Imnunology 3

Innate immunity mechanisms

Introduction

- Barriéres
- **<u>Nonspecific mechanisms</u>**

- activated or almost activated
- starting at once
- recognition of broad spectrum of agenses
- destruction or phagoctosis and destruction
- inflamation (localisation of infection)

Recognition of antigens

- **PRR - Pattern recognition receptors** – present on cells of nonspecific immunity
- **PAMP – pathogen associated molecular patterns** – molecules present on foreign cells
- Innate mechanisms are able to recognise self and nonself

PAMP

- Peptidogycan
- LPS
- non specific antigens of viruses and other microbes

PRR

Extracelular proteins on membranes

bound on phagocyting cells

- **TLR** – recognition of broad spectrum of pathogens., transmission of signal to the nucleus, activation of genes encoding production of cytokínes stimulating inflamation
- **opsonins** – molecules binding on the surface of microbes, that make them more attractive for phagocytes

Several receptors can be activated at once

Preformed receptors

- present as part of **innate immunity**
- enable rapid reaction

PRR – on soluble molecules and host cells

TLR – present on host cells

KAR – on NK cells

KIR – on NK cells

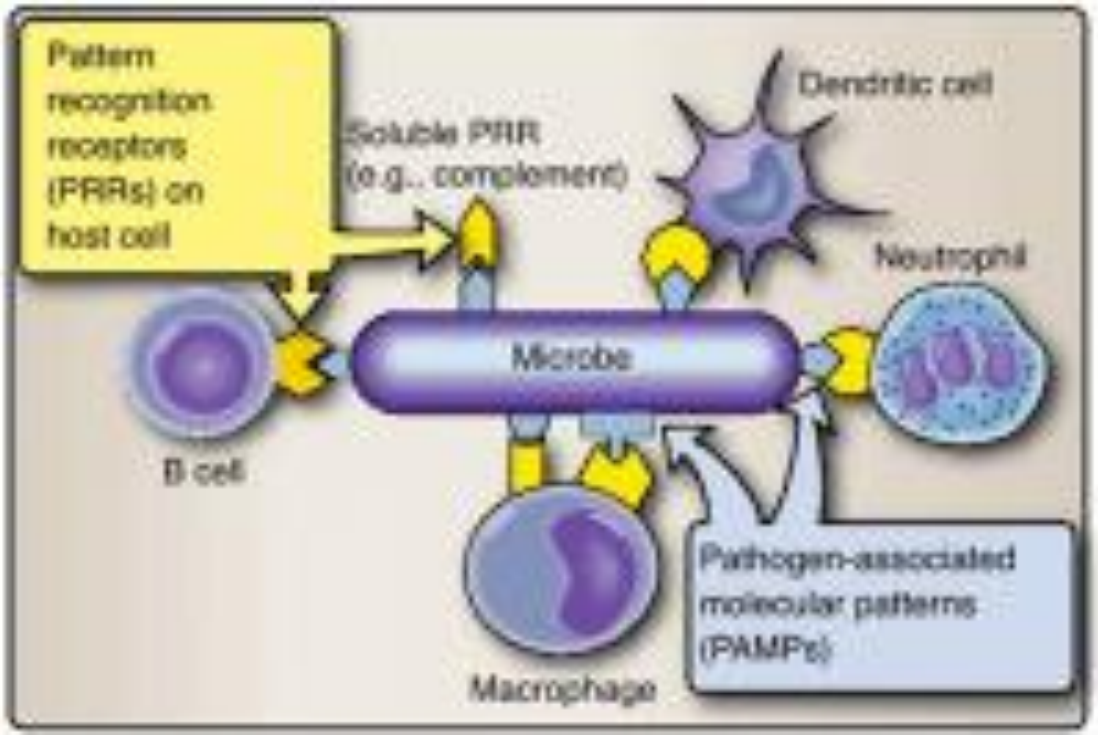
CR – on soluble molecules, phagocytes, on B cells

FcR – on phagocyting cells

PRR – pattern recognition receptors

- present on host cells or in soluble forme (proteins of complement
- recognise different motives (patterns) present on microbes and not on self cells PAMP – pathogen associated molecular patterns
- this bound starts different forms of inflamation with the aime to kill the pathogen

PRR – pattern recognition receptors



TLR – toll like receptors

- present on host cells
- bind PAMP of microbes
- start transcription, synthesis and secretion of cytokins stimulating inflamatin and attraction of macrophages, NK cells, neutrofils and dendritic cells to the site of infection

Molecules detectiong changes of self

- molecules of thermal shock, molecules MICA, MICB – produced:

- by cells infected by virus
- cells on cancerogenesis

Recognised by TLR of phagocyting cells

activationg KAR - Killer Activating Receptors on NK cells

Humoral mechanisms

- Besides activity of cells, innate machanisms engage also soluble molecules

- destruction of cells (infected by virus)
- increase activity of other mechanisme (Phagocytosis)

Interferon type I

Defensins

Complement

Cytokines

Interferon type I

- produced by subgroups of dendritic cells (IFα), fibroblastes (IFγ)
- after binding viral PAMP and PRR
- start activation of antiviral mechanisms (activity of macrofages, dendritic cells...)

Defensins

Many cells: **epitelial, neutrofils, macrophages in skin or mucose membranes** secrete peptids rich on cysteín

These peptides form chanals in cell membrane of bacteria this enable influx of ions and bacterial death.

Other molecules with microbicidal functions: **lysosym, Dnase, Rnase**

Cytokines and chemokines

- **Cytokines -** secreted by leucocytes and other cells
  - engaged in innate immunity, adaptive immunity a inflamation
  - antigen nonspecific way
  - induction of broad spectrum of physiological changes.
- **Chemokines** subgroup of cytokines with low molecules
  - engaged in chemotaxis (chemically induced migration)

Complement

- System of enzymes and proteins engaged in specific and adaptive immunity mechanisms
- In innate mechanisms this systome is activated by
  - alternative path
  - MBL (manan binding lectin) path

Complement

- Consists of innactive circulating glycoproteins activated in cascade way after innitial stimulation

- 3 paths of stimulation:
  - c*lassic (antigen + antibody*)
  - alternative (microbes and their products)
  - MBL path

- Results in production of:
  MAC membrane attact complex
  it is bound on cell surface (of microbe) formation of disruptions in surface memgrane that leads to lysisof cell

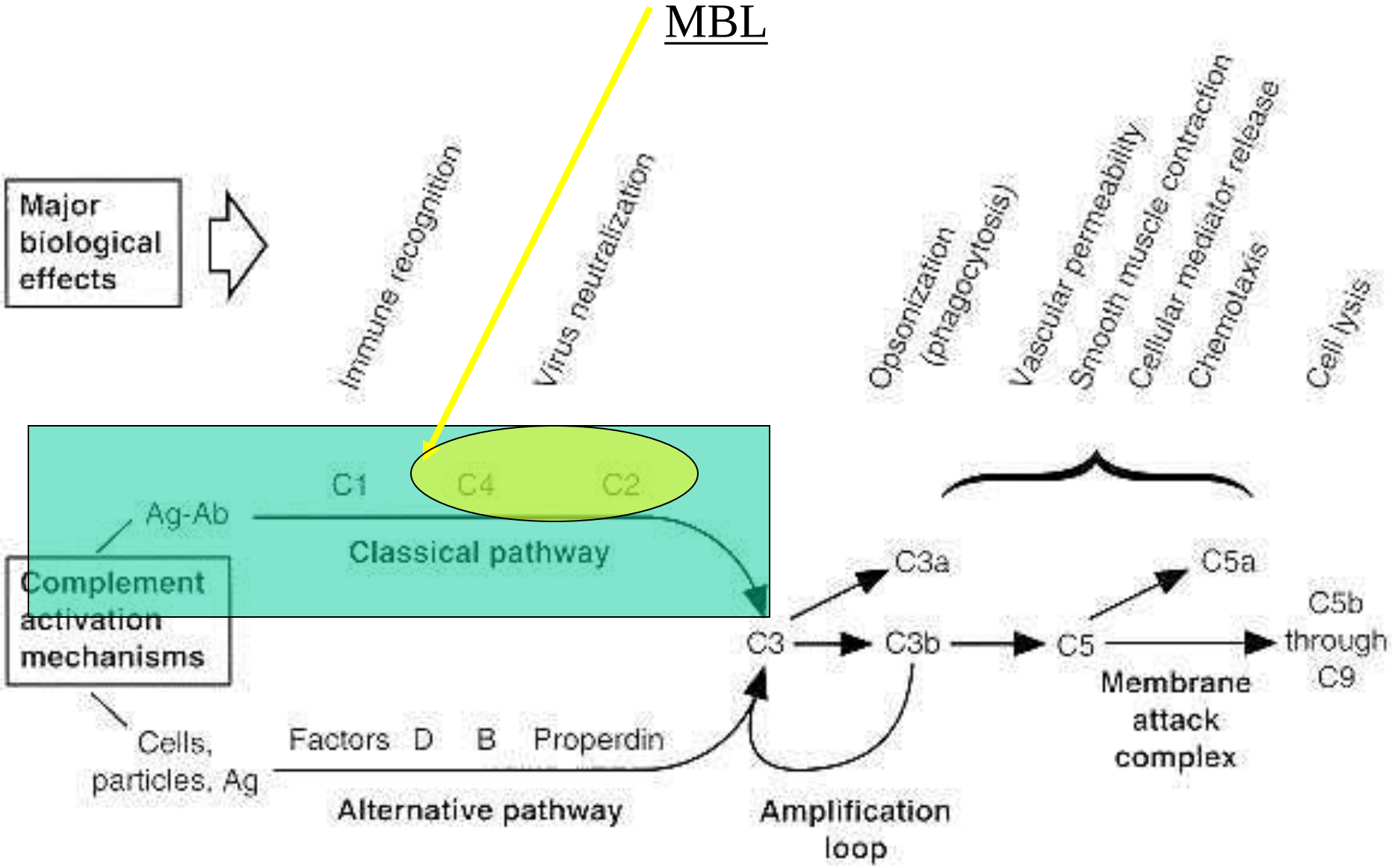
C

- - Complement components C1 to C9, B, D a Properdin are proteins present in serum
- - Fragments of native components of complement are described by small letters,C3b Bb). Smaller fragmentsa “a“, bigger fragments by letter „b“.

- - Horizontal line is indicateing proteins or complexes of complement with enzymatic activity $\overline{C4bC2b}$.

Alternative path

- Initiated by cell surface products recognised as foreign for host cell (LPS)
- Many enzymes (calicreín, plasmin, elastasa) disrupt C3 part of serum complement present concentration 1300 mg/l in several small fragments i.e. shorty living and not stabil C3b fragment.
  It is important **opsonin** binding on receptors on cell surfaces


MBL
Major biological effects
Immune recognition
Virus neutralization
Opsonization (phagocytosis)
Vascular permeability
Smooth muscle contraction
Cellular mediator release
Chemotaxis
Cell lysis
C1
C4
C2
Ag-Ab
Classical pathway
Complement activation mechanisms
C3a
C5a
C3
C3b
C5
C5b through C9
Membrane attack complex
Cells, particles, Ag
Factors D B Properdin
Alternative pathway
Amplification loop

MBL – path

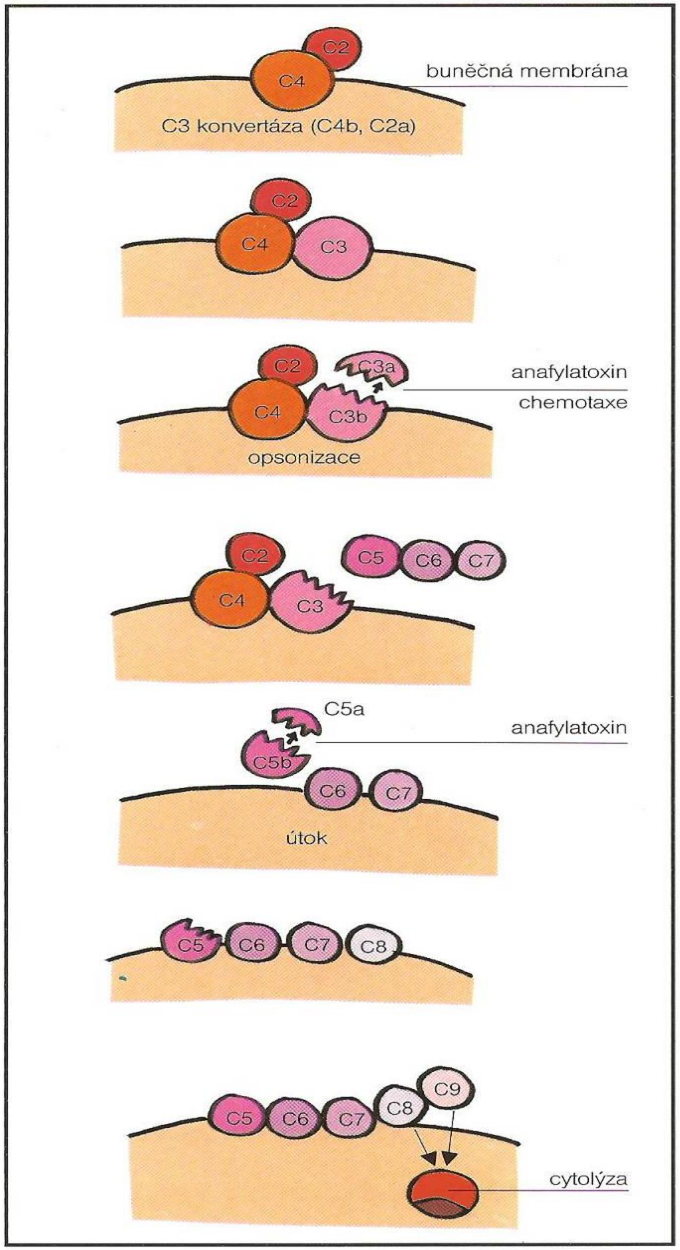
Activated by binding of **lectin on** mannose containde in rests of glycoproteins of some microbes *Listéria, Salmonella*, *Candida albicans.*

MBL is protein of acute phase inflamation.

MBL bound on mannose cooperates with **Mannose Aktivated Serine Protease** to activate C2, C4 a C3

MAC

- C5a — chemotaxis anaphylatoxin
- C3a
- **C3b**C5bC6C7C8C9
- opsonisation



Obr. 11: *Vysvětlení v textu.*

Lysis

- Binding of C5b on bacterial membrane starts formation of MAC and lysis
- C5b start consecutive attachement of C6, C7 a C8.
- C8 is responsible for firme anchoring in the membrane and attachment of C9 molecule, then the pores in membrane are formesd.
- Disrupted integrity of membrane results in nonregulated flow of electrolytes and lytical death of cell

Cellular mechanisms

- Besides soluble (humoral immunity) mechanisms innate immunity engages cells mediated mechanisms
- Receptors recognising ligands (antigenic molecules) of pathogens start inflamation and destruction of microbes by **fagocytes**.
- **NK bunky** – kills infected and transformed cells.

Fagocytosis

- engulfment and degradation of microbes and other corpuscular parts of cells: macrophages, dendritic cells, neutrofils and even B lymfocytes

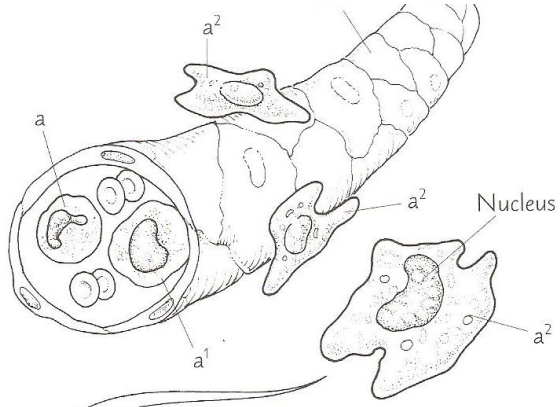
Are part of cleaning mechanisms of the body

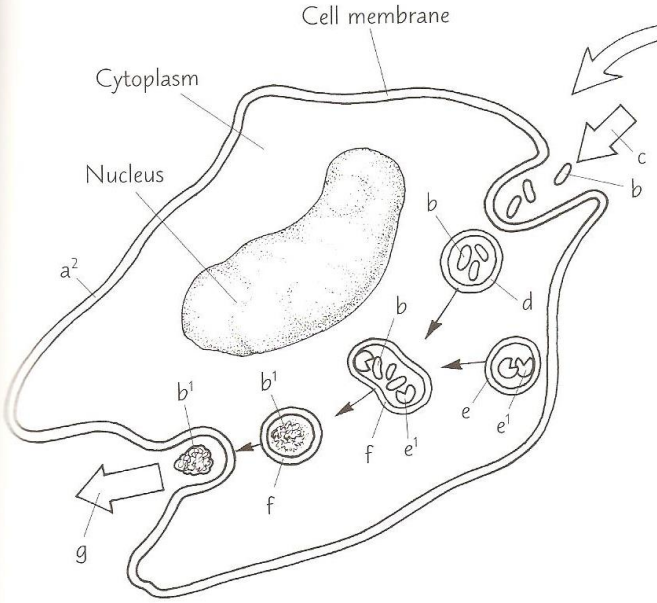
- protect body by ingestion
- disrupt rests of cells and parts

- 1. **translocation** of leu throught intercellular binding of endotel and **adherence** on endotel
- 2. enter leu in interstitium and its activation by chemical substances produced in sites where microbes are present as answer to disruption - **chemotaxis**
- 3. antigen is covered by molecules that make ingestion easier - **opsoniation** *fibronectin, **IgG* *specific antibodies*, C3
- 4. adherence of Ag on neutrofils starts - **internalisation,**
- 5. formation of **fagosomes** and their fusion with primary (hydrolytical and proteolytical enzymes) and secondary granules (lactoferin, cytochrome b)

PHAGOCYTES

NEUTROPHIL a
MONOCYTE a^1
MACROPHAGE a^2



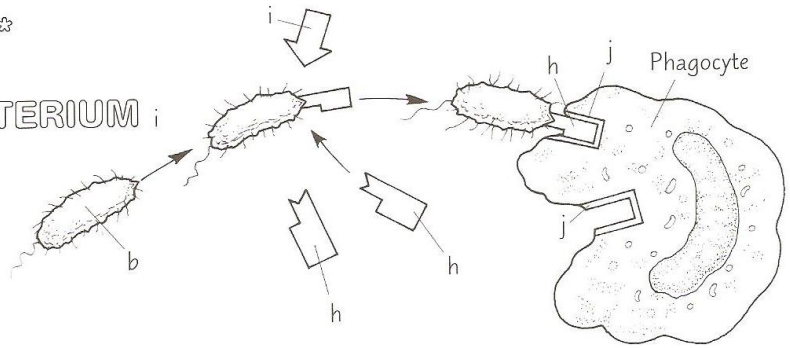


PHAGOCYTOSIS

BACTERIUM b
ENDOCYTOSIS c
PHAGOSOME d
LYSOSOME e
ENZYME e^1
PHAGOLYSOSOME f
BACTERIAL FRAGMENT b^1
EXOCYTOSIS g

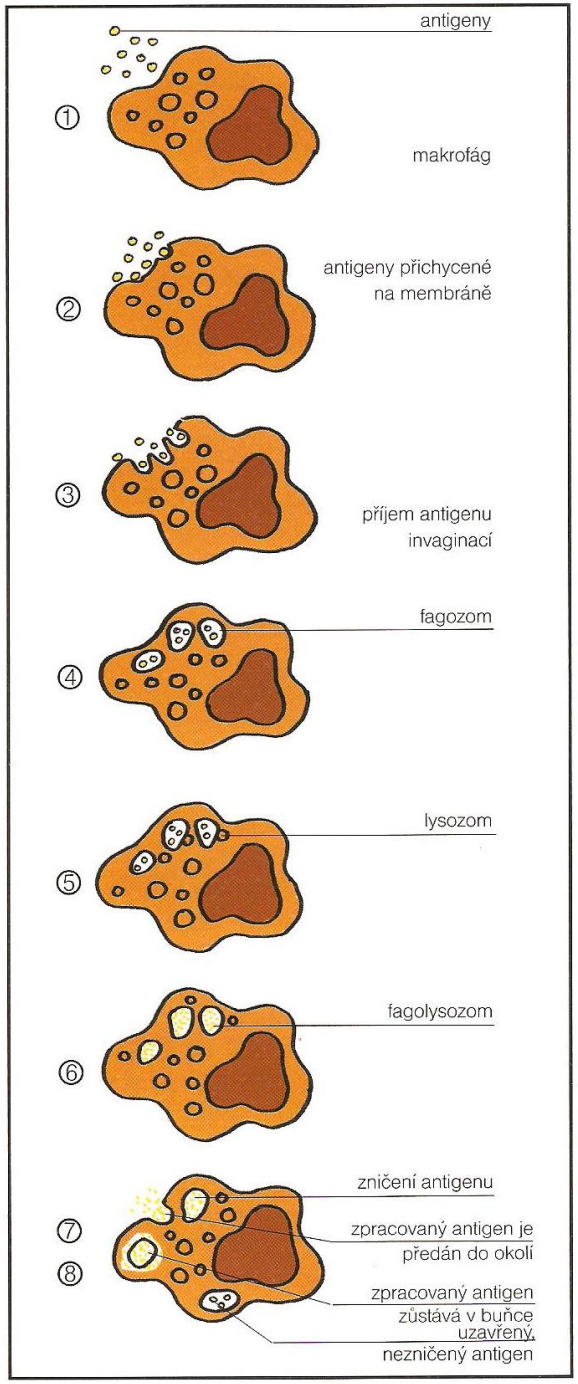
OPSONIZATION

COMPLEMENT h
OPSONIZED BACTERIUM i
RECEPTOR SITE j



Fagocytosis

- **direct mechanism of struggle against infection**
  - engulfment and degradation of microbes by **fagocyting cells -** they secrete cytokines and chemokines
  - attracting and activationg other cells of innate mechanisms
  Oxidative burst – formation of highly reactive **oxygen metabolits**, **- degradation enzymes** are important for degradation of engulfed microbes



Obr. 18: Fagocytóza pomocí makrofágů. Antigeny se dostávají do kontaktu s makrofágem, který se může amébovitě pohybovat (1).
Antigeny se přichytí na membránu makrofága (2) a jsou jí uzavřeny v kráteru (invaginace) (3). Antigen je uzavřen do váčku, který se nazývá fagozom (4) a fagozomy se dostávají do styku s lysozomy (5). Rozpouštějí se za vzniku fagolysozomu (6) a antigen je stráven (7). Po zničení může být antigen vypuzen do okolí a prezentován lymfocytům (8), které na samotné antigeny, t. zn. bez přítomnosti makrofágů, nemohou reagovat. Strávené antigeny mohou také zůstávat v makrofágu; některé antigeny jako např. bakterie tuberkulózy mohou přetrvávat v makrofágu nestrávené.

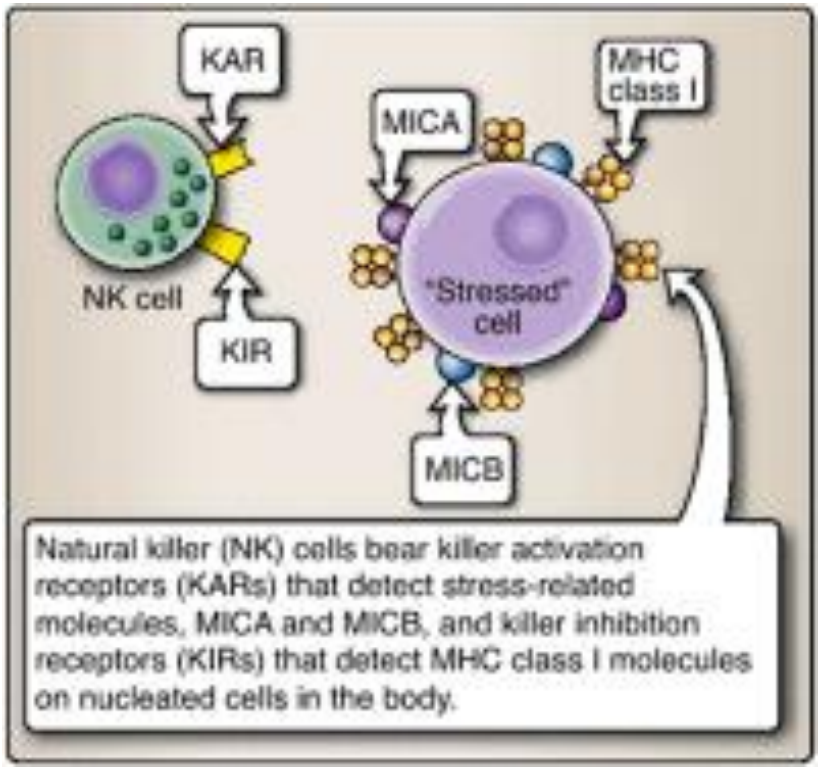
NK cells

- NK cells recognise changed cells and direct them to destruction
- NK cells **contain KAR – killer activation receptors** – that recognise stress molecules, incl. **MICA a MICB** in on surface of inected and transformed cell

KIR, KAR on NK- natural killers

- NK cells – part of lymphocytic line
- Receptors recognising changes on self cells molecules (after viral infection, or changed by Ca - gennic processes)
- **KAR** – **killer activation receptors** – recognise MICA, MICB (stress molecules) on self cells that activates NK cells to kill self cell.
- **KIR** – **killer inhibition receptors** – monitors MHC I molecules. Tumor and virus infected cells decrease number of MHC I, that decrease the possibility of binding to MHC I molecules and decrease the inhibítion of killers

KIR, KAR – on natural killers NK



Inflamation

- - aktivation of complement by alternative or lectin binding path,
- - attraction and activation of phagocyting cells that secrete cytokines and chemokines,
- - aktivation of NK cells,
- - changes of vascular permeability
- - rise of body temperature

Signs

ache

warm

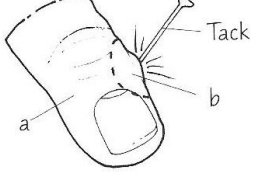
redness

oedema

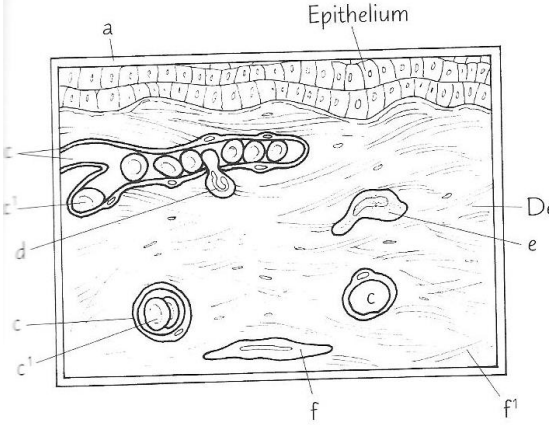
loss of function

(dolor, calor, rubor, tumor, functio laesa)

INFLAMMATION ☆

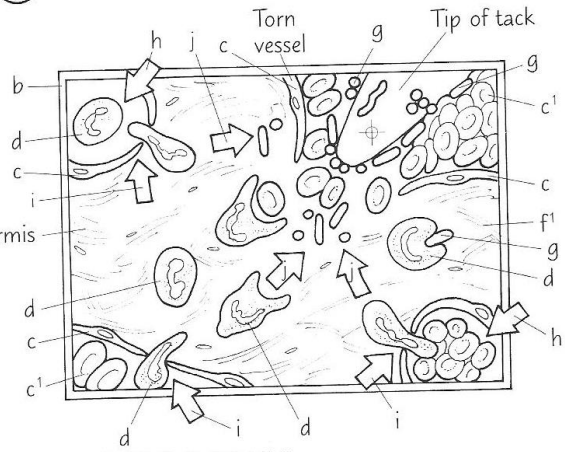


① NORMAL SKIN a

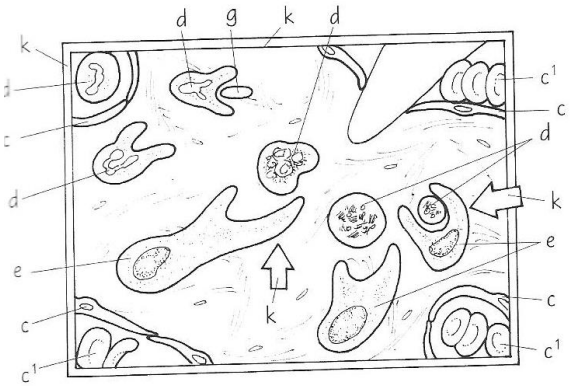


BLOOD VESSEL c / RBC c¹
NEUTROPHIL d
MACROPHAGE e
FIBROBLAST f / FIBER f¹

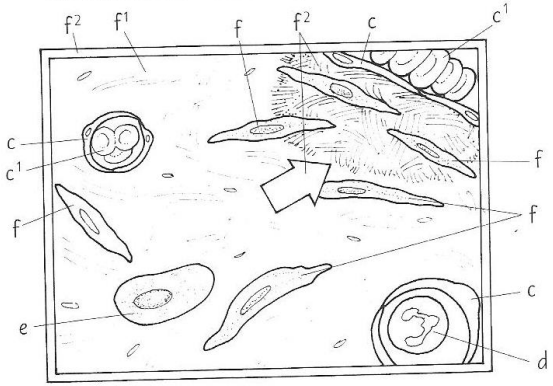
② INFLAMED SKIN b



BACTERIUM g
VASODILATATION h
DIAPEDESIS i
CHEMOTAXIS j



③ PHAGOCYTOSIS OF DEAD NEUTROPHILS k



④ HEALING: FIBROSIS f²