CYTOKINES

CONTENTS

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1. INTRODUCTION The term cytokine is derived from a combination of two Greek words - "cyto" refers to cell and

"kinos" the cell movement.

Cytokines are basically the cell signaling molecules that aid cell to cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. Cytokines exist in peptide, protein and glycoprotein forms.

Cytokines affect nearly every biological process in the human body, including;

- Embryonic development
- Disease pathogenesis
- Non-specific response to infection
- Antigenic response
- Cognitive function changes and
- Progression of degenerative process of aging
- Stem cell differentiaton, vaccine efficacy and allograft rejection are the certain functions exerted by the cytokines.[1]

The most current terminology describes cytokines as "**Immunomodulating agents**."[2]

2. SOURCES OF CYTOKINES Cytokines are produced by a broad range of cells, including;

- Immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells

- Endothelial Cells
- Fibroblasts
- Various stromal cells (**Figure 1**)

A given cytokine may be produced by more than one type of cell. [3,4]

Figure 1: Cytokines. Image Credit: Designua / Shutterstock

1. MECHANISM OF ACTION Cytokines have a fundamental role in communication within the immune system and between

the immune system and host tissue cells to exchange information.

Cytokines act via binding to a receptor that in turn sends a signal to the recipient cell, leading to

a change in function or phenotype. Such signal cascades are complex and integrate a variety of

environmental factors.

Cytokines and their receptors exhibit very high affinity for each other. Because of this high

affinity, even picomolar concentrations of cytokines can mediate a biological effect. [5]

3.1 SIGNALING MODES Cytokines have been shown to be involved in autocrine, paracrine and endocrine signaling as

immunomodulating agents.

A particular cytokine may exhibit;

Autocrine action- by binding to receptors on the membrane of the same cell that secreted it

Paracrine action- by binding to receptors on a target cell in close proximity to the producer cell

Endocrine activity- by traveling through circulation and acting on target cells in distant parts of

the body. [6]

Figure 2: Signaling modes of Cytokines

2. IMPORTANT ATTRIBUTES OF CYTOKINES Cytokines can regulate cellular activity in a coordinated, interactive way due to the following

attributes;

Pleiotrophy - One cytokine has different effects on different types of target cells.

Redundancy - Multiple cytokines have same effects.

Synergism - Cooperative effect of multiple cytokines occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of individual cytokines.

Antagonism - The effect of one cytokine inhibits or offsets the effects of another cytokine. [7]

3. CYTOKINE NOMENCLATURE Cytokines are glycoproteins that regulate the functions of the immune system. Their definitions are imprecise because of the redundancy of both the function and the capacity of tissue parenchymal cells and leukocytes to produce them. Hence the terms lymphokine and monokine previously used have been dropped. Originally described by their perceived major function, the term IL has been adopted. When an agreed characterization of a cytokine is broadly accepted, a number is attributed (e.g., IL-6). However, the use of descriptive names for some key cytokines persists, including IFNs (α, β, and γ), TNF (TNF- α and TNF- β), colony stimulating factors (granulocyte colony–stimulating factor [G-CSF] and granulocyte–macrophage colony–stimulating factor [GM-CSF]), and some growth factors(TGF-b and PDGF). [8]

4. TYPES OF CYTOKINES

Major classes of cytokines include;

- Interleukins (IL)
- Interferons (IFN)
- Tumor Necrosis Factors-Alpha and Beta (TNF)
- Colony Stimulating Factors (CSF)
- Chemokines [9]

5. CYTOKINE RECEPTORS Cytokine receptors exist in structurally related families and comprise high-affinity molecular signaling complexes that facilitate cytokine-mediated communication.

Cytokine Receptors Fall within five families;

Receptors for the various cytokines are quite diverse structurally, but almost all belong to one of five families of receptor proteins:

- Class I cytokine receptor family (also known as the hematopoietin receptor family)
- Class II cytokine receptor family (also known as the interferon receptor family)
- TNF receptor family (TNFR)
- Chemokine receptor family
- TGF-beta receptors family [10]

6. TUMOUR NECROSIS FACTORS (TNF) Tumor Necrosis Factors or the TNF-family refer to a group of cytokines family which are mainly secreted by macrophages and can induce cell death of certain tumor cell lines.

8.1 TYPES & RECEPTORS Following two types are so far included in the family**;**

1. Tumor necrosis factor-alpha (TNF-α) - the most well-known member of this class
2. Tumor necrosis factor-beta (TNF-β), also known as lymphotoxin.

TNF act via the TNF Receptor (TNF-R) and is part of the extrinsic pathway for triggering apoptosis. [11]

7. COLONY STIMULATING FACTORS (CSFs) Colony-stimulating factors are secreted glycoproteins, primarily involved in directing the division and differentiation of bone marrow stem cells, and the precursors of blood leucocytes. They bind to receptor proteins on the surfaces of hematopoietic stem cells and activate intracellular signaling pathways, which can cause the cells to proliferate and differentiate into a specific kind of blood cell.

9.1 TYPES Colony-stimulating
factors include;

1. **CSF1** – Macrophage colony-stimulating factor
2. **CSF2** - Granulocyte macrophage colony-stimulating factors (also called GM-CSF and Sargramostim-Generic name)
3. **CSF3** - Granulocyte colony-stimulating factors (also called G-CSF and Filgrastim-Generic name)
4. **Nerve Growth Factor** (NGF) [12]

8. CHEMOKINES Chemokines are chemotactic cytokines mainly involved in facilitating chemotaxis i.e. chemical

stimulated movement in immune cells. The name is derived from their ability to induce directed chemotaxis in nearby responsive cells. [13] They are the cytokines that share the ability to stimulate leukocyte movement (chemokinesis) and directed movement (chemotaxis) and are particularly important in inflammation. Some chemokines are considered pro-inflammatory and can be induced during an immune response to recruit cells of the immune system to a site of infection, while others are considered homeostatic and are involved in controlling the migration of cells during normal processes of tissue maintenance or development.[14]

10.1 TYPES AND RECEPTORS Chemokines have been classified into four main subfamilies: CXC, CC, CX3C and XC.

They exert their biological effects by interacting receptors. Chemokine receptors are G protein-linked transmembrane receptors selectively found on the surfaces of their target cells.They are divided into four different families, CXC chemokine receptors, CC chemokine receptors, CX3C chemokine receptors and XC chemokine receptors.[15]

11. INTERLEUKINS (ILs) Interleukins are a large group of cytokines, essentially important for the function of the immune

system—both innate and adaptive. The function of the immune system depends in a large part on interleukins, and rare deficiencies of a number of them have been described, all featuring autoimmune diseases or immune deficiency. The primary function of interleukins is to modulate growth, differentiation, and activation during inflammatory and immune responses.[16]

Figure 3: Crystallographic structure of human Interleukin

11.1 PRODUCTION OF INTERLEUKINS Initially they were believed to be made by leukocytes (white blood cells) to act primarily on

other leukocytes, so named as interleukins, meaning “between leukocytes.” They were thought to function only as modulators of immune functions. Afterwards it was discovered that interleukins are produced by other cells too and are also involved in many other physiological functions. So the role that interleukins play in the body is much greater than was initially understood. The majority of interleukins are synthesized by T lymphocytes, as well as monocytes, macrophages, and endothelial cells.[17]

11.2 MECHANISM OF ACTION 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’s behaviour. They have paracrine, autocrine and endocrine action.[18]

11.3
TYPES

ILs can be divided into four major groups based on distinguishing structural features. However, their amino acid sequence similarity is rather weak (typically 15–25% identity). The human genome encodes more than 50 interleukins and related proteins.[19]

11.4 GENERAL
PROPERTIES

- Interleukin production is a self-limited process. These molecules are rapidly secreted once synthesized.
- Cellular responses to interleukins include up- and down-regulatory mechanisms with the induction and participation of genes that encode inhibitors of the cytokine receptors.
- The set of interleukins stimulated by a specific infectious agent determines which cells will respond to the infection and influences some of the clinical manifestations of the disease.
- Interleukins have redundant functions. For instance, IL-4, IL-5, and IL-13 are B-cell

growth factors and stimulate B-cell differentiation.

- Interleukins often influence other interleukin synthesis and actions. For instance, IL-1 promotes lymphocyte activation that leads to the release of IL-2.
- They have both Autocrine and Paracrine functions, for instance, IL-2 produced by T cells operates on the same T cells that made it or on a nearby cell. Besides, they also show endocrine activity as they may enter the circulation and act far from the site of production, for example, IL-1 is an endogenous pyrogen that works on the central nervous system (CNS) and causes fever.

11.5 CLINICAL SIGNIFICANCE

Clinical significance of some interleukins is listed below;

- IL-1 acts on the hypothalamus to induce fever and is therefore called an endogenous pyrogen. It operates on hepatocytes to increase synthesis of specific serum proteins. It causes fall in blood pressure or shock in large amounts.
- IL-12 overproduction causes allergic disorders.
- IL-27 treatment suppressed autoimmune diabetes.
- IL-28 may be sufficient treatment of HCV patients.
- IL-29 is a marker of osteoarthritis as joint inflammation implicates it.
- IL-36 also seems to play a significant role in human psoriasis.
- Elevated IL-37 levels in comparison with healthy controls were correlated with high disease activity in lupus patients.
- Recent studies point to an association between IL-38 and IL 39 and autoimmune diseases.

- IL-40 expression in several human B-cell lymphomas suggests that it may play a role in the pathogenesis of these diseases.[20]

12. INTERFERONS (IFNs) IFNs are signaling proteins that belong to the large class of proteins known as cytokines.

They are named after their ability to "interfere" with viral replication within host cells produced very early in infection and are the first line of resistance to a great many viruses. They are produced in response to the presence of pathogens such as viruses, bacteria or parasites — or tumor cells.

12.1 SOURCES OF INTERFERONS Interferons are released by T lymphocytes, as well as through monocytes, macrophages, and

endothelial cells.[21]

12.2. TYPES AND RECEPTORS Interferons are currently classified into three groups: Type I IFNs, Type II IFN & Type III IFNs

Type I IFNs are Interferon-alpha, -beta, -tau, and -omega, with relatively similar amino acid sequences. Humans have 12 different IFNαs and a single IFNβ. They are produced by almost every cell in the body. They are known primarily for their ability to make cells resistant to viral infections. All type I IFNs bind to the same interferon alpha/beta receptor (IFNAR) which consists of two major subunits: IFNAR1 and IFNAR2c.

Type II IFN include only one class i.e. IFNγ. The type II interferon-gamma is produced only by specialized cells in the immune system known as T lymphocytes and natural killer cells. This interferon is known for its ability to regulate overall immune system functioning.

IFNγ binds to a distinct receptor, the interferon gamma receptor (IFNGR) consisting of the two subunits IFNGR1 and IFNGR2.

Type III IFNs are the more recently described. They are IFNλ2, IFNλ3 and IFNλ1.They are alternatively known as IL-28 and IL-29 as they are structurally more closely related to the interleukins. They signal through the IFN-λ receptor containing a unique IFNλ chain. [22,23,24,25]

12.3 FUNCTIONS 1. Interferons induce antiviral and antiproliferative responses in **animal** cells and are major

defense against viral infections and abnormal growths (neoplasms).

2. Interferons play their role in stimulating the entire immune system to fight disease.

3. They can promote or hinder the ability of some cells to differentiate. They can inhibit cell division, the reason they hold promise for stopping cancer growth.

4. Interferons are species-specific proteins. In contrast to antibodies, interferons are not virus specific but host specific. Thus, viral infections of human cells are inhibited only by human interferons.

12.4 MEDICAL APPLICATIONS OF INTERFERONS

- Interferon-alpha had been approved by the Food and Drug Administration (FDA) as a viable therapy for hairy-cell **leukemia.**
- This class had also been approved for the treatment of **genital warts, chronic hepatitis C**, cancers like **Hodgkin's lymphoma** and malignant melanoma or skin cancer and **Kaposi's sarcoma** (a form of cancer that appears frequently in patients suffering from AIDS).
- Interferon-gamma, has received FDA approval for the treatment of a form of **multiple sclerosis.**

- It has also been used to treat **chronic granulomatous diseases** (an inherited immune disorder in which white blood cells fail to kill bacterial infections, causing severe infections in the skin, liver, lungs, and bone).
- Administered intranasaly in very low doses, interferon is extensively used in Eastern Europe and Russia as a method to prevent and treat **viral respiratory diseases** such as cold and flu.

12.5 FUTURE PROSPECTS Biotechnological advances in **genetic engineering** are making protein drugs like interferons

more available for study and use. Using **recombinant DNA** technology, or **gene splicing**, genes that code for ineterferons are identified, cloned, and used for experimental studies and in making therapeutic quantities of protein.

Another particular area of interest is the use of interferons to enhance other therapies. For example, studies have shown that a combination of **interferon-alpha and tamoxifen** may be a more effective therapy for breast cancer than either used alone. Future studies will focus more on combining interferons with other drug therapies.

Recent studies found that **interferon-tau** may play an important role in the early biological processes of **pregnancy**. It has been shown to **block tumor cell division** and may **interfere with the replication** of the **AIDS** virus. Since it has fewer unwanted side-effects (flu-like symptoms and decreased blood cell production) than the other interferons, so it is becoming a **new focal point for research.** [26]

13. SIGNALING OF CYTOKINES: JAK–STAT Signaling Pathway

JAK-STAT signaling pathway is the major pathway in cytokine receptor signaling. The effects

of this signaling are often more highly seen in cells of the immune system.[27] The pathway is a chain of interactions between proteins in a cell, and is involved in processes such as immunity, cell division, cell death and tumour formation. The pathway communicates information from chemical signals outside of a cell to the cell nucleus, resulting in the activation of genes through a process called transcription. There are three key parts of JAK-STAT signalling: Janus kinases (JAKs), signal transducer and activator of transcription proteins (STATs), and receptors (which bind the chemical signals). Disrupted JAK-STAT signalling may lead to a variety of diseases, such as skin conditions, cancers, and disorders affecting the immune system. [28]

13.1 STRUCTURE OF JAKS AND STATS STATs were firstly found in 1988 as proteins that bind to interferon (IFN)-stimulated response

elements of DNA sequences to stimulate the transcription of type I IFNs [10]. Then, JAKs were discovered in 1992 by three separate labs and the JAK-STAT pathway was coined [11]. The name of the JAK comes from a Roman two-faced god that implies two domains, including a catalytic domain and a kinase-like domain. [27]

There are 4 JAK proteins: JAK1, JAK2, JAK3 and TYK2.[1] JAKs contains a FERM domain (approximately 400 residues), an SH2-related domain (approximately 100 residues), a kinase domain (approximately 250 residues) and a pseudokinase domain (approximately 300 residues). [29] The kinase domain is vital for JAK activity, since it allows JAKs to phosphorylate (add phosphate groups to) proteins.

There are 7 STAT proteins: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6.[28] STAT proteins contain many different domains, each with a different function, of which the most conserved region is the SH2 domain.[29] STATs also have transcriptional activation domains (TAD). STATs also contain: tyrosine activation, amino-terminal, linker, coiled-coil and DNA-binding domains.[30]

The binding of cytokine to its receptor causes receptor dimerization and subsequently, JAKs are activated following close proximity. These activated JAKs initiate trans-phosphorylation on

specific tyrosine residues (also named transactivation), generating docking sites for recruitment of latent cytoplasmic transcription factors known as STATs. Phosphorylation is the most common modification in the cell biology, which plays a crucial role in the regulation of multitude of signaling pathways. Unphosphorylated STATs (Off) reside in the cytoplasm. If phosphorylation of STATs (On) and STAT dimerization occur upon activation of JAKs, phosphorylated STATs abandon docking sites on the receptors. Therefore, they translocate to the nucleus and bind to specific DNA sequences either to activate or suppress gene transcription. [27]

Figure 4. Cytokine signaling through the Janus kinase-signal transduction and activation of transcription (JAK–STAT) pathway. Binding of cytokine to the receptor leads to activation and phosphorylation of

JAK and phosphorylation of the receptor. This in turn leads to phosphorylation and dimerization of STAT. Activated STAT dimer migrates to the nucleus and binds to specific DNA-binding sites regulating gene transcription. This culminates in alteration of cellular function. [31]

13.3 ROLE IN CYTOKINE RECEPTOR SIGNALING Given that many JAKs are associated with cytokine receptors, the JAK-STAT signaling pathway

plays a major role in cytokine receptor signaling. A main subgroup of cytokines, ranging from over 60 factors, binds to receptors termed type I and type II cytokine receptors. These cytokines are inevitable for initiating and orchestrating of innate and adaptive immunities. Type I- and II receptors are constitutively associated with JAKs. [27]

For example, JAK3 activation in response to IL-2 is vital for lymphocyte development and function. JAK1 is needed to carry out signalling for receptors of the cytokines IFNγ, IL-2, IL-4 and IL-10. STAT1 can enable the transcription of genes which inhibit cell division and stimulate inflammation. STAT4 is able to activate NK cells (natural killer cells), and STAT5 can drive the formation of white blood cells. [32]

14. CYTOKINE STORM "Cytokine storm" is the phenomenon that has been mapped as one of the key elements of a

severe immune overreaction –which can both sicken and kill patients who are infected with certain strains of flu virus.

A cytokine storm is an overproduction of immune cells and their activating compounds (cytokines) in a flu infection. It is often associated with a surge of activated immune cells into the lungs. The resulting lung inflammation and fluid buildup can lead to respiratory distress and can be contaminated by a secondary bacterial pneumonia -- often enhancing the mortality in patients.

Cytokine storms are a **common complication** not only of **Covid-19 and flu** but of other

respiratory diseases caused by coronaviruses such as **SARS and MERS.**

14.1 CYTOKINE STORM SYMPTOMS

Cytokine storm syndromes (CSS) are a group of disorders representing a variety of inflammatory causes. The primary symptoms of a cytokine storm are high fever, swelling and redness, extreme fatigue and nausea. In some cases the immune reaction may be fatal. .[33][34]

14.2 CYTOKINE STORM TREATMENT

The clinical presentations of all cytokine storm syndromes (CSS) can be strikingly similar, creating diagnostic uncertainty. However, clinicians should avoid the temptation to treat all CSS equally, because failure to identify and address the underlying trigger results in delayed, inoptimal, or potentially harmful consequences.

Drugs for the treatment of cytokine storm can be classified into the following types: OX40 IG, ACE inhibitors (Prils) and Angiotensin II Receptor Blockers (Sartans), Corticosteroids, Gemfibrozil, Free radical scavengers, TNF-alpha blockers.[35]

15. CYTOKINE THERAPY Advances in the understanding of the role of cytokines in immune and inflammatory disorders

have led to the development of cytokine-based therapies. The benefits of cytokines as therapeutic

targets are as follows:

(i) Unlike in chemical drugs, specific protein which mediate the inflammatory process can be

inhibited.

(ii) Cytokines are well studied in animal models using neutralizing antibodies or genetic models

like knockout mice; thus the process in which these cytokines are involved can be thoroughly

researched.

(iii) With the advancement of biotechnology techniques, the expression and isolation of highly purified recombinant proteins becomes a relatively easier and cheaper process than in the past years.

The drawbacks of cytokine therapy come due to the basic properties of cytokines:

(i) Cytokines are pleiotropic, i.e. they affect several processes in parallel.

(ii) Cytokines are also known to have redundancy, meaning that the effects achieved by blocking one specific cytokine activity can be compensated by others.

(iii) The cytokine network is a regulated and balanced system and its alteration may lead to impaired immune response. For example, inhibiting proinflammatory cytokines can result in compromised host defense against infections. On the other hand, inhibition of regulatory cytokines can result in autoimmunity or tissue damage.

(iv) The production and manufacturing of biologics is still an expensive process, since their production requires sterile conditions and multiple stages of purification.

(v) Compared to chemical drugs, recombinant cytokines and antibodies have limited shelf half-life, require special/controlled storage conditions, and are typically administrated by a physician.[36]

Therapies have been developed with the aim to **block/inhibit or restore** the activity of specific cytokines. Cytokines delivered by **gene therapy** and **antisense oligonucleotide treatment** are also being assessed.

Currently, the most utilized approach to cytokine therapy is that of blocking or neutralizing cytokine action with **monoclonal antibodies** (mAbs). Drugs that block inflammatory cytokines, such as tumor necrosis factor **(TNF)-α**, are among the **most successful therapeutics approved** for clinical use.[37]

Non specific inhibition or stimulation of particular components of the immune system may

sometimes be of benefit. **The best results** have been obtained with cytokines and among these **interferon-α (IFN- α)** is the most widely used mainly for its antiviral properties. **Interferon beta- 1a and beta- 2b** are used to treat and control multiple sclerosis, an autoimmune disorder. **Interferon therapy** is used (in combination **with chemotherapy and radiation**) as a treatment for many **cancers**. This treatment is most effective for treating hematological malignancy; leukemia and lymphomas including hairy cell leukemia, chronic myeloid leukemia, nodular lymphoma, cutaneous T-cell lymphoma. Both **hepatitis B and hepatitis C** are treated with **IFN-α**, often in combination with other antiviral drugs.

IFN therapy causes **immunosuppression**, in particular through neutropenia and can result in some infections manifesting in unusual ways.

The **most striking** clinical effect of a cytokine has been that of **G-CSF** in **restoring bone marrow function after anti cancer therapy**. [38]

16. CYTOKINE THERAPY IN AUTOIMMUNE DISEASES The pathogenesis of autoimmune disease involves mainly the genetic susceptibility and previous infections[39].Unregulated levels of cytokines are central mediators of many inflammatory diseases. Targeting these cytokines using recombinant anti-inflammatory cytokines, recombinant soluble receptors, or antibodies against cytokines has demonstrated preferable clinical outcomes in patients with autoimmune diseases, which are refractory to glucocorticoids treatments[36].

In cases, where manifestations of different diseases result from an overproduction of cytokines, cytokine antagonists make desirable therapeutic drugs.[38]

Cytokine inhibitors can be used for severe or chronic inflammatory conditions. Various ways of **inhibiting TNF and IL-1** have proved valuable **in rheumatoid arthritis** and more controversially in **septic shock** and **severe malaria**.[40]

17. EMERGING APPROACHES & BIOLOGICS FOR CYTOKINE TARGETING

17.1 NEED FOR CYTOKINE TARGETING Cytokine therapy emerged from the need to increase immunity against tumors. High doses of

IL-2 were administered to patients bearing renal cell carcinoma (RCC) and melanoma in order to increase antitumor immunity[41,42]. Unfortunately, systemic administration of IL-2 has been related to severe toxicity mainly capillary leak syndrome, associated with edema and hypotension, damage to the kidneys, heart, and brain (as well as tachycardia, atrial fibrillation, fever and chills, muscle and joint pain, and catheter related urinary tract infections)[42,43] . In spite of numerous restrictions and warnings, a recombinant modified version of IL-2 (aldesleukin) was approved in 1992 for metastatic RCC and in 1998 for metastatic melanoma patients[44].

Another example is of IFNα. IFNα in a PEGylated form is given in order to increase antiviral immunityin chronic hepatitis-B virus (HBV) and hepatitis-C virus (HCV)[45,46] or in the case of immediate treatment for acute HCV. The IFNα can be given alone[47,48] or together with the nucleoside analog, ribavirin[49]. This treatment facilitates the clearance of the HCV virus and can prevent the chronic disease which can result in cirrhosis and hepatocellular carcinoma[50]. However, this type I IFN cytokine can cause serious adverse effects that can result in limitation of the doses given or even in discontinuation of the treatment. Among these adverse effects are decreased granulocytes and thrombocytes production in the bonemarrow, flu-like symptoms, neuropsychiatric disorders, and autoimmunity syndromes, mainly thyroiditis [51].

The severe adverse effects associated with these therapies called for discovering alternate approaches. So over the past few years, new innovative biological agents for blocking and regulating cytokine activities have emerged. Some of the most recent approaches for cytokine targeting are focusing on; (FIGURE 5)

- Anti-TNF antibodies or recombinant TNF decoy receptors,

- Recombinant IL-1 receptor antagonist (IL-1Ra) and anti-IL-1 antibodies
- Anti-IL-6 receptor antibodies
- TH17 targeting antibodies

17.2 ANTI-TNF-α BIOLOGICS TNF-α is a proinflammatory cytokine appearing early during the response to trauma or bacterial

infections. It is a central alarm cytokine. The role of TNF receptor signaling has been correlated

FIGURE 5: Biological drugs strategies for targeting inflammatory cytokines. The biologics can be composed of anticytokine or antireceptor neutralizing antibodies (1) or a soluble receptor that binds the cytokine (2). An inflammatory cytokine, like IL-1β, binds the IL-1R1 and the coreceptor IL-1R accessory protein (3) and transmits cell signaling, while an antagonist, like IL-1Ra, binds the receptor without recruiting the coreceptor (4), thus inhibiting signaling from the receptor and reducing the inflammation. Inflammation-dependent anticytokine strategy: enzymes such as neutrophil serine proteases or macrophage caspase-1 are released into the environment and cleave the two parts of the chimeric-IL-1Ra inactive precursor into an active antagonist (5), which blocks the receptors of tissue cells and the inflammatory cells.[37]

with several diseases including rheumatoid arthritis (RA), Crohn's disease, atherosclerosis,

psoriasis, sepsis, diabetes and obesity [52].

The TNF-α inhibitor **Etanercept** was the first biologic on the market for the treatment of RA. It

is a FC fused recombinant form of a soluble TNF receptor[53]. **Infliximab** a monoclonal human-

mouse anti-TNF antibody, was also approved by the FDA together with Etanercept in1998. Later

on, by 2002, a fully human monoclonal antibody **Adalimumab** against TNF-α was approved as well.

Etanercept and anti-TNF antibodies carry differences in their abilities to bind TNF. These differences appear in the effectiveness against different inflammatory diseases[54]. Etanercept was first approved only for the treatment of RA. Infliximab was first approved for the treatment of severe Crohn's disease and later on for RA also. It was further approved for ulcerative colitis, psoriatic arthritis, ankylosing spondylitis, and chronic plaque psoriasis. Etanercept was further approved for psoriatic arthritis, ankylosing spondylitis, chronic plaque psoriasis, and juvenile idiopathic arthritis in children. Adalimumab is approved for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, moderate-to-severe chronic psoriasis, juvenile idiopathic arthritis, and noninfectious uveitis.

These days, **Certolizumab** and **Golimumab** are the newer anti-TNF-α antibodies most recently approved by the FDA for the treatment of RA, psoriatic arthritis, ankylosing spondylitis, Crohn's disease unresponsive to regular medications (Certolizumab), and ulcerative colitis (Golimumab). Although the TNF inhibitors were shown effective for the treatment of skin and joint inflammation[55], they carry the risk of several adverse effects, mainly concerning infections. As TNF-α is a fundamental factor for fighting intracellular bacteria it is therefore not surprising that its inhibition showed to increase the risk for reactivation of tuberculosis[56]. Additionally, RA patients treated with anti-TNF antibodies experienced a higher rate of outbreaks of herpes zoster virus (HZV) compared to Etanercept or disease-modifying antirheumatic drug (DMARD) treatments[57]. Patients treated with anti-TNF therapy were also reported for increased risk for demyelinating disorders, like multiple sclerosis, optic neuritis, and acute transverse myelitis[58].

17.3 ANTI-IL-1 THERAPY Following the failure to use IL-1 as a therapeutic agent in order to treat

neutropenic patients and

the increasing data demonstrating the potency of this cytokine to induce inflammation, it was comprehended that IL-1 inhibition rather than IL-1 administration could be beneficial. **Anakinra** a recombinant nonglycosylated form of IL-1Ra (IL-1 receptor antagonist) was approved in 2001 for the treatment of RA in adult patients not responding to other antirheumatoid drugs, like DMARDs. Anakinra was shown beneficial for the treatment of RA by reducing symptoms and joint damage; however it is recommended to use when other biologics, like anti-IL-6 or anti-TNF therapies which are preferable, are refractory or contraindicated [59-61].

Anakinra is also approved for the treatment of patients suffering from a form of Cryopyrin-Associated Periodic Syndromes (CAPS) called Neonatal-Onset Multisystem Inflammatory Disease (NOMID). CAPS is a common name for three autoinflammatory syndromes Since IL-1 is the major mediator of these autoinflammatory diseases so anakinra which blocks IL-1 activity, is preferable for therapy.

It was also shown to be effective in case of nonhereditary chronic systemic inflammatory diseases like the adult-onset Still disease[62,63], which involves arthritis, fever, and systemic inflammation or the childhood version—systemic-onset juvenile idiopathic arthritis (SJIA)[64-66]. [In addition to vast types of other inflammatory disorders, inflammatory diseases and conditions like gout, type 2 diabetes, hemodialysis patients, postmyocardial infarction cardiac remodeling also have also been shown responding to Anakinra [36].

Anakinra has a short half-life of about 6 h; so the treatment therefore requires frequent subcutaneous injections. The most common side effect of anakinra is injection site reaction. The short half-life of anakinra allows immediate withdrawal of the treatment if needed.

During the administration of anakinra, the immune systems ability to fight infections is reduced. Meta-analysis of four RA trials using anakinra showed increased risk of infections, mainly pneumonia but also osteomyelitis, cellulitis, bursitis, herpes zoster, infected bunion, and

gangrene[67]. Anakinra is forbidden to patients receiving TNF blockers or patients getting live vaccines. The combination of anakinra together with corticosteroids or other immunosuppressive drugs increases the risk of infections.[68]. Chance for reactivation of tuberculosis during administration of anakinra is high[67].

Rilonacept termed as IL-1 trap was approved as biological drug in 2008, and **Canakinumab**, a monoclonal anti-IL-1β antibody that was also shown beneficial for the treatment of CAPS[36], was approved in 2009. Like Anakinra, both were shown to reduce symptoms in additional inflammatory diseases, such as gout[69,70], and canakinumab was also shown to be effective for SJIA. Side effects associated with Canakinumab resemble those of Anakinra, such as increased risk of infections[71, neutropenia, and low platelet count[72]; therefore it is not recommended for patients with a high risk for infections. Canakinumab is administered once every four to eight weeks, dependent on disease severity, due to its extended half-life. Nonetheless, withdrawal will not terminate the effects of the drug immediately, like in the case of anakinra.

17.4. ANTI-IL-6

IL-6 is another major proinflammatory cytokine with pleotropic effects on the immune system. IL-6 is the ligand for IL-6 receptor (IL-6R). IL-6R is restricted to hepatocytes, monocytes, macrophages, and lymphocytes. The **myeloma receptor antibody** (**MRA**), is a humanized antibody against IL-6R was trialed first in 2003. MRA was renamed as **Tocilizumab** and approved by FDA in 2010 for the treatment of RA patients refractory to TNF inhibitors; additionally it was also shown efficient in treatment of SJIA[73] so in 2011 FDA expanded the use of the antibody to the treatment of SJIA patients. Unfortunately, together with the benefits of IL-6 inhibition came adverse effects including serious infections mainly pneumonia, gastroenteritis, urinary tract infections, opportunistic infections (such as tuberculosis,

candidiasis), gastrointestinal perforation,and anaphylactic reactions, neutropenia and increased lipid levels, which are assumed to induce cardiovascular events[74].

Siltuximab is a human-mouse chimeric anti-IL-6 antibody approved in 2014 for HIV-negative and herpes virus-8 negative patients for the treatment of multicentric Castleman's disease, a lymphoproliferative disorder associated with increased IL-6 in the enlarged hyperplastic lymph nodes[75]. Siltuximab was further studied for its beneficial anti-IL-6 effects in other malignancies, like multiple myeloma, myelodysplastic syndrome, prostate cancer, ovarian cancer and lung cancer, and cancer-associated cachexia and anorexia. However, the treatment with siltuximab increases the risk of upper respiratory tract infections and other adverse effects including nausea, fatigue pruritus, increased weight gain, rash, hyperuricemia, thrombocytopenia, dyspnea,leukopenia, and neutropenia[36].

17.5 BIOLOGICS TARGETING TH17 CYTOKINES Ustekinumab is a targeted human monoclonal antibody, works by inhibiting the similar p40 subunit of the interleukin IL-12 and IL-23. Both IL-12 and IL-23 proteins are necessary to activate a cascade of inflammatory mediators responsible in the pathogenesis of psoriasis. The inhibition of the IL-12/23 pathway produces a profound suppression of both the Th1 and Th17. TH17 cells are named after IL-17 cytokine which they produce and are correlated with autoimmunity disorders including RA, lupus, colitis, and EAE[76,77]. IL-12 and IL-23 and their associated T helper cells are correlated to psoriasis which is an immune-mediated chronic inflammatory skin disease, and psoriasis patients have an increased risk to develop psoriatic arthritis[78]. Ustekinumab was shown to be more effective compared to etanercept[79] and was

approved in 2009 for plaque psoriasis and in 2013 for psoriatic arthritis. However, ustekinumab treated patients are recommended to receive prophylactic treatment due to increased risk of tuberculosis reactivation[80] as well as the issue of reduced CD4+

lymphocytes during this treatment, that should be taken into account[81,82].

Secukinumab a human anti-IL-17A antibody was approved by the FDA in 2015 for plaque psoriasis. Secukinumab was also reported for its efficiency for psoriatic arthritis[83]and ankylosing spondylitis[84] and was approved for these indications. In March 2016 an additional monoclonal anti-IL-17 antibody **Ixekizumab** was approved for patients with plaque psoriasis[85,86]. Longterm data from experiences of these antib odies targeting effector helper T cells cytokines is required for further evaluation of the adverse effects and safety of these biologics.

17.6 CYTOKINE SIGNAL TRANSDUCTION INHIBITION Blocking cytokine signaling pathways can effectively prevent cytokine participation in inflammatory diseases. A number of small molecular weight inhibitors have progressed to clinical trial; however, specificity and toxicity have limited their progress to the clinic.

17.6.1 Janus Kinase Inhibitors (Jakinibs) Janus kinase (JAK) inhibitors are small molecules with multiple effects on cytokine signaling pathways that inhibit the effects of cytokine-induced cell activation and consequent pathologic inflammation[8].

Pharmacological inhibition of JAKs block the actions of type I/II cytokines, and in past few years therapeutic JAK inhibitors, or Jakinibs, have become available to rheumatologists. Jakinibs have proven effective for the treatment of rheumatoid arthritis and other inflammatory diseases. Adverse effects of these agents are largely related to their mode of action and include infections and hyperlipidemia. Jakinibs are currently being investigated for a number of new indications, and second-generation selective Jakinibs are being developed and tested. Targeting STATs could be a future avenue for the treatment of rheumatic diseases, although substantial challenges remain. Nonetheless, the ability to therapeutically target intracellular signalling pathways has already created a new paradigm for the treatment of rheumatologic disease[88].

For instance, Tofacitinib preferentially inhibits JAK-1 and JAK-3. In clinical trials, the degree of benefit in resistant RA was similar in efficacy to adalimumab, a TNF-α inhibitor. It may lack specificity because side effects, including sepsis, disturbed liver function tests, raised creatinine, and neutropenia, were reported during its use.

17.7 CYTOKINE GENE THERAPY Gene therapy has been demonstrated to be an effective way of treating pathologic inflammation.

Rheumatoid synovia are arthroscopically removed from patients awaiting joint replacement and transfected with the gene for IL-1RA. Reimplantation of this transfected synovia back into the joint attenuated the disease. This technique has also been successfully used in collagen arthritis[8].

Since systemic cytokine blocking suffers from a number of serious limitations. The lack of danger signals which is crucial for adequate immune cell activation and hematopoiesis alterations being common features in all biologics, expose the host to increased risks of infections. In addition, the pleiotropic nature of most cytokines and their necessity to the function of multiple cell types across different organs make it almost impossible to inhibit their signaling cascade in a long-term therapy without severe complications. Therefore, new approaches based on **site-restricted biologics**, which could maintain the cytokine activity in other sites, are highly required[39].

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