Pattern Recognition Receptors (PRRs)

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- PRRs expressed by **innate immune cells** are essential for detecting invading pathogens and initiating the innate and adaptive immune response.
- There are multiple families of PRRs including the
  - **Membrane** associated
    - Toll-like receptors (TLRs), C-type lectin receptors (CLRs)
  - **Cytosolic**
    - NOD like receptors (NLRs), RIG-I-like receptors (RLRs), and AIM2-like receptors (ALRs).
- PRRs are activated by
  - PAMPs
  - DAMPs (exposed on the surface of, or released by damaged cells)

- ligand recognition by PRRs trigger intracellular signal transduction cascades that result in the expression of
  - pro-inflammatory cytokines
  - chemokines and
  - antiviral molecules
- **In contrast**, activation of some ALRs and NLRs leads to the formation of multi-protein inflammasome complexes that causes activation of Caspase-1.
  - Caspase-1 promotes the maturation and secretion of IL-1 and IL-18, which further amplifies the pro-inflammatory immune response
- Since a single pathogen can simultaneously activate multiple PRRs, **crosstalk** between different receptors may also play a role in enhancing or inhibiting the immune response.

1. **Toll-like Receptors (TLRs)**
2. **C-type Lectin Receptors (CLRs)**

Membrane Receptors

3. **NOD-like Receptors (NLRs)**
4. **RIG-I-like Receptors (RLRs)**
5. **AIM2 like Receptors (ALRs)**

Cytosolic Receptors

Toll-like Receptors (TLRs)

- Toll-like receptors (TLRs) are a family of type I transmembrane pattern recognition receptors (PRRs) that are expressed by a number of different immune and non-immune cells including
  - monocytes,
  - macrophages,
  - dendritic cells,
  - neutrophils,
  - B cells,
  - T cells,
  - fibroblasts,
  - endothelial cells,
  - epithelial cells.

- TLRs initiate the immune response following recognition of either
  - PAMPs
  - DAMPs
- There are 10 functional TLRs in humans and 12 in mice.
- Of the human TLRs,
  - TLR1, 2, 4, 5, 6, and 10 are expressed on the cell surface
    - primarily recognize microbial membrane and/or cell wall components,
  - TLR3, 7, 8, and 9 are expressed in the membranes of endo-lysosomal compartments
    - recognize nucleic acids

- TLRs have a variable number of ligand-sensing, leucine-rich repeats at their N-terminal ends and a cytoplasmic Toll/IL-1 R (TIR) domain.
- The TIR domain mediates interactions between TLRs and adaptor proteins involved in regulating TLR signaling including MyD88, TRIF, TRAM, and TIRAP/MAL.
- Signaling promote the expression of pro-inflammatory cytokines, chemokines, and type I and type III interferons.
  - As a result, additional immune cells are recruited to the infection site and pathogenic microbes and infected cells are eliminated.
- Although TLRs provide protection against a wide variety of pathogens**, inappropriate** or **unregulated** activation of TLR signaling can lead to chronic inflammatory and autoimmune disorders.

C-type Lectin Receptors (CLRs)

- CLRs are a diverse family of soluble and transmembrane proteins that contain one or more C-type lectin-like domain (CTLD).
- Multiple members of the CLR family are considered to be PRRs
  - recognize PAMPs
  - induce intracellular signaling pathways that regulate the immune response.
  - Most CLRs belong to either
    - the Dectin-1
    - or Dectin-2 subgroups.

- Members of these subgroups are transmembrane proteins
  - primarily expressed by monocytes, macrophages, and dendritic cells,
  - recognize fucose, mannose, or glucan carbohydrate structures.
- Signaling pathways activated by CLRs either directly regulate gene expression or modulate TLR signaling
- **Dectin-1** and **Dectin-2** receptors have been shown to promote NFkB signaling through activation of spleen tyrosine kinase (**SYK**) and a multi-protein complex (**CARD9, Bcl-10, MALT1**)

- signaling initiated by either receptor can precisely control the expression of numerous cytokines that direct the innate and adaptive immune response.
- CLRs are particularly important for antifungal immunity
  - with an increased susceptibility to a variety of fungal pathogens

NOD-like Receptors & RIG-I-like Receptors

- The NOD-like receptors (NLRs) are cytoplasmic proteins that regulate **inflammatory** and **apoptotic** responses
- Nucleotide-binding, oligomerization domain (NOD)-like receptors (NLRs) and retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) are **cytosolic receptors** that provide a second line of defense against invading pathogens.
- The NLR family consists of 22 human proteins and at least 34 mouse proteins.
- NOD1 and NOD2 recognize components of bacterial peptidoglycan (PGN).

- Upon activation, they homo-oligomerize and recruit signaling molecules that drive **the NFkB-/AP-1-dependent** expression of pro-inflammatory cytokines and the **IRF3-/IRF7-dependent** expression of type I interferons.
- Other NLRs (NLRP1, NLRP3, and NLRC4), are activated by a number of different pathogens or endogenous danger signals and oligomerize to form multi-protein inflammasome complexes.
- Inflammasome oligomerization induces the cleavage and activation of Caspase-1, which promotes the processing and secretion of IL-1β and IL-18, and may induce an inflammatory form of cell death known as pyroptosis

- **RIG-I-like receptors (RLRs)** are a subset of cytosolic pattern recognition receptors (PRRs) that detect viral RNA.
- The RLR (RIG-I and MDA5) receptors activates NFkB- and **IRF3-/IRF7-dependent** gene expression.

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