Cytokines

Luděk Šefc

Cytokines

- Protein regulators of cellular communication

Cytokines x hormones

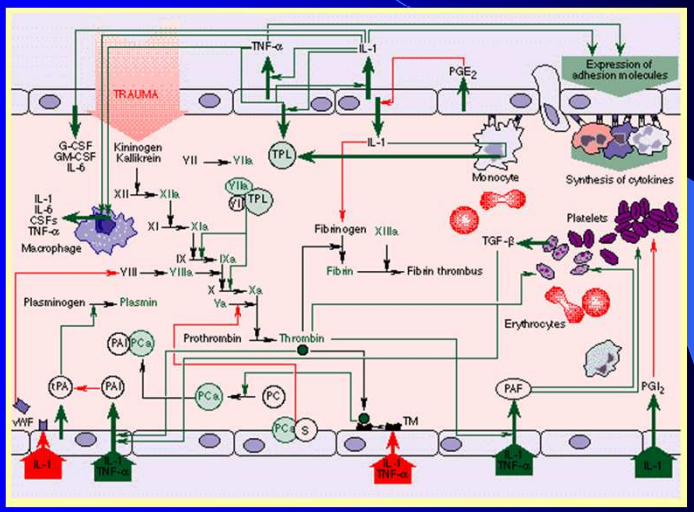
	Hormones	**Cytokines**
Production sites	few	many
Cell targets	few	many
Presence in blood	yes	rarely
Biological role	homeostasis	infection tissue reparation
Pleiotropic effects	low	high

Cytokines are not produced by specialized cells which are organized in specialized glands, i. e. there is not a single organ source for these mediators .

Cytokine properties

- mostly glycoproteins, they bind to a specific membrane receptor on target cells
- effective in extremely low concentrations (10^{-9} - 10^{-12} M)
- many different producing cells
- almost all cytokines are pleiotropic effectors showing multiple biological activities.
- multiple cytokines often have overlapping activities
- high conservation during phylogenesis – low species specifity

Cytokine regulatory network



Cytokine receptors

- transmembrane proteins
- mostly composed of different subunits
- similar receptors – members of receptor family

Cytokine receptor family - type 2

α chain

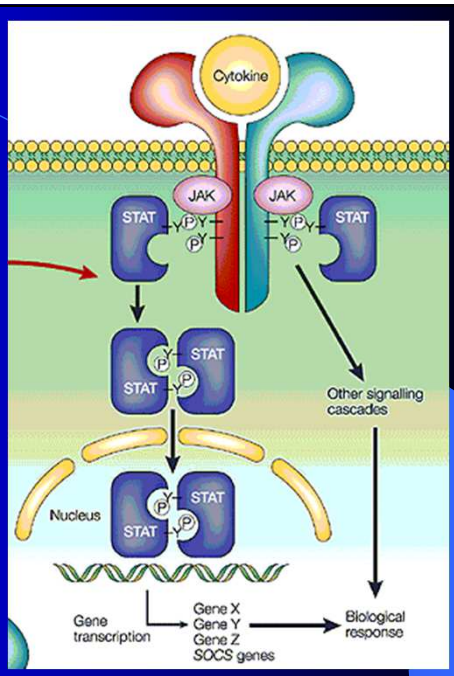
⇓

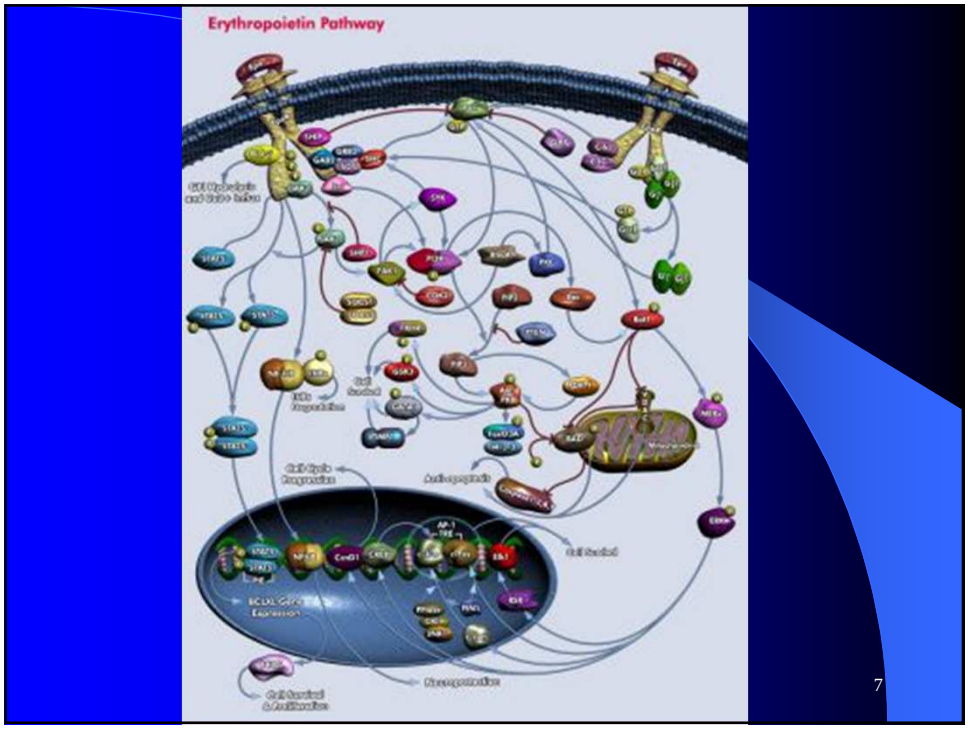
ligand-receptor interaction

β chain

⇓

signal transduction





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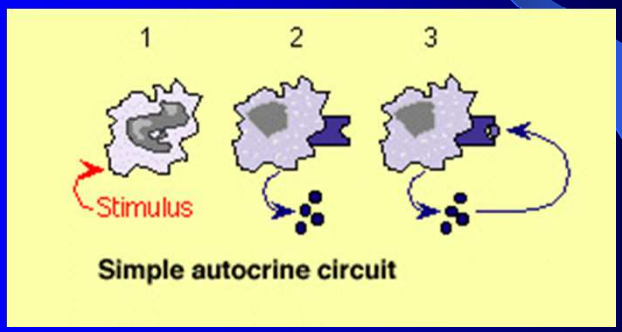
Autocrine regulation



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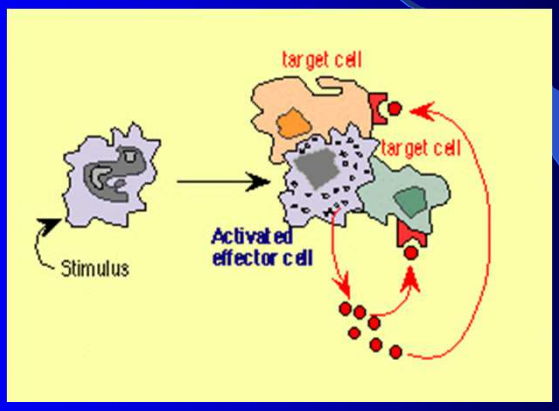
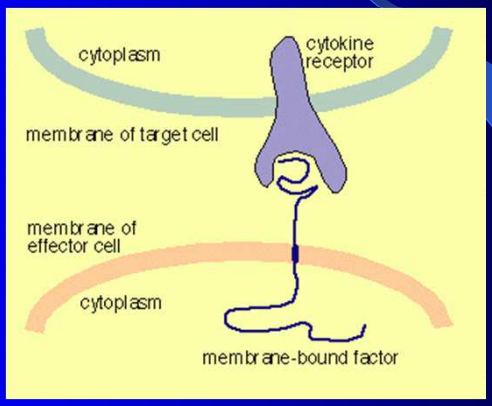
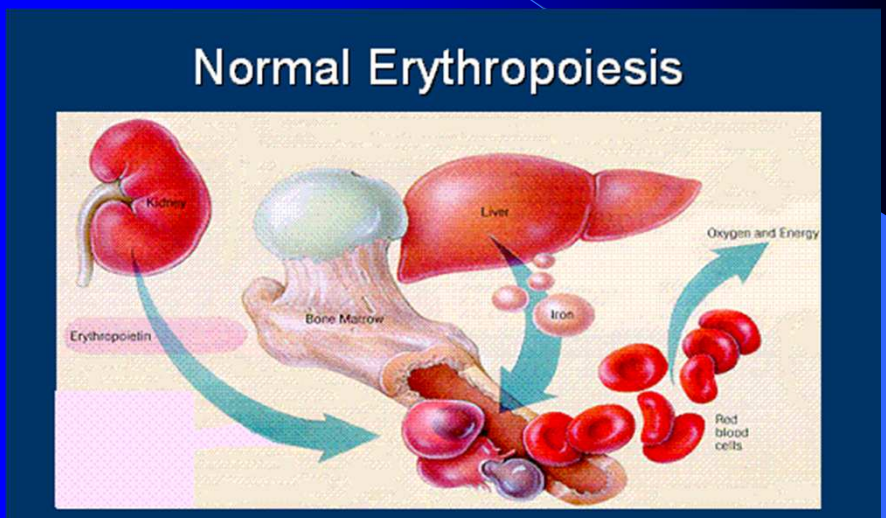
Paracrine regulation



Juxtacrine regulation



Endocrine regulation



Cytokine groups

Cytokines exert pleiotropic effects, producing cell range can be wide ⇒ no simple classification

There exist several cytokine groups, which can partially overlap

- Hematopoietic growth factors

SCF, IL-3, GM-CSF, G-CSF, TPO, Epo, … MIP-1 α, IL-10

- Interferons (IFN)

IFN-α, IFN-β, IFN-γ, limitin, TP-1, …

- Interleukins

up to date IL-1 to IL-38

- Lymfokines

IL-2, IL-10

- Monokines

interleukins, chemokines …

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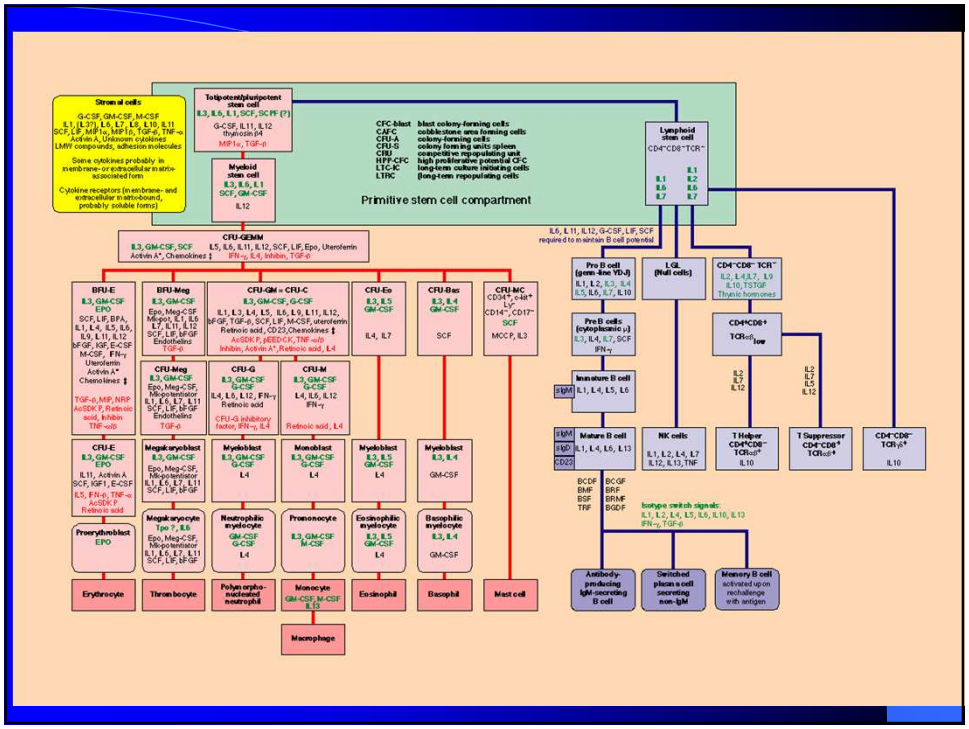
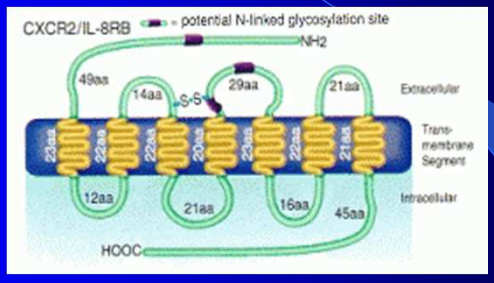


Chemokines

- chemotaxis, migration, activation of immunocompetent cells
- small proteins (8-10 kDa)
- high homology
- CXC chemokines: PF4, IL-8 , ⇒ neutrophiles
- CC chemokines: MIP-1α ,β, RANTES ⇒ monocytes
- C chemokines: IL-16

Chemokine receptors



- „serpentine receptors“
- promiscuity
- CXCR-1, CCR-3, …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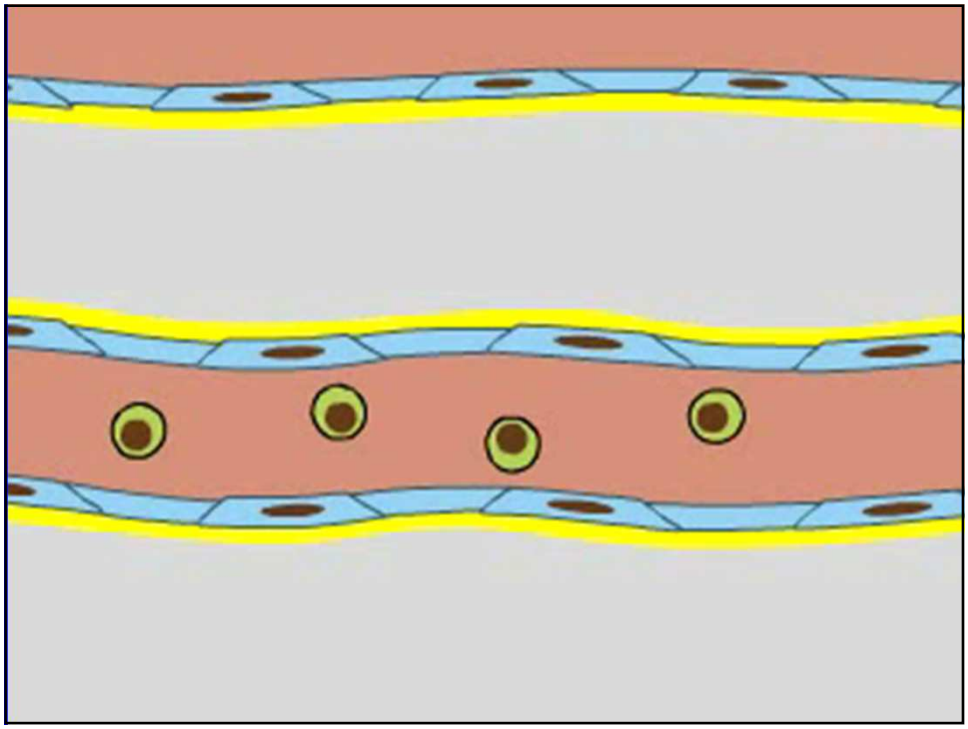
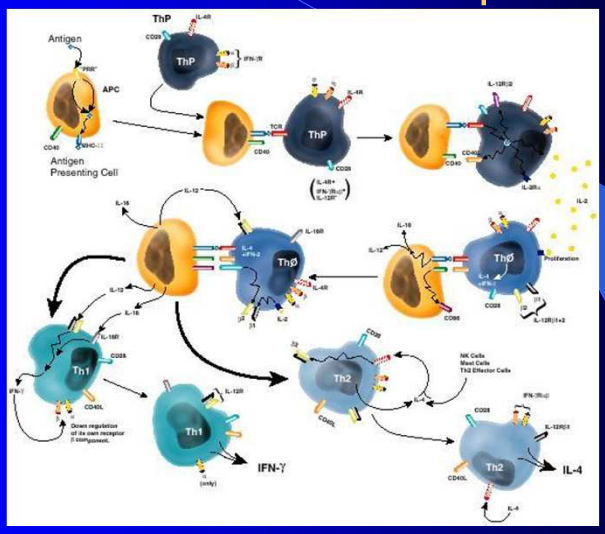


Inflammatory cytokines

- many different cytokines
- monokines, lymphokines, chemokines, interferons, interleukins…
- key role of macrophages: inflammation triggering cytokines IL-1, TNF-α, IL-6

- TGF-β, LIF – (cannot be classified) – receptors present on all somatic cells, high diversity of effect depends on tissue type and state
- …..

Activation of naive CD4+ T lymphocytes towards Th1 a Th2 response



Cytokines in pathogenesis and therapy

Hematopoietic growth factors

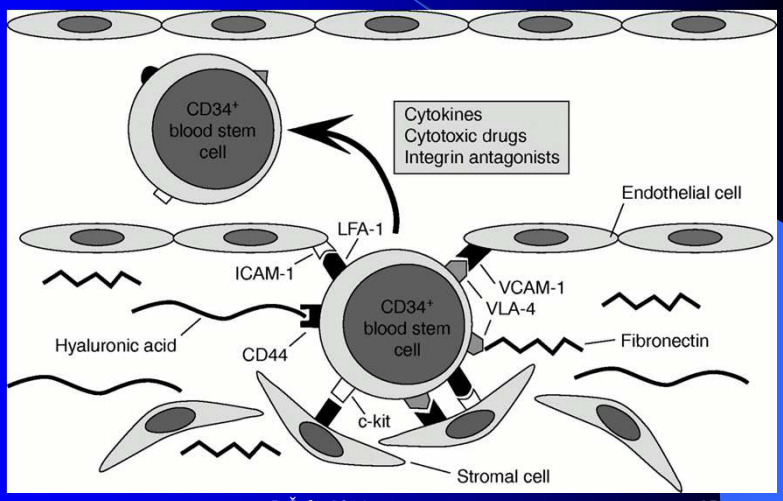
- anemia (Epo)
- neutropenia (G-CSF, GM-CSF)
- thrombocytopenia (Tpo)

Stem cells

- in the bone marrow
- in the peripheral blood

Stem cell mobilization into the blood stream

G-CSF
GM-CSF



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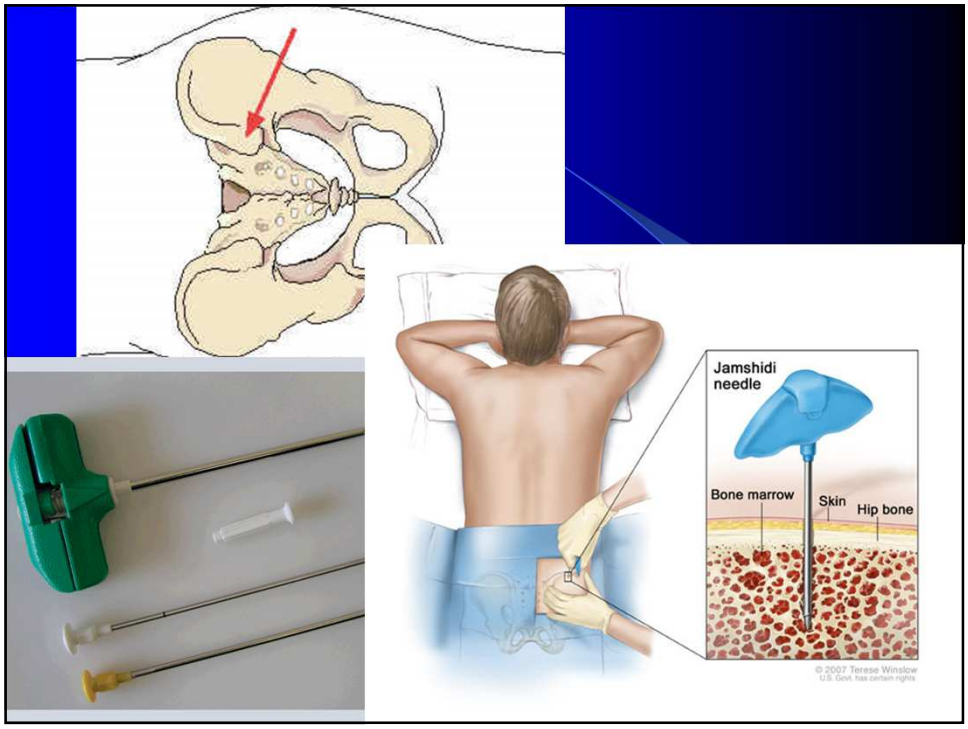
Jamshidi needle
Bone marrow
Skin
Hip bone
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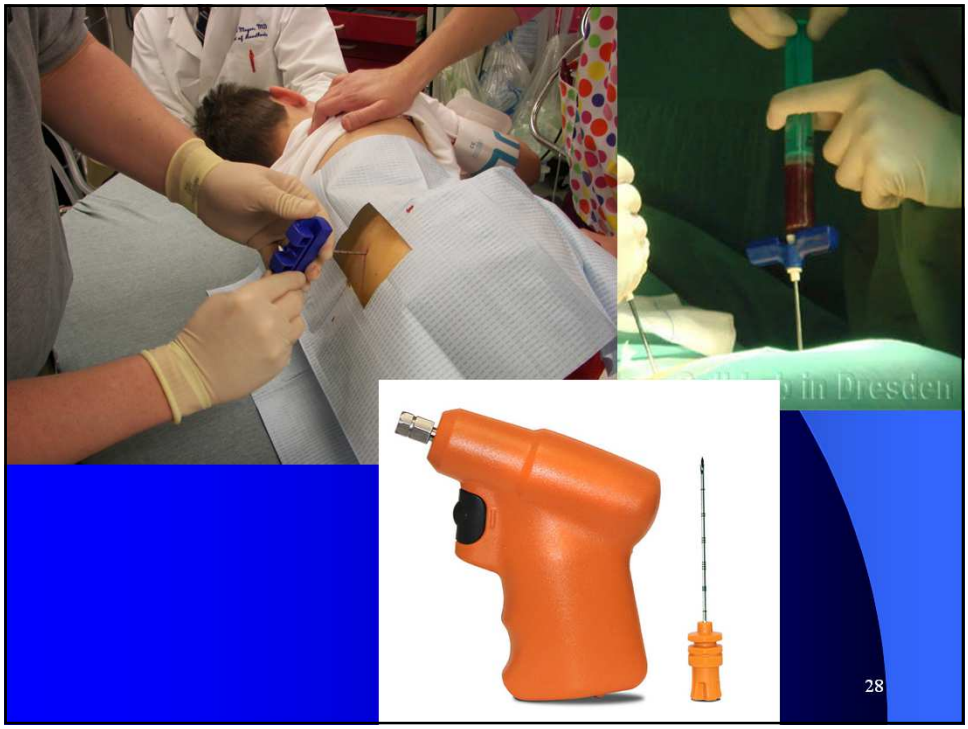
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Two Sisters


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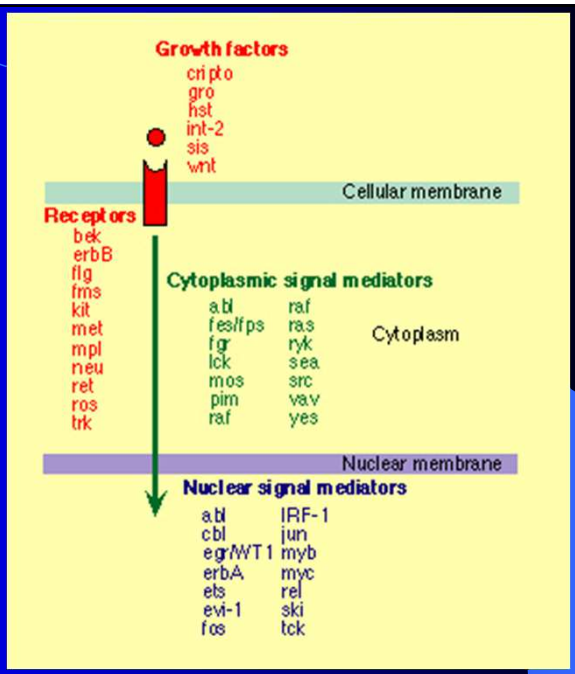
Graft purging

- autologous graft containing leukemic cells – *in vitro* cultivation with cytostatics (Mafosfamide)
- proliferative block of healthy stem cells – MIP-1α

Oncogenes



Adoptive immunotherapy

- LAK cells: melanoma, renal carcinoma, colorectal carcinoma, prevention of GVHD

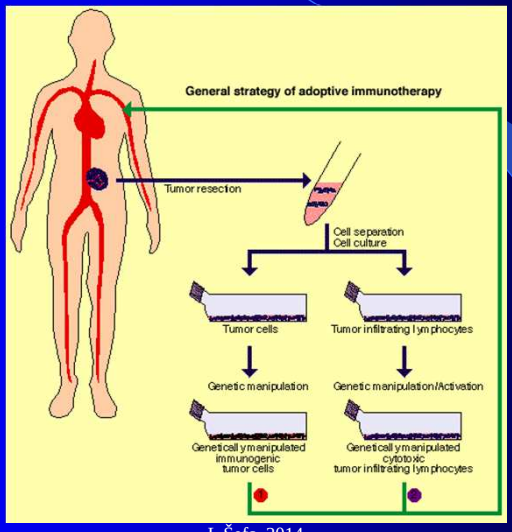
  a) IL-2 i.v.

  b) leukaferesis

  c) *in vitro* cultivation with IL-2

  d) reinfusion of $10^{10} – 10^{11}$ LAK cells

Adoptive immunotherapy



AIDS

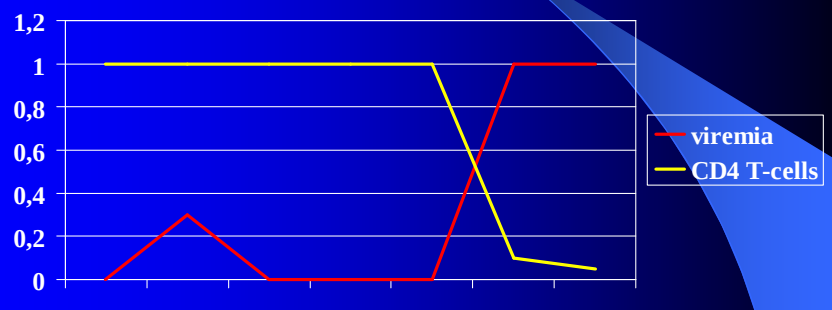
HIV-1 receptors : CD4 + coreceptor

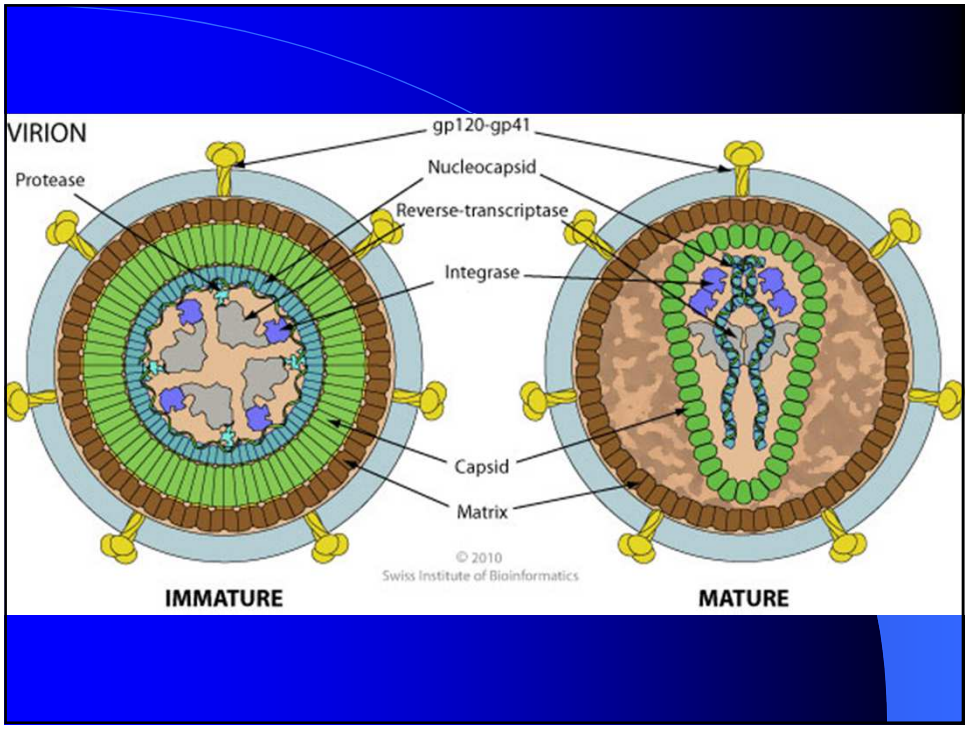
infected cells:

CD4 T-lymphocytes — CXCR-4

monocytes — CCR-5

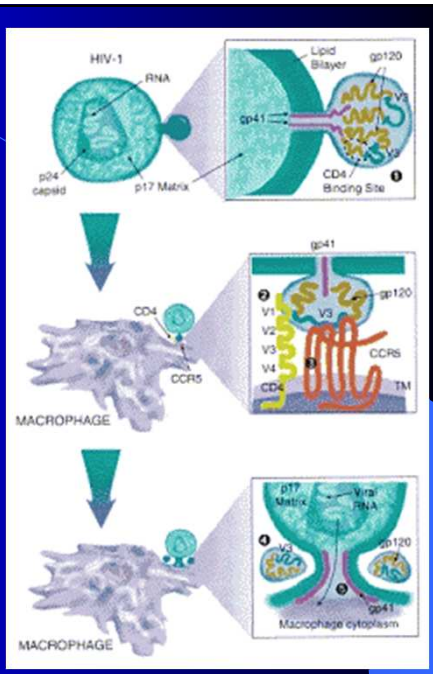
HIV-1 infection course

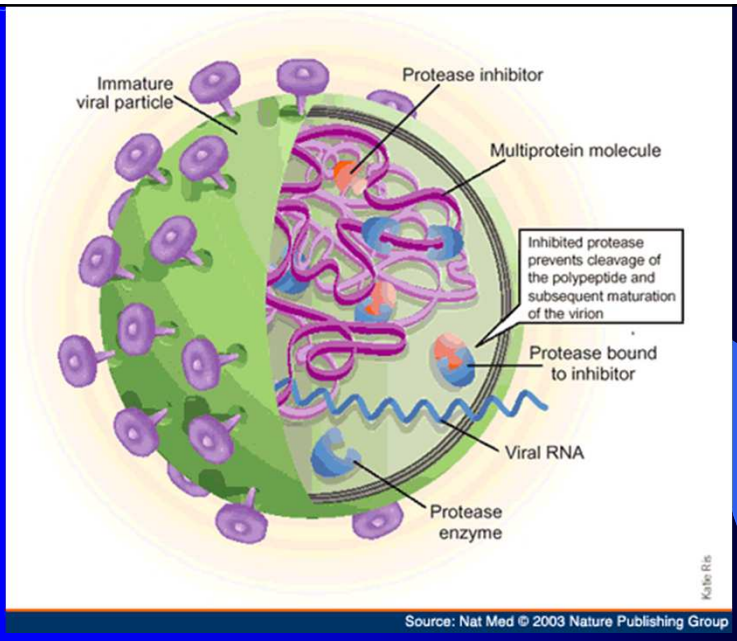




HIV-1 infection

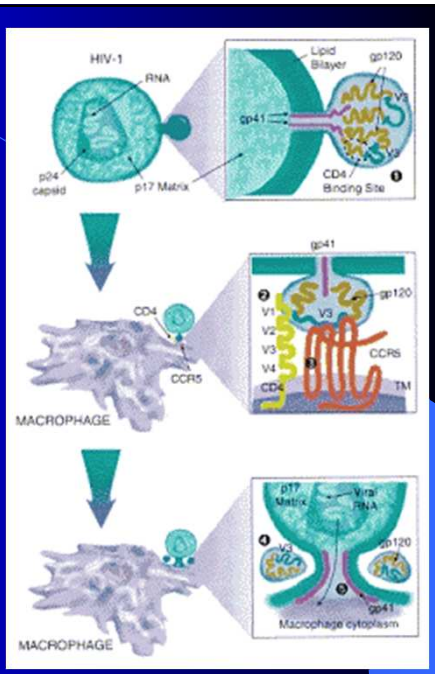
- gp160 ⇒ gp120 + gp41
- protease inhibitors
  (Norvir, Katera)

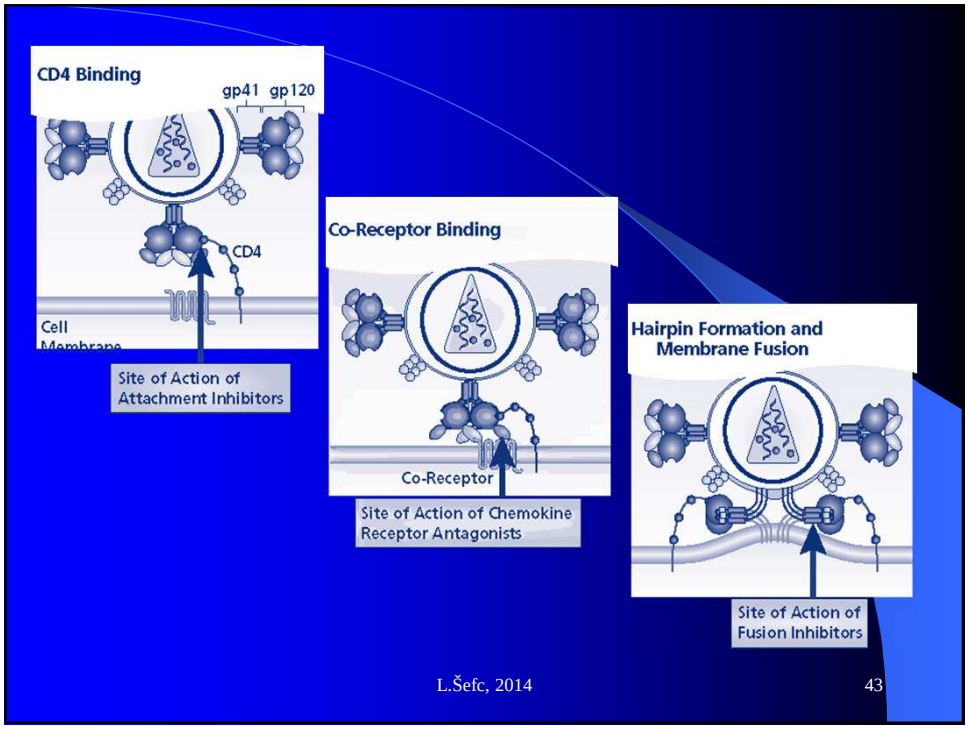


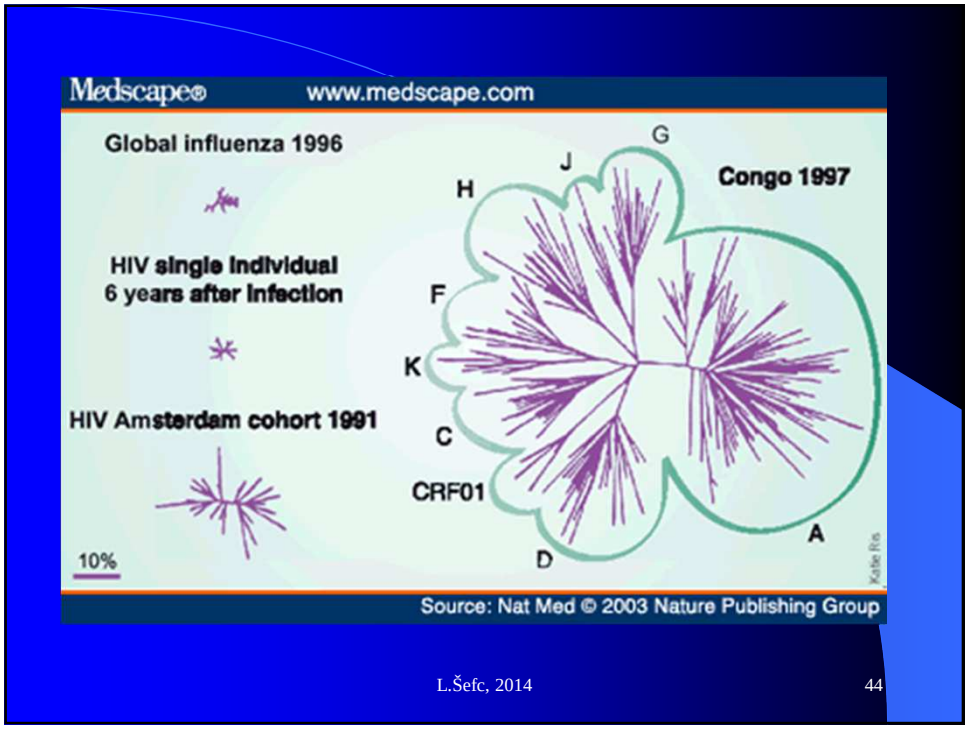


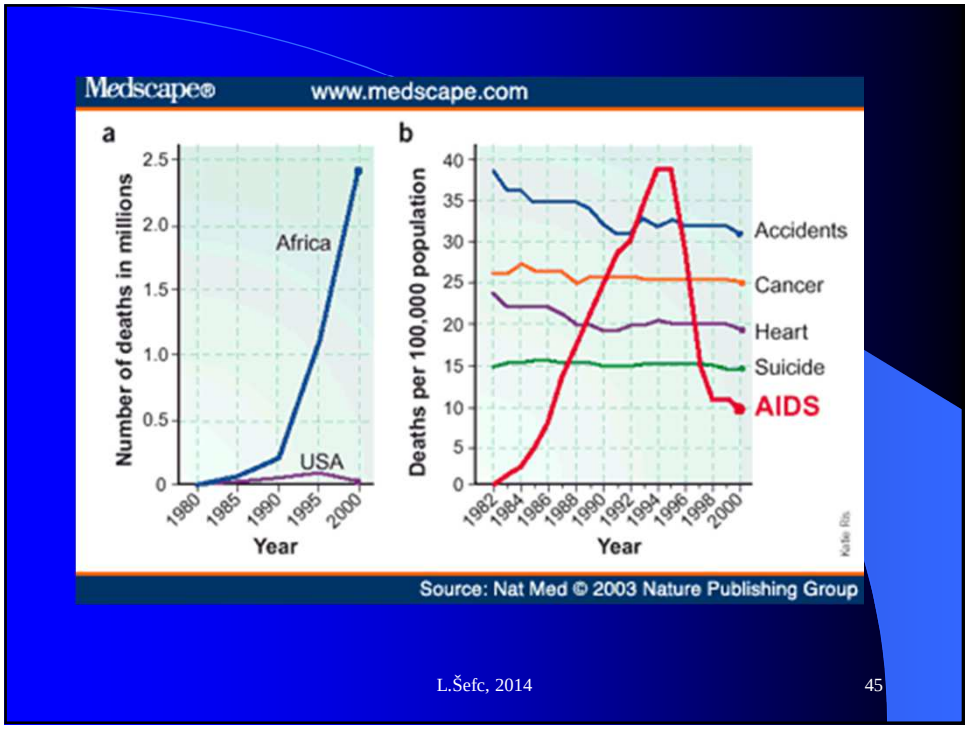
HIV-1 infection

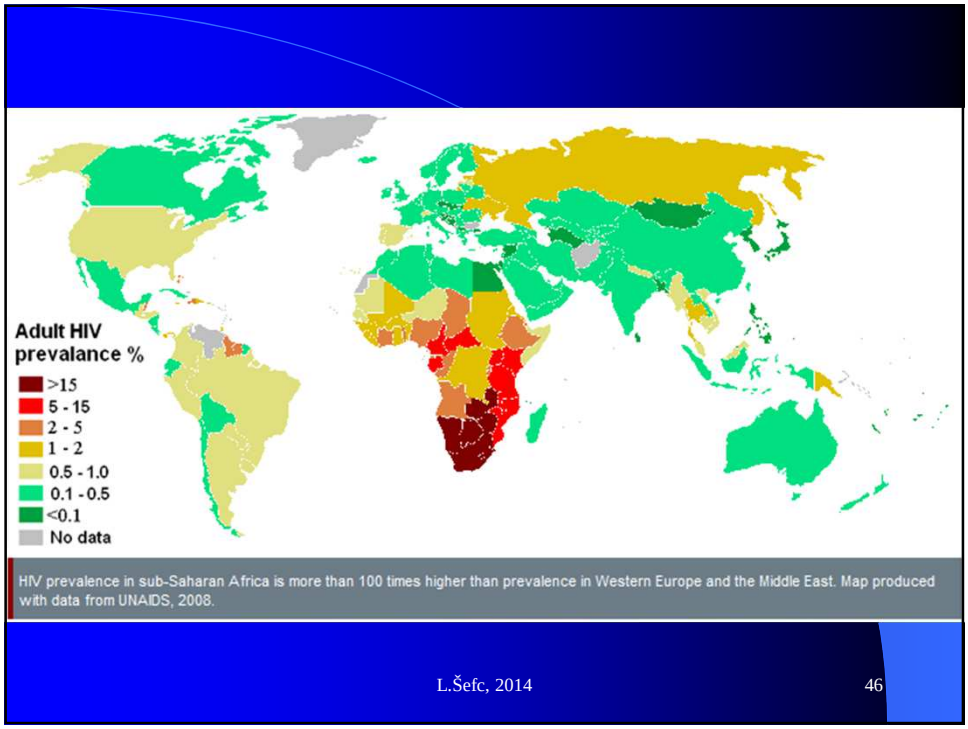
- gp160 ⇒ gp120 + gp41
- protease inhibitors
  (Norvir, Katera)
- fusion inhibitors
  (Fuzeon)




CD4 Binding
gp41 gp120
CD4
Cell
Site of Action of
Attachment Inhibitors
Co-Receptor Binding
Co-Receptor
Site of Action of Chemokine
Receptor Antagonists
Hairpin Formation and
Membrane Fusion
Site of Action of
Fusion Inhibitors


Medscape®
www.medscape.com
Global influenza 1996
HIV single individual
6 years after infection
HIV Amsterdam cohort 1991
10%
G
J
H
Congo 1997
F
K
C
CRF01
A
D
Source: Nat Med © 2003 Nature Publishing Group


Medscape®
www.medscape.com
a
b
Number of deaths in millions
Africa
USA
Year
Deaths per 100,000 population
Accidents
Cancer
Heart
Suicide
AIDS
Year
Source: Nat Med © 2003 Nature Publishing Group


Adult HIV prevalance %
>15
5 - 15
2 - 5
1 - 2
0.5 - 1.0
0.1 - 0.5
<0.1
No data
HIV prevalence in sub-Saharan Africa is more than 100 times higher than prevalence in Western Europe and the Middle East. Map produced with data from UNAIDS, 2008.

Septic shock

- systemic expression of multiple inflammatory mediators
- Gram-negative septicemia – endotoxin
- (tampons contaminated with Staphylococcus aureus - exotoxin ⇒ toxic shock)
- hypotension, insufficient tissue perfusion, uncontrollable bleeding
- multisystem organ failure, disseminated intravascular coagulation

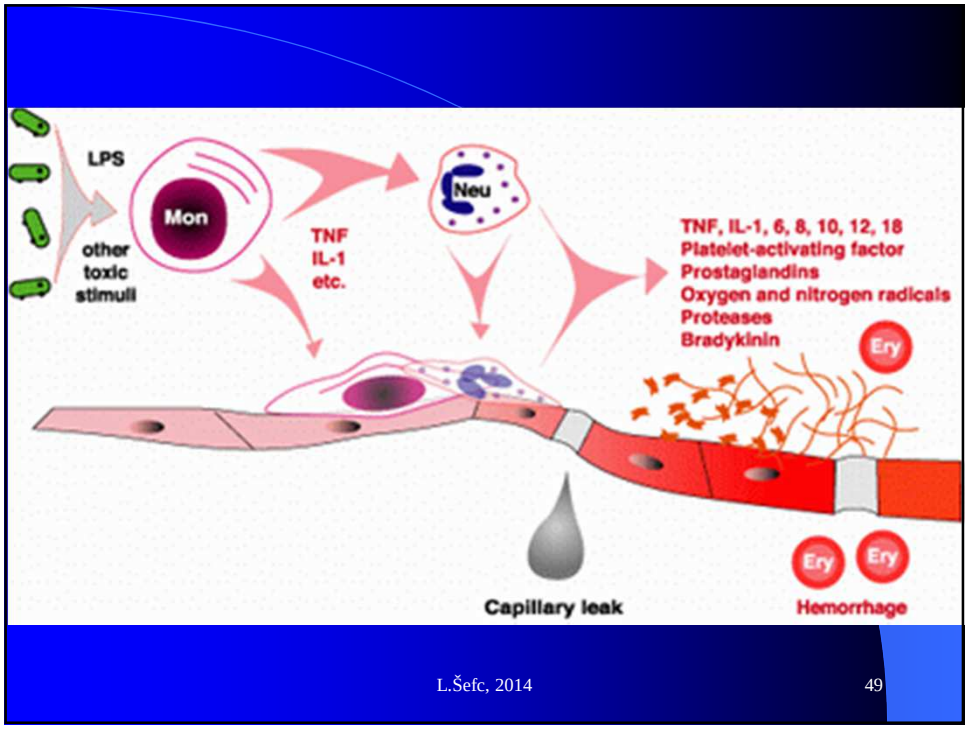
Septic shock

- > 150 cytokines, „cytokine storm“

IL-1⇒ tachycardia and hypotension, ↑ IFN-γ, chemokines, …

TNF-α ⇒ ↑ pro-coagulation activity of endothelial cells, > 1 ng/ml ⇒ lethal prediction

IL-6 ⇒ induction of acute phase proteins

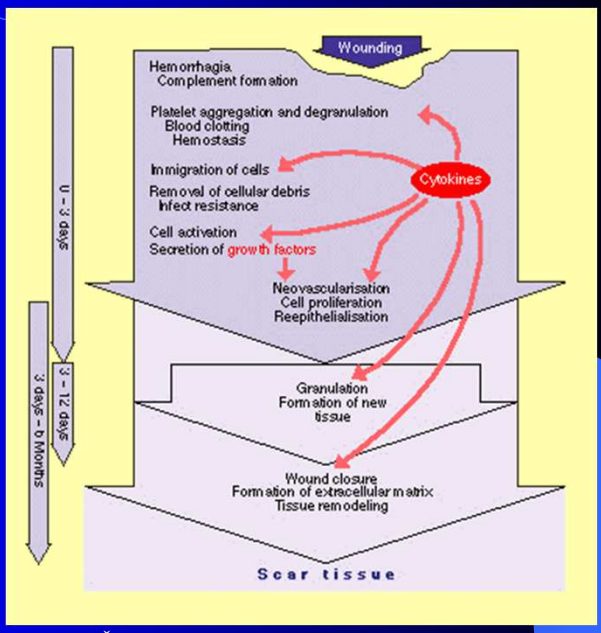


Septic shock - therapy

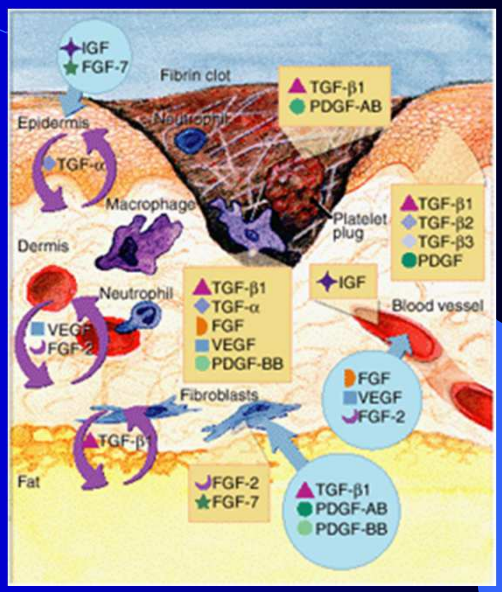
- antibodies against TNF-α
- IL-1Ra
- sTNF-αR
- IL-4, IL-10

Wound healing

- EGF, FGF
- TGF-β
- chemokines
- angiopoietins

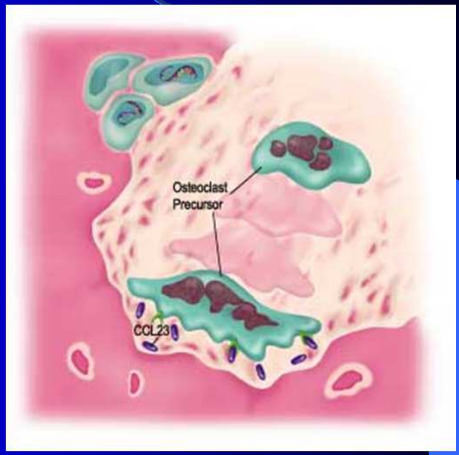


Wound healing



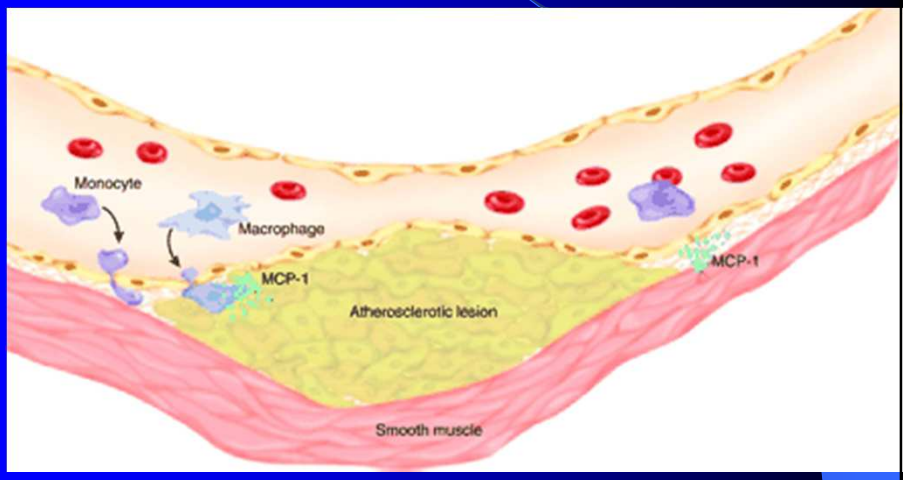
Bone remodelation

osteoblasts
⇓
chemokine CCL23
⇓
osteoclast
chemotraction



Aterosclerosis

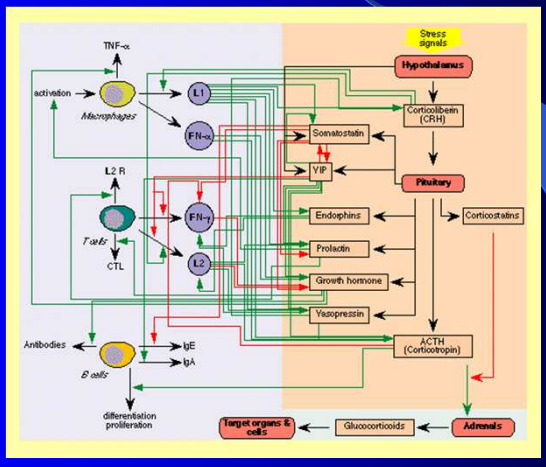
MCP-1 – macrophage chemoattractant protein-1



Neuroimmune network

- interactions between the immune system and neuroendocrine organs
- hypothalamo-pituitary-immune axis
- innervations of lymphatic organs (sympaticus, parasympaticus)
- cytokine production in CNS during injury, infection, and neurodegenerative processes
- hypofysectomy impairs humoral and cell immunity

Hypotalamo-pituitary-immune axis and cytokines



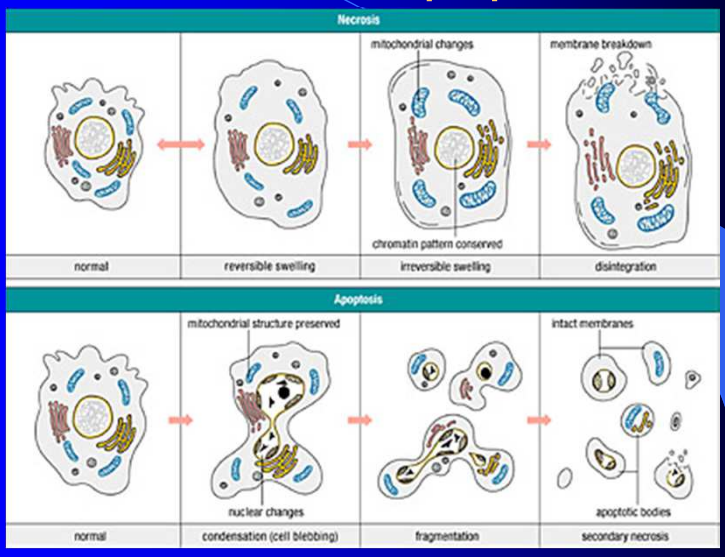
Cytokine fusion toxins

- chimeric proteins: DT (diphtheria toxin) and PE (Pseudomonas exotoxin)
- targetted against cells bearing a specific receptor
- cancer cells, lymphoma
- prevention of GVHD

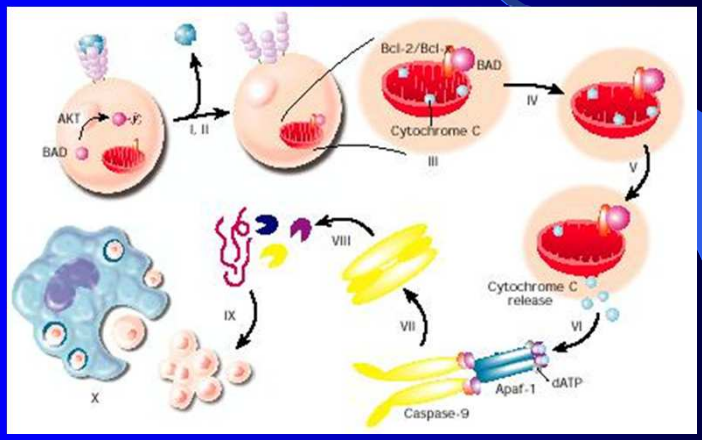
Necrosis x apoptosis

- Necrosis: passive ⇒ inflammation
- Apoptosis: active and energy dependent ⇒ no inflammation

Necrosis x apoptosis



Negative apoptosis regulation
(hematopoietic cells)



Positive apoptosis regulation
(lymphocytes, cancer cells)

- „death factors“ – TNF-α, Fas-L
- „death receptor“ activation
- pro-caspase activation (caspase 8 – FLICE)

⇓

apoptosis

Positive apoptosis regulation
(lymphocytes, cancer cells)