Cytokines

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Abstract: Cytokines are a group of cell signaling molecules that play roles in aid cell-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. Cytokine molecules can be peptide, protein and glycoprotein.
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Cytokines are a group of cell signaling molecules that play roles in aid cell-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. Cytokine molecules can be peptide, protein and glycoprotein.

Cytokines are a group of small proteins (about 5–20 kDa) that are important in cell signaling and immunology. They are synthesized and released by cells and affect the cells including the cells releasing the cytokines and other cells. Cytokines include chemokines, interferons, interleukins, lymphokines, tumour necrosis factor, etc. Cytokines are produced by cells including immune cells such as macrophages, B lymphocytes, T lymphocytes and mast cells endothelial cells, fibroblasts and various stromal cells; etc.

Cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Cytokines act through receptors. Some cytokines enhance or inhibit the action of other cytokines in complex ways. They are different from hormones that are also important cell signaling. Hormones circulate in much lower concentrations and hormones tend to be made by specific kinds of cells.

Cytokines are important in health and disease that responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction.

Interferon-alpha, an interferon type I, was discovered in 1957 as a protein that interfered with viral replication. The activity of interferon-gamma was identified in 1965, and macrophage migration inhibitory factor was identified in 1966. In 1969 Dudley Dumonde proposed the term lymphokine to describe proteins secreted from lymphocytes and the proteins derived from macrophages and monocytes in culture were called as monokines, and named as cytokines later.

Cytokines could circulate in a concentration of picomolar (10^{-12} M) (such as IL-6) and hormones norlly circulate in nanomolar (10^{-9} M). The immunomodulating effects of cytokines are systemic rather than local. Cytokines have been classed as lymphokines, interleukins and chemokines according to their functions, secretion cells and function target. Such as, the interleukin targets leukocytes.

The following are some cytokines related to their producing or functions:

- Lymphokines, produced by lymphocytes
- Monokines, produced by monocytes
- Interferons, involved in antiviral responses
- Colony stimulating factors, support the growth of cells in semisolid media
- Chemokines mediate chemoattraction between cells.

The inflammatory cytokines can be induced by oxidative stress, and cytokines can trigger the release of other cytokines. The cytokine receptors are important in the immunology, and they can be classified based on their three-dimensional structure and function. Type I cytokine receptors have certain conserved motifs in their extracellular amino-acid domain. Type II cytokine receptors are receptors mainly for interferons. Immune cells can produce signalling factors called cytokines, which trigger inflammation.

Chemokines are a family of small cytokines, or signaling proteins secreted by cells. The major role of chemokines is to act as a chemoattractant to guide the migration of cells. Cells that are attracted by chemokines follow a signal of increasing chemokine concentration towards the source of the chemokine. Some chemokines control cells of the immune system during processes of immune surveillance, such as

directing lymphocytes to the lymph nodes so they can screen for invasion of pathogens by interacting with antigen-presenting cells residing in these tissues. These are known as homeostatic chemokines and are produced and secreted without any need to stimulate their source cell(s).

Interferons (IFNs) are a group of signaling proteins[1] made and released by host cells in response to the presence of pathogens, such as viruses, bacteria, parasites, or tumor cells. In a typical scenario, a virus-infected cell will release interferons causing nearby cells to heighten their anti-viral defenses. IFNs belong to the large class of proteins known as cytokines, molecules used for communication between cells to trigger the protective defenses of the immune system that help eradicate pathogens. Interferons are named for their ability to "interfere" with viral replication[2] by protecting cells from virus infections. IFNs also have various other functions: they activate immune cells, such as natural killer cells and macrophages; they increase host defenses by up-regulating antigen presentation by virtue of increasing the expression of major histocompatibility complex (MHC) antigens. Certain symptoms of infections, such as fever, muscle pain and "flu-like symptoms", are also caused by the production of IFNs and other cytokines.

Interleukin are a group of cytokines that were first seen to be expressed by white blood cells (leukocytes). The function of the immune system depends in a large part on interleukins, and rare deficiencies of a number of them have been described, all featuring autoimmune diseases or immune deficiency. The majority of interleukins are synthesized by helper CD4 T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells. Interleukin receptors on astrocytes in the hippocampus are also known to be involved in the development of spatial memories in mice.

Lymphokines are a subset of cytokines that are produced by a type of immune cell known as a lymphocyte. They are protein mediators typically produced by T cells to direct the immune system response by signalling between its cells. Lymphokines have many roles, including the attraction of other immune cells, including macrophages and other lymphocytes, to an infected site and their subsequent activation to prepare them to mount an immune response. Circulating lymphocytes can detect a very small concentration of lymphokine and then move up the concentration gradient towards where the immune response is required. Lymphokines aid B cells to produce antibodies.

Tumor necrosis factors (or the TNF family) refer to a group of cytokines that can cause cell death (apoptosis). The first two members of the family to be identified were: (1) Tumor necrosis factor (TNF), formerly known as TNFα or TNF alpha, is the best-known member of this class. TNF is a monocyte-derived cytotoxin that has been implicated in tumor regression, septic shock, and cachexia. The protein is synthesized as a prohormone with an unusually long and atypical signal sequence, which is absent from the mature secreted cytokine. A short hydrophobic stretch of amino acids serves to anchor the prohormone in lipid bilayers.[5] Both the mature protein and a partially processed form of the hormone can be secreted after cleavage of the propeptide. (2) Lymphotoxin-alpha, formerly known as Tumor necrosis factor-beta (TNF-β), is a cytokine that is inhibited by interleukin 10.

Toll-like receptors (TLRs) play important roles in the immune system. Toll-like receptor 4 (TLR 4) is one of toll-like receptors that detects lipopolysaccharide (LPS) from Gram-negative bacteria and is important in the activation of the living bodies' innate immune system (Medzhitovm 1997; Rock, 1998). TLR 4 is a kind of cluster of differentiation 284 (CD284). The structure of TLRs is conserved from Drosophila to human beings and the structural and functional are similar in different species. They recognize pathogen-associated molecular patterns (PAMPs) that are expressed to respond infectious factor for the development of effective immunity. TLR 4 is expressed abundantly in the animal placenta. It cooperates with CD14 to regulate the signal transduction induced by LPS found in most gram-negative bacteria. The molecular weight of TLR 4 is approximately 95 kD. TLRs exist in both the vertebrates and invertebrates. TLRs are conserved components of the immune system. Toll-like receptors are one of the key molecules related to the immune system reacting to the microbial infections. Both mammalian and invertebrate require Toll genes for innate immunity. TLRs were identified also in the mammalian nervous system, which were detected on glia, neurons and on neural progenitor cells in which they regulate cell-fate decision. Most mammalian species have 10 to 15 types of Toll-like receptors, and 13 TLRs (TLR1 to TLR13) have been identified in humans and mice together, and equivalent forms of many of these have been found in other mammalian species. TLR3 is the only Toll-like receptor which does not use the MyD88 dependent pathway. TLRs seem to be involved only in the cytokine production and cellular activation in response to microbes, and do not play a significant role in the adhesion and phagocytosis of microorganisms. Toll-like receptors bind and become activated by different ligands, which,

in turn, are located on different types of organisms or structures. They also have different adapters to respond to activation and are located sometimes at the cell surface and sometimes to internal cell compartments. Immune cells can produce signalling factors called cytokines, which trigger inflammation. In the case of a bacterial factor, the pathogen might be phagocytosed and digested, and its antigens presented to CD4+ T cells. In the case of a viral factor, the infected cell may shut off its protein synthesis and may undergo programmed cell death (apoptosis). Immune cells that have detected a virus may also release anti-viral factors such as interferons. (Ma, et al, 2014).

Toll-like receptor 4 (TLR 4) is a toll-like receptor that detects lipopolysaccharide from Gram-negative bacteria and is thus important in the activation of the innate immune system. TLR 4 has also been designated as CD284 (cluster of differentiation 284). Stimulation of unrestricted somatic stem cells with either lipopolysaccharide (LPS) or flagellin resulted in a marked increase of interleukin (IL)-6 and/or IL-8 production although levels differed significantly between both stimuli (van den Berk, Jansen et al. 2009). Apoptosis of implanted MSCs limits the efficiency of MSC therapy. Wang et al showed the ligands of Toll-like receptors (TLRs) could control the function of these cells. The appropriate treatments with LPS can protect MSCs from oxidative stress-induced apoptosis and improve the survival of MSCs via the TLR4 and PI3K/Akt pathway. Endotoxin LPS is a structural component of gram-negative bacteria membranes and a potent proinflammatory agent. Epidemiologic reports indicate that exposure to endotoxin can cause inflammatory airway diseases in agricultural workers and can exacerbate reactive airway disease in those with asthma and in wheezing children. A single exposure to aerosolized LPS can induce airflow obstruction that commences within min of challenge and persists for up to 48 h. Inhaled LPS leads to neutrophil recruitment and the release of proinflammatory molecules, including interleukin (IL), tumor necrosis factor (TNF), and the chemokines macrophage inflammatory protein-2, keratinocyte-derived chemokine (Hollingsworth, et al, 2004; Ma and Yang, 2011).

Cytokines have been developed into drugs in the medical therapy.

Cytokines are molecular messengers between cells, with regard to arthritis, cytokines regulate various inflammatory responses.

The body produces different types of cytokines:

• colony stimulating factors (stimulate production of blood cells)

• growth and differentiation factors (function primarily in development)

• immunoregulatory and proinflammatory cytokines (interferon, interleukins, and TNF-alpha that function in the immune system). The immune cells and proteins do different jobs, and cytokines are among those proteins. Biologic drugs have been developed to inhibit IL-1 or TNF-alpha.

Cell signalling is a complex system of communication that play roles in the basic cellular activities and coordinates cell actions. The ability of cells in the microenvironment Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and diabetes.

The immune system is a biological structures and processes within an life body that protects against disease such as inflammation and bacteria infection. To function properly, an immune system must detect a wide variety of agents, such as pathogens, from viruses to bacteria, and distinguish them from the life body itself. In many species, the immune system can be classified into subsystems, such as the innate immune system versus the adaptive immune system, or humoral immunity versus cell-mediated immunity.

Pathogens can evolve and adapt, and thereby avoid to be detected and neutralized by the living bodies' immune system. The multiple defense mechanisms are evolving to recognize and neutralize pathogens. The simple unicellular organisms such as bacteria possess the rudimentary immune system also, twhich are in the form of enzymes that protect against bacteriophage infections. Other basic immune mechanisms evolved in ancient eukaryotes and remain in their modern descendants, such as plants and insects. These mechanisms include phagocytosis, antimicrobial peptides and the complement system. The vertebrates including humans have even more sophisticated defense mechanisms including the ability to adapt over time to recognize specific pathogens more efficiently. The adaptive immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen.

Disorders of the immune system can result in autoimmune diseases, inflammatory diseases and cancer. Immunodeficiency occurs when the immune system is less active than normal, resulting in recurring and life-threatening infections. In humans, immunodeficiency can either be the result of a genetic disease such as severe combined immunodeficiency, acquired conditions such as HIV/AIDS, or the use of immunosuppressive medication. In contrast, autoimmunity results from a hyperactive immune system attacking normal tissues as if they are foreign organisms. Common autoimmune diseases include

Hashimoto's thyroiditis, rheumatoid arthritis, diabetes mellitus type 1, and systemic lupus erythematosus. Immunology covers the study of all aspects of the immune system (Wikipedia., 2015).

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