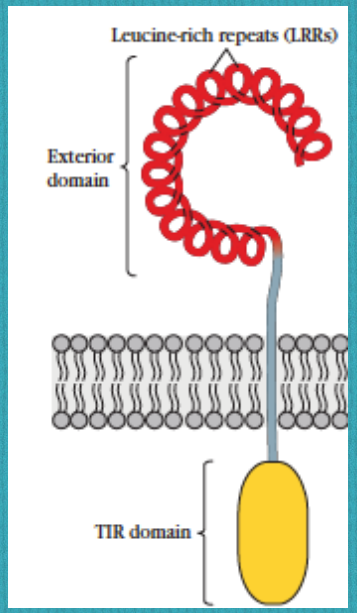
Curso de Ciencias Biologicas
Disciplina BMI-296 – Imunologia basica



Aula 4 – Imunidade inata

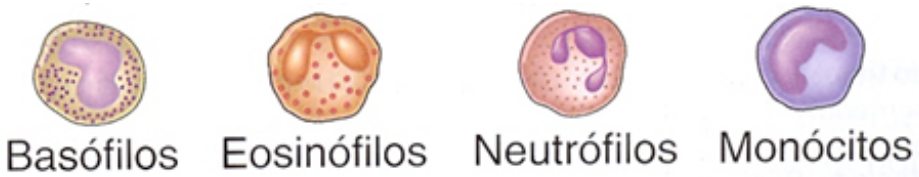
Alessandra Pontillo

Lab. Imunogenetica/Dep.Imunologia/ICB/USP

Reconhecimento

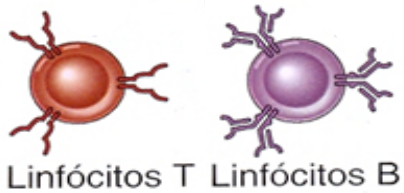
SISTEMA IMUNE

Imunidade inata



PADROES MOLECULARES (PAMPs, DAMPs)

Imunidade adaptativa

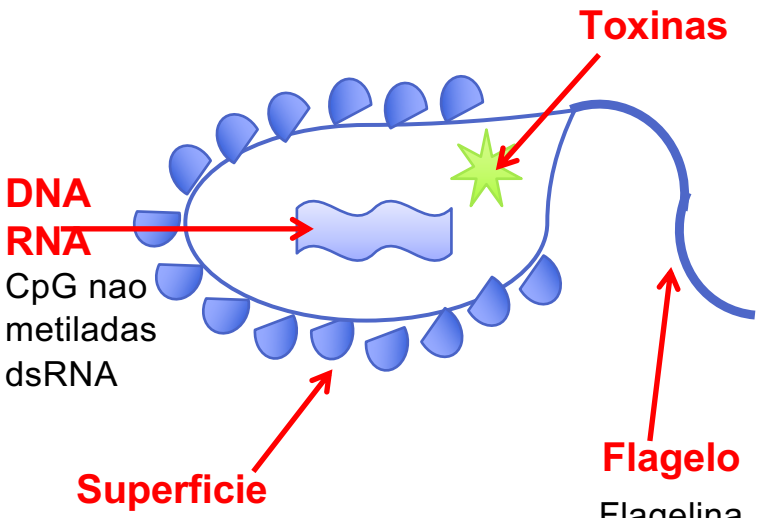


ANTIGENOS ESPECIFICOS

PAMPs & DAMPs

PAMPs

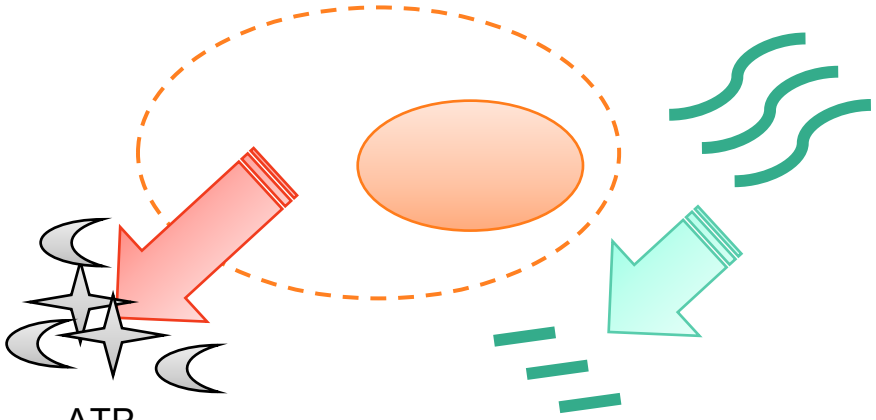
Moleculas ou porçoes de moleculas do microrganismo que nao existem no hospedeiro. Essenciais para sobrevida ou patogenicidade



Lipopolisacarideo (LPS)
Peptidoglicano (PG)
Acido Lipoteicoico (LTA)
Mannosio terminal nas glicoproteinas
Proteinas do envelope viral
Zymosan (fungo)
Profilina (T gonodii)

DAMPs

Moleculas do hospedeiro (endogenas) produzidas por celulas danificadas/mortas ou produtos de degradaçao de proteinas (celular ou extracelular)

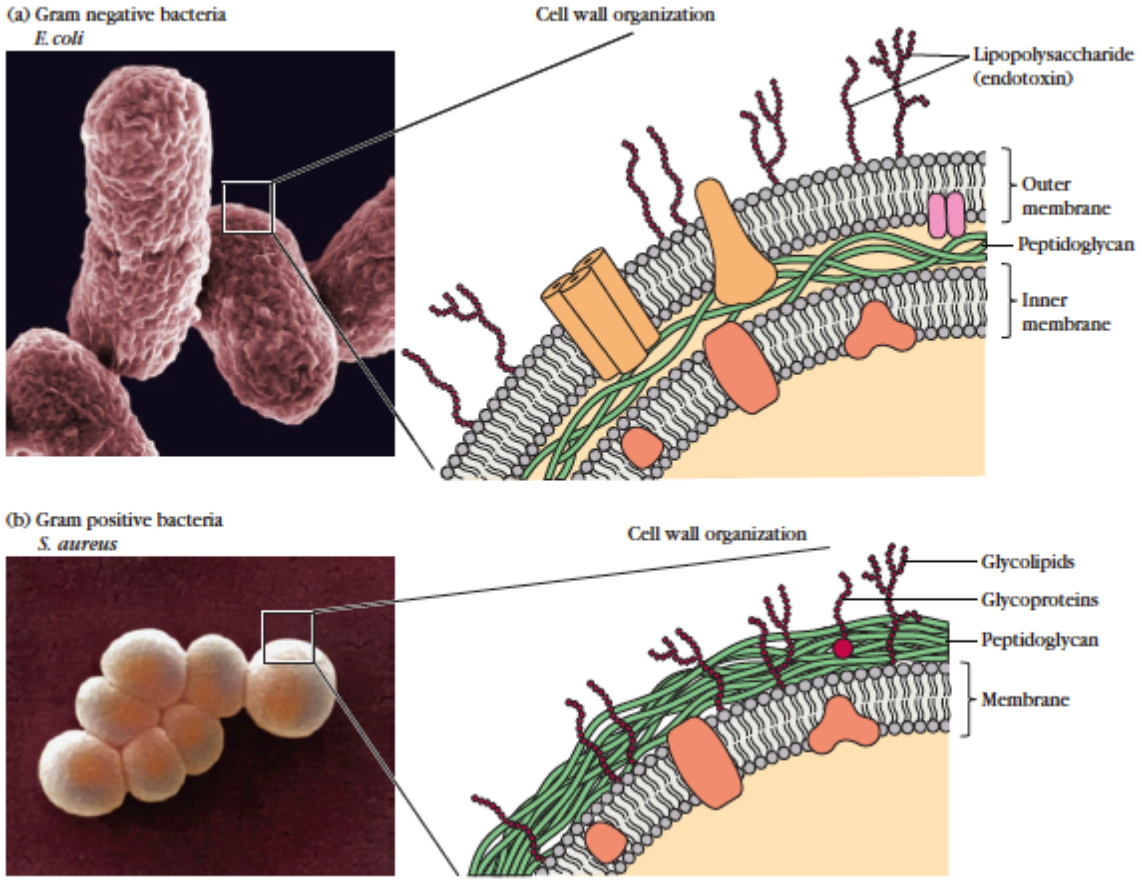


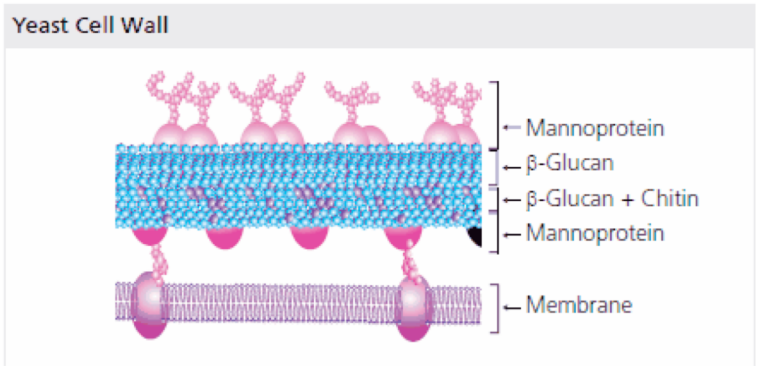
ATP
DNA/RNA
Acido urico
HMGB1
HSP
Metabolic intermediates
High Cholesterol
High Glucose
ß-amiloid

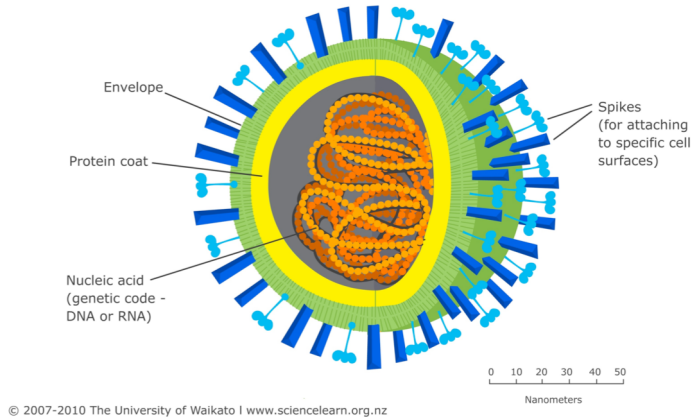
Heparansolfato
Hialuronano

PAMPs & DAMPs

O microbo carrega multiplos PAMPs





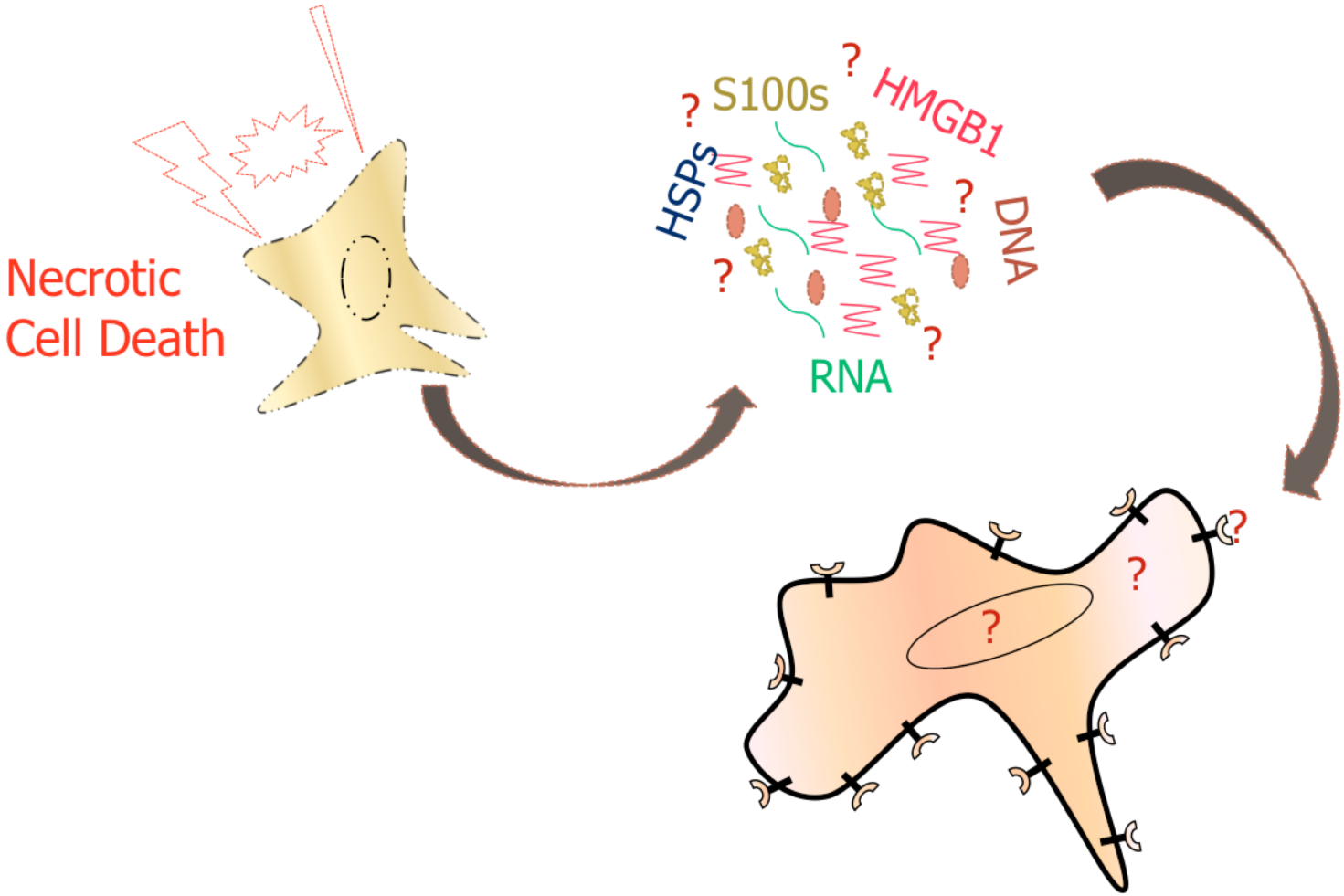


Pode gerar dano (DAMPs)

(Exclusivo de organismos patogenicos!)

PAMPs & DAMPs

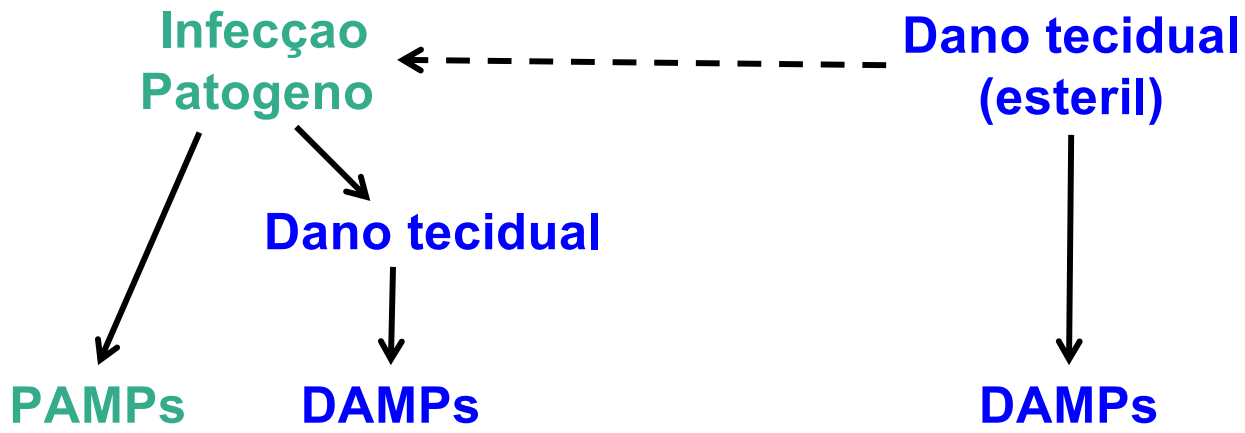
O dano/stress pode gerar multiplos DAMPs



VAMPs: venenom-associated molecular patterns

ACAMPs: apoptotic cells molecular patterns (fosfatidilserina, anexina)

Reconhecimento

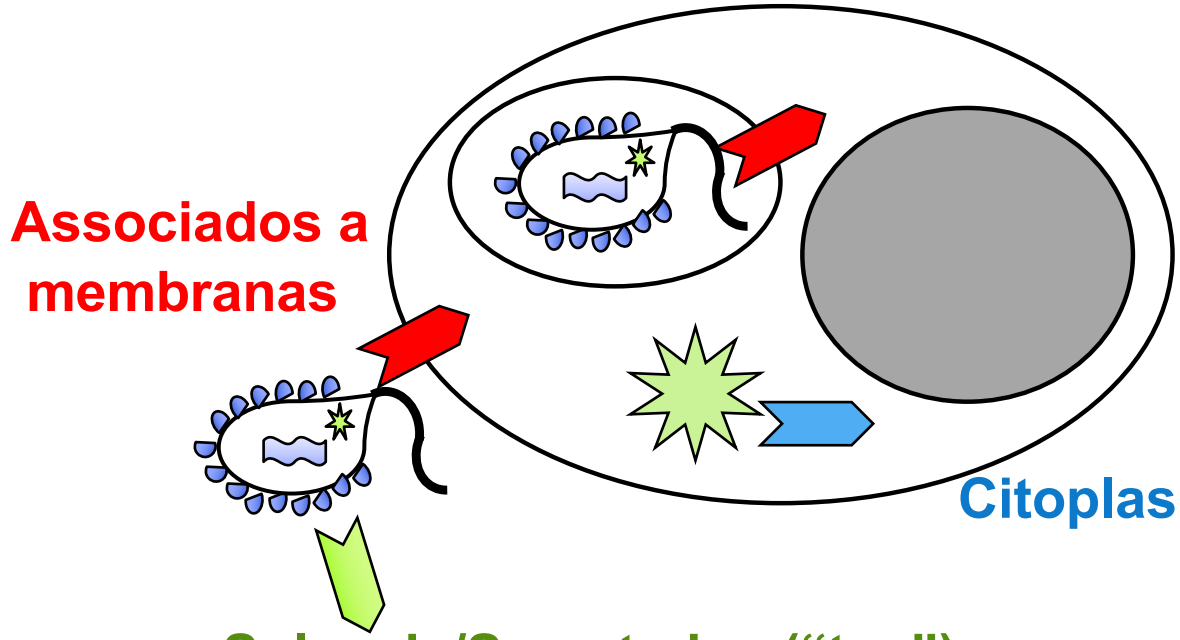


Sistema imune inato = "orgao de percepçao"

Reconhecimento feito por quase todas as celulas somaticas

Receptores de reconhecimento de padroes: PRRs

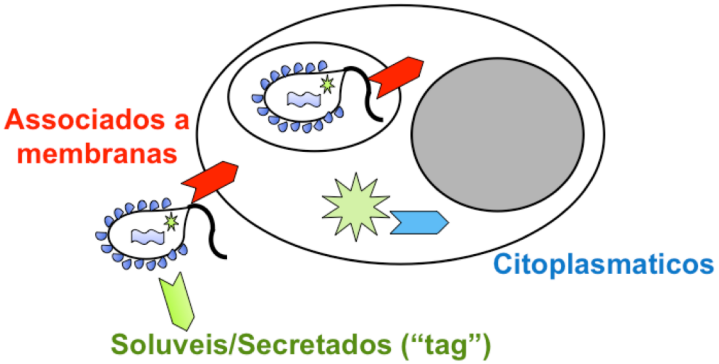
PRRs



Ativaçao do sistema imune inato

- Opsonizaçao
- Ativaçao complemento
- Fagocitose
- Mediadores inflamatorios
- IFNs
- Morte da célula infectada/danificada

PRRs



Celulares

Associados a membrana
- Toll-like receptors (TLRs)
- Receptores de carboidratos (CLRs)
- Receptores Scavanger
- TKRs (plantas)

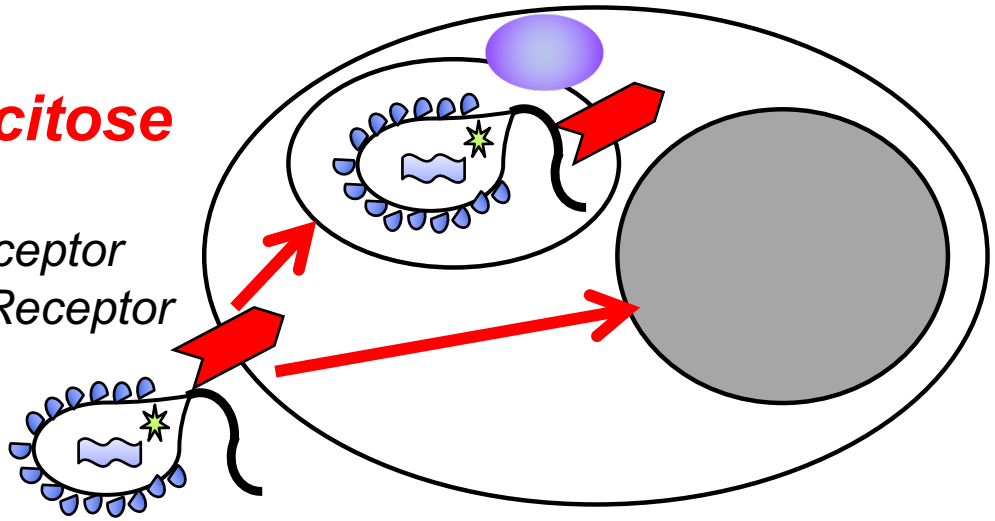
Citoplasmáticos
- Receptores com domínios NBD and LRR (NLRs)
- Sensores de DNA
- RIG-I like receptors (RLRs)

Secretados (PRMs) por figado (cel.imunes)
- S. Complemento
- Collectinas, ficolinas e pentraxinas

PRRs associados a membranas

Fagocitose

PRR
- *Mannose receptor*
- *Scavanger Receptor*

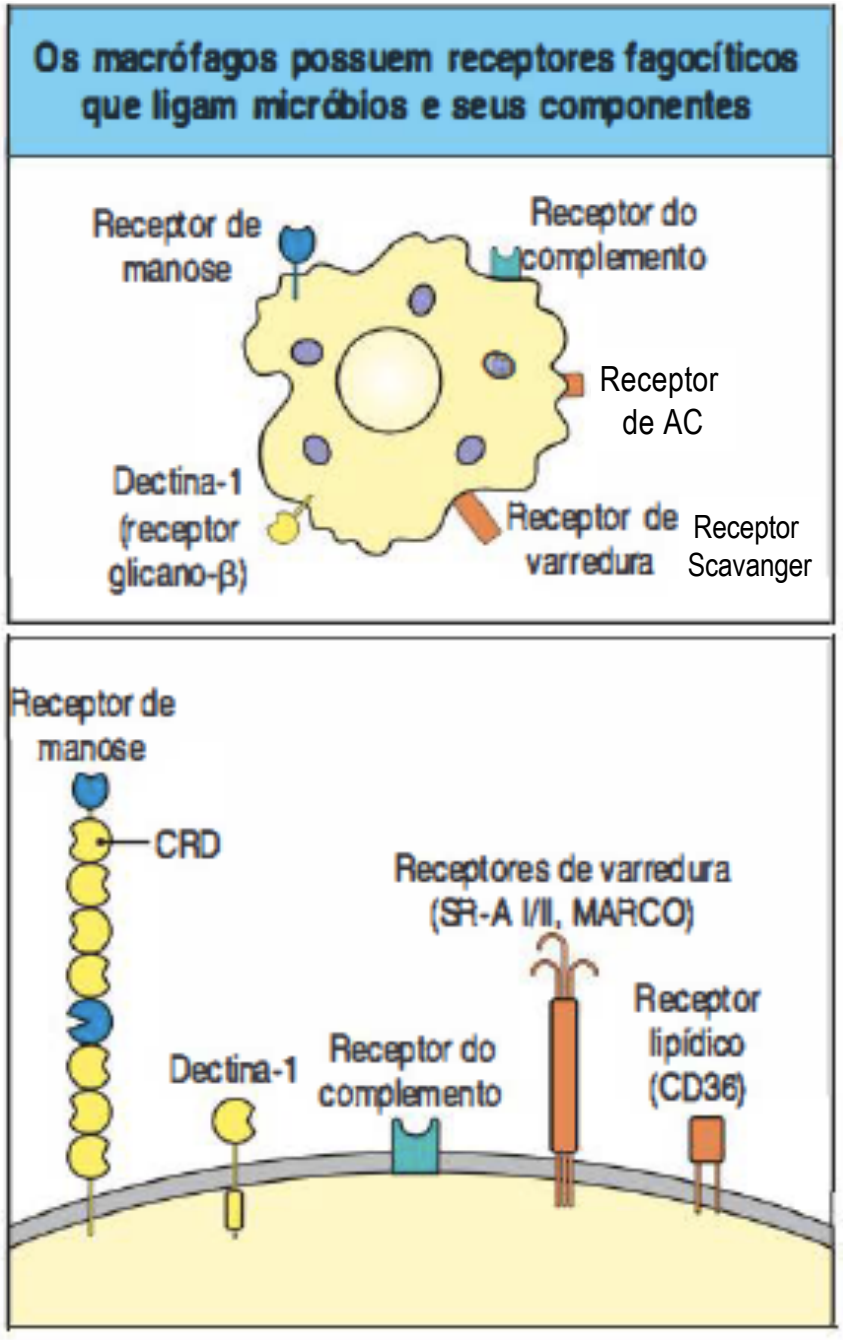


PRR
reconhecimento indireto
- *CR*
- *FcR*

Via de sinalizaçao intracelular
Trascriçao geni de defesa
- NF-kB: citocinas, quimiocinas, AMPs
- IRFs: interferon tipo I

PRR
- *TLRs*

Receptores de fagocitose



PRRs

- ***CLRs*** *(Receptor de Manose, Dectin-1, DC-SIGN)*
- ***Receptores Scavenger*** *(SR-A, SR-B)*

Reconhecimento indireto

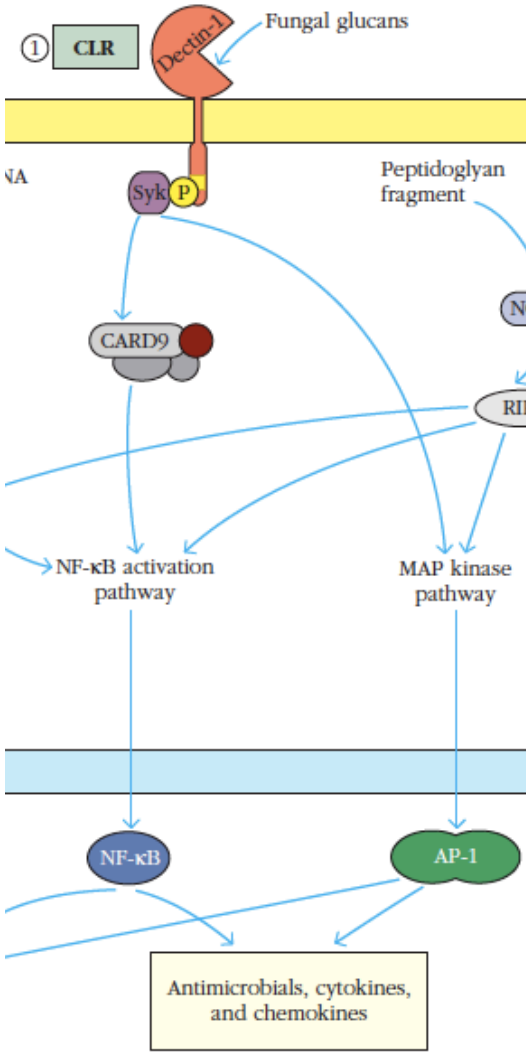
Receptores de opsoninas

- ***CR*** *(CR1, CR3, CR4)*
- ***FcR*** *(FCγR, FCαR, FCεR)*

Receptores de fagocitose

Receptores de carboidrados (CLRs)

Examples	Ligands
	Microbial ligands (found on microbes)
Mannose receptor	Mannans (bacteria, fungi, parasites)
Dectin 1	β-glucans (fungi, some bacteria)
DC-SIGN	Mannans (bacteria, fungi, parasites)



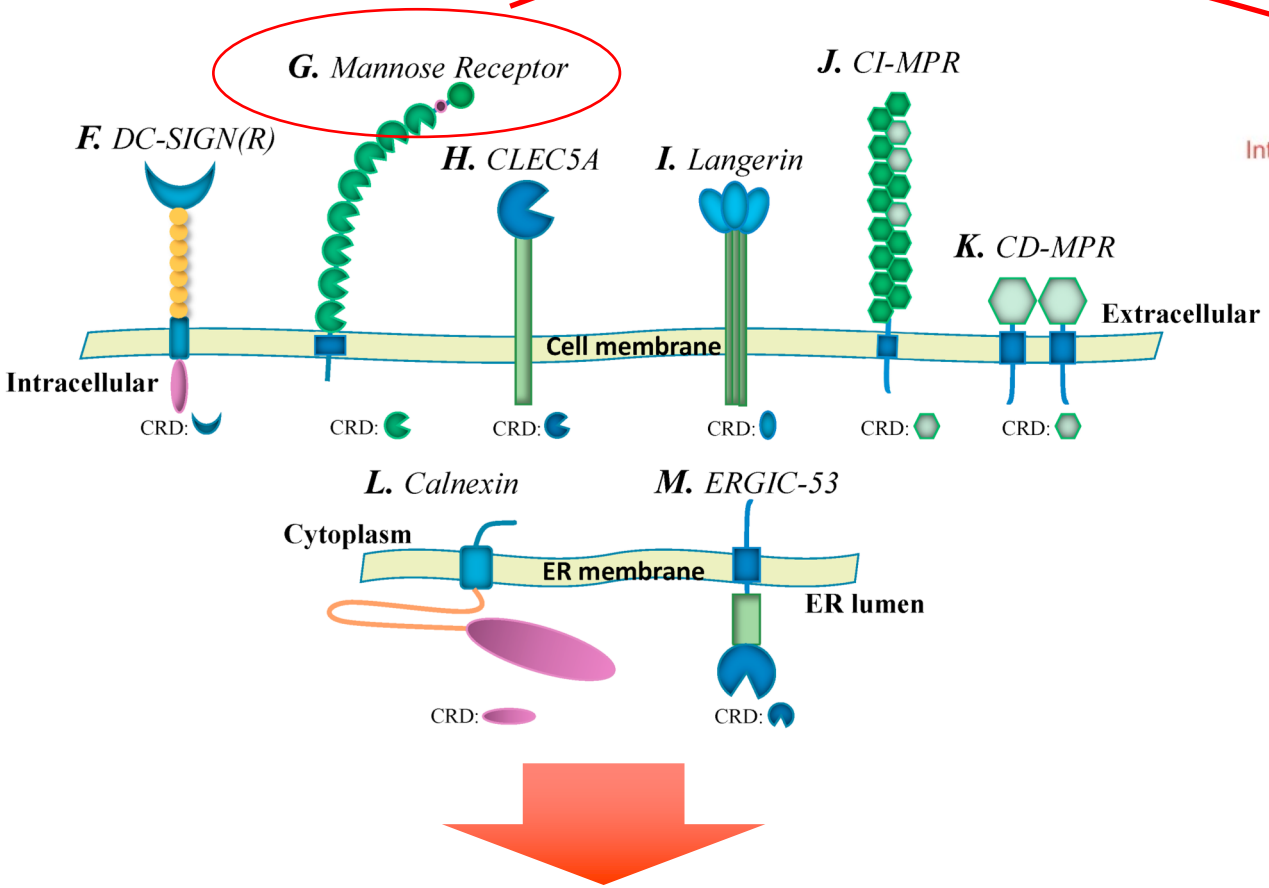
From Kuby 7 ed

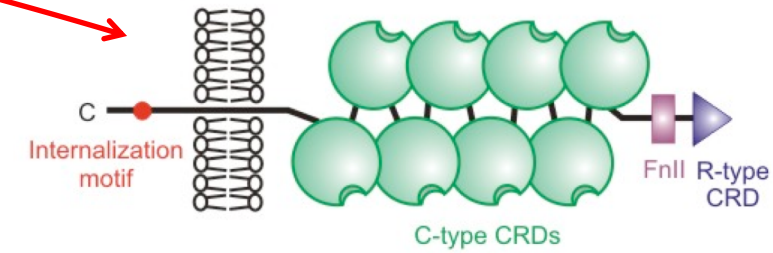
✓ Fagocitose

✓ NF-kB

Receptores de fagocitose

Receptor de manose





SP-D_CTLD	VYSNWAPGEPNDDGGSEDCV-	20
MBL_CTLD	TYTNWNEGEPNNAGSDEDCV-	20
MR_CTLD4	SYENWAYGEPNNYQNVEYCG-	20
Langerin_CTLD	SVRFWIPGEPNNAGNNEHCG-	20
DC-SIGN_CTLD	FKQYWNRGEPNNVGE-EDCAE	20
DC-SIGNR_CTLD	FQRYWNSGEPNNSGN-EDCAE	20
SP-A1_CTLD	NYTNWYRGEPAGRGK-EQCVE	20
Aggrecan_CTLD	QFENWRPN---QPDNF-FAAGEDC	20
Neurocan_CTLD	QFENWREN---QPDNF-FAGGEDC	20
Versican_CTLD	QYENWRPN---QPDSF-FSAGEDC	20
ASCPR-H1_CTLD	GFKNWRPE---QPDDW-YGHGLGG	20
SRCL_CTLD	DYKNWKAG---QPDNWGHGHGPG-	20
Endo180_CTLD1	KYLNWESD---QPDNP-SEENCGV	20
Tetranectin_CTLD	---NWETEITAQPDGG-KTENCAV	20

✓ Fagocitose

✓ NF-kB

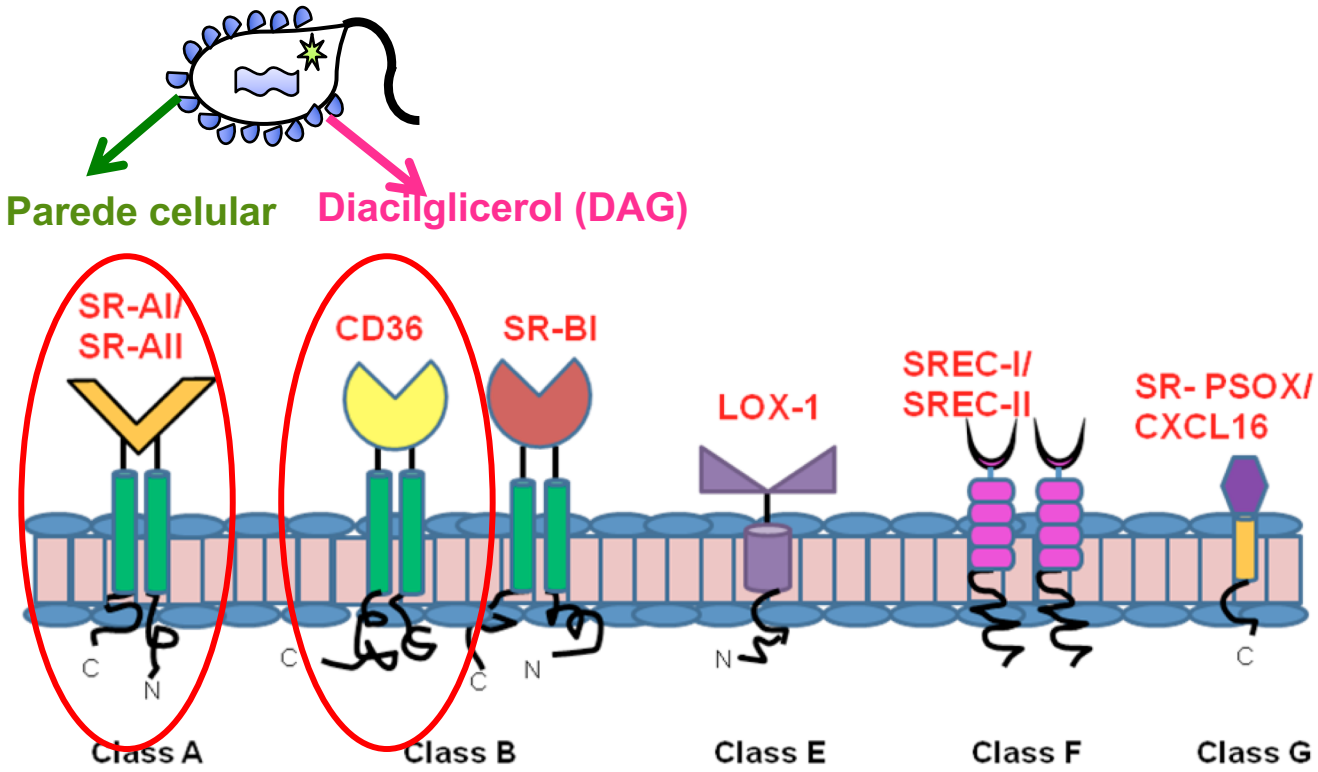
Yang Liu et al, 2015

Receptores de fagocitose

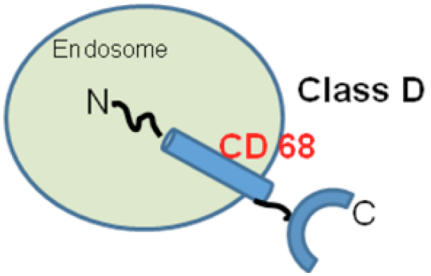
Receptores Scavanger

PAMPs: LPS, acido lipoteicoico, acidos nucleicos, ß-glucanas e proteinas.

DAMPs: LDL, HDL



SR-A	Lipopolysaccharide (LPS), lipoteichoic acid (LTA) (bacteria)
SR-B	LTA, lipopeptides, diacylglycerides (bacteria), β-glucans (fungi)

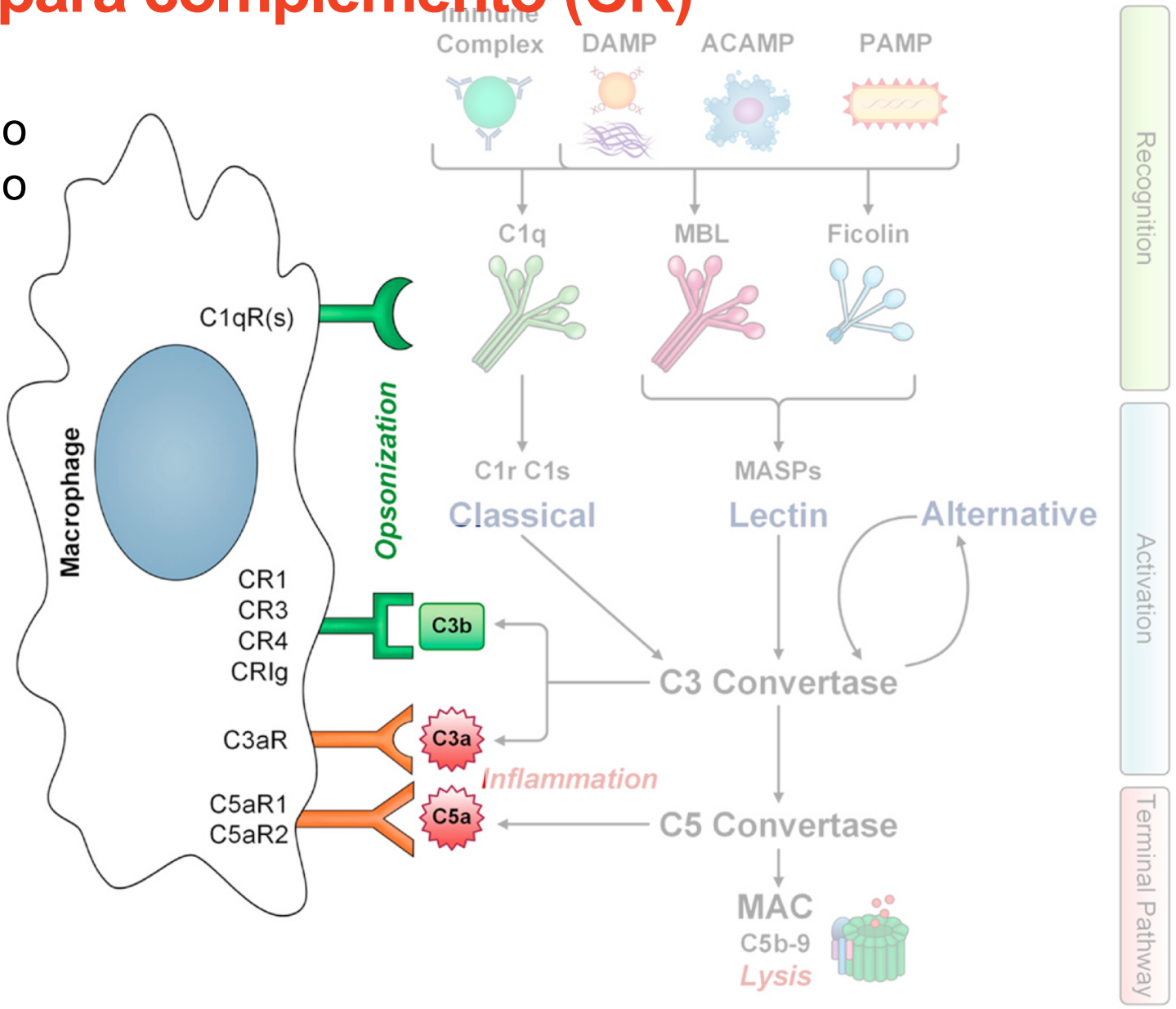


From Kuby 7 ed

Reconhecimento indireto

Receptores para complemento (CR)

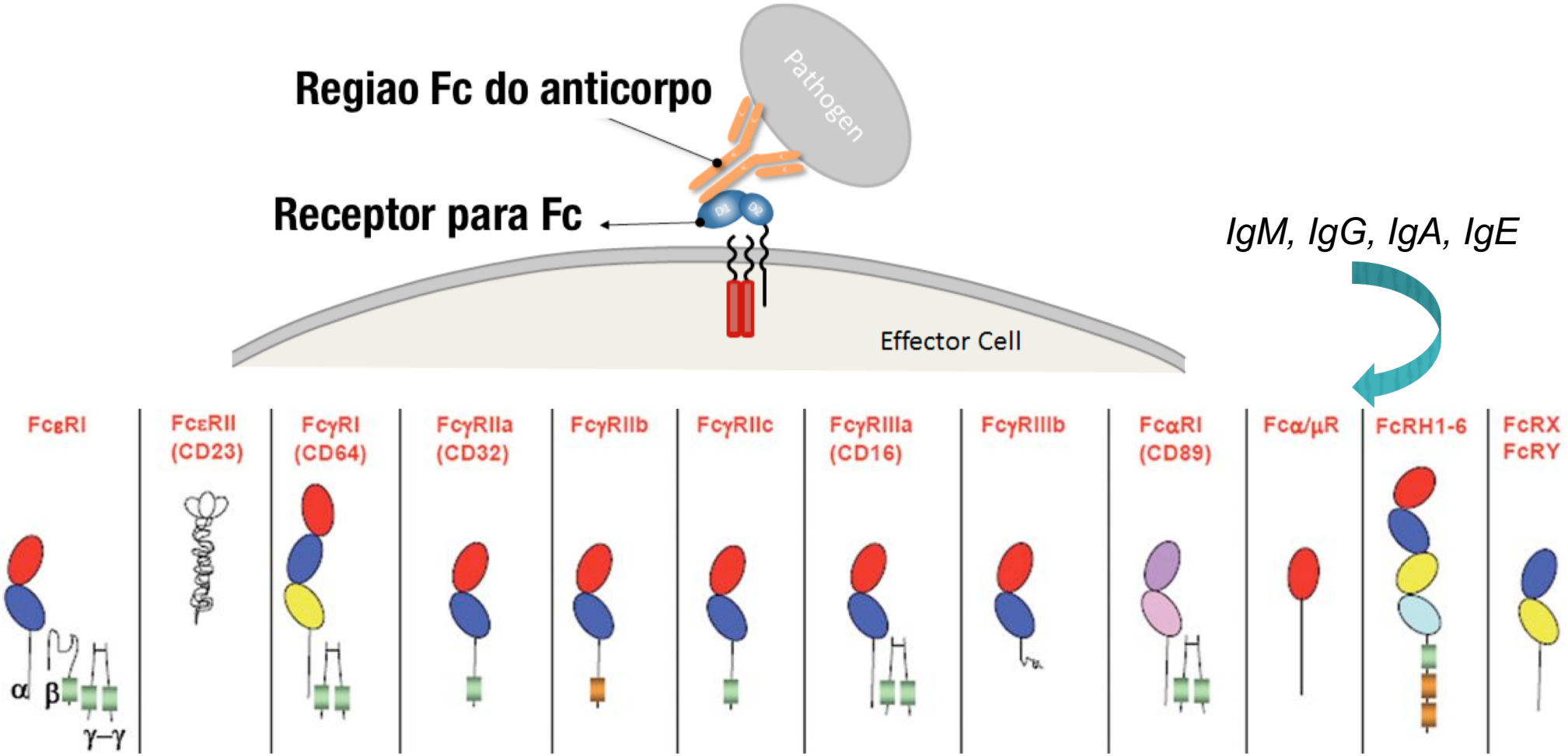
- Fagocitose
- Desgranulaçao
- Pro-inflamaçao



Reconhecimento indireto

Receptores para Fc dos AC (FcR)

- Fagocitose (muito aumentada na presença de AC!)
- Desgranulaçao



PRRs e indução de respostas inatas

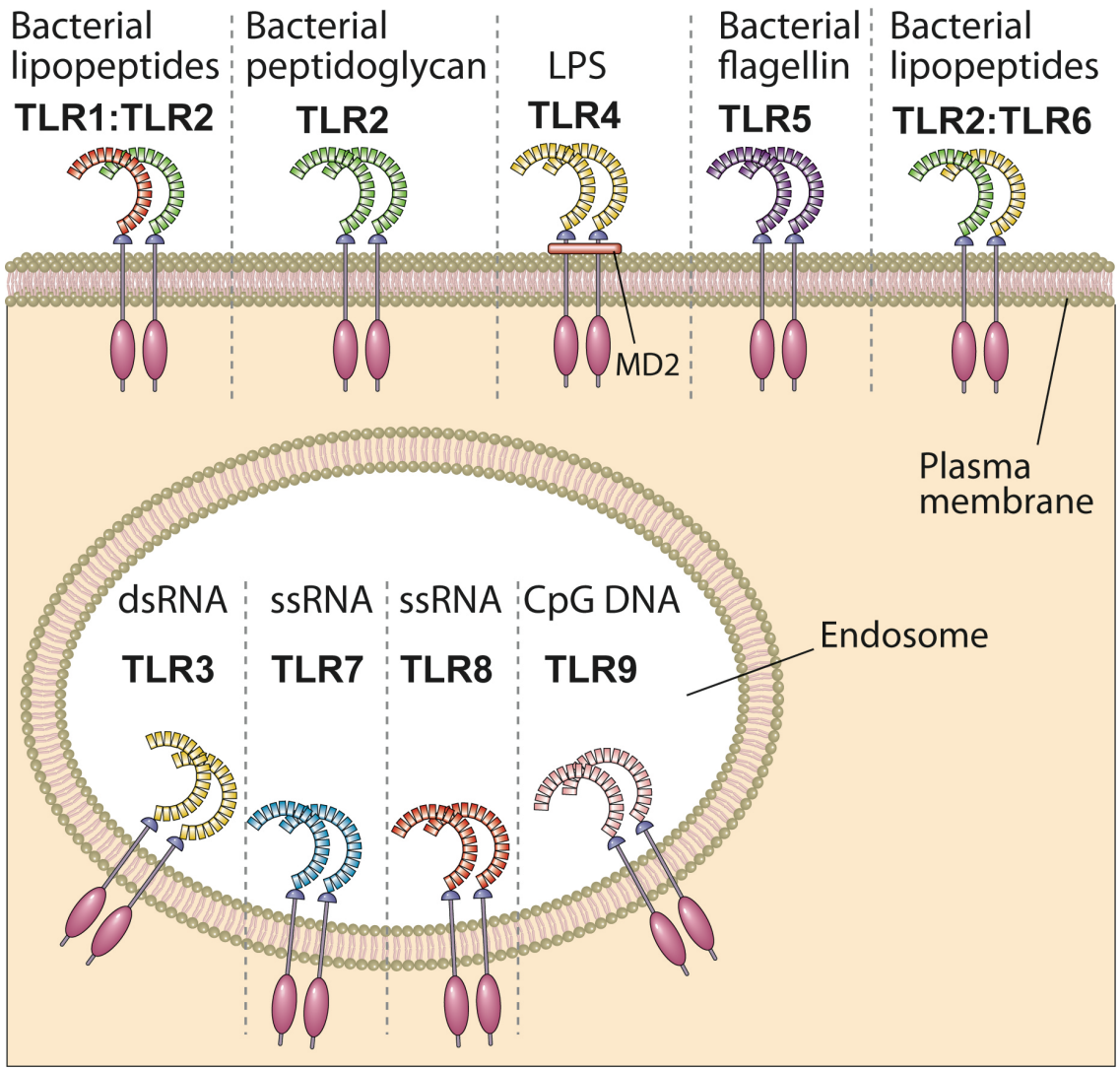
Existem receptores que nao estao envolvidos na fagocitose e que desenvolvem um papel importante na imunidade inata

Ativando vias de sinalizaçao que levam a expressao de genes imunes:

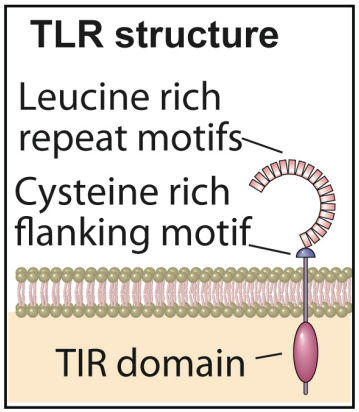
- moleculas antimicrobianas (AMPs, IFNs)
- Enzimas (iNOS)
- Quimiocinas
- Citocinas

Tanto de membrana (**TLR**s) que citosolicos (**NLRs**)
Expressos in leucocitos e celulas non-imunes

Receptores semelhantes a Toll (TLRs)



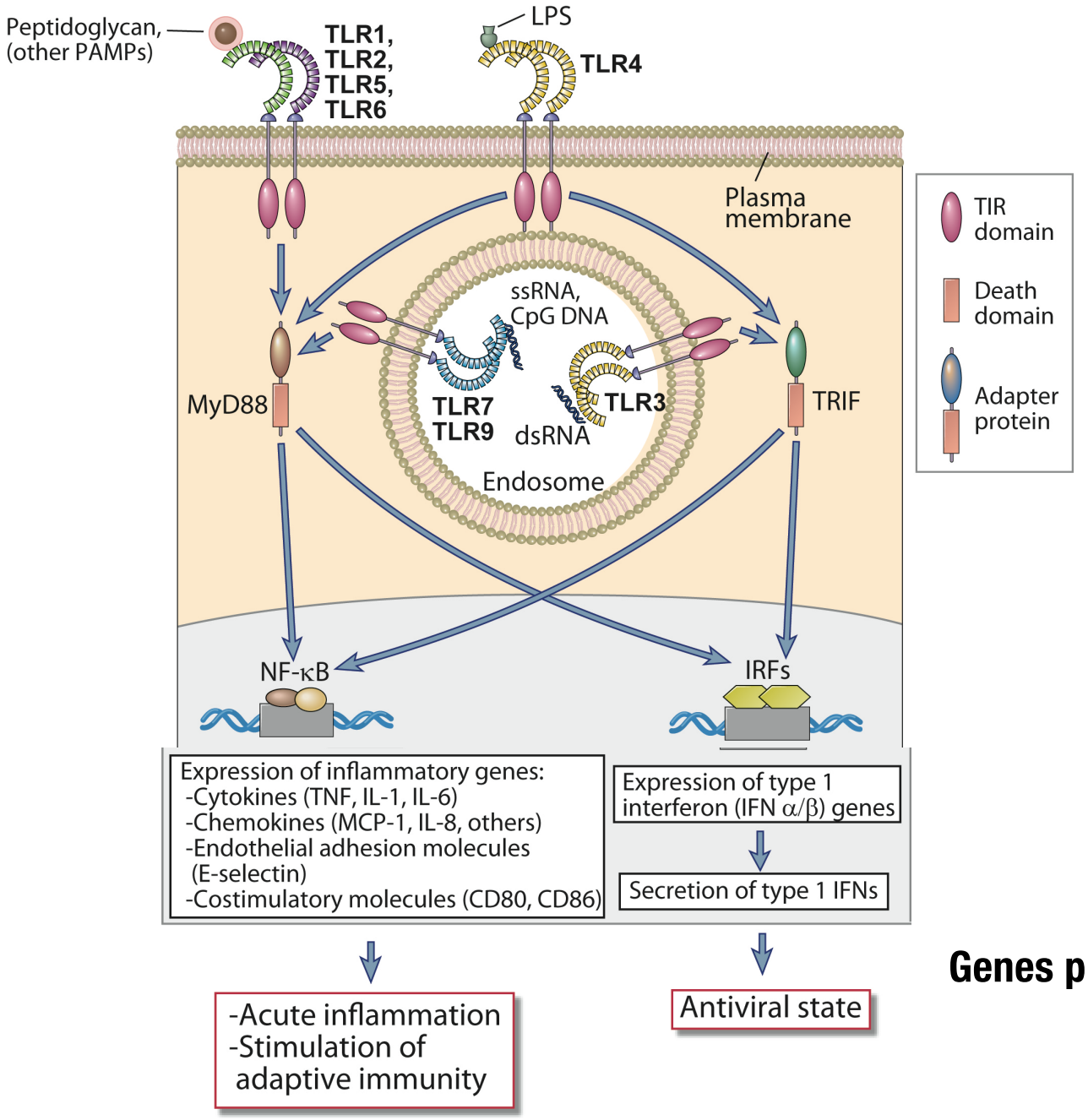
- Dimeros (homo ou hetero)
- Membrana celular (bacteria PAMPs)
- Endosomes (viral PAMPs)



TLRs

Reconhecimento imune inato pelos TLRs de mamíferos		
Receptor TCR	**Ligante**	**Distribuição celular**
Heterodímero TLR-1:TLR-2 Heterodímero TLR-2:TLR-6	Lipomananos (micobactérias) Lipoproteínas (lipopeptídeos diacil; lipopeptídeos triacil) Ácidos lipoteicoicos (bactérias gram-positivas) β-glicanos de parede celular (bactérias e fungos) Zimosano (fungos)	Monócitos, células dendríticas, mastócitos, eosinófilos, basófilos
TLR-3	dsRNA (vírus)	Células NK
TLR-4 (mais MD-2 e CD14)	LPSs (bactérias gram-negativas) Ácidos lipoteicoicos (bactérias gram-positivas)	Macrófagos, células dendríticas, mastócitos, eosinófilos
TLR-5	Flagelina (bactérias)	Epitélio intestinal
TLR-7	ssRNA (vírus)	pDCs, células NK, eosinófilos, células B
TLR-8	ssRNA (vírus)	Células NK
TLR-9	DNA com CpG não metilado (bactérias e herpes-vírus)	pDCs, eosinófilos, células B, basófilos
TLR-10	Desconhecido	pDCs, eosinófilos, células B, basófilos
TLR-11 (somente em camundongos)	Profilina e proteínas semelhantes à profilina (*Toxoplasma gondii*, bactérias uropatogênicas)	Macrófagos, células dendríticas, células epiteliais do fígado, dos rins e da bexiga

TLRs



Dimerizaçao

Sinalizaçao
Myd88,TRIF

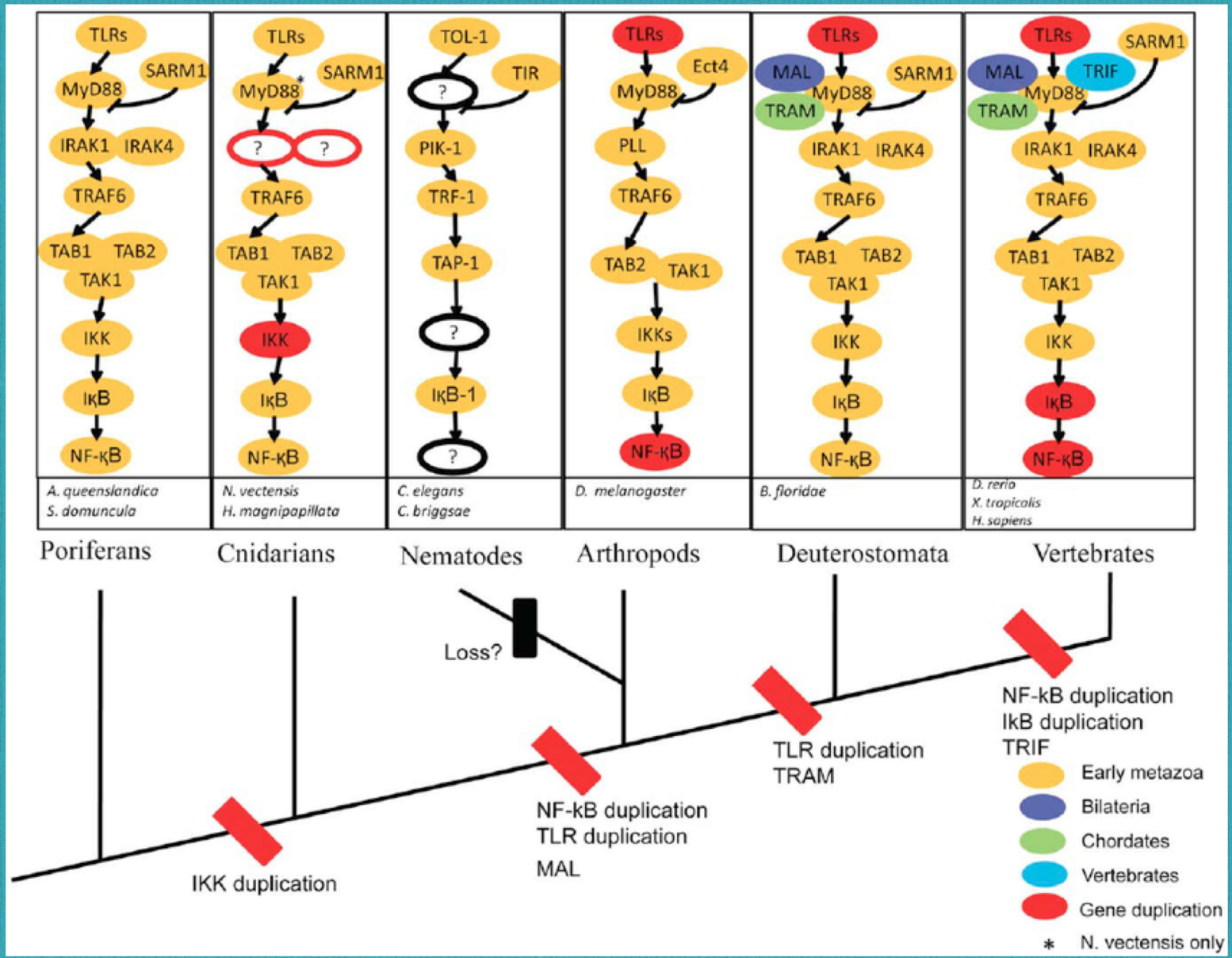
NF-kB **IRFs**

Expressao genica

Genes pro-inflamatorios

Interferon de tipo I

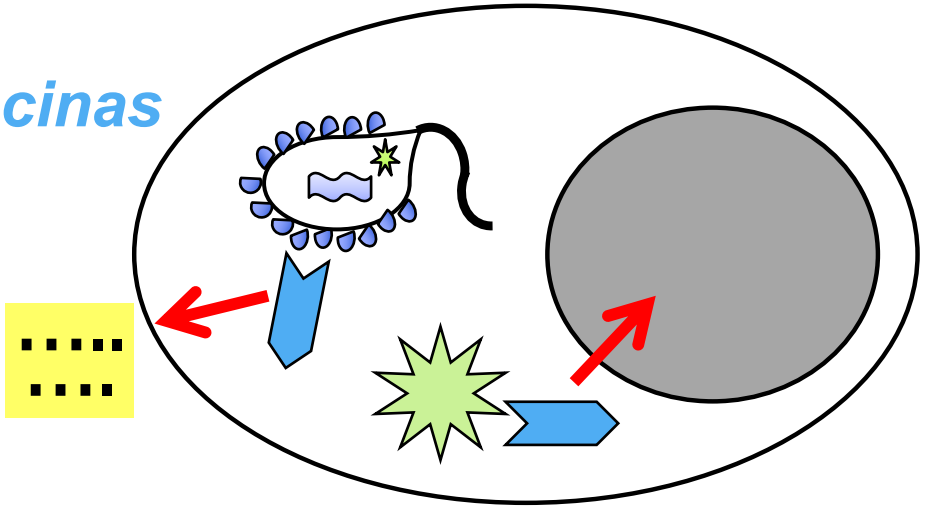
Filogenia dos TLRs



PRRs citoplasmaticos

Liberaçao citocinas

PRR
- *NLRs*



Via de sinalizaçao intracelular
Trascriçao geni de defesa ou MORTE

- NF-kB: citocinas, quimiocinas, AMPs
- IRFs: interferon tipo I

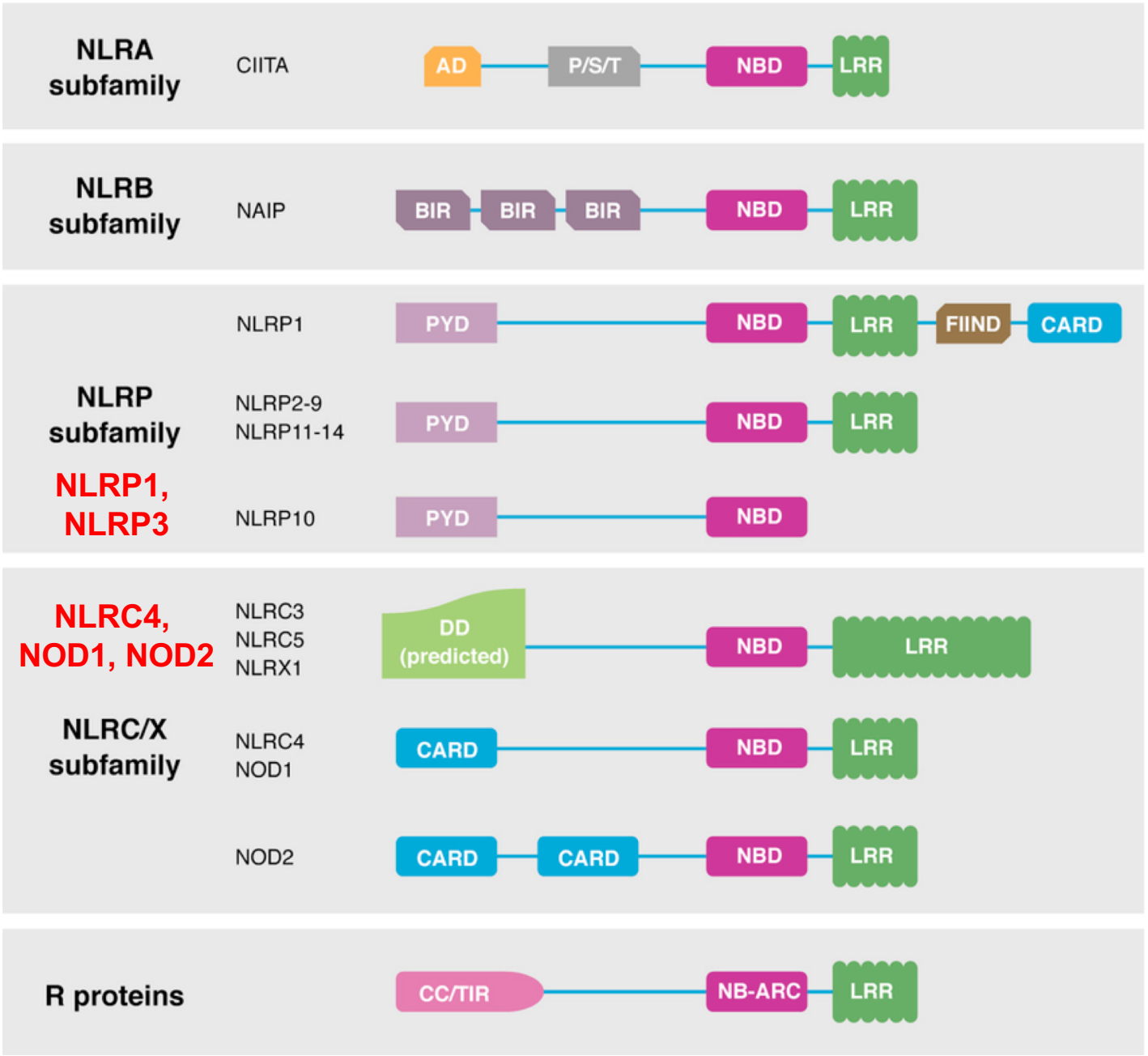
PRR
- *NLRs*
- *ALRs*

Receptores com NBD e LRR (NLRs)

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

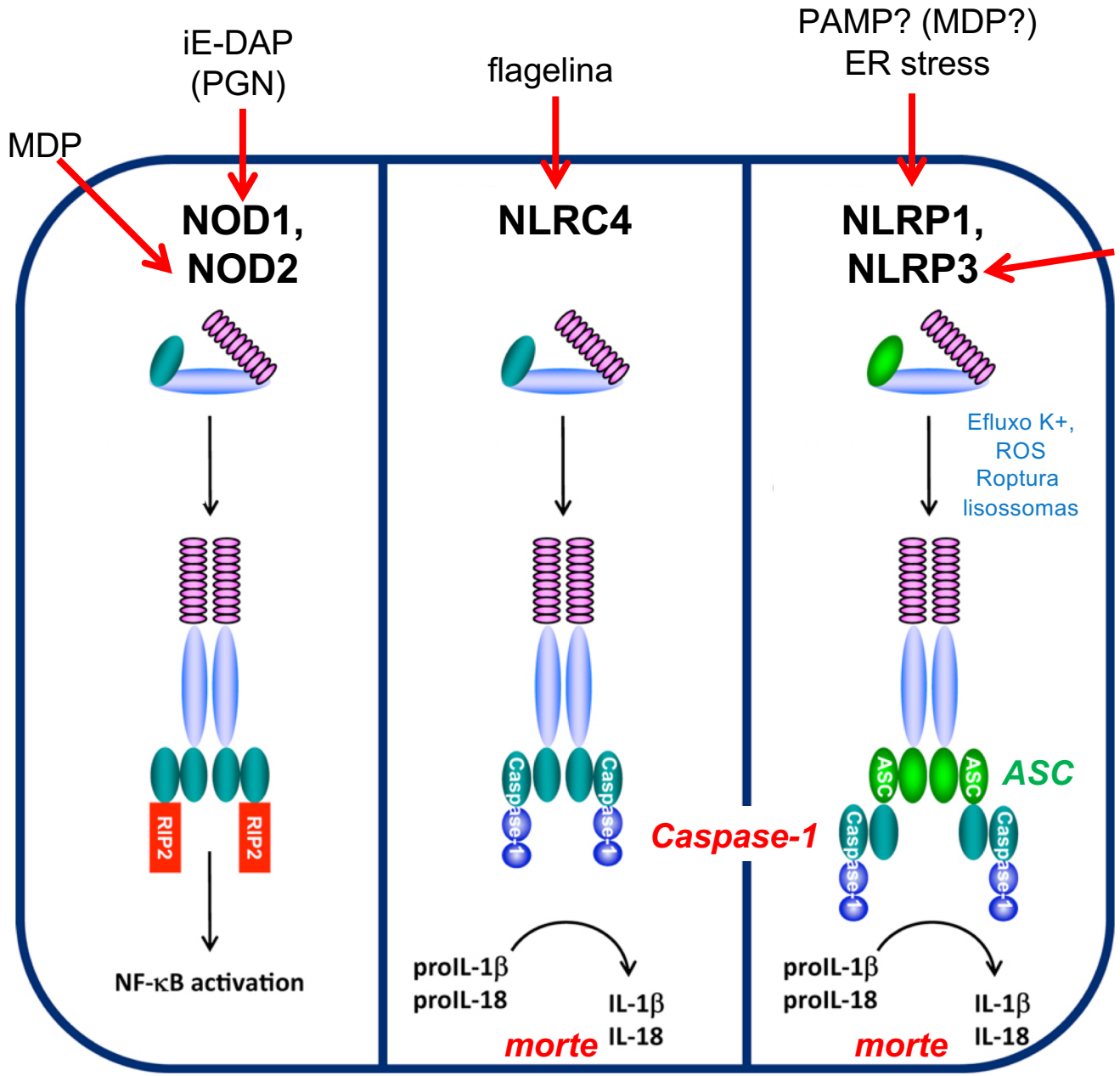
- PYD pyrinico (NLRP)
- CARD recrutamento caspase (NLRC)

- NLRs montam inflamassomas: NLRP1, NLRP3, NLRC4
- NLRs attivam NF-kB: NOD1, NOD2



Tuncer, 2014

Receptores com NBD e LRR (NLRs)

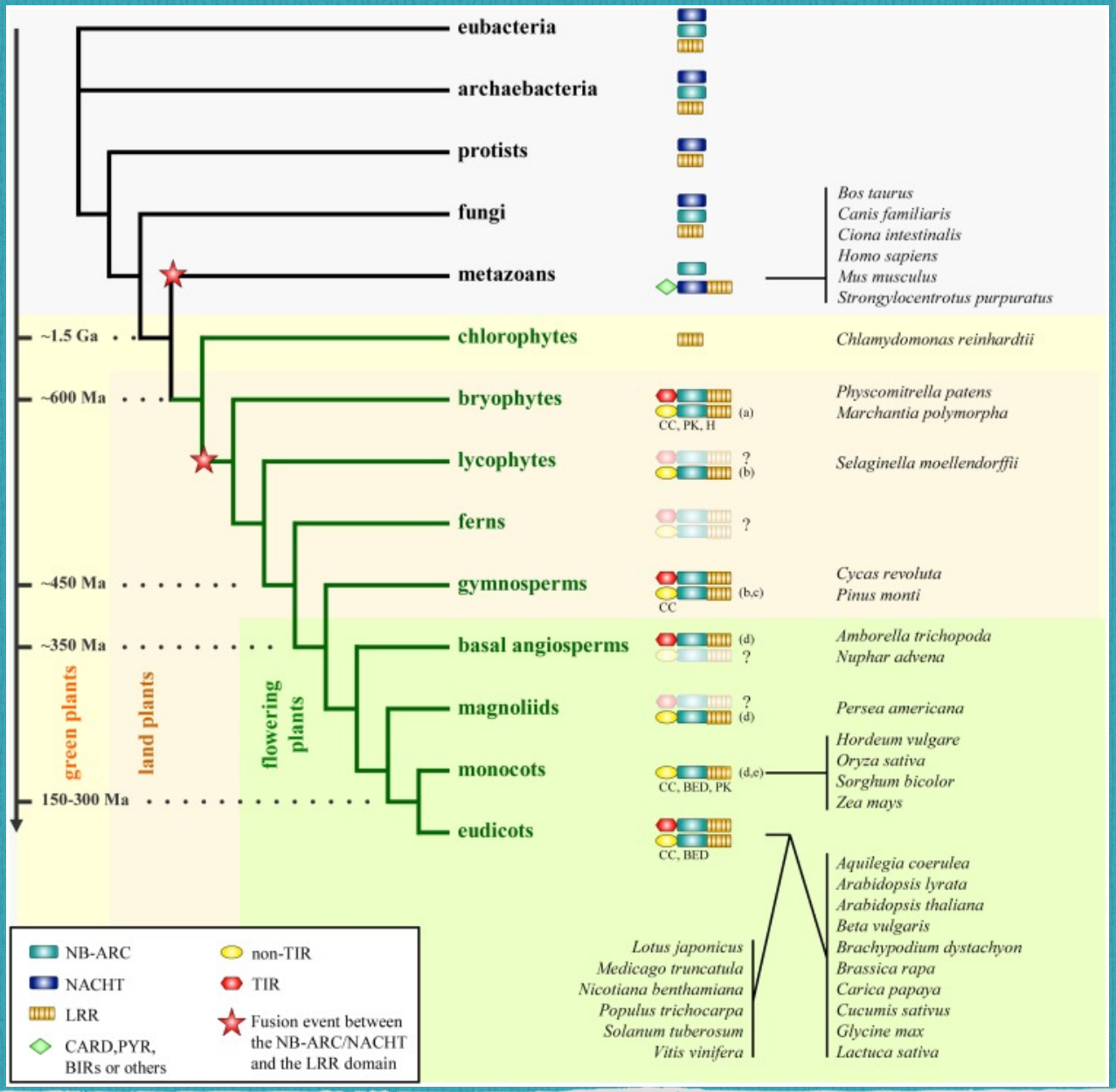


Bacteria
Viruses
Fungi
Protozoa
Toxins
DNA, RNA

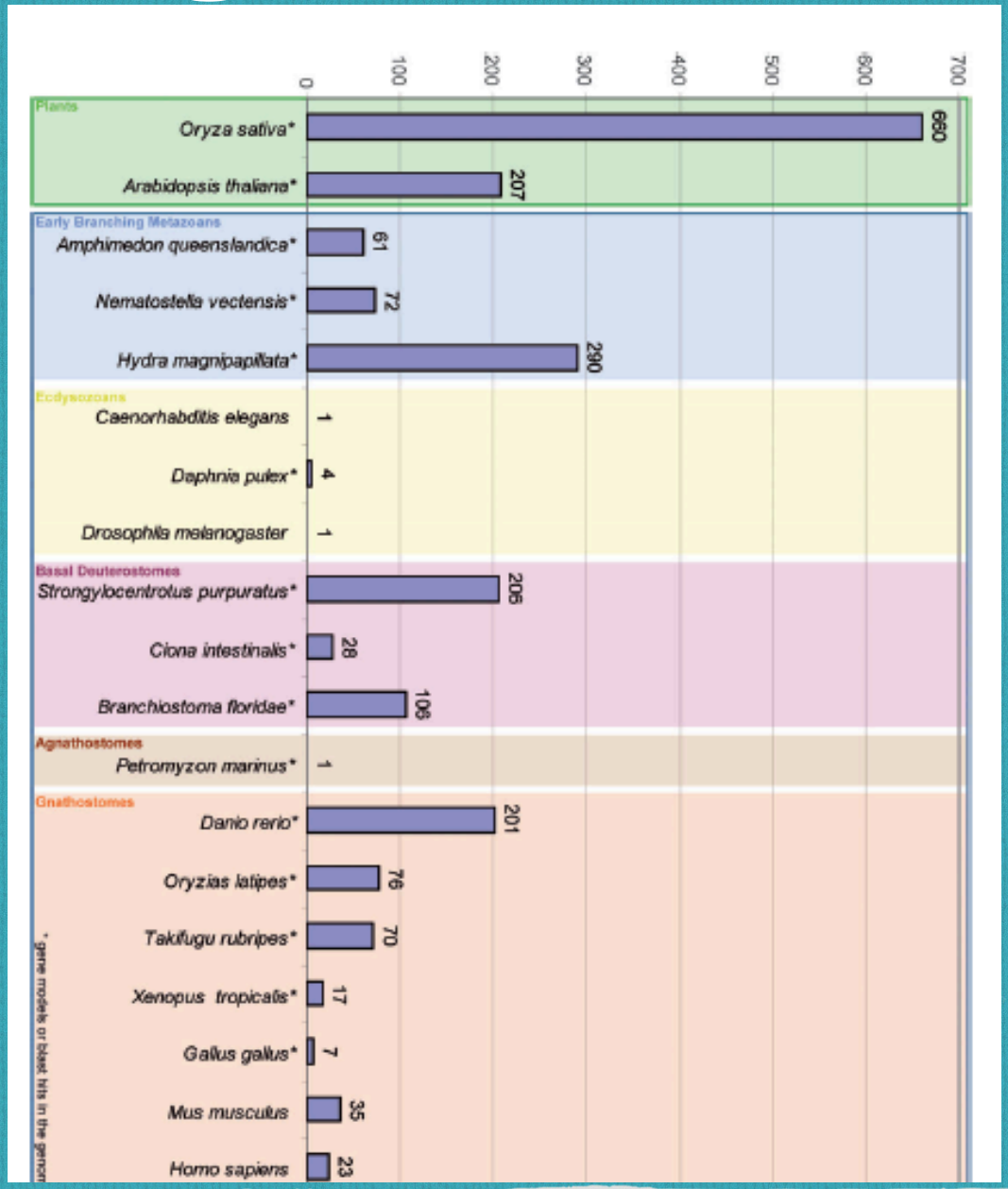
Enviromental DAMPs:
silica, asbestos, alum

Endogenous DAMPs:
ATP, uric acid, ß-amyloid,
cholesterol crystal,
saturated fatty acid

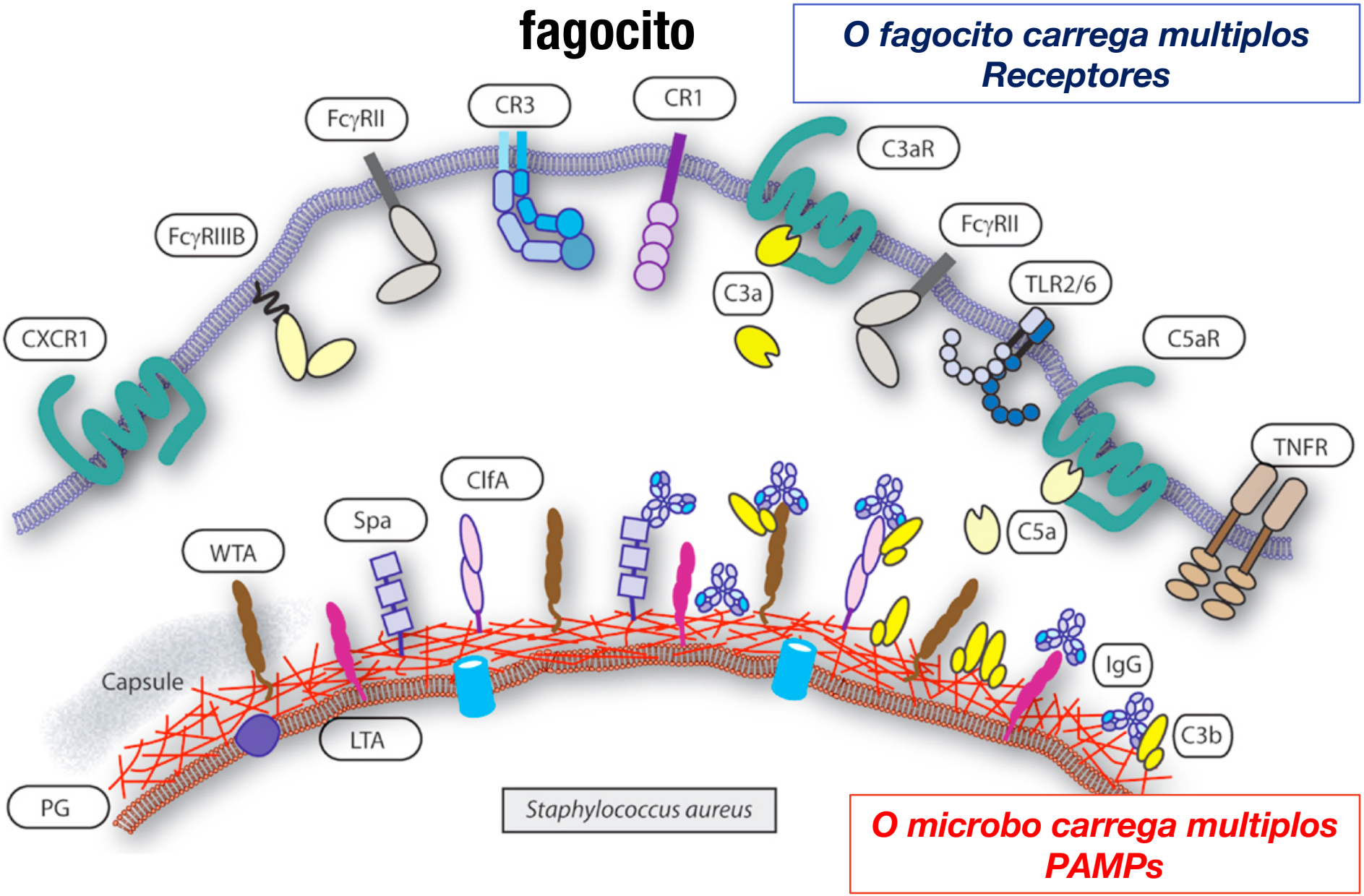
Filogenia dos NLRs



Filogenia dos NLRs



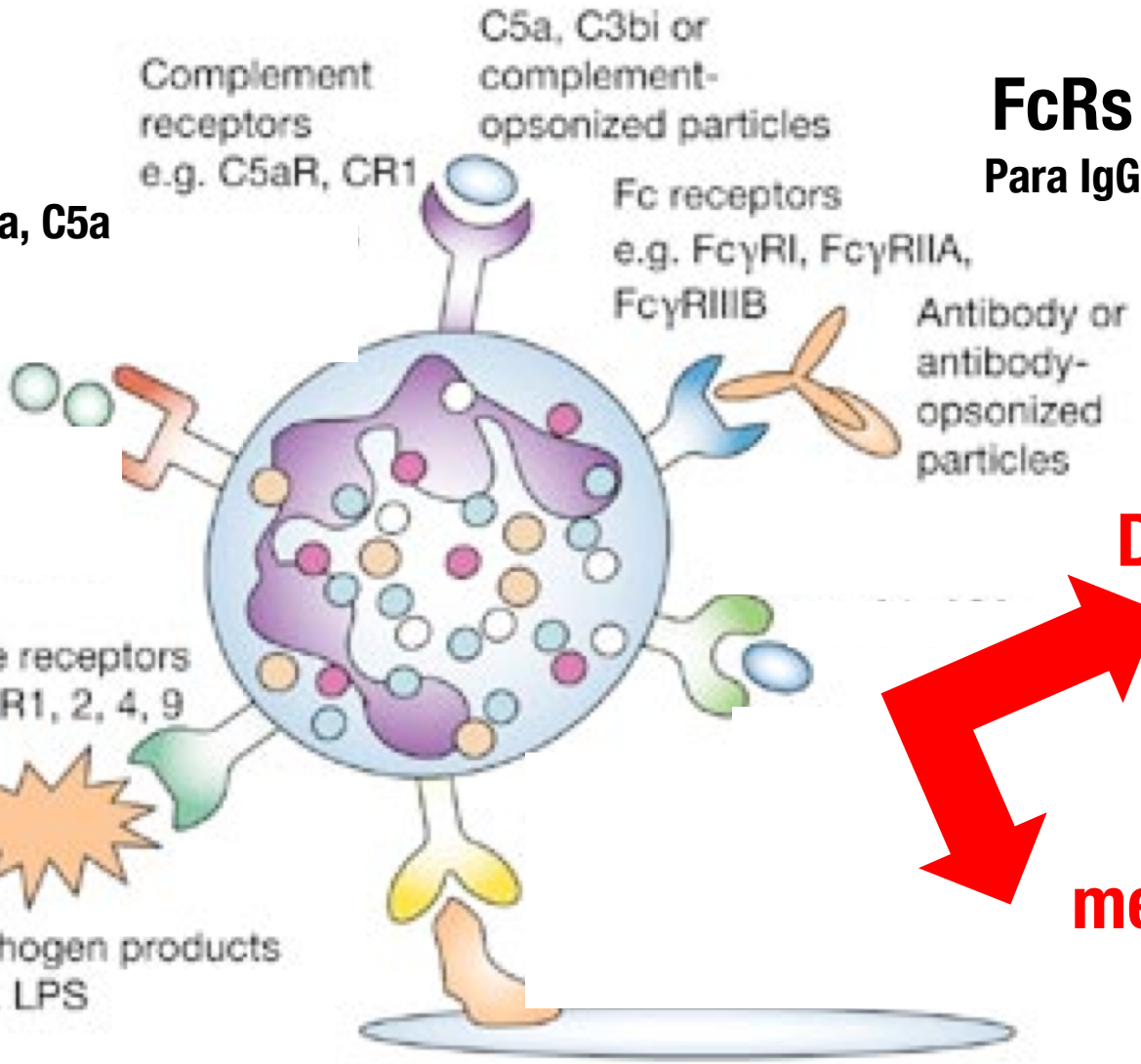
Reconhecimento



Reconhecimento por neutrofilo

CRs
Para C3b, C3a, C5a

FcRs
Para IgG

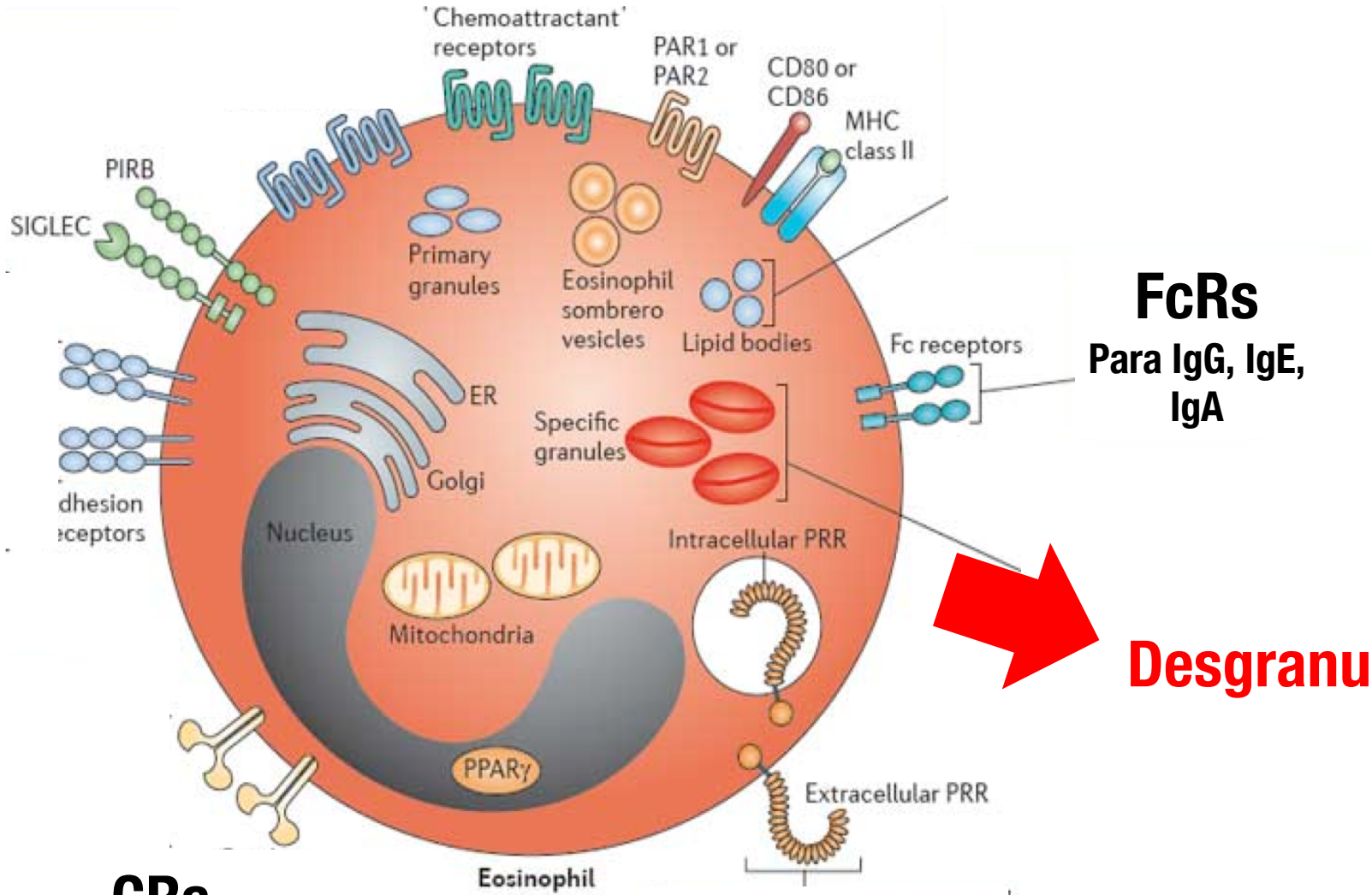


PRRs
TLRs, NLRs

Fagocitose
Desgranulaçao
NETs

mediadores

Reconhecimento por eosinofilo



FcRs

Para IgG, IgE, IgA

Desgranulaçao

CRs

PRRs

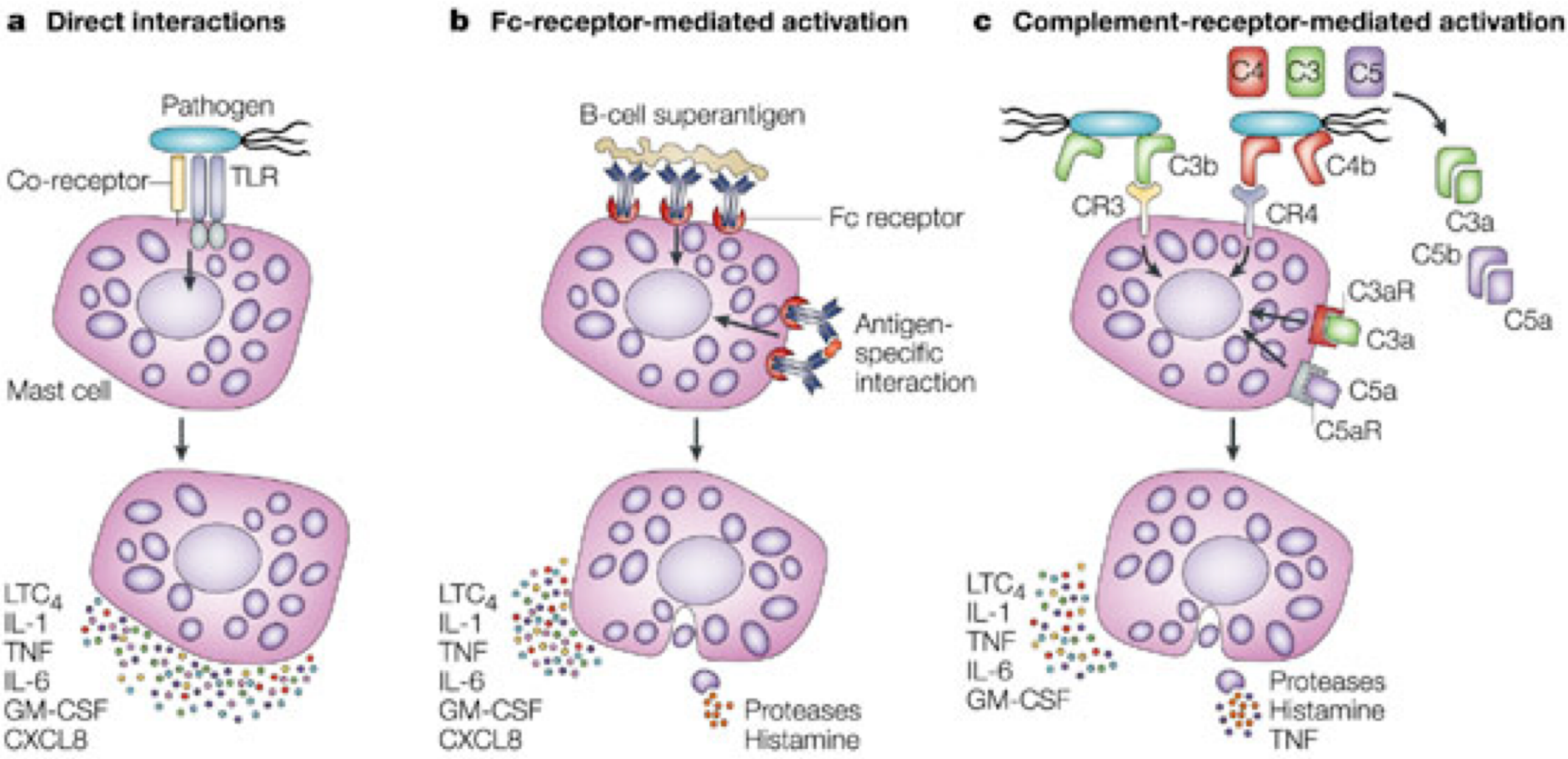
TLRs, NLRs

Reconhecimento por mastocitos

PRRs
TLRs, NLRs

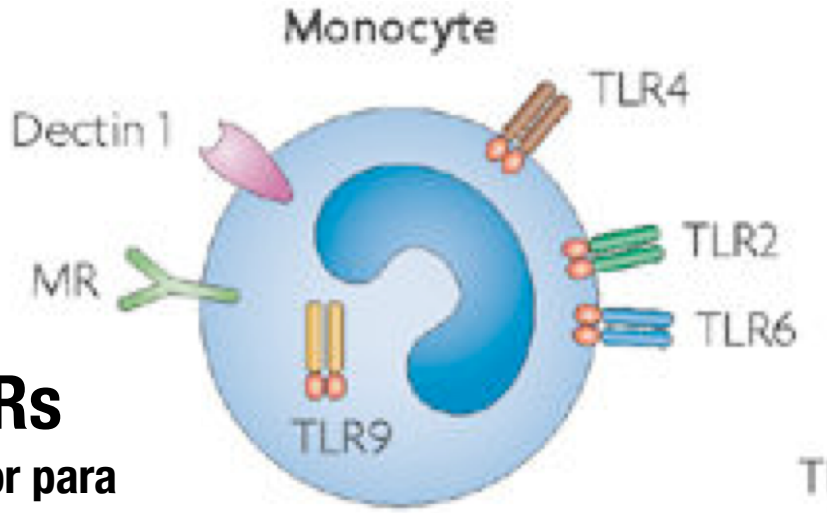
FcRs
para IgG, IgE

CRs
C3b, C4b, C3a, C5a



Desgranulaçao

Reconhecimento por monocitos/Mø

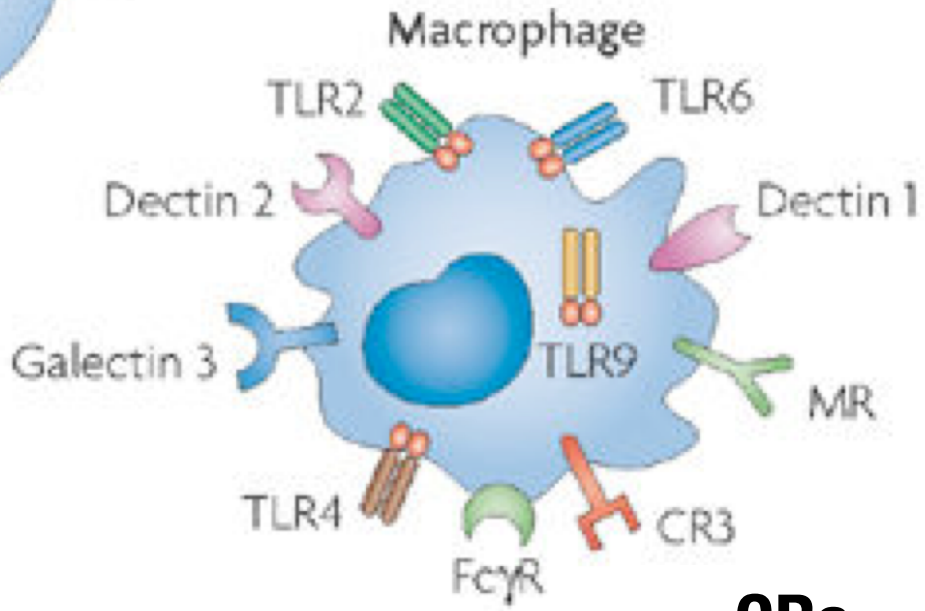


PRRs

TLRs, NLRs

PRRs

Receptor para Manose, Scavanger



Fagocitose

mediadores

FcRs

Para IgG

CRs

C3b, C3a, C5a

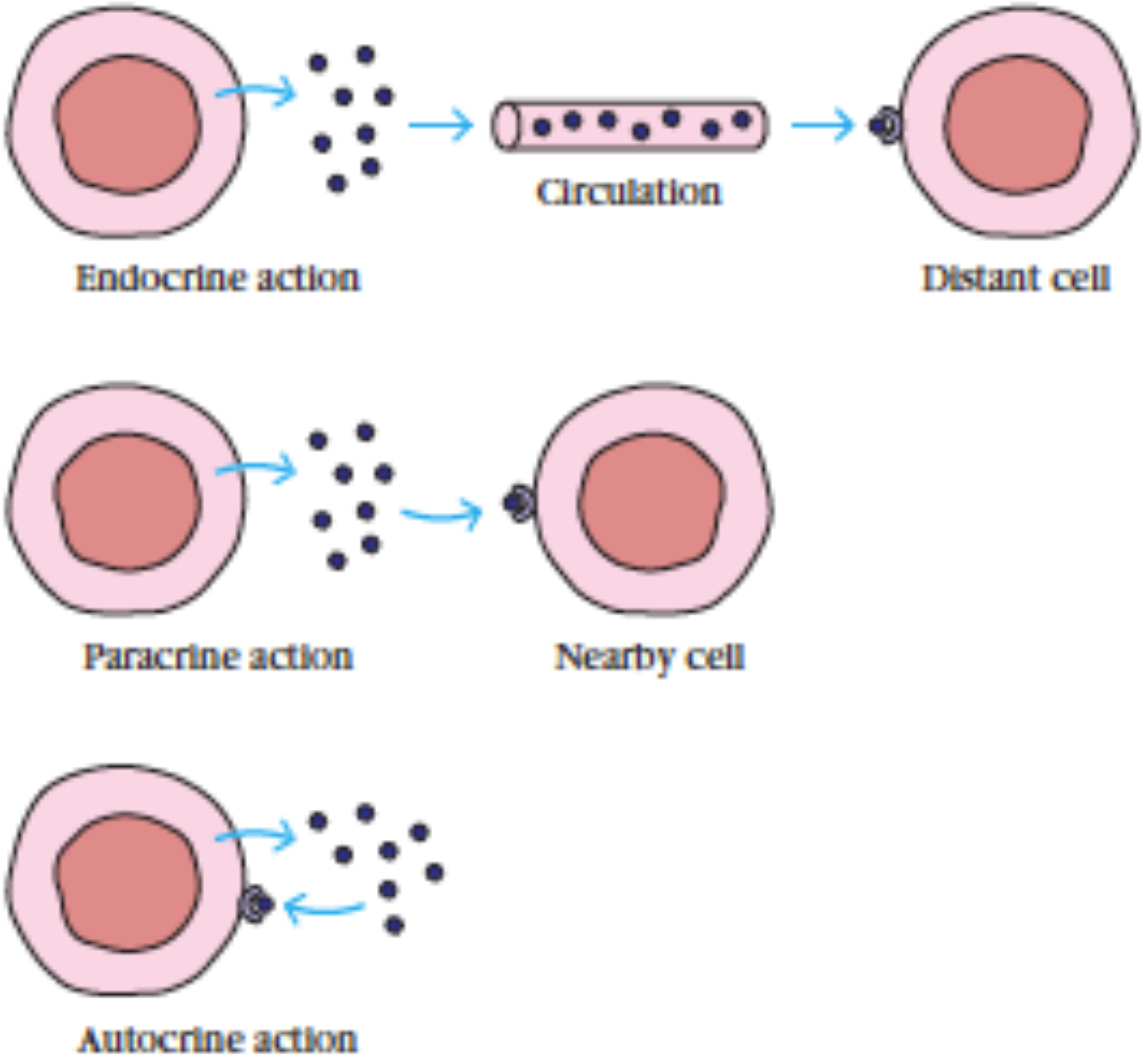
Moleculas induzidas pelos PRRs

Açao anti-microbicida direta

PRRs — *antimicrobicida*; *citocinas*; *quimiocinas*

Inflamaçao

NF-kB: inflamaçao
IRFs: IFNs



Moleculas induzidas pelos PRRs

citocinas	Produtor	Alvo	Acao
IL-6	Monocytes, macrophages, dendritic cells, NK cells, epithelial cells, vascular endothelial cells	Lymphocytes	Regulates activity
		Bone marrow	Promotes hematopoiesis → neutrophils
		Vascular endothelium	Activates; increases vascular permeability
		Liver	Induces acute-phase response
		Hypothalamus	Fever
TNF	Monocytes, macrophages, dendritic cells, mast cells, NK cells, epithelial cells	Macrophages	Activates
		Vascular endothelium	Activates, increases vascular permeability, fluid loss, local blood clotting
		Liver	Induces acute-phase response
		Hypothalamus	Fever
		Tumors	Cytotoxic for many tumor cells
GM-CSF	Macrophages, vascular endothelial cells	Bone marrow	Stimulates hematopoiesis → myeloid cells

Moleculas induzidas pelos PRRs

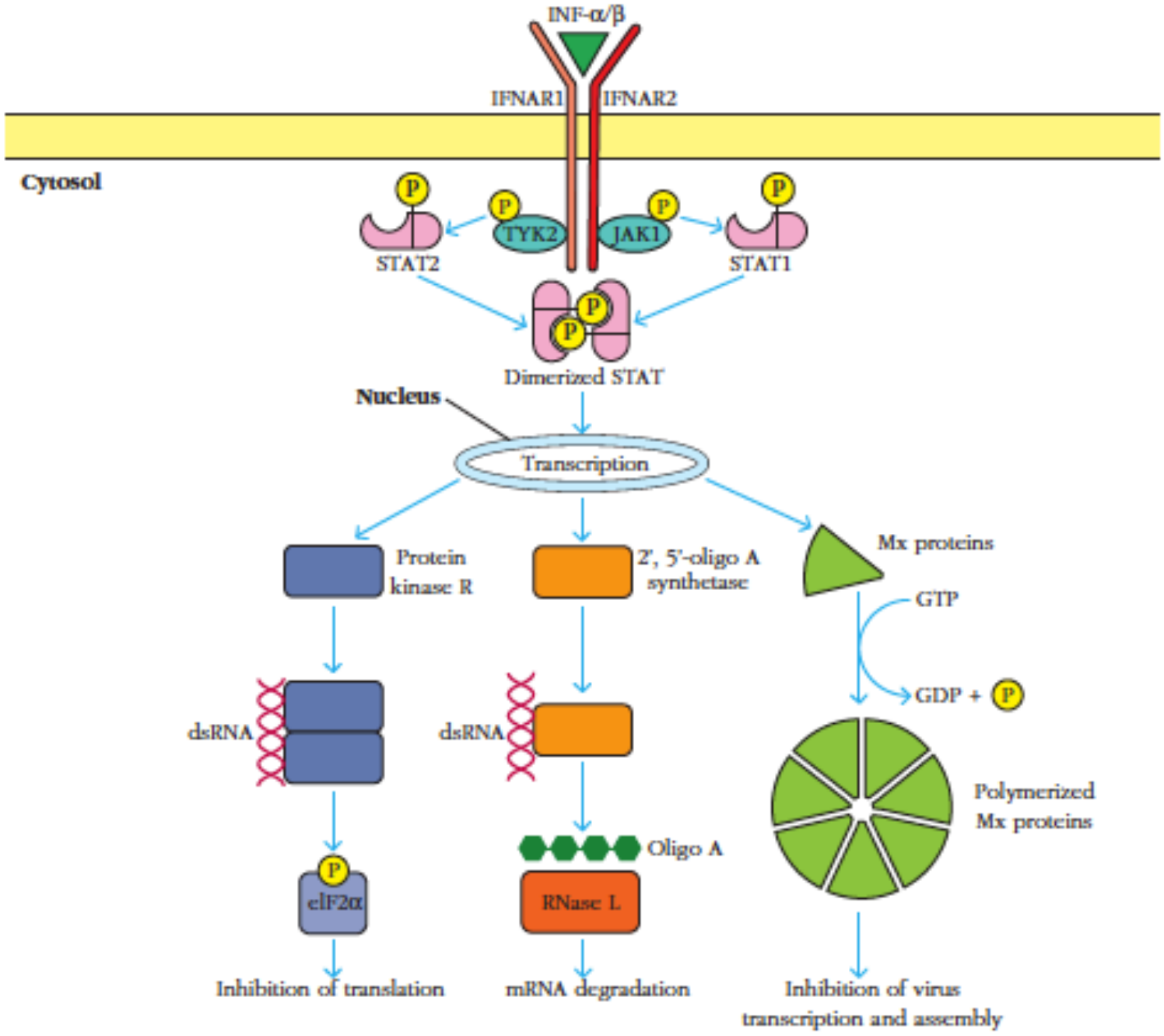
citocinas	***Produtor***	***Alvo***	***Acao***
IL-1ß	Monocytes, macrophages, dendritic cells, keratinocytes, epithelial cells, vascular endothelial cells	Lymphocytes Bone marrow Vascular endothelium Liver Hypothalamus	Enhances activity Promotes neutrophil production Activates; increases vascular permeability Induces acute-phase response Fever
IL12, IL-18	Monocytes, macrophages, dendritic cells	Naïve CD4 T cells Naïve CD8 T cells, NK cells	Induce T_H1 phenotype, IFN-γ production Activate

quimiocinas	***Produtor***	***Alvo***	***Acao***
IL-8/CXCL-8	Macrophages, dendritic cells, vascular endothelial cells	Neutrophils, basophils, immature dendritic cells, T cells	Chemoattracts cells to infection site

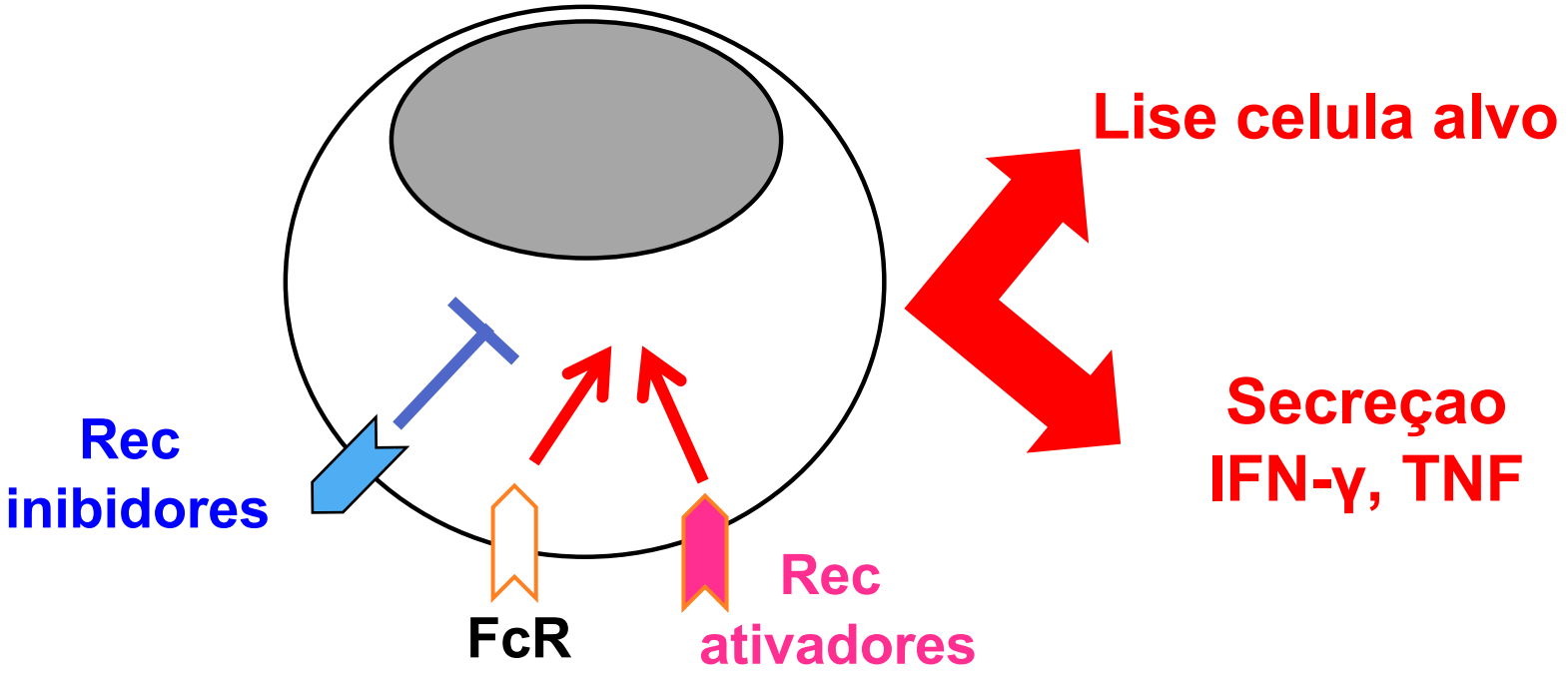
Moleculas induzidas pelos PRRs

antimicrobial	***Produtor***	***Alvo***	***Acao***
Defensinas Catelicidina	Epithelia (e.g., oro/nasal, respiratory, intestinal, reproductive tracts; skin keratinocytes, kidney); NK cells	Pathogens	Inhibit, kill
		Monocytes, immature dendritic cells, T cells	Chemoattractant; activate cytokine production
		Mast cells	Activate degranulation
IFN-α, -β	Virus-infected cells, macrophages, dendritic cells, NK cells	Virus-infected cells	Inhibit virus replication
		NK cells	Activate
		Macrophages, T cells	Regulate activity
iNOS	Phagocytes, epithelia	Pathogens	NO production, killing
COX2	Phagocytes, mast cells	Leukocytes, endothelial cells Epithelial cells	Converting arachidonic acid into prostaglandins (inflammation)

Acao anti-viral dos IFN tipo I



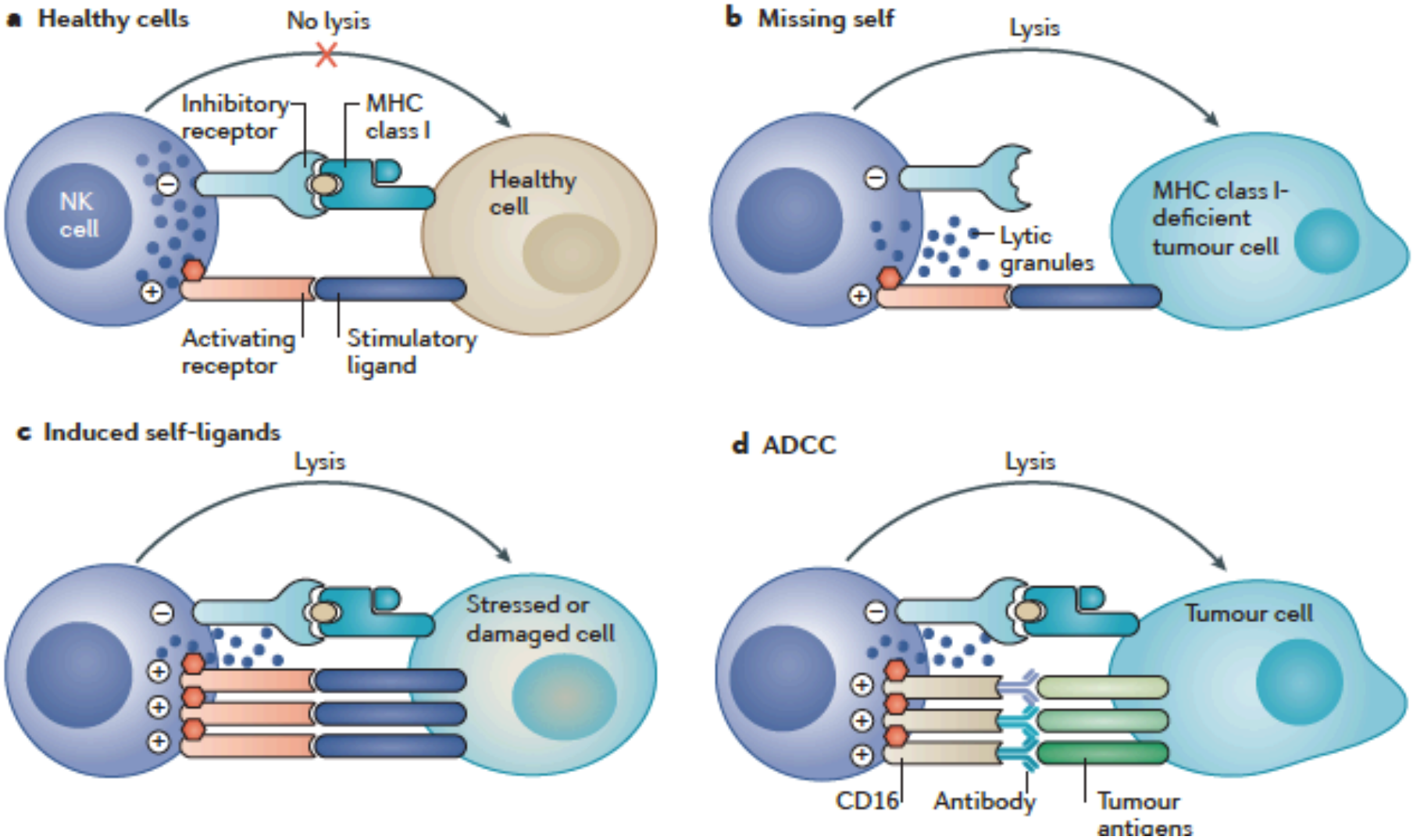
Reconhecimento por celulas NK



Receptores de celulas danificadas/infectadas

- **Inibidores** reconhecem ligandos nas celulas saudaveis
- *Rec Inib para MHC-I*
- **Ativadores** reconhecem ligandos nas celulas danificadas/infectadas
- **FcγR** ligam AC (ADCC)

Reconhecimento por celulas NK



Moleculas induzidas pelos NK R

citocinas	Produtor	Alvo	Acao
TNF	Monocytes, macrophages, dendritic cells, mast cells, NK cells, epithelial cells	Macrophages	Activates
		Vascular endothelium	Activates, increases vascular permeability, fluid loss, local blood clotting
		Liver	Induces acute-phase response
		Hypothalamus	Fever
		Tumors	Cytotoxic for many tumor cells
IFN-γ	NK cells, T lymphocytes	Mø, NK cells, B lymphocytes	Activate Mø and increase killing activity Increase NK activity, modulate AC production by B lymphocytes

Moleculas liticas

perforina	NK cells, T CD8+ lymphocytes	Celulas danificadas, Infectadas, tumorais	Pore formation in plasma membranes
granzima	NK cells, T CD8+ lymphocytes	Celulas danificadas, Infectadas, tumorais	Induçao de apoptose

Acao litica de perforina/granzimas