Review Article

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Journal of Biomedical Sciences
2254-609X

2022
Vol. 11 No. 10: 83

An Insight of Interleukin -6 and Fibrinogen: In Regulating the Immune System

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Citation: Obeagu EI, Muhimbura E, Kagenderezo BP, Nakyeyune S, Obeagu GU (2022) An Insight of Interleukin -6 and Fibrinogen: In Regulating the Immune System. J Biomed Sci, Vol. 11 No. 10: 83

Abstract

The role of the liver as a critical part of the immune system involved in both innate and adaptive immunity. As a major source of acute phase proteins, including components of the complement system. Hepatocytes are an important part of innate immunity and play an important role in controlling inflammatory responses throughout the body. Acute-phase protein production in hepatocytes is controlled by various cytokines released during the inflammatory process, with IL-6 and IL-1 type cytokines acting as key regulators, cascading and synergistic regulation or it functions as a cascade network with inhibition. Effects on acute-phase protein expression. The pro inflammatory cytokine interleukin-6 is an endogenous biochemical active during B cell maturation and inflammatory processes. Interleukin-6 plays an important role in regulating acute-phase protein synthesis in human hepatocytes.

Keywords: Interleukin-6; Fibrinogen; Immune system; Inflammatory cytokines; Aute phase proteins; B Cell

Received: 21-Sep-2022, Manuscript No. IPJBS-22-13019; **Editor assigned:** 23-Sep-2022, PreQC No. IPJBS-22-13019 (PQ); **Reviewed:** 07-Oct-2022, QC No. IPJBS-22-13019; **Revised:** 12-Oct-2022, Manuscript No. IPJBS-22-13019 (R); **Published:** 19-Oct-2022, DOI: 10.36648/2254-609X.11.10.83

Introduction

Interleukin-6 (IL-6) initiates a rapid and transient response to infection and injury and contributes to host defence by stimulating acute-phase, haematopoiesis, and immune responses. Interleukin-6 is a multifunctional cytokine with multiple biological activities; cytokines are signalling peptides, proteins, or proteins involved in the inference, suppression of inflammation in response to pathogens, foreign molecules, or toxins. Interleukin-6 is a mediator of the immunoglobulin class that replaces and regulates the acute phase response. This is a marker or indicator of inflammation in the body. The proinflammatory cytokine interleukin-6 is an endogenous biochemical active during B cell maturation and inflammatory processes. It may act as a pyrogen causing fever in infectious, non-infectious and autoimmune diseases. In chronic or acute inflammation, IL-6 is produced in situations such as cancer, trauma, burns, and infections [1-6].

Fibrinogen is a positively regulated acute phase reactant that plays a key role in hemostasis. Polypeptide chains, Aα, Bβ, and ϒ (Aα, Bβ, and ϒ) that form pseudodimers form fibrinogen. A coordinated accumulation of α, β, and β mRNA is observed during the acute inflammatory phase, and this effect can be mimicked by recombinant IL-6. Fibrinogen biosynthesis is regulated by hormone- and cytokine-mediated mechanisms under normal and pathophysiological conditions. Glucocorticoids and cytokines regulate fibrinogen biosynthesis [2,4]. Originally called leukocyte endogenous mediator and hepatocyte stimulating factor, the cytokines that mediate fibrinogen production are now shown to be derived from a single gene family of cytokines called IL6.

Interleukin-6 (Il-6)

Interleukin 6 is a cytokine with a wide range of biological activities. It is a mediator of immunoglobulin class displacement and regulation of acute-phase responses. It is also an indicator

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of inflammation in the body. It is a research marker for the development of bacteremia [7]. IL-6 is synthesized by macrophages and monocytes in response to other inflammatory cytokines, including tumor necrosis factor (TNF) beta and interleukin-11. IL-6 is an endogenous biochemical that is activated during B cell maturation and inflammatory processes. As a pyrogen, it can cause fever during infections and also in non-infectious and autoimmune diseases [8]. IL-6 is also produced in situations of chronic or acute inflammation, as well as cancer, trauma, burns and infections [9]. IL-6 is also thought to increase susceptibility to systemic forms of juvenile rheumatoid arthritis and diabetes mellitus [10]. According resting receptors for IL-6 are present on normal activated B cells, cells of liver and myeloid cell lines, and normal T lymphocytes. IL-6 is also present on B cells modified by Epstrin-Barr virus. IL-6 is produced through the inflammatory response by initiating transcription factors that are present in multiple inflammatory pathways. Its origin occurs in protein kinase C, cAMP/protein kinase A, and the release of calcium occurs. IL-6 has various functions and forms depending on its production, and also has pleiotropic activities [11]. IL-6 is produced by macrophages and monocytes during the early stages of infectious inflammation, shortly after stimulation of Toll-like receptors (TLRs) by different pathogen-associated molecular patterns (PAMPs).

When non-infectious inflammation such as trauma or burns occurs, damage-associated molecular patterns (DAMPs) from the injury site activate TLRs to produce IL-6 [12]. IL-6 expression plays a major role by activating various cell populations. Broad-spectrum acute-phase proteins such as chymotrypsin initiate C-reactive protein is an excellent biomarker of inflammation in laboratory tests, and its expression is associated with the activation of IL-6 in hepatocytes. The iron transporter ferroportin 1 is present in intestinal epithelia, hepatocytes and macrophages and can lead to anemia, chronic inflammation and hypoferremia Triggering IL-6-enhanced TGF-β autoimmune tissue damage Differentiation of IL-17 to produce T helper r cells that play a key role in the differentiation of IL-17. Induction of CD8+ T cells by IL-6 aids in T cell production. Activation of hematopoietic stem cells and maturation of megakaryocytes into platelets is induced by IL-6 in hematopoiesis. Activation of the NF-κB ligand receptor is activated by IL-6 production in bone marrow stromal cells that are important for the activation and differentiation of bone resorption and osteoporosis. IL-6 in inflammatory lesions, such as those found in rheumatoid arthritis synovial tissue, is due to excess vascular endothelium

Structure of il-6 and its receptor

Originally, IL-6 was identified under several names in the 1980s [13]. Liver is involved. Subsequent cloning of these proteins showed that they were all identical and were given the common name IL-6.

It is typically a cytokine with four bundles of α-helices, with a short α-helix within the CD loop plus the expected up-up-down-down arrangement of the α-helices. The extracellular region of IL-6Rα is composed of three domains, an N-terminal Ig-like domain and two Fn3 domains that constitute the IL-6 binding CHR. The N-terminal Ig domain adopts a distorted Ig-like fold and is essential for cytokine binding and biological activity (. IL-6 binds to the surface formed by the two Fn3 domains D2 and D3 that make up CHR [14]. At the C-terminus of the structured extracellular domain (D1–D3) is a long linker region (52 residues) that is predicted to be disordered, linking the structured extracellular domain and membrane [15, 16].

Receptors and signalling of il-6

IL-6 receptor belongs to the class I cytokine receptor family. Signaling and ligand-binding components are present at higher affinities in class I receptors. IL-6R has two separate components. It has a ligand-binding portion of 80 kDa and is associated with IL-6. It can exist in two forms, soluble and membrane-bound. On the other hand, the signalling portion of IL-6R is composed of glycoprotein 130 and can be called the IL-6Rb chain. GP130 has the ability to signal IL-6 and establish a binding site. Gp130 is a key molecule across the family of IL-6 signaling cytokines. When IL-6Ra binds to the soluble form of IL-6, a circulating complex is formed. This soluble form binds to cells expressing gp130, resulting in gene expression and signal transduction. This complex leads to the expression of gp130, known as transsignaling, and is critical for mediating pro inflammatory responses. Ligand activation of gp130 occurs in a variety of ways, including activation of cytoplasmic tyrosine kinases and activation of transcription factors. Transcription signal transducers and activators (STATs) occur through kinase activation that occurs through tyrosine phosphorylation of potential cytoplasmic transcription factors. STAT3 and Ras proteins are activated by gp130 and IL-6. Ras protein activation results in hypophosphorylation of mitogen-activated protein kinases (MAPKs) and increased serine/threonine kinase activity. The NF-IL6 factor (IL-6 core factor) is phosphorylated by MAPK at threonine 235 and serine 231, which are important for DNA binding. Various acute phase proteins are activated with the help of NF-IL6.

Functions of Il-6

Role in diseases

a. Immediate and transient expressions of IL-6 are generated in response to environmental stressors such as infection and tissue injury. This expression triggers alarm signals and activates host defence mechanisms against stress. Multiple sclerosis [17]. In many diseases such as neuromyelitis optica spectrum disorder (NMOSD), diabetes, atherosclerosis, depression, Alzheimer's disease and systemic lupus, which are stimulated by IL6 impairment, there are inflammatory and autoimmune processes. Prostate cancer, Behcet's disease, rheumatoid arthritis [18].

b. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects 1% of the female population worldwide. Anti-IL-6 is the first FDA-approved treatment for rheumatoid arthritis. IL-6 is a pleiotropic cytokine involved in autoantibody production and B-cell maturation, leading to activation of C-reactive protein that plays an important role in the pathogenesis of rheumatoid arthritis. IL-6 is involved in the production of pro-inflammatory lymphocytes, Th17. It

enhances the adaptive immune response, transitions from acute to chronic inflammation, develops joint pathology, increases joint erosion, and improves extracellular turnover [19].

c. **Cancer**

Anti-IL-6 therapy has been used for autoimmune therapy, but IL-6 blockade is also being evaluated for cancer therapy because of IL-6's role in chronic inflammation. IL-6 has been found to play a role in regulating the tumor microenvironment, producing breast cancer stem-like cells, metastasis by downregulating E-cadherin, and altering DNA methylation in oral cancer.

Role of il-6 as a myokine: Anti-IL-6 therapy has been used for autoimmune therapy, but IL-6 blockade is also being evaluated for cancer therapy because of IL-6's role in chronic inflammation [20,21]. IL-6 has been found to play a role in regulating the tumor microenvironment, producing breast cancer stem-like cells, metastasis by downregulating E-cadherin, and altering DNA methylation in oral cancer.

Role of il-6 in immunity

Acute phase response of il-6: The organism's response to injury due to neoplastic growth, immunological disorders, infection and tissue damage is involved in the acute phase response. It is believed to be beneficial for damaged organisms to maintain homeostasis after infection. IL-1, IL-6, and interferon are involved in acute responses and various functions such as clot and platelet accumulation, monocyte and granulocyte activation, and vascular leakage.

The innate immune system is enhanced by IL-6, which activates the acute phase and provides protection against tissue damage [22]. Acute-phase protein release into the plasma occurs via hepatocytes, whereas release of other proteins is suppressed. IL-6 increases the production of two major proteins, serum amyloid A and C-reactive protein (CRP). CRP is used to increase the phagocytic rate of bacteria and SAA is used to alter the gene transcription rate of proteins. Fibrinogen, an essential clotting factor, is increased by IL-6, while transferrin and albumin levels are decreased. This leads to systemic responses including increased glucocorticoid production, complement activation, fever, increased erythrocyte sedimentation and coagulation.

Role of Il-6 in B- And T-Lymphocytes: IL-6 increase production of immunoglobulin A, G and M by directly activating the B cells and enhance production of IL5 and IL-4. It plays important role terminal differentiation of B cells into secretions of immunoglobulin.

Fibrinogen

Fibrinogen is a thrombin-clotting glycoprotein produced in the liver [23] and present in the blood of vertebrates. The structure of human fibrinogen includes alpha, beta, and gamma polypeptide chains known from amino acid and nucleic acid sequencing. It is functionally bivalent. The intact molecule has a tripartite dimeric structure. The most important physiological function of fibrinogen is the formation of fibrin, which binds platelets and some plasma proteins into hemostatic plugs. Fibrinogen is a substrate for her three major enzymes: thrombin, plasmin, and factor XIIIa. In pathological situations, the network traps large numbers of red and white blood cells and forms a thrombus that can occlude blood vessels. Fibrinogen and fibrin are multifunctional proteins. Fibrinogen is essential for platelet aggregation. It also binds to several plasma proteins, but the biological function of this interaction is not fully understood. Fibrin is an essential matrix for regulating fibrinolysis and promoting cell adhesion in wound healing.

A variety of congenital and acquired human fibrinogen-related disorders result in fibrinogen depletion and/or dysfunction. These diseases represent a group of rare diseases that can have severe episodes of pathological bleeding and thrombosis. These diseases are treated by increasing the level of fibrinogen in the blood or by preventing the blood from clotting [24, 25]. These disorders can also cause certain liver and kidney diseases. Fibrinogen is a "positive" acute phase protein. H. Its blood levels rise in response to systemic inflammation, tissue injury, and certain other events. It is also elevated in many types of cancer. Inflammation and elevated levels of fibrinogen in cancer and other conditions are implicated in the thrombosis [26-30] and vascular injury associated with these conditions.

Structure

Human fibrinogen is made up of three pairs of polypeptide chains, designated Aα, Bβ and γ, with molecular masses of 66,500, 52,000, and 46,500 Da, respectively. The co- and post-translational addition of N-linked carbohydrate to the Bβ and γ chains brings the total molecular mass to about 340 kDa. It has a molecular weight of 340 kDa [31-38]. Fibrinogen has a biological half-life of about 100 h and is synthesized predominantly in the liver.

Conversion of fibrinogen to fibrin

The conversion of fibrinogen to fibrin is one of the main consequences of the enzymatic cascade of blood clotting and is essential for hemostasis (hemostasis) and vessel occlusion or thrombosis. This occurs in two main stages, enzymatic and non-enzymatic. An enzymatic step results in thrombin-catalyzed cleavage of fibrinopeptides from fibrinogen to form fibrin monomers. Thrombin becomes a highly specific serine protease upon activation of prothrombin [39-45], a zymogen normally present in the blood. In a non-enzymatic step, monomeric fibrin spontaneously self-assembles to produce fibrin oligomers, which elongate to form double-stranded protofibrils. Protofibrils aggregate both laterally and longitudinally into fibers that branch off to form a three-dimensional gelling network called a clot. Finally, fibrin polymers are stabilized by covalent cross-linking by plasma transglutaminase [46, 47], factor XIIIa, to form mature fibrin clots that are mechanically and chemically more stable.

Relationship between Interleukin-6 and Fibrinogen

Interleukin-6 (IL-6) is produced rapidly and transiently in response to infection and tissue injury and contributes to host defence by stimulating acute-phase responses, haematopoiesis, and immune responses. During the early stages of inflammation [48-55],

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IL-6 is synthesized in local lesions and transported through the bloodstream to the liver, followed by rapid induction of various acute-phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA), fibrinogen, haptoglobin, α1-antichymotrypsin

Acute phase systemic response

One of the relationships between IL-6 and fibrinogen in regulating immune response is seen in acute phase response [56, 57]. Acute phase response is a systemic reaction against inflammation, infection, or tissue injury, which is characterized by leukocytosis, fever, increased vascular permeability, alteration in plasma metal and steroid concentration, along with increased levels of acute phase proteins. The production of acute phase proteins by hepatocytes is regulated by several soluble factors, such as IL-1, tumor necrosis factor (TNF) and HSF. Among these factors, only HSF could induce the full acute phase proteins. It was demonstrated that recombinant IL-6 can function as HSF [58, 59]. It can induce various acute phase proteins, such as fibrinogen, α_1-antichymotrypsin, α_1-acid glycoprotein, and haptoglobin, in a human hepatoma cell line. In addition, IL-6 induces serum amyloid A, C reactive protein, and α_1-antitrypsin in human primary hepatocytes.

Fibrinogen is an acute phase reactant. Blood levels of fibrinogen along with other acute phase reactants rise sharply with conditions causing acute tissue inflammation or damage, nephrotic syndrome, liver disease, pregnancy, estrogen therapy, and/or compensated intravascular coagulation [60-62]. Tests for these acute phase reactants, including fibrinogen, may be performed to determine the extent of inflammation in the body.

Conclusion and Recommendation

Injuries such as bacterial or parasitic infections, physical and chemical trauma's, malignant tumours and immunological disorders that lead to immune response from the innate immune system. Innate immune system enhances Interleukin 6, which is a major regulator of the acute phase proteins synthesis which leads towards protection against tissue damage. Fibrinogen is one of the proteins produced for the process. IL-6 plays a key function in regulating the proteins synthesis in the hepatocytes as well as the secretion as seen in inflammatory states in the body.

I recommend that if there is infections that triggers immune response the reactant proteins should be estimated as a marker to prevent cytokine storm which leads to organ dysfunction and subsequent organ death.

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