Cytokines (CKs)

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Objectives

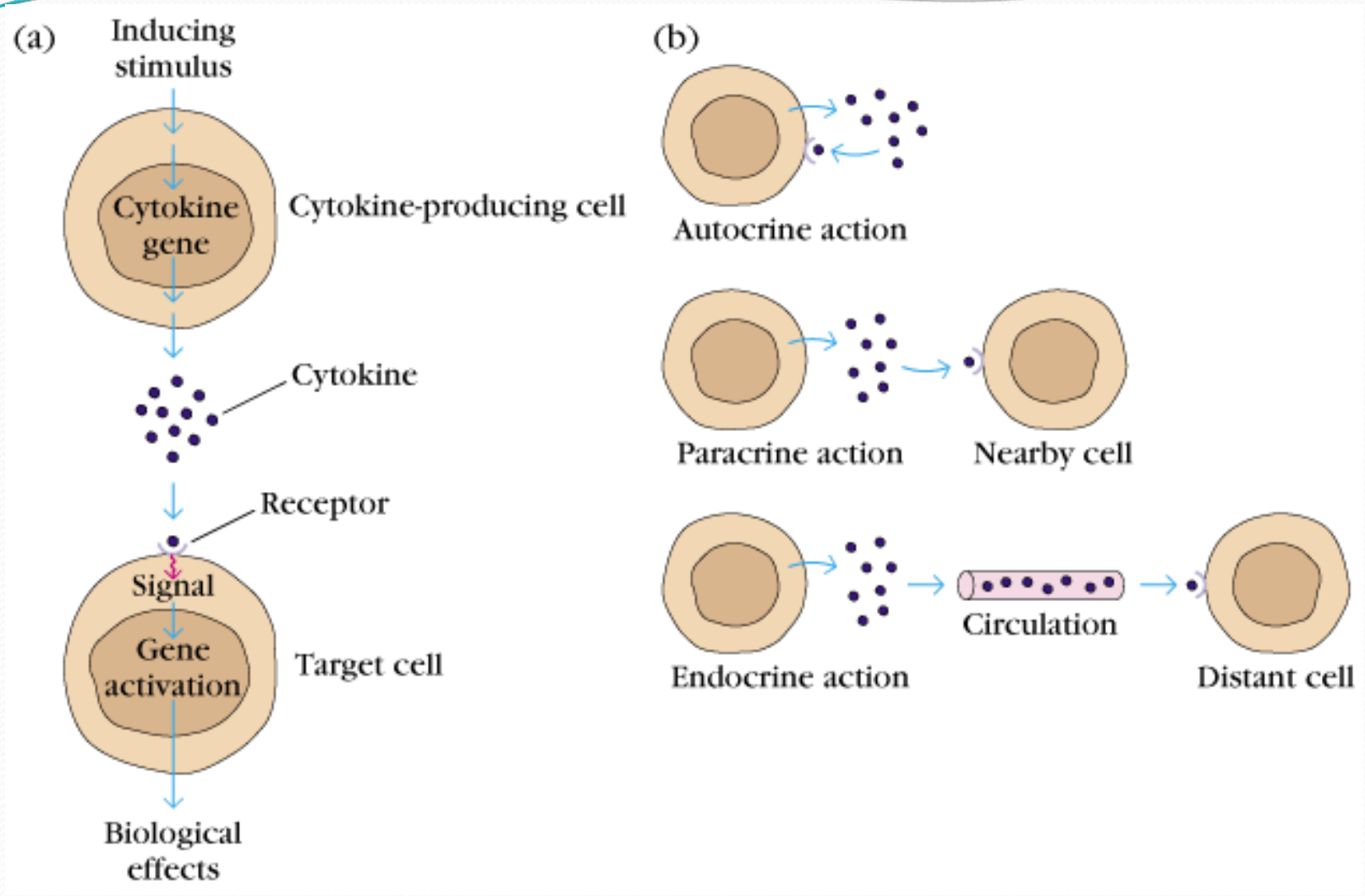
- Definition and general properties of cytokines
- Classification of cytokines
- Cytokine receptor
- Biological functions of cytokines
- Cytokine and disease

Definition

- A group of low molecular weight polypeptides or proteins which are secreted by activated immunocytes or some matrix cells and possess high activity and various functions.
- Cytokine or immunocytokine is a generic name used to describe a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to-picomolar concentrations
- Their major functions are to mediate and regulate immune response and inflammatory reactions.

General Properties

- Most cytokines are low molecular weight polypeptides or glycoprotein (8~80 KD), and most of them are monomer
- Natural cytokines are secreted by activated cells such as activated immune cells, matrix cells and tumor cells
- One kind of cytokines can be produced by different cells. One kind of cells can secrete different cytokines
- Cytokines initiate their actions by binding to specific membrane receptors on target cells.
- Cytokines can act on the cells that produce them (autocrine), on other cells in the immediate vicinity (paracrine), or on cells at a distance (endocrine) after being carried in blood or tissue fluids.

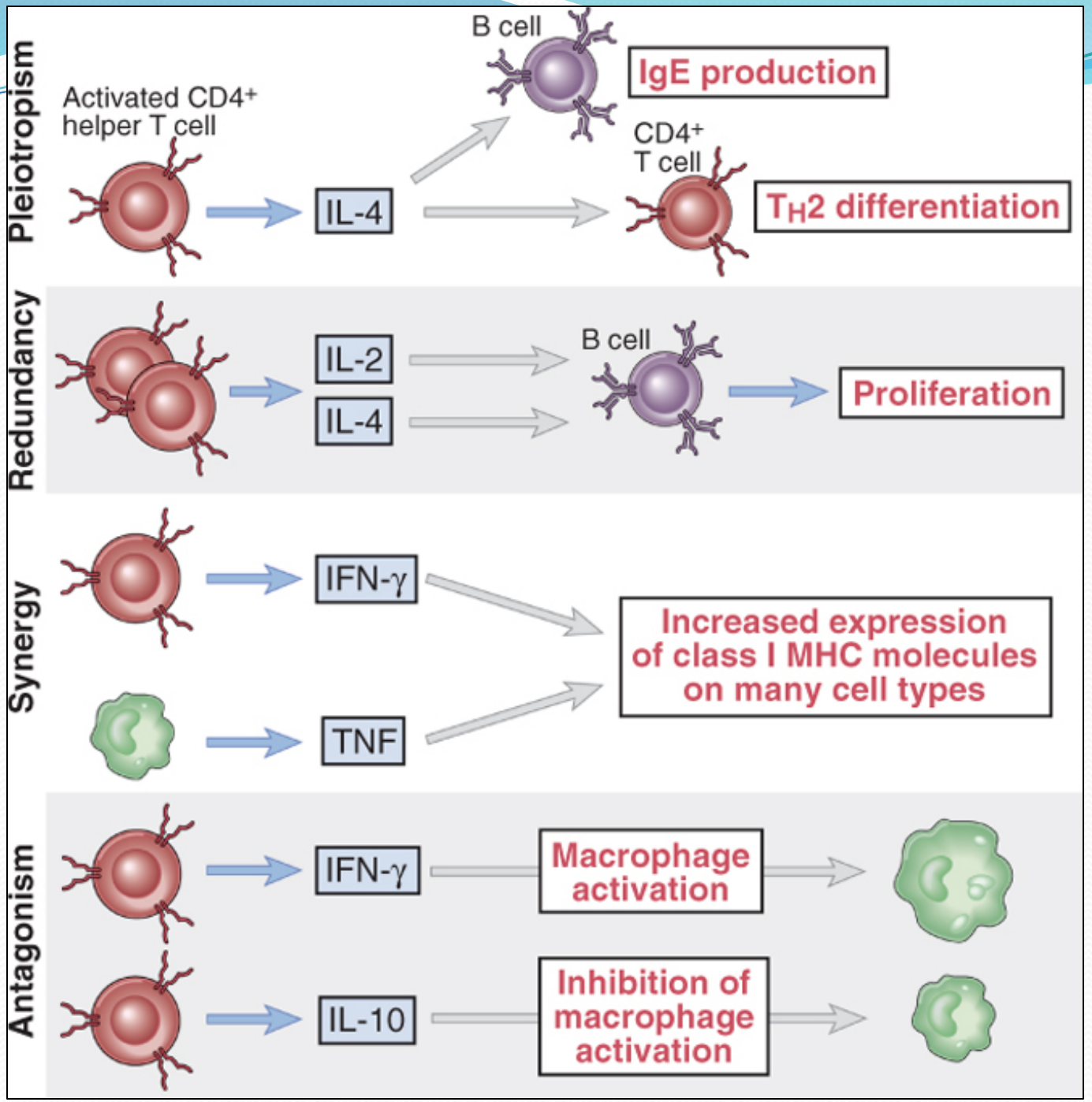

(a)
Inducing stimulus
Cytokine gene
Cytokine-producing cell
Cytokine
Receptor
Signal
Gene activation
Target cell
Biological effects
(b)
Autocrine action
Paracrine action
Nearby cell
Circulation
Endocrine action
Distant cell

Cytokine Names

- Interleukins - produced exclusively by leukocytes
- Lymphokines - produced by lymphocytes
- Monokines - produced exclusively by monocytes
- Interferons - involved in antiviral responses
- Colony Stimulating Factors - support the growth of cells in semisolid medias
- Chemokines - promote chemotaxis

Effects of Cytokines

- Pleiotropism refers to the ability of one cytokine having multiple effects on diverse cell types.
- Redundancy refers to the property of multiple cytokines having the same or overlapping functional effects.
- Synergy refers to the property of two or more cytokines having greater than additive effects.
- Antagonism refers to the ability of one cytokine inhibiting the action of another.


Pleiotropism
Activated CD4+ helper T cell
IL-4
B cell
IgE production
CD4+ T cell
TH2 differentiation
Redundancy
IL-2
IL-4
B cell
Proliferation
Synergy
IFN-γ
TNF
Increased expression of class I MHC molecules on many cell types
Antagonism
IFN-γ
Macrophage activation
IL-10
Inhibition of macrophage activation

Cytokine General Actions

- Development of cellular and humoral immune responses
- Induction of inflammation
- Regulation of hematopoiesis
- Control of cellular proliferation and differentiation
- Induction of wound healing
- Chemotaxis

Classification of cytokines

- Interleukin, IL
- Interferon , IFN
- Tumor necrosis factor, TNF
- Colony stimulating factor, CSF
- Chemokine
- Transforming growth factor

1. Interleukin (IL)

- Cytokines secreted by leukocytes that have the ability to act as signal molecules between different population of leukocytes
- IL-1~IL-29
  - Th1: IL-2
  - Th2: IL-4, IL-5
  - Th3/Treg: IL-10
  - Th17: IL-17

2. Interferon (IFN)

- A group of glycoproteins that produced by human or animal cells following the infection of virus and exposure to various inducing agents

	Types	Produced cells	Main functions
IFN-α	Type I	leukocyte	anti-virus, immune regulation
IFN-β	Type I	fibroblast	anti-tumor
IFN-γ	Type II	Th1, NK	weaker anti-virus effect, stronger immune regulation effect, anti-tumor

3. Tumor Necrosis Factor (TNF)

- TNFs were originally thought of as selective antitumour agents, but are now known to have a multiplicity of actions.
- TNF-α is produced mainly by LPS activated monocytes and macrophages.
- TNF-β is produced mainly by activated Th0 and Th1.

4. Colony-Stimulating Factors (CSF)

- Cytokines that stimulate proliferation or differentiation of pluripotent hematopoietic stem cell and different progenitors.
  - Multi-CSF (IL-3)
  - Granulocyte macrophage-CSF (GM-CSF)
  - Monocyte-CSF (M-CSF)
  - Granulocyte-CSF (G-CSF)
  - Stem cell factor (SCF)
  - Erythropoietin (EPO)

5. Chemokine

- Chemokines are cytokines which recruits monocytes, granulocytes and lymphocytes in blood to the sites of inflammation.

➢ CXC chemokines (α subgroup)

➢ CC chemokines (β subgroup)

➢ C chemokines (γ subgroup)

➢ CX_3C chemokines (δ subgroup)

6. Transforming Growth Factor

- Growth-factor are cytokines which stimulate the growth of their target cells.

➢ Transforming growth factor-β (TGF- β)

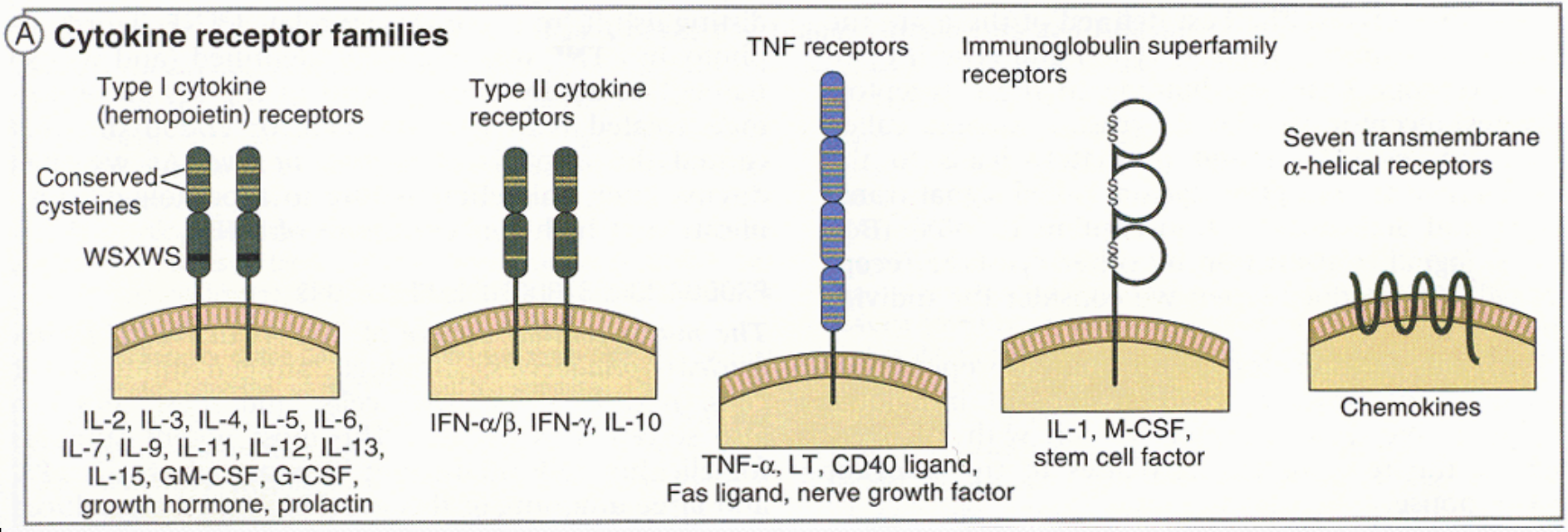
➢ Epithelia growth factor (EGF)

➢ Vascular endothelia cell growth factor (VEGF)

➢ Fibroblastic growth factor (FGF)

CK receptor

- Membrane-binding cytokine receptors:
- The receptor consists of extra-cellular region, trans-membrane region and cytoplasmic region.
- CK receptors can be grouped into five families according to structure and function:
  - Ig receptor superfamily
  - Type I CK receptor superfamily
  - Type II CK receptor superfamily
  - Type III CK receptor superfamily
  - G-protein linked receptor superfamily


A Cytokine receptor families
Type I cytokine (hemopoietin) receptors
Conserved cysteines
WSXWS
IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, GM-CSF, G-CSF, growth hormone, prolactin
Type II cytokine receptors
IFN-α/β, IFN-γ, IL-10
TNF receptors
TNF-α, LT, CD40 ligand, Fas ligand, nerve growth factor
Immunoglobulin superfamily receptors
IL-1, M-CSF, stem cell factor
Seven transmembrane α-helical receptors
Chemokines

Functional Categories

- Mediate/regulate innate immunity
  - TNF, IL-1, IL-12, IFN type1, IL-10
- Mediate/regulate adaptive immunity
  - IL-2, IL-4, IFN-γ, TGF-β
- Stimulates hematopoiesis
  - IL-3, IL-7

Specific Interleukins Functions

- **IL1:** Play role in inflammation
- **IL2:** Growth factor for B and T cells (clonal expansion)
- **IL3:** Haematopoetic growth factor which stimulates colony formation of blood cells
- **IL4:** Stimulates development of Th2 cells from naïve Th cell. Stimulates Ig class switch from IgG1 to IgE (allergy)
- **IL5:** Produced by Th2 cells and aids in the growth and differentiation of eosinophils
- **IL6:** acute phase response
- **IL10:** Suppresses inflammatory responses and Inhibits production of IFN-γ, IL-2, IL-3, TNFα, GM-CSF

Cytokines and Clinical Applications

- Cytokines and cytokines inhibitors can be used in many clinical applications and treatments.
  - Advantages: Known ligands, receptors and mechanisms of action
  - Problems with cytokine therapies: Effective dose levels, short half-life, can cause unpredictable side effects
- **Colony stimulating factors (CSFs):** hematological disorders associated with cancer therapy
- **Erythropoietin (EPO):** anemia associated with kidney disease
- **Interferon α:** antiviral therapy (chronic Hepatatis B and C)
- **IFN-β**: multiple sclerosis
- **IFN-γ**: chronic granulomatous disease (CGD)
- **IL-2:** kidney cancer, melanoma