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Cytokines that Mediate and Regulate Immune Responses

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ABSTRACT

Cytokines are the proteins which stimulate or inhibit the activation, proliferation and differentiation of various target cells up on antigen activation, there by influence the activity of various other cells such as macrophages, mast cells, B-cells, T-cells, Natural Killer (NK) cells involved in the immune response. Redundancy, synergy and pleiotropism are the characteristics of cytokine action and account for the effectiveness of these proteins in regulating immune response. Cytokines that mediate and regulate innate immunity are mainly produced by activated macrophages which includes- Tumor necrosis factor (TNF) and Interleukin(IL)-1 are mediators of acute inflammatory reactions to microbes; IL-12 stimulate production of the macrophage activating cytokine Interferon (IFN)-γ and IL-10 is an inhibitor of macrophages and dendritic cells. Cytokines that mediate and regulate adaptive immune responses are produced mainly by antigen stimulated T lymphocytes, and they include the following: IL-2 is a T cell growth factor and an essential regulator of T cell responses; IL-4 stimulates. Immunoglobulin E production and the development of TH2 cells from naive helper T cells; IL-5 activates eosinophils; IL-13 promotes IgE production, mucus secretion, and tissue fibrosis in the setting of allergic disease; IFN-γ is an activator of macrophages and contributes to differentiation of IFN-γ producing helper T cells; and Transforming growth factor-β inhibits the proliferation of T lymphocytes and the

activation of leukocytes. Cytokines contribute to the specialization of immune responses by activating different types of effector cells. Administration of cytokines is a possible approach for modifying biological effects associated with immune diseases. Hence the cytokines may address as a potential therapeutics in future.

Content: 1. Introduction; 2. Cytokines Nomenclature; 3. General Properties; 4. Function; 5. Cytokine receptor; 6. Cytokine antagonists; 7. Cytokines that mediate and regulate innate immune response (TNF, IL-1, IL-12 & IL-10); 8. Cytokines that mediate and regulate adaptive immune response (IL-2, IL-4, IL-5, IFN-γ, IL-13 & TGF-β).

Keywords: Cytokine; TNF; IL-1; IL-12; IL-10; IL-2; IL-4; IL-5; IL-13; IFN-γ; TGF-β

INTRODUCTION

Cytokines are small glycoproteins produced by a number of cell types, predominantly leukocytes that regulate a number of physiological and pathological functions including innate immunity, acquired immunity and a plethora of inflammatory responses. During the effector phases of natural and acquired immune responses, cytokines are produced from various sources such as immune and inflammatory responses. They often have multiple effects on the same target cell and may induce or inhibit the synthesis and effects of other cytokines. After binding to specific receptors on the cell surface of the target cells, cytokines produce multiple signals which regulate the expression of cytokine receptors and these target cells responds by new mRNA and protein synthesis, which results in a specific biological response [1] (Figure1).

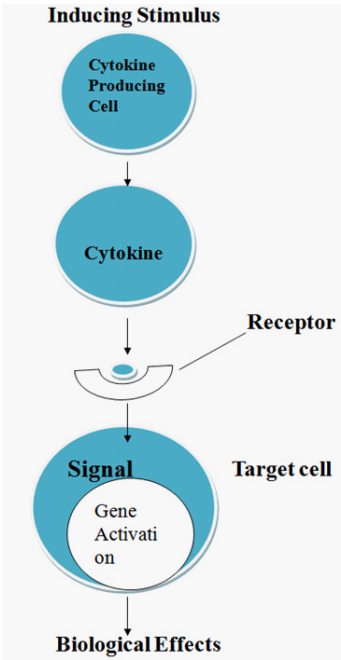

Figure 1: Cytokines leading to biological effects [74].

Cytokines play an essential role in orchestrating normal immune system maturation and in regulating defence against infectious disease [2]. They are produced in response to microbes and other antigens which stimulate diverse responses of cells involved in immunity and inflammation. In the activation phase of adaptive immune responses, cytokines stimulate the growth and differentiation of lymphocytes, and in the effector phases of innate and adaptive immunity, they activate different effector cells to eliminate microbes and other antigens. In clinical medicine, cytokines are important as therapeutic agents and as targets for specific antagonists in numerous immune and inflammatory diseases [3].

CYTOKINES NOMENCLATURE

Most of the cytokines are named according to the Interleukin nomenclature subcommittee of the international union of immunological societies. Although the definition of cytokines is quite broad, but together they can be classified as lymphokines, interleukins, interferons, chemokines etc. depending on their function, cell of secretion, or target of action [4].

General Properties of Cytokines

1. Most cytokines are low molecular weight water soluble polypeptides or glycoprotein (8~80 KD), and mainly they are monomers.

2. Generally they act over short distances and short time spans.

3. They act by binding to specific membrane receptors and induce specific gene expression via a second messenger

4. Cytokines are often produced in a cascade, as one cytokine stimulates its target cells to secrete additional cytokines.

5. Cytokines act on target cells by the way of paracrine, autocrine or endocrine-they can act on the cells that produce them (autocrine), on other cells in the immediate vicinity (paracrine), or on cells at a distance (endocrine) after being carried in blood or tissue fluids (Figure 2).

6. Cytokines initiate their actions by binding to specific membrane receptors on target cells- Receptors for cytokines often bind their ligand with high affinities.

- Low concentration (pmol/L).
- Most cells express low levels of cytokine receptors, and this is adequate for inducing response.
- So only small quantities of cytokines are needed to occupy receptors and elicit biologic effects.

7. The effects of cytokines are often pleiotropism, redundant, synergy, antagonism, and form a cytokine network (Figure 3).

- Pleiotropism refers to the ability of one cytokine having multiple effects on diverse cell types.
- Redundancy refers to the property of multiple cytokines having the same or overlapping functional effects.
- Synergy refers to the property of two or more cytokines having greater than additive effects.
- Antagonism refers to the ability of one cytokine inhibiting the action of another.

8. Cytokines are produced de novo in response to an immune stimulus.

9. Responses to cytokines include increasing or decreasing expression of membrane proteins (including cytokine receptors), proliferation, and secretion of effector molecules.

10. Cytokines are released by many cell populations, but the predominant producers are helper T cells (TH) and macrophages.

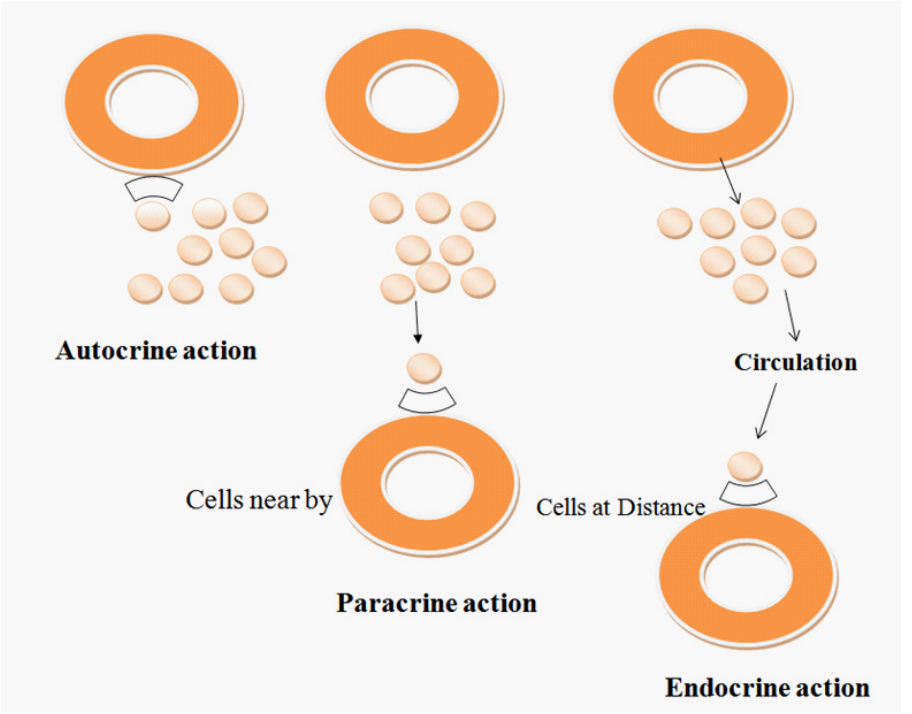

Figure 2: Cytokines action on the target cells [74].

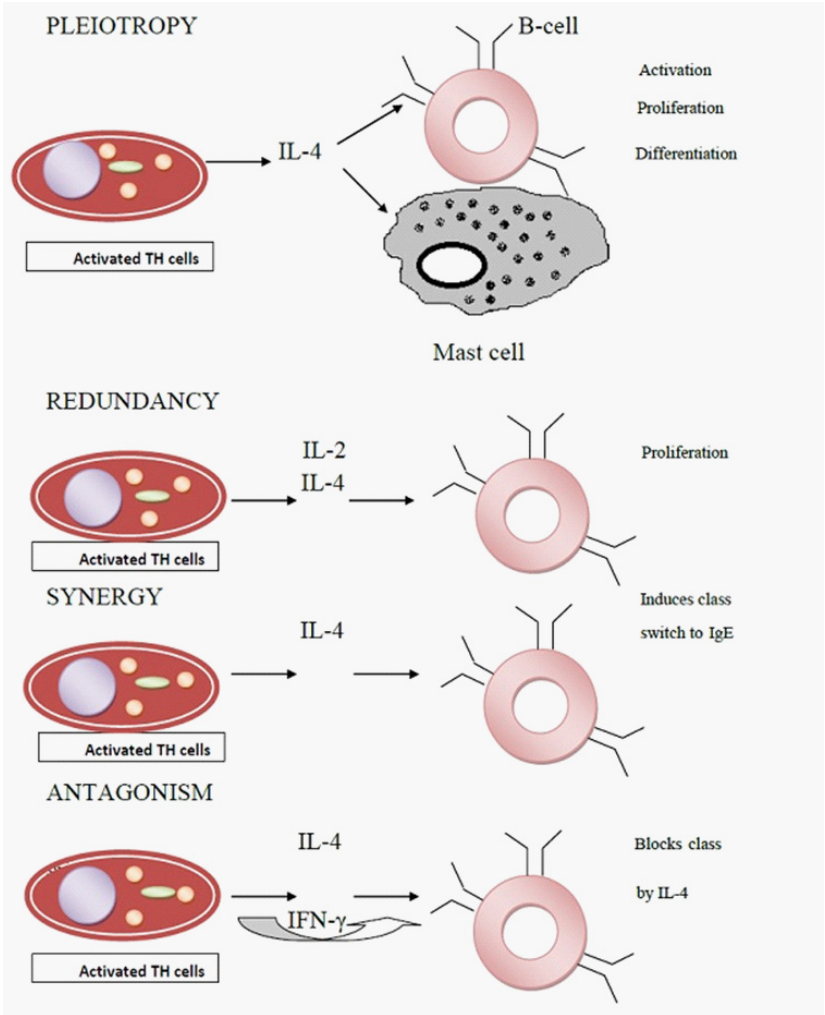

Figure 3: Effects on cytokines [74].

Functions of Cytokines

Cytokines generally function as intercellular messenger molecules that evoke particular biological activities after binding to a receptor on a responsive target cell.

1. The two principal producers that can secrete cytokines are the Th cell and the macrophage (Figure 4).

2. The main biological activities of a number of cytokines include

- Both cellular and humoral immune responses,
- Induction of inflammatory responses,
- Regulation of hematopoiesis,

- Control of cellular proliferation and differentiation,
- Induction of wound healing.

3. Cytokines rarely act alone in vivo. Instead a target cell is exposed to a milieu containing a mixture of cytokines whose combined synergistic or antagonistic effects can have very different consequences.

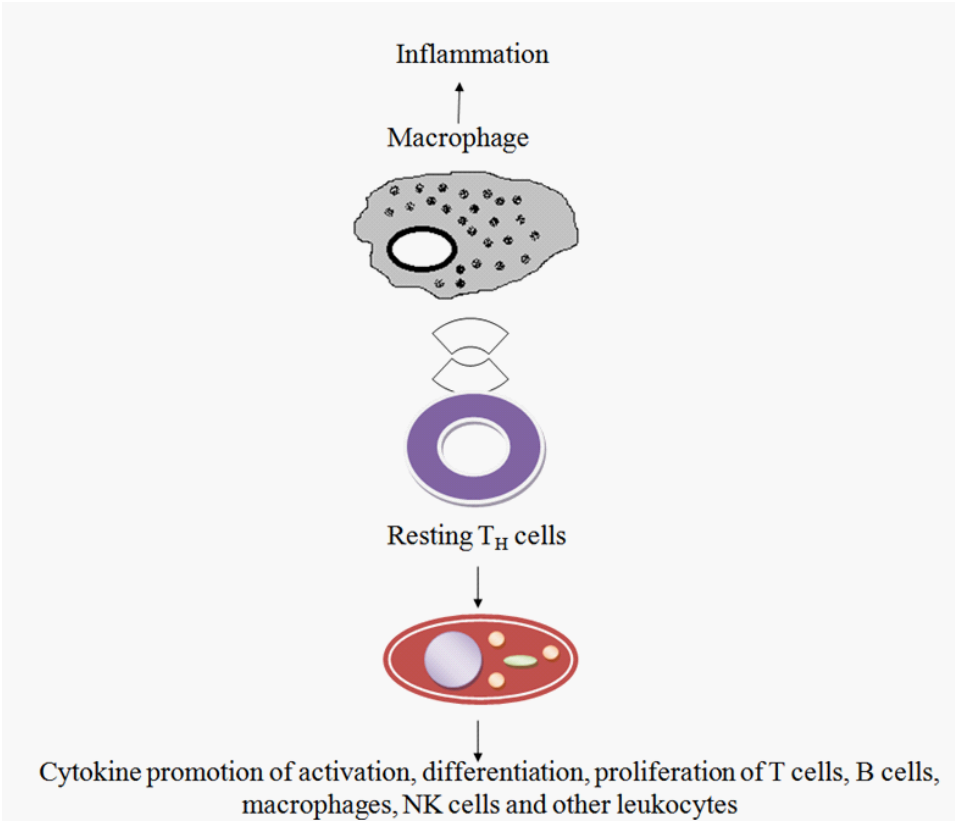

Figure 4: Biological activities of Cytokines. The interaction of antigen with macrophages and the subsequent activation of resting TH cells leads to release of numerous cytokines there by involves in biological activities [74].

4. Cytokines often induce the synthesis of other cytokines resulting in cascades of cytokine activity in which later cytokines may influence the activity of earlier cytokines.

5. Cytokines are nonspecific in their actions, the specificity of an immune response is determined by Ag recognition by B and T cells.

- One way specificity is maintained by careful regulation of the cytokine receptors on cells. Often cytokine receptors are expressed on a cell only after the cell has interacted with Ag. In this way nonspecific cytokine activation is limited to Ag primed lymphocytes.

- Another means of maintaining specificity may be a requirement for cell to cell interaction to generate effective concentrations of a cytokine at the juncture of interacting cells.

- Additionally, the half life of cytokines in the bloodstream or other extracellular fluids into which they are secreted is usually very short, ensuring that they act for only a limited period of time.

Cytokine Receptors

Cytokines exert their biological effects through specific receptors expressed on the membrane of responsive target cells.

- These receptors are expressed by many cell types as cytokines can affect a diverse array of cells.

- Biochemical characterization of cytokine receptors initially progressed at a very slow rate because of their low concentration on the cell membrane.

- Cloning of the genes encoding cytokine receptors has led to rapid advances in the identification and characterization of these receptors.

- All cytokine receptors have at least one extracellular domain, a membrane spanning domain, and a cytoplasmic tail.

There are 5 families of receptor proteins (Figure 5)

1. Immunoglobulin (Ig) superfamily receptors- Interleukin (IL)-1, Macrophage colony stimulating factor (M-CSF).

2. Hematopoietin receptor family (class I cytokine receptor family) - IL-2,4,13,15, Granulocyte Macrophage colony stimulating factor (GM-CSF), Granulocyte colony stimulating factor (G-CSF).

3. Interferon receptor family (class II cytokine receptor family)-Interferon – γ.

4. Tumour Necrosis factor (TNF) receptor family – TNF-α, β, Fas, Cluster Differentiation (CD) 40, Nerve growth factor.

5. Chemokine receptor family -IL8, Regulated on Activation Normal T cell expressed and secreted (Rantes), Macrophage inflammatory protein (MIP)-1, Platelet Factor.

6. (PF)-4, Monocyte chemotactic and activating Factor (MCAF), Neutrophil activating protein (NAP).

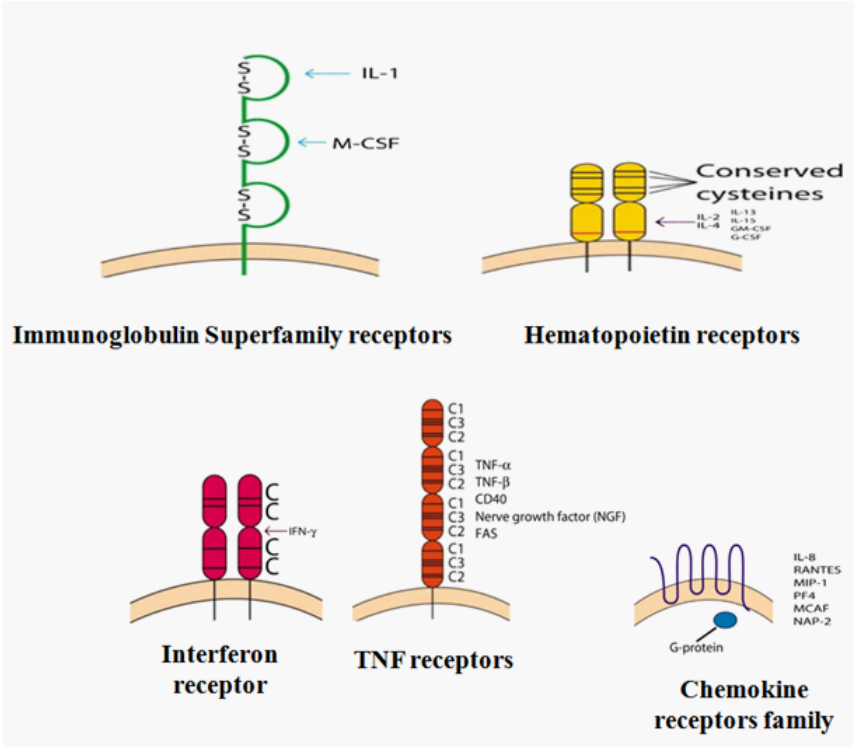

Figure 5: Receptor Families [74].

Many cytokine receptors have 2-3 polypeptide chains: An α chain which is cytokine specific and a (non-cytokine specific) β chain which is the signal transducing subunit.

Cytokine Antagonists

- A number of proteins that inhibit the biological activity of cytokines have been identified. These proteins can act in either of two ways:

(1) They bind directly to a cytokine receptor but fail to activate the cell or

(2) They bind directly to the cytokine inhibiting its activity.

- The best characterized inhibitor is the IL-1 R antagonist IL-1Rα which binds to the IL-1 receptor has no activity but blocks binding of IL-1. Production of IL-1Rα appears to play a role in regulating the intensity of the inflammatory response.

- A second group of cytokine inhibitors are soluble cytokine receptors that are able to bind to the cytokine and neutralize its activity. Enzymatic cleavage of the extracellular domain of the receptor releases a fragment that retains its cytokine binding capabilities.

Table 1: Cytokines of immune responses.

Cytokines of Innate immunity		
Cytokines	**Source**	**Biologic effects**
Tumor necrosis factor (TNF)	Macrophages, T cells	Cell destruction, Activation of endothelial cells, T cell proliferation
Interleukin-1 (IL-1)	Macrophages, Dendritic cells	Endothelial cells activation, endogenous pyrogen (rise in body temperature)
Interleukin-12 (IL-12)	Macrophages, dendritic cells	Th1 differentiation, NK cell activation, IFN-γ synthesis, Cytotoxic activity
Interleukin-10 (IL-10)	Macrophages, T cells	Inhibition of Th1 cytokines, costimulator of the proliferation of mast cells with IL-4
Cytokines of Adaptive immunity		
Interleukin-2 (IL-2)	T cells	T cell proliferation, NK cell activation and proliferation, B-cell proliferation
Interleukin-4 (IL-4)	CD4+T cells, mast cells	Promotes CD4+ differentiation, isotype switch to IgE
Interleukin-5 (IL-5)	CD4+ T cells	Eosinophil activation and generation
Interferon (IFN)	T cells, NK cells	Activates macrophages, increases expression of MHC class I and Class II molecules; increases antigen presentation
Interleukin-13 (IL-13)	CD4+ T cells	B-cells isotype switching to IgE
Transforming growth factor (TGF-β)	T cells, Macrophages	Inhibits Tcell proliferation and effector functions; inhibits B cell proliferation; promotes isotype switch to IgE; inhibits macrophages

Th1: T-helper 1 cells; NK: Natural killer; IFN-γ: Interferon-γ; IgE: Immunoglobulin E.

CYTOKINES THAT MEDIATE AND REGULATE INNATE IMMUNE RESPONSES

Tumor Necrosis Factor (TNF)

TNF (17kDa) super family of cytokines located at 6p21.33 represents a multifunctional proinflammatory cytokine which activate signalling pathways for cell survival, apoptosis, inflammatory responses and cellular differentiation. It is mainly secreted by macrophages, lymphoid cells, mast cells, fibroblasts and can induce cell death of certain tumor cell lines [5]. It is potent pyrogen causing fever by direct action or by stimulation of interleukin-1 secretion and is implicated in the induction of cachexia, under certain conditions it can stimulate cell proliferation and induce cell differentiation [6]. TNF is produced upon activation by the immune system, able to exert significant cytotoxicity on many tumor cell lines and to cause tumor necrosis in certain animal model systems [7]. The two molecular species of TNF are known as TNF-α and TNF-β which are stimulated by interferons.

TNF receptors

The members of the TNF ligand family exert their biological functions via interaction with their cognate membrane receptors, comprising the TNF receptor (TNF-R) family [8]. The members of TNF–R family contains two receptors TNF-R1 (TNF receptor type 1; CD120a; p55/60) and TNF-R2 (TNF receptor type 2; CD120b; p75/80) bind not only to membrane-integrated TNF (mem TNF) and soluble TNF (sTNF) but also the secreted homotrimeric molecule lymphotoxin-α

(LTα) [9]. TNF-R1 is constitutively expressed in most tissues, whereas expression of TNF-R2 is highly regulated and is typically found in cells of the immune system. In the vast majority of cells, TNF-R1 appears to be the key mediator of TNF signalling, whereas in the lymphoid system TNF-R2 seems to play a major role [10]. TNFR1 is activated in most human tissues by the binding of TNFα and TNFR2 is primarily expressed in immune cells and is activated by both TNFα and TNFβ. TNFα elicits its pro-inflammatory signals by initially binding to receptors, TNFR1 (p55) and TNFR2 (p75) on the cell surface. Activation by TNFα results in the trimerization of the TNFR1 receptor and association of death domains located on the cytoplasmic region of the TNFR1 protein [11].

Biological action

- TNF is found predominantly on monocytes and T-cells after cell activation which is also biologically active and mediates cell destruction by direct cell to cell contacts [12].

- *In vivo* TNF in combination with IL-1 is responsible for many alterations of the endothelium which inhibits anticoagulatory mechanisms and promotes thrombotic processes and therefore plays an important role in pathological processes such as venous thromboses, arteriosclerosis and vasculitis [13].

- TNF is a potent promoter of angiogenesis *in vivo* where as it inhibits the growth of endothelial cells *in vitro*. The angiogenic activity of TNF is significantly inhibited by IFN-γ [14].

- TNF is a growth factor for normal human fibroblasts, promotes the synthesis of collagenase and prostaglandin E_2 which functions as an autocrine growth modulator for human chronic lymphocytic leukemia cells *in vivo* and has been described to be an autocrine growth modulator for neuroblastoma cells in which the autocrine growth promoting activity is inhibited by IL-4 [15].

- TNF enhances the proliferation of T-cells induced by various stimuli in the absence of IL-2 where as in the presence of IL-2, it promotes the proliferation and differentiation of B-cells [16].

- TNF mediates part of the cell mediated immunity against obligate and facultative bacteria and parasites [17].

- TNF-α has been shown to protect hematopoietic progenitors against irradiation and cytotoxic agents, suggesting that it may have some potential therapeutic applications in aplasia induced by chemotherapy or bone marrow transplantation [18].

Interleukin-1 (IL-1)

IL-1 (17kDa) is an important inflammatory cytokine located at 2q13 mainly produced by tissue macrophages, monocytes, fibroblasts and dendritic cells, but it is also expressed by B lymphocytes, NK cells and epithelial cells. It increases the expression of adhesion factors on endothelial cells to enable transmigration of immunocompetent cells, such as phagocytes and lymphocytes to the

site of infection. They also affect the activity of the hypothalamus, the thermoregulatory center, which leads to a rise in body temperature by which IL-1 is called an endogenous pyrogen. Besides fever, IL-1 also causes hyperalgesia (increased pain sensitivity), vasodilatation and hypotension [19]. IL-1 shows two functionally almost equivalent forms of IL1-α and IL1-β that are encoded by two different genes where IL1-β is the predominant form in humans while it is IL1-α in mice [20].

IL-1 receptors

Interleukin-1 receptor (IL-1R) consists of type I and type II receptors. The type I receptor is

primarily responsible for transmitting the inflammatory effects of IL-1 while type II receptors acts as a suppressor of IL-1 activity by competing for IL-1 binding. The IL-1 receptor accessory protein (IL1RAP) is a transmembrane protein that interacts with IL-1R and is required for IL-1 signal transduction [21].

Biologic action

- The main biological activity of IL-1 is the stimulation of T-helper cells which are induced to secrete IL-2 and to express IL-2 receptors. Virus-infected macrophages produce large amounts of an IL-1 inhibitor that may support opportunistic infections and transformation of cells in patients with T-cell maturation defects.

- It acts directly on B-cells, promoting their proliferation and the synthesis of immunoglobulins and also functions as one of the priming factors that makes B-cells responsive to IL-5 [22].

- It stimulates the proliferation and activation of NK-cells, fibroblasts, thymocytes and glioblastoma cells. The IL-1 mediated proliferation of lymphocytes is inhibited by TGF-β1 and TGF-β2.

- IL-1causes many alterations of endothelial functions in vivo. It promotes thrombotic processes and attenuates anticoagulatory mechanisms.

- It also influences the functional activities of Langerhans cells of the skin which are not capable of eliciting primary immune responses which convert these cells into potent immunostimulatory dendritic cells. The Langerhans cells therefore constitute an in situ reservoir for immunologically immature lymphoid dendritic cells. The increased ability of maturated Langerhans cells to process antigens is decreased by TNF-α [23].

- IL-1 in combination with other cytokines is an important mediator of inflammatory reactions.

- It is also a strong chemoattractant for leukocytes which leads to the local accumulation of neutrophils at the site of injection in vivo and also activates oxidative metabolism in neutrophils.

Interleukin-12 (IL-12)

IL-12 (70kDa) is a heterodimeric pro-inflammatory cytokine composed of two covalently-linked subunits, IL-12p35 (35 kDa) and IL-12p40 (40 kDa) which are expressed on 3q25.33 and 5q33.3 chromosomes. It is an important immunoregulatory cytokine mainly produced by antigen-presenting cells. The sequence of the p35 gene is homologous to that of IL-6 and granulocyte-colony stimulating factor whereas the sequence of the p40 chain has a homology to the extracellular domain of the IL-6 receptor (IL-6R) α-chain and the ciliary neurotropic factor which explains some of the redundant actions of these cytokines [24,25]. Although p35 transcripts are found in many cell types, free p35 is not secreted without the p40 subunit. IL-12p40 is produced predominantly by activated monocytes, macrophages, neutrophils and dendritic cells and has been shown to act as a chemoattractant for macrophages and promotes the migration of stimulated dendritic cells. The p40 subunit is associated with several pathogenic inflammatory responses such as silicosis, graft rejection and asthma, but it is also found to be protective in a mycobacterial infection model [26]. IL-12 has multiple biological functions and importantly, it bridges the early nonspecific innate resistance and the subsequent antigen-specific adaptive immunity [27].

IL-12 receptors

IL-12 binds to a membrane receptor complex composed of two subunits: IL-12R β1 and IL-12R β2, which are members of the class I cytokine receptor family including IL-6, IL-11 and leukocyte inhibitory factor related to glycoprotein gp130 [28]. IL-12R β1 is required for high-affinity binding to the IL-12p40 subunit and it is associated with the Janus kinase (Jak) family member tyrosine kinase (Tyk-2), while the IL-12R β2 chain mediates signal transduction via three tyrosine residues that act as a docking site for STAT4 and is associated with Jak-2. IL-12R β2 recognizes either the heterodimer IL-12 or the IL-12p35 subunit and is expressed at low levels after T cell receptor stimulation. Expression of this receptor subunit is critically influenced by IL-12 and IFN-γ. The initial expression of functional IL-12 receptors is further enhanced when IL-12 is present at the time of priming, working as a positive feedback loop regulator [29].

Biological action

- IL-12 is produced mainly by dendritic cells, Macrophages and to a lesser extent by human B cells but not murine B cells following CD40 ligation [30].

- Non-immune cells such as infected-keratinocytes and osteoblasts, epithelial and endothelial cells have also been shown to produce some amounts of IL-12 [31].

- Pathogen associated molecular patterns such as lipopolysaccharide (LPS), teichoic acid, peptidoglycan, and bacterial CpG DNA, can induce IL-12 production.

- The production of IL-12 is regulated by positive and negative feedback mechanisms involving Th1 cytokines (e.g., IFN-γ), Th2 cytokines (e.g., IL-10) and type 1 IFN [32].

- It induces differentiation of naive CD4+ T cells to Th1 cells and activates NK cells. Upon activation, these cells produce IFN-γ and other type-1 cytokines [33].

- It also protects CD4+ Th1 cells from antigen-induced apoptotic death [34].

- It plays a role in T cell trafficking and migration by inducing functional adhesion molecules such as P- and E-selectin ligand expression on Th1 cells but not Th2 cells; therefore, these cells are selectively recruited to sites where Th1 immune responses are needed [35].

- Stimulation of macrophages derived IL-12 also plays a major role in the induction of resistance in parasitic infestation [36].

- The biological activity and quantity of IL-12 can be determined using molecular approaches based on IL-12-induced proliferation of phyto heagglutinin (PHA) stimulated lymphocytes and also on the ability of IL-12 to induce IFN-γ secretion from activated T-lymphoblast [37] (Figure 6).

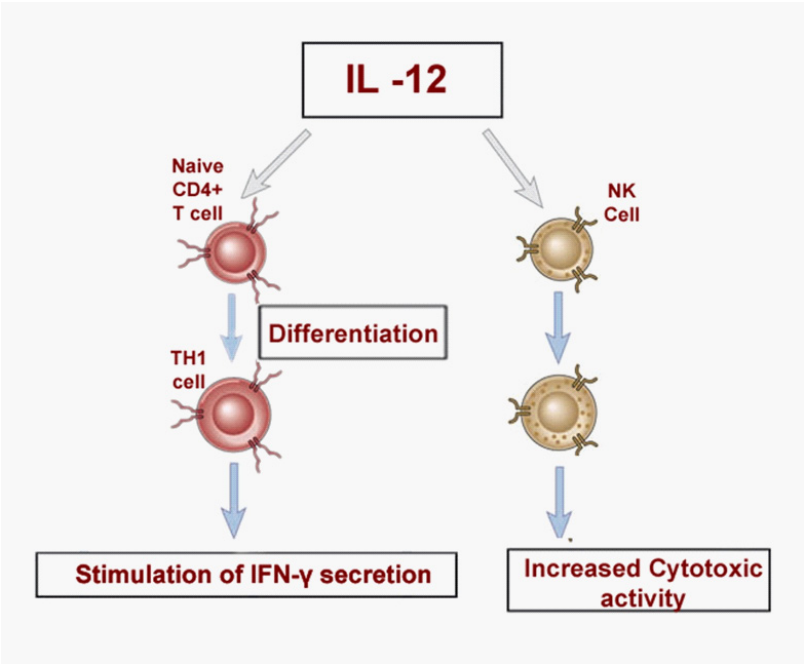

Figure 6: Biological effects of IL-12: IL-12 acts on T lymphocytes and NK cells to stimulate IFN-γ production and cytotoxic activity [75].

Interleukin-10 (IL-10)

IL-10(37kDa) is a pleiotropic, immunoregulatory cytokine located at 1q32.1 that protects from infection-associated immunopathology, autoimmunity and allergy. IL-10 was initially named as a cytokine-synthesis inhibitory factor. It can also act as an immunosuppressive cytokine where it suppresses the production of IFN-γ, IL-2 and other pro inflammatory cytokines [38,39]. It can be expressed by both innate and adaptive immune cells which include dendritic cells (DC),

macrophages, mast cells, natural killer cells (NK), eosinophils, neutrophils, B cells, CD8+ T cells, TH1, TH2 and TH17 CD4+ T cells [40].

IL-10 receptor

Functional IL-10 receptor complex is a tetramer consisting of two identical ligand binding subunits (IL10R1) induced on stimulated hematopoietic cells and two identical accessory signalling subunits (IL10R2) expressed on most cells and tissues [41]. These receptor subunits transduce signals through the Tyk2 ending in tyrosine phosphorylation and activation of STAT3 and STAT1. However, the genetic and biochemical evidence implicates STAT3 as the only STAT required to generate the IL-10 inhibitory signal [42,43].

Biological action

- IL-10 inhibits the synthesis of Th1 but not of Th2 cytokines, antagonized by IL-4 and was shown to be a physiologic antagonist of IL-12 [44].

- It inhibits the secretion of TNF *in vivo* and protects against the lethality of endotoxin in a murine model of septic shock, if administered before challenging the mice with bacterial lipopolysaccharides [45].

- It inhibits secretion of Immunoglobulins by T-cell independent antigens induced by IL-5 but not that induced by IL-2 [46].

- It acts as a co stimulator of the proliferation of mast cells and peripheral lymphocytes combination with IL-4, which has the same growth-promoting effects as IL-3 alone. Optimal growth of mast cells is achieved by a combination of IL-3, IL-4 and IL-10. Therefore, IL-10 probably plays a role in the development of mastocytosis frequently observed after parasitic infections by potentiating the effects of IL-3 and IL-4.

- It also acts as co stimulator for the growth of mature and immature thymocytes and functions as a cytotoxic T-cell differentiation factor, promoting a higher number of IL-2 activated precursors of cytotoxic T-lymphocytes to proliferate and differentiate into cytotoxic effector cells [47].

- IL-10 sustains viability of B-cells *in vitro* and also stimulates B-cells and promotes their differentiation. It enhances the expression of MHC class II antigens on B-cells whereas it inhibits MHC class II expression on monocytes [48].

- IL-10 induces the secretion of IgG, IgA and IgM in B-cells activated through their antigen receptors which is synergised by IL-4, while the synthesis of immunoglobulins induced by IL-10 which is antagonized by TGF-β [46].

- Human IL-10 is a potent and specific chemoattractant for T-lymphocyte which is directed towards cells expressing CD8 and not towards CD4 + cells.

CYTOKINES THAT MEDIATE AND REGULATE ADAPTIVE IMMUNE RESPONSES

Interleukin-2 (IL-2)

IL-2 (15kDa) is a single polypeptide chain of 133 amino acid residues located at 4q27. When T helper cells immune regulatory binds to an APC (Antigen presenting cells), it is produced by CD4+ cells. It supports the proliferation and differentiation of any cell that has high-affinity towards its receptors and it is necessary for the activation of T cells. Resting T lymphocytes belonging to either the CD4+ or the CD8+ subsets possess few high-affinity IL-2 receptors, but stimulation with specific antigen, there is a substantial increase. The binding of IL-2 with its receptors on T cells induces their proliferation and differentiation and also releases other cytokines. L-2 is required for the generation of CD8+ cytolytic T cells, which are important in antiviral responses. It increases the effector function of NK cells. It enhances the ability of the immune system to kill tumor cells and may also interfere with the blood flow to the tumors. It not only induces lymphoid growth but also maintains peripheral tolerance by generation of regulatory T cells. IL-2 knockout mice produce a wide range of auto antibodies and many die of autoimmune haemolytic anaemia, which suggests that it plays a role in immune tolerance [1].

IL-2 receptors

IL-2 binds to and signals through a receptor complex consisting of three distinct subunits designated as IL-2Rα (CD25), IL-2Rβ (CD122), and common γ -chain (CD132). All three subunits are required for high-affinity binding to IL-2 where in the absence of IL-2 Rα expression, IL-2Rβ and γc can form an intermediate affinity receptor which is competent to signal, appears to be the only physiologically relevant form of the IL-2R. IL-2 with closely related cytokine IL-15, signals through the β and γc subunits of the IL-2R but utilizes a unique IL-15Rα chain instead of CD25 there by both cytokines generate identical intracellular signals. The signal transduction pathways shared between IL-2R and IL-15R might imply that they have similar functions and responses such as induction of T-cell proliferation, involvement in the differentiation of cytotoxic T lymphocytes, generation, activation and persistence of natural killer cells as well as stimulation of B-cell proliferation and immunoglobulin synthesis. Nevertheless, the cytokines have distinct in vivo properties, most likely due to different expression patterns of the cytokines and their respective α receptor subunits [49].

Biological action

- IL-2 is an antigen-unspecific proliferation factor for T-cells that induces cell cycle progression in resting cells and thus allows clonal expansion (Figure 6) of activated T-lymphocytes which is modulated by hormones such as Prolactin [50].
- The p55 receptor subunit is expressed in adult T-cell leukaemia (ATL), while freshly

isolated leukemic cells also secrete IL-2 and respond to it. IL-2 may also function as an autocrine growth modulator for these cells capable of worsening ATL.

- It also promotes the proliferation of activated B-cells in presence of additional factors, such as IL-4.

- Due to its effects on T-cells and B-cells, IL-2 is a central regulator of immune responses which plays a role in anti-inflammatory reactions and also in tumor surveillance.

- The induction of the secretion of tumoricidal cytokines apart from the activity in the expansion of LAK cells (lymphokine-activated Killer cells) are probably the main factors responsible for the antitumor activity.

A dimeric form of human IL-2, produced by the action of a transglutaminase isolated from regenerating fish optic nerves, has been shown to be a cytotoxic factor for rat brain oligidendrocytes in culture. It has been suggested that dimerization of IL-2 may provide a mechanism to permit nerve growth under the conditions in which oligodendrocytes inhibit neuronal regeneration [51].

IL-2 has additional effects on other components of the cellular immune system, including B-cells, macrophages and induces the secretion of other soluble mediators, including TNF-α, TNF-β and IFN-γ which contributes to the antitumor activity of IL-2 as well as to its dose-related toxicity.

Cellular immunodeficiency diseases, those with impaired IL-2 production are successfully treated by daily injections of human IL-2 (hIL-2).

IL-2 is also effective in some of the patients with antibody deficiency, probably which is caused by the lack of T-cell help for B-cells [52].

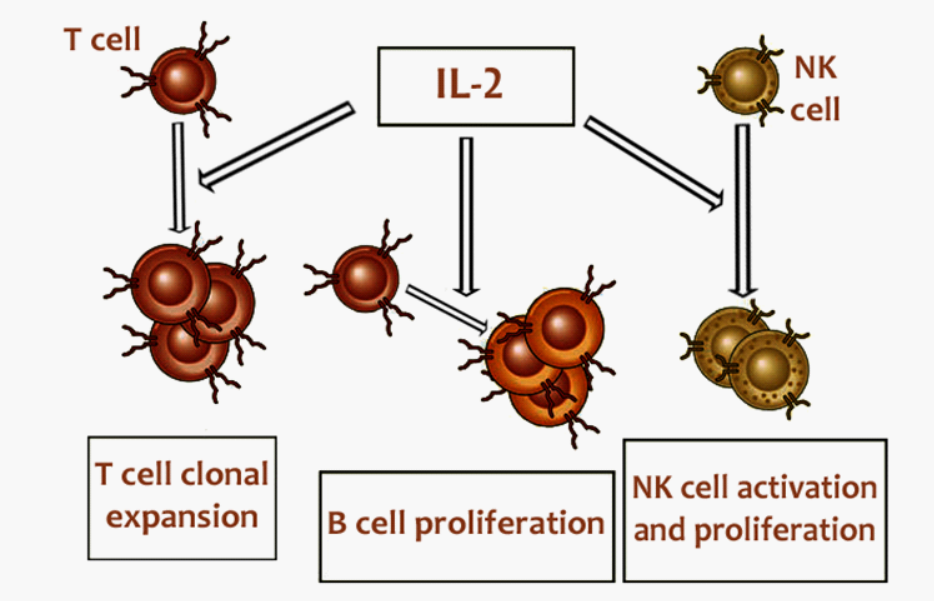

Figure 7: Biological effects of IL-2: IL-2 stimulates the proliferation of B cells, Clonal expansion of T cells and activation of NK cells [75].

Interleukin-4

IL-4 (18kDa) is a pleiotropic cytokine of 129 amino acids located at 5q31.1 produced by TH2 cells, mast cells and NK cells, some specialized subsets of T cells, basophils and eosinophils. It regulates the differentiation of antigen-activated naive T cells and then develop to produce other TH2 type cytokines including IL-5, IL-10 and IL-13. IL-4 suppresses the production of TH1 cells. It is required for the production of IgE and is the principal cytokine that causes isotype switching of B cells from IgG expression to IgE (Figure 8). As a result, it regulates allergic disease. It leads to a protective immunity against helminths and other extracellular parasites. It mediates its effects via specific IL-4 receptors that are expressed on a number of tissues including hematopoietic cells, endothelium, hepatocytes, epithelial cells, fibroblasts, neurons and muscles [1].

IL-4 receptors

IL-4 receptor consists of an α chain that binds IL-4 with high affinity. Although artificial homodimerization of the IL-4Rα chain can result in the generation of biochemical signals within the cell, physiologic signalling depends upon IL-4-mediated hetero dimerization of the IL-4Rα chain with a second chain [53].The gamma common chain (γ c), first identified as a component of the IL-2 receptor, appears to be the dominant chain involved in this heterodimerization in many cell types [54]. Molecular binding studies have indicated that γ c chain recognises a complex of IL- 4 and IL-4 Rα chain. Although the γ c chain only moderately increases the observed affinity of the IL-4R complex for IL-4, it is required for the activation of signalling pathways [55].

Biologic action

- IL-4 is probably an autocrine growth modulator for Hodgkin's lymphomas [56].
- It enhances expression of MHC class II antigens on B-cells and promote their capacity to respond to other B-cell stimuli to present antigens for T-cells. This may be one way to promote clonal expansion of the immune system [57].
- It is important in the treatment of inflammatory diseases and autoimmune diseases since it inhibits the production of IL-1, IL-6 and TNF-α by monocytes [58].
- It plays an essential role in the pathogenesis of chronic lymphocytic leukemia disease, which is characterized by the accumulation of slow-dividing and long-lived monoclonal B-cells arrested at the intermediate stage of their differentiation by preventing both the death and the proliferation of the malignant B-cells [59] (Figure7).

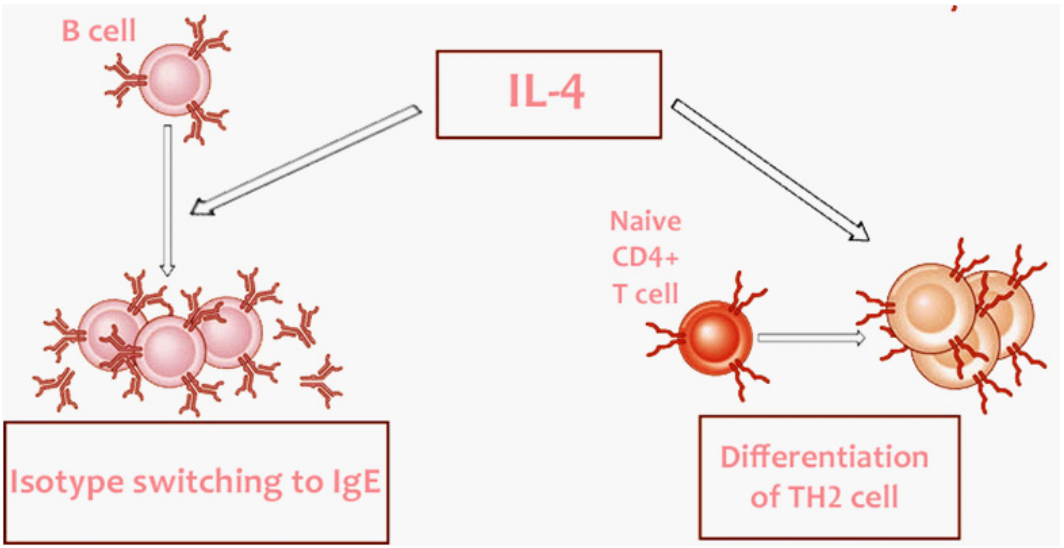

Figure 8: Biologic actions of IL-4. IL-4 stimulates B cell isotype switching to IgE and differentiation of naive T cells to the TH2 subset [75].

Interleukin-5

IL-5 (45-50kDa) located at 5q31.1 is secreted predominantly by TH2 lymphocytes and also found in mast cells and eosinophils which regulates the growth, differentiation, activation and survival of eosinophils. It contributes to eosinophil migration, tissue localization and its function, blocks their apoptosis. Eosinophils play an important role in the pathogenesis of allergic disease and asthma and in the defense against helminths and arthropods.

IL-5 receptors

The IL-5 receptor is a heterodimer of α and β subunits. The α subunit is specific, whereas the

β subunit is common to IL-3, IL-5, and granulocyte/macrophage colony-stimulating factor (GM-CSF) receptors and is crucial for signal transduction [1].

Biologic action

- IL-5 stimulates proliferation and differentiation of antigen-induced B lymphocytes and the production of IgA.

- TH2 cytokines like IL-4 and IL-5 play a central role in the induction of airway eosinophilia and air way hyperresponsiveness (AHR). It is a main player in inducing and sustaining the eosinophilic airway inflammation.

- During the disease state in humans, number of eosinophils are elevated where high levels of IL-5 and its mRNA can be found in the circulation, tissue and bone marrow. For disease of the respiratory tract, hematopoietic system, gut, skin and allergic or nonallergic respiratory diseases.

- Another way of interfering with IL-5 or IL-5R synthesis is by the use of antisense oligonucleotides which results in the inhibition of the transcription and processing of mRNA. The administration of IL-5-specific antisense oligonucleotides results in reduced lung eosinophilia in animal models. However, there is no complete inhibition of antigen-specific late-phase AHR, suggesting that in addition to IL-5, other pathways may also be involved in airway hyperreactivity [1].

Interferon-γ

IFN-γ (50kDa) located at 12q15 modulates a number of components of the immune response and is produced by activated T lymphocytes (TH1 and CD8+ cells), NK cells, B cells, NKT cells and professional APCs. The cell self-activation and activation of nearby cells in part may result from IFN-γ production by professional APCs, which include monocyte/macrophage and dendritic cells. The early host defense against infection is likely to utilize IFN-γ secreted by NK and professional APCs. IFN-γ is a potent activator of mononuclear phagocytes. The expression of both MHC class I and class II molecules is augmented by IFN-γ as it induces upregulation of MHC class I molecules which have a pivotal role for host defense against intracellular pathogens, resulting in to an increased susceptibility to cytolytic T cells for recognition and consequent promotion of cell-mediated immune response (Figure 9). IFN-γ is an inhibitor of cell growth, proliferation and also induces the costimulatory molecules on the macrophages, which increases cell-mediated immunity. As a consequence, there is activation and increase in the tumoricidal and antimicrobial activity of mononuclear phagocytes, granulocytes and NK cells. The activation of neutrophils by IFN-γ includes an increase in their respiratory burst. IFN-γ stimulates the cytolytic activity of NK cells. It is an activator of vascular endothelial cells, promoting CD4+ T lymphocyte adhesion and morphological alterations, which facilitates lymphocyte extravasation. IFN-γ promotes opsonization by stimulating the production of IgG subclasses that activate the complement pathway [1].

IFN-γ receptors

Functional IFN-γ receptor (IFNγR) is comprised of two ligand-binding IFNγR1 chains associated with two signal-transducing IFNγR2 chains and associated signaling machinery. IFNγR1 and IFNγR2 chains form a small angle of V structure when bind ligand by two IgG like folds that constitutes extracellular domain. IFNγR1 chain usually an additional where as IFNγR2 chain is the limiting factor in IFN-γ responsiveness which is constitutively expressed but its expression levels regulated according to the state of cellular differentiation or activation. IFN-γ effects the CD8+T-cell and B-cell adaptive immune response which extend from a profound regulatory role in stimulating the proliferation, activation and generation of existing memory CD8+cytotoxic T cells (CTLs) to the stimulation of lymphocyte activated killer (LAK) activity [60].

Biologic action

- IFN-γ has antiviral and antiparasitic activities and also inhibits the proliferation of a number of normal and transformed cells. IFN-γ synergises with TNF-α and TNF-β in inhibiting the proliferation of various cell types. The growth inhibitory activities of IFN-γ are more pronounced than those of the other interferons. However, the main biological activity of IFN-γ appears to be immunomodulatory in contrast to the other interferons that are mainly antiviral.

- In T-helper cells, IL-2 induces the synthesis of IFN-γ and other cytokines. IFN-γ acts synergistically with IL-1 and IL-2 and appears to be required for the expression of IL-2 receptors on the cell surface of T-lymphocytes. Blocking of the IL-2 receptor by specific antibodies also inhibits the synthesis of IFN-γ and thus influences cell mediated mechanisms of cytotoxicity.

- IFN-γ is a modulator of T cell growth and functional differentiation. It is a growth-promoting factor for T-lymphocytes and potentiates the response of these cells to mitogens or growth factors.

- IFN-γ regulates the expression of MHC class II genes and is the only interferon that stimulates the expression of these proteins.

- IFN-γ also stimulates the expression of Ia antigens on the cell surface, the expression of CD4 in T-helper cells, and the expression of high-affinity receptors for IgG in myeloid cell lines, neutrophils and monocytes. In monocytes and macrophages IFN-γ induces the secretion of TNF-α and the transcription of genes encoding G-CSF and M-CSF. In macrophages IFN-γ stimulates the release of reactive oxygen species. It is also involved in processes of bone growth and inhibits bone resorption probably by partial inhibition of the formation of osteoclasts.

- IFN-γ inhibits the proliferation of smooth muscle cells of the arterial intima *in vitro* and *in vivo* and therefore probably functions as an endogenous inhibitor for vascular overreactions such as stenosis following injuries of arteries.

- IFN-γ inhibits the proliferation of endothelial cells and the synthesis of collagens by

myofibroblasts. It thus functions as an inhibitor of capillary growth mediated by myofibroblasts and fibroblast growth factors.

- IFN-γ specifically induces the transcription of a number of genes. These genes contain regulatory DNA sequences within their promoter regions Interferon-stimulated response element (ISRE), Interferon response element (IRS) that function as binding sites for a number of transcription factors and which are also expressed in response to other interferons.

- IFN-γ may be used in the treatment of opportunistic infections in AIDS patients. It has also been shown to reduce inflammation, clinical symptoms and eosinophilia in severe atopic dermatitis [61-64].

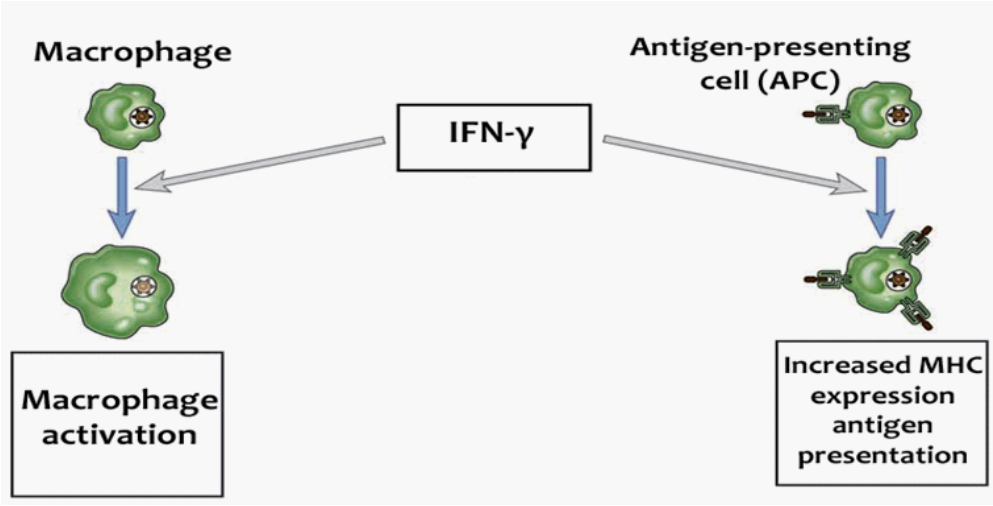

Figure 9: Biologic actions of IFN-γ. FN-γ activates macrophages and APCs for activation and increased MHC expression [75].

Interleukin-13

IL-13 (15kDa) belongs to the same α-helix superfamily as IL-4, and their genes are located 12 kb apart on chromosome 5q31.1. It was originally identified for its effects on B cells and monocytes, which included isotype switching from IgG to IgE, inhibition of inflammatory cytokines and enhancement of MHC class II expression. Initially, IL-13 appeared similar to IL-4 until its unique effector functions were recognized. Nevertheless, IL-13 and IL-4 have a number of overlapping effects [1].

IL-13 receptors

For signal transduction, IL-13 require the receptor subunit, IL-4Rα, a heterodimeric receptor complex organises through signalling molecules associated with its large intracellular domain. Signalling is initiated by recruiting and binding of the ligand to a second receptor subunit, which can be either γc (type 1receptor) or IL-13Rα1 (type 2 receptor). Type 1 receptor complexes can be formed only by IL-4, not by IL-13 responsible for signalling in T-cells, which do not express

functional IL-13Rα1. Type 2 receptor complexes can be formed by either IL-4 or IL-13 and are activated by both ligands. A difference between the two ligands is that IL-4 contacts first IL-4Rα and then IL-13Rα1, a sequence of events which is reversed for IL-13. However, the resulting dimeric receptor subunit assembly is identical [65].

Biologic action

- IL-13 plays an essential role in resistance to most Gastro Intestinal (GI) nematodes. It regulates mucus production, inflammation, fibrosis and tissue remodelling. It is a therapeutic target for a number of disease states including asthma, idiopathic pulmonary fibrosis, ulcerative colitis, cancer and others.

- IL-13 is believed to inhibit TH1 responses, which will inhibit the ability of the host to eliminate the invading pathogens. The role of IL-13 in the etiology/ pathogenesis of allergic disease/asthma has drawn broad attention.

- It induces AHR and goblet cell metaplasia, which result in airway obstruction and cause allergic lung disease. IL-13/chemokine interactions play a key role in the development of AHR and mucus production. IL-13 induces the expression of eotaxins. These chemokines recruit eosinophils into the site of inflammation in synergy with IL-5. Eosinophils release IL-13 and induce the production of IL-13 from TH2 cells, which is mediated via IL-18. IL-13 then, through its effects on epithelial and smooth muscle cells, aids in the development of AHR and mucus production. In addition to its potent activation of chemokines, it is also an inducer of adhesion molecules which are involved in asthma [1].

TRANSFORMING GROWTH FACTOR β

TGF-β (25kDa), a pleiotropic cytokine located at 19q13.2 acts as a regulatory molecule with numerous effects on cell proliferation ,differentiation, migration and survival that affect multiple biological processes, including development, carcinogenesis, fibrosis, wound healing and also suppresses immune response in the periphery to prevent an autoimmune responses. The family of TGF-β contains the three closely related isoforms, namely TGF-β1, TGF-β2 and TGF-β3, which are synthesized as large latent, inactive complexes where proper folding, interaction with critical interacting partners such as the latent TGF-β binding proteins (LTBPs) or fibronectin and secretion/release from storage sites is controlled by disulfide bonds and many different activation factors [66].

TGF-β receptors

TGF-β family members consists of type I and type II heterotetrameric transmembrane receptors which initiates intracellular signalling. Types I and II have an N-glycosylated extracellular domain that is rich in cysteine residues, one transmembrane domain, and an intracellular serine/ threonine kinase domain. The type II receptor kinase is a constitutively active kinase, whereas the type I receptor kinase needs to be activated by the type II receptor kinase. Upon ligand induced

formation of the heteromeric complex, the type II receptor phosphorylates the type I receptor rich in glycine and serine/threonine residues which changes the conformation of the type I receptor, thereby activating its kinase which later propagates the signal by phosphorylating specific intracellular proteins [67]. Thus, the type I receptor acts downstream of the type II receptor and consistent with this notion, has been shown to determine signalling specificity. In addition to the signalling type I and type II receptors, TGF-β can bind to receptor-associated transmembrane proteins, such as betaglycan (also called TβR-III) and endoglin. These receptors do not have any intrinsic enzymatic activity but have been shown to modulate TGF-β signalling [68,69].

Biological action

- The various TGF-β isotypes share many biological activities and their actions on cells are qualitatively similar in most cases although there are a few examples of distinct activities. The most pronounced differences in the TGF-β isoforms is their spatially and temporally distinct expression of both the mRNAs and proteins in developing tissues, regenerating tissues, and in pathologic responses [70].

- TGF-β is the most potent known growth inhibitor for normal and transformed epithelial cells, endothelial cells, fibroblasts, neuronal cells, lymphoid cells, hepatocytes and keratinocytes.

- TGF-β inhibits the proliferation of T-lymphocytes by downregulating predominantly IL-2 mediated proliferative signals. It also inhibits the growth of natural killer cells in vivo and deactivates macrophages. TGF-β blocks the antitumor activity mediated *in vivo* by IL-2.The latent form of TGF- β is a strong inhibitor of erythroleukemia cell lines [71].

- TGF-β also regulates the expression of plasminogen activator and plasminogen activator inhibitor. The gene encoding plasminogen activator I inhibitor contains a specific TGF-β1 responsive element in its promoter region which mediates the binding of specific transcription factors [72].

- TGF-β has mainly suppressive effects on the immune system since it inhibits the IL-2 dependent proliferation of T cells and B-lymphocytes. TGF-β inhibits the proliferation of B-lymphocytes, and proliferation of thymocytes induced by IL-2 and IL-1, respectively. It also inhibits the maturation of B-cells. It also suppresses the interferon induced cytotoxic activity of natural killer cells, the activity of cytotoxic T-lymphocytes and the proliferation of the precursors of lymphokine-activated killer cells [73].

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