INFLAMMATION
**INFLAMMATION**

reaction to physical, chemical and biological injury

purpose:
  - to dilute, neutralize or destroy foreign cause of injury, to heal damaged tissue

- increased blood flow
- increased capillary permeability
- increased cell migration

**acute** – mast cells, platelets, granulocytes
**chronic** – mononuclear cells
  (monocytes/macrophages and lymphocytes)

calor, dolor, rubor, tumor
CELLS OF ACUTE INFLAMMATION I

**mast cells** (degranulation)
- secrete:
  - histamine, serotonin, bradykinin – vasodilatation, increased vascular permeability
  - LTB4 – chemotaxis of neutrophils and eosinophils

**platelets**
- secrete serotonin: vasodilatation, increased vascular permeability
- clump and clot blood vessels, prevent bleeding

LTB4 - leukotriene B4
CELLS OF ACUTE INFLAMMATION II

neutrophils
- most abundant cells in inflammation
- chemotaxis (C5a, LTB4, IL-8)
- phagocytosis and extracellular degranulation

eosinophils
- chemotaxis
- phagocytosis and degranulation
- specialized for parasitic infections

→ both eosinophils and neutrophils can damage healthy tissues by degranulation

eosinophils important in allergy
### CHEMICAL MEDIATORS OF ACUTE INFLAMMATION

**complement system**  
chemotaxis, opsonization, lysis

**coagulation system**  
forming of blood clot, then fibrinolysis  
factor XII activates kinin system

**kinin system**  
kininogens – kallikreins – bradykinin  
activity: vasodilatation, vascular permeability

**acute phase proteins**  
CRP: facilitates phagocytosis of bacteria

blood clot in addition to preventing bleeding also prevents spreading of pathogen into circulation
# CELLS OF CHRONIC INFLAMMATION

**lymphocytes**
- extravasation, chemotaxis
- CD8, NK: cytotoxicity
- CD4: cytokines – activation of macrophages + other cells

**plasma cells (PC)**
- activation of B cells through antigen presentation
- proliferation of B cells
- differentiation into PC $\Rightarrow$ secretion of antibodies

**macrophages**
- phagocytosis, digestion of damaged tissue and microorganisms, termination of inflammation

mononuclear cells
# CYTOKINES IN INFLAMMATION

## INTERLEUKIN-1 (IL-1)

**pro-inflammatory cytokine**

**secreted by:**

- activated macrophages, some other cells
  (neutrophils, endothelial cells,...)

**activity:**

- induces secretion of other cytokines, production of cytotoxic effector cells, production of inflammatory cells in bone marrow
- causes fever and shock

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pro-inflammatory (IL-1, TNF, IFN-γ) and anti-inflammatory (IL-10) cytokines
(regulation, resolution of inflammation)
CYTOKINES IN INFLAMMATION
TUMOR NECROSIS FACTOR (TNF)

pro-inflammatory cytokine

secreted by:

activated macrophages, some other cells

activity:

activation of endothelial cells, macrophages and granulocytes, stimulation of leukocyte adherence, MHC-I expression and secretion of other cytokines, secretion of acute phase proteins, co-stimulation of T and B cell proliferation

causes fever, hypotension and rapid weight loss (cachexia)
<table>
<thead>
<tr>
<th>CYTOKINES IN INFLAMMATION INTERFERON-γ (IFN-γ)</th>
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<tbody>
<tr>
<td>pro-inflammatory cytokine</td>
</tr>
<tr>
<td>secreted by:</td>
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<tr>
<td>activated T cells, NK cells</td>
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<tr>
<td>activity:</td>
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<tr>
<td>activation of macrophages, stimulation of</td>
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<tr>
<td>expression of MHC-I in most of the cells,</td>
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<tr>
<td>MHC-II in antigen-presenting cells, adhesion</td>
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<td>molecules in endothelial cells, stimulation</td>
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<tr>
<td>of T cell and NK cell cytotoxicity,</td>
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<tr>
<td>stimulation of TNF and IL-1 secretion</td>
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<td><strong>CYTOKINES IN INFLAMMATION</strong></td>
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<tr>
<td><strong>INTERLEUKIN-10 (IL-10)</strong></td>
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</table>

anti-inflammatory cytokine

**secreted by:**

- **macrophages**

**activity:**

blocks activation of macrophages and dendritic cells, blocks production of pro-inflammatory cytokines
CYTOKINES IN INFLAMMATION
INTERLEUKIN-2 (IL-2)

secreted by:
activated T cells

activity:
promotes proliferation of T cells (autocrine activity), B cells (transformation into plasma cells), activation of NK cells (LAK), activation of macrophages (increased cytotoxicity)
ADAPTIVE IMMUNITY, ANTIBODIES
ADAPTIVE (SPECIFIC) IMMUNITY

- requires prior encounter with antigen
- coupled with major histocompatibility molecules (MHC, HLA)*
- specific recognition of particular antigen
- immunological memory

Effectors: T cells (TCR) and B cells (BCR)

- MHC = major histocompatibility complex
- HLA = human leukocyte antigens

Adaptive immunity is also called acquired immunity
ANTIGEN RECOGNITION

- **BCR**: recognizes soluble or cell-bound Ag in native form; can be membrane-bound (BCR) or soluble and secreted (antibody)
- **TCR**: recognizes only processed Ag in complex with MHC molecules on surface of presenting cells; TCR is always only membrane-bound

Ag = antigen
one B cell always makes antibodies of the same specificity
### ANTIBODIES

**immunoglobulins IgG, IgA, IgM, IgD, IgE**

**bifunctional molecules**
- antigen binding
- effector functions – interaction with other immune mechanisms, humoral (complement) and cellular (immunocytes with FcR)

**class depends on structure**
- two same light (κ, λ) and
- two same heavy chains (α, δ, γ, μ, ε)
one cell always makes either kappa or lambda chains; one antibody has two same chains (kappa or lambda)
next three slides on the example of IgG, other isotypes are little different, but the principle of structure is the same
hinge region, flexibility
hypervariable regions on both heavy and light chain
hinge region, flexibility
Fab – antigen binding; Fc - crystallizable
EFFECTOR FUNCTIONS OF ANTIBODIES

neutralization of toxins
complement activation (classical pathway)
interaction with other cells by receptors
### EFFECOTOR FUNCTIONS OF ANTIBODIES

Receptors for interaction with immunoglobulins (all but T cells)

**IgG receptors:** FcγRI (CD64) and FcγRII (CD32): phagocytes, FcγRIII (CD16): phagocytes and NK cells (ADCC)

**IgE receptors:** FcεRI: mast cells and basophils; FcεRII (CD23): eosinophils

**IgA receptors:** FcαRI (CD89): phagocytes
ANTIBODY BINDING TO ANTIGEN

types of bonds (all are noncovalent)
hydrogen
electrostatic
Van der Waals
hydrophobic

<table>
<thead>
<tr>
<th>Noncovalent forces</th>
<th>Origin</th>
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<tr>
<td>Electrostatic forces</td>
<td>Attraction between opposite charges</td>
</tr>
<tr>
<td>Hydrogen bonds</td>
<td>Hydrogen shared between electronegative atoms (H, O)</td>
</tr>
<tr>
<td>Van der Waals forces</td>
<td>Fluctuations in electron clouds around molecules oppositely polarize neighboring atoms</td>
</tr>
<tr>
<td>Hydrophobic forces</td>
<td>Hydrophobic groups interact unfavorably with water and tend to pack together to exclude water molecules. The attraction also involves van der Waals forces</td>
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multiple bonds enable sufficient strength of binding
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<th>ANTIBODY PROPERTIES</th>
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<tr>
<td><strong>affinity</strong></td>
</tr>
<tr>
<td>strength of antigen – antibody binding at one binding site</td>
</tr>
<tr>
<td><strong>avidity</strong></td>
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<tr>
<td>sum total strength of antibody binding to antigen</td>
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<tr>
<td><strong>specificity</strong></td>
</tr>
<tr>
<td>capability of recognizing total configuration of antigen epitope (amino acid sequence, spatial configuration, electric charge)</td>
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ANTIBODY PROPERTIES

affinity and avidity
10^{11} different antibodies for different antigens (about 20000 genes in human genome)
IMMUNOGLOBULIN CLASSES - IgG

- IgG1-IgG4
- 70-75% Ig in serum
- 146 KDa
- major Ig of secondary response
- major antitoxin Ig
- complement activation by classical pathway
- opsonization – phagocytes (FcγR)
- ADCC – NK cells (FcγR)

classes = isotypes
**IMMUNOGLOBULIN CLASSES – IgA**

- IgA1 and IgA2
- 15-20% Ig in serum
- 160 kDa
- major component of seromucous secretions, most abundant Ig in mucosae
- secretory IgA is dimer
- doesn’t activate complement
IMMUNOGLOBULIN CLASSES - IgM

- 10% Ig in serum
- pentamer (970 kDa)
- major Ig of primary response
- against antigenically complex microorganisms
- complement activation by classical pathway
IMMUNOGLOBULIN CLASSES - IgD

- < 1% Ig in serum
- predominates among membrane-bound Ig on B cells (BCR) together with IgM
IMMUNOGLOBULIN CLASSES - IgE

- <1% Ig in serum
- on basophil and mast cell membrane (FcεR)
- anti-parasitic activity
- allergies (asthma)