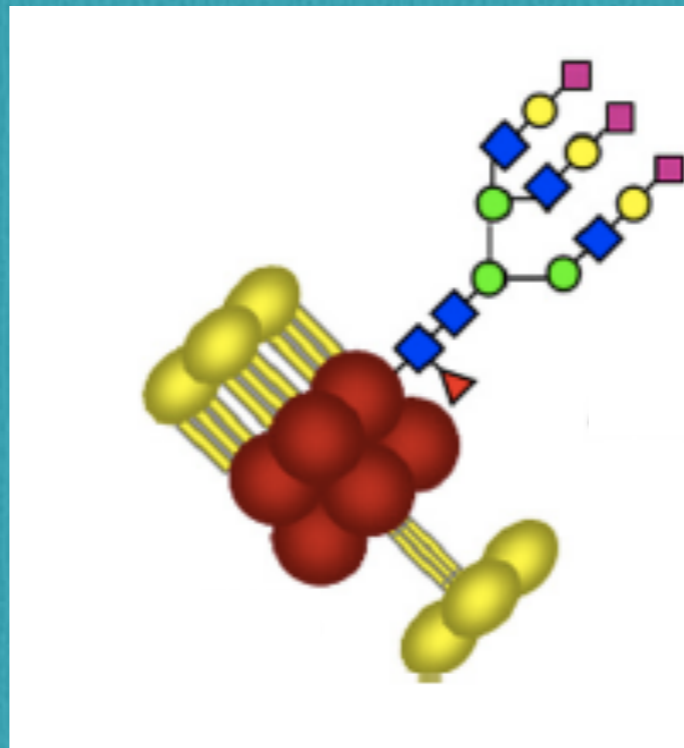


Programa de Pós-graduação em Imunologia ICB/USP

Disciplina BMI 5904
Reconhecimento no Sistema Imune



Aula 1

Alessandra Pontillo

Lab. Immunogenetica/Dep.Imunologia/ICB/USP

The Danger Model: A Renewed Sense of Self

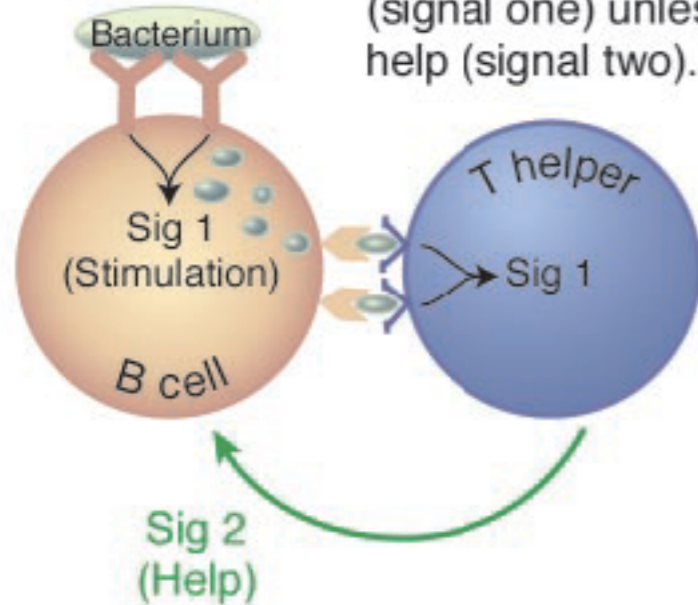
Polly Matzinger

Modelos de Ativação

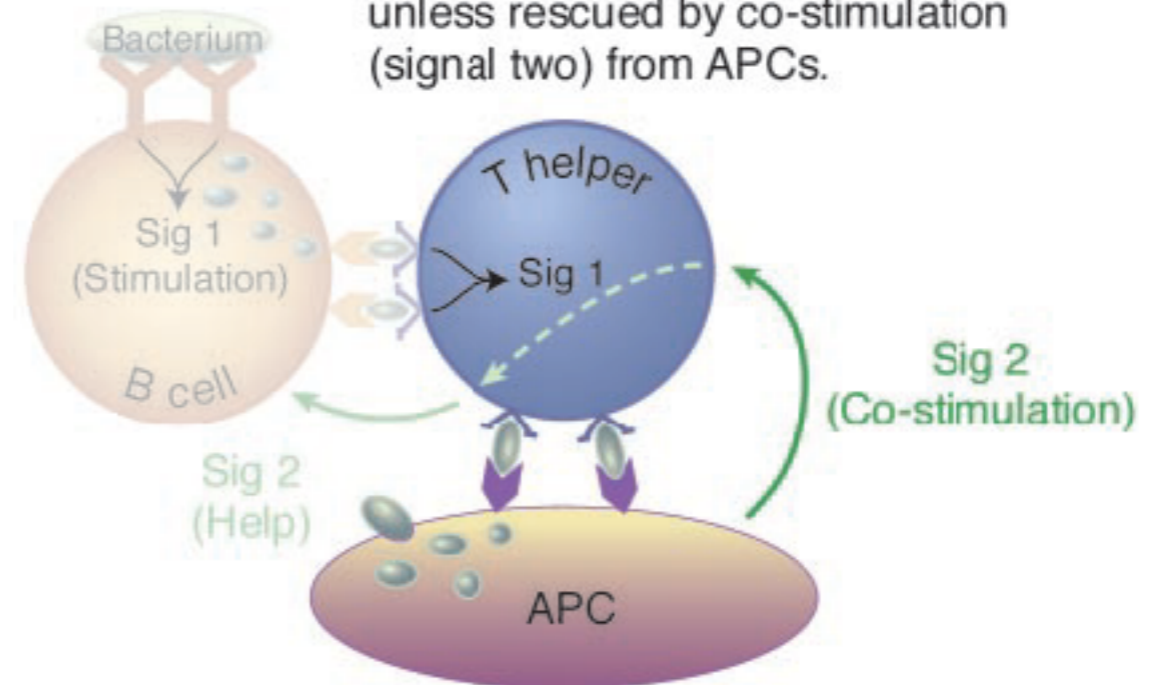
A history of immunological models.



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

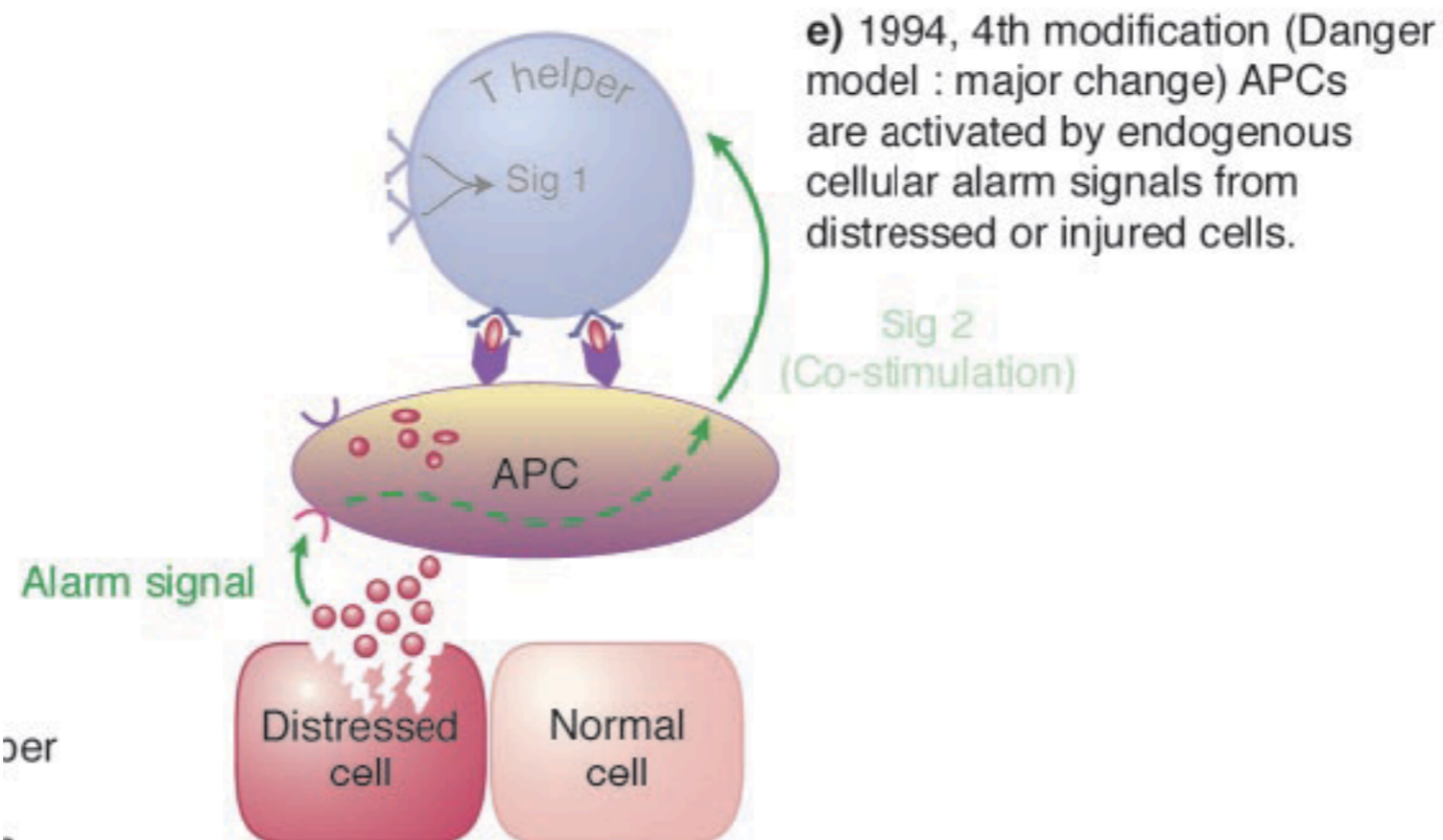
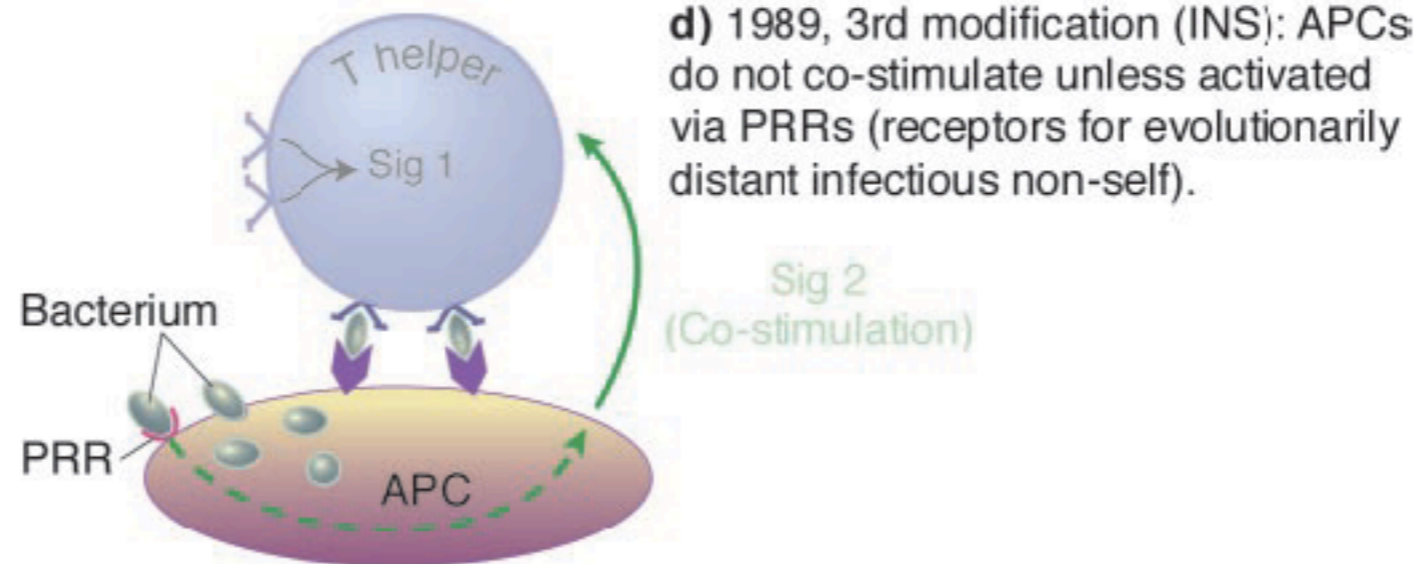


b) 1969, 1st modification: B cells die when they see antigen (signal one) unless rescued by help (signal two).



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

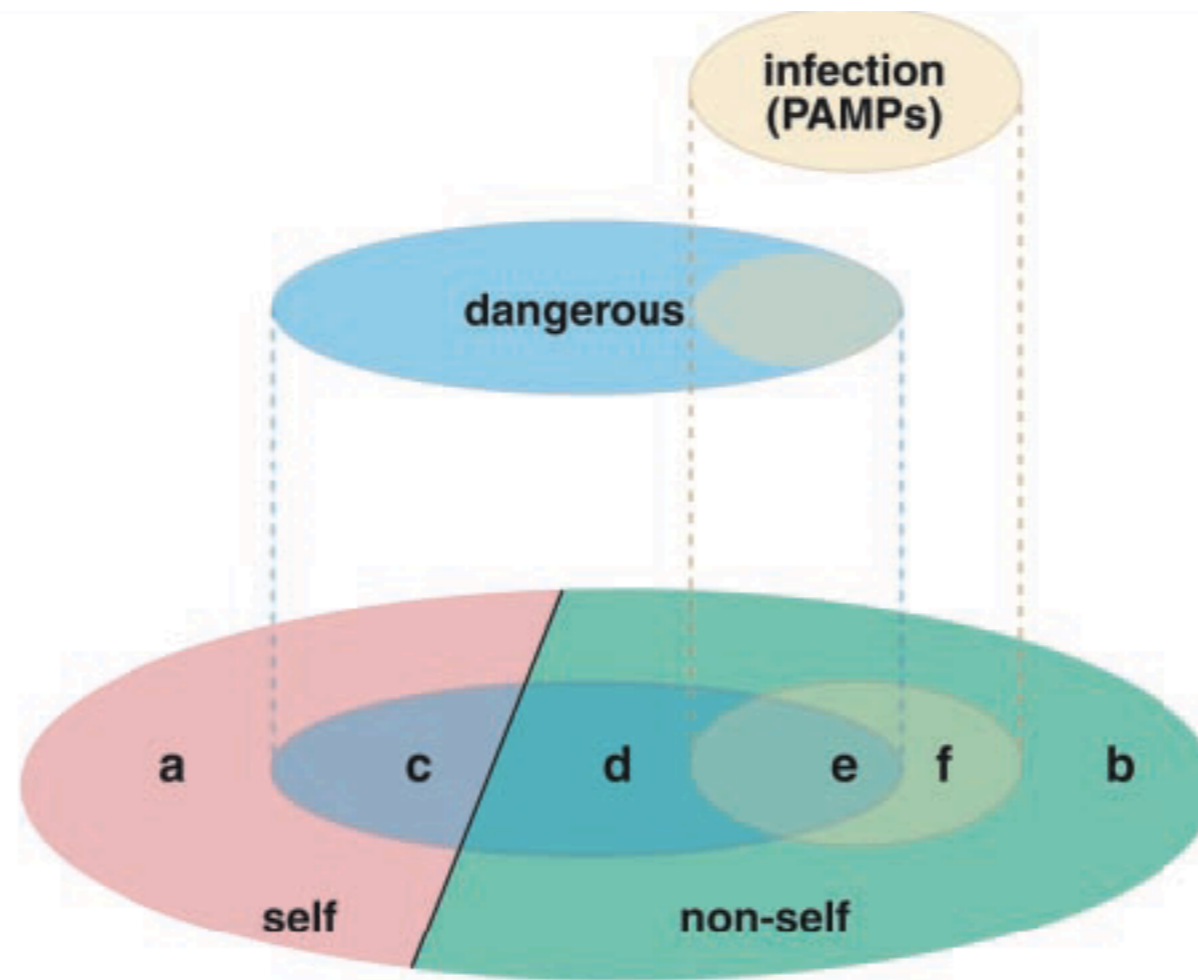
1

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



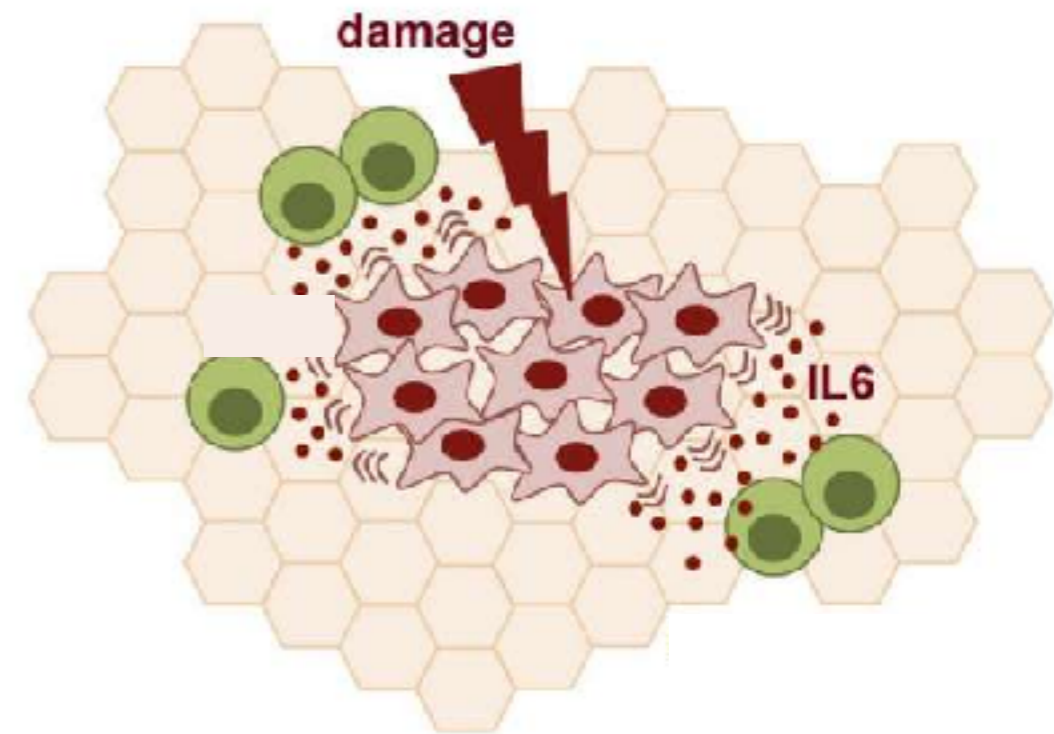
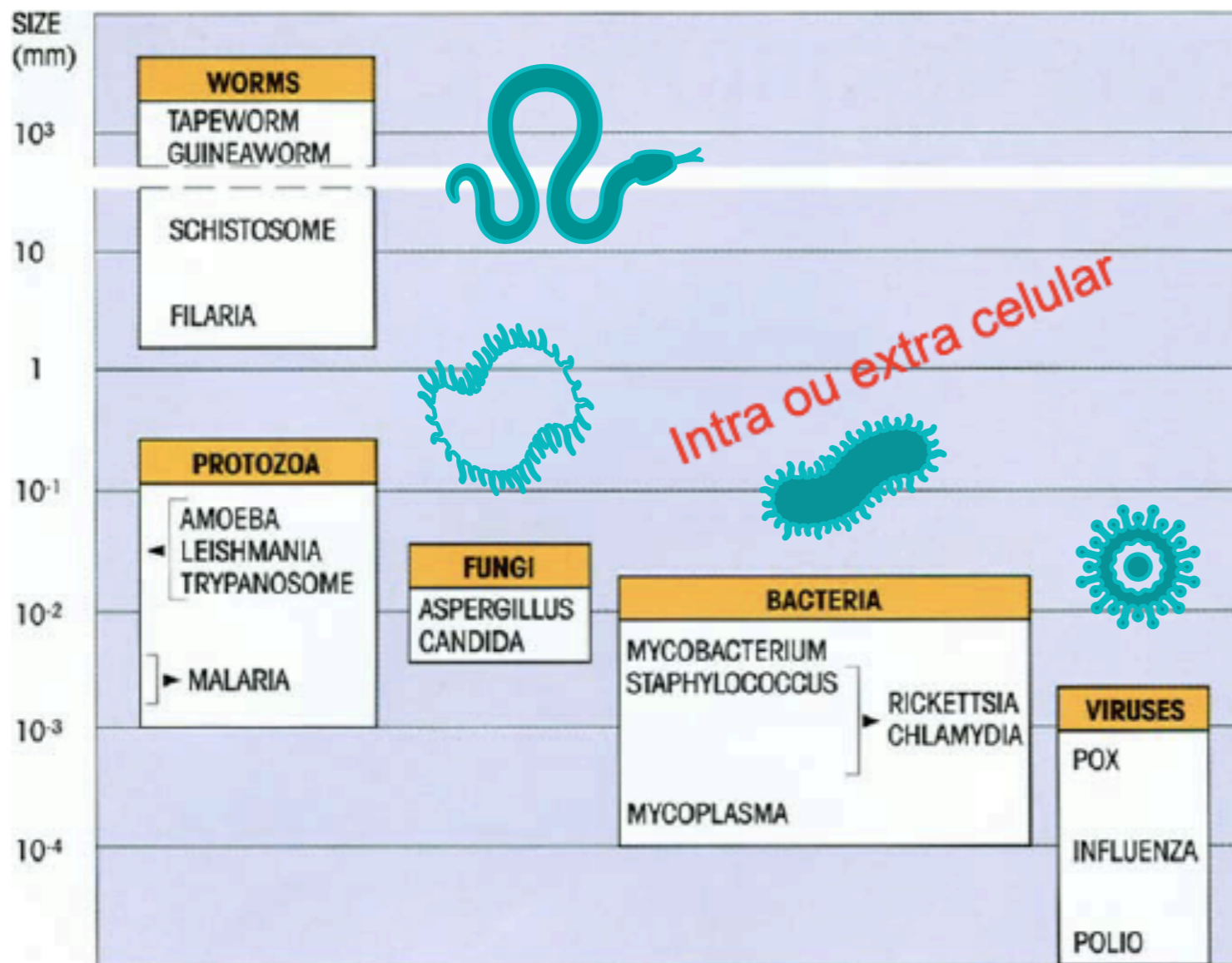
| Responses to each set predicted by: | | | | | | | |
|---|--------|---|---|---|---|---|---|
| | | a | b | c | d | e | f |
| } SNS INS Danger | SNS | - | + | - | + | + | + |
| | INS | - | - | - | - | + | + |
| | Danger | - | - | + | + | + | - |

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



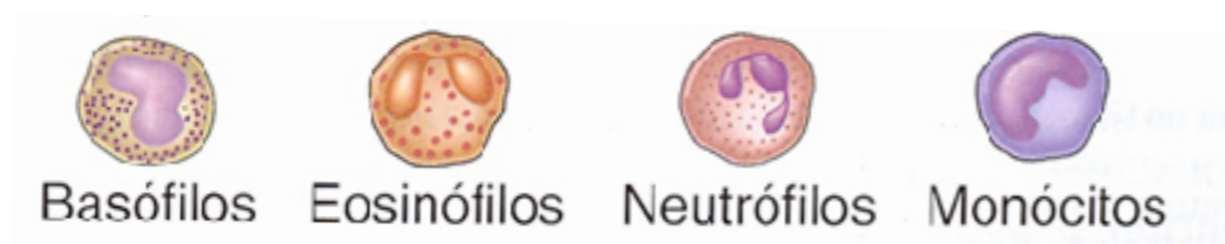
NK Rec



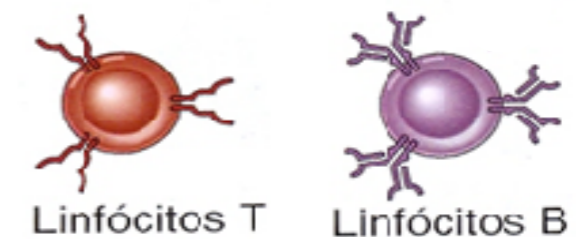
PRRs



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.

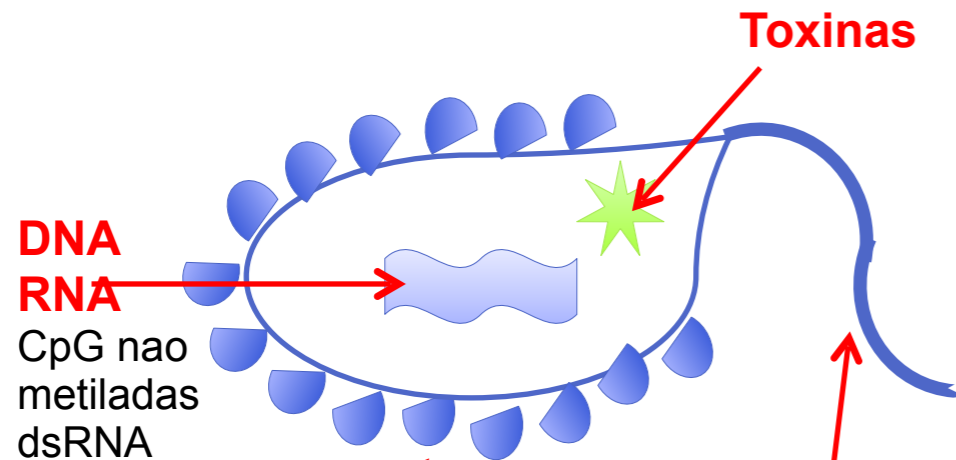
VAMPs: venom-associated molecular patterns

ACAMPs: apoptotic cells molecular patterns (fosfatidilserina, anexina)

PAMPs & DAMPs

PAMPs

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



Superfície

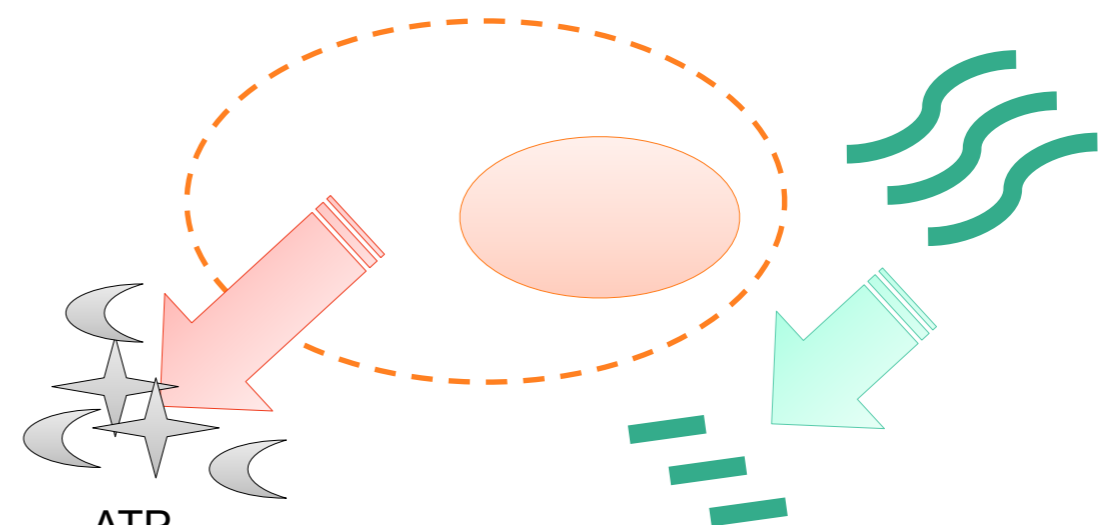
- Lipopolisacarideo (LPS)
- Peptidoglicano (PG)
- Acido Lipoteicoico (LTA)
- Mannosio terminal nas glicoproteinas
- Proteinas do envelope viral
- Zymosan (fungo)
- Profilina (T gonodii)

Flagelo

Flagelina

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

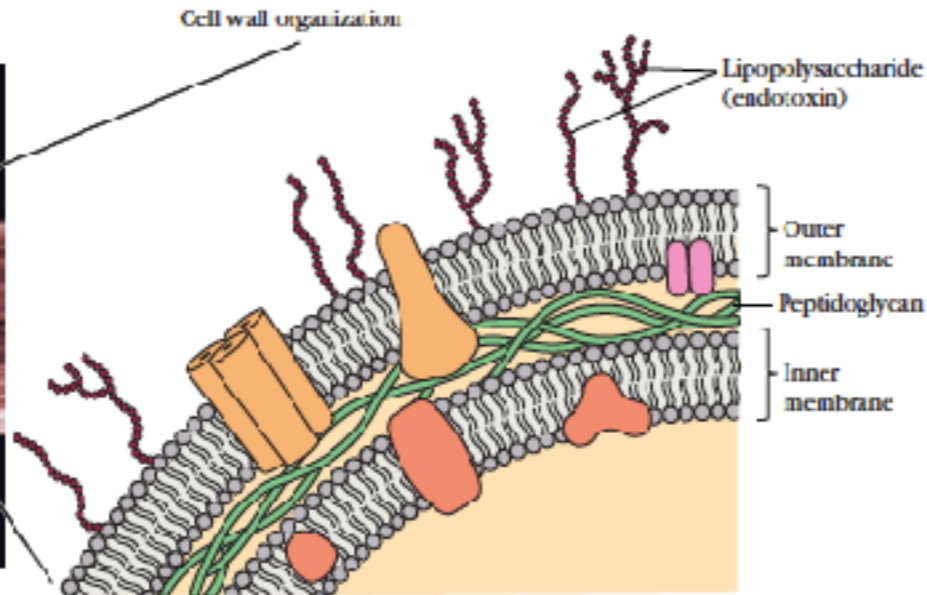
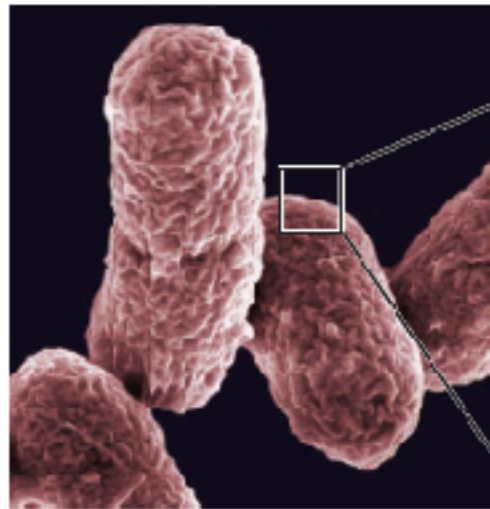
Heparansulfato

Hialuronano

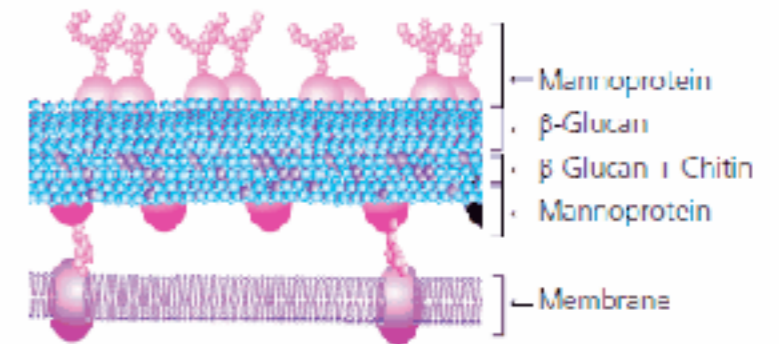
PAMPs & DAMPs

O microbo carrega multiplos PAMPs

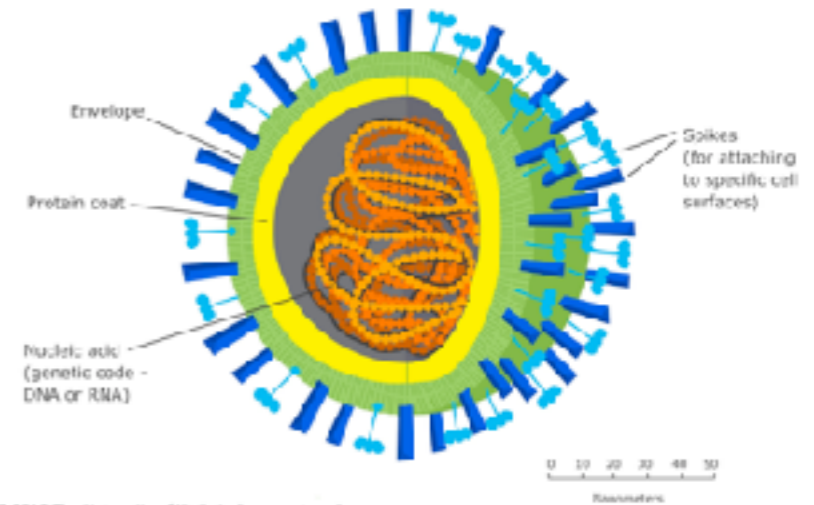
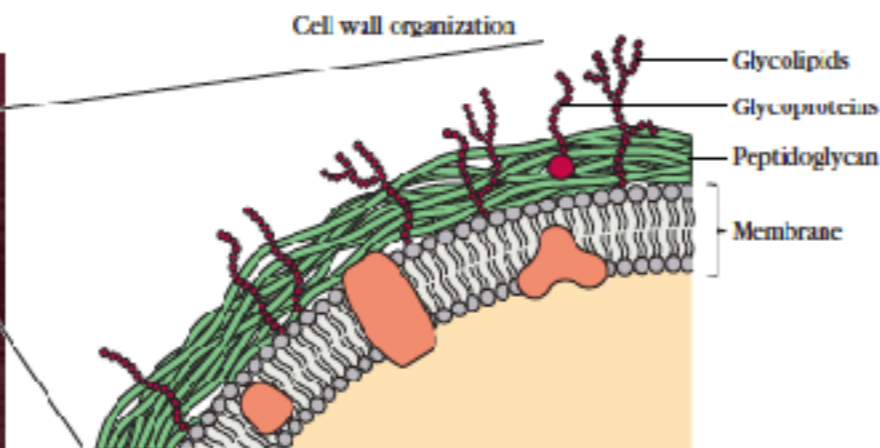
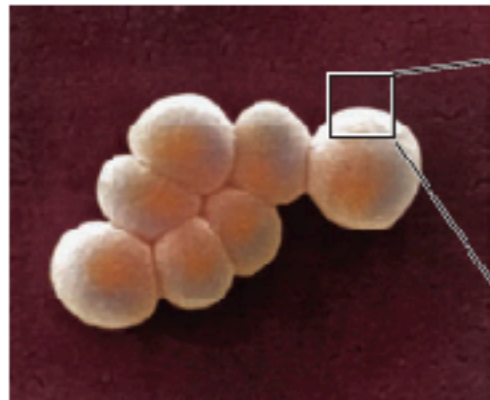
(a) Gram negative bacteria
E. coli



Yeast Cell Wall



(b) Gram positive bacteria
S. aureus

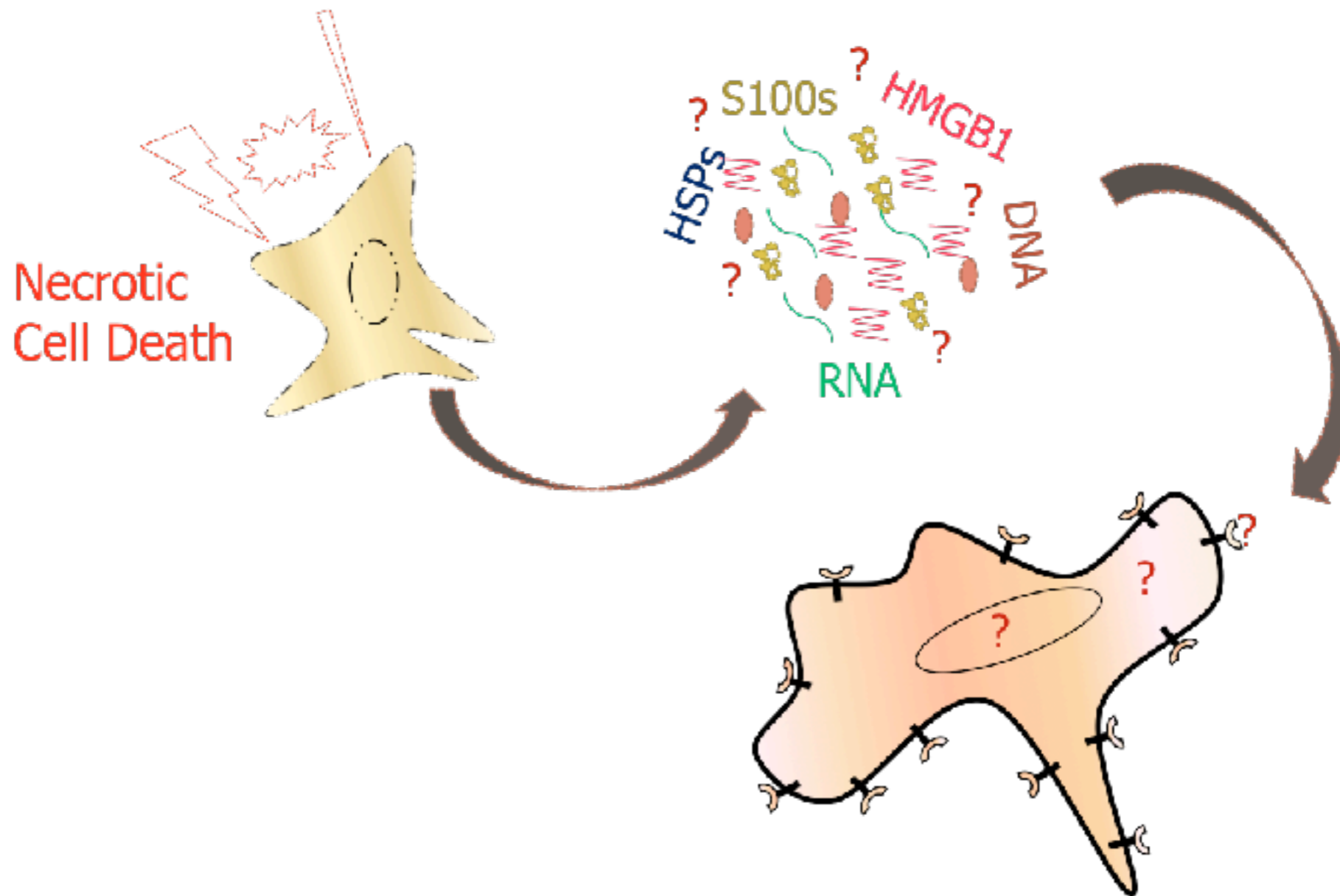


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Pode gerar dano (DAMPs)
(Exclusivo de organismos patogênicos!)

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

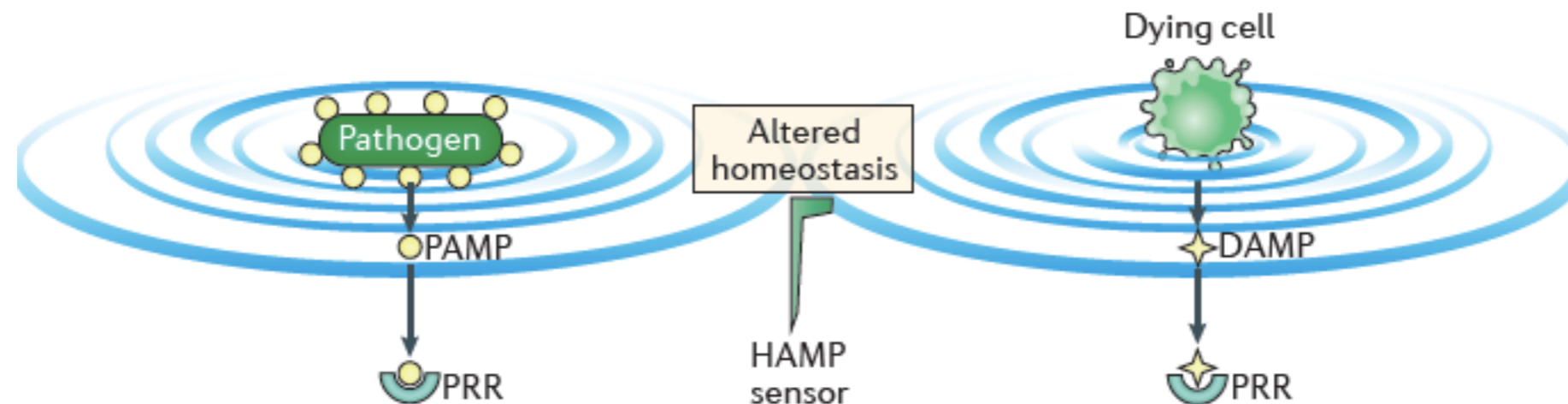
Burns cause skin cells to die prematurely by a non-programmed mechanism leading to inflammation



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

Homeostasis-altering molecular processes

HAMPs: perturbações da homeostasia celular (perturbações citoplasmáticas)

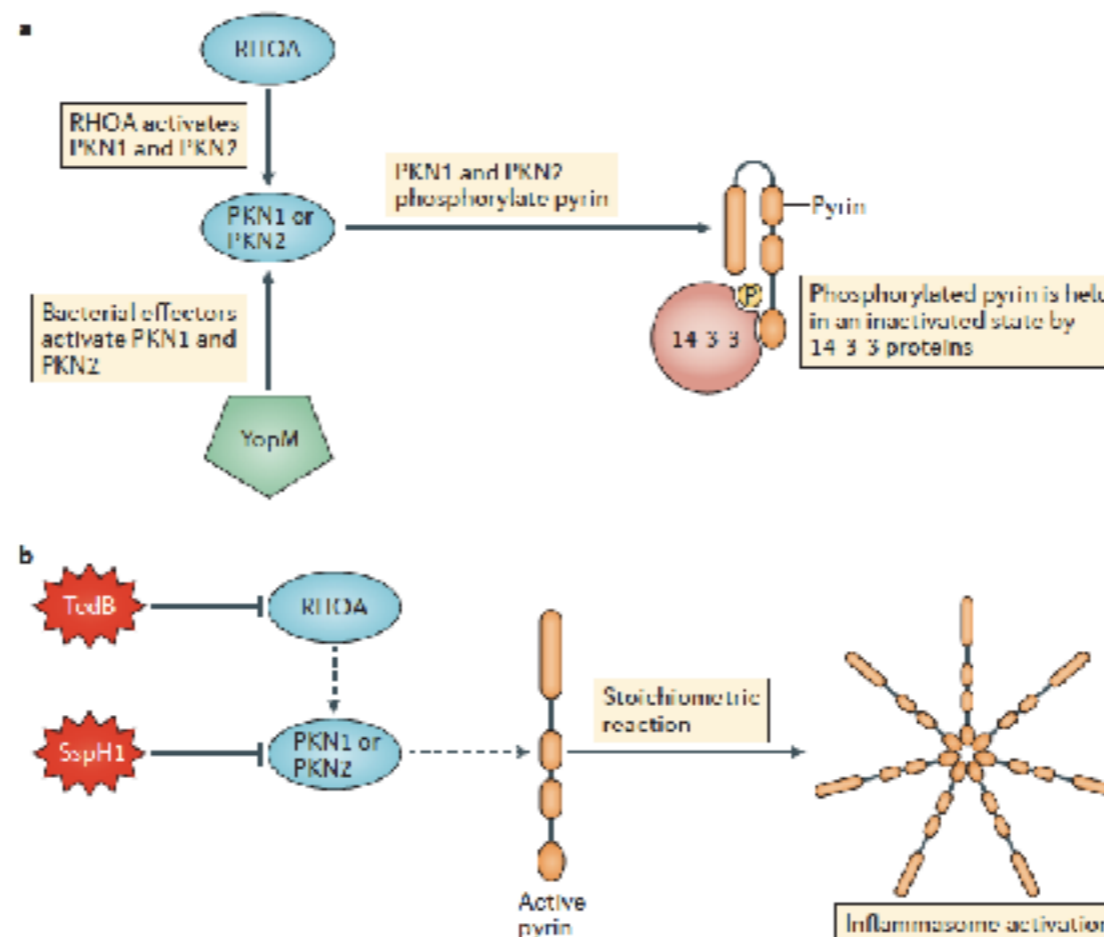


*Detectar as consequências funcionais do patógeno/dano nos processos celulares
Flexibilidade na capacidade do sistema imune inato de reconhecer infecções/dano
Amplia o repertório dos mecanismos de reconhecimento do sistema inato*

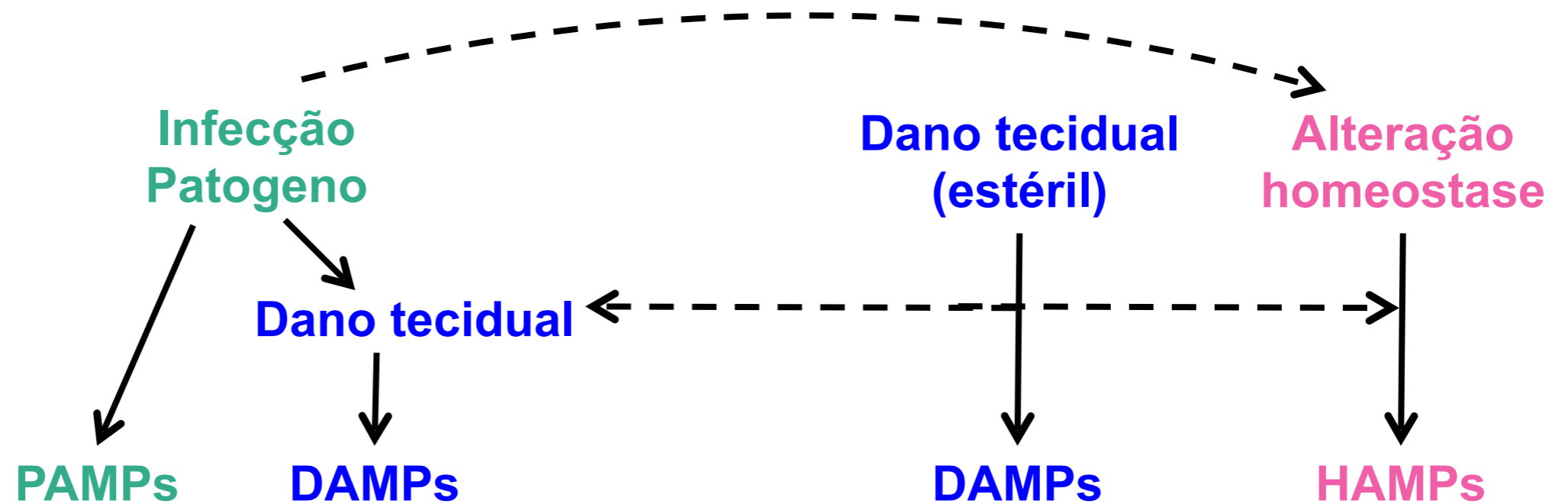
*MAS ... o custo dessa sofisticação é o risco de desenvolver inflamação
inapropriada (HAMPs>DAMPs>>PAMPs)*

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