Biological Effects of Tumor Necrosis Factor Alpha (TNF-α) in Systemic Inflammation. Running title: TNF-α for systemic inflammation

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Abstract

Aim. The purpose of this article review is to investigate the biological effects of TNF-α in systemic inflammation at moderate levels. TNF-α is a product of macrophages, one of the body's defence systems that is active in the presence of a bacterial infection.

Background. TNF-α plays a role in host defence for bacterial, viral and parasitic infections. TNF-α is produced by macrophages and is activated by T cell lymphocytes, antigens, NK cells, and mast cells. TNF-α is usually not detected in healthy individuals but is often found in conditions of inflammation and infection in the serum. TNF-α works against leukocytes and endothelium, induces acute inflammation at low levels because TNF-α is a strong pyrogen. TNF-α plays a role in systemic inflammation at moderate levels. TNF-α causes pathological abnormalities in high levels of septic shock, because TNF-α is cytotoxic.

Riview Results. In the review of this article we get results about the biological effects of TNF-α on systemic inflammation at moderate levels and their role in the humoral and cellular immune systems.

Conclusion. TNF-α has a biological effect on systemic inflammation at moderate levels and has a strong role in the humoral and cellular immune systems.

***Keywords**: Tumor Necrosis Factor Alpha (TNF-α), Humoral, Cellular Immune, Systemic Inflammation*

Background

Tumor necrosis factor alpha (TNF-α) is a pleiotropic cytokine which plays a role in the inflammatory process, initiates polymorphonuclear (PMN) and activites it so that PMN can reach the site of infection. Tumor necrosis factor alpha (TNF-α) is the main cytokine in the acute inflammatory response to Gram negative bacteria and other microbes. [1]

Severe infections can trigger the production of large amounts of TNF-α which results in a systemic reaction. The main sources of TNF-α are mononuclear phagocytes and T cells that are activated by antigens, NK cells, and mast cells. Lipopolysaccharide is a patent stimulation of macrophages to secrete TNF-α. IFN-γ produced by T cells and NK cells also stimulates macrophages, including increasing synthesis of TNF-α.[2] TNF-α has several functions in the inflammatory process, which can increase the pro-thrombotic role and stimulate adhesion molecules from leukocyte cells and induce endothelial cells, play a role in regulating macrophage activity and immune responses in tissues by stimulating growth factors and other cytokines, functioning as regulators of hematopoietic and commitogen for T cells and B cells and neutrophil cell and macrophage activity. [3]

TNF-α also has beneficial additional functions including its role in the immune response to bacteria, viruses, fungi, and parasitic invasion. Almost all

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inflammatory processes result in activation of tissue macrophages and blood monocyte infiltration. This activation causes many changes in cells, including the production of TNF, IL-1, and IL-6, namely cytokines that cause multiple effects on the host. [4]

Among the many proinflammatory cytokines, tumor necrosis factor α (TNF-α) has an important role in the occurrence of systemic inflammation. Preclinical and clinical studies have reported that suppressing TNF-α expression can reduce the development of inflammation in many diseases, including typhoid fever caused by Salmonella typhi bacteria. Using anti-TNF antibodies can reduce systemic inflammation that occurs during the infection process. Besides the dissolved TNF-α receptor has the ability to reduce the induction of ischemia and the sequestration of neutrophils which play a role in injury to the infected intestine. [5]

Endogenous pyrogens, which can cause inflammation, apoptotic cell death, and mediate the release of various cytokines such as IL-6, IL-8 and IL-1 by stimulation of macrophages. Excessive production of TNF-α can cause various diseases in humans including atherosclerosis, cancer, and inflammatory bowel disease. [6] However, it is still unclear, and many studies are directly related to TNF-α. The molecular mechanism of TNF-α from clinical studies found that a decrease in levels of TNF-α in the blood level can control the inflammation that is currently occurring in the host in systemic inflammation. [7]

Riview Results

TNF-α plays a role in host defence for bacterial, viral and parasitic infections. TNF-α is produced by macrophages and is activated by T cell lymphocytes, antigens, NK cells, and mast cells. [8] TNF-α is usually not detected in healthy individuals but is often found in conditions of inflammation and infection in the serum. TNF-α works against leukocytes and endothelium, induces acute inflammation at low levels because TNF-α is a strong pyrogen. TNF-α plays a role in systemic inflammation at moderate levels. TNF-α causes pathological abnormalities in high levels of septic shock, because TNF-α is cytotoxic. The biological effects of TNF-α are as follows: [9]

1. Deployment of neutrophils and monocytes to the site of infection and activate these cells to get rid of microbes.

2. Encouraging the expression of molecular adhesion of vascular endothelial cells to leukocytes.

3. Stimulates macrophages to secrete chemokines and induces chemotaxis and leukocyte deposition.

4. Stimulate mononuclear phagocytes to secrete IL-1 with effects such as TNF-α.

5. Induces the same inflammatory cell apoptosis.

6. Stimulates the hypothalamus which induces heat, so-called endogenous pyrogens.

7. Production of large amounts of TNF-α can prevent myocardial contractility and vascular smooth muscle tone which lowers blood pressure or shock and weak cells that cause of kaheksia (severe metabolic disorders such as blood sugar drops to levels that are not possible to live).

8. Complications of septic shock syndrome caused by gram-negative or gram-positive bacteria characterized by vascular collapse. Some of the biological functions of TNF-α comprise cellular proliferation and differentiation, tumorigenesis, apoptosis or necrotic cells death, immunoregulators, lipid metabolism, coagulation and endothelial function.

TABLE 1 : Biological Effects of TNF-α [9]

Number	Location Target	Biological effect
1	Neutrophils	Deployment of neutrophils to the site of infection and activate these cells to get rid of microbes.
2	Monocytes	Deployment of monocytes to the site of infection and activate these cells to get rid of microbes.
3	Endothelial cells	Encouraging the expression of molecular adhesion of vascular endothelial cells to leukocytes.
4	Macrophage	Stimulates macrophages to secrete chemokines and induces chemotaxis and leukocyte deposition.
5	Mononuclear cells	Stimulate mononuclear phagocytes to secrete IL-1 with effects such as TNF-α.
6	Hypothalamus	Stimulates the hypothalamus which induces heat, so-called endogenous pyrogens.
7	Cardiac myocardial cells	Production of large amounts of TNF-α can prevent myocardial contractility and vascular smooth muscle tone
8	Vascular	Complications of septic shock syndrome caused by gram-negative or gram-positive bacteria characterized by vascular collapse
9	Inflamation Cell	Induces the same inflammatory cell apoptosis

Discussion

After invading mammalian tissue, bacteria activate complement and macrophage tissue. Activated macrophages secrete proinflammatory cytokines such as TNF-α, interleukin-1β (IL-1β) and IL-8 which

play a role in phagocytosis and enhance the T cell immune response. [10] In the blood, bacteria or bacterial products causal systemic inflammation characterized by activation of macrophages in the reticuloendothelial system, leukocytosis, release of cytokines and hypotension8. Some gram-positive organisms have a thick peptidoglycan layer that inhibits insertion of the C5b-9 membrane attack complex on bacterial cell membranes. Salmonella typhi can induce an inflammatory response in the respiratory tract through activation of TNFR. [11] The complex mechanism of host response to invasion by microbial pathogens includes the production and release of proinflammatory and immunomodulating cytokines, which are very necessary in stimulating leukocytes and other cells by pathogens. [12]

Cytokine synthesis is needed for host defence against infection. But an excessive inflammatory response will cause organ dysfunction and host death. Bacterial products in the form of peptidoglycan cell wall fragments and lipoteikoic acid have characteristics as immunostimulators, which can induce the release of TNF-α, IL-1β, IL-6, IL-8 and IL-10 from monocyte macrophage culture in mice. [13]

Salmonella typhi has several strategies to fight the killing of neutrophils, by releasing Chemotaxis Inhibitory Protein (CHIP), and Extracellular adherence protein and binding to endothelial ICAM-1 adhesion molecules. ICAM-1 inhibition prevents leukocyte adhesion, diapedesis and extravasation of blood flow to the infected part. After arriving at the site of infection, neutrophils release antimicrobial substances, including antimicrobial peptides, ROS, RNS, proteases and lysozyme. [14]

Defence against ROS from Salmonella typhi by releasing large amounts of antioxidant enzymes (eg catalase, pigments, superoxide dismutase) which neutralizes ROS and RNS. Severe bacterial infections usually cause host to improve the specific immunity response within 7 to 10 days to limit ongoing infections and reinfection. Immunity Response due to Salmonella infection in typhi. [15]

3. 1 The Role of TNF-α Humoral and Cellular Immunology

Two types of adaptive immunity, humoral immunity and cellular immunity, are mediated by different cells and molecules and each is designed to provide defence against extra and intra-cellular microbes. [16]

Humoral Immunity

Humoral immunity is mediated by proteins called antibodies, which are produced by cells called lymphocytes B. Antibodies enter the circulation and mucous fluid, then neutralize and eliminate microbes and microbial toxins that are outside the host cells, in the blood, extracellular fluid which originates from the plasma and inside the lumen of mucous organs, such as the gastrointestinal tract and the respiratory tract.

One of the most important functions of antibodies is to stop microbes which are on the mucosal surface and in the blood so that they do not gain access to host cells and do not form colonies in the cells and connective tissue of the host. In this way, antibodies prevent infection from developing. Antibodies cannot reach microbes that live and divide in infected cells. [17]

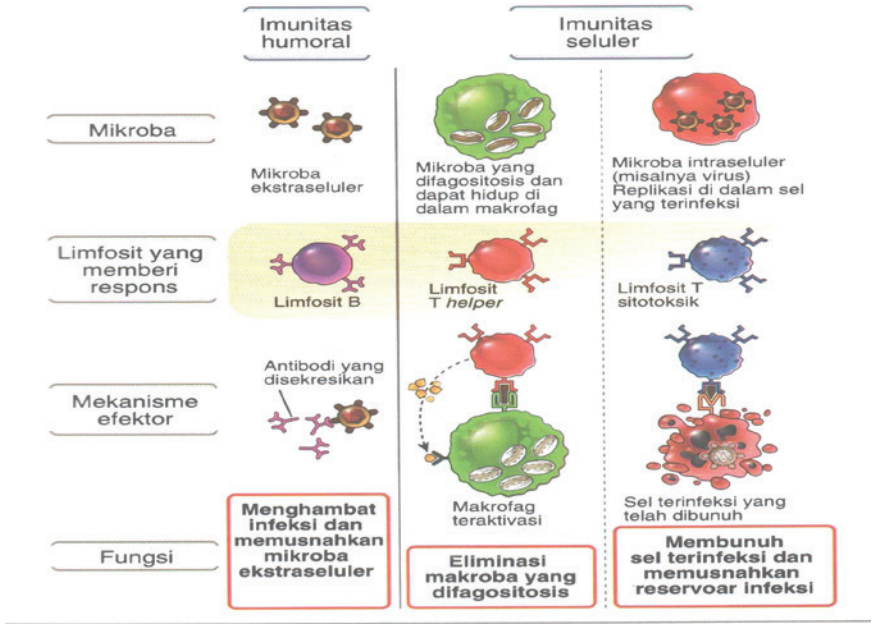

Figure 1

Humoral and cellular immunity [17]

One of the most important functions of antibodies is to stop microbes that are on the mucosal surface and in the blood so that they do not gain access to host cells and do not form colonies in the cells and host connective tissue (Fig. 1). In this way, antibodies prevent infection from developing. Antibodies cannot reach microbes that live and divide in infected cells. [18]

Once tied, B cells receive a signal to begin secreting this form of immunoglobulin, which is a process that initiates an optimal antibody response with the intention of eliminating antigens from the host. Antibodies are a heterogeneous mixture of serum globulins, which work together to demonstrate the ability to bind specific antigens. All serum globulins with antibody activity are called immunoglobulins. [19]

The bond between antigens and antibodies is not covalent, but depends on various bonds with weak forces, such as hydrogen bonds, van der Waals, hydrophobic bonds. Because of the weak nature of the bond, the success of the bond between the antigen and the antibody depends on the area that is very close and appropriate, which can be imagined as the contact between the lock and the lock (a lock and a key). Another important element in the humoral immune response is the complement system. [20]

The reaction between antigens and antibodies activates this complement system, which consists of a series of serum enzymes, and the end of the complement activation reaction is target cell lysis or increases the phagocytosis process by phagocytic cells. Complement activation also results in PMN (phagocytic polymorphonuclear) cell recruitment, which is part of the immune system's acquisition. This activity maximizes the effectiveness of the humoral immune response to invading agents. [21]

Humoral defence consists of complement, acute phase protein, mediator of phospholipid origin, cytokine IL-1, IL-6, TNF-α. Complement consists of a large number of proteins which, when activated, provide protection against infection and play a role in the inflammatory response. Complement acts as opsonin which increases phagocytosis, as a chemotactic factor and also causes bacterial and parasite lysis. [22]

Acute phase protein consists of CRP, lectin, and other acute phase proteins α1-antitrypsin, serum amyloid A, haptoglobin, C9, factor B and fibrinogen. The mediator from phospholipids is needed for the production of prostaglandins and leukotrienes. Both increase the inflammatory response through increased vascular permeability and vasodilation. [23]

The nonspecific immune system uses various soluble molecules. Other soluble factors are produced in a more distant place and are deployed to target tissues through circulation such as complement, acute phase proteins, mediators of the origin of phospholipids and cytokines such as IL-1, IL-6, and TNF-α. [24]

The main actors in the humoral specific immune system are B lymphocytes or B cells. B cells stimulated by foreign objects will proliferate, differentiate, and develop into plasma cells that produce antibodies. The main function of antibodies is defence against extracellular infections, viruses, and bacteria and neutralizes their toxins. [25]

Cellular Immunity

The defence against intracellular microbes is called cellular immunity because the process is mediated by cells called T lymphocytes. Some T lymphocytes activate phagocytes to destroy microbes that have been eaten by phagocytic cells into intracellular phagocytes. Other T lymphocytes kill various types of host cells infected with infectious microbes in their cytoplasm. In both cases, T cells recognize antigens that are displayed on the cell surface, which indicates the presence of microbes in the cell. [26]

There are various T cell subpopulations, each of which has the same specificity for an antigenic determinant (epitope), although the function is different. This is analogous to different classes of immunoglobulins, which have identical specificity but different biological functions. Existing functions originate from various T cell subsets, namely: [27]

1. Working with B cells, increasing antibody production. Such T cells are called helper T cells (TH) and the functions caused by the released cytokines provide various activation signals for B cells.

2. Inflammatory effects. When activating, certain subpopulations of T cells release cytokines, which induce migration and activation of monocytes and macrophages, which cause delayed-type hypersensitivity inflammatory reactions, and that subset of T cells is TDTH cells.

3. Cytotoxic effects. T cells in this subset become cytotoxic kiler cells which if contact with target cells will cause target cell death. These cells are called cytotoxic T cells (Tc).

4. Regulatory effects. Helper T cells can be divided into subsets of different functions determined by the cytokines they release, namely TH! And Mr. Both can regulate each other with negative effects.

5. Signal via cytokine. T cells and other cells involved in the immune system (eg macrophages) affect the effects of various lymphoid and non-lymphoid

cells, through the different cytokines that they release. So, directly or indirectly T cells communicate and collaborate with various cell types.

Over the years, researchers in the field of immunology have known that antigen-activated cells show a variety of effector phenomena. Only in the last century have they noticed the complexity of the events that exist with the activation of antigens and communication with other cells. [28]

Conclusions

The results can be concluded that there are TNF-α have the most significant biological effects on the systemic inflammatory process, namely the deposition of neutrophils and monocytes to the site of infection, stimulating the expression of molecular adhesion of vascular endothelial cells to leukocytes and stimulating chemokine secreting macrophages and induces chemotaxis and leukocyte deposition.

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