Cytokines, CK (brief introduction)

Ning Pan

- **Department of Pathogen biology and Immunology Medical School , Southeast University**

Cytokine

- Common features
- Classification
- biological activities
- Receptors

Communications between cells

- **Cell-cell contact**

- **Soluble cytokines through binding of their receptors**

Cytokines

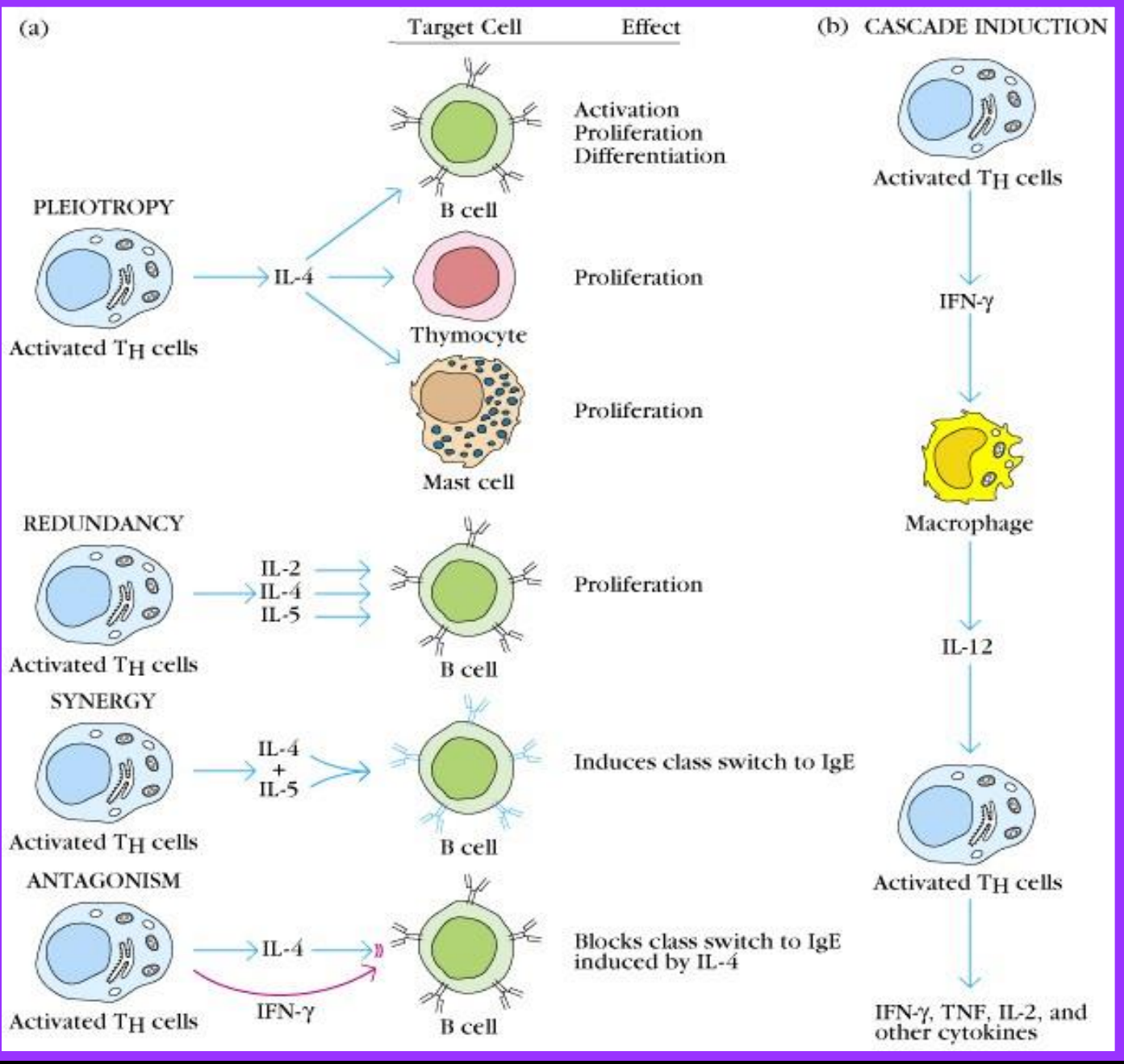
- A group of soluble proteins that mediate communication among cells are collectively designated cytokines.
- Regulate the intensity and duration of the immune response by stimulating or inhibiting the activation, proliferation, and/or differentiation of various cells and by regulating the secretion of antibodies or other cytokines.
- Many types: monokine, lymphokine, colony stimulating factor,CSF…

Common characteristics

- **Low-molecular-weight proteins or glycoproteins**
- **Function through receptor**
- **Secreted mainly by local various type of tissues and cells (autocrine, paracrine, and endocrine)**
- **high affinity (Act as very low concentration)**

Cytokines function in a network manner

- **Attributes**
  - *Pleiotropy. CK X causes this and that*
  - *Redundancy. CK X and CK Y causes this*
  - *Synergy. CK X plus CK Y causes this*
  - *Antagonism. CK X stops CK Y from causing this*


(a)
Target Cell
Effect
(b) CASCADE INDUCTION
PLEIOTROPY
Activated TH cells
IL-4
B cell
Activation
Proliferation
Differentiation
Thymocyte
Proliferation
Mast cell
Proliferation
REDUNDANCY
Activated TH cells
IL-2
IL-4
IL-5
B cell
Proliferation
SYNERGY
Activated TH cells
IL-4
+
IL-5
B cell
Induces class switch to IgE
ANTAGONISM
Activated TH cells
IL-4
IFN-γ
B cell
Blocks class switch to IgE induced by IL-4
Activated TH cells
IFN-γ
Macrophage
IL-12
Activated TH cells
IFN-γ, TNF, IL-2, and other cytokines

Classification of cytokines

1. Interleukins, IL
2. Tumor necrosis factor, TNF
3. Interferon, IFN
4. Colony-stimulating factors, CSF
5. Chemokine
6. Growth factor, TGF

1. Interleukins

- Interleukin (IL) is often used to describe cytokines produced by leukocytes although some cytokines are produced by other cell populations

TABLE 12-1 SELECTED FUNCTIONS OF SOME CYTOKINES

		Major biological functions	
Cytokine	Secreted by*	Target cells/tissues	Activity
Interleukin 1 (IL-1α, IL-1β)	Monocytes, macrophages, B cells, dendritic cells, endothelial cells, other cell types	T_H cells	Co-stimulates activation
		B cells	Promotes maturation and clonal expansion
		NK cells	Enhances activity
		Vascular endothelial cells	Increases expression of ICAMs†
		Macrophages and neutrophils	Chemotactically attracts
		Hepatocytes	Induces synthesis of acute-phase proteins
		Hypothalamus	Induces fever
Interleukin 2 (IL-2)	$T_H1$cells	Antigen-primed T_H and T_C cells	Induces proliferation
		Antigen-specific T-cell clones	Supports long-term growth
		NK cells (some) and T_C cells	Enhances activity
Interleukin 3 (IL-3)	T_H cells, NK cells, mast cells	Hematopoietic cells	Supports growth and differentiation
		Mast cells	Stimulates growth and histamine secretion
Interleukin 4 (IL-4)	T_H2 cells, mast cells, NK cells	Antigen-primed B cells	Co-stimulates activation
		Activated B cells	Stimulates proliferation and differentiation; induces class switch to IgG1 and IgE
		Resting B cells	Up-regulates class II MHC expression
		Thymocytes and T cells	Induces proliferation
		Macrophages	Up-regulates class II MHC expression; increases phagocytic activity
		Mast cells	Stimulates growth

TABLE 12-1 SELECTED FUNCTIONS OF SOME CYTOKINES

Cytokine	Secreted by*	Major biological functions: Target cells/tissues	Major biological functions: Activity
Interleukin 5 (IL-5)	T_H2 cells, mast cells	Activated B cells	Stimulates proliferation and differentation; induces class switch to IgA
		Eosinophils	Promotes growth and differentiation
Interleukin 6 (IL-6)	Monocytes, macrophages, T_H2 cells, bone-marrow stromal cells	Proliferating B cells	Promotes terminal differentiation into plasma cells
		Plasma cells	Stimulates antibody secretion
		Myeloid stem cells	Helps promote differentiation
		Hepatocytes	Induces synthesis of acute-phase proteins
Interleukin 7 (IL-7)	Bone-marrow, thymic stromal cells	Lymphoid stem cells	Induces differentiation into progenitor B and T cells
		Resting T cells	Increases expression of IL-2 and its receptor
Interleukin 8 (IL-8)	Macrophages, endothelial cells	Neutrophils	Chemokine; chemotactically attracts; induces adherence to vascular endothelium and extravasation into tissues
Interleukin 9 (IL-9)	T_H cells	Some T_H cells	Acts as mitogen, supporting proliferation in absence of antigen
Interleukin 10 (IL-10)	T_H2 cells	Macrophages	Suppresses cytokine production and thus indirectly reduces cytokine production by T_H1 cells
		Antigen-presenting cells	Down-regulates class II MHC expression

ILs applied in clinical practice

2. Tumor necrosis factor

- Tumor necrosis factor α: TNF α
- Tumor necrosis factor β : TNF β

TABLE 12-1 SELECTED FUNCTIONS OF SOME CYTOKINES

		Major biological functions	
Cytokine	Secreted by*	Target cells/tissues	Activity
Tumor necrosis factor α (TNF-α)	Macrophages, mast cells	Tumor cells Inflammatory cells	Has cytotoxic effect Induces cytokine secretion and is responsible for extensive weight loss (cachexia) associated with chronic inflammation
Tumor necrosis factor β (TNF-β)	T_H1 and T_C cells	Tumor cells	Antiinflammatory, antiproliferative for stem cell, monomyelocytic cell, and lymphocytes
		Macrophages and neutrophils	Promotion of fibroblast proliferation and wound healing

3. Interferon

- Interferon, first discovered for that it can interfere with viral replication
- Consisting of large family of secretory proteins
- functions
  - Anti virus
  - Modulate immune response

FUNCTIONS OF IFN

TABLE 12-1 SELECTED FUNCTIONS OF SOME CYTOKINES

		Major biological functions	
Cytokine	Secreted by*	Target cells/tissues	Activity
Interferon alpha (IFN-α)	Leukocytes	Uninfected cells	Inhibits viral replication
Interferon beta (IFN-β)	Fibroblasts	Uninfected cells	Inhibits viral replication
Interferon gamma (IFN-γ)	T_H1, T_C, NK cells	Uninfected cells Macrophages Many cell types	**Promotion of cell-mediated immunity**
		Proliferating B cells	**Upregulation of MHC expression**
		T_H2 cells Inflammatory cells	**Activation of macrophages, neutrophils and NK cells**

Type I IFN

Type II IFN

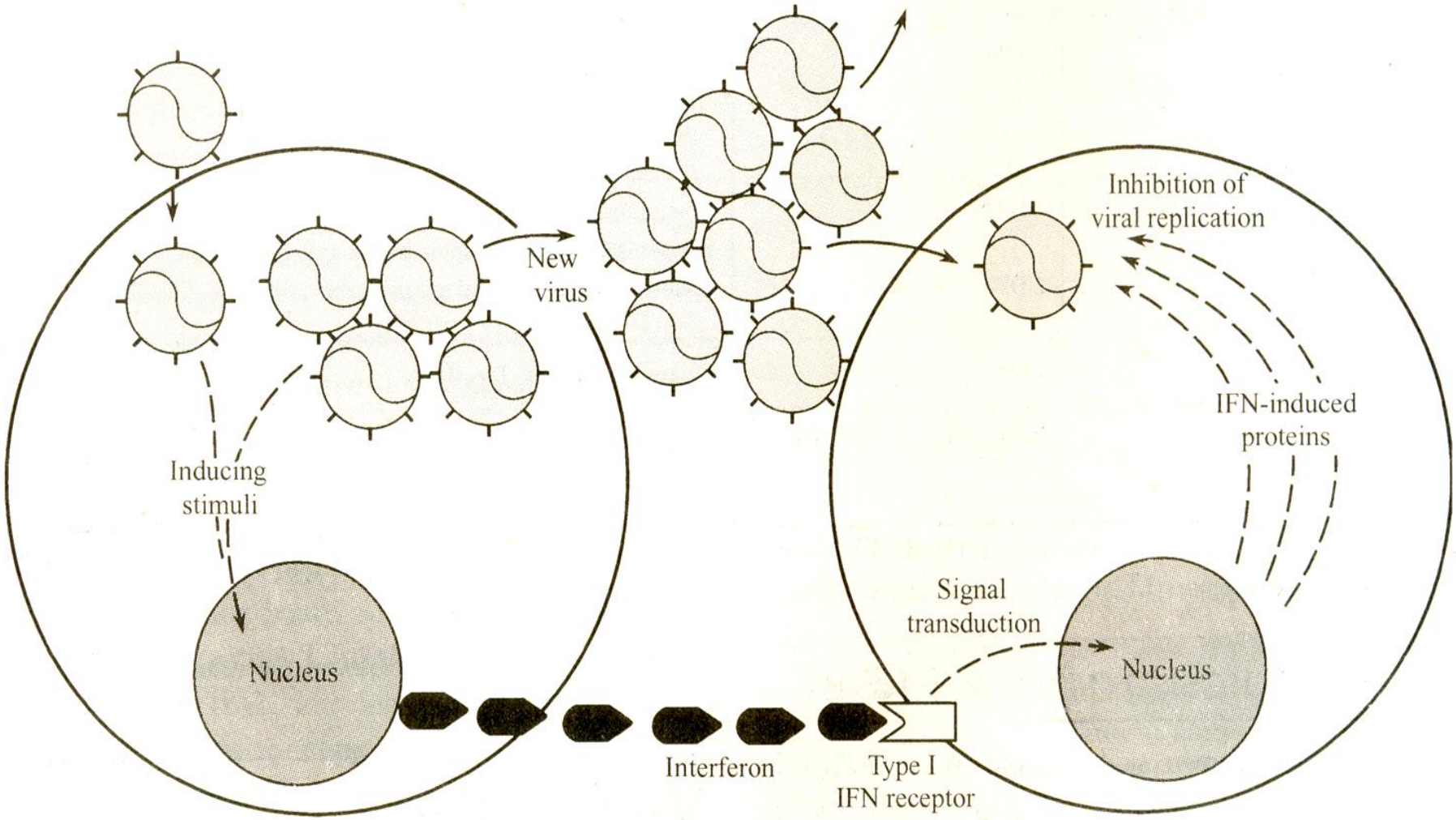
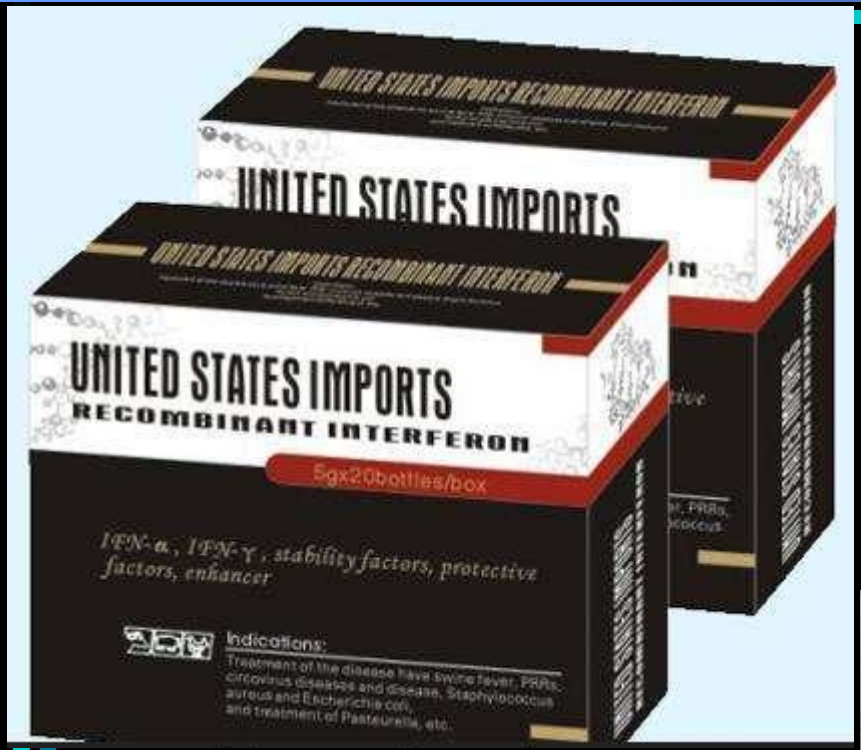


Figure 6-1 Schematic representation of the induction and activity of a type 1 interferon.


UNITED STATES IMPORTS RECOMBINANT INTERFERON
UNITED STATES IMPORTS
UNITED STATES IMPORTS RECOMBINANT INTERFERON
UNITED STATES IMPORTS
RECOMBINANT INTERFERON
5gx20bottles/box
IFN-α, IFN-γ, stability factors, protective factors, enhancer
Indications:

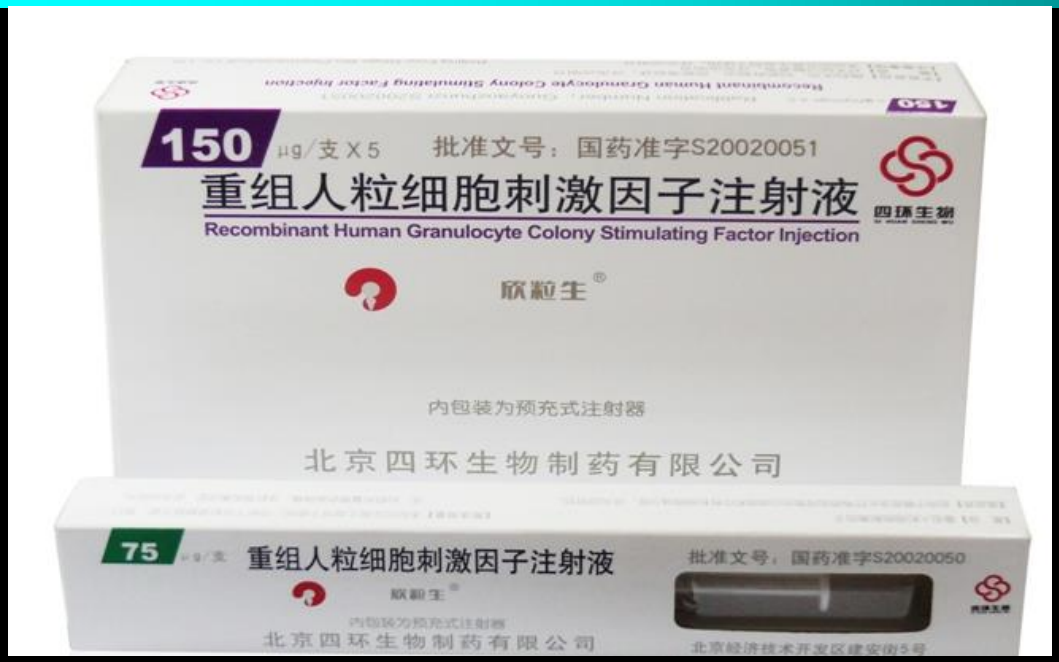

重组人干扰素α1b注射液
运德素
10
重组人干扰素α1b注射液
Recombinant Human Interferon α1b Injection
运德素
10微克：1毫升/支×10支
10
三元基因

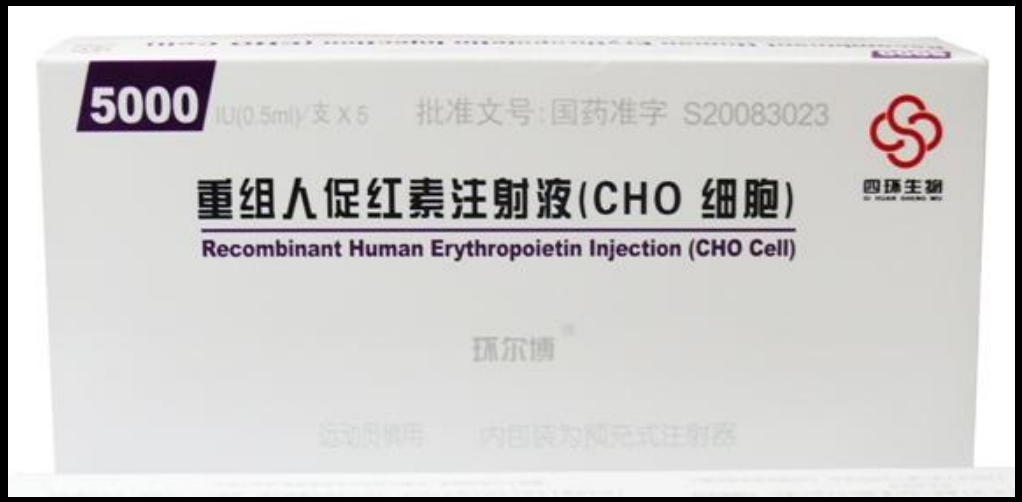

150万国际单位/支X10支
铁草
注射用重组猫干扰素ω(冻干型)
用于猫病毒性疾病，传染性结膜炎、传染性腹膜炎等。
北京铁草科技有限公司


500万IU/支×10支
注射用重组
犬γ干扰素(冻干型)
用于多种犬顽固性皮肤病及各种原因引起的免疫力低下症
北京中科拜克生物技术有限

4. Colony-stimulating factors, CSF

- **CSF: Cytokines that support the production of particular mature blood cell types from pluripotent stem cells or committed progenitors in the bone marrow.**
- **Classification**
  - **GM-CSF: granulocyte-monocyte colony-stimulating factor**
  - **M-CSF: monocyte colony-stimulating factor**
  - **G-CSF: granulocyte colony-stimulating factor**
  - **EPO (erythropoietin)**
  - **SCF (stem cell factor)**
  - **…**


150 μg/支 X 5
批准文号：国药准字S20020051
重组人粒细胞刺激因子注射液
Recombinant Human Granulocyte Colony Stimulating Factor Injection
四环生物
欣粒生®
内包装为预充式注射器
北京四环生物制药有限公司
75
重组人粒细胞刺激因子注射液
批准文号：国药准字S20020050
欣粒生®
北京四环生物制药有限公司


5000 IU(0.5ml)/支 X 5
批准文号：国药准字 S20083023
四环生物
重组人促红素注射液(CHO 细胞)
Recombinant Human Erythropoietin Injection (CHO Cell)
环尔博®

5. Growth factor

Stimulating particular tissue growth and differentiation

- **Epidermal Growth Factor (EGF)**
- **vascular endothelial growth factor (VEGF)**
- **Nerve Growth Factor (NGF)**
- **Transforming growth factor β (TGFβ)**

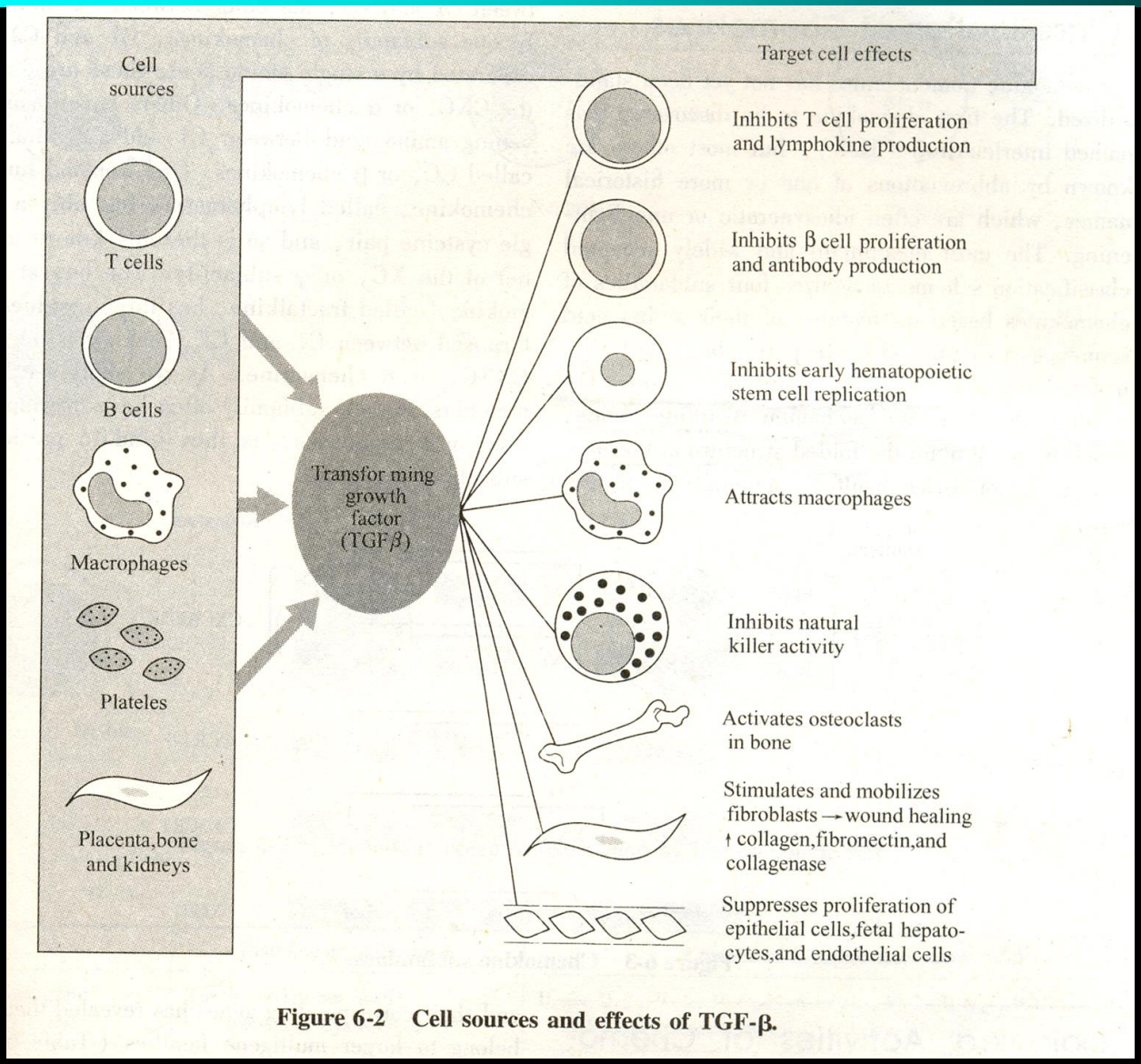


Figure 6-2 Cell sources and effects of TGF-β.

TGFβ: Negative regulator of immunity and hematopoiesis

6. Chemokines

Cytokines that have potent chemoattractant activity for monocytes and neutrophils

Over 35 such chemoattractant cytokines have been characterized, and additional members are being discovered at an accelerating rate , making this one of the largest functional groups of cytokines known.

Main functions of CK

- **Immune regulation**
- **Play a role in the development and differentiation of immune cells**
- **Regulate cell apoptosis**
- **Enhance tissue repair**

Cytokine Receptor

- **There are several cytokines receptor families**
- **Some receptors use common subunits**
- **Receptors of different affinity**

CLINICAL APPLICATION

- **IL-2, IFN-γ, IFN-α are approved to treat infectious microbes and tumors**
- **CSF for treatment of some blood diseases**
- **…**

More than in medical practice

Rh-epidermal growth factor

Cytokine Summary

- Definition
- Common features
- Classification
- Functions of IL-2, IL-4, IL-10, IFN, and TGFβ