KUBY IMMUNOLOGY-W. H. FREEMAN (2018)

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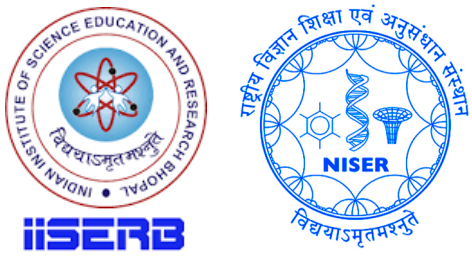

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1 CHAPTER 1 - OVERVIEW OF THE IMMUNE SYSTEM

1.1 INTRODUCTION

This documentation focuses on Chapter 1 of "Kuby's Immunology, 8th edition" as part of our comprehensive reading project. It provides an overview of the chapter's events and explores key terminologies, significant learnings, and a summary. This chapter plays a crucial role in advancing the central themes and narrative arc of the book, offering valuable insights into the field of immunology. By closely examining its content and analysing its concepts, I have deepened my understanding of immunology. The chapter covers the fundamentals of immunology and briefly discusses its evolutionary history, from the initial understanding of the immune system's ability to memorize pathogen interactions to present-day efforts in combating evolving pathogens and related diseases. This documentation presents a concise overview of the topics covered in the chapter, key terminologies, and concludes with a brief reflection. Its purpose is to share the knowledge I have acquired from studying this chapter.

1.2 KEY TERMINOLOGIES

- **Immunity** is the state of protection from infectious diseases.
- A **vaccine** is a weakened or attenuated strain of a pathogen administered to provide immunity against the disease.
- **Herd immunity** reduces the number of individuals capable of spreading an infectious agent, thereby lowering the risk of susceptible individuals becoming infected.
- **Antibiotics** are chemical agents designed to destroy specific types of bacteria, but they are ineffective against other infectious agents and certain bacterial species.
- **Gamma globulin (now immunoglobulin)** is a fraction of serum responsible for neutralizing toxins, precipitating toxins, and agglutinating bacteria.
- **Antibodies**, the active soluble molecules in the immunoglobulin fraction of serum, are produced by B cells and confer humoral immunity, combating pathogens in bodily fluids.
- **Humoral immunity** refers to the immunologic events in which antibodies, produced by B cells, combat pathogens and are present in bodily fluids.
- **Antiserum** refers to the antibody-containing serum fraction from an individual exposed to a specific pathogen.
- **Passive immunity** refers to immune protection transferred between individuals, such as the presence of maternal antibodies in newborn infants.
- **Active immunity** is the host's production of its own immunity against pathogens.

- **Cell-mediated immunity** is immunity imparted by specific cells, involving pathogen-specific T lymphocytes that directly eliminate infectious agents and aid other cells in their function.
- **Lymphocytes**, including T lymphocytes (T cells) and B lymphocytes (B cells), are white blood cells responsible for both cellular and humoral immunity.
- **Side-chain receptors**, expressed on blood cells, bind to infectious agents and inactivate them.
- **Antigens** are substances that elicit a specific response from B or T lymphocytes.
- **The clonal selection theory** explains that each lymphocyte expresses a specific receptor before exposure to an antigen, and binding to the antigen activates the cell, leading to the production of daughter cells with the same receptor specificity.
- Organisms causing disease are referred to as **pathogens**, and the process by which they induce illness in the host is known as **pathogenesis**. Pathogens can be categorized into viruses, fungi, parasites, and bacteria.
- **Cytotoxic T lymphocytes (CTLs or Tc cells)** play a crucial role in the cellular arm of immunity, as they recognize viral proteins in the cytosol and alert the cell to the presence of an invader.
- **T helper cells (T cells)** guide the behaviour of other immune cells, including B cells, and determine the pathway of the immune response.
- **Pathogen-associated molecular patterns (PAMPs)** are common foreign structures recognized by DNA-encoded receptors of the innate immune system.
- **Pattern recognition receptors (PRRs)**, found on white blood cells, specifically recognize sugar residues and other common foreign structures.
- **Tolerance** is the principle of self/nonself discrimination in the immune response.
- **The danger or damage model** suggests that the immune system evaluates encounters based on their potential danger or safety to the host, rather than solely considering self-versus nonself.
- **Innate immunity** encompasses molecular and cellular mechanisms that are evolutionarily primitive and aimed at preventing infection or swiftly eliminating common invaders. It includes physical and chemical barriers, as well as DNA-encoded receptors that recognize pathogens' common chemical structures. These mechanisms are inherited and provide a rapid response through the recognition and destruction of pathogens. However, the innate immune system's recognition elements are fast but lack specificity, unable to distinguish minor differences in foreign antigens.

- Innate immunity also involves pre-existing serum proteins known as **complement**, which bind to common pathogen-associated structures and initiate a cascade of labelling and destruction events.

- **Adaptive immunity**, involving B and T lymphocytes, is highly sensitive to subtle molecular differences. It takes longer to activate but exhibits greater antigen specificity. Usually, an

- Communication within the immune system occurs through direct cell-to-cell interactions and the secretion of messenger proteins known as **cytokines**.

- **Chemokines** are a subset of soluble signals with chemotactic activity, recruiting specific cells to infection sites.

- **Immunologic memory** enables a swifter and more efficient immune response during subsequent exposures to the same pathogen.

- **Primary Immunodeficiencies** result from inherited genetic factors, while **secondary immunodeficiencies** arise from disruptions or damage caused by chemical, physical, or biological agents.

- **Severe combined immunodeficiency (SCID)** is a rare but severe deficiency that affects both B and T cells, severely impairing adaptive immunity.

- **Opportunistic infections** are caused by microorganisms that are typically harmless in individuals with a competent immune system but pose a risk in cases of underlying immune deficiency.

1.3 KEY LEARNINGS

- Vaccination exposes individuals to safe forms of infectious agents, resulting in acquired protection or immunity against real and more dangerous pathogens. When a group has high protection against an infectious agent, either naturally or through vaccination, it reduces the likelihood of spreading and inadvertently protects unvaccinated individuals in the group. Some pathogens are not amenable to vaccination due to factors like molecular variants, complexity of generating protective immunity, or inability to establish necessary immunologic memory responses.

- Passive immunity provides a quick but temporary solution, while active immunity through natural infection or vaccination generates renewable, long-lasting protection by producing one's own immunity.

- The immune response involves both cell-mediated and humoral components, with B cells producing antibodies that bind to foreign proteins and T cells using surface-bound receptors to sense antigens. In the humoral response, B cells interact with antigens, differentiate

into antibody-secreting cells, and help clear foreign proteins or infectious agents. The cell-mediated response involves various T lymphocytes with diverse functions, including secretion of messengers and killing of infected cells.

- Recognition molecules bind to pathogens, initiating an immune response that involves cellular immunity (recognition and killing of pathogens by cells) and humoral immunity (labeling and destruction of pathogens by soluble proteins). During initial infection stages, receptors recognize the foreign agent, categorizing it and tailoring the subsequent immune response with specialized pathways. Diversity is generated in B and T lymphocytes, resulting in a range of cells expressing unique recognition molecules that can respond to any antigen.

- The immune response consists of innate and adaptive arms. Innate responses are rapid but less specific, using inherited recognition molecules and phagocytic cells. Adaptive responses are slower but highly specialized, relying on randomly generated recognition receptors.

- Memory is a unique capacity arising from adaptive responses, with no memory component in innate immunity.

- Immune dysfunction or failure can fall into categories such as hypersensitivity (allergy), autoimmune disease, immune deficiency, or immune imbalance, which leads to aberrant immune cell activity and inflammation.

1.4 CONCLUSION

The mammalian immune response is a complex network of molecules, cells, and organs that defends against diverse microbial invaders. While immunology is a relatively young field, societies have applied its principles for centuries to combat infectious agents. Recent advancements have revealed that the immune system maintains a delicate balance between aggression and regulation. Furthermore, it is now understood that the immune system is influenced by the environment and interacts with other body systems. This newfound understanding opens up possibilities for innovative medical treatments and raises new questions that were previously unexplored in the study of the immune response.

2 CHAPTER 2 - CELLS, ORGANS, AND MICRO-ENVIRONMENTS OF THE IMMUNE SYSTEM

2.1 INTRODUCTION

This documentation focuses on Chapter 2 of "Kuby's Immunology, 8th edition" as part of our comprehensive reading project. It provides an overview of the chapter's events and explores key terminologies, significant learnings, and a summary. This chapter offers a comprehensive overview of the processes involved in the production, activation, proliferation, and differentiation of immune cells. In this chapter, we delve into hematopoiesis, the process of HSC differentiation into mature blood cells. We explore the characteristics and functions of different cell types derived from HSCs, and examine the anatomy and microanatomy of primary lymphoid organs where hematopoiesis occurs. Our focus lies on the lymph nodes and spleen as we discuss secondary lymphoid organs. This documentation presents a concise overview of the topics covered in the chapter, key terminologies, additional learning I have gained through web related to some of the given topics and concludes with a brief reflection. Its purpose is to share the knowledge I have acquired from studying this chapter.

2.2 KEY POINTS

- Primary lymphoid organs—including the bone marrow and the thymus—are sites where immune cells develop from immature precursors.
- Secondary lymphoid organs—including the spleen, lymph nodes, and specialized sites in the gut and other mucosal tissues—are sites where the mature antigen-specific lymphocytes first encounter antigen and begin their differentiation into effector and memory cells.
- Two circulatory systems—blood and lymphatic vessels—connect these organs, uniting them into a functional whole.
- Notably, all mature blood cells, encompassing red blood cells, granulocytes, macrophages, dendritic cells, and lymphocytes, originate from a singular cell type known as the hematopoietic stem cell (HSC).
- Embryonic stem cells possess the remarkable ability to generate nearly every specialized cell type within an organism, making them pluripotent. On the other hand, adult stem cells are characterized by their capacity to produce diverse cell types specific to a particular tissue, thus being multipotent.
- Various organs in adults harbor tissue-specific stem cells capable of generating cells unique to that particular tissue. The hematopoietic stem cell (HSC) was the first identified tissue-specific stem cell, serving as the origin for all red blood cells (erythroid cells) and white blood cells (leukocytes) in our body.

- Hematopoietic stem cells (HSCs) consist of diverse subpopulations distinguished by their quiescence and self-renewal abilities. Long-term HSCs, the most dormant and long-lasting, give rise to short-term HSCs. The latter, in turn, can differentiate into more proliferative multipotent progenitors (MPPs) responsible for generating lymphoid and myeloid cell types.

- During HSC differentiation, self-renewal diminishes from LT-HSCs to ST-HSCs and MPPs. Two lineage choices emerge: myeloid progenitors, also known as a common myeloid progenitor (CMPs) for red blood cells, platelets, and myeloid cells, and lymphoid progenitors, also referred to as a common lymphoid progenitor (CLPs) for B and T lymphocytes, ILCs, and specific dendritic cells. Myeloid cells are part of innate immunity, while B and T lymphocytes contribute to adaptive immunity. ILCs combine features of both innate and adaptive cells.

- As hematopoietic stem cell (HSC) descendants progress in their respective lineages, their ability to contribute to other cellular lineages diminishes gradually. For instance, when multipotent progenitors (MPPs) express the Flt-3 receptor, they lose the potential to become erythrocytes and platelets, transforming into lymphoid-primed, multipotent progenitors (LMPPs). Further commitment to the lymphoid lineage is marked by a decline in c-Kit and Sca-1 stem-cell antigen levels, accompanied by the expression of RAG1/2 and TdT enzymes involved in lymphocyte receptor generation. Cells expressing RAG1/2 are identified as early lymphoid progenitors (ELPs), some of which migrate to the thymus as T-cell progenitors, while the remaining ELPs remain in the bone marrow as B-cell progenitors. ELPs in the bone marrow, characterized by increased interleukin-7 receptor (IL-7R) levels, develop into common lymphoid progenitors (CLPs) that lack myeloid potential but retain the ability to mature into T cells, B cells, or ILCs (innate lymphoid cells).

- Various factors regulate quiescence, proliferation, and differentiation of hematopoietic stem cells (HSCs). The "top ten" factors, including GATA-2, RUNX1, Scl/Tal-1, Lyl1, Lmo2, Meis1, PU.1, ERG, Fli-1, and Gfi1b, along with other factors, play significant roles. Transcriptional regulators also impact myeloid versus lymphoid lineage choices. For instance, Ikaros is essential for lymphoid but not myeloid development, as its absence results in severe immunocompromise. PU.1 levels affect lymphoid differentiation, with low levels favoring it and high levels directing cells toward myeloid fate. Notch1 activity plays a role in driving lymphoid progenitors to develop into T lymphocytes rather than B lymphocytes. GATA-1 directs myeloid progenitors toward erythroid (red blood cell) development instead of the granulocyte/monocyte lineages. Furthermore, PU.1 regulates the choice between erythroid and other myeloid cell lineages.

- All granulocytes have multilobed nuclei that make them visually distinctive and easily distinguishable from lymphocytes, whose nuclei are round.

- Neutrophils, upon reaching the infected tissue, perform phagocytosis (engulfing) of bacteria and release various proteins with antimicrobial properties and the ability to remodel tissues.

- Eosinophils combat multicellular parasites, like helminths, by clustering around them and releasing granule contents that damage their membranes.
- Basophils release histamine, increasing vessel permeability and muscle activity, enabling immune cell access to infection sites. They also secrete cytokines, which attract other immune cells like eosinophils and lymphocytes.
- Myeloid progenitors generate three phagocytic cell groups: monocytes, macrophages, and dendritic cells. Each of these cells possesses professional antigen-presenting cell (pAPC) function.
- Two main categories of monocytes have been identified. Inflammatory monocytes rapidly migrate to tissues in response to infection. Patrolling monocytes move slowly along blood vessels, monitoring tissue repair and serving as a reservoir for tissue-resident monocytes during non-infectious periods. Additionally, patrolling monocytes can suppress immune responses rather than initiating them.
- The presence of specific antibodies to an antigen increase the rate of phagocytosis by 4000-fold compared to when the antibodies were absent. This highlights antibodies as opsonins, molecules that bind antigens and enhance their recognition and uptake by phagocytes.
- As peripheral sentinels, immature dendritic cells capture antigens through three methods: phagocytosis, receptor-mediated endocytosis, or pinocytosis.
- Follicular dendritic cells (FDCs) are functionally distinct from dendritic cells, as they do not arise from hematopoietic stem cells. Unlike dendritic cells, FDCs are not pAPCs and do not activate naïve T cells. Their primary function is to regulate the activation of B cells.
- In mammals, erythrocytes lack a nucleus, while nonmammalian vertebrates retain their nuclei. Erythrocytes are primarily involved in gas exchange but also contribute to immunity. They express surface receptors for antibodies, bind antibody complexes, and can be cleared by macrophages. Additionally, erythrocytes generate compounds, such as nitric oxide, which can directly damage microbes.
- Antigen contact triggers lymphocyte proliferation and differentiation into effector and memory cells. Effector cells combat pathogens, while memory cells provide faster and more efficient responses upon re-exposure.
- B lymphocytes improve antigen binding through somatic hypermutation and generate diverse antibodies via class switching. Activated B lymphocytes are the only non-myeloid cell that can act as a pAPC. Activated B cells also express costimulatory molecules required to activate T cells. Through direct antigen presentation, B cells receive T-cell help in the form of cytokines, promoting their differentiation into plasma cells and memory cells responsible for antibody production.

- T-cell receptors recognize processed antigen fragments bound to MHC molecules. MHC exists in two forms: MHC class I is expressed by most nucleated cells, while MHC class II is mainly expressed by pAPCs. CD4+ T cells function as helper cells, recognizing antigen-MHC class II complexes, while CD8+ T cells act as cytotoxic cells, recognizing antigen-MHC class I complexes.

- Naïve CD8 T cells survey APCs surfaces with their TCRs. Upon binding to an MHC-peptide complex, they activate, proliferate, and differentiate into cytotoxic T lymphocytes (CTLs). CTLs play a critical role in monitoring and eliminating cells displaying non-self-antigen with MHC class I. For optimal proliferation and differentiation, naïve CD8 T cells require assistance from mature CD4 T cells.

- Similarly, Naïve CD4 T cells activate into various effector subsets. T helper type 1 (T1) and T helper type 17 (T17) cells regulate the response to intracellular pathogens, while T helper type 2 (T2) and T follicular helper (Tfh) cells regulate the response to extracellular pathogens. Each CD4 T-cell subtype produces distinct cytokines that facilitate the activation of B cells, T cells, macrophages, and other immune response participants.

- NK cells employ two strategies to eliminate abnormal cells effectively. Firstly, they target cells lacking MHC class I molecules, which can occur due to viral infection or tumor-related mutations. Secondly, NK cells express Fc receptors (FcRs) that can bind to antibodies. By binding to pathogenic protein-specific antibodies, NK cells engage in antibody-dependent cell cytotoxicity (ADCC), releasing granules to induce cell death upon contact with target cells.

- Hematopoiesis occurs in the bone marrow, which consists of the endosteal and perivascular niches. Quiescent long-lived HSCs reside in the perivascular niche, nurtured by perivascular and endothelial cells. B lymphocytes develop primarily in the bone marrow, associated with osteoblasts in the endosteal niche. Additionally, the bone marrow serves as a site for both lymphoid and myeloid cell development, as well as a destination for fully mature myeloid and lymphoid cells to return.

- Thymocytes with high-affinity self-MHC/peptide binding undergo induced cell death through negative selection, while those with intermediate affinity undergo positive selection and mature in the thymic medulla before entering circulation.

- Immature thymocytes are called double negative (DN) and do not express CD4 or CD8 antigens. In the cortex, they become double positive (DP) by upregulating both CD4 and CD8. As they mature, they become single positive (SP) by losing either CD4 or CD8.

- The thoracic duct is the largest lymphatic vessel and connects to the left subclavian vein, collecting lymph from the entire body except the right arm and right side of the head. Lymph from these areas is collected by the right lymphatic duct, which drains into the right subclavian vein.

- Activated B cells can follow two paths: some become plasma cells, producing antibodies, while others re-enter the follicle to form a germinal center. A follicle with a germinal center is called a secondary follicle, while one without is called a primary follicle.

- Memory T cells residing in secondary lymphoid organs are termed central memory cells, exhibiting distinct phenotypes and functional potentials compared to circulating effector memory T cells. Another population, tissue-resident memory cells, settle in peripheral tissues long-term and demonstrate a rapid response upon re-infection with a pathogen.

2.3 KEY DEFINITIONS

- **Hematopoiesis** is the formal process through which hematopoietic stem cells (HSCs) undergo differentiation, resulting in the production of mature blood cells.

- The temporary elevation in the quantity of circulating neutrophils is termed **leukocytosis**, which serves as a medical indicator of infection.

- **Antigen presentation** is the process in which professional antigen-presenting cells (APCs), serving as crucial links between the innate and adaptive immune systems, become activated upon contact with a pathogen at the infection site. They communicate this encounter to T lymphocytes in the lymph nodes by presenting peptides derived from the pathogen.

- The modification of antigens with opsonins is called **opsonization**.

- **Megakaryocytes** are large myeloid cells that reside in the bone marrow and give rise to thousands of platelets, very small cells (or cell fragments) that circulate in the blood and participate in the formation of blood clots.

- **Natural Killer T (NKT)** cells exhibit characteristics of both adaptive and innate immune cells. They possess T-cell receptors (TCRs) like T cells and some express CD4. Unlike typical T cells, NKT cells have limited TCR diversity and recognize lipids and glycolipids presented by CD1 molecules, related to MHC proteins. Upon activation, NKT cells release cytotoxic granules to kill target cells and secrete cytokines that can modulate the immune response.

- **Innate lymphoid cells (ILCs)** are derived from common lymphoid progenitors but lack antigen-specific receptors. They are classified into three groups (ILC1, ILC2, and ILC3) based on their secretion of cytokines, which resemble those produced by specific helper T-cell subsets.

- A site of active infection and immune activity is often referred to as a **tertiary lymphoid tissue**.

2.4 ADDITIONAL LEARNING

- Totipotency - is the ability of a single cell to divide and produce all of the differentiated cells in an organism. Spores and zygotes are examples of totipotent cells.
- In cell biology, pluripotency refers to a stem cell that has the potential to differentiate into any of the three germ layers: endoderm (gut, lungs, yolk sac), mesoderm (muscle, skeleton, blood vascular, urogenital, dermis), or ectoderm (nervous, sensory, epidermis), but not into extra-embryonic tissues like the placenta.
- Multipotency is when progenitor cells have the gene activation potential to differentiate into discrete cell types. For example, a hematopoietic stem cell —and this cell type can differentiate itself into several types of blood cell like lymphocytes, monocytes, neutrophils, etc., but it is still ambiguous whether HSC possess the ability to differentiate into brain cells, bone cells or other non-blood cell types.
- In biology, oligopotency is the ability of progenitor cells to differentiate into a few cell types. It is a degree of potency. Examples of oligopotent stem cells are the lymphoid or myeloid stem cells.
- In cell biology, a unipotent cell is the concept that one stem cell has the capacity to differentiate into only one cell type. It is currently unclear if true unipotent stem cells exist. Hepatoblasts, which differentiate into hepatocytes (which constitute most of the liver) or cholangiocytes (epithelial cells of the bile duct), are bipotent. A close synonym for unipotent cell is precursor cell.
- MHC - The major histocompatibility complex (MHC) is a large locus on vertebrate DNA containing a set of closely linked polymorphic genes that code for cell surface proteins essential for the adaptive immune system. These cell surface proteins are called MHC molecules.
- Pinocytosis - the ingestion of liquid into a cell by the budding of small vesicles from the cell membrane.
- Co-stimulation is a secondary signal which immune cells rely on to activate an immune response in the presence of an antigen-presenting cell.
- Plasma cells are the antibody-secreting effector cell derived from the B lineage, whereas Plasma refers to the cell-free, fluid component of blood that encompasses all clotting factors.
- Chemokines released by infected or damaged cells form a concentration gradient. Attracted cells move through the gradient towards the higher concentration of chemokine.
- A systemic infection earns its name by being spread throughout the systems of the body. It can be compared to a local infection, in which the pathogen or symptoms are localized to one area. Such infections are sometimes known as local infections.

2.5 CONCLUSION

Hematopoietic stem cells in the bone marrow give rise to all blood cells. Immune cell differentiation occurs in primary lymphoid organs, such as the bone marrow and thymus for T lymphocytes. From there, immune cells circulate through the blood and lymphatics to secondary lymphoid organs like lymph nodes and spleen. In secondary lymphoid organs, lymphoid cells search for antigens. Innate immune cells act as the initial defence against pathogen invasion, while antigen-presenting cells and antigens migrate to lymph nodes, activating T and B lymphocytes. Activated cells proliferate and differentiate to become either short-lived effector cells, aiding in pathogen clearance, or memory cells provide long-term protection against reinfection.

3 CHAPTER 3 - RECOGNITION AND RESPONSE

3.1 INTRODUCTION

This documentation focuses on Chapter 3 of "Kuby's Immunology, 8th edition" as part of our comprehensive reading project. It provides an overview of the chapter's events and explores key terminologies, significant learnings, and a summary. This chapter covers cellular receptors and their adaptations in the immune system. It discusses antigen receptors (BCRs and TCRs) and their interactions, as well as innate immune receptors. Cytokine receptors and chemokines are also explored. Signal transduction is explained as the process of communicating receptor-ligand interactions to evoke cellular responses. The outcomes of immune system recognition are briefly summarized. This documentation presents a concise overview of the topics covered in the chapter, key terminologies, additional learning I have gained through web related to some of the given topics, references and concludes with a brief reflection. Its purpose is to share the knowledge I have acquired from studying this chapter.

3.2 KEY DEFINITIONS

- **The dissociation constant (K)** relates the concentration of the receptor-ligand pair ([SL]) to the product of the concentrations of free receptor sites ([S]) and free ligand ([L]). K is measured in molarity (M) and indicates the affinity of the interaction, with lower K values representing higher affinity. When 50% of the binding sites are occupied, [SL] equals [S], and K is equal to the concentration of free ligand.

$$\mathcal{K} = \frac{[S][L]}{[SL]}$$

- Within the BCR molecule, **the complementarity-determining regions (CDRs)** are situated in loosely folded regions and are responsible for contacting the antigen. These CDRs have the ability to adopt various conformations without compromising the fundamental β-sandwich framework structure of the molecule.

- **The immunoglobulin superfamily** refers to a group of structurally related proteins that share a common ancestral gene responsible for encoding the fundamental structure of the immunoglobulin domain.

- The amino-terminal domains of antibody heavy and light chains are known as **variable or V regions**, while the carboxyl-terminal regions are referred to as **constant or C regions**. Subscripts are used to distinguish the light and heavy-chain regions.

- **Complementarity-determining regions (CDRs)** are hypervariable, loosely folded polypeptide loops located at the end of the variable region Ig domains. CDRs make direct contact with the bound antigen and play a crucial role in antibody specificity. CDR3, particularly in the heavy chain, exhibits the highest sequence variability among the Ig CDRs.

- The molecules recognized by innate immune cells are commonly known as **pathogen-associated molecular patterns (PAMPs)**. These patterns can be expressed by microbes, irrespective of their pathogenicity, and are sometimes referred to as **microbe-associated molecular patterns (MAMPs)**. Additionally, certain innate immune receptors have the ability to recognize antigens associated with dead or dying cells, which are known as **damage-associated molecular patterns (DAMPs)**.

- **Cytokines** are proteins that facilitate communication between cells in the immune system. Cytokines exhibit the properties of redundancy, pleiotropy, synergy, antagonism, and cascade induction. **Interleukins** are cytokines that mediate communication between white blood cells (leukocytes). **Chemokines** are cytokines that attract cells with specific chemokine receptors to areas of highest chemokine concentration. **Endocrine** cytokines travel through the bloodstream to reach their target cells, while **paracrine** cytokines act on nearby cells by diffusing short distances. **Autocrine** signaling occurs when a cell receives a signal from a cytokine it has secreted itself.

- Some chemokines can bind to glycosaminoglycans on endothelial cell membranes, creating a gradient along blood vessels and guiding leukocyte movement to infection sites. This movement induced by soluble factors is called **chemotaxis**, and the molecules responsible are known as **chemoattractants**.

- Receptors, known as **G protein-coupled receptors (GPCRs)** or seven-pass transmembrane receptors, threads through the membrane seven times and transmit ligand signals by interacting with polymeric GTP/GDP-binding "G proteins."

- The process by which ligand binding to a cellular receptor is translated into a modification in cellular activity is referred to as **signal transduction**.

- The **upstream component**s of a signaling pathway are those closest to the receptor; the **downstream components** are those closest to the effector molecules that determine the outcome of the pathway.

- Receptors known as **receptor tyrosine kinases (RTKs)** undergo dimerization upon ligand binding. This dimerization brings the tyrosine residues of one receptor in proximity to the kinase activity of the partner molecule.

- **Adapter proteins** lack intrinsic enzymatic or receptor functions and do not act as transcription factors. They are characterized by having multiple surface domains with precise binding specificities for specific molecular structures. Their role is to bind to specific motifs or domains on proteins or lipids and facilitate the redistribution of molecules within the cell in response to signals.

- **Scalable signaling** allows for activation of different targets depending on the strength of the received signal.
- **Proteasomes** are cylindrically shaped organelles that contain **proteases** located on the inner surface of the cylinder. These proteases normally break down cellular proteins that have outlived their usefulness.
- Neutrophils and macrophages undergo an **oxidative burst**, a metabolic shift that generates toxic chemicals like hypochlorous acid, peroxide, superoxide radicals, and reactive nitrogen species. These substances are concentrated in the phagolysosomes of these cells and exhibit high toxicity towards engulfed microbes.

3.3 KEY LEARNINGS

- Receptor molecules bind to ligands through weak noncovalent interactions, including hydrogen bonds, ionic bonds, hydrophobic interactions, and van der Waals forces. These interactions provide sufficient binding energy and duration for the receptor to receive molecular signals indicating ligand binding. Due to the individually weak nature of these interactions, multiple interactions are required for a biologically relevant receptor-ligand connection. Moreover, since each interaction operates over a short distance (about 1 Ångström), a high-affinity interaction relies on a close fit or complementarity between the receptor and ligand surfaces.
- By using different combinations of protein chains, the immune system can increase the variety of different receptor binding sites. For example, three different class 1 cytokine receptor alpha (α) chains bind the same beta (β) chain to form receptors for interleukins 3 and 5 (IL-3 and IL-5) and granulocyte-macrophage colony-stimulating factor (GM-CSF), respectively.
- The diversity in the adaptive receptor repertoire is achieved by the unique strategy of recombination between DNA sequences encoding small segments of receptor chains that are recombined in different ways in individual cells.
- Receptor expression patterns may change when a cell is activated, making it more or less responsive to particular signals.
- Cell-cell interactions allow the directional release of ligands, creating locally high concentrations and increasing signal strength.
- The immunoglobulin fold is composed of a pair of β sheets formed from β strands, which are connected by loops that define the protein-binding specificity.
- Most immunoglobulin domains contain approximately 110 amino acids, and each β sheet contains three to six strands. The pairing of β sheets within each domain is stabilized by intrachain disulfide bonds. Neighbouring domains are connected to one another by a stretch of relatively unstructured polypeptide chain.

- Upon stimulation, a B cell releases a soluble form of its receptor, which differs in sequence from the membrane-bound BCR at the C terminus but retains the same antigen binding site. Through differential mRNA splicing, the hydrophobic region responsible for anchoring the membrane-bound form to the B cell surface is replaced with a soluble (hydrophilic) amino acid sequence in the secreted antibody. Both soluble antibodies and membrane-bound BCRs belong to the immunoglobulin family of proteins, and consist of two identical heavy (H) chains and two identical light (L) chains.

- Immune receptors may be located on the plasma membrane, on intracellular membranes of endosomes and lysosomes, in the cytosol, or even floating in the tissue fluids.

- The antigen-binding sites of antibodies consist of components from both the heavy and light chains, resulting in two binding sites per four-chain antibody molecule. Each light chain comprises two immunoglobulin domains, while each heavy chain contains four or five Ig domains.

- Glycosylation is important in maintaining the solubility of the secreted antibody and in preserving the overall structure and flexibility of the molecule.

- There are two primary classes of light-chain constant region sequences: kappa (κ) and lambda (λ). Among the lambda light chains, there are four subtypes, with the majority belonging to subtype $\lambda 1$.

- The constant region of the antibody heavy chain can be categorized into five major sequence types known as isotypes: mu (
mu), delta (δ), gamma (γ), alpha (α), and epsilon (ϵ). Each isotype corresponds to a specific antibody class: IgM, IgD, IgG, IgA, and IgE, respectively. The gamma heavy chain is further divided into four subclasses, with the majority falling under the $\gamma 1$ subclass.

- During development, immature B cells express only membrane-bound IgM. Mature, unstimulated B cells express both membrane-bound IgD and IgM. Interestingly, upon antigen stimulation, IgD is lost from the cell surface. The expression of membrane-bound and soluble forms of IgM and IgD is controlled by alternative RNA splicing. On the other hand, the expression of other antibody classes (IgG, IgA, and IgE) requires an additional irreversible DNA recombination step. The regulation of specific heavy chain classes relies on cytokines released by T cells and antigen-presenting cells near the activated B cell.

- The B-cell receptor (BCR) is noncovalently associated with three transmembrane molecules on the membrane: CD19, CD21 (also known as a coreceptor), and CD81 (TAPA-1). The innate immune system tags pathogens by binding a C3d protein fragment to them. CD21 specifically binds to C3d, enhancing antigen binding to B cells. CD19 and CD81 assist in transmitting antigen signals across the B-cell membrane.

- Each membrane-bound B-cell receptor (BCR) is associated with a heterodimer, Igα, Igβ (CD79α,β), which transduces the antigen signal into the cell. Igα and Igβ are transmembrane proteins with intracytoplasmic tails containing immunoreceptor tyrosine-based activation motifs (ITAMs). The two tyrosine residues placed approximately 10 residues apart within ITAMs become phosphorylated (pYs) upon activation, serving as docking sites for downstream signaling molecules. Proteins with SH2 and PTB domains bind to these phosphorylated tyrosine residues, participating in signal transduction. Thus, the BCR complex is divided into a recognition component (BCR and CD21) and a signal transduction component (Igα, Igβ).

- There are two types of T-cell receptors (TCRs): $\alpha\beta$ TCRs and $\gamma\delta$ TCRs. The majority of T cells have $\alpha\beta$ TCRs, composed of an α chain and a β chain. These TCRs recognize complex antigens consisting of antigenic peptide fragments presented on MHC class I or class II molecules. The second subset of T cells express $\gamma\delta$ TCRs, which have a different pair of protein chains but a similar overall structure. $\gamma\delta$ T cells often localize to mucosal and skin tissues and can be activated by nontraditional antigens, with or without MHC platforms.

- TCR chains have two immunoglobulin domains: a variable (V) domain for antigen binding and a constant (C) domain that lifts the antigen-binding site away from the membrane. The chains are connected by a disulfide bond and anchored in the membrane by a transmembrane region. The $\alpha\beta$ TCR's CDR1 and CDR2 regions interact with MHC proteins, while the antigenic peptide interacts with the CDR3 regions.

- CD4 and CD8 are accessory molecules associated with TCRs involved in antigen recognition. CD4 is a monomeric glycoprotein with extracellular immunoglobulin-like domains, a transmembrane region, and a cytoplasmic tail. CD8 exists as either an $\alpha\beta$ heterodimer or an $\alpha\alpha$ homodimer, with an extracellular immunoglobulin-like domain, stalk region, transmembrane region, and cytoplasmic tail. CD28, another coreceptor, requires interaction with CD80 or CD86 on antigen-presenting cells for full activation, but it does not directly interact with the MHC-peptide antigen complex.

- The CD3 complex consists of three dimers: $\delta\epsilon$, $\gamma\epsilon$, and either$\zeta\zeta$ or $\zeta\eta$. The γ, δ, and ϵ chains have one ITAM unit each, while the$\zeta$and η chains have three each. The phosphorylation of tyrosine residues in these chains determines the strength of the signal produced.

- The IL-1 cytokine family consists of IL-1α, IL-1β, IL-18, and IL-33. IL-1α is biologically active in its pro-form, often found in a membrane-bound state, while pro-IL-1β requires processing by caspase-1 to become functional. Caspase-1 is part of an inflammasome protein complex. The immune system regulates cytokine signaling strength by adjusting the balance of functional receptors, inhibitory receptors, and soluble inhibitory molecules.

- The class 1 cytokine receptor family consists of three subfamilies defined by their common subunits: β, gp130, and γ. These subunits combine with various α chains to form specific

cytokine receptors. The α subunit is responsible for cytokine binding, while the accompanying chain (β, gp130, or γ) mainly facilitates receptor signaling, although their contribution to cytokine affinity varies.

- There are three subfamilies of interferons: type I (IFN-α and IFN-β), type II (IFN-γ), and type III (IFN-λ). Type I interferons include IFN-α (about 20 related proteins) and IFN-β, secreted by activated macrophages, dendritic cells, and virally infected cells. Type II interferon is known as IFN-γ and is produced by activated T cells and cytotoxic NK cells. IL-10 is also considered a type II interferon. Type III interferons, or IFN-λ, are secreted by plasmacytoid dendritic cells. Interferon receptors are heterodimers with conserved cysteine residues and consist of 12 receptor chains, binding a total of 27 different class 2 cytokines.

- The TNF family consists of soluble and transmembrane proteins. They have short intracytoplasmic N-terminal regions and longer extracellular C-terminal regions containing a TNF homology domain for receptor interaction. TNF-α and LT-α (also called TNF-β) are soluble proteins produced by activated macrophages, lymphocytes, fibroblasts, and keratinocytes. Binding of LT-α can increase MHC glycoprotein and adhesion molecule expression. Important membrane-bound TNF family members include lymphotoxin-β, BAFF, APRIL, CD40 ligand (CD40L), and Fas ligand (FasL). TNF family cytokines form trimers, either homo- or heterotrimeric, regardless of their soluble or membrane-bound forms.

- IL-17A, released by activated T cells, binds to receptors on neutrophils, keratinocytes, and other nonlymphoid cells, inducing proinflammatory cytokine secretion. T 17 cells secrete IL-17A and related cytokines. IL-17E (IL-25) promotes anti-inflammatory T 2 cell differentiation and suppresses T 17 cell responses. IL-17 family members typically exist as homodimers, including IL-17A and IL-17F heterodimers. The IL-17 receptor family consists of five transmembrane protein chains (IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE) that form various homo- and heterodimeric and trimeric receptor units.

- Upon ligand binding, TCRs or BCRs undergo noncovalent association (oligomerization) on the membrane surface and migrate to specialized lipid raft regions of the lymphocyte membrane. In B cells, the tyrosine kinase Lyn phosphorylates tyrosine residues on the Igα and Igβ molecules, initiating the signaling cascade. In T cells, the kinase Lck performs a similar function by phosphorylating the ITAMs on CD3 molecules.

- Signal transduction pathways can culminate in cellular functions such as the release of effector molecules from preformed vesicles, the destruction or modification of particular proteins, the alteration of mRNA stability, or the initiation of apoptosis.

- The nature of the innate immune receptor engaged in a dendritic cell determines what cytokines the dendritic cell secretes. These, in turn, determine the type of T-cell response that it initiates.

- Following antigen binding, phosphatidylinositol-3-kinase (PI3 kinase) is activated and binds to an adapter protein complex generated by antigen signaling. PI3 kinase phosphorylates an inner membrane phospholipid, which activates the protein kinase Akt. Akt plays various roles in cell activation, including phosphorylating and inactivating molecules that promote apoptosis. This extends the lifespan of antigen-activated lymphocytes.

3.4 ADDITIONAL LEARNINGS

- Signal transduction is the process of transferring a signal throughout an organism, especially across or through a cell.

- In molecular biology, a protein domain is a region of a protein's polypeptide chain that is self-stabilizing and that folds independently from the rest. Each domain forms a compact folded three-dimensional structure. Many proteins consist of several domains, and a domain may appear in a variety of different proteins. Molecular evolution uses domains as building blocks and these may be recombined in different arrangements to create proteins with different functions. In general, domains vary in length from between about 50 amino acids up to 250 amino acids in length.

- The immunoglobulin domain, also known as the immunoglobulin fold, is a type of protein domain that consists of a 2-layer sandwich of 7-9 antiparallel β-strands arranged in two β-sheets with a Greek key topology, consisting of about 125 amino acids. The backbone switches repeatedly between the two β-sheets.

- Beta sheets consist of beta strands (β-strands) connected laterally by at least two or three backbone hydrogen bonds, forming a generally twisted, pleated sheet. They can be oriented in parallel or antiparallel fashion.

- Glycosylation is the controlled enzymatic modification of an organic molecule, especially a protein, by the addition of a sugar molecule.

- Upstream and downstream are used to distinguish which event happens when in relation to each other. So something that's downstream of Enzyme A happens after the activation of that enzyme. Something upstream happens first, and may need to happen in order for the next step to occur. So, downstream/upstream are indicators of placement, and also importance, because some events (downstream) can't happen without events that happen first (upstream).

3.5 REFERENCES

https://youtu.be/Prd5ixp3_Vc

3.6 CONCLUSION

Communication and coordination among immune cells are vital for an effective immune response. Small molecules like chemokines attract cells to the site of infection, while cytokines induce cell differentiation for targeted immune responses. Adhesion molecule expression allows cells to leave circulation and respond to injuries. Dual recognition of antigens and coreceptor ligands prevents autoimmune responses. The immune system comprises innate and adaptive cells, with innate cells activating rapidly and adaptive cells requiring division and differentiation. Despite diverse receptors, similar signal transduction strategies are employed. Integration of multiple signals enables appropriate immune responses.

4 CHAPTER 4 - INNATE IMMUNITY

4.1 INTRODUCTION

This documentation focuses on Chapter 4 of "Kuby's Immunology, 8th edition" as part of our comprehensive reading project. It provides an overview of the chapter's events and explores key terminologies, significant learnings, and a summary. This chapter describes the components of the innate immune system, including physical and chemical barriers, a battery of protective cellular responses carried out by numerous cell types, and inflammatory responses. It illustrates how they act together to defend against infections. We will also conclude with an overview of innate immunity in plants and invertebrates. This documentation presents a concise overview of the topics covered in the chapter, key terminologies, key learning, additional learning I have gained through web related to some of the given topics, and concludes with a brief reflection. Its purpose is to share the knowledge I have acquired from studying this chapter.

4.2 KEY DEFINITIONS

- **The epidermis** contains several tiers of tightly packed epithelial cells; its outer layer consists mostly of dead cells filled with a waterproofing protein called keratin.
- The **dermis** is composed of connective tissue and contains blood vessels, hair follicles, sebaceous glands, sweat glands, and scattered myeloid leukocytes such as dendritic cells, macrophages, and mast cells.
- **Mucus**, the viscous fluid secreted by specialized cells of the mucosal epithelial layers, entraps foreign microorganisms; mucins, glycoproteins found in mucus, can prevent pathogen adherence to epithelial cells.
- Adherence of these and other bacteria to mucous membranes is generally mediated by hairlike protrusions on the bacteria, called **fimbriae or pili**, that have evolved the ability to bind to certain glycoproteins or glycolipids expressed only by epithelial cells of the mucous membrane of particular tissues.
- **Lysozyme** is an enzyme found in saliva, tears, and fluids of the respiratory tract that cleaves the peptidoglycan components of bacterial cell walls. **Lactoferrin and calprotectin** are two proteins that bind and sequester metal ions needed by bacteria and fungi, limiting their growth.
- **Psoriasin**, a small protein of the S-100 family with potent antibacterial activity against Escherichia coli, an enteric (intestinal) bacterial species.
- The epithelium of the respiratory tract secretes a variety of lubricating lipids and proteins called **surfactants**. Two surfactant proteins, SP-A and SP-D, which are present in the lungs

as well as in the secretions of some other mucosal epithelia, are members of a class of microbe-binding proteins called collectins.

- **Inflammasomes** are large complexes of NLRs, caspases, and other proteins. They detect intracellular pathogens and danger signals, leading to the release of pro-inflammatory cytokines essential for the immune response and tissue homeostasis.
- The **AIM2-like receptors (ALRs)** are cytosolic receptors that bind bacterial and viral DNA. They have a PYD (pyrin domain) at the N-terminus and one or two HIN (hematopoietic expression, interferon inducibility, nuclear localization) domains at the C-terminus, acting as the DNA-binding unit. They are also referred to as the PYHIN family.
- **Plasmacytoid dendritic cells (pDCs)** are specialized immune cells with a distinctive shape resembling plasma cells. They are highly effective producers of type I interferons, particularly in response to viral infections.
- Genes turned on by IFN are known as **interferon-stimulated genes (ISGs)**. Four ISGs important for inhibiting viral replication are Protein kinase R (PKR), 2',5'-Oligoadenylate A synthetase (OAS), Mx group proteins, and The IFIT (IFN-induced proteins with tetratricopeptide repeats) proteins. They increase the expression of MHC class I proteins, making the cells better targets for T cell–mediated killing; activate NK cells; and regulate the activities of macrophages and T cells.
- **Chemoattractants** are small protein agents that guide cell movement towards higher concentrations. They recruit cells into, within, and out of tissues, playing a vital role in immune responses, wound healing, and tissue repair.
- Bacterial pathogens like Listeria evade immune responses by replicating in the cytosol, avoiding phagocytosis. However, they are susceptible to **autophagy**, an intracellular process where the bacteria are enclosed in an autophagosome, derived from the endoplasmic reticulum. The autophagosome then fuses with lysosomes, leading to pathogen destruction. Autophagy is triggered by NLRs (NOD1 and NOD2), which are part of the innate immune system.
- Cell death induced by receptor-activated signaling pathways is called **regulated cell death**.
- **NETs** are extracellular traps formed by neutrophils. They are filaments that can extend up to 10 to 15 times the size of the originating cell. The process of forming NETs and accompanying cell death is called NETosis. NETs are vital in trapping and killing pathogens to enhance the immune response against infections. Other granulocytes—eosinophils, mast cells, and basophils—can also form extracellular traps.
- **Extravasation** is the process in which cells, guided by chemokines and cell adhesion molecules, adhere to vascular endothelial cells in inflamed regions and then pass through capillary walls to enter tissue spaces.

- **Sepsis** is a severe systemic response to infection characterized by fever, elevated heart rate, breathing rate, low blood pressure, and compromised organ function. It can lead to **septic shock**, with a high mortality rate of 90%. The primary cause of sepsis from gram-negative bacteria like Salmonella and E. coli is the cell wall component LPS (endotoxin), which activates TLR4 receptors. Other pathogens can also cause sepsis.

- **LPS tolerance**, also known as endotoxin tolerance, is a state of reduced responsiveness in macrophages continuously exposed to the TLR4 ligand LPS. Initially, these macrophages produce antimicrobial and proinflammatory mediators in response to LPS. However, over time, inhibitors like IkB and the short form of MyD88 are induced, blocking further responses to LPS. This state prevents prolonged exposure to LPS from leading to septic shock during a bacterial infection.

- **Adjuvants** are materials that enhance immune responses in animals and humans. Many adjuvants contain ligands for TLRs or other PRRs, playing a crucial role in activating the immune system. They are essential in vaccine development to improve immune response and protection against infections.

- **Melanization**—the deposition of a melanin clot around invading organisms that prevents their spread.

4.3 KEY LEARNINGS

- Innate immunity is the most ancient form of defense, found in all multicellular plants and animals, while adaptive immunity is a much more recent evolutionary invention, having arisen in vertebrates.

- The primary elements of innate immunity are the external barriers that protect the body from microbial invasion. These barriers consist of epithelial layers, such as the skin and tissues connected to body openings, which act as physical shields to prevent pathogens from entering the body. Additionally, these epithelial barriers play a crucial role in generating active chemical and biochemical defenses by producing antimicrobial molecules like peptides and proteins that aid in combating pathogens.

- The skin, the outermost physical barrier, consists of two distinct layers: a thin outer layer, the epidermis, and a thicker layer, the dermis.

- Proteins produced by intestinal epithelia include members of a family of lectins (carbohydrate-binding proteins), the RegIII proteins, which bind carbohydrates on bacterial cell walls, preventing them from contacting the intestinal epithelial cells. RegIII proteins also are directly bactericidal; they generate membrane pores that kill the cells.

- SP-A and SP-D bind differentially to sets of carbohydrate, lipid, and protein components of microbial surfaces and help to prevent infection by blocking and modifying surface components and promoting pathogen clearance.

- Antimicrobial peptides differ from antimicrobial proteins in that they are generally less than 100 amino acids long.

- Antimicrobial peptides are essential components of innate immunity in humans. They are characterized by being cysteine-rich, cationic, and amphipathic, which allows them to interact with microbial membranes. By forming pores and disrupting the lipid bilayers of bacteria, fungi, parasites, and viruses, these peptides can enter the microbes and exert toxic effects, inhibiting DNA, RNA, or protein synthesis, and activating antimicrobial enzymes, ultimately leading to cell death.

- The main types of antimicrobial peptides in humans are α- and β-defensins, cathelicidin (specifically LL-37, the only cathelicidin expressed in humans), and histatins. Defensins and LL-37 are continuously secreted by epithelial cells in various tissues and are also stored in neutrophil granules, contributing to microbial killing during phagocytosis. Additionally, dermcidin, secreted by sweat glands onto the skin, exhibits antibacterial and antifungal activities.

- The innate immune system's second line of defence consists of an array of cells expressing membrane receptors that recognize microbial components. These receptors then activate a variety of cellular defence mechanisms against the invaders.

- There are 13 TLRs that function as PRRs in both humans and mice. TLRs are membrane proteins that possess a common structural element in their extracellular region known as leucine-rich repeats (LRRs). The extracellular ligand-binding domain of the TLR polypeptide chain is composed of multiple LRRs, forming a horseshoe-shaped structure. When TLRs interact with their PAMP or DAMP ligands through their extracellular LRR domains, they undergo dimerization, forming either a homodimer (e.g., TLR3/3) or a heterodimer.

- The expression of the potent antiviral type I interferons, IFN-α and IFN-β, is induced by pathways downstream of the TLRs that bind viral components. The activation of the interferon regulatory factors (IRFs) is essential for initiating the transcription of genes encoding IFN-α and IFN-β.

- The two key adaptors that are recruited to TLR dimers are MyD88 (myeloid differentiation factor 88) and TRIF (TIR domain–containing adaptor-inducing IFN-b factor). MyD88 is the adaptor used by most TLRs—all of the plasma membrane TLRs and most of those in endosomes. TRIF uniquely associates with TLR3 and also with TLR4 when it localizes to endosomes.

- The IKK (inhibitor of κB kinase) complex consists of NEMO (NF-κB essential modifier), IKKα, and IKKβ.

- In particular, TLRs that bind bacterial PAMPs stimulate the production of antimicrobial proteins and peptides, enzymes, as well as proinflammatory cytokines, including IL-1β and tumor necrosis factor (TNF), along with chemokines essential for antibacterial responses. On the other hand, all intracellular TLRs that bind viral PAMPs, after internalization and endosomal release of viral nucleic acids, induce the synthesis and secretion of type I interferons, which effectively inhibit the replication of the virus in infected cells.

- CLRs (C-type lectin receptors) recognize carbohydrates in pathogens like fungi, mycobacteria, viruses, parasites, and allergens (e.g., peanut and dust mite proteins). Humans have at least 15 CLRs functioning as PRRs, capable of detecting specific sugar moieties like mannose (mannose receptor, DC-SIGN), fucose (dectin-2, DC-SIGN), and glucans (dectin-1).

- NLRs are cytosolic proteins activated by intracellular pathogens and danger signals. They play critical roles in initiating innate immune and inflammatory responses. The human genome has about 23 NLR genes, and the mouse genome has around 34. NLRs are divided into NLRCs (with CARDs), NLRBs (with BIR domains), and NLRPs (with PYDs). They can trigger both beneficial and harmful inflammation.

- NOD1 and NOD2 are cytosolic NLRs that recognize breakdown products of bacterial cell wall peptidoglycans. Diaminopimelic acid and muramyl dipeptides are specific PAMPs that bind to NOD1 and NOD2, respectively. These PAMPs are generated during the synthesis or degradation of peptidoglycans from cytosolic or endocytosed bacteria. NOD1 and NOD2 activation plays a crucial role in defending against bacterial infections. Additionally, NOD1 provides protection against the intracellular protozoan parasite Trypanosoma cruzi, causing Chagas disease, while NOD2 activates responses to certain viruses, including influenza.

- In addition to inducing expression of genes encoding antimicrobial proteins and peptides, NOD1 and NOD2 contribute to the elimination of cytosolic bacteria by initiating autophagy, in which membrane from the endoplasmic reticulum surrounds the bacteria, forming an autophagosome, which then fuses with lysosomes, killing the bacteria.

- Proteases called caspases play a crucial role in converting inactive procytokines into smaller, mature forms of important cytokines like IL-1β and IL-18. These mature forms are then secreted by activated cells. Caspase activation can also lead to pyroptosis, a form of cell death in activated macrophages, facilitating the release of mature IL-1β and IL-18.

- Members of the RIG-I–like receptor (RLR) family of PRRs, RIG-I and MDA5, bind viral dsRNA in the cytosol.

- Cytosolic DNA from viruses or bacteria activates the DNA sensor cGAS (cyclic GMP-AMP synthase), which produces cGAMP (2',5'-cyclic GMP-AMP dinucleotide). This DNA-derived dinucleotide, along with other dinucleotides released by intracellular bacteria, activates the ER membrane-associated protein STING (stimulator of interferon genes). STING, in turn, initiates signaling pathways that activate IRF3 and NF-κB, leading to the synthesis of type I IFNs and cytokines.

- Induced effector mechanisms consist of both antimicrobial molecules and cellular responses that directly combat pathogens or infected cells.

- Binding of the IFN dimer to IFNAR triggers receptor dimerization, activating the JAK/STAT signalling pathway. This pathway is utilized by many cytokines to initiate specific responses. The IFNAR dimer activates JAK1 and TYK2, which phosphorylate inactive STAT transcription factors. Phosphorylated STAT1 and STAT2 then form dimers and enter the nucleus, where they initiate the transcription of specific genes. This process plays a key role in the cellular response to interferons.

- Three of the most important cytokines are IL-1, TNF-α, and IL-6, the major proinflammatory cytokines.

- Two enzymes, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX2), are produced in response to PRR-activated signaling pathways. iNOS plays a vital role in generating nitric oxide, which kills phagocytosed microbes. COX2, induced by PRR activation in various immune cells, is crucial for producing proinflammatory prostaglandins from arachidonic acid. These enzymes contribute to the generation of antimicrobial and proinflammatory mediators in the immune response.

- Monocytes in the blood and macrophages, neutrophils, and dendritic cells in tissues are the primary cell types responsible for phagocytosis. Phagocytosis involves the cellular uptake and destruction of particulate materials larger than 0.5 microns (µm) in size, such as bacteria.

- Some, but not all, PRRs induce phagocytosis. Notably, TLRs (Toll-like receptors) are a significant class of PRRs that do not trigger phagocytosis.

- Phagocytosis can also be indirectly activated through opsonization, where phagocytes recognize soluble proteins bound to microbial surfaces, enhancing phagocytosis. These phagocytosis-enhancing proteins, called opsonins, often bind to conserved components on microbial surfaces, such as carbohydrates and lipopolysaccharides, and are referred to as soluble pattern-recognition proteins. The complement component C1q also acts as an opsonin, binding to bacterial cell wall components and certain viral proteins, triggering phagocytosis through the CR1 opsonin receptor.

- Neutrophils, macrophages, and dendritic cells employ highly toxic reactive oxygen species (ROS) and reactive nitrogen species (RNS) to attack phagocytosed microbes. These ROS and RNS damage microbial membranes and intracellular components. The unique NADPH oxidase enzyme complex in phagocytes generates ROS when microbes bind to phagocytic receptors, while the transcriptional activation of the iNOS gene is required for RNS production. The respiratory burst provides the necessary oxygen for ROS production. ROS and RNS can also be released from activated neutrophils and macrophages to kill extracellular pathogens.

- CD47, expressed on many cell types throughout the body, is recognized by the SIRPα (signal regulatory protein α) receptor on macrophages, which transmits signals that inhibit phagocytosis.

- ILC group 1 includes both NK cells and ILC1 cells, as they share production of IFN-$\gamma$and TNF-α; however, significant cytotoxic activity is restricted to NK cells.

- The cytokines produced by ILC2 cells, IL-4, -5, -9, and -13, are important for innate protection against parasitic worms (helminths).

- Different types of pathogen-associated molecular patterns (PAMPs) activate dendritic cells to secrete specific cytokines, leading to distinct T-cell differentiation. Extracellular bacteria and endosomal nucleic acids induce IL-12 secretion, leading to T1 cell differentiation, which secretes IFN-$\gamma$to activate macrophages and NK cells. PAMPs from helminths and certain bacteria/fungi block IL-12 production, leading to T2 cell differentiation, activating mediators to clear these pathogens. Fungal PAMPs activate dectin-1, inducing T17 cell differentiation, which releases IL-17 to recruit inflammatory cells for fungal infection clearance. Additionally, TLR2/6 activation with vitamin A induces regulatory T cell formation, inhibiting other immune responses.

- TLR4 binding of LPS can induce B cells to proliferate and differentiate into antibody-secreting plasma cells, even without T-cell help, when LPS is present at low concentrations. At high concentrations of LPS, all B cells are activated regardless of their antigen-binding specificity, leading to polyclonal activation. LPS is considered a T-independent antigen. Human B cells do not respond to LPS as they lack TLR4, but they can be activated by microbial CpG DNA through TLR9.

- Plants lack phagocytes or circulating cells that can be recruited to infection sites for protective responses. Instead, they depend on local innate immune responses to defend against infections.

- Similarity between innate and adaptive immunity are: The complement pathway can be activated by both, also just as innate immunity uses opsonins for opsonisation, in adaptive immunity some classes of antibodies work as opsonins.

4.4 ADDITIONAL LEARNINGS

- **Sebaceous glands** secrete sebum into hair follicles, whereas sweat glands secrete sweat. **Sebum** is an oily substance, while sweat is a viscous and odorous substance.
- **Cathelicidin antimicrobial peptide (CAMP)** is a polypeptide that is primarily stored in the lysosomes of macrophages and polymorphonuclear leukocytes (PMNs).
- **Autophagy** - destruction of damaged or redundant cellular components occurring in vacuoles within the cell.
- **Autophagosomes** - a double membrane-bound vesicle that encloses cellular constituents and fuses with lysosomes, which digest these cellular constituents during autophagy.
- **Pyroptosis** is a highly inflammatory form of lytic programmed cell death that occurs most frequently upon infection with intracellular pathogens and is likely to form part of the antimicrobial response. This process promotes the rapid clearance of various bacterial, viral, fungal, and protozoan infections by removing intracellular replication niches and enhancing the host's defensive responses.
- **Interferons (IFNs)** are a group of signaling proteins made and released by host cells in response to the presence of several viruses. In a typical scenario, a virus-infected cell will release interferons causing nearby cells to heighten their anti-viral defenses.
- **Caspases** are intracellular proteases that cleave substrate proteins at specific aspartic acid residues.
- There are two forms of cell death: 1. Programmed death of cells called **Apoptosis**. 2. An uncontrolled death of cells called **Necrosis**.
- **Oxidative stress** is an imbalance between free radicals and antioxidants in your body.
- **Antioxidants** - a substance that inhibits oxidation, especially one used to counteract the deterioration of stored food products.
- **Normal cell turnove**r refers to the continuous renewal of cells in the body.
- **Polymorphism** - the presence of genetic variation within a population, upon which natural selection can operate.
- **Vasculature** - the vascular system of a part of the body and its arrangement.
- **Septicemia** - a serious illness in which an infection spreads through the bloodstream.

4.5 CONCLUSION

The chapter discusses the importance of innate immunity as the first line of defence against infections. Epithelial layers, such as the skin and mucosal tissues, provide the initial barrier to prevent pathogens from entering the body. Chemical substances, including antimicrobial peptides and proteins, also aid in controlling pathogens at these sites. However, if infections manage to establish themselves inside the body, the second line of defence, consisting of myeloid leukocytes like macrophages, monocytes, neutrophils, and dendritic cells, recognizes the infection through pattern recognition receptors (PRRs) and mounts a response appropriate for the specific pathogen. The innate immune responses, such as phagocytosis, complement activation, and the production of antimicrobial proteins, are often effective in clearing pathogens within a short period. In cases where innate responses are insufficient, the adaptive immune system, with its B and T cells equipped with diverse antigen-specific receptors, comes into play as the third and last line of defence. The innate immune system still plays a critical role in guiding the adaptive immune response by influencing the differentiation of T cells through specific PRR activation. Overall, the chapter emphasizes that the innate immune system is essential for enhancing the potency of the adaptive immune response and contributing to a comprehensive defence against pathogens.