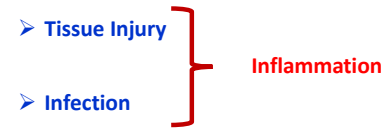


DAMPENING INFLAMMATION BY MODULATING TLR SIGNALLING

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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



- 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 IκB 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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