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"Review On Cytokines and Their Role in Autoimune Diseases"

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ABSTRACT

Cytokines are small, non-structural proteins with low molecular weights which have a complex regulatory influence on inflammation and immunity. Cytokines are proteins produced by cells, and they serve as molecular messengers between cells. Proteins which are produced by cytokines regulate and influence immune response. Cytokines has low molecular weight soluble proteins (polypeptides) produced in response to microbes and other antigens. They act via cell surface receptors to mediate and regulate the amplitude and duration of the immune inflammatory responses, through activation of macrophages, controlling growth and differentiation of T and B cells. Cytokines play a vital role in the pathogenesis of autoimmune diseases. Cytokines has also other names that are lymphokine (lymphokines are produced from lymphocytes), monokine (cytokines produced by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines produced by single leukocyte)

KEYWORDS : Cytokines, Inflammation, Lymphokine

I. INTRODUCTION

- Cytokines previously called as Lymphokines(Cytokines produced by lymphocytes), or Monokines(Cytokines produced by monocytes).However it is now known that are considerable overlap e.g. TNF – a,IL-6 are made by both cell types so this nomenclature is not in wideuse.
- Interleukins are describe as molecular messengers acting between leukocytes. Two other related group of molecules have been described they are Interferons and Growthfactors.
- Cytokines are a wide group of intercellular proteins that regulate not only local and systemic immune and inflammatory response butalso
  - Woundhealing.
  - Hematopoiesis and many biologicalprocess.
  - Over 100 structurally similar and dissimilar and genetically unrelated cytokines have been identified todate.
  - These cytokines are not only released from lymphocytes and monocytes but also from variety of other cells like fibroblasts and endothelium that interact with cells of the immune system and participate in inflammatory reaction[1]
- Cytokines are small secreted proteins which mediate and regulate immunity, inflammation, andhematopoiesis.
- They generally (although not always) act over short distances and short time spans and at very lowconcentration.
- They act by binding to specific membrane receptors, which then signal the cell via second messengers, often tyrosine kinases, to alter its behavior (geneexpression).
- Responses to cytokines include increasing or decreasing expression of membrane proteins (including cytokine receptors), proliferation, and secretion of effector molecules.
- Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrineaction).[2]

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CLASSIFICATION OF CYTOKINES

1. **Interleukins:**
- Interleukin1
- Interleukin2
- Interleukin3
- Interleukin4
- Interleukin5
- Interleukin6
- Interleukin7
- Interleukin12
- Interleukin14

2. **Chemokine:**
- α:CXC,
- β:CC

3. **Interferon**
4. **Tumor NecrosisFactor**
5. **Colony StimulatingFactor**[3]

1. INTERLEUKINS :

- Interleukins are a subset of a larger group of cellular messenger molecules called cytokines, which are modulators of cellularbehavior.
- Like other cytokines, Interleukins are not stored within cells but are instead secreted rapidly, and briefly, in response to a stimulus, such as an infectious agent. Once an interleukin has been produced, it travels to its target cell and binds to it via a receptor molecule on the cell's surface. This interaction triggers a cascade of signals within the target cell that ultimately alter the cell'sbehavior.
- Interleukins are a group of cytokines that are expressed and secreted by white blood cells as well as some other bodycells.
- The human genome encodes more than 50 interleukins and relatedproteins.
- The first interleukins were identified in the1970s.
- Initially investigators believed that interleukins were made chiefly by leukocytes (white blood cells)to act primarily on other leukocytes, and for this reason they named them interleukins, meaning "between leukocytes." Because leukocytes are involved in mounting immune responses, interleukins were thought to function only as modulators of immunefunctions.
- Although this is an important function of interleukins, it is now known that interleukins also are produced by and interact with a host of cells not involved in immunity and are involved in many other physiological functions. Thus the role that interleukins play in the body is much greater than was initiallyunderstood.[4]

A. INTERLEUKIN: 1

- Interleukin-1 is a very potent multifunctional cytokine that appears to be a central regulator of the inflammatory and immuneresponses.
- The term Interleukin-1 was introduced in1979.
- IL-1 is a Pleotropic cytokine with a variety ofactivities.
- It includes osteoclast activating factor (OAF) because of stimulation of osteoclasts and lymphocyte activating factor (LAF) because of its ability to stimulate proliferation of phytohemagglutination-treatedT-cells.[5]
- It is secreted by monocytes, macrophages, B-cells, fibroblasts, neutrophils, and epithelialcells.
- Bacterial Lipopolysaccharide is a potent commonly used stimulus for IL-1production.
- IL-1 synthesis is suppressed by several endogenous factors, such as Corticosteroids, Prostaglandins, Cytokines like IFN-α,IL-4.
- Some of the other cytokines share biologic activities with IL-1, most importantly IL-6 and TNF factor.
- There are 2 principal forms of IL-1 that have agonist activity. IL-1α, IL IB. with a third ligand, IL-1 receptor agonist (IL-Ira) that functions as a competitiveinhibitor.
- Two IL-1 receptors are found on the surface of the target cells, designated IL-1 receptor-1 and IL-1 receptor2.
- IL-IRI is generally thought to mediate most of the responses toIL-1.
- IL-1R2 has been reported to function principally as a decoyreceptor.[6]

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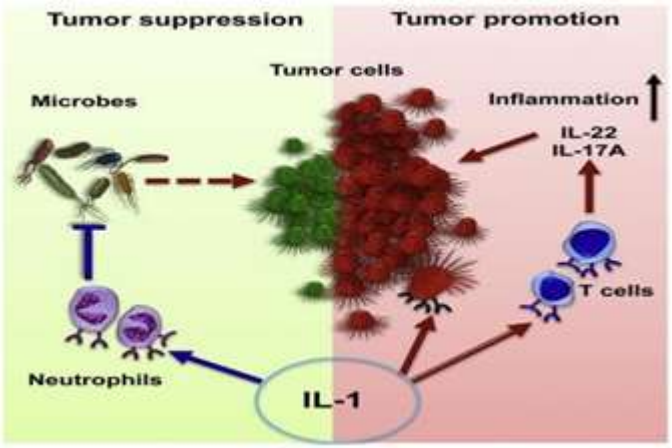

Fig 1a: Schematic diagram of IL-1

Biologic effects IL1 include: Lymphocyte activation, macrophage activation, Natural killer stimulation, Prostaglandin formation, Fever induction, Anorexia, Acute phase protein release, Adrenocorticotrophic release, Corticosteroid release, Cytokine gene expression, Plasminogen activator, Endothelial cell activation, Tumor cell growth inhibition, and suppression of lipoprotein lipase geneexpression.[7]

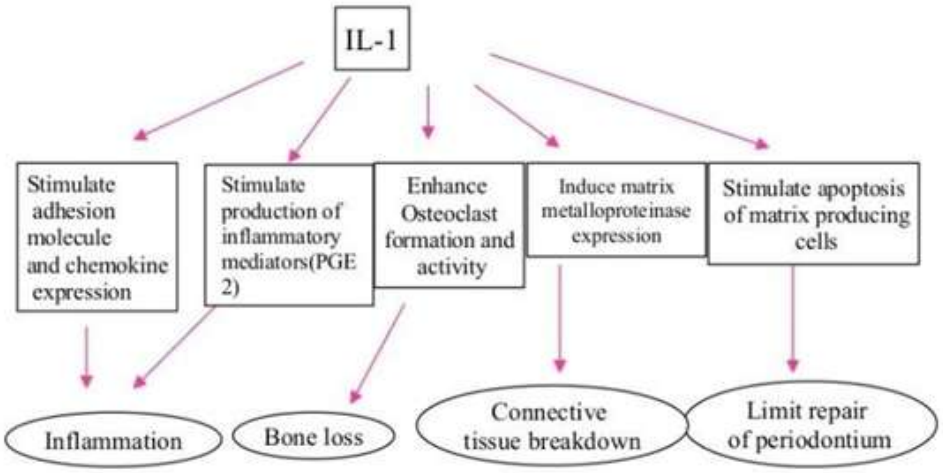

Fig 1b: Schematic Diagram of IL-1 Source: Adapted from Wikipedia

B. INTERLEUKIN 2:

- IL-2 (α andß) was originally called T-cell growth factor because of its effect on mitogen or antigen activating T-cells and is known to play a general role in immuneresponses.
- IL-2 also stimulates macrophage functional activity, modulates natural killer function and induces natural killer prolife ration.
- It is secreted by helper T cells and natural killercells.
- The molecular weight of IL-2 is approximately 20,000KD.[8]

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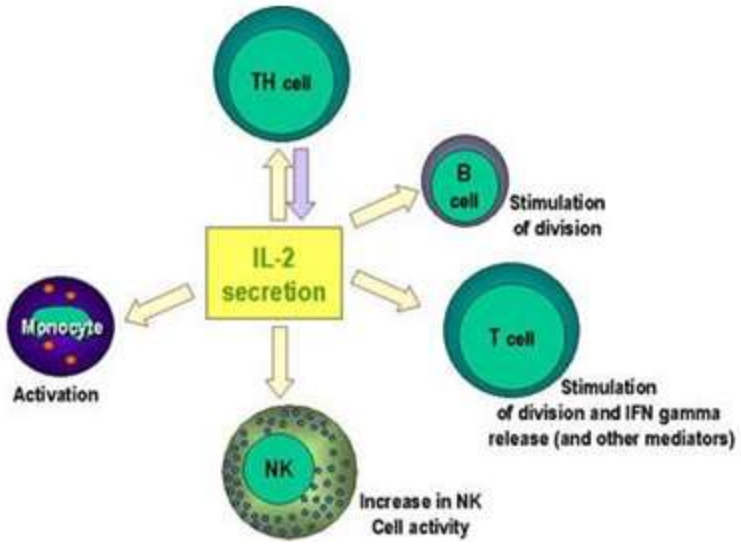

Fig 2: Schematic diagram of IL-2
Source: Adapted from Microbiology and Immunology On-line

Interleukin 2 receptors :

- Three different forms of the human IL-2 receptors have been identified. These receptors interact with IL-2 with characteristically different affinities, specifically high, intermediate and lowaffinities.
- The high affinity IL-2 receptors comprise at least two different IL-2 binding subunits termed IL-2Rα andIL-2RB.

Clinical aspects :

- Used in Tumors immunotherapy, either using IL-2 alone or in combination with in-vitro activated lymphokine-activated killercells.
- The potential for IL-2 as a cancer treatment is based on activation of cells, which are cytotoxic to thetumor.
- Adverse effects: fever, chills, fatigue, nausea, vomiting, capillary leakage syndrome or vascular leakage syndrome, characterized by the accumulation of edema fluid in pleural cavities.[9]

C. INTERLEUKIN:3

- IL-3 is a distinct hematopoietic factor affecting multiple hematopoietic celllineages.
- IL-3 also known as burst-promoting factor, B-cells stimulating factor, hemopoietic cell growth factor and multi colony stimulating factor is produced primarily by activated helper T type I and IIcells.
- This molecule stimulates the growth of colonies of mast cells, neutrophils, macrophages, eosinophil, and megakaryocytes.
- It is secreted by activated helper T cells, natural killercells.
- IL-3 acts as a link between the T lymphocytes and mast cells of the immune system, and the hematopoietic system, which generates the accessory cells granulocytes, phagocytes, and platelets, which carry out repair and defenseresponses.[10]

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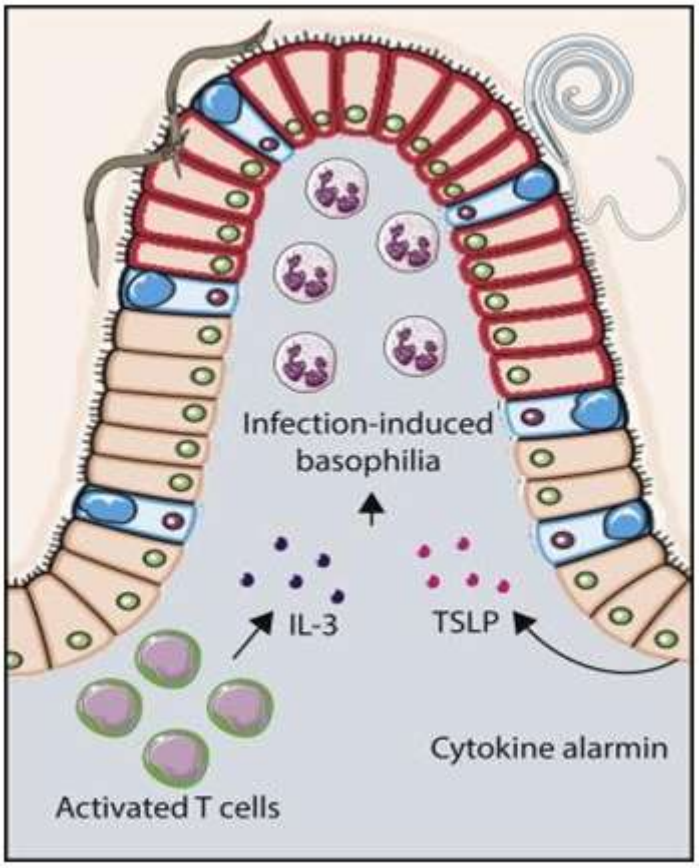

Fig 3: Schematic diagram of IL-3
Source: Adapted from sciencedirect.com

D.INTERLEUKIN :4

- IL-4 originally called T-cell-derived B-cell growth factor (BCGF-1) because of its activation of Bcells.
- Also called as migration inhibitionfactor.
- It is also play a role in the activation, proliferation and differentiation of B cells, T-cell growth, macrophage function, and growth of mastcells.
- IgE synthesis by B cells is also induced byIL-4.
- It is secreted by helperTcells.
- Mwt 15000 to20000.
- Receptors for this cytokine found on T-cells, B-cells, mast cells, myeloid cells, fibroblasts, neuroblasts, stromal cells, endothelial cells andmonocytes

❖ **Effects onmacrophages:**

- It can activate macrophage cytocidal function and increase macrophage expression of class II major histocompatibility complexproteins.
- It suppresses the synthesis of proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF-α and activated monocytes.[11]

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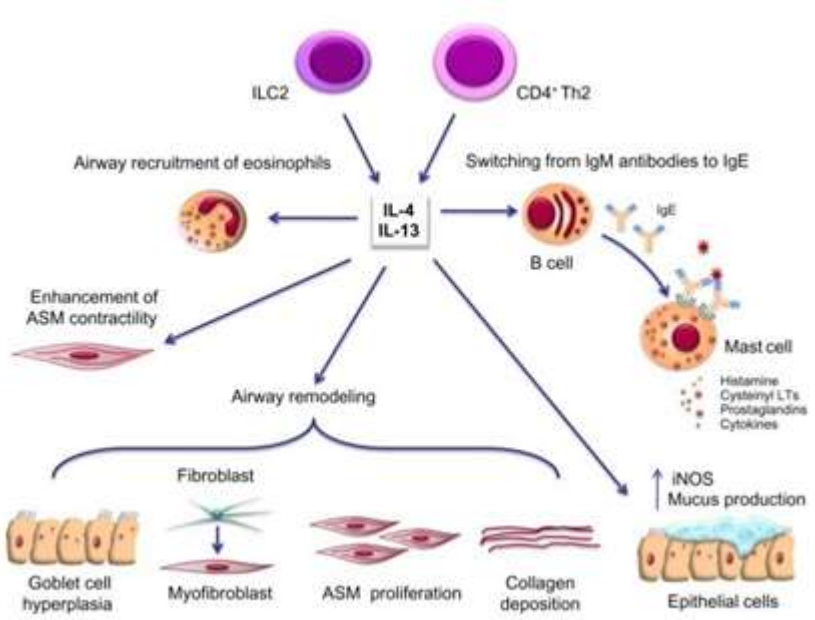

Fig 4: Schematic diagram of IL-4 Source: Adapted from ResearchGate.net

D. INTERLEUKIN:5

- It is the name given to a lymphokine (a cytokine produced bylymphocytes).
- Coffman and colleges found that IgA enhancing factor was IL-5 when the protein is sequenced.
- Thus initially known as B- cells growth and differentiation factor, IgA enhancing factor, eosinophil colony stimulatingfactor.
- IL-5 is heterogeneous glycoprotein with a molecular weight of 4000050000.
- The major function of IL-5 in humans is to stimulate the production ofeosinophils.

IL-5 not only increases the number of eosinophils but also has been reported to increase their function. [12]

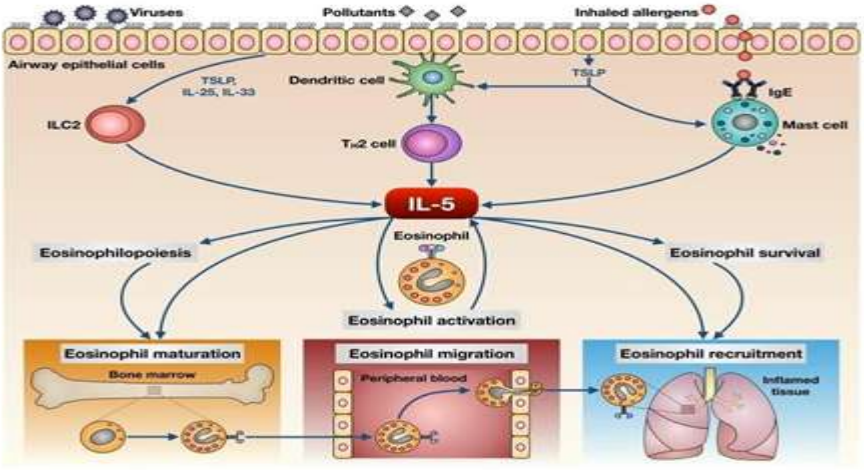

Fig 5: Schematic diagram of IL-5 Source: Adapted from Frontiersin.org

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E. INTERLEUKIN:6

- Interleukin-6 is a multifunctional cytokine produced by various cells such as activated monocytes or macrophages, endothelial cells, activated T cells, andfibroblasts.
- Formerly these molecules were known as B-cells stimulatory factor II, interferon B2 and plasmacytoma growthfactor.
- Its effect on B cells is to promote growth and facilitate maturation of the B cells causing immunoglobulinsecretion.
- IL-6 increases in sites of gingival inflammation and plays a role in boneresorption.[13]

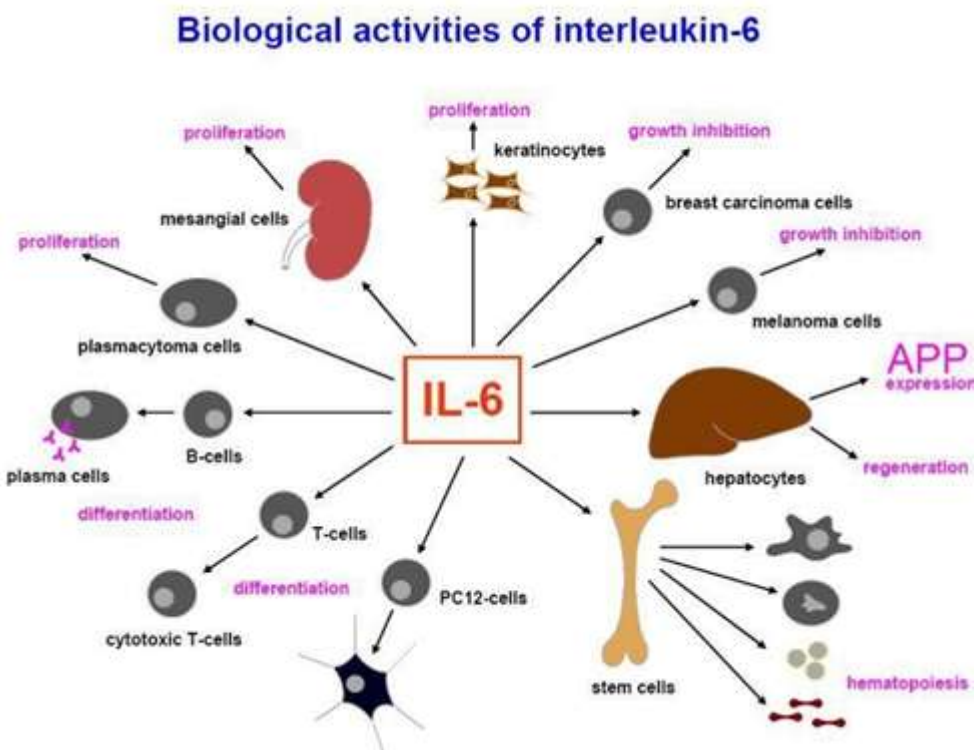

Fig 6: Schematic diagram of IL-6 Source: Adapted from Pinterest.com

F. INTERLEUKIN:7

- Secreted by thymus, spleen and bone marrow stromal cells that functions as a growth factor for T and B cellsprecursors.
- It was formerly known as lymphopoitin 1 based on its capacity to influence early lymphopoiesis.
- IL-7 enhances the function of mature activated lymphocytic cells, particularly those with cytotoxic activity. At higher concentrations, IL-7 also increases macrophage cytotoxic

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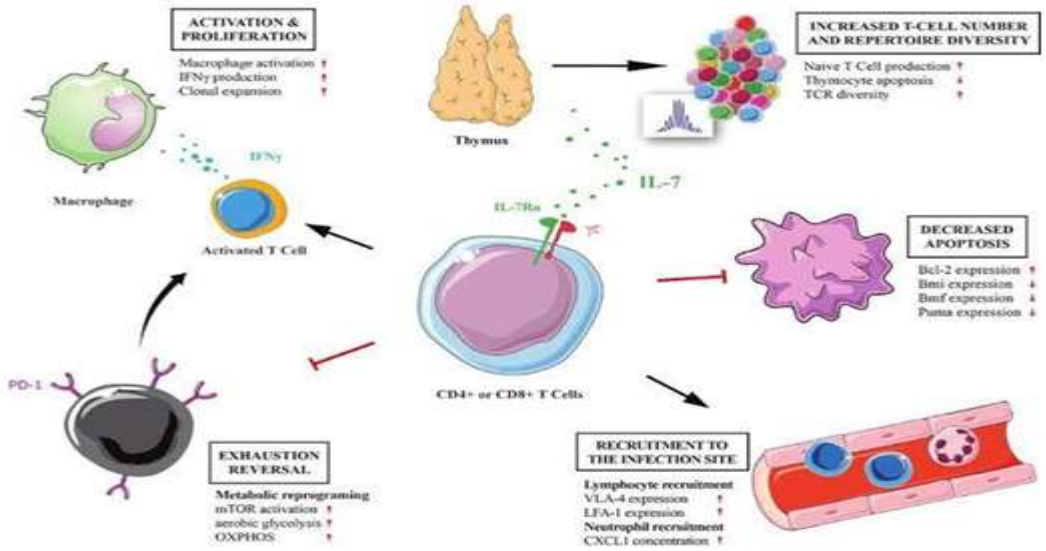

Fig 7: Schematic diagram of IL-7 Source: Adapted fromResearchGate.com

G. INTERLEUKIN:12

- It was originally called cytotoxic lymphocytes maturation factor (CLMF) or NK cell stimulatoryfactors.
- Its molecular wt about 35000 to40000.
- It is produced predominantly on activation by B cells andmacrophages.
- It acts synergistically with IL-2 to induce IFN-y by T-cells and NKcells
- It is a key factor in the development of Th1 cells, stimulating both their proliferation and differentiation.
- It suppresses Th2 dependent functions, such as the production of IL-4, IL 10, IgE antibodies.
- IL-12 also induces the production of GM-CSF, TNF, IL-16, IL-2.c activity and induces cytokine secretion bymonocytes.

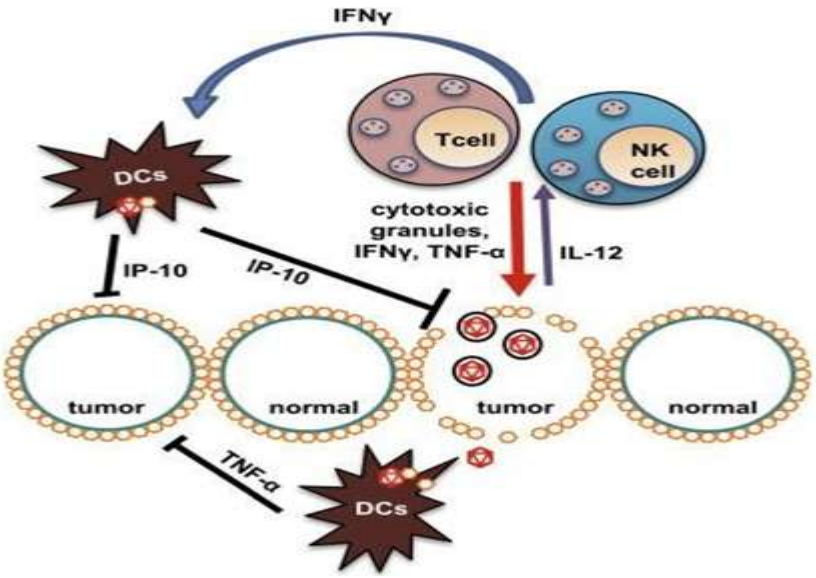

Fig 8: Schematic diagram of IL-12 Source: Adapted from ScienceDirect.com

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H. Interleukin :14

- IL-14 is a 50-60 KD glycosylated cytokine otherwise known as the high mol wt B cell growthfactor.
- IL-14 is thought to play a role in the development of B cellmemory.
- It enhances the proliferation of activated B cells and inhibits the synthesis of immunoglobulin.
- It is produced by follicular dendritic cells and activated Tcells.
- IL-14 receptors are found only in cells of the B cellslineage.
- IL-14, participates mainly in secondary humoral immuneresponses.

2. CHEMOKINE:

- Chemokines are a family of small heparin-binding homologous proteins involved in the regulation of cell migration under both inflammatory and physiological conditions.
- Chemokines are classified according to the presence of a conserved tetra cysteine motif.
- They generally have low molecular weights, ranging from 7-14 KDa, and stimulate recruitment ofleukocytes.
- Chemokine are secondary proinflammatory mediators, i.e., they are typically induced by primary proinflammatory mediators such Interleukin-1 orTNF.
- By recruitment of leukocytes, chemokine activity leads to activation of host defense mechanisms and stimulates the early events of woundhealing.
- There are two major chemokine subfamilies based upon the portion of cysteine residues i.e. CXC andCC.
- The CXC family members also known as the alpha Chemokine. They primarily stimulateneutrophils.
- C chemokine are also known as the beta Chemokine. They stimulate Basophiles, eosinophil, T-lymphocytes and NKcells.

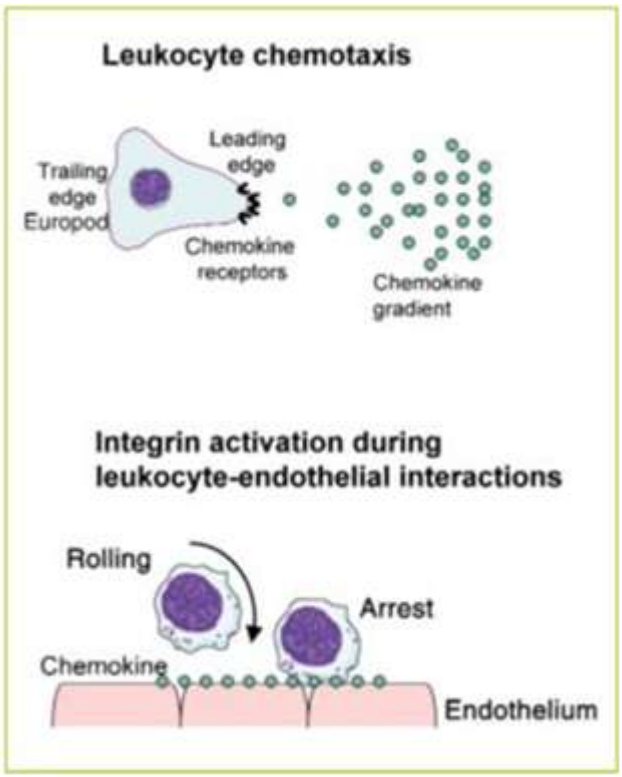

Fig 9: Schematic diagram of Chemokine Source: Adapted from immunology.org

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3. INTERFERON:

- Interferons are a group of proteins belonging to a class of signaling molecules known as cytokines and are released by a variety of cells during the inflammatoryresponse.
- Interferon have been divided into two types: Type I an viral interferon has been further divided into alpha and beta subcategories. Type II or immune interferon is referred to as gammainterferon.
- IFN-alpha is leukocyte derived whereas IFN-beta is derived from fibroblasts. IFN- gamma is however derived from stimulated T cells of both CD4+ and CD8+lineage.
- Both IFN-a and B are characterized by their antiviral activity, IFN Y appears to be more integrated part of the immunesystem.
- IFN y is stimulated by IL-2 has a molecular wt of 35 -70 KD and in addition to its antiviral activity appears to have an important role in the stimulation of cytotoxic T cells and NK cellsactivity.[14]
- It also plays an important role in B-cells differentiation and in production of Igs under someconditions.
- Interferons are a group of signaling proteins made and released by host cells in response to the presence of severalviruses.
- In a typical scenario, a virus-infected cell will release interferons causing nearby cells to heighten their anti-viraldefenses.
- Interferons are categorized as cytokines, small proteins that are involved in intercellular signaling.
- Interferon is secreted by cells in response to stimulation by a virus or other foreign substance, but it does not directly inhibit the virus'smultiplication[15]

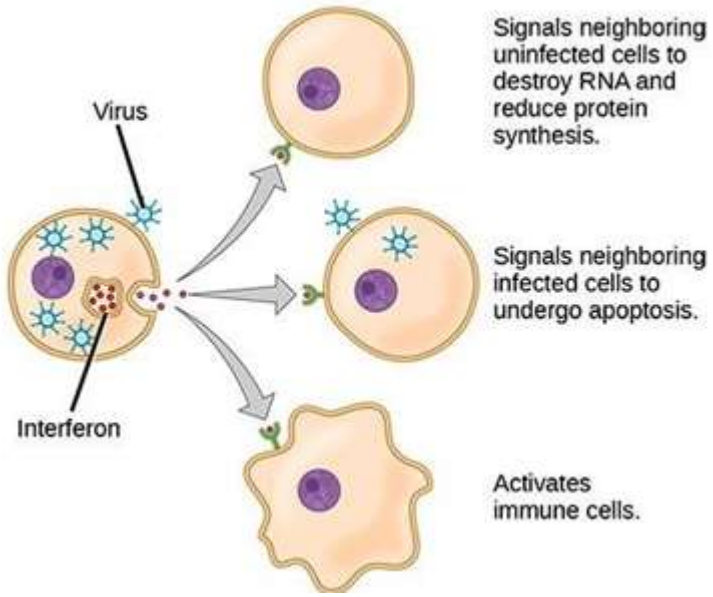

Fig 10: Schematic diagram of Interferon. Source: Adapted from lecturio.com

4. TUMOR NECROSIS FACTOR:

- TNF is a principal mediator in the host inflammatoryresponse.
- The main cell type secreting TNF is the mononuclearphagocyte.
- The main stimulus for release is the Lipopolysaccharide of bacterial cellwalls.
- There are two structurally and functionally similar forms of TNF α and ß but they differbiochemically.
- TNF a is 17 KD is derived from stimulated macrophages and appears to have significant stimulatory activity on the cytoxic T lymphocytes (CTL) responsible for lysing tumor or virally infectedcells.
- TNF-β is a 25 KD glycoprotein derived from activated T cells with a 28% homology toTNF-α
- B Form is occasionally known as lymphotoxin

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these virtually have similar actions, which includes CTL stimulation, osteoclast activation of PMNLs and antiviral activity.

- TNF also appears however to act synergistically with cytokines and induces release ofIL-1.
- TGF β was initially discovered as a growth factor for fibroblasts and promotes wound healing.
- T lymphocytes produceTGFβ.
- Humans express at least three forms of TGF ß called TGF β1, TGF β-2,TGFβ-3.
- These are products of separate genes, but they all bind to 5 types of high affinity cell surface receptors.
- TGFβ has anti proliferative effects on a wide variety of cell types including macrophages, endothelial cells and T andB-lymphocytes.
- TGF is a chemo attractant and promotes many functional activities offibroblasts.
- TGF β is a potential mediator of inflammation because it is a product of activated macrophages, a potent chemo attractant for macrophages and can activate macrophages to produceIL-1.
- It is chemo attractive for neutrophils and monocytes and it stimulates monocyte expression of adhesionproteins

5. COLONY STIMULATING FACTOR:

- Colony-stimulating factors (CSFs) are secreted glycoproteins that bind to receptor proteins on the surfaces of hematopoietic stem cells, thereby activating intracellular signaling pathways that can cause the cells to proliferate and differentiate into a specific kind of blood cell, usually white bloodcells.
- They play part in the hosts response to injury and infection, and although they were originally defined as haematopoietic cell growth factors, colony-stimulating factors (CSFs) have been shown to have additional unique biological functions, suggesting that they could be used to target specificconditions.
- The colonies consisted of growing granulocytes. Their growth was in direct proportion to the presence of some factor called, for the time, colony-stimulating factor, or CSF. Today these factors are known to be of immense significance in the treatment of low white blood cell levels following chemotherapy in cancerpatients.

CYTOKINES ROLE IN AUTOIMMUNE DISEASES

Introduction :

- Cytokines are peptides synthesized and released by white blood cells and tissue macrophages that stimulate or suppress the functional activity of lymphocytes, monocytes, neutrophils, fibroblast cells, and endothelialcells.
- Cytokines are substances released by leukocytes and other cells that control the development of the immuneresponse.
- Often termed the hormones of the immune system, they modulate the differentiation and division of hematopoietic stem cells and activation of lymphocytes andphagocytes.
- Corticosteroids were among the earliest compounds found to have immune suppressive activity.
- The binding of the glucocorticoids to their receptors blocks the synthesis or release of lymphokines andcytokines.
- This results in an inhibition of T-cell response to stimulation, a redistribution of lymphocytes from the vascular to the lymphatic system, and a decrease in the number of circulating T-cells andB-cells.
- The cellular immune response is blunted, but almost no immuno suppressive effect is seen in the humoral response (antibodyproduction).
- Cytokines are soluble proteins that interact with specific cellular receptors that are involved in the regulation of the growth and activation of immune cells and mediate normal and pathologic inflammatory and immuneresponses.
- Cytokines are peptides used by cells for intercellular communication and for controlling the inner environment of the cells in which theyoperate.
- They are produced by cell types that have important roles in the immune response, inflammation, hemopoiesis, healing, and systemic response toinjury.
- Many cytokines can be measured by bioassay and immunoassay.[16]

i. RHEUMATOID ARTHRITIS:

- Cytokines are cell molecules that are secreted

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by immune cells and aid cell to cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection andtrauma.

- So, the cytokines are the main part of the immune network to provide the communication in rheumatoid arthritis (RA) too. In RA, cytokines may be classified into four groups: pro-inflammatory cytokines, inflammatory cytokines in joints, anti-inflammatory cytokines and natural cytokineantagonists.
- After the initial stimuli have occurred, cytokines play a role in communication between the parts of immune system in every step of the pathophysiology process of RA.
- The differentiation of nerve T cells into Th17 cells results in inflammation (synovitis) in joints. B cells further the pathogenic process through antigen presentation and autoantibody and cytokineproduction.
- The release of cytokines, especially tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1, causes synovial inflammation. In addition to their articular effects, pro-inflammatory cytokines promote the development of systemic effects (anemia, cardiovascular disease, fatigue and depression). So, cytokines are the main molecules contributing to all facets of thedisease.[17]

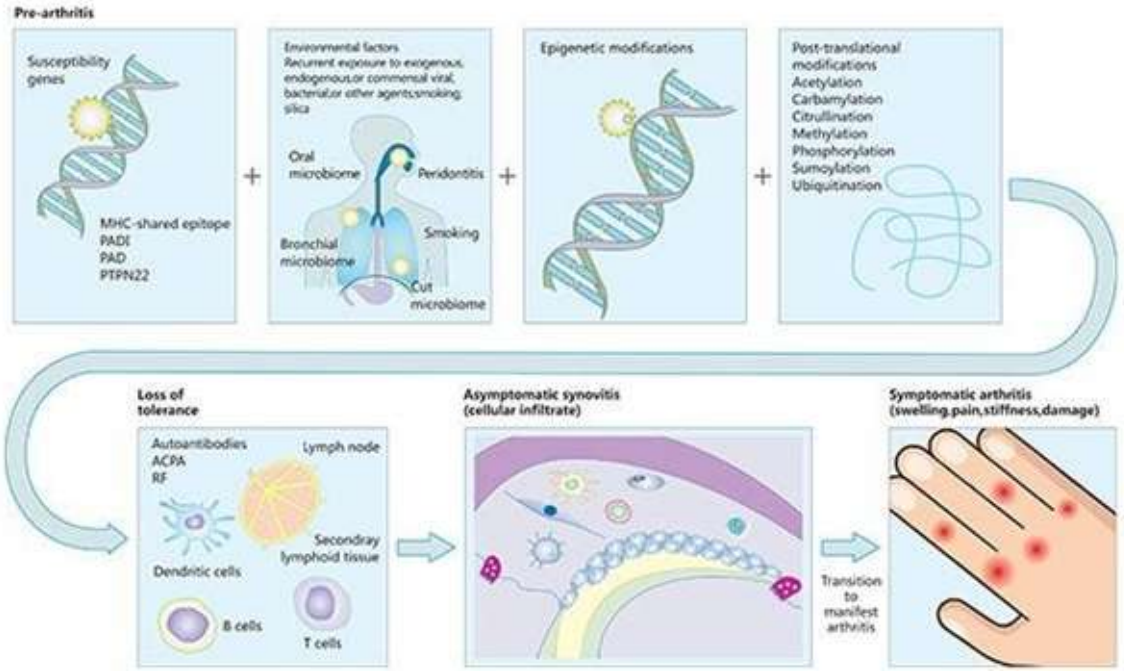

Fig 11 : Schematic diagram of pathways of rheumatoid arthritis
Source: Adapted from CUSABIO.com

ii. COVID19:

- The role of inflammatory cytokines in CRS based on recent studies, it was strikingly shown that the level of inflammatory cytokines is increased inCOVID-19.
- An overview of the literature indicates that IL-6, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IFN- γ, inducible protein (IP)-10, TNF-α, MCP-1, macrophage inflammatory protein (MIP)-1α play a crucial role in the pathogenesis of COVID-19.
- Besides, Liu et al. (2015) evaluated 48 cytokines in the blood plasma of COVID-19 patients. Compared to healthy subjects, 38 out of 48 cytokines were remarkably elevated in patients withCOVID-19.
- In addition, there was a strong linear association between severe lung injury and the level of 15 cytokines including, IFN-γ, IFN-α2, IL-1ra, IL-2, 4, 7, 10, 12, and 17, as well as chemokines such as IP-10, macrophage colony-stimulating factor (M-CSF) and G-

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CSF. The levels of Th1, Th2, and Th17 cells were increased,too.

- With this evidence, a great deal of attention has been paid to dampening signaling pathways of inflammatory cytokines aiming to reduce inflammatory responses and mortality in patients suffering fromCOVID-19.
- According to the literature, cytokines have a key role in regulating immunological and inflammatoryprofiles.
- Among the cytokines, IL-6 is known as a causative factor in the pathogenesis and severity of COVID-19 due to various pleiotropic functions. Therefore, continuous measurement of IL-6 level is suggested in affected subjects with COVID-19. Multiple clinical trials are ongoing to evaluate the benefit of cytokine blockade by corresponding inhibitors. Taken together, we concisely describe inflammatory markers responsible for CRS and possible therapeutic approaches in thisregard.

Cytokine storm :

- The first documented use of the term "cytokine storm," also referred to as hypercytokinemia, appears in a 1993 article discussing graft-versus-host disease. However, since 2000, cytokine storms have been referenced in various infectious diseases, which is why this term is most commonly used to describe an uncontrollable inflammatory response by the immune system.
- In general, acute inflammation begins with five key symptoms including rubor, or redness, tumor, or swelling, calor, or heat, dolor, or pain and function laesa, which translates from Latin into a loss offunction.
- Regardless of where the inflammation occurs, increased blood flow will typically follow these symptoms to allow plasma proteins and leukocytes to reach the sites of injury. Although this cellular response is advantageous for host defense against bacterial infections,they often occur at the expense of local organ function.
- In addition to this normal response to inflammation, a cytokine storm can also occur. During a cytokine storm, various inflammatory cytokines are produced at a much higher rate than normal. This overproduction of cytokines causes positive feedback on other immune cells to occur, which allows for more immune cells to be recruited to the site of injury, that can lead to organdamage.

Treating cytokine storm in COVID-19 :

- Recent research has found that a critical period of 5-7 days exists between the time of COVID-19 diagnosis and multiple organ dysfunction syndrome (MODS). Whereas about 80% of patients tend to improve after this window, about 20% of patients will experience severe pneumonia and approximately 2% will ultimately succumb to thisvirus.
- A huge range of anti-inflammatory therapies are being looked at for treating the cytokine storm in COVID-19. To directly reduce the deleterious effects that the cytokine storm can have on individuals who test positive for COVID-19, researchers have recommended that immunotherapy is administered at the time of cytokine stormdiagnosis.
- Some notable immunotherapeutic strategies that have been proposed for this purpose include neutralizing antibodies, which can be obtained from the plasma of patients who previously survived COVID-19 infection, IFN inhibitors, and oxidized phospholipid (OxPL) inhibitors, and sphingosine-1-phosphate receptors 1 (S1P1)antagonists.
- Further clinical studies must still be performed to fully evaluate the ability of these treatment options to successfully inhibit the cytokine storm induced byCOVID-19.

II. CONCLUSION

In conclusion, cytokines are ubiquitous molecules which act as key messengers for and between immune cells and help to maintain a delicate and intricate balance in the immune system. Cytokines affect nearly every biological process viz. embryonic development, disease pathogenesis, non-specific response to infection, specific response to antigen, changes in cognitive functions and progression of the degenerative processes of aging. They are also involved in stem cell differentiation, vaccine efficacy and allograft rejection. Such regulation of immune homeostasis is crucial for health and disease, and disruption of this balance results in many chronic pathophysiological states. Thus, it is imperative that therapeutic targeting of cytokine pathways holds great promises for patients suffering from several intractable chronic diseases.

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