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''REVIEW ON IMMUNE SYSTEM AND IMMUNOLOGICAL FACTORS''

Kanchan P. Saraf[1*], Madhuri Shingade[2]

[1*]M.B.B.S M.D(General Medicine), Shivaji University, Kolhapur
[2]M.B.B.S M.D(General Medicine), Rashtrasant Tukadoji Maharaj Nagpur University

***Corresponding author:** Kanchan P. Saraf
*M.B.B.S M.D(General Medicine), Shivaji University, Kolhapur

ABSTRACT-
The body has a collection of physical barriers to prevent infection, but once these are overcome, we rely on our immune systems to protect us against a wide variety of infections. The complex mechanisms through which this is achieved are grouped into two lines of defence called the "innate" and "adaptive" immune systems. The innate immune system provides a rapid and tailored response to infection or injury often associated with inflammation. Innate immunity also promotes the development of acquired immunity. Specific, long-lasting responses against a particular infection are dependent on acquired immunity, and these provide immune memory, such that if we encounter the same pathogen again, we are better protected. Many diseases are related to defects in immune function which can lead to either a weakened or overactive immune response. Autoimmune diseases (where the immune system attacks tissues or organs) and allergies (where the immune system responds inappropriately to substances in our environment) are just two examples of conditions resulting from immune function defects. Improved understanding of immune processes provides tremendous opportunities for enhanced immunization strategies and immune-based therapies.

KEYWORDS- *Immune System, Factors, Function, Defence Mechanism*

INTRODUCTION-

The immune system comprises distinct innate and adaptive arms, each of which contains many layers to provide a coordinated, sequential immune response to insults [1,2]. The cells underpinning these arms of the immune system develop in multiple waves and locations throughout the life course through defined developmental pathways to yield a complex set of specialized cells across both myeloid and lymphoid lineages [3,4]. These immune cells collectively serve to maintain health throughout the life course, which includes the elicitation of transient inflammation when appropriate in response to various insults [5]. However, chronic inflammation is pathogenic and underpins a number of disease states [6,7].

The immune system: innate and adaptive immunity

The immune system refers to a collection of cells, chemicals and processes that function to protect the body from infection and damage. At areas in contact with disease-causing organisms such as bacteria, viruses, fungi and parasites (collectively referred to as pathogens), the immune system provides ongoing active defence against infection. This activity is particularly important at body surfaces which interact with the external environment, such as the skin, airways, and gastrointestinal

and reproductive tracts. In addition, the immune system protects us against cancer cells and toxins throughout the body. Beyond the structural and chemical barriers which protect us from infection, the immune system can be simplistically viewed as having two "lines of defence", known as innate immunity and adaptive immunity. Innate immunity represents the first line of defence to an intruding pathogen. It is a defence mechanism that is used by the host immediately, or within hours, of encountering a pathogen or tissue damage. The innate immune response can be triggered by common chemical signals associated with multiple pathogens, such as structures found on bacterial or fungal cell walls. Adaptive immunity, on the other hand, is antigen-dependent and antigen-specific, which means it responds to a very precise chemical structure(s) (antigen[s]), and involves a lag time between exposure to the antigen and maximal response. The important hallmark of adaptive immunity is the capacity for memory, which enables the host to mount a more rapid and efficient immune response upon subsequent exposure to the antigen. This memory response allows the host to vigorously combat infection, and it is the basis for vaccination strategies. Innate and adaptive immunity are not mutually exclusive mechanisms of host defence, but rather are complementary and interactive, with defects in either system resulting in host vulnerability or inappropriate responses. Often, the innate immune response aids in directing a more rapid and effective acquired response to infection [1, 2].

Innate immunity

Innate immunity can be viewed as comprising four types of defensive barriers: anatomic (skin and mucous membrane), physiologic (temperature, low pH and chemical mediators), endocytic and phagocytic, and inflammatory. Table 1 summarizes the non-specific host-defence mechanisms for each of these barriers. Cells and processes that are critical for effective innate immunity to pathogens that evade the initial anatomic barriers have been widely studied. Innate immunity to pathogens often relies on pattern recognition receptors (PRRs) which allow a limited range of immune cells to detect and respond rapidly to a wide range of pathogens that share common structures, known as pathogen associated molecular patterns (PAMPs). Examples of these include bacterial cell wall components, such as lipopolysaccharides (LPS), and double-stranded ribonucleic acid (RNA) produced during viral infection. In addition, the innate immune system responds to signals from dead and dying cells, allowing innate immunity to mobilize if the physical barriers that protect the body are damaged. These processes involve chemicals known as "alarmins" and damage-associated molecular patterns (DAMPs) produced in response to cell and tissue damage.

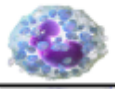
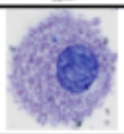
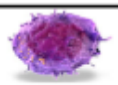
An important function of innate immunity is the rapid recruitment of immune cells to sites of infection and inflammation through the production of cytokines and chemokines (proteins involved in immune cell–cell communication and recruitment). Cytokine production during innate immunity mobilizes defence mechanisms throughout the body while also activating local cellular responses to infection or injury. Key inflammatory cytokines released during the early response to bacterial infection are tumour necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6). These cytokines are critical for aiding in cell recruitment and the local inflammation and increased mucus production which is essential for clearance of many pathogens. They also contribute to the development of fever. Dysregulated production of such inflammatory cytokines, so that they are produced excessively without infection, is often associated with inflammatory or autoimmune disease, making them important therapeutic targets. Chemokines, such as CXCL8 (IL-8) and CCL2, direct the movement of critical immune cells, such as neutrophils and monocytes, into tissues to combat infection. Cytokines and chemokines produced during the innate immune response also aid in the proper development of an effective adaptive immune response by enhancing the activity of antigen-presenting cells (APCs) (discussed later) and increasing the accumulation of cells within lymph nodes draining infection sites.

The complement system is a biochemical cascade that functions to identify and opsonize (coat) bacteria and other pathogens. It renders pathogens susceptible to phagocytosis, a process by which immune cells engulf microbes and remove cell debris, and kills some pathogens and infected cells directly. The phagocytic action of the innate immune response promotes clearance of dead cells or antibody complexes and removes foreign substances present in organs, tissues, blood, and lymph. It

can also activate the adaptive immune response through the mobilization and activation of APCs [1, 3].

Numerous cells are involved in the innate immune response such as phagocytes (macrophages and neutrophils), dendritic cells, mast cells, basophils, eosinophils, natural killer (NK) cells, and innate lymphoid cells. The main characteristics and functions of these cells are summarized in Fig. 1 [1, 3, 4].

Fig. 1

Cell	Image	% in adult blood	Nucleus	Functions	Lifetime	Main targets
Macrophage*		Varies Mainly in tissues	Varies	• Phagocytosis • Antigen presentation to T cells	Months – years	• Various
Neutrophil		40-75%	Multi-lobed	• Phagocytosis • Degranulation (discharge of contents of a cell)	6 hours – few days	• Bacteria • Fungi
Eosinophil		1-6%	Bi-lobed	• Degranulation • Release of enzymes, growth factors, cytokines	8-12 days (circulate for 4-5 hours)	• Parasites • Various allergic tissues
Basophil		< 1%	Bi- or tri-lobed	• Degranulation • Release of histamine, enzymes, cytokines	Lifetime uncertain; likely a few hours – few days	• Various allergic tissues
Mast cell		Common in tissues but not in blood	Central, single-lobed	• Degranulation • Release of histamine, enzymes, cytokines	Months to years	• Parasites • Various allergic tissues
Lymphocytes (T cells, B cells and innate lymphoid cells [ILCs])		20-40%	Deeply staining, eccentric	• T helper (Th) cells (CD4+): immune response mediators • Cytotoxic T cells (CD8+): cell destruction • B cells: antibody production and immune regulation • ILCs: innate immune regulation	Weeks to years	• Th cells: intracellular bacteria • Cytotoxic T cells: virus infected and tumour cells • Natural killer cells: virus-infected and tumour cells
Monocyte		2-6%	Kidney shaped	• Differentiate into macrophages and dendritic cells to elicit an immune response	Hours – days	• Various
Natural killer (NK) cell (specialized subset of lymphocytes)		15% (varies) and also in tissues	Single-lobed	• Tumour rejection • Destruction of infected cells • Release of perforin and granzymes which induce apoptosis	7-10 days	• Viruses • Tumour cells

Characteristics and function of cells involved in innate immunity [1, 3, 4]. *Include alveolar macrophages (within pulmonary alveolus), histiocytes (connective tissue), Kupffer cells (liver), microglial cells (neural tissue), epithelioid cells (granulomas), osteoclasts (bone), mesangial cells (kidney)

Passive vs. active immunization

Acquired immunity is attained through either passive or active immunization. Passive immunization refers to the transfer of *active* humoral immunity, in the form of "ready-made" antibodies, from one individual to another. It can occur naturally via transplacental or breast milk transfer of maternal antibodies, or it can be induced artificially by injecting a recipient with antibodies that are usually manufactured for this purpose and that are targeted to a specific pathogen or toxin. The latter is used when there is a high risk of infection and insufficient time for the body to develop its own immune response, or to reduce the symptoms of chronic or immunosuppressive diseases. Examples include antibodies to respiratory syncytial virus (RSV) which can be given to high-risk infants to prevent RSV infection, or pooled Ig provided to subjects who, for genetic or other reasons, do not mount appropriate antibody responses on their own.

Active immunization refers to the production of antibodies against a specific antigen or pathogen *after* exposure to the antigen. This process, in the form of vaccination, has been highly effective in preventing or reducing the severity of many infectious diseases, including influenza and coronavirus disease (COVID-19). A vaccine can consist of inactivated organisms, specific proteins

or carbohydrates known to induce immunity, or messenger RNA for important proteins for the pathogens. Attenuated (weakened) pathogens are also sometimes used for immunization. Through vaccinations, the immune system develops a memory response to the potential pathogen. If it is encountered in the future, the immune system can either combat it completely, so that the individual does not get ill, or it can reduce the severity of infection substantially. Effective active immunization often requires the use of "adjuvants" which improve the ability of the immune system to respond to antigen injection.

Acquired immunity can also be acquired through natural infection with a microbe, and protection from further infection with the same microbe can be life-long.

The development and function of immune cells, extending to the regulation of inflammation, is moderated by a rich network of immune factors, notably including cytokines, chemokines, growth factors and other signaling proteins [8,9,10], as well as the numerous molecules that serve to regulate their action [11,12,13]. These proteins are required for normal immune cell development and function, but many are also perturbed in a variety of inflammatory disease states [14,15,16].

This Special Issue brings together a diverse set of authors and topics to consider 'Immune Factors, Immune Cells and Inflammatory Diseases' from a variety of perspectives. This includes the delineation of the role played by specific factors and regulators in the development and function of particular immune cell populations, such as the integrin lymphocyte function-associated antigen 1 (LFA-1) in regulatory T cells [17] and the negative feedback regulator cytokine-inducible SH2-domain containing (CISH) protein in myeloid cells [18]. This further extends to the function of such regulators in disease, specifically with respect to the cytokine vascular endothelial growth factor (VEGF) and the chronic inflammation associated with asthma [19]. The other contributions to this Special Issue explore the role of cytokine receptor-associated Janus kinase (JAK) proteins in keratinocyte susceptibility to virus infection that is relevant to various immune-related diseases, the cell surface LY108 molecule in lupus-prone mice and biomarkers of immunogenic cell death in the context of severe acute pancreatitis.

Together, these articles have added to our understanding of this important area of study. Such research has proven to have direct clinical significance, underpinned by the exciting results already seen in modulating immune factors in relevant inflammatory and other diseases [20,21].

Immunopathology

As mentioned earlier, defects or malfunctions in either the innate or adaptive immune response can provoke illness or disease. Such disorders are generally caused by an overactive immune response (known as hypersensitivity reactions), an inappropriate reaction to self (known as autoimmunity) or ineffective immune responses (known as immunodeficiency).

Hypersensitivity reactions

Hypersensitivity reactions refer to undesirable responses produced by the normal immune system. There are four types of hypersensitivity reactions :

- Type I: immediate hypersensitivity
- Type II: cytotoxic or antibody-dependent hypersensitivity
- Type III: immune complex disease
- Type IV: delayed-type hypersensitivity

3 Types of hypersensitivity reactions [7, 8]

Type I –

hypersensitivity is the most common type of hypersensitivity reaction. It is an allergic reaction provoked by re-exposure to a specific type of antigen, referred to as an allergen. Unlike the normal immune response, the type I hypersensitivity response is characterized by the secretion of IgE by plasma cells. IgE antibodies bind to receptors on the surface of tissue mast cells and blood basophils, causing them to be "sensitized". Later exposure to the same allergen cross-links the bound IgE on sensitized cells resulting in degranulation and the secretion of active mediators, such as histamine,

leukotrienes, and prostaglandins, that cause vasodilation and smooth-muscle contraction of the surrounding tissue. Common environmental allergens inducing IgE-mediated allergies include pet (e.g., cat, dog, horse) epithelium, pollen, house dust mites, and molds. Food allergens are also a common cause of type I hypersensitivity reactions (see *IgE-mediated Food Allergy* article in this supplement); however, these reactions are more frequent in children than adults. Treatment of type I reactions generally involves trigger avoidance, and in the case of inhaled allergens, pharmacological intervention with bronchodilators, antihistamines and anti-inflammatory agents. Some types of allergic disease can be treated with immunotherapy (see *Allergen Immunotherapy* article in this supplement). Severe cases of type 1 hypersensitivity, such as anaphylaxis (see *Anaphylaxis* article in this supplement), may require immediate treatment with epinephrine.

Type II –
hypersensitivity reactions are rare and take anywhere from 2 to 24 h to develop. These types of reactions occur when IgG and IgM antibodies bind to the patient's own cell-surface molecules, forming complexes that activate the complement system. This, in turn, leads to opsonization, red blood cell agglutination (process of agglutinating or "clumping together" if the antigen is on the surface of red blood cells), cell lysis and death. Some examples of type II hypersensitivity reactions include erythroblastosis fetalis, Goodpasture syndrome, and autoimmune anaemias in which autoantibodies bind to red cells on other tissues, such as the lung.

Type III –
hypersensitivity reactions occur when IgG and IgM antibodies bind to soluble proteins (rather than cell surface molecules as in type II hypersensitivity reactions) forming immune complexes that can deposit in tissues, leading to complement activation, inflammation, neutrophil influx, and mast cell degranulation. This type of reaction can take days, or even weeks, to develop and treatment generally involves anti-inflammatory agents and corticosteroids. Examples of type III hypersensitivity reactions occur in systemic lupus erythematosus, serum sickness, and reactive arthritis.
Unlike the other types of hypersensitivity reactions, type IV reactions are cell-mediated and antibody-independent. They are the second most common type of hypersensitivity reaction, and usually take 2 or more days to develop. Type IV reactions are caused by the overstimulation of T cells and monocytes/macrophages which leads to the release of cytokines that cause inflammation, cell death and tissue damage. In general, these reactions are easily resolvable through trigger avoidance and the use of topical corticosteroids. An example of a type IV reaction is the inflamed skin response to poison ivy.

Autoimmunity-
Autoimmunity involves the loss of normal immune homeostasis such that the organism produces an abnormal response to its own tissue. The hallmark of autoimmunity is the presence of self-reactive T cells, auto-antibodies, and inflammation. Prominent examples of autoimmune diseases include: rheumatoid arthritis, type 1 diabetes mellitus and Graves' disease [9].

Inflammation-
Defects in immune regulation are associated with many chronic inflammatory diseases, whether they are autoimmune in nature or their causes are less well understood. Poorly regulated inflammatory responses and tissue damage as a result of inflammation are often immunopathological features. Inflammatory diseases include: rheumatoid arthritis, psoriasis, inflammatory bowel disease and chronic asthma. The classical features of inflammation are heat, redness, swelling and pain. Inflammation can be part of the normal host response to infection and a required process to rid the body of pathogens, or it may become uncontrolled, ongoing, and lead to chronic inflammatory disease. The overproduction of inflammatory cytokines (such as TNF, IL-1, and IL-6) as well as the recruitment of inflammatory cells (such as neutrophils and monocytes) through the function of chemokines are important drivers of the inflammatory process. Additional mediators produced by

recruited and activated immune cells induce changes in vascular permeability and pain sensitivity. Therapies for inflammation include both agents that block these mediators and, more recently, agents that target the cytokines driving the inflammatory process directly.

Immunodeficiency-

Immunodeficiency refers to a state in which the immune system's ability to function properly to fight infectious disease, or function appropriately in other ways, is substantially compromised. Immunodeficiency disorders may result from a primary genetic defect (primary immunodeficiency [also referred to as inborn errors of immunity [IEI]—see *IEI* article in this supplement) which can effect either innate or acquired immune function through inhibition of selected immune cells or pathways [10], or they may be acquired from a secondary cause (secondary immunodeficiency—see *Secondary Immunodeficiency* article in this supplement), such as viral or bacterial infections, malnutrition, autoimmunity or treatment with drugs that induce immunosuppression, such as certain anti-cancer drugs [11]. Certain diseases can also directly or indirectly impair the immune system such as leukemia and multiple myeloma. Immunodeficiency is also the hallmark of acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV). HIV directly infects Th cells and impairs other immune system responses indirectly [11].

Conclusion

Innate immunity is the first-line immunological, non-pathogen-specific mechanism for fighting against infections. This immune response is rapid, occurring minutes or hours after aggression, and is mediated by many enhanced barrier activities to prevent infection, numerous cells including phagocytes, mast cells, basophils, and eosinophils, as well as the complement system. Adaptive immunity develops in conjunction with, and is enhanced by, innate immunity to eliminate infectious agents and defend against re-infection. It relies on the tightly regulated interplay between T cells, APCs, and B cells. A critical feature of adaptive immunity is the development of immunologic memory or the ability of the system to learn or record its experiences with various pathogens, leading to effective and rapid immune responses upon subsequent exposure to the same or similar pathogens. The adaptive immune response, particularly the production of antibodies and cytokines can, in turn, enhance the function of innate immune processes, such as complement-mediated destruction of pathogens and the ability of phagocytes to kill bacteria.

There is a great deal of synergy between the adaptive immune system and its innate counterpart, and defects in either system can lead to immunopathological disorders, including autoimmune diseases, immunodeficiencies and hypersensitivity reactions. The remainder of this supplement will focus on the appropriate diagnosis, treatment and management of some of these more prominent immune-mediated disorders.

References-

1. Tomar N., De R.K. A brief outline of the immune system. Methods Mol. Biol. 2014;1184:3–12. doi: 10.1007/978-1-4939-1115-8_1. [DOI] [PubMed] [Google Scholar]
2. Mills C.D., Ley K., Buchmann K., Canton J. Sequential immune responses: The weapons of immunity. J. Innate Immun. 2015;7:443–449. doi: 10.1159/000380910. [DOI] [PMC free article] [PubMed] [Google Scholar]
3. Cool T., Forsberg E.C. Chasing Mavericks: The quest for defining developmental waves of hematopoiesis. Curr. Top. Dev. Biol. 2019;132:1–29. doi: 10.1016/bs.ctdb.2019.01.001. [DOI] [PMC free article] [PubMed] [Google Scholar]
4. Kobayashi M., Yoshimoto M. Multiple waves of fetal-derived immune cells constitute adult immune system. Immunol. Rev. 2023;315:11–30. doi: 10.1111/imr.13192. [DOI] [PMC free article] [PubMed] [Google Scholar]
5. Soliman A.M., Barreda D.R. Acute inflammation in tissue healing. Int. J. Mol. Sci. 2022;24:641. doi: 10.3390/ijms24010641. [DOI] [PMC free article] [PubMed] [Google Scholar]

6. Purushothaman A.K., Nelson E.J.R. Role of innate immunity and systemic inflammation in cystic fibrosis disease progression. Heliyon. 2023;9:e17553. doi: 10.1016/j.heliyon.2023.e17553. [DOI] [PMC free article] [PubMed] [Google Scholar]
7. Fernandes Q., Inchakalody V.P., Bedhiafi T., Mestiri S., Taib N., Uddin S., Merhi M., Dermime S. Chronic inflammation and cancer; the two sides of a coin. Life Sci. 2024;338:122390. doi: 10.1016/j.lfs.2023.122390. [DOI] [PubMed] [Google Scholar]
8. Kelly A., Houston S.A., Sherwood E., Casulli J., Travis M.A. Regulation of innate and adaptive immunity by TGFbeta. Adv. Immunol. 2017;134:137–233. doi: 10.1016/bs.ai.2017.01.001. [DOI] [PubMed] [Google Scholar]
9. Leonard W.J., Lin J.X., O'Shea J.J. The gammac family of cytokines: Basic biology to therapeutic ramifications. Immunity. 2019;50:832–850. doi: 10.1016/j.immuni.2019.03.028. [DOI] [PubMed] [Google Scholar]
10. Zimmerman K.A., Hopp K., Mrug M. Role of chemokines, innate and adaptive immunity. Cell Signal. 2020;73:109647. doi: 10.1016/j.cellsig.2020.109647. [DOI] [PMC free article] [PubMed] [Google Scholar]
11. Yoshimura A., Ito M., Chikuma S., Akanuma T., Nakatsukasa H. Negative regulation of cytokine signaling in immunity. Cold Spring Harb. Perspect. Biol. 2018;10:a028571. doi: 10.1101/cshperspect.a028571. [DOI] [PMC free article] [PubMed] [Google Scholar]
12. Sobah M.L., Liongue C., Ward A.C. SOCS proteins in immunity, inflammatory diseases and immune-related cancer. Front. Med. 2021;8:727987. doi: 10.3389/fmed.2021.727987. [DOI] [PMC free article] [PubMed] [Google Scholar]
13. Li Y., Ming M., Li C., Liu S., Zhang D., Song T., Tan J., Zhang J. The emerging role of the hedgehog signaling pathway in immunity response and autoimmune diseases. Autoimmunity. 2023;56:2259127. doi: 10.1080/08916934.2023.2259127. [DOI] [PubMed] [Google Scholar]
14. Edderkaoui B. Chemokines in cartilage regeneration and degradation: New insights. Int. J. Mol. Sci. 2023;25:381. doi: 10.3390/ijms25010381. [DOI] [PMC free article] [PubMed] [Google Scholar]
15. Ferreira L.B., Williams K.A., Best G., Haydinger C.D., Smith J.R. Inflammatory cytokines as mediators of retinal endothelial barrier dysfunction in non-infectious uveitis. Clin. Transl. Immunol. 2023;12:e1479. doi: 10.1002/cti2.1479. [DOI] [PMC free article] [PubMed] [Google Scholar]
16. Liu W. The involvement of cysteine-X-cysteine motif chemokine receptors in skin homeostasis and the pathogenesis of allergic contact dermatitis and psoriasis. Int. J. Mol. Sci. 2024;25:1005. doi: 10.3390/ijms25021005. [DOI] [PMC free article] [PubMed] [Google Scholar]
17. Klaus T., Wilson A., Fichter M., Bros M., Bopp T., Grabbe S. The role of LFA-1 for the differentiation and function of regulatory T cells-lessons learned from different transgenic mouse models. Int. J. Mol. Sci. 2023;24:6331. doi: 10.3390/ijms24076331. [DOI] [PMC free article] [PubMed] [Google Scholar]
18. Naser W., Maymand S., Dlugolenski D., Basheer F., Ward A.C. The role of cytokine-inducible SH2 domain-containing (CISH) protein in the regulation of basal and cytokine-mediated myelopoiesis. Int. J. Mol. Sci. 2023;24:12757. doi: 10.3390/ijms241612757. [DOI] [PMC free article] [PubMed] [Google Scholar]
19. Gomulka K., Tota M., Brzdak K. Effect of VEGF stimulation on CD11b receptor on peripheral eosinophils in asthmatics. Int. J. Mol. Sci. 2023;24:8880. doi: 10.3390/ijms24108880. [DOI] [PMC free article] [PubMed] [Google Scholar]
20. Heimberger A.B., Tripathi S., Platanias L.C. Targeting cytokines and their pathways for the treatment of cancer. Cancers. 2023;15:5224. doi: 10.3390/cancers15215224. [DOI] [PMC free article] [PubMed] [Google Scholar]
21. Lu L., Li J., Jiang X., Bai R. CXCR4/CXCL12 axis: "old" pathway as "novel" target for anti-inflammatory drug discovery. Med. Res. Rev. 2024. ahead of print . [DOI] [PubMed]