Cytokines

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Cytokines

- Proteins secreted by the cells of innate and adaptive immunity that mediate many of the functions of the cells.
- In the activation phase of adaptive immune responses, cytokines stimulate the growth and differentiation of lymphocites.
- In the effector phase, activate different effector cells to eliminate microbes and other antigens.
- Stimulate the development of hematopoietic cells.
In Clinical Medicine

- Important as therapeutic agents and as targets for specific antagonists in numerous immune and inflammatory disease.
Nomenclature

- Monokines are produced by mononuclear phagocytes
- Lymphokines are produced by lymphocytes
- Interleukines: made by leukocytes (macrophages and lymphocytes) and act on other leukocytes
General properties of Cytokines
Cytokine secretion is a brief, self-limited event.
The actions of cytokines are often pleiotropic and redundant.
Cytokines often influence the synthesis and actions of other cytokines.
Cytokine actions maybe local and systemic

- Autocrine action
- Paracrine action
- Immune synapse: Tcells often secrete cytokines at the site of contact with APC.
- Endocrine action
Cytokines initiate their actions by binding to specific membrane receptors on target cells.

- Receptors for cytokines often bind their ligands with high affinities, $K_d$ values $10^{-10} - 10^{-12}$M.

- For comparison: antibodies bind antigens at $K_d$ values $10^{-7} - 10^{-11}$M and that T cell antigen receptors bind MHC-associated peptides with a $K_d$ of $10^{-7} - 10^{-11}$M.

- Consequence: only small quantities of a cytokine are needed to occupy receptors and elicit biologic effects.
External Signals regulate the expression of cytokine receptors and thus the responsiveness of cells to cytokines

- During an immune response, the antigen-specific lymphocytes are the preferential responders to secreted cytokines.

- Receptor expression is also regulated by cytokines themselves, including the same cytokine that binds to the receptor, permitting positive amplification or negative feedback.
The cellular responses to most cytokines consist of changes in gene expressions in target cells, resulting in the expression of new functions and sometimes in the proliferation of the target cells.
Cytokines that mediate and Regulate Innate Immunity
Tumor Necrosis Factor

- The principal mediator of the acute inflammatory response to gram-negative bacteria and other infectious microbes and is responsible for many of the systemic complications of severe infections.

- The major cellular source: activated mononuclear phagocytes, other source: antigen-stimulated T cells, NK cells and mast cells.

- Most potent stimulus for eliciting TNF production by macrophages is LPS (gram negative bacteria).

- IFN-γ, produced by T-cells and NK cells augments TNF synthesis by LPS-stimulated macrophages.
Tumor Necrosis Factor

- Principal cell targets and biologic effects:
  - Endothelial cells: activation (inflammation, coagulation).
  - Neutrophils: activation
  - Hipothalamus: fever
  - Many cell types: apoptosis
  - Liver: synthesis of acute phase proteins
  - Muscle, fat: catabolism (cachexia)
Effect of TNF on the body:

- **Low quantities (plasma conc. <10^{-9} M)**:
  - Local inflammation
    - Endothelial cell: Adhesion molecule, IL-1, chemokines
    - Leukocyte: Activation

- **Moderate quantities**:
  - Systemic effects
    - Brain: Fever
    - Liver: Acute-phase proteins
    - Bone marrow: Leukocytes

- **High quantities (plasma conc. ≥10^{-7} M)**:
  - Septic shock
    - Heart: Low output
    - Blood vessel: Thrombus, low resistance
    - Liver: Hypoglycemia

Interleukin-1

- The principal mediator of the acute inflammatory response to gram-negative bacteria and other infectious microbes and is responsible for many of the systemic complications of severe infections.

- The major cellular source: activated mononuclear phagocytes, other source neutrophils, epithelial cells and endothelial cells.
Interleukin-1

- Principal cell targets and biologic effects:
  - Endothelial cells: activation (inflammation, coagulation).
  - Hypothalamus: fever
  - Liver: synthesis of acute phase proteins
Chemokines

- A large family of structurally homologous cytokines that stimulate leukocyte movement and regulate the migration of leukocytes from the blood to tissues.
- Chemotactic cytokine
- Subfamily: CC and CXC
- Size: 8-12 kD polypeptides
- Produced by leukocytes, and also endothelial cells, epithelial cells, platelets and fibroblasts
Chemokines

- Principal cell targets and biologic effects:
  - Leukocytes: chemotaxis, activation;
  - migration into tissues.
Interleukin-12
IL-12

- Principal mediator of the early innate immune response to intracellular microbes and is a key inducer of a cell mediated immunity, the adaptive immune response to these microbes: activator NK cell cytotoxic function, stimulate IFN-γ production by T-cells and NK-cells.
Source

- activated mononuclear phagocytes and dendritic cells.
Biologic Actions

- stimulate IFN-γ production by T-cells and NK-cells.
- Stimulates the differentiation of CD⁴⁺ helper T lymphocytes into IFN-γ producing $T_{H1}$ cells.
- Enhances the cytolytic function of activated NK-cells and CD⁸⁺ cytolytic T lymphocytes (CTLs).
Type-1 Interferons
IFN-α and IFN-β mediates the early innate immune response to viral infections.

Major source of IFN-α is mononuclear phagocytes, sometimes called leucocyte interferon.

Major source of IFN-β is fibroblasts, sometimes called fibroblast interferon.
Biologic actions

- Inhibits viral replication.
- Increases expression of class I MHC molecules.
- Stimulates the development of $T_H^1$ cells in humans.
Interleukin-10
Inhibitor of activated macrophages and dendritic cells and is thus involved in the control of innate immune reactions and cell-mediated immunity.
Production

- Activated macrophages, T-lymphocytes and keratinocytes.
Biologic actions

- Inhibits the production of IL-12 by activated macrophages and dendritic cells.
- Inhibits the expression of costimulators and class II MHC molecules on macrophages and dendritic cells.
Cytokines that Mediate and Regulate Adaptive Immunity
Interleukin-2

- **Cell sources:** T-cells.

- **Principal cell targets and biologic effects:**
  - T cells: proliferation, increased cytokine synthesis; potentiates Fas-mediated apoptosis.
  - NK cells: proliferation, activation
  - B cells: proliferation, antibody synthesis (in vitro)
Interleukin-4

- **Cell sources:** $\text{CD}^{4+}$ cells ($\text{T}_{\text{H}}2$ cells), mast cells.

- **Principal cell targets and biologic effects:**
  - Isotype switching to IgE.
  - T cells: $\text{T}_{\text{H}}2$ differentiation, proliferation.
  - Macrophages: inhibition of IFN-$\gamma$-mediated activation.
  - Mast cells: proliferation *(in vitro)*.
Interleukin-5

- **Cell sources:** $\text{CD}^{4+}$ cells ($\text{T}_{\text{H}}2$ cells)
- **Principal cell targets and biologic effects:**
  - Activation, increased production
  - B cells: proliferation, IgA production
Interferon-γ

- **Cell sources:** CD$^{8+}$ cells ($T_H^1$ cells), NK cells.
- **Principal cell targets and biologic effects:**
  - Macrophages: activation (increased microbicidal function)
  - B cells: isotype switching to opsonizing and complement fixing IgG subclasses.
  - T-cells: $T_H^1$ differentiation.
  - Various cells: increased expression of class-I and class-II MHC molecules, increased antigen processing and presentation to T cells.
Lymphotoxin

- Cell sources: T cells
- Principal cell targets and biologic effects:
  - Recruitment and activation of neutrophils