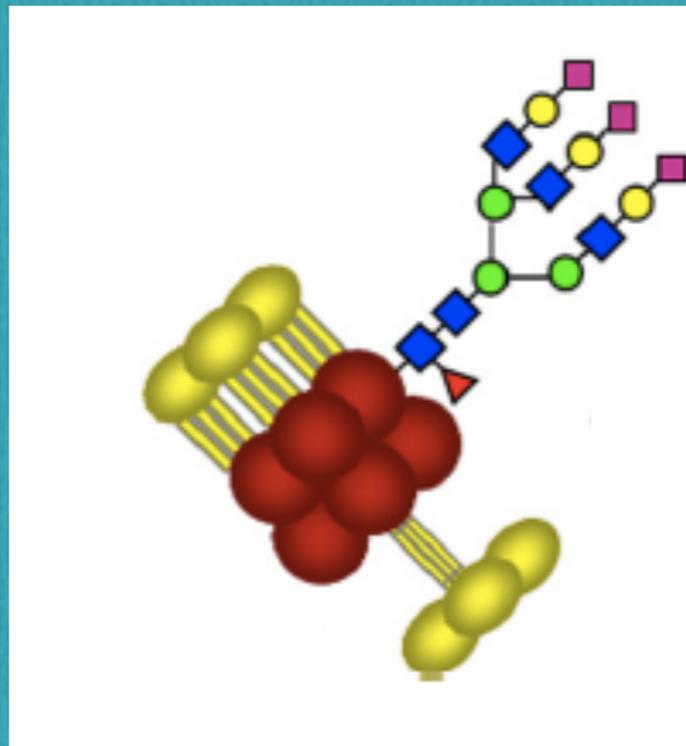


Programa de Pós-graduação em Imunologia ICB/USP

Disciplina BMI 5904

Reconhecimento no Sistema Imune



Aula 1

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Lab. Immunogenetica/Dep.Imunologia/ICB/USP

The Danger Model: A Renewed Sense of Self

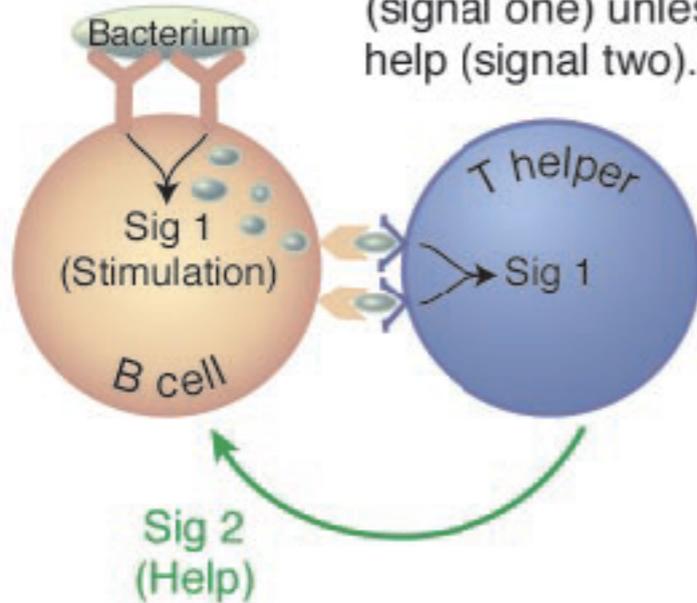
Polly Matzinger

Modelos de Ativação

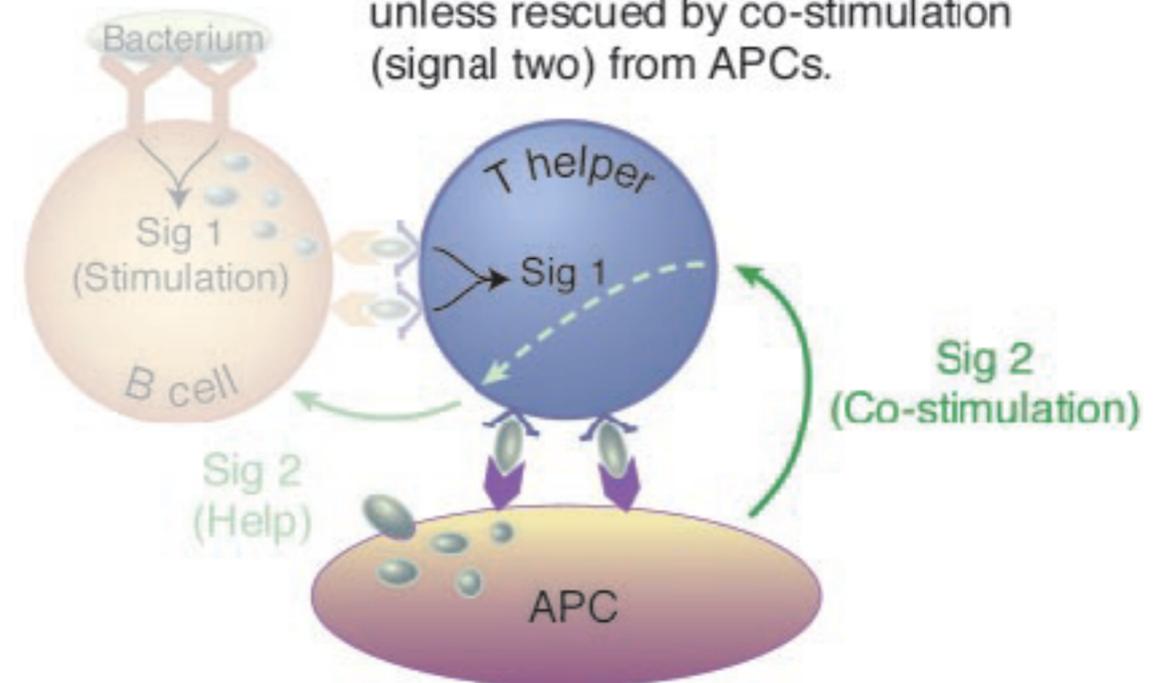
A history of immunological models.



a) 1959, original SNS model said that lymphocytes are activated by recognition of foreign things.

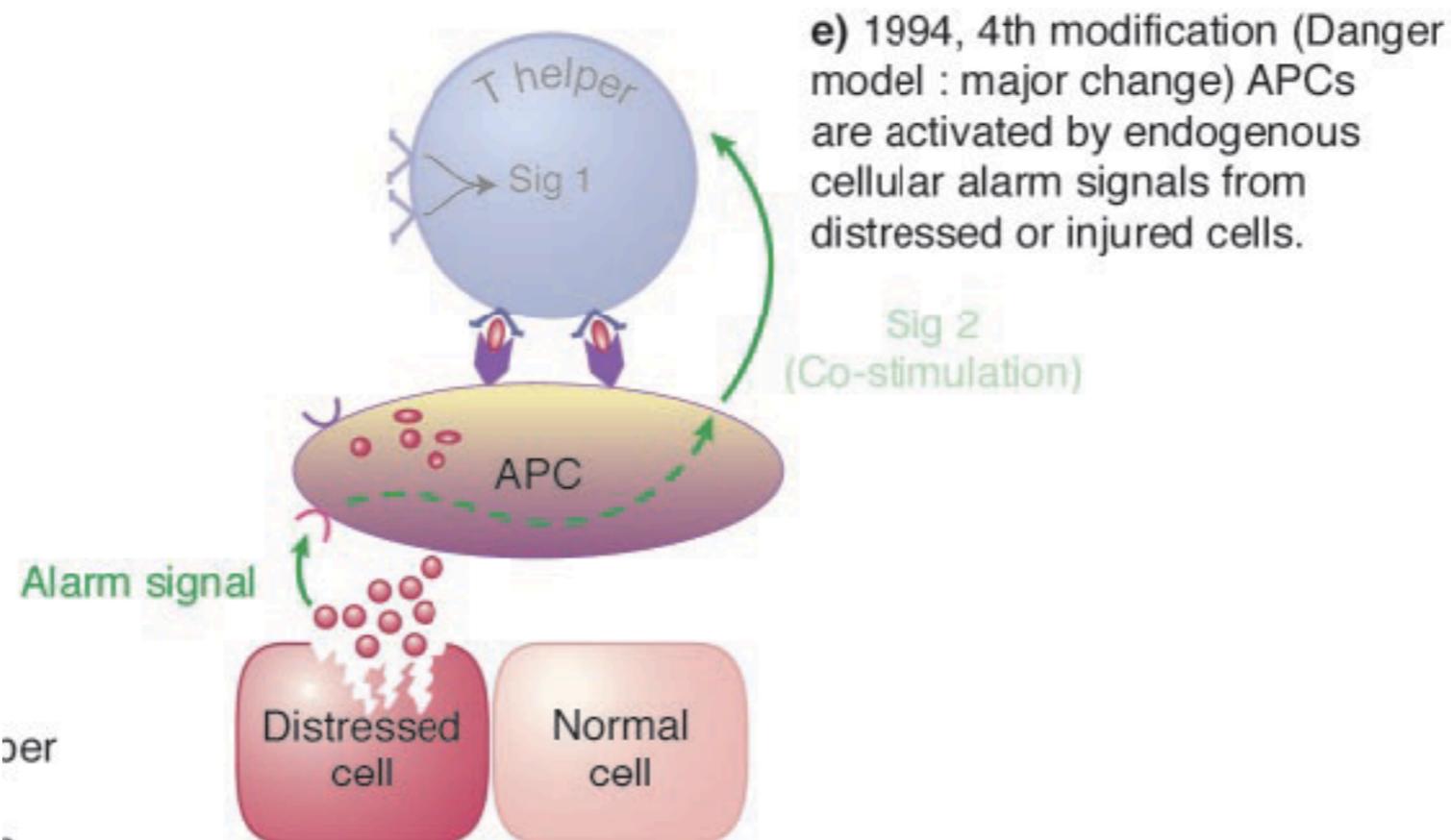
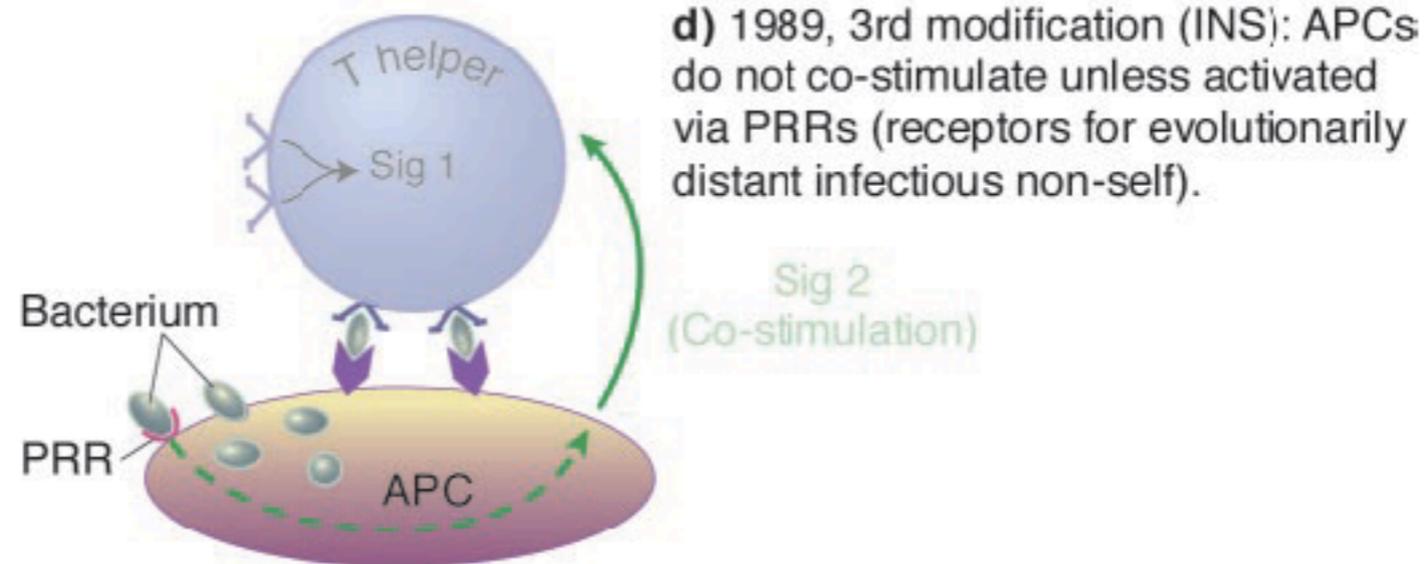


b) 1969, 1st modification: B cells die when they see antigen (signal one) unless rescued by help (signal two).



c) 1975, 2nd modification: T helper cells die when they see antigen unless rescued by co-stimulation (signal two) from APCs.

Modelos de Ativação



per

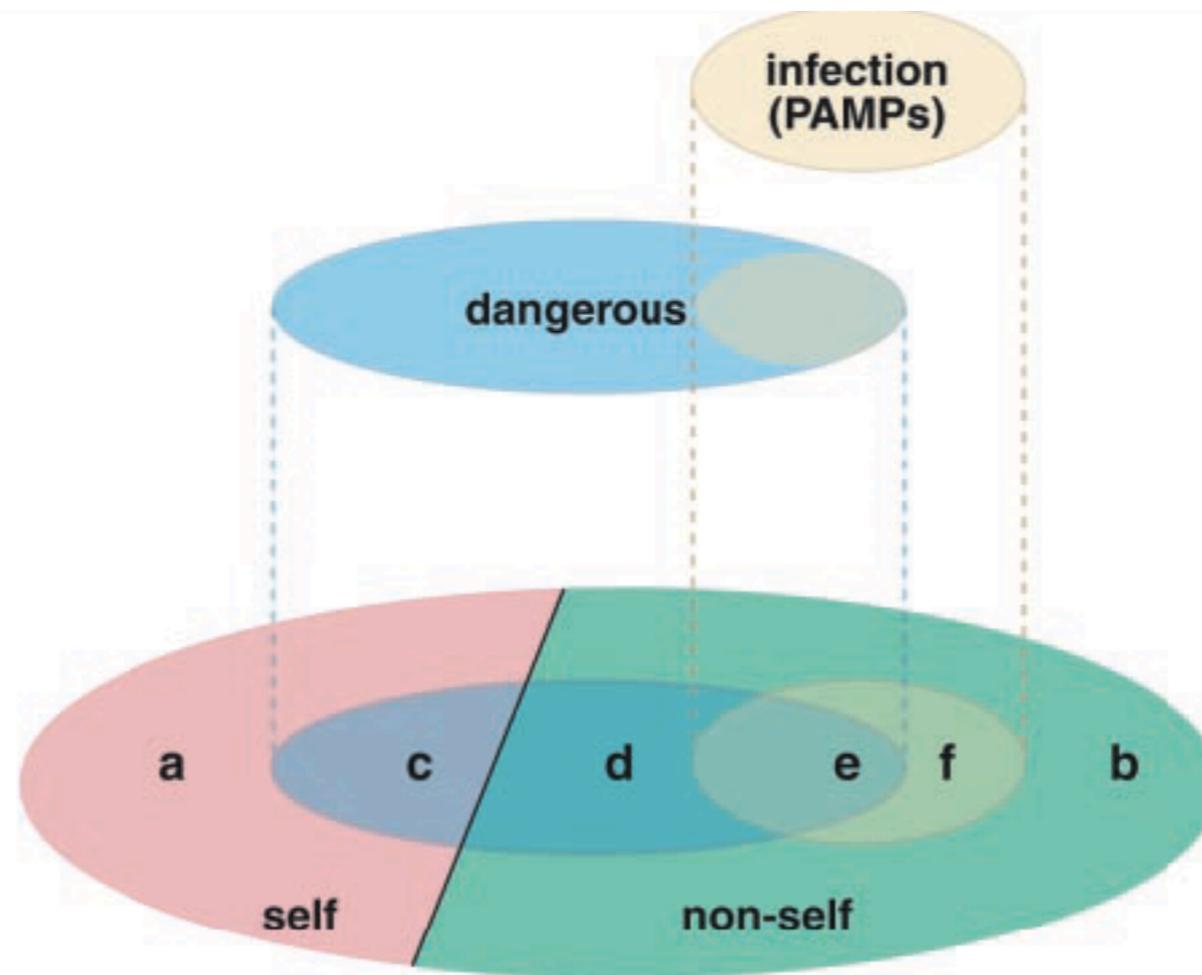
1

Modelos de Ativação

SNS: a (self) vs b (non-self)

INS: a vs f (infectious non-self)

Danger: c (dangerous self) vs e (dangerous non-self pathogen) ou d (dangerous non self environmental); set f = non self but not dangerous



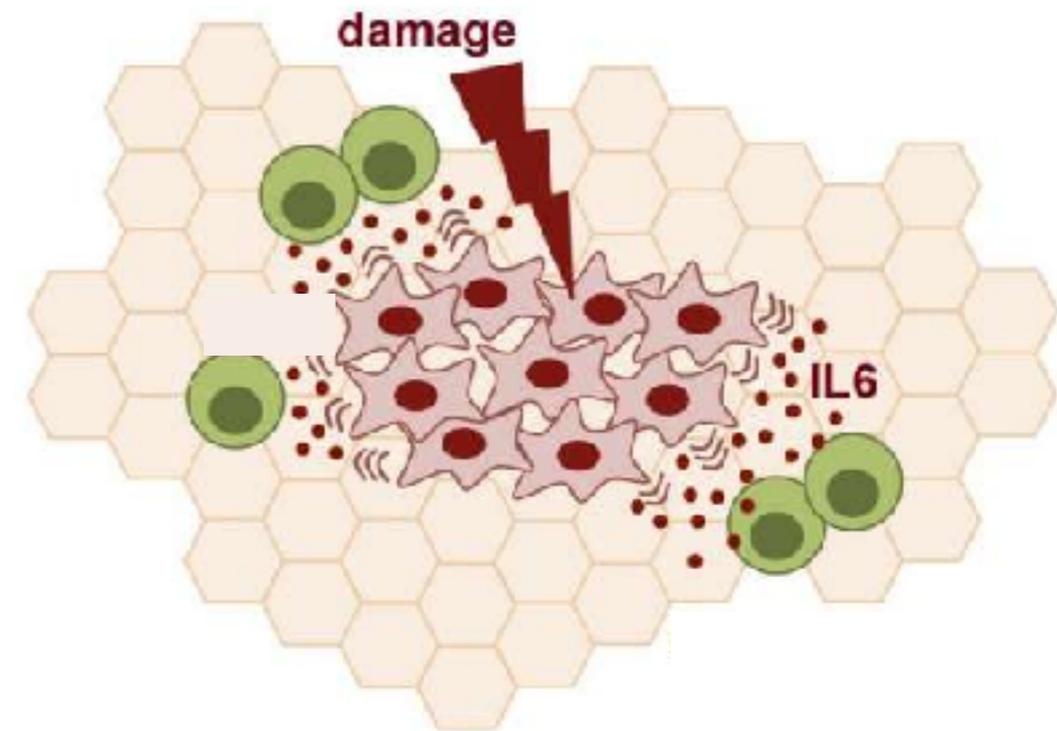
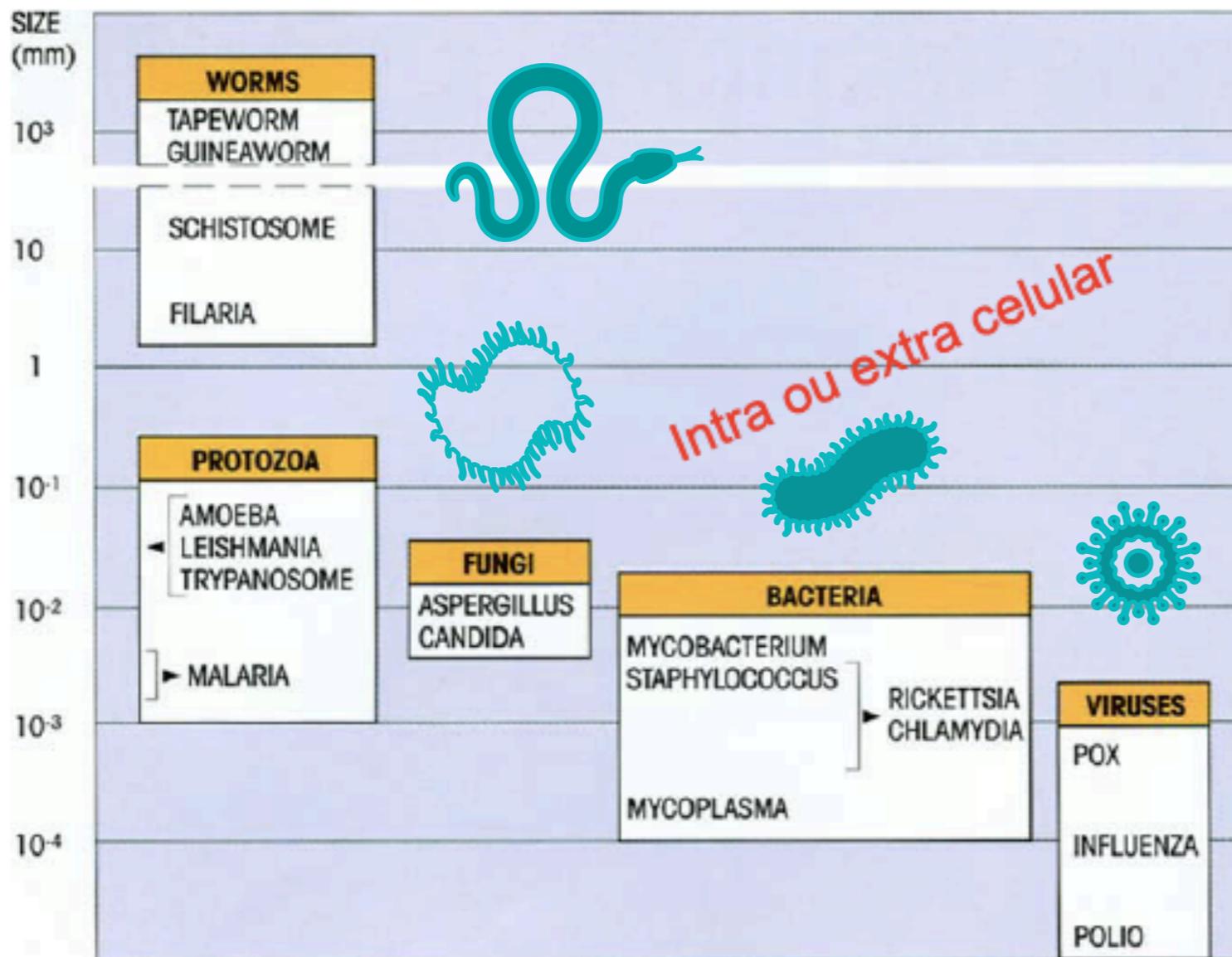
Responses to each set predicted by:	}	SNS	a	b	c	d	e	f
		INS	-	+	-	+	+	+
		Danger	-	-	+	+	+	-

Resposta imune

Eliminação do “insulto”

MICROORGANISMO

PROPRIO TECIDO



destruição do patógeno e/ou da célula

Reconhecimento

SISTEMA IMUNE

“SELF”
ALTERADO

PADRÕES MOLECULARES
(MAMPs, PAMPs, NAMPs,
DAMPs, HAMPs, VAMPs....)

ANTIGENOS
ESPECIFICOS



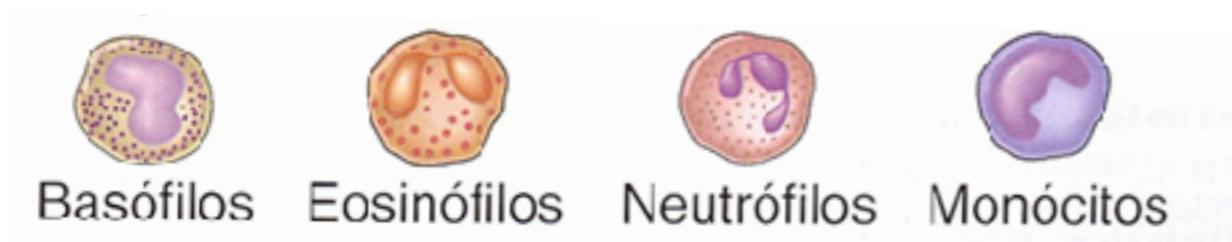
NK Rec



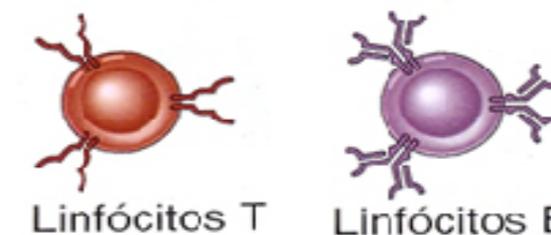
PRRs



TCR, BCR, Ig



Basófilos Eosinófilos Neutrófilos Monócitos



Linfócitos T Linfócitos B

&...todas as outras células

*20-40 genes para reconhecer um limitado
numero de pattern "mais prevalentes e
conservados"*

*Rec com potencial de
reconhecer um amplo leque
de antígenos (recombinação
somática randômica)*

Padrões moleculares

MAMPs or PAMPs: Moléculas com estrutura química/ padrões geralmente conservadas em varias classes de organismos “non-self” MAS ausentes nas moléculas “self”.

MAMPs: Microbe-associated molecular patterns

PAMPs: Pathogen-associated molecular patterns

DAMPs: Danger/Damage-associated molecular patterns

Moléculas “self” liberadas/originadas em resposta a dano (trauma, isquemia, cancer, ...). Podem ser localizadas no núcleo da célula, no citoplasma, nos exosomos, na matriz extracelular. Também agentes físicos e químico que danifica o hospedeiro.

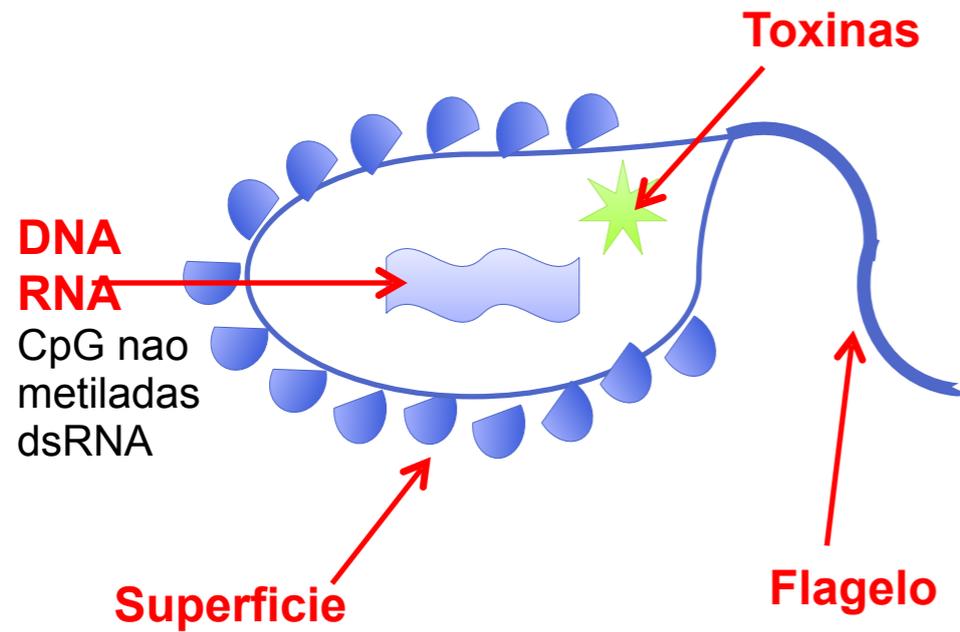
VAMPs: venom-associated molecular patterns

ACAMPs: apoptotic cells molecular patterns (fosfatidilserina, anexina)

PAMPs & DAMPs

PAMPs

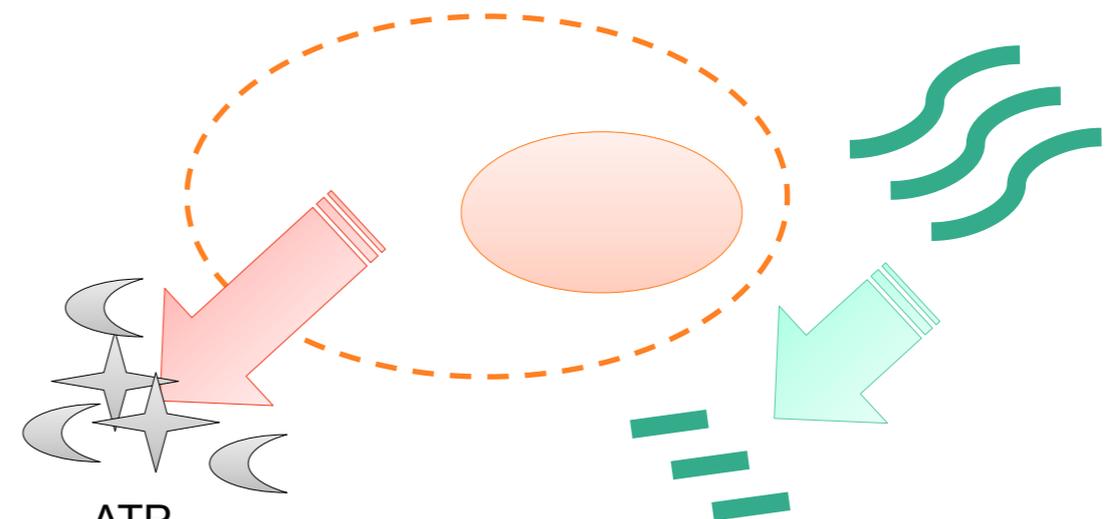
Moléculas ou porções de moléculas do microrganismo que não existem no hospedeiro.



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

DAMPs

Moléculas do hospedeiro (endógenas) produzidas por células danificadas/mortas ou produtos de degradação de proteínas (celular ou extracelular); ou moléculas exógenas (agentes físicos ou químicos)



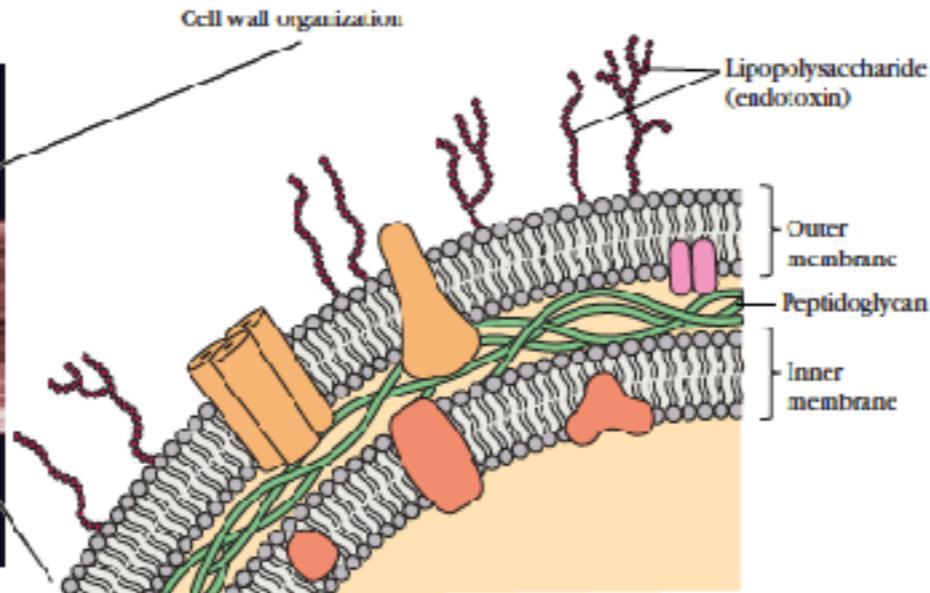
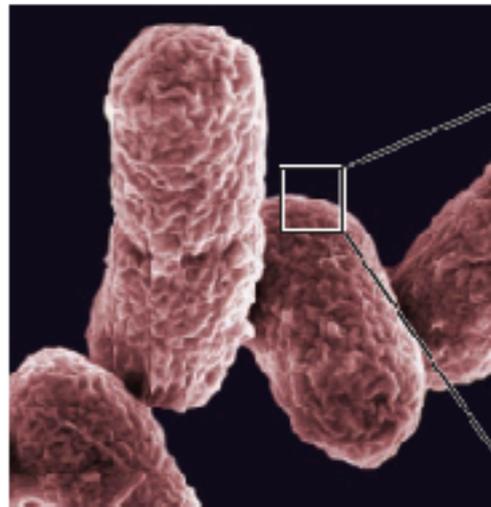
- ATP
- DNA/RNA
- Acido urico
- HMGB1
- HSP
- Metabolic intermediates
- High Cholesterol
- High Glucose
- β-amiloid

- Heparansulfato
- Hialuronano

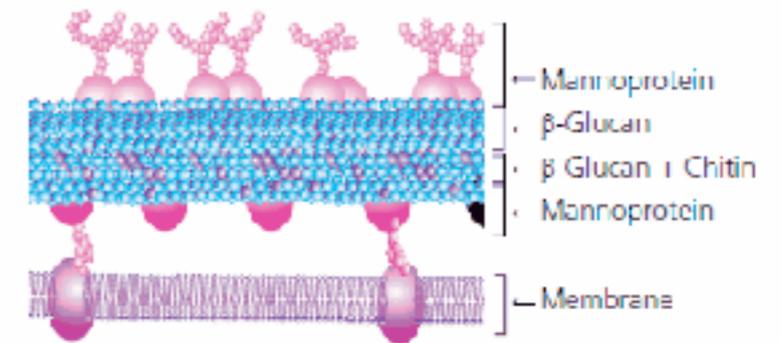
PAMPs & DAMPs

O microbo carrega multiplos PAMPs

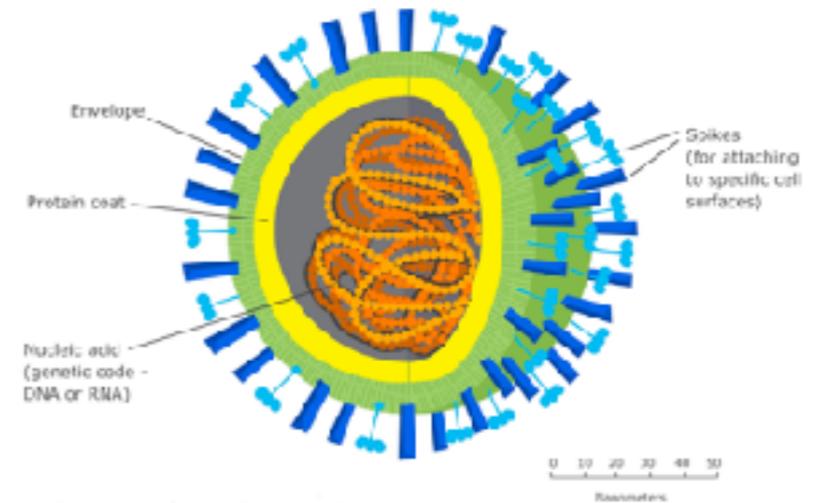
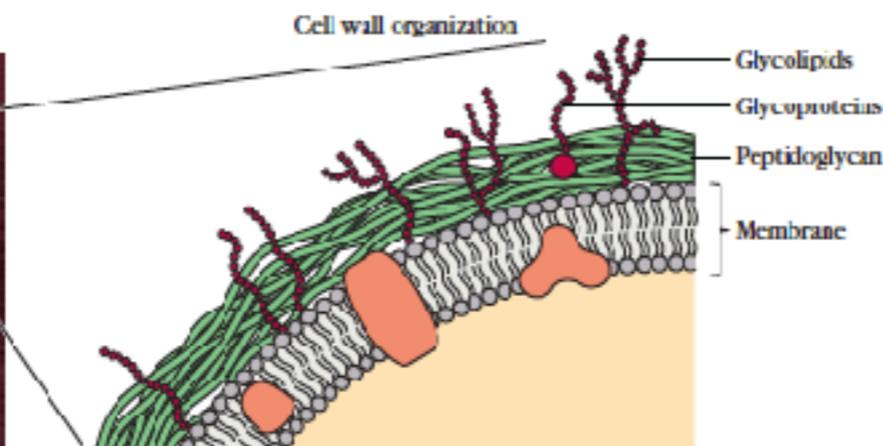
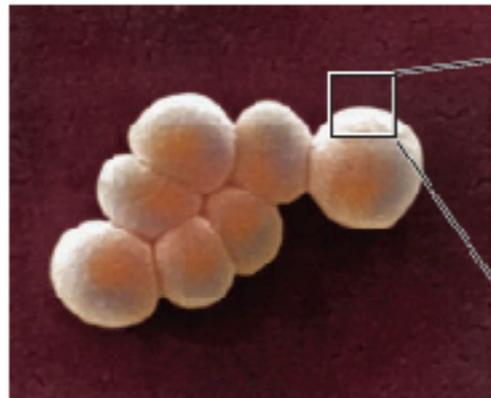
(a) Gram negative bacteria
E. coli



Yeast Cell Wall



(b) Gram positive bacteria
S. aureus

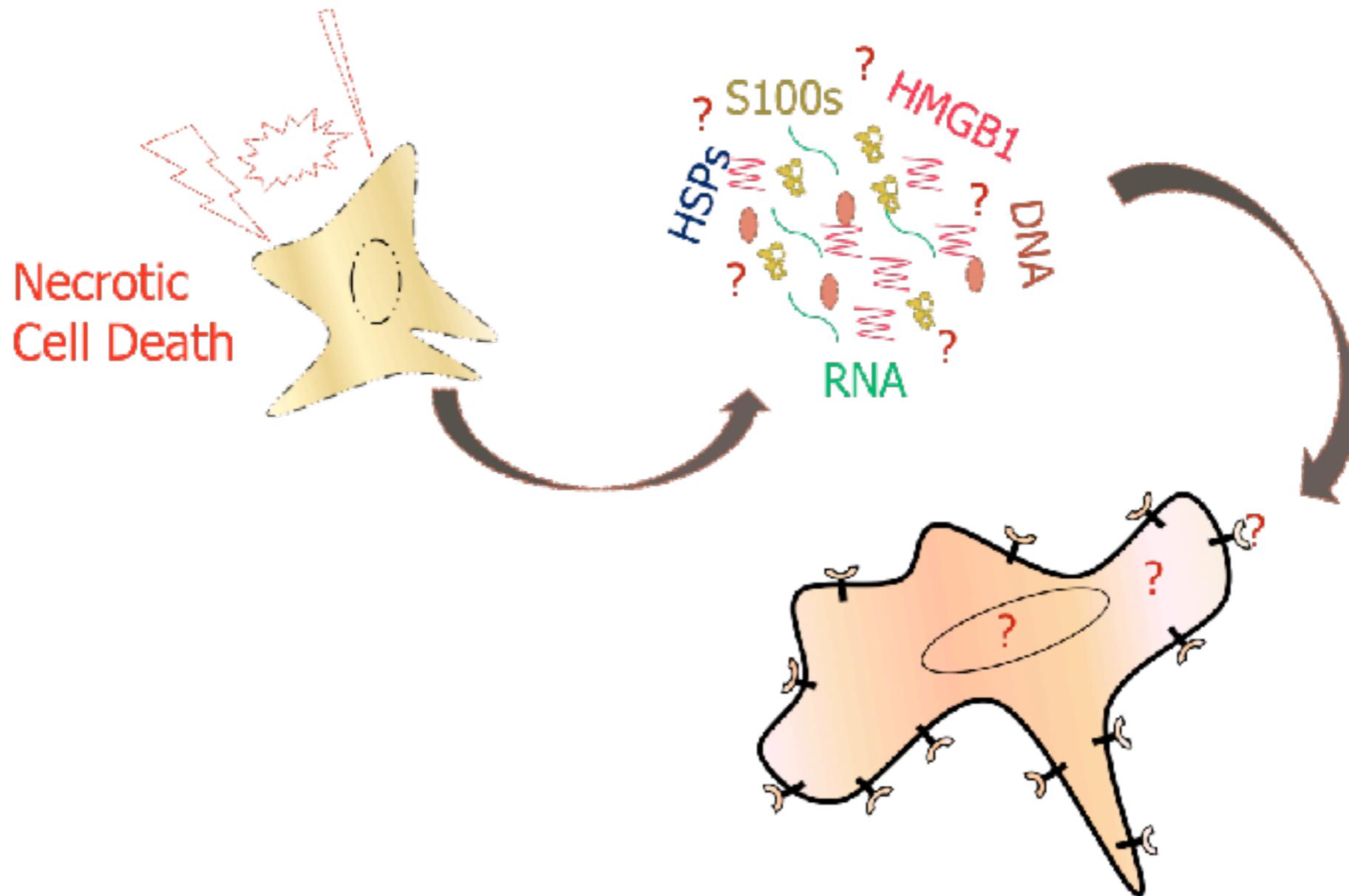


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Pode gerar dano (DAMPs)
(Exclusivo de organismos patogênicos!)

PAMPs & DAMPs

O dano/stress pode gerar múltiplos DAMPs



Danger, damage, death

Dano, morte & ativação do S.I.

DANO → MORTE → resposta imune / inflamação



Staphylococcal
infection

Sunburnt skin

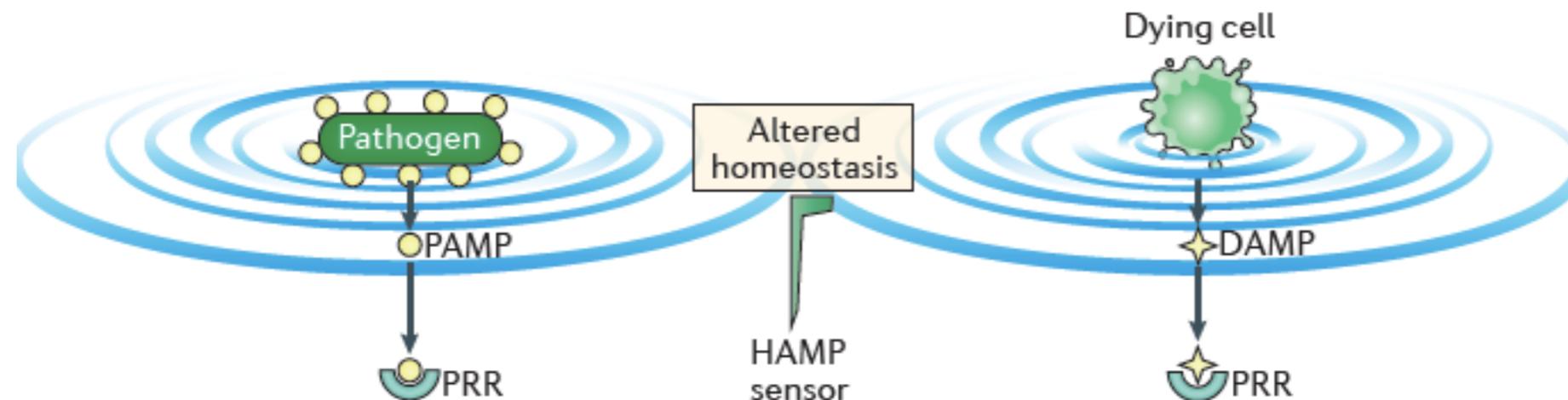
Burns cause skin cells to die prematurely by a non-programmed mechanism leading to inflammation



MORTE...qual tipo?
“necrose” versus “apoptose”

Homeostasis-altering molecular processes

HAMPs: perturbações da homeostasia celular (perturbações citoplasmáticas)

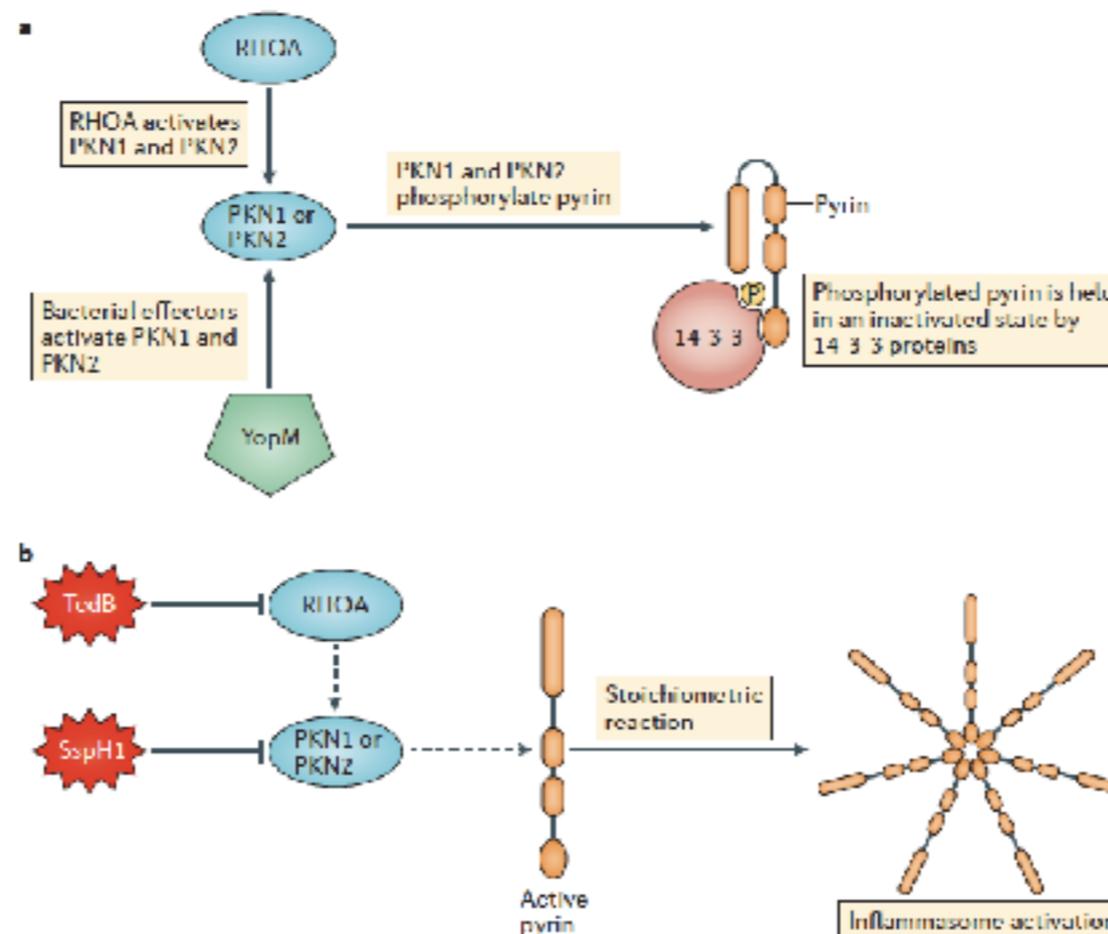


*Detectar as consequências funcionais do patógeno/dano nos processos celulares
Flexibilidade na capacidade do sistema imune inato de reconhecer infecções/dano
Amplia o repertório dos mecanismos de reconhecimento do sistema inato*

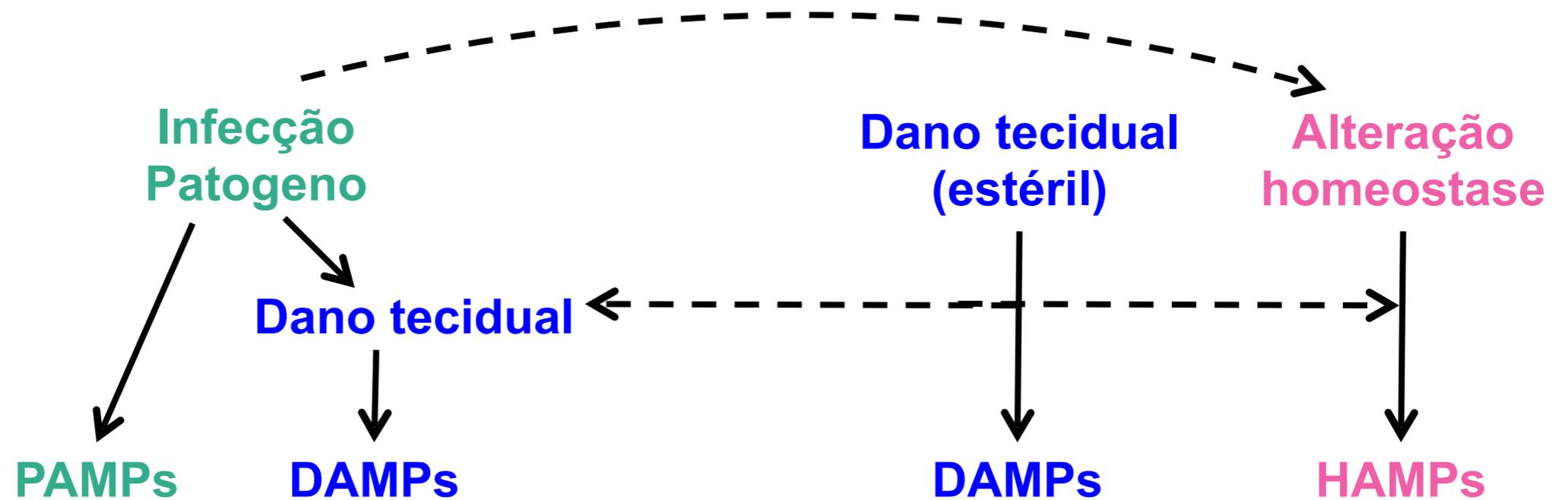
*MAS ... o custo dessa sofisticação é o risco de desenvolver inflamação
inapropriada (HAMPs>DAMPs>>PAMPs)*

Homeostasis-altering molecular processes

Molecular trigger of innate immunity	Source of trigger	Host recognition mechanism	Potential molecular variety in triggers
PAMP	Foreign (for example, bacterial LPS)	Molecular pattern (for example, LPS recognition by TLR4)	Constrained
DAMP	Self (for example, cellular ATP)	Molecular pattern (for example, ATP recognition by P2X7)	Constrained
HAMP	Self (for example, RHOA inactivation)	Molecular process (for example, loss of pyrin phosphorylation)	Broad



Reconhecimento de padrões



Sistema imune inato = “órgão de percepção”
Reconhecimento feito por quase todas as células somáticas

Receptores de reconhecimento de padrões: PRRs