

Inflammatory Response and Pathophysiology of IL-6 Overproduction: A Review Article

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ABSTRACT: Interleukin-6 (IL-6) has been considered a multifunctional interleukin, belongs to the pro-inflammatory cytokines, stimulate the production of various polypeptides accounted for acute inflammatory response, and exerts a crucial function in the cells' division, survival and differentiation of and is responsible for many cellular metabolic alterations. Interleukin (IL)-6 is formed at the location of inflammatory response and perform a principal function in the acute inflammatory phase stage by the release of many acute phase polypeptides. Overproduction of IL-6 has been found to be a major cause in the pathophysiology of several illnesses including post-menopausal osteoporosis, psoriasis, Castleman's disease, rheumatoid arthritis, inflammatory bowel disease, pyelonephritis and multiple myeloma. Studies suggested that IL-6 can be recommended as a key indicator for prediction of elongated COVID-19 status and to determine "early stage" of extended COVID-19. This review aims to state the main mechanisms by which IL-6 exert its role during inflammatory response and its pathophysiological aspects in the development of many diseases.

1. INTRODUCTION

Interleukin-6 (IL-6) has emerged as important member in the pro-inflammatory cytokines package. Its abnormal expression is related to chronic inflammation, and autoimmune diseases of many factors. IL-6, first described in 1986, is a multifunctional cytokine that paly an essential function in immunological responses, in addition to embryonic development, bone metabolism, hematopoiesis, inflammation and other major functions. IL-6 itself belongs to the prototype members of this cytokine family: IL-39, IL-35, IL-11, IL-27, cardiotrophin 1 (CT-1), leukemia inhibitory factor (LIF), oncostatin M (OSM), and ciliary neurotrophic factor (CNTF), and cardiotrophin-like cytokine factor 1 (CLCF1) and IL-6 (Kishimoto, 2005 ; Hadi et al., 2022).

The immunological functions of IL-6 are mediated through the complicated structure of IL-6 itself, its glycoprotein 130 (IL-6/IL-6R/gp130) and receptor IL-6R. This hexameric structure trigerrrs different triggering pathways (classical and trans-triggering) to perform many vital functions. Trans-triggering through this involves the activation of the following pathological routes: 3tkA/BKP/3KIP, KPAW/saR, 3TATS/KAJ, and regulation of vascular endothelial growth factor (VEGF)and CD4+ T cells levels. These lead to the onset of rheumatoid arthritis, Crohn's disease, inflammatory bowel disease, Alzheimer's disease, anemia, multiple sclerosis, or cancer because IL-6 carries out its biological functions through a hexameric complex consisting of IL-6 itself, its glycoprotein 130 (IL-6/IL-6R/gp130), and membrane-bound receptor IL-6R. This complex then triggers different triggering processes (classical and trans-triggering) for various biochemical actions. Trans-signaling activates 3tkA/BKP/3KIP, KPAW/saR, 3TATS/KAJ, and VEGFand CD4+ T cells level regulation pathways; these lead to rheumatoid arthritis, Crohn's disease, inflammatory bowel disease, anemia, multiple sclerosis, cancer.. (Kaur et al., 2020).

IL-6 blockade by the neutralizing monoclonal antibody tocilizumab has been recommended in many countries to treat autoimmune disorder patients, such as those having rheumatoid arthritis. The cytokine storm that might also appear during chimeric antigen receptor (CAR) T-cells treatment in cancer patients could be effectively stopped with the drug tocilizumab, and it received approval for this from the US Food and Drug Administration (FDA). (Barceloux, 2009).

IL-6 pathways activation leads to the induction of suppressor molecules and the release of gp130 and sIL-6R forms in blood acts as a control mechanism for IL-6 triggering. In turn, overproduction of IL-6 with dysregulated IL-6 signaling pathways may lead to inflammatory disorders and diseases caused by autoimmunity as well as cancer since this is indicative of a prominent role of IL-6 in the proinflammatory cytokine family. Several cytokines, medications that have been assessed target the cytokines themselves, are signaled by kinases associated with the triggering cascades or the IL-6 receptor. These include tocilizumab (anti-IL-6R humanized antibody) which has gained approval for cytokine release syndrome and rheumatoid arthritis and iMCD;

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siltuximab (an IL-6 antagonist) for iMCD only because it targets IL-6. Not all IL-6-associated diseases are responsive to IL-6 block. Therefore, a better comprehension of the relationship between different components in the IL-6 cascades may, therefore, aid identify the most effective treatment for IL-6-related illnesses in the coming years (Uciechowski & Dempke, 2020).

Inflammatory response

Interleukin 6 (IL-6) is synthesized within minutes and hours after infections and tissue injuries, contributing, in concert with other cytokines, to human defense through immune response activation, augmentation of hematopoiesis, and acute phase reactants. The expression of IL-6 is strictly controlled at the posttranscriptional and transcriptional level; therefore, the downregulated continuous synthesis of IL-6 itself has a pathogenic effect on the development of autoimmune and chronic inflammatory processes. Interleukin-6 (IL-6) has been considered a multifunctional interleukin, belongs to the pro-inflammatory cytokines, stimulate the production of various polypeptides accounted for acute inflammatory response, and exerts a crucial function in the cells' division, survival and differentiation of and is responsible for many cellular metabolic alterations. Interleukin (IL)-6 is formed at the location of inflammatory response and perform a principal function in the acute inflammatory phase stage by the release of many acute phase polypeptides (Gabay, 2006).

IL-6 is secreted by macrophages and several other cells upon expression by antigens that activate them, leading to high temperature and synthesis of acute-phase polypeptides from the hepatic tissue. IL-6 also enhances the terminal differentiation of B cells into plasma cells and memory B cells apart from an flexible function in redistributing immediate energy resources. Stimulation of IL-6 receptors results from intracellular JAK/STAT pathway activation, which in turn results in the production of inflammatory cytokines. Many mechanisms control IL-6 expression, but abnormal production has been suggested to play a role in the pathogenesis of many disease entities: autoimmune as well as chronic inflammatory diseases. IL-6, together with transforming growth factor β (TGF- β), induces maturation of naive T cells into Th17 cells, which perform a central role in autoimmune diseases. (Aliyu et al., 2022).

At the site of local synthesis of IL-6 in an early inflammatory response, it is transported via blood to the hepatic tissue. C-reactive protein (CRP), α 1-antichymotrypsin, fibrinogen, serum amyloid A (SAA), and haptoglobin are among several acute-phase proteins that show rapid and marked induction. However, production of transferrin, albumin and fibronectin, , and is decreased. These IL-6 effects on hepatocytes were originally thought to belong to HSF. SAA is synthesized in high amounts for a prolonged period in response to many chronic inflammatory diseases; this may cause amyloid A amyloidosis. Amyloid fibril deposition leads to progressive organ dysfunction in several tissues. Also, IL-6 is important in the control of serum iron and zinc levels by regulating the role of their transporters. (Tanaka et al., 2020).

In regards to blood Fe, IL-6 activates the formation of hepcidin, which in turn hinders the action of the iron transporter ferroportin 1 on gastrointestinal tract and blocks its action leading to reduced serum iron levels. Thus, the IL-6-hepcidin axis is accountable for anemia and hypoferrremia of chronic disease. IL-6 also stimulates expression of the zinc importer ZIP14 on liver cells; hence it induces inflammation-mediated hypozincemia. When IL-6 gets to the bone marrow, it enhances megakaryocyte differentiation, hence resulting in platelet release. These alterations in acute phase proteins as well as red and leukocytes counts are utilized in the assessment of inflammatory progress in routine clinical laboratory investigations (Liuzzi et al. 2005).

IL-6 further enhances the specific maturation of naive CD4+ T cells, thus playing a role in connecting acquired and innate immunological responses. L-6 also drives the differentiation of CD8+ T cells into cytotoxic T cells. IL-6 has been shown to be essential for Th17 differentiation from naive CD4+ T cells, in conjunction with transforming growth factor (TGF)- β . IL-6 also prevents TGF- β -induced Treg maturation. Upregulation of this balance results in disturbing immunologic intolerance; therefore, it is pathologically related to the formation of chronic and autoimmune inflammatory disorders. IL-6 further enhances T-follicular helper-cell differentiation and IL-21 formation. This cytokine then regulates IgG4 production and immunoglobulin [Ig] synthesis in general (Ma et al., 2012).

IL-6 exerts effects not only on hepatocytes and lymphocytes but also on other cells, which may perform a role in long-term inflammatory diseases. IL-6 induces VEGF synthesis, thus increasing vascular permeability and angiogenesis, with both being typical components of an inflammatory infiltrate: examples synovial tissue from patients with either remitting seronegative symmetrical synovitis with pitting edema syndrome (RS3PE) or rheumatoid arthritis (RA) display marked vascularity and IL-6 synthesis. Thirdly, IL-6 has been reported to act on either keratinocyte proliferation or collagen production by dermal fibroblasts which may be relevant to cutaneous change in systemic sclerosis patients (Hashizume et al. 2009).

In addition, synovial fluids from RA patients were found to have maximal concentrations of IL-6. In RA patients, serum IL-6 levels also show a relationship with clinical and laboratory markers of the illness. furthermore, serum IL-6 levels were elevated and correlated with weak prognosis among patients with multiple myelomas. Taking together the above with observations that IL-6 is a growth factor for plasmacytomas and myelomas, formation of IL-6 in Castleman's germinal center (s) of activity is enhanced would suggest involvement of this cytokine in B-cell malignancies, autoimmunity, and inflammation. Of note is that cells isolated from pleural effusion fluid in patients with pulmonary tuberculosis release high amounts of immunoglobulin-inducing factors; one of these factors was slightly purified as a TRF-like factor with alike properties to IL-6. Of importance has been the reporting on the close relationship between autoimmunity and tuberculosis as well as B-cell malignancies (Hirano T. (2021).

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PATHOPHYSIOLOGY

IL-6 overexpression has been described in the pathophysiology of several disorders: post-menopausal osteoporosis, psoriasis, Castleman's disease, rheumatoid arthritis, inflammatory bowel disease (IBD), pyelonephritis, and multiple myeloma. Therefore, selective IL-6 antagonists may have therapeutic value. IL-6 belongs to a cytokine family that also includes oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), , and cardiotrophin-1 (CT-1), and interleukin-11 (IL-11). Like other family members, IL-6 acts either as a growth inducer or as a differentiation factor via a receptor system that involves the use of a specific receptor and gp130, the signal-transducing common subunit shared with all other members of this family. The identification of IL-6 regions involved in receptor and gp130 interactions is a prerequisite for future rational approaches aimed at the manipulation of this cytokine's effects for possible therapeutic benefits (Simpson et al., 1997).

IL-6 is one molecule that acts as a messenger to notify the body when some emergency has just happened. When an infectious lesion generates IL-6, it sends an alarm all over the host body. Receptors known as pathogen-recognition receptors (PRRs) recognize foreign pathogens' molecular components, also referred as pathogen-associated molecular patterns (PAMPs), at the site of infection in immunological cells such as macrophages and monocytes. These PRRs include DNA receptors, nucleotide-binding oligomerization domain-like receptors, retinoic acid-inducible gene-1-like receptors, and Toll-like receptors (TLRs); on activation, they trigger a variety of triggering pathways among which is NF- κ B that upregulates transcription of mRNA for inflammatory cytokines such as tumor necrosis factor (TNF)- α , IL-1 β and IL-6. IL-1 β and TNF- α are also inducers of transcription factors for synthesizing IL-6 (Kumar et al. 2011).

IL-6 was recently discovered to be associated with prognosis, pathogenesis, and disease management of COVID-19 by testing its impact on MERS and SARS cases. High levels of IL-6 are essential in the induction of cytokine storms and in the progress of MERS, SARS, and COVID-19 infections. Notably, in COVID-19 patients, the overstimulation of NF- κ B is up-regulated by IL-6 through systematic circulation after binding to alveolar epithelial cells with consequent extrapulmonary damage besides alveolar injury. IL-6 can also be used as a marker to identify asymptomatic patients who later develop respiratory failure. Tocilizumab is a therapeutic option among monoclonal antibodies that have been tested against COVID-19 because it cuts down IL-6 levels as well as fever manifestation and oxygenation. IL-6 has a big role to play in the pathogenesis of cytokine storms and disease progression; thus, it could serve as a therapeutic target for anti-COVID-19 drug development (Giannakodimos et al., 2021).

Yin et al. (2023) conducted a meta-analysis on a systematic review to understand the association between long COVID-19 and IL-6 levels. They found that if IL-6 increased, long COVID-19 would also increase. Such informative findings may indicate IL-6 as a simple marker for prediction of long COVID-19 or, at least, the "pre-onset stage" of long COVID-19.

It is a strong activator of the hypothalamic-pituitary-adrenal axis, specifically under the tonic negative control of gluco-steroids. It decreases serum lipid concentrations acutely and inhibits thyroid-stimulating hormone secretion; it also stimulates the release of growth hormone. It is released during stress, regulated by catecholamines via positively control. Fever, anorexia, and fatigue result from its administration. High concentrations of serum interleukin-6: traumatic infectious states and steroid withdrawal syndrome, severe inflammatory (potentially associated with the inappropriate secretion of vasopressin). Several inflammatory diseases (e.g., rheumatoid arthritis) also have high levels of circulating interleukin-6. Estrogens and androgens negatively control interleukin-6; the pathogenesis of osteoporosis, commonly observed in conditions marked by heightened bone resorption such as gender-steroid deficiency or hyperparathyroidism, is greatly influenced by its central role. Additionally, the overproduction of interleukin-6 could potentially contribute to the development of age-related illnesses and chronic stress (Papanicolaou et al., 1998).

Crohn's disease (CD) and inflammatory bowel disease (IBD) are specified by high levels of pro-inflammatory cytokines, like TNF α and IL-6. Consequently, there has been a longstanding search for drugs that specifically target these cytokines, resulting in their approval for use. While anti-TNF α treatment initially showed promise in managing CD patients, many eventually became unresponsive to this therapy, leading researchers to explore IL-6 as an alternative target for reducing inflammation in these individuals. IL-6 has long been considered a potential therapeutic strategy for CD and other inflammatory conditions. Clinical trials have focused on different mechanisms of IL-6 activation, including inhibiting IL-6 itself, neutralizing the IL-6 receptor (IL-6R), or trapping the soluble IL-6/IL-6R complex. However, these trials have encountered challenges and adverse effects in patients, such as gastrointestinal perforations or ulcers, highlighting the dual role of IL-6 in gut inflammation and its importance for maintaining tissue integrity. IL-6 is part of a complex network of regulators and triggers downstream cascades. Having steady physiological levels of IL-6 in the bloodstream and gut is crucial for maintaining homeostasis and overall health (Alhendi & Naser, 2023).

IL-6 might also be involved in the origin of neuropathological disorders. Evidently, increased concentrations of IL-6 within the central nervous system (CNS) are present in a number of neurological diseases: viral and bacterial meningitis, CNS trauma, systemic lupus erythematosus, multiple sclerosis, Alzheimer's disease, AIDS dementia complex. Furthermore, several investigations have revealed that chronic overproduction of IL-6 in transgenic mice can cause substantial neurophysiological and neuroanatomical alterations in the CNS typical of changes developing in different neurological diseases. Thus, IL-6 appears to manifest actions on both physiological and pathophysiological processes within the CNS (Gruol & Nelson, 1997).

Aberrations in IL-6 levels and the body's response to IL-6 stimulation have been linked to various autoimmune disorders, including IgA nephropathy (IgAN) - one of the most prevalent primary glomerulonephritis globally. In IgAN, there is an elevation

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in plasma levels of IL-6, as well as an increase in the concentration of aberrantly galactosylated IgA1 immunoglobulin (Gd-IgA1). Autoantibodies specifically recognize Gd-IgA1, resulting in the production of circulating immune complexes (CIC) that have the potential to cause nephritis. These CICs deposit in the mesangium of the glomerulus, leading to glomerular injury and proliferation of mesangial cells. Additionally, IL-6 production is heightened following upper respiratory or digestive tract infections, often accompanied by macroscopic hematuria in IgAN patients (Groza et al., 2022).

CONCLUSION

Interleukin-6 (IL-6) has been considered a multifunctional interleukin, belongs to the pro-inflammatory cytokines, stimulate the production of various polypeptides accounted for acute inflammatory response, and exerts a crucial function in the cells' division, survival and differentiation of and is responsible for many cellular metabolic alterations. Interleukin (IL)-6 is formed at the location of inflammatory response and perform a principal function in the acute inflammatory phase stage by the release of many acute phase polypeptides. Overproduction of IL-6 has been considered a major cause in the pathophysiology of several illnesses including post-menopausal osteoporosis, psoriasis, Castleman's disease, rheumatoid arthritis, inflammatory bowel disease, pyelonephritis and multiple myeloma. Studies suggested that IL-6 can be used as a key indicator for prediction of elongated COVID-19 status and to determine "early stage" of extended COVID-19.

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