JOURNAL CLUB:
"Toll Like Receptors & BioDetection: A Review"

Reference: Ruslan Medzhitov and Charles A. Janeway, Jr.,"Decoding the Patterns of Self and Nonself by the Innate Immune System”
Science 2002 April 12; 296: 298-300

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RECOGNITION

• 3 States of recognition:
  – Nonself: discriminate between (infectious non-self and non-infectious self)
  – Makers of normal self
  – Markers of abnormal self (viral infection)
RECOGNITION

- Nonself: PAMP pathogen associated molecular patterns (LPS, peptidoglycan)
- These are recognized by pattern recognition receptors (PRR)
- Subset of PRR are TLR
- TLRs play a role in adaptive immune response through antigen-presenting cell (APC), such as dendritic cells
RECOGNITION

Normal healthy cell

Infected or transformed cell

Senescent or apoptotic cell

Necrotic cell

Assisted apoptosis

Phagocytosis

Tissue repair

Marker of normal self. Ligand for inhibitory receptors.
Marker of infected, stressed, or transformed cell. Ligand for activating receptors.
Marker of apoptotic and senescent cells. Ligand for phagocytic receptors.
Markers of tissue damage. Ligands for receptors that induce tissue repair responses.
Toll Like Receptors (TLRs)

• Single spanning transmembrane protein: First Human TLR is described in 1997. Now there are 10 of them.
  – Outside: Ligand recognition and signal transduction (LRR region: leucine rich region)
  – Inside: TIR: Toll Interleukin resistance genes (mostly conserved sequence)

• Similar to Drosophila (Toll pathway)
  – drosophila toll doesn’t function as PRR: spatzle (another molecule) activates Toll
  – Toll pathway is similar to mammalian IL-IR pathway
Toll Like Receptors (TLRs)

- TLR ligands are diverse in structure and origin and TLR can recognize structurally unrelated ligands
- For example: TLR4 recognize LPS, G- (with the help of other molecules), TLR2 peptidoglycans G+
- Cooperative behavior between TLRs are observed TLR6+TLR1, TLR2+TLR1
Toll Like Receptors (TLRs)

- Pathway: Shared signaling and specific signaling. 4 major components:
  - Adaptor protein
  - Adaptor protein
  - IRAK (kinase)
  - TOLLIP
- X-Ray structure for toll proteins are not known. (work in progress)
UNDERSTANDING THE PATHOGEN MECHANISM: TOLL LIKE RECEPTORS

Toll identified in Drosophila, and similarity shown in human (1997): Toll like.

TLR is a single spanning transmembrane protein

TLR: 1-10 known (6 available, 4 patented !!!)

Phagocytosis: mouse cell engulfs a bacterium. Toll-like receptors may help such cells recognize microbes (Vol 160, 10, 2001, Science-NEWS)

Filtering mechanism of TLRs. Can we recreate the same mechanism?
TLR5 + Flagellin

Two approaches: FRET + SPR

Hayashi et al. (2001) Nature v410, 1099
Gewirtz et al. (2001), J Immunol, v167, 1882

Aderem’s group (U. Washington) is working on kinetic data of TLRs
MORE OPEN QUESTIONS

• What are the full compliments of PAMPs and other ligands recognized by TLRs? (Taxol is a non-PAMP and recognized by TLR-4)
• What are the differences between individual TLRs in the induction of cellular and immune responses?
• What is the mechanism of ligand recognition by TLRs? (Many molecules, CD14, LBP, MD2, help TLR4 in the LPS recognition)
• Can TLRs detect any features of pathogens that are important for the choice of effector responses? (TLR-PAMP libraries: can we create them?)
• What is the biological significance of differential TLR expression?
• Why are the TLRs not continuously activated by commensal microflora?
• SPECIFICITY in terms of RECOGNITION!!!!
DISCUSSIONS

WHAT IS NEXT?
Study Group

- Topics are quantitative bioscience, biomimetics, biophysics (what are these!!!)
- NIH/NSF Proposal: Education-research grants
- Internal collaborations
- Time to introduce: Self introduction