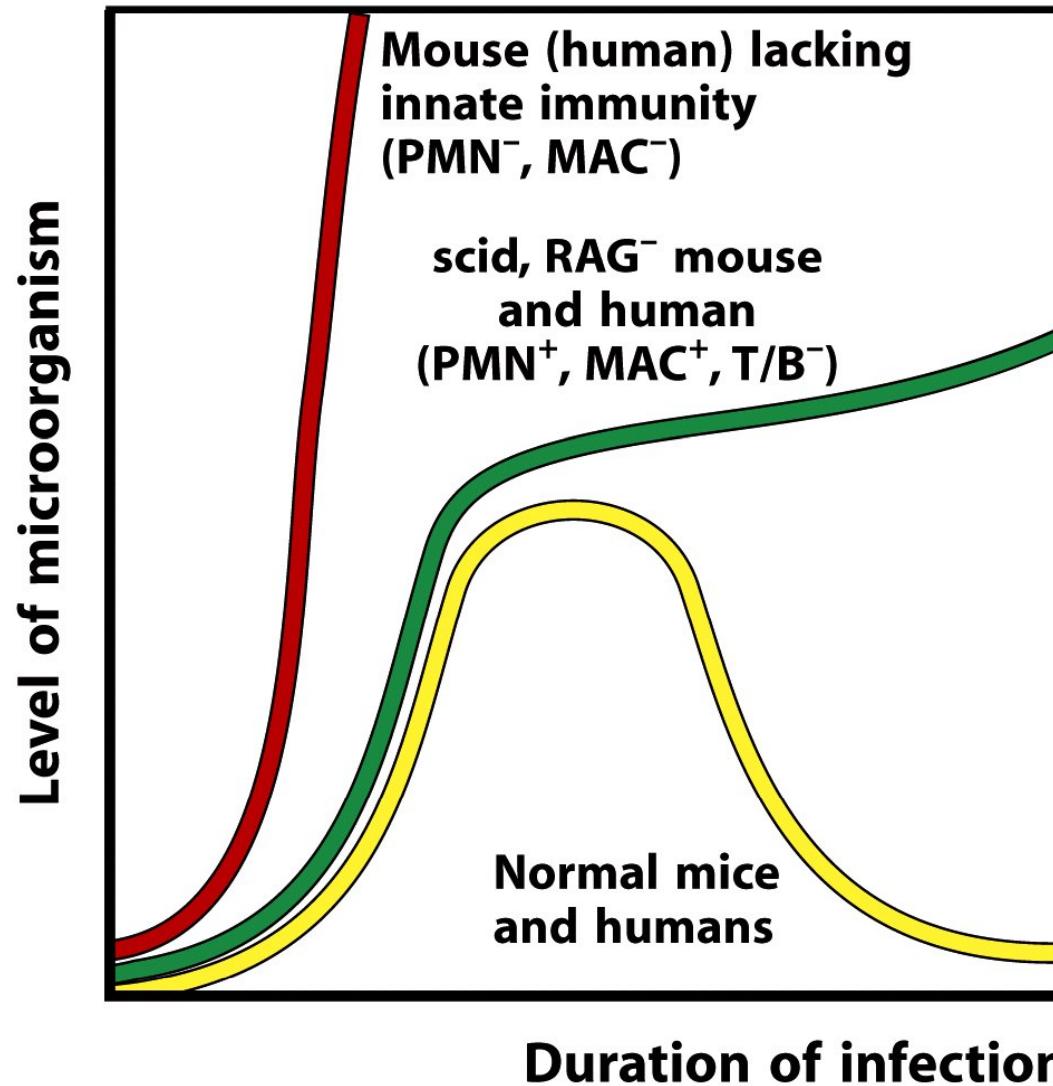


Das angeborene Immunsystem:

Nutzen oder Schaden?

Hermann Wagner

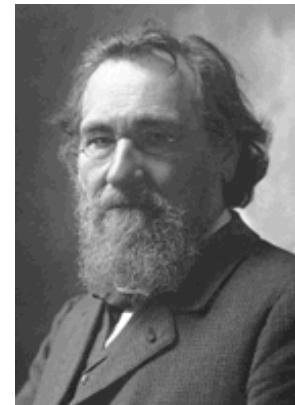
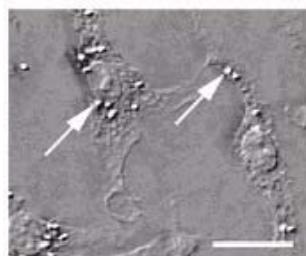
Innate and adaptive immunity is required



Immunity



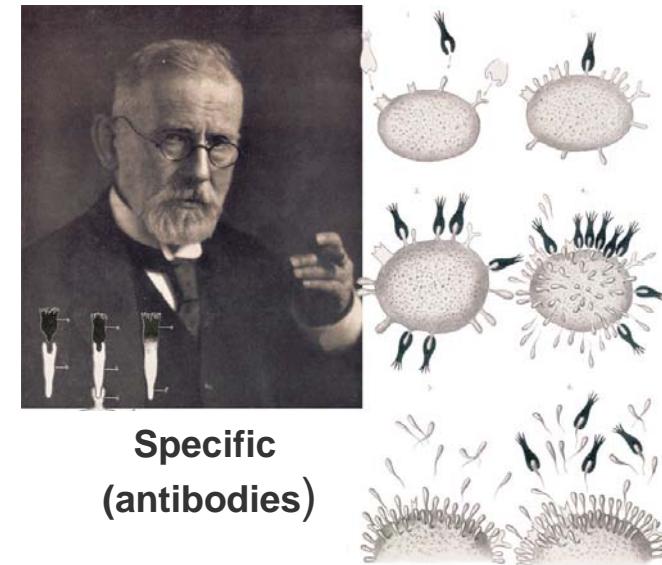
Innate
(angeboren)



Non-specific
(phagocytosis)

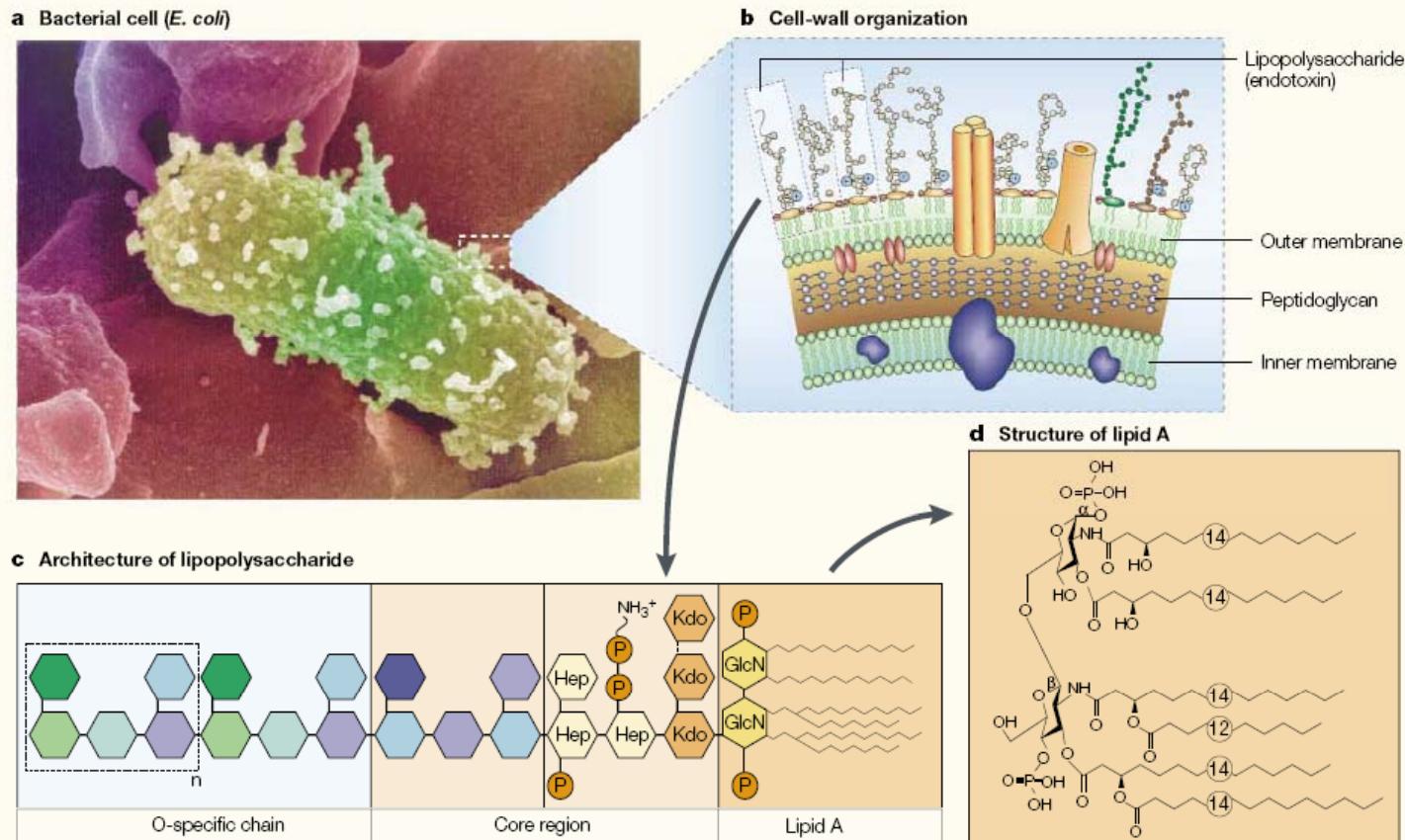


Adaptive
(erworben)



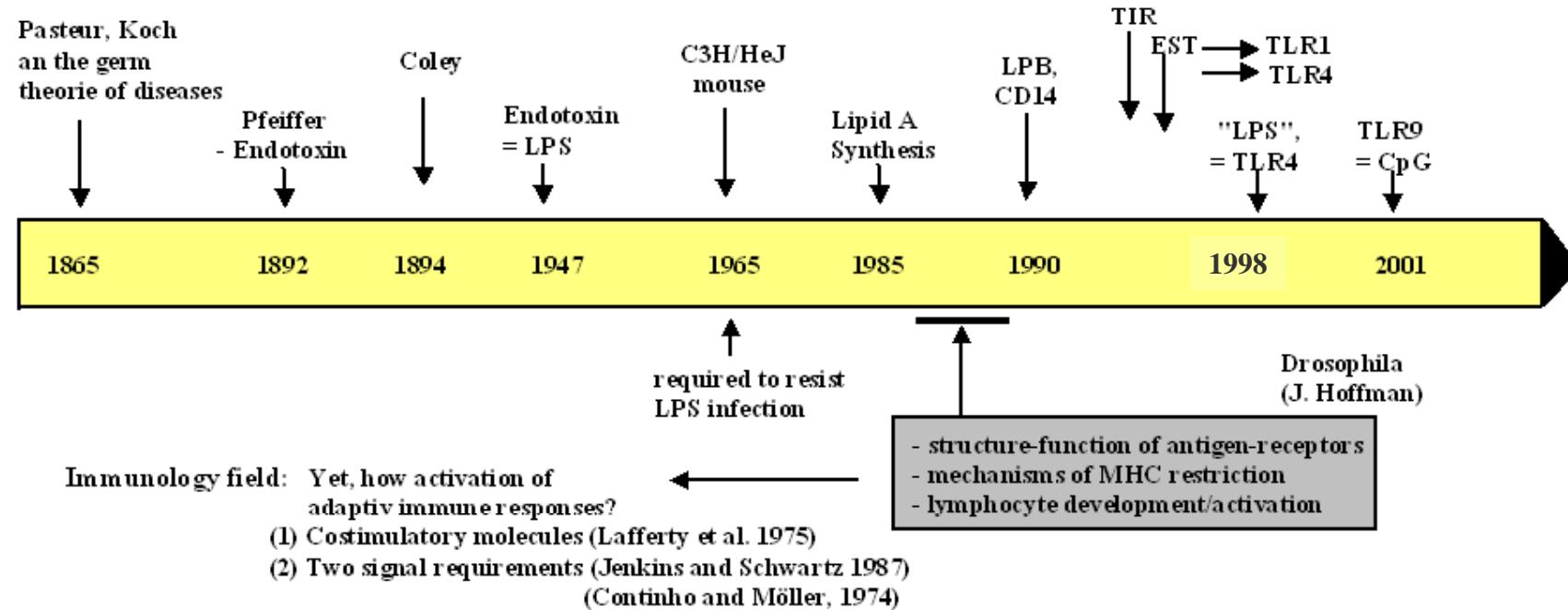
Specific
(antibodies)

Ilya Metschnikow **Nobelprice 1908** Paul Ehrlich



Time line "Innate Immune Recognition"

The Endotoxin field:



Janeways Hypothesis (1989, Cold Spring Harb. Symposium)

- inducible co-stimulation
- induced by conserved microbial products
- postulated receptors of innate immune cells
- = germ line encoded pattern recognition

Innate Immunity

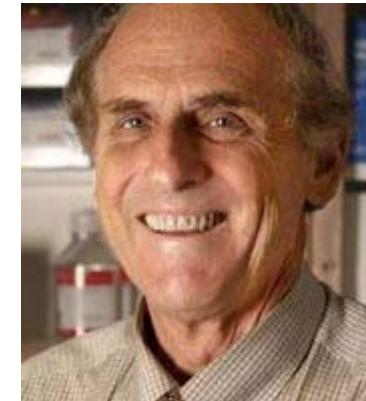
Julius Hoffmann



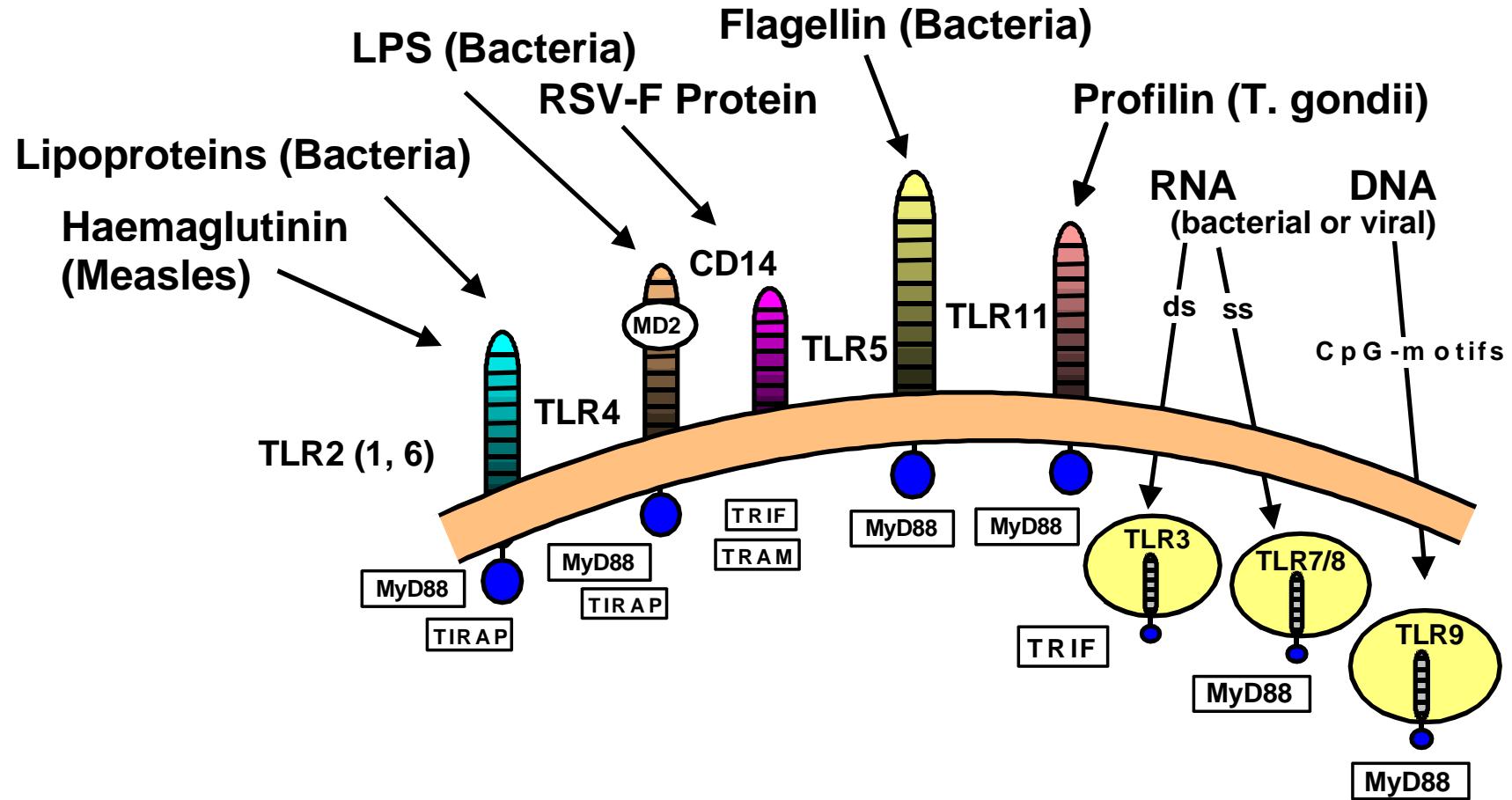
Bruce Beutler



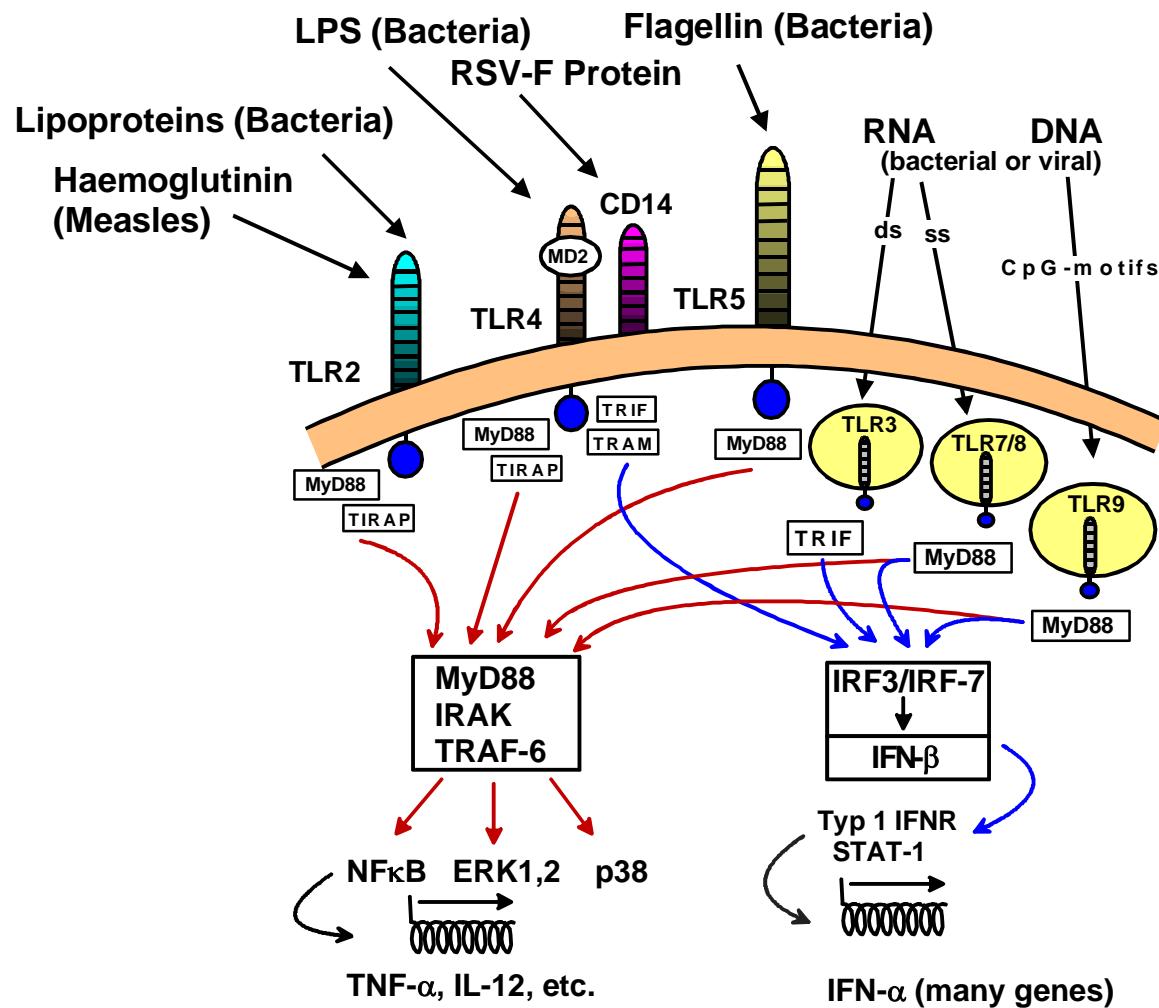
Ralph Steinman

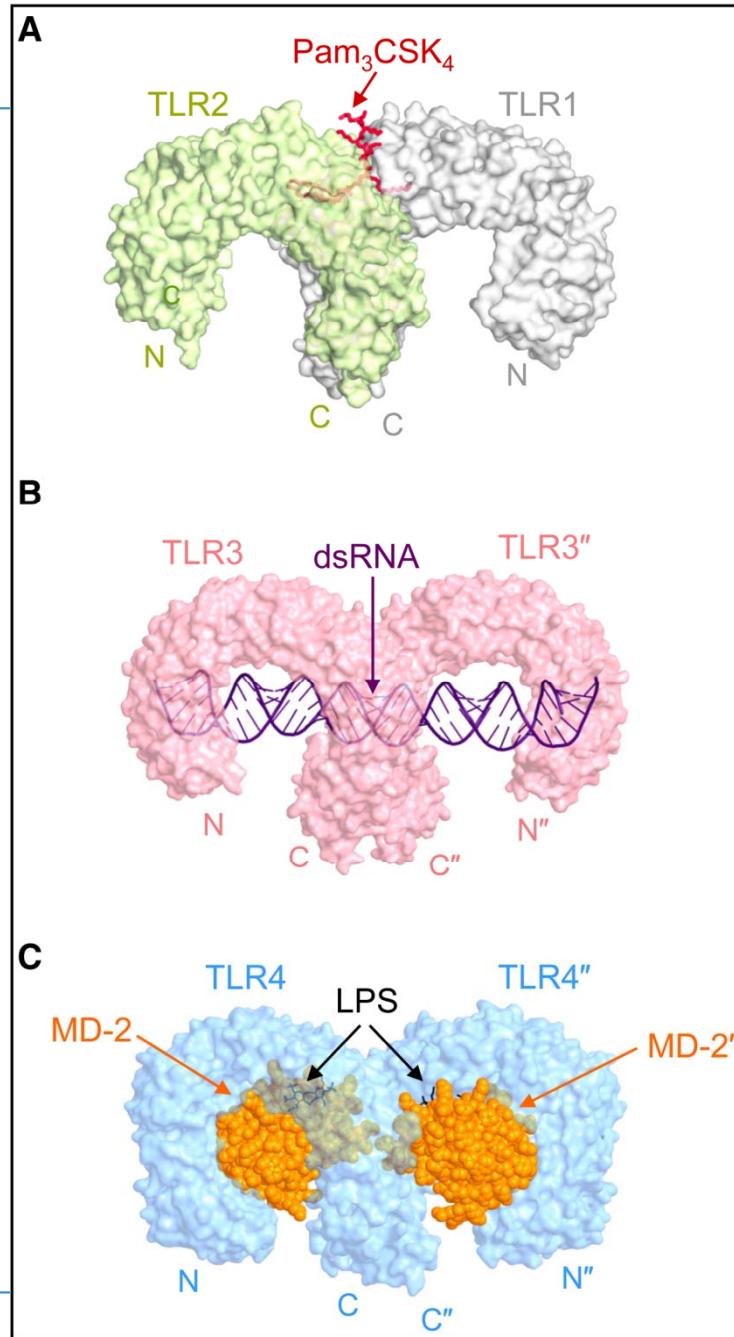


Nobelprice 2011



TLR signalling pathways

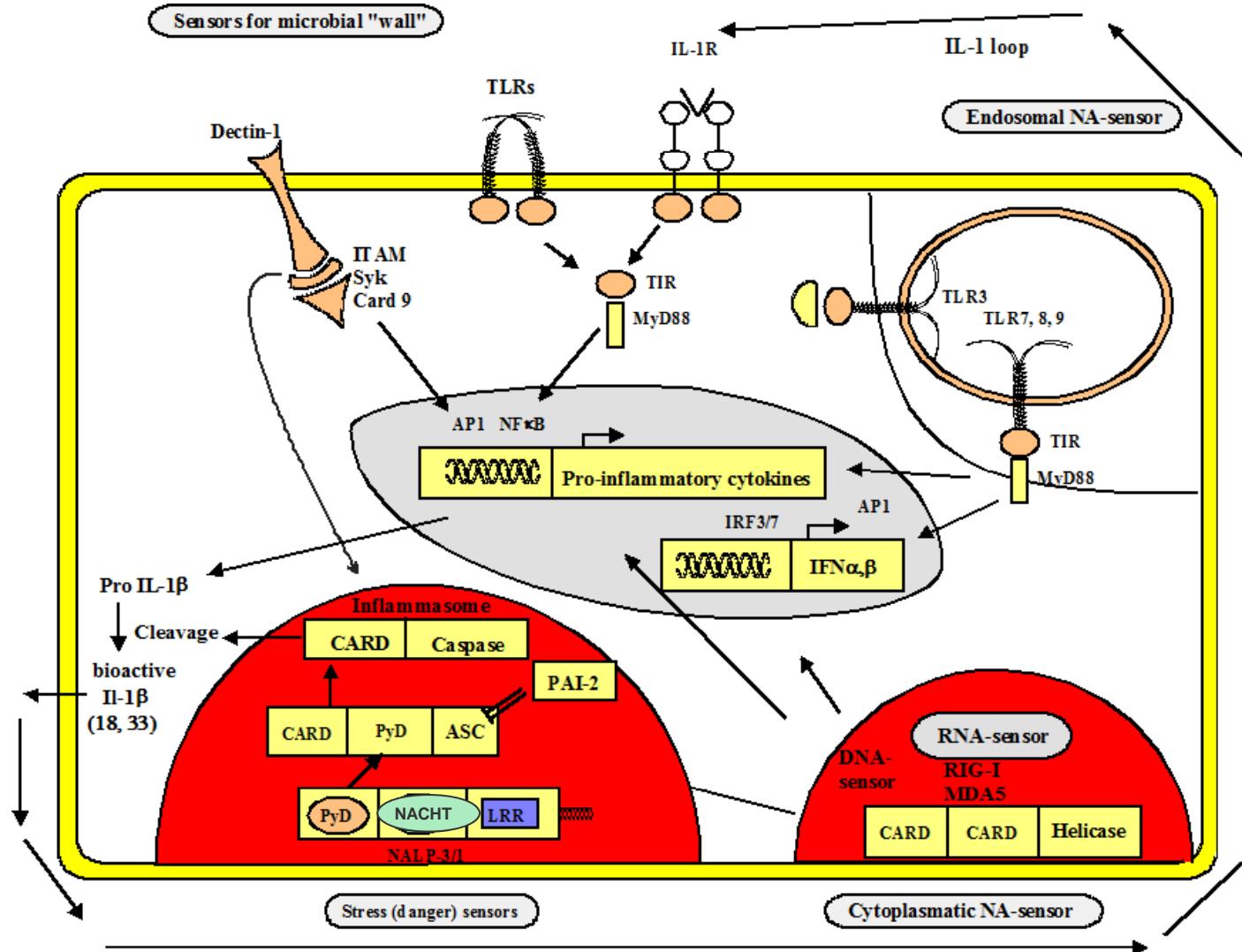


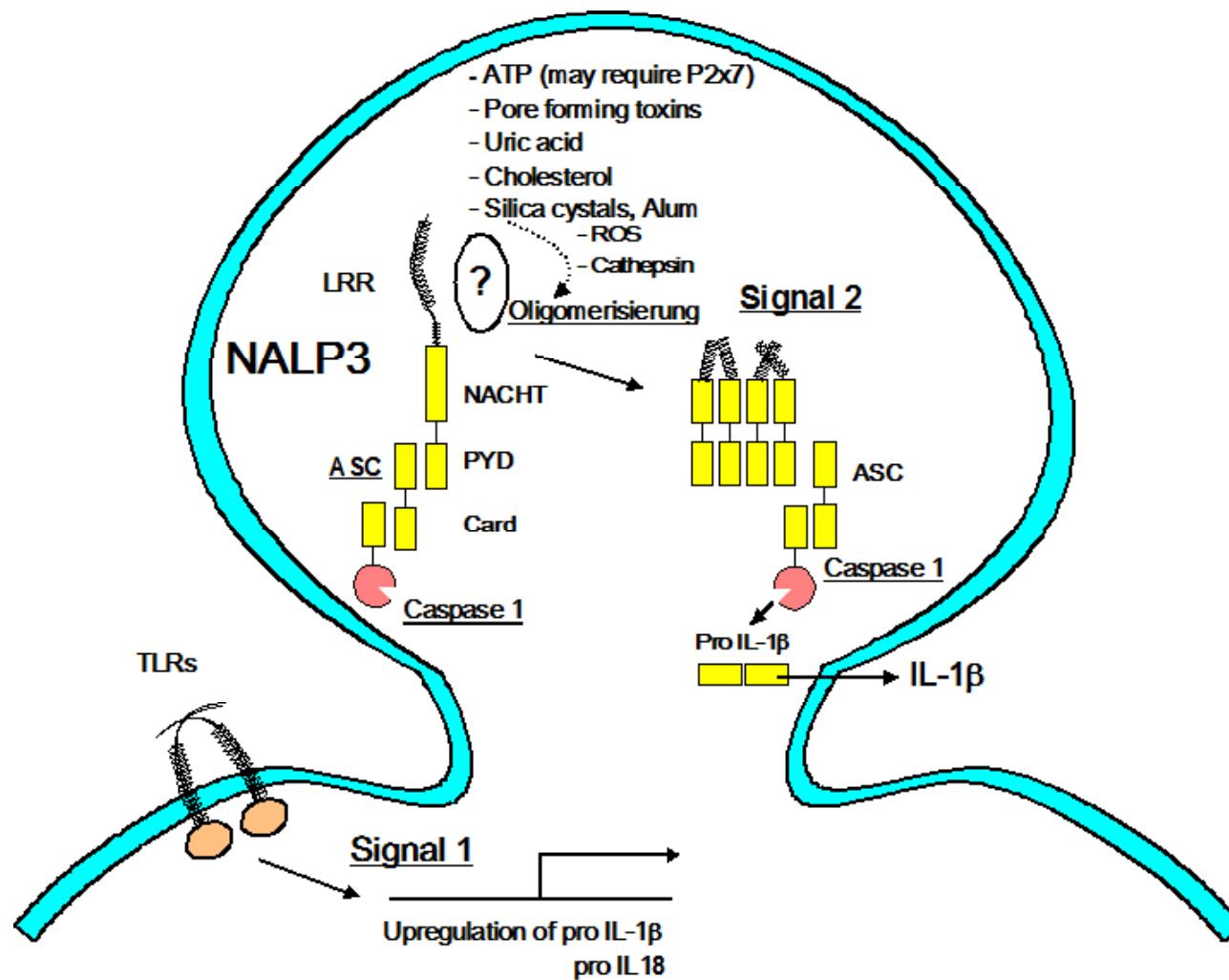


Jin and Lee, Immunity
(2008) 29:182

**Cytoplasmic Receptors:
NLR 's: Nucleotide-binding oligomerisation domain-like receptors**

| | <u>N-terminus</u> |
|--------|-------------------|
| NOD1 | CARD |
| NOD2 | CARD |
| (n=5) | |
| NLR P3 | <u>N-terminus</u> |
| NLR P6 | PYD |
| (n=13) | PYD |

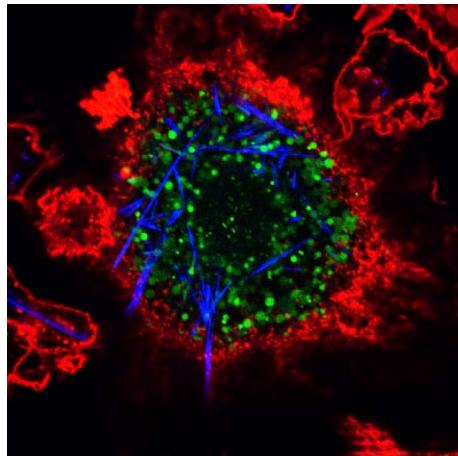




Endogenous danger signals activate the NALP3 Inflammasome

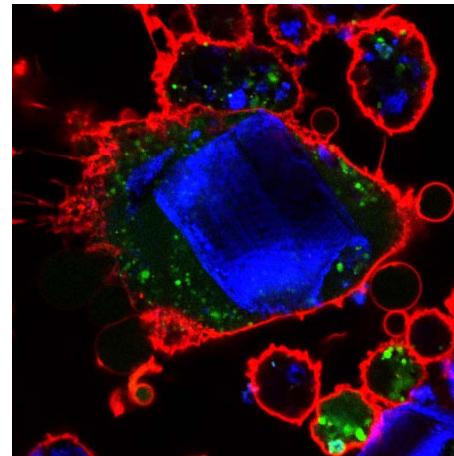
Macrophage activation via endogenous ligands like ...

**Uric acid crystals
(Gout)**

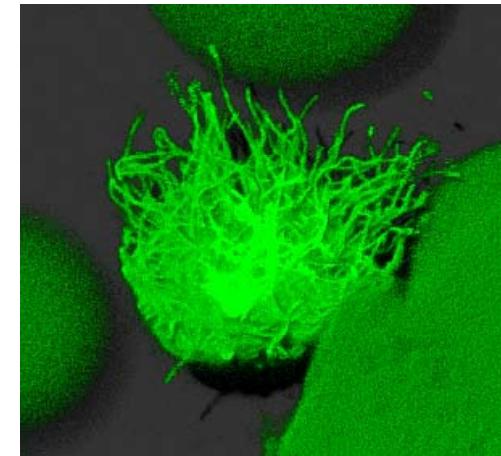


or

**Cholesterol crystals
(Arteriosclerosis)**



**drive inflammasome
aggregation**



PAMPS versus DAMPS

(pathogen-derived)

- Lipopeptide
- LPS
- Flagellin
- ss RNA
- DNA
- Haemozoin

etc.

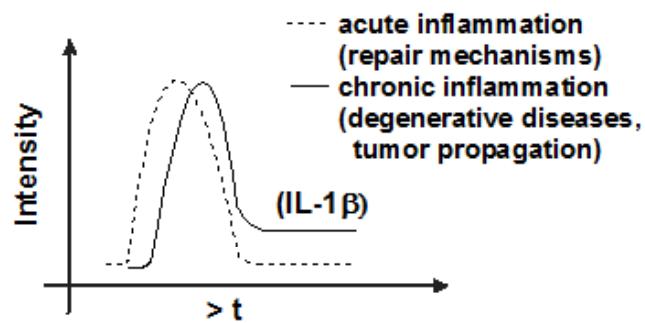
(modified self)

- Heat shock proteins
- HMGB's
- MRP-8/14
- Hyluronan
- Heparin sulfate
- modified Lipids
- (OxLDL)
- β -amyloid
- Surfactant Protein A

Matrix components

concern: contamination (LPS etc.)

Chronic inflammation / diseases



Alzheimer Disease:

- protracted inflammatory response of microglia (brains macrophages)
- amyloid β (fibrillar A β 1 - 42)

Artherosclerosis:

Oxidized low density lipoprotein (LDL) accumulates in plaques

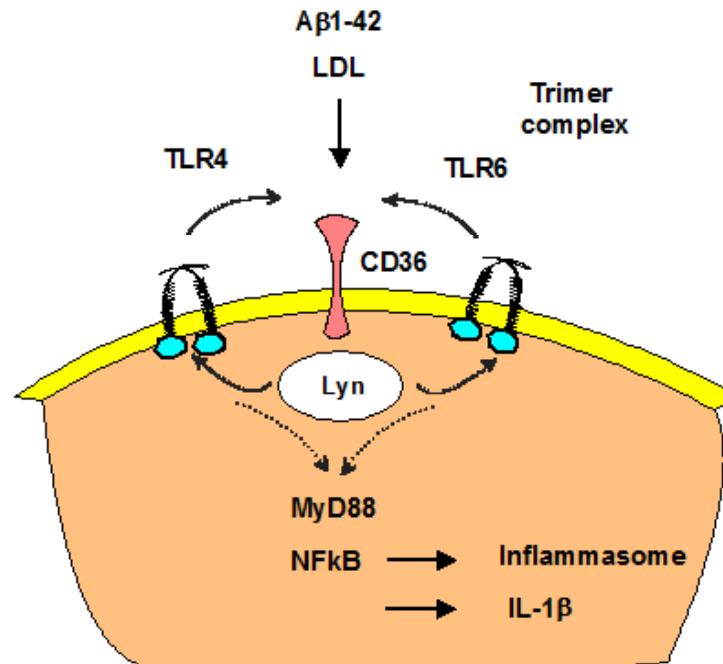
Typ 2 Diabetes:

role of IL-1 β

Gout / hereditary fever:

role of IL-1 β

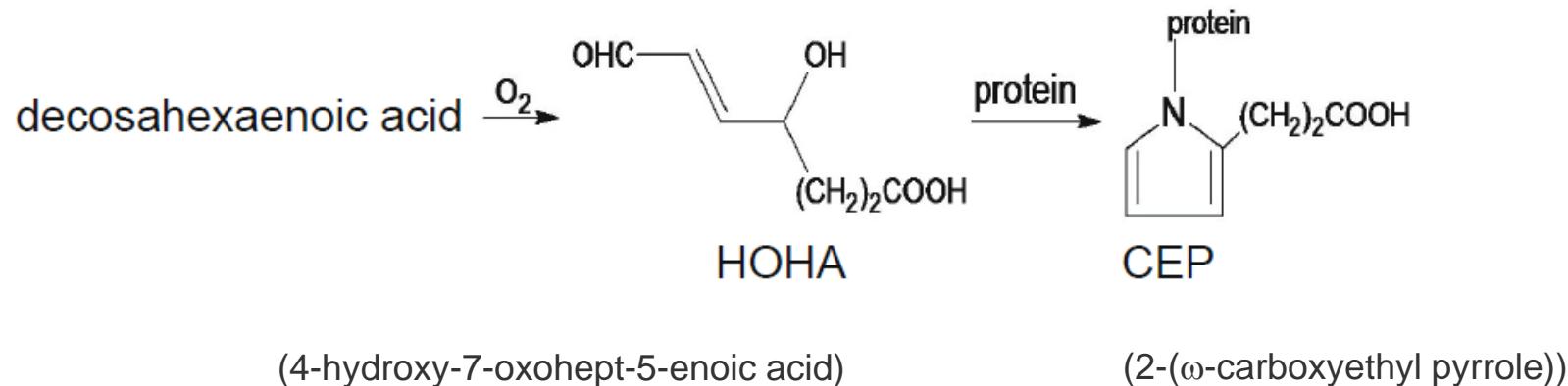
Coreceptor CD14, LPB
CD-36: polyanionic ligands
- Staph aureus LTA recognition via TLR2/6
- endocytosis of altered self (LDL, amyloid proteins, etc.)



(Stewart et al, Nat. Immunol. 2010)

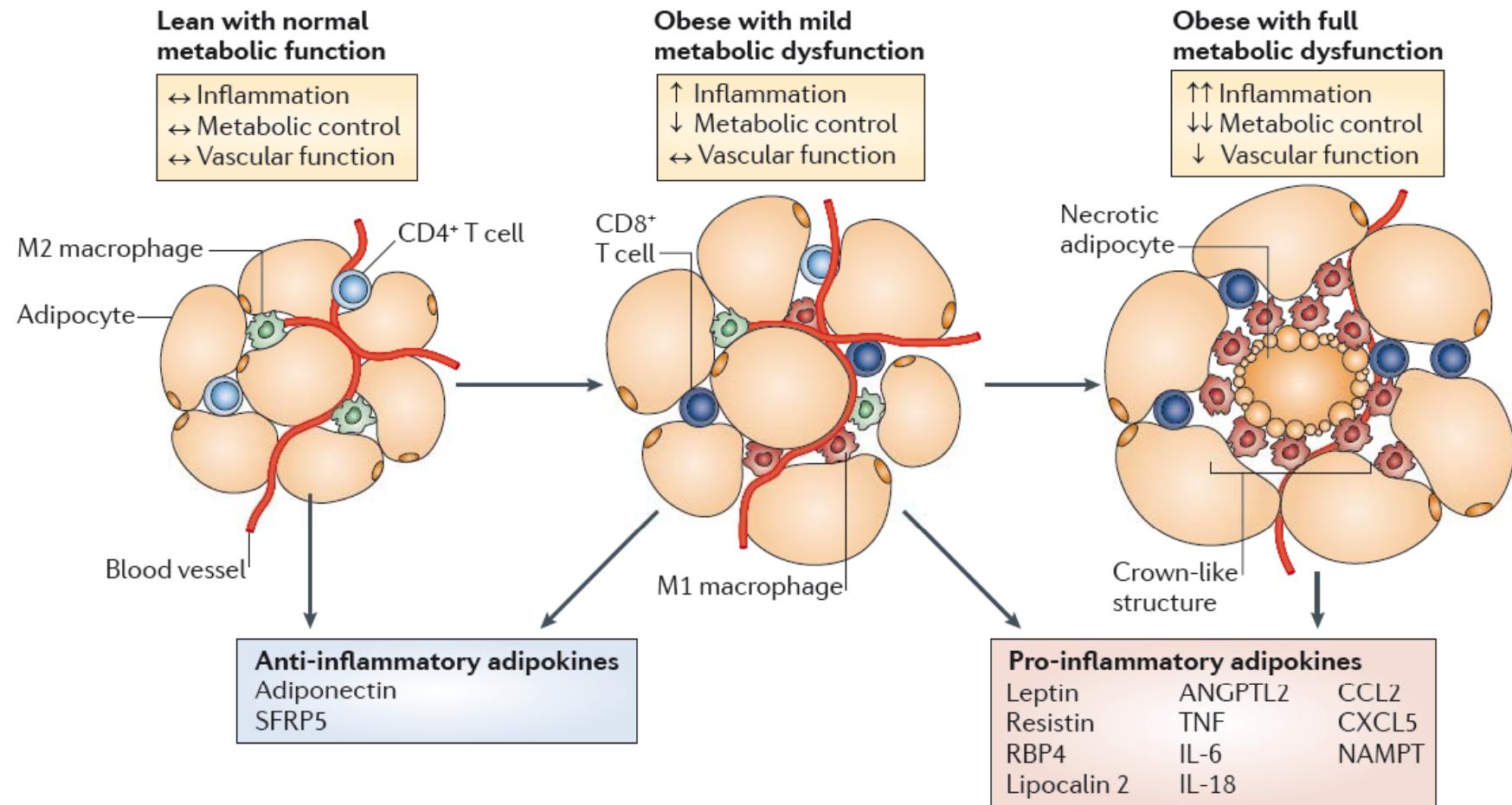
Question: role of co-receptors in sterile inflammation ?

TLR2 senses Endproducts of Lipid Oxydation (Carboxyethyl pyrrole (CEPs))

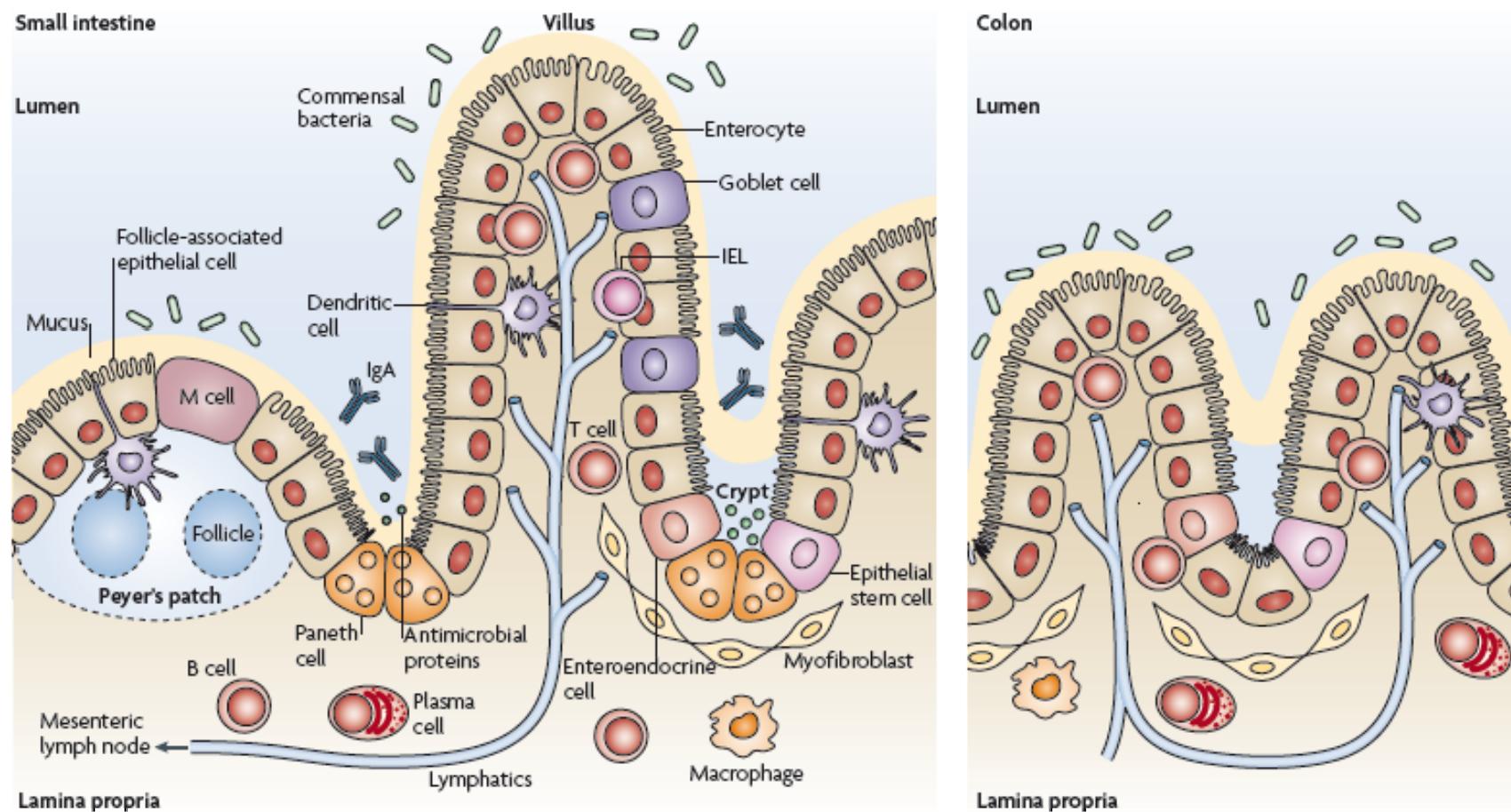


- CEPs are generated during inflammation/wound healing
- accumulate in ageing tissues and highly vascularised melanomas
- CEPs are recognized by TLR2 leading to angiogenesis that is independent of vascular endothelial growth factor (VEGF)
- both TRL2 and MyD88 are required
- CEPs – present in low-density lipoprotein – accumulate in arteriosclerotic plaques and are found in the retina (choroidal neovascularization and age-related macular degeneration)

Adipositas / Inflammation / Metabolic diseases



Gut anatomy & function

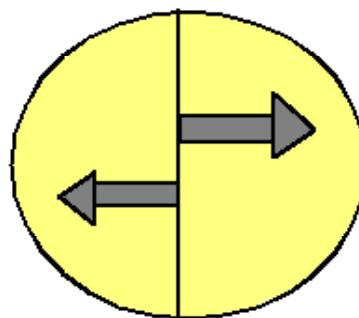


Modified from Abreu, Nat. Rev. Immunol. (2010)

Two faces of Innate Immunity

(Infection)
Protection

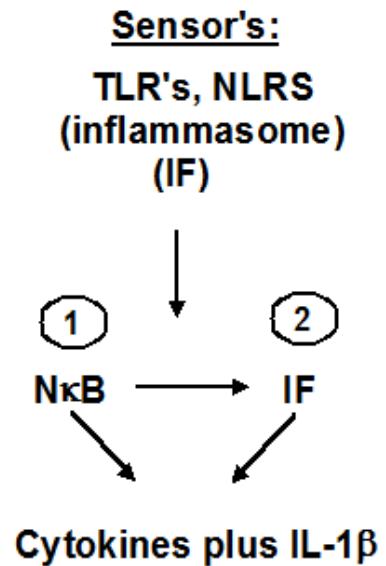
(acute inflammation)



Disease Promotion
(chronic inflammation)

- Diabetis
- Artheriosklerosis
- Alzheimer Disease
- cardiovascular disease

PAMPs
(pathogen derived)
LPS, CpG-DNA,
Lipoproteins,
Flagellin
RNA (U-rich)



DAMPs
(self derived)
Alzheimer peptide
m.o. LDL
I (usulin) a (sciated) pp
Crystals (Ureic acid,
Cholesteriol, Alum salt,
Silica), ATP