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Cytokines & Mediators

1. Introduction

Cytokines and inflammatory mediators are small soluble proteins and bioactive molecules that play a central role in the **regulation of immune responses, inflammation, hematopoiesis, and cell communication.** They act as **signaling molecules** between immune cells and other tissues, helping the body to respond to infections, tissue injury, and malignancies. Dysregulation of cytokines and mediators can lead to chronic inflammatory diseases, autoimmune disorders, and cancer progression.

2. Definition

Cytokines are low–molecular weight proteins secreted mainly by immune cells such as lymphocytes, macrophages, dendritic cells, and natural killer cells. They exert their effects by binding to specific receptors on target cells, leading to changes in gene expression and cellular behavior.

2.1 General characteristics of cytokines:

- Act at very low concentrations
- Have short half-lives
- Often act locally (paracrine or autocrine action)
- Show pleiotropy (one cytokine has multiple effects)
- Exhibit redundancy (different cytokines can perform similar functions)

3. Classification of Cytokines

Cytokines can be classified based on their function and source:

1. Interleukins (ILs)

- Secreted mainly by leukocytes
- Regulate immune cell growth, differentiation, and activation
- Examples:
  - **IL-1**: pro-inflammatory, induces fever
  - **IL-2**: T-cell proliferation
  - **IL-4**: B-cell activation and IgE class switching

2. Interferons (IFNs)

- Important in antiviral defense
- Types:
  - **IFN-α and IFN-β**: inhibit viral replication
  - **IFN-γ**: activates macrophages and enhances antigen presentation

3. Tumor Necrosis Factors (TNFs)

- Major mediators of inflammation
- **TNF-α** plays a key role in septic shock and chronic inflammatory diseases

4. Colony-Stimulating Factors (CSFs)

- Regulate hematopoiesis
- Examples: G-CSF, GM-CSF

5. Chemokines

- Specialized cytokines that induce cell migration (chemotaxis)

- Guide leukocytes to sites of infection or inflammation

4. Inflammatory Mediators

Inflammatory mediators are substances released during tissue injury or infection that initiate and regulate inflammation. They may be derived from cells or plasma proteins.

1. Cell-Derived Mediators

- **Histamine**: released from mast cells; increases vascular permeability
- **Prostaglandins**: cause vasodilation, fever, and pain
- **Leukotrienes**: promote bronchoconstriction and leukocyte recruitment
- **Nitric Oxide (NO)**: vasodilation and antimicrobial activity

2. Plasma-Derived Mediators

- **Complement system**: enhances phagocytosis and cell lysis
- **Kinins (e.g., bradykinin)**: pain, vasodilation, increased permeability
- **Coagulation factors**: link inflammation and clot formation

5. Mechanism of Action of Cytokines

Cytokines exert their effects through binding to specific cell surface receptors. This binding activates intracellular signaling pathways such as:

- JAK-STAT pathway
- MAP kinase pathway
- NF-κB pathway

These pathways regulate gene transcription, leading to:

- Cell activation
- Proliferation

- Differentiation
- Apoptosis

6. Biological Functions of Cytokines and Mediators

- Regulation of innate and adaptive immunity
- Activation and differentiation of T and B lymphocytes
- Recruitment of immune cells to sites of infection
- Induction of fever and acute-phase response
- Promotion of tissue repair and wound healing

7. Cytokines in Disease

1. Cytokine Storm

An excessive and uncontrolled release of cytokines, seen in:

- Severe infections
- Sepsis
- Certain viral diseases

2. Autoimmune and Inflammatory Diseases

- Rheumatoid arthritis (TNF-α, IL-6)
- Inflammatory bowel disease
- Asthma and allergies

3. Cancer

- Cytokines can promote tumor growth or anti-tumor immunity
- Used therapeutically (e.g., IFN-α, IL-2)

8. Therapeutic Applications

- Anti-TNF drugs (Infliximab, Etanercept)
- IL-6 receptor blockers
- Interferon therapy
- Cytokines as vaccine adjuvants

Lec. 4 Hypersensitivity: Types and Diseases Caused by Hypersensitivity

1. Introduction

Hypersensitivity is an exaggerated, inappropriate, or harmful immune response that occurs when the immune system reacts excessively to an antigen. hypersensitivity reactions lead to tissue injury and disease rather than protection, such as **allergic disorders, autoimmune diseases, inflammatory conditions, and transplant rejection**.

2. Hypersensitivity reactions are classified into **four main types (Type I–IV)** according to the Gell and Coombs classification.

2.1 Type I Hypersensitivity (Immediate or IgE-Mediated Hypersensitivity)

Type I hypersensitivity is an **immediate immune reaction mediated by IgE antibodies**, occurring within minutes of exposure to an allergen.

Immunological Mechanism

B cells switch to IgE production then IgE binds to FcεRI receptors on mast cells and basophils. Re-exposure to the same allergen causes mast cell degranulation.

Mediators Released

- Histamine
- Prostaglandins
- Cytokines (IL-4, IL-5, IL-13)

Diseases Caused by Type I Hypersensitivity

- Allergic rhinitis
- Bronchial asthma
- Atopic dermatitis
- Food allergies
- Anaphylaxis

2.2 Type II Hypersensitivity (Antibody-Mediated Hypersensitivity)

Type II hypersensitivity is caused by **IgG or IgM antibodies directed against antigens on cell surfaces or extracellular matrix components**, leading to cell damage or functional alteration.

Immunological Mechanism: Antibody binding to target antigen then Complement activation, Opsonization and phagocytosis, and Antibody-dependent cellular **cytotoxicity** (ADCC)

Diseases Caused by Type II Hypersensitivity

- Autoimmune hemolytic anemia
- Hemolytic disease of the newborn
- Goodpasture syndrome
- Myasthenia gravis
- Graves' disease

2.3 Type III Hypersensitivity (Immune Complex–Mediated Hypersensitivity)

Type III hypersensitivity results from the formation of **antigen–antibody immune complexes** that deposit in tissues and induce inflammation.

Immunological Mechanism: Formation of circulating immune complexes, Deposition in blood vessels, kidneys, joints, or lungs,Complement activation,Neutrophil recruitment and tissue damage

Diseases Caused by Type III Hypersensitivity

- Systemic lupus erythematosus (SLE)
- Serum sickness
- Arthus reaction
- Post-streptococcal glomerulonephritis
- Immune complex vasculitis

2.4 Type IV Hypersensitivity (Delayed-Type Hypersensitivity)

Type IV hypersensitivity is a **cell-mediated immune reaction** that does not involve antibodies and usually appears **24–72 hours** after antigen exposure.

Immunological Mechanism: Secretion of cytokines (IFN-γ, TNF-α), Macrophage activation and inflammation.

Diseases Caused by Type IV Hypersensitivity

- Contact dermatitis (nickel, latex)
- Tuberculin skin test reaction
- Type 1 diabetes mellitus
- Multiple sclerosis
- Rheumatoid arthritis

Comparison of Hypersensitivity Types

Type	Immune Mechanism	Key Mediators	Examples
I	IgE-mediated	Histamine, leukotrienes	Asthma, anaphylaxis
II	IgG/IgM antibodies	Complement, ADCC	Hemolytic anemia
III	Immune complexes	Complement, neutrophils	SLE
IV	T-cell mediated	Cytokines	Contact dermatitis

Clinical Importance

- Helps in diagnosis of allergic and autoimmune diseases
- Guides treatment with antihistamines, corticosteroids, and biologics
- Essential for understanding vaccine reactions and transplant rejection

Mnemonic: "**ACID**

A – Type I = **A**llergic (Immediate)
C – Type II = **C**ytotoxic
I – Type III = **I**mmune complex
D – Type IV = **D**elayed (cell-mediated)