Immunology – Part II

Innate Immunity

26. April 2017, Ruhr-Universität Bochum
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Nomenclature

Cytokine: proteins that are made by cells and affect the behavior of other cells. „Hormones“ of the immune system
Abbreviation: IL for Interleukin=Cytokine

Chemokine: Small chemoattractant proteins that stimulate the migration and activation of cells.
Abbreviation: CCL and CXCL

Clusters of differentiation: groups of antibodies identifying the same cell-surface molecule.
Abbreviation: CD

Leucocytes: all white blood cells, these are differentiated by their microscopic appearance and expression of CD molecules
Unspecific/Innate Immune Response

- genetically fixed (innate)
- not directed toward specific pathogens but against pathogen associated molecular patterns PAMPs
- reduces invasion of pathogens into the tissue
- reacts immediately, slows down distribution of pathogen until specific immunity has evolved

- e.g.: **humoral**: protease, complement, Interferons….
  **cellular**: macrophages, granulocytes…

humoral = solubilized in blood (lat. umor = Liquid)
Conserved structures of pathogens are detected by „Pattern Recognition Rezeptoren“

<table>
<thead>
<tr>
<th>Receptor characteristic</th>
<th>Innate immunity</th>
<th>Adaptive immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity inherited in the genome</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Expressed by all cells of a particular type (eg, macrophages)</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Triggers immediate response</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Recognizes broad classes of pathogen</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Interacts with a range of molecular structures of a given type</td>
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<td>No</td>
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<tr>
<td>Encoded in multiple gene segments</td>
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<td>Yes</td>
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<tr>
<td>Requires gene rearrangement</td>
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<td>Yes</td>
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<tr>
<td>Clonal distribution</td>
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<tr>
<td>Able to discriminate between even closely related molecular structures</td>
<td>No</td>
<td>Yes</td>
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Figure 2-10 Immunobiology, 6/e. (© Garland Science 2005)
Innate immunity evolved early in evolution

<table>
<thead>
<tr>
<th></th>
<th>Drosophila (insect)</th>
<th>Sea urchin (echinoderm)</th>
<th>Sea squirts (ascidian)</th>
<th>Lamprey (agnathan)</th>
<th>Shark (chondrichthyes)</th>
<th>Carp (teleost)</th>
<th>Frog (amphibian)</th>
<th>Snake (reptile)</th>
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<td>MHC molecules</td>
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<td>complement pathway</td>
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</table>

Figure 15-10 Immunobiology, 6/e. (© Garland Science 2005)

MASP=MBL associated serine protease
Stages of the immune response to infectious microbes

1. Adherence to epithelium
2. Local infection, penetration of epithelium
3. Local infection of tissues
4. Lymphatic spread
5. Adaptive immunity

Protection against infection:

- Normal flora and local chemical factors inhibit microbial growth
- Wound healing induced by antimicrobial proteins and peptides, phagocytes, and complement destroy invading microorganisms
- Complement activation: Dendritic cells migrate to lymph nodes, phagocyte action, NK cells activated
- Pathogens trapped and phagocytosed in lymphoid tissue
- Infection cleared by specific antibody

Figure 10-2 Immunobiology, 6/e. (© Garland Science 2005)
Innate Immunity – First Defense

Prevention of infiltration of pathogens into the body:

• **Mechanic barrier** (skin, mucosa)

  Airway epithelium:
  red = mucus secreting goblet cells
  yellow = ciliated epithelium

• **Chemical barrier** (pH-value, enzymes)
  - blood, lymph 7,4
  - saliva 6,4
  - stomach 1,9 – 2,6
  - urine 4,5 – 8,2
  - sweat 4,0 – 6,8
**Innate Immunity - Second Defense**

**Humoral immune response**

1) **lysozyme**: enzyme that is able to cleave peptidoglycan of bacterial cell walls

2) **Antimicrobial peptides**: e.g. **Defensin** (direct bactericidal activity by pore formation in the cell wall)

3) **Complement system** (chemotaxis of leucocytes, opsonization of pathogens, destruction of pathogens)
The complement system as a part of the innate immune response

- more than 30 proteins soluble and membrane-bound plasma and other body fluid proteins are involved
- complement mediate the effect of antibodies
- facilitate the destruction of pathogenic microorganisms by phagocytes or by lysis (Opsonisation)
- direct cell-destructive properties*
- many complement proteins are proteases, which are activated by proteolytic cleavage (Zymogens)

*are tightly regulated
Different ways of how the complement system protects against an infection

1. Production of activated complement proteins, which bind covalently to pathogens and "opsonise" them, so that an incorporation by phagocytes, which carry CR, will facilitate (opsonization).

2. Smaller fragments that can be released after complement activation act as chemoattractants (attract phagocytes and activate these) (anaphylatoxin).

3. Destruction of pathogens by pore formation (bacteriolysis).
Three different mechanisms of complement activation

Classical pathway
- Antigen-antibody-complex
- Attraction of inflammatory cells

MB-lectin pathway
- Lectin binds on the surface of the pathogen
- Opsonisation of pathogens

Alternative pathway
- Pathogen surfaces
- Destruction of pathogens
Essential components and effector impacts of the complement system

**Classical way**
- Antigen: antibody-complexes (pathogen surfaces)
- Recognition: C1q, C1r, C1s, C4, C2

**MB-lektin way**
- Mannan binding lectin binds mannose on the pathogen surface
- Recognition: MBL, MASP-1, MASP-2, C4, C2

**Alternative way**
- Pathogen surfaces
- Recognition: C3, B, D

**C3-convertase**
- **Effect**: C4a*, C3a, C5a
  - Inflammatory mediated peptides, attraction of phagocytes
- **Effect**: C3b
  - Binds on complement receptors on the phagocytes
  - Opsonisation of pathogens
  - Removal of immunocomplexes
- **Effect**: Terminal complement components C5b, C6, C7, C8, C9
  - Membrane offending complex, lyse of specific pathogens and cells
Innate Immunity – Third defense
NK cells
Innate Immunity - NK cells

Natural killer cells

- Found in tissue and blood
- Characteristic marker CD56, Fc\(\gamma\) III Receptor
From innate to adaptive immunity

Time line of development

- Production of IFN-α, IFN-β, TNF-α, and IL-12
- NK-cell-mediated killing of infected cells
- T-cell-mediated killing of infected cells

Time after viral infection (days)

Virus titer

Figure 2-49 Immunobiology, 6/e. (© Garland Science 2005)
Inhibition of NK cell activation by normal cells

MHC class I on normal cells is recognized by killer cell immunoglobulin-like receptors (KIRs) or by lectin-like CD94:NKG2.

NK cell does not kill the normal cell.

Figure 2-50 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)
Activation of NK cell by altered cell surface

Mechanism I

'Altered' or absent MHC class I cannot stimulate a negative signal. The NK cell is triggered by signals from activating

Activated NK cell releases granule contents, inducing apoptosis in target cell

Figure 2-50 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)
Activation of NK cell by altered cell surface
Mechanism II

Antibody binds antigens on the surface of target cells

Fc receptors on NK cells recognize bound antibody

Figure 9-34 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)
Activation of NK cell by altered cell surface

Mechanism II

Cross-linking of Fc receptors signals the NK cell to kill the target cell

Target cell dies by apoptosis

Figure 9-34 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)
Innate Immunity – Third defense
Mast cells
Innate Immunity - Mast cells

mast cells

- cells found in tissue
- characteristic markers: c-kit, Fcε Receptor,
- cytoplasmatic granula stains blue with Methylene-Blue
Activation of mast cells in allergic disease

Mast cell

Allergen

IgE

FcεR

Histamine

Leukotriene

Figure 12-16 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)
But mast cells have also some very useful functions...

**Yellow scorpion** (*Leiurus quinquestriatus*)

(Mast cell deficient mice)

Innate Immunity – Third defense
Eosinophilic granulocytes
Innate Immunity - Eosinophilic granulocytes

**Eosinophilic granulocytes**

- cells found in tissue and blood
- characteristic marker: EPO eosinophil peroxidase
- cytoplasm stains red with EosinY
Atopic asthma is a disease where inflammation is triggered by eosinophils
However, similar to the mast cell eosinophilic granulocytes can have some useful functions too...

Eosinophilic granulocytes attacking IgE coated parasite
Innate Immunity – Third defense
Phagocytes
Innate Immunity - Phagocytes

**Phagocytic cells:**
- macrophages of tissues
- monocytes of blood
- neutrophilic granulocytes
Phagocytosis of yeast particles by neutrophils (left) and macrophages (right)
Mechanism of Phagocytosis

1. Chemotaxis and adherence of microbe to phagocyte
2. Ingestion of microbe by phagocyte
3. Formation of a phagosome
4. Fusion of the phagosome with a lysosome to form a phagolysosome
5. Digestion of ingested microbe by enzymes
6. Formation of residual body containing indigestible material
7. Discharge of waste materials
Formation of neutrophil extracellular traps (NET)

NETosis
- Chromatin decondensation
- Nuclear membrane disintegration

NET formation is associated with bacterial clearance but also with thrombosis, sepsis and SLE
Innate Immunity – Third defense
Dendritic Cells
Dendritic cells
Found in tissue and blood
Characteristic marker CD1a, CD11c, MHC II

uptake of antigen via endocytosis
The blood contains different subsets of dendritic cells.
Dendritic cells bridge innate and adaptive immune response via presentation of antigens to T-lymphocytes
Dendritic cells bridge innate and adaptive immune response via presentation of antigens to T-lymphocytes

unreife dendritische Zellen in den peripheren Geweben treffen auf Pathogene und werden durch PAMP aktiviert

TLR-Signale aktivieren CCR7 und verstärken die Prozessierung von Antigenen der Pathogene

CCR7 lenkt die Zelle in die lymphatischen Gewebe und verstärkt die Expression von co-stimulierenden Molekülen und MHC-Molekülen

eine reife dendritische Zelle in der T-Zell-Zone prägt naive T-Zellen (Priming)
PRR Receptors of Innate Immune Cells

- Pattern recognition receptors (PRR) detect pathogen associated molecular patterns (PAMPs).

**Two types of PRR are known:**
1. Toll like receptors = TLR
2. Lectin-receptors
The receptor Toll was identified in Drosophila

Receptor Toll was identified 1996 as a key receptor for immune response against fungi

Human Toll-like receptors (TLR) are homologous to Drosophila toll-protein and have a key function in mediation of the immune response
**Known ligands for the Toll-like receptors**

<table>
<thead>
<tr>
<th>TLR1/2: triacyl-Lipoprotein</th>
<th>TLR5: Flagellin</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR2/6: diacyl-Lipoprotein</td>
<td>TLR7: ssRNA</td>
</tr>
<tr>
<td>TLR3: dsRNA</td>
<td>TLR8: ssRNA</td>
</tr>
<tr>
<td>TLR4: LPS</td>
<td>TLR9: unmethylated CpG oligonucleotides</td>
</tr>
<tr>
<td></td>
<td>TLR10: ??</td>
</tr>
<tr>
<td></td>
<td>TLR11: uropathogenic bacteria</td>
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<tr>
<td></td>
<td>TLR12: Profilin of T. gondii</td>
</tr>
<tr>
<td></td>
<td>TLR13: rRNA</td>
</tr>
</tbody>
</table>
IRAK=Interleukin-1 receptor-associated kinase
MKK= Mitogen-activated protein kinase kinase kinase
IKK=IκB kinase
TIR domain=Toll-Interleukin receptor
MyD88=Myeloid differentiation response
The importance of the TLR signal transduction is apparent in MyD88 knock out mice when they become infected with bacteria.

Mice lacking MyD88 failed to control infection and died.

Figure 10-10 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)
Phagocytes induce inflammation

After activation of TLRs by PAMPs phagocytes release a specific pattern of cytokines triggering inflammation that results in Inflammation: calor (heat), dolor (pain), rubor (redness) and tumor (swelling)
Proinflammatory cytokines have a broad spectrum of functions

IL-1/IL-6/TNF-α

Liver
- Acute-phase proteins (C-reactive protein, mannose-binding lectin)
  - Activation of complement Opsonization

Bone marrow endothelium
- Neutrophil mobilization
  - Phagocytosis

Hypothalamus
- Increased body temperature
  - Decreased viral and bacterial replication
    - Increased antigen processing
    - Increased specific immune response

Fat, muscle
- Protein and energy mobilization to allow increased body temperature

Dendritic cells
- TNF-α stimulates migration to lymph nodes and maturation
  - Initiation of adaptive immune response

Figure 2-46 Immunobiology, 6/e. (© Garland Science 2005)
An example for the endocrine activity of IL6

Bacteria induce macrophages to produce IL-6, which acts on hepatocytes to induce synthesis of acute-phase proteins.

C-reactive protein binds phosphocholine on bacterial surfaces, acting as an opsonin, and also activating complement.

Mannose-binding lectin binds mannose residues on bacterial surfaces, acting as an opsonin, and also activating complement.
LPS of gram-negative bacteria

TLR-4

TLR-2

Lipopeptide of gram-positive bacteria

Inflammation

Additionaly controlled by Inflammasome activation!

IL-1

IL-8

TNF-α

IL-6
Maturation of Interleukin-1β by the Inflammasome
NALP Inflammasom

- **Caspase Recruitment Domain**
- **Leucin rich repeats-Domain**
  - Important as stress sensor!
- **NACHT associated Domain**
- **Nucleotid binding Domain**:
  - Important for oligomerization!
- **Pyrin-Domain**: 95 amino acids
  - „death domain superfamily“
Activation of the inflammasome leads to recruitment of Caspase-1.

Known activators for inflammasome:
- Uric acid
- ATP
- Alum

Pro IL-1β binds to Pyrin Domain after oligomerization!
## Dysregulated Inflammasome activation is involved in Inflammatory disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical features</th>
<th>Gene mutated</th>
<th>Etiologic agent</th>
<th>Inflammasome involvement</th>
<th>Anakinra response</th>
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<tbody>
<tr>
<td>Familial cold autoinflammatory syndrome (FCAS)</td>
<td>Fever, arthralgia, cold-induced urticaria</td>
<td>NALP3</td>
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<td>Muckle-Wells syndrome (MWS)</td>
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<td>Chronic infantile neurological cutaneous and articular syndrome (CINCA, NOMID)</td>
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<td>Hyperimmunoglobulin D syndrome (HIDS)</td>
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<td>Mevalonate kinase</td>
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<td>Gout</td>
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</table>
Another group of pattern recognition receptors are the c-Typ Lectins

- **Carbohydrate Recognition Domain (CRD)**
- Type 1 (more than one CRDs)
- Type 2 (only one CRD)
- Binding of sugar is Ca\(^{2+}\) dependent
- Can facilitate endocytosis of antigens
- Some have also signaling properties

Quelle: Figdor et al. 2002
<table>
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<tr>
<th>CTLR (Trivia)</th>
<th>Organismus</th>
<th>Polysaccharid Liganden</th>
<th>Signale</th>
<th>Quelle</th>
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<td>Homo Sapiens</td>
<td>Mannose reiche Fucose reiche Le(^A), Le(^B), Le(^X), Le(^Y)</td>
<td>Induktion IL-10</td>
<td>Hovius et al., 2008</td>
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<td>DCIR (CLEC4A, CLEC5F6)</td>
<td>Homo Sapiens</td>
<td>Sulfatierte LacNAc, Lac N-glycane</td>
<td>Inhibition TNF Inhibition IL-12 Inhibition IFNα</td>
<td>Meyer-Wentrup et al., 2009 Hsu et al., 2009</td>
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<td>DCAL-2 (MICL, CLEC12A)</td>
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<td>Chen et al., 2006</td>
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<td>Dectin-2 (CLEC6A)</td>
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<td>Mannose reiche Cysteinyll Leucotrien Synthese</td>
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<td>Barrett et al., 2009 Sato et al., 2006</td>
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<td>BDC-2 (CLEC4C, CD303)</td>
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<td>Sulfatierte LacNAc, Lac N-glycane</td>
<td>Inhibition IFN Inhibition TNF Inhibition IL-7 Induktion IL-10</td>
<td>Cao et al. 2007 Dzionek et al. 2001 Rock et al. 2007 Hsu et al., 2009</td>
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