DAMPENING INFLAMMATION BY MODULATING TLR SIGNALLING

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- Both **infection** and **sterile tissue injury** generate strong immune responses
- Among the cellular receptors that sense these danger signals, Toll-like receptors (**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 into the extracellular milieu
  - Others are ECM molecule fragments that are **released** upon tissue damage **or** ECM molecules that are specifically **upregulated** 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 recognized by TLR3
  - **Single stranded RNA** – sensed by TLR7 and 8
- **IgG chromatin complexes** recognized by TLR9

- **E. coli** produce many of these endogenous molecules **recombinantly**, and the fact that most endogenous proteins activate **TLR2 and 4**,
- **TLR3** was also shown to recognize cells **undergoing necrosis** during acute inflammatory events

Mechanisms of TLR Activation by DAMPs versus PAMPs

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
- three diverse modes of exogenous ligand recognition exists by TLRs

- 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** was shown to down regulate peptidoglycan and zymosan induced **NFκB activation** and TNFα secretion by binding to the extracellular domain of **TLR2**
- 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 other than CD14 and MD-2, like Biglycan

TLR Signalling and Biological Outcomes

- Ligand-induced receptor homo- or heterodimerization leads the **cytoplasmic signalling 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 signalling pathways** can be activated by TLRs.

- The first, a **MyD88-dependent pathway**, is activated by **all TLRs** except TLR3
  - It involves the
    - IL-1R-associated kinases (IRAK),
      - IRAK-1 and IRAK-4,
    - TNF receptor-associated factor 6 (TRAF-6)
    - mitogen-activated kinases (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 diseases occur by
  - **Inhibition of DAMP** Action
  - Targeted **Deletion of DAMPs**
  - Or use of **DAMP Antagonists**

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