DAMPENING INFLAMMATION BY MODULATING TLR SIGNALLING

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- Both **infection** and **sterile tissue injury** generate strong immune responses
- Among the cellular receptors sense these signals, **TLRs** represent a key molecular link between

  - **Tissue Injury**
  - **Infection**

  } **Inflammation**

- 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

Endogenous Activators of TLRs

- heat shock protein 60 (**HSP60**) - induce cytokine synthesis through TLR4
- TLR2 and TLR4 stimulation occur by
  - **Heat shock proteins** (HSP70, Gp96, HSP22, HSP72, HMGB1)
  - **ECM molecules** (biglycan, tenascin-C, versican)
  - **Fragments of ECM**
    - oligosaccharides of hyaluronic acid
    - heparan sulfate
- **Self-nucleic acids** have also been described as endogenous danger signals
  - **mRNA** is recognized by TLR3
  - **Single stranded RNA** – sensed by TLR7 and TLR8
- **IgG-chromatin complexes** -- recognized by TLR9
- **TLR3** was also shown to recognize cells **undergoing necrosis** during acute inflammatory events

Mechanisms of TLR Activation

Exogenous Ligand Recognition

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

TLR Signaling and Biological Outcomes

- Ligand-induced receptor homo- or hetero-dimerization leads the **cytoplasmic signaling domains** of TLRs to **dimerize**
- 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**

- Video of TLR signaling via MyD88 pathway

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