2021-2022

Some reactions of innate immunity

against: …microbes
…damaged/necrotic cells

Lecture outline

- Recognition
- NK cells
- Main reactions against virally-infected cells
- Phagocytosis
- Some cytokine actions

Read carefully:

- In innate system, a single cell has a group of receptor types with each receptor type able to recognize structures shared by multiple different classes of microbes

…while in adaptive system, a T cell will have a single type of T cell receptor (TCR) specific for a specific structural detail on a microbe (antigen…and particularly: epitope (the small part of an antigen that is actually recognized and bound by the receptor))

…also a B cell has a single type of BCR (immunoglobulin) for a specific antigen (or again: epitope)

…and also remember that:

- In innate system, the receptor types are identical on all cells of the same lineage (all neutrophils for example)

  …this is called “Nonclonal distribution of receptors”

  …while in adaptive system, the TCR is the same on all T cells of a specific clone (not all T cells in the body)

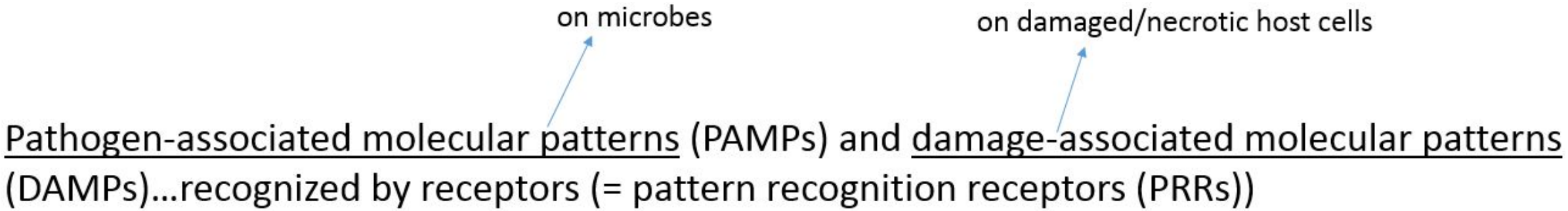
  …and so the BCR (immunoglobulin) on B cells

  … = clonal distribution of receptors

Recognition

- In innate system, we are not talking about TCR, BCR or antigen

…we are talking about:

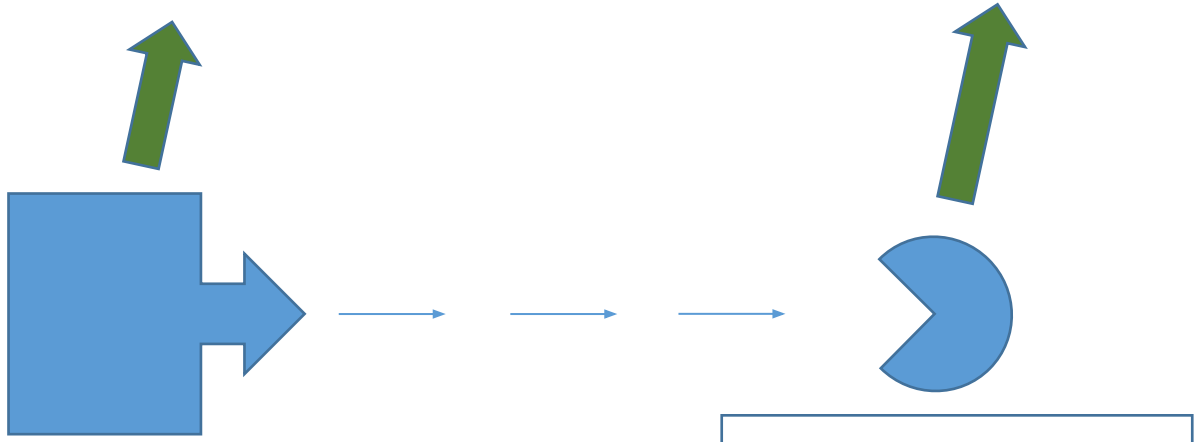


Recognition

By this, the innate system discriminates between self and non-self

on microbes (PAMPs)
or damaged cells (DAMPs)
not host cells

on host cells
not microbes



*PRR genes do not undergo somatic modification (they are conserved/germline)

Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)

Pattern recognition receptors (PRRs)

PRRs

* Cellular PRRs

…on/in phagocytes, dendritic cells and others

or

* Soluble extracellular PRRs

…like what?

***Main families:**

1-Toll-like receptors (TLRs)

2-NOD-like receptors (NLRs)

…and the inflammasome

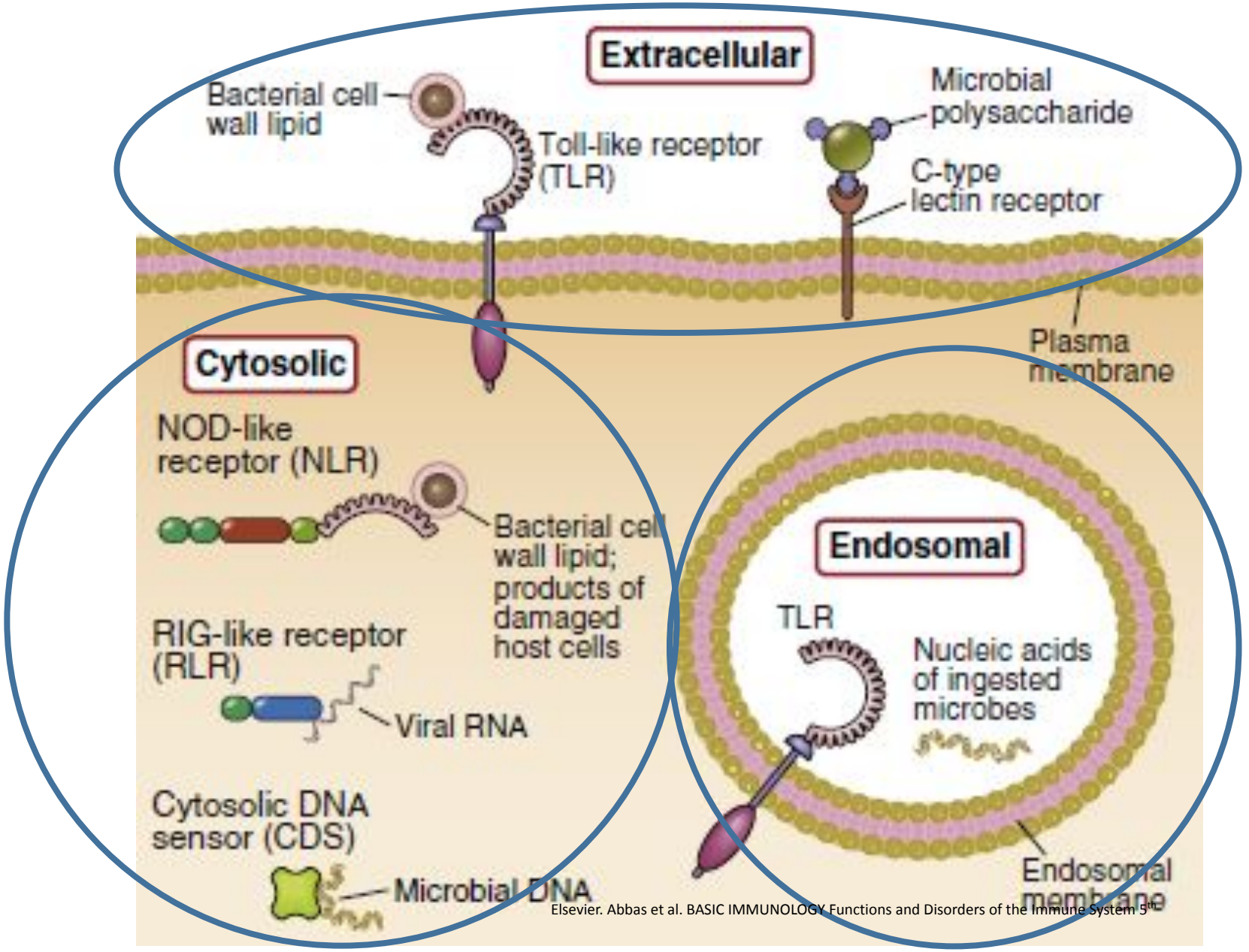
3-RIG-like receptors (RLRs)

4-Cytosolic DNA sensors (CDSs)

5-Lectin (carbohydrate-recognizing) receptors

6-A receptor on phagocyte cell surface that recognizes peptides beginning with *N*-formylmethionine

Cellular PRRs…3 main locations



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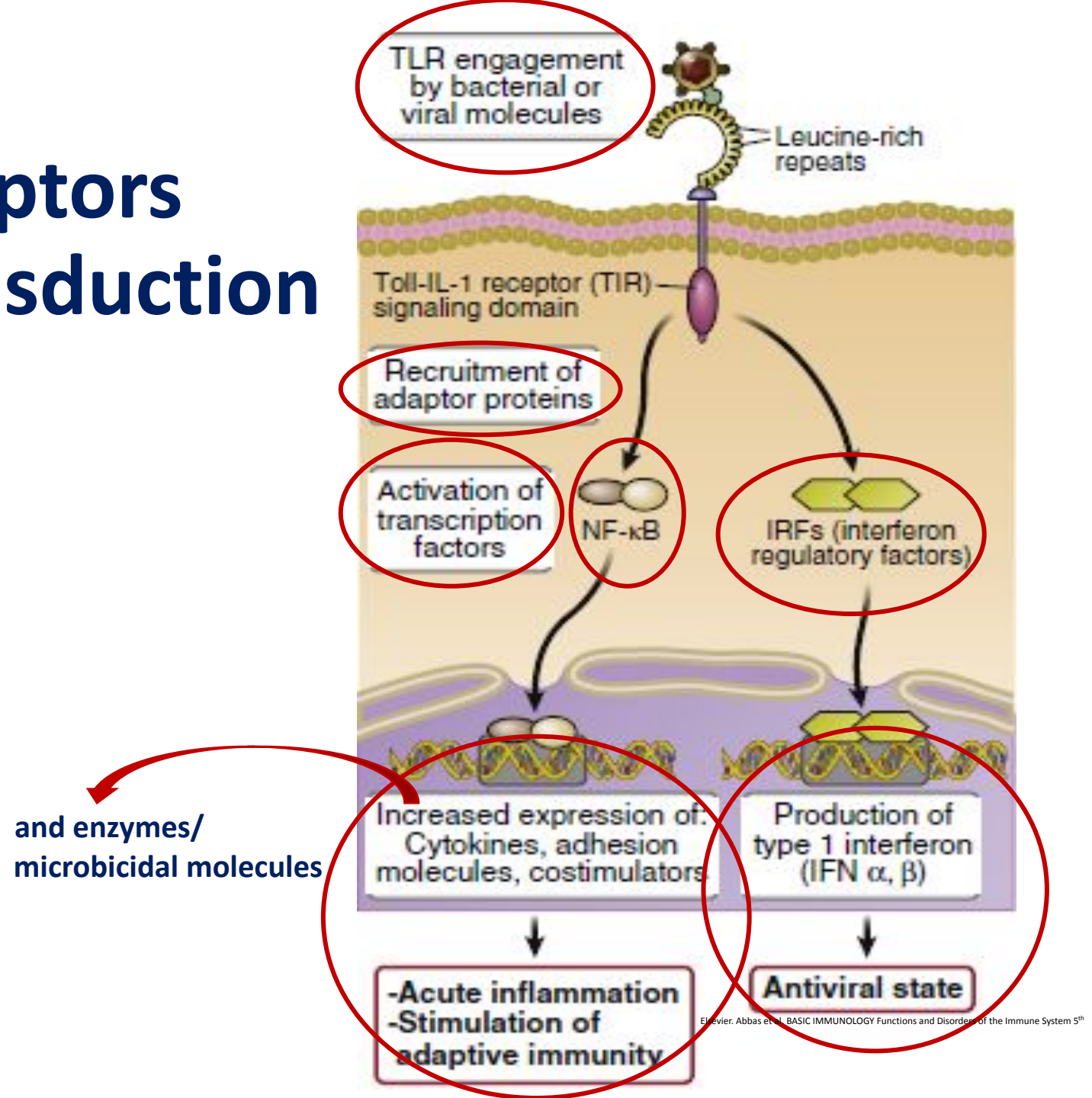
Toll-like receptors

can be: -sugar
-protein
-lipid
-nucleic acid

Toll-like receptor (TLR) …on the cell surface or endosomal	Pathogen-associated molecular pattern (PAMP)
TLR-2	Peptidoglycan and several bacterial and parasitic glycolipids
TLR-3, -7, and -8	Viral RNA
TLR-4	Bacterial lipopolysaccharide (endotoxin)
TLR-5	Flagellin (a bacterial flagellar protein)
TLR-9	Unmethylated CpG DNA, which is more abundant in microbial genomes than in mammalian DNA

endosomal

Toll-like receptors …signal transduction



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NOD-like receptors (NLRs)

- Cytosolic

- They recognize
  - -products of necrotic cells (uric acid, released ATP…etc.)
  - -ion disturbances (e.g., loss of K+)
  - -crystals (urate, cholesterol…etc.)
  - -some microbial products

- 3 important NLRs:
  - -NOD-1…recognizes peptidoglycan and activates NF-κB transcription factor
  - -NOD-2…recognizes peptidoglycan and activates NF-κB transcription factor
  - -NLRP-3…part of inflammasome cytosolic protein complex
    - …caspase-1 (part of the inflammasome complex) when activated it will cleave a precursor form of the cytokine interleukin-1β (IL-1β) to generate biologically active IL-1β

…mention 3 diseases associated with this mechanism

Other cellular PRRs

- RIG-like receptors (RLR) …recognizes viral RNA in the cytosol
  …leads to type I interferon production

- Cytosolic DNA sensors (CDSs) …recognizes viral DNA in the cytosol
  …leads to type I interferon production

- Lectin (carbohydrate-recognizing) receptors …plasma membrane receptors
  …recognize carbohydrates on
  fungi and bacteria
  …lead to phagocytosis and inflammatory
  response to these microbes

Other cellular PRRs, cont'd

- A receptor on phagocyte cell surface that recognizes peptides beginning with *N*-formylmethionine

  Specific to bacterial proteins

- Scavenger receptors: …plasma membrane receptors

  …on macrophages for example: recognize modified LDL…role in atherosclerosis (the foamy macrophages in the atherosclerotic plaque)

Markers of abnormal self

this also happens to cells in cancerous transformation

- Viruses: ↓ MHC class I molecules on infected host cells

  ……also expression of "stress signals" on cell surface

HSPs

(heat shock proteins)

-MICA

-MICB

..detected by: -TLR2

-TLR4

-KARs (killer activation receptors) of NK cells

NK cells

Killer activation receptors (KARs) **VS** Killer inhibition receptors (KIRs)

-MICA

-MICB

MHC I

How do NK cells kill the target cells?

- Perforin…creating pores
- Granzyme…proteolysis and apoptosis
- Fas ligand…apoptosis

Main reactions against virally-infected cells

- Killing by natural killer cells

- Interferon I production by the infected cells to prevent infection of other cells

  …plasmacytoid dendritic cells are the main producers

  …their TLR-3 recognizes viral ds-RNA

  …actions of interferon I -production of antiviral molecules…RNA-dependent protein kinase (PKR) (by adjacent cells)

  -apoptosis

  -activation of phagocytes, CD8, Th1, and NK cells

Phagocytosis

- Special areas in the phagocyte membrane are called: clathrin-coated pits…these contain different receptors (PRRs, complement receptors…etc.)

- **Phagocyte activation:**

-Lysosomal destruction of microbe: -acid hydrolases (proteases, lipases, nucleases..etc)

-<u>oxygen free radicals</u>

..this process is called: ….

-nitrous oxide (NO)

-acidity

-…etc

-Secretion of cytokines and chemokines

**Remember the enzymes:
1- NADPH oxidase
2- Myeloperoxidase

Some cytokine actions

-IL-1 and IL-6: fever, also vascular permeability

-TNF-alpha: vascular permeability, also fever

-IL-8 and IL-12: chemotaxis of neutrophils and NK cells, respectively

Thank You