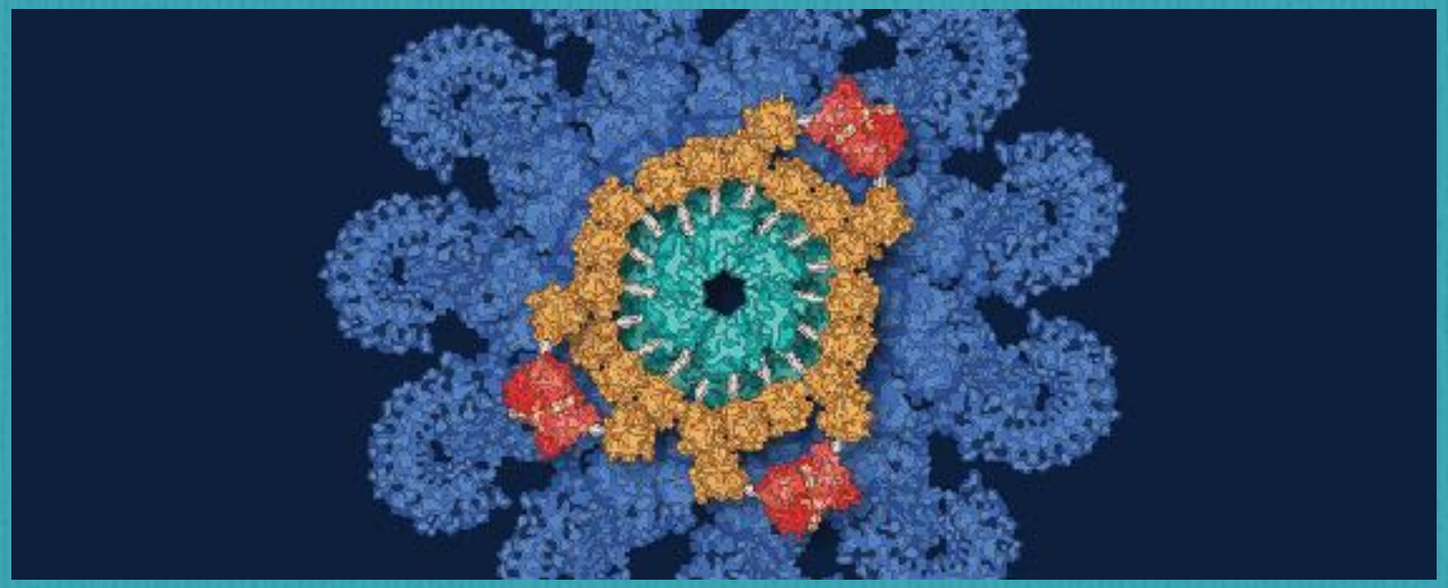
Programa de Pôs-graduação em Imunologia ICB/USP
Disciplina BMI 5904 – Reconhecimento no Sistema Imune

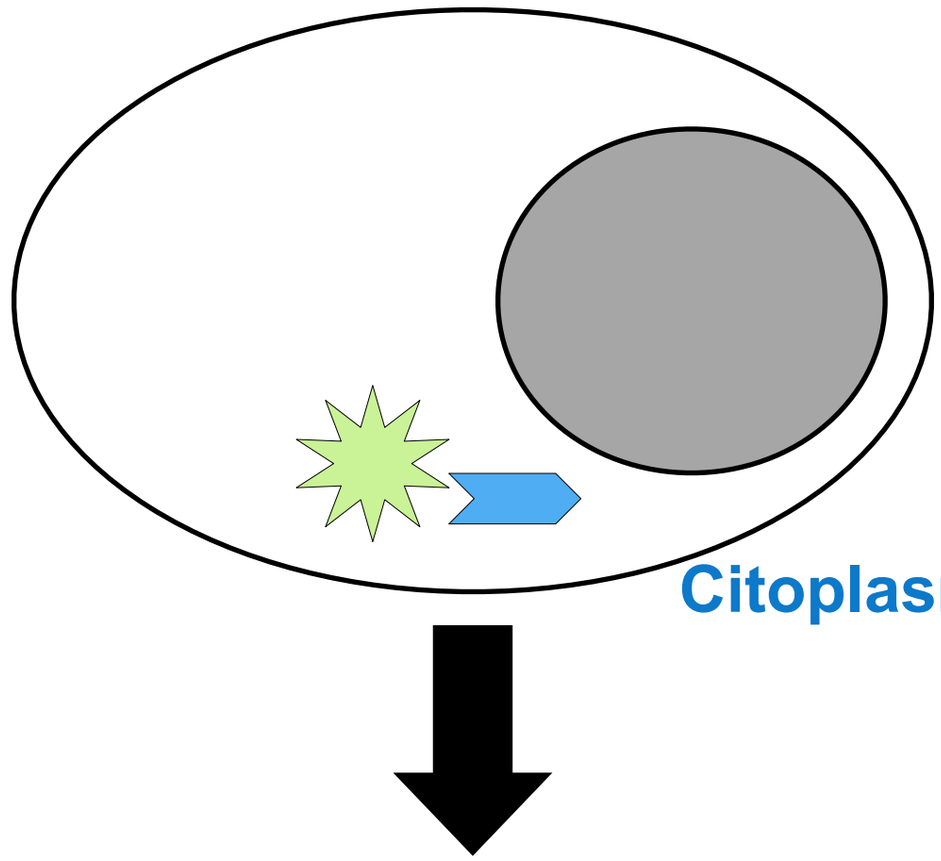


Aula 4

Alessandra Pontillo

Lab. Imunogenetica/Dep.Imunologia/ICB/USP

Cytosolic PRRs



Citoplasmaticos

RECEPTORES DE SINALIZACAO

NACHT and LRRs containing receptors (NLRs)
PYD and HIN containing receptors (PYHIN)
RIG-like receptors (RLRs)

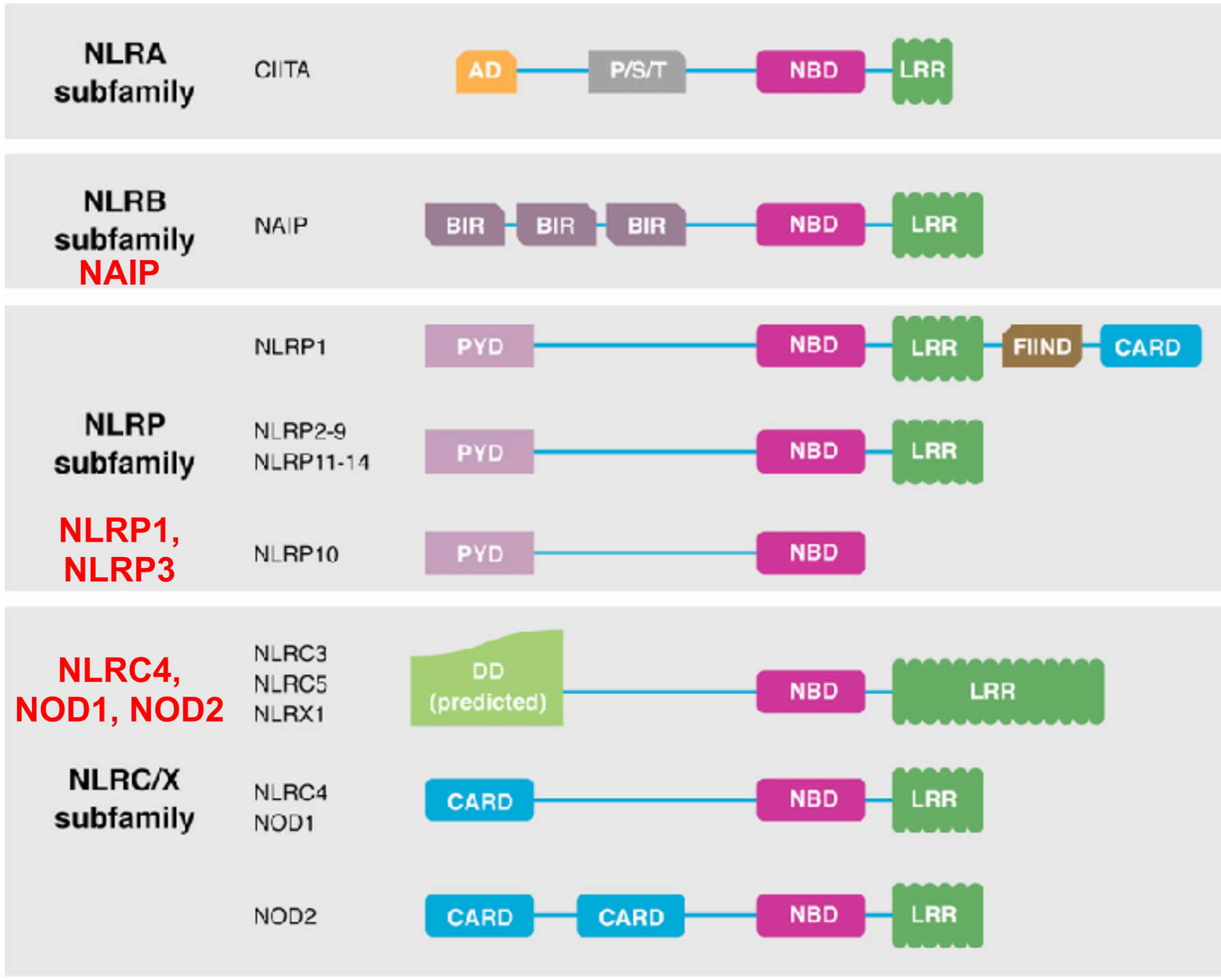
morte (da célula infectada)

Receptores com NBD e LRR (NLRs)

- 22 genes em humanos
- Citoplasmaticos
- NBD e LRR comuns
- N-terminal especifico

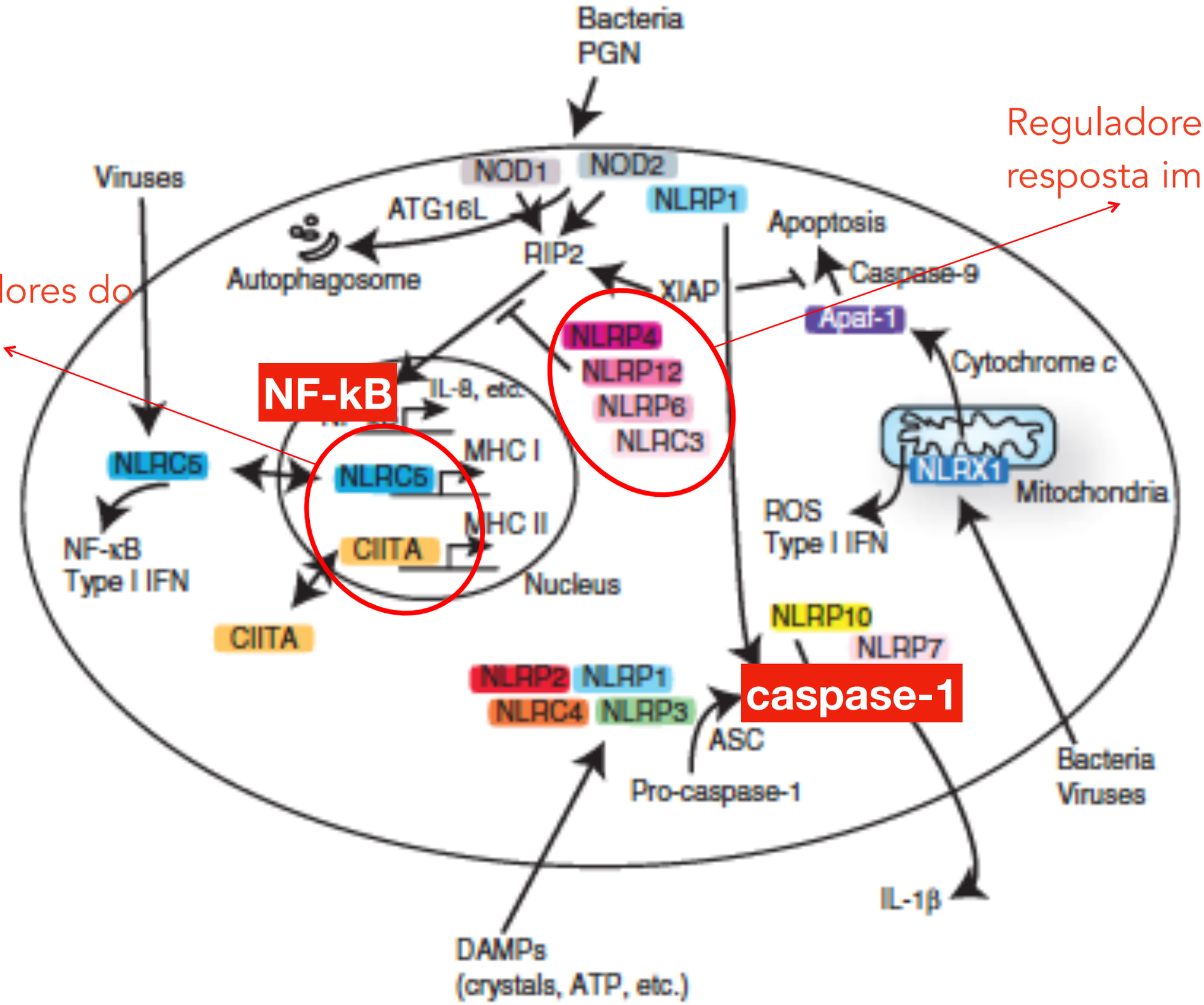
- PYD pirinico (NLRP)
- CARD recrutamento caspase (NLRC)

- LRRs não é domínio de reconhecimento!



Tuncer, 2014

Funções dos NLRs

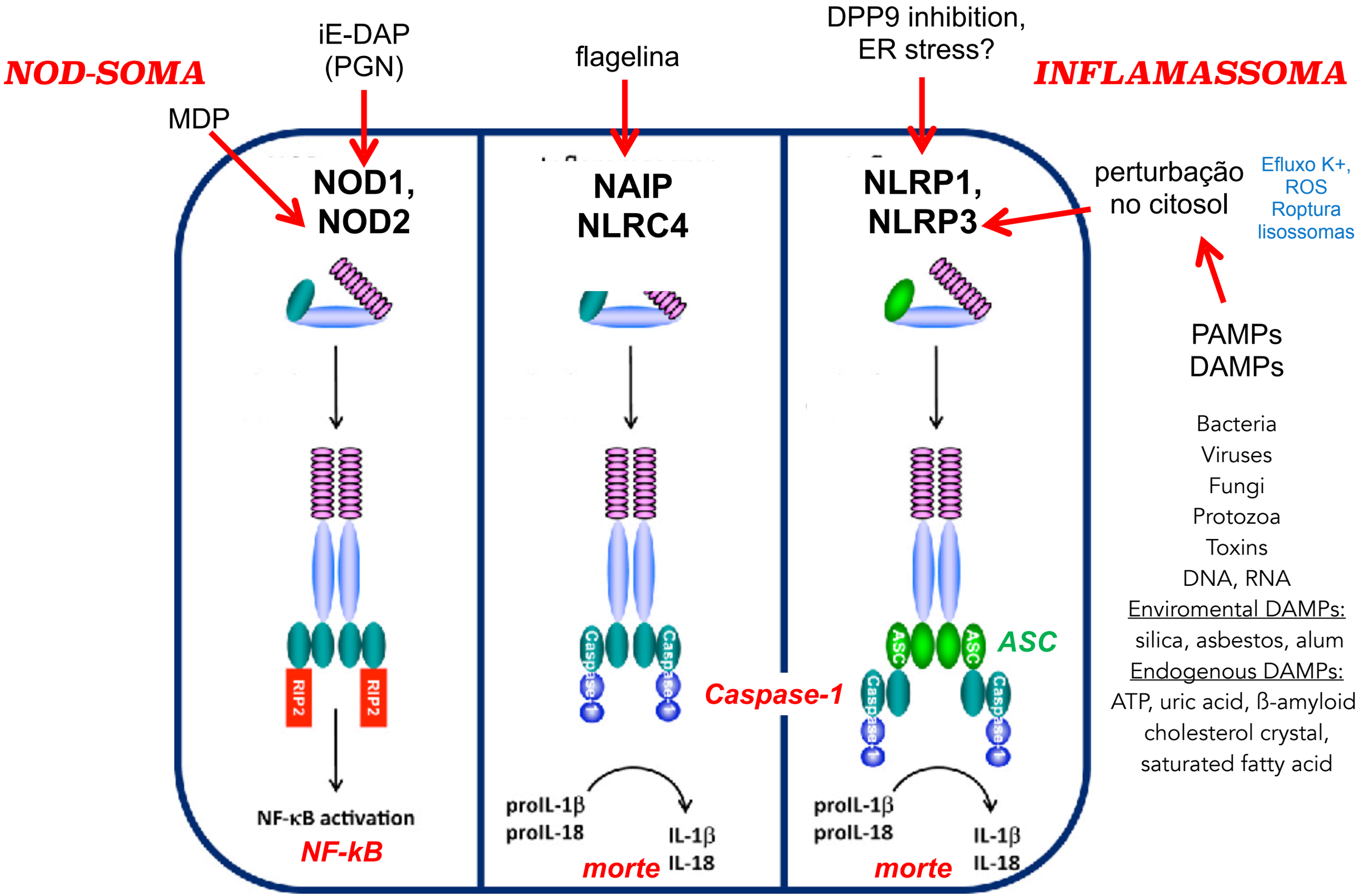


Reguladores da resposta imune

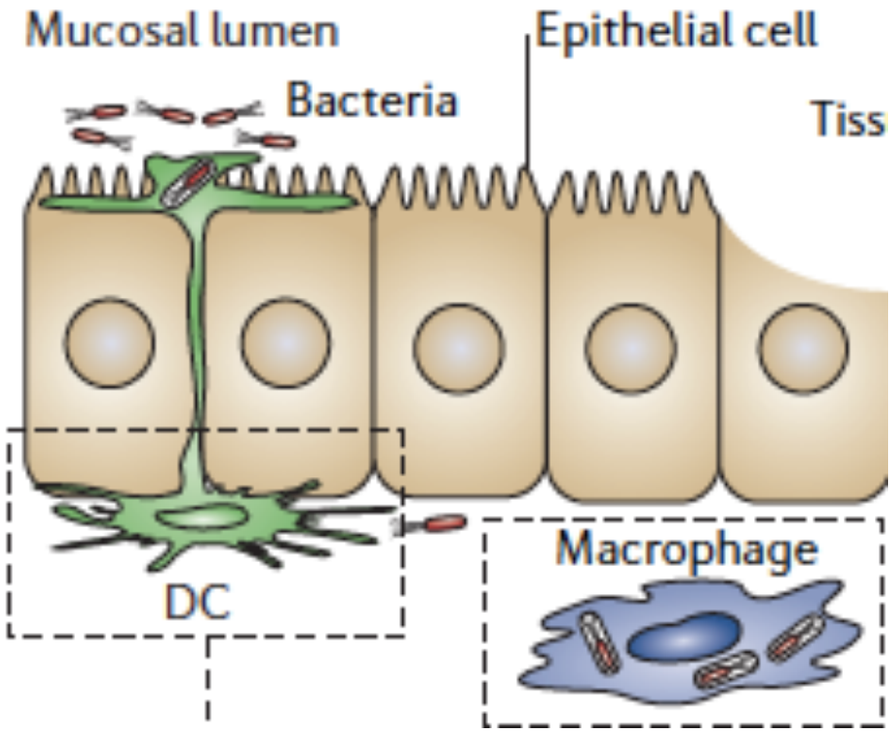
Transativadores do MHC

From Kufer 2011

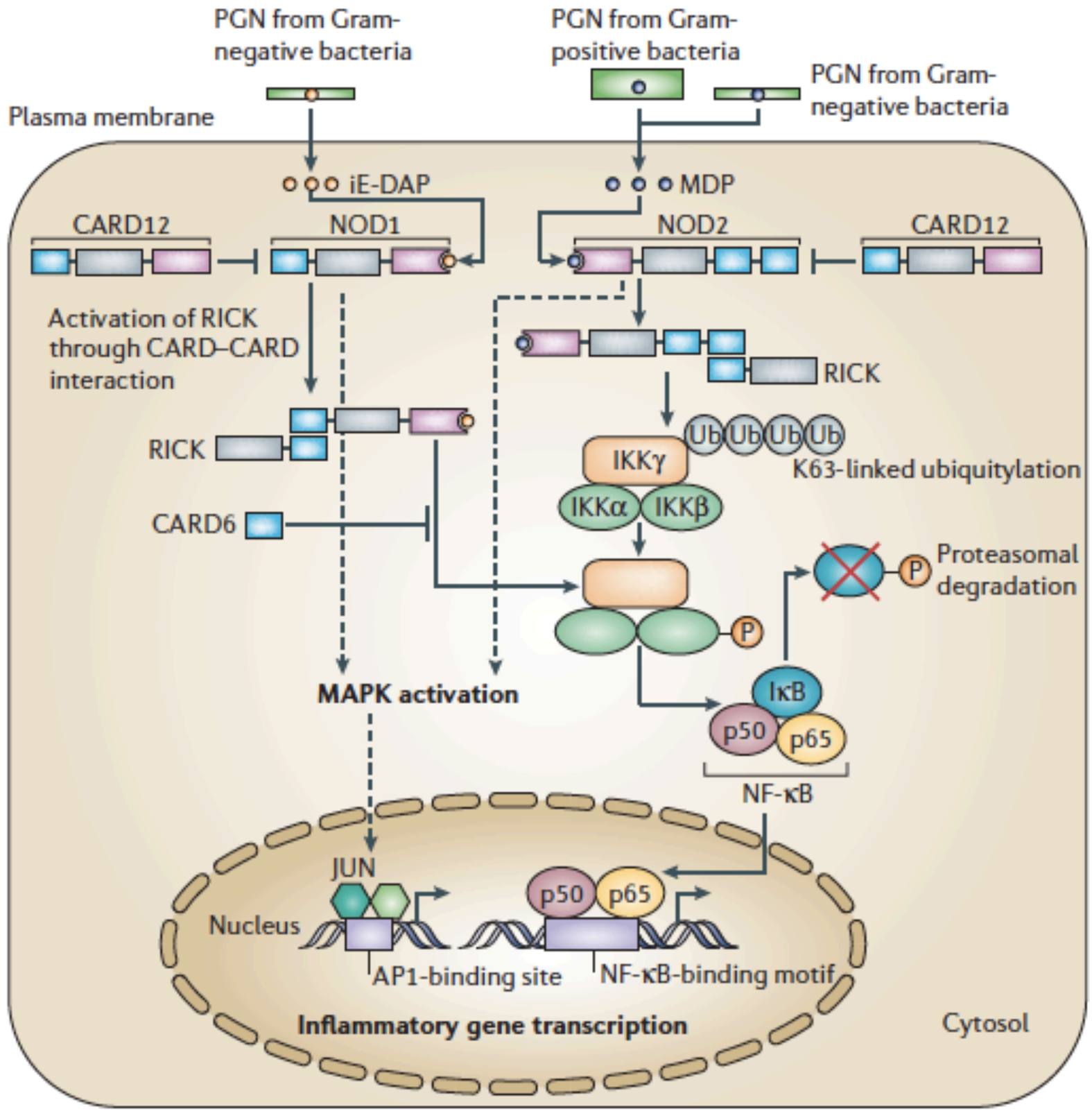
NLRs


NOD-SOMA
INFLAMASSOMA
iE-DAP
(PGN)
MDP
flagelina
DPP9 inhibition,
ER stress?
NOD1,
NOD2
NAIP
NLRC4
NLRP1,
NLRP3
perturbação
no citosol
Efluxo K+,
ROS
Roptura
lisossomas
PAMPs
DAMPs
Bacteria
Viruses
Fungi
Protozoa
Toxins
DNA, RNA
Enviromental DAMPs:
silica, asbestos, alum
Endogenous DAMPs:
ATP, uric acid, ß-amyloid,
cholesterol crystal,
saturated fatty acid
RIP2
RIP2
NF-κB activation
NF-kB
Caspase-1
Caspase-1
Caspase-1
ASC
ASC
ASC
Caspase-1
proIL-1β
proIL-18
IL-1β
IL-18
morte
proIL-1β
proIL-18
IL-1β
IL-18
morte

NODosoma

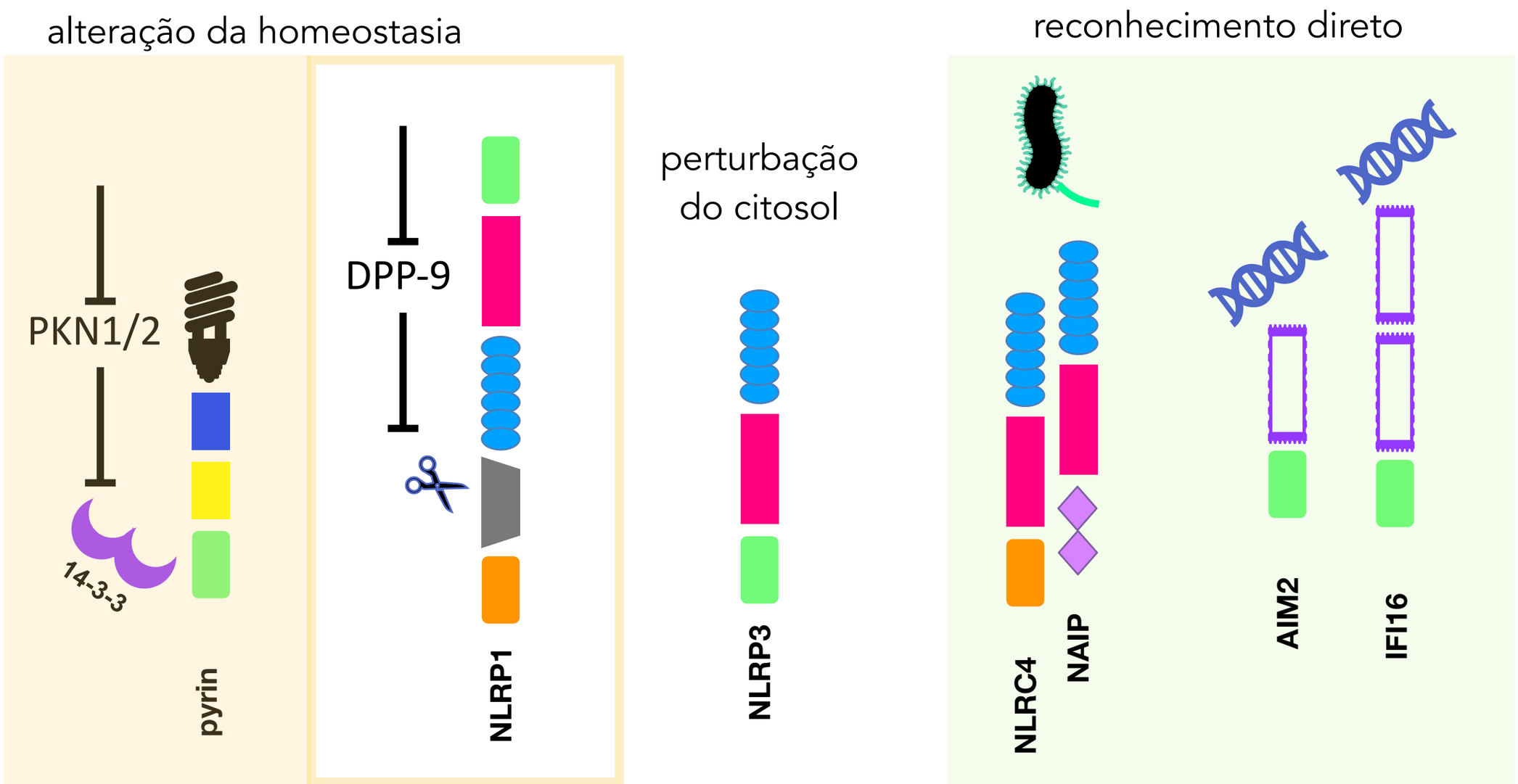


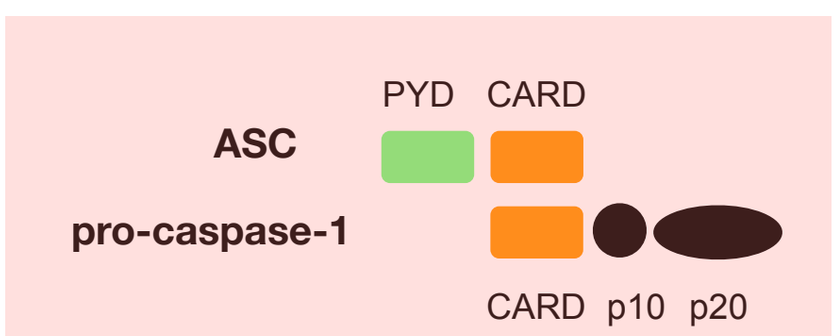
Mutuações Perda-de-função estão associadas a doença de Crohn

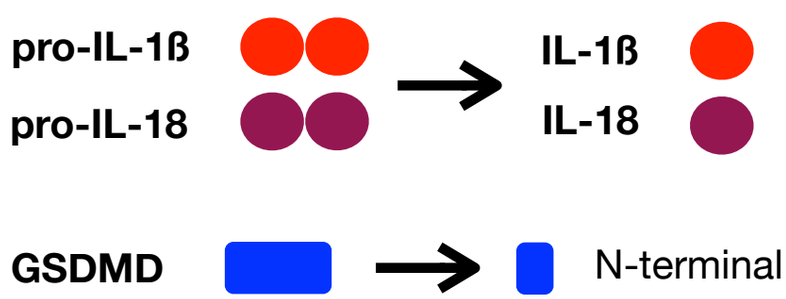


Strober, 2005

Inflamassoma 2022







NLRP3 & PAMPs/DAMPs

DAMPs

Self-derived	ATP, cholesterol crystals, monosodium urate crystals, calcium pyrophosphate dihydrate crystals, calcium oxalate crystals, soluble uric acid, neutrophil extracellular traps, cathelicidin, α-synuclein, amyloid-β, serum amyloid A, prion protein, biglycan, hyaluronan, islet amyloid polypeptide, hydroxyapatite, haeme, oxidized mitochondrial DNA, membrane attack complex, cyclic GMP–AMP, lysophosphatidylcholine, ceramides, oxidized phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine and sphingosine
Foreign-derived	Alum, silica, aluminium hydroxide, nanoparticles, carbon nanotubes, chitosan, palmitate (also self-derived), UVB, imiquimod (R837)/CL097 and resiquimod (R848)

COMO "SENTIR" TUDO ISSO???

NLRP3

PAMPs

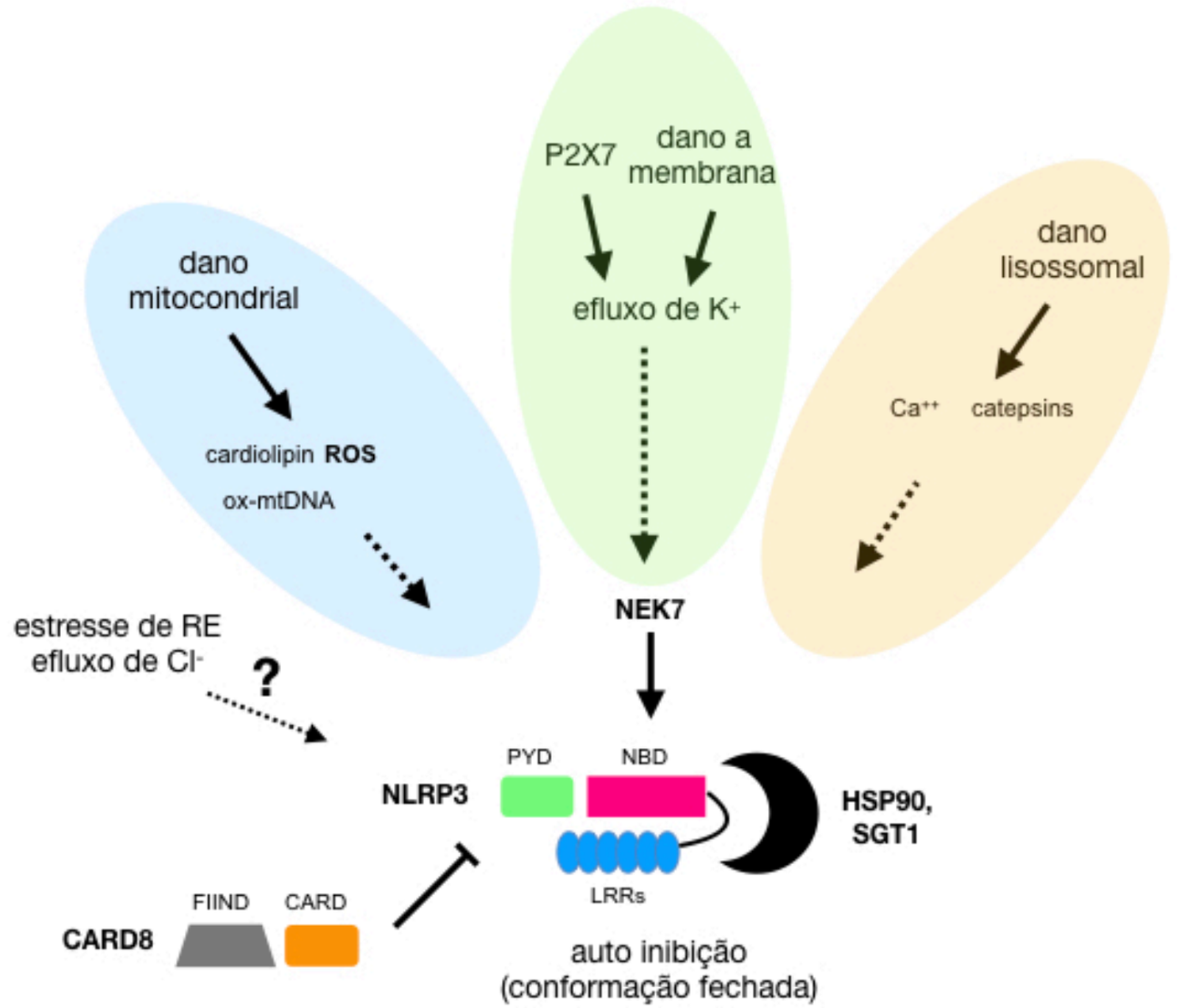
Bacterial	Lipopolysaccharide, peptidoglycan, muramyl dipeptide, trehalose-6,6'-dibehenate, c-di-GMP–c-di-AMP, bacterial RNA and RNA–DNA hybrid
	Toxins: nigericin (*Streptomyces hygroscopicus*), gramicidin (*Brevibacillus brevis*), valinomycin (*Streptomyces fulvissimus* and *Streptomyces tsusimaensis*), β-haemolysin (*Streptococcus* sp. 'group B'), α-haemolysin (*Staphylococcus aureus*), M protein (*Streptococcus* sp. 'group A'), leucocidin (*Staphylococcus aureus*), tetanolysin O (*Clostridium tetani*), pneumolysin (*Streptococcus pneumoniae*), listeriolysin O (*Listeria monocytogenes*), aerolysin (*Aeromonas hydrophila*), streptolysin O (*Streptococcus pyogenes*), enterohaemolysin (*Escherichia coli* O157:H7), haemolysin BL (*Bacillus cereus*), adenylate cyclase toxin (*Bordetella pertussis*), M protein (*Streptococcus* sp. 'group A') and maitotoxin (*Marina* spp. dinoflagellates)
Viral	Double-stranded RNA and single-stranded RNA
Fungal	β-Glucans, hyphae, mannan and zymosan

From Swanson et al 2019

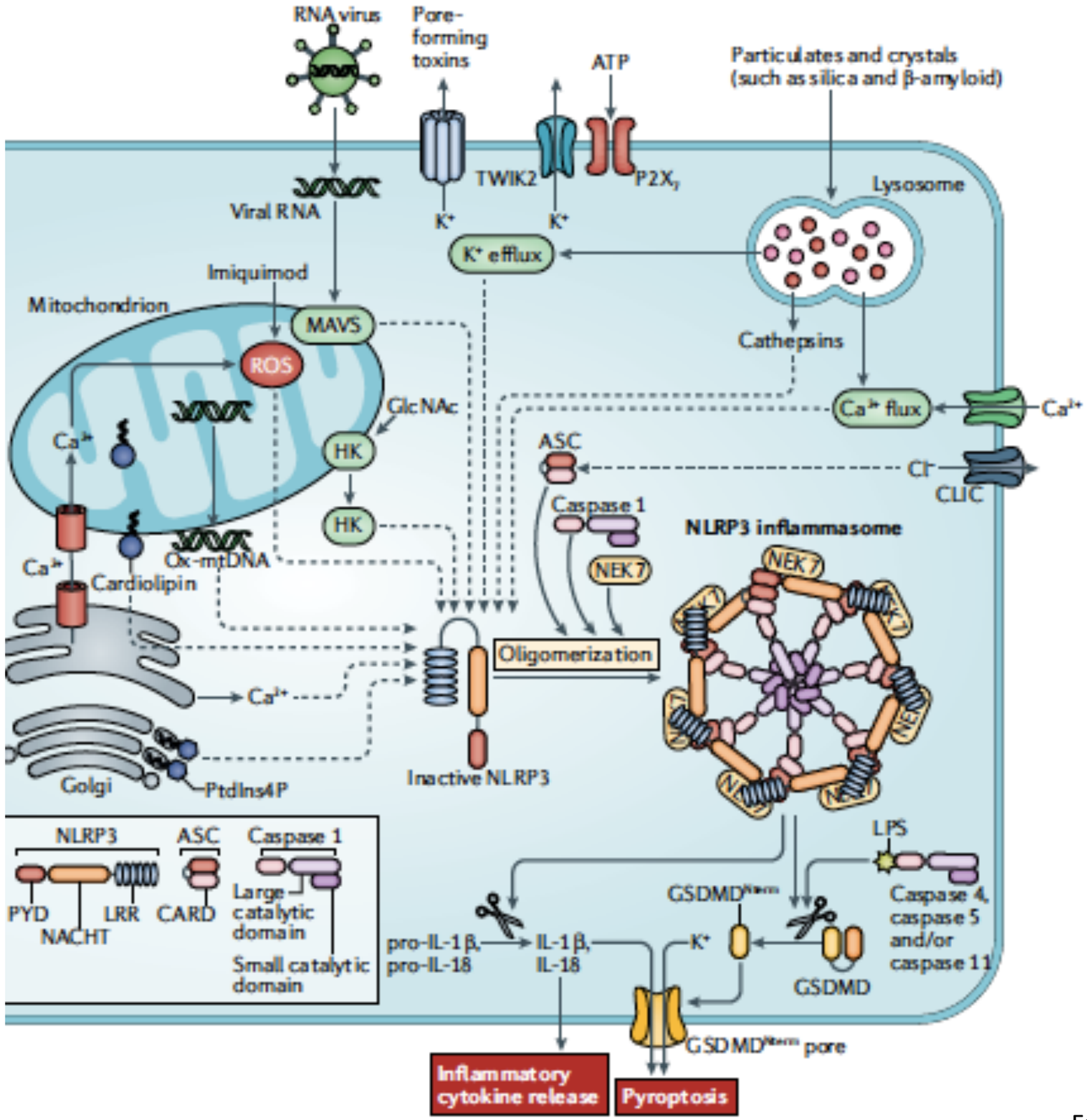
Ativação de NLRP3

PAMPs
toxinas bacterianas
LPS, Esx-1 SS, type VII SS
genoma viral, viroporina 2B,
proteina Tat *etc,* hemozoin
Zymosan and mannana fungica

DAMPs
elevada $[ATP]_{extra}$, elevada $[glucose]_{extra}$, cristais de acido urico ou colesterol, ß-amilode, proteinas "*unfolded*", material particulado inorganico, UV

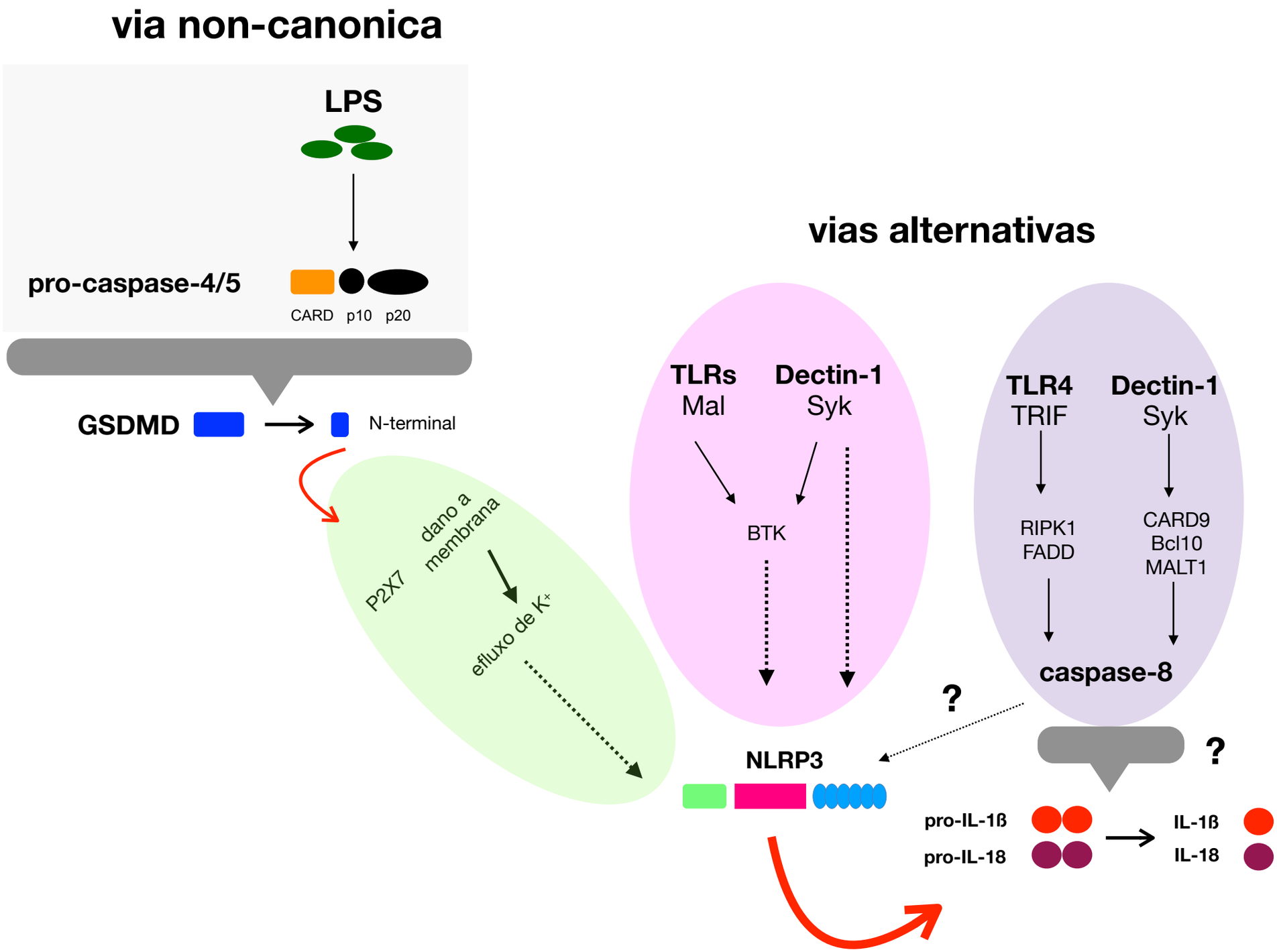


Ativação de NLRP3



From Swanson et al 2019

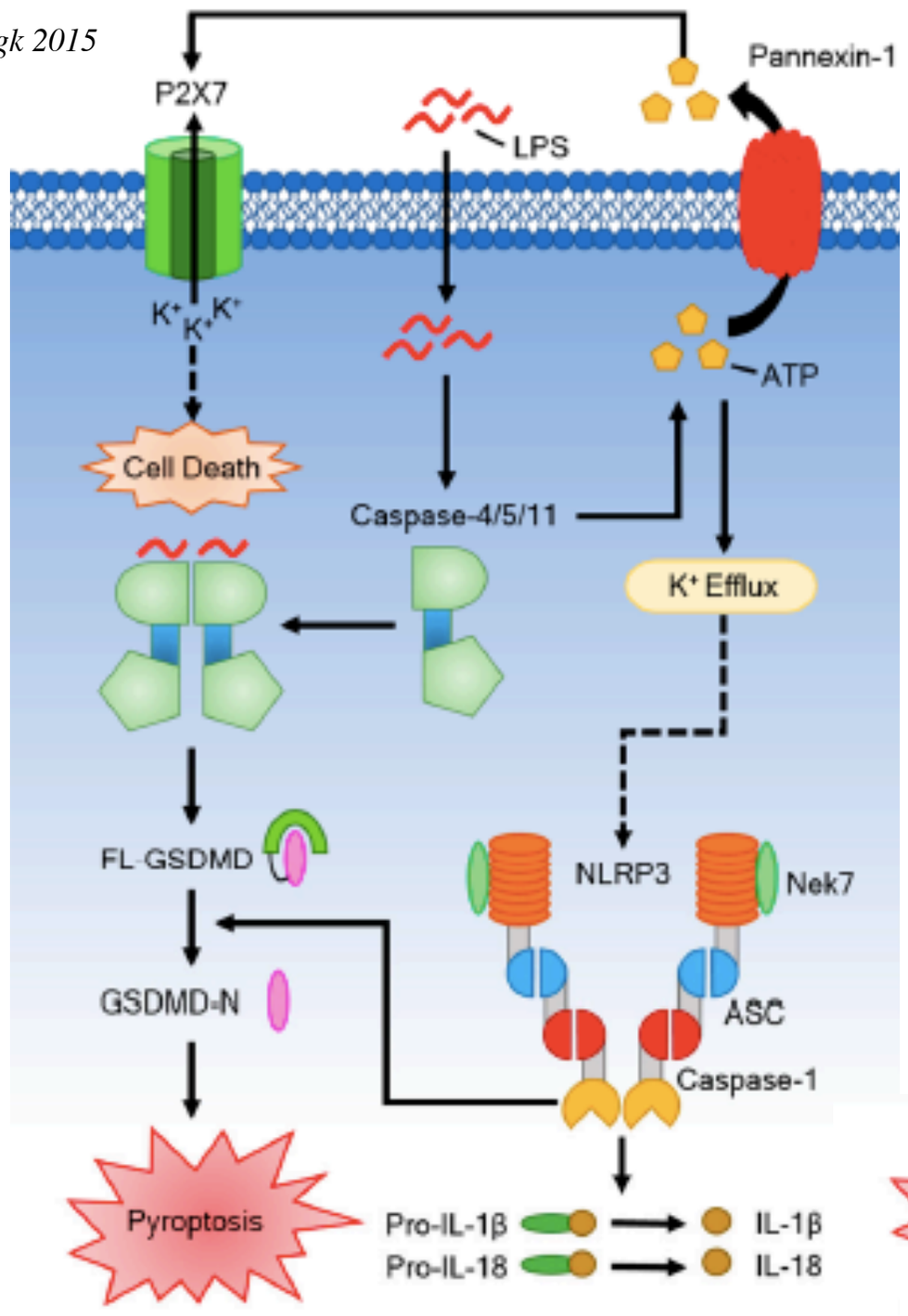
Ativação de NLRP3 (2)



Ativação non-canonica e alternativa

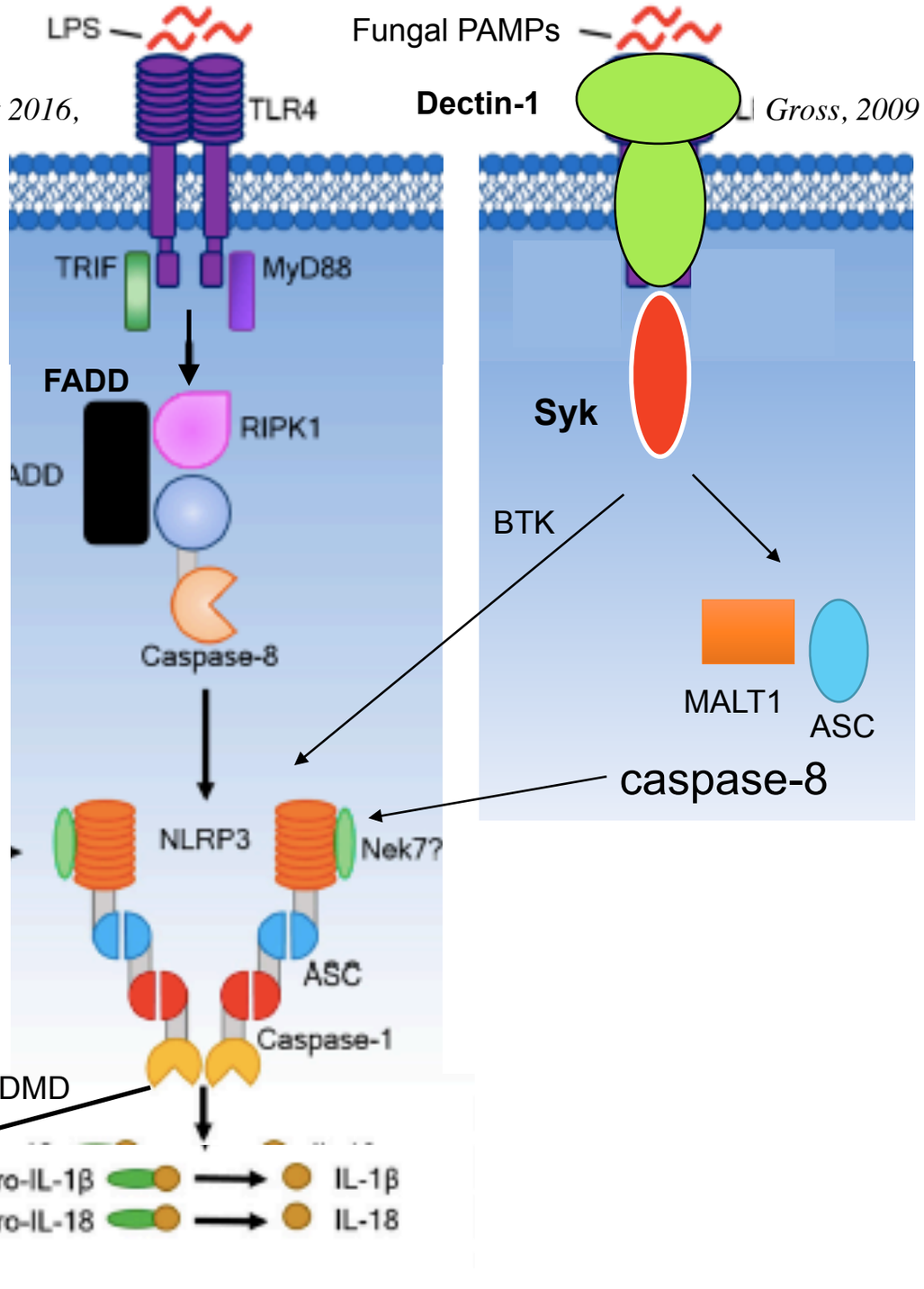
Non-canonical NLRP3 activation

Baker 2015
Schmid-Burgk 2015



Alternative pathways for NLRP3 activation

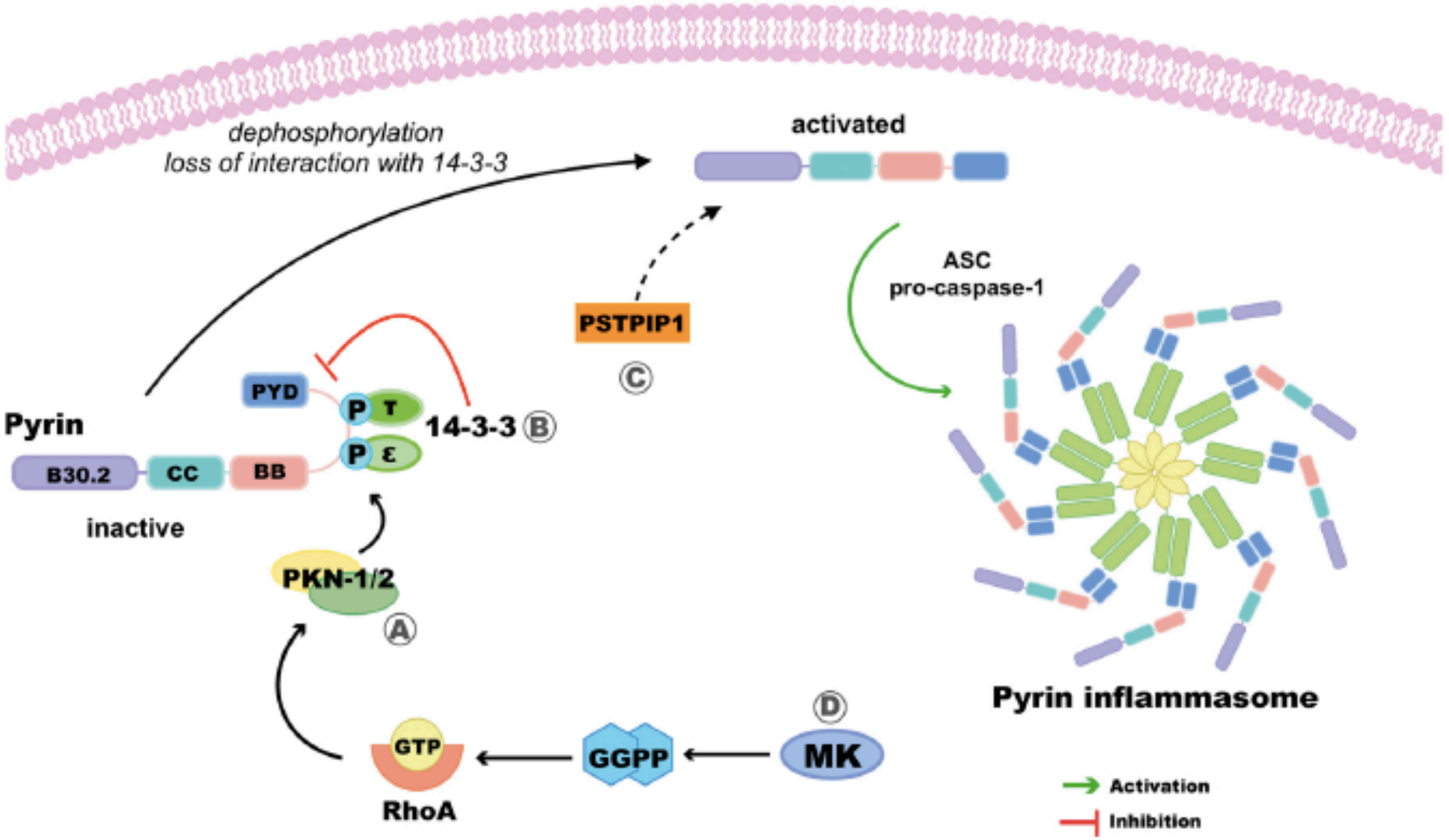
Gaidt 2016,



Gross, 2009

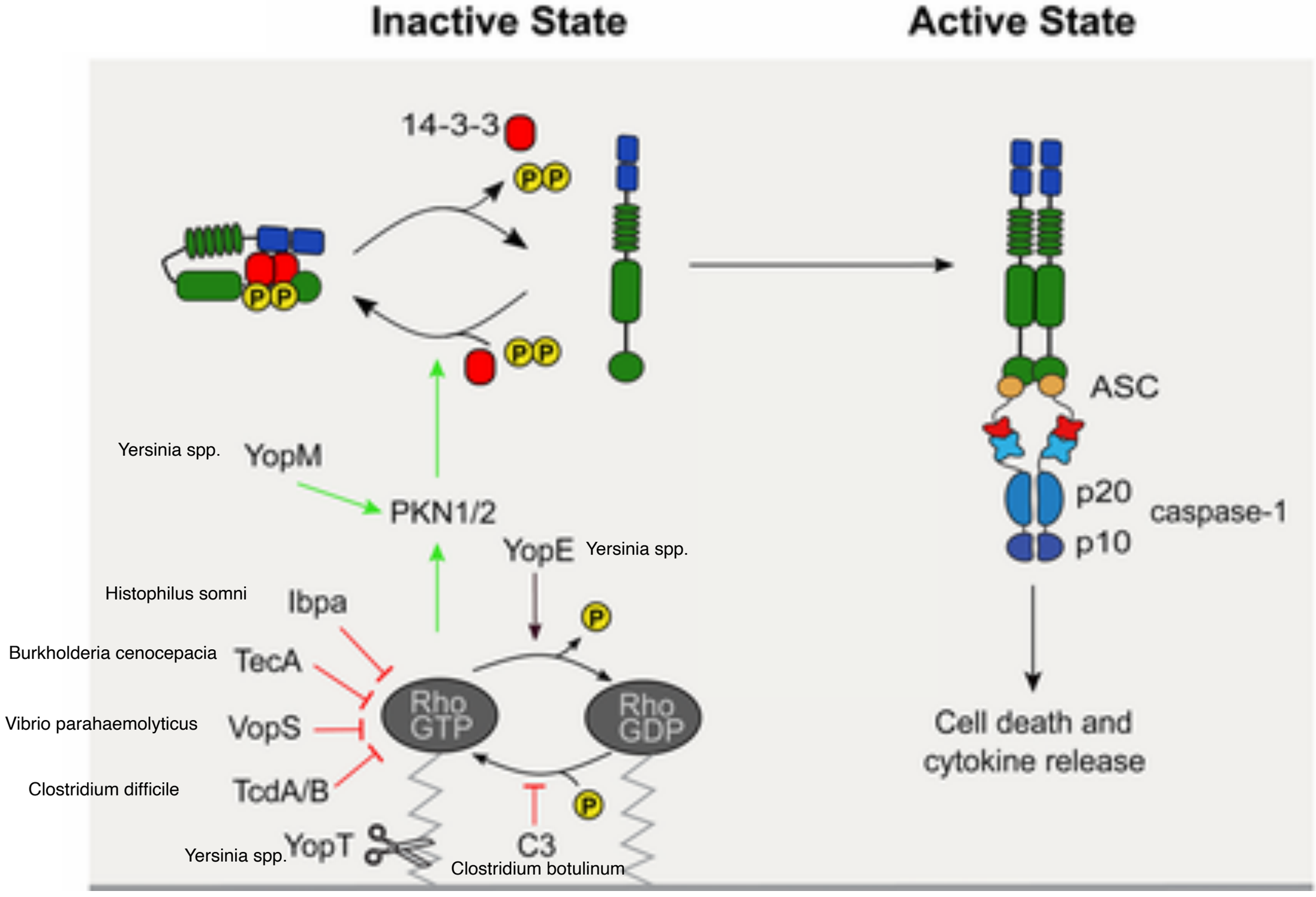
From Kelley et al 2019

HAMPs & inflamassoma



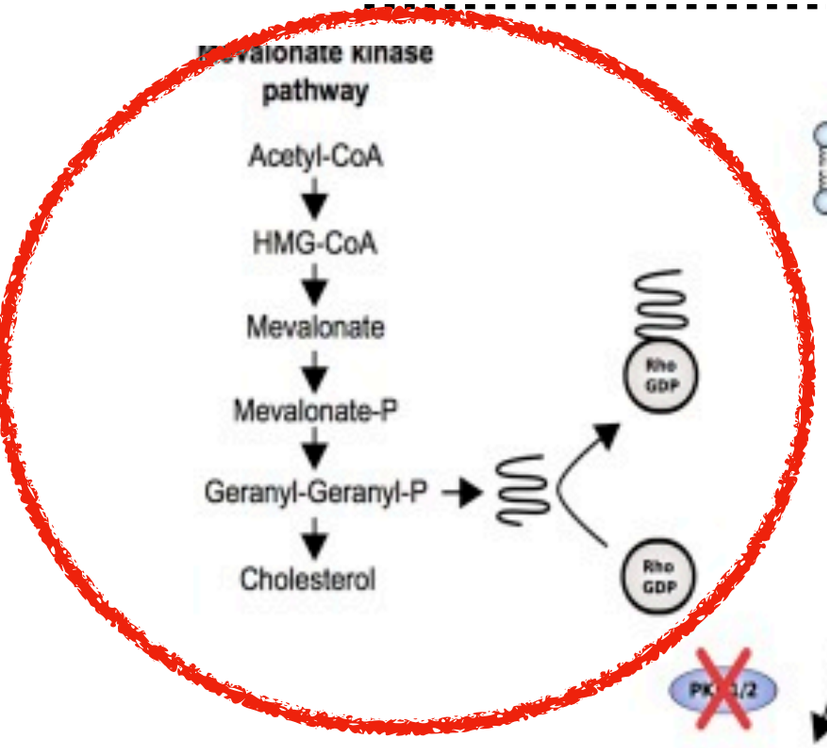
Yamada & Pontillo 2022

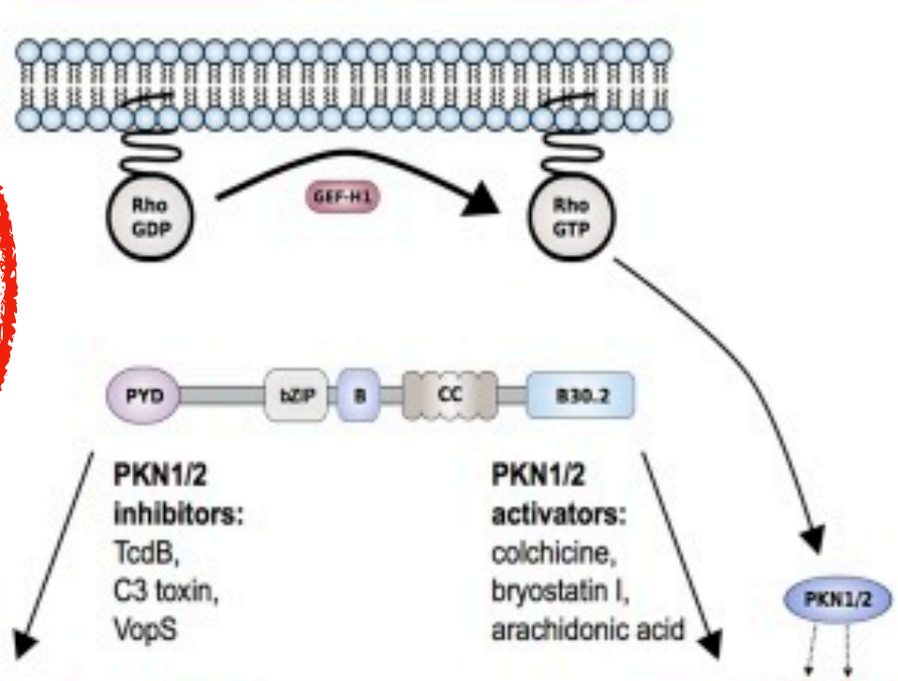
Ativação da Pirina (Pyrin/MEFV)

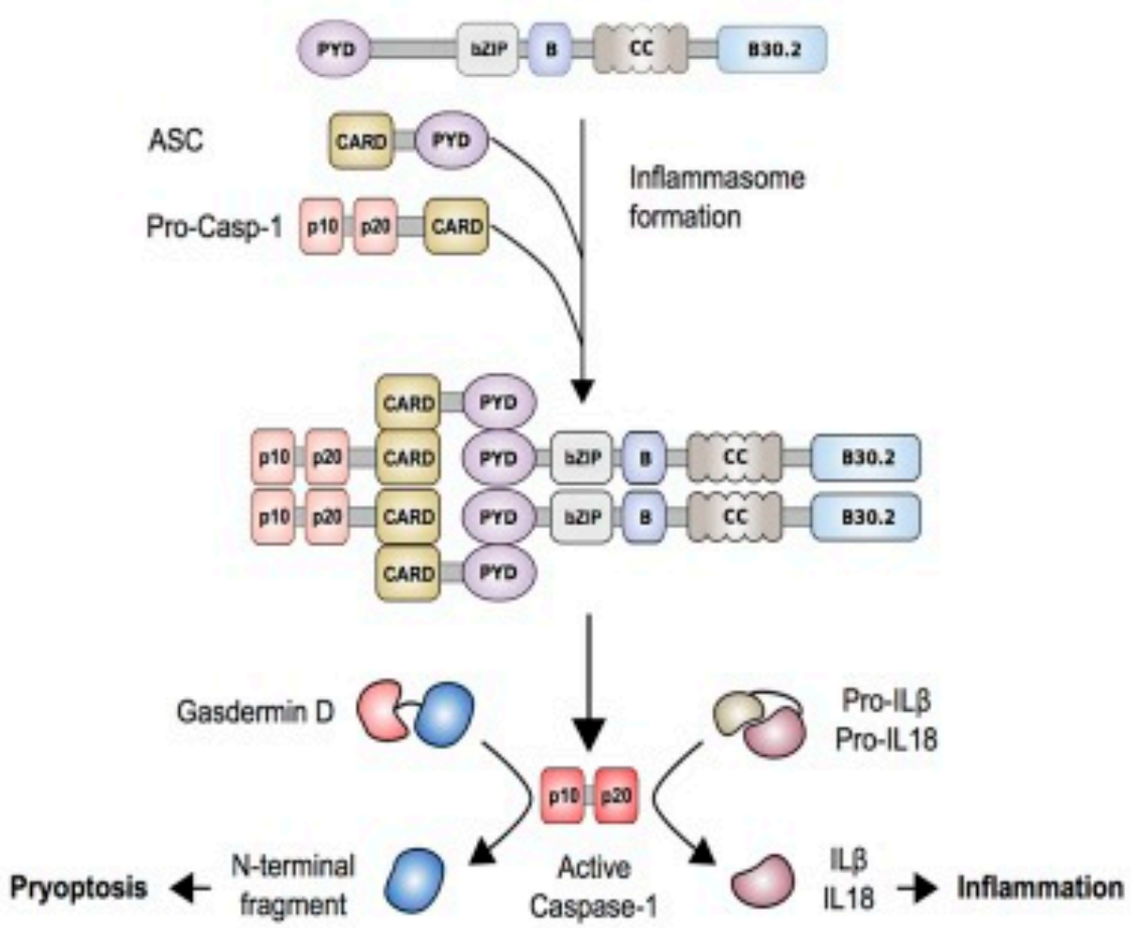


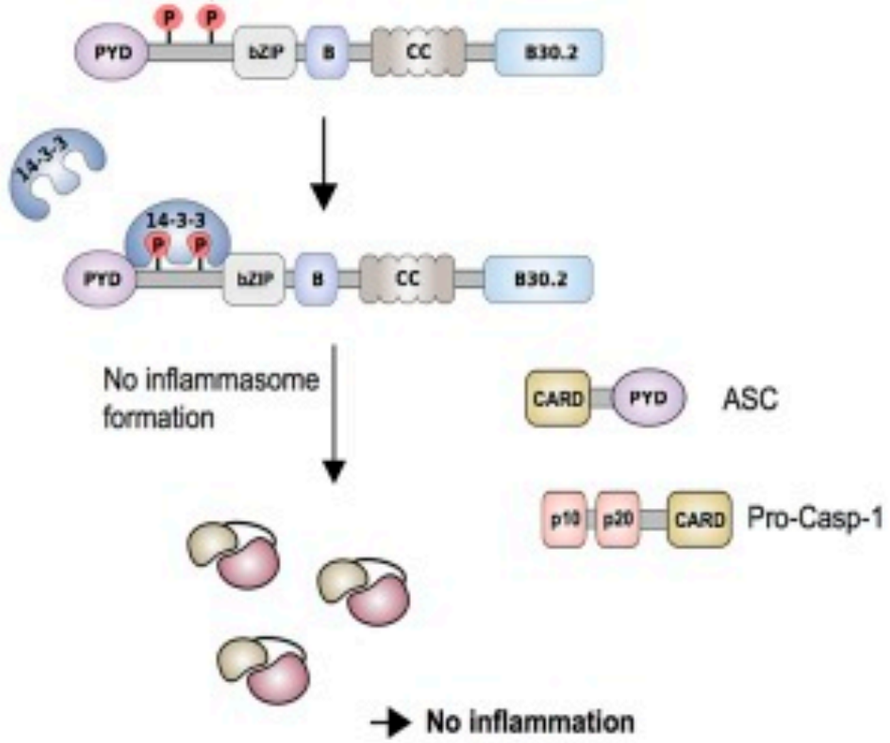
Heilig & Broz, EJI 2017

Ativação da Pirina (Pyrin/MEFV)



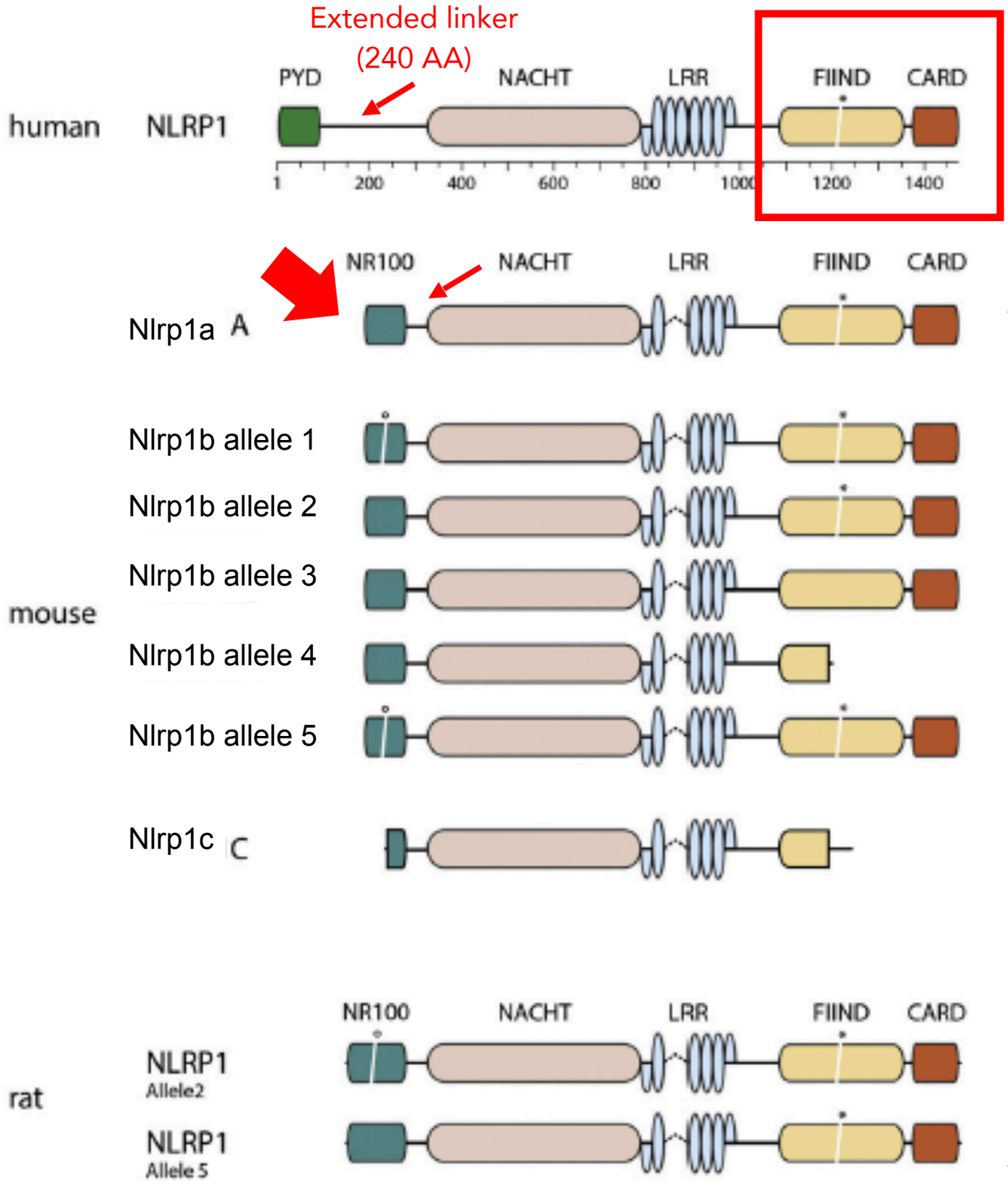






Schnappauf,2019

NLRP1

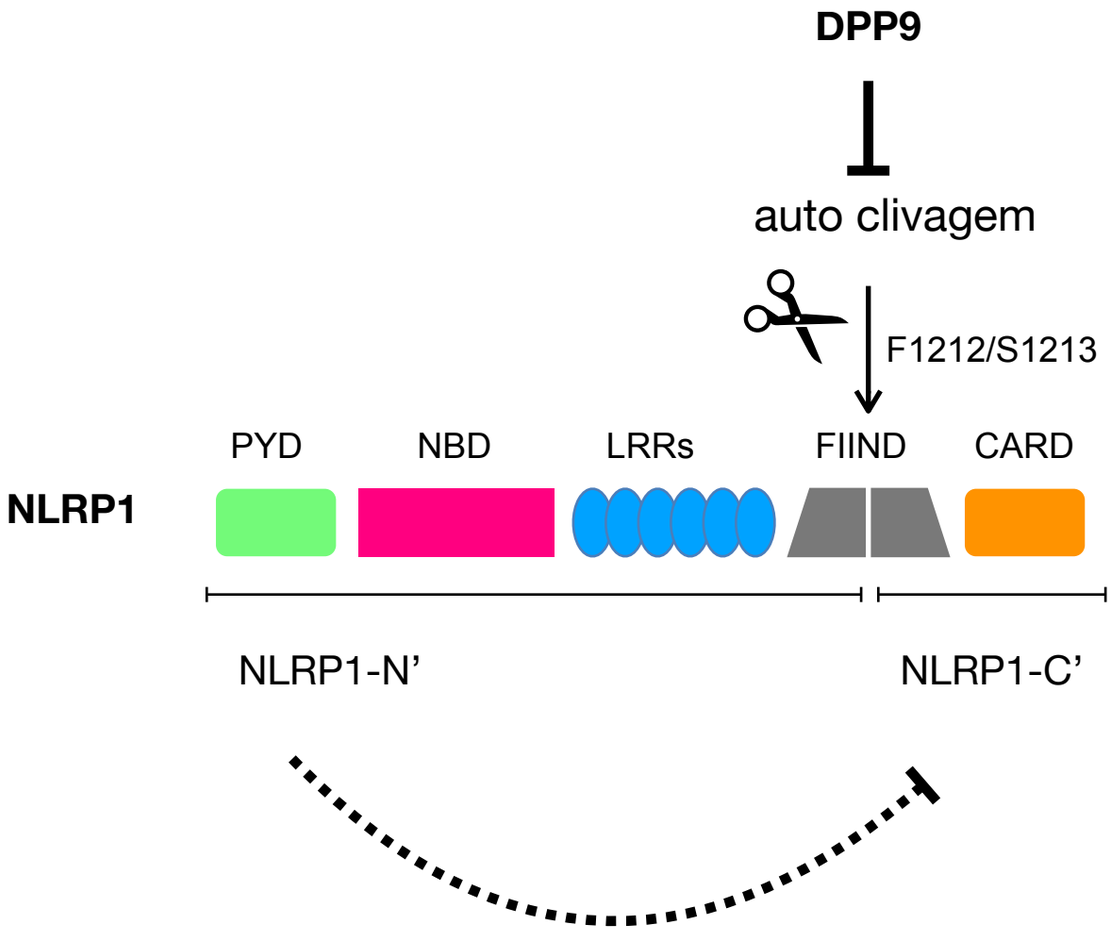


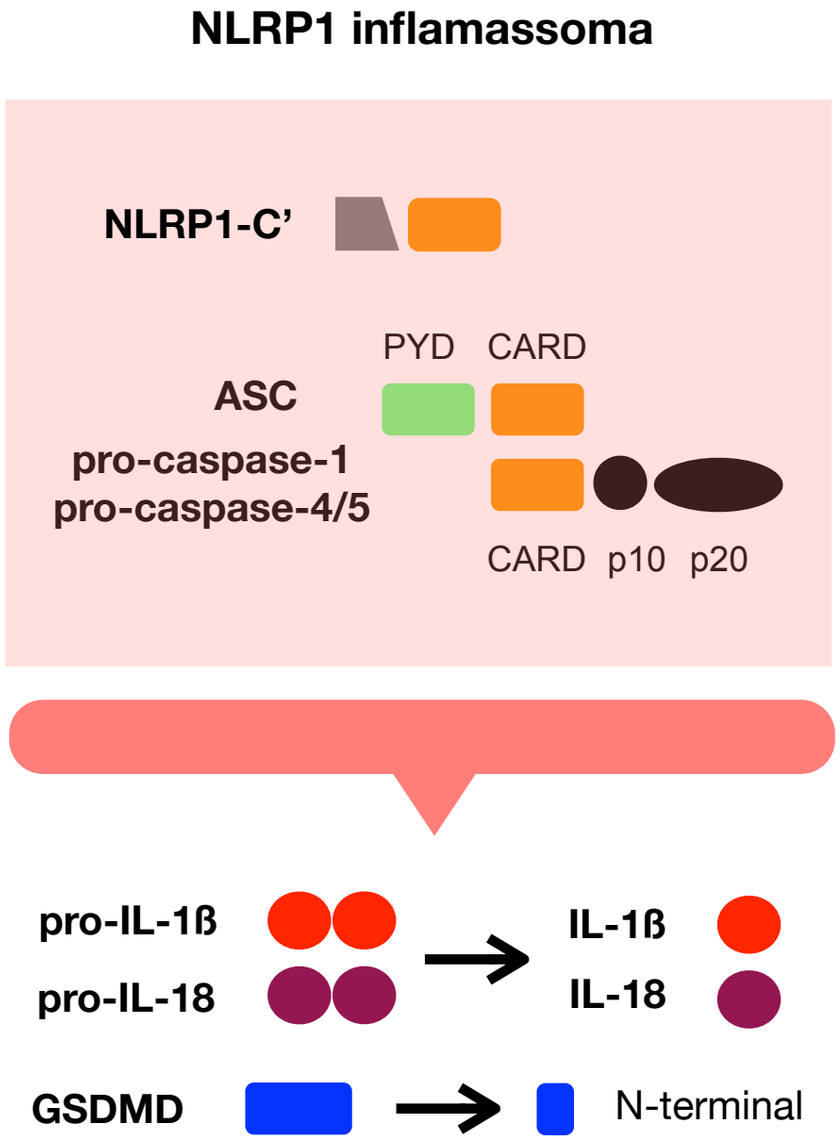
Unique domain composition!

Broad genetic diversification

From Yu & Masters, 2018

Ativação do NLRP1 (2020)





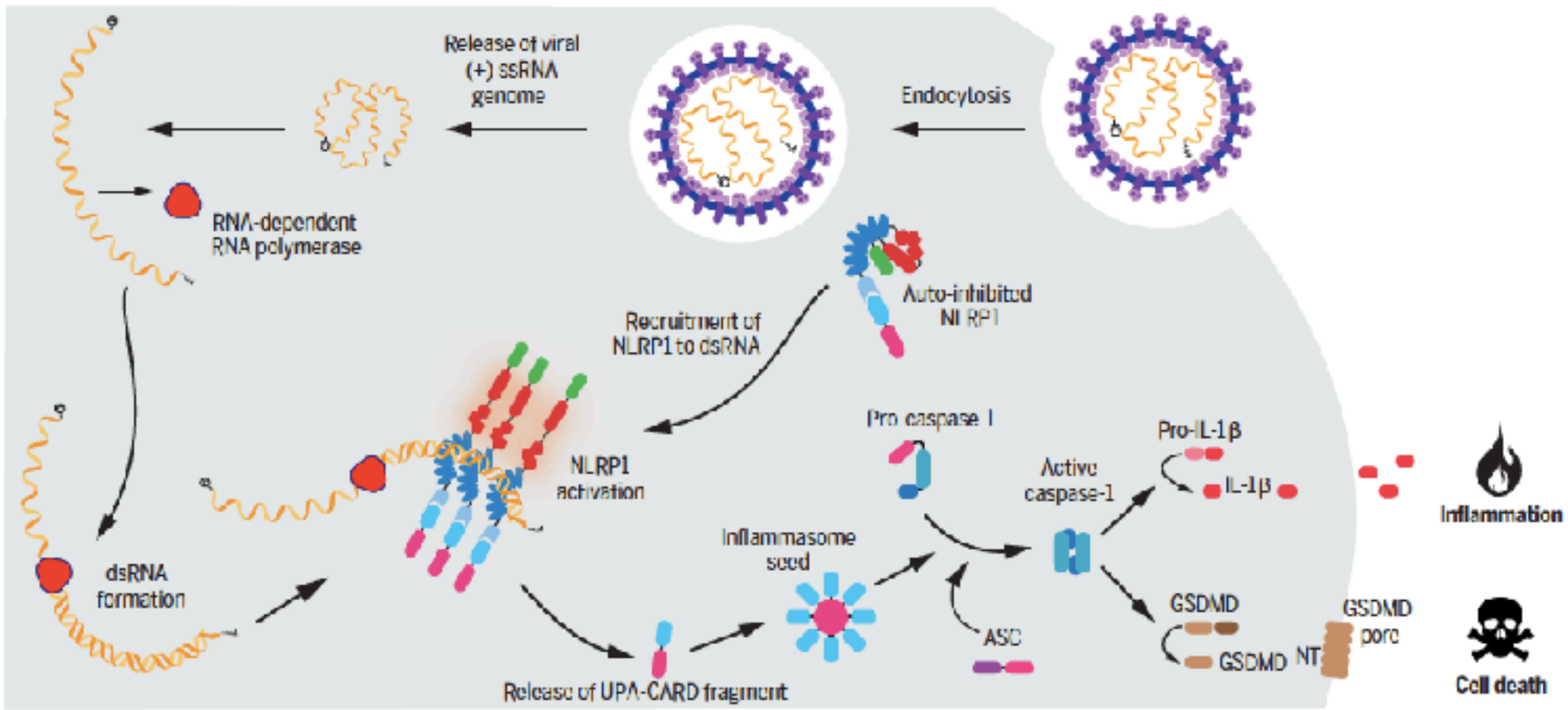
Ativação do NLRP1 (2021)

RESEARCH ARTICLE SUMMARY

INNATE IMMUNITY

Human NLRP1 is a sensor for double-stranded RNA

Stefan Bauernfried, Matthias J. Scherr, Andreas Pichlmair, Karl E. Duderstadt, Veit Hornung*

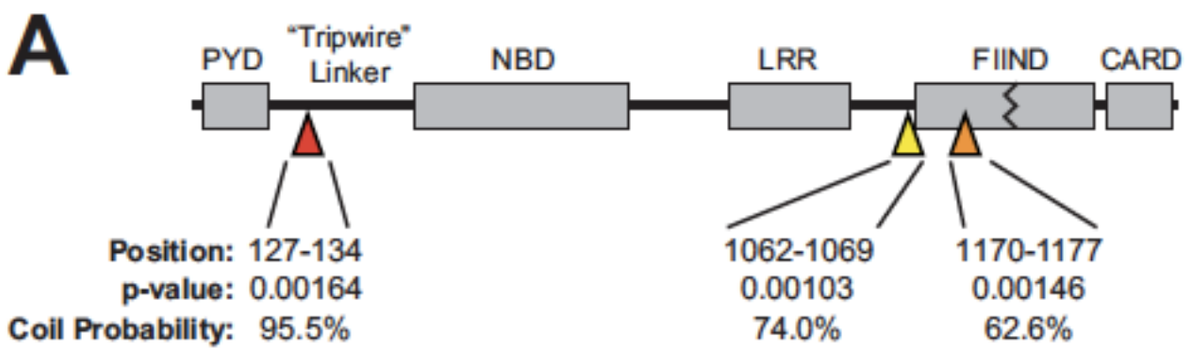


Ativação do NLRP1 (2021)

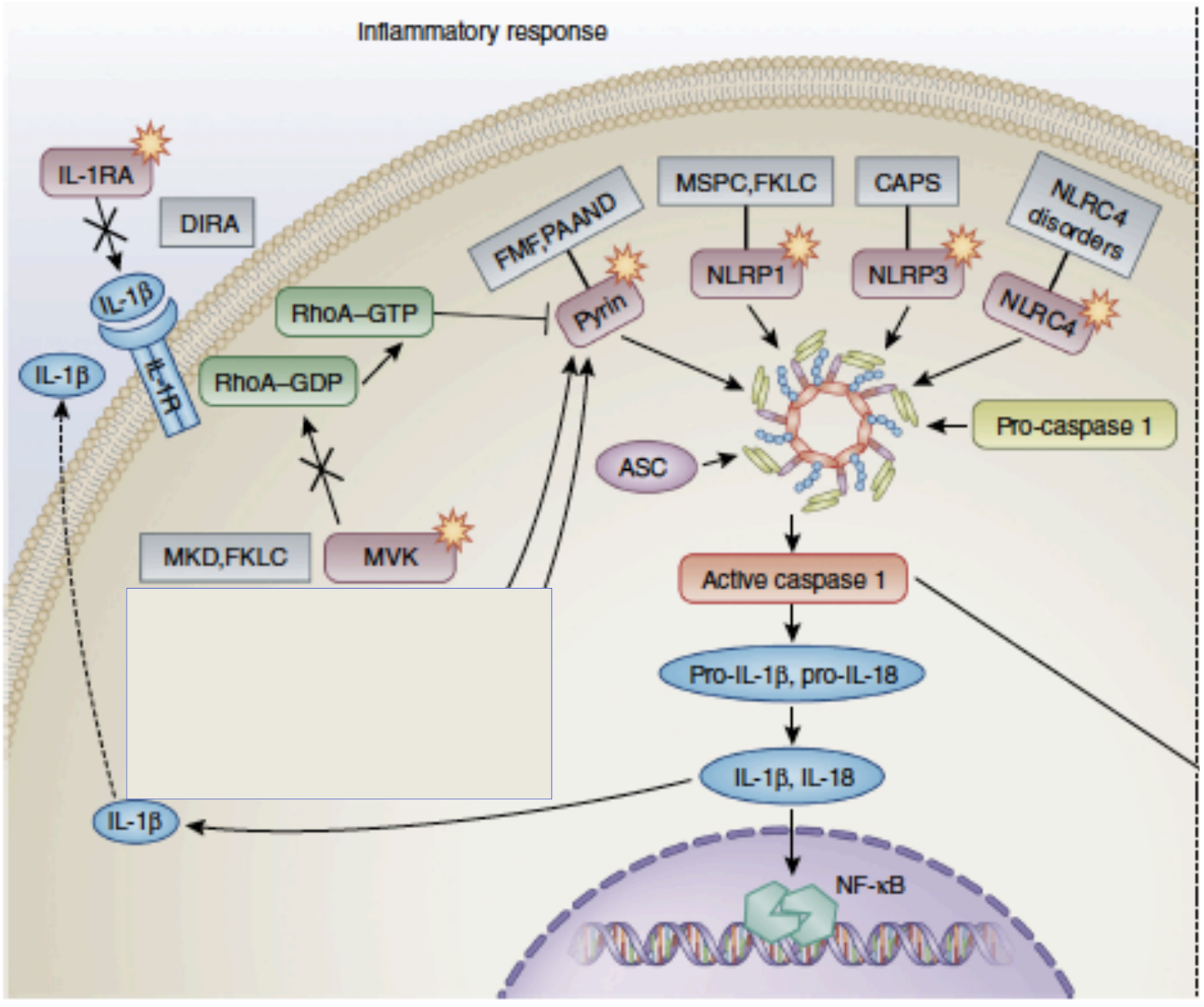
Diverse viral proteases activate the NLRP1 inflammasome

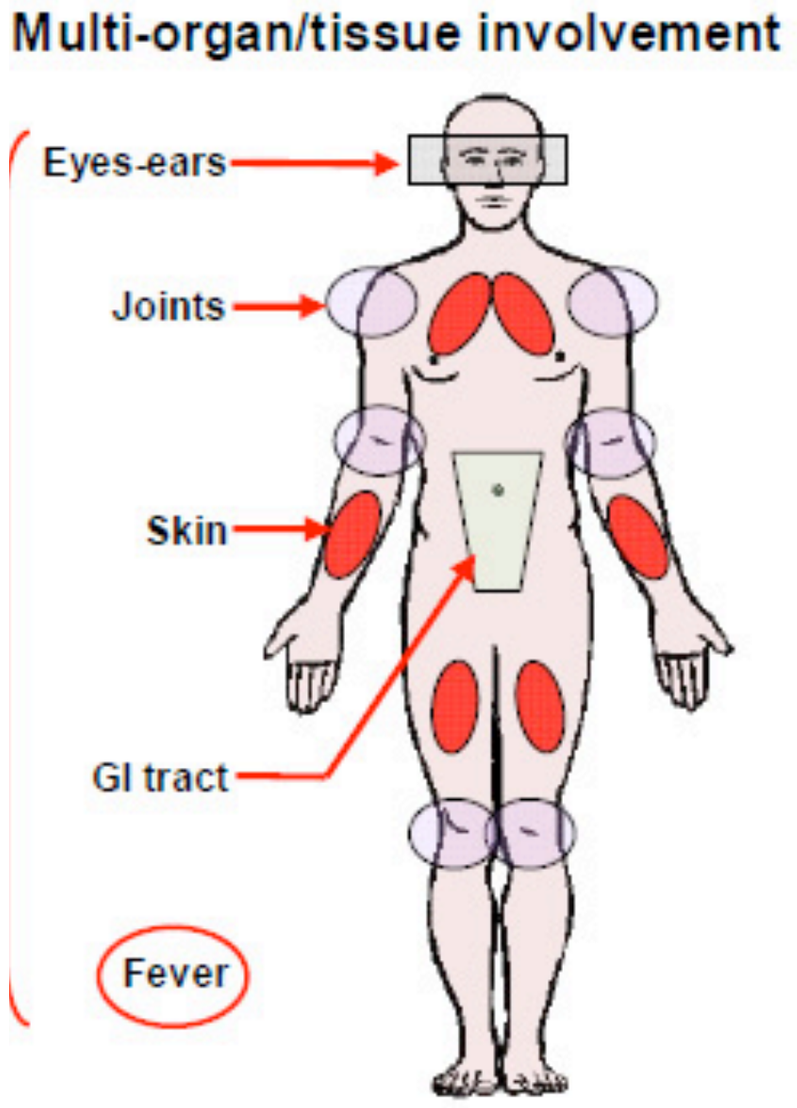
Brian V Tsu[1†], Christopher Beierschmitt[1†], Andrew P Ryan[1], Rimjhim Agarwal[2], Patrick S Mitchell[2,3], Matthew D Daugherty[1*]

[1]Division of Biological Sciences, University of California San Diego, San Diego, United States; [2]Division of Immunology & Pathogenesis, University of California Berkeley, Berkeley, United States; [3]Department of Microbiology, University of Washington, Seattle, United States



Gain-of-function mutations





↓ inflammasome activation threshold

↑↑ IL-1ß (IL-18?)

but distinct phenotype!! → cell specific activity