IMMUNE SYSTEM: AN OVERVIEW OF THE CELLS INVOLVED IN IMMUNITY

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Abstract
We live in an environment that is highly contaminated with diseases and infections. Our body’s immune system plays a significant role in overcoming this. They create a barrier against the microorganism. Immune dysfunction can lead to several disorders like cancer, allergy, asthma, arthritis, and infection. Immunity is composed of two types: innate and adaptive immunity. Immune cells are involved in the phagocytosis of the microorganism. Cells may be of the myeloid and lymphoid progenitors. It involves neutrophils, basophils, eosinophils, natural killer cells, dendritic cells, and mast cells. These cells activate by recognizing potentially harmful molecules through their pattern recognition receptors (PRRs). PRRs can be categorised into different types of receptors. These include membrane-bound receptors such as TLRs (Toll-like receptors) and CLRs (C-type lectin receptors), as well as cytoplasmic receptors like RIG-1-like receptors (RLRs) and NOD-like receptors (NLRs). Cytokines are small secreted proteins that regulate immune responses against microorganisms. Interleukin-2 (IL-2), Interleukin-4 (IL-4), Interleukin-6 (IL-6), Interleukin-7 (IL-7), Interferon Gamma (INF-γ), Tumor necrosis factor alpha (TNF-α), Tumor necrosis factor-13 (TNF-13), and leukaemia inhibitory factors, are the soluble cytokine receptors that have been detected. Some of the immunoglobulins like Immunoglobulin A (IgA), Immunoglobulin G (IgG), Immunoglobulin M (IgM), Immunoglobulin E (IgE), and Immunoglobulin D (IgD) produce immune responses directed against various pathogens, chemicals, synthetic material, bacteria, viruses, fungi and parasites. Immune cells play a very important role in overcoming various diseases and also to overcome autoimmune diseases. This review provides more knowledge about the cells and receptors which play a significant role in the immune system.

Keywords: Immunity, phagocytosis, cytokines, receptors.

1 BACKGROUND:
The epidemics and pandemics of the past have had a significant impact on shaping human history. Similarly, emerging infectious diseases possess the same potential to influence the course of future human history. Immunity is nothing but the body's defence mechanism to protect itself from the invasion of pathogens and provide defence against microorganisms. Immune dysfunction can lead to several disorders like cancer, allergy, asthma, arthritis and infection[1]. This study involves the investigation of substances with the potential to alter immune responses. Thereby offering potential for the treatment or prevention of diverse diseases, has emerged as a captivating area of research in recent times. Nevertheless, the pursuit of novel natural immunomodulators remains significant due to the limitations of certain existing medications, which may exhibit reduced efficacy or induce undesirable side effects[2]. The immune system safeguards the host from invading pathogens using innate and adaptive immunity[3].

2 MAIN TEXT:
2.1 IMMUNITY:
Immunity is the defence mechanism that protects against the microorganism. Immunity is mainly due to the presence of immune cells. These cells originate from the lymph node, spleen, thymus and bone marrow[4]. Immunity has been the most important concern for several decades for humans. During COVID-19 herbal medicines and plant-based foods are most commonly used for enhancing immunity[5]. Immunity is divided into innate and adaptive immunity. The types of immunity are given in the Figure 1.
Figure 1: Cells of innate and adaptive immune response

2.2 TYPES OF IMMUNITY:

2.2.1 INNATE IMMUNITY:

The human body has two types of immune systems that protect against various pathogens. These are innate or natural immunity and adaptive or acquired immunity. The innate immunity is the inherent resistance that is present from birth and is often demonstrated. When the body encounters pathogens for the first time without any prior exposure it activates the immune cells\(^6\). Anatomical and physiological barriers establish the initial line of defence against pathogens. These barriers encompass unbroken skin, robust mechanisms for mucociliary clearance, a low pH in the stomach and bacteriolytic lysozyme found in tears, saliva and other secretions. The vulnerability to infections seen in individuals with severe cutaneous burns or primary ciliary dyskinesia highlights the fact that the innate and adaptive immune system alone cannot compensate for the breakdown of crucial anatomical and physiological barriers\(^7-8\). Chemical, biological or mechanical barriers are the first line of defence against outside threats. These barriers include skin, mucous membranes, body fluids and normal bacterial flora\(^6\).

2.2.2 Physical barrier:

The stratum corneum, which is largely supported by corneocytes, is essential to preventing the epidermis barrier function. Ceramides, cholesterol, and free fatty acids are stacked like “Bricks and Mortar” to form cells\(^9\). The stratum corneum consists of three layers and serves as a dual barrier. The epidermis serves as an external barrier, effectively safeguarding against the intrusion of foreign substances and microorganisms. Simultaneously, it functions as an internal shield, preventing the escape of water\(^10\). Some of the components such as junctional adhesion molecules (JAMS), Zonula occludins-1 (ZO-1), claudins and occludins are found in the layers of the epidermis\(^11-12\). The weakening of the skin’s physical barriers can be the cause of the inflammation of the skin. This is observed in patients with atopic dermatitis, where the skin showcases decreased levels of ZO-1 and claudin-1 expression\(^13\).

2.2.3 Biomolecules of the skin:

The primary biomolecules involved in skin defence against bacterial infections are antimicrobial peptides (AMP) and lipids. These compounds work by rupturing the membranes of the bacteria\(^14-16\). Amphipathic peptides, or AMPs, are synthesized constitutively or after a cell becomes active in response to stimulation causing inflammation or homeostasis. Defensins and cathelicidins are the two most extensively investigated AMP families in human skin. Different skin cells including keratinocytes, fibroblasts, dendritic cells, monocytes and macrophages as well as sweat and sebaceous glands are involved in the production of these peptides\(^15\). In particular antimicrobial peptides have a major influence on the immunological response of the host. For instance, LL-37 a human AMP, has been found to stimulate the differentiation of dendritic cells derived from monocytes. This stimulation leads to the production of cytokines and the expression of CD86, a co-stimulatory molecule\(^17\). Furthermore, ß defensins and LL-37 may function
as alarmins for keratinocytes, promoting their migration and proliferation\(^{18}\). In addition, LL-37 works with additional mediators of inflammation like IL-1β to show its alarmin effects on immune system cells. On the other hand, immature dendritic cells, memory and naive T-cells, and activated neutrophils have all been drawn to human α and β-defensins as chemoattractants\(^{19,20}\).

### 2.2.4 Skin pH:

The skin’s pH level ranges from 5.4 to 5.9 creating an unfavourable environment for potential pathogens\(^{21-22}\). A significant difference in pH levels between the skin and blood where the latter has a pH-7.4. This difference serves as a secondary defence mechanism in case microbes breach the skin tissue and enter the bloodstream. The breakdown of filaggrin, a protein that binds keratin fibres, into histidine and its further processing by histidase, expressed by corneocytes into the acidic metabolite trans-urocanic acid, has been linked to the acidification of the stratum corneum\(^{23}\).

Additionally, fatty acids produced in the stratum corneum and acidic electrolytes and lactic acid from sweat glands contribute to the skin’s acidity, promoting epidermal turnover\(^{24-26}\).

### 2.2.5 Immune cells of the skin:

In maintaining homeostasis, skin resident immune cells play a crucial role in promoting tissue function and serving as sentinels by actively sampling environmental antigens. The skin contains both myeloid and lymphoid cells. A lymph node is the organ where the immune cell migrates into it to promote tolerance towards self-antigens present in the tissue or initiate robust immune responses. When faced with challenges such as infections or tissue injuries the immune cells present in the skin, as well as those infiltrating from the periphery, collaborate to establish a complex defence network\(^{27}\).

### 2.3 ADAPTIVE IMMUNITY:

The innate immune system aids in the development of adaptive immunity, which is essential when innate immunity is ineffective in getting rid of pathogenic microbes. The identification of particular "non-self" antigens and their differentiation from "self" antigens, the creation of pathogen-specific immune effector pathways that eradicate particular pathogens or pathogen-infected cells, and the establishment of an immune memory capable of promptly eliminating a particular pathogen in the event of recurrent infections are the main function of the adaptive immune response\(^{28}\).

#### 2.3.1 Active immunity:

Active immunity is the term used to describe the production of a particular response to an antigen. It is an essential component of our immune system’s ability to respond effectively upon re-exposure to the same antigen, as well as in the administration of vaccines. Active immunity is the term used to describe the process of exposing the body to an antigen to trigger an adaptive immune response. This response may take several days or weeks to develop, but it can provide long-lasting and, in some cases, lifelong protection. Active immunity can be categorized as either natural or acquired. For instance, when a person becomes infected with the hepatitis A virus (HAV) and subsequently recovers, their body naturally develops an active immune response that typically offers lifelong protection. Similarly receiving two doses of the hepatitis A vaccine stimulates an acquired active immune response, which also provides long-lasting protection\(^{29}\).

#### 2.3.2 Passive immunity:

Passive immunity is a method of safeguarding against infection by providing IgG antibodies. This type of immunity offers immediate protection, but it is short-lived, lasting only a few weeks to a maximum of 3 or 4 months. Passive immunity is categorized as either natural or acquired. The transfer of maternal tetanus antibody primarily IgG, through the placenta provides natural passive immunity to the newborn for several weeks or months until the antibody degrades and is lost. Acquired Passive immunity is acquired by injecting concentrated immunoglobulin fraction obtained from immune individuals to protect susceptible individuals\(^{29}\).

#### 2.3.3 Naturally acquired:

##### 2.3.3.1 Maternal passive immunity:

Maternal passive immunity is a form of passive immunity that is acquired naturally. It refers to the transfer of antibody-mediated immunity from a mother to her foetus or infant. This type of immunity can be acquired during pregnancy or through breastfeeding. In humans, maternal antibodies are transferred to the foetus through the placenta via an FcRn receptor on placenta cells. This transfer occurs mainly during the third trimester of pregnancy and is reduced in premature babies. Immunoglobulin G (IgG) is the only antibody isotope that can pass through the human placenta and is the most prevalent antibody among the five types found in the body\(^{30}\).

##### 2.3.3.2 Artificially acquired passive immunity:

Passive immunity acquired through artificial means involves the transfer of antibodies and can be achieved through various methods such as human or animal blood plasma or serum, pooled human immunoglobulin for i.v or i.m use, high-titre human IVIG or IG from immunized donors or donors recovering from the disease and monoclonal antibodies. This type of immunity is used to prevent disease or as a prophylactic measure for immunodeficiency diseases like hypogammaglobulinemia. It is also used to treat acute infections and poisoning. The immune response from passive immunization can be prolonged for several weeks up to three months and there may be a potential risk associated with hypersensitivity reactions and serum sickness, in particular gamma globulin of unhuman origin\(^{31-32}\).
3. CELLS INVOLVED IN IMMUNE SYSTEM:

Leukocytes also known as WBC are the major cells that can be categorized into two: myeloid cells and lymphoid cells. The myeloid cells, which make up the majority of the innate immune system, consist of macrophages, mast cells, dendritic cells, neutrophils, basophils and eosinophils. The lymphoid cells which make up the other major class of immune cells, consist of three cell types: T-lymphocytes, B-lymphocytes and natural killer cells (NK). T and B lymphocytes play a crucial role in the adaptive immune system and possess the ability to produce highly specific cell surface receptors. These receptors namely T-cell receptors (TCRs) and B-cell receptors (BCRs) can be generated to recognize specific molecular structures called antigens.[33]

3.1 COMMON LYMPHOID PROGENITOR:

3.1.1 T lymphocyte:

T lymphocytes are derived from precursor stem cells found in the foetal liver and bone marrow. After migrating to the thymus, they differentiate into various mature cell types.[34] These cells can be classified based on specific functions. Cytotoxic T lymphocytes, which express the surface protein cluster of differentiation CD8 are responsible for defending against intracellular pathogens and monitoring for tumours. Helper T lymphocytes on the other hand express the surface protein CD4.[35] T cells possess T cell antigen receptors (TCR) on their surface which are accountable for identifying an antigen/major histocompatibility complex (HCA complex).[36-37] Once activated helper (CD4+) T cells can be categorized into at least three primary functional subtypes based on their release of cytokines. These subtypes include the Th1 subtypes, which are primarily involved in cell-mediated tissue damaging reactions. The Th2 subset stimulates B cells to produce antibodies and Th17 cells which play a role in immune responses to infectious agents and the maintenance of autoimmune disease.[38-39] Th1 cells produce TNF-β, interferon IFN-γ and IL-2. Th2 cells primarily secrete IL-4, IL-5, IL-13 and IL-6. Th17 cells secrete IL-17.[40-41]

3.1.2 T regulatory (Treg) cells:

T regulatory cells (Treg) a distinctive subtype of T lymphocytes have been identified among the various types of cells involved in the pathophysiological process of (Autoimmune Thyroid disease) AITD.[39-42] T regulatory cells, which are part of the T helper CD3+, CD4+ cells family can be classified into five distinct groups based on the molecules expressed on their surface. These groups promote specific immunosuppressive features such as CD4+, CD25+, FOXP3+, T regulatory cells (iTregs), peripheral (P Tregs), Tr1 type Tregs (IL-10 Dependent), Th3 type Tregs (TGF-alpha dependent, CAP+) and CD8+ Tregs.[43]

3.1.3 B lymphocyte:

Hematopoietic stem cells give rise to B-lymphocytes during their development. The maturation process of B cells occurs in the bone marrow, while their activation takes place in secondary lymphoid organs like lymph nodes and the spleen.[44] B cells primarily contribute to humoral immunity. In the case of Graves’ disease B cells play a crucial role as they are responsible for producing pathognomonic activating autoantibodies Thyrotropin receptor antibody (TRAB) against Thyroid-stimulating hormone receptors (TSHR).[45] These TRABs bind to the receptor and chronically stimulate it. TSHR is expressed on thyroid follicular cells, leading to increased production and secretion of thyroid hormones T4 and T3 as a consequence of this chronic stimulation.[46-47] B cells can act as APCs due to their possession of a transmembrane receptor known as BCR, which is a surface immunoglobulin. This receptor allows them to recognize particular antigens, which they then use to initiate an immune response and produce antibodies. Additionally, B cells present fragments of these antigens to CD4+ cells through the use of MHC class II molecules.[45][48-49]

3.1.4 Natural killer cells (NK cells):

An essential member of the innate lymphoid cell (ILC) family is the natural killer cell or NK cell. During adulthood, common lymphoid progenitors (CLPs) in the bone marrow give rise to NK cells. It is evident that they play a crucial role in protecting mice and humans from infections. The regulation of adaptive immune responses to control infection is significantly influenced by NK cells. It has been discovered that NK cells can destroy T cells that are specific to a virus and antigen-presenting cells. They can also produce cytokines that reduce inflammation, like IL-10, which can suppress immune responses.[50] Also by encouraging adaptive immunity's activation, NK cells can also favourably influence the regulation of adaptive immunity.[51]

3.1.5 Maturation of NK cells:

On the other hand in NK cells, both precursor and immature, may also migrate to secondary lymphoid tissues (SLTs), including the tonsils, lymph nodes, and spleen, according to studies done on humans and mice. The NK cells in these SLTs go through terminal maturation before moving into circulation. The first stage of the NK cell differentiation process is the commitment of human stem cells to the myeloid/lymphoid lineage rather than the erythroid/megakaryocyte lineage. Hematopoietic stem cells expressing Lin−CD34+ CD133+ CD244+ move forward to CLPs upon the expression of the CD45RA molecule while the differentiation of human NK cells. These CLPs then express CD38, CD7, CD10, and the cytokine CD127 (IL-7 receptors α), developing into lymphoid-primed multipotent progenitors (LMP). CLPs can differentiate into B, T and NK cell progenitors, as well as other lymphoid cells.[52] NK expansion and activation are triggered by IL-15, which is produced by macrophages and IL-12, a powerful inducer of
IFN-γ and cytolytic activity. Once activated, NK cells eliminate infected and tumour cells through lysis and release proinflammatory cytokines such as IL-1, IL-2 and particularly IFN-γ[53].

3.2 MYELOID PROGENITOR:

Granulocytic and phagocytic leukocytes, or myeloid cells, may travel through solid tissues and also through blood. As sentinels, these cells rapidly trigger an innate immune response upon encountering virus-infected cells or virus-damaged tissue. The complicated reaction entails the release of cytokines to direct other leukocytes in putting up a strong defense as well as the activation of cell signalling cascades. Evidence from recent studies indicates that neutrophils and inflammatory monocytes, two subsets of myeloid cells, are more important than previously thought in recognizing and stopping viral infections[54]. Myeloid cells are essential for reconstructing the extracellular matrix’s tissue structure, which controls the development of blood vessels and organ growth[55].

3.2.1 Neutrophils:
The predominant cell type found in human blood is polymorphonuclear leukocytes, also referred to as neutrophils. In the bone marrow, these cells are produced at a rate of about 10^11 per day. Functioning as effector cells within the innate immune system, neutrophils are significant [56]. Through the activation of the NADPH oxidase complex, neutrophils perform a variety of microbicidal functions by producing Reactive oxygen species (ROS) that efficiently destroy pathogens[57].

3.2.2 Neutrophil phagocytosis and activation:

At infection sites, neutrophils bind and ingest invasive microorganisms through a process known as phagocytosis. PAMPs, or pathogen-associated molecular patterns, include a variety of molecules, including flagellin, lipoprotein lipoteichoic acid (LTA), and lipopolysaccharide (LPS). Microbes typically have these PAMPs on their surface, but not the host cell. These molecules interact with the neutrophil membrane's surface receptors. Numerous receptors are expressed by neutrophils, such as the peptidoglycan recognition protein and TLRs 1, 2, 4–10. Neutrophil pattern recognition receptor ligation typically stimulates signal transduction pathways, which in turn supports several beneficial effects, including increased adhesion, phagocytosis, and the release of chemokines, ROS, and cytokines[58].

3.2.3 Eosinophil:

One of the main characteristics of eosinophils, a subset of innate immune granulocytes, is their ability to cause cytotoxicity[59]. They may lead to tissue damage in allergic diseases and are essential in harming parasitic pathogens during helminth infections. About 6% of the nucleated cells in the bone marrow are eosinophils. Eosinophilia is defined as having an absolute count of more than 450–500 cells/μl of eosinophils. The standard threshold for defining blood hypereosinophilia is 1500 cells/μl. In the absence of other possible causes, blood hypereosinophilia is categorized as hypereosinophilia syndrome (HES) if it is linked to documented organ damage caused by eosinophils[60].

3.2.4 Eosinophil phagocytosis, cell killing and antigen presentation:

Major Basic Protein (MBP) and Eosinophil Cationic Protein (ECP) are delivered to intracellular phagosomes by eosinophils, just like neutrophils, enabling them to phagocyte and kill invasive pathogens intracellularly[61]. Antigen presentation comes from this process[62]. Additionally, extracellular DNA trapping, degranulation, respiratory bursts through EPO, and the release of cytokotyes are among the extracellular killing mechanisms that eosinophils possess[63–64]. Eosinophil degranulation is a strictly controlled process involving cells in the extracellular environment being exposed to trace amounts of particular cytokotyes[65].

3.2.5 Eosinophil mechanism:

Reactive oxygen species (ROS) and nitric oxide (NO) produced by eosinophil peroxidase cause oxidative stress in target cells, which in turn causes necrosis and apoptosis. Furthermore, the production of different cytokines, such as TNF-α, IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, and IL-13, as well as the release of inflammatory lipid mediators like prostaglandins (PGE2) and leukotrienes (LTC4, LTD4, LTE4), further stimulates the inflammatory process. Tissue remodelling is assisted by elastase enzymes as well as growth factors such as TGF-β, platelet-derived growth factors (PDGF), and vascular endothelial growth factor (VEGF)[66].

3.2.6 Basophil:

Less than 1% of peripheral blood leukocytes are basophils, which come from progenitors in the bone marrow. Even though they are normally absent from tissues, they can accompany eosinophils to inflammatory sites and become mobilized there. Similar mediators to those found in mast cells are present in the granules of basophils. Additionally, basophils express FcεR1, bind IgE and can be stimulated by IgE-antigen complexes potentially playing a role in immediate hypersensitivity reactions[67]. Basophils possess surface molecules essential for antigen-presenting cell (APC) function, including MHC class II and co-stimulatory molecules like CD80, CD86 and CD40. They are capable of processing and presenting antigens as well as providing IL-4 to naïve CD4 T cells, thereby promoting their differentiation into the Th2 cell subtype[68].

3.2.7 Dendritic cells:

Dendritic cells (DCs) have essential functions in not only initiating a defensive immune response against invading pathogens but also in promoting immune tolerance towards harmless antigens[69]. Dendritic cells are extensively
acknowledged as the most important antigen-presenting cells (APCs) furthermore they play a crucial role in maintaining the intricate equilibrium between immunity and tolerance. Through cell–cell contact or the secretion of cytokines, they engage in interaction with other immune system cells. DCs can inhibit autoimmunity through two distinct mechanisms. Firstly, they can trigger apoptosis in autoreactive T cells within the thymus thereby promoting central tolerance. Secondly in the periphery, DCs can collaborate with regulatory T cells (Treg) to induce anergy, deletion or tolerance thus establishing peripheral tolerance[70].

3.2.8 Mast cells:
Mast cells (MCs) play a crucial role in type 1 allergic reactions, also known as anaphylactic responses. In this MCs are activated when specific antigens crosslink with cell-surfaced bound FcεRI-IgE complexes. This activation triggers a three-step response:

a) Immediate degranulation of mast cell secretory granules
b) Release of lipid mediators such as thromboxane, prostaglandins and leukotrienes.
c) Secretion of a wide range of newly synthesized mediators including cytokines, chemokines and growth factors[71]

Moreover, mast cells possess an array of surface receptors that enable them to detect a wide range of pathogen-associated patterns (PAMPs), danger-associated molecular patterns (DAMPs), cytokines, chemokines, neuropeptides and other molecules[72]. CD3+ Mast cells develop via hematopoietic precursors in the bone marrow and don’t typically appear in the blood. As immature cells, these precursors disappear from the bone marrow and circulate to peripheral tissues. After that, they go through differentiation according to the particular circumstances of their environment. Mature mast cells are positioned beneath the skin and mucous membrane, next to blood vessels and on nerves. They play a critical role in triggering acute inflammatory reactions and are particularly prevalent in areas that have direct contact with the environment[73].

3.2.9 Macrophages:
Monocytes make up 3-8% of the leukocytes found in the bloodstream and can differentiate into macrophages and myeloid dendritic cells within the connective tissue or parenchyma of organs. Both monocytes and macrophages are highly effective phagocytes responsible for engulfing pathogens and cellular debris. Unlike neutrophils, macrophages can reside in tissue for extended periods, serving as vigilant sentinels[74]. Recently a proposal has been made regarding the existence of three subpopulations of macrophages activated, tissue repair and regulator macrophages. The first subpopulation consists of classic macrophages that exhibit tumoricidal and microbicidal activity. These macrophages secrete a significant amount of proinflammatory mediators and cytokines that present antigens to T cells and play a crucial role in cellular immune response. The second subpopulation activated by IL-4, primarily contributes to tissue repair by stimulating fibroblasts and facilitating extracellular matrix deposition. The third subgroup releases the anti-inflammatory cytokine IL-10, which has regulatory effects[75]. Macrophages serve as antigen-presenting cells (APCs) in inflammatory responses, promoting T and B cell activation by expressing co-stimulatory molecules. They also release chemokines and proinflammatory cytokines like TNF-α, IL-1, IL-6, and IL-12. Reactive oxygen species (ROS) are also produced by macrophages. These include the superoxide anion, hydroxyl radical, hydrogen peroxide (H₂O₂), and reactive nitrogen intermediates, of which nitric oxide (NO) is the principal example[76].

4. RECEPTORS INVOLVED IN THE IMMUNE SYSTEM:
The defence mechanism relies on the innate immune system's capacity to promptly identify potentially harmful molecules through its pattern recognition receptors (PRRs). These receptors are responsible for recognizing conserved damage-associated patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs)[77,78]. PRRs can be categorised into different types of receptors. These include membrane-bound receptors such as TLRs (Toll-Like Receptors) and CLRs (C-type Lectin Receptors) as well as cytoplasmic receptors like RIG-1-like receptors (RLRs) and NLRs. Upon binding their agonists, these receptors initiate an innate immune response by activating specific signalling cascades. These cascades ultimately stimulate the transcription factors, including nuclear factor kappa B (NFκB), Activator Protein-1 (AP-1), ETS domain-containing protein Elk-1, Activating Transcription Factor-2 (ATF2), phosphoprotein P53 and members of the Interferon-Regulatory Factor (IRF) family[79-80].

4.1 Toll-like receptors (TLRs):
The toll-like receptors serve as the archetypal receptors for innate pattern recognition, detecting molecular patterns associated with danger and microbes[81]. Toll-like receptors are a family of 10 type I transmembrane PRR proteins with extracellular leucine-rich repeats that bind a variety of PAMPs and activate protective host response to pathogens. Various structural components of pathogens, such as lipopolysaccharides, lipopeptides, polysaccharides, RNA, and DNA, are identified by receptors. Some TLRs are in the plasma membrane and others are found in the endosomes[82-84].

4.2 C-type lectin receptors:
The C-type lectin receptors also known as CLRs, form a significant group of PRRs that have a crucial function in antimicrobial immunity. The CLR superfamily is categorized into 17 groups based on their distinct structure and phylogeny, encompassing over 1000 proteins[85-86]. The carbohydrate recognition domain (CDR) was initially identified
as the calcium-dependent carbohydrate-binding motif that defines the CLRs. However, further research revealed the existence of structurally conserved domains, known as C-type lectin-like domains (CTLD), which are capable of binding various ligands such as glycans, lipids and proteins[87-88].

4.3 RIG-1 like receptors:
The RIG-1-like receptors (RLRs) are a small group of cytosolic receptors that serve as viral RNA sensors. Currently, there are three known members: retinoic acid-inducible gene-1 (RIG-1), its homology melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2). Alongside endosomal TLRs, the RIG-1-like receptors detect nucleic acids within cells. However, unlike TLRs which operate within the lumen of endosomes, RLRs are situated in the cytosol[89-90].

4.4 NOD-like receptors:
The NLR family of receptors is primarily expressed in the cytosol of immune cells, including macrophages, dendritic cells and lymphocytes. However, NLRs are also found in certain non-immune cells such as epithelial and mesothelial cells. These receptors play a crucial role in detecting molecules associated with intracellular infection and stress. As a result, they are capable of sensing various generic stimuli that indicate intracellular microbial infection and damage such as changes in ion concentrations and the production of Reactive oxygen species (ROS). Downstream of NLRs, three major signalling pathways can be activated: nuclear factor-kB (NF-kB) signalling, mitogen-associated protein kinase (MAPK) signalling and inflammasome activation. Some NLRs are specifically designed to facilitate the activation of an intracellular complex known as inflammasomes[91].

5. CYTOKINE ROLE IN IMMUNE SYSTEM:
Cytokines and chemokines play a crucial role in cellular communication, similar to hormones and neurotransmitters. These signalling molecules are small proteins with significant impact, facilitating intercellular communication. They are predominately produced by various cell types, particularly those within the immune system[92]. Some of the cytokines produced by the cells are given below in figure 2.

5.1 Interleukin-6:
Interleukin-6 consists of four α-helices, similar to other members of the IL-6 family. It is a protein that is 184 amino acids long and undergoes glycosylation. This protein is secreted by T-cells, monocytes, endothelial cells and fibroblasts. Notably, IL-6 was initially identified for its impact on adaptive immunity, such as its role in promoting the production of IL-21 and the differentiation of CD4+ T-cells towards Th2 and Th17 cells[93].

5.2 Interleukin 1 family:
Interleukin-1α and IL-1β are produced by separate genes, yet they can both interact with IL-1 receptor (IL-1R)[94]. Although IL-1α exhibits a stronger binding affinity towards IL-1R1, IL-1β shows a greater affinity for the soluble IL-1R2[95]. Both cytokines are initially synthesized as 31 kDa precursor proteins and subsequently cleaved into smaller 17 kDa, albeit with distinct amino-acid sequences[96]. Upon exposure to stimuli such as oxidative stress or cytokines, the...
IL-1α mRNA can be induced. However, it remains unclear whether post-translational modifications are necessary for IL-1α to become active. Unlike IL-1β and IL-33, the progenitor form of recombinant adult IL-1α and IL-1α exhibits similar biological activity by stimulating the production of IL-6 and TNF-α in human peripheral blood mononuclear cells (PBMCs) and lung cancer cells[97].

5.3 Tumor Necrosis Factor- Alpha (TNF-α):

In 1975, Carswell et al; first reported the discovery of TNF-α[98]. This protein exhibits cytotoxic effects on Tumor cells through immune cells, leading to its name TNF. Initially, TNF is expressed as a type II transmembrane protein called mb TNF-α. However, it can be cleaved into its soluble form, TNF-α, which possesses enhanced biological activity[99]. The enzyme responsible for this cleavage is TNF converting enzyme (TACE) or ADAM17[100]. The mbTNF-α is composed of 233 amino acids, weighs 26 kDa and forms homotrimers[101]. TACE cleaves the mbTNFα complex, resulting in a 51 kDa form[102]. TNF-α exerts its effect through two type I transmembrane receptors TNF receptor 1 (TNFR-1 or CD120a) and TNF receptor II (TNFR-11 or CD120b), which serve as its targets[103].

5.4 Interleukin-10:

In 1989, Fiorentino et al first described IL-10 as a cytokine synthesis inhibitory factor (CSIF)[104]. It consists of a homodimer with each unit containing a sequence of 178 amino acids[105]. Notably, IL-10 is among the few anti-inflammatory cytokines, alongside IL-2, TGF and the more recently discovered IL-25, IL-35 and IL-37[106]. Biologically, IL-10 is typically found as a dimer and shares certain structural and functional characteristics with interferon (IFN-γ)[107]. However, CD4+ T-cells are the primary producers. For example, FOXP3+ regulatory CD4+ T-cells (Tregs, thymus and periphery-derived) and FOXP3- regulatory CD3+ T-cells (Tr1 cells). Specifically attenuate T-cells and Th17 response through IL-10[108-109].

5.5 Interleukin-8:

Interleukin-8 was initially discovered for its ability to attract granulocytes, particularly neutrophils, in laboratory settings, and is also referred to as chemokine C-X-C motif ligand 8 or CXCL-8[110]. It is encoded by the CXCL-8 gene. Studies using transfected cell culture models have identified NF-kB, JNK and AP-1 as crucial pathways for the inducible expression of IL-8[111]. Notably, all cells with TLR can produce and release IL-8, including macrophages and smooth muscle cells[112]. Additionally, endothelial cells store IL-8 in vesicles called Weibel-Palade bodies[113]. The primary receptors for IL-8 are G-protein coupled receptors CXCR1 and CXCR2[114].

6. IMMUNOGLOBULIN (Ig):

Plasma cells develop the glycoproteins known as antibodies, or immunoglobulins (Ig). Bacterial proteins are a specific kind of immunogen that directs B cells to differentiate into plasma cells. The humoral immune responses that target different pathogens, chemicals, synthetic materials, bacteria, viruses, fungi, and parasites are mediated by protein-producing cells called plasma cells. Immunoglobulins make up about 20% of the proteins in plasma[115]. Types of immunoglobulins are:

- IgM
- IgG
- IgA
- IgE
- IgD[116]

6.1 Immunoglobulin M (IgG):

With a molecular weight of 970 Kd, IgM is found in serum at an average concentration of 1.5 mg/ml. It is mainly generated during the initial immune response to pathogenic microbes or antigens. It is a pentamer that opens the conventional path of the complement system. IgM is believed to be a potent agglutinin, and its monomer is used as a B cell receptor (BCR)[117].

6.2 Immunoglobulin G (IgG):

IgG is a monomer with a molecular weight of about 146 Kd and a serum concentration of 9.0 mg/ml. IgG is referred to as daventable because it has two identical antigen-binding sites comprised of two L chains and two H chains joined by disulfide bonds. IgG synthesis primarily takes place during the secondary immune system response to infections. IgG can activate the classical pathways of the complement system and is very protective. The subclasses of IgG are IgG1, IgG2, IgG3, and IgG4. IgG1 makes up around 65 percent of all IgG. The host's defense against encapsulated bacteria is greatly enhanced by IgG2. The only immunoglobulin that can cross the placenta's barrier is the Fc fragment of IgG, which attaches to receptors on the surface of the embryo[118].

6.3 Immunoglobulin A (IgA):

IgA is found in two distinct molecular forms serum-bound monomeric and secretory dimeric forms. The molecular weight of serum IgA is 160 Kd, and its concentration in the blood is 3mg/ml. IgA is the predominant antibody in secretions, which include respiratory, gastrointestinal, colostrum, saliva and tears. It shields the intestinal, respiratory
and genitourinary system epithelial surfaces. A secretory component of IgA inhibits its enzymatic digestion. It initiates the complement system’s alternative pathway for activation\textsuperscript{[119]}.

6.4 Immunoglobulin E (IgE):

IgE is a very potent monomer. It has a serum concentration of 0.00005 mg/mL and a molecular weight of 188 Kd. It causes allergic reactions by binding to high-affinity receptors on mast cells and basophils and providing protection against parasites. IgE is thought to be the primary host defence against a variety of parasite infections, such as trichinella spiralis and Strongyloides stercoralis\textsuperscript{[120,122]}.

6.5 Immunoglobulin D (IgD):

The molecular weight of the immunoglobulin D monomer is 184 Kd. IgD has a tiny concentration in the serum (0.003 mg/mL) and is not known to have any protective properties against infections. It is thought to be a B-cell receptor. IgD may be crucial for the differentiation of lymphocytes triggered by antigens\textsuperscript{[123]}.

7. CONCLUSION:

The immune system is crucial to maintaining human health. Both innate and adaptive immunity are possible. The first line of defence against infections is innate immunity. It is primarily found in tears, saliva, mucous membranes, and skin. The elimination of pathogens that recur frequently is greatly aided by adaptive immunity. The majority of immune-related cells are derived from pluripotent hematopoietic stem cells. They could be myeloid or lymphoid cell precursors. T cells, B cells, NK cells, dendritic cells, neutrophils, basophils, eosinophils, mast cells, and monocytes are the cells primarily involved. These cells function through receptors such as NOD-like, C-type lectin, RIG-1-like, and toll-like receptors. Understanding molecular mechanisms better offers a fresh viewpoint on the identification of relevant biomarkers that could be useful in predicting severe or complex cases when they present clinically. Future diagnostics will be made possible by the ongoing discovery of receptors, other proteins, and cytokines. Both pro- and anti-inflammatory cytokines may be present in these cells. Phagocytic cells, lymphocytes, platelets, mast cells, and basophils have receptors that bind immunoglobulins. This binding can activate the cells to perform some function. Future studies are conducted via these cells and their mechanisms to combat a variety of life-threatening illnesses.

Abbreviations:

PRRs - Pattern Recognition Receptors
TLRs - Toll-like receptors
CLRs - C-type lectin receptors
RLRs - RIG-1 like receptors
NLRs - NOD-like receptors
IL - Interleukin
Ig - Immunoglobulin
JAMS - Junctional adhesion molecule
ZO-1 - Zonula occludins-1
AMP - Antimicrobial peptides
HAV - Hepatitis A virus
FeRn - Neonatal fragment crystallizable (Fc) receptor
TCRs - T-cell receptors
BCRs - B-cell receptors
HCA - Histocompatibility
AITD - Autoimmune Thyroid disease
TSHR - Thyroid-stimulating Hormone receptor
APC - Antigen-presenting cells
MHC - Major histocompatibility complex
DAMPs - Damage-associated patterns
PAMPs - Pathogen-associated molecular patterns
NfKB - Nuclear factor kappa B
CDR - Carbohydrate recognition domain
MAPK - Mitogen-associated protein kinase

REFERENCES:


