



الجمهورية الجزائرية الديمقراطية الشعبية
People's Democratic Republic of Algeria
وزارة التعليم العالي والبحث العلمي
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Immunity and associated pathologies

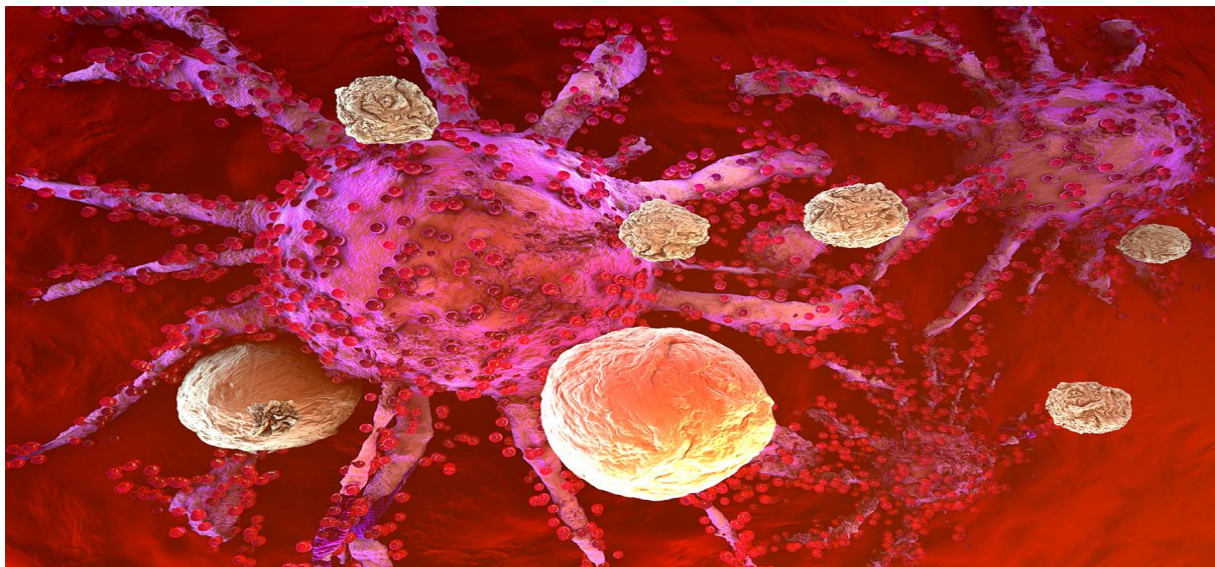
IPA

Course polycopy

Intended for 1st year Master student of Molecular and Cellular Biology

Presented by Dr Arbia ABBES

MCA



2025/2026

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Learning Objectives:

Immunology is the scientific study of the immune system, which plays a crucial role in protecting the body from foreign agents such as viruses and bacteria. This field examines how the immune system distinguishes between self and non-self, and how it can malfunction, leading to autoimmune diseases where the body's defenses mistakenly target its own cells. Immunology encompasses two primary types of immune defense: humoral immunity, which involves antibodies produced by B lymphocytes, and cell-mediated immunity, which is orchestrated by T cells and natural killer (NK) cells. Autoimmune diseases represent a spectrum of disorders, ranging from organ-specific conditions like Hashimoto's disease and type 1 diabetes to systemic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.

Treatment approaches generally focus on managing symptoms and may include medications to suppress the immune response. While immunology has advanced significantly since its inception, many aspects, including the precise triggers of autoimmune diseases and the mechanisms of immune regulation, remain areas of active research. Understanding how the immune system operates not only aids in treating autoimmune conditions but also enhances our overall knowledge of immune health. The complexity of the immune response highlights the importance of further exploration in this vital area of biomedical science, which reflects its deep relevance to human health across diverse populations.

This manuscript addresses the fundamental concepts of immunology to enable students to acquire knowledge regarding the immune system, its fundamentals, its role in signaling, and its dysfunction in the context of various pathologies and to learn how to analyze immunology articles on a specific topic, summarize them, and present them to the class and a panel of instructors.

Recommended prior knowledge:

Students must possess the required knowledge of the pathophysiology of major physiological functions, as well as general pharmacology and toxicology.

Content of the material:

Origin and evolution of the immune system. Immune organs and cells; ontogeny and differentiation of T and B lymphocytes. Innate and adaptive immunity. Structure of antigen receptors; genetics of antigen-specific receptors: structure and synthesis of immunoglobulins. Cytokines and chemokines. Structure and function of MHC molecules; genetic diversity of MHC molecules. The complement system. Autoimmunity and autoimmune diseases. Auto-proliferative diseases. Immunodeficiencies. HIV and the immune system. Antitumor immunity. The concept of immunosurveillance. Molecular and cellular bases of the antitumor immune response. Immunochemical methods. Immunological therapies.

Chapter I: Origin and evolution of immune system

I.1. Origin and evolution of the immune system

The primary function of the immune system is to defend the body from pathogens, which are disease-causing organisms such as viruses and bacteria. Tissues, cells, and proteins in the immune system work together to achieve this function. . To fight infections, the immune system must be able to identify pathogens. Pathogens have molecules called antigens on their surface. Antigens provide a unique signature for the pathogen that enables immune system cells to recognize different pathogens and distinguish pathogens from the body's own cells and tissues.

I.1.1. Immunity

Immunity is divided into two parts determined by the speed and specificity of the reaction. These are named the innate and the adaptive responses, although in practice there is much interaction between them. The term innate immunity is sometimes used to include physical, chemical, and microbiological barriers, but more usually encompasses the elements of the immune system (neutrophils, monocytes, macrophages, complement, cytokines, and acute phase proteins) which provide immediate host defence. The highly conserved nature of the response, which is seen in even the simplest animals, confirms its importance in survival. Adaptive immunity is the hallmark of the immune system of higher animals. This response consists of antigen-specific reactions through T lymphocytes and B lymphocytes. Where as the innate response is rapid but sometimes damages normal tissues through lack of specificity, the adaptive response is precise, but takes several days or weeks to develop. The adaptive response has memory, so that subsequent exposure leads to a more vigorous and rapid response, but this is not immediate (Delves and Roitt , 2000).

I.1.2. Evolution of the immune system

From early on in evolution, organisms have had to protect themselves from pathogens. Mechanisms for discriminating “self” from “non-self” evolved to accomplish this task, launching a long history of host–pathogen co-evolution. Evolution of mechanisms of immune defense has resulted in a variety of strategies. Even unicellular organisms have rich arsenals of mechanisms for protection, such as restriction endonucleases, antimicrobial peptides, and RNA interference.

In multicellular organisms, specialized immune cells have evolved, capable of recognition, phagocytosis, and killing of foreign cells as well as removing their own cells changed by damage, senescence, infection, or cancer. Additional humoral factors, such as the complement cascade, have developed that co-operate with cellular immunity in fighting infection and maintaining homeostasis. Defensive mechanisms based on germline-encoded receptors constitute a system known as innate immunity. In jaw vertebrates, this system is supplemented with a second system, adaptive immunity, which in contrast to innate immunity is based on diversification of immune receptors and on immunological memory in each individual.

In 1989, Charles Janeway Jr. first proposed the paradigm of innate immunity controlling adaptive immunity, providing a solid foundation for subsequent research. Virtually all organisms have at least one form of defense that helps repel disease-causing organisms. Advanced vertebrate animals, a group that includes humans, defend themselves against such microorganisms by means of a complex group of defense responses collectively called the immune system. This protective system evolved from simpler defense mechanisms, but the evolutionary twists and turns that led to its development are not entirely clear. To unravel the path that the vertebrate immune system followed in its evolution, investigators have studied the defense responses of various living organisms. They also have examined the genes of immune system proteins for clues to the genetic origins of immunity (Volchenkov and al., 2012).

I.1.3. Development of immunity

The development of immunity in major animal groups Because the immune system is composed of cells and tissues that do not lend themselves to fossilization, it is impossible to trace the evolution of immunity from the paleontological record. But, because all animals exhibit some general ability to recognize self and to repel foreign substances, it is possible to study the immune capacity of living animals and, based on the relative positions of these animals in the evolutionary tree, to extrapolate a reasonable evolutionary history of the development of immunity.

I.2. Genetic origins of the immune system

Researchers have found many similarities between the structures of proteins involved in antigen recognition and those in cell-to-cell recognition in the immune system. (Antigens are the foreign proteins that antibodies recognize and bind to.) These proteins include the antigen receptors of lymphocytes, the (MHC) proteins, the coreceptors involved in cell-to-cell recognition in immune reactions (such as the receptors named CD4, CD8, and CD28), and the F_C receptor that binds to the stem of the Y-shaped immunoglobulin molecule.

A number of proteins not involved in the immune system also share structural features with these proteins. The main feature similarity is a structure called the immunoglobulin domain. Each protein is composed of one or more Ig domains of nearly identical size. The domains are formed into a loop by bonds between sulfur atoms on the amino acids at the ends. Although each domain is different and serves a different function in the molecule as a whole, the number and order of the amino acids forming each domain are far more similar than would be expected if each had arisen independently in the course of evolution. Equally remarkable is the fact that nerve cells, thymus cells, and T lymphocytes (T cells) in mice and rats carry a surface protein called Thy-1 (thymus-1 antigen) that also has this same basic structure and a similar arrangement of amino acids (Flajnik and Kasahara, 2010).

I.3. Immune system regulatory genes

The similarities suggest that the genes for all these molecules originated from some primitive gene involved in the recognition of one cell by another, which is required for orderly development of a complex, multicellular organism, and that during evolution they had acquired different functions. Researchers named this group of genes and their protein products the immunoglobulin superfamily. The processes where by one ancestral gene could have given rise to such a family of genes include gene duplication, crossing over, and mutation, all of which are discussed in detail in genetics.

Not surprisingly, molecules that have a similar function in different species (e.g., immunoglobulins or MHC components) show an even closer resemblance. By analyzing the number of differences in the amino acids and their position in the polypeptide chains that make up IgM and IgG molecules in, for example, humans, mice, and rabbits and by making reasonable assumptions about mutation rates, scientists can estimate roughly how many

generations would have had to elapse and hence how much time for the present immunoglobulins of these species to have evolved from a common ancestral IgM-like molecule. Such calculations suggest that divergence from the ancestral immunoglobulin took place some 200 million years ago. That was about the same time amphibians are thought to have diverged from the main vertebrate line. So one may conclude that a functional immune system arose even earlier and has continued to provide a defense against foreign agents ever since (Humphrey et al., 1984).

II. The Immune system

II.1. The organs and cells of the immune system

The immune system is the body's primary defense system; it protects the body against pathogens such as bacteria, viruses, and parasites. It consists of specialized cells, organs, and immune cells that work in close collaboration (Delves and Roitt, 2000). Our immune system is made up of individual cells and proteins, as well as entire organs and organ systems. The organs of the immune system include skin and mucous membranes, blood and the organs of the lymphatic system (Fig. 01).

Which organs function as barriers?

The skin and mucous membranes form a barrier that prevents many harmful substances from entering the body. They act as a physical barrier with support from Antibacterial substances, Mucus, Stomach acid and Harmless bacteria on our skin and many of the mucous membranes in our body are also a part of the immune system (Delves and Roitt, 2000).

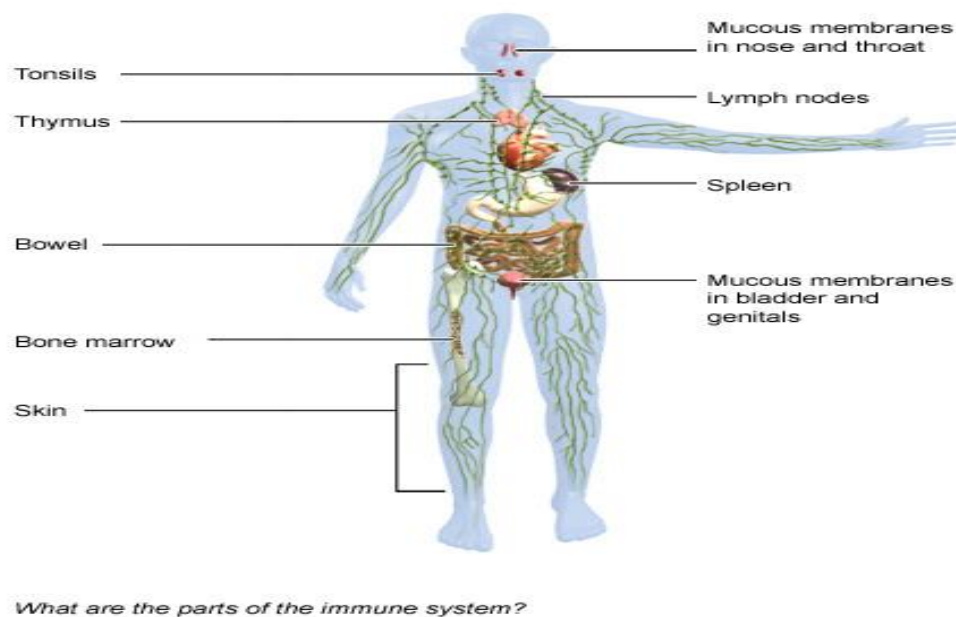


Fig. 01. Different parts of the immune system (Menche N, 2023)

lymphoid organs

Lymphoid organs are defined as specialized structures that provide a stationary framework for the generation, maturation, and interaction of migratory immune cells with antigens, including primary organs like the thymus and bone marrow, and secondary organs such as lymph nodes and the spleen . These primary and secondary organs perform many functions which are crucial for the immune system. The lymphatic system is made up of **Primary and secondary lymphoid organs** (Brandes et al., 2019).

II.1.1. Bone marrow

Bone marrow is found in the medullary cavities, the centres of bones. The bone marrow is where circulating blood cells are produced ; a process known as haematopoiesis. That's where most immune system cells are made and then also multiply. These cells move to other organs and tissues through the bloodstream. At birth, many bones contain red bone marrow, which actively creates immune system cells. Early on in a human's life, this takes place in many bones, but during development haematopoiesis increasingly centres on flat bones so that by puberty, blood production takes place predominantly in the sternum, vertebrae, iliac bones and ribs (Smith, 2007).

II.1.2. Thymus

The thymus is an organ that is critically important to the immune system which serves as the body's defense mechanism providing surveillance and protection against diverse pathogens, tumors, antigens and mediators of tissue damage. Special types of immune system cells called thymus cell lymphocytes (T cells) mature in the thymus. The immune system comprises a complex network of cellular and molecular components subdivided into thymus-independent (innate) and thymus-dependent (adaptive) arms which function synergistically in all immune responses (Markert et al., 2003).

II.1.3. Lymph nodes

Lymph transported through collecting lymphatic vessels is concentrated in the draining lymph node, which is the key location where adaptive immune responses are initiated. The unique lymph node microenvironment is organized to provide optimal conditions for naïve lymphocytes. Lymph nodes are small bean-shaped clumps of tissue found along the lymphatic vessels. The outgoing efferent lymph is composed of a greater number of B cells, together

with T cells that have surveyed antigens in that particular lymph node. Myeloid cells usually turn over locally without exiting the lymph node.

II.1.4. Spleen

The spleen is found in the upper left abdomen, beneath the diaphragm, and is responsible for many different jobs:

- It stores various immune system cells. When needed, these cells travel to other organs in the bloodstream. Scavenger cells (phagocytes) in the spleen act as a filter for germs that get into the bloodstream.
- It breaks down red blood cells (erythrocytes).
- It stores and breaks down platelets (thrombocytes), which are responsible for the clotting of blood, among other things.

Spleen tissue always has a lot of blood flowing through it. It is also very soft, so it can tear easily – for example, when injured in an accident. Surgery is then usually needed because otherwise there's a risk of bleeding to death. If the spleen needs to be removed completely, other immune system organs can carry out its job instead.

II.1.5. Tonsils

The tonsils are lymphoepithelial structures that provide a protective immunological ring at the openings of both digestive and respiratory tracts. Because of their location in the throat and roof of the mouth, they can stop germs entering the body through the mouth or the nose. The tonsils also contain a lot of white blood cells, which are responsible for killing germs.

The human palatine tonsils and the nasopharyngeal tonsil were considered the defense mechanism against ingested or inhaled foreign pathogens. The current findings suggest that the tubal tonsils possess abilities of active transportation of foreign antigens, and will act as inductive and effector sites in the mucosal immune system (Perry and Whyte, 1998).

II.1.6. Mucous membranes

Mucous membranes line the body's internal cavities, including the respiratory, gastrointestinal, and urogenital tracts. These membranes possess unique structural and

immunological features that enable them to defend against pathogens while maintaining normal physiological functions

Mucous membranes support the immune system in other parts of the body, too – such as the respiratory and urinary tracts, and the lining of the vagina. The immune system cells are directly beneath the mucous membranes. They prevent bacteria and viruses from settling and growing there. The mucosal epithelium is composed of specialized cells that secrete mucus, a viscous substance that acts as a physical barrier, trapping and preventing pathogens from reaching underlying tissues. Mucosal surfaces also contain cilia, which move in coordinated patterns to propel mucus and trapped pathogens out of the body(Brandtzaeg, 2009).

II.2. Cells of the immune system

Leukocytes, or white blood cells, are the cellular effectors of immune defence against infectious agents and foreign material. The five main leukocyte types (neutrophils, eosinophils, basophils, monocytes and lymphocytes) all derive from a common multipotent precursor in the bone marrow, the haematopoietic stem cell (Janeway et al., 2001). The innate immune system relies on phagocytes, mast cells, eosinophils, basophils and natural killer (NK) cells. These cells detect and eliminate pathogens rapidly, and several of them also help to initiate the adaptive immune response (Janeway et al., 2001; Marshall et al., 2018).

Neutrophils and macrophages are the main professional phagocytes. Neutrophils are the most abundant phagocytes in the circulation. During acute inflammation they leave the blood and are usually the first cells to reach an infected site, where they engulf and kill microorganisms (Burn et al., 2021). Figure 02 (Brinkmann, 2005) shows a neutrophil in the process of engulfing bacteria. Macrophages, by contrast, reside in tissues. Besides releasing a wide range of soluble mediators, they clear senescent cells and debris and act as antigen-presenting cells that help to activate adaptive immunity (Mass et al., 2023).

Dendritic cells (DCs) are also phagocytic. They are particularly abundant in tissues exposed to the external environment, such as the skin and the mucosae of the nose, lungs, stomach and intestine. After capturing antigens, DCs present them to T cells, one of the central cell types of adaptive immunity; they therefore form the main bridge between innate and adaptive responses (Cabeza-Cabrerizo et al., 2021).

Mast cells are located mainly in connective tissues and beneath mucosal surfaces. By releasing preformed and newly synthesised mediators, they regulate inflammation, and they are best known for their involvement in allergy and anaphylaxis (Dahlin et al., 2022). Eosinophils and basophils are granulocytes, like neutrophils; their mediators contribute to defence against parasites and to allergic diseases such as asthma (Janeway et al., 2001; Marshall et al., 2018). Finally, NK cells are innate lymphocytes that recognise and kill tumour cells and virus-infected cells (Wolf et al., 2023).

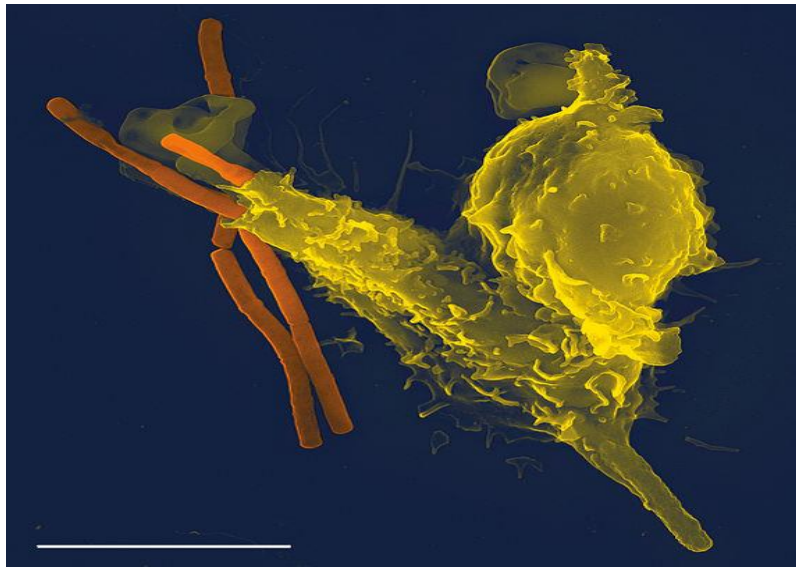


Fig. 02. Scanning electron micrograph (false color) of a neutrophil (yellow) engulfing rods of *Bacillus anthracis* (orange), the causative agent of anthrax. (Brinkmann, 2005)

Adaptive immunity, in contrast, depends on lymphocytes. B and T lymphocytes, the two major lymphocyte classes, also arise from haematopoietic stem cells in the bone marrow (Fig. 03), but they recognize antigens in fundamentally different ways (Janeway et al., 2001; Marshall et al., 2018).

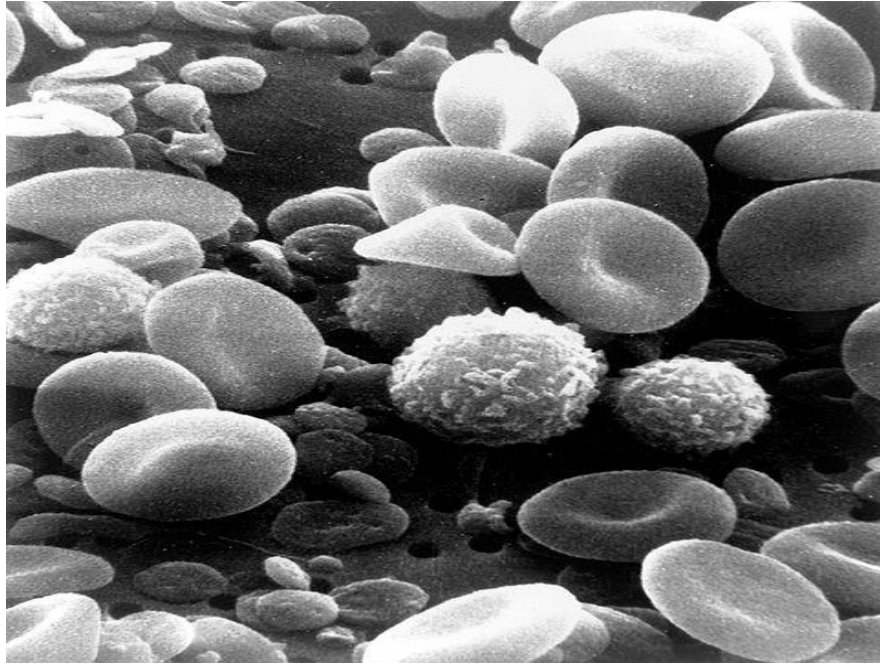


Fig. 03. Blood Cells: *Red blood cells, several white blood cells including lymphocytes, a monocyte, a neutrophil, and many small disc-shaped platelets (Menche N, 2023)*

T cells do not recognize free antigen. Their receptor binds a “non-self” target, such as a pathogen-derived peptide, only after the antigen has been processed and displayed at the cell surface by a “self” major histocompatibility complex (MHC) molecule (Marshall et al., 2018). Two main subsets of conventional T cells are distinguished. Cytotoxic (killer) T cells, which are mostly CD8⁺, kill cells infected with viruses or other pathogens, as well as damaged or dysfunctional cells. Helper T cells, which are mostly CD4⁺, do not directly kill infected cells or eliminate pathogens; instead, they regulate innate and adaptive responses and determine the type of immune response mounted against a given pathogen (Marshall et al., 2018). A third, less abundant population, the $\gamma\delta$ T cells, can recognize intact antigens that are not presented by MHC molecules (Ribot et al., 2021).

B cells recognize antigen differently. Their antigen receptor is a membrane-bound antibody that binds native antigens, including whole pathogens, without any need for processing. Because each B-cell clone expresses a distinct antibody, the B-cell receptor repertoire as a whole corresponds to the full range of antibodies that the organism can produce (Marshall et al., 2018).

II.3. Ontogeny and differentiation of T and B lymphocytes

T and B lymphocytes are the only cells able to recognize individual antigenic epitopes specifically, and they are therefore responsible for acquired, antigen-specific immunity. B cells can differentiate into antibody-secreting plasma cells and mediate humoral immunity, whereas T cells are the effectors of cell-mediated immunity (Janeway et al., 2001; Marshall et al., 2018). The following sections describe how each lineage develops, from haematopoietic progenitors to mature naïve lymphocytes.

At rest, T and B lymphocytes cannot be distinguished by morphology. Both are small cells, 8–10 µm in diameter, with a large nucleus containing dense heterochromatin and a narrow rim of cytoplasm with few mitochondria, ribosomes and lysosomes (Janeway et al., 2001; Cano & Lopera, 2013). After antigenic stimulation they enlarge, and their cytoplasm and organelle content increase. What distinguishes the two lineages is their antigen receptor: the T-cell receptor (TCR) or the B-cell receptor (BCR). The genes encoding these receptors are assembled by somatic DNA recombination, a process that generates an immense diversity of antigen specificities (Schatz & Swanson, 2011).

II.3.1. T lymphocytes (T cells)

Ontogeny

T-cell development begins outside the thymus. Haematopoietic stem cells (HSCs), located first in the fetal liver and later in the bone marrow, give rise to multipotent progenitors. A subset of them initiates transcription of the recombination-activating genes *RAG1* and *RAG2*, giving rise first to lymphoid-primed multipotent progenitors and subsequently to common lymphoid progenitors (CLPs) (Rothenberg et al., 2008). The thymus contains no self-renewing progenitors, so thymopoiesis depends throughout life on the continuous import of blood-borne thymus-seeding progenitors (Hosokawa & Rothenberg, 2021).

Only a small number of these cells enter the thymus, where they become early thymic progenitors (ETPs) and are gradually reprogrammed into mature, functional T cells. Each step of this programme is coupled with migration of the developing thymocytes through distinct thymic niches, which provide the stage-specific signals needed for further differentiation (Fig. 04; Rothenberg et al., 2008).

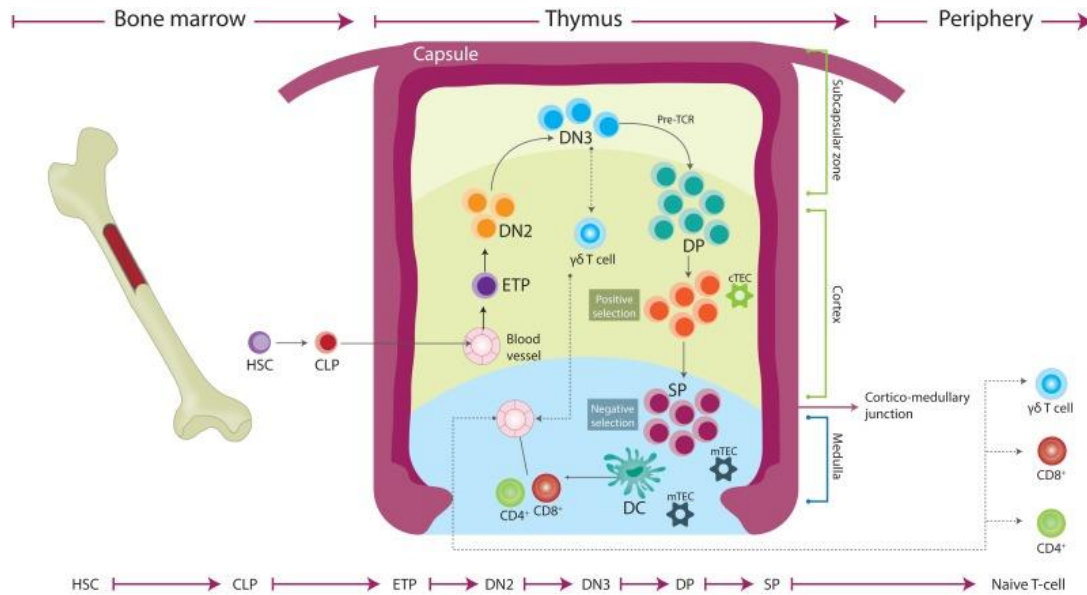


Fig.04. Overview of T Cell development and maturation (Rothenberg *et al*, 2008.). Abbreviations. *HSC*: Haematopoietic stem cells, *CLP*: Common lymphoid progenitors, *ETP*: Early thymic progenitors, *DN*: Double negative; *DP*: Double positive, *SP*: Single positive, *DC*: Dendritic cells, *cTECs*: Cortical thymic epithelial cells, *mTECs*: Medullary thymic epithelial cells.

ETPs form a small, heterogeneous and highly proliferative population that can still generate B cells, NK cells, myeloid cells and DCs in addition to T cells (Hosokawa & Rothenberg, 2021). Progenitors enter the thymus near the corticomedullary junction, guided by the chemokine receptors CCR7 and CCR9 and their respective ligands, CCL19/CCL21 and CCL25 (Zlotoff et al., 2010). In the thymic stroma they encounter abundant Notch ligands and growth factors such as Kit ligand and interleukin-7 (IL-7), which trigger and sustain their proliferation and differentiation at the earliest stages of T-cell development. Engagement of the Notch1 receptor by Delta-like ligands is indispensable for T-lineage specification and, at the same time, blocks alternative fates: when Notch1 is inactivated, B cells develop in the thymus instead of T cells (Radtke et al., 1999; Hosokawa & Rothenberg, 2021).

Early thymocytes express neither CD4 nor CD8 and are therefore called double-negative (DN) cells. In the mouse, DN cells are subdivided according to CD44 and CD25 expression; ETPs belong to the CD44⁺CD25⁻ DN1 fraction, and acquisition of CD25 marks the transition to the CD44⁺CD25⁺ DN2 stage (Rothenberg et al., 2008). During these stages the cells lose their B-cell potential and begin to express the proteins required for TCR gene rearrangement, such as RAG1 and RAG2, together with molecules needed for TCR assembly and signalling, including the CD3 chains, the kinases LCK and ZAP-70, and the adaptor protein LAT (Hosokawa & Rothenberg, 2021). At the DN3 stage, cells follow one of two pathways. Cells that express a $\gamma\delta$ TCR give rise to $\gamma\delta$ T cells, a population with distinct functional properties, whereas cells that express a TCR β chain continue along the $\alpha\beta$ lineage and will later generate CD4⁺ or CD8⁺ T cells (Hosokawa & Rothenberg, 2021; Ribot et al., 2021). The main features of these two T-cell lineages are compared in Table 1.

In $\alpha\beta$ -lineage cells, the newly rearranged TCR β chain pairs with the invariant pre-TCR α chain to form the pre-TCR. Signalling through this receptor, a checkpoint known as β -selection, drives proliferation and induces co-expression of CD4 and CD8 (Hosokawa & Rothenberg, 2021). The resulting double-positive (DP) thymocytes form the largest cell population in the thymus. Once the TCR α locus has rearranged, DP cells express a complete $\alpha\beta$ TCR and undergo positive selection in the cortex, where cortical thymic epithelial cells present self-peptides on MHC class I and class II molecules (HLA-I and HLA-II in humans). Only thymocytes whose TCR binds these complexes with intermediate affinity and avidity receive survival signals (Klein et al., 2014; Ashby & Hogquist, 2024). Most DP cells, about 75–80%, fail to bind HLA-I or HLA-II adequately and die by apoptosis, a process termed death by neglect (Klein et al., 2014; Yates, 2014). Once negative selection is also taken into account, only about 1–5% of DP thymocytes eventually complete their maturation (Cano & Lopera, 2013; Yates, 2014).

Table 1. Main features of $\alpha\beta$ and $\gamma\delta$ T cells. Adapted from Carding and Egan (2002) and updated with Ribot et al. (2021) and Nanda and Alphonse (2024). CTL: cytotoxic T lymphocyte; IEL: intraepithelial lymphocyte; MHC: major histocompatibility complex; TCR: T-cell receptor.

Feature	$\alpha\beta$ T cells	$\gamma\delta$ T cells
Antigenreceptor	$\alpha\beta$ TCR associated with the CD3 complex	$\gamma\delta$ TCR associated with the CD3 complex
Theoreticalreceptordiversity	$\sim 10^{15}$	$\sim 10^{20}$
Antigen recognition	Peptides presented by MHC molecules	Protein and non-protein antigens (e.g. phosphoantigens), mostly without MHC presentation
MHC restriction	Yes	Rare
Phenotype	CD4 ⁺ or CD8 ⁺	Mostly CD4 ⁻ CD8 ⁻ ; intestinal IELs often CD8 $\alpha\alpha$ ⁺
Frequency	65–75% of blood lymphocytes	1–5% of blood lymphocytes; 25–60% of T cells in the gut
Tissue distribution	Blood and lymphoid tissues	Blood, epithelial tissues and lymphoid tissues
Effectorfunctions	Cytotoxicity (mainly CD8 ⁺ CTLs) and cytokine secretion	Cytotoxicity and cytokine secretion (e.g. IFN- γ , IL-17)
Main roles	Antigen-specific protection and pathogen clearance	Immunoregulation, immunosurveillance (including of tumours) and tissue homeostasis

Positive selection also sets the co-receptor fate of each cell. Thymocytes selected on HLA-I become CD4⁻CD8⁺ single-positive (SP) cells, whereas those selected on HLA-II become CD4⁺CD8⁻ SP cells (Klein et al., 2014). SP thymocytes then move to the medulla, where a second checkpoint, negative selection, takes place. There, medullary thymic epithelial cells (mTECs) and DCs expose the thymocytes to a broad array of self-antigens. mTECs achieve this through promiscuous gene expression, an unusual transcriptional programme, controlled largely by the autoimmune regulator AIRE, that allows low-level expression of many tissue-restricted self-antigens normally found only in peripheral organs (Anderson & Su, 2016). SP cells that bind self-peptides presented by HLA-I or HLA-II with high affinity or avidity are eliminated by apoptosis, which removes most potentially autoreactive clones (Klein et al., 2014; Ashby & Hogquist, 2024).

Cells that survive negative selection complete their maturation and become naïve T cells, so called because they have not yet encountered the antigen recognised by their TCR. They then exit the thymus and recirculate continuously through the secondary lymphoid organs, where antigen encounter leads to their priming and differentiation into effector cells with specialised phenotypes (Ashby & Hogquist, 2024).

II.3.2. B lymphocytes (B cells)

Ontogeny

Unlike T cells, B cells complete their early development in the bone marrow. This process takes place in specialised microenvironments, or “niches”, formed by stromal cells. These niches deliver stimuli that activate transcription factors, which in turn induce or repress the target genes controlling the survival, proliferation and differentiation of B-cell precursors; among these factors, stromal-derived IL-7 is critical for early B-cell development (Pieper et al., 2013). As shown in Fig. 05, HSCs give rise successively to early lymphoid progenitors (ELPs) and CLPs. CLPs can generate NK cells and DCs, as well as a B220⁺ progenitor population termed common lymphoid progenitor-2 (CLP-2). Described in the mouse, CLP-2 is not yet restricted to the B lineage, since it retains both B- and T-cell potential (Martin et al., 2003). Commitment to the B-cell fate is established later, as cells progress through the pro-B, pre-B and immature B-cell stages (Pieper et al., 2013). Whereas T-cell development requires

Notch1 signalling, B-cell development in the bone marrow depends on its absence or suppression (Radtke et al., 1999; Pieper et al., 2013).

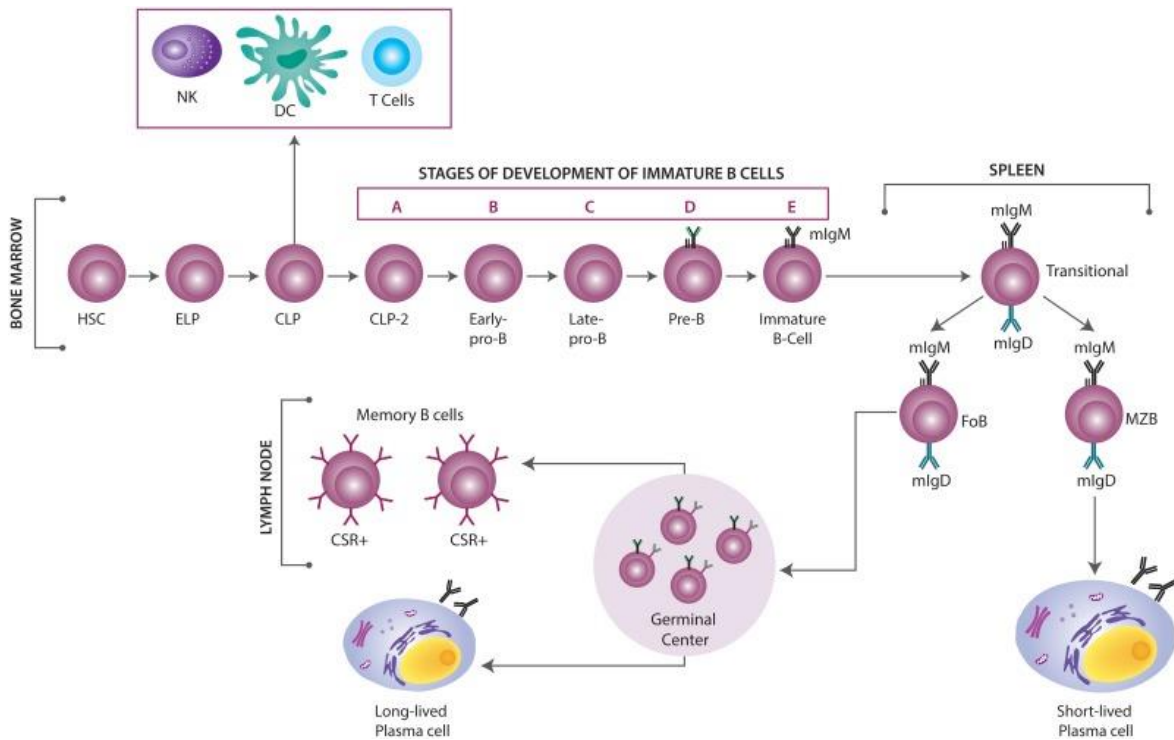


Fig. 05. Cell development and B Cell subsets Abbreviations. *HSC*: haematopoietic stem cell, *ELP*: early lymphoid progenitor *CLP*: common lymphoid progenitor, *CLP-2*: common lymphoid progenitor-2, *NK*: Natural Killer cell, *DC*: Dendritic Cell, *CSR*: classswitch recombination, *mIgM*: membrane-bound immunoglobulin M, *mIgD*: membrane-bound immunoglobulin D, *FoB*: follicular B Cells, *MZB*: marginal zone B Cells. Adapted from Cano and Lopera (2013).

The diversity of the BCR repertoire is generated by V(D)J recombination. In developing B cells, the immunoglobulin heavy-chain locus rearranges first: a diversity (D) segment is joined to a joining (J) segment, and a variable (V) segment is then joined to the DJ unit. The light-chain genes, which have no D segments, are assembled later by V–J joining (Schatz & Swanson, 2011). Recombination is initiated by the RAG1–RAG2 complex, which recognises the recombination signal sequences (RSSs) flanking each gene segment and introduces a DNA double-strand break between the RSS and the coding segment; the broken ends are then joined by the non-homologous end-joining pathway (Schatz & Swanson, 2011). The resulting membrane-bound immunoglobulins (mIg) form the antigen-binding part of the BCR. The size of the repertoire generated in this way is difficult to measure, and published estimates vary:

the naïve human antibody repertoire is thought to comprise at least 10^{12} unique antibodies (Briney et al., 2019), and Cano and Lopera (2013) report that the BCR repertoire can recognise more than 5×10^{13} different antigens.

Although each B cell carries two heavy-chain alleles and several light-chain alleles (at the κ and λ loci), a mature B cell expresses a receptor of a single specificity. This allelic exclusion results from two features of the recombination process: rearrangement is activated on one allele at a time, and the expression of a functional chain sends a feedback signal that prevents further rearrangement of the other allele (Vettermann & Schlissel, 2010).

The pre-BCR is the checkpoint that tests the product of heavy-chain recombination. The μ heavy chain (Ig μ) pairs with the surrogate light chain (SLC), a heterodimer of two invariant, germline-encoded proteins, VpreB and $\lambda 5$, and associates with the signalling subunits Ig α (CD79a) and Ig β (CD79b) to form the pre-BCR of B-cell precursors (Fig. 06A; Herzog et al., 2009; Winkler & Mårtensson, 2018). The pre-BCR does not need antigen to signal. In the mouse, this signalling has been linked to positively charged arginine residues in the non-immunoglobulin tail of $\lambda 5$, which promote receptor aggregation (Ohnishi & Melchers, 2003) and interaction with negatively charged heparan sulfate on stromal cells (Bradl et al., 2003). In humans, stromal galectin-1 has been identified as a ligand of the pre-BCR (Gauthier et al., 2002).

Once expressed at the cell surface, the pre-BCR triggers a burst of proliferation that expands the pool of pre-B cells carrying a functional heavy chain. Pre-BCR signalling then promotes light-chain rearrangement and is therefore needed for further B-cell differentiation (Herzog et al., 2009). The pre-BCR also appears to limit the development of autoantibody-producing B cells, and defects at this checkpoint may contribute to multifactorial autoimmune diseases (Keenan et al., 2008; von Boehmer & Melchers, 2010).

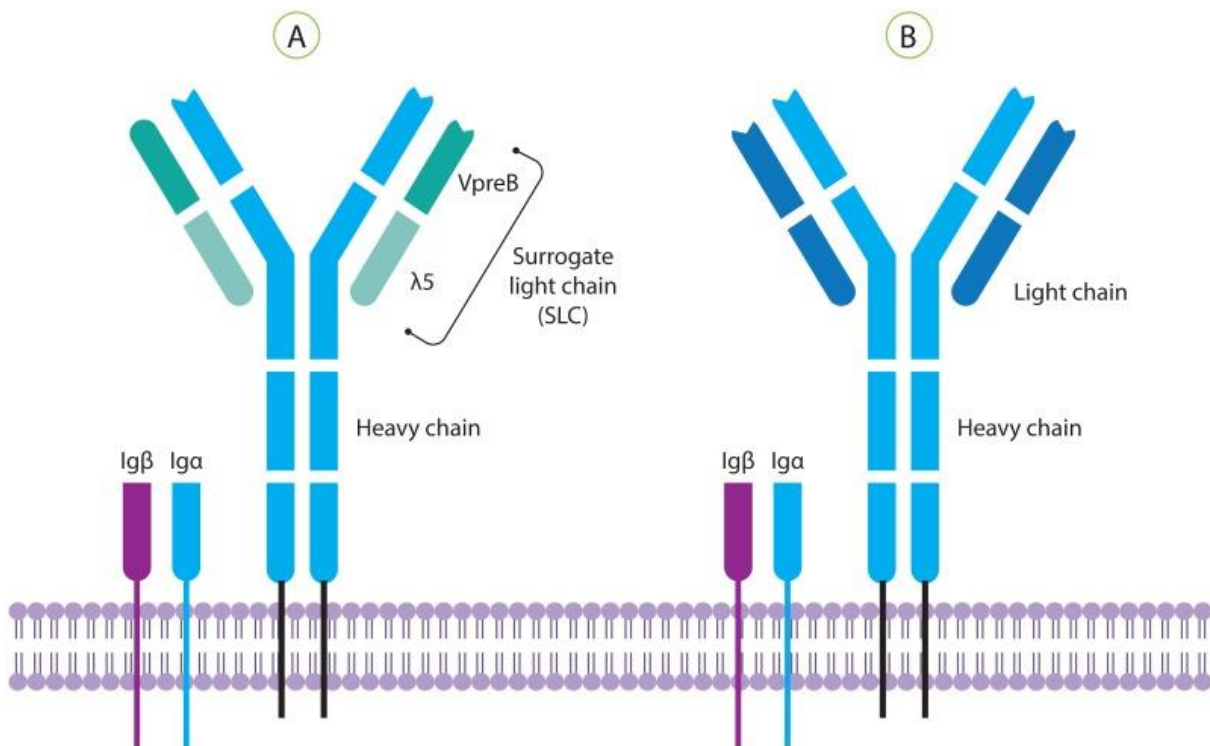


Fig. 06. A) pre-B Cell receptor. **B)** B cell receptor. *Ig α* : Accessory Immunoglobulin alpha (CD79a), *Ig β* : Accessory Immunoglobulin beta (CD79b) (Pieper and al., 2013).

II.4. Structure of antigen receptors

The key to mounting an immune response is that the host cells must be coordinated to generate an appropriate immune response against the pathogenic invaders. Antigen receptors recognize specific molecular structures and recruit adaptors through their effector domains, triggering trans-membrane transduction signaling pathway to exert immune response. The T cell antigen receptor (TCR) and B cell antigen receptor (BCR) are the primary determinant of immune responses to antigens. Their structure determines the mode of signaling and signal transduction determines cell fate, leading to changes at the molecular and cellular level. Studies of antigen receptor structure and signaling revealed the basis of immune response triggering, providing clues to antigen receptor priming and a foundation for the rational design of immunotherapies.

In recent years, the increased research on the structure of antigen receptors has greatly contributed to the understanding of immune response, different immune-related diseases and even tumors. In this review, we describe in detail the current view and advances of the antigen structure and signaling. Antigen receptors are formed of pairs of polypeptide chains: α/β or γ/δ in the T-cell receptor (TCR) and heavy (H)/light (L) in immunoglobulin (Ig). TCR molecules are heterodimers, and Ig molecules are tetramers of two H and two L chains.

One of the central problems encountered in understanding adaptive immunity is to explain how lymphocytes recognize the enormous diversity of microbes that may invade the body. Given that microorganisms change rapidly, the immune system must be able to respond not only to existing organisms but also, within reason, to newly evolved organisms. The ability of the adaptive immune responses to respond specifically to an enormous number of foreign antigens implies the existence of an enormous number of different lymphocytes, each with its own specific antigen receptors. This then raises the question, How do lymphocytes generate such an enormous diversity of antigen-specific receptors?

The ability of a receptor to bind an antigen is determined by the shape of its binding site. This shape depends on the folding of its peptide chains, which is governed, in turn, by their amino acid sequences. Each amino acid in a peptide chain exerts an influence on its neighboring amino acids, which determines their relative configuration. The shape of a peptide chain therefore represents the contributions of all amino acids in the chain as the peptide assumes its most energetically favorable conformation. The folding of a protein is determined by its amino acid sequence, and that sequence is determined by the sequence of bases in the DNA coding for that protein. The diversity of antigen receptors implies either a corresponding diversity in the genes coding for these receptors or a mechanism that generates diversity from a limited pool of receptor genes. This second mechanism is now known to be the method employed by the adaptive immune system.

II.4.1. Receptor-Antigen Binding

When an antigen and its receptor bind, they interact through the chemical groups on the surface of the antigen and on the complementarity determining regions (CDRs) of the receptor. In classic chemical reactions, molecules are assembled through the establishment of firm, covalent bonds. These bonds can be broken only by the input of a large amount of energy, energy that is not readily available in the body. In contrast, the formation of noncovalent bonds provides a rapid and reversible way of forming complexes and permits

reuse of molecules in a way that covalent bonding would not allow. However, noncovalent bonds act over short intermolecular distances and, as a result, form only when two molecules approach each other very closely. The binding of an antigen to a BCR or TCR is exclusively noncovalent, so the strongest binding occurs when the shape of the antigen and the shape of the receptor conform to each other. This requirement for a close conformational fit has been likened to the specificity of a key for its lock.

The major bonds formed between an antigen and its receptor are hydrophobic (Fig. 07). When antigen and antibody molecules come together, they exclude water molecules from the area of contact. This frees some water molecules from constraints imposed by the proteins and is therefore energetically stable. (The bond can be likened to two wet glass microscope slides stuck together. Anyone who has tried to separate two wet glass slides can confirm the effectiveness of this type of bonding.)

A second type of binding between an antigen and its receptor is through hydrogen bonds. When a hydrogen atom covalently bound to one electronegative atom (e.g., an—OH group) approaches another electronegative atom (e.g., an O=C—group), the hydrogen is shared between the two electronegative atoms. This situation is energetically favorable and is called a hydrogen bond. The major hydrogen bonds formed in antigen-receptor interaction are O—H—O, N—H—N, and O—H—N. Hydrogen bonds are already present between proteins and water molecules in aqueous solution, so the binding of an antigen to its receptor by hydrogen bonds requires relatively little net energy change.

Electrostatic bonds formed between oppositely charged amino acids may contribute to antigen-receptor binding, but the charge on many protein groups is commonly neutralized by electrolytes in solution. As a result, the importance of electrostatic bonding is unclear.

When two atoms approach very closely, a nonspecific attractive force, called a van der Waals force, becomes operative. It occurs as a result of a minor asymmetry in the charge of an atom because of the position of its electrons. This force, although very weak, may become collectively important when two large molecules come into contact. It can therefore contribute to antigen-receptor binding.

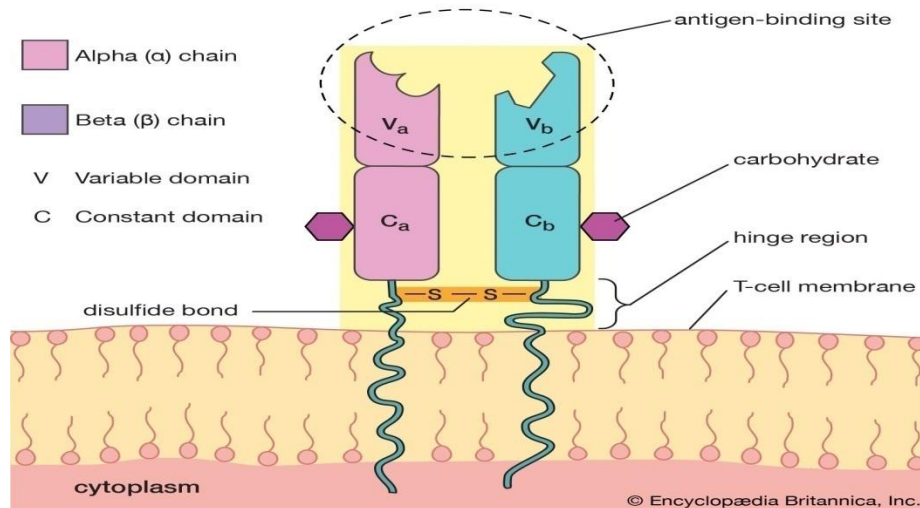


Fig. 07. The basic structure of a typical T-cell antigen receptor. Klenerman, P. (2025).

The binding of a receptor to its antigen is therefore mediated by multiple noncovalent bonds. Each bond is relatively weak in itself, but collectively the bonds may have a significant binding strength. All these bonds act only across short distances and weaken rapidly as that distance increases. Electrostatic bond and hydrogen bond strengths are inversely proportional to the square of the distance between the interacting molecules; the van der Waals forces and hydrophobic bonds are inversely proportional to the seventh power of that distance. Thus the strongest binding between an antigen and its receptors occurs when their shapes match perfectly and multiple noncovalent bonds form. Antigens can bind to receptors when they fit less than perfectly, although the strength of this binding will be much reduced.

II.4.2. Antigen Receptor Genes

The information needed to make all proteins, including antigen receptors, is stored in an animal's genome. All that is required for the production of these molecules is that the necessary genes be turned on. Once the appropriate genes are activated, they can be transcribed into RNA and translated into the appropriate receptor protein on B or T cells. It has been estimated that mammals can produce up to 10^{15} different antigen receptors to be expressed on B and T cells. In order to produce this enormous diversity, they use fewer than 500 genes!

Multiple genes code for each receptor peptide chain. Several genes code for each variable region, whereas only one codes for a constant region. As a result, the single constant-region

gene can be combined with any one of several different variable-region genes to make a complete receptor chain (Fig. 08). Instead of having genes for all possible receptor chains, it is only necessary to have genes for all the variable regions and to join these to an appropriate constant-region gene as required. In addition, antigen receptor chains may be paired in different combinations to yield even greater diversity, a process called combinatorial association.

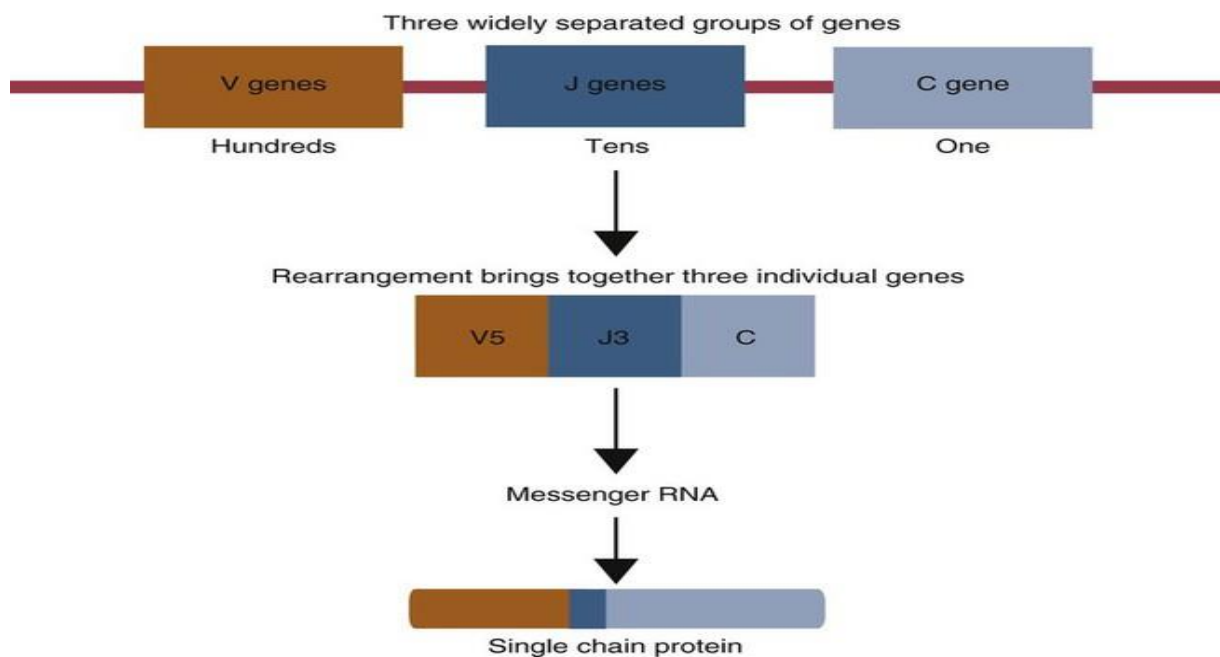


Fig. 08. Antigen receptor chains are coded for by three genes originating in three widely separated groups. The genes for a complete receptor chain are assembled by joining one gene selected from each group (Kindt and al., 2007).

II.5. Structure and synthesis of immunoglobulins

Antibodies are the secreted form of the B-cell receptor. An antibody is identical to the B-cell receptor of the cell that secretes it except for a small portion of the C-terminus of the heavy-chain constant region. In the case of the B-cell receptor the C-terminus is a hydrophobic membrane-anchoring sequence, and in the case of antibody it is a hydrophilic sequence that allows secretion. Since they are soluble, and secreted in large quantities, antibodies are easily obtainable and easily studied. For this reason, most of what we know about the B-cell receptor comes from the study of antibodies.

Antibody molecules are roughly Y-shaped molecules consisting of three equal-sized portions, loosely connected by a flexible tether. Three schematic representations of antibody structure, which has been determined by X-ray crystallography, are shown in Fig.09. The aim of this part of the chapter is to explain how this structure is formed and how it allows antibody molecules to carry out their dual tasks—binding on the one hand to a wide variety of antigens, and on the other hand to a limited number of effector molecules and cells. As we will see, each of these tasks is carried out by separable parts of the molecule. The two arms of the Y end in regions that vary between different antibody molecules, the V regions. These are involved in antigen binding, whereas the stem of the Y, or the C region, is far less variable and is the part that interacts with effector cells and molecules.

An antibody molecule consists of two heavy chains (approximately 50 kDa each) and two light chains (approximately 25 kDa each). These chains are interconnected by disulfide bonds, resulting in a characteristic Y-shaped structure with a total molecular weight of approximately 150 kDa. Each antibody molecule possesses distinct variable and constant regions.

The variable region confers an antibody's antigen-binding specificity. This region contains two fragment antigen binding (Fab) domains, each capable of binding a specific epitope (the part of an antigen recognized by an antigen). Consequently, a single antibody molecule can simultaneously bind two identical epitopes on the same antigen.

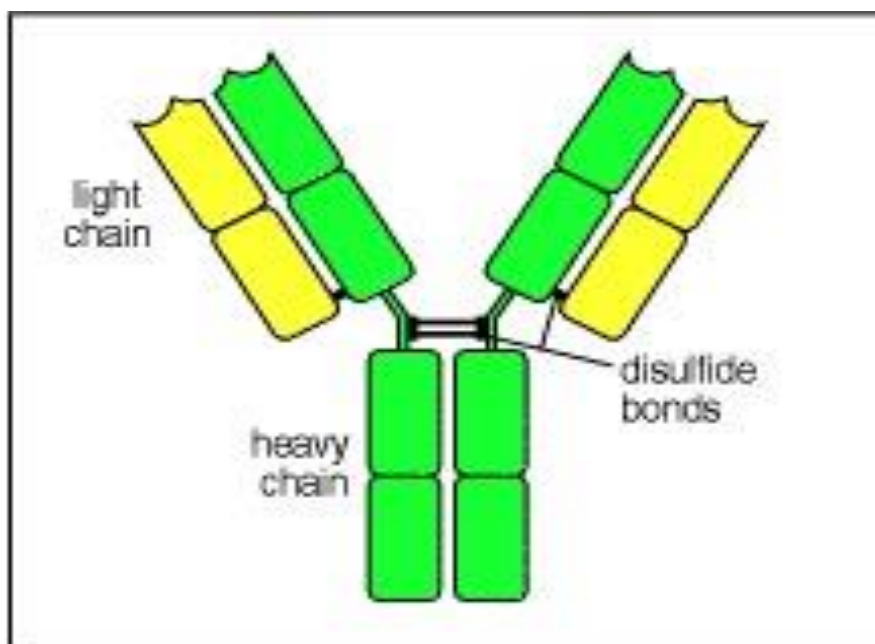


Fig. 09. Immunobiology (Janeway and al., 2001)

The constant region of an antibody houses the fragment crystallizable (Fc) region, which mediates interactions with Fc receptors expressed on the surface of immune cells such as leukocytes (white blood cells), macrophages, and natural killer cells. These interactions are crucial for triggering various effector functions of the immune system. Two hinge regions link the Fab and Fc portions of each antibody molecule.

II.5. 1. Types of antibodies and their roles

There are five main types (isotypes) of antibodies, each with distinct structures and functions: IgG, IgM, IgA, IgE, and IgD. Alberts, B., Bray, D., Hopkin, K., Johnson, A. D., Lewis, J., Raff, M., ... & Walter, P. (2015). *Essential cell biology*. Garland science.

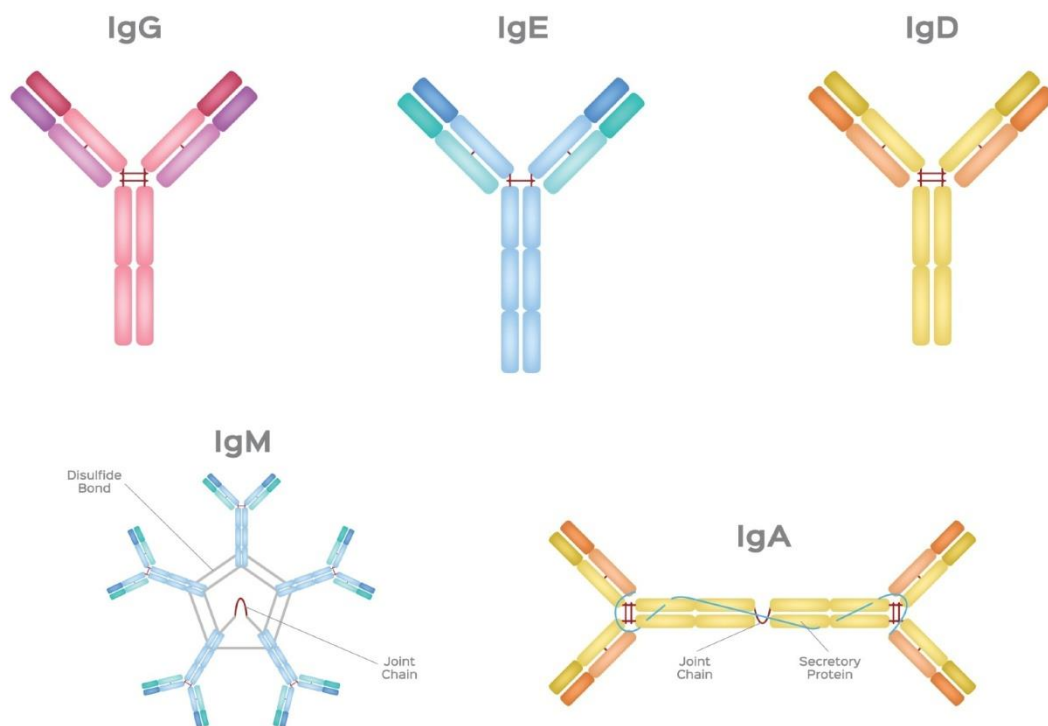


Fig.09. the five major antibody (immunoglobulin) types: IgG, IgE, IgD, IgM, and IgA, each with its unique structural configuration and functional properties. Image Credit: gritsalak karalak/Shutterstock.com

IgG - Immune defense and passive immunity

IgG is the most abundant immunoglobulin in human serum, comprising 70–75% of the total immunoglobulins present in the blood. Structural variations, primarily in the hinge region (size and flexibility) and the number and position of disulfide bonds, lead to four distinct IgG subclasses: IgG1, IgG2, IgG3, and IgG4, each with unique effector functions. Protein antigens typically elicit IgG1 and IgG3 responses, whereas IgG2 and IgG4 are generally associated with responses to polysaccharide antigens. IgG's high abundance makes it the principal component of the humoral immune system, which relies on antibodies (immunoglobulins) present in extracellular fluids to neutralize pathogens. Owing to its small, monomeric structure and high diffusibility, IgG is the most abundant type of immunoglobulin in the extracellular fluid. Its ability to bind Fc receptors on phagocytic or other lytic effector cells enables the initiation of antibody-dependent cell-mediated cytotoxicity (ADCC).

ADCC is a cell-mediated immune mechanism whereby effector cells, including phagocytes and natural killer cells, lyse antibody-coated target cells. IgG promotes phagocytosis by initiating opsonization, a process whereby pathogens (e.g., bacteria) are coated with antibodies, thereby enhancing their recognition and subsequent engulfment by phagocytes.

IgG plays a crucial role in both passive and active immunity. IgG is the only immunoglobulin capable of placental transfer, conferring passive immunity to the developing fetus and neonates for the first few months after birth. Studies have demonstrated the positive impact of heat-treated colostrum on serum IgG concentrations in newborn calves, thereby enhancing passive immunity. However, this approach may also have associated side effects. In contrast, active immunity can be induced through vaccination. For instance, a single dose of a COVID-19 mRNA vaccine may generate high levels of IgG targeting the receptor-binding domain (RBD) of SARS-CoV-2 and elicit surrogate neutralization in individuals with a prior COVID-19 diagnosis.

IgM - Early response and complement activation

IgM is the largest antibody isotype and the first to be secreted during a primary immune response to an antigen or microbe. It thereby provides immediate immune responses, regulates immune functions, and maintains immunological tolerance. Representing approximately 5% of serum immunoglobulins, IgM is typically found as a pentamer composed of five identical subunits connected by disulfide bonds and a J chain. This

pentameric form is the predominant structure of IgM. In addition to the pentameric form, IgM also exists as secretory IgM, which is synthesized by plasma cells in mucosal-associated lymphoid tissue (MALT) and other glandular tissues. A monomeric form of IgM is expressed on the surface of B cells, enabling recognition and B-cell activation. Because of its large size and polymeric structure, IgM is largely confined to the intravascular space and exhibits a lower binding affinity for individual epitopes compared to IgG. Despite this lower affinity, the pentameric form of IgM possesses ten antigen-binding sites, resulting in high avidity (overall binding strength). This high avidity makes IgM a highly efficient excellent activator of the classical complement pathway and a potent inducer of agglutination.

IgM antibodies are frequently used as a diagnostic criterion for acute or recent disease, but unconventional IgM-specific responses have been described in SARS-COV-2 infection.

IgA - Mucosal protection and neonatal defense

IgA represents 10–15% of the total immunoglobulins in serum and is found in various secretions, including nasal mucus, saliva, breast milk, and intestinal fluid. Two subclasses of IgA exist—IgA1 and IgA2—which are distinguished primarily by structural differences in their hinge regions. IgA plays a crucial role in mucosal immunity, providing the first line of defense against pathogens encountered at mucosal surfaces, such as those of the respiratory and gastrointestinal tracts. The importance of IgA in maintaining mucosal immunity is highlighted by the increased susceptibility to infections observed in individuals with IgA deficiency. Studies have shown that IgA is critical for clearing gastrointestinal viral pathogens such as rotavirus and preventing reinfection. Furthermore, selective IgA deficiency appears to be a significant risk factor for recurrent chest infections, particularly in asthmatic patients.

IgE - Allergies and parasite defense

IgE is the least common immunoglobulin in serum, present at concentrations roughly 10,000 times lower than those of IgG in healthy individuals. Clinically, however, IgE levels rise dramatically in type I hypersensitivity reactions, including allergic diseases like bronchopulmonary aspergillosis and parasitic infections such as schistosomiasis. In response to pathogens, IgE antibodies bound to mast cells through high-affinity receptors undergo cross-linking upon antigen binding. This cross-linking triggers mast cell degranulation, releasing inflammatory mediators that recruit eosinophils to the site of infection. The

eosinophil-mediated killing of the pathogen can then occur through mechanisms resembling antibody-dependent cell-mediated cytotoxicity (ADCC).

IgD - B and T cell regulation

IgD is primarily known for its role as a B-cell antigen receptor (BCR) on the surface of B cells. It is thought to participate in various B-cell processes, including maturation, maintenance of peripheral tolerance, activation, and potentially even silencing. The precise mechanisms and full extent of IgD's functions are still under investigation. Still, current evidence suggests a role in regulating B-cell selection and maintaining B-cell homeostasis, thus influencing humoral immune responses.

II.5.2. Where are antibodies produced?

Antibodies are produced by B cells (specialized white blood cells). When an antigen comes into contact with a B cell, it causes the B cell to divide and clone. These cloned B cells or plasma cells — release millions of antibodies into your bloodstream and lymph system. Antibodies are located in various areas of your body, including your skin, lungs, tears, saliva and even breast milk. In fact, high amounts of antibodies are present in colostrum (a thick fluid secreted by the breasts for a few days after giving birth). That's why breastfeeding can boost your baby's immune system.

II.5.3. Antibody synthesis by B cells

Since their discovery, the development of B and T cells and antibody synthesis have been extensively studied in several vertebrate species. Today, we know that their complex development starts with B cell maturation in the primary lymphoid tissue (mammals – fetal liver and adult marrow, birds, bursa of Fabricius) followed by differentiation and activation in the secondary lymphoid tissue (lymph nodes and spleen), with or without the help of T cells. In their differentiated stage, antibodies produced by B cells are not secreted, but instead, they are expressed and bound to the plasma membrane where they will serve as antigen receptors. A mature B cell is coated with thousands of these receptors on its surface.

At this point, fully mature B cells circulate in the vast network of lymphatic vessels between the lymph nodes and the spleen until they encounter an antigen. The antigen-dependent

activation of B cells results in the development of memory B cells, which express membrane-bound antibodies and have long half-lives; or plasma cells, also known as effector B cells, which secrete large amounts of the specific antibody and have relatively short half-lives.

The activation process is irreversible and it creates plasma or memory cells which will only produce a specific antibody during their entire lifetime. To guarantee a successful immune response, the organism often develops antibodies that are specific to different epitopes (i.e. different parts of the antigen) of the same antigen; thus, increasing the chances of successful immune response and elimination of the virulent, pathogenic or toxic component.

The activation of B cells is a complex process occurring in two stages. In the first stage, the antigen binds to the B cells receptors on the surface of the mature lymphocytes, leading to the internalization and digestion of these molecules and subsequent complexation with the major histocompatibility complex (MHC II) located on the surface of B cells. The second activation stage can either be a T cell-dependent or independent process. Some microbial components (e.g. bacterial polysaccharides) can activate B cells directly without the help of T cells, however, for the vast majority of antigens, T cell-mediated activation is the most common route of activation. In this case, the antigen complexed with the MHC II is recognized by effector T cells initially primed by other antigen-presenting cells (APC) to recognize the same antigen. This cross-linked recognition triggers the activation of the T cell which, in turn, secretes cytokines that induce the quick differentiation and proliferation of the B cell. This process results in thousands of clonal copies of the activated B cell that secrete antibodies with the same recognition pattern.

The activation process is irreversible and it creates plasma or memory cells which will only produce a specific antibody during their entire lifetime. To guarantee a successful immune response, the organism often develops antibodies that are specific to different epitopes (i.e. different parts of the antigen) of the same antigen; thus, increasing the chances of successful immune response and elimination of the virulent, pathogenic or toxic component.

II.6. Innate immune system

The innate immune response represents the first line of defense against pathogens within the body. Consequently, we outline the components and the key functions of the innate immune system to enhance understanding. A central feature of the innate reaction is recruitment and activation of neutrophils at the site of infection to eradicate pathogens. The same process occurring inappropriately leads to the inflammation of connective tissue diseases, vasculitis, and the systemic inflammatory response syndrome. There is intense interest in the mechanisms underlying the process for the development of new antiinflammatory therapies. During the very early stages of infection or tissue damage, there is release of cytokines from activated macrophages. Two of these, granulocyte and granulocytemacrophage colony stimulating factors, stimulate division of myeloid precursors in the bone marrow, releasing millions of cells into the circulation and causing a characteristic neutrophil leucocytosis. Neutrophils, like most cells involved in immune responses, are not static within a particular compartment, but are mobile cells that travel round the body. They normally flow freely in the blood as the circulating pool, or roll along the vascular endothelium as the marginating pool. To home to a site of infection, neutrophils use a multistep process involving proinflammatory mediators, adhesion molecules, chemoattractants, and chemokines. Although most work was initially done within the neutrophil system, it is now clear that all leucocytes, including lymphocytes, use this mechanism of localisation. The recruited neutrophils phagocytose organisms by making pseudopodia (projections of cytoplasmic membrane) which form a membrane-bound vesicle (phagosome) around the particle. This fuses with neutrophil cytoplasmic granules to form the phagolysosome. In this protected compartment killing of the organism occurs by a combination of two mechanisms. The oxygen-dependent response or respiratory burst, involves the sequential reduction of oxygen by an NADPH oxidase leading to production of toxic oxygen metabolites, such as hydrogen peroxide, hydroxyl radicals, and singlet oxygen. The oxygen-independent response, uses the highly toxic cationic proteins and enzymes (eg, myeloperoxidase and lysozyme) contained within the neutrophil cytoplasmic granules. Ingestion and killing of organisms is fold more effective if the particle is first opsonised with specific antibody or complement (C'). These molecules bind to neutrophil Fc and C' receptors, increasing adhesion between particle and phagocyte and priming the cell for activation. Some encapsulated organisms, such as pneumococcus and haemophilus are not susceptible to neutrophil phagocytosis unless first coated with antibody.

This explains why individuals with antibody deficiency are so susceptible to this type of infection, despite normal neutrophil numbers and function. The innate immune system serves as a rapid and broadspectrum defense mechanism. This section delves into the primary functions of the innate immune system, highlighting how it recognizes pathogens, initiates inflammatory responses, and adapts through trained immunity.

II.7. Adaptive immune system

In this section, we will provide a detailed overview of the adaptive immune system and its components, focusing on the key role of T and B cells in the immune response. We will describe antigen recognition and cellular immunity of T cells, humoral immunity of B cells, and how the adaptive immune system generates immune memory to safeguard the body's long-term immune defenses. The characteristic of adaptive immunity is the use of antigen-specific receptors on T and B cells to drive targeted effector responses in two stages. First, the antigen is presented to and recognised by the antigen specific T or B cell leading to cell priming, activation, and differentiation (Fig.10), which usually occurs within the specialised environment of lymphoid tissue. Second, the effector response takes place, either due to the activated T cells leaving the lymphoid tissue and homing to the disease site, or due to the release of antibody from B cells. Formation of antigen-specific receptors on T and B cells B and T lymphocytes develop from progenitor cells within the bone marrow. B cells remain within the marrow for the duration of their development, but T cells migrate to the thymus at an early stage as thymocytes. The production of antigen-specific receptors in both cell types is the result of an unusual process of random rearrangement and splicing together of multiple DNA segments that code for the antigen-binding areas of the receptors (complementarity-determining regions). Gene rearrangement occurs early in the development of the cells, before exposure to antigen, which leads to the production of a repertoire of over 10¹¹ T-cell receptors and antibody specificities, adequate to cover the range of pathogens likely to be encountered in life.

The process for B-cell receptor rearrangement will be described, but the mechanism is similar for the T-cell receptor. There are four segments of gene involved in receptor formation called the variable (V), diversity (D), joining (J), and constant (C) regions. These are found on different chromosomes within the developing cell.

The segments are cut out by nucleases and spliced together using ligases (a product of the recombination activation genes, RAG-1 and RAG-2). This forms the final gene sequence from which protein will be transcribed to form the receptor molecule. There are several ways

in which clonal diversity occurs. First, there is a multiplicity of all these regions within the DNA (V=25–100 genes, D~25 genes, and J~50 genes), but only one of each is needed. There is combinational freedom in that any one of the genes can join with any one other to form the final VDJ region. Second, the splicing is inaccurate and frameshift in basepairs leads to the production of a different aminoacid (junctional diversity). Third, the enzyme deoxyribonucleotidyltransferase can insert nucleotides to further alter the sequence. A greater repertoire of B-cell receptors is produced as further immunoglobulin gene rearrangement occurs during B-cell division after antigen stimulation (somatic hypermutation).

In T lymphocytes the receptor has two forms. The most common consists of a heterodimer of an α and β chain, each with a constant and variable domain. The other form (<10% T cells) has γ and δ chains (the function of this type of T-cell receptor bearing cell remains uncertain).

The T-cell receptor forms a complex with the CD3 molecule, with its associated signalling molecules (Fig.10). In B cells the gene product is a membranebound form of IgM, initially expressed alone and later with IgD. Early in B-cell development this molecule acts as the antigen receptor, being able to induce signal transduction in a similar way to the T-cell receptor. The membrane bound molecule can also internalise antigen, inducing processing, and re-expression for antigen presentation to T cells. After B-cell activation the secreted form of antibody is produced by plasma cells. Despite the similarities in gene rearrangement processes, the T and B cell receptors recognise antigen differently. The T-cell receptor binds linear peptides usually of eight to nine aminoacids. This generally means antigen that has been broken down by intracellular processing. Antibody recognises the conformational structure (shape) of epitopes, and such antigens do not require processing.

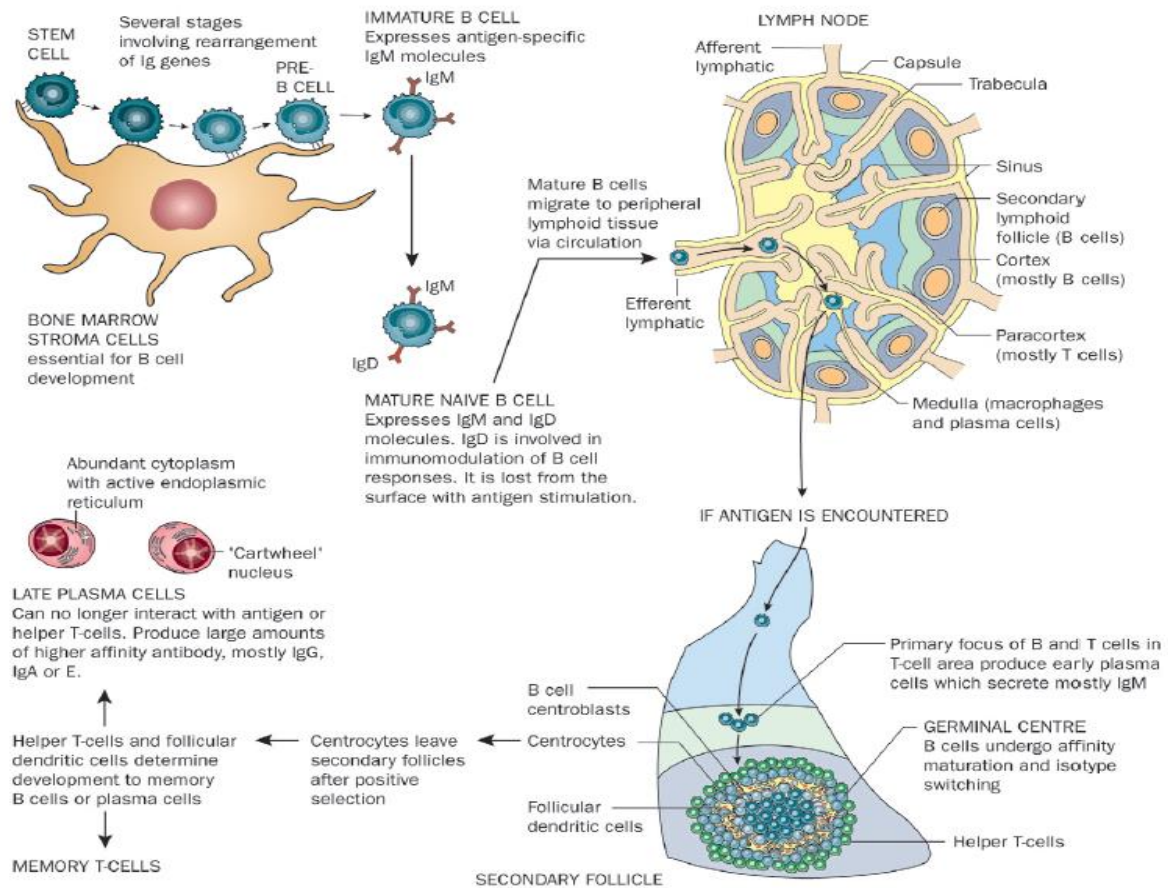


Fig.10. The role of T and B lymphocytes in specific immunity (Garred et al., 1995)

III. Cellular communication

In order for cells to work effectively they need to be recruited to sites of inflammation and appropriately activated. This is achieved by the interaction of cellular receptors which signal internally to the nucleus, and external factors, such as cytokines, which are able to bind the receptors, and with other adhesion molecules. Cytokines and chemokines are secreted proteins with growth, differentiation, and activation functions that regulate the nature of immune responses. Cytokines are involved in nearly every facet of immunity and inflammation, from induction of the innate immune response to the generation of cytotoxic T cells and the development of antibodies by the humoral immune system. The combination of cytokines that are produced in response to an immune insult determines which arm of the immune system will be activated. For this update, recent advances in our understanding of cytokines will be discussed, which includes the IL-10, IL-17, and IL-27 families. (Allergy,. 2006).

Cytokines are involved in virtually every facet of immunity and inflammation, including innate immunity, antigen presentation, bone marrow differentiation, cellular recruitment and activation, and adhesion molecule expression (Fig. 10). Which cytokines are produced in response to an immune insult determines initially whether an immune response develops and subsequently whether that response is cytotoxic, humoral, cell-mediated, or allergic. For presentation in this review, cytokines are grouped according to those that are predominantly mononuclear phagocytic-derived or T-lymphocyte-derived; those that predominantly mediate cytotoxic (antiviral and anticancer), humoral, cell-mediated, or allergic immunity; and those that are immunosuppressive. Fig. 11. Summary of actions of cytokines and chemokines. Cytokines derived predominantly from mononuclear phagocytic cells are uniquely important in innate immunity and both initiate immune responses and generate symptoms associated with infections and inflammatory disorders. Phenotype of the subsequent immune response is a function of the repertoire of cytokines produced by the responding T-helper lymphocytes. TH1-like lymphocytes are characterized by their production of IFN- γ and primarily contribute to cellular immunity. TH2-like lymphocytes are characterized by their production of IL-4, IL-5, IL-9, and IL-13 and contribute to humoral and allergic responses. TH3-like lymphocytes have immunosuppressive tendencies and are characterized by their production of IL-10 and TGF- β .

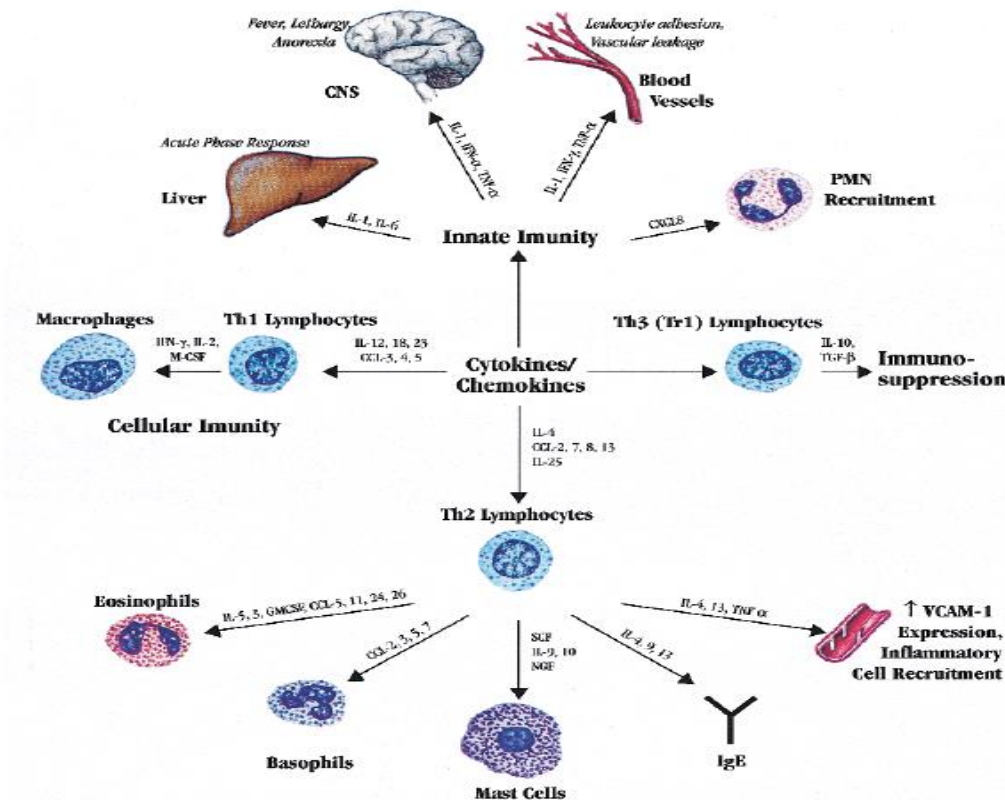


Fig. 11. Actions of cytokines and chemokines. Borish and Steinke (2003).

III.1. Chemokines

Chemokines are particular members of the cytokine family that have a key role in leucocyte migration (table 2). They have substantial chemotactic function (inducing the directional movement of cells). Chemokines are named by the position of two cysteine (C) residues compared with the other amino acids (X). The two main subgroups are CXC (chemokines) and CC (chemokines). Chemokines are produced by most cells on stimulation with proinflammatory cytokines or bacterial products and chemokine receptors are found on all leucocytes. The effects of chemokines are more prolonged than other chemoattractants such as complement activation products, as they bind to glycosamino-glycans on cell surfaces and the extracellular matrix. Chemokines that cause recruitment of leucocytes are termed inflammatory. Additionally, there are lymphoid chemokines which regulate leucocyte positioning within the spleen and other lymphoid tissues (Cyster., 1999).

Table. 02. Chemokines and associated function(Cyster., 1999).

*Refers to a double cysteine amino acid structure (-CC-) within the cytokine; in some cases this is interspersed with another amino acid (-CXC-). RANTES=regulated on activation, normal T-cell expressed and secreted.

Chemokine	Class*	Sites of production	Biological activity
Macrophage chemoattractant protein-1	-CC-	Macrophages, fibroblasts, keratinocytes	Attracts monocytes and memory T cells to inflammatory sites
Macrophage inflammatory protein-1 α	-CC-	Macrophages	Attracts monocytes and T cells
MIP-1 β macrophage inflammatory protein-1 β	-CC-	Monocytes, macrophages, endothelial cells, T and B cells	Attracts monocytes and CD8+ T cells
RANTES	-CC-	Platelets and T cells	Attracts monocytes, T cells, and eosinophils
Interleukin 8	-CXC-	Macrophages	Attracts neutrophils, naive T cells

Chemokines are a group of small (8 to 12 kD) molecules able to induce chemotaxis in a variety of cells including neutrophils, monocytes, lymphocytes, eosinophils, fibroblasts, and keratinocytes. These molecules regulate activity through interactions with members of the 7-transmembrane, G-protein-coupled receptor superfamily. This chapter will use the new systematic nomenclature with the common names listed in parentheses the first time the chemokine is described.⁵⁸ To date, 47 chemokines and 18 chemokine receptors have been described, which are listed in Table III, along with the known chromosomal location and physiological properties of each. Many of the chemokine receptors can bind more than one ligand, allowing extensive overlap and redundancy of chemokine function. Although chemotaxis stands as the hallmark feature of chemokines, their physiological role is more complex than originally described, and new functions continue to be identified. Originally, chemokines were described as inflammatory, being produced at the site of infection or in response to a proinflammatory stimulus. The inflammatory chemokines recruit and activate leukocytes to mount an immune response and initiate wound healing. Other chemokines have now been shown to have a homeostatic or housekeeping function. These functions are involved in adaptive immune responses including lymphocyte trafficking, hematopoiesis,

antigen sampling in secondary lymphoid tissue, and immune surveillance.⁵⁹ Homeostatic chemokines tend to be expressed in specific tissues or organs, whereas inflammatory chemokines can be produced by many cell types in multiple locations.

III.1.1. Classification of chemokines

As a group, the chemokines exhibit between 20% and 50% homology and are characterized by the presence of three to four conserved cysteine residues. They can be subdivided into four families, based on the positioning of the N-terminal cysteine residues (Table 3). The C-X-C subfamily is characterized by the separation of the first two cysteines by a variable amino acid. In the C-C subfamily, the cysteine residues are adjacent to each other. The majority of the known chemokines are contained in these two families. In addition, these groups may be distinguished by their primary target cell: the C-X-C subfamily primarily targeting neutrophils and the C-C family targeting monocytes and T cells. A new family of chemokines has been identified that lack the first and third cysteine, containing a single cysteine residue in the conserved position, and are referred to as the “C” subfamily. This subfamily includes the lymphocyte-specific chemotactic peptide XCL1 (lymphotactin). A fourth subfamily (CX3C) has been identified in which the two N-terminal cysteine residues are separated by three variable amino acids. To date, this family only has one member, CX3CL1 (fractalkine), and it is unique in that it is the only membrane-bound chemokine with a mucin-like glycosylated stalk.

III.2. Cytokines

Cytokines are small molecular weight messengers secreted by one cell to alter the behaviour of itself or another cell (table. 04). Cytokines send intracellular signals by binding to specific cell-surface receptors. Although most are soluble, some may be membrane-bound, making the differentiation between cytokine and receptor difficult. Cytokines are produced by virtually all cells and have a wide variety of functions. The biological effect depends on the cytokine and the cell involved, but typically these molecules will affect cell activation, division, apoptosis, or movement. They act as autocrine, paracrine, or endocrine messengers. Cytokines produced by leucocytes and having effects mainly on other white cells are termed interleukins. Cytokines that have chemoattractant activity are called chemokines. Those that cause differentiation and proliferation of stem cells are called colony-stimulating factors. Those that interfere with viral replication are called interferons.

Table.03. Cytokines (Kumar, P., & Clark, M. L. (2012).

Cytokine	Source	Mode of action
Interleukin 1	Macrophages	Immune activation; induces an inflammatory response
Interleukin 2	Mainly T cells	Activates T (and natural killer) cells and supports their growth. Formerly called T cell growth factor
Interleukin 3	T cells	Mainly promotes growth of haemopoietic cells
Interleukin 4	T helper cells	Lymphocyte growth factor; involved in IgE responses
Interleukin 5	T helper cells	Promotes growth of B cells and eosinophils
Interleukin 6	Fibroblasts	Promotes B cell growth and antibody production, induces acute phase response
Interleukin 7	Stromal cells	Lymphocyte growth factor; important in the development of immature cells
Interleukin 8	Mainly macrophages	Chemoattractant
Interleukin 10	CD4 cells, activated monocytes	Inhibits the production of interferon α , interleukin 1, interleukin 6, tumour necrosis factor α , and stops antigen presentation
Interleukin 12	Monocyte/macrophages	Augments T helper 1 responses and induces interferon γ
Interleukin 13	Activated T cells	Stimulates B cells
Granulocyte colony stimulating factor	Mainly monocytes	Promotes growth of myeloid cells
Monocyte colony stimulating factor	Mainly monocytes	Promotes growth of macrophages
Granulocyte-macrophage colony stimulating factor	Mainly T cells	Promotes growth of monomyelocytic cells
Interferon α	Leucocytes	Immune activation and modulation
Interferon β	Fibroblasts	Immune activation and modulation
Interferon γ	T cells and natural killer cells	Immune activation and modulation
Tumour necrosis factor α	Macrophages	Stimulated generalised immune activation as well as tumour necrosis. Also known as cachectin
Tumour necrosis factor β	T cells	Stimulates immune activation and generalised vascular effects. Also known as lymphotoxin
Transforming growth factor β	Platelets	Immunoinhibitory but stimulates connective tissue growth and collagen formation

III.3. Interferons

Interferons are a major class of cytokine that have a particular role in immunity. They are divided into type 1 (and interferons) and type 2 (or immune interferon). Type 1 interferons have potent antiviral activity and are produced mainly by fibroblasts and monocytes as a reaction to infection. Both and interferon bind to the same cellular receptor and protect uninfected cells by inducing the intracellular production of molecules that inhibit or interfere with viral RNA and DNA production. They increase the expression of MHC class I molecules leading to enhanced recognition of virally infected cells by specific cytotoxic T lymphocytes. Type 1 interferons also have antiproliferative function. interferon is used in the treatment of chronic hepatitis B and C infections in combination with antiviral drugs as well as in some forms of leukaemia. interferon reduces the relapse rate in subgroups of patients with multiple sclerosis. Interferon has different functions, acting directly on the immune system to activate macrophage and neutrophil intracellular killing, stimulate natural killer cell function, and enhance antigen presentation by increasing MHC class II expression on antigen presenting cells. Interferon γ is only produced by cells of the immune system and uses a separate

receptor to that of the type 1 interferons. It is used in the treatment of a specific congenital neutrophil defect (chronic granulomatous disease) and in patients with defects in the production of interferon γ or its receptor, and in the adjunct therapy of some macrophage-based infections (leishmaniasis, atypical mycobacterial disease).

The Major Histocompatibility Complex (MHC) is a vital component of the immune system, governing immune recognition, antigen presentation, and tissue compatibility. Its diverse and polymorphic nature allows for the recognition of a wide range of antigens and plays a critical role in adaptive immune responses. Beyond immune functions, the MHC is associated with disease susceptibility and has implications in transplantation, vaccine development, and even evolutionary biology. Advancements in understanding the MHC and its interactions with T cells have paved the way for innovative approaches in immunotherapy and personalized medicine. Manipulating MHC presentation holds promise for enhancing immune responses against cancer, infectious diseases, and autoimmune disorders. Furthermore, continued research on the MHC may uncover its roles in non-immune processes, contributing to our understanding of development, reproduction, and tissue homeostasis. The Major Histocompatibility Complex (MHC) is a highly diverse and essential part of the immune system in vertebrates. Also known as the Human Leukocyte Antigen (HLA) complex in humans, MHC molecules play a crucial role in presenting antigens to T cells, regulating immune responses, and facilitating tissue compatibility. In this study one will delve into the intricacies of the MHC, exploring its structure, functions, and implications beyond immune responses.

III.4. Structure and classes of MHC molecules

MHC molecules are transmembrane proteins that are classified into two main classes: MHC class I and MHC class II. MHC class I molecules are found on the surface of almost all nucleated cells and present antigens derived from intracellular pathogens to cytotoxic T cells. MHC class II molecules are primarily expressed on antigenpresenting cells, such as dendritic cells, macrophages, and B cells, and present antigens to helper T cells. MHC and tissue compatibility The MHC also plays a crucial role in determining tissue compatibility for transplantation. The compatibility of MHC molecules between the donor and recipient is crucial for successful organ or tissue transplantation. Mismatched MHC molecules can trigger immune responses, leading to graft rejection. Matching MHC profiles between donors and recipients is a key consideration in transplantation medicine. Lei F (2023)

There are two classes of MHC molecules involved in adaptive immunity, MHC I and MHC II (Fig.11). MHC I molecules are found on all nucleated cells; they present normal **self**-antigens as well as abnormal or nonself pathogens to the effector T cells involved in cellular immunity. In contrast, MHC II molecules are only found on macrophages, dendritic cells, and B cells; they present abnormal or nonself pathogen antigens for the initial activation of T cells. Both types of MHC molecules are transmembrane glycoproteins that assemble as dimers in the cytoplasmic membrane of cells, but their structures are quite different. MHC I molecules are composed of a longer α protein chain coupled with a smaller β_2 microglobulin protein, and only the α chain spans the cytoplasmic membrane. The α chain of the MHC I molecule folds into three separate domains: α_1 , α_2 and α_3 . MHC II molecules are composed of two protein chains (an α and a β chain) that are approximately similar in length. Both chains of the MHC II molecule possess portions that span the plasma membrane, and each chain folds into two separate domains: α_1 and α_2 , and β_1 , and β_2 . In order to present abnormal or non-self-antigens to T cells, MHC molecules have a cleft that serves as the antigen-binding site near the “top” (or outermost) portion of the MHC-I or MHC-II dimer. For MHC I, the antigen-binding cleft is formed by the α_1 and α_2 domains, whereas for MHC II, the cleft is formed by the α_1 and β_1 domains (Fig. 12).

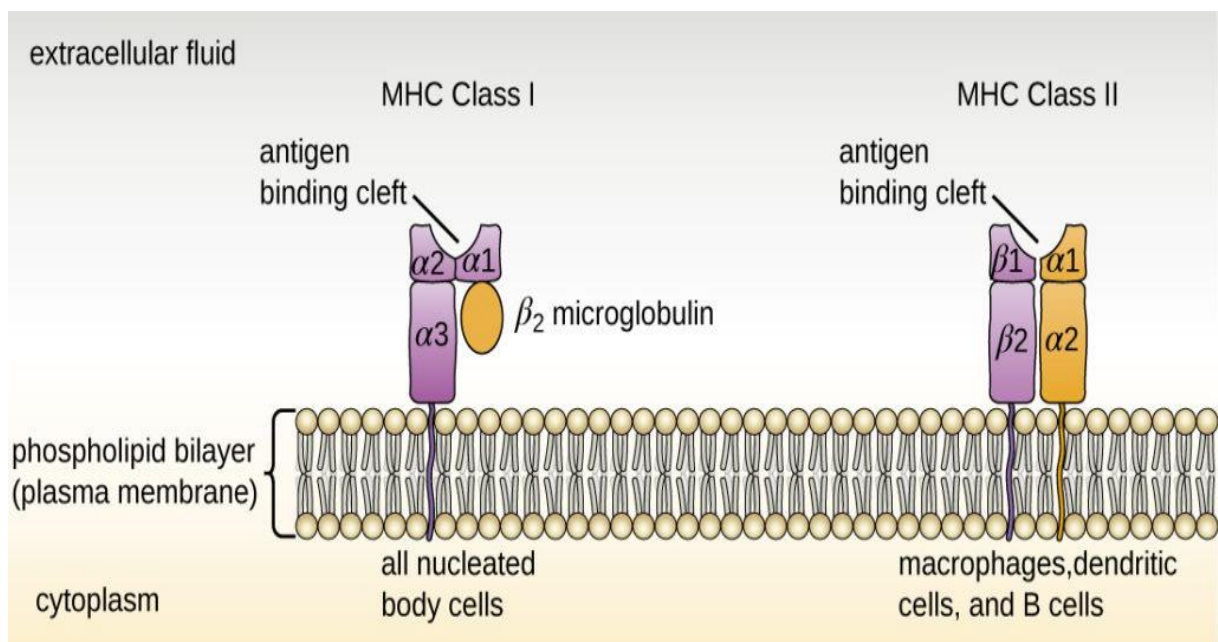


Fig.12. MHC I are found on all nucleated body cells, and MHC II are found on macrophages, dendritic cells, and B cells (along with MHC I). The antigen-binding cleft of MHC I is formed by domains α_1 and α_2 . The antigen-binding cleft of MHC II is formed by domains α_1 and β_1

Lei F (2023).

III.5. Complement

The complement system has several important functions in innate immunity and consists of at least 20 serum glycoproteins, some being regulatory. These are activated in a cascade sequence, with amplification stages. This means that activation of a single molecule will lead to thousands of molecules being generated. There are three pathways of complement activation that can be driven by the presence of a foreign substance (figure 1), the classical by antigen-antibody reactions, the alternative by polysaccharides from yeasts, and gram negative bacteria. The more recently identified mannan binding lectin pathway feeds into the classical sequence by activating it independently of the C1rs complex and is stimulated by mannose containing proteins and carbohydrates on microbes, including viruses and yeasts. Many of the components of the classical and alternative pathway are homologous, suggesting the pathways were initially derived from the same sequence. All three pathways converge with the activation of the central C3 component. This leads to a final common pathway, with assembly of C5–C9 forming a transmembrane pore (membrane attack complex) in the cell surface and death by osmotic lysis. The perforins, which are produced by cytotoxic T lymphocytes and natural killer cells, have a similar structure. Complement activation is focused on the surface of a cell or organism, which forms a protected site where the inhibitory proteins have limited access. Normal host cells bear the complement receptor type 1 and decay accelerating factor, which inhibit C3 convertase and prevent progression of complement activation. However, microbes lack these molecules and are susceptible to complement. In addition to lysis of organisms, complement has other anti-infective functions. There is the opsonic action of C3b, the release of soluble C3a and C5a, which are anaphylatoxins and increase vascular permeability allowing proteins, such as antibody, to penetrate the tissue, and the chemotactic activity of C5a that induces an inflammatory infiltrate. Complement also has a role within the specific immune response; its activation and deposition within immune complexes helps to target these to complement-receptor bearing antigen-presenting cells, such as B lymphocytes and follicular dendritic cells.

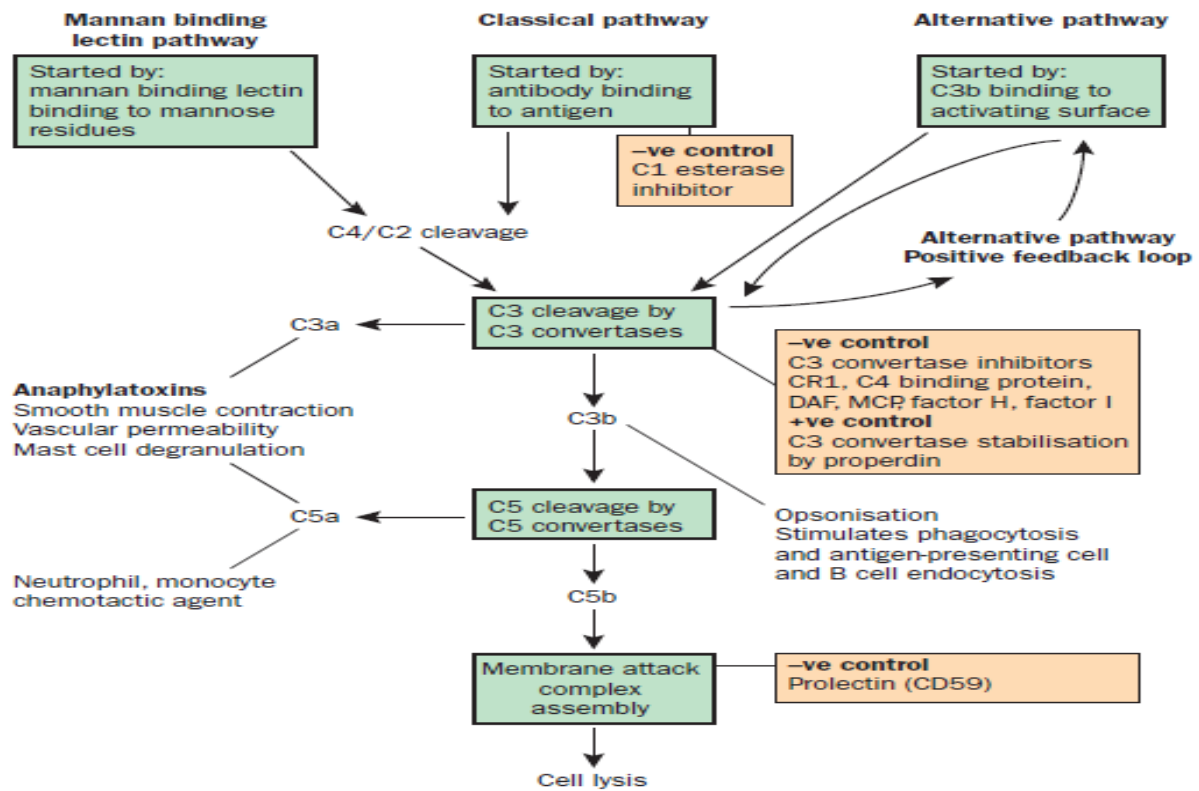


Fig.13. Complement pathways The three pathways of complement activation. Regulatory proteins are shown in orange. Components of activation pathways are shown in green. (MacKay and al., 2000).

III.6. Genetic diversity of MHC molecules

Protein products of the major histocompatibility complex (MHC, termed human leukocyte antigen, HLA, in humans) play a fundamental role in immune processes of vertebrates. In particular, antigens coded by MHC class I genes are responsible for recognition of cells containing proteins of foreign origin. Individual alleles of MHC genes code proteins that differ in the spectrum of short peptides they bind and transport across the cellular membrane. On the cell surface, MHC glycoproteins present these peptides to T-cells. Under normal conditions, negative selection in the thymus eliminates most self-peptide reactive T-cells. Therefore, mature T-cells can recognize and be activated only by foreign-peptide presenting cells. Activation of T-cells is the principal component of both cellular and antibody immune response (Austyn and Wood, 1994). The immune system is in a constant arms race with pathogens, driven by mutation, genetic diversity, selection, and recombination. As a result, the immune system has evolved to be highly adaptable, enabling it to protect the body against

a wide array of pathogens. The adaptability and evolution of the major histocompatibility complex (MHC) are primarily shaped by two key factors: polymorphism and polygeny.

The MHC gene is polygenic, meaning it contains multiple different MHC class I and class II genes that interact additively to determine the final receptor product. This process, also known as codominance, ensures that the protein products of each gene are expressed and capable of presenting antigens to T cells. Because of this polygeny, individuals typically express at least three different MHC class I molecules and three to four class II molecules on their cells.

The MHC genes are among the most polymorphic in the genome, with over 200 variants of most MHC class I and II genes. These genes also exhibit the largest number of single nucleotide polymorphisms (SNPs) linked to nearly 500 traits and diseases. In fact, the MHC region remains one of the least characterized parts of the human genome. Due to their high polymorphism, most people express at least six different MHC class I molecules and eight different MHC class II molecules on their cells. The likelihood of inheriting two identical MHC genes is negligible, further increasing the genetic diversity and the range of pathogen-derived peptides the MHC can present. Moreover, the protein products from a single MHC gene can differ by up to 20 amino acids, making each protein distinct. This variation, which is concentrated in the peptide-binding groove, directly influences antigen presentation. The amino acid residues in the peptide-binding groove, known as the sequence motif, dictate the binding specificity of the MHC for different peptides. This variability enhances the diversity of antigen presentation, allowing the immune system to recognize and respond to a broad spectrum of pathogens. Understanding these sequence motifs can aid in the development of therapeutics, such as vaccines, by identifying which pathogenic peptides are likely to bind to specific MHC molecules Hedrick (2002)

Although the most important known function of the gene products of the MHC is the processing and presentation of antigens to T cells, many other genes map within this region; some of these are known to have other roles in the immune system, but many have yet to be characterized functionally. Fig. 13 shows the detailed organization of the human MHC.

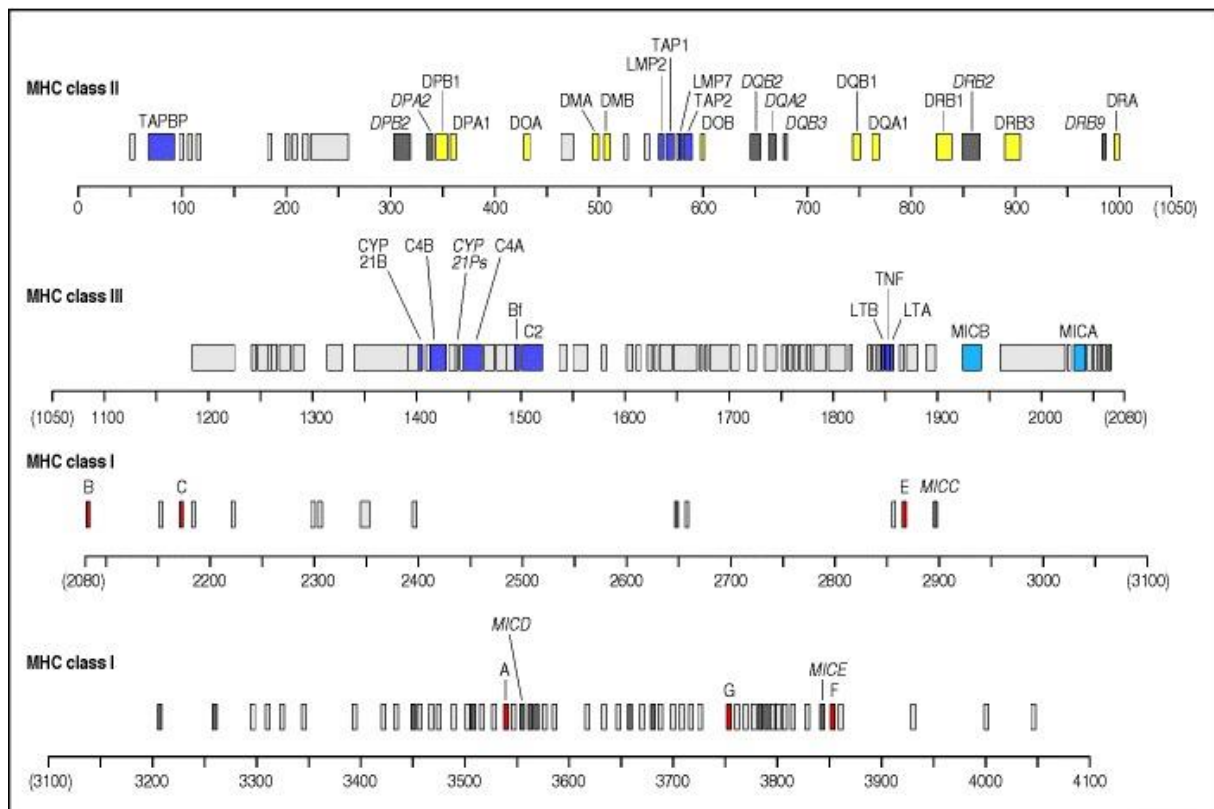


Fig. 14. Detailed map of the human MHC (Hedrick, P. W. (2002).

The organization of the class I, class II, and class III regions of the human MHC are shown, with approximate genetic distances given in thousands of base pairs (kb). Most of the genes in the class I and class II regions are mentioned in the text. The additional genes indicated in the class I region (for example, E, F, and G) are class I-like genes, encoding class IB molecules; the additional class II genes are pseudogenes. The genes shown in the class III region encode the [complement](#) proteins C4 (two genes, shown as C4A and C4B), C2 and factor B (shown as Bf) as well as genes that encode the cytokines tumor necrosis factor- α (TNF) and lymphotoxin (LTA, LTB). Closely linked to the C4 genes is the gene encoding 21-hydroxylase (shown as CYP 21B), an enzyme involved in steroid synthesis. Genes shown in gray and named in *italic* are pseudogenes. The genes are colour coded, with the MHC class I genes being shown in red, except for the MIC genes, which are shown in blue; these are distinct from the other class I-like genes and are under different transcriptional control. The MHC class II genes are shown in yellow. Genes in the MHC region which have immune functions but are not related to the MHC class I and class II genes are shown in purple.

IV. Immunity and associated pathologies

IV. 1. Autoimmunity and autoimmune diseases

Autoimmunity can be considered as the presence of self-reactive adaptive immune components, and autoimmune diseases can be thought of as autoimmunity plus clinically apparent pathology. Although proposals have been made regarding approaches to define autoimmunity and specific autoimmune diseases, there are still no commonly agreed-upon general criteria for these. This lack of consensus in autoimmune disease definitions, and even agreement on which specific illnesses constitute the autoimmune diseases, impede research and clinical care, and the development of international stakeholder-defined consensus on these issues would greatly enhance further progress in the field.

The precise mechanisms for the development of autoimmunity and autoimmune diseases remain unclear, however, a growing consensus has developed that they evolve from still-to-be-defined gene-environment interactions. As a result of technological advances made possible by the human genome project and related investigations, many genetic risk factors for autoimmune diseases have been identified, but there has been relatively little progress in deciphering the even more profound impact of environmental influences. This is not surprising given the difficult tasks of assessing the doses, durations, and effects of the myriad combined environmental exposures we experience over a lifetime and the complex impacts they have on the maturation and function of the immune system (Ayensu et al., 2004).

IV. 1.1. Initiation of autoreactivity

➤ Environmental Triggers

Even in a genetically predisposed person, some trigger an environmental exposure or a change in the internal environment is usually required for frank autoreactivity. Studies of genetically similar populations living in different conditions strongly suggest the importance of environmental triggers. For example, the incidence of both type 1 diabetes and multiple sclerosis in a population changes as the members migrate to different regions (Noseworthy et al., 2000)

➤ Infectious agents

Microbial antigens have the potential to initiate autoreactivity through molecular mimicry, polyclonal activation, or the release of previously sequestered antigens. Molecular mimicry

has clearly been demonstrated in herpes keratoconjunctivitis in mice: T cells that react to the viral protein UL6 cross-react with a peptide derived from a corneal antigen (Zhao et al., 1998).

➤ **Noninfectious Triggers**

Many autoimmune diseases are much more common in women than in men, and estrogens exacerbate systemic lupus erythematosus in murine models of the disease by altering the B-cell repertoire in the absence of inflammation. Drugs can also alter the immune repertoire. Procainamide regularly induces antinuclear antibodies and sometimes induces a lupus like syndrome. Moreover, systemic lupus erythematosus is a regular feature of homozygosity for deficiencies of the C1 or C4 components of the complement cascade; and such deficiencies cause, among other problems, defective elimination of dead cells (Fig. 15).

B-cell activation is mediated by antigen binding to the B-cell receptor. This results in the activation of kinases. Many other molecules affect the process; some enhance activation and some inhibit activation. The overexpression (shown in blue) of genes encoding cell-surface signaling molecules that enhance activation can result in autoimmunity. Two such defects have been described: one is a mutation of CD45 that results in the overexpression of CD45, the other is transgenic overexpression of CD19. Two defects of inhibitory signaling pathways have been described. The first is a knockout (shown in red) of the inhibitory Fc γ receptor II. This receptor recognizes the Fc region of immunoglobulin in the immune complexes, and when it is cross-linked with the B-cell receptor (which recognizes the antigen in the immune complex), it inhibits the activation of B cells. The second is a knockout of any of the components of the CD22 signaling complex — phosphorylated (P) CD22, lyn (which phosphorylates CD22), and the protein tyrosine phosphatase SHP-1 that mediates the down-regulation of the activation of B cells. The other types of defects that can result in excessive activation of B cells are related to decreased clearance of antigen in the form of immune complexes as a result of the underexpression of C1q and C4. C1q and C4 bind to C3d, which, in turn, bind to the immune complexes. Autoimmunity can also result from defective clearance of apoptotic particles owing to the underexpression of DNase I, which breaks down apoptotic particles, and serum amyloid protein (SAP), which coats the particles and enhances their clearance. All the defects shown lead to a systemic lupus erythematosus phenotype. Systemic lupus erythematosus can also be induced by the overexpression of costimulatory molecules such as BAFF (B-cell-activating factor belonging to the tumor necrosis factor family), the underexpression of regulatory molecules such as PD-1 (programmed death 1), and the inhibition of apoptotic pathways.

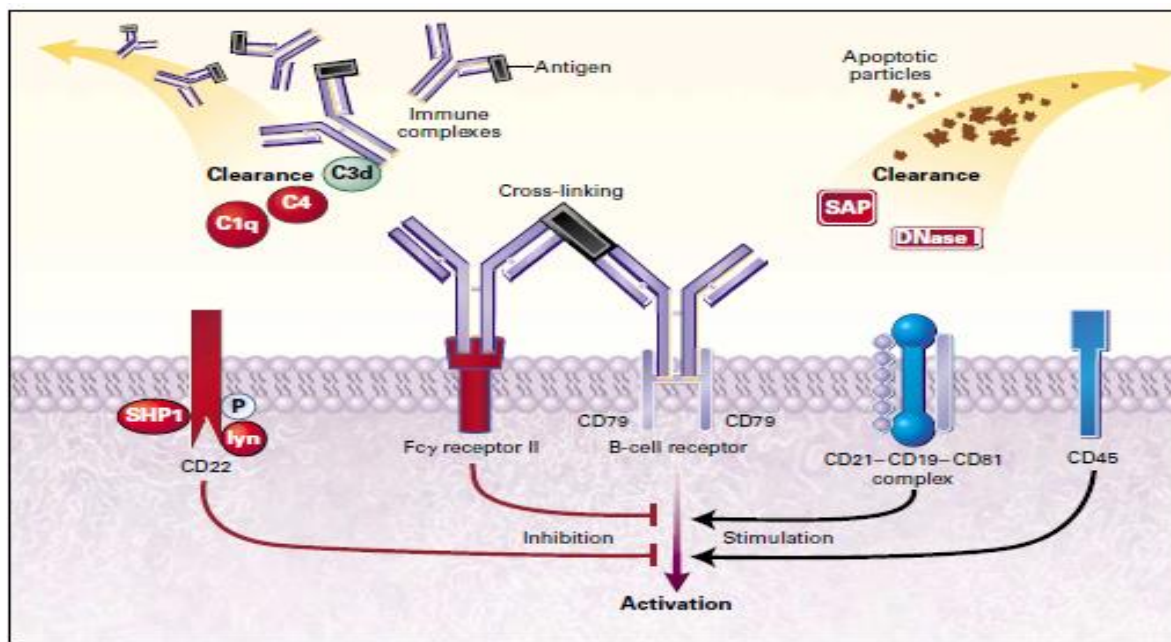


Fig. 15. Defects in B-Cell Activation (Salvetti et al., 2000)

IV. 1.2. Pathogenic Mechanisms

It has become apparent, primarily through studies in animals, that the initial mechanisms causing autoreactivity in an autoimmune disease may be superseded by different effector cells and inflammatory mediators as the disease progresses (table. 04). Naive lymphocytes are activated at the initiation of disease and may continue to be recruited by epitope spreading later in the disease, but it is unknown whether naive cells or memory cells cause progression and flares of disease. There are many examples of the evolution of the mechanisms as an autoimmune disease progresses. For example, antibody against Fas protein prevents the onset of multiple sclerosis in mice but blocks remission if it is given after the onset of disease because it averts the death of activated cells. Moreover, cytokines can have different effects, depending on the stage of the autoimmune disease: transforming growth factor β , for example, suppresses autoreactivity when the disease begins, but once the disease is established, it contributes to fibrotic organ damage.

For example, underexpression of interleukin-1–receptor antagonist leads to arthritis, whereas defects in interleukin-3 lead to a demyelinating syndrome. Since the substances listed are pleiotropic molecules, it is hard to predict on the basis of their known functions what will happen when they are overexpressed or underexpressed. Multiple different defects can lead to

the same disease, especially in the case of inflammatory bowel disease and systemic lupus erythematosus. These molecules are starting to be exploited therapeutically, as exemplified by the use of etanercept and interleukin-1–receptor antagonist for rheumatoid arthritis. Drugs that block costimulation are also becoming available.

Table. 4. Defects in Cytokine Production or Signaling That Can Lead to Autoimmunity.
(McCartney-Francis et al., 1998).

Cytokine or Protein	Defect	Result
 Tumor necrosis factor α	Overexpression	Inflammatory bowel disease, arthritis, vasculitis
 Tumor necrosis factor α	Underexpression	Systemic lupus erythematosus
 Interleukin-1–receptor antagonist	Underexpression	Arthritis
 Interleukin-2	Overexpression	Inflammatory bowel disease
 Interleukin-7	Overexpression	Inflammatory bowel disease
 Interleukin-10	Overexpression	Inflammatory bowel disease
 Interleukin-2 receptor	Overexpression	Inflammatory bowel disease
 Interleukin-10 receptor	Overexpression	Inflammatory bowel disease
 Interleukin-3	Overexpression	Demyelinating syndrome
 Interferon- γ	Overexpression in skin	Systemic lupus erythematosus
 STAT-3	Underexpression	Inflammatory bowel disease
 STAT-4	Overexpression	Inflammatory bowel disease
 Transforming growth factor β	Underexpression	Systemic wasting syndrome and inflammatory bowel disease
 Transforming growth factor β receptor in T cells	Underexpression	Systemic lupus erythematosus

IV. 1.3. Classification of autoimmune diseases

For clinicians, autoimmune diseases appear to be either systemic (as in the case of systemic lupus erythematosus) or organ-specific (as in the case of type 1 diabetes mellitus). This classification, although clinically useful, does not necessarily correspond to a difference in causation. A more useful division distinguishes between diseases in which there is a general alteration in the selection, regulation, or death of T cells or B cells and those in which an aberrant response to a particular antigen, self or foreign, causes autoimmunity. An example of

a general defect is the absence of the Fas protein or its receptor proteins involved in cell death and a representative antigenspecific disorder is the demyelination syndrome that follows enteric infection with *Campylobacter jejuni*. This classification is useful in deciding on therapy, which may differ according to the pathogenic mechanism. Although this mechanistic classification can be used for animal models, we often cannot determine whether a human disease is due to a global abnormality in lymphocyte function or an antigen-specific abnormality (Mackay and al., 2000)

VI. 2. Autoproliferative diseases

In immunology, immunoproliferative disorders are disorders of the immune system that are characterized by the abnormal proliferation of the primary cells of the immune system, which includes B cells, T cells and natural killer (NK) cells, or by the excessive production of immunoglobulins (also known as antibodies). Immunodeficiency disorders result in a full or partial impairment of the immune system. Primary immunodeficiencies are the result of genetic defects, and secondary Immunodeficiencies are caused by environmental factors, such as HIV/AIDS or malnutrition. This briefing explains the two different types of immunodeficiencies and how they are currently treated. It also discusses the future research required in this field to develop better curative treatments for immune disorders.

In healthy individuals the immune response comprises two phases. The first line of defence is the innate system, made up of specialised cells that provide a rapid response that is not tailored to the specific microbe that has infiltrated the body. Sometimes this can clear the infection alone but usually the innate response will contain the infection long enough for the adaptive immune system to activate. The adaptive response is the second line of defence and takes several days to assemble. The response is specific to the microbe and leaves a lasting immune memory, which makes the response to future reinfection more efficient (see here for more information). In a person with an immunodeficiency disorder, one or more components of either the adaptive or innate immune response is impaired, resulting in the body being unable to effectively resolve infections or disease. This leaves immunodeficient individuals at high risk of recurrent infection, and vulnerable to conditions that would not usually be of concern to otherwise healthy individuals.

- There are two types of immunodeficiency disorder:

1. Primary immunodeficiency (PID) .inherited immune disorders resulting from genetic mutations, usually present at birth and diagnosed in childhood.

2. *Secondary immunodeficiency (SID)* : acquired immunodeficiency as a result of disease or environmental factors, such as HIV, malnutrition, or medical treatment (e.g. chemotherapy).

IV. 2. 1. Primary immunodeficiency (PID)

PID disorders are inherited conditions sometimes caused by single-gene mutations, or more often by an unknown genetic susceptibility combined with environmental factors. Although some PIDs are diagnosed during infancy or childhood, many are diagnosed later in life. PIDs are categorised based on the part of the immune system that is disrupted.

Examples of primary immunodeficiency disorders

B cell immunodeficiencies (adaptive)

B cells are one of two key cell types of the adaptive immune system. Their main role is to produce antibodies, which are proteins that attach to microbes, making it easier for other immune cells to detect and kill them. Mutations in the genes that control B cells can result in the loss of antibody production. These patients are at risk of severe recurrent bacterial infections.

T cell immunodeficiencies (adaptive)

T cells are the second of two key cell types of the adaptive immune system. One role of the T cell is to activate the B cell and pass on details of the microbe's identity, so that the B cell can produce the correct antibodies. Some T cells are also directly involved in microbe killing. T cells also provide signals that activate other cells of the immune system. Mutations in the genes that control T cells can result in fewer T cells or ones that do not function properly. This can lead to their killing ability being disrupted, and can often cause problems with B cell function too. Therefore, T cell immunodeficiencies can often lead to combined immunodeficiencies, where both T and B cell function is defective. Some forms of CIDs are more severe than others.

- ***Severe combined immune deficiencies (adaptive)***

Severe combined immune deficiencies disorders are very rare but extremely serious. In *immune deficiencies* patients there is often a complete lack of T cells and variable numbers of B cells, resulting in little-to-no immune function, so even a minor infection can be deadly. SCID patients are usually diagnosed in the first year of life with symptoms such as recurrent infections and failure to thrive.

- ***Phagocyte disorders (innate)***

phagocytes include many white blood cells of the innate immune system, and these cells patrol the body eating any pathogens they come across. Mutations typically affect the ability of certain phagocytes to eat and destroy pathogens effectively. These patients have largely functional immune systems but certain bacterial and fungal infections can cause very serious harm or death.

- ***Complement defects (innate)***

complement defects are some of the rarest of all the PIDs, and account for less than 1% of diagnosed cases. Complement is the name given to specific proteins in the blood that help immune cells clear infection. Some deficiencies in the complement system can result in the development of autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis (please see our autoimmune briefing for more information). Patients who lack certain complement proteins are highly susceptible to meningitis.

IV. 2. 2. Secondary immunodeficiency

SIDs are more common than PIDs and are the result of a primary illness, such as HIV, or other external factor such as malnutrition or some drug regimens. Most SIDs can be resolved by treating the primary condition.

- **Examples of secondary immunodeficiency disorders**

- ✓ ***Malnutrition***

Protein-calorie malnutrition is the biggest global cause of SIDs which can affect up to 50% of the population in some communities in the developing world. T cell numbers and

function decrease in proportion to levels of protein deficiency, which leaves the patient particularly susceptible to diarrhoea and respiratory tract infections. This form of immunodeficiency will usually resolve if the malnutrition is treated.

✓ ***Drug regimens***

There are several types of medication that can result in secondary immunodeficiencies, but these drugs also perform critical roles in certain areas of healthcare. Immunosuppression is a common side-effect of most chemotherapies used in cancer treatment. The immune system usually recovers once the chemotherapy treatment has finished. Another common use for immunosuppressive drugs is the prevention of transplant rejection, where medication is required to suppress the transplant recipient's immune system and prevent it from targeting the transplanted tissue. These drugs can have significant side-effects and often suppress more areas of the immune system than are required, leading to susceptibility to opportunistic infections. Use of a new generation of medicines called biologics are becoming more widespread in treating transplant rejection. These drugs are derived from biological sources like cells, rather than chemical structures. Monoclonal antibodies are one such class of biologics and these drugs are made by farming antibodies from B cells that will act against a specific part of the disease process. These agents are more specific in their action than traditional drugs and have fewer side effects on non-target immune cells.

✓ **Chronic infections**

There are a number of chronic infections which can lead to SID disorders, the most common of which is acquired immune deficiency syndrome (AIDS), resulting from HIV infection. The virus attacks CD4⁺ T cells, a type of white blood cell that plays a critical role in preventing infection, and gradually depletes their numbers. Once the T cell count is less than 200 cells per ml of blood, symptoms of AIDS begin to manifest and the patient is at high risk of recurrent infections that will eventually lead to death. Anti-viral therapies, such as the HAART regimen (Highly Active Antiretroviral Therapy), allow the T cell population a chance to recover and resume normal function. These drugs have had a huge impact on increasing the life expectancy for HIV/AIDS patients and improving their quality of life. Prior to the introduction of HAART, patients with HIV diagnosed at age 20 had an average of 10 years before developing AIDS. Nowadays on average, patients diagnosed at age 20 can expect

to live well into their 60. However, these drugs must be taken every day for life as they are not curative, and are only available to patients and healthcare systems that can afford them.

IV. 3. Human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV), a member of the retrovirus family, is the causative agent of acquired immunodeficiency syndrome (AIDS). HIV invades various immune cells (e.g., CD4⁺ T cells and monocytes) resulting in a decline in CD4⁺ T cell numbers below the critical level, and loss of cell-mediated immunity therefore, the body becomes progressively more susceptible to opportunistic infections and cancer.

IV. 3. 1. HIV invasion of immune cells

HIV infects T cells via high-affinity interaction between the virion envelope glycoprotein (gp120) and the CD4 molecule. The infection of T cells is assisted by the T-cell co-receptor called CXCR4 while HIV infects monocytes by interacting with CCR5 co-receptor (Fig. 16). As illustrated in Figure 16, after gp120 binds to CD4 on the T cell. Nucleocapsids containing viral genome and enzymes enters the target cell. Following the release of viral genome and enzymes from the core protein, viral reverse transcriptase catalyses reverse transcription of ssRNA to form RNA-DNA hybrids (Fig. 17) . To yield HIV dsDNA the viral RNA template is partially degraded by ribonuclease H and the second DNA strand is synthesized . The viral dsDNA is translocated into the nucleus and integrated into the host genome by the viral integrase enzyme . Transcription factors transcribe the proviral DNA into genomic ssRNA , which is exported to cytoplasm . In the cytoplasm, host-cell ribosomes catalyse synthesis of viral precursor proteins . The viral precursor proteins are cleaved into viral proteins by viral proteases . HIV ssRNA and proteins assemble beneath the host-cell plasma membrane forming virion buds from it . Maturation occurs either in the forming buds or after budding from the host cell . During maturation, HIV proteases cleave the poly-proteins into individual functional HIV proteins. The mature virions are able to infect another host cell.

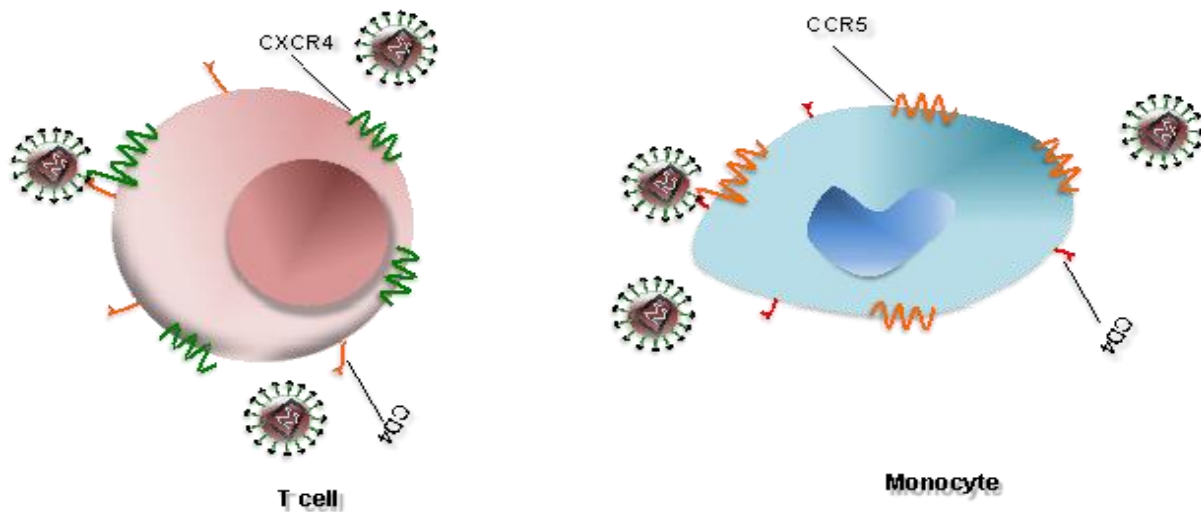


Fig. 16. Interaction between HIV and coreceptors of a T cell and a monocyte (Makvandi-Nejadand et al., 2015).

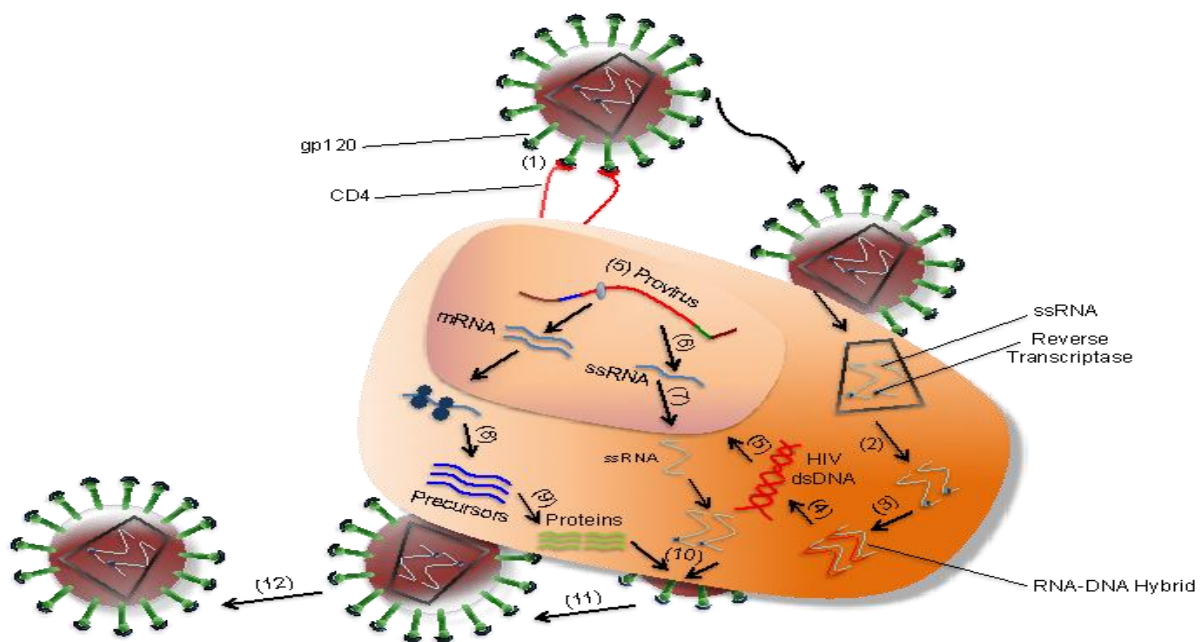


Fig. 17. The release of viral genome and enzymes from the core protein (Makvandi-Nejadand et al., 2015).

IV. 3. 2. Innate immune response to HIV

Innate immune cells (e.g., dendritic cells and natural killer cells) are the first line of defence which HIV encounters upon entry to the body.

Macrophages.

Tissue macrophages are one of the target cells for HIV. These macrophages harbour the virus and are known to be the source of viral proteins. However, the infected macrophages are shown to lose their ability to ingest and kill foreign microbes and present antigen to T cells. This could have a major contribution in overall immune dysfunction caused by HIV infection.

Dendritic cells (DCs)

DCs are large cells with dendritic cytoplasmic extensions. These cells present processed antigens to T lymphocytes in lymph nodes. Epidermal DCs, expressing CD1a and Birbeck granules, are probably among the first immune cells to combat HIV at the mucosal surfaces. These cells transport HIV from the site of infection to lymphoid tissue. The follicular DCs, found in lymphoid tissue, are also key antigen-presenting cells that trap and present antigens on their cell surfaces. In the lymph node follicles, DCs provide signals for the activation of B lymphocytes.

Natural killer (NK) cells.

NK cells have lytic activity against cells that have diminished expression of major histocompatibility complex (MHC) I antigens. Because the presence of MHC class I is required for peptide presentation to T cell receptors, NK cells are important line of defence when HIV escapes the cellular immune response. NK cells proliferate in response to type 1 interferon secreted by DCs. These stimulated NK cells release cytokines such as interferon γ (IFN- γ), tumour necrosis factor α (TNF- α), and chemokines to activate T-cell proliferation (cellular immune response). NK cells also inhibit viral replication by releasing IFN- γ .

IV. 3. 3. Adaptive immune response to HIV

Cellular immune response to HIV. The cellular immune response is induced upon the entry of HIV into the target cells (e.g., T cells) and synthesis of viral proteins (Fig. 18). MHC class I on the cell surface displays the intracellularly degraded HIV peptide fragments for recognition by T-cell receptors (TCR) on CD8⁺ T cells (Fig. 18). CD8⁺ T cells lyse HIV infected cells and secrete cytokines, i.e. interferon- γ (IFN- γ), tumor necrosis factor α (TNF- α), and chemokines, i.e. MIP-1 α , MIP β and RANTES, that inhibit virus replication and block viral entry into CD4⁺ T cells. Development of CD8⁺ T cells is crucial for control of HIV replication. This results in declining viraemia after primary infection. In the early stages of infection, CD4⁺ T cells lose their proliferative capacity and therefore their contribution to viral control is minor. However, during chronic infection CD4⁺T cells are present and secrete interleukin-2 (IL-2) or cytokines, such as IFN- γ , to control viraemia.

IV. 3. 4. Humoral response to HIV

The humoral immune response occurs later in infection; therefore, the level of antibodies during the acute infection is very low. Non-neutralising antibodies to structural proteins (i.e. P17 and P24) are first to appear and generally do not persist. Later neutralising antibodies specific to proteins, involved in the entry of the virus into the cells, will be generated. These antibodies are specific to: (1) the variable region of gp120 (V3); (2) CD4 binding sites and chemokine receptors (i.e., CXCR4 and CCR5); (3) the transmembrane protein gp41. Potent neutralizing antibodies have been shown to play a major role in controlling HIV infection in a few symptom-free HIV⁺ individuals who maintain high level of CD4⁺ T cells and low viral load.

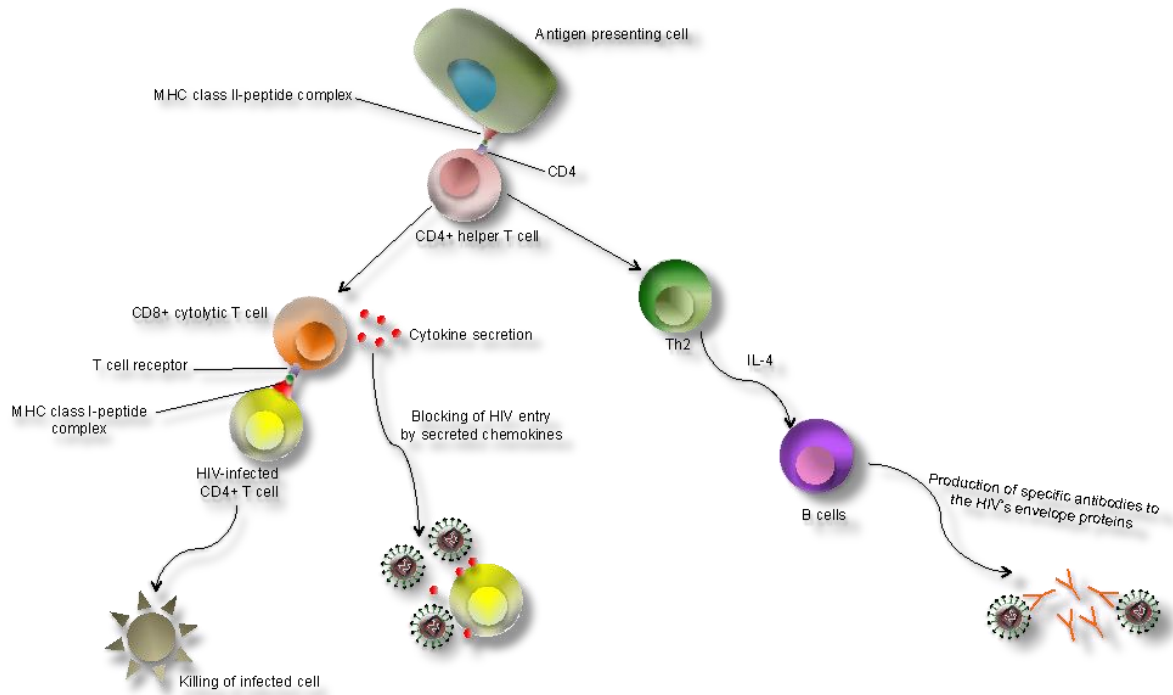


Fig. 18. Cellular & humoral immune responses to HIV (Makvandi-Nejadand al., 2015).

Why does the immune system fail to fight the HIV virus?

There are various reasons which can contribute to the failure of the immune system to control HIV infection and prevent AIDS development. By infecting CD4+ T cells, HIV is able to replicate predominantly in activated T cells and paralyse one of the main components of adaptive immune system. HIV can also establish latent infection in CD4+ T cells and remain invisible to CD8+ T cells and therefore replication can occur later in the infection and generate new virions. Antigenic mutation within the T-cell epitopes can affect the binding capacity of MHC molecules to the viral peptides, resulting in the inability of the TCRs to recognise the MHC-peptide complex. Finally, HIV is able to hide from anti-HIV antibodies by expressing non-immunogenic glycans on key antibody epitopes.

IV.4 . Cancer

Cancer, as a systemic disease, induces many functional and compositional changes throughout the immune system, the first of which occurs as a result of dysregulation of the immunosurveillance role. As the disease progresses, the overall immune landscape beyond the eventual tumor is significantly altered. The classification of cancers into solid and hematologic cancer can help us to better understand the role that the immune system plays in the pathogenesis of cancer.

IV. 4. 1. Immunity of solid tumor

The cancer-immunity cycle Although the role of the immune system, and in particular immune surveillance, in cancer has been studied for decades, clinical observations and immune-therapy. To better integrate clinical care, in 2013 Daniel S. Chen and Ira Mellman introduced the concept of the CI cycle: immune cells neither respond nor function on their own, but rather exist in the context of a series of steps. These steps interact with each other, and any single step has the potential to limit the rate at which optimal immunity is produced. In detail, the cancer immune cycle is divided into seven steps (Chen and Mellman, 2013).

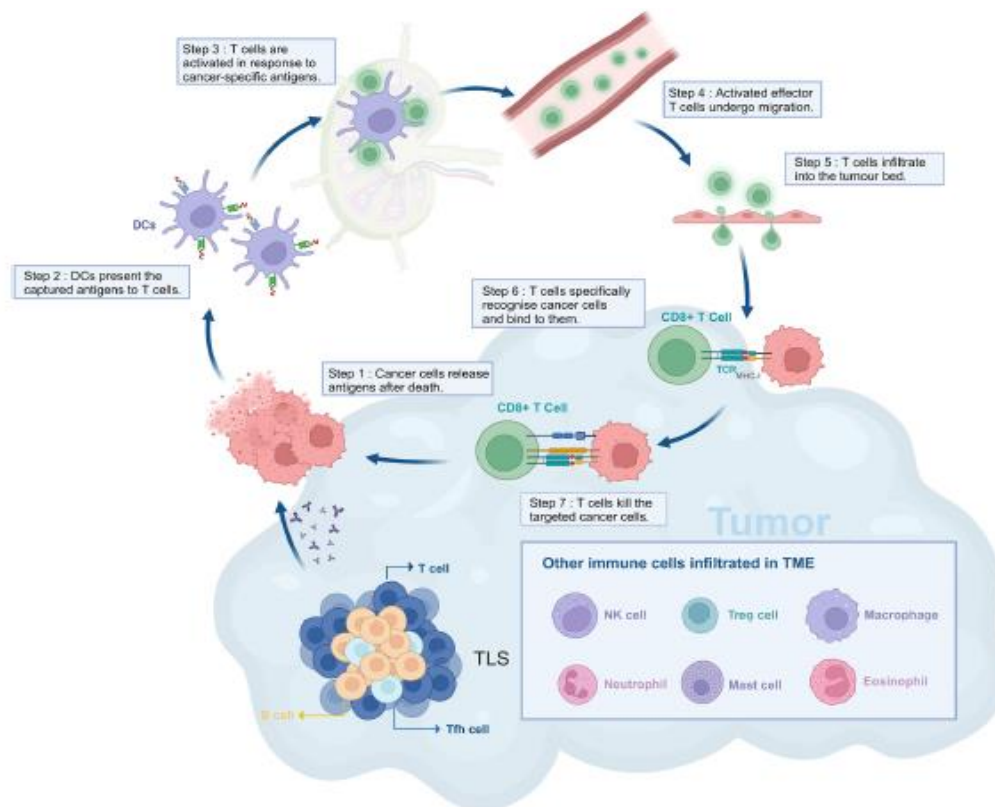


Fig. 19. The cancer-immunity cycle and TME. The figure shows the components of cancer immunity (Fridman and al., 2023).

The upper part shows the core of cancer immunity, a cyclical process of accumulation of immunostimulatory factors and amplification of the killing effect. This cycle can be simplified into seven steps, starting with the release of antigens from the death of cancer cells and ending with the killing of cancer cells by T cells. The other components of the TME are

shown below. The TLS has an inner zone of CD20+ B cells surrounded by T cells, similar to the structure of lymphoid follicles in secondary lymphoid organs. First, antigens generated by tumor cells are released and taken up by DCs by the immunophenotype of the tumor. The three classical immunophenotypes immunoinflammatory, immune-excluded, and immune-deserted are defined as follows: tumors with abundant immune infiltration, tumors where T cell infiltration is restricted to the tumor mesenchyme rather than the parenchyma, and tumors lacking immune infiltration, respectively. Although this classification is now generally accepted and more commonly used, it has been found to be an oversimplification as studies have been carried out. The three classical immunophenotypes immunoinflammatory, immuneexcluded, and immune-deserted are defined as follows:

tumors with abundant immune infiltration, tumors where for processing. Next, the antigen is presented to T cells. These molecules are perceived as foreign or inadequately tolerated, and can thus trigger and activate effector T cellspecific immune responses against cancer cells. Finally, the activated effector T cells move and infiltrate toward the tumor site, specifically identifying and binding to the cancer cells, and subsequently destroying them. Dead cancer cells release additional tumor-associated antigens, thus returning to the initial step and amplifying the immune response in subsequent cycles. Furthermore, the efficiency of this cycle differs markedly in different tumors and is mainly determined T cell infiltration is restricted to the tumor mesenchyme rather than the parenchyma, and tumors lacking immune infiltration, respectively. The tumor microenvironment (TME) comprises not only T cells, but also cells of the innate immune system, B cells, and nonimmune cells like cancer-associated fibroblasts. On the one hand, these cells can work together to inhibit T cell function and physically limit their migration into the tumor nests tolimit T cell immunity.On the other hand, TME can also promote the formation of peripheral lymphoid aggregates and tertiary lymphoid structures, which can more rapidly produce more specific immune cells and thus suppress tumor growth (Fridman andal., 2023).

IV. 4. 2. The concept of immune surveillance

The immune system plays a major role in the surveillance against tumors. To avoid attack from the immune system, tumor cells develop different strategies to escape immune surveillance. Evidence of immune surveillance comes from both animal models and clinical observations. Mice with a wide variety of immunodeficiencies have a high rate of tumor incidence and are more susceptible to transplanted or chemical carcinogen-induced tumors.

Immunosuppressed patients have a high incidence of tumors. However, many patients develop cancer even in the presence of an apparently normal immune system. This indicates that tumor cells are able to escape immune surveillance.

Immune surveillance is a critical biological mechanism by which the body's immune system identifies and eliminates early-stage tumor cells before they progress into clinically detectable malignancies (Catena et al., 2025). The concept of immune surveillance, first proposed decades ago, has significantly reshaped our understanding of cancer biology, emphasizing the intricate interactions between tumor initiation and host immunity. Central to this protective mechanism are diverse cellular players, including natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), dendritic cells (DCs), and various cytokines, all collaborating within a highly coordinated network to prevent tumor establishment and growth (Coënon et al., 2024). While traditional immunotherapies target advanced stages, emerging evidence supports targeting immune surveillance specifically during precancerous stages. Recent studies have demonstrated that CD8⁺ T cells actively infiltrate early lesions and exert tumor-suppressive effects in melanoma models. This suggests that immune surveillance remains active and targetable at precancerous stages. Although substantial progress has been achieved in harnessing the immune system to treat advanced cancers, particularly through immune checkpoint inhibitors and adoptive cell therapies, these strategies often face challenges, such as limited efficacy, immunerelated adverse events, and resistance mechanisms emerging in later stages. Consequently, shifting the focus to the early stages of cancer progression or even precancerous conditions could significantly enhance therapeutic outcomes. Targeting immune surveillance pharmacologically at these initial stages provides an appealing strategy, potentially halting malignant transformation long before invasive disease becomes established (Liu et al., 2025).

Accumulating experimental evidence supports the potential efficacy of immune interventions at the early stages of tumor formation. Specifically, studies in melanoma provide robust examples where immune surveillance mechanisms effectively control or eliminate early-stage lesions (Eyles et al., 2010). For instance, preclinical mouse models have demonstrated that antigen-specific CD8⁺ T cells infiltrating early melanoma lesions can effectively mediate complete tumor regression or sustained growth control (Matsushita et al., 2012).

IV. 4. 3. Molecular and cellular bases of the antitumor immune response

The tumor microenvironment is known to suppress the immune system, which enables that tumor to escape immune surveillance. The tumor and its microenvironment produce various chemokines and cytokines that inhibit the maturation of APCs and T cells, which finally leads to the suppression of the functional activity of the T cell arm of antitumor immunity. Immunosuppression caused by the action of substances secreted by the tumor environment leads to the failure of standard treatments for malignant tumors. Therefore, the development of antitumor therapies based on the activation of the immune system is topical today. DCbased vaccines are considered as one of the most effective ways to overcome immunodeficiency on the basis of body resources.

Today, methods based on the activation of the immune system are of particular importance in cancer therapy. Dendritic-cell- (DC)-based vaccines capable of triggering and maintaining a tumor-specific T and B cell immune response stand out among various approaches. DCs are professional antigen-presenting cells (APCs) the main function of which is to capture foreign antigens and process and present them on the cell surface in complexes with major histocompatibility complex (MHC) class I and II molecules to naive T cells. This interaction results in the maturation and activation of tumor- specific cytotoxic T lymphocytes (CTLs) capable of migrating to tumor sites, identifying tumor cells, and destroying them. In addition, the interaction triggers a response by type 1 and 2 T helper cells (Ths), which stimulates the T and B cell arms of the antitumor immune response. Additional stimulation by DC-secreted cytokines promotes the proliferation of tumor-specific CTL clones. The challenge today is to develop DCbased vaccines for the effective treatment of cancers and overcoming tumor-induced immunodeficient conditions. To better contextualize the dynamic interplay between immune surveillance and early tumor evolution, Figure 1 provides a conceptual overview of cellular and molecular events during the precancer-to-cancer transition. It illustrates key immune cell subsets (e.g., CD8⁺ T cells, Tregs, MDSCs), immunosuppressive cytokines (TGF- β , IL6), and inhibitory pathways such as PD-1/PD-L1 signaling. These events are shown progressing over time, reflecting opportunities for pharmacological interventions such as checkpoint blockade, Treg modulation, and dendritic cell activation to restore immune equilibrium before full tumor establishment. As shown, during the precancerous phase, immune surveillance mechanisms primarily involving CD8⁺ cytotoxic T cells and CD4⁺

helper T cells actively monitor and attempt to eliminate aberrant cells. However, a gradual shift occurs as immune evasion mechanisms intensify, including T cell dysfunction, expansion of immunosuppressive Tregs, and the emergence of CAFs. These changes create an immune-suppressive microenvironment, facilitating malignant progression (Fig. 20).

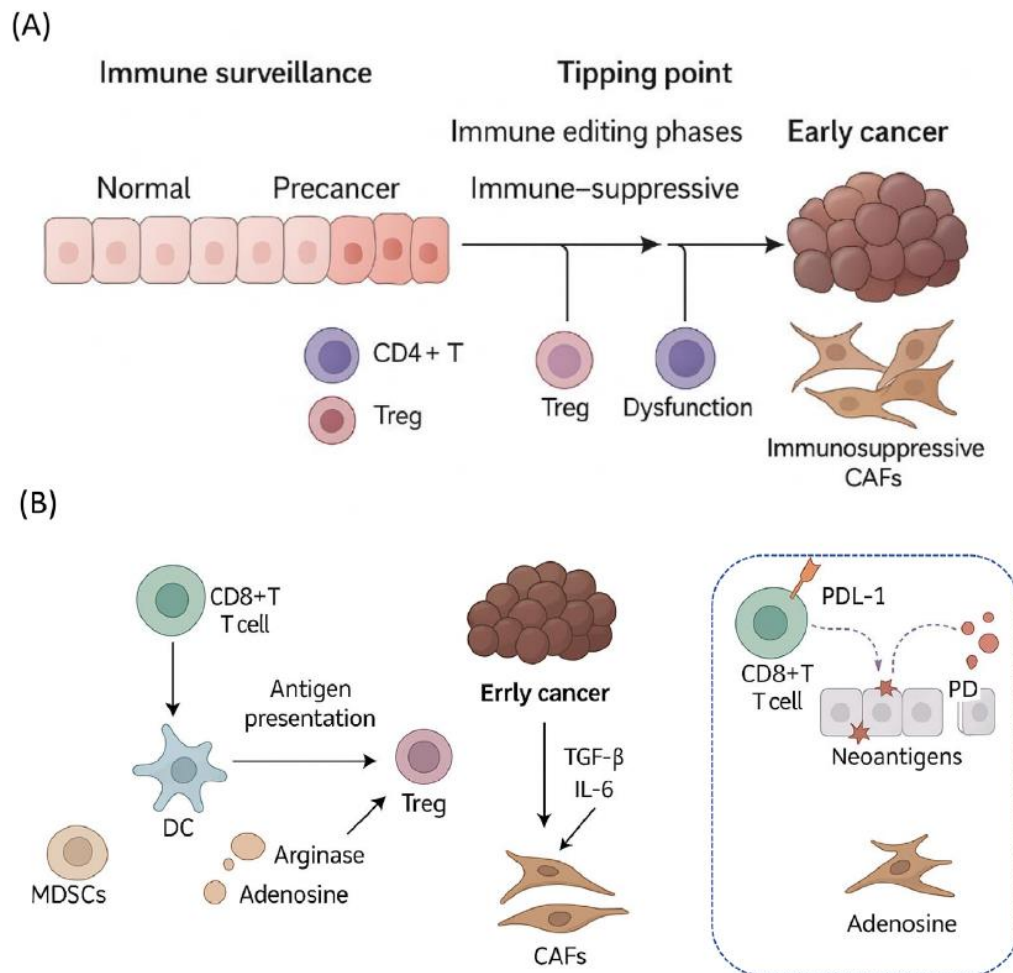


Fig. 20. Immune surveillance failure and early immunosuppressive remodeling during the precancer-to-cancer transition (Liu et al., 2025).

This schematic illustrates the temporal and cellular progression from effective immune surveillance to immune escape. (A) Overview of the immune surveillance phases during early tumorigenesis. In normal tissues, immune homeostasis is maintained. During precancerous stages, immune editing begins with infiltration of CD4+ T cells and Tregs. At the tipping point, immunosuppressive mechanisms intensify, including T cell dysfunction and the emergence of immunosuppressive CAFs, ultimately facilitating early cancer formation. (B) Key mechanisms of early immune evasion. Myeloid-derived suppressor cells (MDSCs) and tumor-derived factors (e.g., arginase, adenosine) inhibit antigen presentation by dendritic cells

(DCs) and promote Treg differentiation. Early tumors and CAFs secrete TGF- β and IL-6 to reinforce immune suppression. Neoantigen-specific CD8⁺ T cells become functionally impaired through PD-1/PD-L1 interactions, leading to immune escape and tumor progression.

V. Immunochemical methods

Immunochemical methods are based on antigen-antibody interaction. Using these methods, we determine the presence of pathogens or demonstrate whether or not a sample contains specific antibodies to a given antigen. An antigen is a macromolecular substance of natural or artificial origin that the organism recognizes as foreign. When an antigen (in this case an immunogen) is introduced into an organism, it elicits an immune response. Lymphocytes are stimulated, which after differentiation produce plasma cells capable of secreting antibodies. Thus, an antibody is a molecule that is able to bind to an antigen and thereby trigger a defense response. We distinguish polyclonal antibodies (directed against multiple epitopes of a particular antigen), monoclonal antibodies (directed against a single epitope of an antigen) and recombinant antibodies.

V.1. Immunoprecipitation methods

V.1.1. Immunodiffusion methods

simple radio-immunodiffusion method

Antigen samples are applied to the wells on an agarose gel containing the specific antibody. During 2-3 days of incubation at room temperature, the antigen diffuses radially in this gel. Upon reaction of the antigen with a specific antibody, an immunoprecipitation ring is formed, the area of which is proportional to the amount of antigen. We evaluate the results of the samples using a special ruler, where we measure the area of the rings and thus determine the concentration of antigen in the samples.

V.1.2. Immunodiffusion methods

Immunodetection by optical methods in solution

Immunoprecipitation associated with immunoturbidity

Immunoprecipitation is based on antigen-antibody interaction and immunoprecipitate formation. The condition is the presence of a polyvalent antigen (antigen reaction with multiple epitopes). If we put a constant amount of antibody and an increasing amount of antigen in several tubes, those immunoprecipitates will be formed. The essence of the immunoprecipitate is the spatial lattice, where the epitopes (binding sites A) of the antigen are connected with the paratopes (binding sites P) of the antibodies. After a while,

it reaches a certain size, when it finally precipitates. The expression of the amount of immunoprecipitate on the amount of antibody and antigen is described by the so-called immunoprecipitation curve .

If we determine the concentration of antigen in an unknown sample (eg plasma proteins), we use the method of immunoturbidimetry . The reaction of the antigen with the antibody produces turbidity. Using spectrophotometry , we measure the intensity of light that was not scattered by turbidity and determine the concentration of antigen in an unknown sample (we use only the ascending part of the curve, where the concentration of antigen is directly proportional to the concentration of precipitate).

V.1.3. Immunonephelometry

The method is based on measuring the intensity of scattered light coming from the solution in all directions . It is measured at an angle that is different from the direction of the incident radiation (usually 45 ° or 90 °). We determine the antigen concentration in the same way as in immunoturbidimetry. We use a nephelometer , where the radiation source is usually a laser .

V.1.4. Immunoanalytic methods with labeled reactants

The methods are based on labeling an antigen or antibody with a substance that is more sensitive than immunoprecipitate detection. The label can be an enzyme (enzyme immunoassay), a radioisotope, but also a fluorescent or chemical substance

V.1.5. Enzyme immunoassay

These methods use enzymes to label an antigen or antibody. Peroxidase or alkaline phosphatase serve as a marker. There are two main techniques, ELISA (Enzyme-Linked Immunosorbent Assay) and EMIT (Enzyme Multiplied Immunoassay Technique) .

Homogeneous enzyme analysis

A sample containing the antigen of interest is mixed with a known amount of the same antigen with bound enzyme (conjugate) and the appropriate antibody in limited amounts. In an immunochemical reaction , the unlabeled antigen competes with the conjugate for binding to a limited amount of antibody . Upon binding of the antibody to the conjugate enzyme, a conformational change in the enzyme associated with loss of activity may occur. The more

unlabeled antigen in the sample, the more antibody molecules react with it and the more enzymatic activity in the conjugate is retained. This method is used to determine low molecular weight substances (drugs, hormones).

Heterogeneous enzyme analysis

One of the methods is the so-called ELISA, where we determine the amount of antigen or antibodies. Here, the antigen or antibody is firmly anchored to a solid phase, which may be either the surface of a microtiter well, a tube, or a magnetic particle. ELISA methods are divided into competitive and non-competitive (sandwich).

V.2. Competitive technique

In this type of assay, unlabeled ligand competes for binding to a limited number of binding sites on the solid surface of immobilized antibodies with the enzyme-labeled ligand. After a short incubation, the complex is separated from the free. After washing (removal of unbound molecules), substrate is added and the enzyme present in the bound fraction converts it into a colored product. The amount of product formed is inversely proportional to the concentration of unlabeled ligand in the test sample. The absorbance of the samples is measured. Wells that contain only the ligand-enzyme conjugate are most intensely stained and the color loss in the wells is proportional to the amount of unconjugated antigen. Standard curves are obtained by plotting antigen concentration and absorbance. We determine the concentration from the curve antigen samples (or we have it done by PC - Elisa reader).

V.3. Non-competitive (sandwich) technique

Using this method, we determine antibodies or antigens that have at least two different determinants. A specific antigen is bound to the surface of the wells of the microtiter strips. In unknown samples that we add to the wells, we investigate the presence of antibodies against this antigen. If the samples contain a given antibody to a given antigen, they bind to the antigen and form an immunocomplex. After washing the unbound components of the sample, the immune complexes are detected by the conjugate (enzyme-bound protein). A so-called "sandwich" is created, which consists of antigen in the strip wall, antibody and conjugate. The amount of bound labeled antibodies is visible by the enzymatic reaction. After washing, add the substrate which is converted to a colored product by peroxidase. It stops the enzyme

reaction by adding STOP solution (weak acid). According to the intensity of the staining, we evaluate whether the samples contained antibodies or not.

VI. Immunotherapies

VI.1. Selective immunotherapies for autoimmune diseases

The goal of replacing blanket immunosuppression by selective immunotherapy for autoimmune diseases now seems attainable, with the many possible “points of engagement” evident from figure 21. Antigen (or autoantigen) engages a B cell receptor directly and also is endocytosed by an antigen presenting cell (typically a dendritic cell, but B cells also serve), in which intracellular degradation generates antigenic peptides. These are presented on a class II molecule of the major histocompatibility complex (MHC II) to the receptor of a naive CD4 helper T cell (Th0). Binding is facilitated by CD4 interaction, as shown. Engagement of CD80/86 on the antigen presenting cell with CD28 on the T cell delivers a costimulatory signal necessary for activation. The naive T cell becomes a Th1 or Th2 T cell under the influence of various cytokines (dotted lines). Slightly different conditions apply to the activation of a CD8 T cell.

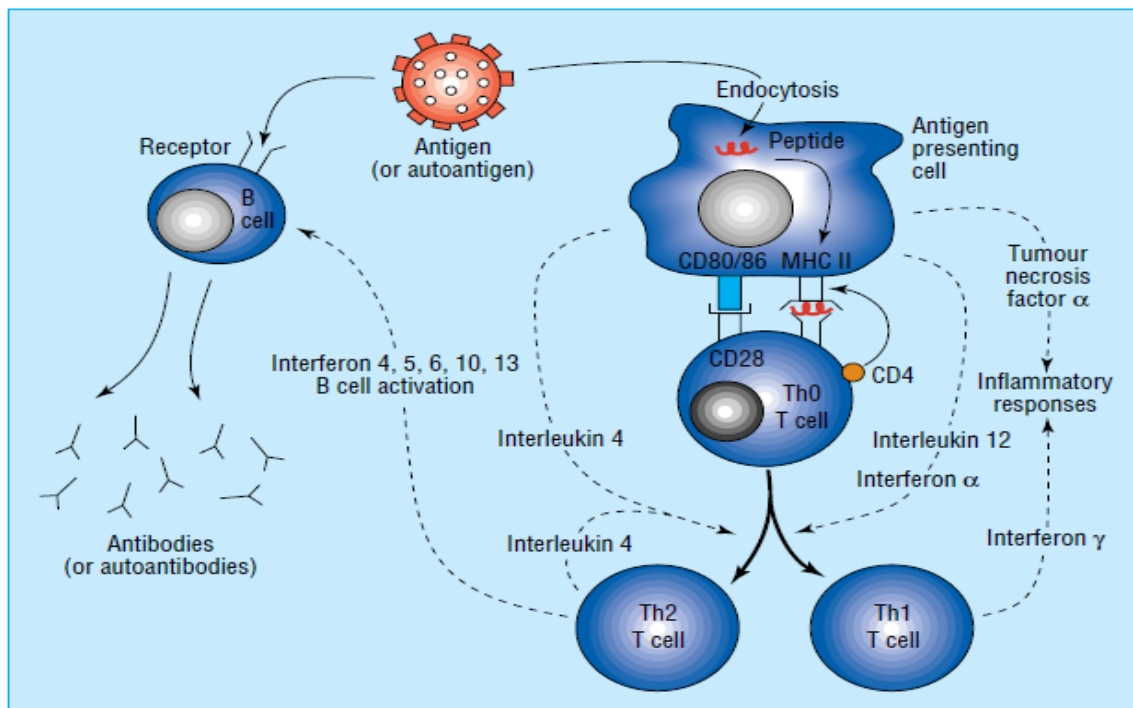


Fig. 21. Components of immune (and autoimmune) responses (Greenfield et al., 1998).

The agents in use or under development (table 5) include monoclonal antibodies or blocking antagonists against the T cell synapse (represented by the binding site for the major

histocompatibility complex, T cell receptor, and autoantigen), interactions between costimulatory molecules and ligands, or interactions between cytokines or chemokines with their receptors; counter-regulatory cytokines such as interleukin ; or the T cell downregulatory molecule CTLA-4.

Table. 5. Selective immunotherapies for autoimmune diseases (Mackay, 2000).

Selective immunotherapies for autoimmune diseases
Monoclonal antibodies or blocking antagonists • Against T cell synapse (used for multiple sclerosis) • Against cytokines such as tumour necrosis factor α (used for rheumatoid arthritis) • Against receptor for cytokines such as tumour necrosis factor α (used for rheumatoid arthritis) • Against receptors for chemokines CCR5 and CXCR3 (under development)
CTLA-4 • Downregulates activated T cells (trial use for psoriasis)
Regulatory cytokines • Interferon β possibly inhibits interleukin 12 (used for multiple sclerosis) • Interleukins 10 and 4 divert Th1 response to Th2 response (used in animal models)
Restoration of tolerance • Antigen specific desensitisation (used for multiple sclerosis, type 1 diabetes) • Stem cell replacement (used for various diseases) • Gene therapy (under development)

Examples in current practice include copolymer 1 (copaxone, glatimer acetate), which interferes with the interaction between the major histocompatibility complex and a neural autoantigen to prevent relapses in multiple sclerosis²⁴; monoclonal antibodies or soluble receptor for tumour necrosis factor α , which block the inflammatory effects of tumour necrosis factor α in rheumatoid arthritis and inflammatory bowel disease; and CTLA-4, which limits graft versus host disease in bone marrow transplantation and alleviates psoriasis. An alternative approach is to “rewire” the immune system for tolerance. Firstly, antigen based desensitisation (oral tolerance), by repetitive mucosal administration of autoantigens, can prevent or reverse autoimmune disease in animal models. So far, results for human diseases are not so encouraging (multiple sclerosis, rheumatoid arthritis, uveitis) or not yet available (type 1 diabetes).

The problem may be that longstanding autoimmune disease is maintained by memory-type T lymphocytes that are difficult to render tolerant. Secondly, immune ablation by intensive

immunosuppression and replacement by infusion of peripheral blood CD stem cells is proving successful in severe refractory autoimmune diseases, lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and multiple sclerosis, but whether this is simply due to heavy immunosuppression or indicates reprogramming for tolerance as well remains uncertain. Thirdly, for the more distant future, gene therapy for autoimmune disease has been considered for type 1 diabetes; but the principles would be applicable to other autoimmune diseases.

VI.2. Therapeutic strategies for specific diseases

Two major challenges lie ahead if the promise of new therapeutic approaches is to be fulfilled. First, we need reproducible and reliable serologic and clinical methods of assessing the risk of a specific disease and of identifying active disease and remission. The use of the criteria of the American College of Rheumatology for a response in patients with rheumatoid arthritis allows clinicians to compare the efficacy of various drugs in different trials (Felson et al., 1995).

The establishment of international standards for screening tests for diabetes will enhance the reliability of these assays. Registries of patients are being established for rarer autoimmune diseases to allow clinical studies to proceed. Nevertheless, there is an urgent need to identify markers of disease activity, remission, and impending relapse in most autoimmune diseases. The second challenge is to determine which approach to use in each disease. Perhaps different therapeutic interventions are needed at different stages in the disease process. It is clear, for example, that the treatments that block the recruitment of naive cells differ from those that prevent the activation of memory cells. The hope is that some approaches will work in more than one disease (Roep et al., 1999).

VI.2.1. Rheumatoid Arthritis

The treatment of rheumatoid arthritis has been markedly improved by the recognition that bone erosions occur early in the disease and that therapy should be instituted promptly in many patients. Although methotrexate remains the first-line disease-modifying agent, there are some promising new drugs. The fact that activated macrophages contribute to synovial inflammation in this disease has led to the development of modulators of macrophage-derived cytokines. Blockade of TNF- α by a soluble TNF- α receptor–IgG1 fusion protein (etanercept) or monoclonal antibody against TNF- α (infliximab) is highly effective in preventing erosions when it is used in combination with methotrexate. Etanercept can also be used alone, since it

is not immunogenic in humans. Blockade of TNF- α is also effective in Crohn's disease and is useful in refractory psoriatic arthritis and ankylosing spondylitis, a disease for which no other disease-modifying therapy has been available. Leflunomide, a pyrimidine antagonist that blocks the enzyme dihydroorotate dehydrogenase, thereby blocking the synthesis of DNA, has an efficacy similar to that of methotrexate and can be used either alone or in combination with methotrexate. Blockade of interleukin-1 receptors with a recombinant interleukin-1-receptor antagonist is less effective than blockade of TNF- α in patients with rheumatoid arthritis, but it may retard the development of bone erosions. The long-term safety of these new agents, particularly with respect to the risk of infections, cancer, and other autoimmune diseases, remains to be ascertained (Weinblatt et al., 1999).

VI.2.2. Multiple Sclerosis

Advances have been made in the treatment of multiple sclerosis with the use of interferon beta-1a and copolymer I. Although the indications for and timing of the use of these agents are still debated, a recent study suggests that interferon beta-1a can delay the onset of frank disease when given after a first episode of optic neuritis. Copolymer I is a nonspecific inhibitor of T cells *in vitro*, although it may also act by immune deviation from type 1 to type 2 helper T cells. Treatment with altered peptide ligands derived from myelin basic protein was efficacious in murine models of the disease, but two recent phase 1 trials of such peptides were associated with clinically significant toxicity: one caused hypersensitivity reactions, and the second resulted in exacerbations of multiple sclerosis. Thus, studies of animal models of disease cannot substitute for clinical trials, and these must proceed with caution.

Blockade of TNF- α , with or without methotrexate, has been effective in refractory psoriasis. Psoriasis responded to treatment with interleukin-10 in several small and short-term clinical trials. Benefit was also achieved with the use of CTLA-4-Ig, a recombinant fusion protein in which the extracellular domain of CTLA-4 is linked to the constant region of IgG1. CTLA-4-Ig blocks the activation of most naive T cells as well as both primary and secondary antibody responses. However, CTLA-4-Ig exacerbated diabetes in a mouse model in which activation of regulatory cells is thought to prevent initiation of the disease. A number of other biologic agents have also been successfully used to treat psoriasis in small pilot studies. These include antibodies against CD4, antibodies against the high-affinity interleukin-2 receptor CD25 (daclizumab), and antibodies against the CD11a component of the adhesion molecule leukocyte function-associated antigen type 1 (also referred to as $\alpha 1\beta 2$ integrin and

CD11aCD18) that mediates migration of T cells into the skin. A humanized antibody against CD11a is currently being evaluated in a clinical trial in a large cohort of patients with psoriasis (Gottlieb et al., 2000).

VI.2.3. Type 1 Diabetes

Therapeutic efforts in type 1 diabetes have focused on prevention. Relatives of patients with diabetes who are at risk for the disease can be identified with near certainty; however, screening of the general population is associated with high false positive rates that preclude intervention studies. Prevention trials are currently assessing the efficacy of inducing antigen-specific immune tolerance through the intra- venous or subcutaneous administration of insulin in persons at risk who have evidence of decreased beta cell mass or through the oral administration of insulin in those who have antibodies against insulin but in whom insulin secretion is normal. Initial results with oral insulin have been disappointing, but the results of systemic insulin are not yet available (Pozzilli et al., 2000) .

VI.2.4. Systemic Lupus Erythematosus

Clinical trials in patients with systemic lupus erythematosus are plagued by the wide range of disease manifestations; the relapsing–remitting nature of the disease, which results in high rates of response in groups given a placebo; and the lack of standardized criteria for remission. Whether or not abnormal serologic results should prompt treatment in the absence of clinical signs of the disease remains debatable. Blockade with CTLA-4–Ig or antibodies against CD40 ligand has been highly effective in the prevention or treatment of nephritis in murine models but not in humans. Two recent clinical trials of monoclonal antibodies against CD40 ligand were unsuccessful; one did not show efficacy, and the other found unexpected toxicity. Polymorphisms of the interleukin-10 gene are associated with systemic lupus erythematosus; a pilot study suggests that treatment of active disease with antibodies against interleukin-10 may be effective (Llorente and al., 2000).

VI.3. Future therapeutic approaches

Four general approaches to therapy are being explored (Table 05): altering thresholds of immune activation, modulating antigen-specific responses, reconstituting the immune system with autologous or allogeneic stem cells, and sparing of target organs. Interference with costimulation, signaling, chemokines, cytokines, and other molecules critical to immune

activation is designed to restore homeostasis in the immune system and dampen the autoimmune response. It is based on the concept that small changes in the availability of proteins that control interactions between cells or participate in intracellular signaling can divert the immune system away from autoreactivity. Antigen-specific therapies aim to induce tolerance to a particular antigen. Exposure of the immune system to autoantigens or appropriate peptides delivered either by ingestion to induce oral tolerance or by injection has worked well in animals but not in humans. Perhaps this approach can only work during the initial activation of autoreactive cells, because once disease is clinically apparent, the immunologic milieu may be inflammatory and epitope spreading may have occurred. However, the rate of concordance for autoimmune disease of less than 50 percent in monozygotic twins argues against attempting preventive strategies. We may need to combine antigen blockade to expose lymphocytes to the antigen in the absence of inflammation. Alternatively, some autoimmune diseases may be sustained by memory cells that resist the induction of tolerance.

An approach involving stem-cell transplantation has engendered much excitement recently. Pilot studies of reconstitution with autologous and allogeneic stem cells are proceeding in patients with systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and multiple sclerosis. The hope is to restore homeostasis with regulatory cells. The efficacy and safety of this approach are unknown. The complex causes of autoimmune diseases not only present a challenge to the development and testing of new therapies but also offer a framework that allows the identification of subgroups of patients who might benefit from particular approaches. Although we will encounter both successes and setbacks, continued studies of autoimmune diseases in humans and animals are necessary to help identify the most appropriate strategies for each disease (Mizuno et al. 2000).

- Abbey JL, O'Neill HC. Expression of T Cell receptor genes during early T cell development. *Immunol Cell Biol.* 2008;86:166–74.
- Alberts, B., Johnson, A., Lewis J., Raff, M., Roberts, K., Walter, P. *Molecular Biology of the Cell.* 4th edition. New York: Garland Science. 2002. B Cells and Antibodies. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK26884/>
- Ali, F., Mahmoud, N., El-Sayed, A., Abdelmaksoud, M., Shata, A., & Fouad, S. (2021). Selective IgA Deficiency a Probable Risk of Recurrent Chest Infections in Asthmatics. *Journal of Asthma and Allergy*, 14, 1323 - 1333. <https://doi.org/10.2147/JAA.S329531>.
- Anderson G, Takahama Y. Thymic epithelial cells: working class heroes for T cell development and repertoire selection. *Trends Immunol.* 2012;33:256–63.
- Anderson, M. S., & Su, M. A. (2016). AIRE expands: New roles in immune tolerance and beyond. *Nature Reviews Immunology*, 16(4), 247–258. <https://doi.org/10.1038/nri.2016.9>
- Arikan, A., Doluca, O., Akhan, S., Şanlıdağ, T., & Sayan, M. (2022). Evaluation of lateral flow and ELISA techniques for detecting IgG and IgM antibodies in COVID-19 cases in Türkiye. *Eastern Mediterranean health journal*, 29 2, 91-99. <https://doi.org/10.26719/emhj.23.011>.
- Ashby, K. M., & Hogquist, K. A. (2024). A guide to thymic selection of T cells. *Nature Reviews Immunology*, 24(2), 103–117. <https://doi.org/10.1038/s41577-023-00911-8>
- Ayensu, W. K., Tchounwou, P. B., & McMurray, R. W. (2004). Molecular and cellular mechanisms associated with autoimmune diseases. *International Journal of Environmental Research and Public Health*, 1(1), 39-73.
- Baniyash M. TCR zeta-chain downregulation: curtailing an excessive inflammatory immune response. *Nat Rev Immunol.* 2004;4:675–87.
- Berkowska MA, Driessen GJ, Bikos V, et al. Human memory B cells originate from three distinct germinal center-dependent and -independent maturation pathways. *Blood.* 2011;118:2150–8. [PMC free article] Bhandoola A, Sambandam A. From stem cell to T cell: one route or many? *Nat Rev Immunol.* 2006;6:117–26.
- Bhandoola A, Sambandam A. From stem cell to T cell: one route or many? *Nat Rev Immunol.* 2006;6:117–26.
- Blutt, S., Miller, A., Salmon, S., Metzger, D., & Conner, M. (2012). IgA is Important for Clearance and Critical for Protection from Rotavirus Infection. *Mucosal immunology*, 5, 712 - 719. <https://doi.org/10.1038/mi.2012.51>.
- Borish, L. C., & Steinke, J. W. (2003). 2. Cytokines and chemokines. *Journal of Allergy and Clinical Immunology*, 111(2), S460-S475
- Bousso P. T Cell activation by dendritic cells in the lymph node: lessons from the movies. *Nat Rev Immunol.* 2008;8:675–84.
- Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. *Nat Rev Immunol.* 2012;12:180–90.
- Bradl, H., Wittmann, J., Milius, D., Vettermann, C., & Jäck, H.-M. (2003). Interaction of murine precursor B cell receptor with stroma cells is controlled by the unique tail of $\lambda 5$ and stroma cell-associated heparan sulfate. *The Journal of Immunology*, 171(5), 2338–2348. <https://doi.org/10.4049/jimmunol.171.5.2338>
- Brandes R, Lang F, Schmidt R. *Physiologie des Menschen: mit Pathophysiologie.* Berlin: Springer; 2019.

- Brandtzaeg, P. (2009). Mucosal immunity: induction, dissemination, and effector functions. *Scandinavian journal of immunology*, 70(6), 505-515.
- Brilhante-Da-Silva, N., De Oliveira Sousa, R., Arruda, A., Santos, E., Marinho, A., Stabeli, R., Fernandes, C., & Pereira, S. (2021). Camelid Single-Domain Antibodies for the Development of Potent Diagnosis Platforms. *Molecular Diagnosis & Therapy*, 25, 439 -456. <https://doi.org/10.1007/s40291-021-00533-7>.
- Briney, B., Inderbitzin, A., Joyce, C., & Burton, D. R. (2019). Commonality despite exceptional diversity in the baseline human antibody repertoire. *Nature*, 566(7744), 393–397. <https://doi.org/10.1038/s41586-019-0879-y>
- Brinkmann, V. (2005). *Bacillus anthracis, the causative agent of anthrax* [Micrograph]. *PLoS Pathogens*, 1(3).<https://doi.org/10.1371/image.ppat.v01.i03>
- Brownlie RJ, Zamoyska R. T cell receptor signalling networks: branched, diversified and bounded. *Nat Rev Immunol*. 2013;13:257–69.
- Burn, G. L., Foti, A., Marsman, G., Patel, D. F., & Zychlinsky, A. (2021). The neutrophil. *Immunity*, 54(7), 1377–1391. <https://doi.org/10.1016/j.immuni.2021.06.006>
- Cabeza-Cabrerizo, M., Cardoso, A., Minutti, C. M., Pereira da Costa, M., & Reis e Sousa, C. (2021). Dendritic cells revisited. *Annual Review of Immunology*, 39, 131–166. <https://doi.org/10.1146/annurev-immunol-061020-053707>
- Cano, R. L. E., & Lopera, H. D. E. (2013). Introduction to T and B lymphocytes. In J.-M. Anaya, Y. Shoenfeld, A. Rojas-Villarraga, R. A. Levy, & R. Cervera (Eds.), *Autoimmunity: From bench to bedside*. El Rosario University Press. <https://www.ncbi.nlm.nih.gov/books/NBK459471/>
- Carding, S. R., & Egan, P. J. (2002). $\gamma\delta$ T cells: Functional plasticity and heterogeneity. *Nature Reviews Immunology*, 2(5), 336–345. <https://doi.org/10.1038/nri797>
- Carding SR, Egan PJ. Gammadelta T cells: functional plasticity and heterogeneity. *Nat Rev Immunol*. 2002;2:336–45.
- Carding SR, Egan PJ. Gammadelta T cells: functional plasticity and heterogeneity. *Nat Rev Immunol*. 2002;2:336–45.
- Cerutti A, Cols M, Puga I. Activation of B cells by non-canonical helper signals. *EMBO Rep*. 2012;13:798–810.
- Chatzigeorgiou A, Lyberi M, Chatzilymperis G, Nezos A, Kamper E. CD40/CD40L signaling and its implication in health and disease. *Biofactors*. 2009;35:474–83.
- Chen DS, Mellman I. Oncology meets immunology: the cancer immunity cycle. *Immunity*. 2013;39(1):1-10.
- Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat Rev Immunol*. 2013;13:227–42. [PMC free article]
- Choi MY, Kipps TJ. Inhibitors of B Cell receptor signaling for patients with B Cell malignancies. *Cancer J*. 2012;18:404–10. [PMC free article]
- Choudhary, O. P., Sarkar, R., Choudhary, P., & Kalita, A. (2021). Preparation of blood samples for electron microscopy: The standard protocol. *Annals of Medicine and Surgery*, 70, Article 102895. <https://doi.org/10.1016/j.amsu.2021.102895>

- Cornec D, Devauchelle-Pensec V, Tobon GJ, Pers JO, Jousse-Joulin S, Saraux A. B cells in Sjogren's syndrome: from pathophysiology to diagnosis and treatment. *J Autoimmun.* 2012;39:161–7.
- Cox MA, Kahan SM, Zajac AJ. Anti-viral CD8 T cells and the cytokines that they love. *Virology.* 2013;435:157–69.
- Cruickshank MN, Ulgiati D. The role of notch signaling in the development of a normal B Cell repertoire. *Immunol Cell Biol.* 2010;88:117–24.
- Cyster JG. Homing of antibody secreting cells. *ImmunolRev.* 2003;194:48–60.
- Dahlin, J. S., Maurer, M., Metcalfe, D. D., Pejler, G., Sagi-Eisenberg, R., & Nilsson, G. (2022). The ingenious mast cell: Contemporary insights into mast cell behavior and function. *Allergy*, 77(1), 83–99. <https://doi.org/10.1111/all.14881>
- Delves PJ, Roitt IM. The immune system. Part 1. *N Engl J Med* 2000; 343: 3–49
- Demonbreun, A., Sancilio, A., Velez, M., Ryan, D., Saber, R., Vaught, L., Reiser, N., Hsieh, R., D'Aquila, R., Mustanski, B., McNally, E., & McDade, T. (2021). Comparison of IgG and neutralizing antibody responses after one or two doses of COVID-19 mRNA vaccine in previously infected and uninfected individuals. *EClinicalMedicine*, 38. <https://doi.org/10.1016/j.eclinm.2021.101018>.
- Dillon SR, Gross JA, Ansell SM, Novak AJ. An APRIL to remember: novel TNF ligands as therapeutic targets. *Nat Drug Rev Discov.* 2006;5:235–46.
- Dustin ML, Depoil D. New insights into the T cell synapse from single molecule techniques. *Nat Rev Immunol.* 2011;11:672–84. [PMC free article]
- EA YTC. B Cell Antigen Receptor. *Encyclopedia of Biological Chemistry.* 2004:155–
- Eyerich S, Eyerich K, Pennino D, et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. *J Clin Invest.* 2009;119:3573–King C. New insights into the differentiation and function of T follicular helper cells. *Nat Rev Immunol.* 2009;9:757–66.
- Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727-35.
- Flajnik, M. F., & Kasahara, M. (2010). Origin and evolution of the adaptive immune system: genetic events and selective pressures. *Nature Reviews Genetics*, 11(1), 47-59.
- Fonseca, M., Silva, M., Pinto, A., De Melo, A., Oliveira, F., De C Araújo, F., & De Andrade, L. (2022). Persistently positive SARS-CoV-2-specific IgM during 1-year follow-up. *Journal of Medical Virology*, 94, 4037 - 4039. <https://doi.org/10.1002/jmv.27822>.
- Garred P, Madsen HO, Hofmann B, Svegggaard A. Increased frequency of homozygosity of abnormal mannan-binding protein alleles in patients with suspected immunodeficiency. *Lancet* 1995;
- Gaudino, S. J., Kumar, P. Cross-Talk Between Antigen Presenting Cells and T Cells Impacts Intestinal Homeostasis, Bacterial Infections, and Tumorigenesis. *Front. Immunol.* 2019; 10:360.
- doi:10.3389/fimmu.2019.00360.. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;343:938-52.

- Gauthier, L., Rossi, B., Roux, F., Termine, E., & Schiff, C. (2002). Galectin-1 is a stromal cell ligand of the pre-B cell receptor (BCR) implicated in synapse formation between pre-B and stromal cells and in pre-BCR triggering. *Proceedings of the National Academy of Sciences of the United States of America*, 99(20), 13014–13019. <https://doi.org/10.1073/pnas.202323999>
- Girard JP, Moussion C, Forster R. HEVs, lymphatics and homeostatic immune cell trafficking in lymph nodes. *Nat Rev Immunol*. 2012;12:762–73.
- Gonzalez-Garcia S, Garcia-Peydro M, Alcain J, Toribio ML. Notch1 and IL-7 receptor signalling in early T Cell development and leukaemia. *Curr Top Microbiol Immunol*. 2012;360:47–73.
- Gottlieb A, Krueger JG, Bright R, et al. Effects of administration of a single dose of a humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. *J Am Acad Dermatol* 2000; 42:428-35.
- Greenfield EA, Nguyen KA, Kuchroo VK. C28/B7 costimulation: a review. *Crit Rev Immunol* 1998;18:389-418.
- Hedrick, P. W. (2002). Pathogen resistance and genetic variation at MHC loci. *Evolution*, 56(10), 1902-1908..
- Hemdan NY, Birkenmeier G, Wichmann G, et al. Interleukin-17-producing T helper cells in autoimmunity. *Autoimmun Rev*. 2010;9:785–92.
- Herzog, S., Reth, M., & Jumaa, H. (2009). Regulation of B-cell proliferation and differentiation by pre-B-cell receptor signalling. *Nature Reviews Immunology*, 9(3), 195–205. <https://doi.org/10.1038/nri2491>
Herzog S, Reth M, Jumaa H. Regulation of B Cell proliferation and differentiation by pre-B Cell receptor signalling. *Nat Rev Immunol*. 2009;9:195–205.
- Ho IC, Tai TS, Pai SY. GATA3 and the T Cell lineage: essential functions before and after T-helper-2-cell differentiation. *Nat Rev Immunol*. 2009;9:125–35. [PMC free article]
- Hosokawa, H., & Rothenberg, E. V. (2021). How transcription factors drive choice of the T cell fate. *Nature Reviews Immunology*, 21(3), 162–176. <https://doi.org/10.1038/s41577-020-00426-6>
- Humphrey, J. H., Grennan, D., & Sundaram, V. (1984). The origin of follicular dendritic cells in the mouse and the mechanism of trapping of immune complexes on them. *European journal of immunology*, 14(9), 859-864.
- Janeway, C. A., Jr., Travers, P., Walport, M., & Shlomchik, M. J. (2001). *Immunobiology: The immune system in health and disease* (5th ed.). Garland Science. <https://www.ncbi.nlm.nih.gov/books/NBK27092/>
Janeway, C. A. Jr., Travers, P., Walport, M., Shlomchik, M. J. *Immunobiology: The Immune System in Health and Disease*. 5th edition. New York: Garland Science. 2001. B-cell activation by armed helper T cells. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK27142/>
- CA Jr, Travers P, Walport M, et al. *The Immune System in Health and Disease*. 5th edition. Janeway New York: Garland Science; 2001.
- Kaiko GE, Horvat JC, Beagley KW, Hansbro PM. Immunological decision-making: how does the immune system decide to mount a helper T Cell response? *Immunology*. 2008;123:326–
Kapsenberg ML. Dendritic-cell control of pathogen-driven T Cell polarization. *Nat Rev Immunol*. 2003;3:984–93.
- Kato A, Hulse KE, Tan BK, Schleimer RP. B-lymphocyte lineage cells and the respiratory system. *J Allergy Clin Immunol*. 2013;131:933–57.

- Keenan, R. A., De Riva, A., Corleis, B., Hepburn, L., Licence, S., Winkler, T. H., & Mårtensson, I.-L. (2008). Censoring of autoreactive B cell development by the pre-B cell receptor. *Science*, 321(5889), 696–699. <https://doi.org/10.1126/science.1157533>
- Keenan RA, De Riva A, Corleis B, et al. Censoring of autoreactive B cell development by the pre-B cell receptor. *Science*. 2008;321:696–9.
- Keenan RA, De Riva A, Corleis B, et al. Censoring of autoreactive B cell development by the pre-B cell receptor. *Science*. 2008;321:696–9.
- Kindt, T. J., Goldsby, R. A., Osborne, B. A., & Kuby, J. (2007). *Kuby immunology*. Macmillan.
- Kindt, T. J., Goldsby, R. A., Osborne, B. A., & Kuby, J. (2007). *Kuby immunology*. Macmillan.
- King C. New insights into the differentiation and function of T follicular helper cells. *Nat Rev Immunol*. 2009;9:757–66.
- Klein L, Hinterberger M, Wirnsberger G, Kyewski B. Antigen presentation in the thymus for positive selection and central tolerance induction. *Nat Rev Immunol*. 2009;9:833–
- Klein L, Hinterberger M, Wirnsberger G, Kyewski B. Antigen presentation in the thymus for positive selection and central tolerance induction. *Nat Rev Immunol*. 2009;9:833–44.
- Klein, L., Kyewski, B., Allen, P. M., & Hogquist, K. A. (2014). Positive and negative selection of the T cell repertoire: What thymocytes see (and don't see). *Nature Reviews Immunology*, 14(6), 377–391. <https://doi.org/10.1038/nri3667>
- Klenerman, P. (2025). *The immune system: a very short introduction*. Oxford University Press.
- Kroczek RA, Mages HW, Hutloff A. Emerging paradigms of T Cell co-stimulation. *Curr Opin Immunol*. 2004;16:321–7.
- Kumar, P., & Clark, M. L. (2012). *Kumar and Clark's clinical medicine E-Book*. Elsevier health sciences.
- Kurosaki T. B-lymphocyte biology. *Immunol Rev*. 2010;237:5–9.
- l'invasion des microbes. *Annales Inst Pasteur Paris* 1887; 1: 321.
- Lange H, Zemlin M, Tanasa RI, et al. Thymus-independent type 2 antigen induces a long-term IgG-related network memory. *Mol Immunol*. 2008;45:2847–60.
- Lieberman J. The ABCs of granule-mediated cytotoxicity: new weapons in the arsenal. *Nat Rev Immunol*. 2003;3:361–70.
- Llorente L, Richaud-Patin Y, Garcia-Padilla C, et al. Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. *Arthritis Rheum* 2000;43:1790–800.
- Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. *Nat Rev Immunol*. 2010;10:838–48. [PMC free article] Ma CS, Tangye SG, Deenick EK. Human Th9 cells: inflammatory cytokines modulate IL-9 production through the induction of IL-21. *Immunol Cell Biol*. 2010;88:621–3. [PubMed]
- Macias-Perez IM, Flinn IW. B Cell receptor pathobiology and targeting in NHL. *Curr Oncol Rep*. 2012;14:411–8. [PubMed]
- Mackay, I., Rosen, F. S., Klein, J., & Sato, A. (2000). The HLA system. *New England Journal of Medicine*, 343(10), 702–709.

- Mackay, IR (2000). Tolérance et auto-immunité. *BMJ* , 321 (7253), 93-96.
- Makvandi-Nejad, S., & Rowland-Jones, S. (2015). How does the humoral response to HIV-2 infection differ from HIV-1 and can this explain the distinct natural history of infection with these two human retroviruses?. *Immunology letters*, 163(1), 69-75.
- Malek TR, Bayer AL. Tolerance, not immunity, crucially depends on IL-2. *Nat Rev Immunol*. 2004;4:665–74.
- Markert, M. L., Sarzotti, M., Ozaki, D. A., Sempowski, G. D., Rhein, M. E., Hale, L. P., ... & Mill, M. R. (2003). Thymus transplantation in complete DiGeorge syndrome: immunologic and safety evaluations in 12 patients. *Blood*, 102(3), 1121-1130.
- Marshall, J. S., Warrington, R., Watson, W., & Kim, H. L. (2018). An introduction to immunology and immunopathology. *Allergy, Asthma & Clinical Immunology*, 14(Suppl. 2), Article 49. <https://doi.org/10.1186/s13223-018-0278-1>
- Martin, C., Aifantis, I., Scimone, M., von Andrian, U. H., Reizis, B., von Boehmer, H., & Gounari, F. (2003). Efficient thymic immigration of B220⁺ lymphoid-restricted bone marrow cells with T precursor potential. *Nature Immunology*, 4(9), 866–873. <https://doi.org/10.1038/ni965>
- Mass, E., Nimmerjahn, F., Kierdorf, K., & Schlitzer, A. (2023). Tissue-specific macrophages: How they develop and choreograph tissue biology. *Nature Reviews Immunology*, 23(9), 563–579. <https://doi.org/10.1038/s41577-023-00848-y>
- Mauri C, Bosma A. Immune regulatory function of B cells. *Annu Rev Immunol*. 2012;30:221–41.
- McCartney-Francis NL, Frazier-Jessen M, Wahl SM. TGF-beta: a balancing act. *Int Rev Immunol* 1998;16:553-80.
- Menche N. *Biologie Anatomie Physiologie*. München: Urban und Fischer; 2023.
- Metchnikoff E. *Sur la lutte des cellules de l'organismes centre*
- Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med*. 2009;361:888–98.
- Mizuno M, Nishikawa K, Morgan BP, Matsuo S. Comparison of the Muller MR, Rao A. NFAT, immunity and cancer: a transcription factor comes of age. *Nat Rev Immunol*. 2010;10:645–56. [PubMed]
- Muller MR, Rao A. NFAT, immunity and cancer: a transcription factor comes of age. *Nat Rev Immunol*. 2010;10:645–56. [PubMed]
- Nagasawa T. Microenvironmental niches in the bone marrow required for B Cell development. *Nat Rev Immunol*. 2006;6:107–16.
- Nakken B, Munthe LA, Kontinen YT, et al. B Cells and their targeting in rheumatoid arthritis--current concepts and future perspectives. *Autoimmun Rev*. 2011;11:28–34.
- Nanda, N., & Alphonse, M. P. (2024). From host defense to metabolic signatures: Unveiling the role of $\gamma\delta$ T cells in bacterial infections. *Biomolecules*, 14(2), Article 225. <https://doi.org/10.3390/biom14020225>
- National Cancer Institute. (n.d.). *Red and white blood cells* [Scanning electron micrograph, Electron Microscopy Facility, NCI-Frederick; public domain]. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Red_White_Blood_cells.jpg

- Noelle RJ, Nowak EC. Cellular sources and immune functions of interleukin-9. *Nat Rev Immunol*. 2010;10:683–7.
- Ohnishi, K., & Melchers, F. (2003). The nonimmunoglobulin portion of $\lambda 5$ mediates cell-autonomous pre-B cell receptor signaling. *Nature Immunology*, 4(9), 849–856. <https://doi.org/10.1038/ni959>
- Paul WE, Zhu J. How are T(H)2-type immune responses initiated and amplified? *Nat Rev Immunol*. 2010;10:225–35.
- Perry, M., & Whyte, A. (1998). Immunology of the tonsils. *Immunology today*, 19(9), 414–421.
- Pieper, K., Grimbacher, B., & Eibel, H. (2013). B-cell biology and development. *Journal of Allergy and Clinical Immunology*, 131(4), 959–971. <https://doi.org/10.1016/j.jaci.2013.01.046>
- Pieper K, Grimbacher B, Eibel H. B Cell biology and development. *J Allergy Clin Immunol*. 2013;131:959–71.
- Pillai S, Cariappa A. The follicular versus marginal zone B lymphocyte cell fate decision. *Nat Rev Immunol*. 2009;9:767–77.
- PLoS Pathogens. (2005). PLoS Pathogens issue image | Vol. 1(3) November 2005. *PLoS Pathogens*, 1(3), ev01.i03. <https://doi.org/10.1371/image.ppat.v01.i03>
- Pozzilli P, Pitocco D, Visalli N, et al. No effect of oral insulin on residual residual beta-cell function in recent-onset type I diabetes (the IMDIAB VII). *Diabetologia* 2000;43:1000–4.
- Puga I, Cols M, Barra CM, et al. B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. *Nat Immunol*. 2012;13:170–80.
- Qian, L., Lin, X., Gao, X., Khan, R., Liao, J., Du, S., Ge, J., Zeng, S., & Yao, S. (2023). The Dawn of a New Era: Targeting the "Undruggables" with Antibody-Based Therapeutics. *Chemical reviews*. <https://doi.org/10.1021/acs.chemrev.2c00915>.
- Qriouet, Z., Cherrah, Y., Sefrioui, H., & Qmichou, Z. (2021). Monoclonal Antibodies Application in Lateral Flow Immunochromatographic Assays for Drugs of Abuse Detection. *Molecules*, 26. <https://doi.org/10.3390/molecules26041058>.
- Rabaza, A., Fraga, M., Mendoza, A., & Giannitti, F. (2023). A meta-analysis of the effects of colostrum heat-treatment on its viscosity and IgG concentration, and the transfer of passive immunity in newborn dairy calves. *Journal of dairy science*. <https://doi.org/10.3168/jds.2022-22555>.
- Radtke, F., Wilson, A., Stark, G., Bauer, M., van Meerwijk, J., MacDonald, H. R., & Aguet, M. (1999). Deficient T cell fate specification in mice with an induced inactivation of Notch1. *Immunity*, 10(5), 547–558. [https://doi.org/10.1016/S1074-7613\(00\)80054-0](https://doi.org/10.1016/S1074-7613(00)80054-0)
- Ribot, J. C., Lopes, N., & Silva-Santos, B. (2021). $\gamma\delta$ T cells in tissue physiology and surveillance. *Nature Reviews Immunology*, 21(4), 221–232. <https://doi.org/10.1038/s41577-020-00452-4>
- Roep BO, Atkinson MA, van Endert PM, Gottlieb PA, Wilson SB, Sachs JA. Autoreactive T cell responses in insulin-dependent (type 1) diabetes mellitus: report of the first international workshop for standardization of T cell assays. *J Autoimmun* 1999;13:267–82.
- Rothenberg, E. V., Moore, J. E., & Yui, M. A. (2008). Launching the T-cell-lineage developmental programme. *Nature Reviews Immunology*, 8(1), 9–21. <https://doi.org/10.1038/nri2232>

- Rothenberg EV, Moore JE, Yui MA. Launching the T Cell-lineage developmental programme. *Nat Rev Immunol*. 2008;8:9–21.
- Sakaguchi S, Miyara M, Costantino CM, Hafler DA. FOXP3⁺ regulatory T cells in the human immune system. *Nat Rev Immunol*. 2010;10:490–500.
- Schatz, D. G., & Swanson, P. C. (2011). V(D)J recombination: Mechanisms of initiation. *Annual Review of Genetics*, 45, 167–202. <https://doi.org/10.1146/annurev-genet-110410-132552>
- Schmetterer KG, Neunkirchner A, Pickl WF. Naturally occurring regulatory T cells: markers, mechanisms, and manipulation. *FASEB journal*. 2012;26:2253–76.
- Severinson E, Westerberg L. Regulation of adhesion and motility in B lymphocytes. *Scand J Immunol*. 2003;58:139–44.
- Sharma, P., Joshi, R., Pritchard, R., Xu, K., & Eicher, M. (2023). Therapeutic Antibodies in Medicine. *Molecules*, 28. <https://doi.org/10.3390/molecules28186438>.
- Shevach EM. Mechanisms of foxp3⁺ T regulatory cell-mediated uppression. *Immunity*. 2009;30:636–45.
- Shlomchik MJ, Weisel F. Germinal center selection and the development of memory B and plasma cells. *Immunol Rev*. 2012;247:52–63.
- Siebenlist U, Brown K, Claudio E. Control of lymphocyte development by nuclear factor-kappaB. *Nat Rev Immunol*. 2005;5:435–45.
- Sims GP, Ettinger R, Shirota Y, Yarboro CH, Illei GG, Lipsky PE. Identification and characterization of circulating human tran-sitional B cells. *Blood*. 2005;105:4390–8.
- Smith, L. (2007). Hematopoietic Theory. *Hematology, clinical principles and applications*, 3, 62-64.
- Taghon T, Waegemans E, Van de Walle I. Notch signaling during human T cell development. *Curr Top Microbiol Immunol*. 2012;360:75–97.
- Tian J, Olcott A, Hanssen L, Zekzer D, Kaufman DL. Antigen-based immunotherapy for autoimmune disease: from animal models to humans. *Immunol Today* 1999;20:190-5.
- Townsend MJ, Monroe JG, Chan AC. B Cell targeted therapies in human autoimmune diseases: an updated perspective. *Im-munol Rev*. 2010;237:264–83.
- Trenevska, I., Li, D., & Banham, A. (2017). Therapeutic Antibodies against Intracellular Tumor Antigens. *Frontiers in Immunology*, 8. <https://doi.org/10.3389/fimmu.2017.01001>.
- Turner SJ, Doherty PC, McCluskey J, Rossjohn J. Structural determinants of T Cell receptor bias in immunity. *Nat Rev Immu-nol*. 2006;6:883–94.
- Vantourout P, Hayday A. Six-of-the-best: unique contributions of gammadelta T cells to immunology. *Nat Rev Immunol*. 2013;13:88–100.
- Vengesai, A., Midzi, H., Kasambala, M., Mutandadzi, H., Mduluza-Jokonya, T., Rusakaniko, S., Mutapi, F., Naicker, T., &Mduluza, T. (2020). A systematic and meta-analysis review on the diagnostic accuracy of antibodies in the serological diagnosis of COVID-19. *Systematic Reviews*, 10. <https://doi.org/10.1186/s13643-021-01689-3>.
- Vettermann, C., & Schlissel, M. S. (2010). Allelic exclusion of immunoglobulin genes: Models and mechanisms. *Immunological Reviews*, 237(1), 22–42. <https://doi.org/10.1111/j.1600-065X.2010.00935.x>

- Vinuesa CG, Chang PP. Innate B cell helpers reveal novel types of antibody responses. *Nat Immunol*. 2013;14:119–26.
- Volchenkov, R., Sprater, F., Vogelsang, P., & Appel, S. (2012). The 2011 Nobel Prize in physiology or medicine. *Scandinavian journal of immunology*, 75(1), 1-4.
- von Boehmer, H., & Melchers, F. (2010). Checkpoints in lymphocyte development and autoimmune disease. *Nature Immunology*, 11(1), 14–20. <https://doi.org/10.1038/ni.1794>
- Von Boehmer H, Melchers F. Checkpoints in lymphocyte development and autoimmune disease. *Nat Immunol*. 2010;11:14–20.
- Wei, W., & Wu, Y. (2019). Innovative drug research targeting IgD and IgDR signaling for the regulation of T cell activity. *The FASEB Journal*, Weinblatt ME, Kremer JM, Coblyn JS, et al. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum* 1999; 42:1322-8
- Weinstein E, Peeva E, Putterman C, Diamond B. B Cell biology. *Rheum Dis Clin North Am*. 2004;30:159–74.
- Winkler, T. H., & Mårtensson, I.-L. (2018). The role of the pre-B cell receptor in B cell development, repertoire selection, and tolerance. *Frontiers in Immunology*, 9, Article 2423. <https://doi.org/10.3389/fimmu.2018.02423>
- Wolf, N. K., Kissiov, D. U., & Raulet, D. H. (2023). Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. *Nature Reviews Immunology*, 23(2), 90–105. <https://doi.org/10.1038/s41577-022-00732-1>
- Wolk K, Witte E, Witte K, Warszawska K, Sabat R. Biology of interleukin-22. *Semin Immunopathol*. 2010;32:17–31.
- Wucherpennig KW, Gagnon E, Call MJ, Huseby ES, Call ME. Structural biology of the T Cell receptor: insights into receptor assembly, ligand recognition, and initiation of signaling. *Cold Spring Harb Perspect Biol*. 2010;2:a005140.
- Yang Q, Jeremiah Bell J, Bhandoola A. T Cell lineage determination. *Immunol Rev*. 2010;238:12–22. [PMC free article]
- Yates, A. J. (2014). Theories and quantification of thymic selection. *Frontiers in Immunology*, 5, Article 13. <https://doi.org/10.3389/fimmu.2014.00013>
- Zhao ZS, Granucci F, Yeh L, Schaffer PA, Cantor H. Molecular mimicry by herpes simplex virus-type 1: autoimmune disease after viral infection. *Science* 1998;279:1344-7.
- Zhou F. Perforin: more than just a pore-forming protein. *Int Rev Immunol*. 2010;29:56–76.
- Zlotoff, D. A., Sambandam, A., Logan, T. D., Bell, J. J., Schwarz, B. A., & Bhandoola, A. (2010). CCR7 and CCR9 together recruit hematopoietic progenitors to the adult thymus. *Blood*, 115(10), 1897–1905. <https://doi.org/10.1182/blood-2009-08-237784>tissue. *Science* 1999; 286: 2098–102.