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A REVIEW ON IMMUNOMODULATORY RECEPTORS: A THERAPEUTIC APPROACH IN IMMUNOMODULATION

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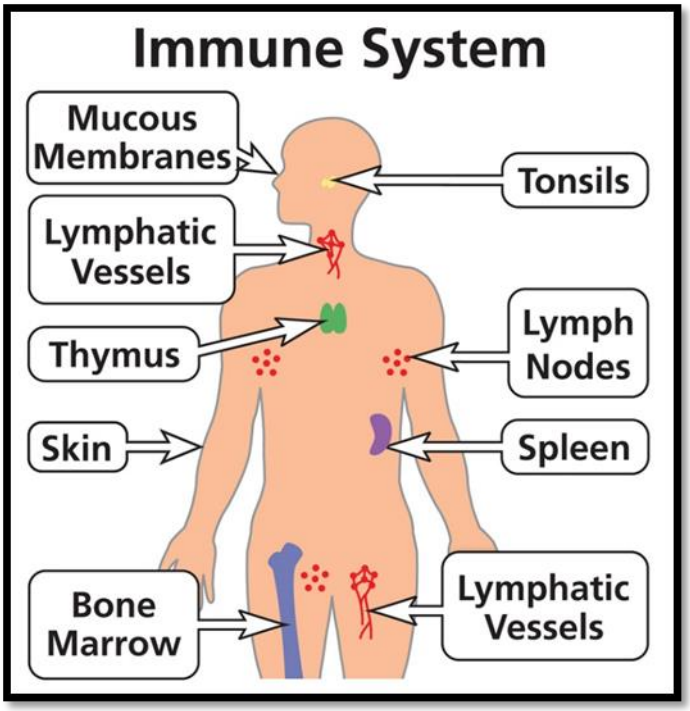
1. Immune system

Good health can be adapted from well-functioning of immune system. Immunity is said to be in balanced condition when human body having proper biological defences against infections, various diseases and allergies. A network of lymphoid organs, various immune cells, humoral factors, and cytokines interact to form the immune system. Several specialized and general strategies can be used to target immune system modulation.



There are two types of immune systems,

1) **Non- specific defence mechanism**- Also called innate immunity. In this defence, mostly immune cells are involved and protect body against various infections, this immunity is first line defence system of body which is present from Birth.
2) **Specific defence mechanism**- Also called as adaptive immunity. Specific immunity can be considered as body's second line defence system. The immune system gets activated due to repeated exposure of same antigen. Here the main two cells provide specific defence are T-lymphocytes and B-lymphocytes.

2. Immunomodulation

A chemical that can affect any immune system component or function, including the innate and adaptive immune systems, in a specific or general way is known as an immunomodulator. By changing the host's immune system, immunomodulation regulates or normalises it by either immunostimulating or immunosuppressing it. Thus, by achieving a balance between regulatory and effector cells, immunomodulators also known as

biological response modifiers improve the host defensive mechanism against illnesses. Immunomodulators are used to treat conditions such as multiple sclerosis, hereditary angioedema, rheumatoid arthritis, and Cryopyrin-associated periodic syndromes, Acute lymphatic leukemia, Crohn's disease, Ulcerative colitis, Pericarditis, Kidney transplant rejection, Capillary leakage syndrome, Familial cold auto-inflammatory syndrome and slow down the progression of the disease.

3. Immunologic receptor

An immune receptor is a receptor that is often found on a cell membrane that binds to a chemical such as a cytokine and triggers an immune response.

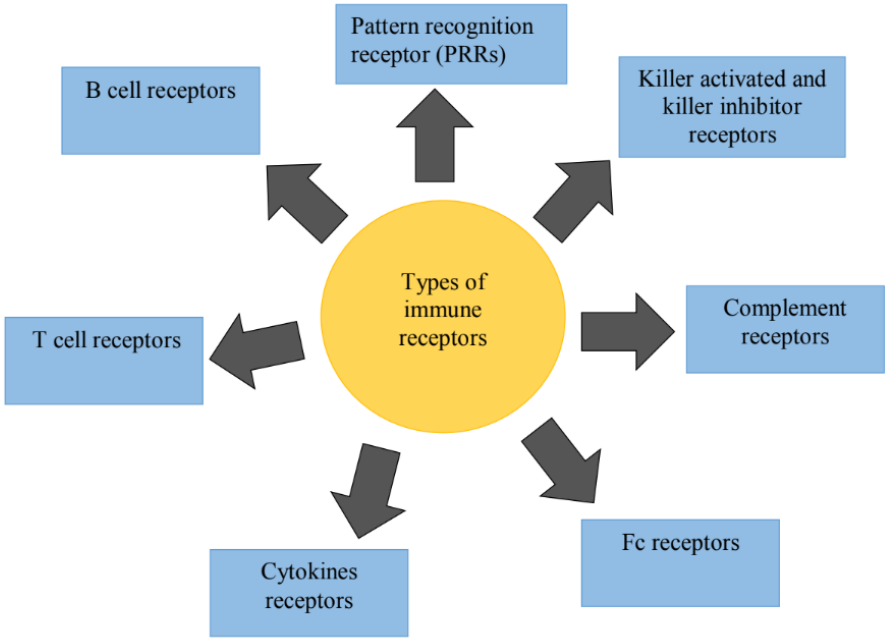


Fig No. 1.1 Types of immunologic receptors.

3.1 Pattern recognition receptors (PRRs)

Pattern recognition receptors (PRRs) are essential for the innate immune system to operate properly. Primitive pattern recognition receptors are another name for them because they emerged before other immune system components, especially before adaptive immunity. They are primarily present on innate immune system cells such dendritic cells, macrophages, monocytes, neutrophils, and epithelial cells that express these proteins. There are several subgroups of PRRs.

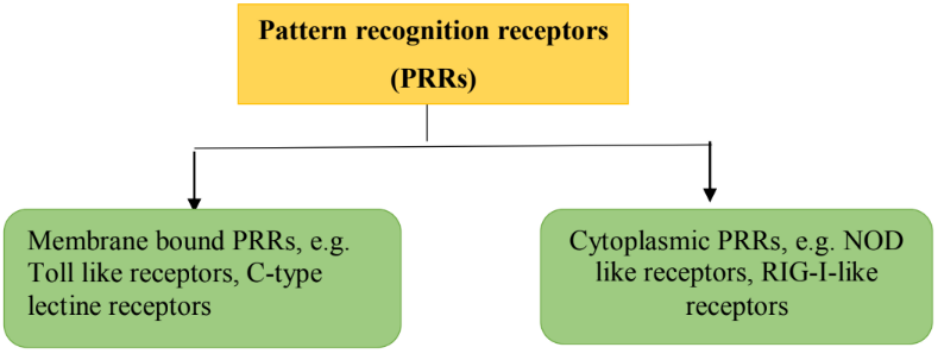


Fig No. 1.2 Types of Pattern Recognition Receptors.

3.1.1 Toll like receptors (TLR)

The best characterised innate receptors are toll-like receptors (TLRs), which are quickly activated and comprise functional modules that are essential for the host's defence against microbial invasion. The TLR family is further classified into extracellular and intracellular receptors. TLR1, 2, 4, 5, 6, and 10 are on the cell surface, while TLR3, 7, 8, and 9 are found in the endoplasmic reticulum and intracellular endosomal/lysosomal compartments. All TLRs are transmembrane proteins with a distinctive cytoplasmic Toll/IL-1 receptor (TIR) domain and a sizable extracellular domain made up of leucine-rich repeats.

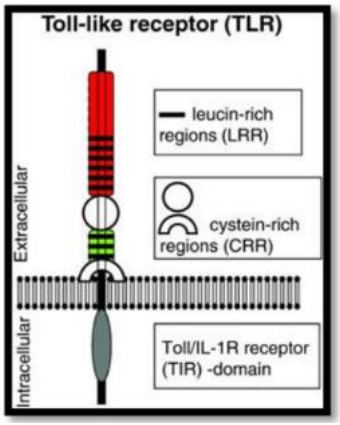


Fig No. 1.3 Structure of Toll-like receptor.

3.1.2 C-type lectin receptors

Myeloid cells are the main source of expression for the family of transmembrane pattern recognition receptors known as C-type lectin-like receptors (CLRs). The C-type nomenclature refers to their need for calcium in order to bind. Functions of proteins with C-type lectin domains include cell-cell adhesion, immunological response to pathogens, and apoptosis. There are two pathways of signaling TLR dependent and TLR independent.

3.1.3 NOD-like receptors (NLR)

These are cytoplasmic proteins which are able to react to endogenous danger signals and preserved microbial structures. NLR mainly transition from innate to adaptive immunity by regulating the transcription of MHC class I and class II molecules. The peptidoglycan fragments generated either by bacterial division in the cytosol or by the lysosome after the destruction of phagocytosed bacteria are recognised by NOD1 and NOD2. In order to cause the creation of inflammatory molecules, it involves activating crucial inflammatory cytokines like IL-1 and/or the NF-B signalling pathway.

3.2 Killer activated and killer inhibitor receptors

Killer Activation Receptors (KAR) and Killer Inhibition Receptors allow natural killer cells to carry out their activity efficiently (KIRs). These receptors can activate NK cells by recognizing cellular stress ligands, major histocompatibility complex class I, and associated substances. The presence of noncovalently coupled subunits with immunoreceptor tyrosine-based activation motifs (ITAMs) in their cytoplasmic domain is a characteristic of these receptors. The tyrosine residues in the ITAMs in the associated chain are phosphorylated by kinases upon the attachment of an activation ligand to an activation receptor complex, and a signal that encourages natural cytotoxicity is sent to the interior of the NK cell. The transduction signal is sent when the ligand binds to the KAR and phosphorylates the ITAMs in the cytoplasmic tail of the receptor by the kinase PTK.

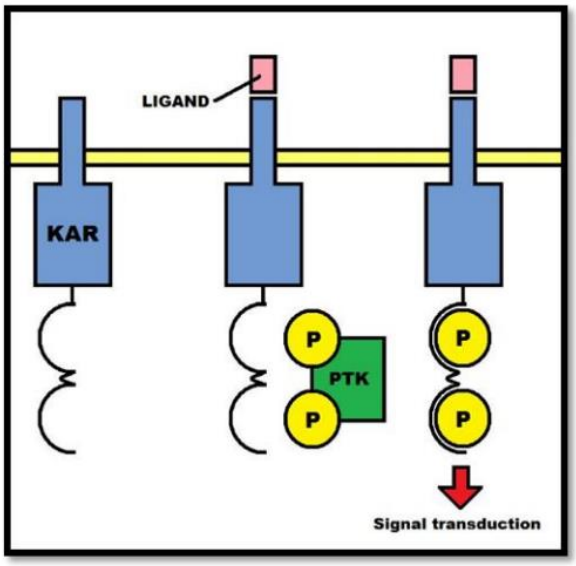


Fig No. 1.4 Signalling of Killer activated and killer inhibitor receptors.

3.3 Complement receptors

A complement receptor is a surface receptor that is a part of the innate immune system's complement system. The complement system, also known as the complement cascade, is a component of the immune system that improves (complements) the capacity of antibodies and phagocytic cells to eliminate microbes and damaged cells from an organism, to cause inflammation, and to attack the cell membrane of the pathogen. The comprehensive way of a target for phagocytosis and the activation of the immune system via soluble anaphylatoxins occur simultaneously as a result of complement activation. It also contributes to inflammatory response and leukocyte extravasation. On their surface, white blood cells, especially monocytes and macrophages, have complement receptors. The complement receptors (CR), 1, 3, and 4 act as opsonins to promote phagocytosis, whereas the co-receptor, CR2, is only found on B cells.

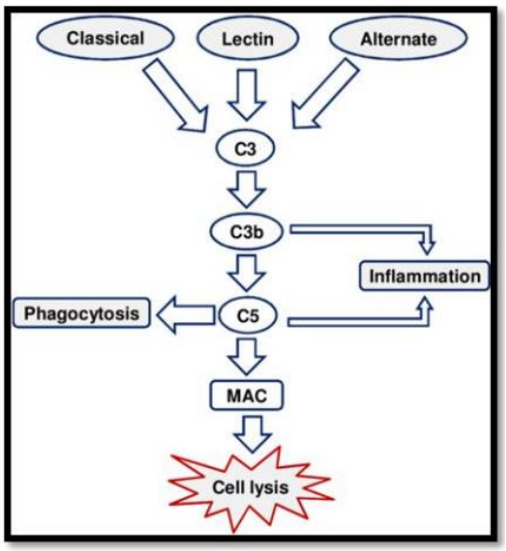


Fig No. 1.5 Schematic representation of the human complement system, which possesses three main pathways: the classical, the lectin and the alternative pathway.

3.4 Fc receptors

These receptors are found on surface of many cells like B lymphocytes, follicular dendritic cells, natural killer cells, macrophages, neutrophils, eosinophils, basophils, human platelets, and mast cells which are involved in protective action of immune system. Two general types of FcR can be separated based on their function: those that are largely expressed by leucocytes and initiate antibody effector activities and those that serve to mediate the transport of immunoglobulins across epithelial or endothelial surface receptors. Receptor follows signalling pathway involving phosphorylation of tyrosine residues. The phosphatases SHP-1 and SHIP-1 prevent Fc receptor activation by removing phosphate groups from tyrosine residues, which regulate the inhibitory activities of these receptors.

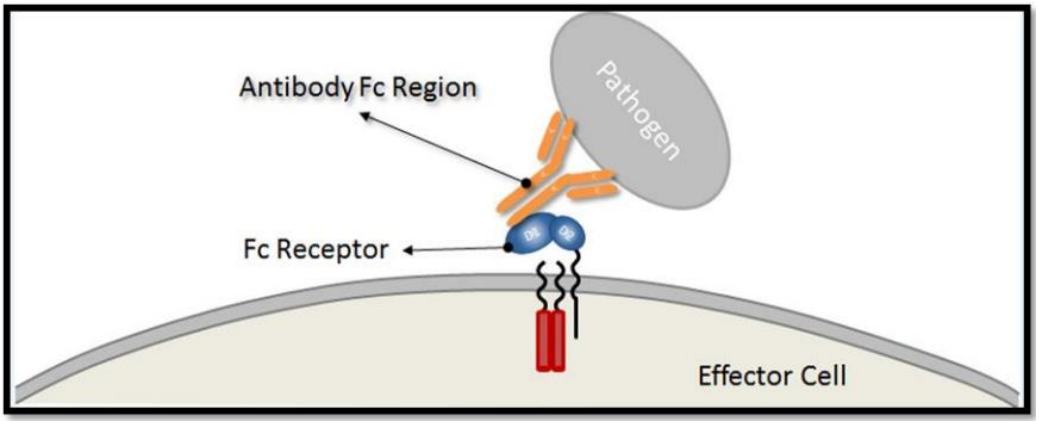


Fig No. 1.6 The illustration of an Fc receptor.

3.5 Cytokines receptors

The receptors known as cytokine receptors bind to cytokines. Additionally, it has been demonstrated that cytokine receptors play a significant part in the pathogenesis of human immunodeficiency virus (HIV) infection. A cytokine receptor categorization based on threedimensional structure. These are Type I cytokine receptors, Type II cytokine receptors, Immunoglobulin

(Ig) superfamily, Tumor necrosis factor receptor family, Chemokine receptors, and TGF-beta receptor family. Cytokine receptors activate the JAK/STAT signaling pathway.

3.6 T cell receptors

The transmembrane heterodimer TCR, a fundamental component of T cells, is made up of either an alpha and beta chain or a delta and gamma chain connected by a disulfide bond. The main obstacle to the successful transplantation of solid organs and bone marrow is the T cell response to polymorphic determinants of the major histocompatibility complex (MHC) molecules. Immune system gives response not only but just recognition of antigen by the TCR but also requires transmembrane signaling. This signal then triggers a series of internal processes that affect cellular reactions, such as the transcriptional activation of the genes for lymphokines and their receptors, cell proliferation, or activation of the proapoptotic effector scheme.

3.7 B cell receptors

A transmembrane protein called the B cell receptor (BCR) is expressed on the surface of a B cell. An immunoglobulin molecule that is membrane-bound and a signalling component make up a B cell receptor. Igα and Igβ regulate transmission through the BCR. The binding event enables the tyrosine kinases of the Src family, such as Blk, Lyn, and Fyn, to phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMs) in the coupled Ig/Ig heterodimer subunits. Like any other antibodies here the receptor binding moiety is composed of a membrane-bound antibodies having two similar paratopes. Here the B cell receptors have two main important role when it combines with the antigen. Firstly it involves signal transduction leads to oligomerization of receptors and secondly to mediate internalization for later antigen processing and peptide presentation to helper T cells.

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