Learning Objectives

1. Describe the following:
   a. cytokines
   b. chemokines
   c. interferons

2. State what is meant by the phrase "Cytokines are pleiotropic, redundant, and multifunctional."

3. Name the two cytokines that are most important in stimulating acute inflammation.

4. Describe specifically how type I interferons are able to block viral replication within an infected host cell.

Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems. They are produced by virtually all cells involved in innate and adaptive immunity, but especially by T-helper (Th) lymphocytes. The activation of cytokine-producing cells triggers them to synthesize and secrete their cytokines. The cytokines, in turn, are then able to bind to specific cytokine receptors on other cells of the immune system and influence their activity in some manner.

Cytokines are pleiotropic, redundant, and multifunctional.

- Pleiotropic means that a particular cytokine can act on a number of different types of cells rather than a single cell type.
- Redundant refers to the ability of a number of different cytokines to carry out the same function.
- Multifunctional means the same cytokine is able to regulate a number of different functions.

Some cytokines are antagonistic in that one cytokine stimulates a particular defense function while another cytokine inhibits that function. Other cytokines are synergistic wherein two different cytokines have a greater effect in combination.
There are three functional categories of cytokines:

1. cytokines that regulate innate immune responses,
2. cytokines that regulate adaptive immune responses, and
3. cytokines that stimulate hematopoiesis.

Cytokines that regulate innate immunity are produced primarily by mononuclear phagocytes such as macrophages and dendritic cells, although they can also be produced by T-lymphocytes, NK cells, endothelial cells, and mucosal epithelial cells. They are produced primarily in response to pathogen-associated molecular patterns (PAMPs) such as LPS, peptidoglycan monomers, teichoic acids, unmethylated cytosine-guanine dinucleotide or CpG sequences in bacterial and viral genomes, and double-stranded viral RNA. Cytokines produced in response to PRRs on cell surfaces, such as the inflammatory cytokines IL-1, IL-6, IL-8, and TNF-alpha, mainly act on leukocytes and the endothelial cells that form blood vessels in order to promote and control early inflammatory responses (Figure \(\PageIndex{1}\)). Cytokines produced in response to PRRs that recognize viral nucleic acids, such as type I interferons, primarily block viral replication within infected host cells (see Figure \(\PageIndex{2}\)A and Figure \(\PageIndex{2}\)B).

**Figure \(\PageIndex{1}\):** Integrins on the surface of the leukocyte bind to adhesion molecules on the inner surface of the vascular endothelial cells. The leukocytes flatten out and squeeze between the endothelial cells to leave the blood vessels and enter the tissue. The increased capillary permeability also allows plasma to enter the tissue.

Examples include:

**a. Tumor necrosis factor-alpha (TNF-a)**

TNF-a is the principle cytokine that mediates acute inflammation. In excessive amounts it also is the principal cause of systemic complications such as the shock cascade. Functions include acting on endothelial cells to stimulate inflammation and the coagulation pathway; stimulating endothelial cells to produce selectins and ligands for leukocyte integrins during diapedesis; stimulating endothelial cells and macrophages to produce chemokines that contribute to diapedesis, chemotaxis, and the recruitment of leukocytes; stimulating macrophages to secrete interleukin-1 (IL-1) for redundancy; activating neutrophils and promoting extracellular killing by neutrophils; stimulating the liver to produce acute phase proteins, and acting on muscles and fat to stimulate catabolism for energy conversion. TNF-a stimulates the endothelial cells that form capillaries to express proteins that activate blood clot formation within the capillaries. This occludes local blood flow to help prevent microbes from entering the bloodstream. In addition, TNF is cytotoxic for some tumor cells; interacts with the hypothalamus to induce fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; and activates macrophages. TNF is produced by monocytes, macrophages,
dendritic cells, T\textsubscript{H}1 cells, and other cells.

b. Interleukin-1 (IL-1)

IL-1 function similarly to TNF in that it mediates acute inflammatory responses. It also works synergistically with TNF to enhance inflammation. Functions of IL-1 include promoting inflammation; activating the coagulation pathway, stimulating the liver to produce acute phase proteins, catabolism of fat for energy conversion, inducing fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; stimulates the synthesis of adhesion factors on endothelial cells and leukocytes (see Figure \(\PageIndex{1}\)) for diapedesis; and activates macrophages. IL-1 is produced primarily by monocytes, macrophages, dendritic cells, endothelial cells, and some epithelial cell.

c. Chemokines

Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation. They increase the affinity of integrins on leukocytes for ligands on the vascular wall (see Figure \(\PageIndex{1}\)) during diapedesis, regulate the polymerization and depolymerization of actin in leukocytes for movement and migration, and function as chemoattractants for leukocytes. In addition, they trigger some WBCs to release their killing agents for extracellular killing and induce some WBCs to ingest the remains of damaged tissue. Certain chemokines promote angiogenesis. Chemokines also regulate the movement of B-lymphocytes, T-lymphocytes, and dendritic cells through the lymph nodes and the spleen. When produced in excess amounts, chemokines can lead to damage of healthy tissue as seen in such disorders as rheumatoid arthritis, pneumonia, asthma, adult respiratory distress syndrome (ARDS), and septic shock. Examples of chemokines include IL-8, MIP-1a, MIP-1b, MCP-1, MCP-2, MCP-3, GRO-a, GRO-b, GRO-g, RANTES, and eotaxin. Chemokines are produced by many cells including leukocytes, endothelial cells, epithelial cells, and fibroblasts.

d. Interleukin-12 (IL-12)

IL-12 is a primary mediator of early innate immune responses to intracellular microbes. It is also an inducer of cell-mediated immunity. It functions to stimulate the synthesis of interferon-gamma by T-lymphocytes and NK cells; increases the killing activity of cytotoxic T-lymphocytes and NK cells; and stimulates the differentiation of naive T4-lymphocytes into interferon-gamma producing T\textsubscript{H}1 cells. It is produced mainly by macrophages and dendritic cells.

e. Type I Interferons

Interferons modulate the activity of virtually every component of the immune system. Type I interferons include 13 subtypes of interferon-alpha, interferon-beta, interferon omega, interferon-kappa, and interferon tau. (There is only one type II interferon, interferon-gamma, which is involved in the inflammatory response.)

The most powerful stimulus for type I interferons is the binding of viral DNA or RNA to toll-like receptors TLR-3, TLR-7, and TLR-9 in endosomal membranes.

a. TLR-3 - binds double-stranded viral RNA;
b. TLR-7 - binds single-stranded viral RNA, such as in HIV, rich in guanine/uracil nucleotide pairs; 
c. TLR-9 - binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral 
genomes but uncommon or masked in human DNA and RNA.

| Flash animation showing toll-like receptors (TLRs) recognizing viral double-stranded RNA. |
| html5 version of animation for iPad showing toll-like receptors (TLRs) recognizing viral double-stranded RNA. |

Signaling pattern recognition receptors located in the cytoplasm of cells such as RIG-1 and MDA-5 also signal synthesis 
and secretion of type-I interferons.

| For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5 |

Type I interferons, produced abundantly by plasmacytoid dendritic cells, by virtually any virus-infected cell, and by other 
defense cells provide an early innate immune response against viruses. Interferons induce uninfected cells to produce 
an enzyme capable of degrading viral mRNA, as well as one that blocks translation in eukaryotic cells. These enzymes 
remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin 
to degrade viral mRNA and block translation in the host cell. This not only blocks viral protein synthesis, it also 
eventually kills the infected cell (see Figure \(\PageIndex{2}\)A and Figure \(\PageIndex{2}\)B). In addition, type I 
interferons also cause infected cells to produce enzymes that interfere with transcription of viral RNA or DNA. They also 
promote body defenses by enhancing the activities of CTLs, macrophages, dendritic cells, NK cells, and antibody-
producing cells, as well as induce chemokine production to attract leukocytes to the area.

| GIF animation showing the antiviral nature of interferon. |

Type I interferons also induce MHC-I antigen expression needed for recognition of antigens by cytotoxic T-lymphocytes ; 
augment macrophages, NK cells, cytotoxic T-lymphocytes, and B-lymphocytes activity; and induce fever. Interferon-
alpha is produced by T-lymphocytes, B-lymphocytes, NK cells, monocytes/macrophages; interferon-beta by virus-
infected cells, fibroblasts, macrophages, epithelial cells, and endothelial cells.

f. Interleukin-6 (IL-6)

IL-6 functions to stimulate the liver to produce acute phase proteins ; stimulates the proliferation of B-lymphocytes ; and 
increases neutrophil production. IL-6 is produced by many cells including T-lymphocytes, macrophages, monocytes, 
endothelial cells, and fibroblasts.

g. Interleukin-10 (IL-10)

IL-10 is an inhibitor of activated macrophages and dendritic cells and as such, regulates innate immunity and cell-
mediated immunity. IL-10 inhibits their production of IL-12, co-stimulator molecules, and MHC-II molecules, all of which 
are needed for cell-mediated immunity. IL-10 is produced mainly by macrophages, and TH2 cells.
h. Interleukin 15 (IL-15)

IL-15 stimulates NK cell proliferation and proliferation of memory T8-lymphocytes. IL-15 is produced by various cells including macrophages.

i. Interleukin-18 (IL-18)

IL-18 stimulates the production of interferon-gamma by NK cells and T-lymphocytes and thus induces cell-mediated immunity. It is produced mainly by macrophages.

A number of human cytokines produced by recombinant DNA technologies are now being used to treat various infections or immune disorders. These include:

1. recombinant interferon alfa-2a (Roferon-A): a cytokine used to treat Kaposi's sarcoma, chronic myelogenous leukemia, and hairy cell leukemia.
2. peginterferon alfa-2a (Pegasys): used to treat hepatitis C (HCV).
3. recombinant interferon-alpha 2b (Intron A): a cytokine produced by recombinant DNA technology and used to treat Hepatitis B; malignant melanoma, Kaposi's sarcoma, follicular lymphoma, hairy cell leukemia, warts, and Hepatitis C.
4. peginterferon alfa-2b (PEG-Intron; PEG-Intron Redipen): used to treat hepatitis C (HCV).
5. recombinant Interferon alfa-2b plus the antiviral drug ribavirin (Rebetron): used to treat hepatitis C (HCV).
6. recombinant interferon-alpha n3 (Alferon N): used to treat warts.
7. recombinant Interferon alfacon-1 (Infergen): used to treat hepatitis C (HCV).

Concept Map for Cytokines Important in Innate Immunity

Summary

1. Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
2. Cytokines are pleiotropic, meaning meaning that a particular cytokine can act on a number of different types of cells rather than a single cell type.
3. Cytokines are redundant, meaning that a number of different cytokines are able to carry out the same function.
4. Cytokines are multifunctional, meaning that the same cytokine is able to regulate a number of different functions.
5. Tumor necrosis factor-alpha (TNF-a) and interleukin-1 (IL-1) are the principle cytokines that mediates acute inflammation.
6. Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the
site of inflammation.

7. Type I interferons, produced abundantly by plasmacytoid dendritic cells, by virtually any virus-infected cell, and by other defense cells provide an early innate immune response against viruses by inducing uninfected cells to produce enzymes capable of degrading viral mRNA and blocking translation in eukaryotic cells. They also enhance the activities of CTLs, macrophages, dendritic cells, NK cells, and antibody-producing cells and induce chemokine production to attract leukocytes to the area.

8. Type II interferon is involved in stimulating an inflammatory response.

Contributors and Attributions

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