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The Effects of Pro-Inflammatory Cytokines on Human Body and Their Relation with Diseases (Review Article)

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Abstract

Cytokines are important mediators in inflammatory disorders that affect the entire body. Signaling molecules called pro-inflammatory cytokines, also known as inflammatory cytokines, are released by the immune system cells including macrophages and T helper cells (Th), which promote inflammation. Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Interleukin-12 (IL-12) are pro-inflammatory cytokines which are released during the inflammations. Other inflammatory cytokines are interleukin-18 (IL-18), interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF) mediate the innate immune response. Immune cells, and activated macrophages release inflammatory cytokines to orchestrate inflammatory responses; however, continuous chronic inflammation release high levels of inflammatory cytokines creating inflammatory microenvironment that are associated with a variety of illnesses, including atherosclerosis, cancer, and other conditions. Although the quantity of inflammation caused by the production of pro-inflammatory cytokines is influenced by ageing, health preservation needs a balance between pro- and anti-inflammatory cytokines. Inflammatory diseases therapy employs monoclonal antibodies that can neutralize inflammatory cytokines or block their receptors.

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Conclusion: A review of previous research shows a strong correlation between cytokines and inflammatory diseases.

Keywords: Effect, Pro-inflammatory cytokines, Human body, Relation with diseases**.**

تأثير السيتوكينات المولدة للالتهابات على جسم الإنسان وعلاقتها بالأمراض

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الخلاصة

السيتوكينات هي مركبات وسطية مهمة في الاضطرابات الالتهابية التي تؤثر على الجسم بأكمله. وهي مواد تحفز الإشارات او الايعازات بين وفي الخلايا وتسمى السايتوكينات المولدة للالتهابات او السيتوكينات الالتهابية, وهي تفرز من خلايا الجهاز المناعي والتي تشمل خلايا البلاعم الكبيرة والخلايا التائية, والتي تولد الالتهاب. الانترلوكين-1 , والانترلوكين-6 , والانترلوكين-12, هي من بين السايتوكينات الالتهابية يتم إطلاقها أثناء الالتهابات . السيتوكينات الاخرى وهي IL-18, IFN-γ, TNF-α, و GM-CSF والتي تَطلق من الخلايا المناعية لتنظيم اوتنسيق الاستجابة المناعية الالتهابية الفطرية. الخلايا المناعية ، والبلاعم الكبيرة المنشطة تطلق السيتوكينات الالتهابية لتنظيم الاستجابات الالتهابية. ومع ذلك ، فإن ان الارتفاع المزمن (طويل الامد) لمستوى السايتوكينات الالتهابية يسبب الالتهابات المرتبطة مع العديد من الامراض مثل تصلب الشرايين, السرطان وغيرها من الامراض. لذلك وللحفاظ على الصحة، يلزم تحقيق توازن بين السيتوكينات المولدة والمضادة للالتهابات. وتتأثر كمية الالتهاب الناجمة عن إنتاج السيتوكينات المولدة للالتهابات أيضا بالشيخوخة والنشاط البدني. يستخدم علاج الأمراض الالتهابية أجساما مضادة وحيدة النسيلة يمكنها تحييد السيتوكينات الالتهابية أو منع مستقبلاتها. من خلال استعراض البحوث السابقة يتبين وجود علاقة ترابطية قوية بين السايتوكينات والامراض الالتهابية.

الكلمات المفتاحية: تأثير، السايتوكينات المولدة للالتهابات، جسم الانسان، العلاقة بالمرض.

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Introduction

Cytokines are small proteins play a crucial role in regulating inflammation during immune response (signaling molecules). Immune cells secrete cytokines to alarm the body as a mechanism defiance against infections that assault the body. Interleukins (IL), interferons (IFN), chemokines, and tumour necrosis factors (TNF) all are examples of cytokines. According to their function; cytokines are categorized into pro-inflammatory and anti-inflammatory cytokines [1]. Pro-inflammatory cytokines are released primarily by innate immune cells especially neutrophils, macrophages, and dendritic cells as well as they are secreted by T helper cells that regulate adaptive immune cells [2]. Dendritic cells, macrophages, CD4+ cells, and Th1 cells release pro-inflammatory cytokines IL-1, IL-2, IL-6, IL-12, IL-17, IL-18, IFN, and TNF. Interleukins (IL), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta-1 (TGF-β1) and granulocyte-macrophage colony-stimulating factor are examples of pro-inflammatory cytokines (GM-CSF) [3]. Pro-inflammatory cytokines often affect immune cells' Proliferation, differentiation, activity, and homing to infection sites to contain and eliminate invasive intracellular pathogens[1]. Pro-inflammatory cytokines play a part in both the development of the inflammatory response and the regulation of the host's tolerance to infections by modulating the innate immune response.[4, 5]. Additionally, neurotic pain is caused by pro-inflammatory cytokines including TNF-, IL-1, and IL-6.[2] . Chronic pro-inflammatory release have negative consequences and contributions to inflammatory conditions that are associated with illnesses including, atherosclerosis, cancer, depression, and other neurological problems [6]. Pro-inflammatory cytokines and anti-inflammatory cytokines balance is necessary to maintain health. Monoclonal antibodies that either neutralize inflammatory cytokines or block their receptors are used to treat inflammatory diseases caused by high levels of pro-inflammatory cytokines [7]. Pro-inflammatory cytokines tends to create disease or causing warning signs linked to disease like fever , inflammation, tissue destruction, and in some cases cytokines storm that lead to shock and finally organ failure

and death [8]. IL-1, IL-6, and TNF- are systemic inflammatory cytokines, and they are essential for coordinating cell-mediated immune responses and are very important in immune system modulation. There are two types of pro-inflammatory Interleukin-1 (IL-1); in reaction to microbial compounds, lymphocytes, macrophages, and monocytes generate the potent pro-inflammatory cytokine IL-1b [1]. Monocytes and macrophages both release interleukin-1, which is also found in nociceptive DRG neurons[4]. The main pro-inflammatory cytokine, IL-6, is a pleiotropic cytokine that its impacts not affect the immune system only, but also other biological systems and several physiological processes, including controlling cell development and the activation, proliferation, differentiation, and survival. Following stimulation, IL-6 is expressed and released by a wide range of cell types, including macrophages, T cells, B cells, mast cells, glial cells, eosinophils, keratinocytes, and granulocytes in addition to monocytes, fibroblasts, and endothelial cells. During microbial invasions various leukocyte subtypes release IL-6 and TNF-α that stimulate the C-reactive protein production from liver. IL-6 is primarily necessary for triggering B-cell differentiation into plasma cells (antibody-forming cells)[2, 3]. An important TNF-α plays a crucial role in local and systemic inflammatory response and it is found in glia and neurons. TNF-α stimulates leukocyte linkages that encourage immune cell penetration and vascular endothelial cell expression. Promoting lymphocyte infiltration to the infection site plays a critical part in the early response to viral infection. TNF-α is frequently engaged in controlling cell apoptosis via several signaling pathways. [1,2,8].

Pro-inflammatory cytokines in renal functions

Ion channels and transporters in kidney nephrons are disrupted by pro-inflammatory cytokines [10,11]. The potassium ion transport channel ; as a result alters the trans-epithelial transport of water and solutes in the kidney. In reactions to lipopolysaccharide (LPS), the proximal tubule of the kidney cells produce pro-inflammatory cytokines which affect potassium ion channels, and this later may be exposed to delayed suppress when stimulated strongly by IFN-γ; additionally, TGF-1 stimulates the KCa3.1 calcium-activated potassium channel, which may contribute to negative consequences [11].

Pro-inflammatory cytokines in Graft-versus-host disease

Graft-versus-host disease (GVHD) is a condition that occurs when donated stem cells or bone marrow (the graft) see the healthy tissues in the patient's body (the host) as foreign and attack them. Host is the recipient body, whereas graft refers to the donated or transplanted organ or tissue. After allogeneic hematopoietic stem cell transplantation, GVHD continues to be the leading cause of morbidity and mortality. By increasing a pro-inflammatory cytokine milieu, graft immune cells are crucial in promoting GVHD. A potential treatment of GVHD involves inhibiting the signaling of propagating pro-inflammatory cytokines, such as targeting of novel T cell–signaling pathways [12]. A side effect of allogeneic bone marrow stem cell transplantation known as GVHD, and it occurs when naive T lymphocytes injected into the recipient tissue cause harm to the tissue. The quantity of naive cells growing along with T regulatory cell, Th1, Th2, or Th17 phenotypes influences the symptoms and severity of GVHD, of which both are varied. Local cytokines substantially impact this maturation. Pro-inflammatory cytokines also have direct impacts on the tissues that GVHD targets. Cytokines play role in orchestrating GVHD in inflammatory conditions in which a predominant T cell is causative of pathology [13-14].

Pro-inflammatory cytokines in lungs cystic fibrosis

In cystic fibrosis, pro-inflammatory cytokines cause hyper-inflammation that destroys lung tissues [15]. Patients with cystic fibrosis have an increased amount of immune cells with a high inflammatory response which makes their lungs less able to get rid of germs and makes them more vulnerable to infections. Asthma symptoms are present in 40–70% of cystic fibrosis patients, perhaps as a result of the loss of the cystic fibrosis transmembrane conductance regulator (CFTR) [16]. T-helper cells create an inflammatory milieu with high amounts of cytokines, which help to enhance the contractility of the smooth muscle in the airways, resulting in asthma [16].

Pro-inflammatory cytokines in cardiovascular disease

A damaged endothelium brought on by atherosclerosis employs immune system cells to repair the damage. Following the stimulation of immune cells by ligands in the vascular heart, pro-inflammatory cytokines mediators lead to inflammation [17]. According to recent studies, exercise can decrease oxidative stress and inflammation in cardiovascular disease. The amount of inflammation caused by released pro-inflammatory cytokines is also affected by ageing and physical activity [18].

Pro-inflammatory cytokines in adipose tissue metabolism and obesity

There may be pro-inflammatory cytokines in adipose tissues. TNF-α and interleukins are produced by adipocytes. This adipose tissue-produced cytokines work as a distant regulator similar to hormones. According to a prior study, Obesity has been linked to high IL-6 and TNF-α levels. The body receives more nutrients as a result of obesity, which causes adipocytes to generate more pro-inflammatory cytokines. In obese people, naturally induced macrophages in visceral fat congregate in adipose tissues and continuously produce pro-inflammatory cytokines, resulting in chronic inflammation. [19, 20].

Pro-inflammatory cytokines in osteoarthritis

Interleukins IL-1, IL-6 and TNF-α, have been reported to have a critical role in cartilage matrix breakdown and bone resorption in osteoarthritis [21]. According to animal model research, inflammatory cytokines drive chondrocytes to produce a cartilage degrading protease such that happens in osteoarthritis condition. Because osteoarthritis in humans is thought to be more complex than in the animal model, this result may not necessarily apply to people [22,23].

Pro-inflammatory cytokines in non-alcoholic fatty liver disease

A significant subset of some individuals with liver inflammation may has fatty liver illnesses, such as alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), which are frequently characterized by lipid buildup[24]. The propensity for inflammation influences

long-term effects of liver disease, such as the emergence liver fibrosis, cirrhosis, and cancer [25,26]. Interleukin (IL) and tumor necrosis factor-alpha (TNF-α) are pro-inflammatory cytokines that are important in several phases of liver disease. These essential cytokines influence all types of liver cells and control the release of several other intermediates that are important in chronic liver disease [27-31].

The organization of inflammatory processes throughout the body is fundamentally influenced by cytokines and adipocytokines, intermediaries produced from adipocytes; additionally, some of these intermediates can control a variety of processes, such as inflammatory, immunological, and metabolic processes like insulin resistance (IR) [31-33]. TNF-α, IL-1, and IL-6, pro-inflammatory cytokines, have a significant role in the pathogenesis of many features of human non-alcoholic fatty liver disease (NAFLD) [27-34]. Due to genetic modification and over-nutrition, the significance of TNF-α in fatty liver disorders has been established. [35,36]. The importance of mediators in reducing inflammation and IR has been demonstrated by vitro experimental studies using anti-inflammatory cytokines, which have potent TNF-α-counteracting properties. [31,35,36]. As a result, the balance between pro- and anti-inflammatory actions appears to be crucial for systemic insulin activity and hepatic action, both of which are thought to play significant roles in the development of NAFLD. [9,36-38].

Pro-inflammatory cytokines in the pathogenesis of viral infection

Pro-inflammatory cytokines are raised during viral infections such as Parvovirus B19, SARS-CoV-2, RSV, and influenza and fall once the virus has cleared the body [2,3,5-7]. Influenza A and SARS-CoV-2 infections with viruses increase the virus' ability to reproduce in respiratory epithelial cells. Infection causes inflammatory reaction that can directly destroy lung cells; as a result, more dead (apoptotic) cells which were phagocyted by pulmonary macrophages accumulate. Following phagocytosis; macrophages release proinflammatory cytokines that stimulate other immune cells and cause acute local inflammation. [2,3,5-7,39,40]. In addition to attracting additional macrophages and monocytes to the infection site to clear the residual pieces of the apoptotic cells, this binding (phagocytosis) raises the levels of the local IL-1 and

IL-8. The viral peptides are delivered by macrophages to T-helper cells, which activate, differentiate, and produce and release Th1 pro-inflammatory cytokines. Local IL-6, IFN-γ, and chemokines are released during this activation and differentiation and are then transported into the circulation by n-graft anti-inflammatory cytokines [39,40]. The pro-inflammatory cytokines IL-12 and IL-8 are generated in SARS-CoV-2 to trigger IFN-γ production, which draws monocytes and T lymphocytes to promote apoptosis and kill the infected cells [3]. The infection site attracts the regulatory T cells. For the regulation and management of the intensity of cellular immune responses to viral infections, they are crucial middlemen. They exude IL-10, a crucial regulatory cytokine that suppresses the immune system's overactive T cell response and sense of balance [40].

Pro-inflammatory cytokine regulation

Pro-inflammatory cytokines and chemokines at higher levels are associated with a primary viral infection. Therefore, maintaining the immune system's hemostasis depends on controlling cytokine production. Severe inflammation can be brought on by dysregulated cytokine production. It has been suggested that changes in the balance of the Th1/Th2 cytokine response or an uneven pro-inflammatory cytokine pattern play a part in the adjustment of the viral infection and cause Parvovirus (viral persistence) [7]. By reducing immunity (innate and acquired) several interleukins help to decrease and controlling of the inflammation. The condition known as cytokine release syndrome or cytokine storm results from an immunological response that is not properly controlled. The intense pro-inflammatory reaction and weak anti-inflammatory response characterize this singularity [41]. A cytokine release syndrome can have a variety of origins, but it gained attention in medical research since it is thought to be the primary factor in the morbidity and mortality of viral illnesses like SARS-CoV-2 infection [42]. Sepsis, toxic shock syndrome, macrophage activation syndrome, hem phagocytic lymphohistiocytosis, and malignancy-associated syndrome of hyper inflammation (MASH) are just a few of the disorders that have been identified as being characterized by a cytokine storm [43, 44]. Interferons, TNF-α, IL-1, and most significantly IL-6 are crucial markers for disorders that include a cytokine storm [45].

Clinical treatments

The biological activity of pro-inflammatory cytokines can be reduced to lessen the severity of disease attacks [9]. Inflammatory bowel illness and rheumatoid arthritis patients have found great relief by inhibiting IL-1 or TNF-α [46], or graft-vs-host disease (GvHD) [9,12]. But in sepsis-stricken individuals, this treatment has not yet proved effective [9]. The therapeutic benefits of acupuncture may be connected to the body's capacity to inhibit a variety of pro-inflammatory cytokines, including IL-1, IL-6, IL-10, and TNF [47].

Estrogen have been demonstrated to assist healing by decreasing the production of a variety of pro-inflammatory cytokines, such as IL-6 [48], TNF-α [49], and macrophage migration inhibitory factor (MIF). MIF levels are frequently reported to be elevated in the vicinity of chronic wounds that never heal. If estrogen-based healing is effective, their levels can drop significantly. According to experimental data, "estrogen governs healing almost entirely through MIF down-regulation. Clinical research on ageing skin and skin wounds has linked estrogen's ability to inhibit MIF to aiding healing. Sadly, according to the American Cancer Society, estrogen therapy has recognized carcinogenic consequences (higher rates of breast cancer in women) [50].

On the other hand, examining "downstream impacts on genes/factors that intermediate the effects of estrogen on healing" might lead to important discoveries in the future [51]. Several studies also recommend an immune regulatory effect of vitamin D, which has been revealed to decrease the release of specific pro-inflammatory cytokines [52,53].

Conclusion

A review of previous research shows a strong correlation between cytokines and inflammatory diseases.

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