Innate Immunity

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- Evolutionary View
- Epithelial barriers to infection
- Complement activation
- Four main types of innate recognition molecules
  TLRs, CLRs, NLRs, RLRs
- NF-κB, transcriptional regulator of inflammation
- Inflammasome activation
- Anti-viral innate immunity: the interferon system and killing of virus-infected cells

Innate Immunity: An Evolutionary View

- All multicellular organisms have defense mechanisms against microbial and viral infections
- For vertebrates, immune defense can be divided into innate immunity and adaptive immunity
- Vertebrate innate immune elements are closely related to components of immunity in invertebrates (especially TLRs and complement)
- Innate immunity is "hard wired" into cells, with defined responses to defined pathogen molecules

Innate Immunity: An Evolutionary View

- Innate immune responses have two functions

  A first line of host defense (while clonal expansion occurs by T cells and B cells)

  Directing the type of adaptive immune response (activation vs. tolerance; specialization of T cells and antibody types)

  Also involved in tissue repair

Innate Immunity	Adaptive Immunity
• Immediate response (mins)	• Delayed response (days)
• Occurs at site of pathogen entry (somewhat)	• Occurs in immune organs (LN)
• Based on recognition of common pathogen elements (flagellin, ect)	• Based on recognition of peptides (mainly) specific to pathogen
• Specificity and diversity is limited	• Specificity and diversity is very high
• No memory	• Memory to allow secondary response
• Limited cellular interactions	• Complex cellular interactions (help)

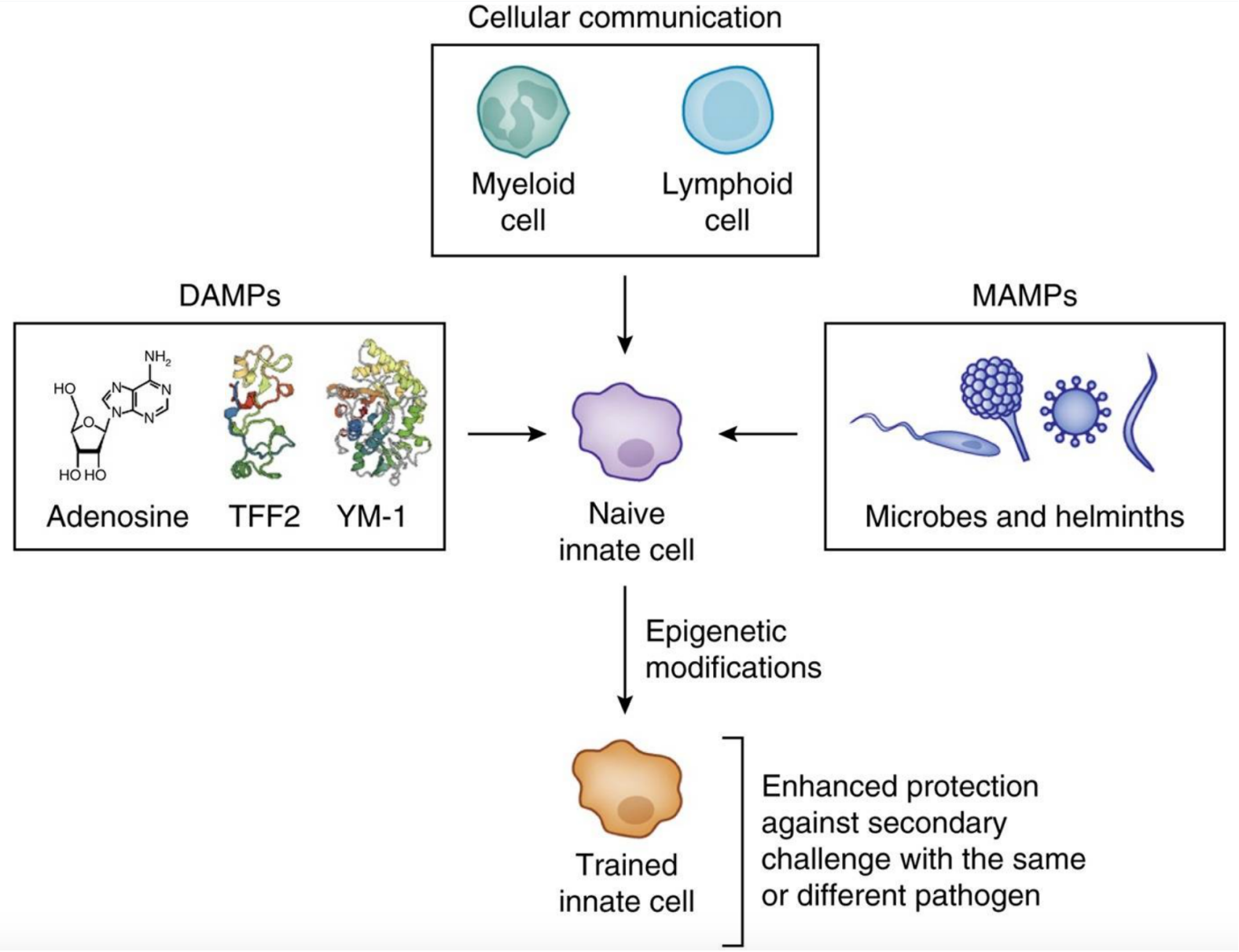
Innate Immunity and memory

Newer term: "Trained Immunity"

- Also called "non-specific memory"
- Concept that some innate cells exposed to one innate stimulus respond better to second (different) innate stimulus
- Seen in NK cells (Lanier Lab as pioneers)
- Monocytes/macrophages → exposed to b-glycans, increased cytokine responses to LPS or other bacterial components
    - increased cytokines
    - altered metabolism (increased glycolysis)
    - reduced H3K4 me3 epigenetic marks
- Pre-activated or "trained" monocytes seen in patients with autoimmune/ autoinflammatory disorders

Arts et al, Front Immunol, 9:298 (2018)

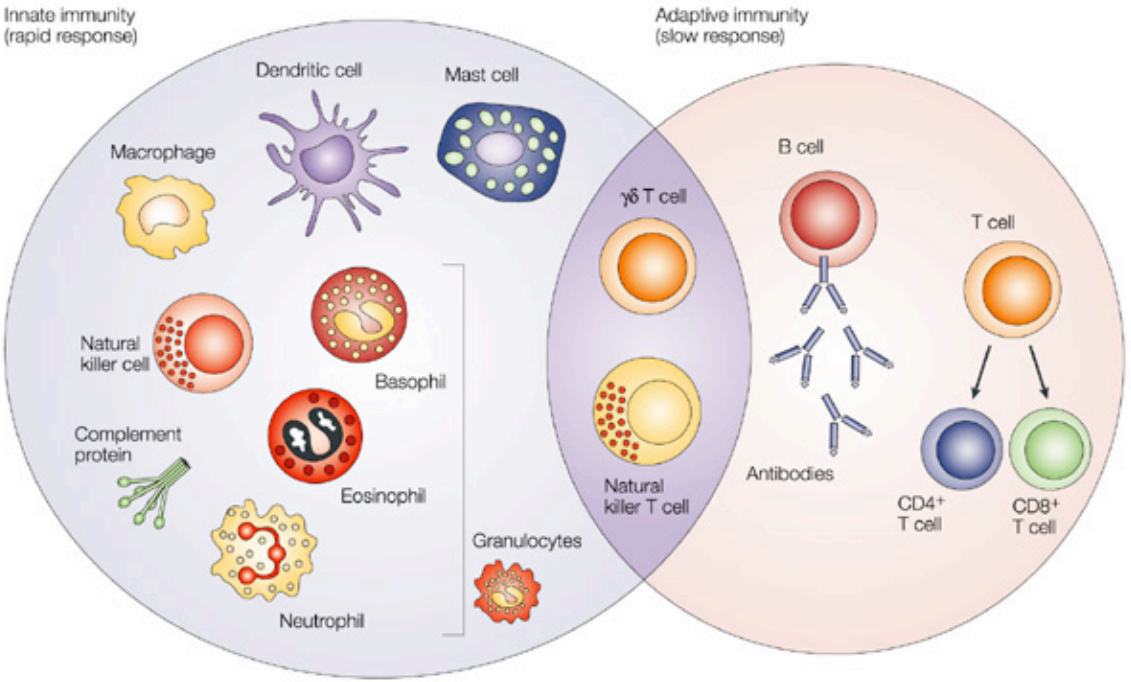
Trained Immunity

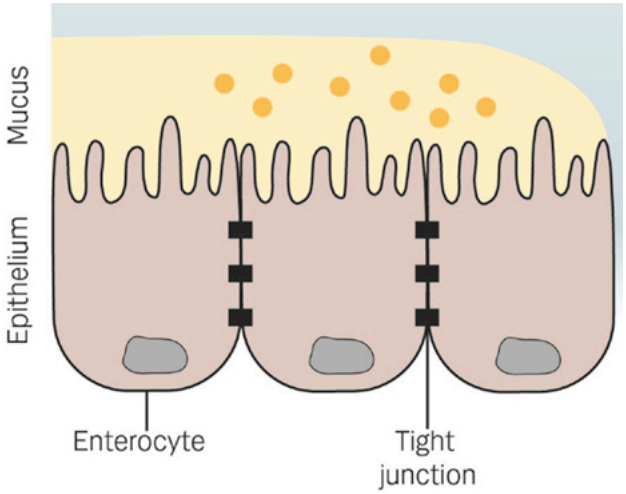


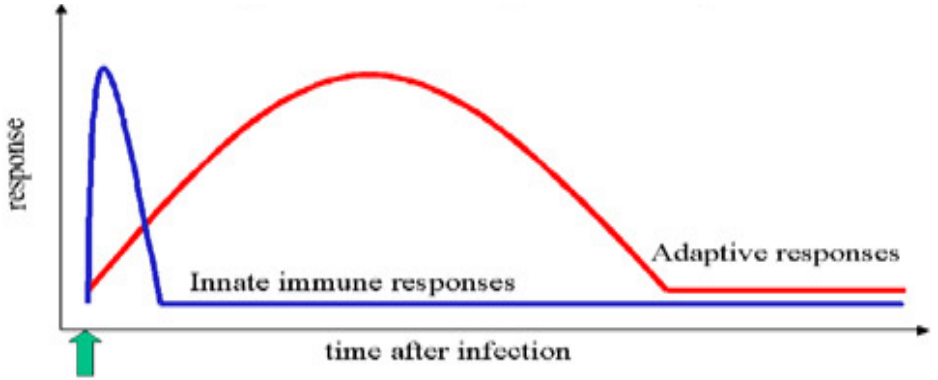
Arts et al, Front Immunol, 9:298 (2018)

Components of Innate Immunity

- Epithelial barriers
- Soluble molecules (complement)
- Cellular (immune)

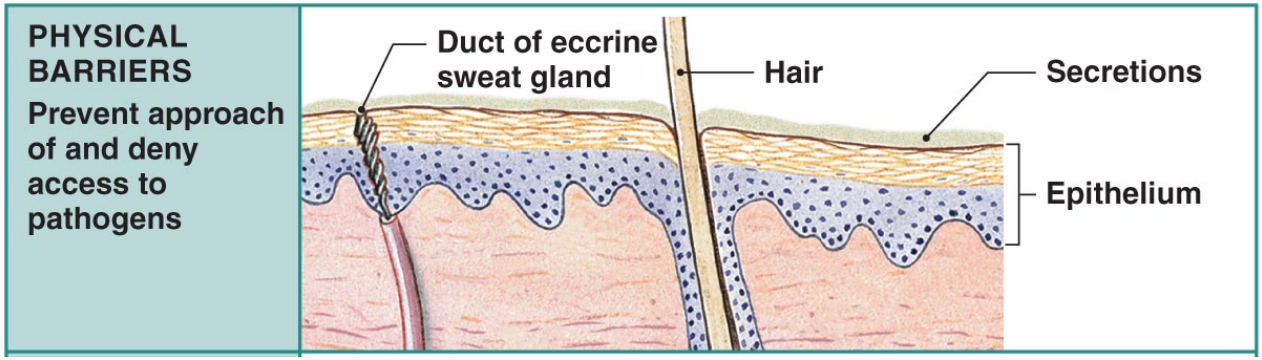




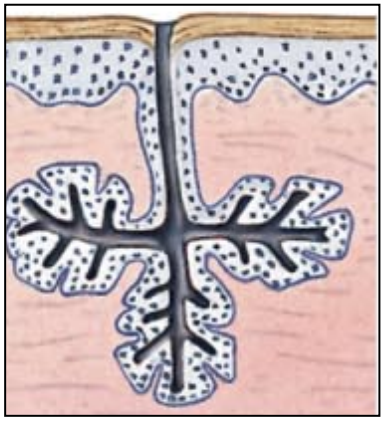


Epithelial barriers as first line of defense

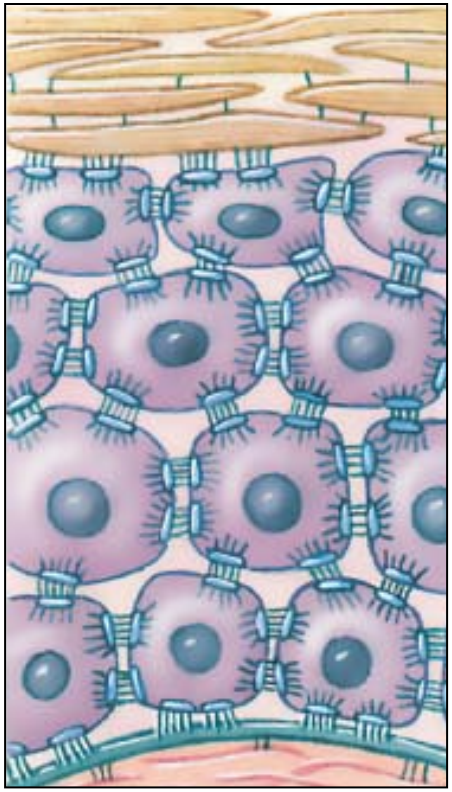
- Surface barriers ward off invading pathogens
- Skin, mucous membranes, and their secretions



Intestinal epithelium



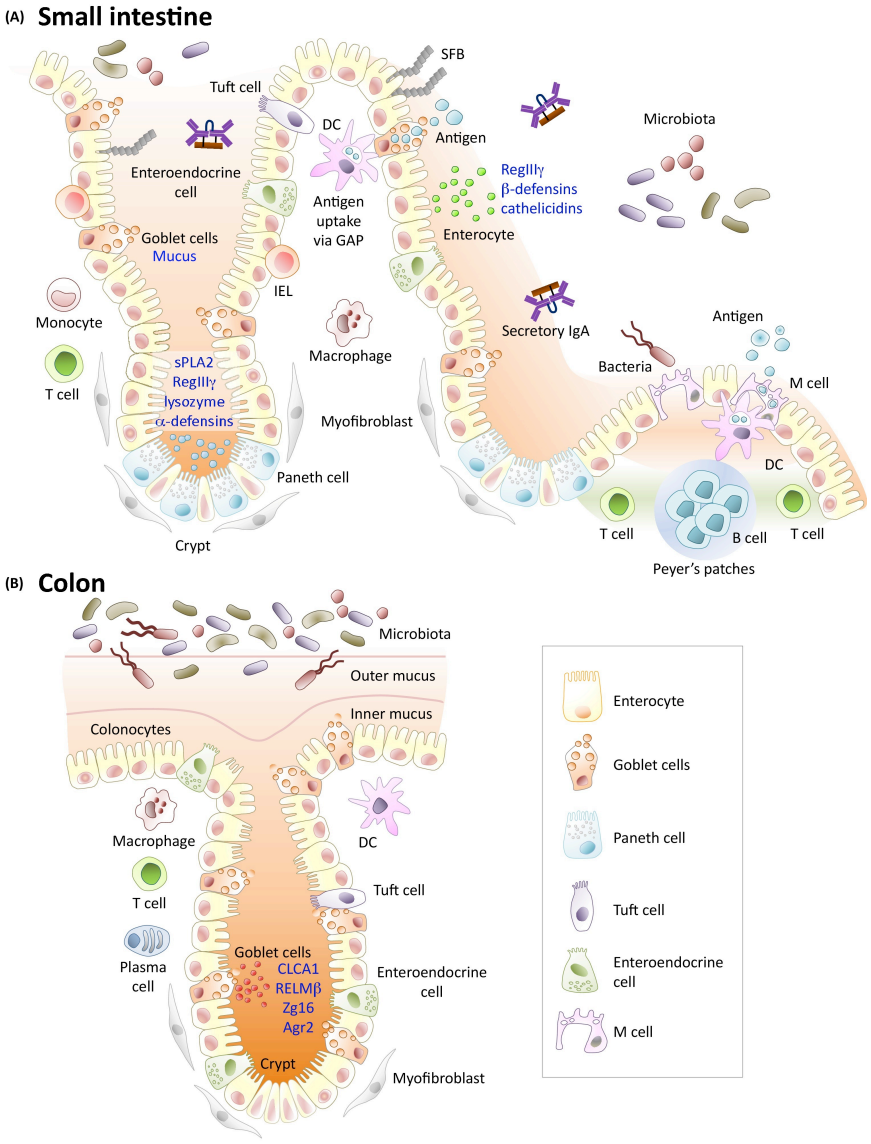
Airway epithelium



The Epithelial Layer: The initial barrier to infection

1. Physical barrier of the epithelial layer (toughness of barrier varies by location due to other functions: air exchange, nutrient uptake, etc.)
2. Acid pH of the stomach
3. Anti-microbial peptides secreted by some epithelial cells (small intestines, small airways of lungs)
4. Mucus/cilia to remove particles, microbes from airways; mucus layer in gut creates spatial separation between epithelial cells and most of bacteria
5. Microbe-binding molecules outside the epithelial layer: IgA; surfactants A/D (lung)

Intestinal epithelial defense mechanisms



multiple cell types:

- enterocytes
- goblet cells (mucin)
- endocrine cells
- Paneth cells (AMP producers)
- M cells (Ag uptake)
- Tuft cells (IL-25)

Close interaction with IELs:

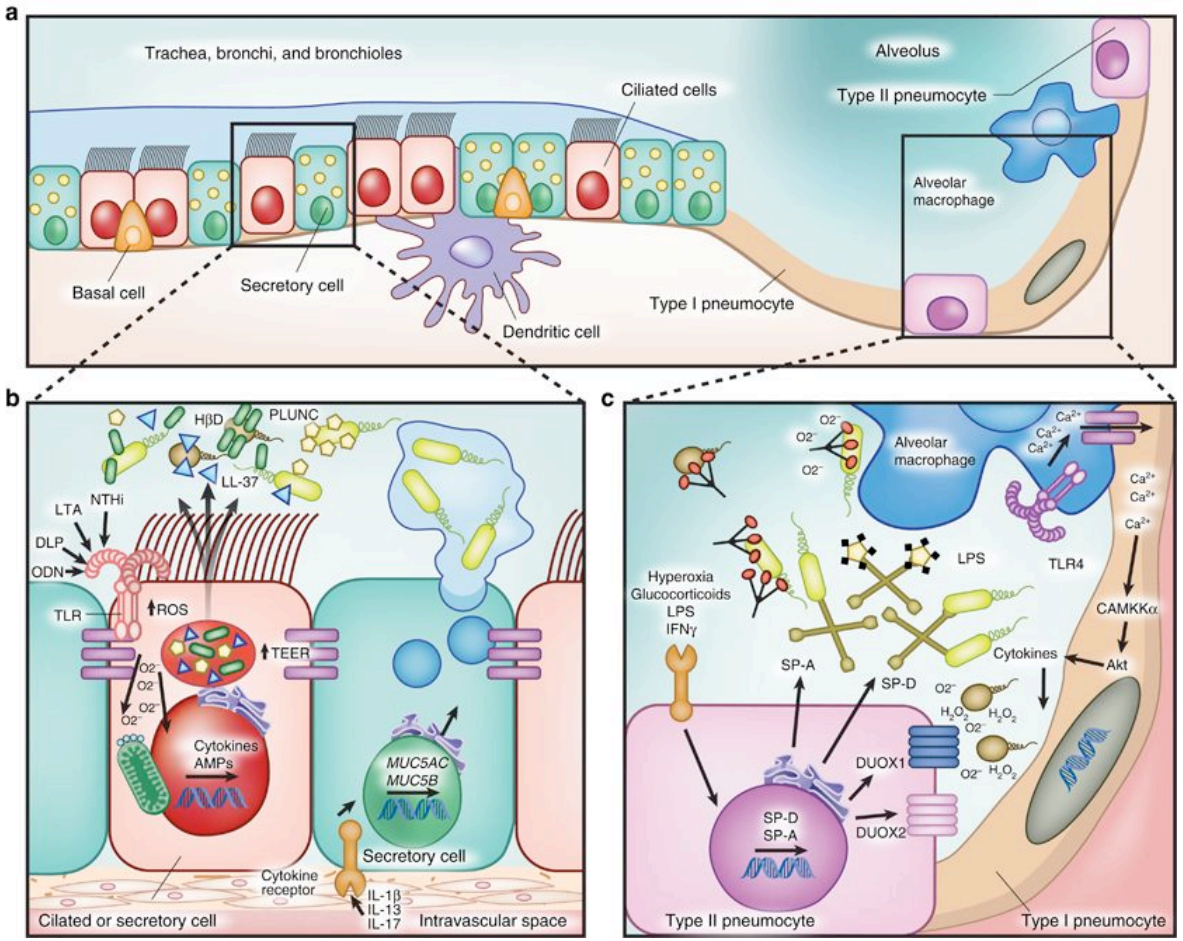
- M cells and Peyers patches
- transcytosis of IgA
- cytokine production (TSLP)

Close interaction with microbiota:

- microbial sensing (TLRs)
- microbial metabolites (SCFA)
- affect microbiome
- inflammasome activation

Allaire et al, Trends Immunol, 39:677 (2018)

Lung epithelial defense mechanisms



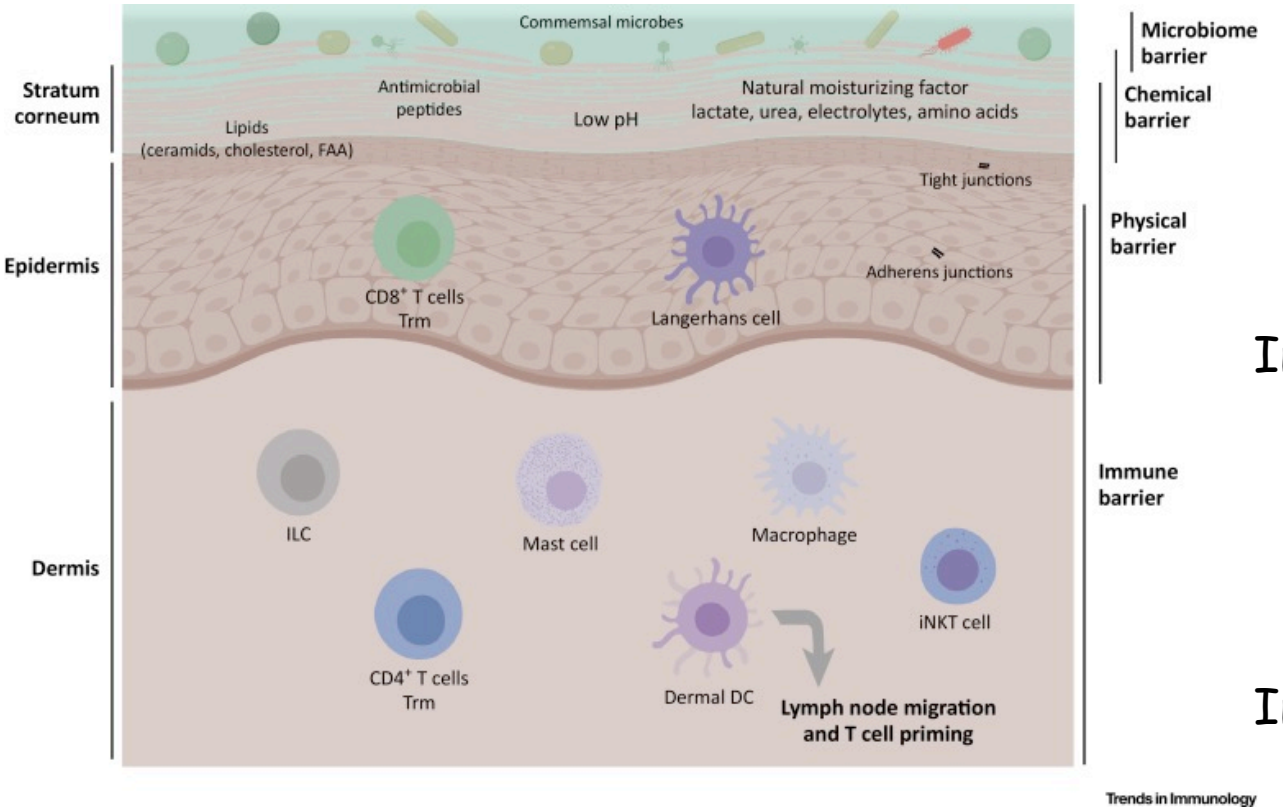
multiple cell types:
- ciliated cells
- secretory cells (mucin)
- ATI
- ATII

Close interaction with DCs:
- DC Ag sensing
- surfactant production
- cytokine production
- APM production

Interaction with microbiota:
- microbial sensing (TLRs)

Leiva-Juárez et al, Mucosal Imm, 11:21 (2018)

Skin epithelial defense mechanisms



multiple cell types:

- keritinocytes
- epidermal cells
- hair follicles

Interaction w/ DCs, lymphs:

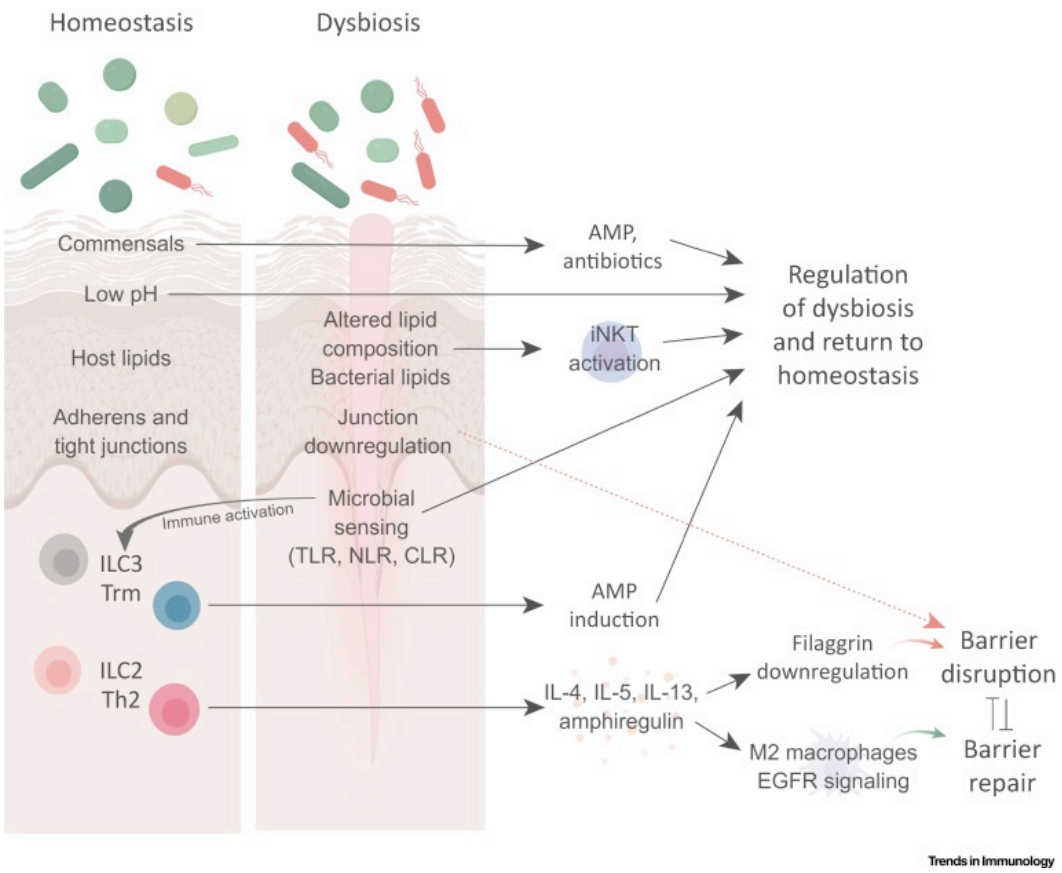
- Langerhan cells
- iNKT, γδT-cells
- cytokine production

Interaction with microbiota:

- microbial sensing (TLRs)

Eyerich et al, Trends Immuno, 39:315 (2018)

Skin epithelial defense mechanisms



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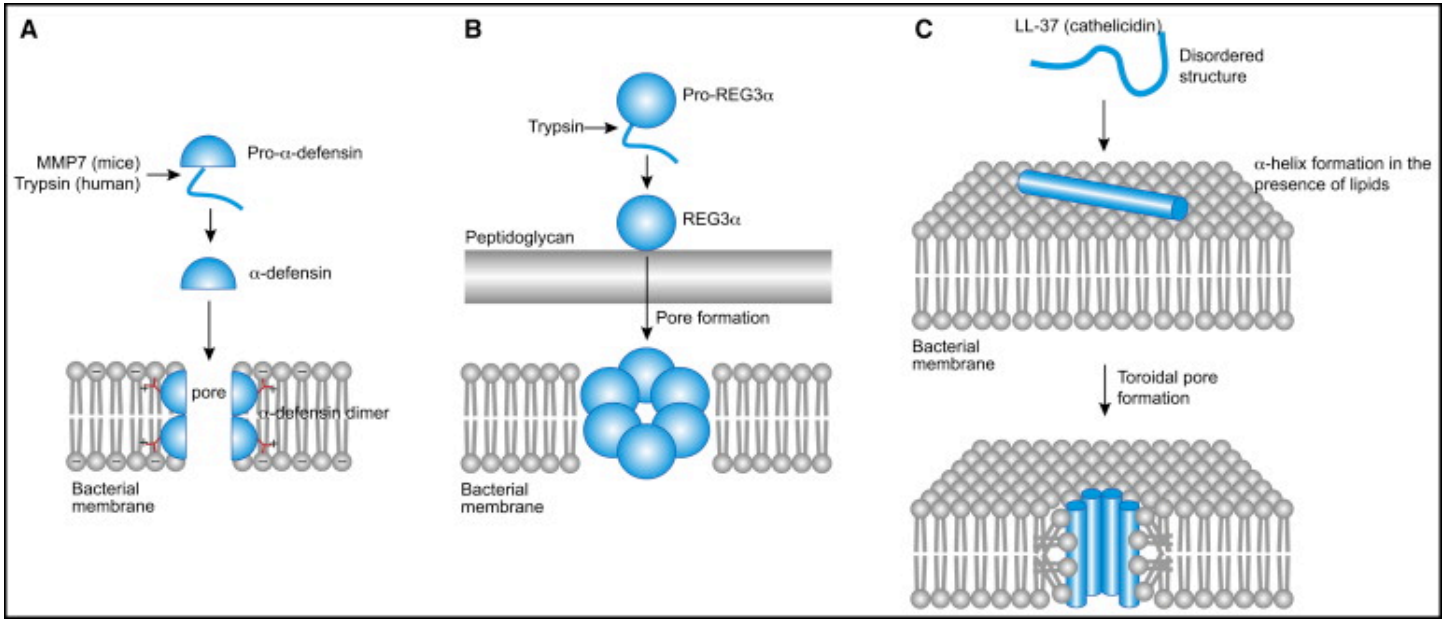
Interaction with microbiota:
- microbial sensing (TLRs)
- AMP production

Eyerich et al, Trends Immuno, 39:315 (2018)

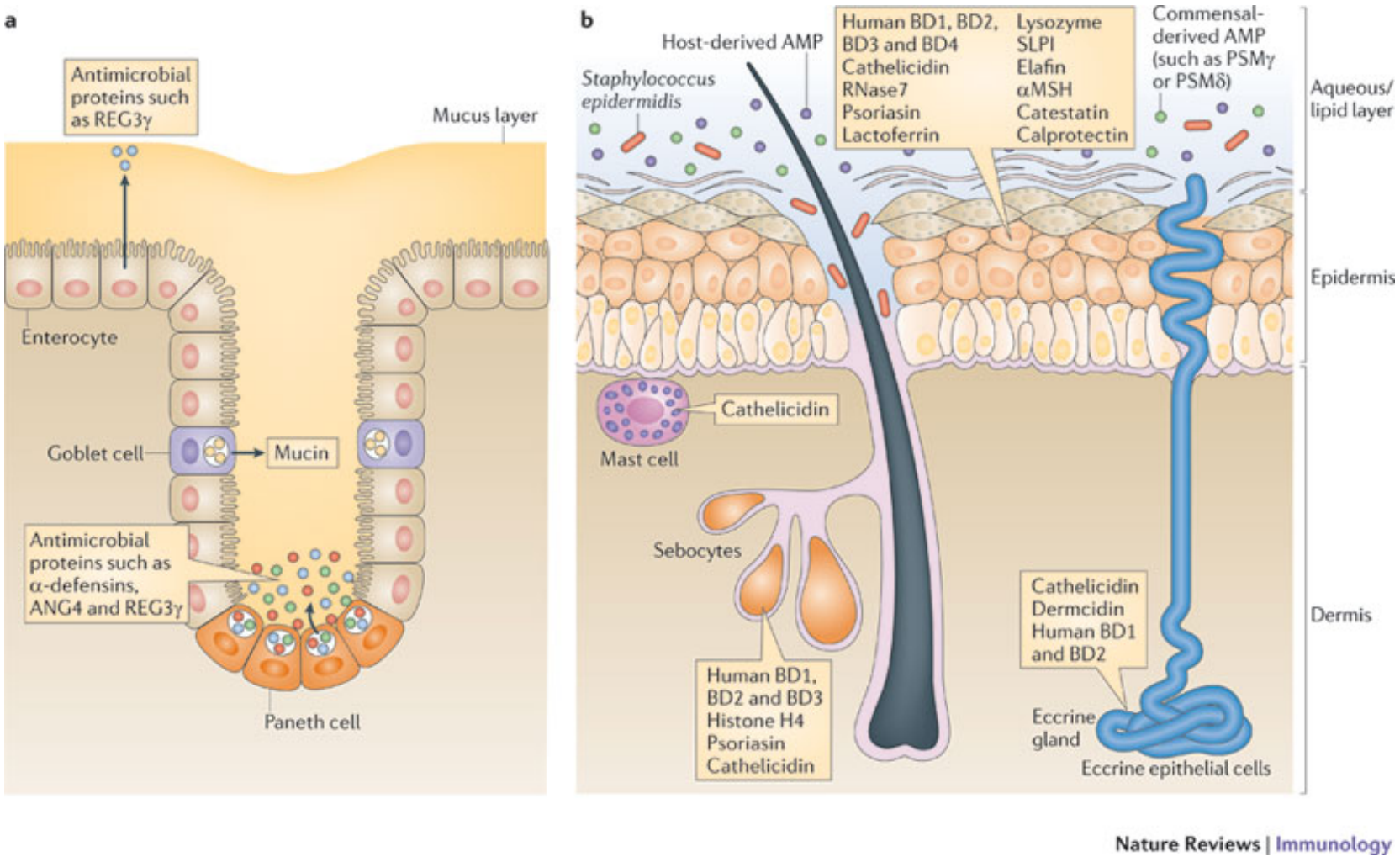
Anti-microbial peptides

- Ancient form of innate immunity
- ~ 1800 different types, from 12 – 50 aa in size
- mainly produced epithelial cells, also immune cells
- highly positively charged with amphipathic structure
- allow for insertion into membranes, form pores. Natural antibiotics
- also activate/modulate immune cells
- dysregulation associated with inflammatory disease
- cathelicidins (LL-37), β-defensins as examples



Mukherjee and Hooper, Immunity, 42:28 (2015)

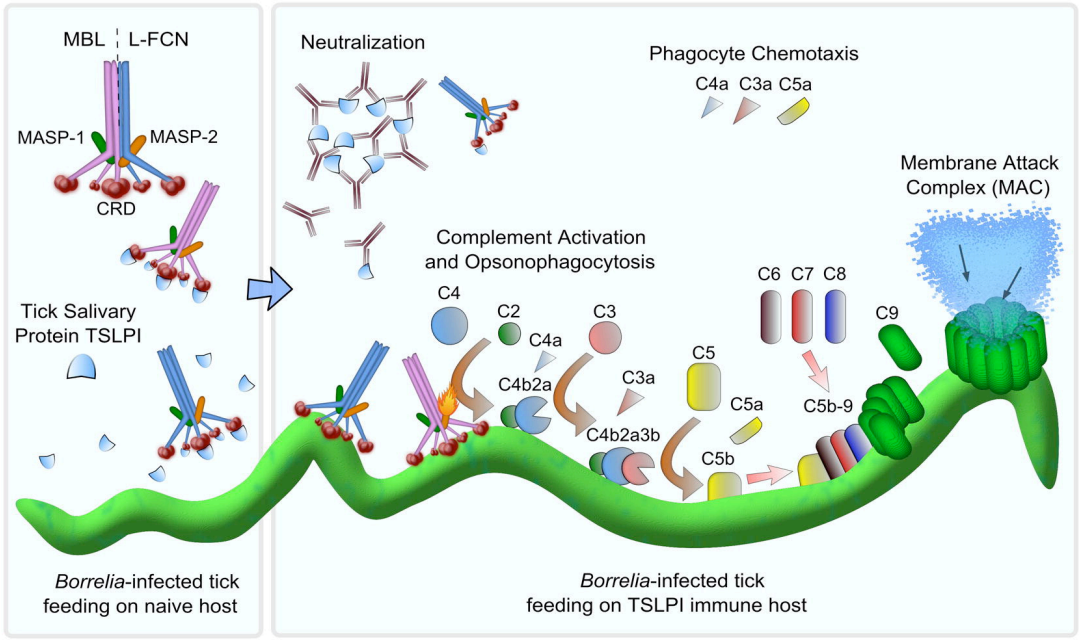
Anti-microbial peptides in the gut and skin



Gallo and Hooper, Nat Rev Immunol, 12:503 (2012)

Soluble innate recognition and complement activation

- recognize foreign carbohydrate structures
- leads to complement activation
- mannose binding lectin, lung surfactants, ficolins
- Immune complexes and complement activation
- Many disease associations



Schuijt et al, Cell Host Microb, 10:136 (2011)

Complement activation
Three ways to get it started

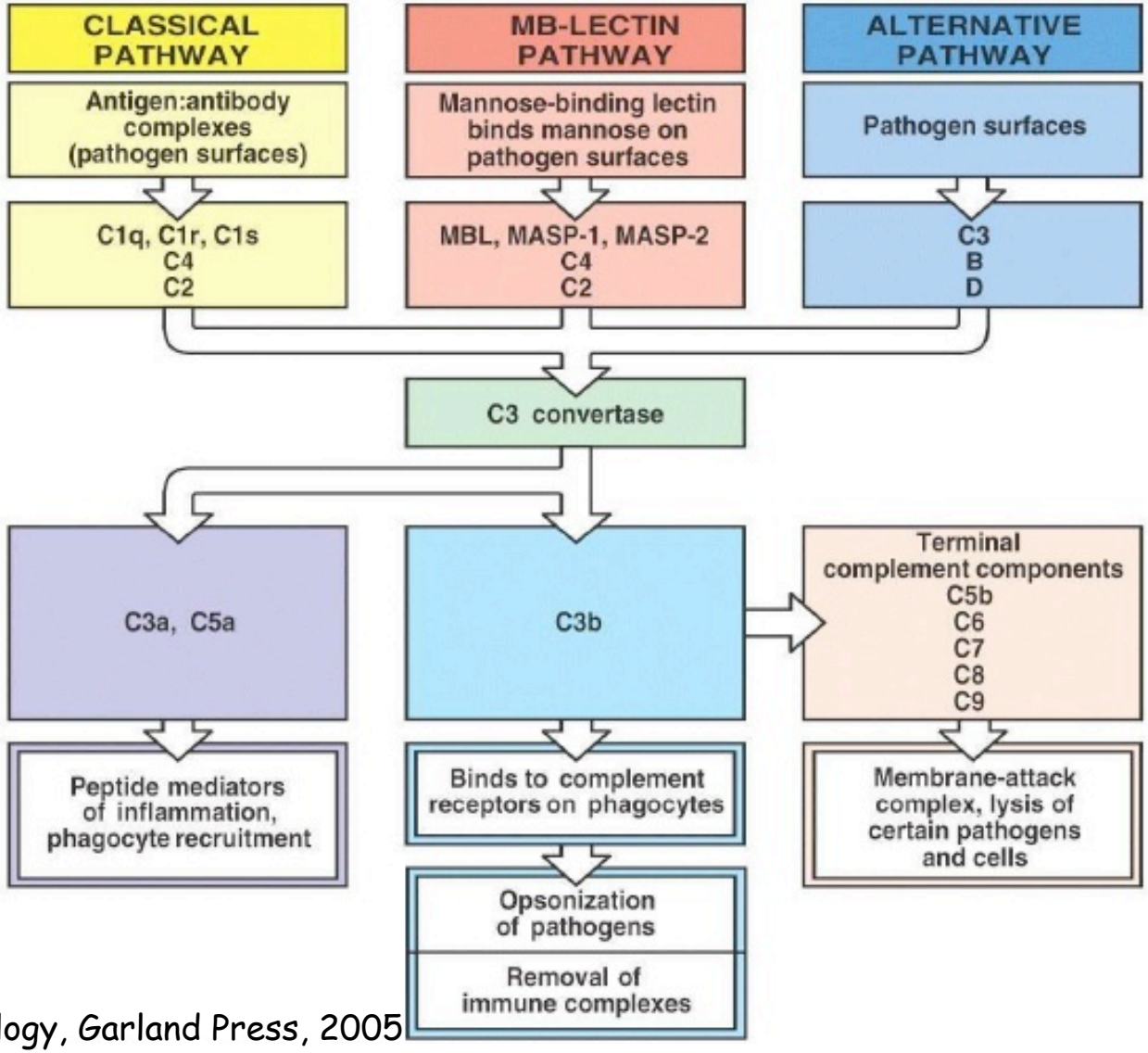
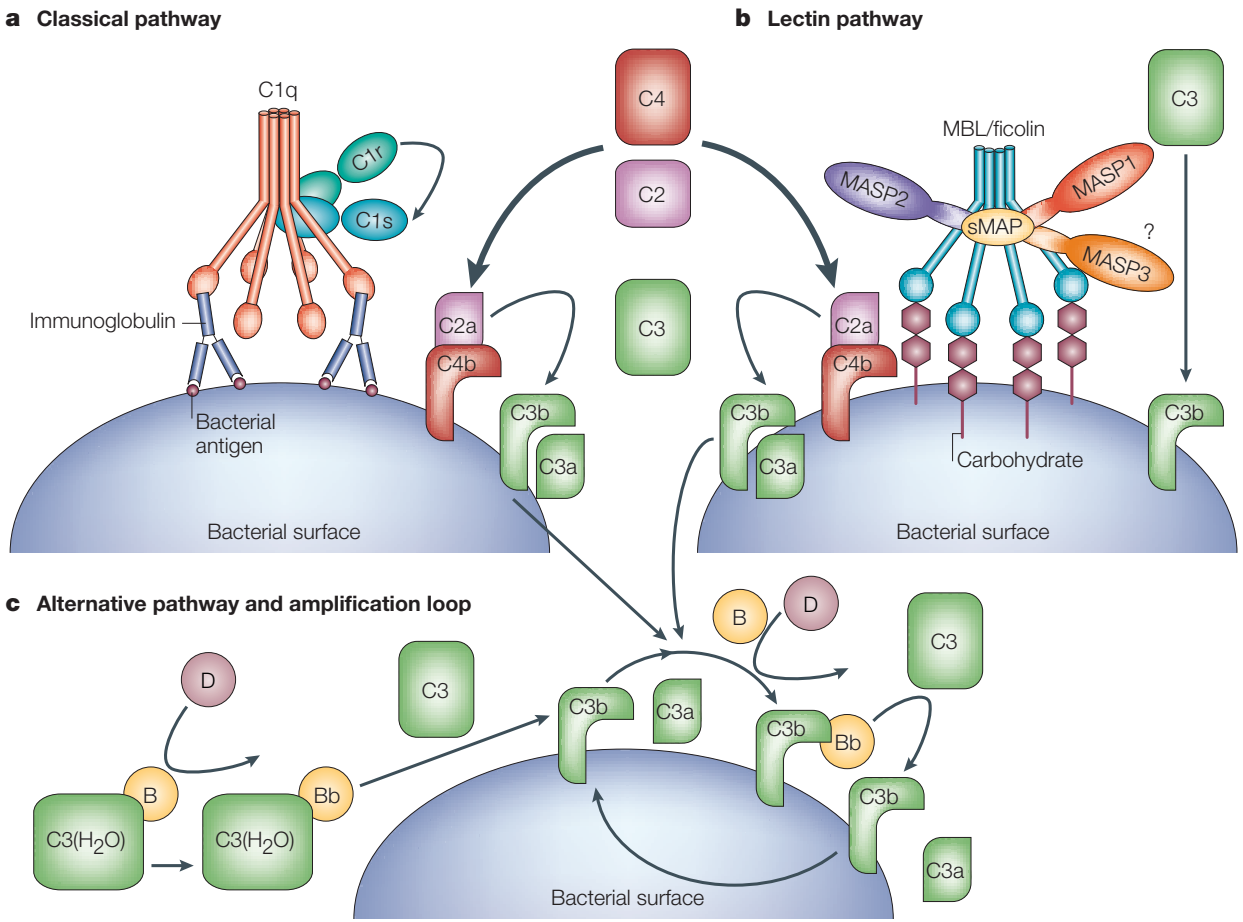


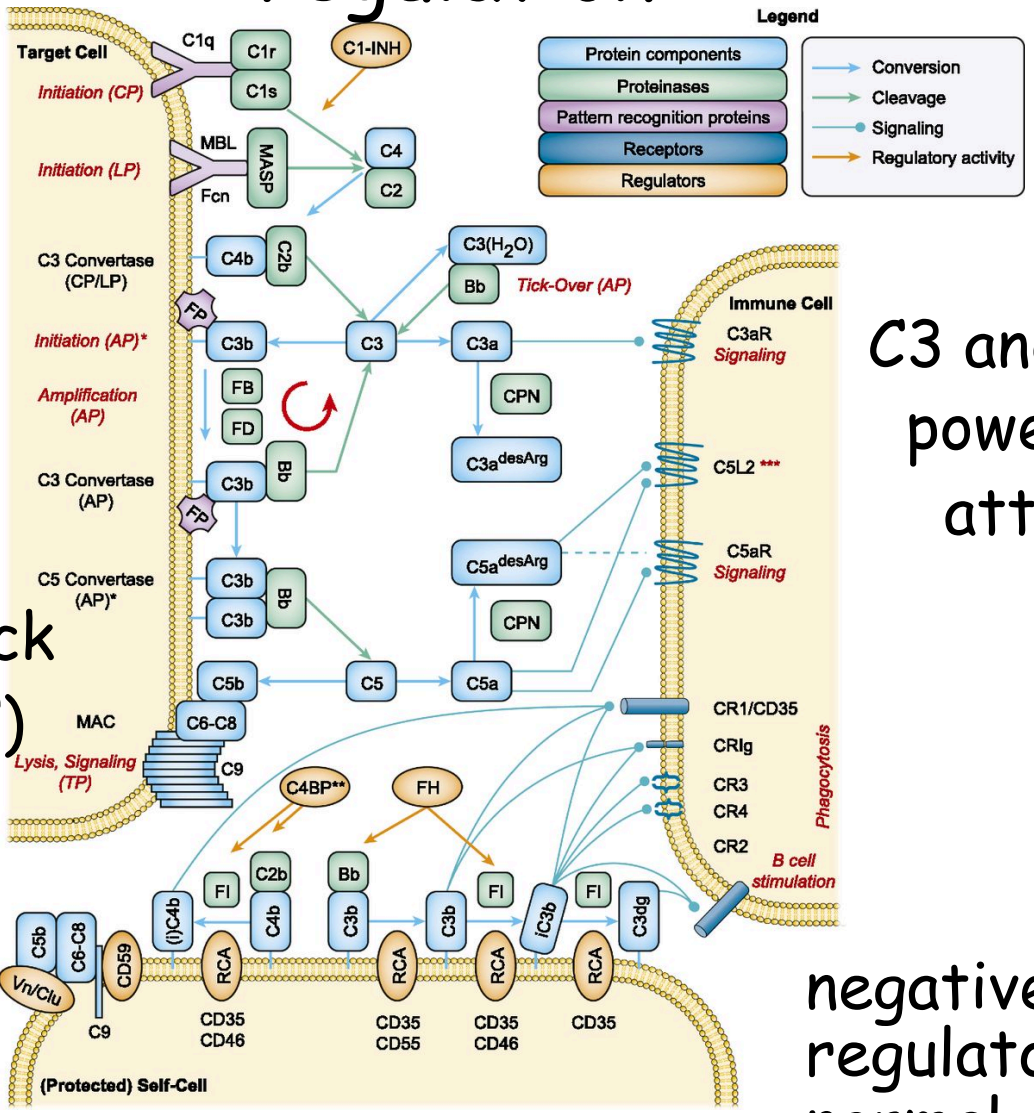
Fig. 2-19, Immunobiology, Garland Press, 2005

Complement activation
Three ways to get it started



Foster, Nat Rev Micro, 3:948 (2005)

Complement activation – receptors and regulation



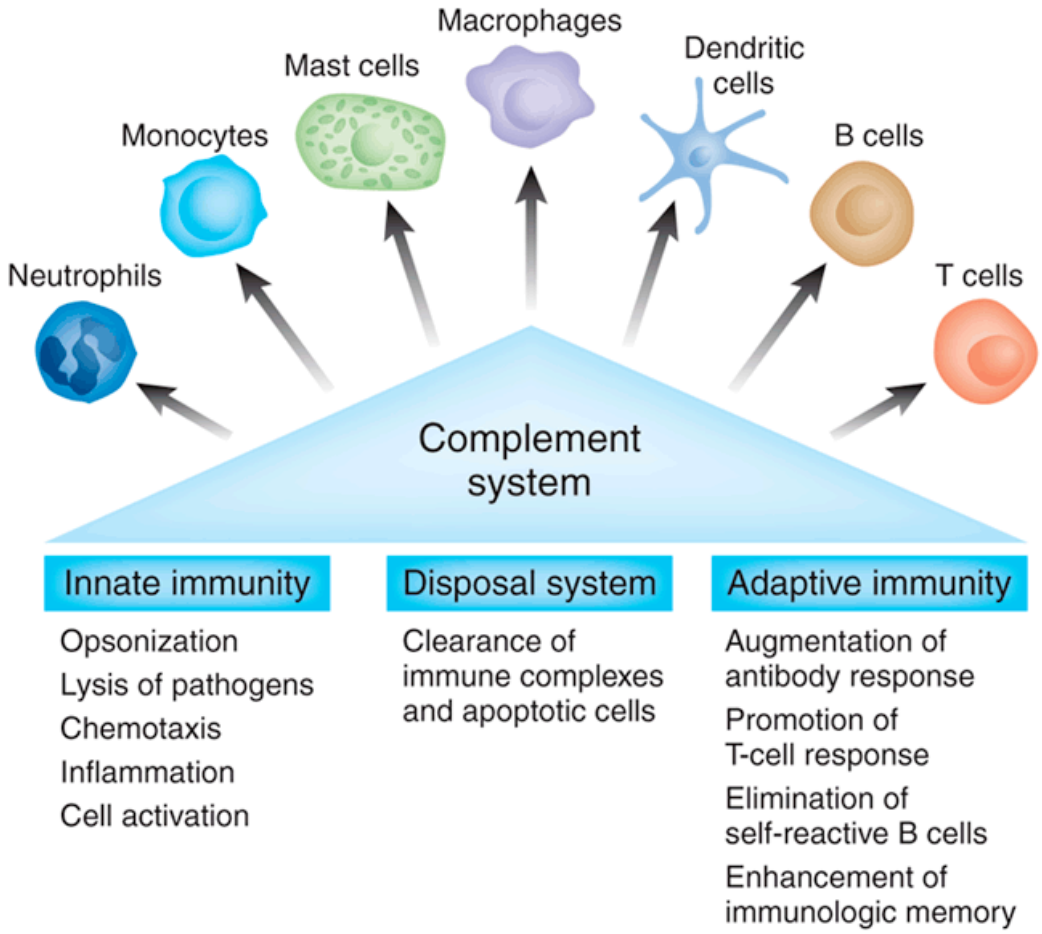
cell killing membrane attack complex (MAC)

C3 and C5 powerful chemo-attractants

negative regulators on normal cells

Ricklin and Lambris, J Immunol, 190:3831 (2013)

Functional outputs of complement activation

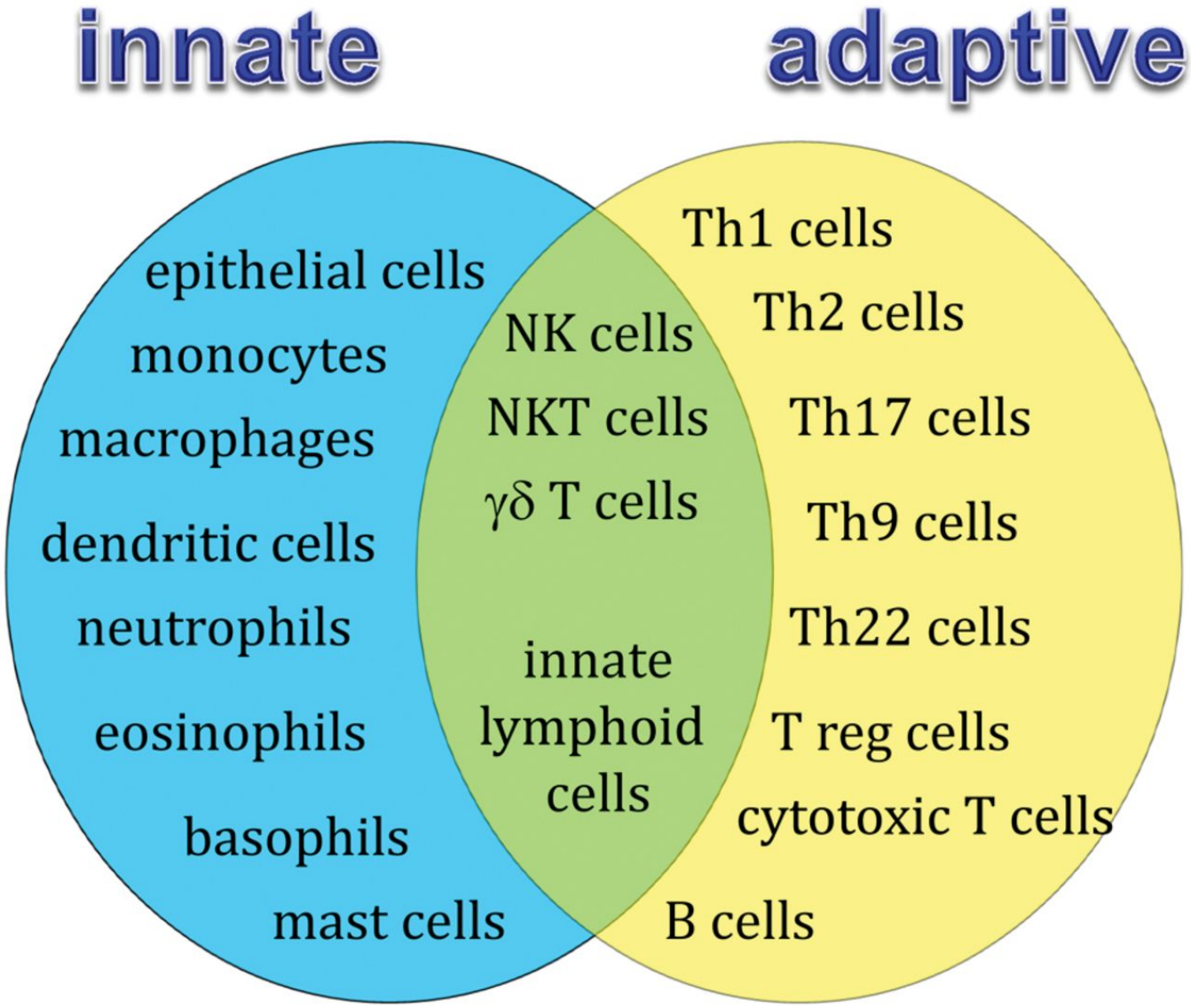


complement activation – disease association

- excessive activation, amplification, tissue injury
- contributes to cycles of inflammation
- Examples:
  - macular degeneration (AMD), factor H polymorphisms
  - Alzheimers, CR1 polymorphisms
  - HUS (kidney) – bacterial or genetic
  - Deficiencies associated with autoimmunity (SLE, RA)
  - PNH – CD55 and CD59 deficiency
  - Nissera infection with C9 deficiency
  - Complement activation ischemia/reperfusion injury
  - Periodontal diseases
  - Trauma induced SIRS

Clinical significance: C3/C5 levels as biomarkers

Cells of the innate immune system



The major receptors by which innate immune cells recognize pathogens

Four major families of pathogen recognition Rs

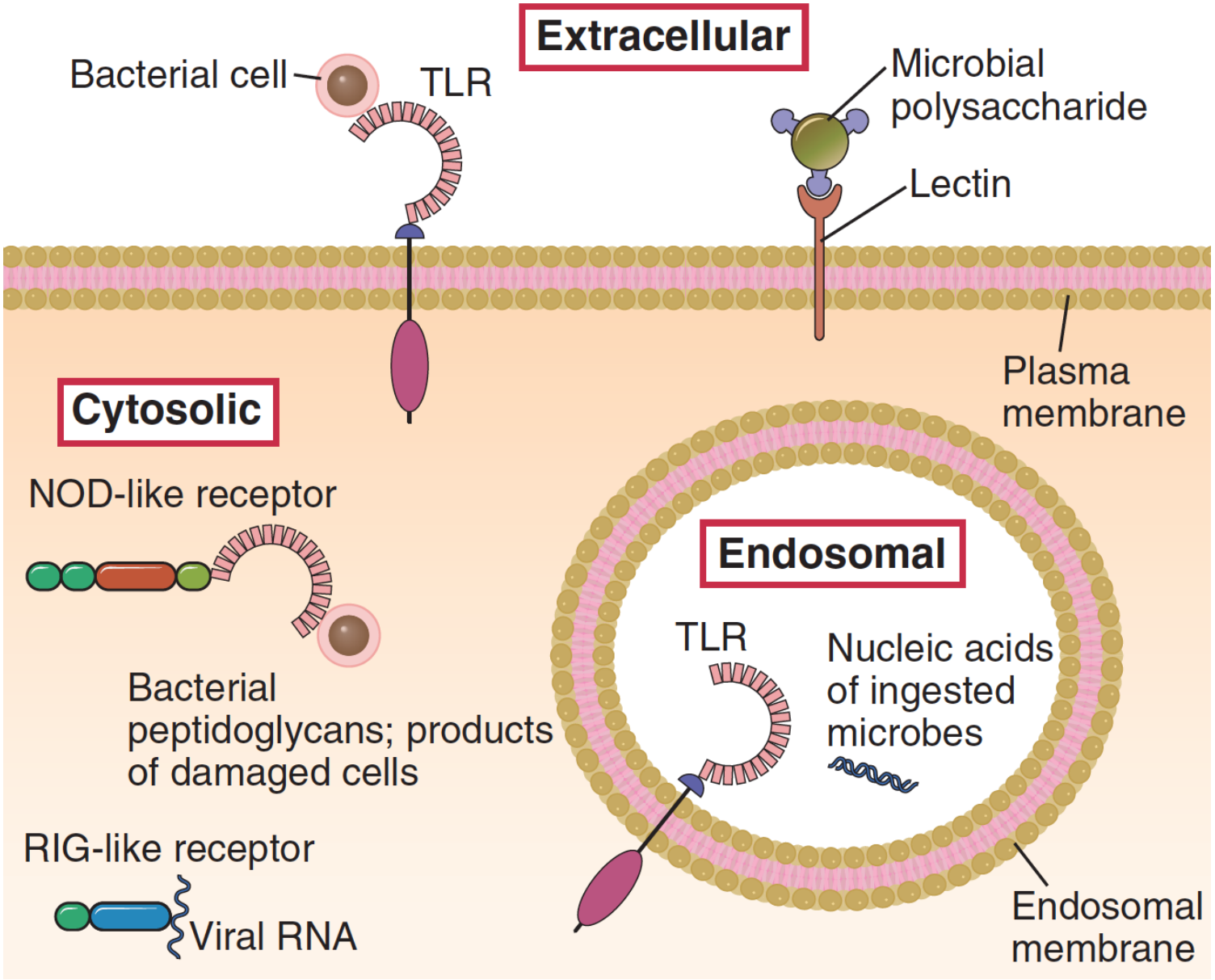
- Toll-like receptors (TLRs)
- C-type lectin-like receptors (CLRs)
  (Lectin: carbohydrate binding protein)
- Nod-like receptors (NLRs)
- Rig-I-like receptors (RLRs)

Other major receptors on innate cells

- FcRs – recognize Ig opsonized particles/Ags
- Complement receptors – comp opsonsized

Present (in different amounts) in all innate cells
- most studied in macrophages and DCs

Innate receptors: location of recognition

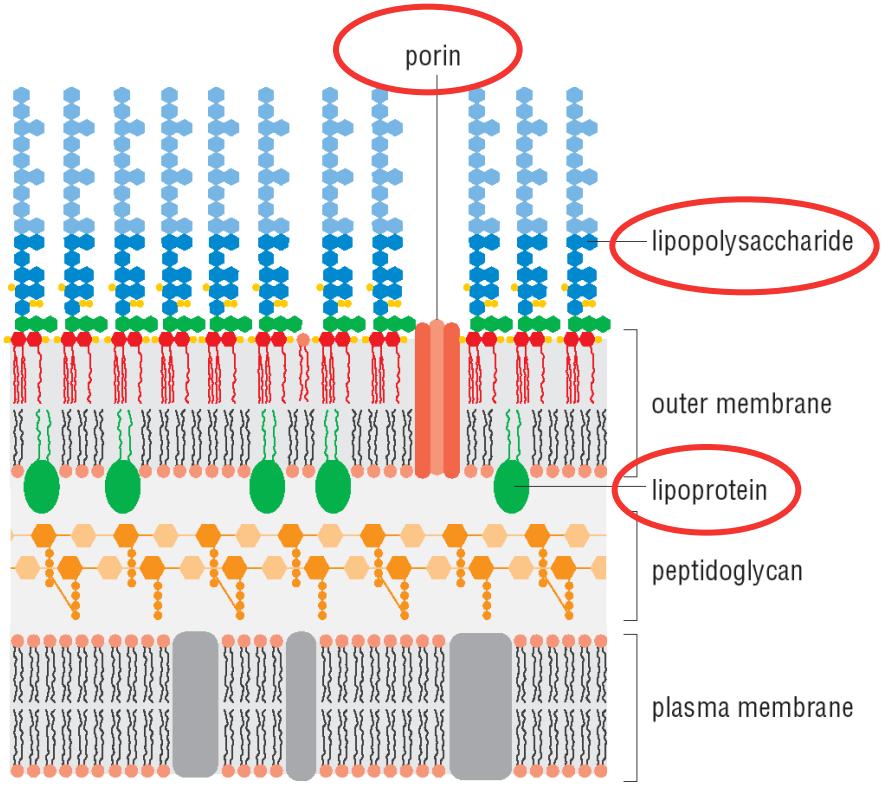


Types of molecules recognized by innate immune receptors

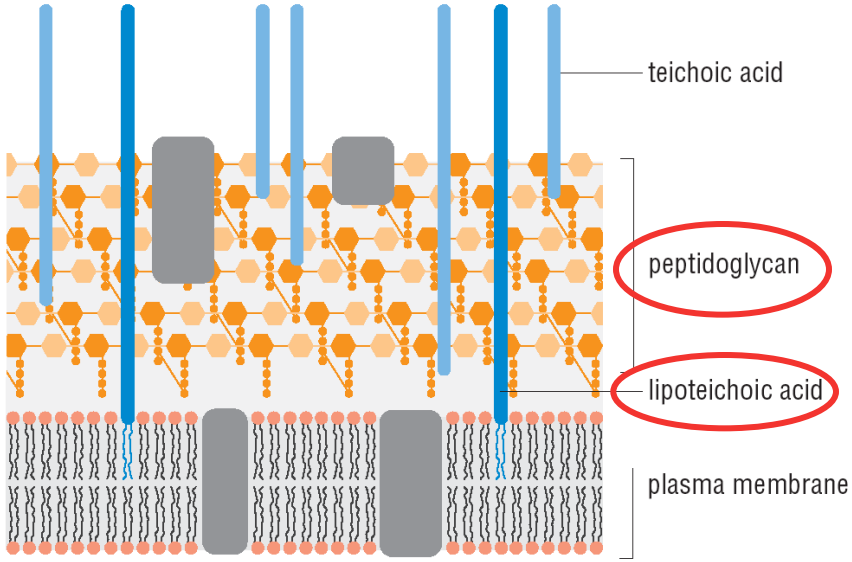
- TLRs, CLRs, NLRs, and RLRs see highly conserved and essential components of microbes
  "Pathogen-associated molecular patterns" (PAMPs)
  examples: nucleic acids, proteins, lipids

- Also see host molecules generated by stress or damage
  "Danger-associated molecular patterns" (DAMPs)
  examples: chromatin (HMGB1), S100, mtDNA

Innate immune recognition of bacterial cell wall components



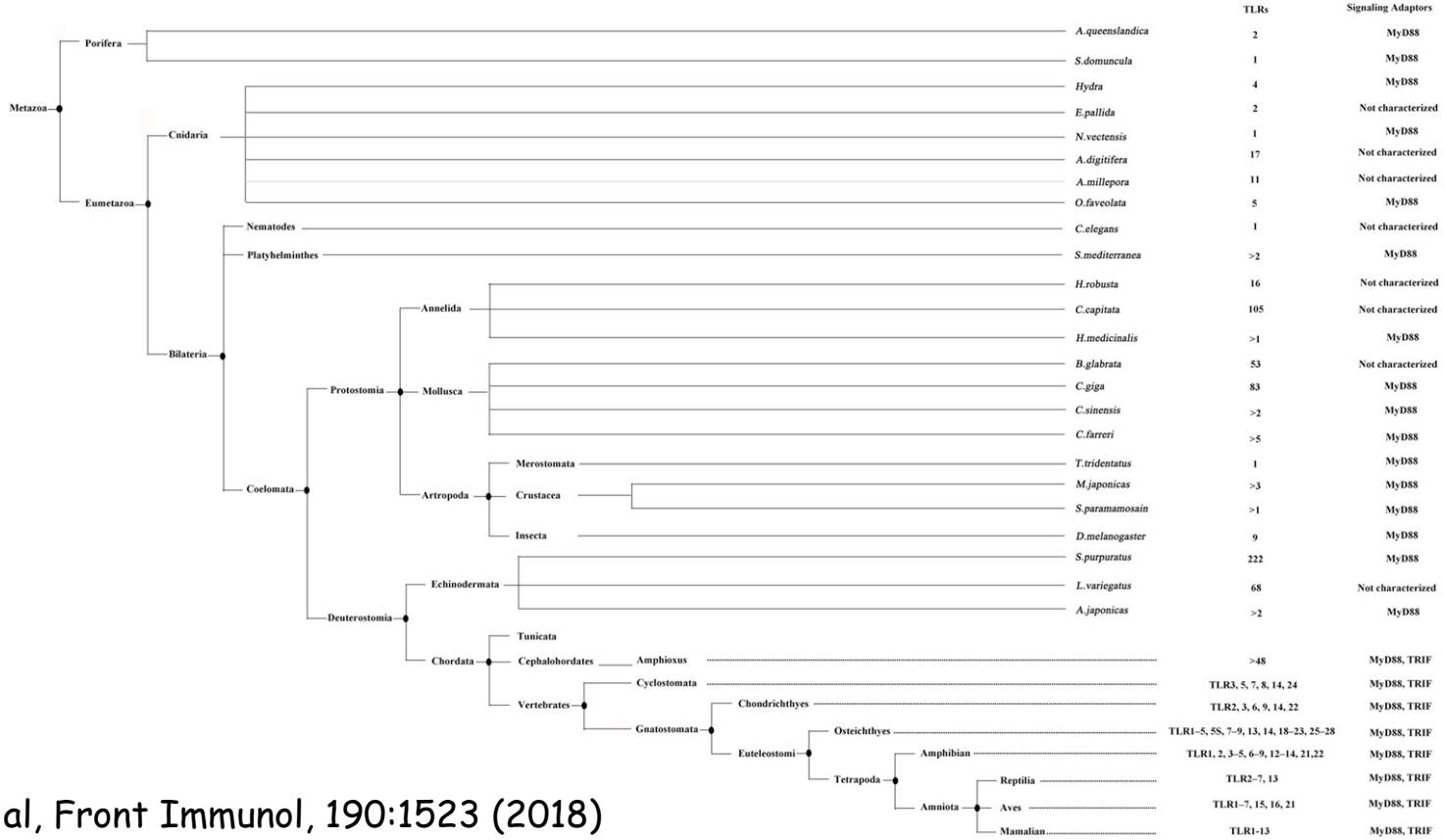
Gram-negative bacteria



Gram-positive bacteria

TLRs are the most ancient of all innate receptors

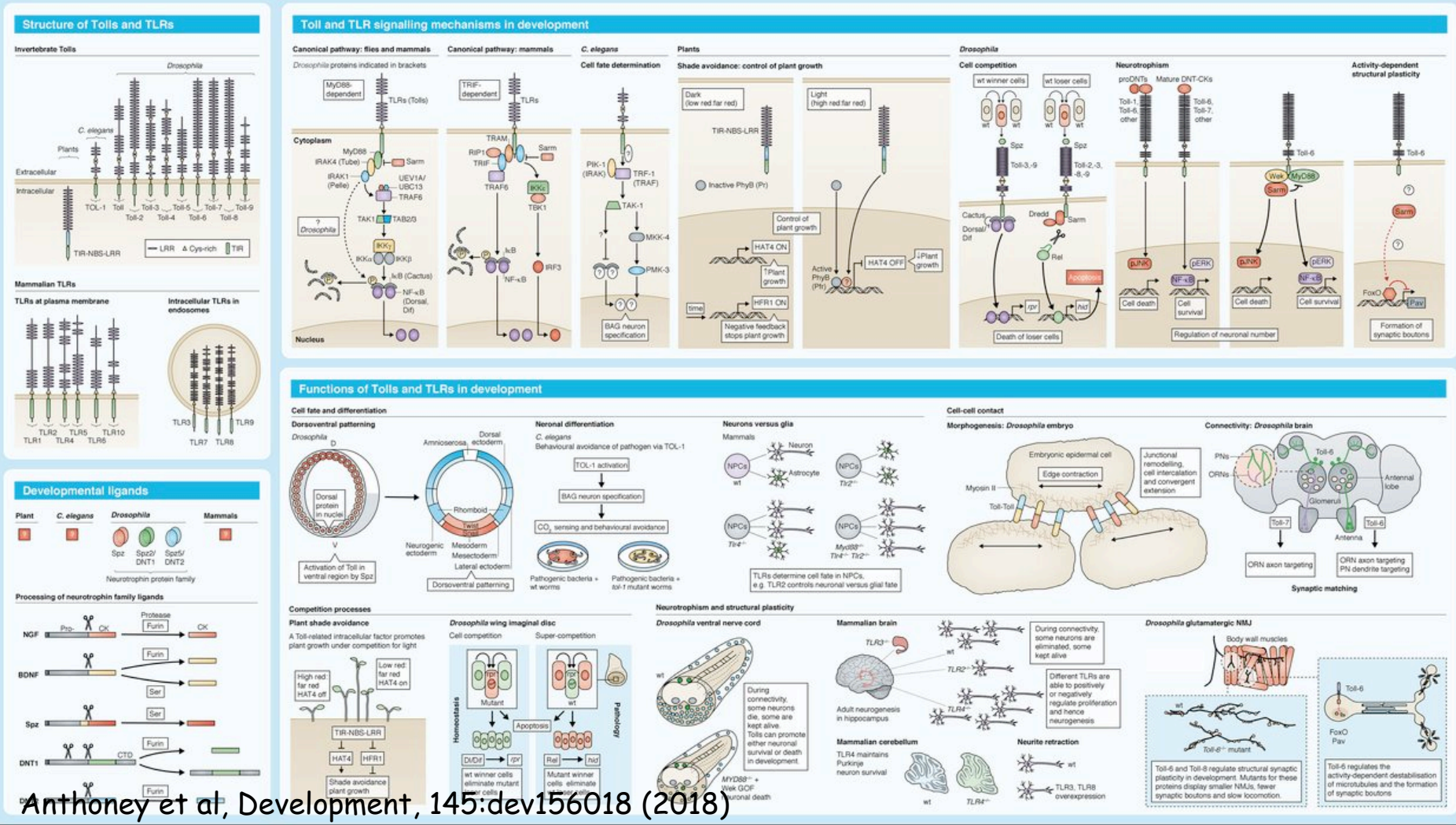
- widest spectrum of pathogen recognition
- present in plants, invertebrates, vertebrates
- generally conserved structures and signaling



Nie et al, Front Immunol, 190:1523 (2018)

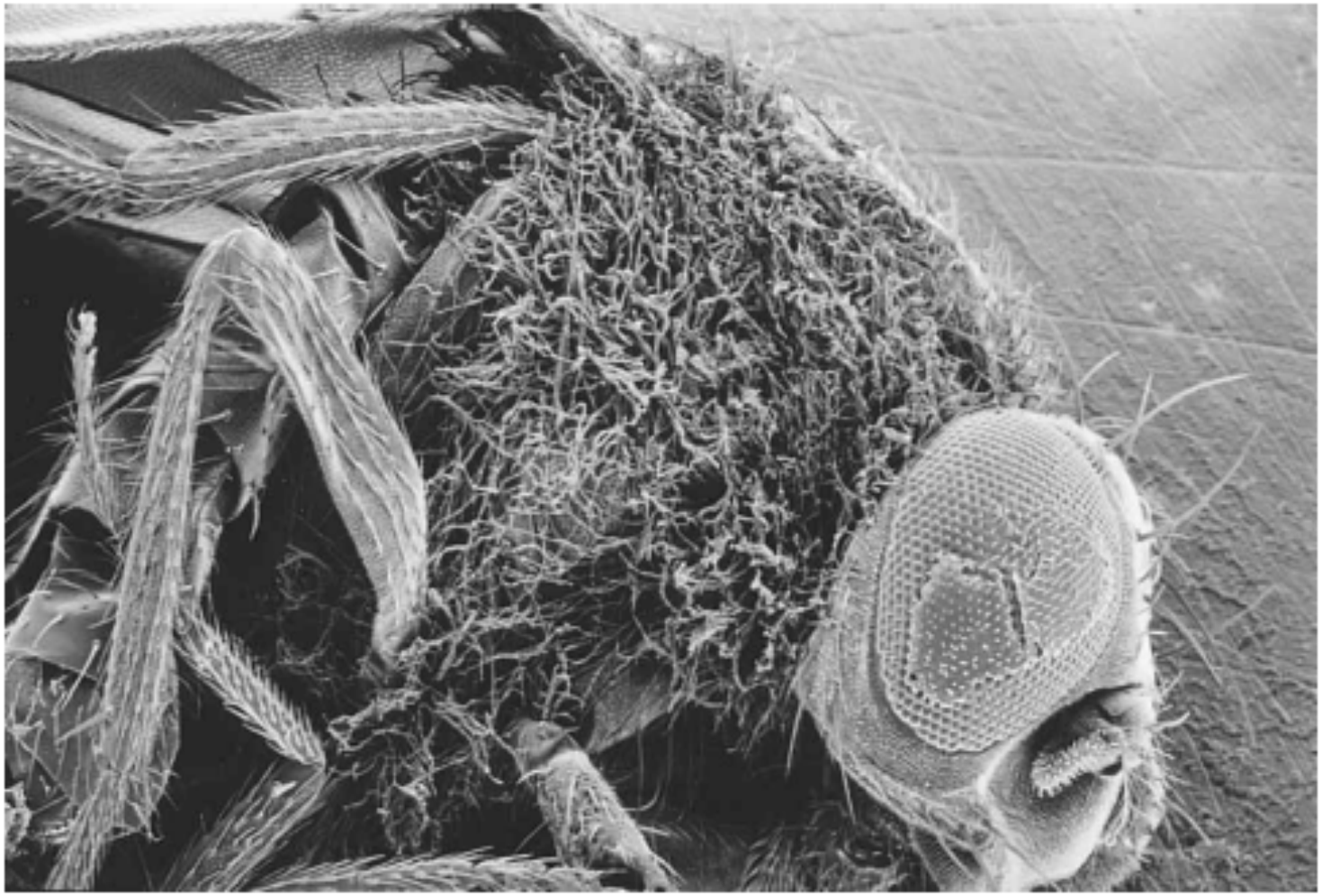
TLRs originally described in fly development

Pathway defined for role in dorsal/ventral patterning in early embryos
Spaetzle->Toll->->Dorsal (NF-κB homolog)



Anthoney et al, Development, 145:dev156018 (2018)

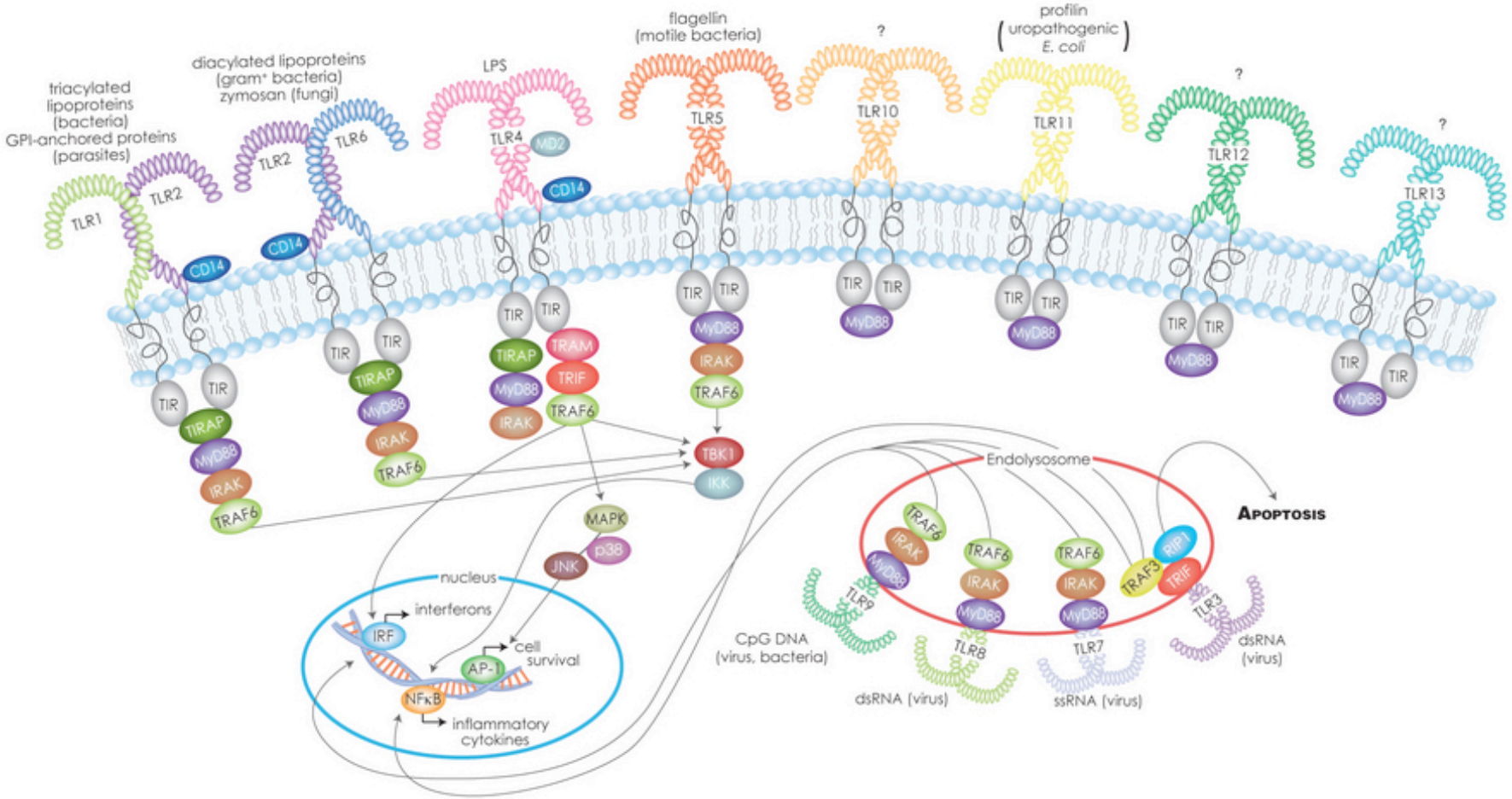
Toll is required for innate defense in flies



J. Hoffmann et al. Cell 1996

2011 Nobel Prize with Bruce Beutler for Innate Immunity

Mammalian Toll-like receptors/ligands



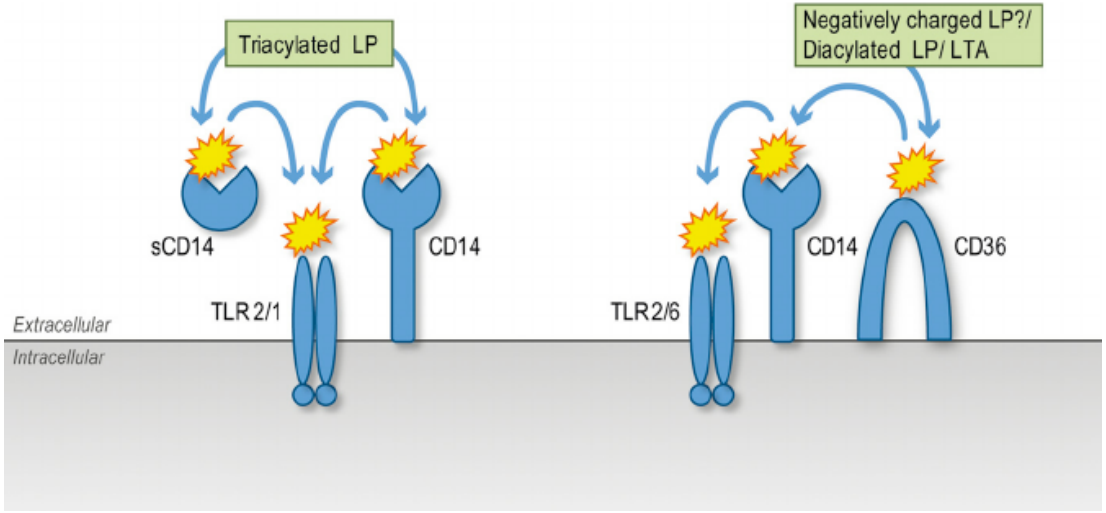
10 -13 different TLRs in mammals (10 in humans)
LRR extracellular domain; TIR domain inside

https://www.caymanchem.com/Article/2190

Toll-like receptors directly bind ligands (mostly)

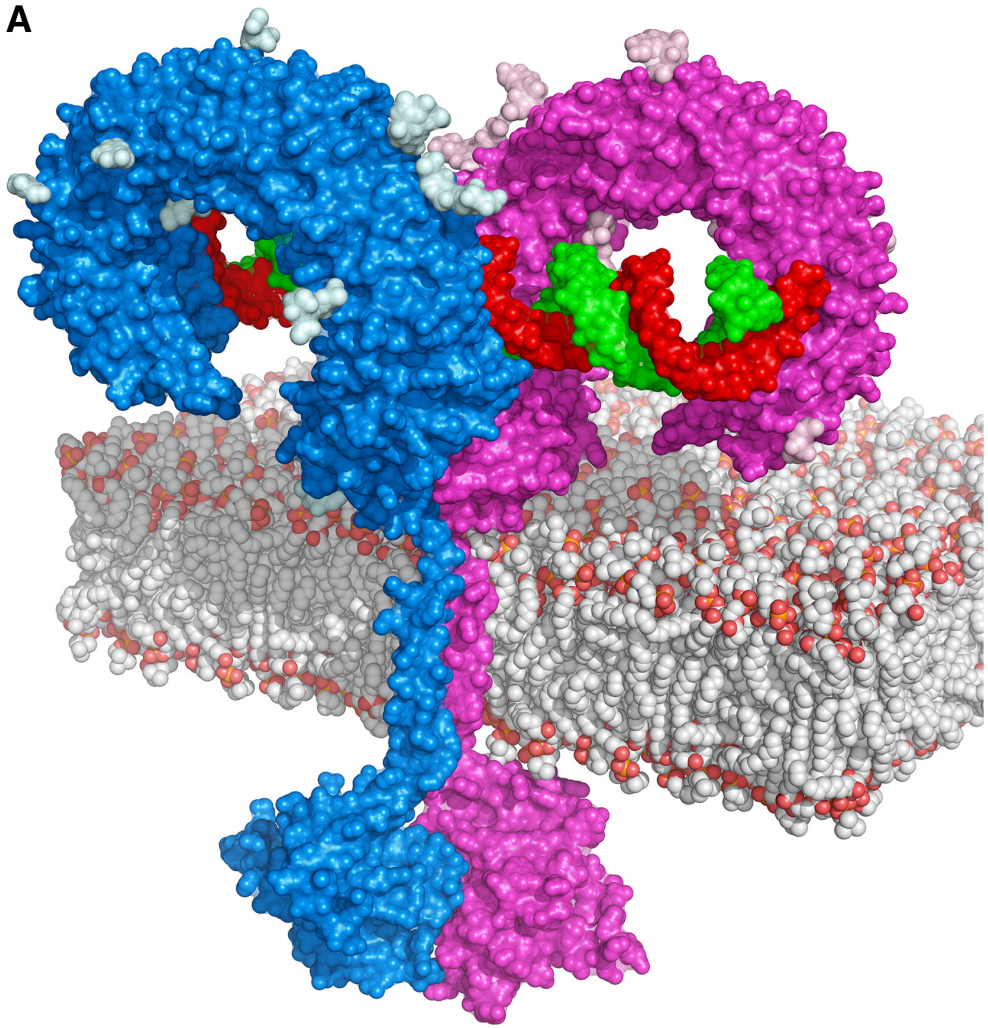
- TLRs recognize pathogen-derived ligands by their ectodomains (leucine rich repeat horseshoe structure), leading to receptor dimerization → intracellular signaling

- Most ligands bind directly (Pam3CSK4 to TLR2 or dsRNA to TLR3) but some associated host proteins needed (CD14 or MD-2 for LPS binding)



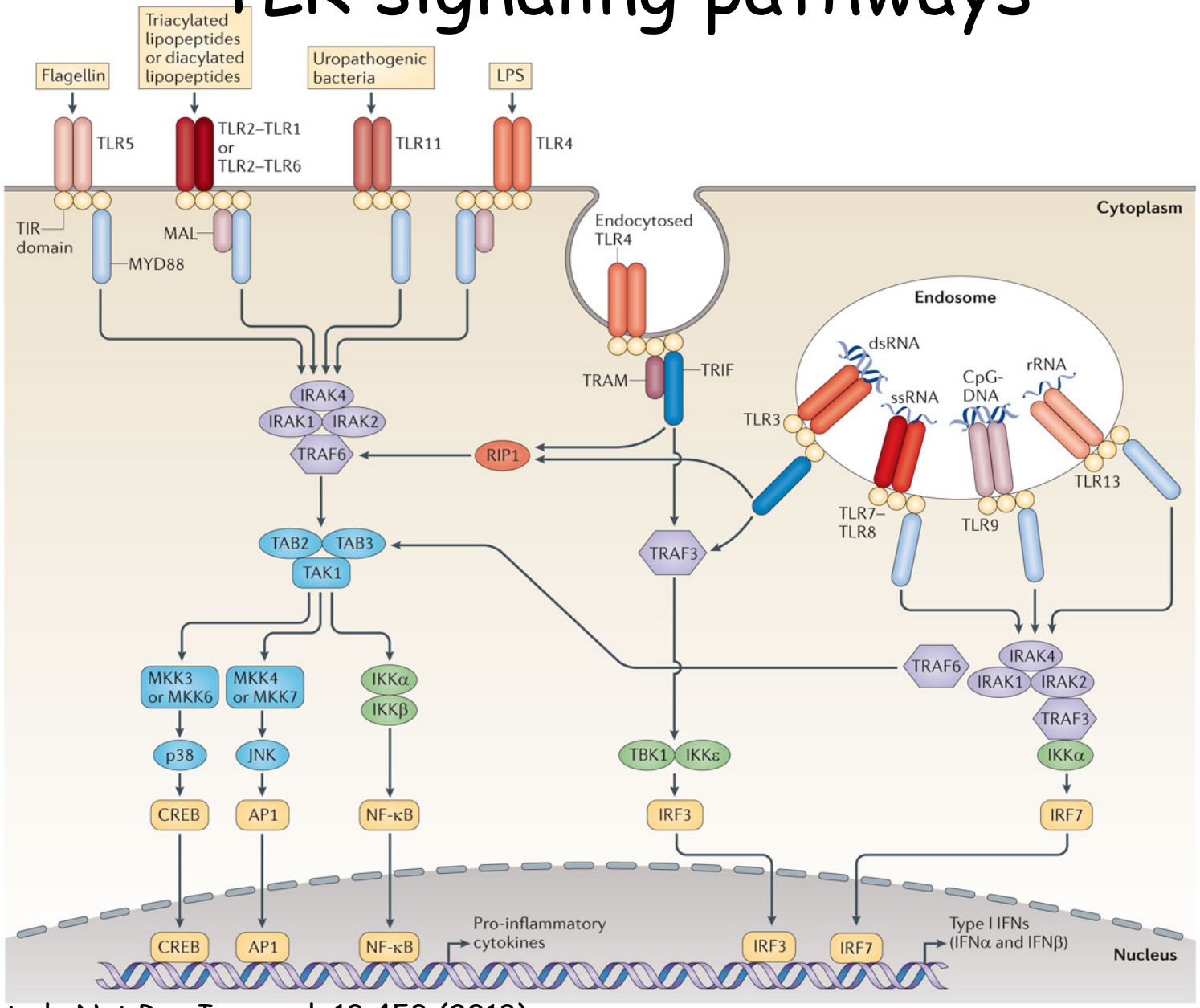
Bergenhenegouwen et al J Leuk Biol 94:885 (2013)

Structure of TLR3 dimer bound to ds RNA



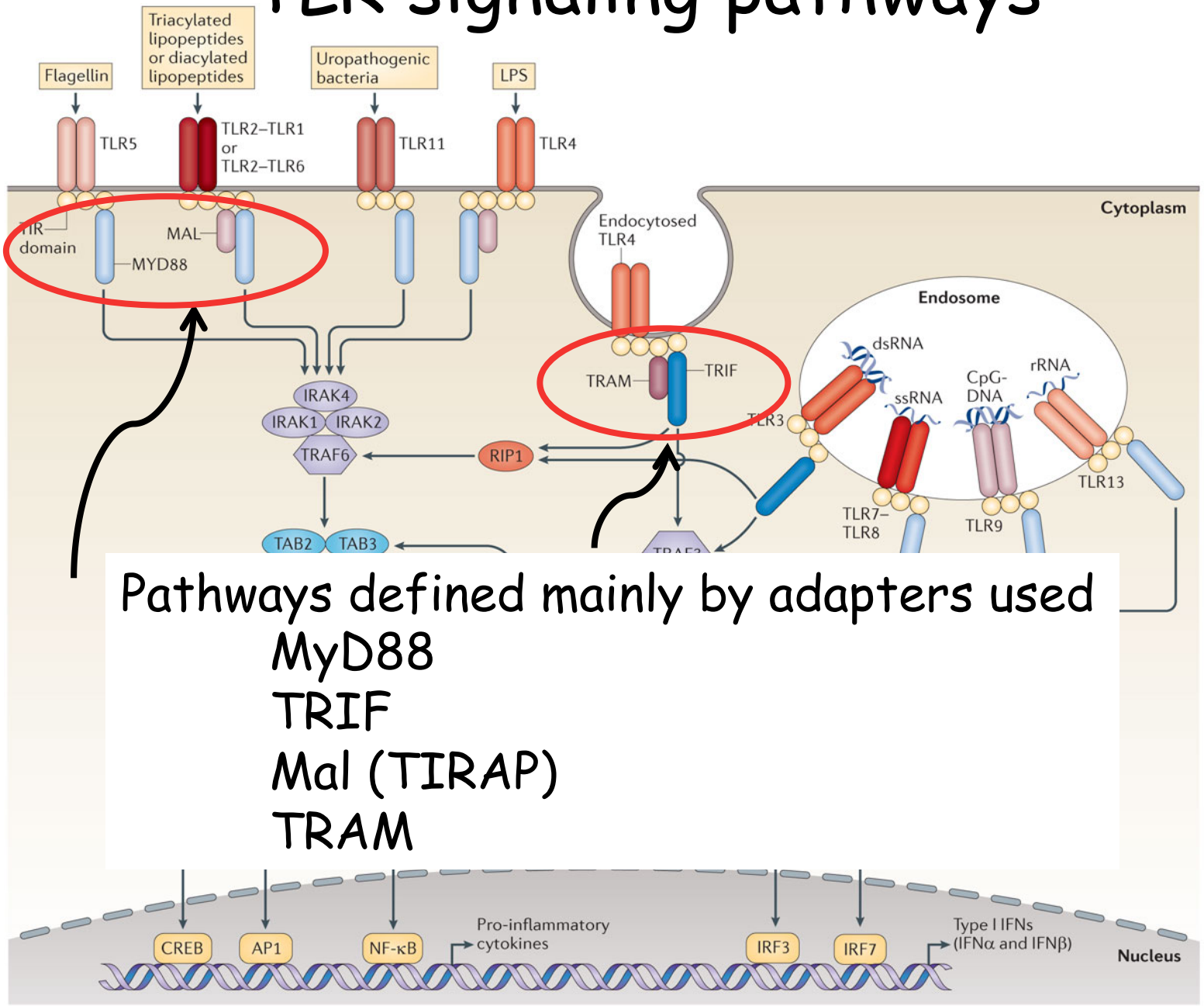
Botos et al., Structure, 19:447 (2011)

TLR signaling pathways



O'Neill et al., Nat Rev Immunol, 13:453 (2013)

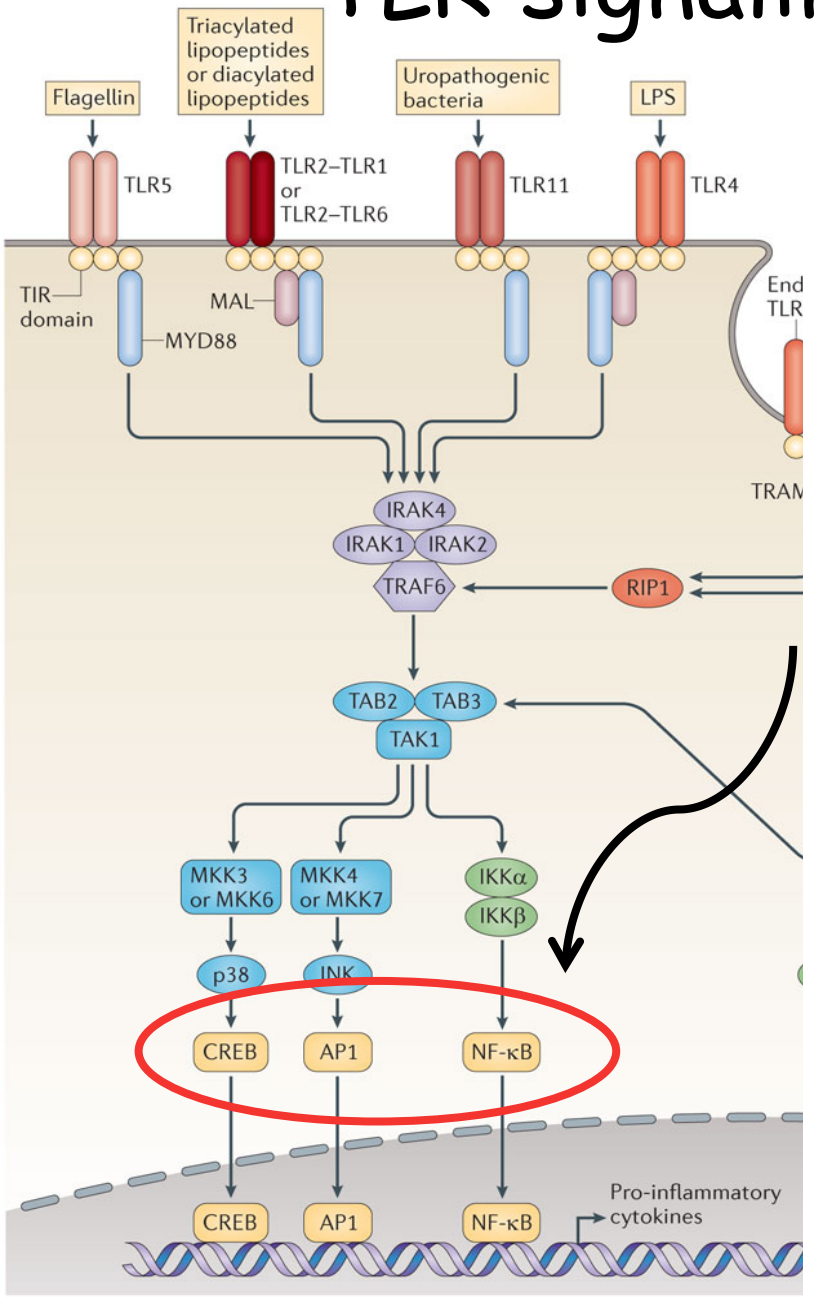
TLR signaling pathways



Pathways defined mainly by adapters used

- MyD88
- TRIF
- Mal (TIRAP)
- TRAM

TLR signaling pathways



MyD88 most dominant signaling pathway

Works through IRAKs (ser/thr kinases)

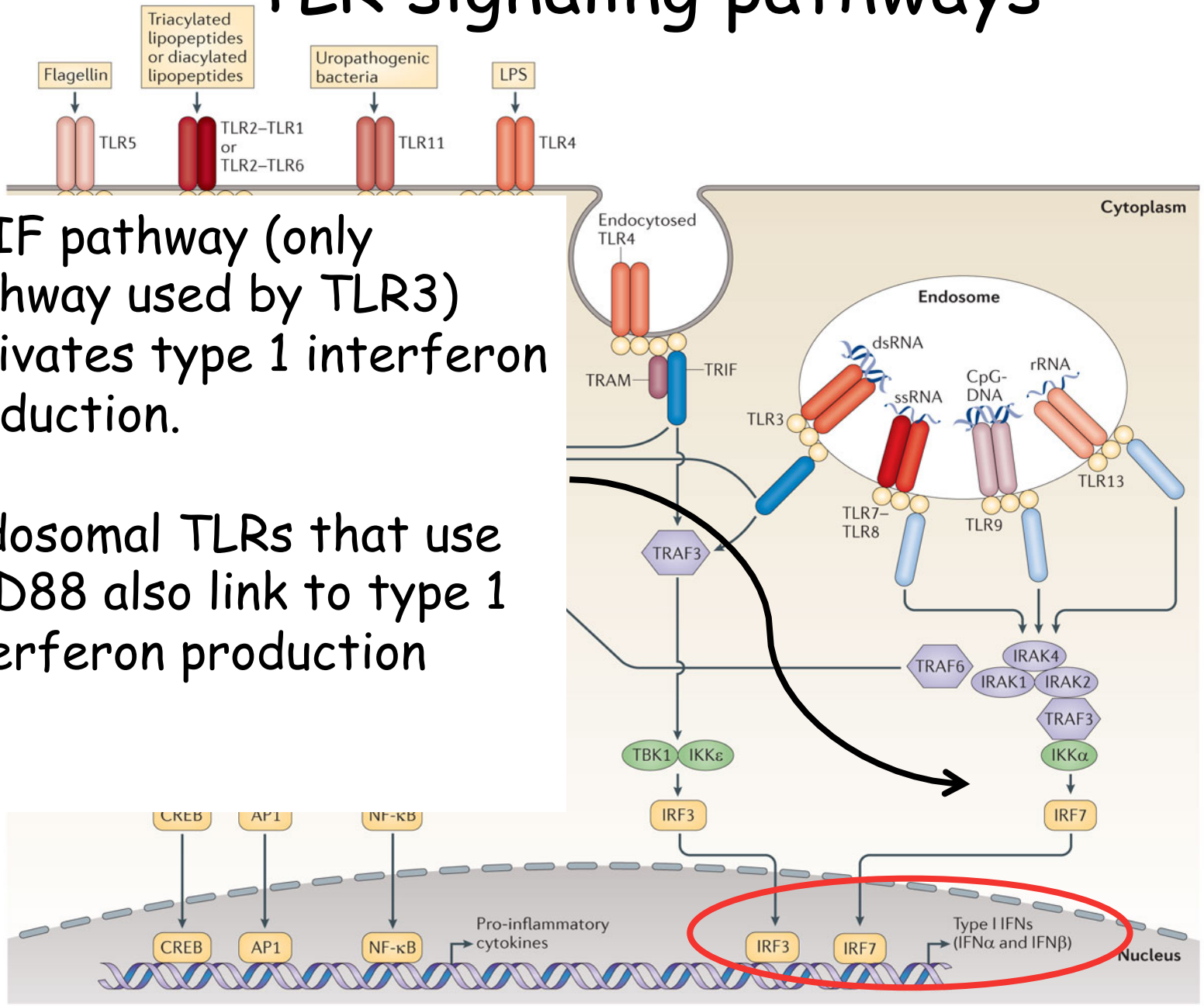
Links to NF-kB activation through IKK degradation

Cell surface receptors also activate MAPK pathways

TLR signaling pathways

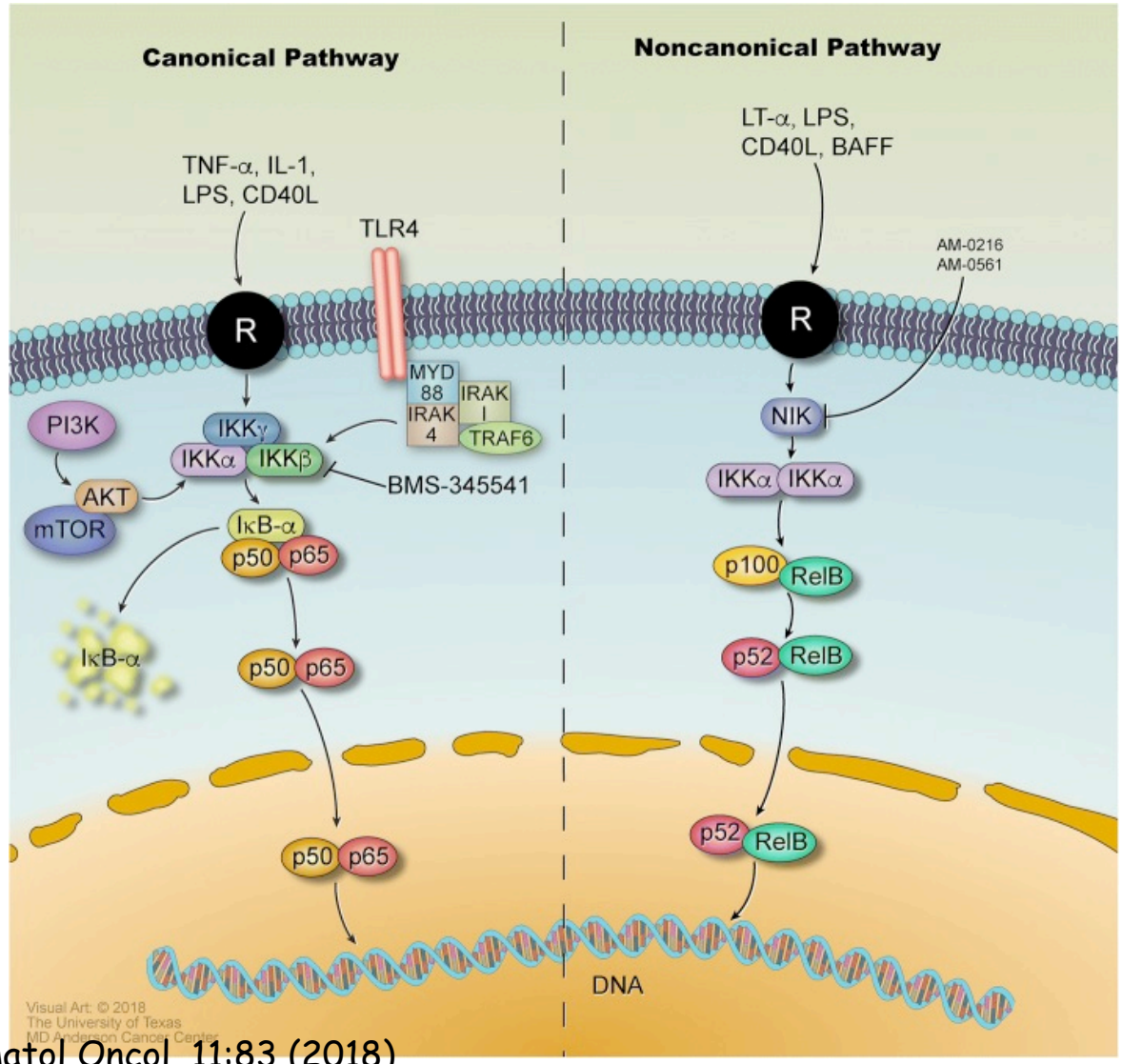
TRIF pathway (only pathway used by TLR3) activates type 1 interferon production.

Endosomal TLRs that use MyD88 also link to type 1 interferon production



Pathways of NF-κB activation

NF-κB is a family of transcription factors: p50, p52, p65 (Rel-A), c-Rel, Rel-B; plus inhibitors (I-κB)



Balaji et al, J Hematol Oncol, 11:83 (2018)

Genes regulated by NF-κB

Cytokines
TNF-α, TNF-β
IL-1-α, IL-1β
IFN-α, IFN-γ
TRAIL, M-CSF
RANTES
FAS ligand
Lymphotoxin α, β
G-CSF, GM-CSF
IL- 2, IL- 6, IL -8, IL- 9, IL-10,
IL-11, IL-12, IL-13, IL-15
NK4, GCP-2 (CXCL6)
Gro α, Gro γ, Gro-1
ICOS
IL-1 receptor antagonist
IP-10, KC, BMP-2
CCL 15, CCL 22,
CCL 28, CCL 5
CD40 ligand
CINC-1, CXCL 11
ENA-78 (CXCL5) Eotaxin
Erythropoietin
MCP-1/JE, MIP-1 α β
MIP-2, MIP-3 α, Mob-1
Neutrophil- activating peptide 78
NK-1R
Stem cell factor
Angiotensinogen
TCA3
TFF3
TSP-1
TSP-2

Receptors
beta2 microglobulin
μ-opioid receptor 2A
A1 Adenosine receptor
Amiloride-sensitive Na channel
Androgen receptor B 7.1
Bradykinin B-1 receptor
BRL-1, CCR 5, CCR 7, CD 137
CD 154, CD 23, CD 40, CD 48
CD 69, CD 83, CD 95
EGFR
Gal 1 receptor, GFBP-2
Glucocorticoid receptor
IGFBP-1
IL-1 receptor antagonist
IL-2 receptor a-chain
Ig γ4, Ig Cγ1, Ig ε heavy chain
Ig κ light chain, invariant chain II
Lox-1, Mdr 1
MHC class (HLA-B7)
MHC class I (H-2Kb)
Neuropeptode YY1- receptor
NMDA receptor subunint NR-1
NMDA receptor subunit Nod 2
Polymeric Ig receptor
RAF receptor 1,RAGE
T -cell receptor β chain
T -cell receptor *CD*3γ
TNF-Receptor, p75/80
DR4, DR5

Early response genes
p62, p22/RPG1, B 94
Egr-1, TIEG

Transcription factors
NF-KB1, NF-KB2, c-Rel, RelB
IkBα
c-fos, p53, c-myb, JunB
E2F3a, Elf3 , ELYS
ETR 1001
IRF-1, IRF-2, IRF-4, IRF-7
Mail, Nurr1, Stat5a, WT1

Metastasis
ICAM-1, VCAM-1
ELAM-1, E-selectin
Endoglin, Fibronectin
MadCAM-1, P-selectin
Tenascin-C, DC-SIGN
MMP-3, MMP-9, CXCR4
KA11/CD82, uPA

Antiapoptosis
Bcl-2, Bcl-XL, Bfl1/A1
TRAF-1, TRAF-2, TRAF6
c-FLIP, IAPs
Survivin, A20, Bax
Caspase-11
FAP-1, Fas-ligand
IEX-1 L, Nr13

Angiogenesis
VEGF

Cell proliferation
COX-2, c-myc

Cell cycle
Cyclin D1, P21, GADD 45
Cyclin D2, Cyclin D3

Viruses
HIV-1
EBV wp promoter
HBV pregenomic promoter
HSV, SV-40
Adenovirus (E3 region)
Avian leukosis virus
Bovine leukemia virus
Cytomegalovirus
JC virus, HPV 16, SIV

Proteins involved in antigen presentation
Tapasin
LMP2
TAP 1
Complement B
Complement receptor 2
Complement component 3

Genes regulated by NF-κB (more)

Kinases
PI3K
PIK3
PKC8
MAP 4K1

P450
CYP2C11
CYP2E1

Oxidative stress
XOD
GST
Mn SOD
INOS

Enzymes
γ-GCS
11bGSD2
12-LOX
5-LOX
ABC transporters
ADH
ARFRP1
Aromatase
BACE
Catepsin B and ceramide glycosyl transferase
Collagenase 1
CRAD1 and 2
Dihydrodiol dehydrogenase
DT –diaphorase

Enzymes (ctd)
Gelatinase B
GSTP1-1
Guanylyl cyclase α
H+-K+-ATPase a2
Heparanase
HO-1
Hyaluronan synthase
Iodothyronine deiodinase
Lysozyme
MKP-1
N- Acethylglucosaminyl transferase 1
NGAL
NQO1
PDE 7A1
PGES\L-PGDS
Phospholipase A2
Phospholipase C δ1
PIM-1
PTGIS
RACK1
REV3
Seprin 2A
SNARK
TERT
Transglutaminase

Miscellaneous
α-1 acid glycoprotein
a1-Antitrypsin,
a2(1)-Collagen
α-Fetprotein
AMH
Apolipoprotein C III
β-Amyloid
Biglycan
Caveolin-1
Claudin-2
Clone 156
Clone 330
Clone 68
Connexin 32
Epsilon-globin
Factor VIII
Gadd45β
Galectin 3
GIF
GS 3686
HMG-14
K15 keratin
K3 keratin
K3 keratin
K6 keratin

Laminin B2 chain
mCGM3
Mts1
MUC-2
Mx1
Neutrophil gelatinaseassosiated lipocalin
NIF 1
P11
PAI-1
Pax 8
PCBD
Perforin
PGK
PSA
RICK
S100A6 (calcyclin)
Spergen-1
Syndecan-4
TFPI-2
Transferrin
Urokin 16
UBE 2M
UCP-2
Vimentin
Wilms' tumor suppressor gene

Importance of TLR signaling revealed in primary immunodeficiency syndromes

Table 1. PIDs due to genetic defects of NF-κB and TLR signaling

Genetic defect	Inheritance	Typical infections	Autoimmune features	Immunological features
MyD88 dependent				
IRAK4, MyD88	AR	Invasive and recurrent bacterial infections, most commonly *Streptococcus pneumoniae, Staphylococcus aureus,* and *Pseudomonas aeruginosa*	None reported	Impaired TLR and IL-1R responses, reduced $IgM^+IgD^+CD27^+$ B cells, impaired TI IgM
NEMO (IKKγ)	XL	Bacterial, fungal, mycobacterial, and viral infections	Arthritis, hemolytic anemia, inflammatory bowel disease-like colitis	Impaired TLR and IL-1R responses, reduced T cell proliferative responses, impaired TI antibodies
IKKβ	AR	Bacterial, fungal, and viral infections	None reported	Hypogammaglobulinemia, reduced CD45RO T cells, impaired T cell proliferative responses
IκBα	AD	Recurrent bacterial infections, pneumocystis pneumonia, chronic mucocutaneous candidiasis	Colitis, recurrent diarrhea	Impaired TLR and TNF-α responses, reduced T cells TI antibodies
MyD88 independent				
TBK1, TLR3, TRAF3, TRIF, UNC93B	AD or AR (TLR3, TRIF) AD (TBK1, TRAF3) AR (UNC93B)	HSV-1 encephalitis	None reported	Impaired TLR3 stimulation of type I interferon

Maglione et al., Annal NY Acad Sci, 1356:1 (2015)

Sepsis Syndrome

- Bacterial septicemia leads to activation of TLRs on monocytes in the blood
- Systemic release of TNF and IL-1 leads to "inflammation" all over the body
- Often referred to as "cytokine storm" or SIRS
- Shock from loss of blood pressure (vasodilation and leakage of fluid into tissues)
- Damage to lung endothelium → ARDS
- Damage to kidney endothelium → renal failure
- TLRs also induce coagulation (via tissue factor)
- The combination of effects can lead to multi-organ failure and death
- Can also occur with tumor lysis

Sepsis Syndrome - cytokines

Table I

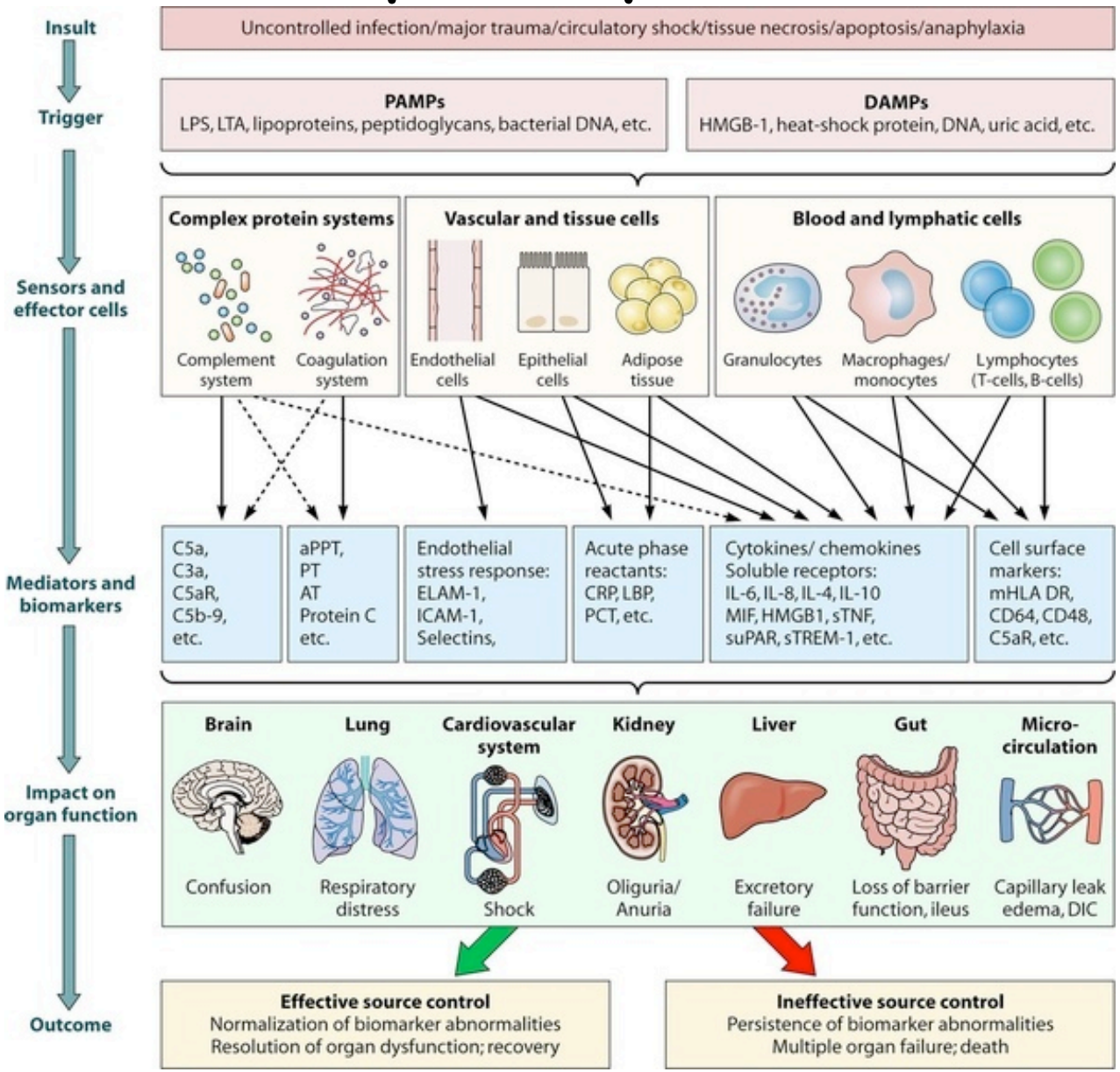
Role of major pro-inflammatory and anti-inflammatory cytokines in sepsis.

Cytokine	Family	Cell origin	Function	Role in sepsis
Pro-inflammatory				
IL-1β	IL-1	Macrophages, monocytes	Cell proliferation, differentiation, apoptosis	Unknown
IL-6	IL-6	T-cells, macrophages, endothelial cells	Cell growth, differentiation, cytokine production	Disease severity, mortality, biomarker
IL-8	CXC	Macrophages, epithelial cells, endothelial cells	Chemotaxis, angiogenesis	Mortality, biomarker
IL-12	IL-12	Dendritic cells, macrophages, B-cells	IFN-γ production, TNF-α production, Th1 differentiation	Unknown
IL-17	IL-17	Helper T-cells	Cytokine/chemokine production, anti-tumor immunity, autoimmunity	Controversial
IL-18	IL-1	Macrophages, monocytes, dendritic cells	IFN-γ production, anti-microbial immunity	Disease severity, biomarker
IFN-γ	IFN	T-Cells, NK cells, NKT cells	Anti-infection, anti-tumor immunity, autoimmunity	Unclear
GM-CSF	IL-4	T-Cells, macrophages, mast cells, endothelial cells, fibroblasts	Cell growth, survival, granulocyte development, monocyte development, autoimmunity	Unclear
TNF-α	TNF	Macrophage, CD4 T-cells, NK cells	Cytokine production, cell proliferation, apoptosis, anti-infection, tumor necrosis	Disease progress, survival, biomarker
Anti-inflammatory				
IL-1Ra	IL-1	Macrophages, monocytes, dendritic cells	IL-1α inhibitor, IL-1β inhibitor	Unknown
IL-4	IL-4	T-Cells, mast cells, basophils	Cell proliferation, Th2 differentiation	Unclear
IL-10	IL-10	Th2 cells, B-cells, monocytes	Potent inhibitor of pro-inflammatory cytokine production	Disease severity, mortality
IL-11	IL-6	Fibroblasts, neurons, epithelial cells	Induction of Th2 cytokines, inhibition of Th1 cytokine production	Unknown
IL-13	IL-4	Th2 Cells	Inhibitor of pro-inflammatory cytokine production	Unknown
TGF-β	TGF-β	Macrophages, T-cells	Proliferation, apoptosis, differentiation, migration, inhibition of pro-inflammatory cytokine production	Unclear

IL: Interleukin; CD: cluster of differentiation; Th: T helper; IFN: interferon; TNF: tumor necrosis factor; TGF: transforming growth factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; CXC: cysteine X cysteine.

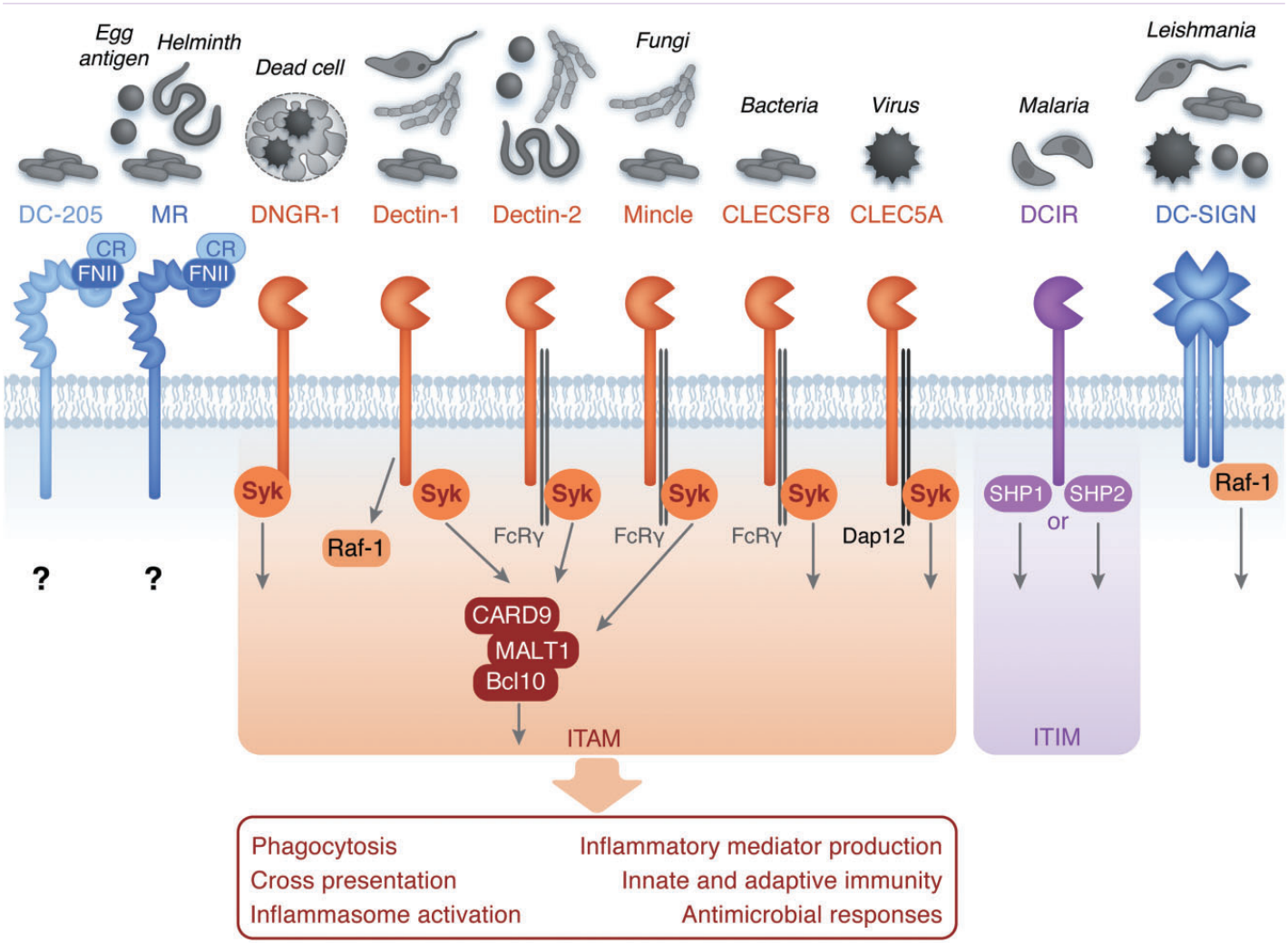
Chaudhry et al., In Vivo, 27:669 (2013)

Sepsis Syndrome



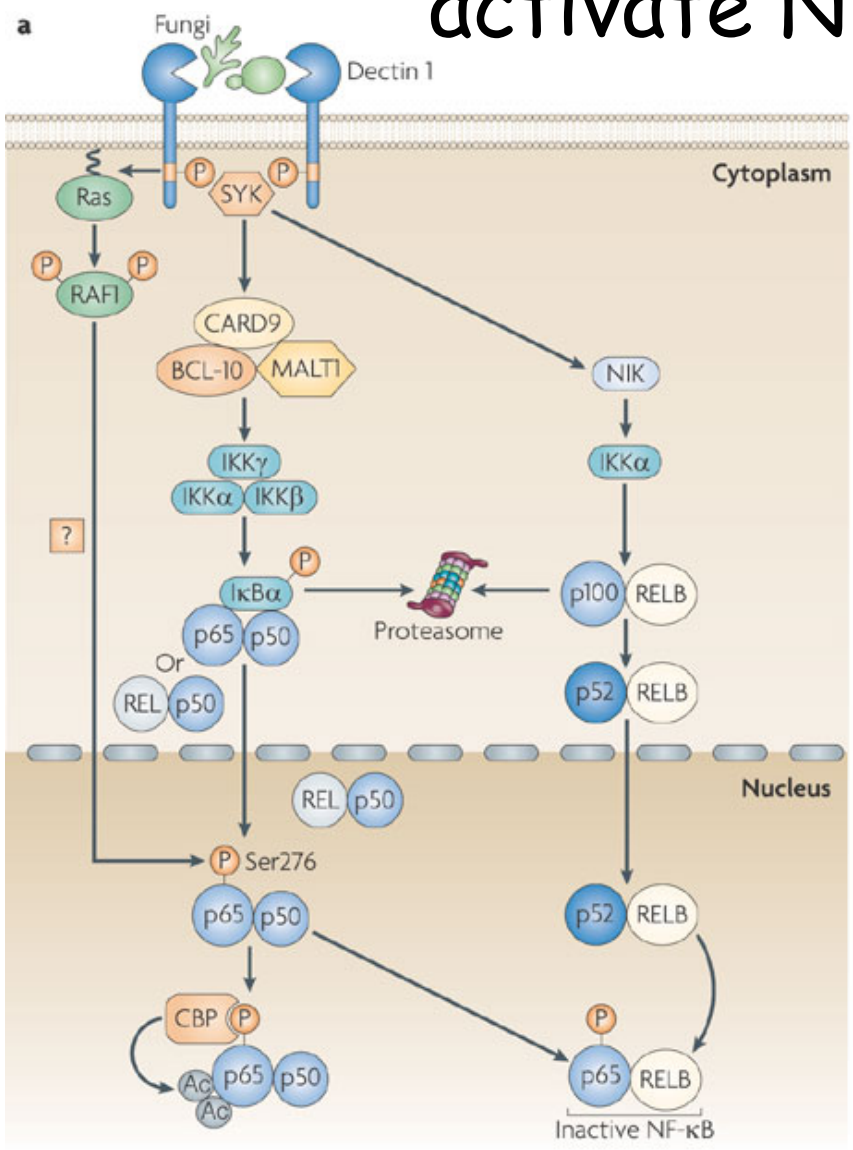
just a nice picture… don't memorize

Examples of C-type lectin receptors



Hoving et al., Cell Microbiol, 16:185 (2014)

CLR signaling through Syk/Card 9 to activate NF-κB

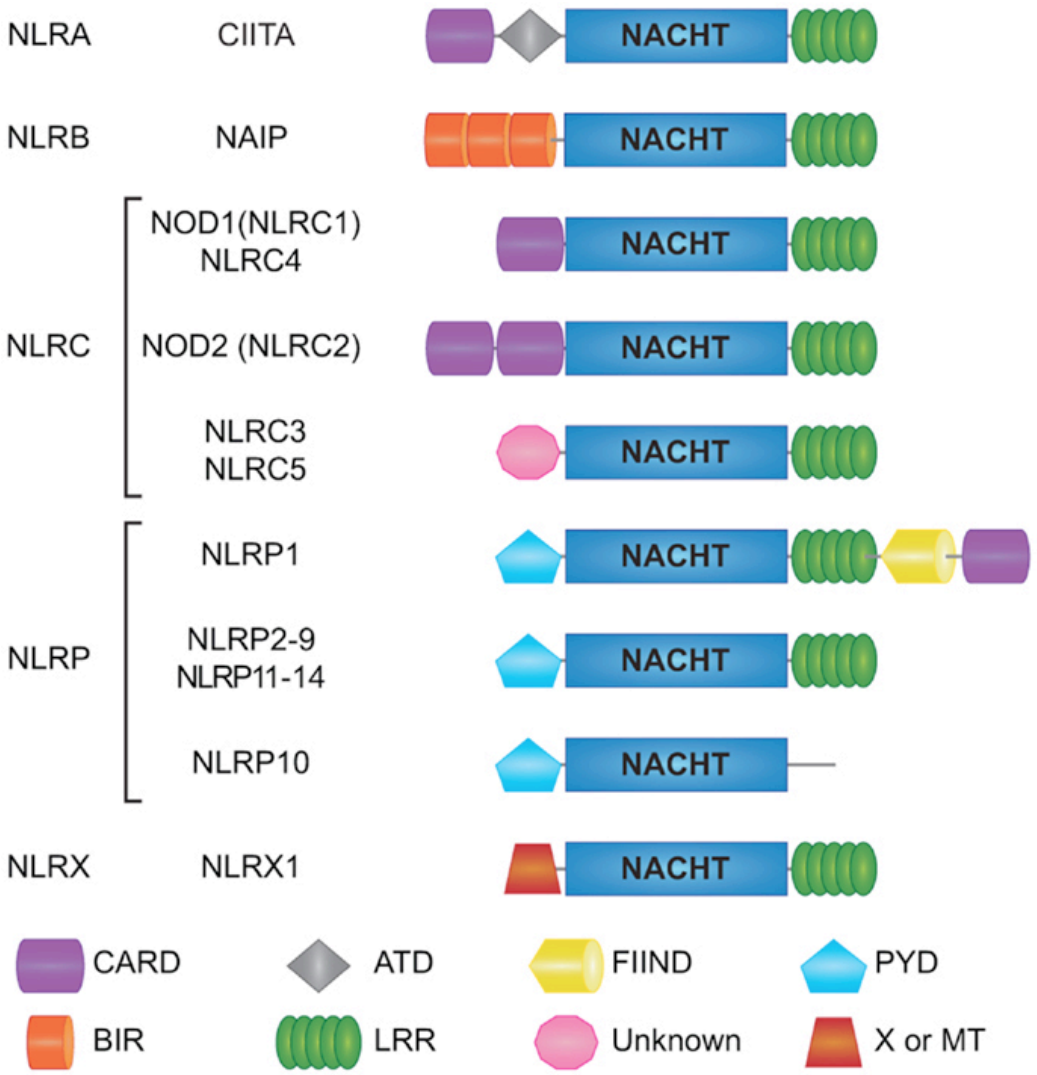


- Genetic deficiency of any components of the CLR pathway (dectin-1, CARD9) lead to increased susceptibility to fungal infections.
- Also, various autoimmune disorders (IBD)

Geijenbeek and Gringhuis, Nat Rev Immunol, 9:465 (2009)

Nod-like receptors (NLRs)

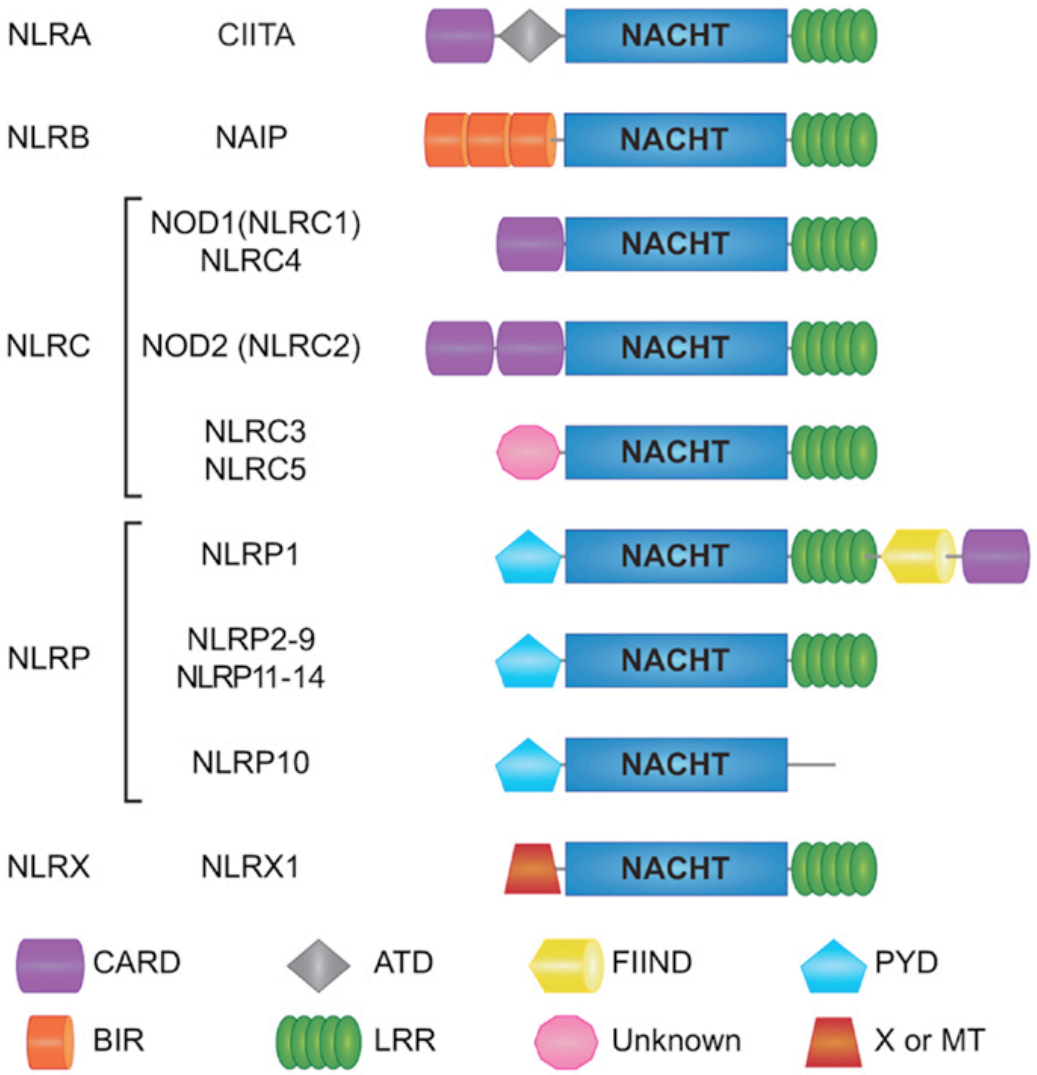
- Nucleotide-binding and oligomerization domain
- Cytosolic
- At least 22 members
- Recognize microbial and intracellular components
- Synergize with TLRs



Saxena and Yeretssian, Front Immunol 5:1 (2014)

Nod-like receptors (NLRs)

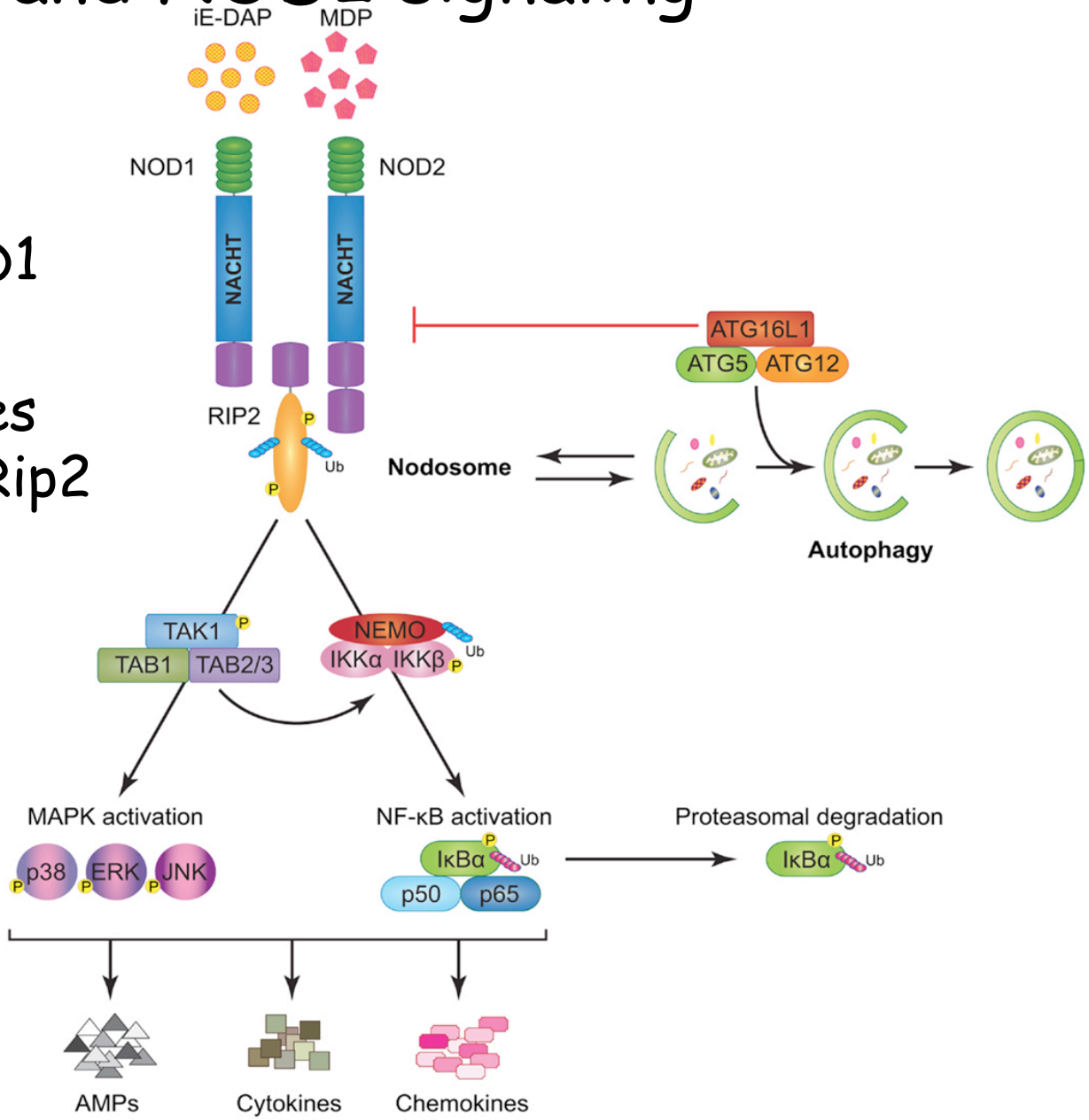
- NAIP family, bacterial components such as flagellin
- NLRC family, bacterial components such as MDP, peptidoglycan, iE-DAP
- NLRP family, bacterial components, LPS, toxins, and DAMPs (uric acid) and fibers (asbestos)



Saxena and Yeretssian, Front Immunol 5:1 (2014)

NOD1 and NOD2 signaling

- MDP induces dimerization of intracellular NOD1 and NOD2
- signaling resembles TNF-R pathway (Rip2 kinase)
- MAPK and NF-κB pathways

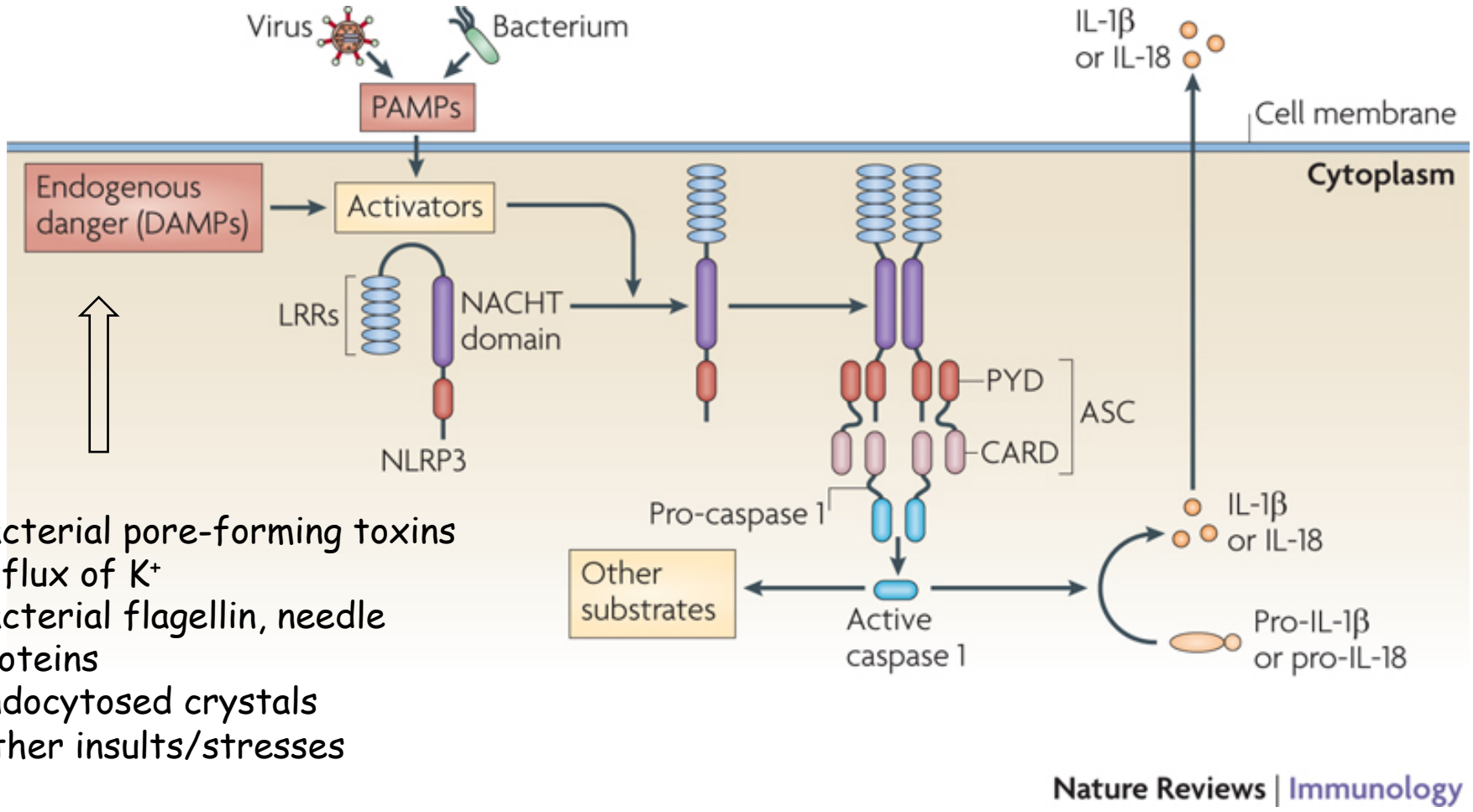


Saxena and Yeretssian, Front Immunol 5:1 (2014)

Common alleles of NOD2 are a genetic risk factor for Crohn's disease

- Several moderately common alleles of the NOD2 gene (7% of total alleles) increase susceptibility to Crohn's disease (a form of inflammatory bowel disease)
- Two copies of these alleles increase susceptibility by 40X
- Evidence that these alleles of are "loss of function" alleles, results in reduced bacterial sensing, increased infections
- NOD1/2 have been shown to have 4 immune functions
  - -activation of inflammatory cytokine gene expression
  - -induction of anti-microbial peptide synthesis by Paneth cells in intestines
  - -activation of inflammasome
  - -autophagy of bacteria in cytoplasm

NLRP family – inflammasome activation



Bacterial pore-forming toxins
Efflux of K^+
Bacterial flagellin, needle proteins
Endocytosed crystals
Other insults/stresses

Tschopp and Schroder, Nat Rev Immunol 10:210 (2010)

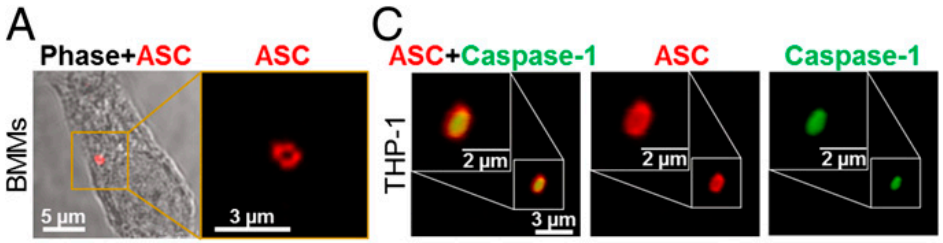
IL-1 family of cytokines

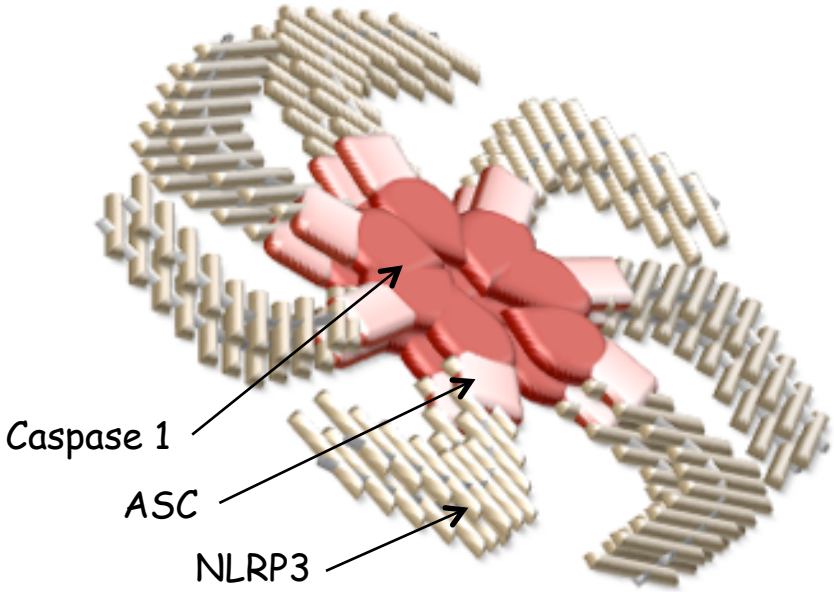
Name	New Name	Receptor Co-Recpt	Function	Released with cell death	Activation protease	Expression	Cells acted on
IL-1α	IL-1F1	IL-1R1 IL-1RAcP	pro-inflammatory	Yes	calpain, NE	macs, DCs, endothelium, keratinocyte fibroblasts	DCs, macs, stromal cells (all types)
IL-1β	IL-1F2	IL-1R1 IL-1RAcP	pro-inflammtory	Yes	Caspase 1	monos, macs and DCs (Langerhan)	DCs, macs, neutrophils, stromal cells
IL-1RA	IL-1F3	IL-R1	ANTI-inflammatory	Yes	none	same cells that produce IL-1α and IL-1β	BLOCKS IL-R1 **Anakinra**
IL-18	IL-F4	IL-18Rα IL-18Rβ	pro-inflammatory	Yes	Caspase 1	monos, macs, intestinal epithelia, skin	Langerhan cells, DCs (migration)
IL-33	IL-1F11	ST2 IL-1RAcP	pro-inflammatory	Yes	Cathepsin G, Caspase 3, 7	Epithelial cells, adipocytes	DCs, to prime Th2 (allergic), macs
IL-36α IL-36β IL-36γ	IL-1F6 IL-1F8 IL-1F9	IL-36R IL-1RAcP	pro-inflammatory	unknown	unknown	monos, macs, epithelial cells	major regulator of skin inflammation
IL-36RA	IL-1F5	IL-36R	ANTI-inflammatory	Yes	none	keratinocytes, kidney, heart, monos, DCs	Blocks binding of IL-36 members
IL-37 IL-38	IL-1F7 IL-1F10	IL-18Rα	ANTI-inflammatory	unknown	none	intestinal epithelia	mainly humans, DCs

Muñoz-Wolf and Lavelle, FEBs J 285:2377 (2018)

NLRP family – inflammasome activation

- Inflammasome activation requires ASC adapter
- Prior exposure to TLRs or NOD1/NOD2 induce synthesis of pro-IL-1 = priming phase
- Oligomerization activates pro-caspase 1 to active protease for IL-1, IL-18 production

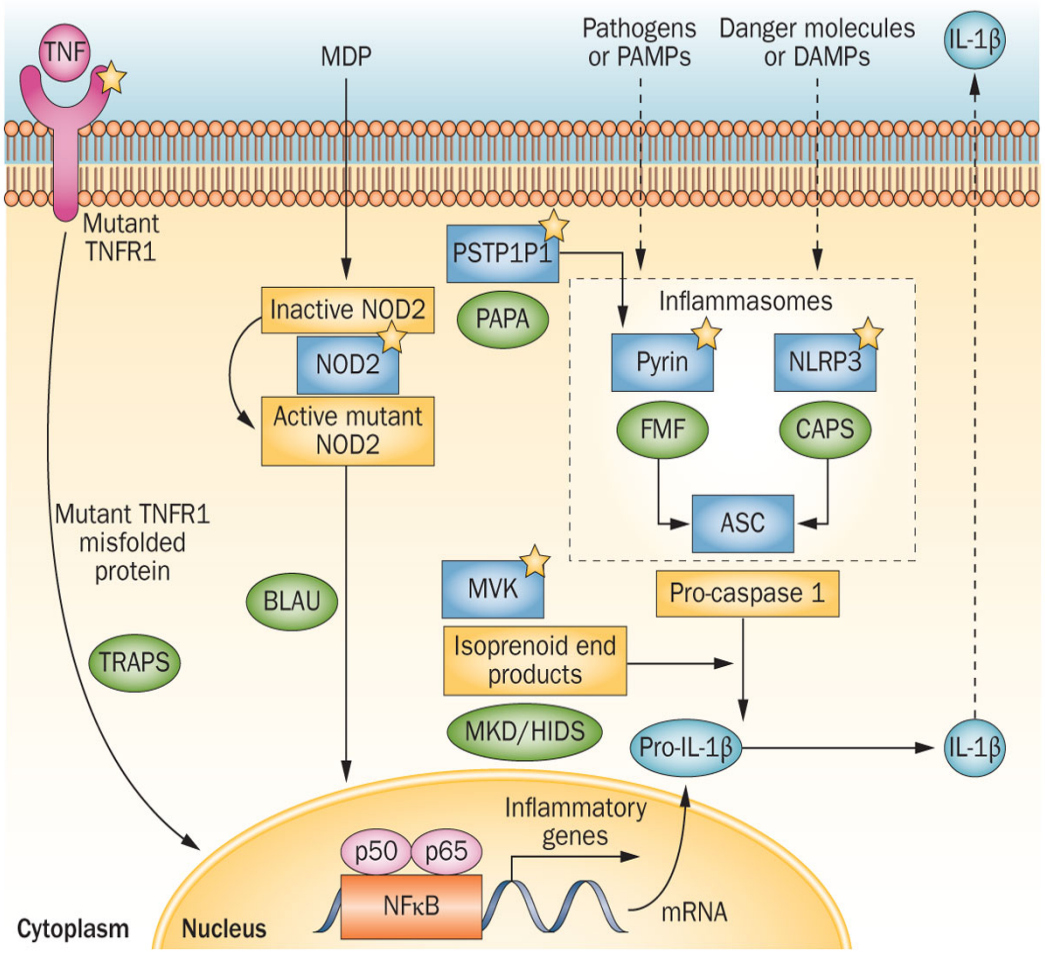




Mann et al, PNAS 11:7403 (2014)

Inflammasome activation in human disease

- Autoinflammatory disorders due to gain of function mutations in NLRP3
- Cryopryrin-associated periodic syndromes (CAPs): Muckle-Wells, FCAS and NOMID
- Autoinflammatory disorders due to gain of function mutations in Pyrin: Familiar Mediterranean Fever (FMF)



Ozen and Bilginer, Nat Rev Rheumatology 10:7135 (2014)

Inflammasome activation -- caspases

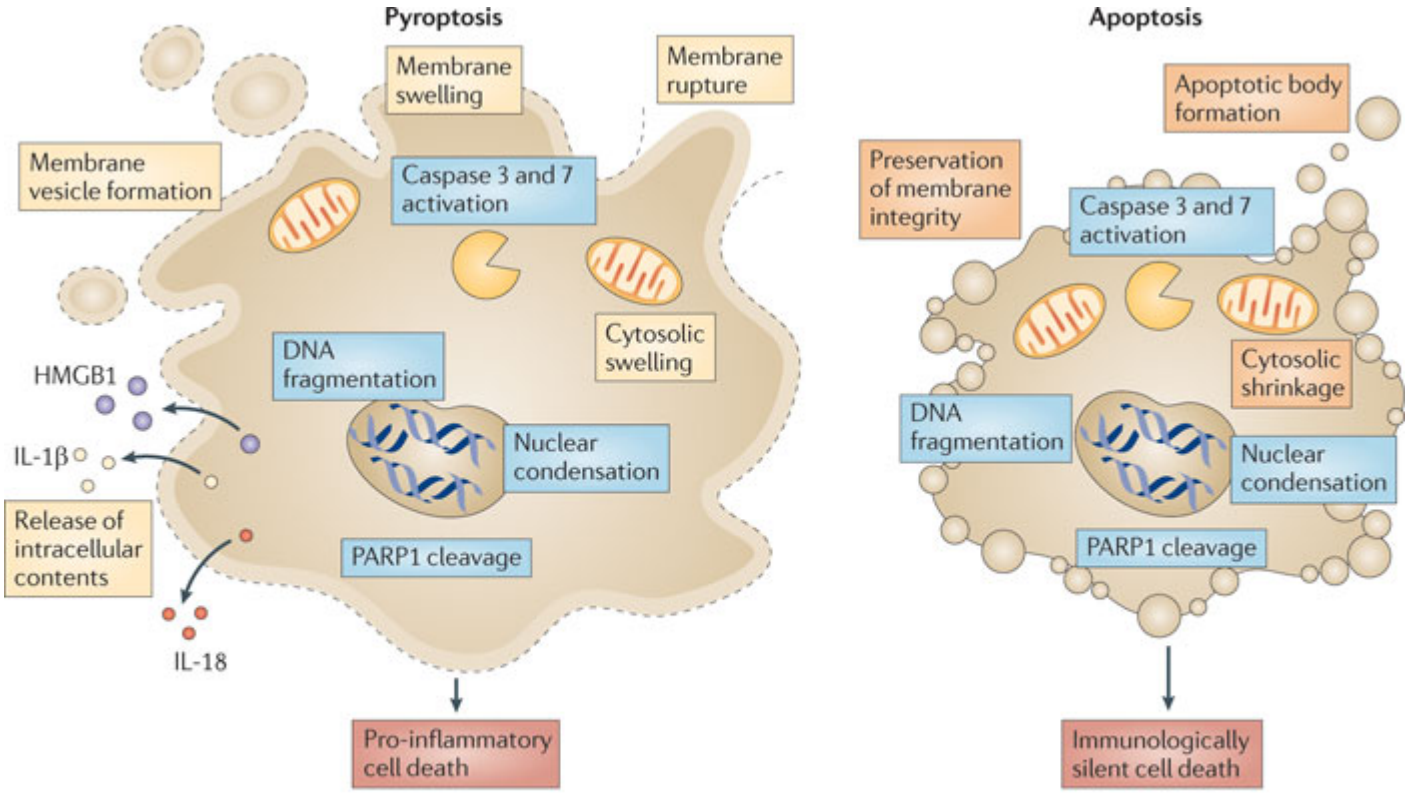
- Cysteine proteases, synthesized as inactive zyomogen, undergo proteolytic activation with inflammasome. Have CARD domain and catalytic domains

- Initiate both IL-1/18 secretion as well as cell death
  "Pyroptosis"

- Initiator (2, 8, 9, 10) and executioner caspases involved in apoptotic pathways (3, 6, 7)

- Inflammatory caspases (1, 11&12 in mouse or 4&5 in human). Also function as direct intracellular sensors of pathogen molecules → **Non-canonical inflammasome activation.**

Cell death associated with inflammasome activation

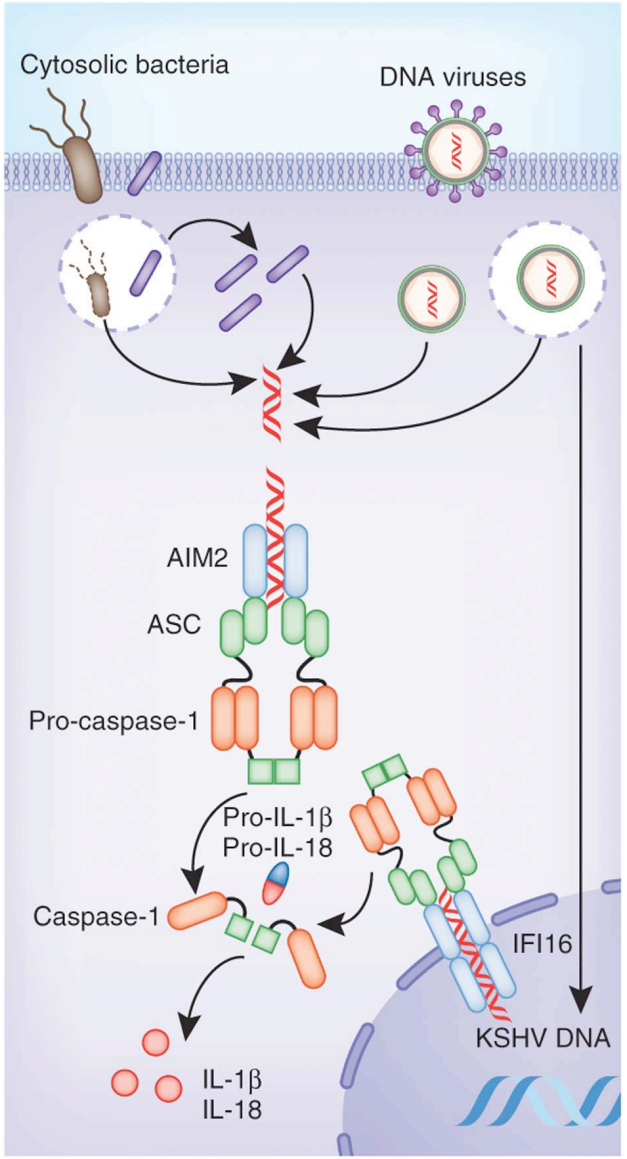


- Pro-inflammatory cell death, release of cytokines (IL-1α)
- Mechanism to limit intracellular bacterial growth
- Mechanism to remove damaged cells

Lamkanfi, Nat Rev Immunol 11:213 (2011)

AIM2 and IFI16 DNA sensors

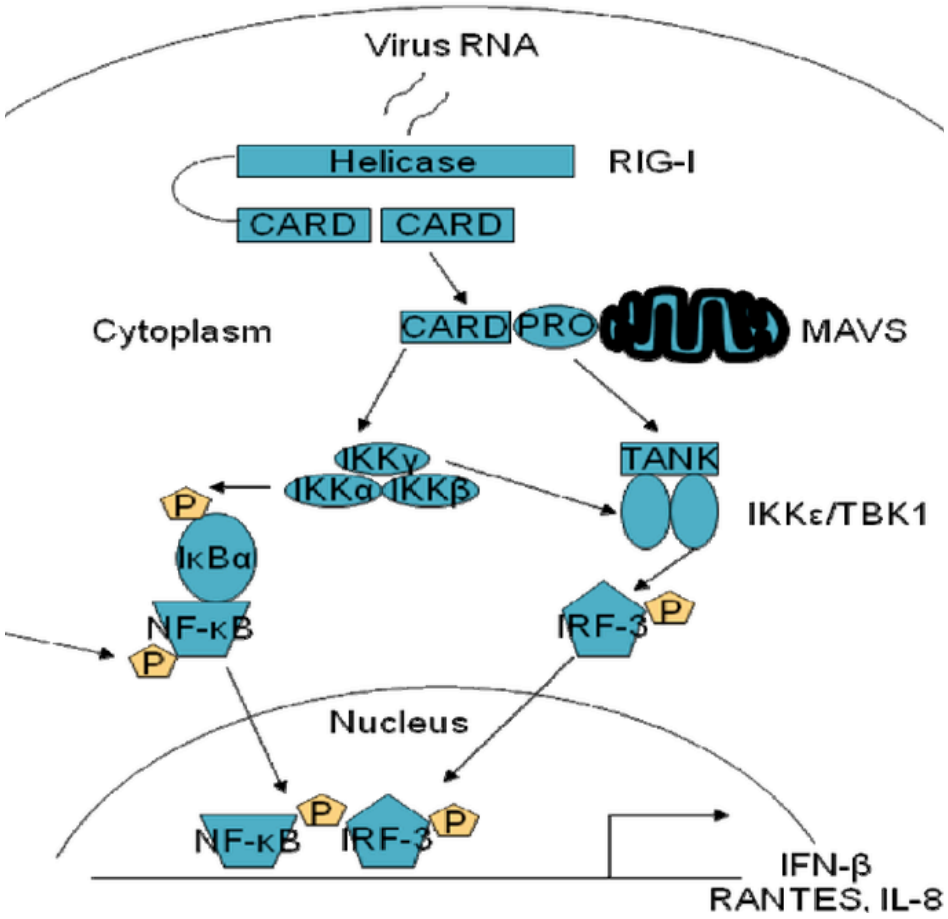
- Examples of non-NLR protein that activates inflammasome
- Sensors of intracellular dsDNA molecules
- Recognition based on length not sequence of DNA
- May play a role in recognition of self-dsDNA in autoimmunity



Rathinam, et al., Nat Rev Immunol 13:333 (2012)

RIG-I RNA sensors

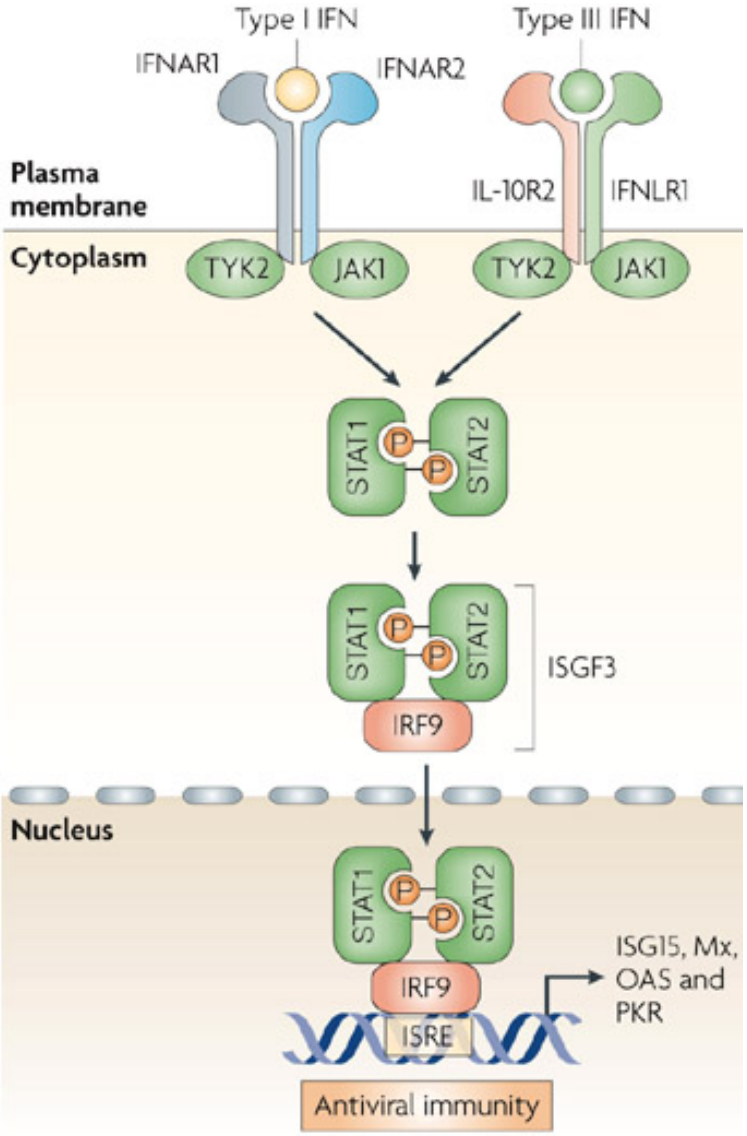
- Two major RLRs: RIG-I and MDA5. Have helicase/CARD domain. Widely expressed
- Sense dsRNA in the cytoplasm. Replicative intermediate of various viral pathogens
- RIG-I an MDA5 induce NF-κB and IRF signaling via CARD domain
- Require MAVS (mitochondrial protein) as adapter for signaling



Kolli, et al., Viruses 4:3551 (2012)

Interferons α/β

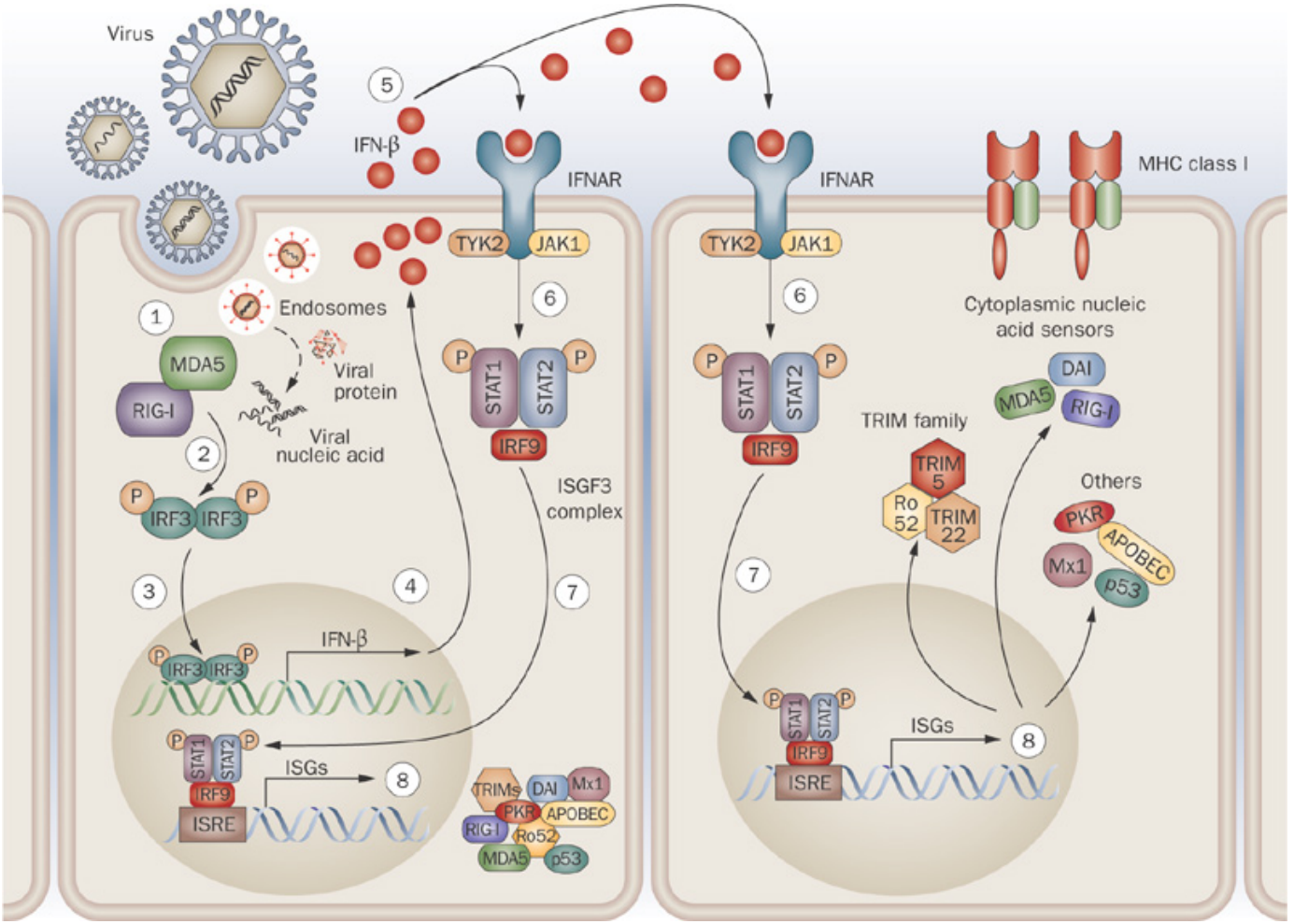
- Type I interferon → signaling through JAK/Stat pathway
- Activate a number of IRFs (interferon response factors)
- Induce transcription of a number of proteins that establish "anti-viral state"
- One infected cell will release type I IFNs to neighboring cells – self amplifying loop
- Type I IFNs implicated in systemic autoimmunity



Sadler and Williams, et al., Nat Rev Immunol 8:559 (2008)

Steps to antiviral immunity

- Upregulation of RNA sensors
- Upregulation of PKR → blocks viral protein synthesis
- Upregulation MHC I
- Increase p53 for cell death
- Upregulation of Apobec3
- Upregulation of Mx GTPase

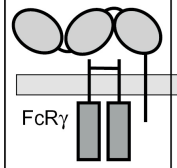
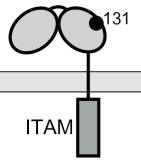
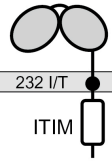
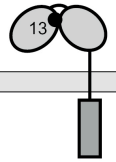
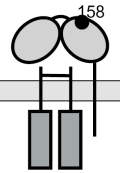
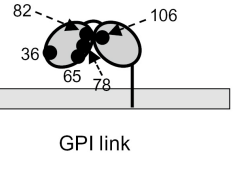


Hall and Rosen, et al., Nat Rev Rheumat 6:40 (2010)

Fc receptors

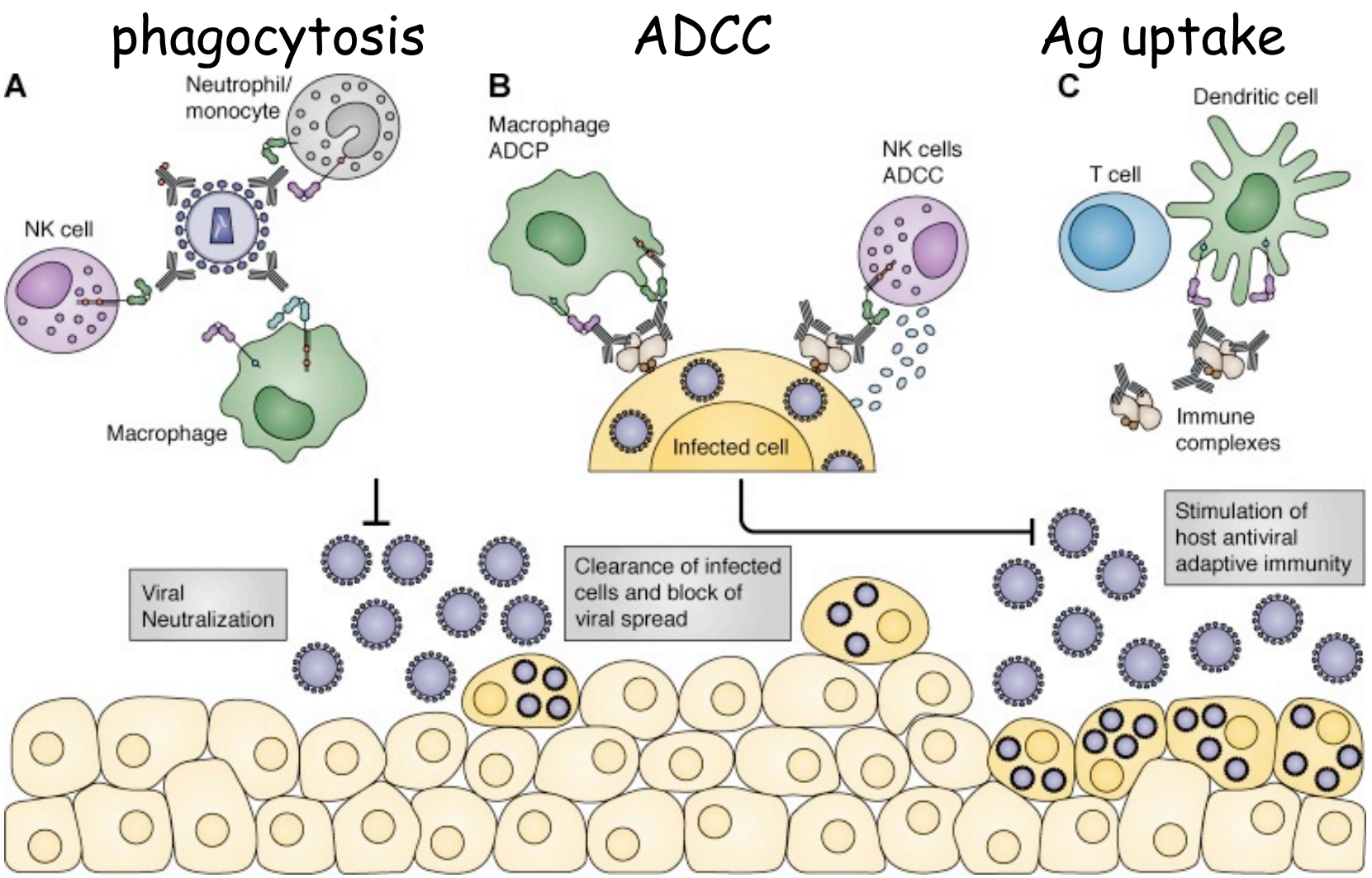
- Recognize Ig bound to particles or antigens
- One Fc for each Ig → FcγR for IgG, FcεR for IgE, etc
- Mediate both particle uptake → phagocytosis and activation of innate immune cell function
- Single inhibitory FcγR → contributor to autoimmunity
- Major receptors that mediate efficacy of therapeutic Abs, such as anti-CD20 (rituximab) via ADCC (antibody dependent cellular cytotoxicity)
- Co-operate with other innate immune receptors to amplify signaling

Fcγ receptors and human disease

	FcγRIA	FcγRIIA		FcγRIIB		FcγRIIC		FcγRIIIA		FcγRIIIB		
												
Alleles		H131	R131	Promoter –386C/ –120A	T232	Q13	stop13	V158	F158	NA1 R36N65A78 D82V106	NA2 S36S65A78 N82I106	SH S36S65D78 N82I106
IgG1	+++	+++	+++	+	+	+	–	+++	++	+++		
IgG2	–	++	+	–	–	–	–	+	–	–		
IgG3	+++	+++	+++	++	++	++	–	+++	+++	+++		
IgG4	+++	+++	++	+	+	+	–	++	–	–		
Expression	Mac, Mono, Neu, DC	Mac, Mono, Neu, Eo, DC LC, Plt		B cell, Mac, Mono, Neu, Baso,DC		Mac, Mono, Neu, NK cell		Mac, Mono, NK cell, DC		Neu, Eo, Baso		
Disease association (polymorphisms)	–	GBS [12], Kawasaki disease [16], Ulcerative colitis [17], Childhood-onset ITP [73]	SLE [13], ITP [14], IgAN [15], APS [74]	SLE [13] (positive association), Lupus nephritis [13] (negative association)	SLE [20], Atopy [75]	Kawasaki disease [22]		IgAN [15],RA severity [30], Childhood chronic ITP [73]	SLE [25], RA [26], Crohn's disease [27], Behcet's disease [28], Severe GBS [29]	IPF [31], ANCA-associated disease [32], Wegener's granulomatosis [32]		
Disease association (copy number variation)						ITP [23], SLE [24]		Anti-GBM disease [8], Sarcoidosis [76]		Glomerulonephritis [9], SLE [9], systemic sclerosis [9], RA [33], IPF [77], Sarcoidosis [76], Kawasaki disease [78]		

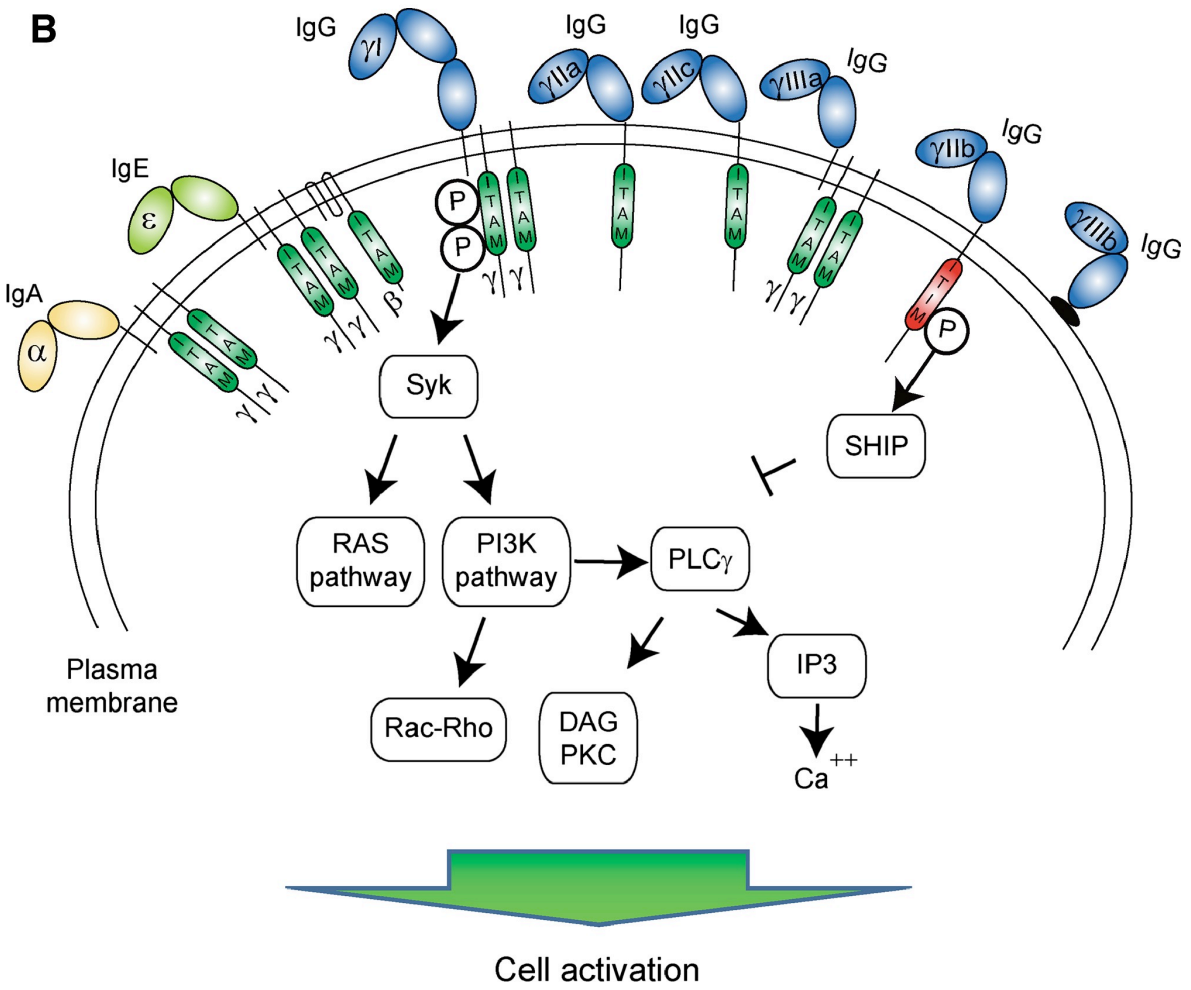
Kaifu and Nakamura, Int Immunol 29:319 (2017)

Effector mechanisms of Fc receptors



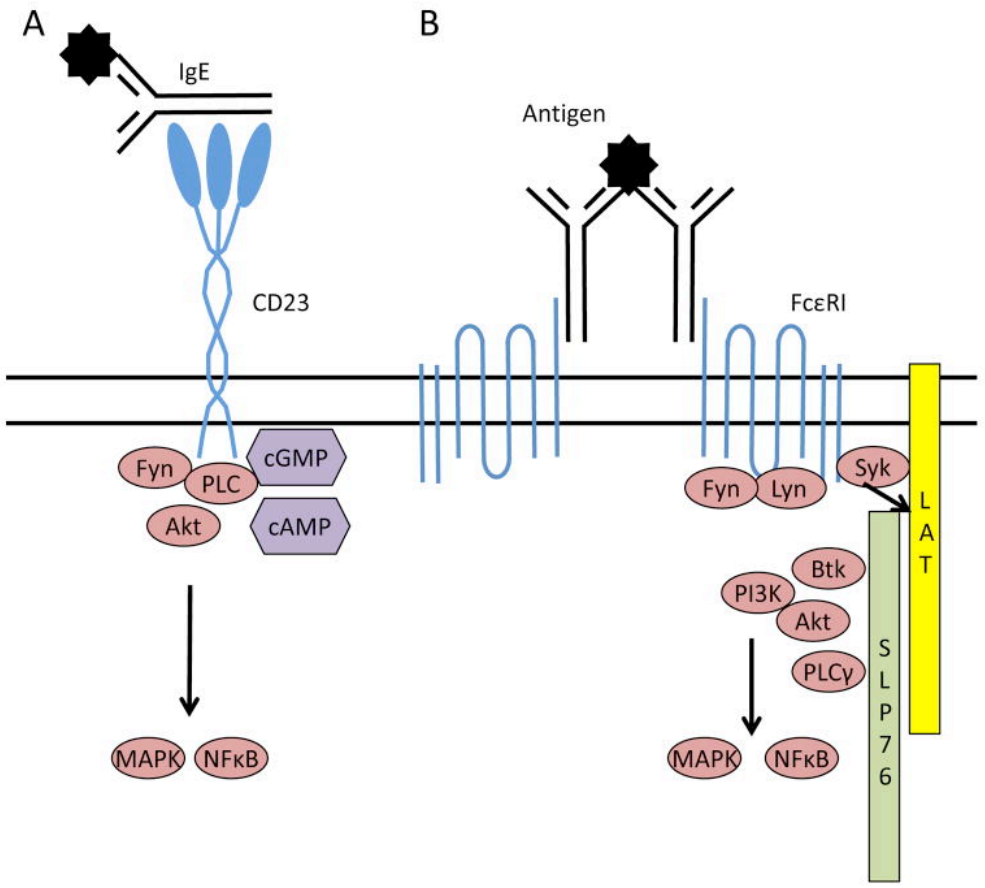
Bournazos, Dilillo, Ravetch, J Exp Med 212:1361 (2015)

Fc receptors signaling pathways -- similar to C-type lectin receptors



van Egmond, Immunol Rev 268:311 (2015)

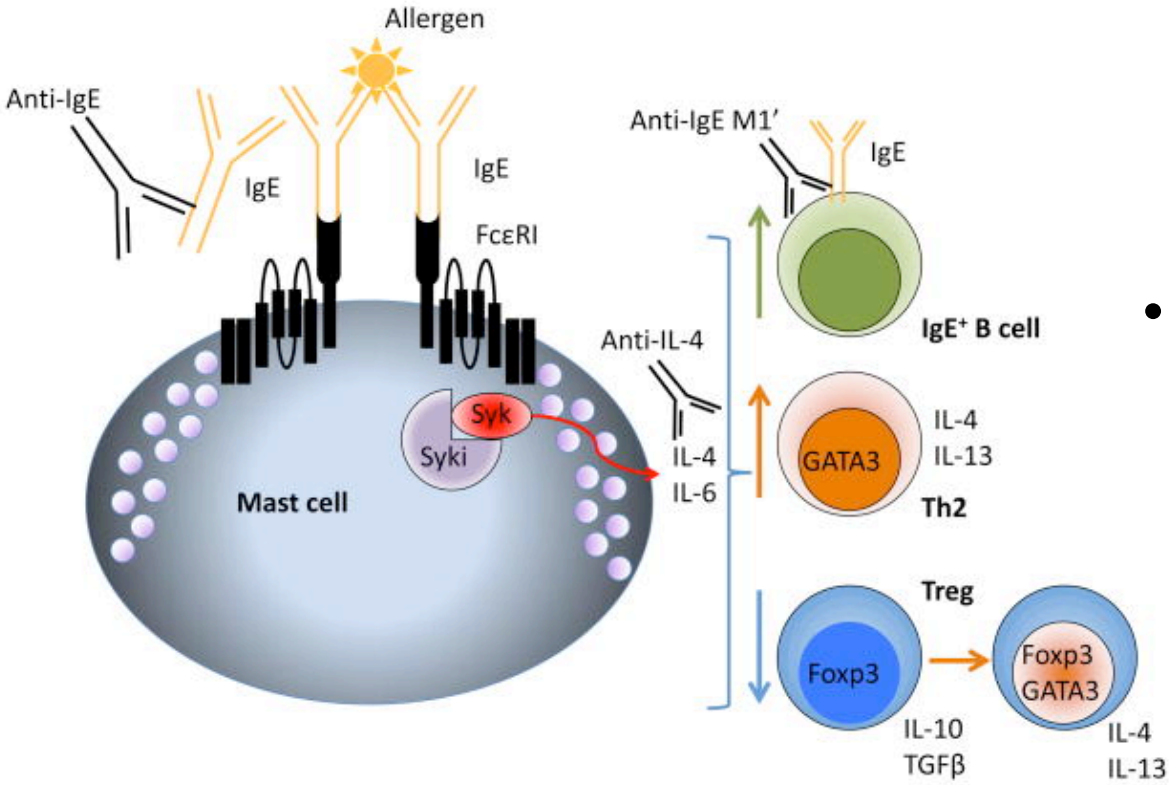
Fcε receptors – major players in allergy



- CD23 -- low affinity
- FceRI -- high affinity
- same signaling path
  PTK to NF-κB

Oettgen and Burton, Curr Opin Immunol 36:109 (2015)

Fcε receptors – major players in allergy

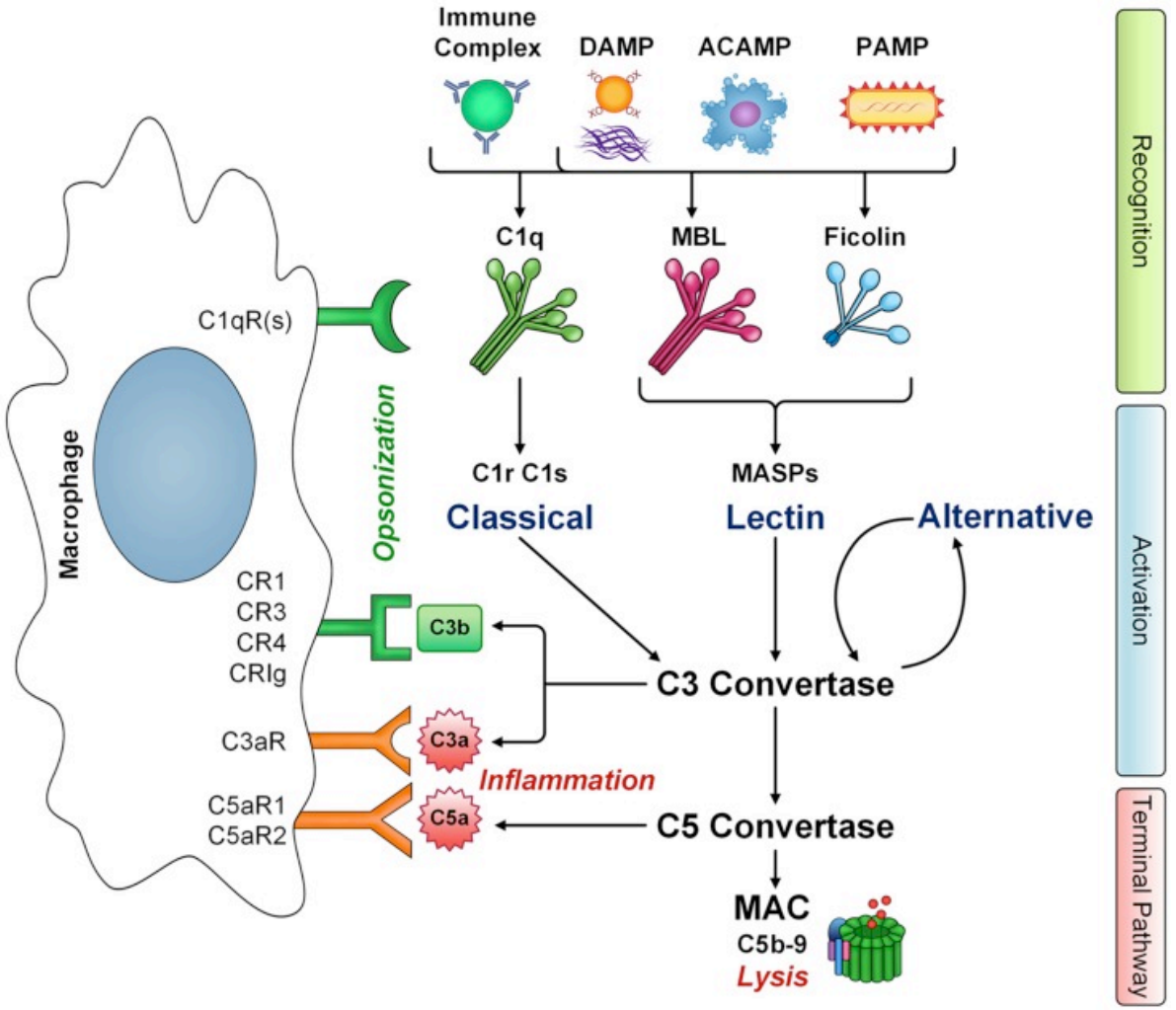


- cytokine and granule release prime Th2 immunity

Oettgen and Burton, Curr Opin Immunol 36:109 (2015)

Complement receptors

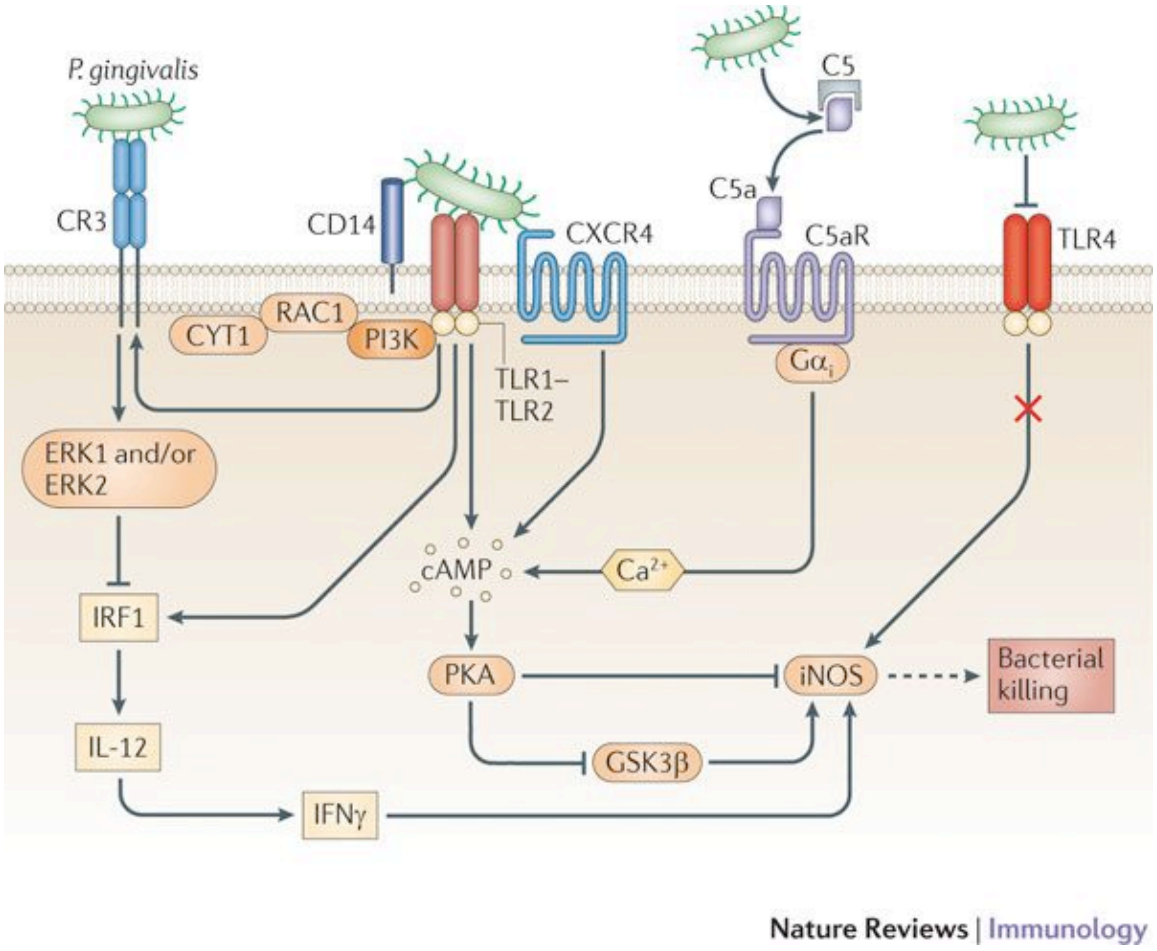
- Similar to FcRs
- Phagocytosis
- Immune activation
- On many innate cell types



Bohlson et al, Frontiers Immunol 5:402 (2014)

Receptor cross-talk in innate immunity

- Additive effect of multiple pathways



Hajishengallis and Lambris, Nat Rev Immunol 11:187 (2011)

TOMORROW:

Cellular effectors of innate immunity