DAMPENING INFLAMMATION BY MODULATING TLR SIGNALLING

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  ➢ Tissue Injury
  ➢ Infection
  ➢ Inflammation

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• number of endogenous molecules generated upon tissue injury that activate TLRs have been identified
  • Some are intracellular molecules normally inaccessible to the immune system that are released extracellularly
  • Others are ECM molecule fragments that are released upon tissue damage
  • Or ECM molecules that are specifically up-regulated in response to tissue injury
• It is also becoming apparent that PAMPs and DAMPs act in quite a different manner in order to stimulate an immune response
Mechanisms of TLR Activation

Exogenous Ligand Recognition

- TLR can interact with a wide variety of ligands ranging from proteins, lipoproteins, nucleic acids, and saccharides, all of which differ in size and chemical properties.
- The extracellular domains (ECDs) of TLRs contain leucine-rich repeat (LRR) motifs responsible for PAMP recognition.

- TLRs also cooperate with other families of receptors to recognize microbial ligands.
  - TLR2 was shown to collaborate with dectin-1 in zymosan recognition or with the macrophage receptor.
  - With collagenous structure in addition to CD14 to respond to cell wall glycolipid from Mycobacterium tuberculosis.

Endogenous Ligand Recognition

- Surfactant protein A when bind to extracellular domain of TLR2 down-regulate peptidoglycan and zymosan induced NFκB activation and TNFα secretion.
- There is also evidence that DAMPs require different co-receptors and accessory molecules to PAMPs.
  - A first group of DAMPs requires both CD14 and MD-2.
  - A second group of DAMPs requires only CD14.
  - A third group comprises DAMPs that have been shown to involve only MD-2.
  - A fourth group includes DAMPs that require molecules like Biglycan.

- The resulting TIR-TIR complex initiates downstream signaling through recruitment of specific adaptor molecules.
- Five adaptors have been described so far:
  - Myeloid differentiation factor 88 (MyD88),
  - MyD88-adaptor like (Mal),
  - TIR domain containing adaptor inducing IFN-beta (TRIF),
  - TRIF-related adaptor molecule (TRAM), and
  - Sterile alpha and HEAT-Armadillo motifs (SARM).
- Depending on the adaptors recruited to the TLRs, two major intracellular signaling pathways can be activated by TLRs.
• The first, a **MyD88-dependent pathway**, is activated by all TLRs except TLR3
  • It involves
    • IL-1R-associated kinases (IRAK),
      • IRAK-1 and IRAK-4,
    • TNF receptor-associated factor 6 (TRAF-6)
    • mitogen-activated protein kinase (MAPK)
  • It culminates in the activation of the **transcription factor NFκB** via the IkB kinase (IKK) complex.
  • In turn, NFκB mediates the **transcription** of pro-inflammatory cytokine genes

• The second pathway, **TRIF pathway**, is independent of MyD88 and can be activated upon stimulation of TLR3 or 4
  • It leads to activation of the **interferon regulated factors** (IRF) family of transcription factors via recruitment of **TRIF** and results in the **synthesis** of interferon (**IFN**) 
  • High levels of DAMPs are associated with **Human Inflammatory Disease**.
  • The amelioration of inflammatory disease occurs by
    • **Inhibition of DAMP** Action
    • **Targeted deletion of DAMPs**
    • Or use of **DAMP antagonists**

**References**


**Video of TLR signaling via MyD88 pathway**