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THE ACTION OF CYTOKINES ANDGROWTH FACTORS IN THE INFLAMMATORY RESPONSE OF THE BODY

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Abstract
Cytokines and growth factors are highly potent proteins (active in picomolar concentrations) that exert a wide range of biological effects. Unlike hormones, which maintain homeostatic balance, cytokines and growth factors provide a response to foreign body invasion, immune damage, inflammation, repair and regeneration. They form a network of communication signals between immune system cells and cells of other organs and tissues. These proteins promote inflammation and immune response, but their secretion may be in response to other stimuli (microorganisms, their waste products). In addition to secretion, cytokines can be expressed on the surface of stimulated cells. They bind to specific receptors on target cells [1,2,3].

Keywords: Target cells, secretion, cytokines, growth factors, inflammation.

Introduction

Like hormones, cytokines act indirectly on target cells, altering their behaviour via secondary messengers. Cytokines can act on the producing cell (autocrine action), on cells neighbouring the producing cell (paracrine action) or, like hormones, on distant cells in organs and tissues (endocrine action). One cytokine often triggers the secretion of a second cytokine by the target cell (cytokine cascade). A cell's own cytokines often alter the nature of the interaction of other cytokines on the same cell. Such interaction can be synergistic, additive, inhibitory, or even lead to the formation of a new effect unknown to any single cytokine of the cell [4,5,6].

The main target cells for cytokines are leukocytes. On the one hand, leukocytes are sources of cytokines, and on the other, they are targets for them. In this regard, they have been given the name ‘interleukins’ [7,8,9].

Interleukin-1 (IL-1) is primarily produced by blood monocytes and tissue macrophages, but many other cell types, including keratinocytes, can also produce this cytokine. It exists as a compound attached to the cell membrane. This enables activated macrophages to induce T-cell proliferation through cell-to-cell contact when IL-1 cannot be detected in the circulating bloodstream. The effect of IL-1 on the immune system includes T-cell proliferation by stimulating IL-2 production and increasing the number of IL-2 receptors, with a simultaneous increase in the release of neutrophils from the bone marrow. The latter event is also influenced by colony-stimulating factor (GM-CSF), which is produced in response to the action of IL-1 on macrophages [8,9,10,11].

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webofjournals.com/index.php/5

The metabolic effects of IL-1 have also been identified, including:

1) an increase in body temperature as a result of the action of prostanoids on the central nervous system; 2) an increase in IL-6 levels and, simultaneously, an increase in the production of acute phase proteins by the liver; 3) a decrease in plasma iron and zinc levels; 4) increased muscle catabolism, although a similar effect may be due to TNF to a greater extent; 5) development of anaemia as a result of stem cells being intensively used up in the formation of leukocytes; 6) wound healing and connective tissue repair. The predominant effect of IL-1 is its ability to increase vascular permeability and procoagulant activity, especially in the presence of increased TNF production [9,10,11,12].

Interleukin-1 is a pleiotropic mediator. Its binding to receptors causes an increase in body temperature, sleep disturbances, anorexia, generalised myalgia, arthralgia, headache, and certain gastrointestinal disorders [13,14,15].

Interleukin-2 (IL-2) is a cytokine produced by T lymphocytes. Its main role is to stimulate cellular immunity and enhance the cytotoxic function of T cells. IL-2 production depends on IL-1 production by macrophages. The nature of IL-2 production and action is well established. The decrease in IL-2 levels is due to the action of a combination of serum depressant factors, in particular increased PGE2 production. Low IL-2 levels correlate with increased mortality in sepsis in animals. Treatment with low levels of IL-2 ibuprofen increases the animals' resistance to infection. A deficiency of this cytokine plays an important role in reducing the resistance to infection in burn patients. On the other hand, increased IL-2 levels can have a negative effect in patients with hypermetabolism and organ failure. This effect is due to the fact that IL-2 causes the release of TNF and gamma interferon, which contribute to increased catabolism [16,17,18].

Interleukin-6 (IL-6) is a member of a family of various phosphoglycoproteins and was initially called hepatocyte-stimulating factor. These cytokines are produced in various tissues, except macrophages, including neutrophils and fibroblasts. IL-6 enters the bloodstream very quickly in response to injury or infection, particularly circulating endotoxin. They have immunological and metabolic effects. Die immunologische Wirkung umfasst eine Erhöhung der B-Zell-Proliferation und der Immunglobulinproduktion. Die metabolische Wirkung besteht in der Stimulierung der Produktion von Akutphasenproteinen in der Leber. Bei Verbrennungsopfern erreicht der Serum-IL-6-Spiegel etwa eine Woche nach der Verbrennung seinen Höchstwert und entspricht dem Endotoxinspiegel, wobei ein sehr hoher Spiegel mit Mortalität einhergeht IL-6 stimulates antibody production (T-cell factor or factor released by T-lymphocytes). It promotes the maturation of B cells into antibody-producing plasma cells [19,20,21].

Thus, IL-1, IL-6, and TNF-α are involved in the regulation of inflammation, immune response, and haematopoiesis [1,2,3].

Natural gamma interferon is a cytokine produced by human T helper cells and certain populations of macrophages. It is the first agent in the implementation of macrophage function. It increases the activity of other cytokines, in particular TNF [20,21].

Colony-stimulating factors are a family of glycoproteins involved in stimulating the formation of various cell lines in the bone marrow. This group includes erythropoietin, granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (GM-CSF). The latter is particularly important in burns [18,19].

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Interleukin-4 (IL-4) stimulates the proliferation of Ig-activated B cells, T lymphocytes, mast cells and thymocytes, regulates the production of IgE and IgG1 by B cells, induces the expression of Ia and Fe receptors on lymphocytes and monocytes, increases the antigen-presenting ability of monocytes, regulates colony formation from haematopoietic precursors in combination with colony-stimulating factor, inhibits the formation of lymphokine-activated killer cells, inhibits the production of IL-1, TNF-α and IL-6, acting as an antagonist of inflammatory cytokines [15,16,17].

Small cytokines are a superfamily of secreted factors with low molecular weight belonging to the platelet-derived growth factor-4 (PDGF-4) superfamily and, along with other immune cytokines, regulate immune-inflammatory responses. All polypeptides of the superfamily, depending on the position of the four cysteine residues they contain, are divided into two branches: C-C and C-X-C. The C-X-C branch includes molecules such as PFT4 and IL-8. The C-C branch includes polypeptides grouped under the name 'RANTES/SIS'. These include six different molecules: RANTES, 1-309, monocyte chemotactic factor-1 (MCF-1), HC14, and macrophage inflammatory proteins (HuMIP-1a and HuMIP-1b) [5,6,7].

A distinctive feature of these molecules is their 'inducibility', i.e. they are hardly secreted (expressed) in unstimulated cells. They play an important role in the migration of various leukocyte populations to the site of damage or introduction of an infectious or other 'antigenic' agent. Another important component of this movement is the homing of circulating lymphocytes [4,5,8].

One of the main proteins in blood serum, alpha2-MG, interacts with a large number of cytokines. In the first stage, the native molecule is converted into a 'fast' form under the influence of endogenous proteins. Then, the 'fast' form binds to the cytokine, and the resulting complex interacts with cytokine receptors on the surface of target cells or with receptors for the 'fast' form of alpha2-MG on the surface of macrophages, hepatocytes, or fibroblasts. Alpha2-MG molecules serve to rapidly eliminate excess cytokines that are not bound to cell receptors, performing a protective function together with natural antibodies. They themselves can be removed from the blood by binding to receptors on the surface of macrophages, fibroblasts, and hepatocytes. In addition to cytokines, alpha2-MG molecules are capable of binding endopeptidases, mitogens, and various ions, including zinc and nickel cations [4,5,6].

Thus, simultaneously with the molecular transformations that cause inflammation, processes begin that are aimed at restoring damaged tissues and healing them, which are associated with the activation and regulation of growth factors [23,24].

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