Princípios da Imunidade Inata: Respostas Inatas induzidas na infecção

Imunologia Modulo CFG2038

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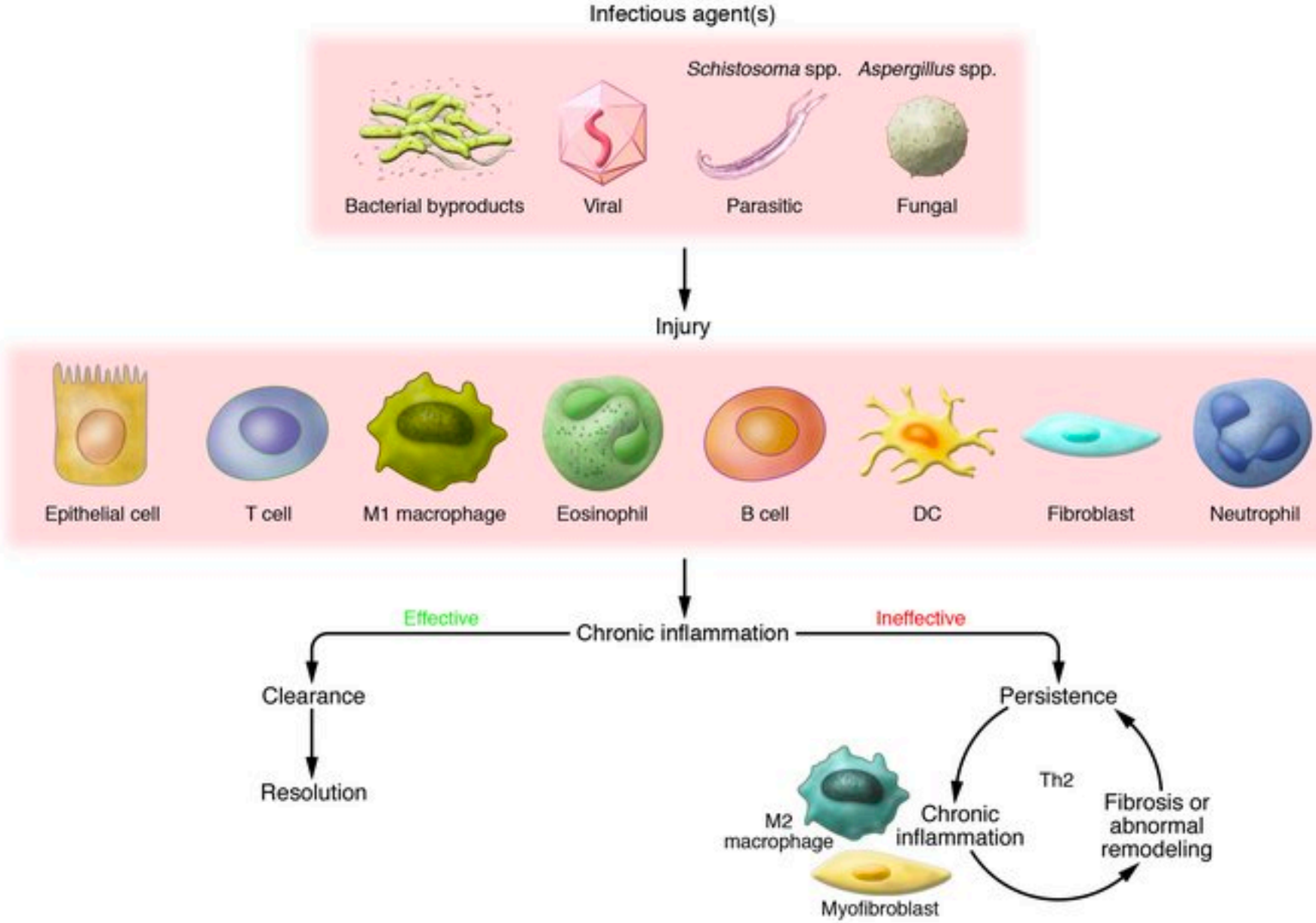
O que o Sistema Imune reconhece?

- ➔Microrganismos
- ➔Parasitas
- ➔Fungos
- ➔Estruturas próprias alteradas
- ➔Estruturas constitutivas
- ➔Substâncias de animais, plantas e insetos
- ➔Componentes de alimentos


Infectious agent(s)
Schistosoma spp.
Aspergillus spp.
Bacterial byproducts
Viral
Parasitic
Fungal
Injury
Epithelial cell
T cell
M1 macrophage
Eosinophil
B cell
DC
Fibroblast
Neutrophil
Effective
Chronic inflammation
Ineffective
Clearance
Resolution
Persistence
Th2
M2 macrophage
Chronic inflammation
Fibrosis or abnormal remodeling
Myofibroblast

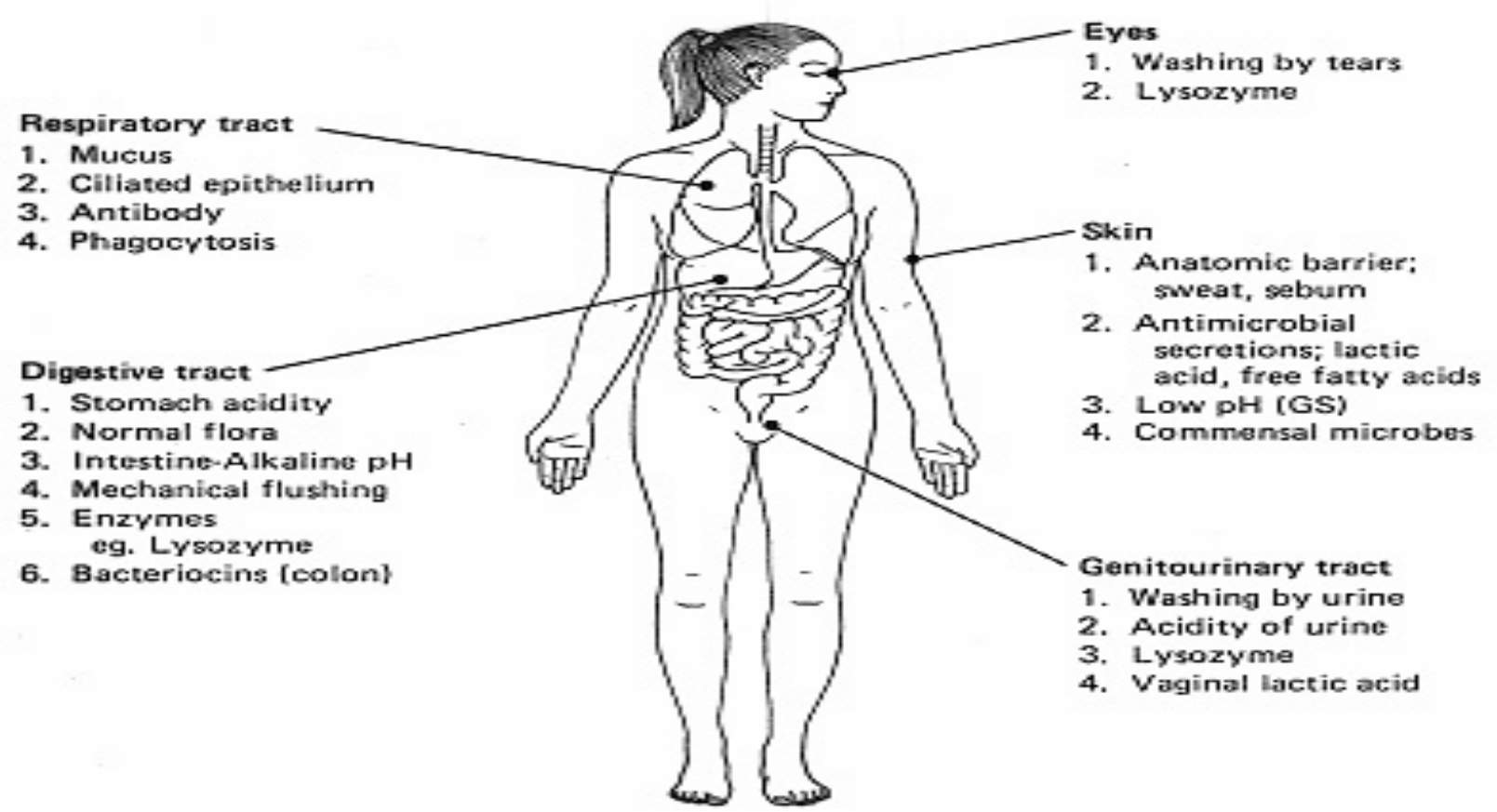
SISTEMA IMUNOLÓGICO

RESPOSTA IMUNE INATA (INESPECÍFICA)
Barreiras biológicas
Inflamação - mecanismo indutor
Ausência de memória (nova teoria propõe "memória dos macrofagos -epigenética)

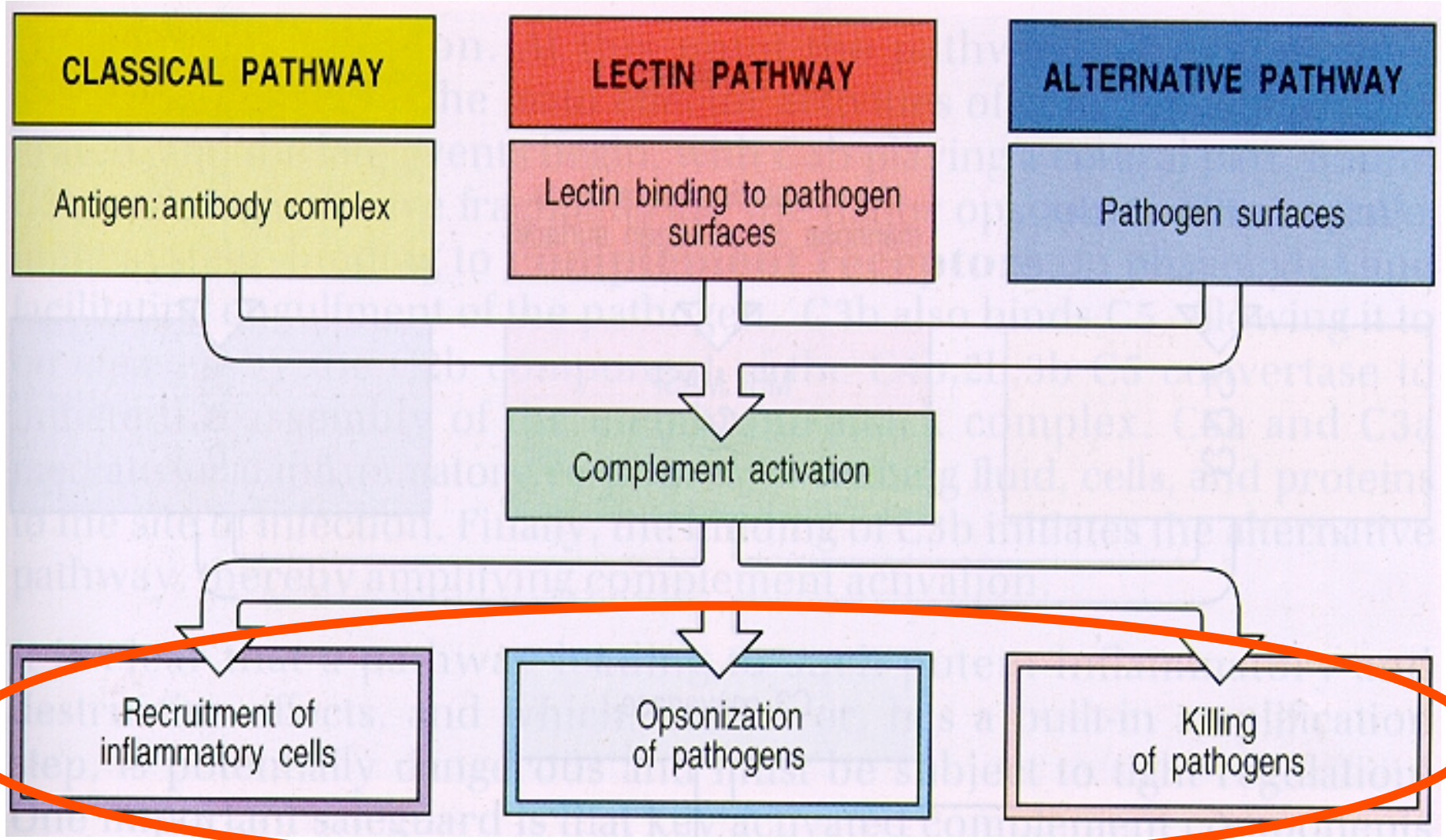
RESPOSTA IMUNE ADAPTATIVA (ESPECÍFICA)
Inflamação - mecanismo efetor
Geração de memória

Elementos da resposta imune inata

BARREIRAS CONSTITUTIVAS
Proteção Física ou Bioquímica



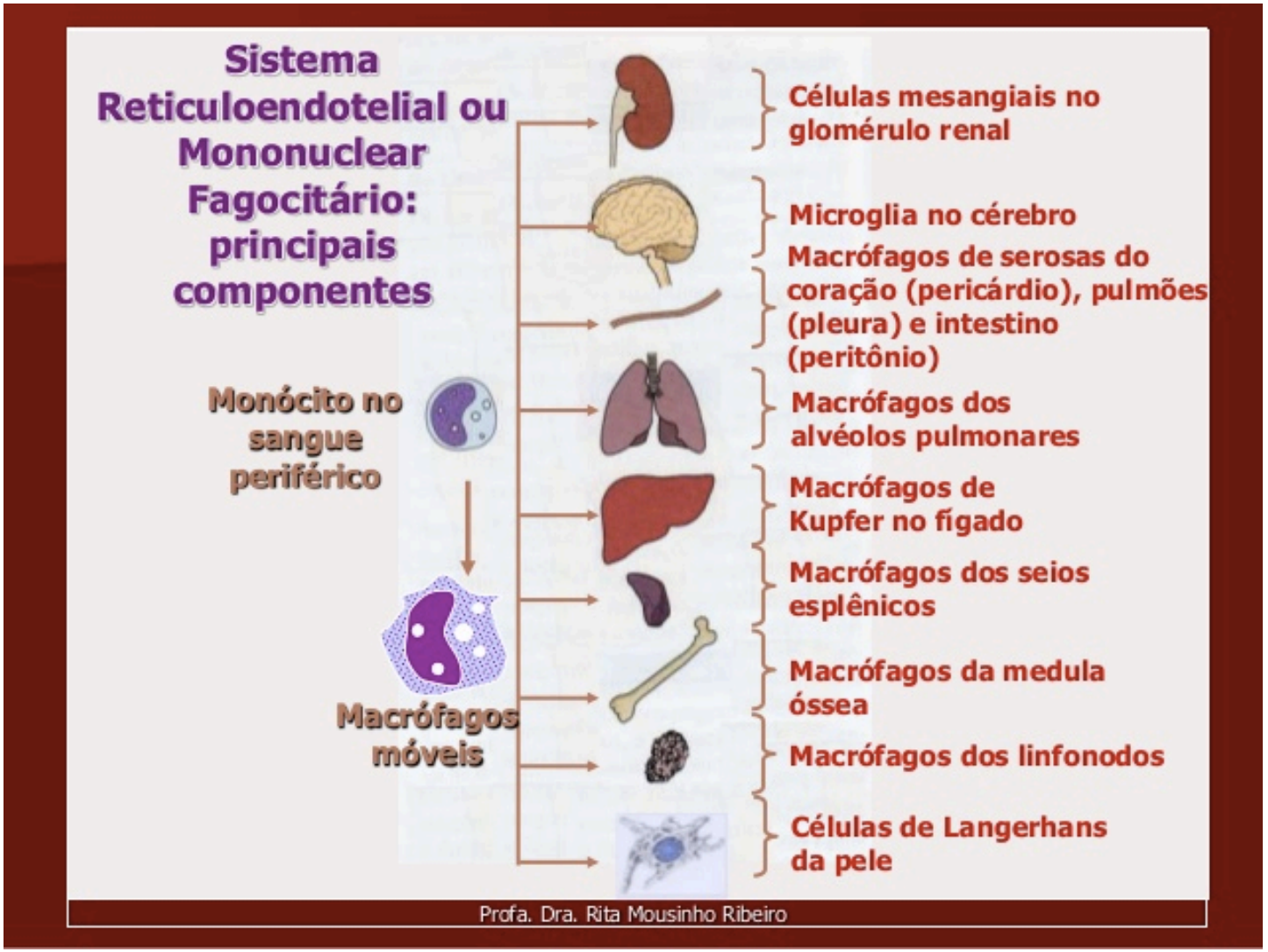
O Sistema Complemento é um dos primeiros elementos da resposta imune inata, que interage com os patógenos que passam as barreiras constitutivas. Sua ativação gera fragmentos importantes para mecanismos de defesa (mecanismos efetores)



Outros Fatores Solúveis da Imunidade Inata que interagem com os patógenos

Lisosima	Digere peptidoglicanas e facilita lise osmótica
Proteína ligante de manose (PRRs)	Opsonização e Ativação do Complemento
Proteína C reativa	Liga-se à carboidratos e lipideos de bactérias, opsonizando-as
Proteína ligante do LPS (LBP)	Liga-se ao LPS e depois ao CD14 das células: fagocitos e ativação

Células do sistema imune residentes nos parênquimas são as primeiras a interagirem com os patógenos. Os macrófagos são as principais e estão em diferentes tecidos onde recebem nomes diversos



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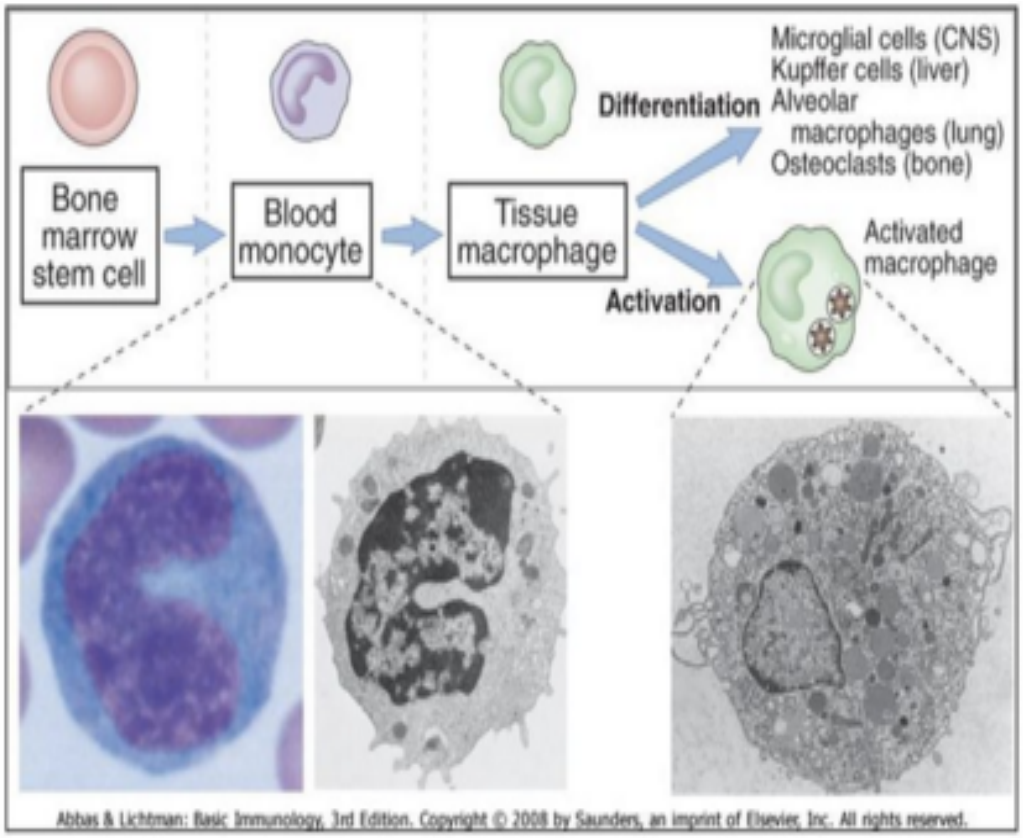
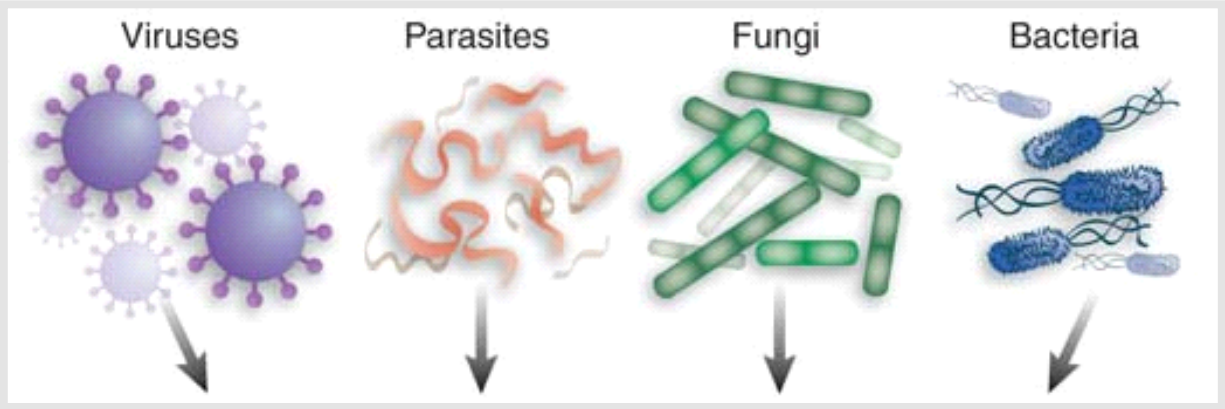
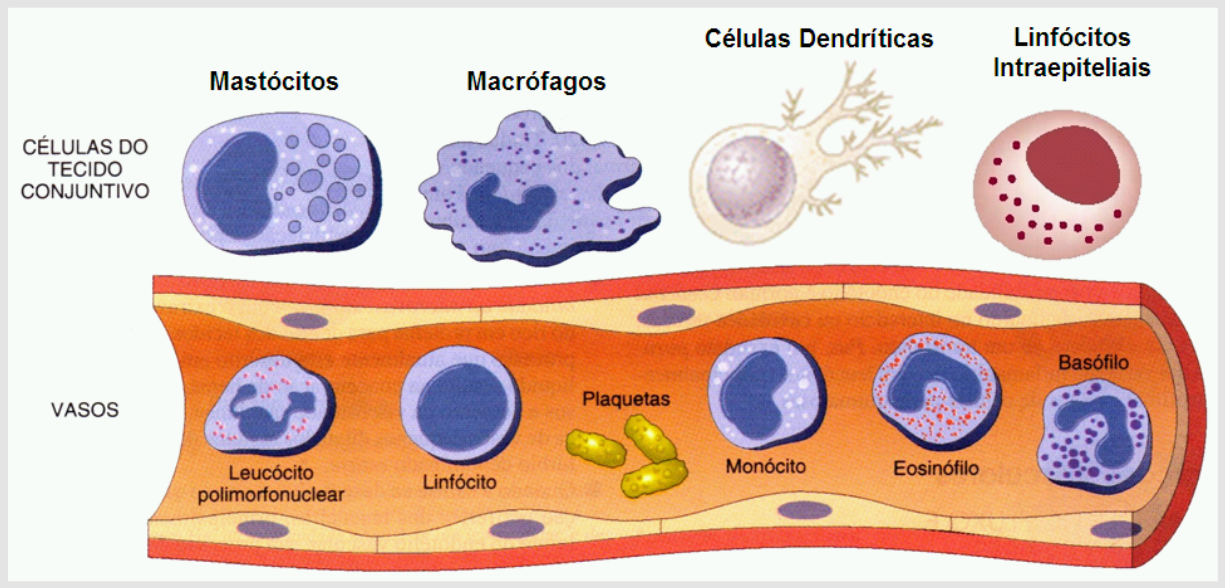


Os Patógenos ou substancias estranhas que ultrapassam as barreiras constitutivas são reconhecidos por células residentes via interação PAMPS/VAMPs e PRRs.
Também podem ativar o sistema do complemento.

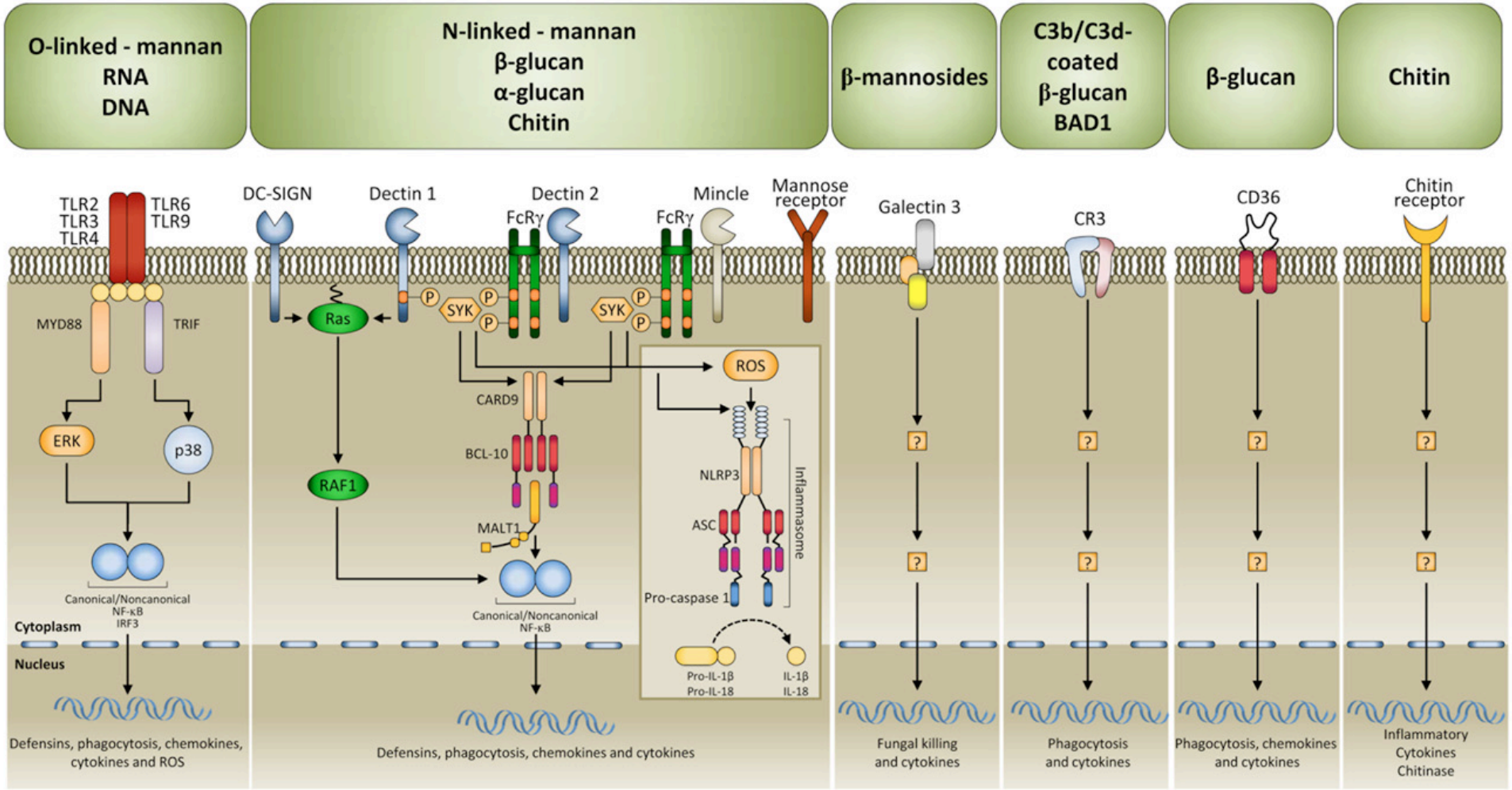
PAMP/VAMPs
Sinal de Invasão

Células de Alarme
PRR



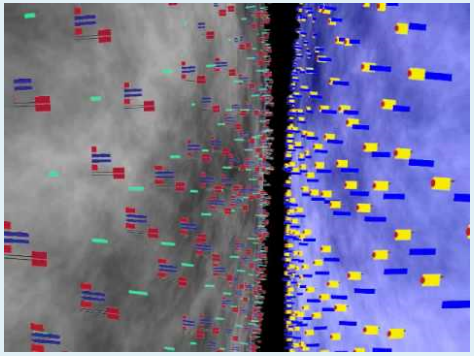


PAMP's Recognition



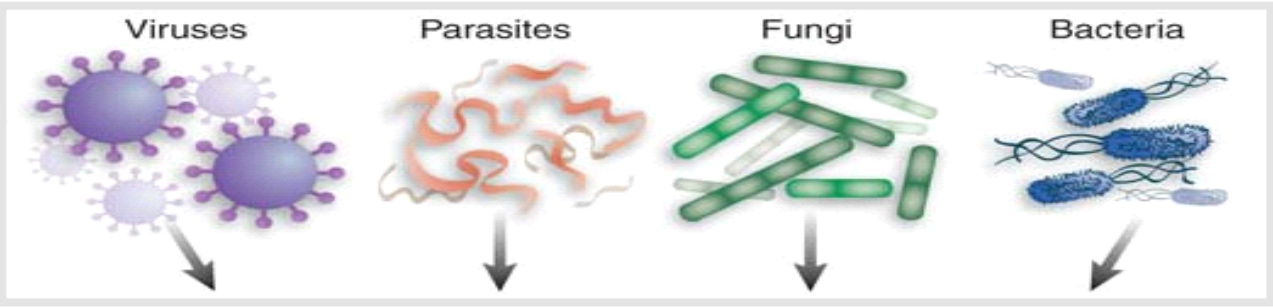
As células do sistema imune reconhecem moléculas do patógeno (PAMPs) via diferentes receptores presentes na sua superfície (PRRs)

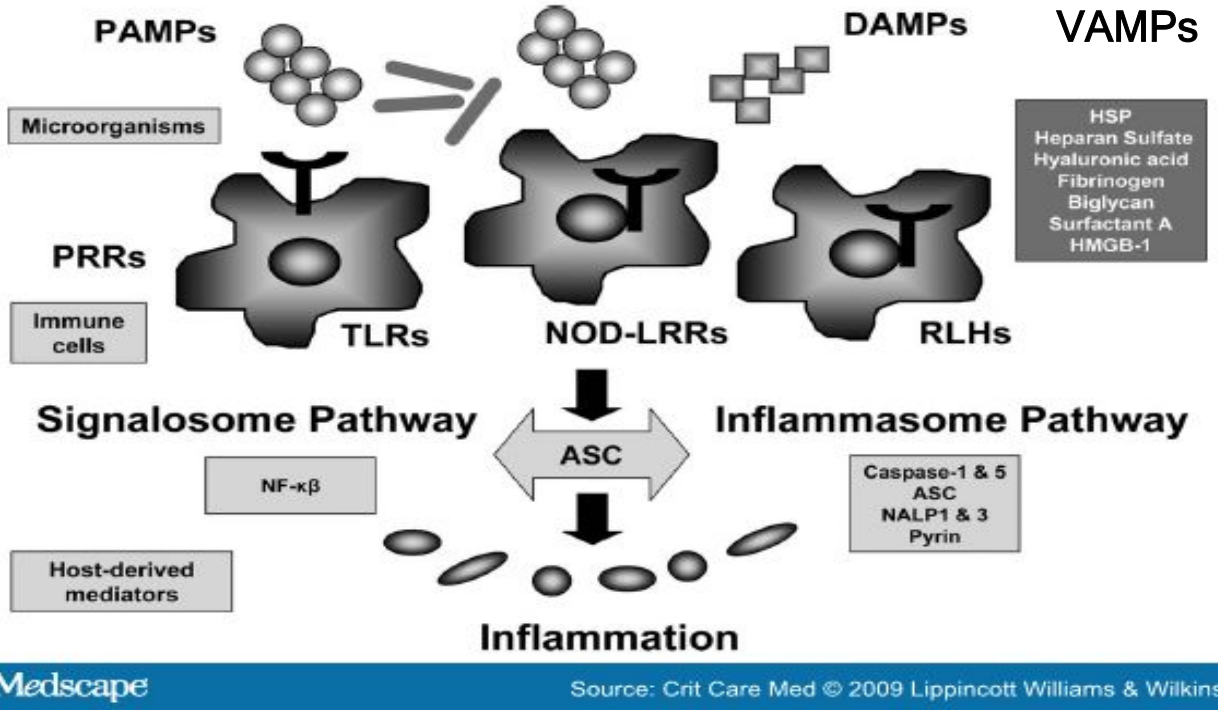
PAMPs
Pathogen-Associated Molecular Pattern
(Moléculas Padrões Associados aos Patógenos)



Pattern Recognition Receptors
Receptores para Reconhecimento das Moléculas Padrões (dos Patógenos)

Na resposta imune inata, os patógenos, peçonhas, venenos e produtos de células são reconhecidos por Células Residentes e Inflamatórias que se tornam ativadas

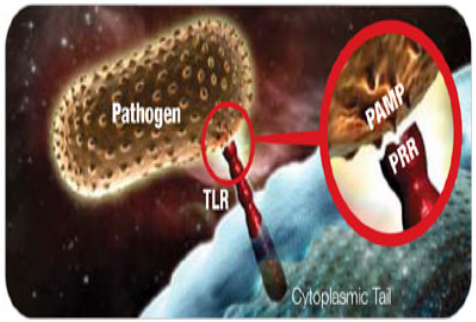


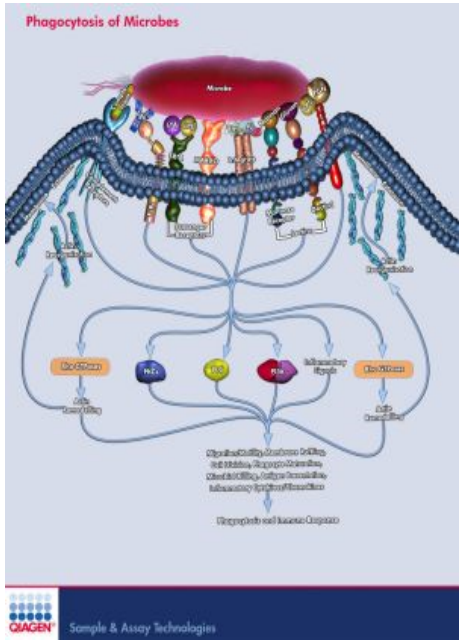


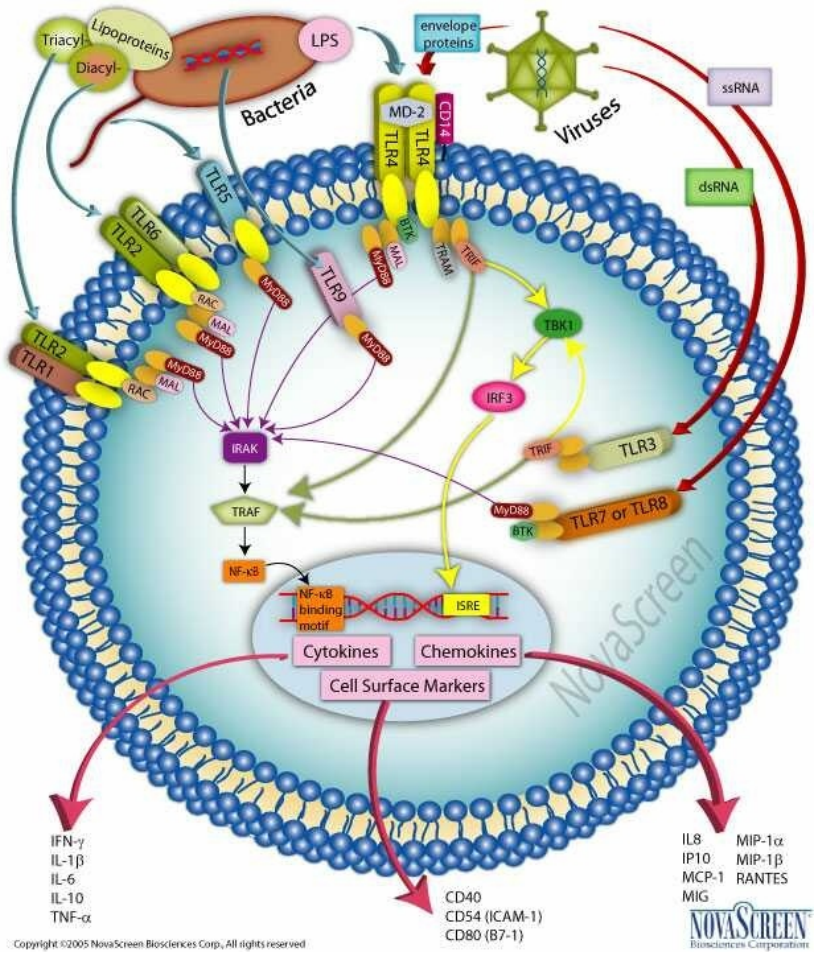
Vários receptores podem estar envolvidos no reconhecimento de um mesmo microrganismos, e a maioria leva à ativação celular

TLRs possuem domínios intracitoplasmáticos que recrutam Moléculas adaptadoras como MyD88, TRIF, TIRAP e TRAM que fazem sinalização intracelular e induzem expressão gênica

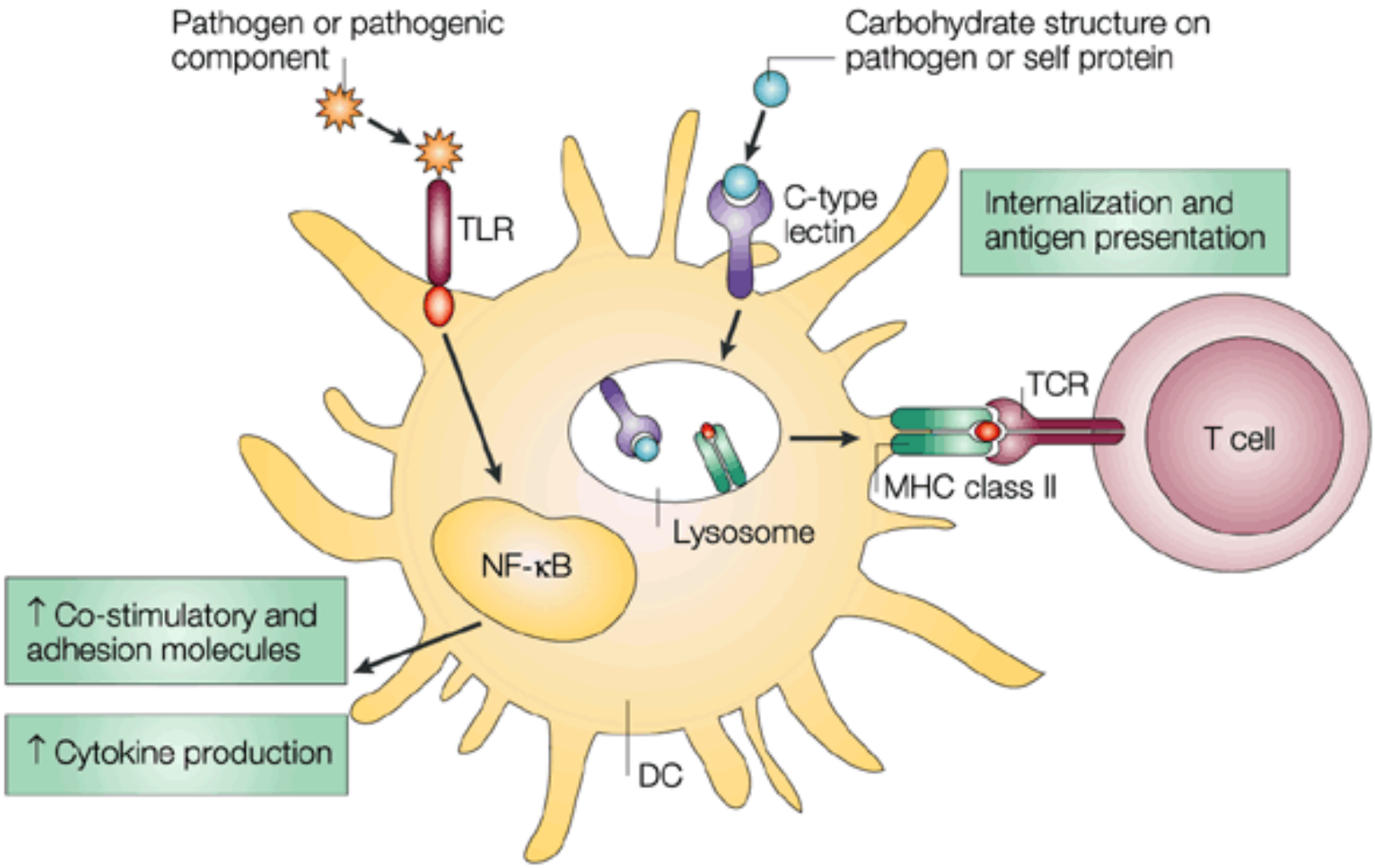
PAMPs ao se ligarem aos PPRs: induzem as células a produzirem mediadores da Inflamação, citocinas, quimiocinas, mediadores lipídicos que ativam a resposta imune



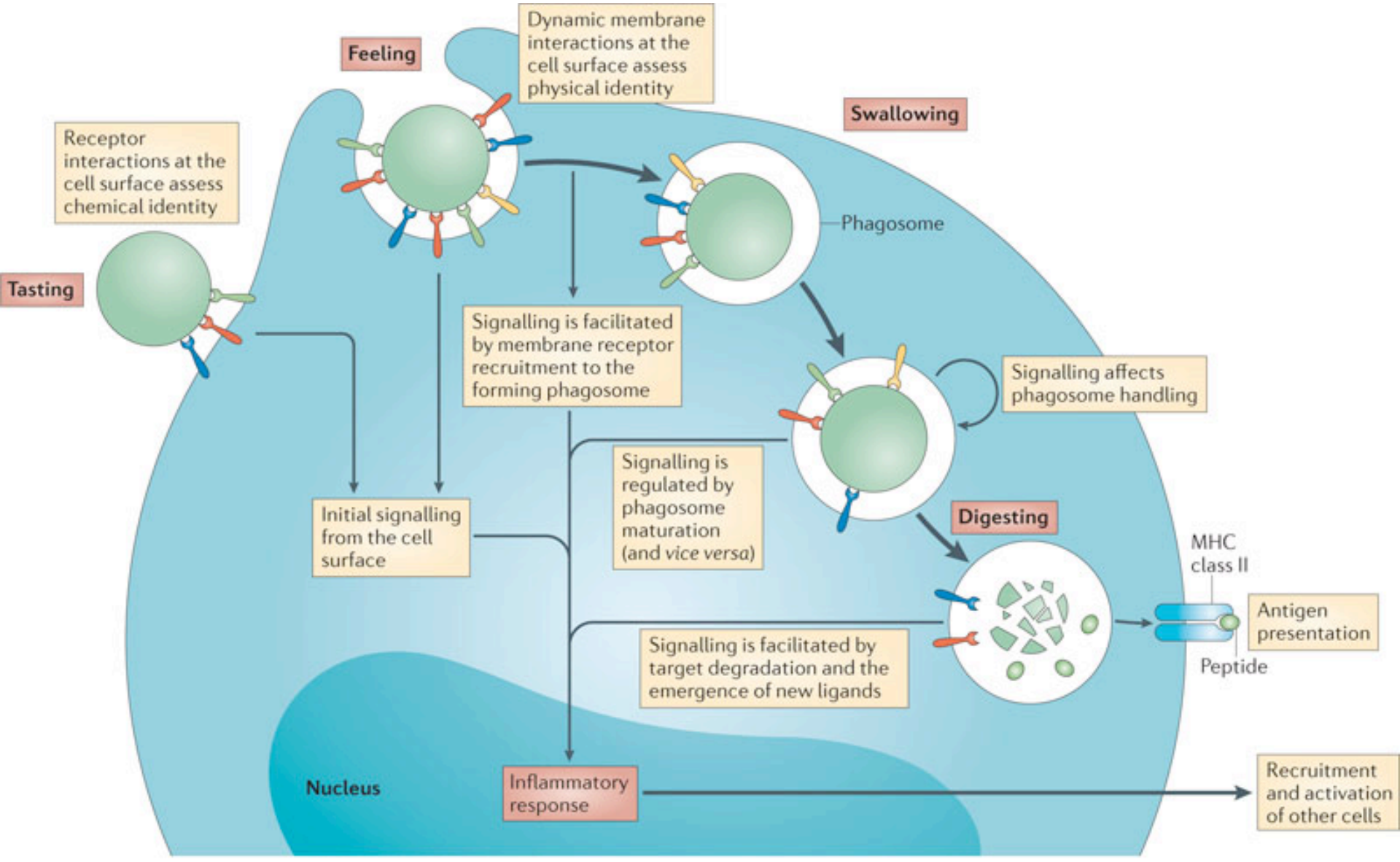




Os PAMPs/VAMPS dos patogenos/venenos, após ligação aos PRRs das DC/Mos estimulam a fagocitose do patógeno, a produção de mediadores e o aumento da expressão de Moléculas do MHC e as co-estimulatórias



Fagocitose



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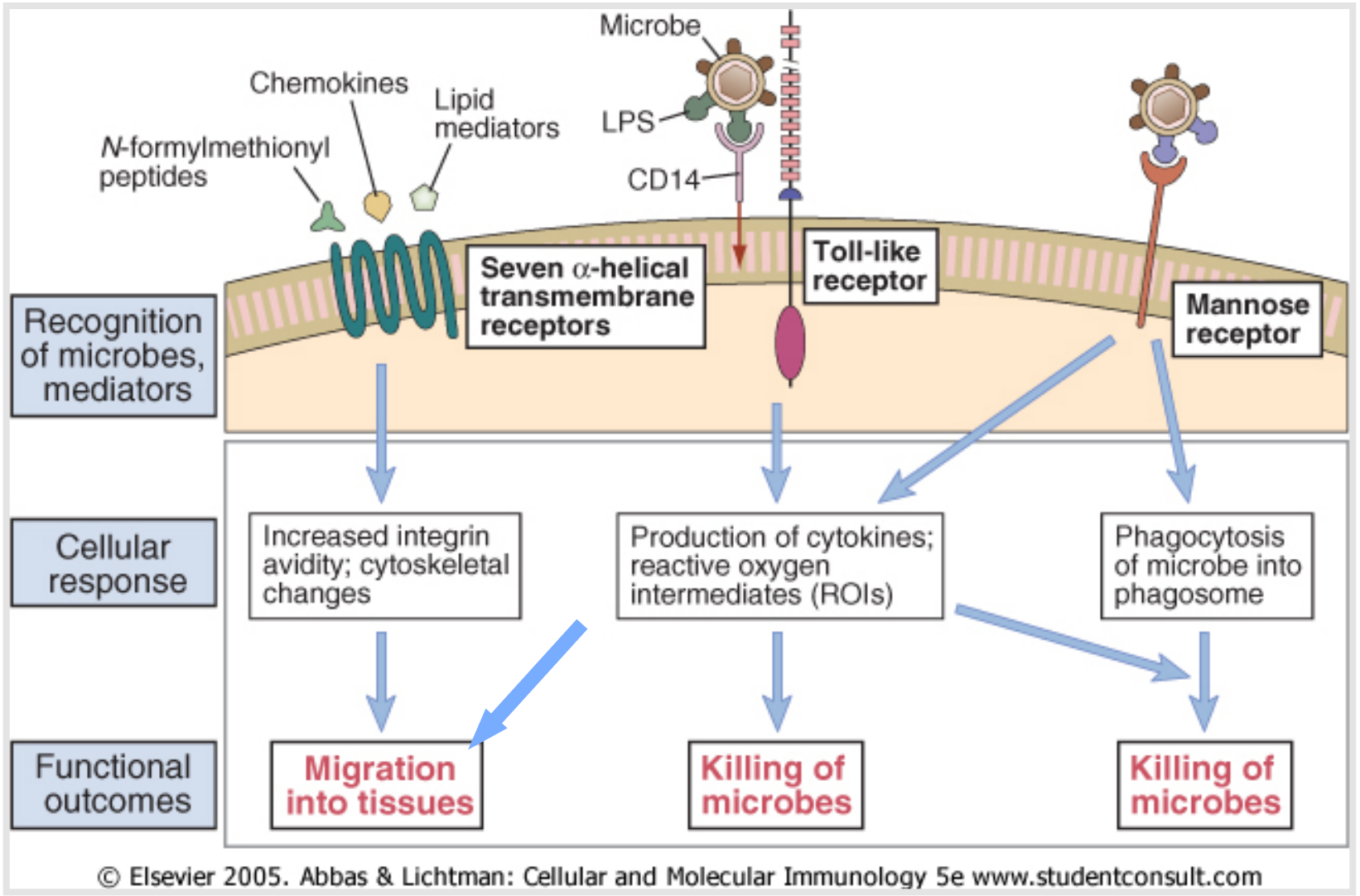
PAMPs ativam células que aumentam a atividade "killing" e a secreção de mediadores



Macrófago possui vários mecanismos para matar os patógenos

Class of mechanism	Specific products
Acidification	pH=~3.5–4.0, bacteriostatic or bactericidal
Toxic oxygen-derived products	Superoxide O_2^-, hydrogen peroxide H_2O_2, singlet oxygen $^1O_2^*$ hydroxyl radical $^*OH$, hypohalite OCl^-
Toxic nitrogen oxides	Nitric oxide NO
Antimicrobial peptides	Defensins and cationic proteins
Enzymes	Lysozyme—dissolves cell walls of some Gram-positive bacteria. Acid hydrolases—further digest bacteria
Competitors	Lactoferrin (binds Fe) and vitamin B_{12}-binding protein

Figure 2-9 Immunobiology, 7ed. (© Garland Science 2008)

Macrófago liberam diferentes citocinas

Cytokines secreted by macrophages and dendritic cells			
Cytokine	**Main producer**	**Acts upon**	**Effect**
IL-1	Macrophages Keratinocytes	Lymphocytes	Enhances responses
		Liver	Induces acute-phase protein secretion
IL-6	Macrophages Dendritic cells	Lymphocytes	Enhances responses
		Liver	Induces acute-phase protein secretion
CXCL8 (IL-8)	Macrophages Dendritic cells	Phagocytes	Chemoattractant for neutrophils
IL-12	Macrophages Dendritic cells	Naive T cells	Diverts immune response to T_H1, pro-inflammatory, cytokine secretion
TNF-α	Macrophages Dendritic cells	Vascular endothelium	Induces changes in vascular endothelium (expression of cell-adhesion molecules (E- and P-selectin), changes in cell–cell junctions with increased fluid loss, local blood clotting)

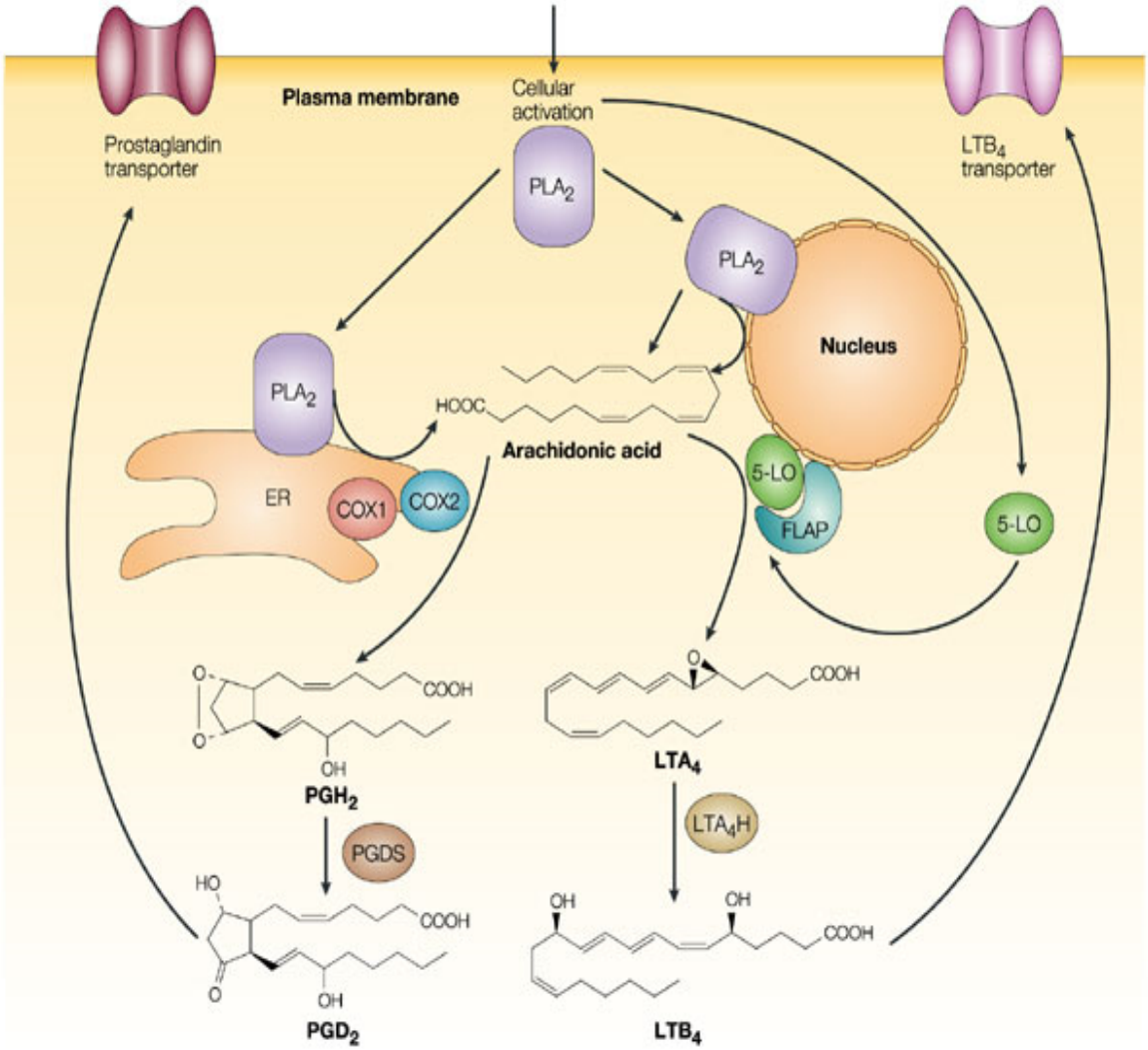
Figure 2-21 Immunobiology, 7ed. (© Garland Science 2008)

Monócitos e macrófagos liberam diferentes quimiocinas

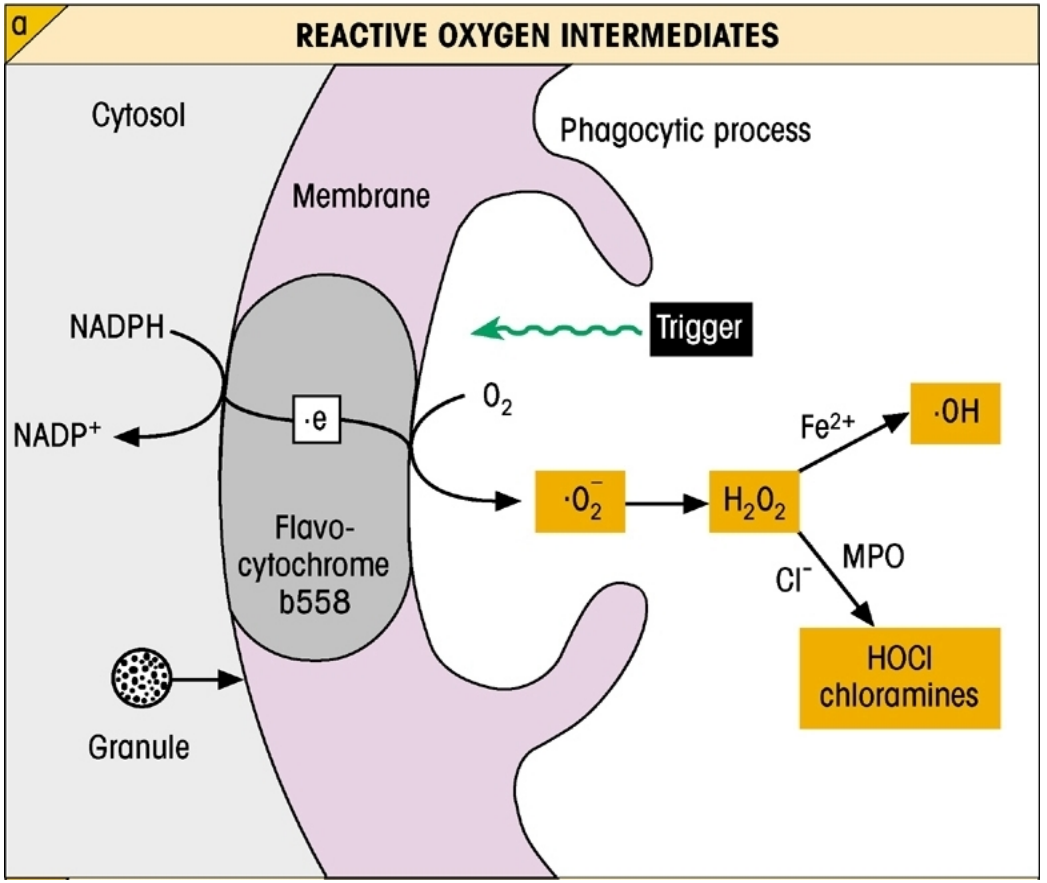
Class	Chemokine	Produced by	Receptors	Cells attracted	Major effects
CXC	CXCL8 (IL-8)	Monocytes Macrophages Fibroblasts Keratinocytes Endothelial cells	CXCR1 CXCR2	Neutrophils Naive T cells	Mobilizes, activates and degranulates neutrophils Angiogenesis
	CXCL7 (PBP, β-TG NAP-2)	Platelets	CXCR2	Neutrophils	Activates neutrophils Clot resorption Angiogenesis
	CXCL1 (GROα) CXCL2 (GROβ) CXCL3 (GROγ)	Monocytes Fibroblasts Endothelium	CXCR2	Neutrophils Naive T cells Fibroblasts	Activates neutrophils Fibroplasia Angiogenesis
	CXCL10 (IP-10)	Keratinocytes Monocytes T cells Fibroblasts Endothelium	CXCR3	Resting T cells NK cells Monocytes	Immunostimulant Antiangiogenic Promotes T_H1 immunity
	CXCL12 (SDF-1)	Stromal cells	CXCR4	Naive T cells Progenitor ($CD34^+$) B cells	B-cell development Lymphocyte homing Competes with HIV-1
	CXCL13 (BLC)	Stromal cells	CXCR5	B cells	Lymphocyte homing

Figure 2-46 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Macrófagos tambem sintetizam mediadores lipídicos como PGE_2 e LTB_4



Produção de reativos de oxigênio e de nitrogênio são importantes para matar microrganismos



Protective mechanism in macrophage

$$2O_2^- + 2H^+ \xrightarrow[\text{catalase}]{\text{superoxide dismutase}} O_2 + H_2O_2$$
$$2H_2O_2 \qquad\qquad 2H_2O + O_2$$

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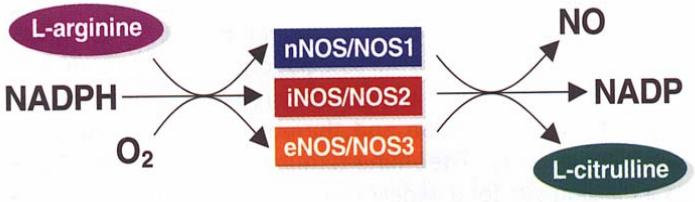
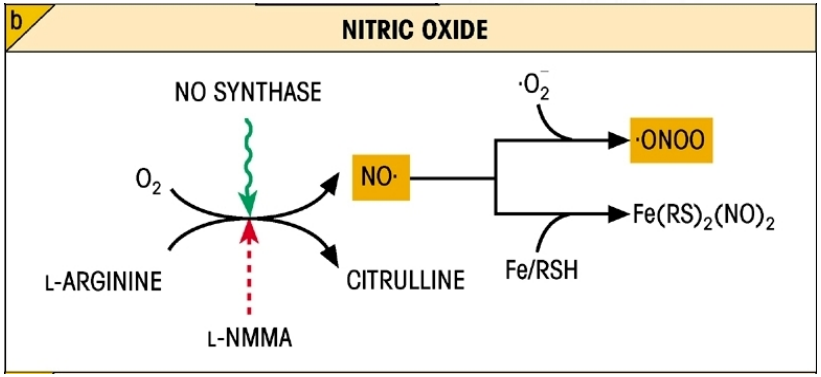
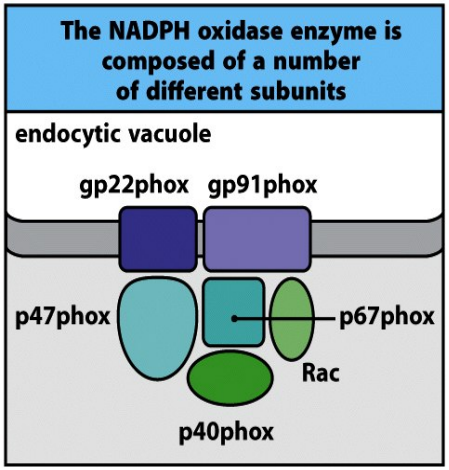






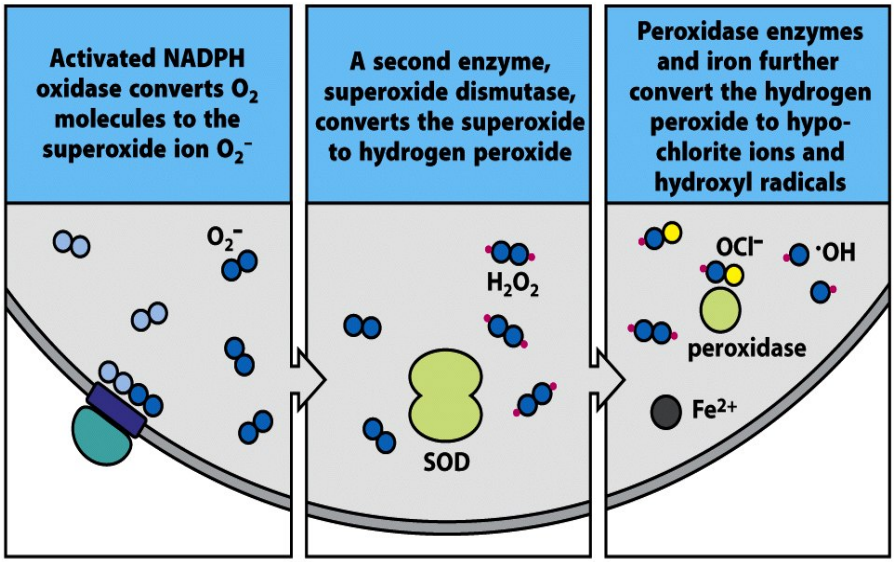


Figure 2-10 Immunobiology, 7ed. (© Garland Science 2008)

RADICAL SUPERÓXIDO: $O_2^{\bullet -}$

$$O_2 + e^- \rightarrow O_2^{\bullet -}$$

RADICAL HIDROXIL: $OH^{\bullet}$

(Reação de Fenton)

$$Fe^{2+}/Cu^{+} + H_2O_2 \rightarrow OH^{\bullet} + OH^{-} + Fe^{3+}/Cu^{2+}$$

(Reação de Haber-Weiss)

$$H_2O_2 + O_2^{\bullet -} \xrightarrow{Fe/Cu} OH^{\bullet} + OH^{-} + O$$

(a partir de peroxinitrito)

$$O_2^{\bullet -} + NO \rightarrow ONOO^{-} \rightarrow ONOO^{-} + H^{+} \rightarrow OH^{\bullet}$$

PERÓXIDO DE HIDROGÊNIO: H_2O_2

$$2O_2^{\bullet -} + 2H^{+} \xrightarrow{SOD} H_2O_2$$

RADICAL HIDROPEROXILA: $HO_2^{\bullet}$

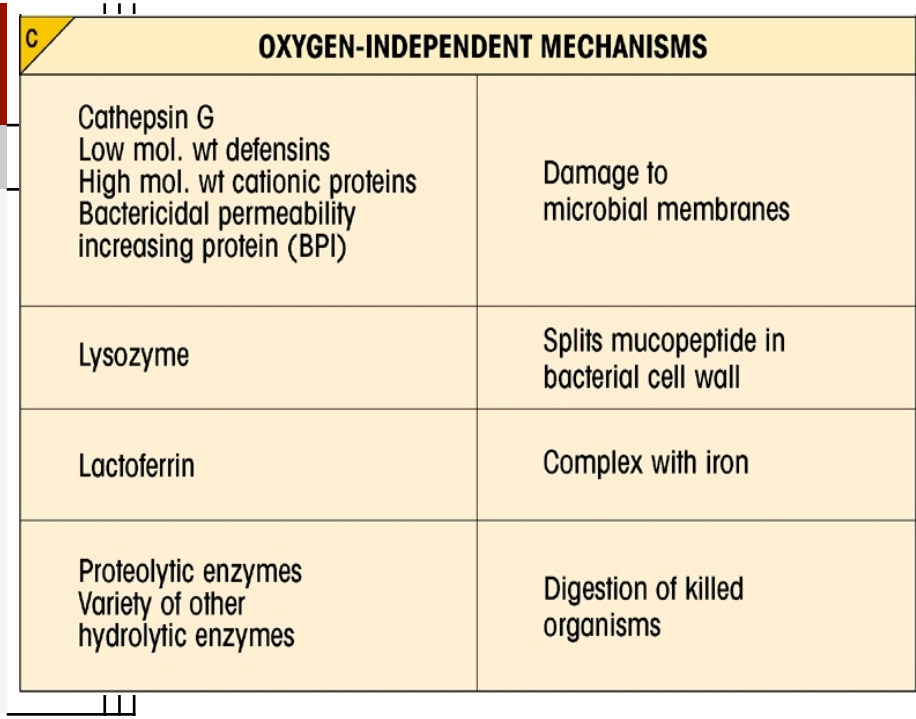
OXIGÊNIO SINGLET: $^1O_2$

RADICAL ÓXIDO NÍTRICO: $NO^{\bullet}$

Mecanismos microbicidas independentes de oxigênio

Table 4. Oxygen-independent mechanisms of intracellular killing

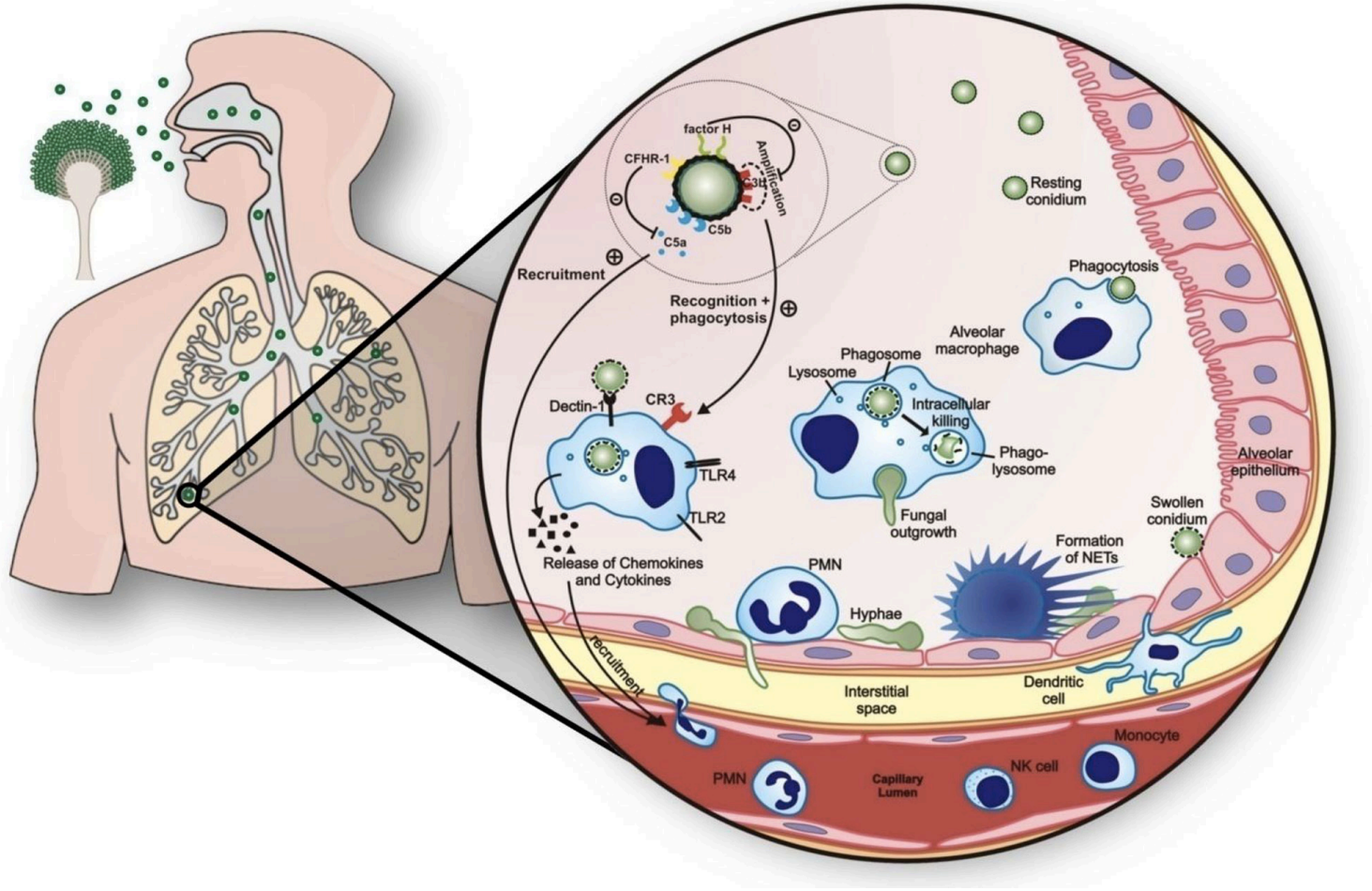
Effector Molecule	Function
Cationic proteins (including cathepsin)	Damage to microbial membranes
Lysozyme	Splits mucopeptide in bacterial cell wall
Lactoferrin	Deprives proliferating bacteria of iron
Proteolytic and hydrolytic enzymes	Digestion of killed organisms



C OXYGEN-INDEPENDENT MECHANISMS	
Cathepsin G Low mol. wt defensins High mol. wt cationic proteins Bactericidal permeability increasing protein (BPI)	Damage to microbial membranes
Lysozyme	Splits mucopeptide in bacterial cell wall
Lactoferrin	Complex with iron
Proteolytic enzymes Variety of other hydrolytic enzymes	Digestion of killed organisms

<Defensinas> familia de proteinas cationicas, ricas em cisteinas (30-35 residuos) presentes nos fagócitos, especialmente nos granulos azurófilos de neutrófilos e que matam bacterias, fungos e virus.

Uma das principais consequências do reconhecimento dos patógenos pelas células residentes nos parênquimas é a indução da inflamação



Todos leucócitos podem ser recrutados no processo inflamatório, mas geralmente os neutrófilos são os primeiros

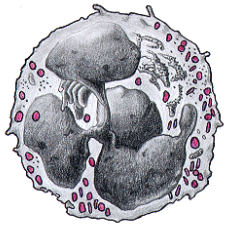


Fig. 8 - Neutrophil

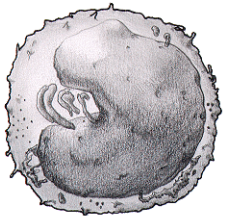


Fig. 12 - Monocyte

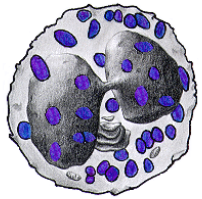


fig. 10 - Basophil

Fig. 11 - Lymphocyte

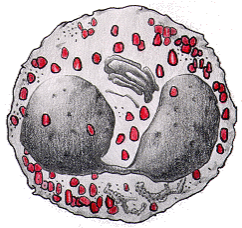
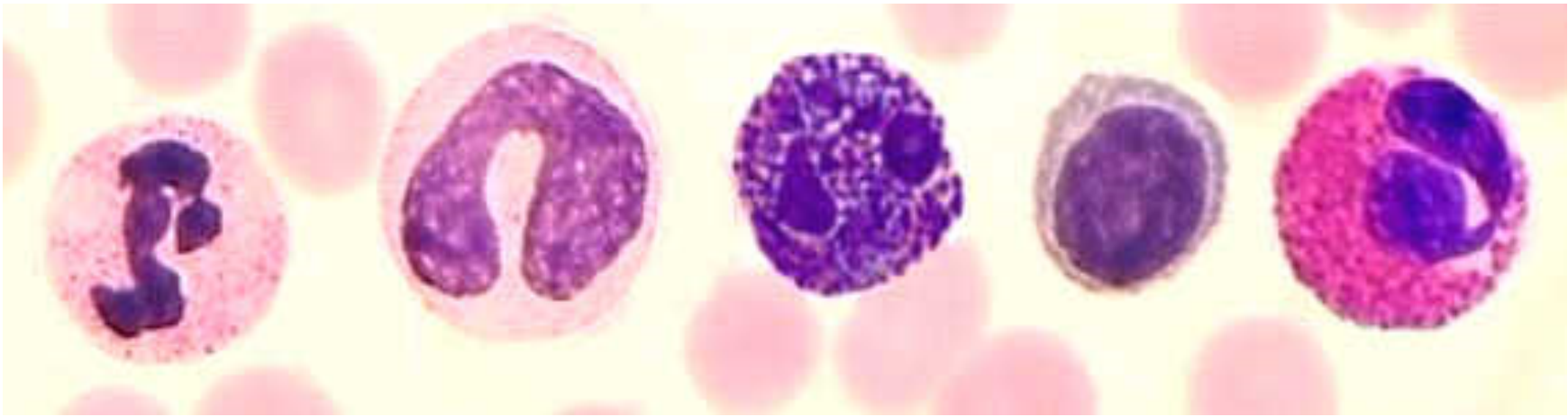


Fig. 9 - Eosinophil



O processo inflamatório

Definição: reação dos tecidos vascularizados a agente agressor como patógenos, toxinas, peçonhas, venenos, traumas, UV, ate mesmo material inerte, entre outros. 'E um evento complexo que envolve a microcirculação e as moléculas de adesão presente em suas células, mediadores inflamatórios, e os leucócitos.

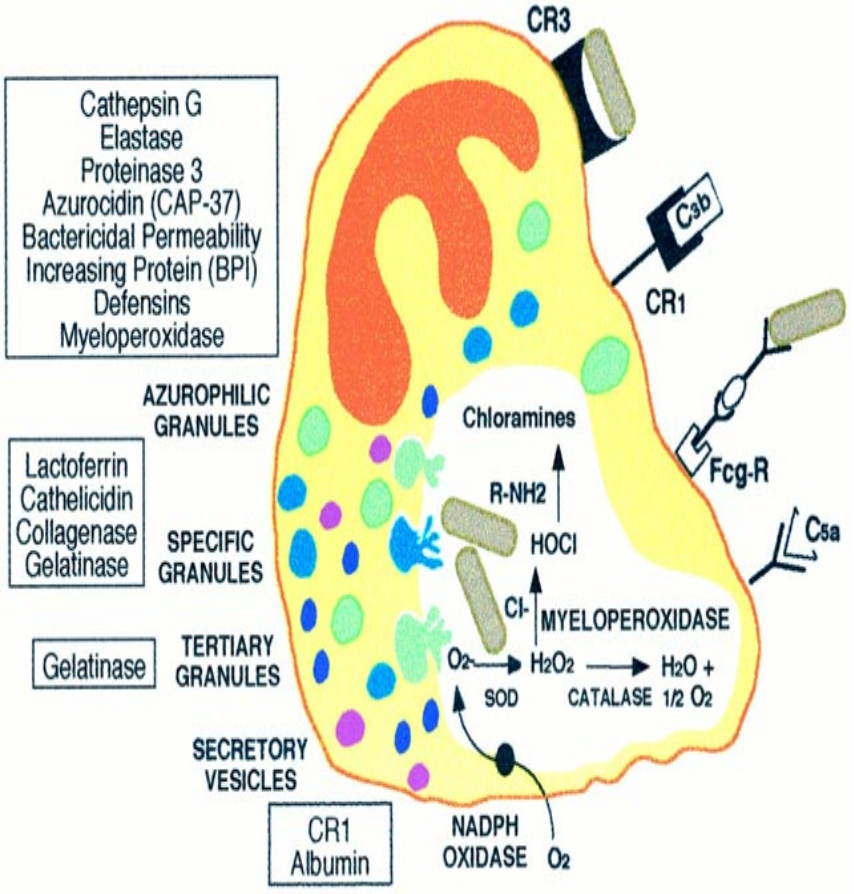
São dois os eventos resultantes:

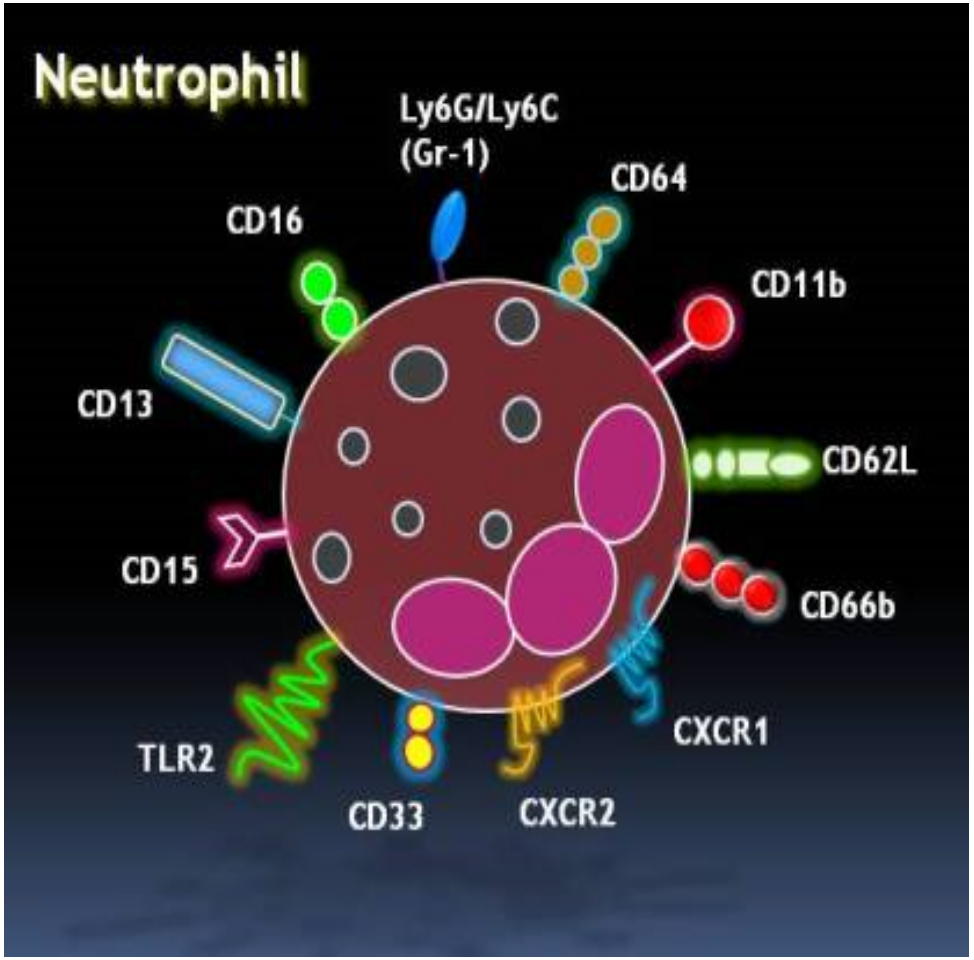
1. **Edema e**
2. **Recrutamento celular**

Inflamação é um mecanismo de defesa (mecanismo efetor) da resposta imune inata, mas ela tem que ser controlada para nao causar danos

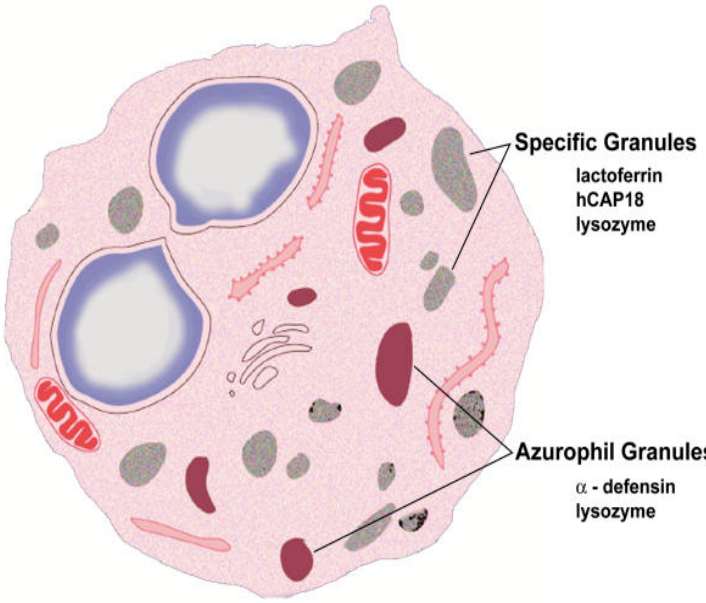
Sinais cardinais da Inflamação

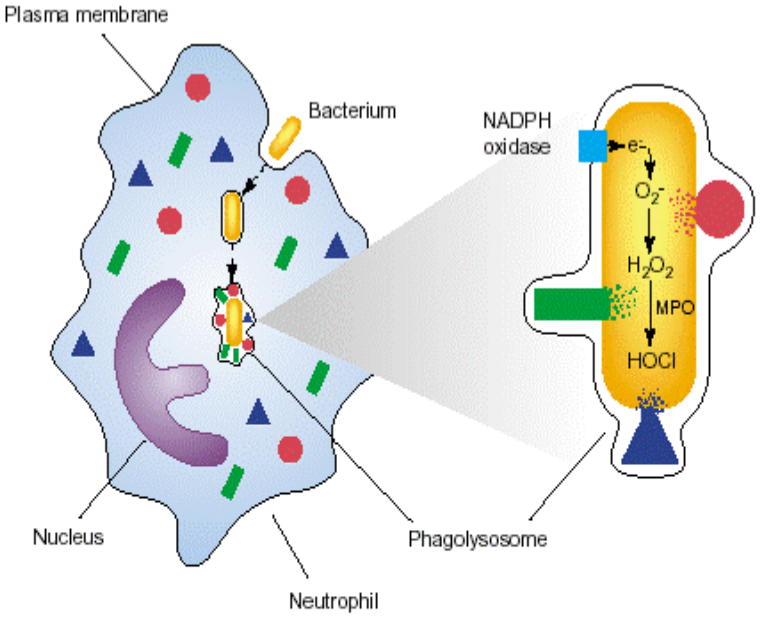
Receptores de Neutrófilos

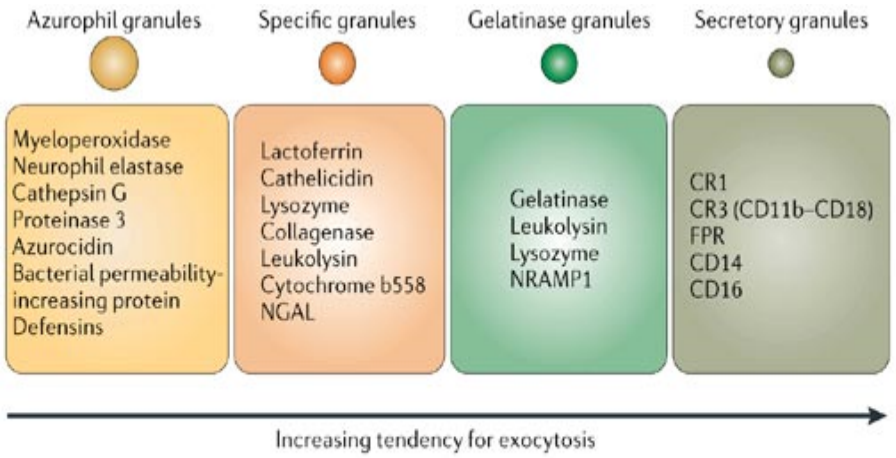


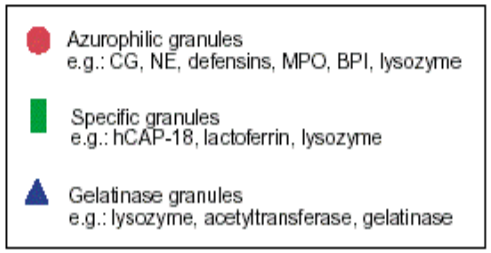


Grânulos no citoplasma dos neutrófilos

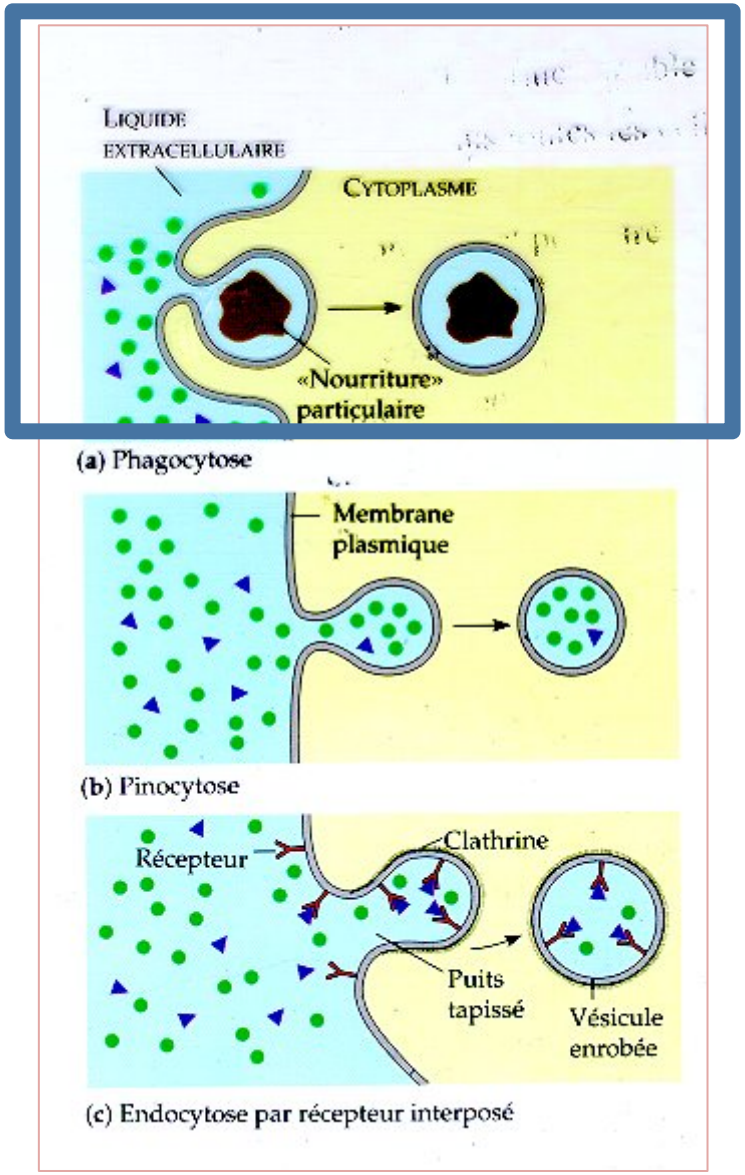


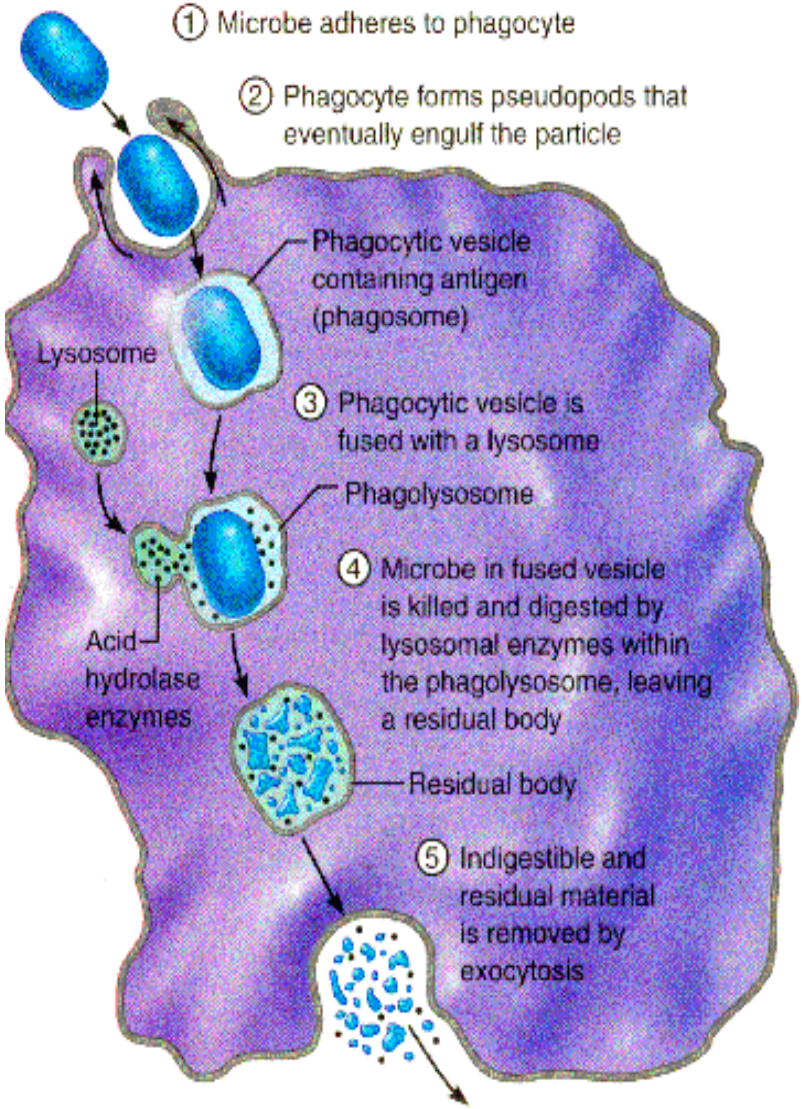


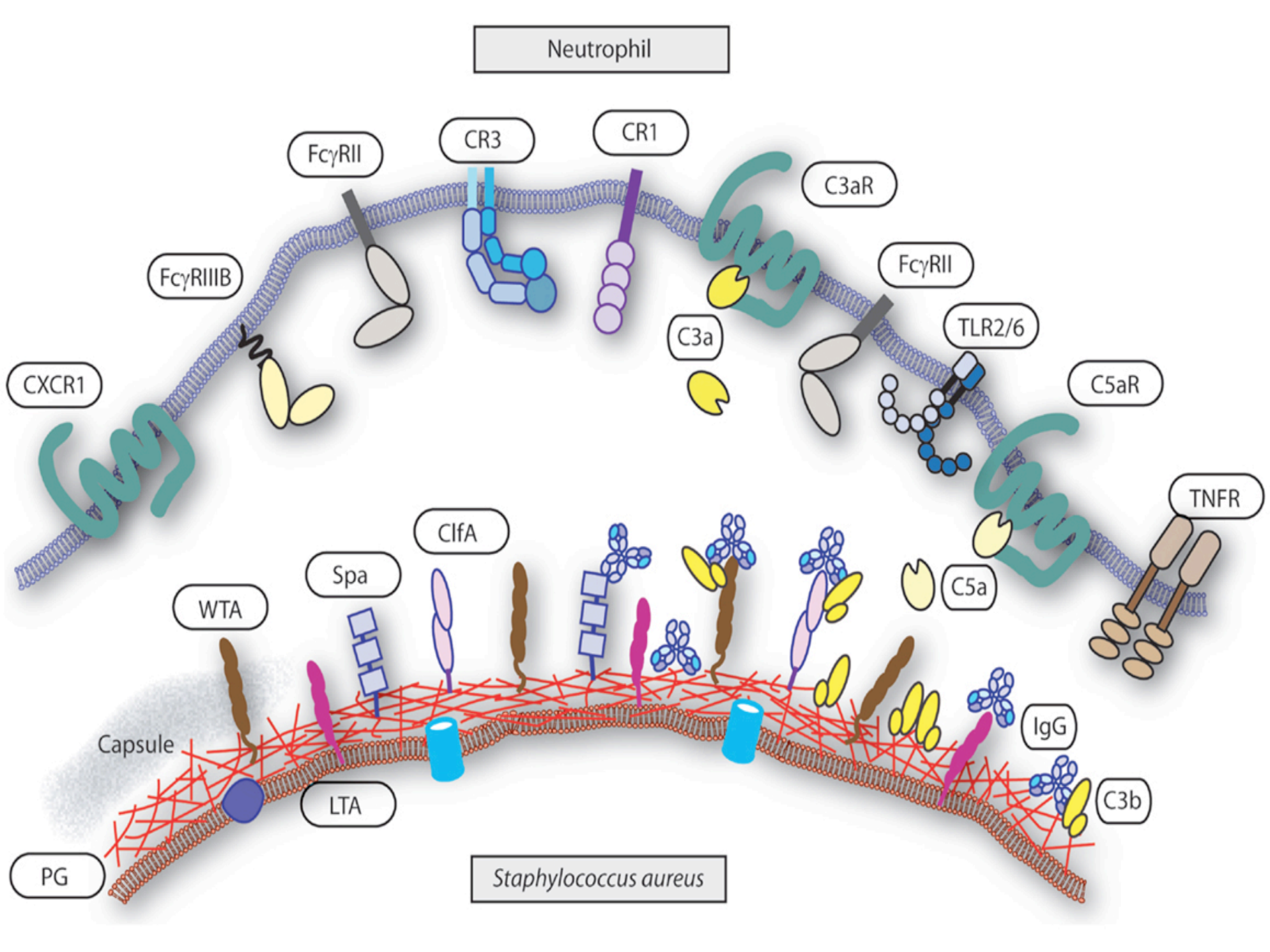




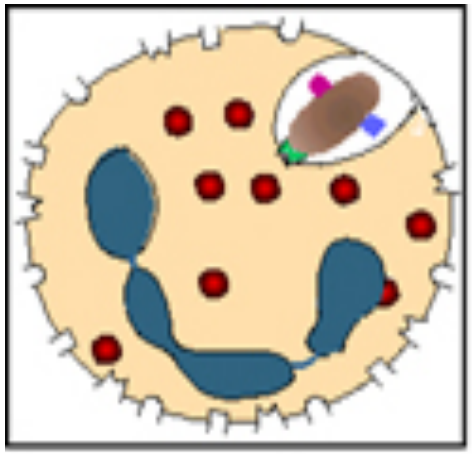
Citoesqueleto dos neutrófilos participa da migraçãodos neutrofilos e também é importante para fagocitose

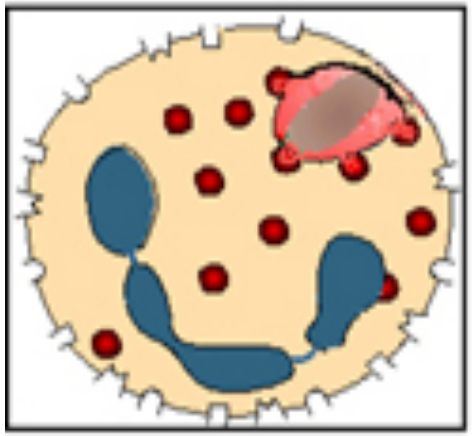





Neutrophil
FcγRII
CR3
CR1
C3aR
FcγRIIIB
FcγRII
C3a
TLR2/6
CXCR1
C5aR
TNFR
ClfA
Spa
C5a
WTA
IgG
Capsule
C3b
LTA
PG
Staphylococcus aureus

Após a fagocitose são ativadas enzimas que geram produtos tóxicos para os microrganismos





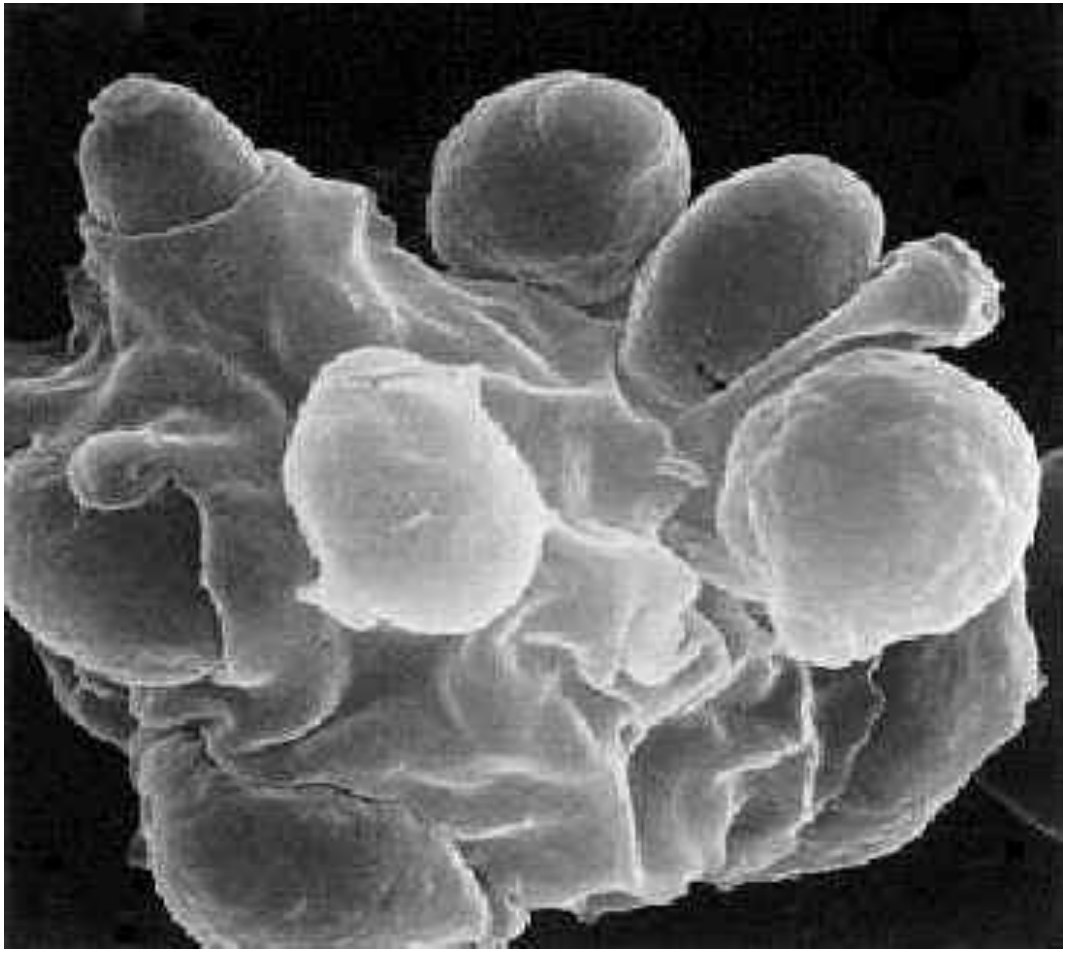
$$H_2O_2 + Cl^- \xrightarrow[\text{myeloperoxidase}]{} OCl^- + H_2O$$

$$OCL^- + H_2O \rightarrow {}^1O_2 + Cl^- + H_2O$$

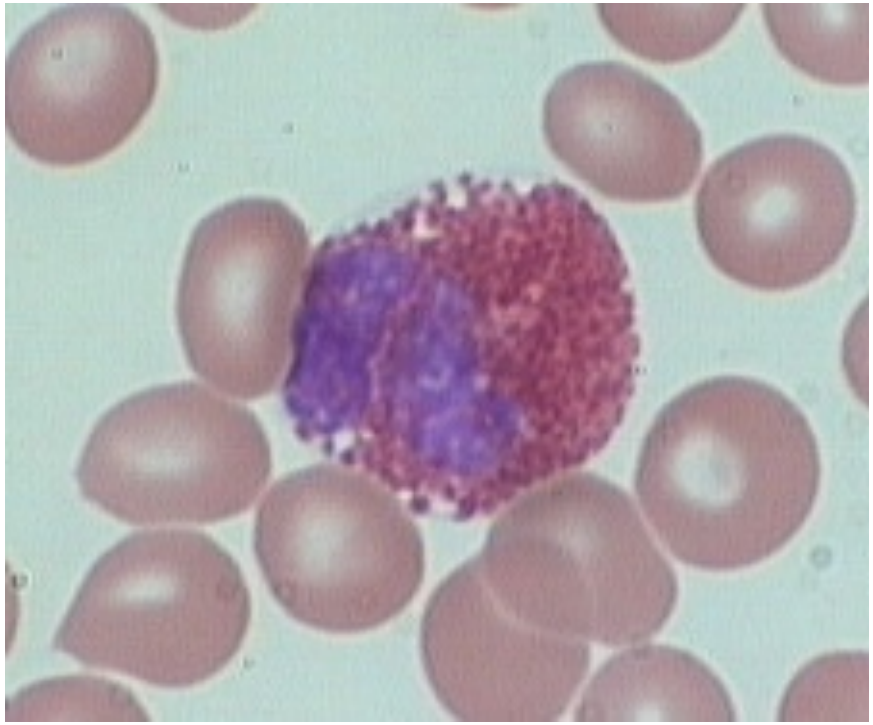
$$2O_2^{\cdot-} + 2H^+ \xrightarrow[\text{Superoxide dismutase}]{} H_2O_2 + {}^1O_2$$

$$2\,H_2O_2 \xrightarrow[\text{catalase}]{} H_2O + O_2$$

Neutrófilo fagocitando leveduras



EOSINÓFILOS



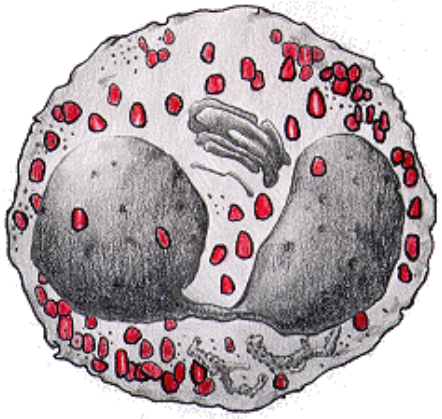
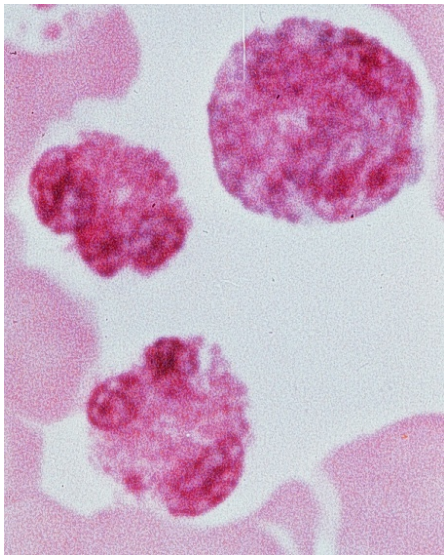
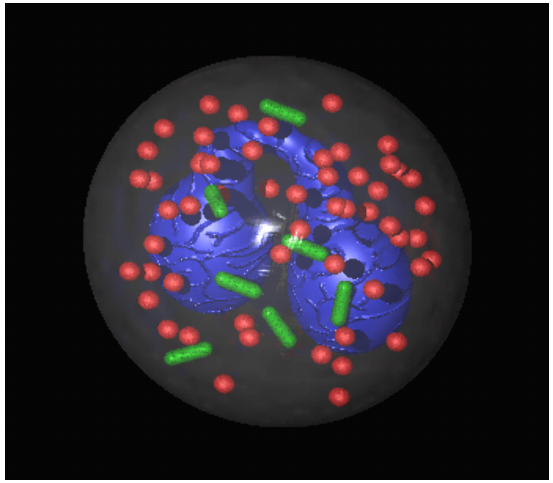
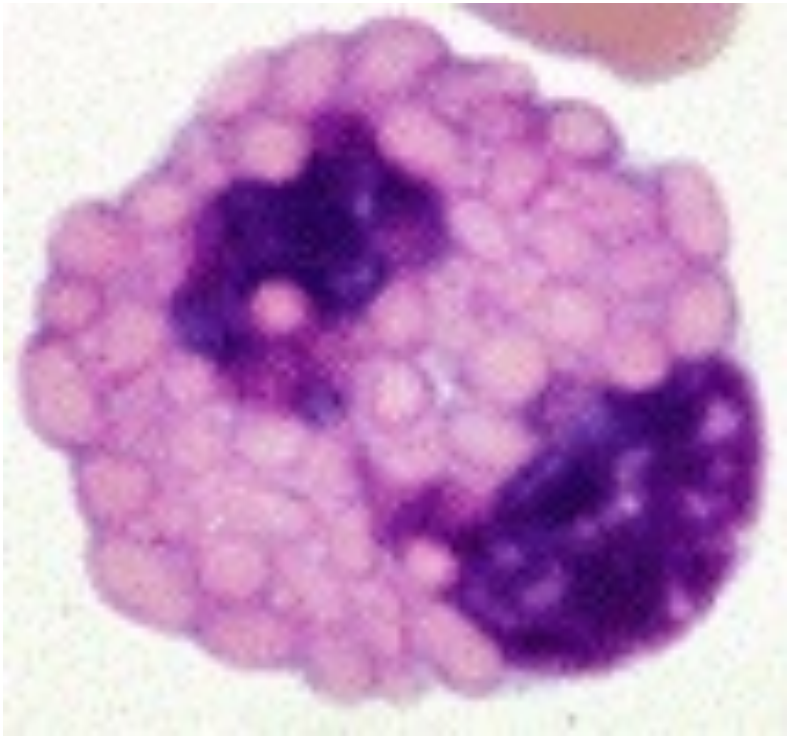


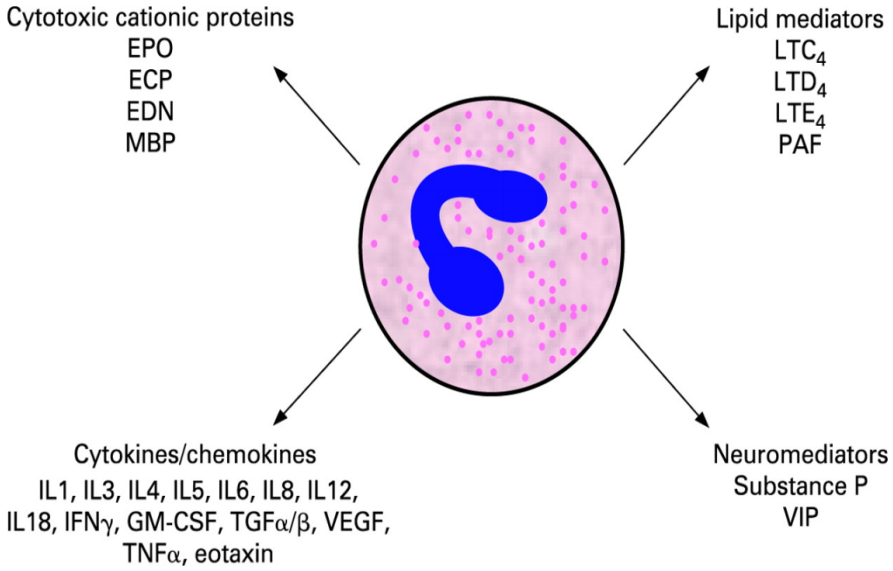
Fig. 9 - Eosinophil

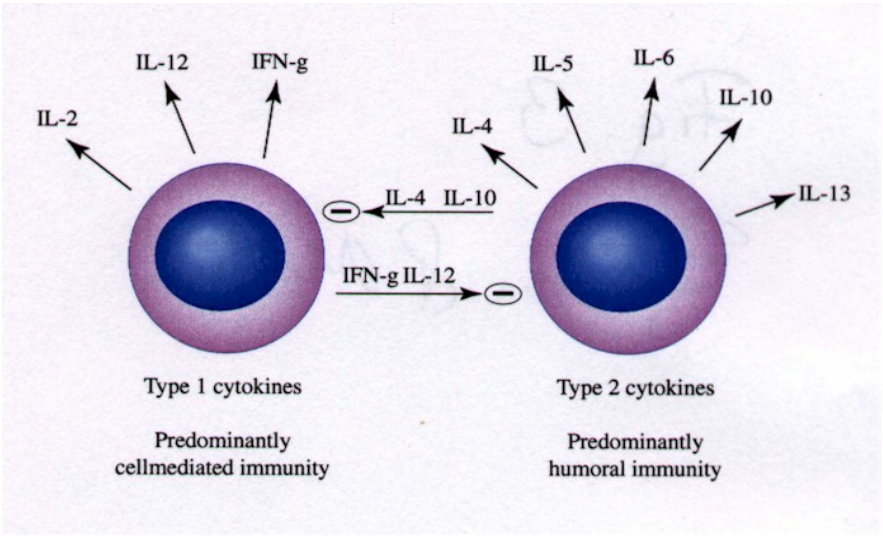


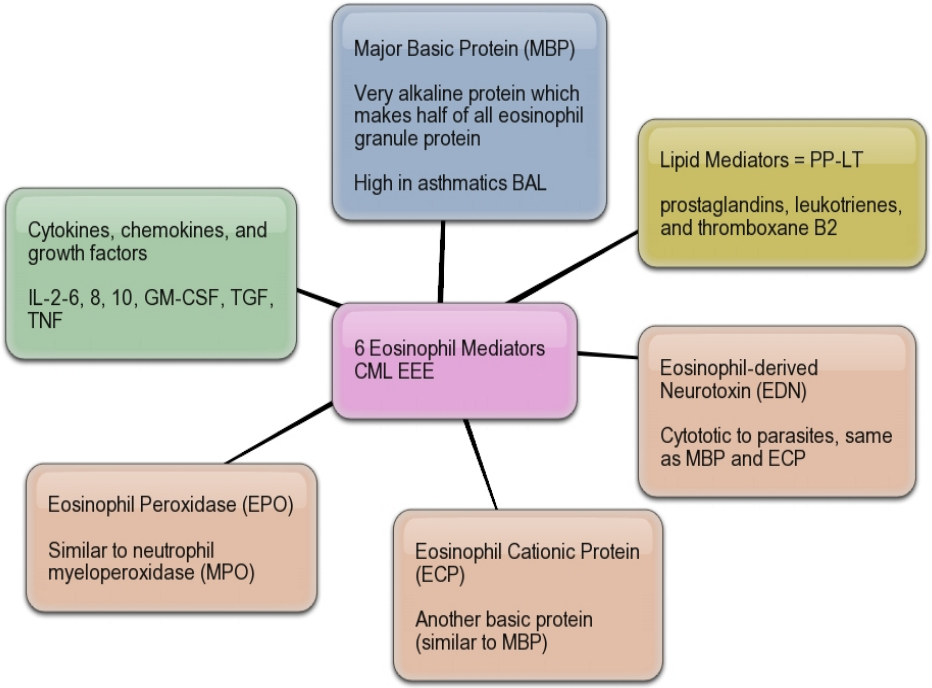




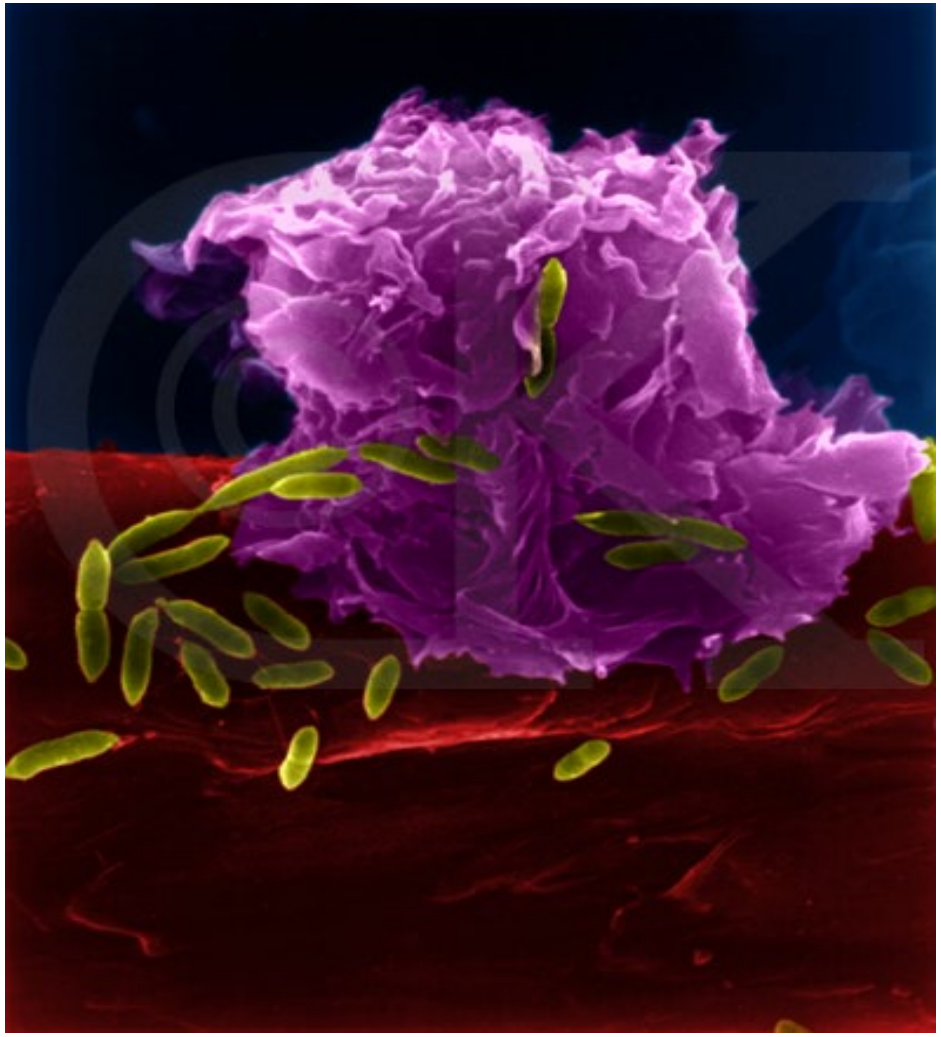
Citocinas e produtos liberados pelos eosinófilos

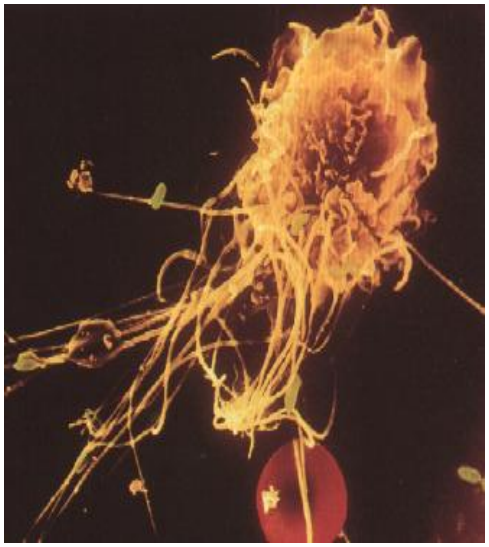


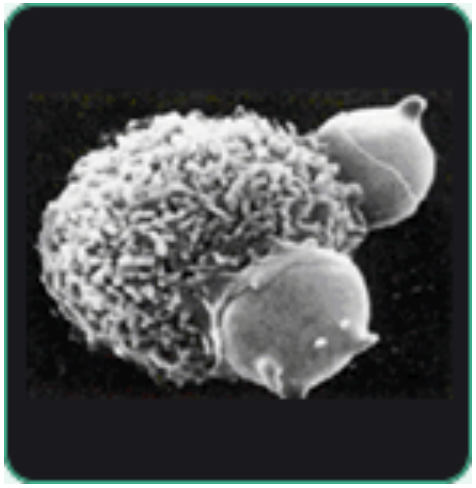




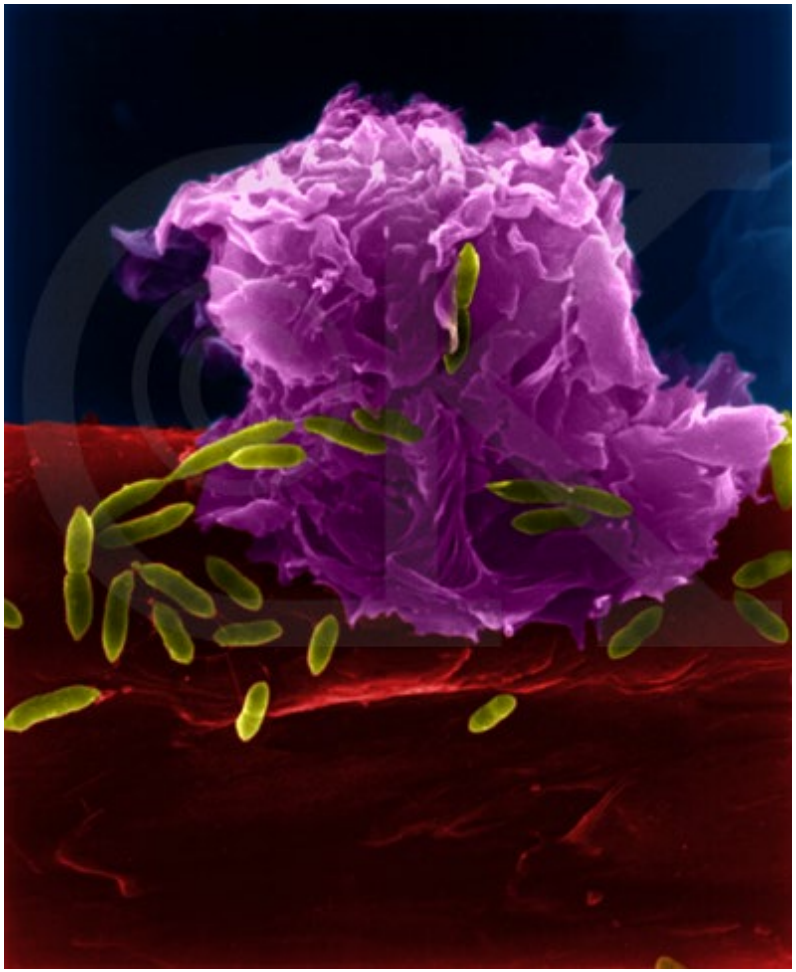
Greek: "big eaters", makros = large, phagein = eat) are cells within the tissues that originate from specific white blood cells called monocytes

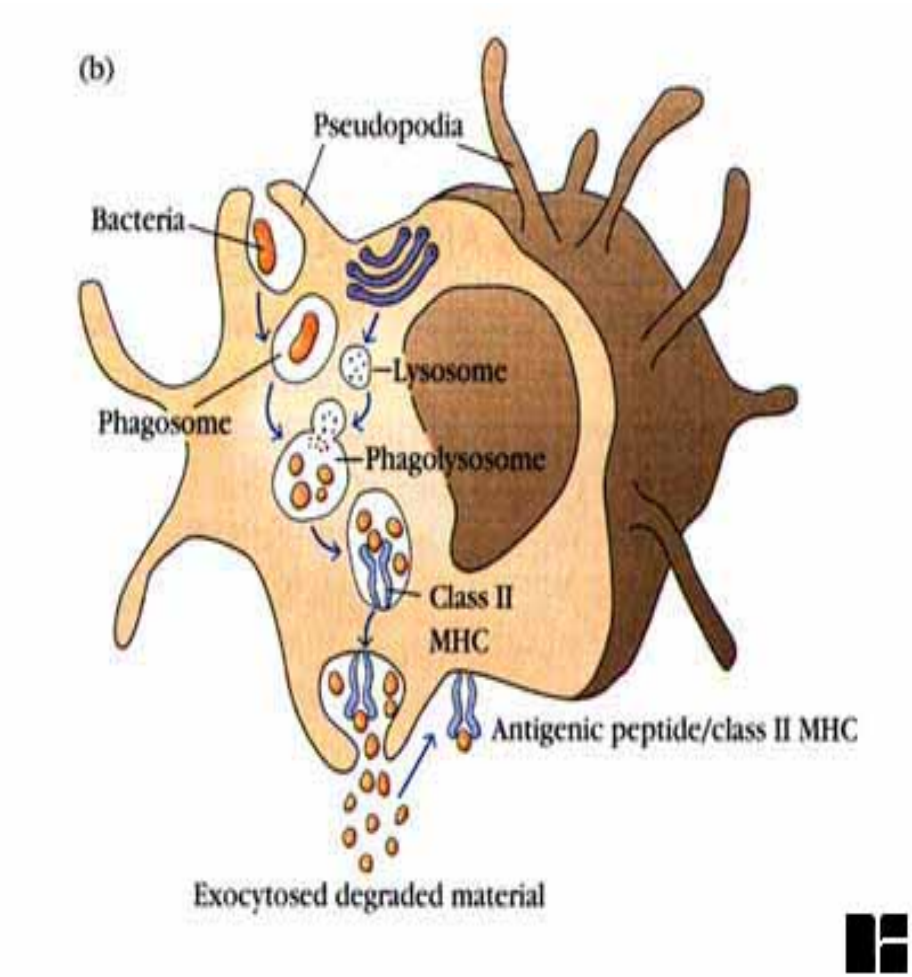






Macrófagos fagocitam microrganismos, matam, digerem e apresentam peptídeos em sua membrana - Os macrófagos são células apresentadoras de antígenos ou APCs





Células Dendríticas são as principais células apresentadoras de antígenos ou APC e expressam moléculas de MHC I e II

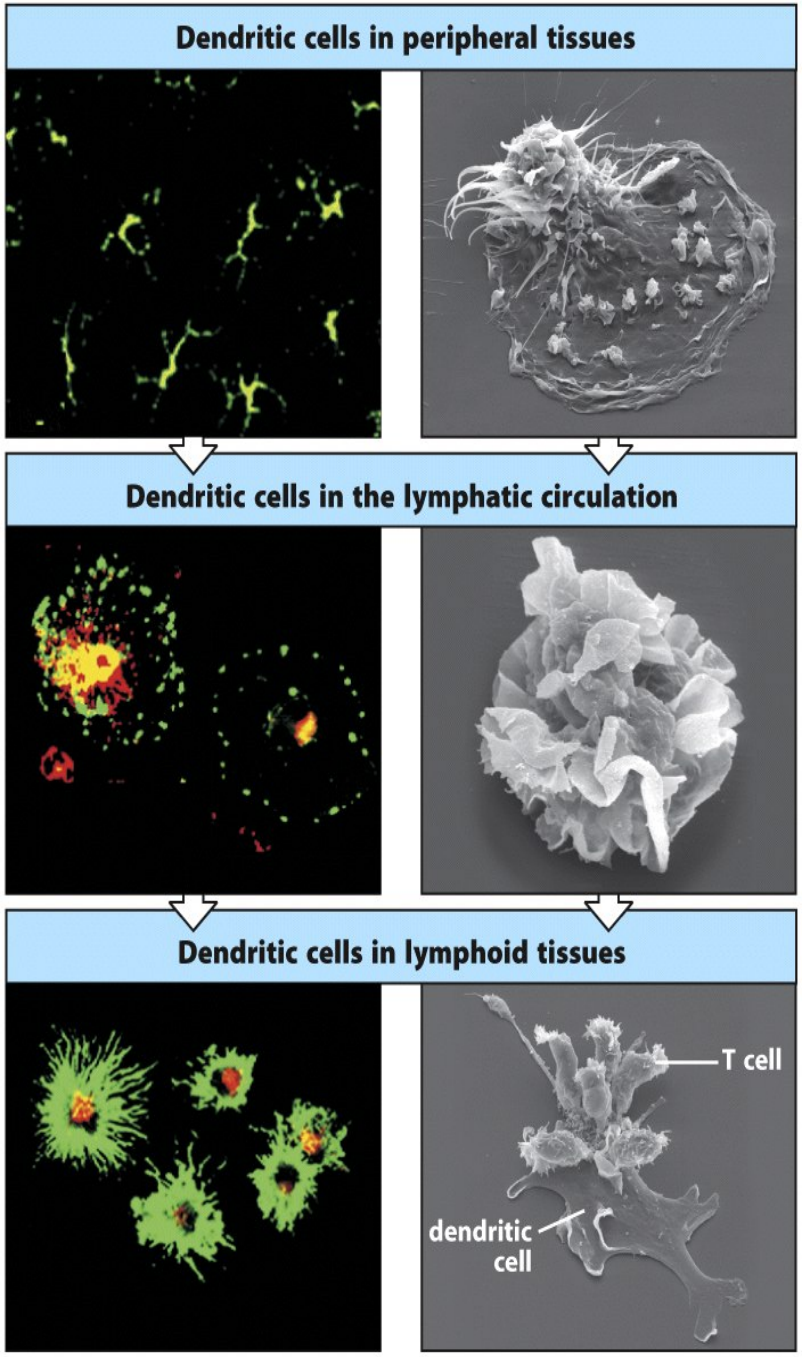
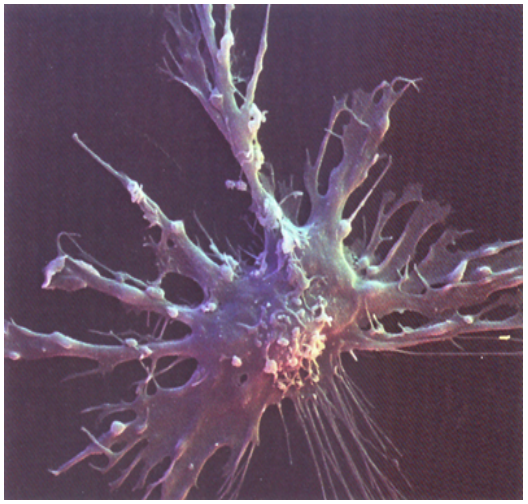
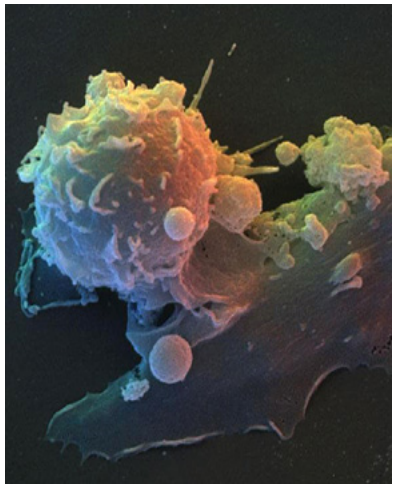
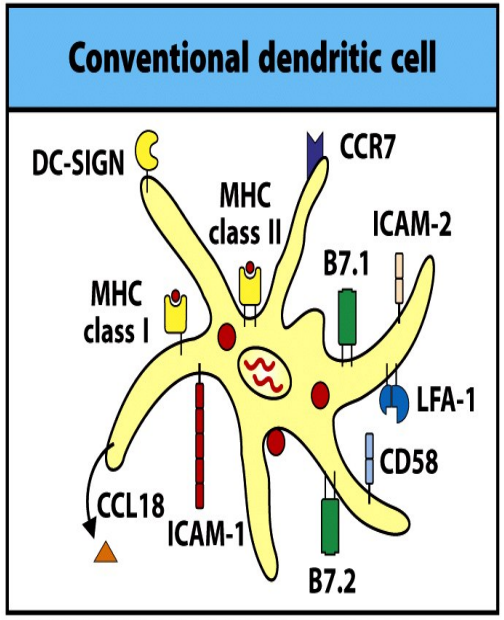


Figure 8-9 Immunobiology, 7ed. (© Garland Science 2008)







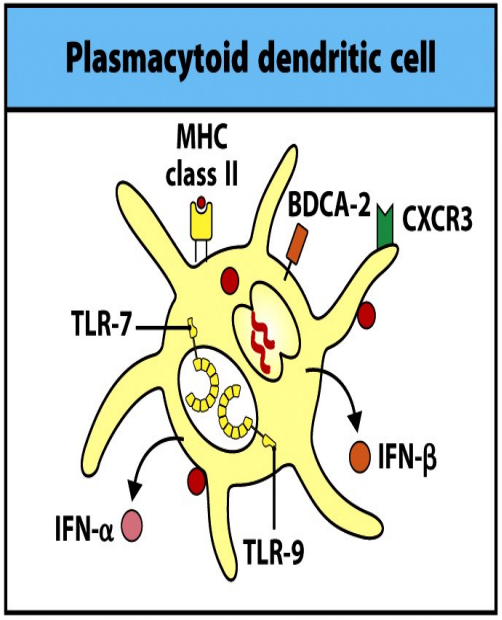
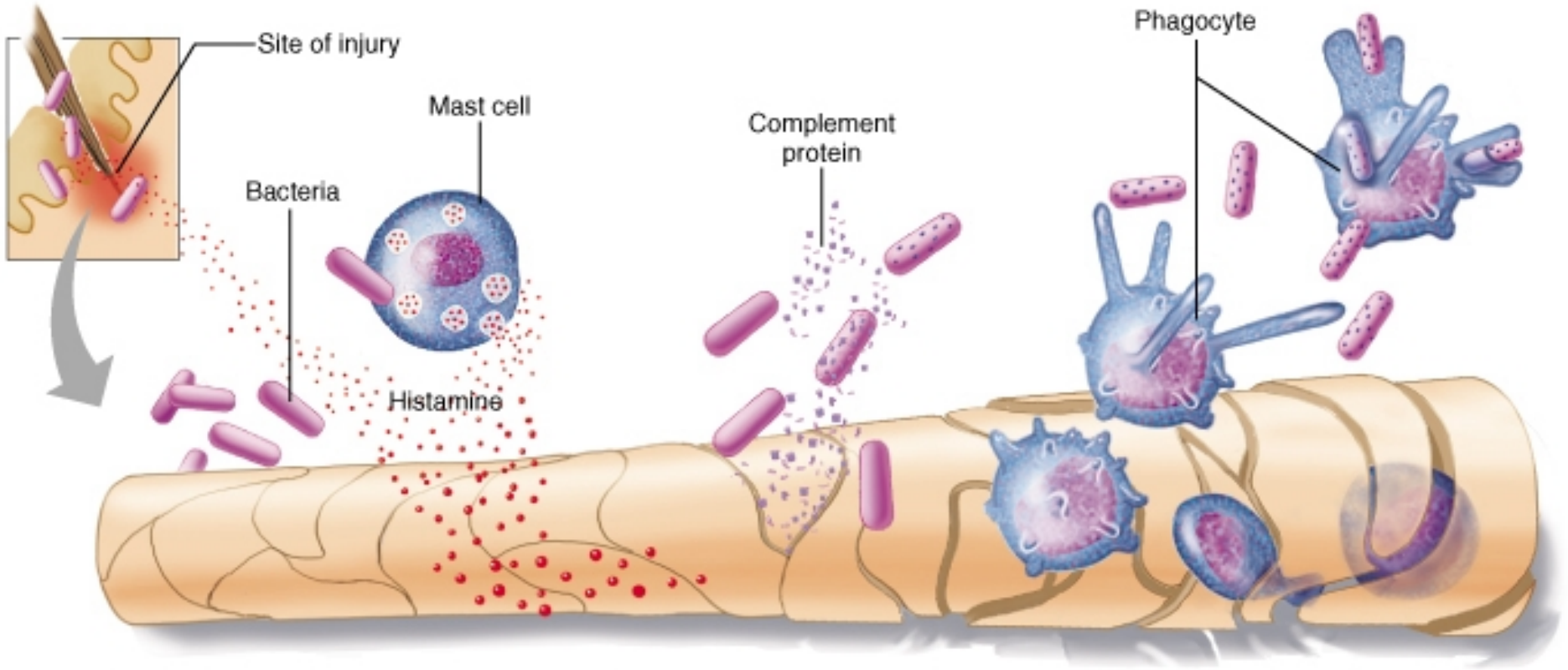


Figure 8-11 Immunobiology, 7ed. (© Garland Science 2008)

Inflamação é parte da resposta imune inata

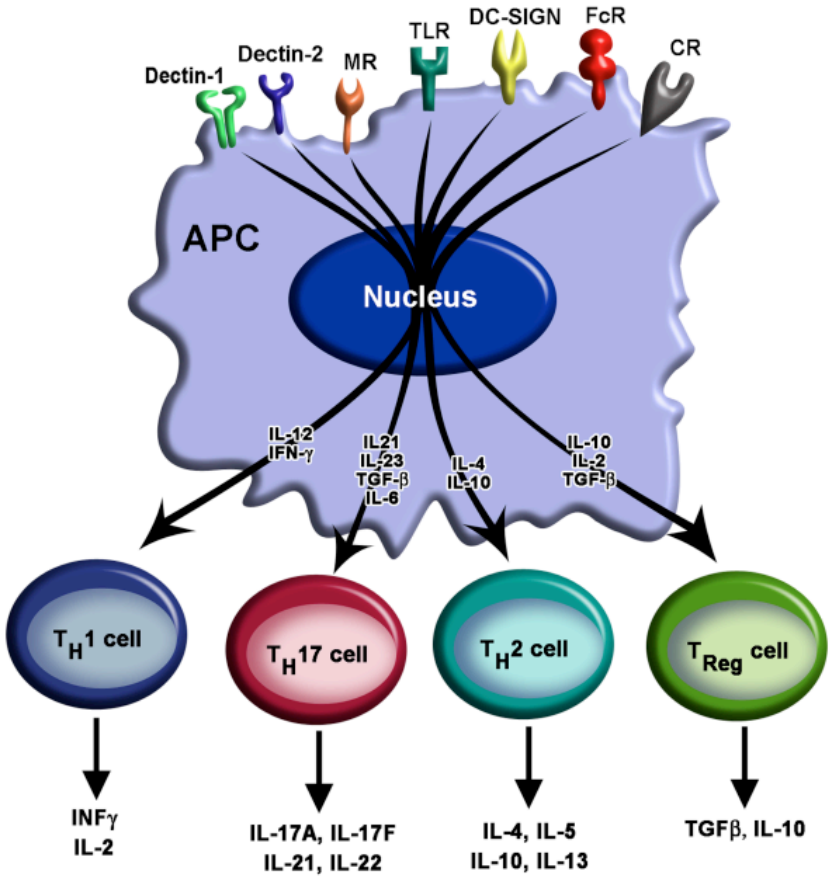


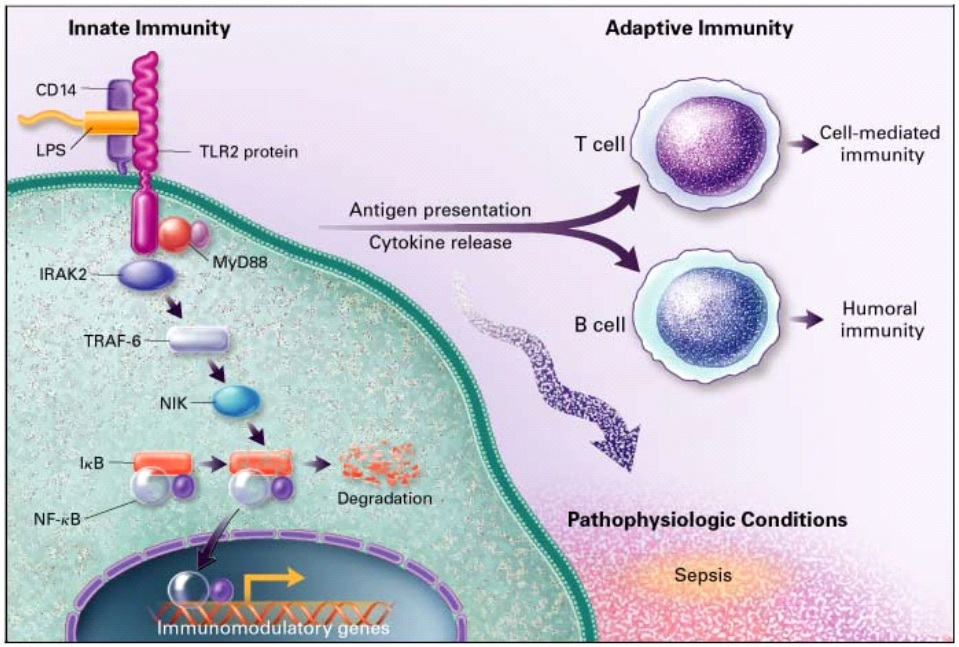
① Damaged cells and mast cells in the area release histamine and other substances. Histamine dilates blood vessels and makes them leaky.

② Complement proteins from plasma diffuse out of leaky capillaries. They mark the bacteria for destruction and sometimes kill them.

③ Attracted by histamine and other chemicals, phagocytes squeeze through the leaky capillary walls and begin attacking and engulfing bacteria and debris.

Interação entre PAMPs e PRRs contribui para ativação da resposta imune adaptativa ou especifica





PAMPs
Sinal de Perigo

PRR
Resposta Imune

Poly Matzinger (1987) -
Danger Signal Hypothesis

Outra função fundamental dos Macrófagos e outras APCs, é apresentar os antígenos aos linfócitos

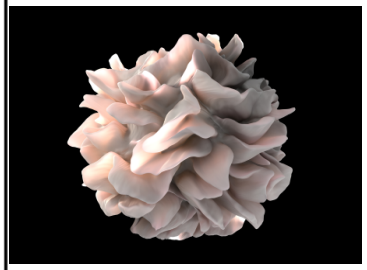
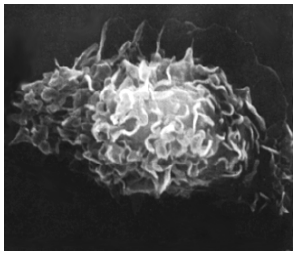
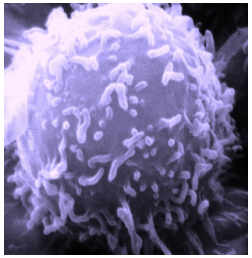
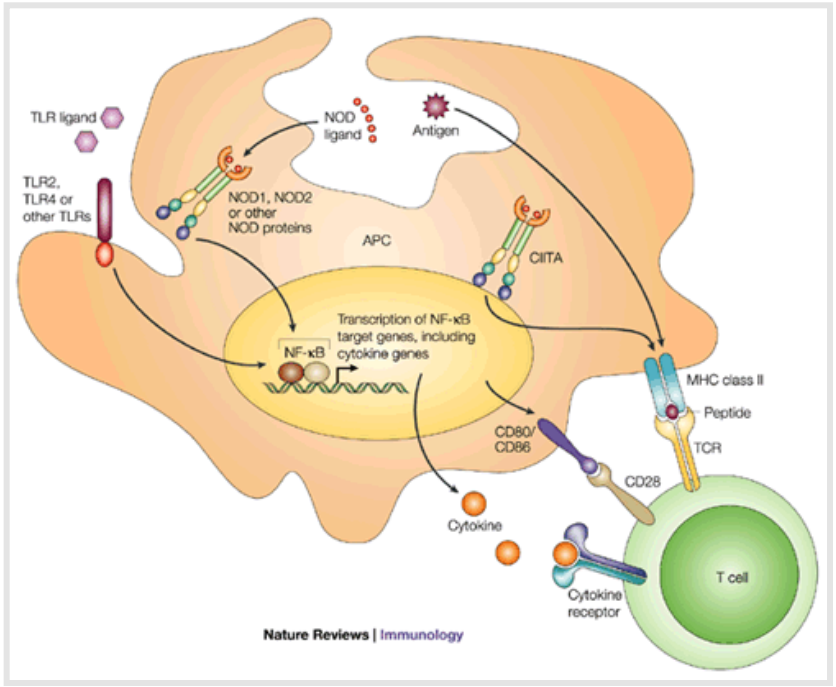
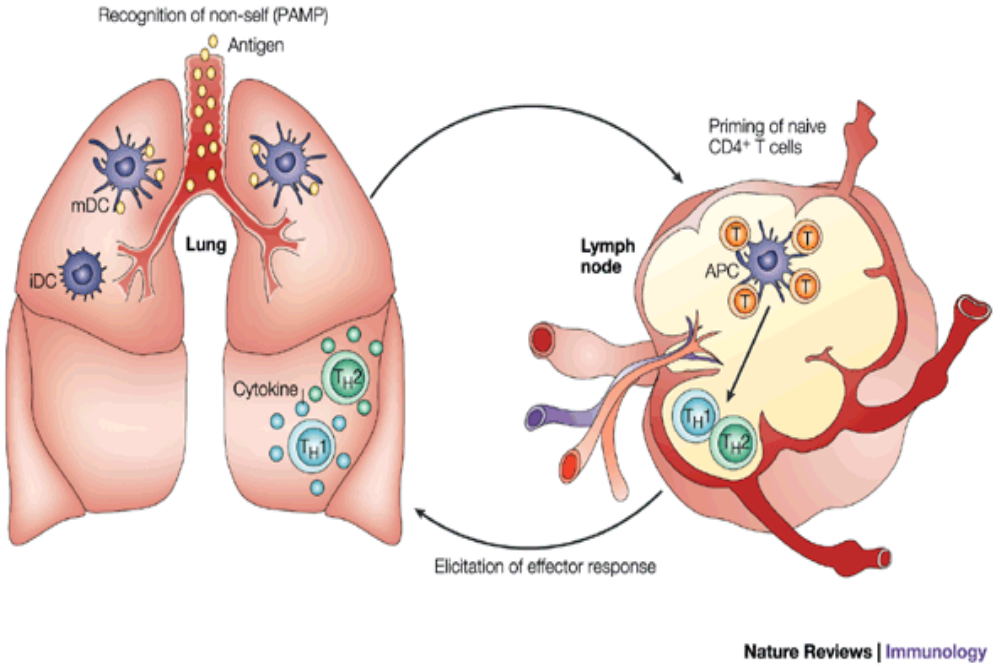
	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible – to +++	Inducible – to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellular and extracellular pathogens	Soluble antigens Toxins Viruses
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

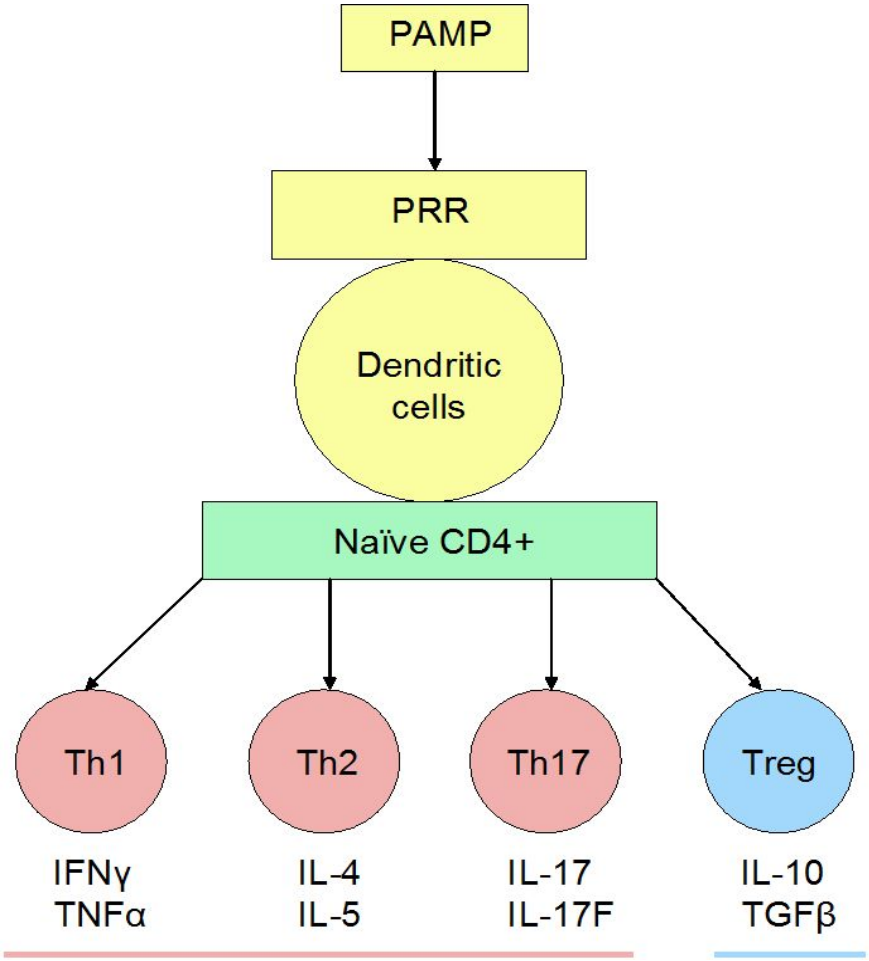
Figure 8-16 Immunobiology, 7ed. (© Garland Science 2008)

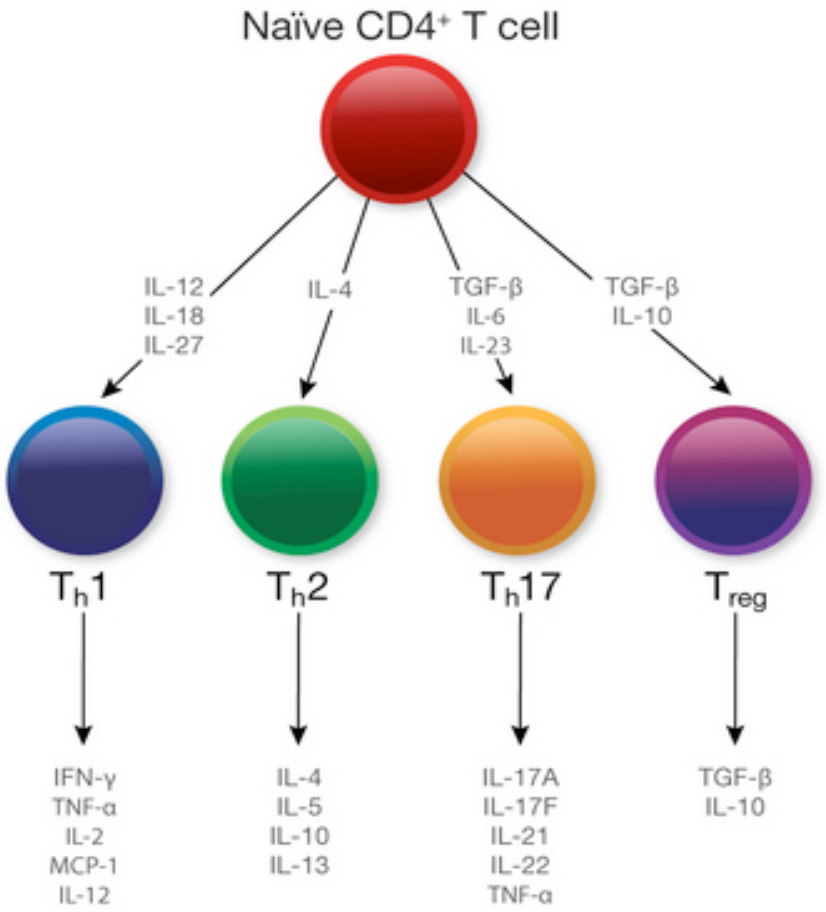
Os PAMPs, após ligação dos PRRs, estimulam células Dendríticas/ Macrófagos para processar o patógeno e mostrar via MHC, induz expressão de moléculas co-estimuladoras de linfócitos, citocinas e as fazem migrar para os Órgãos Linfoides Secundários, onde vao induzir a resposta imune adaptativa





Resposta Imune Th1, Th2, Th17 e Treg





Interação entre PAMPs e PRRs pode ter como consequência, eventos sistêmicos