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Review Article

Interleukin-6: A Dual Edged Sword in Immunity, Disease and Therapy

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Abstract

IL-6 is a multifunctional cytokine that is significant for the regulation of immunity, tissue repair, metabolism, and neurobiology. Even though IL-6 is involved in protective immune responses, it's a condition that may bring about chronic inflammation and multiple pathologies such as autoimmune diseases, cancers, infectious diseases, metabolic syndromes, and recently COVID-19. The dual nature of IL-6 as a mediator of immune defence and driver of inflammatory diseases underlines its importance in health and disease. Therapeutic strategies focused on IL-6 have transformed the treatment of many inflammatory and immune-mediated diseases. Monoclonal antibodies such as tocilizumab and sarilumab have shown impressive efficacy, especially in autoimmune diseases and cytokine storm syndromes. Currently, IL-6-targeted therapies are under way, including small molecule inhibitors, gene-editing technologies, and nanoparticle-based delivery systems, which will help to make better patient outcomes. Among the challenges are drug resistance, increased risk of infection, and high costs of treatment. Besides its therapeutic potential, IL-6 acts as a useful biomarker in disease diagnosis and monitoring, especially in conditions such as sepsis, cancer, and COVID-19. Its inclusion in multi-biomarker panels and its application in personalized medicine open new avenues for improving diagnosis and treatment customization. New findings about the intricate interactions of IL-6 with other cytokines further extend our understanding in aging, neuropsychiatric disorders, and metabolic regulation. Future studies with advancements in technologies promise to provide even finer understanding of IL-6 signalling and to discover novel therapeutic and diagnostic opportunities. The present review underscores the duality of IL-6, its clinical significance, and future directions in research toward improved healthcare outcomes through better-targeted therapies and diagnostic tools.

Keywords: Interleukin-6; Cytokine; Inflammation; Immune Response; Autoimmune Diseases; Cancer; Infectious Diseases; Metabolic Syndromes; COVID-19; Therapeutic Strategies; Monoclonal Antibodies; Cytokine Storm

Introduction

Cytokines are a class of signalling molecules critical to the immune system for mediating a wide array of physiological processes, such as inflammation, immune cell communication, tissue repair, and haematopoiesis [1]. Among the diverse families of cytokines, the interleukins play a pivotal role in regulating immune responses. Interleukin-6 (IL-6), first discovered in the 1980s, has emerged as one of the most versatile and the most studied interleukins because of its profound effects on both physiological and pathological processes. IL-6 was first found to be a factor that induces differentiation of B cells into antibody-producing cells. Since that time, the biological role of IL-6 has been found to extend way beyond adaptive immunity into innate immunity, metabolism, haematopoiesis, and tissue regeneration. As molecular biology advanced over decades, the signalling pathways behind IL-6 were unravelled to be complex. Its duality was pointed out as being pro-homeostatic under normal circumstances and pathogenic when perturbed. IL-6 mediates its effects through two distinct mechanisms of signalling classic and trans-signalling. Classic signalling is mediated by the membrane-bound IL-6 receptor (IL-6Rα) and

is restricted to certain cell types, such as hepatocytes and some leukocytes, and is largely anti-inflammatory and regenerative in nature. Trans-signalling is mediated by the soluble form of IL-6Rα and accounts for most of the pro-inflammatory actions of IL-6. This dual-signalling ability makes IL-6 act in a context-dependent manner, which makes it a critical mediator in both protective immunity and chronic inflammation. The dysregulation of IL-6 is implicated in a wide array of diseases, including autoimmune disorders like rheumatoid arthritis, chronic inflammatory diseases, cancer, and metabolic syndromes. Elevated IL-6 levels have been linked to disease severity in conditions such as sepsis, cardiovascular diseases, and neurodegenerative disorders [2]. More recently, during the COVID-19 pandemic, IL-6 was identified as the major contributor to cytokine storm syndromes. This has highlighted the relevance of IL-6 to acute inflammatory responses. Such recognition has accelerated research into IL-6-targeted therapies, such as monoclonal antibodies such as tocilizumab and sarilumab, which have shown marked efficacy in treating IL-6-mediated diseases. More than its therapeutic potential, IL-6 is critical as a biomarker in diagnosing and monitoring the progression of disease. This marker is directly correlated with the level of severity of diseases such as sepsis, cancer, and autoimmune diseases; hence, it has vast applications in clinical practice. In addition, new strategies involving manipulation of IL-6 signalling continue to emerge through the advancements in biotechnology and molecular medicine, thus holding promise for more targeted and effective therapy in the future [3].

Structure and biology of IL-6

Molecular structure and gene encoding IL-6

Interleukin-6 is a glycoprotein, and its encoding gene lies on chromosome 7 of the human body. In its unprocessed form, it consists of 212 amino acids that are then cleaved to form a mature protein of 184 amino acids. It is categorized as a family of four-helix bundle cytokines, bearing a structural motif in the up-up-down-down topology, and it is significant for binding to receptors. IL6 gene expression is tightly controlled by a myriad of stimuli that include stress, infection, and inflammation. The response elements in the promoter region of the IL6 gene for the transcription factors NF-kB and AP-1 mediate the upregulation of IL6 through inflammatory signals [4] as shown in Figure 1.

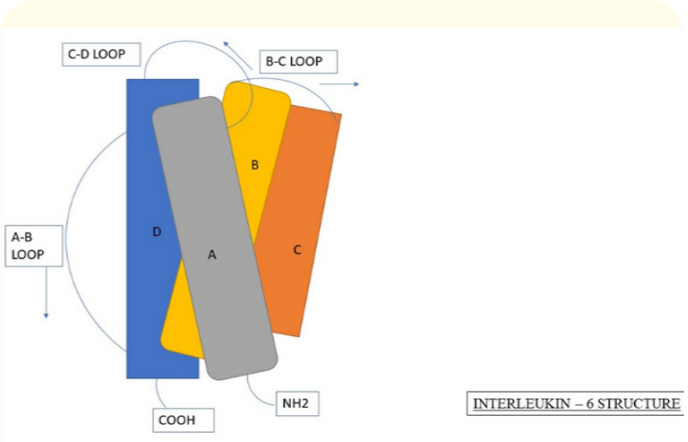

FIGURE.1 STRUCTURE OF INTERLEUKIN -6

Figure 1

IL-6 receptor system: Classic signalling vs. Trans-signalling

The biological functions of IL-6 are performed through the interaction with the receptor complex that consists of two units:

- The IL-6 receptor alpha chain (IL-6Rα), which exists both as a membrane-bound and as a soluble form.
- The signal-transducing subunit gp130, shared by other cytokines in the IL-6 family.

Classic signalling

occurs when the IL-6 binds with the membrane-bound IL-6Rα, generating a complex that associates itself with gp130. Usually, this pathway is restrained to certain cells, especially hepatocytes and some immune cells, that express the receptor. It is mainly employed in anti-inflammatory and regeneration processes.

Trans-signalling

A phenomenon where IL-6 forms a complex with its soluble receptor, sIL-6R, that then activates gp130 on cells that do not have the membrane-bound IL-6Rα. This makes the range of activity for IL-6 significantly larger and often contributes to pro-inflammatory

responses. The physiological and pathological roles of IL-6 are therefore dependent on the balance between these two signalling pathways [5] as shown in Table 1.

Regulation of IL-6 expression

IL-6 production is regulated at the multi-level so that expression is strictly controlled to prevent overreaction in inflammation. Some of the key regulation mechanisms are as follows.

- **Transcriptional Regulation:** IL-6 transcription is caused by inflammatory cytokines, such as TNF-α and IL-1β, microbial components, such as LPS, and cellular stress. NF-κB pathway dominates its transcriptional activation during an immune response.
- **Post-Transcriptional Control:** IL-6 mRNA stability is regulated by RNA-binding proteins and microRNAs that can both increase and decrease its translation.
- **Post-Translational Modifications:** IL-6 is also subject to glycosylation and phosphorylation that determine its stability, secretion, and receptor binding activity [7].

Remaining, the levels of IL-6 are controlled through negative feedback loops mediated by suppressors of cytokine signalling (SOCS) proteins, which block the downstream signalling events to ensure that homeostasis is achieved.

Physiological functions of IL-6

Interleukin-6 is significant in maintaining immune homeostasis and coordinating the different biological processes. Its capacity to act locally and systemically allows it to govern the different physiological functions in the different systems [10]. The following are the primary functions of IL-6 in normal biological processes.

Role in immune response

IL-6 is the central mediator of both innate and adaptive immune responses, bringing the two systems together in order to mount effective defences against pathogens.

- **Innate Immunity:** Immediately after infection or tissue damage, IL-6 is promptly produced by monocytes, macrophages, dendritic cells, and other innate immune cells. The acute-phase response is activated by the stimulation of hepatocytes to produce acute-phase proteins, such as CRP and SAA, which are essential for pathogen opsonization and elimination.
- **Adaptive Immunity:** IL-6 promotes the differentiation of T-helper 17 (Th17) cells, a subpopulation of T cells that play a critical role in combating extracellular pathogens. It also suppresses regulatory T cells (Tregs), which helps to induce an immune response when required. Furthermore, IL-6 promotes B-cell proliferation and antibody production, thereby boosting humoral immunity.

Haematopoiesis

IL-6 is involved in haematopoiesis, especially during stress or inflammation. It favours the differentiation of hematopoietic stem cells into mature blood cells, thereby enabling proper production of leukocytes to combat immune challenges and also works in conjunction with other growth factors to influence megakaryocyte maturation and platelet generation, which are essential functions in wound healing and stopping the bleeding process during acute trauma [8].

Modulation of inflammatory reactions

IL-6 plays two contradictory roles in inflammation - pro-inflammatory and anti-inflammatory depending on the situation.

- **Pro-Inflammatory Effects:** Trans-signalling by IL-6 enhances the recruitment of neutrophils and monocytes to the site of infection or injury, therefore, amplifying the inflammation responses.
- **Anti-Inflammatory Effects:** Classic signalling is achieved by IL-6 as it promotes tissue repair by inducing the production of mediators such as interleukin-10 (IL-10). This ensures resolution of inflammation and prevents any over tissue damage.

Role in metabolism

IL-6 is a key regulator of energy metabolism, exerting its effects on adipose tissue, liver, and skeletal muscle.

- **Liver:** IL-6 stimulates gluconeogenesis and glycogenolysis, processes that ensure energy availability during stress or inflammation.
- **Adipose Tissue:** It influences lipolysis, promoting the release of free fatty acids for energy production.
- **Skeletal Muscle**: IL-6 is secreted by the muscle cells during exercise; it acts in an autocrine or paracrine manner to enhance glucose uptake and lipid oxidation, which contributes to energy balance [9].

Tissue regeneration and wound healing

IL-6 modulates the behaviour of fibroblasts, keratinocytes, and other stromal cells that contribute to tissue repair and regeneration with promotes the proliferation of keratinocytes and fibroblasts, thus accelerating wound closure and tissue remodelling. IL-6 also stimulates angiogenesis, the generation of new blood vessels that will have to supply the oxygen and nutrients to newly forming tissue.

Neurobiology and cognition

IL-6 acts neuroprotective and as a neuromodulator within the central nervous system. Maintains neuronal survival and repair after stress or damage by promoting neurotrophic factor release, but dysregulation in this aspect may lead to impairing cognitive function as well as neurodegenerative progression.

Hormonal and endocrine regulation

IL-6 has a regulatory impact on endocrine functions with respect to the hypothalamic-pituitary-adrenal (HPA) axis. It also increases the secretion of CRH and ACTH by causing cortisol production. Due to its modulation of levels, IL-6 participates in stress responses and adaptation mechanisms in the face of challenges [10].

Pathophysiology of interleukin-6 (IL-6)

The pathophysiology of IL-6 is characterized by its central role in mediating inflammation, immune responses, and tissue damage. While its normal activity is essential for immune defence and tissue repair, dysregulated IL-6 signalling is a driving factor in a wide array of pathological conditions. IL-6-induced pathophysiological effects result from its dual signalling mechanisms-classic signalling and trans-signalling and its widespread influence on various cellular pathways [11] as shown in Figure 2.

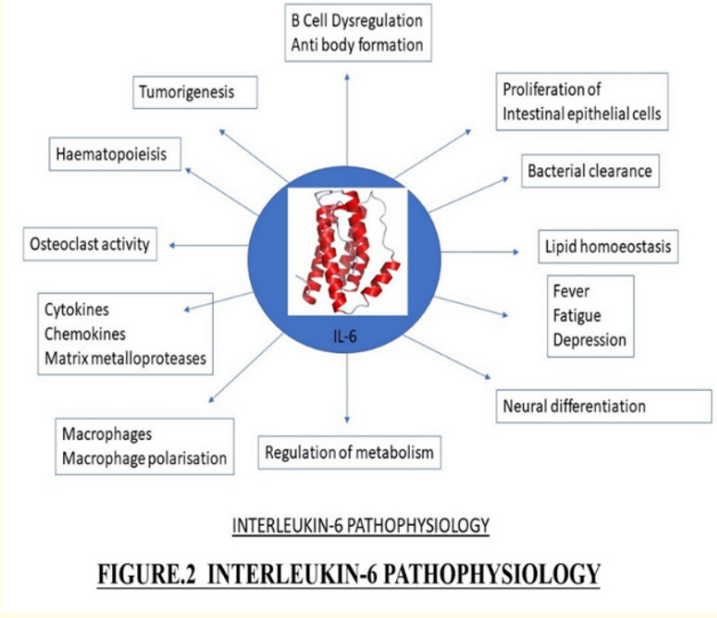

Figure 2

Dysregulated Mechanisms of IL-6 activity

- **IL-6 Overproduction** Chronic or excessive IL-6 production is caused by infections, autoimmune triggers, cancer, and metabolic disturbances. Factors such as persistent activation of nuclear factor-kappa B (NF-κB) and increased toll-like receptor (TLR) signalling contribute to increased synthesis of IL-6.
- **Dysregulation in Signalling Pathways:** Dysregulated trans-signalling is one of the major contributors to the pathological effects of IL-6. While classic signalling is usually limited to regenerative and anti-inflammatory roles, trans-signalling occurs in a wider range of cells, amplifying pro-inflammatory responses and perpetuating chronic inflammation.
- **Prolonged Activation of Downstream Pathways:** IL-6 activates primarily by the JAK/STAT3 pathway, in addition to PI3K/Akt and MAPK pathways. The overactivation of these pathways leads to uncontrolled cellular proliferation, survival, and migration, responsible for autoimmune diseases, cancer, and other chronic maladies [12].

Chronic inflammation and autoimmunity

- **Rheumatoid Arthritis (RA):** IL-6 contributes to joint inflammation, synovial hyperplasia, and osteoclast activation, which causes destruction of cartilage and bone. It also skews the balance of T cells by promoting Th17 differentiation while inhibiting regulatory T cells (Tregs), exacerbating autoimmune responses.
- **Systemic Lupus Erythematosus (SLE):** In lupus, IL-6 triggers the hyperactivation of B cells with the production of pathogenic autoantibodies, causing systemic inflammation and resulting in damage to organs, such as the kidneys-lupus nephritis.
- **Inflammatory Bowel Disease (IBD):** The IL-6-mediated trans-signalling prevents apoptosis of T cells in the intestinal lamina propria, supporting chronic inflammation in Crohn's disease and ulcerative colitis [13].

Function in cancer development and progression

IL-6 is an integral component of the tumour microenvironment and thus exerts an influence on cancer pathophysiology by affecting both tumour cells and stromal cells in the vicinity. Cell Survival and Proliferation**,** IL-6 promotes STAT3, which transcribes genes that have roles in cell survival and proliferation, such as BCL2 and Cyclin D1. This leads to the proliferation of tumours and also renders them resistant to apoptosis. Angiogenesis, IL-6 promotes the expression of vascular endothelial growth factor (VEGF) and stimulates the formation of new blood vessels in support of tumour growth. Metastasis, IL-6 supports epithelial-to-mesenchymal transition, which supports increased invasiveness and metastatic potential of tumour cells. Cancer-Related Inflammation, Prolonged IL-6 production leads to chronic inflammatory conditions in the tumour microenvironment, downregulating immune responses against the tumour while allowing immune evasion by cancer cells [14].

Metabolic dysregulation via IL-6

Obesity and Insulin Resistance, Adipose tissue is the prime source of IL-6 from obesity, which leads to chronic low-grade inflammation. The IL-6 impairs insulin signalling and activates SOCS3-the suppressor of cytokine signalling 3, therefore inhibiting insulin receptor substrate, causing insulin resistance. Type 2 Diabetes, Illumination of IL-6 raises hepatic gluconeogenesis and decreases uptake of glucose in peripheral tissues exacerbating hyperglycaemia and also increasing insulin sensitivity. Dyslipidaemia, IL-6-induced inflammation alters lipid metabolism, thus increasing circulating triglycerides and promoting atherosclerosis [15].

IL-6 and Infectious diseases

Cytokine Storm Syndromes**,** the hallmark of these syndromes, including severe infections like Covid-19, is IL-6 overproduction, causing systemic inflammation through improper regulation of IL-6. This results in multiorgan failure and can be fatal. Sepsis, IL-6 both has protective effects during acute infection and can maintain elevations that promote systemic inflammation, endothelial dysfunction, vascular leakage, and subsequent death in septic shock [16].

Neuroinflammation and neurodegeneration

- **Alzheimer's Disease (AD):** Chronic IL-6 elevation in the brain exacerbates neuroinflammation, amyloid plaque deposition, and neuronal death, accelerating cognitive decline.
- **Multiple Sclerosis (MS):** IL-6 promotes the differentiation of pathogenic Th17 cells, contributing to demyelination and neurodegeneration in MS.

- **Mental Health Disorders:** Elevated IL-6 levels have been linked to depression and anxiety, possibly due to its effects on brain-immune communication and neurogenesis [17].

Cardiovascular pathophysiology

- **Atherosclerosis:** IL-6 promotes the infiltration of inflammatory cells to atherosclerotic plaques, making them more prone to rupture, causing myocardial infarction or stroke.
- **Hypertension:** Continuous IL-6-induced endothelial dysfunction is an underlying factor in vascular inflammation and stiffness, which contribute to hypertension.
- **Heart Failure:** IL-6 is involved in myocardial remodelling and fibrosis, which affects the function of the heart in chronic heart failure.

IL-6 and diseases of aging

- **Inflammation:** IL-6 is considered a central mediator of inflammation, which is chronic low-grade inflammation that develops with age. It can contribute to sarcopenia, frailty, and osteoarthritis among older adults, leading to a decrease in quality of life [18].

Pathological functions of IL-6 in diseases

Even though IL-6 plays an important role in the preservation of physiological homeostasis, its deregulation has been involved in a plethora of diseases. Chronic up-regulation of IL-6 levels, mainly through trans-signalling, causes persistent inflammation, malfunctioning of the immune system, and tissue destruction [20]. An overview of disease category involving specific disease and role of IL-6 in specific disease has been mentioned in Table 2.

Disease Category	Specific Disease	Role of IL-6	Clinical Implications	Reference
Autoimmune	Rheumatoid Arthritis	Promotes joint inflammation, bone erosion	Target for therapies (e.g., Tocilizumab)	
Cancer	Systemic Lupus Erythematosus	Enhances B-cell activation, autoantibody production	Worsens organ damage	
	Breast Cancer	Stimulates tumor growth, angiogenesis	Biomarker and therapeutic target	
	Multiple Myeloma	Supports proliferation of malignant cells	Linked with poor prognosis	
Infectious	COVID-19	Drives cytokine storm syndrome	Predictor of severity, therapeutic target	
Metabolic	Type 2 Diabetes	Contributes to insulin resistance	Marker for metabolic syndrome	
	Obesity	Maintains low-grade inflammation	Implicated in comorbidities	[19]

Table 2: Diseases Associated with IL-6 Dysregulation.

Chronic inflammation and autoimmune diseases

Dysregulated IL-6 production is a feature of many chronic inflammatory and autoimmune diseases.

- **Rheumatoid Arthritis (RA):** IL-6 acts to drive synovial inflammation and pannus formation in RA. It encourages the activation of osteoclasts, which are involved in bone erosion, and upregulates the production of MMPs, thus allowing cartilage degradation.
- **Systemic Lupus Erythematosus (SLE):** In lupus, IL-6 favours the hyperactivation of B cells and stimulates the synthesis of autoantibodies, thereby worsening systemic inflammation and organ damage.
- **Inflammatory Bowel Disease (IBD):** IL-6 maintains intestinal inflammation as it inhibits apoptosis in lamina propria T cells, which is seen in Crohn's disease and ulcerative colitis [20].

Role in infectious diseases

IL-6 has a dual role in diseases caused by infection: The cytokine is associated both with protective immunity and with pathological inflammation.

- **Bacterial Infections:** It plays a crucial role in mediating acute-phase responses triggered by bacterial infections. Conversely, overproduction of this cytokine results in the damage of tissues and even to septic shock in most cases.
- **Viral Infections:** In influenza and HIV, IL-6 exacerbates systemic inflammation, thereby perpetuating disease severity. However, in COVID-19, IL-6 mediates cytokine storm syndromes that lead to respiratory distress and multi-organ failure [21].

Contribution to metabolic disorders

Chronic elevation of IL-6 has been associated with metabolic derangement and implicated in the pathogenesis of obesity, insulin resistance, and type 2 diabetes.

- **Obesity:** IL-6 produced by adipocytes is one of the principal sources in obesity, creating low-grade systemic inflammation. This dysregulates insulin signalling and contributes to metabolic syndrome.
- **Diabetes:** IL-6 blunts glucose homeostasis through enhancing gluconeogenesis in the liver and decreased insulin sensitivity of skeletal muscles and adipocytes [22].

IL-6 in cancer biology

IL-6 is a critical component of the tumour microenvironment, playing a key role in the initiation, progression, and metastasis of tumours.

- **Tumour Growth:** IL-6 acts to promote cell proliferation and survival through the activation of several downstream signalling pathways, including the JAK/STAT3 and PI3K/Akt pathways. These pathways stimulate the expression of anti-apoptotic and pro-proliferative genes.
- **Angiogenesis:** IL-6 stimulates VEGF production, leading to the development of new blood vessels that supply adequate oxygen and nutrients to growing tumours.
- **Metastasis:** IL-6 promotes the epithelial-to-mesenchymal transition (EMT), which is an absolute requirement for tumour cells to acquire invasive and metastatic capacity.
- **Cancer-Related Inflammation:** Increased, chronic production of IL-6 contributes to an inflammatory, tumour-promoting microenvironment, downregulating anticancer immune responses and favouring immune evasion [23].

Neurological diseases and cognitive decline

IL-6 is increasingly linked to neuroinflammatory/neurodegenerative pathologies.

- **Alzheimer's Disease:** The excessive and sustained expression of IL-6 in the brain initiates the formation of the amyloid-beta plaque, besides causing neuronal dysfunction that accentuates cognitive decline.
- **MS:** IL-6 promotes and facilitates the differentiation of pathogenic Th17 cells responsible for demyelination in MS and neurodegenerative changes.
- **Depression and Stress:** Prolonged elevation of IL-6 after chronic exposure to stress correlates with disease and poor neurogenesis at the level of the hippocampus [24].

Cardiovascular diseases

IL-6 plays a critical role in the pathogenesis of cardiovascular diseases due to its pro-inflammatory and pro-coagulant effects.

- **Atherosclerosis:** IL-6 promotes the recruitment of inflammatory cells to vascular plaques, which contributes to their instability and rupture.
- **Heart Failure:** In chronic heart failure, elevated IL-6 levels correlate with myocardial inflammation and fibrosis, impairing cardiac function.
- **Hypertension:** IL-6-driven endothelial dysfunction and vascular inflammation contribute to the development of high blood pressure [25].

Aging-associated diseases

Chronic low-grade inflammation, often referred to as "inflammaging," is driven in part by IL-6. This cytokine is implicated in age-related diseases such as sarcopenia, frailty, and osteoarthritis, reducing the quality of life in the elderly.

Therapeutic applications of IL-6

IL-6 has been one of the most critical drugs for the treatment of chronic inflammatory diseases, immune system disturbances, and excessive cytokine activities. The use of anti-IL-6 drugs changed the entire treatment profile for autoimmune diseases, inflammatory conditions, and cytokine storm syndromes. The following are the principal therapeutic interventions and their uses.

Anti-IL-6 therapies

Blocking IL-6 activity can be achieved through interference at the level of the cytokine itself, its receptors, or downstream signalling pathways.

Monoclonal antibodies against IL-6

- These antibodies directly neutralize IL-6, preventing it from binding to its receptors.
- Mechanism is by binding free IL-6, these therapies inhibit both classic and trans-signalling pathways that result in reduced inflammation and tissue damage.
- Application is Conditions such as Castleman's disease, rheumatoid arthritis, and some cancers have been shown to exhibit significant improvement with these agents.

Monoclonal antibodies against IL-6 receptor

Its Mechanism These drugs prevent the binding of IL-6 to IL-6R, thus inhibiting downstream signalling. Example is Tocilizumab and sarilumab are commonly used in clinical practice, especially in autoimmune and inflammatory diseases. Advantage is Besides controlling systemic inflammation, these treatments can also control localized effects of IL-6.

Small molecule inhibitors

Targeting intracellular signalling pathways downstream of IL-6R, like the JAK/STAT3 pathway, is a promising approach. These inhibitors are more useful in the treatment of diseases in which more than one cytokine is aberrant [26].

Approved drugs targeting IL-6

There have been some regulatory-approved anti-IL-6 therapies that show marked clinical efficacy.

- **Tocilizumab:** Approved for rheumatoid arthritis, giant cell arteritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome (CRS). It has proven effective in controlling severe cases of COVID-19 by blocking cytokine storm syndromes.
- **Sarilumab:** Primarily used for rheumatoid arthritis, sarilumab provides an alternative for patients intolerant to or unresponsive to tocilizumab.
- **Siltuximab:** Approved for Castleman's disease, a rare disorder characterized by systemic inflammation and lymphadenopathy.

Emerging therapies and clinical trials

Ongoing research continues to expand the repertoire of IL-6-targeted treatments, focusing on improving efficacy and minimizing adverse effects.

- **Bispecific Antibodies:** Novel therapies combining anti-IL-6 activity with other immunomodulatory functions are under investigation to enhance therapeutic outcomes in cancers and autoimmune diseases.
- **Gene Silencing Approaches:** Techniques like RNA interference (RNAi) and antisense oligonucleotides aim at reducing IL-6 production at the transcriptional level, offering a new strategy for managing diseases driven by cytokine overexpression.
- **Nanoparticle-Based Delivery:** Advances in drug delivery systems, such as nanoparticles and liposomes, are being explored to enhance the targeted delivery of anti-IL-6 therapies, improving their bioavailability and reducing off-target effects [27].

Challenges and limitations of IL-6-targeted therapies

Despite the successes of IL-6 inhibitors, several challenges remain:

- **Infection Risk:** IL-6 plays a critical role in host defence against infections. Blocking its activity increases susceptibility to opportunistic infections, including tuberculosis and bacterial sepsis.
- **Off-Target Effects:** Systemic blockade of IL-6 may cause unwanted effects like neutropenia, elevated liver enzymes, and lipid abnormalities.
- **Resistance:** Some patients develop resistance to IL-6 inhibitors due to compensatory mechanisms involving other pro-inflammatory cytokines like TNF-α and IL-1β.
- **Cost and Accessibility:** The high cost of biologic therapies remains a barrier to widespread access, particularly in resource-limited settings [28].

Potential applications in emerging diseases

IL-6-targeted therapies have proven efficacious in treating conditions besides those classically autoimmune or inflammatory in nature.

- **Cytokine Storm Syndromes:** Tocilizumab and other IL-6 antagonists have been a life-saver in cytokine release syndrome caused by CAR-T cell therapy as well as in severe infections such as COVID-19.
- **Neurological Disorders:** Emerging evidence suggests a possible benefit of IL-6 blockade in diseases such as multiple sclerosis and neuroinflammatory disorders, though such treatments require further research.
- **Cancer Immunotherapy:** IL-6 Inhibitors and Immune Checkpoint Inhibitors (e.g., Anti-PD-1/PD-L1) Cancer researchers explore their combination to increase antitumor immunity while dampening the pro-tumour consequences of chronic inflammation [29].

IL-6 as a biomarker

Interleukin-6 has become a good biomarker in diagnosing, prognostication, and treatment monitoring for a number of diseases. It is very rapidly induced in inflammatory and pathological processes, and its systemic action makes IL-6 a strong marker of disease activity and progression.

Diagnostic usefulness

IL-6 levels are typically elevated in conditions involving inflammation or immune dysfunction. In this respect, it becomes a diagnostic biomarker for some diseases is Infectious Diseases, Elevated IL-6 levels are found in bacterial sepsis, meningitis, and severe viral infections, including COVID-19. IL-6 measurement can thus help detect systemic inflammation early, leading to timely intervention. Autoimmune Disorders is the diseases like rheumatoid arthritis and lupus, IL-6 levels correlate with disease activity, helping in diagnosis and differentiation from other inflammatory conditions. Cancer generally observed in patients bearing various cancers, including myeloma, lymphomas, and solid tumours in elevated circulating IL-6 that represents tumour-associated inflammation [30].

Prognostic use

The amount of tissue- or circulation-based IL-6 can be used for an advance provision indicating prediction about disease outcome and possible complications are Sepsis and Septic Shock in patient suffering from septic diseases shows a continuously augmented IL-6 level indicating their worsened condition, often culminating in multiorgan dysfunction failure up to death. Tumour Burden, Metastatic Potential, Survival IL-6 concentrations are directly proportional to tumour burden and inversely related to survival in cancers, such as breast, lung, and prostate cancers, offering insights for prognosis. COVID-19 Disease Severity in IL-6 has recently become prominent during the COVID-19 pandemic as a predictive marker for disease severity. Elevated concentrations of IL-6 have a strong association with cytokine storm syndromes, acute respiratory distress syndrome, and mortality risk [31].

Monitoring therapeutic outcomes

IL-6 can be used as an indicator of the efficacy of therapeutic interventions, especially those diseases that are caused by inflammation and immune dysregulation. Autoimmune Diseases in patients treated with IL-6 inhibitors such as tocilizumab, monitoring IL-6 levels provides feedback about the efficacy of the therapy and guides dose adjustments. Cancer Therapy is dynamics of IL-6 are studied to assess response to immunotherapies and to detect early signs of treatment resistance. Post-Surgical Recovery in IL-6 is being monitored in perioperative phases to monitor the likelihood of infection or post-operative complication, mainly after a critical trauma injury or a major transplant operation [32].

Role in cytokine storm syndromes

Cytokine storms, wherein IL-6 is the key cytokine released, lead to devastating life-threatening consequences like COVID-19 is High levels of IL-6 were established as a feature of severe COVID-19 and were used as a biomarker in the treatment of most patients during the pandemic. The measurement of IL-6 has been crucial in stratifying patients for anti-IL-6 therapies such as tocilizumab and to determine the need for intensive care. CAR-T Cell Therapy in CRS is a side effect of CAR-T cell therapy, and it is identified by high levels of IL-6. The prediction of onset and severity of CRS is possible in these patients by measuring IL-6, which makes timely management with anti-IL-6 agents possible [33].

Challenges and limitations

Despite the utility of IL-6 as a biomarker, the following factors limit its general use like Lack of Specificity is IL-6 is elevated in such a wide range of conditions that its interpretation becomes challenging. Temporal Dynamics are the levels of IL-6 change rapidly with acute insults and require measurement at precise times to accurately assess. Standardization Issues are differences in assay techniques and detection thresholds for IL-6 can affect reproducibility and comparability among studies or clinical settings [34].

Emerging applications

Further research into the role of IL-6 in new contexts continues to expand its potential as a biomarker are aging and Chronic Diseases: In conditions like frailty, sarcopenia, and cardiovascular diseases, IL-6 is being explored as an indicator of biological aging and chronic inflammation. Mental Health Disorder are Elevated IL-6 levels have been linked to depression, schizophrenia, and other psychiatric conditions, opening avenues for its use in neuropsychiatric diagnostics. Personalized Medicine is integration of IL-6 data into multi-biomarker panels could enhance precision in diagnosing complex diseases and tailoring treatments to individual patients [35].

Current studies and future trends

Interleukin-6 remains one of the focus areas of biomedical research because of its varied role in health and disease. New information regarding the signalling pathways of IL-6, associated diseases, and the possibility of its application as therapy drives innovation at both basic science and clinical levels. This shows the trend of current research and postulates on the future course of IL-6 studies.

Advances in the understanding of IL-6 signalling and therapeutics

Research into interleukin-6 continues deepening our understanding of what the cytokine has to say about health and disease. The distinction between classic versus trans-signalling is gaining significant attention to develop strategies of therapy that selectively take away pro-inflammatory effects yet retain homeostatic functions. Studies are currently probing for tissue-specific roles of IL-6 trans-signalling in the brain, liver, and lungs, as well as its interaction with other cytokines like TNF-α and IL-1β to disentangle the intricacy of cytokine networks and the control of inflammation. Advancements in therapeutics are developed, such as the development of combination therapies where the inhibitors of IL-6 will be paired with the immune checkpoint inhibitors in treating cancers and anti-TNF agents for autoimmune diseases. Targeted delivery systems based on nanotechnology aim to reduce systemic side effects, while gene-editing tools such as CRISPR-Cas9 and RNA-based approaches, including antisense oligonucleotides, provide precise intervention strategies. Personalized medicine is advancing with efforts to stratify patients based on genetic markers of IL-6 signalling and integrate IL-6 into multi-biomarker diagnostic panels, improving treatment outcomes and disease management [36].

Emerging roles, challenges, and future directions

Beyond its traditional roles in inflammation, IL-6 is being studied in non-traditional areas, such as inflammaging associated with aging, neuropsychiatric disorders, and the regulation of metabolism during exercise. These studies suggest that modulation of IL-6 levels may delay age-related diseases, improve mental health outcomes, and refine treatments for metabolic syndromes. However, challenges remain, including resistance to IL-6 inhibitors, balancing the suppression of harmful inflammation with immune preservation, and addressing the redundancy of cytokine networks. These issues are being overcome by researchers who are using systems biology models and investigating epigenetic regulation of IL-6. Synthetic biology approaches may also allow for the design of engineered IL-6 analogues for novel therapeutic applications. Efforts to study IL-6 in diseases that are prevalent in resource poor settings, such as tuberculosis and malaria, could be used to inform cost-effective diagnostic and therapeutic solution. Artificial intelligence and machine learning are accelerating IL-6 research by predicting outcomes, identifying novel pathways, and optimizing clinical trial designs. These advancements, along with continued innovation, position IL-6 research at the forefront of breakthroughs in diagnostics and therapeutics, promising significant improvements in patient care across diverse medical fields [37].

Conclusion

Interleukin-6 is one of the central players in the immune system, orchestrating all sorts of physiological processes as well as driving pathological conditions when dysregulated. Such a dual nature that it shares—protective immune response and chronic inflammation—certainly makes it significant for health and disease. Indeed, IL-6 is known to be a multifunctional cytokine, involved in immunity, metabolism, tissue repair, and neurobiology, but its activity is also involved in many diseases, including autoimmune, cancers, infectious diseases, and metabolic syndromes. Therapeutic targeting of IL-6 has dramatically changed the management of a wide variety of inflammatory and immune-mediated conditions. Medications like tocilizumab and sarilumab have shown unprecedented success, particularly in autoimmune diseases and cytokine storm syndromes. Further progress in the development of IL-6-targeted therapies-including small molecule inhibitors, gene-editing strategies, and nanoparticle-based delivery systems-may well provide further opportunities for their use and improved patient results. The challenges include issues of resistance, infection risk, and cost. Besides its clinical importance, IL-6 becomes a significant biomarker that is helpful in diagnosis as well as disease management - including sepsis, cancer, and more lately, COVID-19. Being included in multi-biomarker panels and applying them in personalized medicine holds good hope for enhancing the diagnosis process and tailoring the therapy of individual patients. Forward looking, cutting-edge research into IL-6 signalling has progressively deepened our knowledge about the complexity of interplay between other cytokines. Emerging roles in aging, neuropsychiatric disorders, and metabolic regulation make this an exciting focus of study. Addressing the existing gaps through new technologies, the future studies will not only make finer refinements in the knowledge about IL-6 but will unlock new therapeutic and diagnostic possibilities as well [38].

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Conflict of Interest

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Authors Contribution

The authors confirm contribution to the paper: EP: Drafted the Manuscript, VAS. Study conception and design, RG: Review the manuscript. All authors reviewed and approved the final version of the manuscript.

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