

## 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

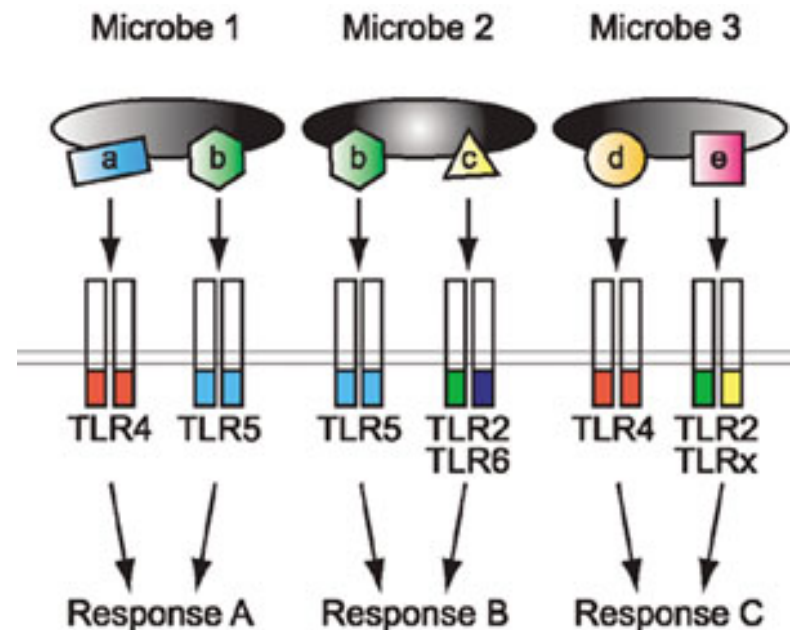
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# RECOGNITION

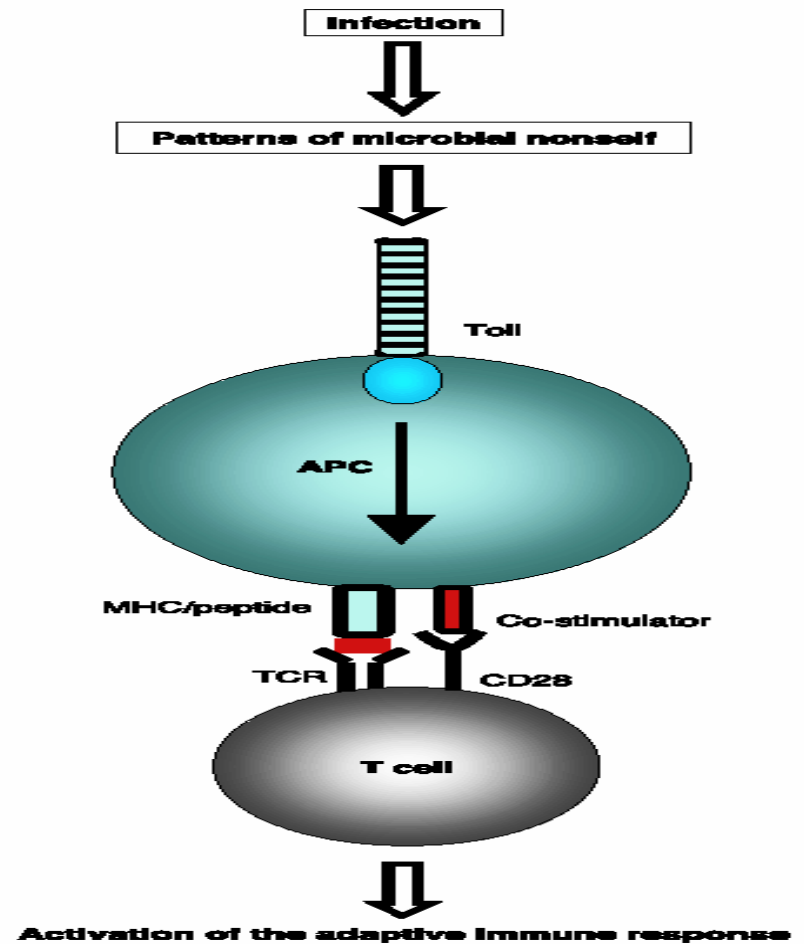
- 3 States of recognition:
  - Nonself: discriminate between (infectious non-self and non-infectious self)
  - Makers of normal self
  - Markers of abnormal self (viral infection)

## BAR CODES of RECOGNITION

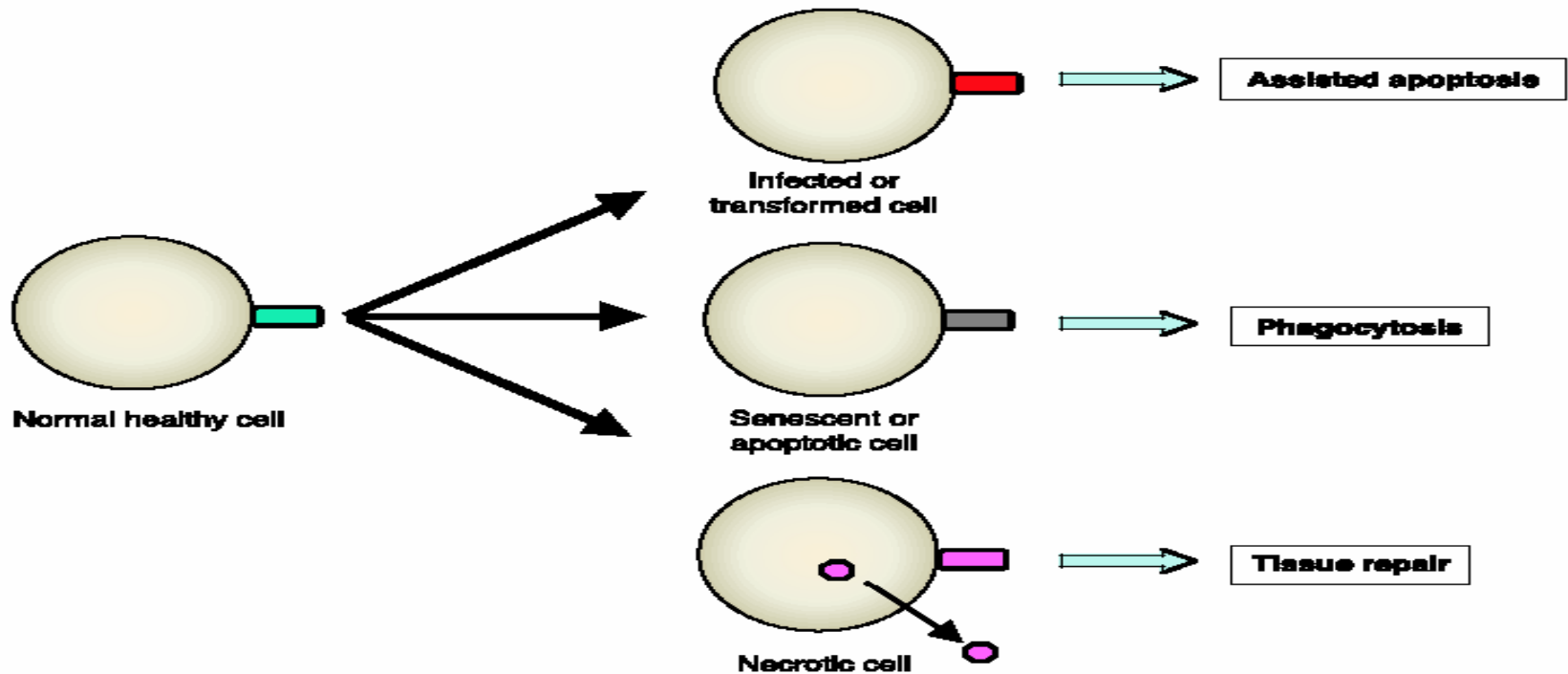






# RECOGNITION

- 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



-  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 response.

# 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)

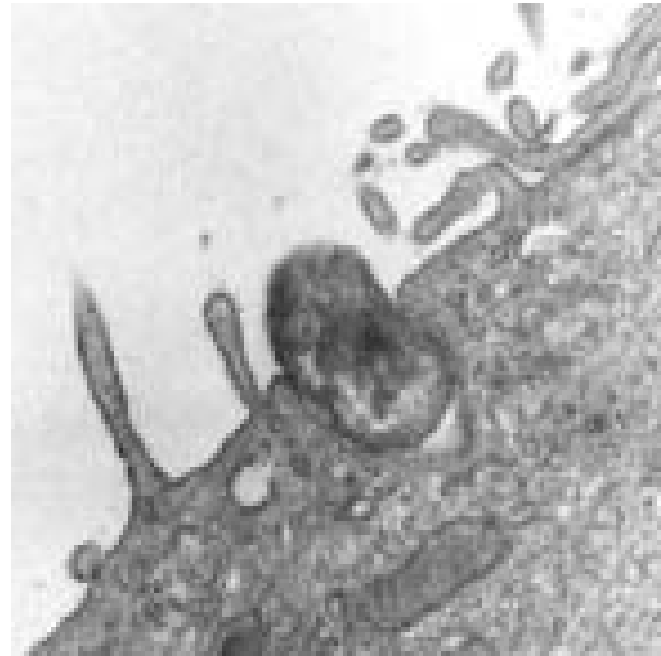
# UNDERSTANDING THE PATHOGEN MECHANISM: TOLL LIKE RECEPTORS

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 !!!)

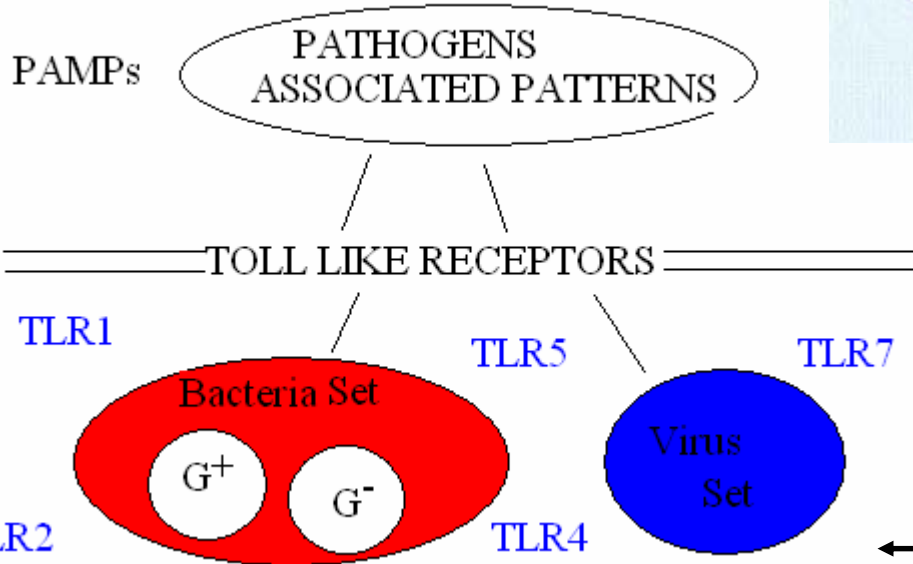
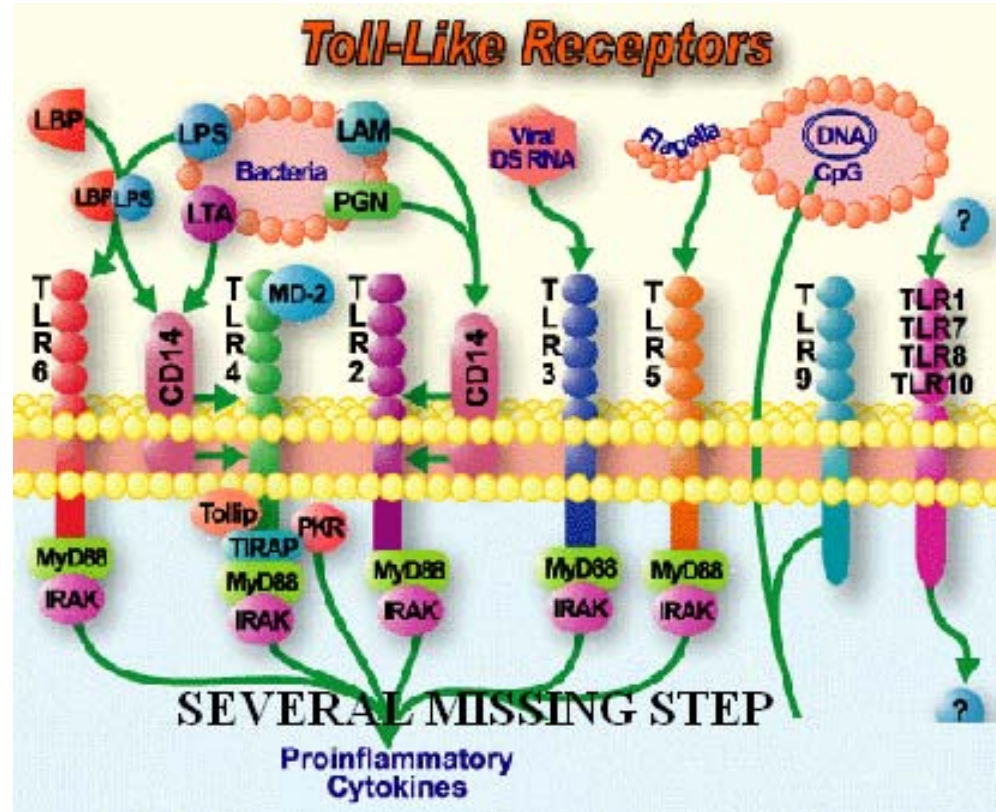
**Medzhitov, Janeway, et al. (1997) *Nature*, v388,394**



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



# TOLL LIKE RECEPTORS (TLR)

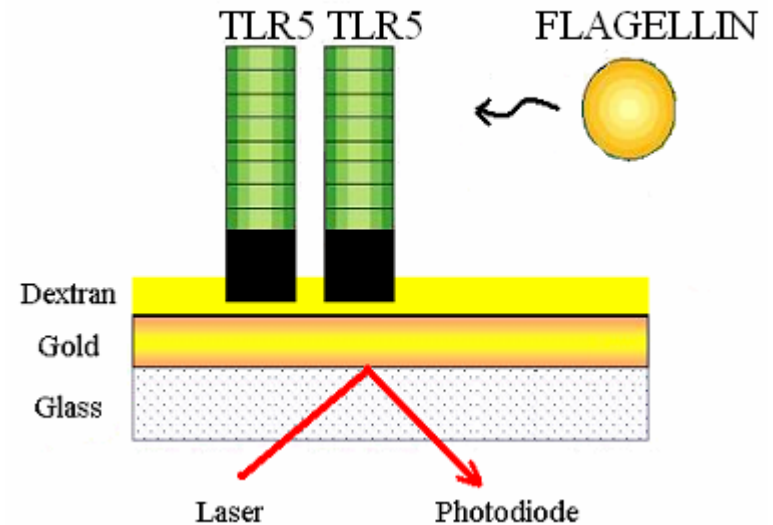
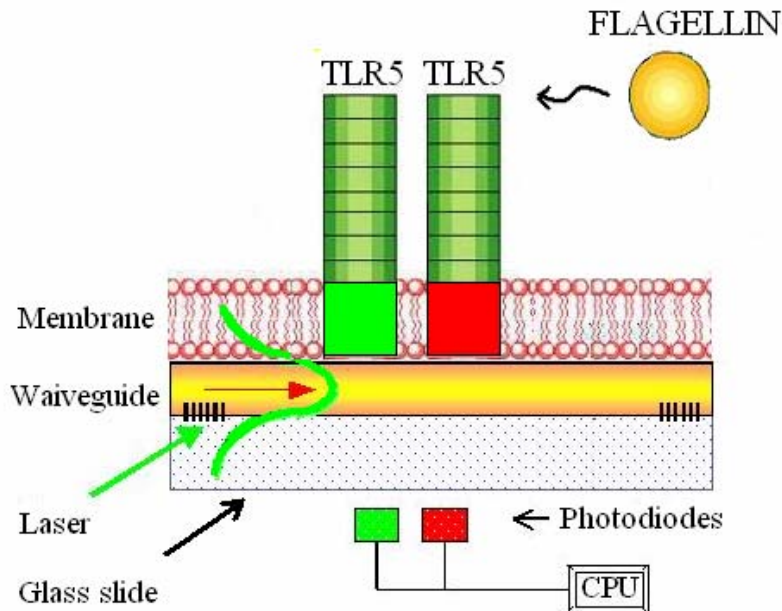


Filtering mechanism of TLRs.  
Can we recreate the same mechanism?



# 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** interms 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