Patogênese Bacteriana – Respostas imunológicas do hospedeiro contra infecções bacterianas

Como entrar no corpo humano, essa fortaleza!

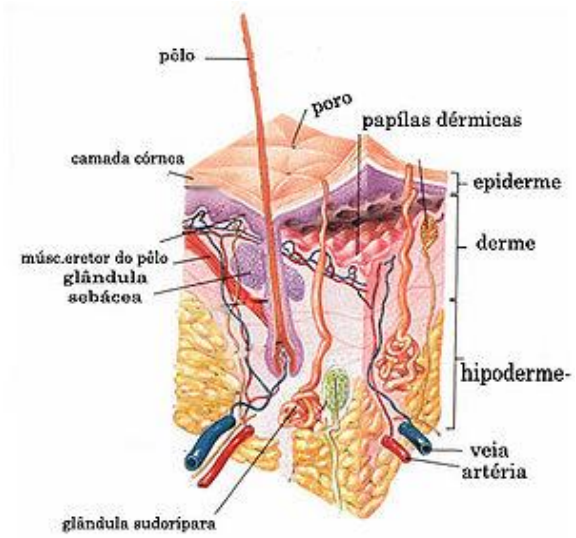
Pele

Saliva

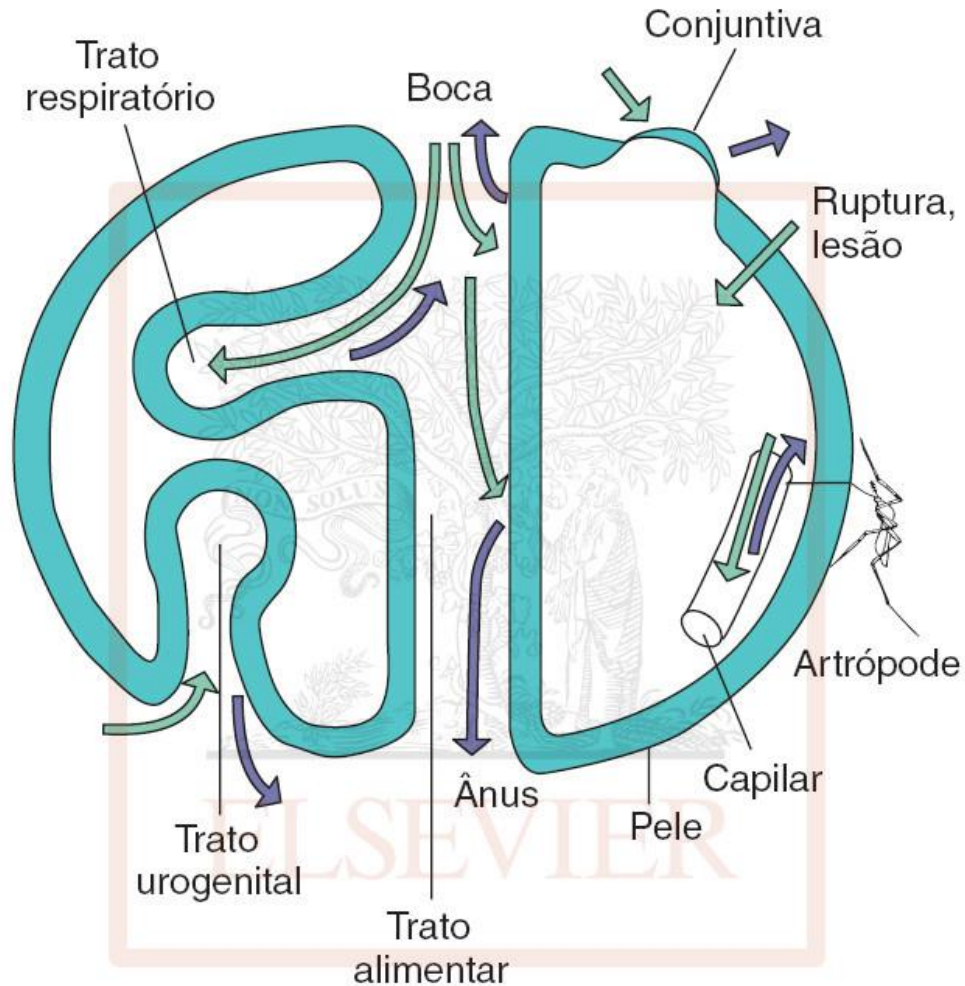
Muco

Lágrimas

Epitélio ciliado



Microbiologia Médica - 6ª Edição
Murray & Rosenthal & Pfaller
ISBN: 9788535234466
Elsevier Editora



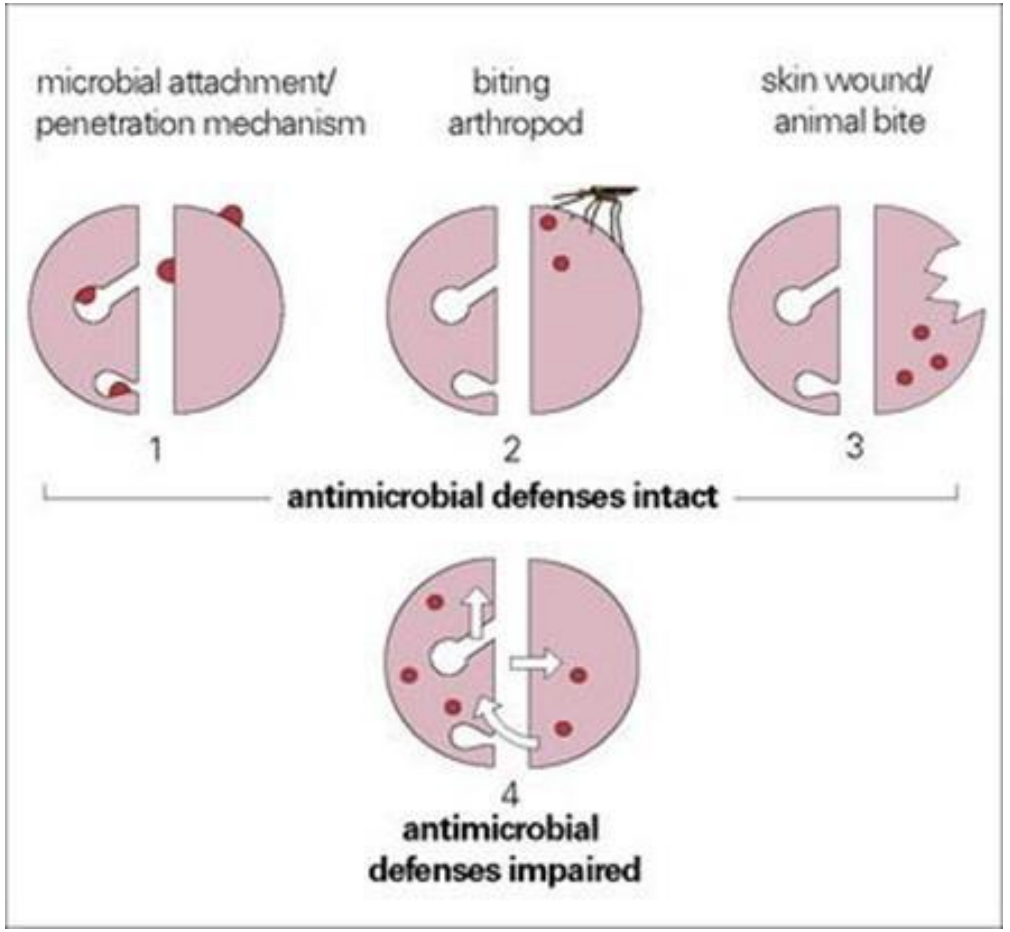
Os microrganismos podem entrar de 4 formas distinta e causar doença :

-microrganismos com mecanismos específicos de aderência e invasão das superfícies corporais do hospedeiro

-microrganismos introduzidos em hospedeiros saudáveis por picadas de artrópodes

- Microrganismos introduzidos em hospedeiros saudáveis, através de feridas na pele ou mordidas de animais

- Microrganismos capazes de infectar hospedeiro saudável apenas quando os mecanismos de defesa estão comprometidos



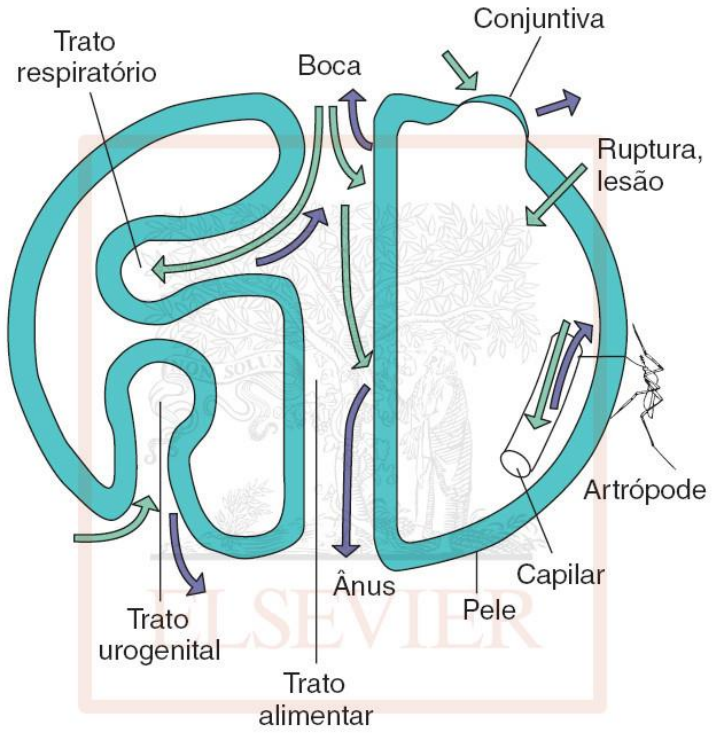
Entrada

Barreiras:

pele:

- Camada rígida formada por células mortas e queratinizadas
- Entrada pelos folículos pilosos e ductos sudoríparos
- Cortes via parenteral = através de perfurações, injeções, mordidas ....

Microbiologia Médica - 6ª Edição
Murray & Rosenthal & Pfaller
ISBN: 9788535234466
Elsevier Editora



Boca, nariz, trato respiratório, ouvidos, olhos, trato urogenital e ânus

- Superfícies revestidas com epitélio ciliado e/ou muco
- Alta concentrações de lisozima
- Meio ácido

- Bactérias podem produzir proteínas que modulam as funções do epitélio

Via preferencial = pré-requisito para causar a doença
Ex. estreptococococos devem ser inalados para causar doença.

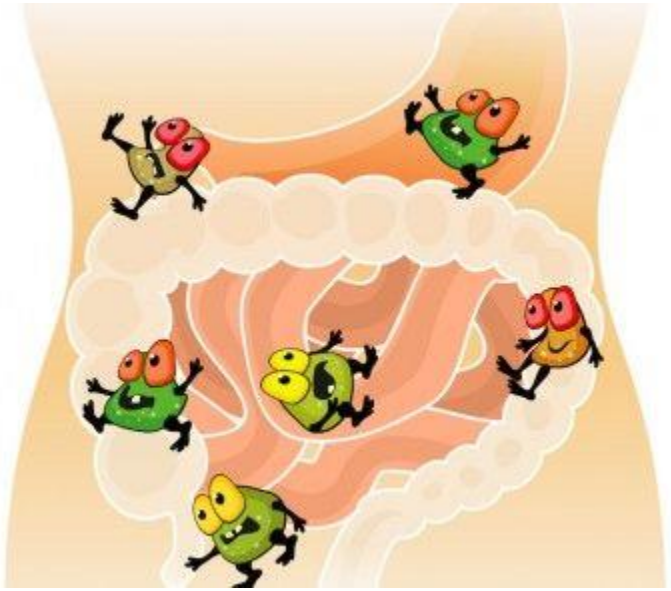
Número de microrganismos invasores:

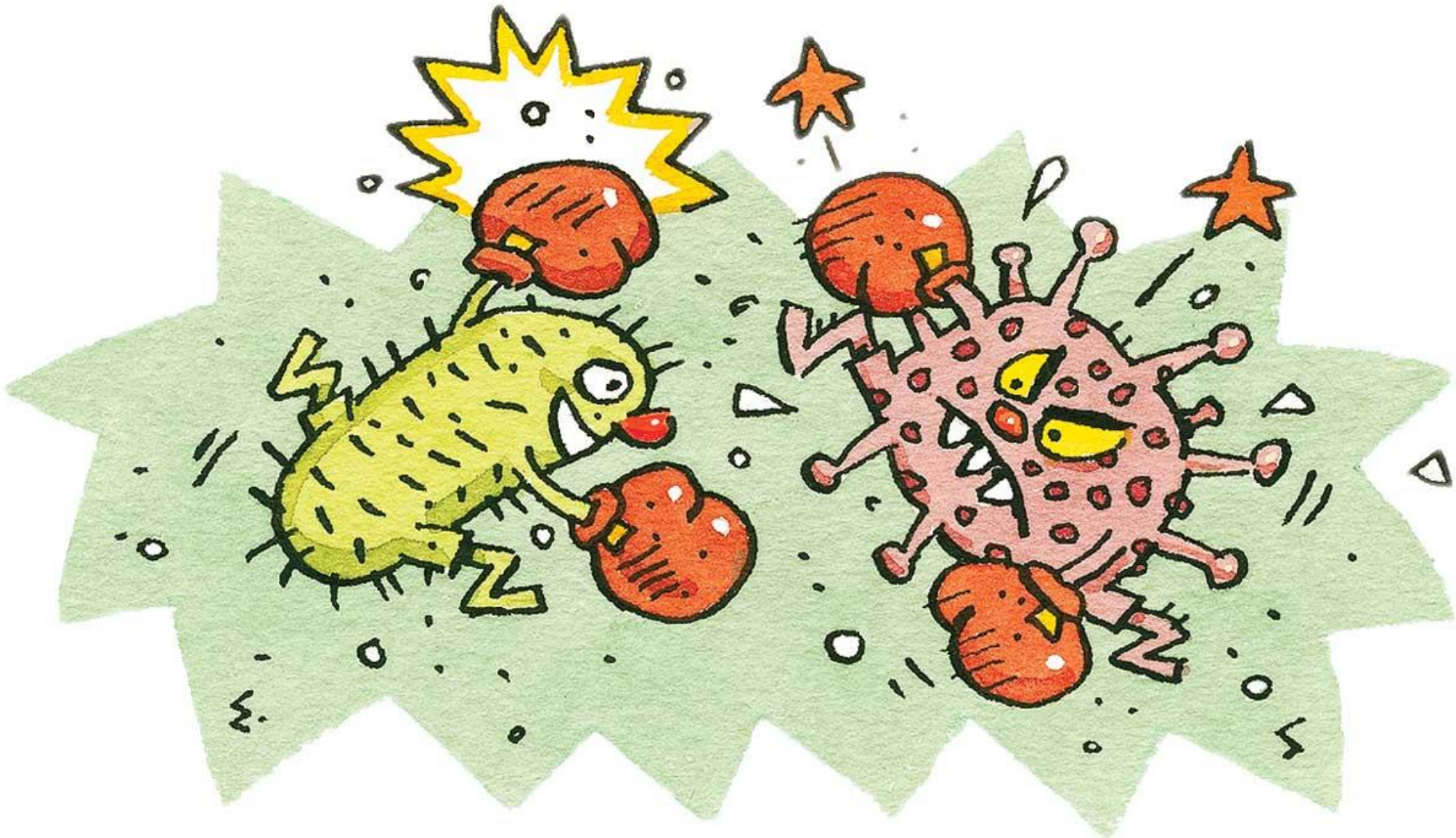
DI_{50} = dose infectante para 50% de uma amostra da população

- varia conforme a porta de entrada

DL_{50} = dose infectante letal para 50% de uma amostra da população (termo geralmente utilizado para toxinas)
0,03 ng/Kg para a toxina botulínica

Uma vez dentro do nosso corpo.....

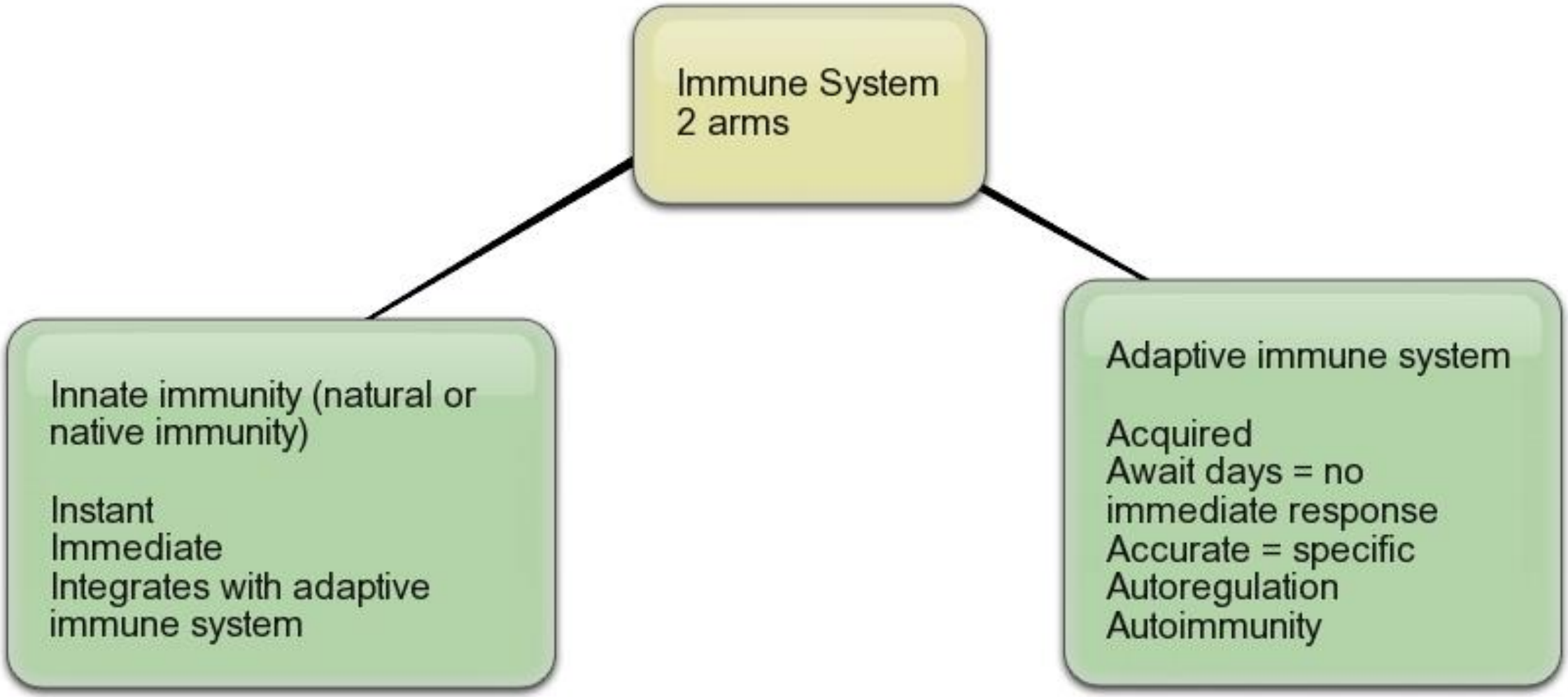




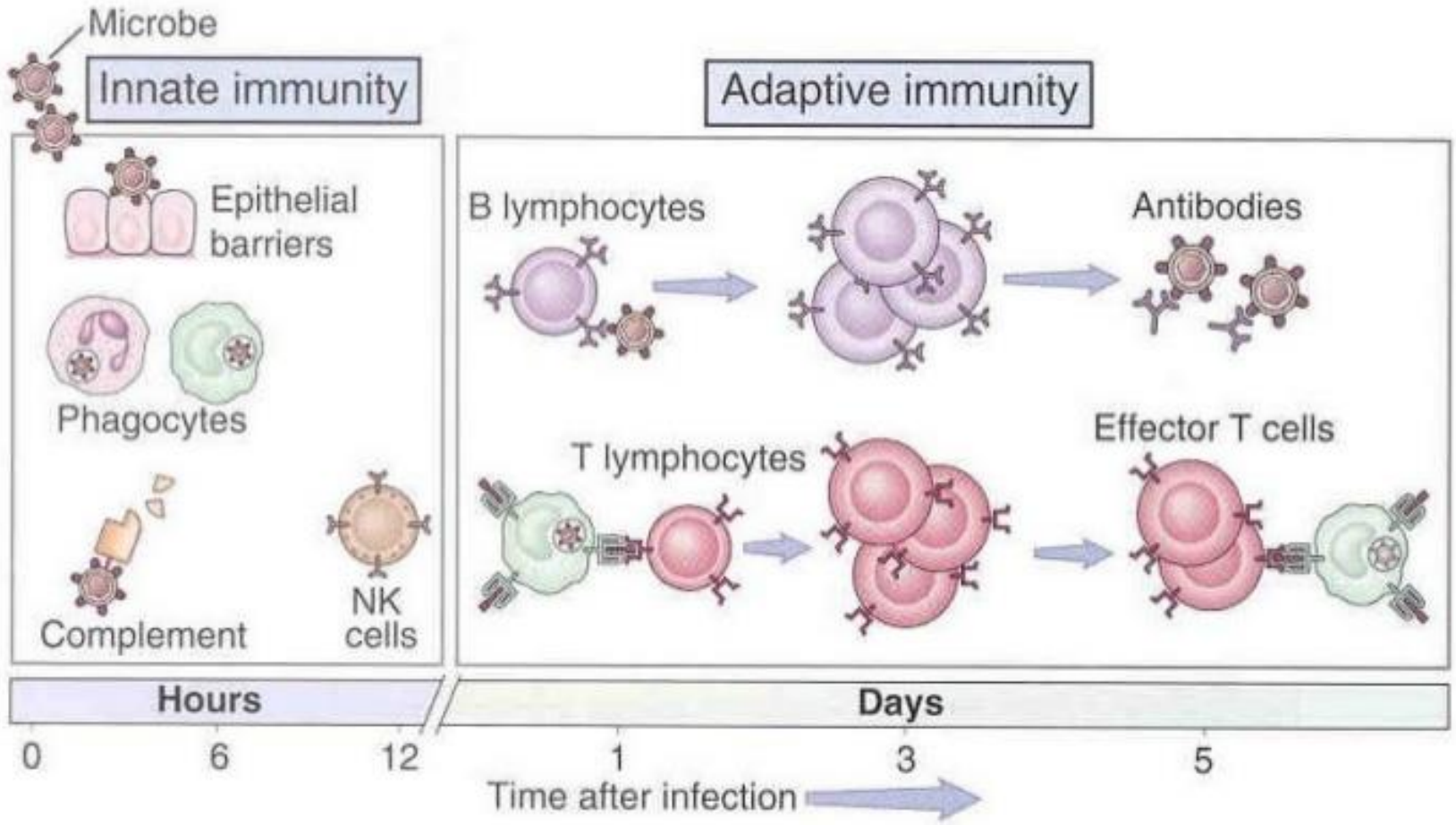
Sistema imune

Respostas inatas – são mecanismos de reconhecimento molecular que realizam uma rápida e efetiva defesa do hospedeiro e não requer uma exposição prévia ao patógeno

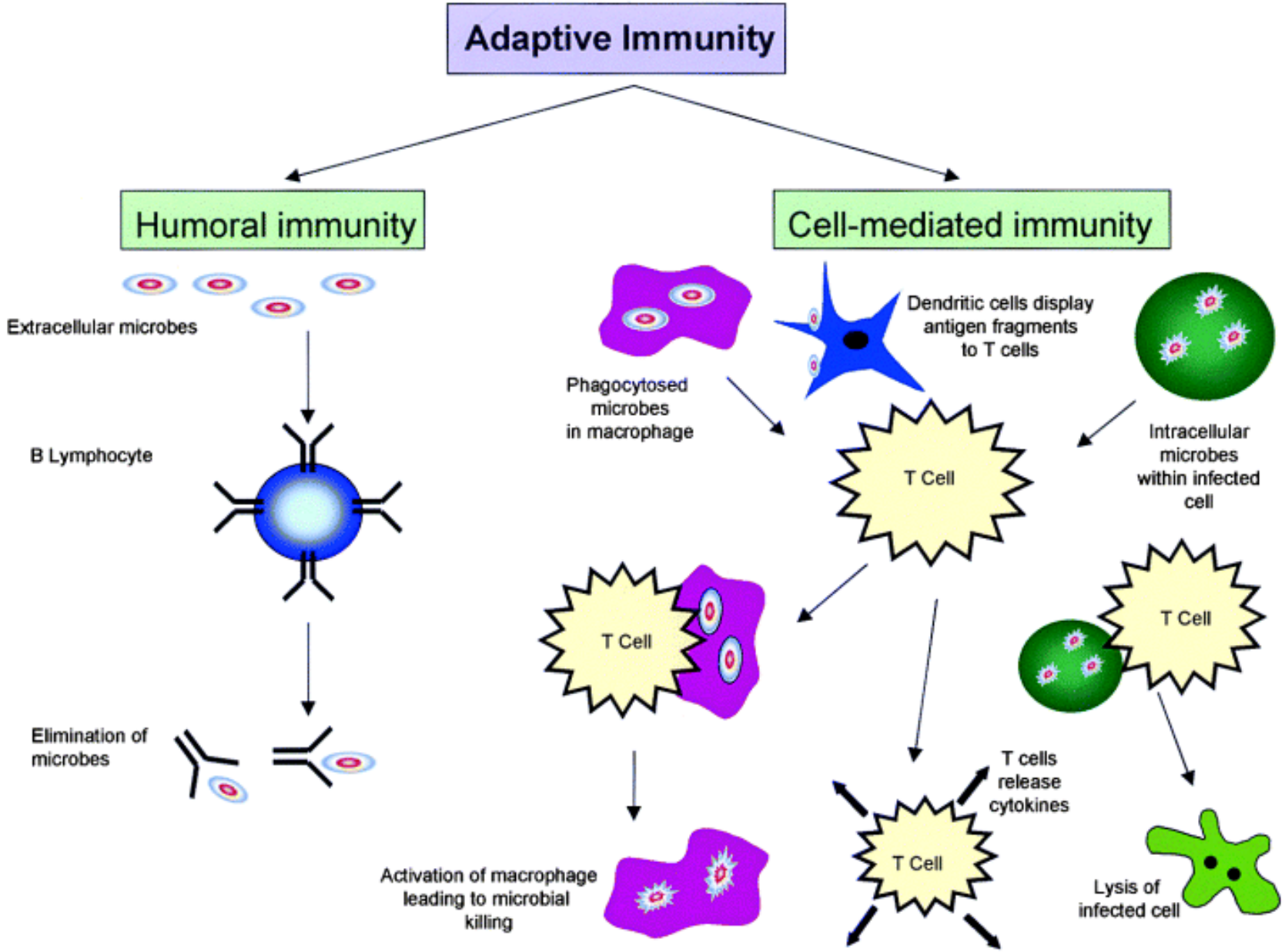
Resposto adaptativa – habilidade ADQUIRADA de reconhecer e destruir um patógeno em particular.


Immune System
2 arms
Innate immunity (natural or native immunity)
Instant
Immediate
Integrates with adaptive immune system
Adaptive immune system
Acquired
Await days = no immediate response
Accurate = specific
Autoregulation
Autoimmunity

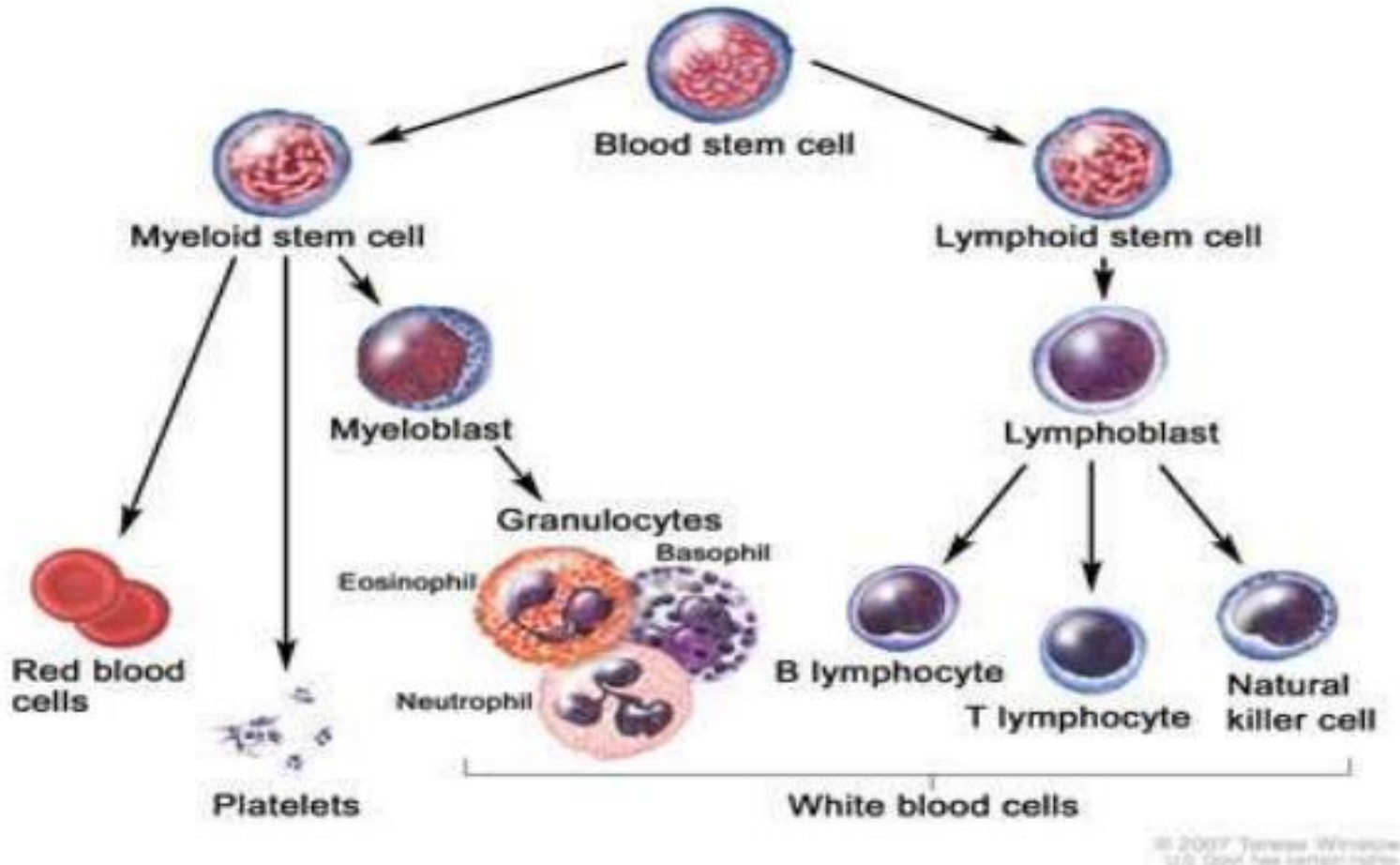
The big picture…Integration of innate and adaptive immunity

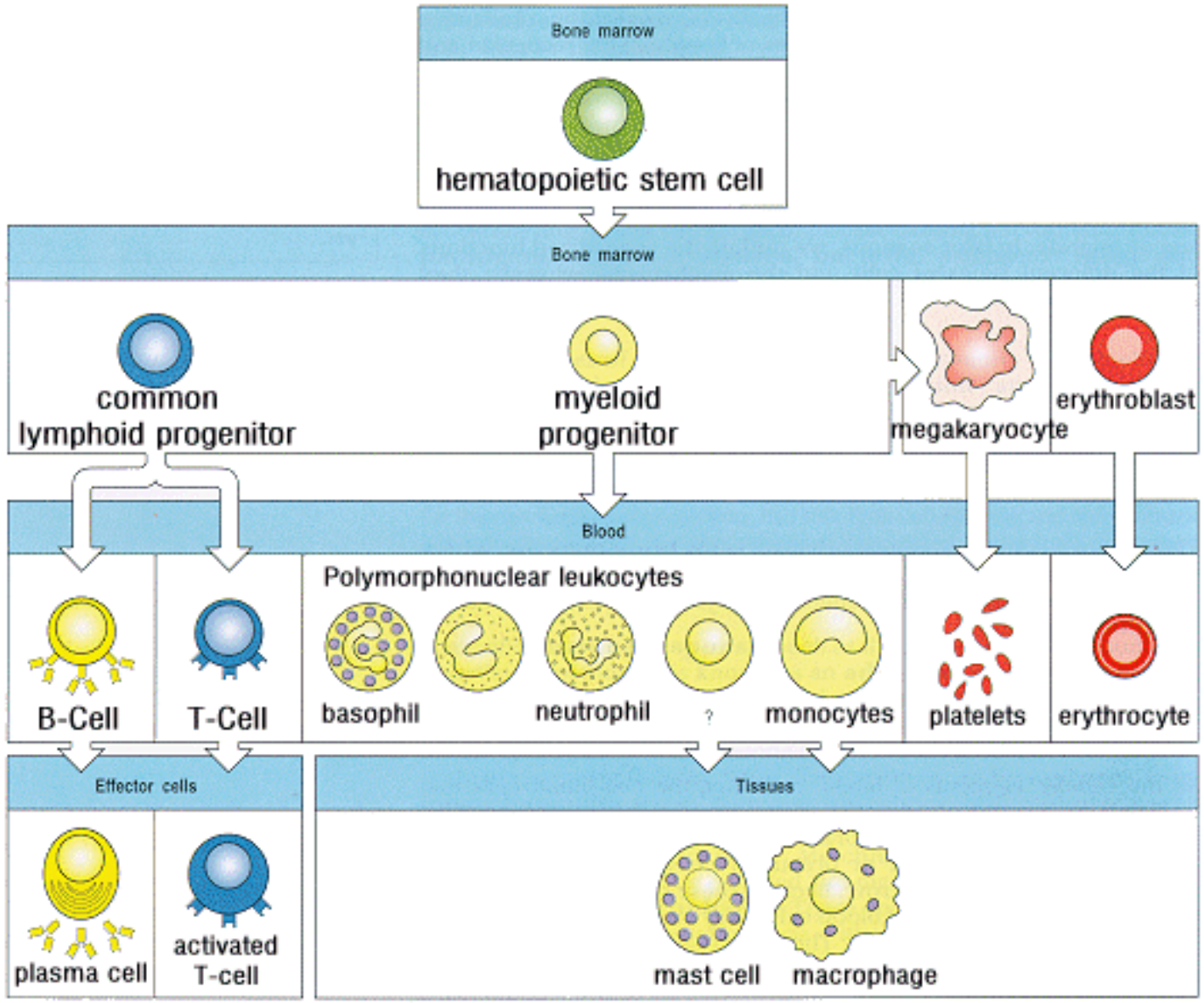


Courtesy: Abbas and Litchman; Basic Immunology

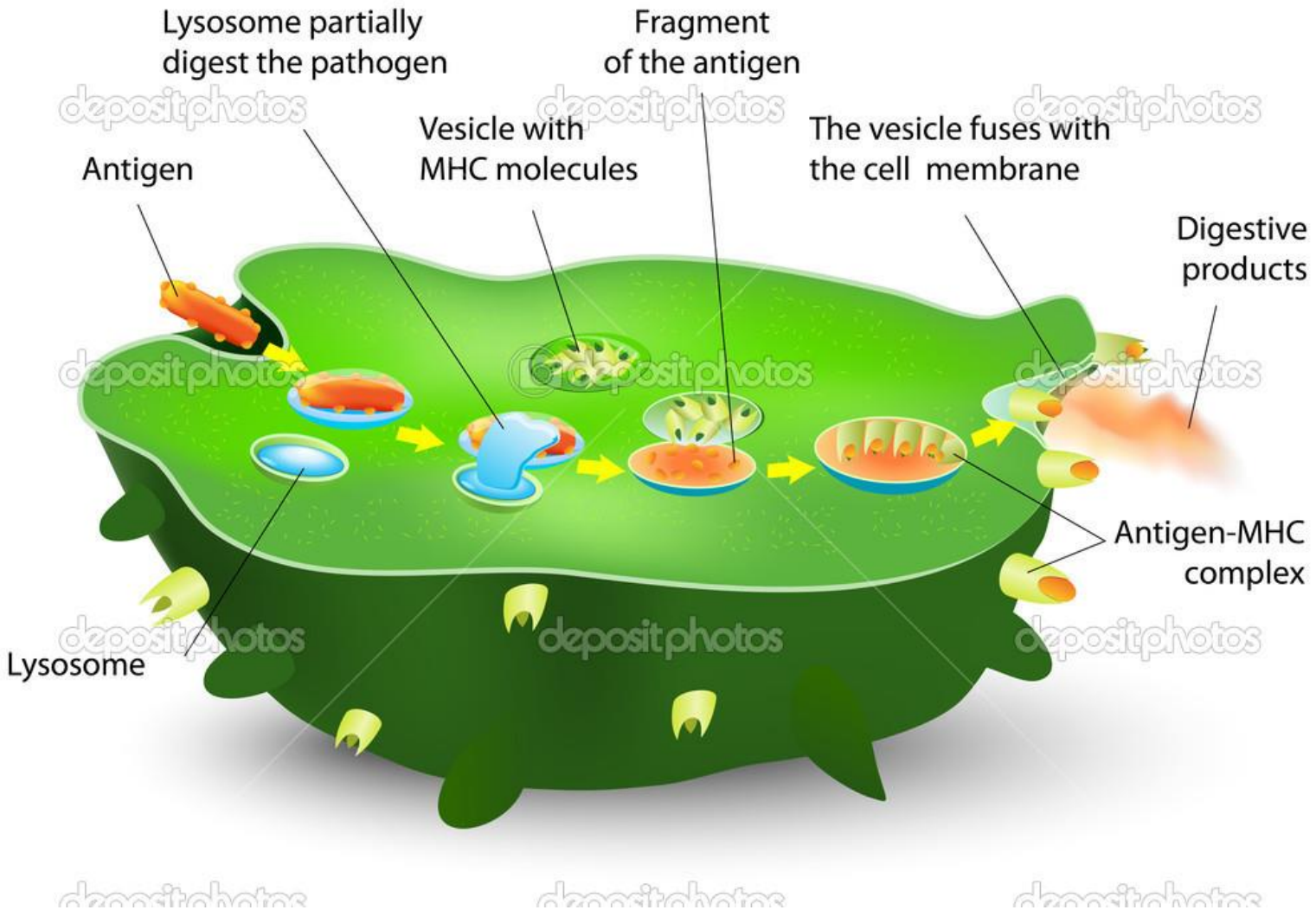

Adaptive Immunity
Humoral immunity
Cell-mediated immunity
Extracellular microbes
B Lymphocyte
Elimination of microbes
Phagocytosed microbes in macrophage
Dendritic cells display antigen fragments to T cells
Intracellular microbes within infected cell
T Cell
T Cell
T Cell
T Cell
T cells release cytokines
Activation of macrophage leading to microbial killing
Lysis of infected cell

CELLS OF THE IMMUNE SYSTEM




Bone marrow
hematopoietic stem cell
Bone marrow
common
lymphoid progenitor
myeloid
progenitor
megakaryocyte
erythroblast
Blood
Polymorphonuclear leukocytes
B-Cell
T-Cell
basophil
neutrophil
?
monocytes
platelets
erythrocyte
Effector cells
Tissues
plasma cell
activated
T-cell
mast cell
macrophage

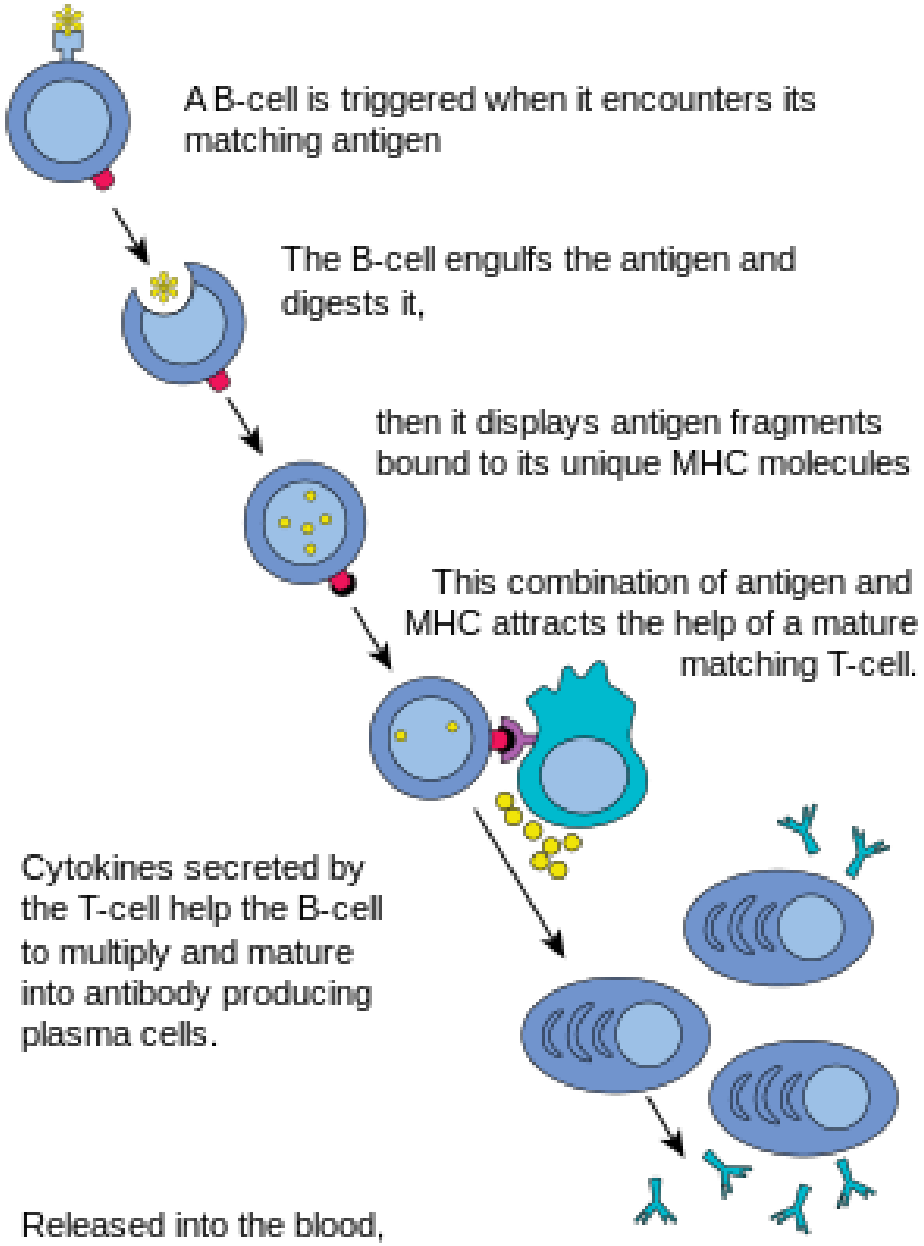
ANTIGEN-PRESENTING CELLS



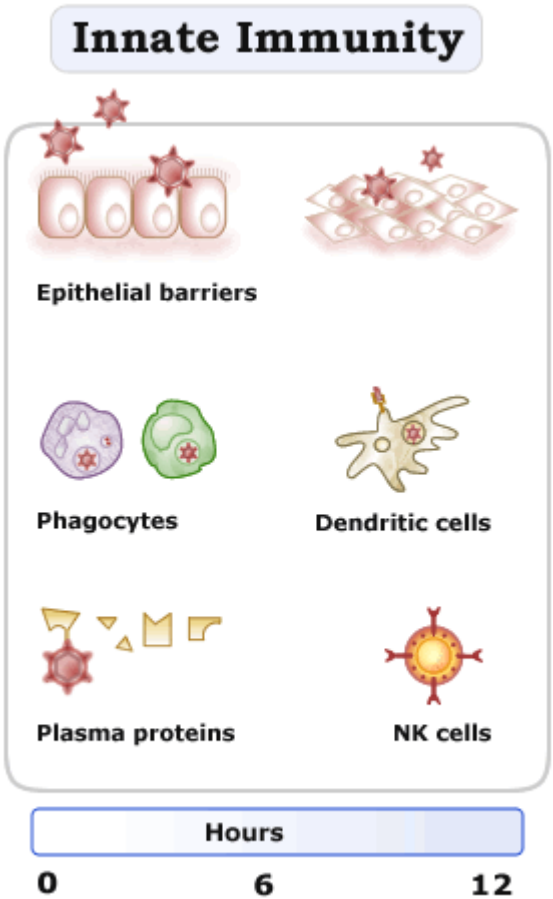
Expressam moléculas classe II do complexo principal de histocompatibilidade (MHC II)

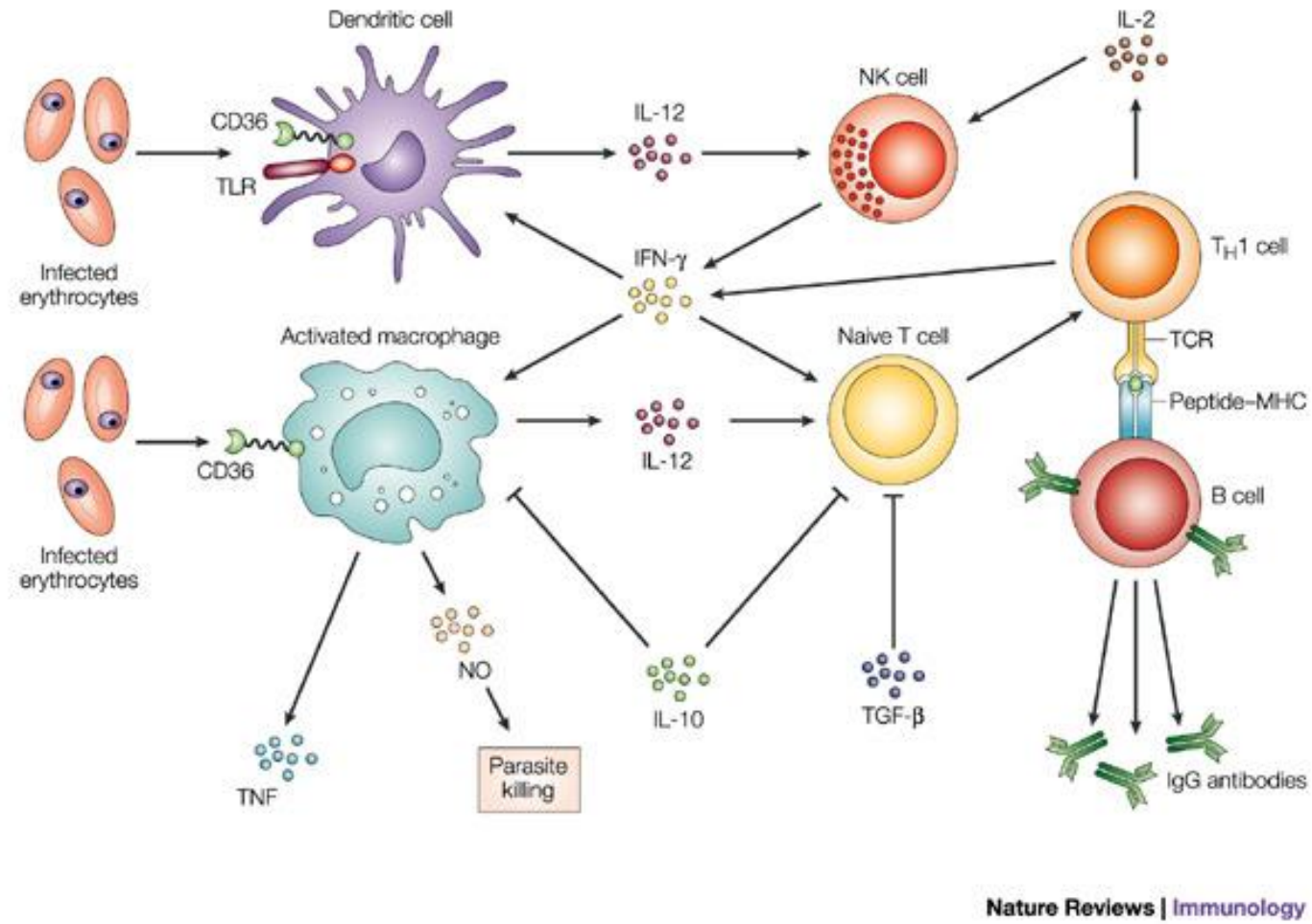
-células dendríticas
-macrófagos
-linfócitos B

Células natural killer – destroem células revestidas por anticorpos e células infectadas por vírus
Neutrófilos – fagocitam e matam bactérias
Eosinófilos – defesa de parasitas e resposta alérgica
Monócitos – liberação de citocinas
Células dendríticas = apresentação de antígenos
Macrófagos – respostas inflamatórias
Basófilo/mastócito – produção de anticorpos
Linfócito B – produção de anticorpos
Linfócito T – controle de resposta imune e matar células infectadas por vírus e tumores

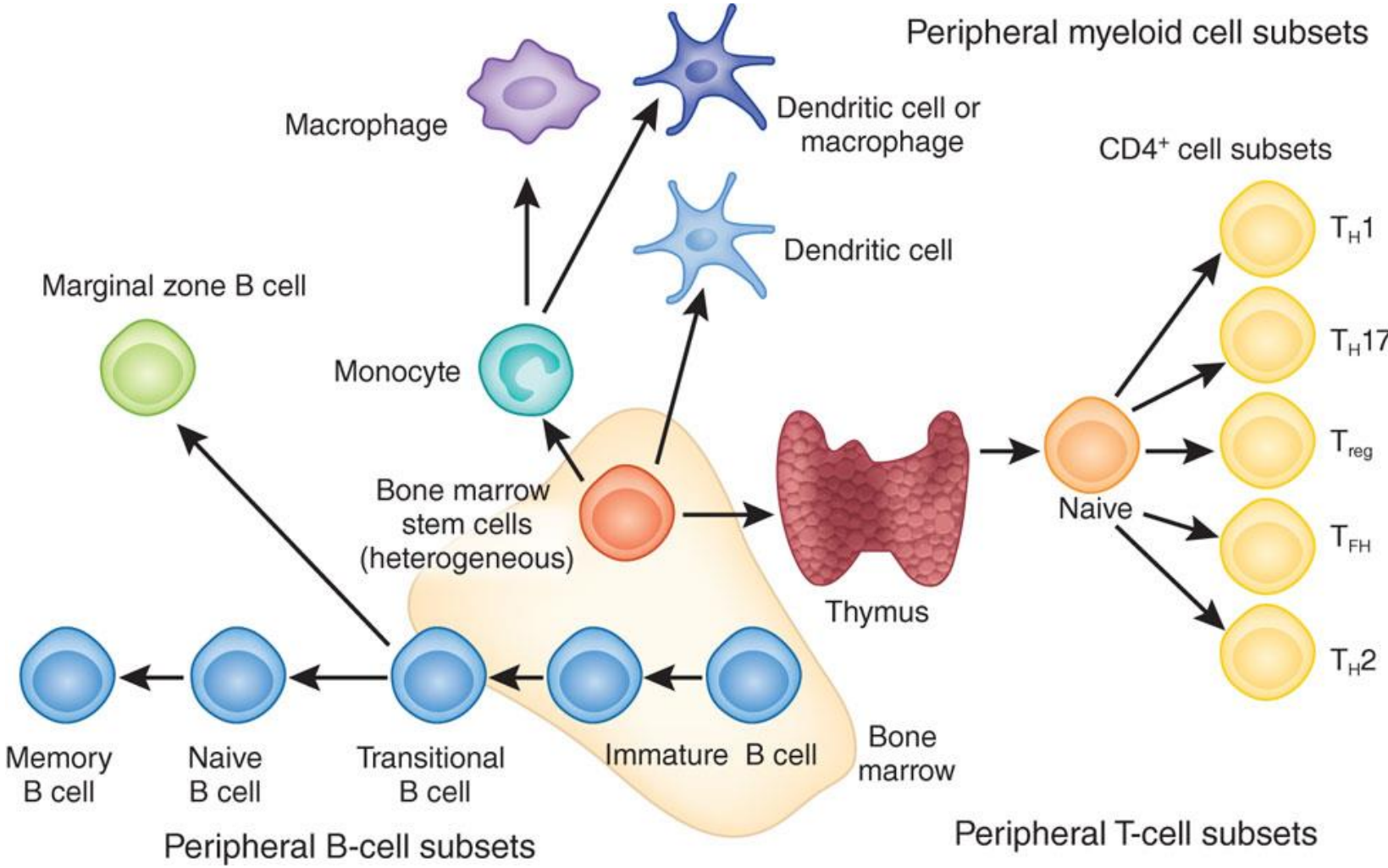

A B-cell is triggered when it encounters its matching antigen
The B-cell engulfs the antigen and digests it,
then it displays antigen fragments bound to its unique MHC molecules
This combination of antigen and MHC attracts the help of a mature matching T-cell.
Cytokines secreted by the T-cell help the B-cell to multiply and mature into antibody producing plasma cells.
Released into the blood, antibodies lock onto matching antigens. The antigen-antibody complexes are then cleared by the complement cascade or by the liver and spleen.

Resposta inata





Células da resposta imune



T_H1 → Resposta inflamatória microrganismos intracelulares

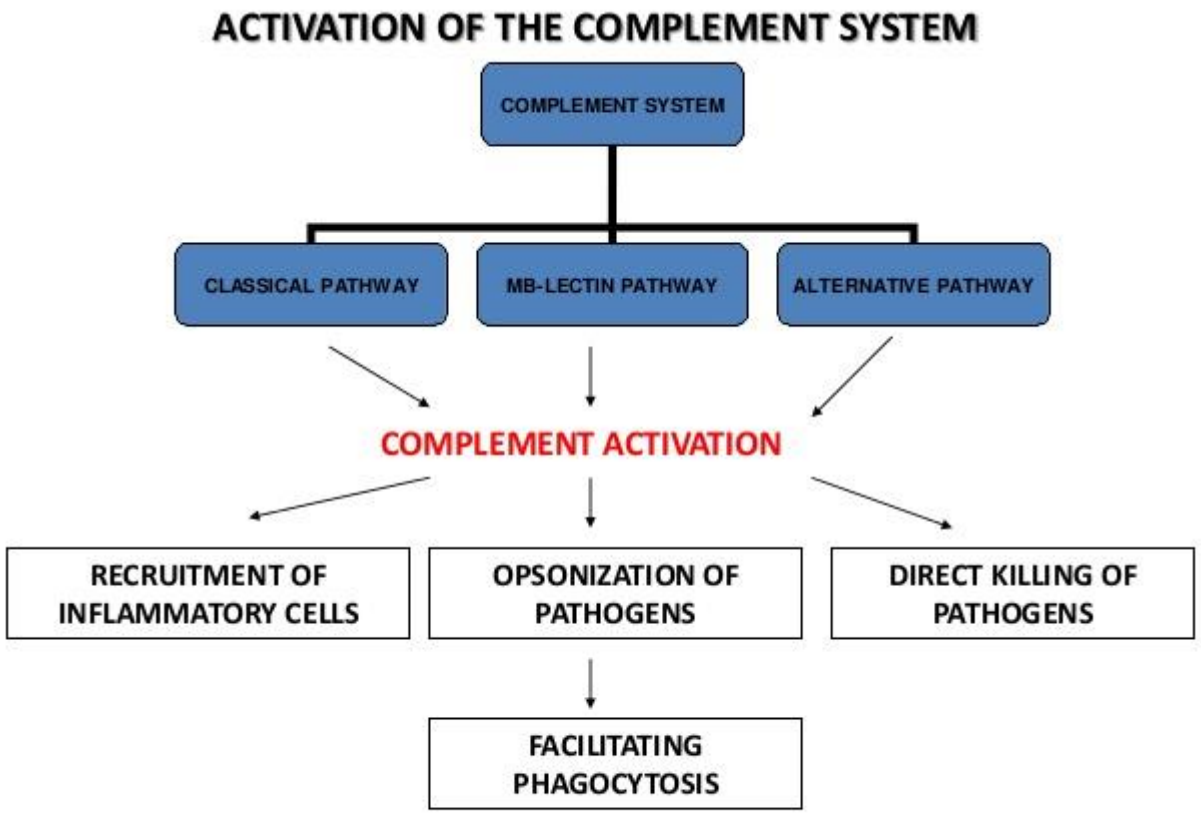
T_H17 → Resposta inflamatória IL17, IL-6 e IL-23

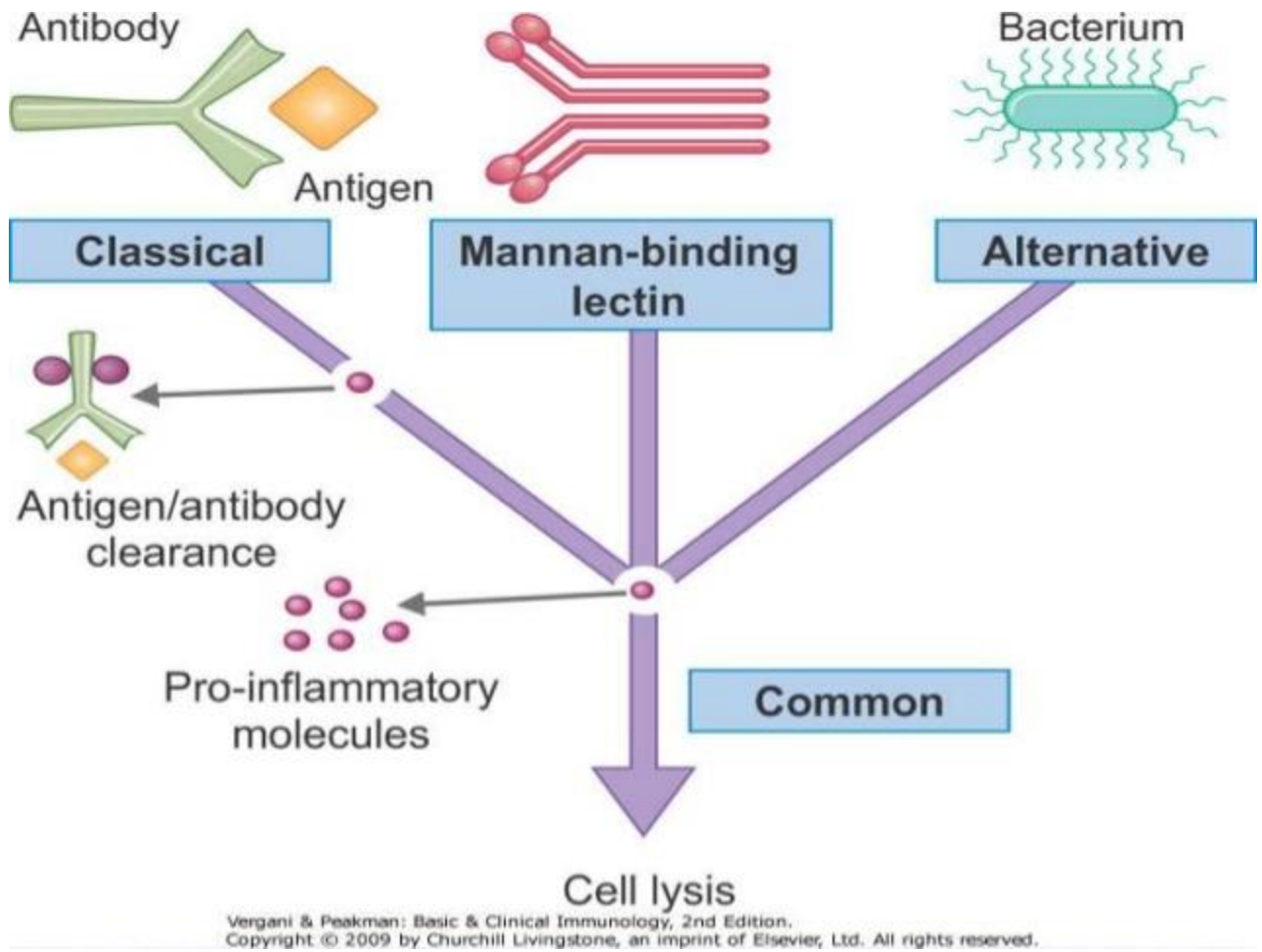
T_{reg} → Controle resposta imune

T_{FH} → Diferenciação de linfócitos B

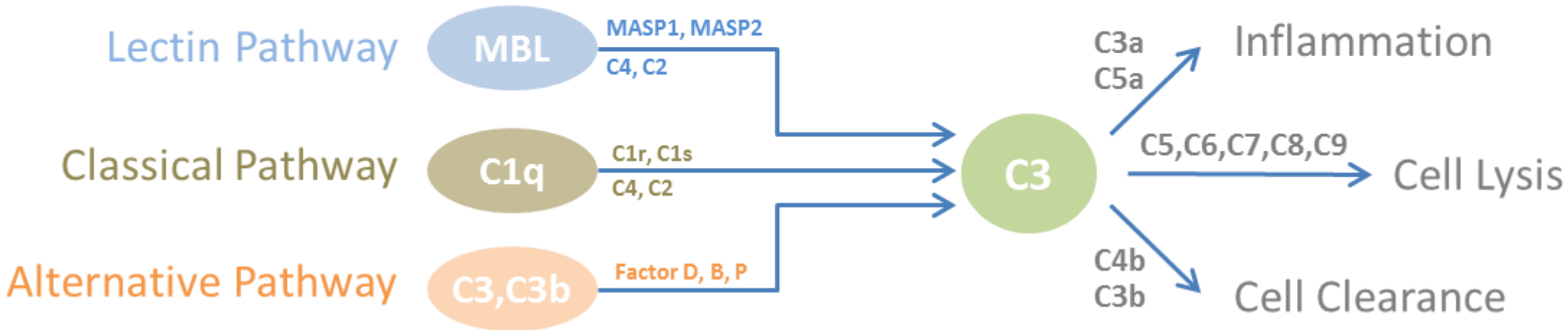
T_H2 → Resposta anticorpos

O sistema complemento é formado por um conjunto de proteínas sanguíneas que marcam de maneira mais permanente patógenos, principalmente bactérias aumentando a capacidade de ligação de anticorpos e células fagocíticas





Three Pathways of the Complement System



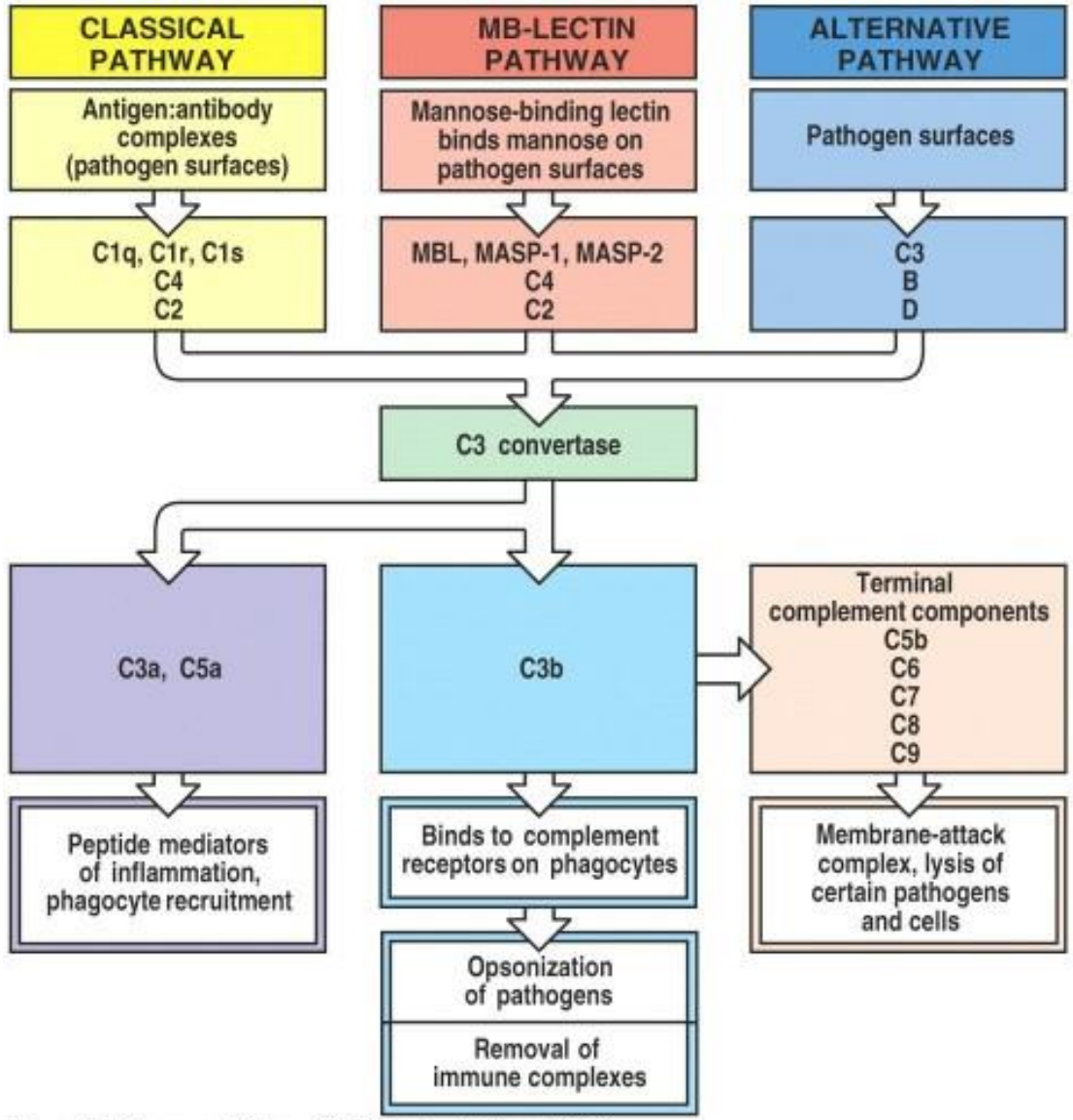
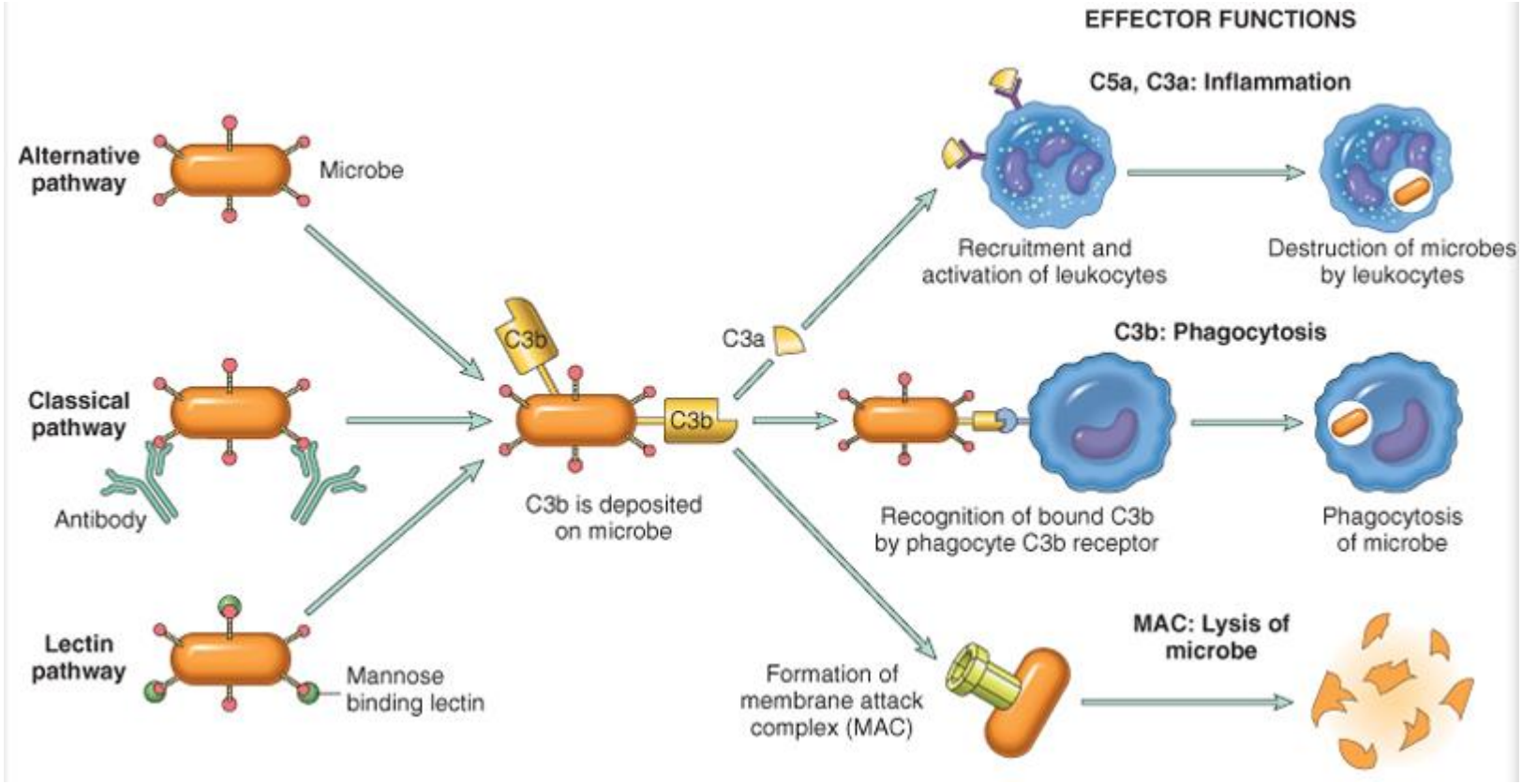
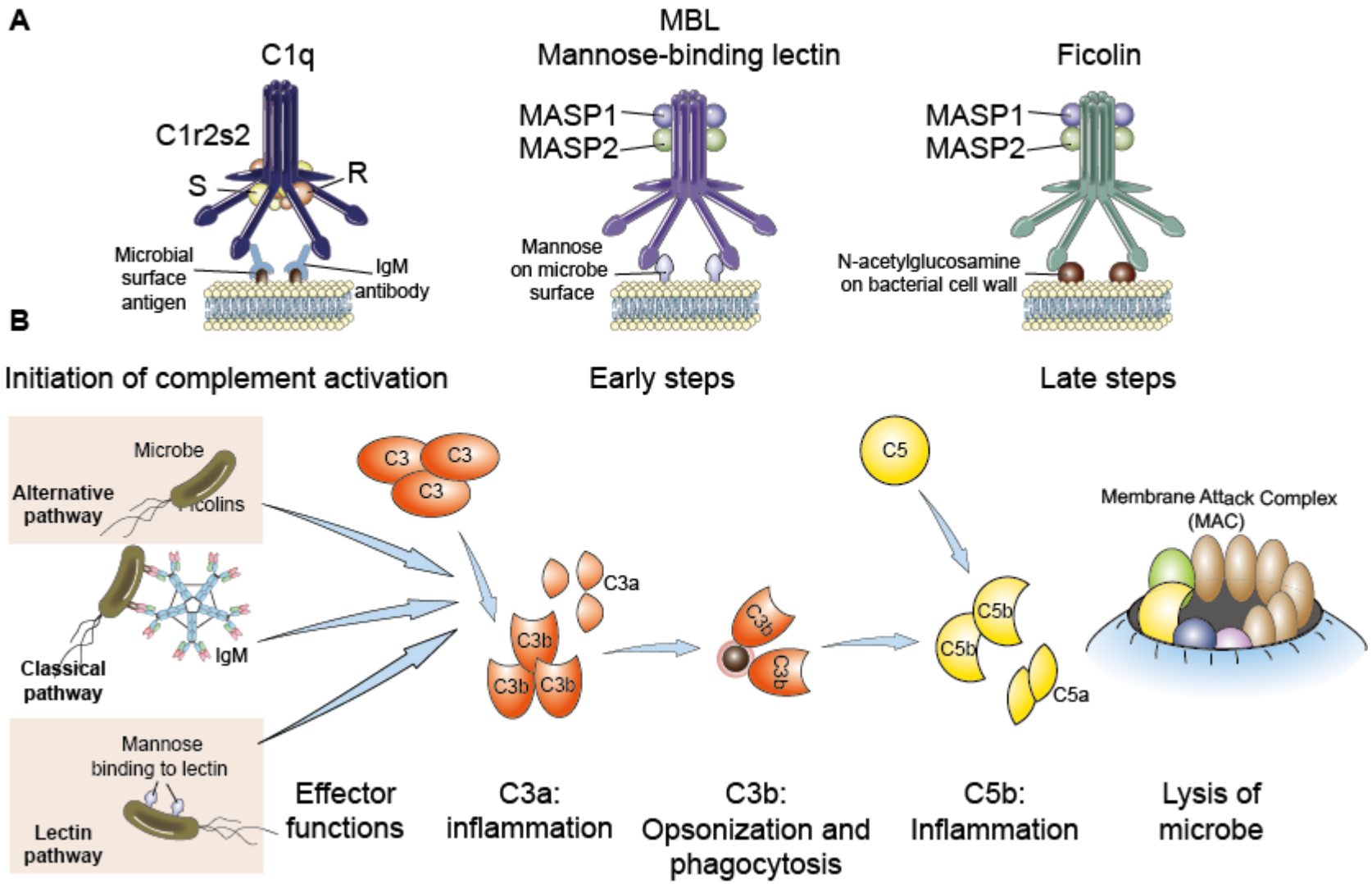


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

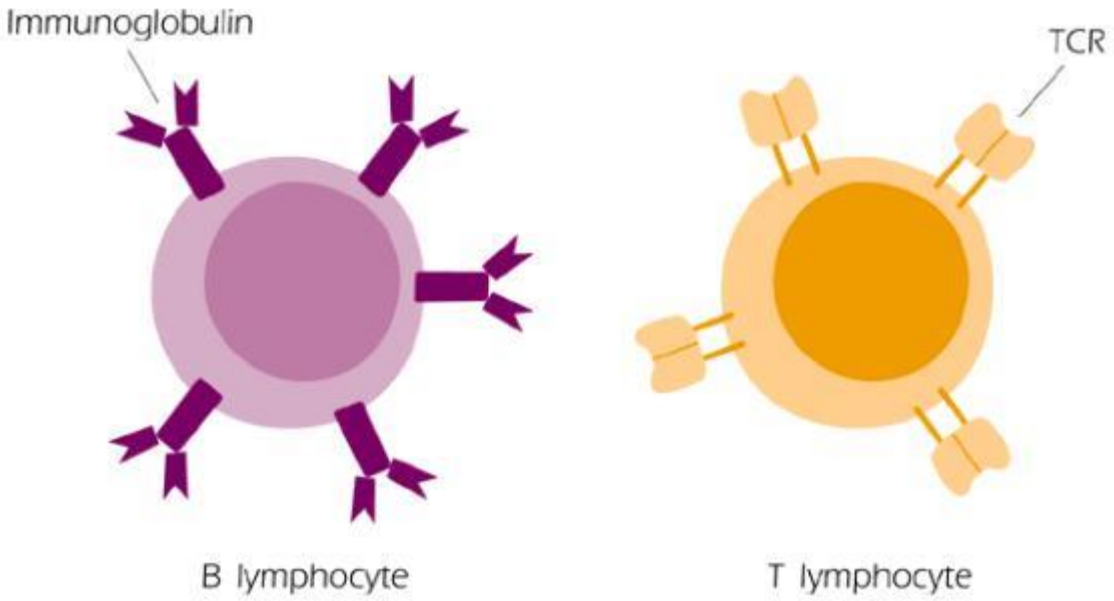
A ativação do complemento pode ocorrer por ácido teicóico, peptidoglicano e LPS



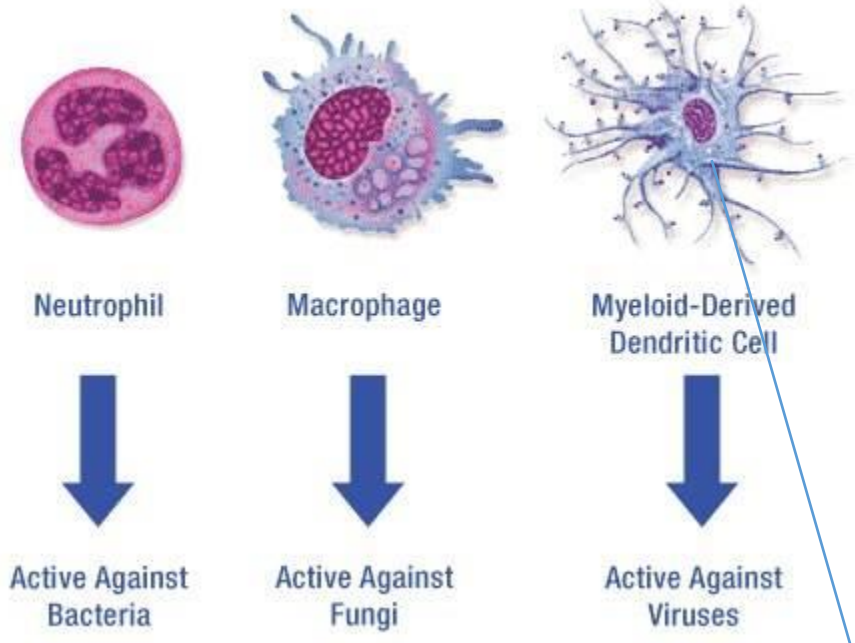
1. Fatores quimiotáticos (C5a) – atrai neutrófilos e macrófagos para a infecção
2. Anafilatoxinas (C3a e C5a) – estimula liberação de histamina pelos mastócitos aumentando a permeabilidade celular
3. Opsoninas (C3b) – ligam às bactérias e promovem sua fagocitose
4. Ativador de célula B (C3d)


A
C1q
C1r2s2
S
R
Microbial surface antigen
IgM antibody
MBL
Mannose-binding lectin
MASP1
MASP2
Mannose on microbe surface
Ficolin
MASP1
MASP2
N-acetylglucosamine on bacterial cell wall
B
Initiation of complement activation
Early steps
Late steps
Microbe
Alternative pathway
Ficolins
Classical pathway
IgM
Mannose binding to lectin
Lectin pathway
C3
C3
C3
C3a
C3b
C3b
C3b
C5
C3b
C3b
C5b
C5b
C5a
Membrane Attack Complex (MAC)
Effector functions
C3a: inflammation
C3b: Opsonization and phagocytosis
C5b: Inflammation
Lysis of microbe

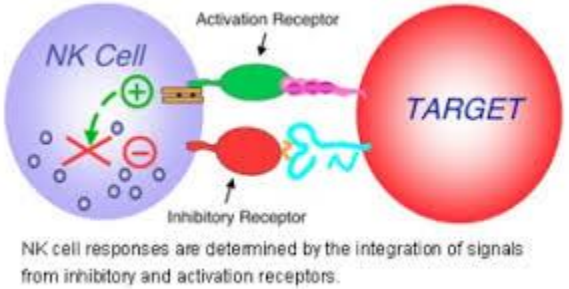
Respostas mediadas por células



Detectam microorganismos e liberam citocinas



Resposta antígeno-específica

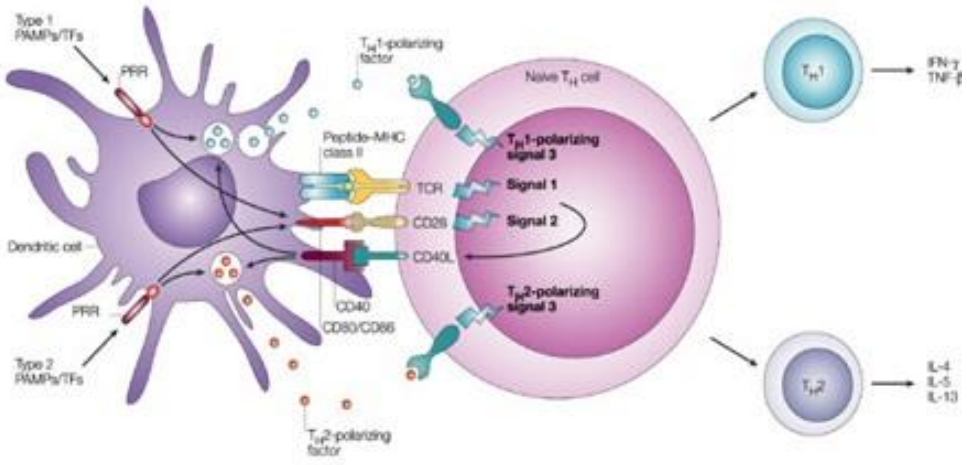


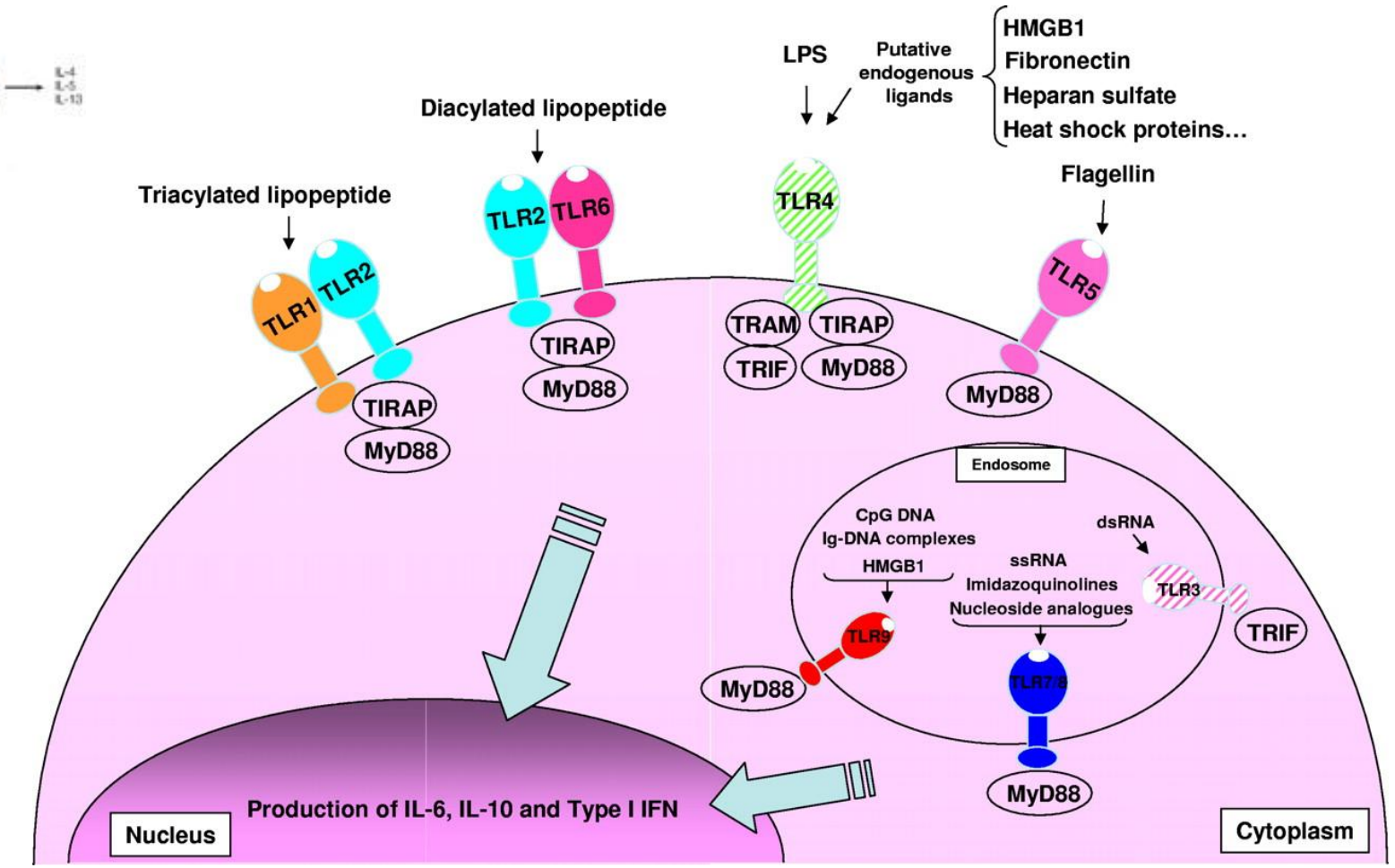
Apresentação de antígenos aos linfócitos T

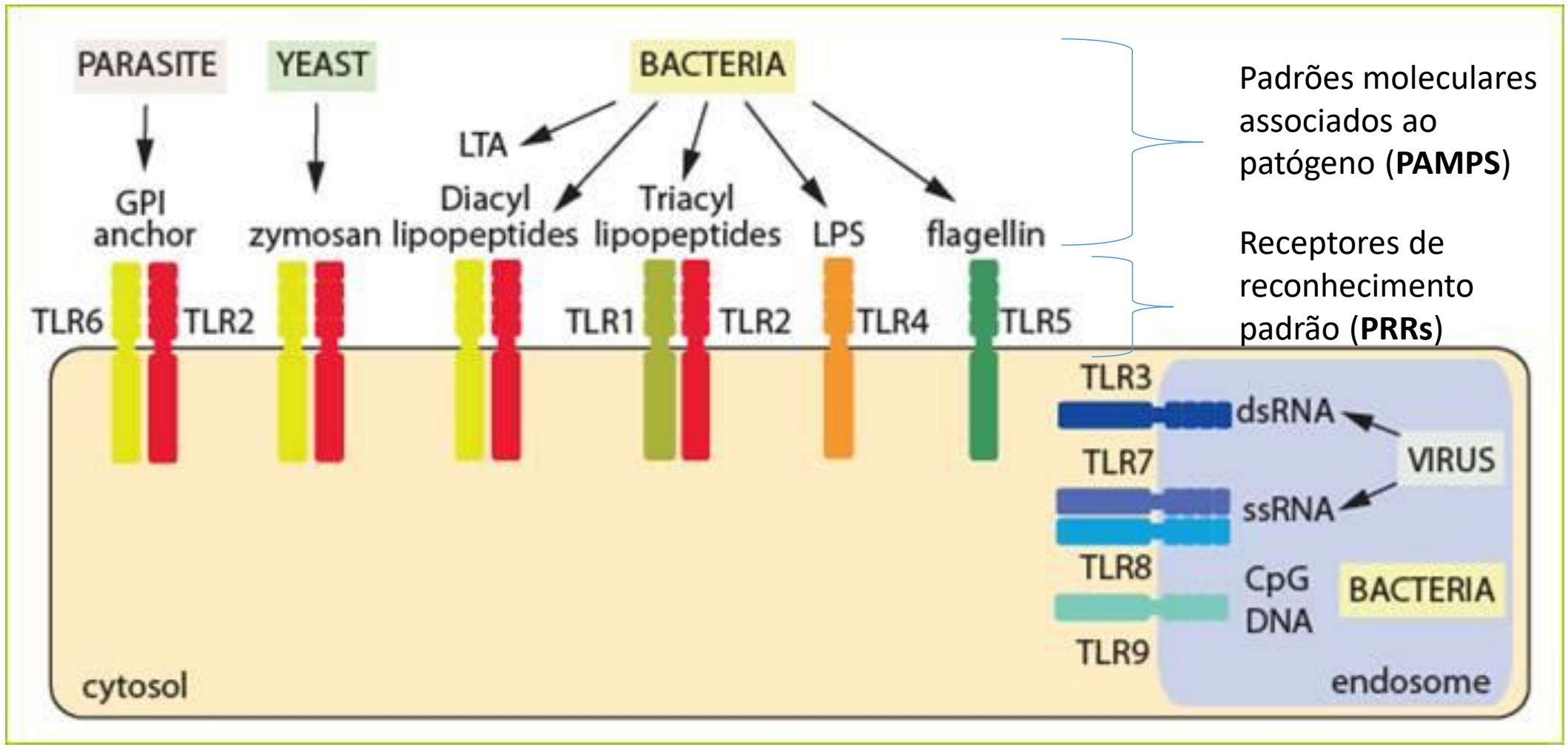
TH1 - inflamatório

humoral

Células dendríticas

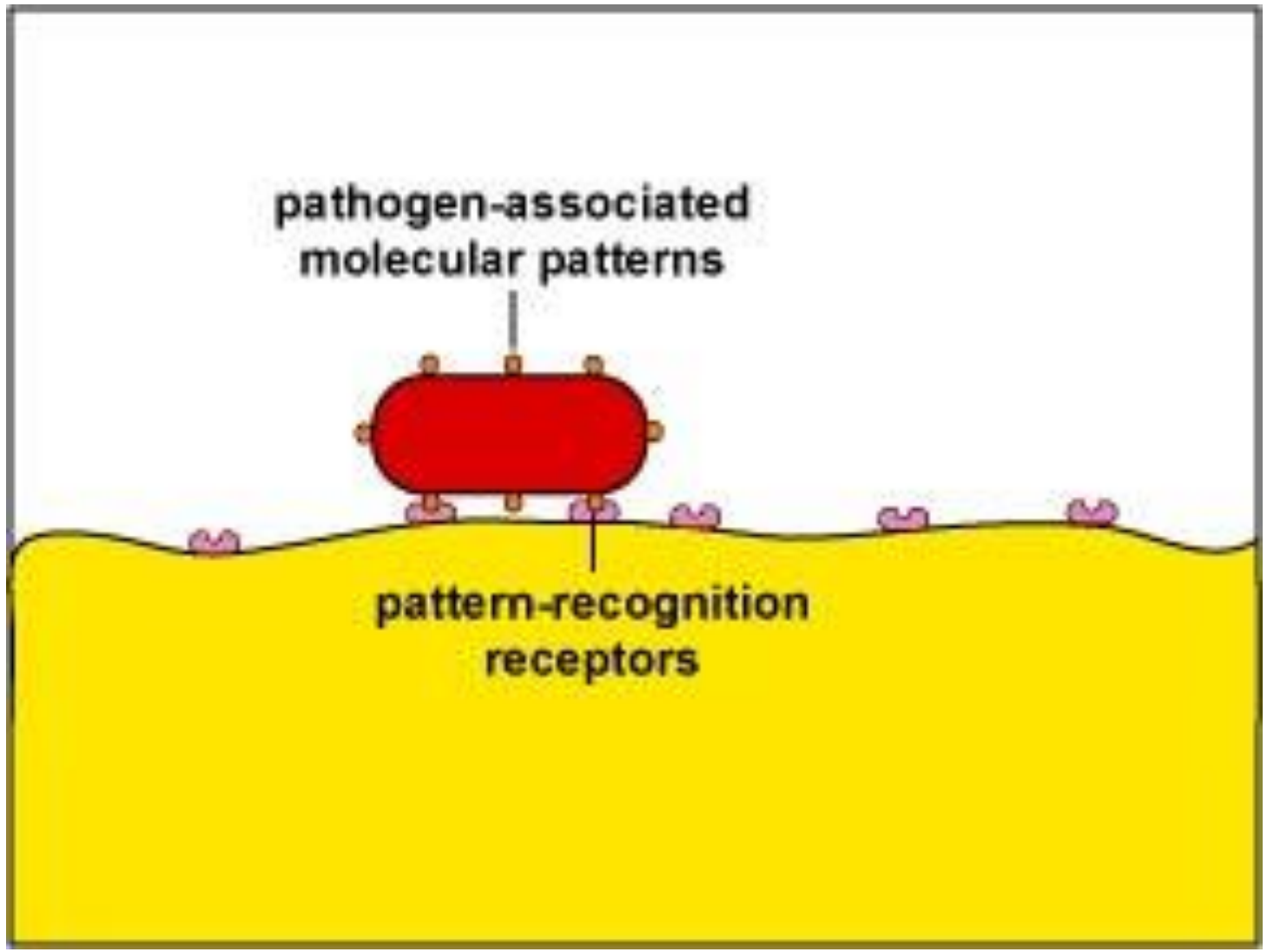


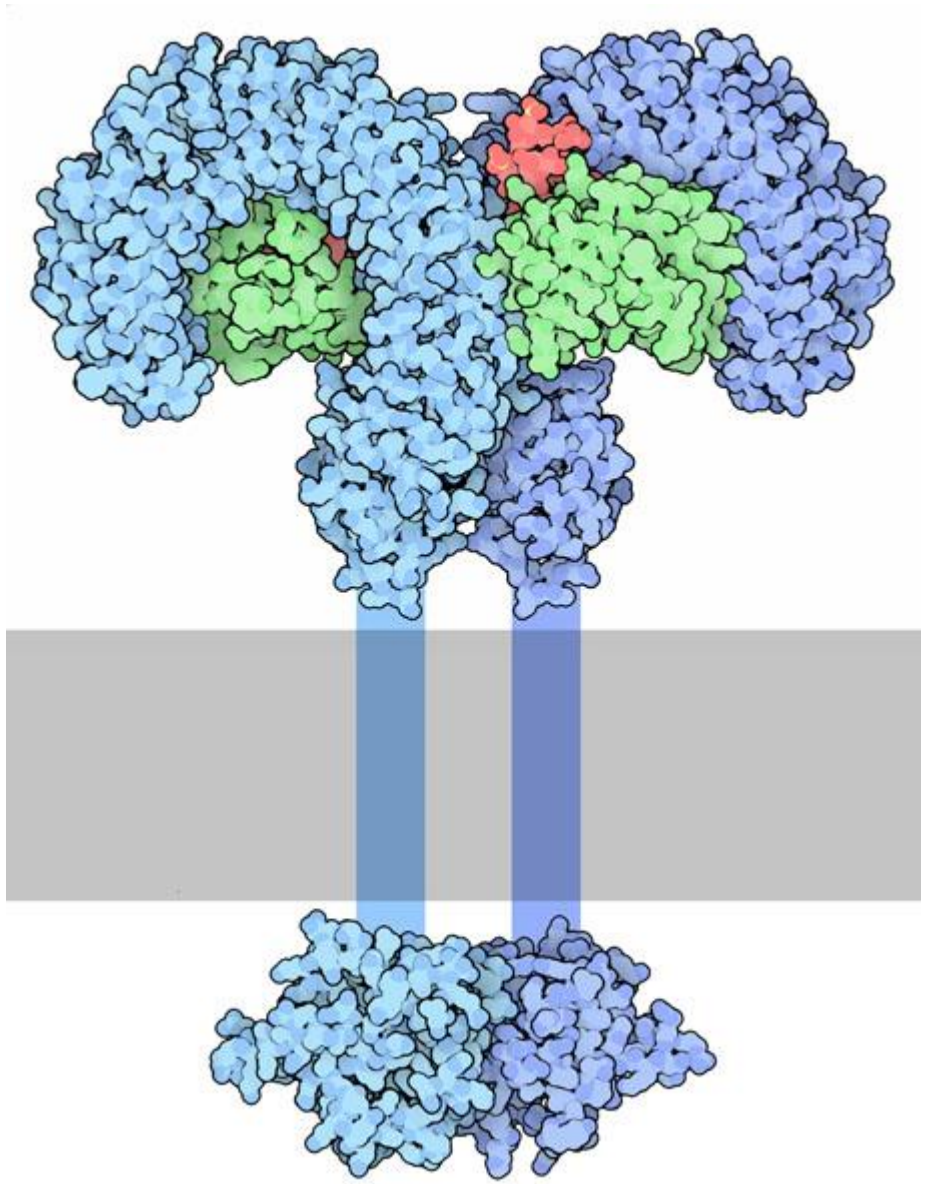




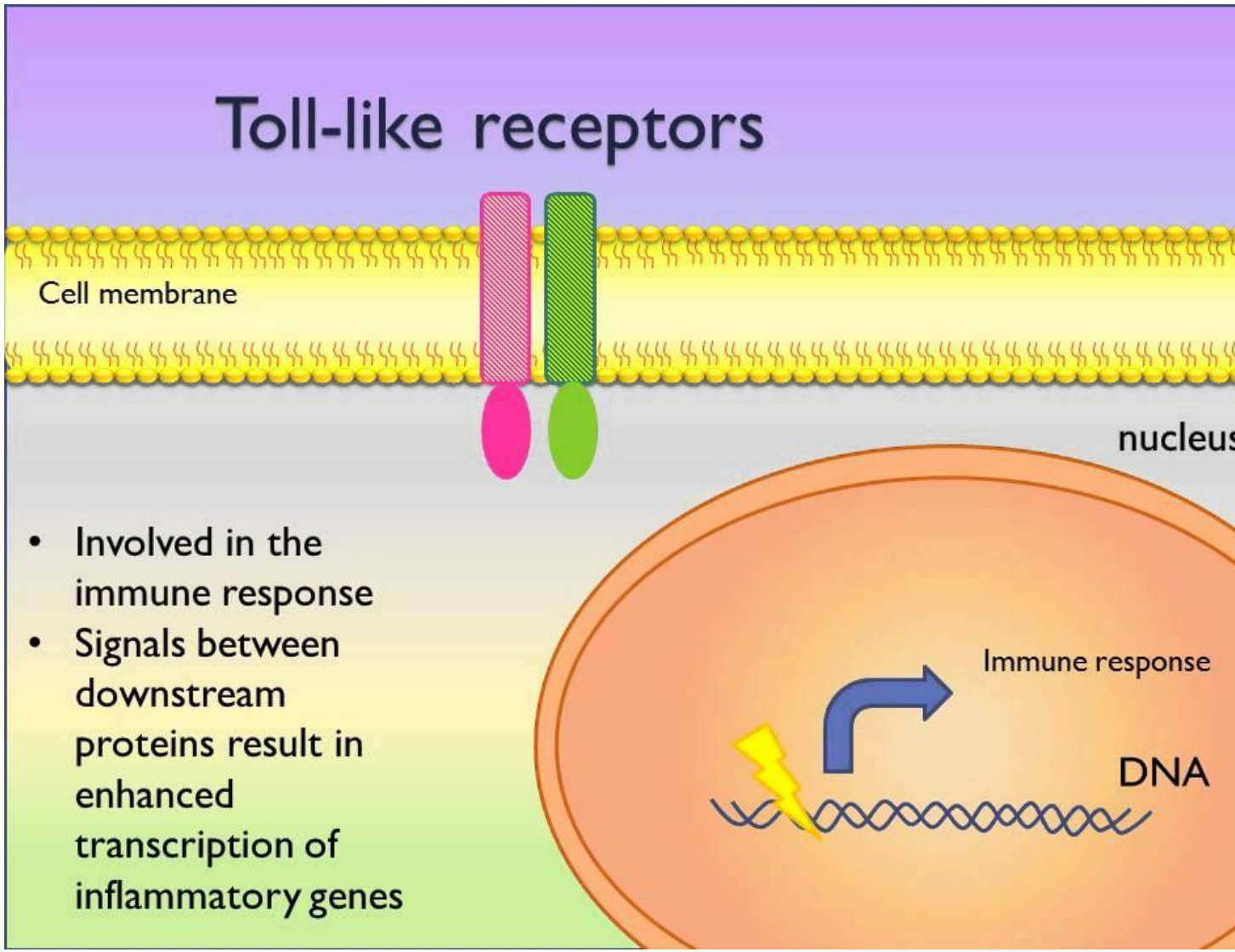
Padrões moleculares associados ao patógeno (**PAMPS**)

Receptores de reconhecimento padrão (**PRRs**)

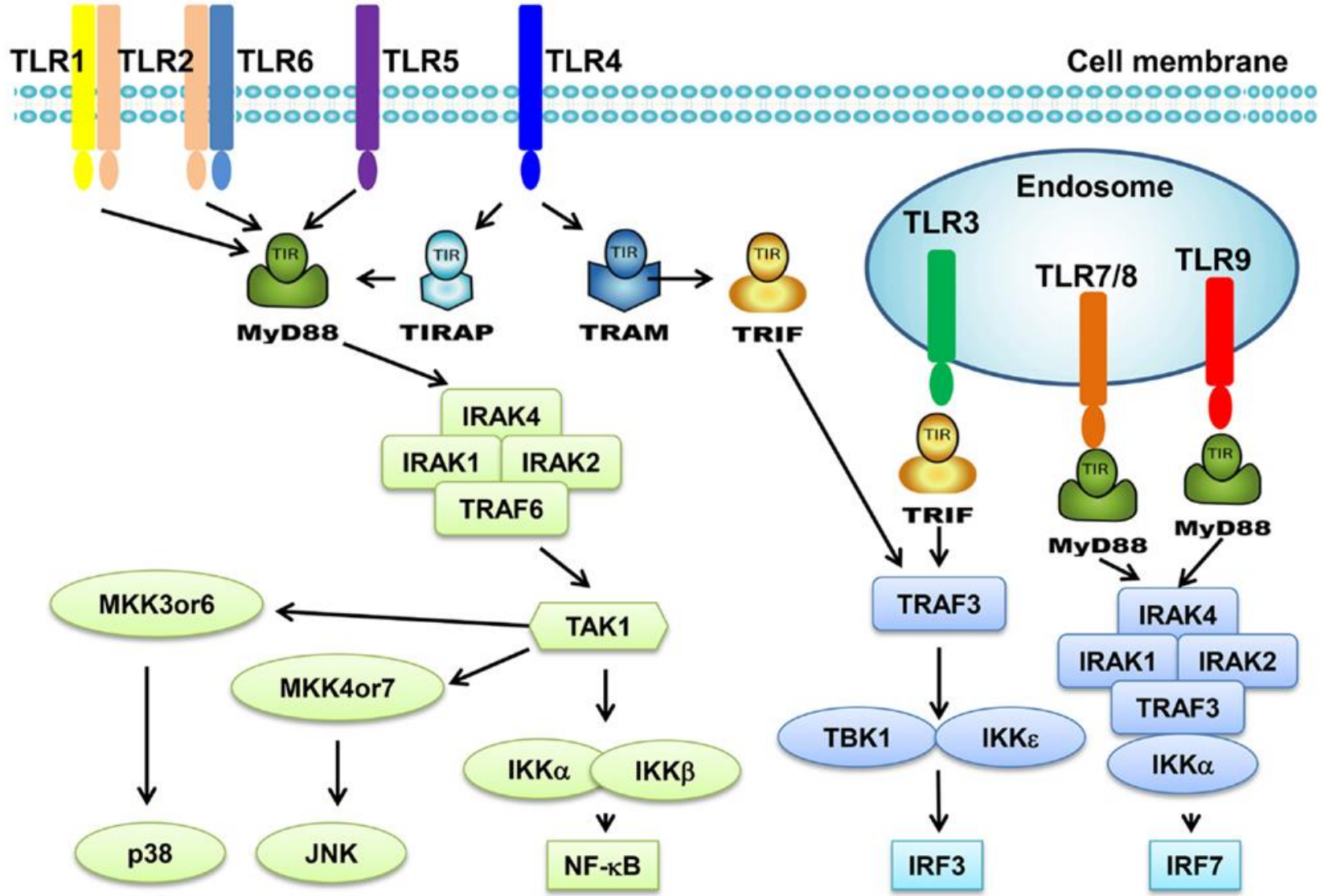

pathogen-associated
molecular patterns
pattern-recognition
receptors



Toll-like receptors



- Involved in the immune response
- Signals between downstream proteins result in enhanced transcription of inflammatory genes


TLR1
TLR2
TLR6
TLR5
TLR4
Cell membrane
TIR
MyD88
TIRAP
TRAM
TRIF
Endosome
TLR3
TLR7/8
TLR9
IRAK4
IRAK1
IRAK2
TRAF6
MKK3or6
TAK1
MKK4or7
IKKα
IKKβ
p38
JNK
NF-κB
TRAF3
TBK1
IKKε
IRF3
IRF7
Pro-inflammatory cytokines
Type 1 IFN

PAMPS

PAMPS recognized by the innate immune system:

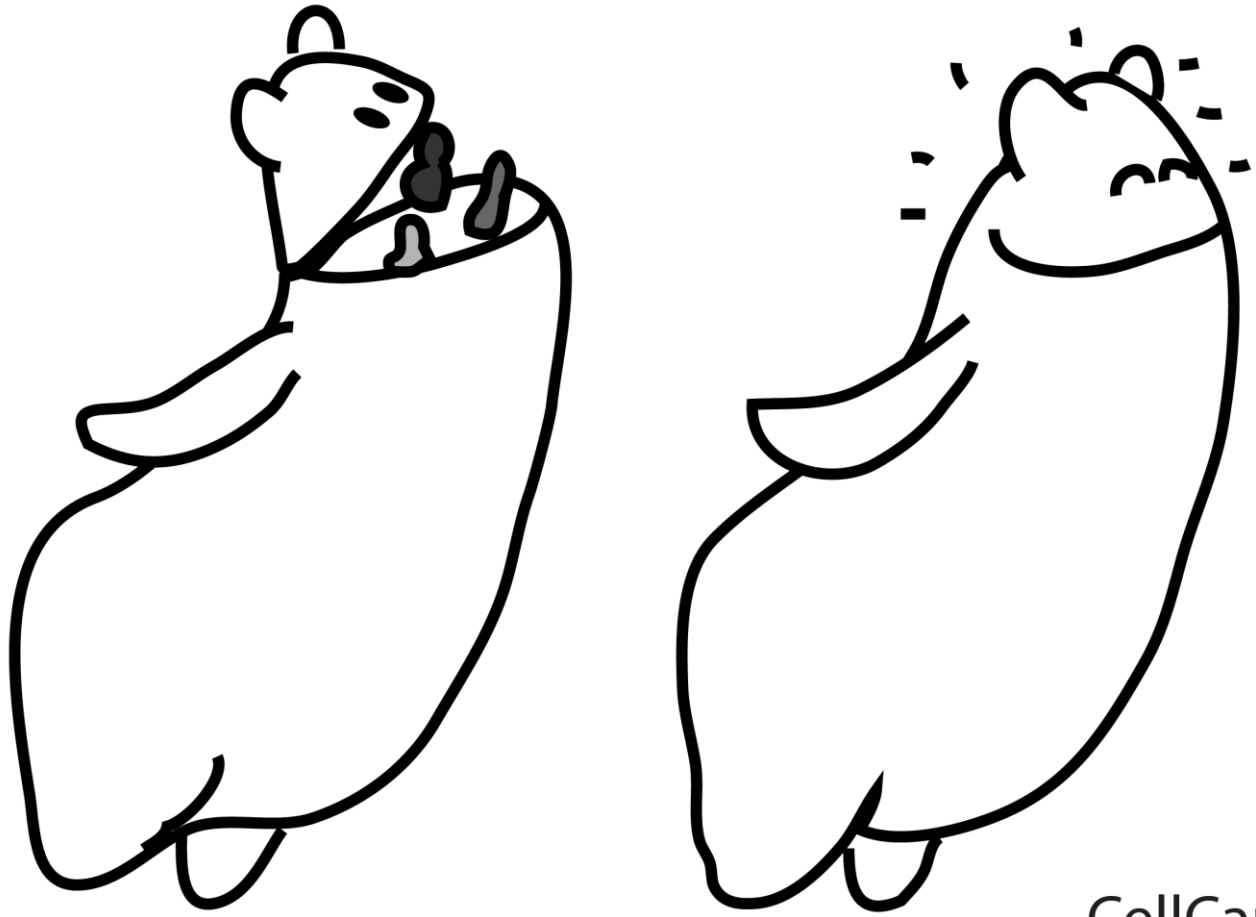
Cell wall constituents or microbial nucleic acids

1. **Lipopolysaccharide** (LPS) from the gram -ve cell wall.
2. **Peptidoglycan** found abundantly in the gram-positive cell wall and to a lesser degree in the gram-negative cell wall .
3. **Lipoteichoic acids** in the gram +ve bacterial cell walls
4. **Lipoarabinomannum** (LAM) in mycobacterial wall
5. **Mannose-rich glycans** (common in microbial glycoproteins and glycolipids but rare in those of humans).
6. **Flagellin** found in bacterial flagella.
7. **Pilin** from bacterial pili.
8. **Bacterial and viral nucleic acid**. Bacterial and viral genomes contain a high frequency of unmethylated cytosine-guanine dinucleotide sequences (a cytosine lacking a methyl or CH3 group and located adjacent to a guanine). Mammalian DNA has a low frequency of cytosine-guanine dinucleotides and most are methylated.
9. **Double-stranded RNA** unique to most viruses.
10. **Lipoteichoic acids, glycolipids, and zymosan** from yeast cell walls.

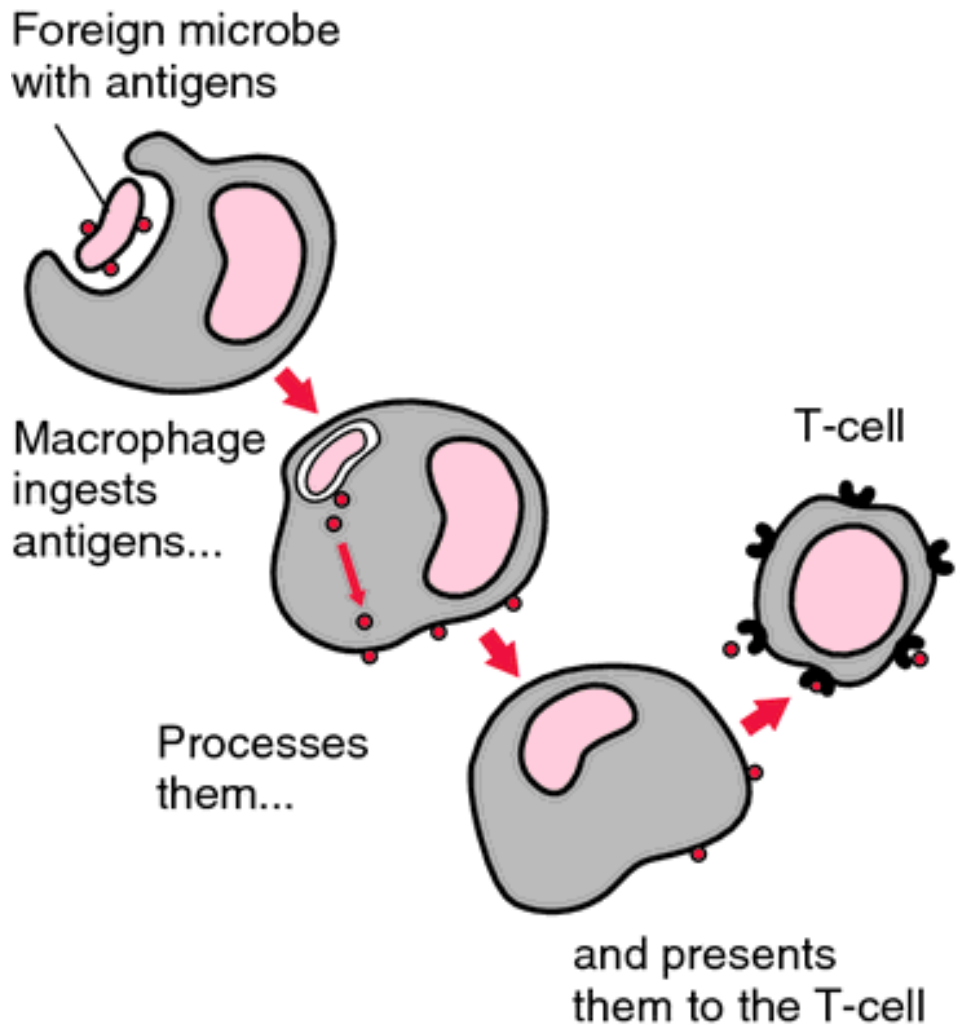
Cell-associated Pattern Recognition Receptors (PRRs)

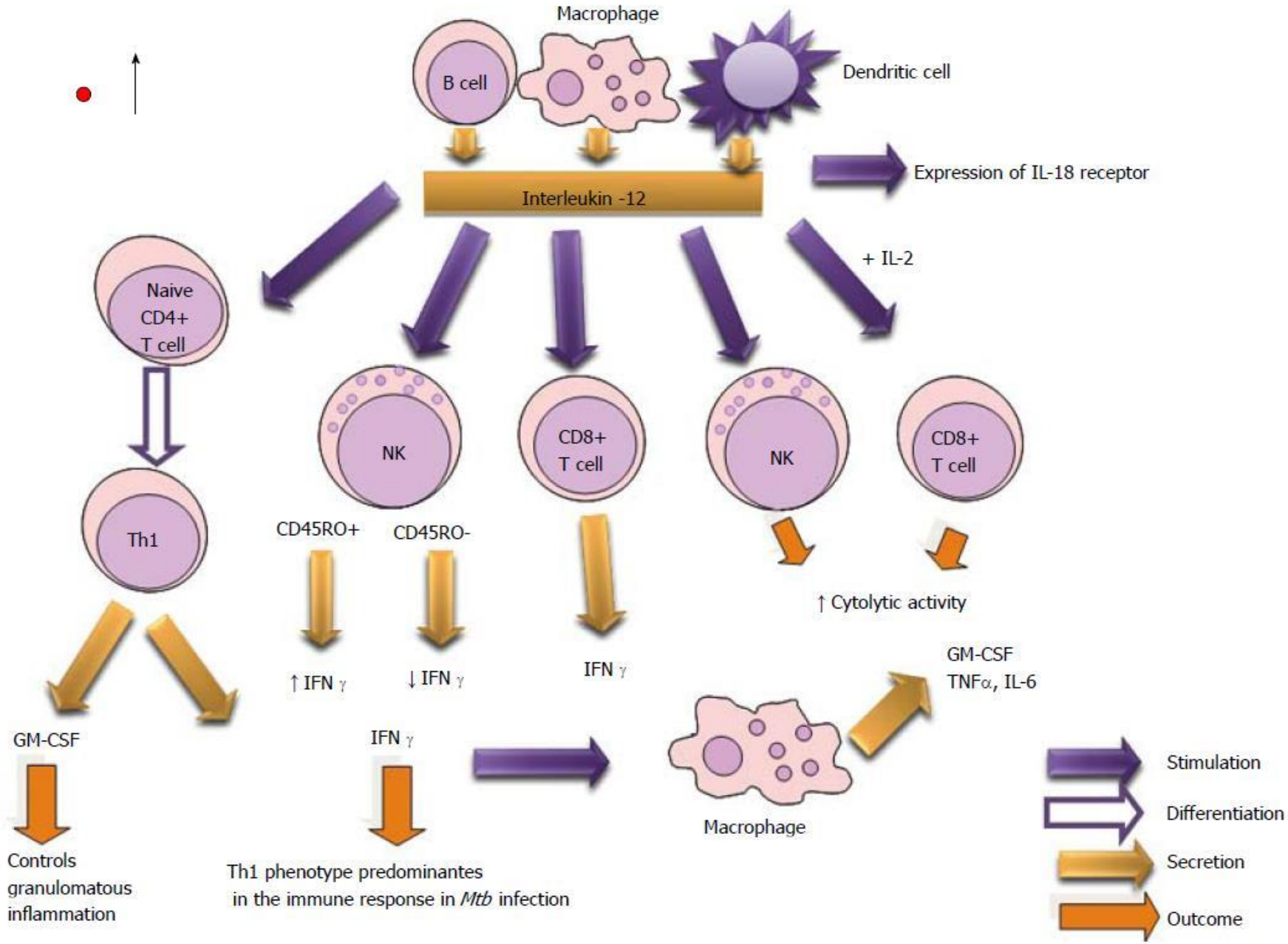
TLR	Ligand	Source
TLR1/2	lipoarabinomannan	mycobacteria
TLR2±6	Zymosan HSP70	Fungi Host
TLR3	DS RNA	Viruses
TLR4	lipopolysaccharide RSV fusion protein HSP70	Gr- bacteria RSV Host
TLR5	Flagellin	Flagelated bacteria
TLR6/2	Diacyl lipopeptides	Mycoplasma
TLR7 and 8	SS RNA Imidazoquinolones	Viruses Synthetic
TLR9	Unmethylated CpG motifs	Bacteria and DNA viruses
TLR10	Unknown	

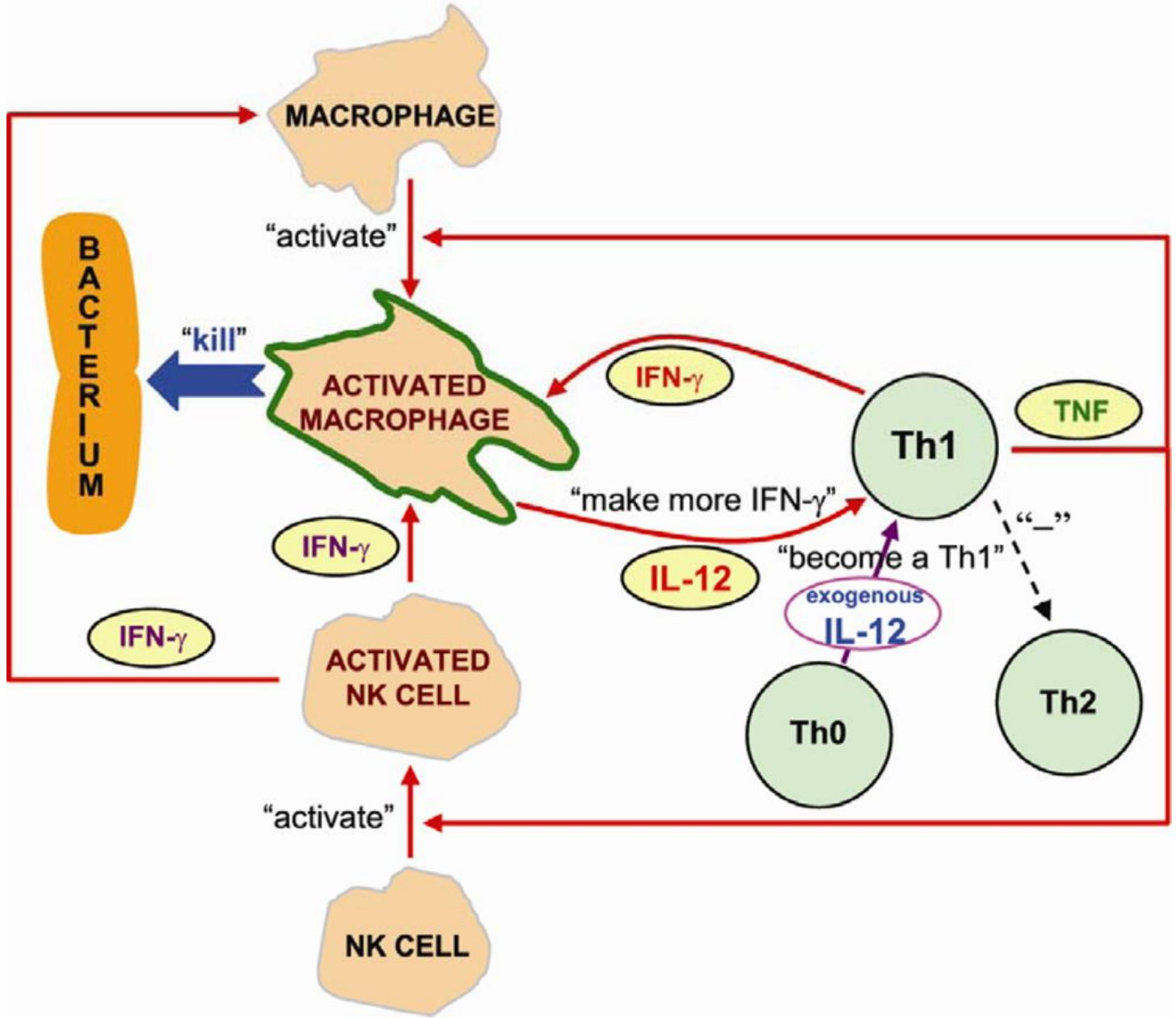
Macrophage



CellCartoons.net


Foreign microbe
with antigens
Macrophage
ingests
antigens...
T-cell
Processes
them...
and presents
them to the T-cell


Macrophage
B cell
Dendritic cell
Interleukin -12
Expression of IL-18 receptor
+ IL-2
Naive
CD4+
T cell
Th1
NK
CD8+
T cell
NK
CD8+
T cell
CD45RO+
CD45RO-
↑ IFN γ
↓ IFN γ
IFN γ
↑ Cytolytic activity
GM-CSF
IFN γ
GM-CSF
TNFα, IL-6
Macrophage
Controls
granulomatous
inflammation
Th1 phenotype predominantes
in the immune response in *Mtb* infection
Stimulation
Differentiation
Secretion
Outcome


MACROPHAGE
"activate"
BACTERIUM
"kill"
ACTIVATED MACROPHAGE
IFN-γ
Th1
TNF
"make more IFN-γ"
"become a Th1"
"–"
IFN-γ
IL-12
exogenous IL-12
IFN-γ
ACTIVATED NK CELL
Th0
Th2
"activate"
NK CELL

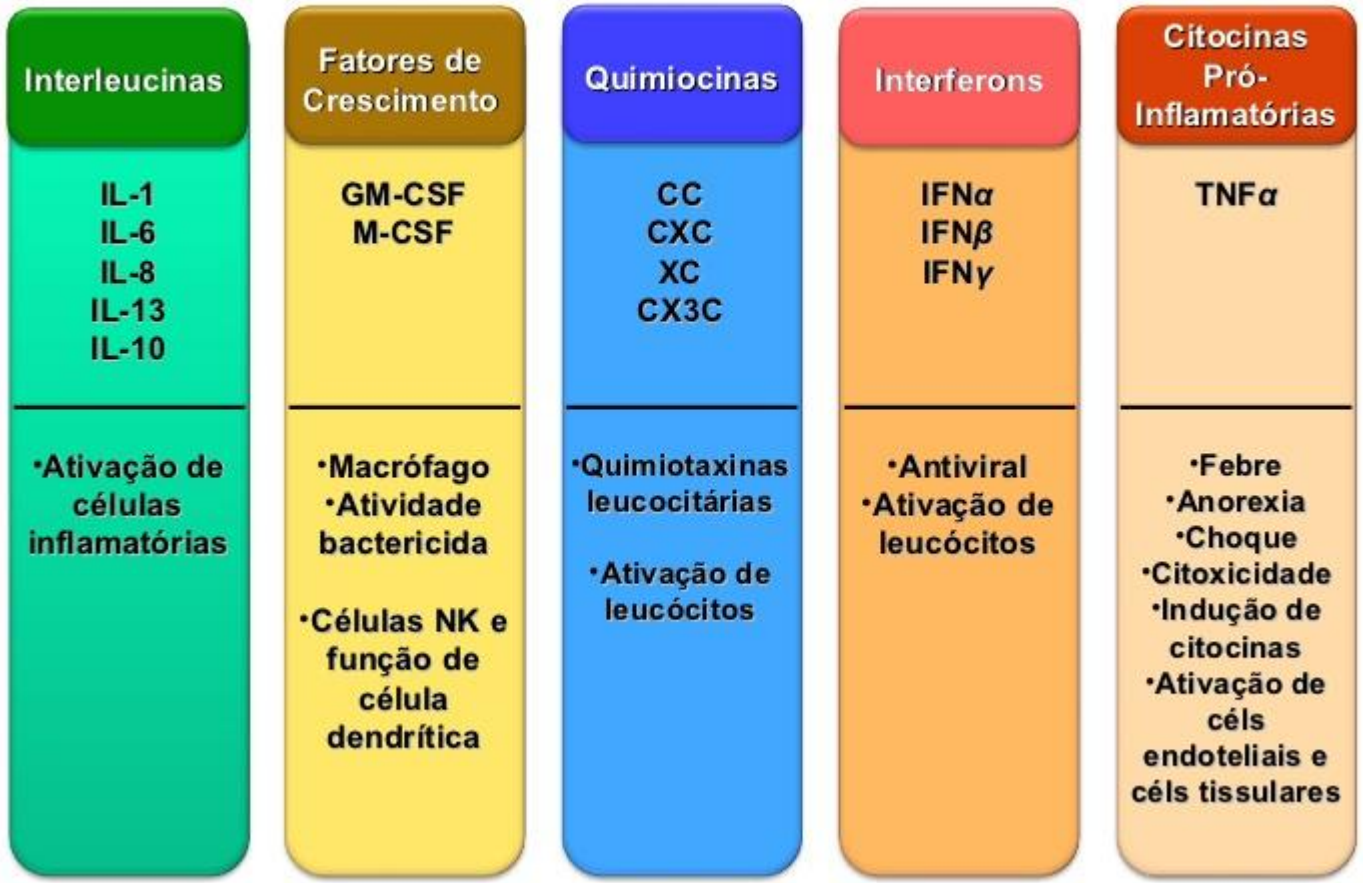
AS células do sistema imune se comunicam por interações de receptores específicos com moléculas solúveis

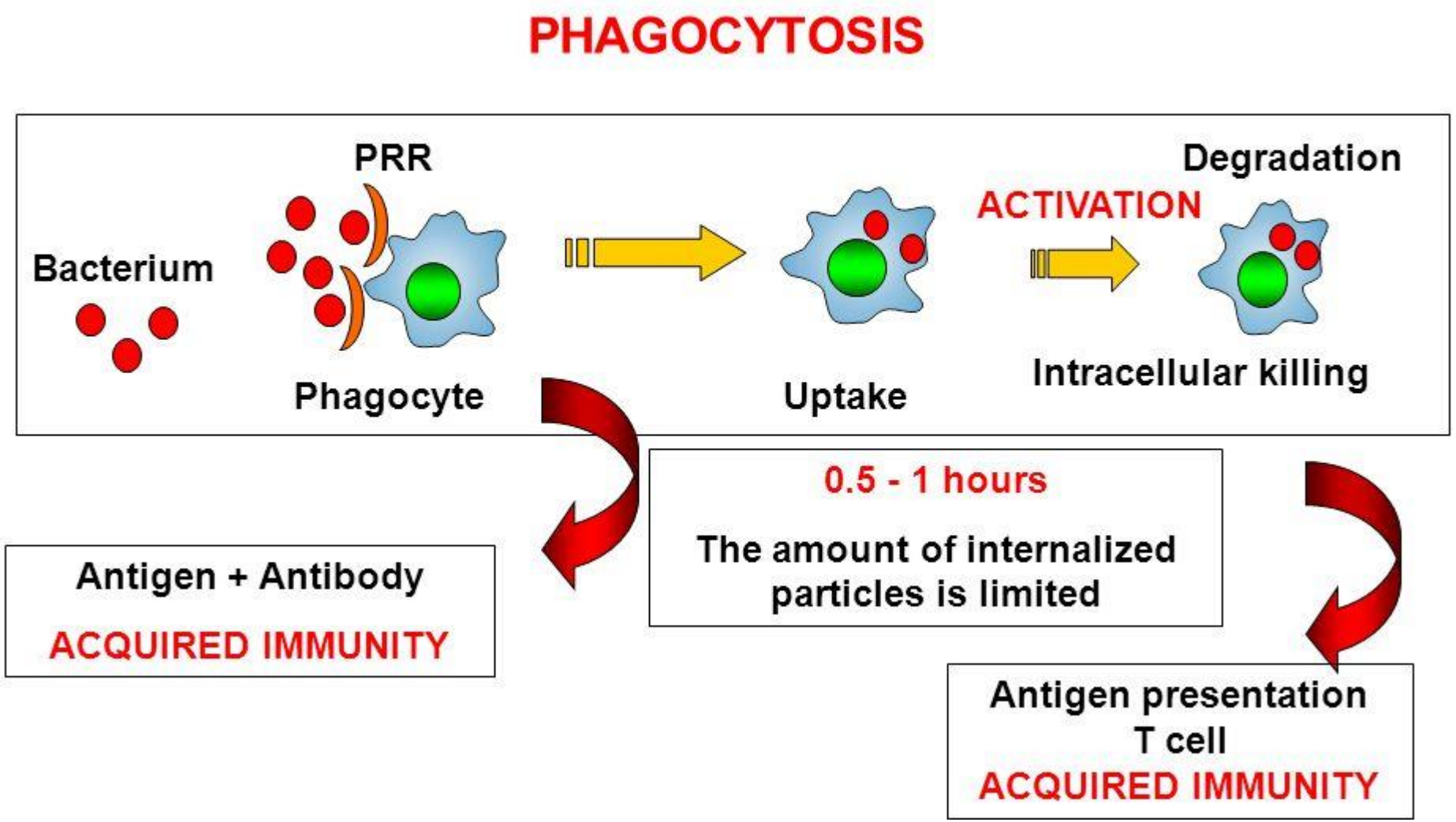
Citocinas – proteínas produzidas por células linfoides que estimulam e regulam outras células durante a resposta imune

Interferons – proteínas produzidas em resposta a infecções virais

Quimiocinas – proteínas associadas a resposta inflamatória

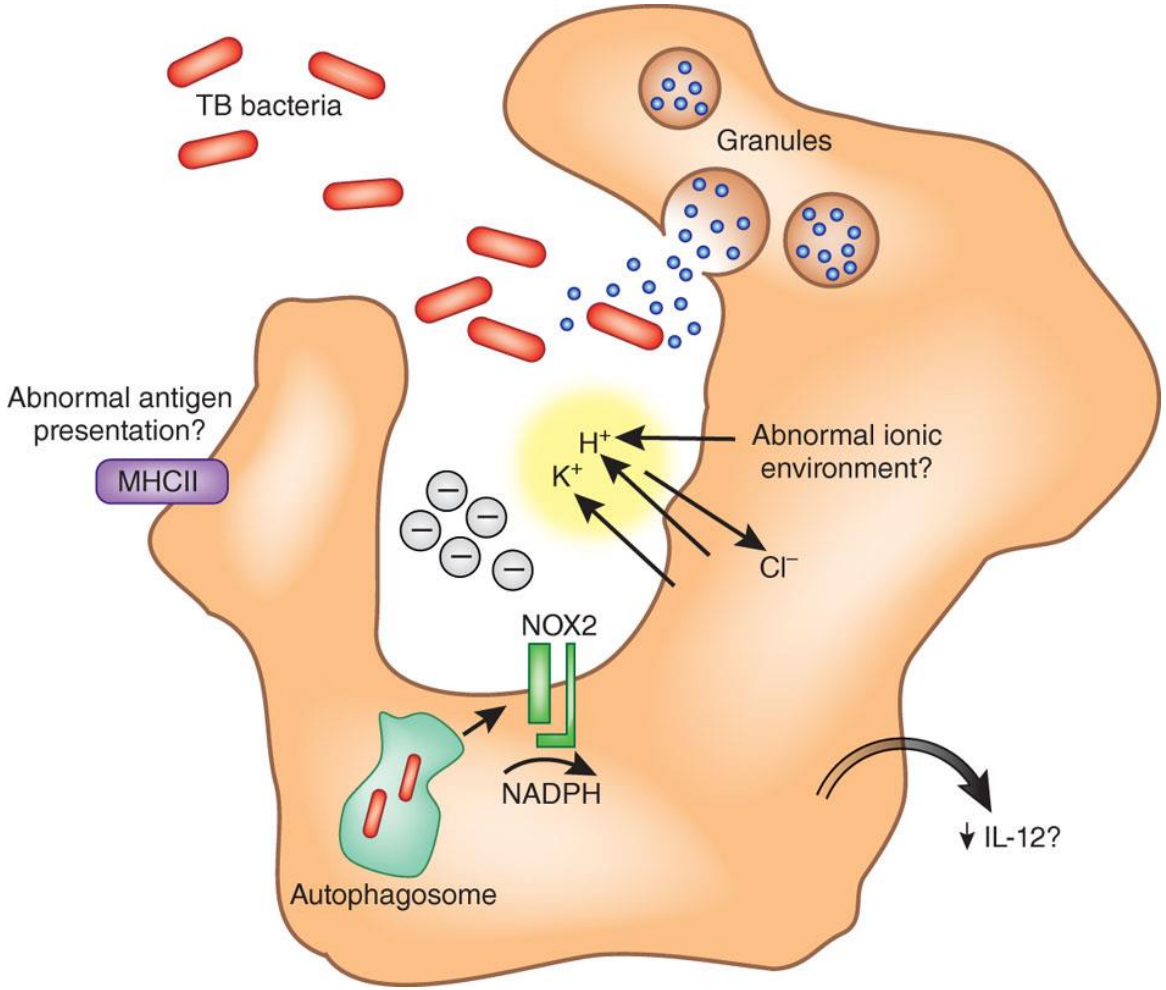
Citocinas Importantes na Inflamação





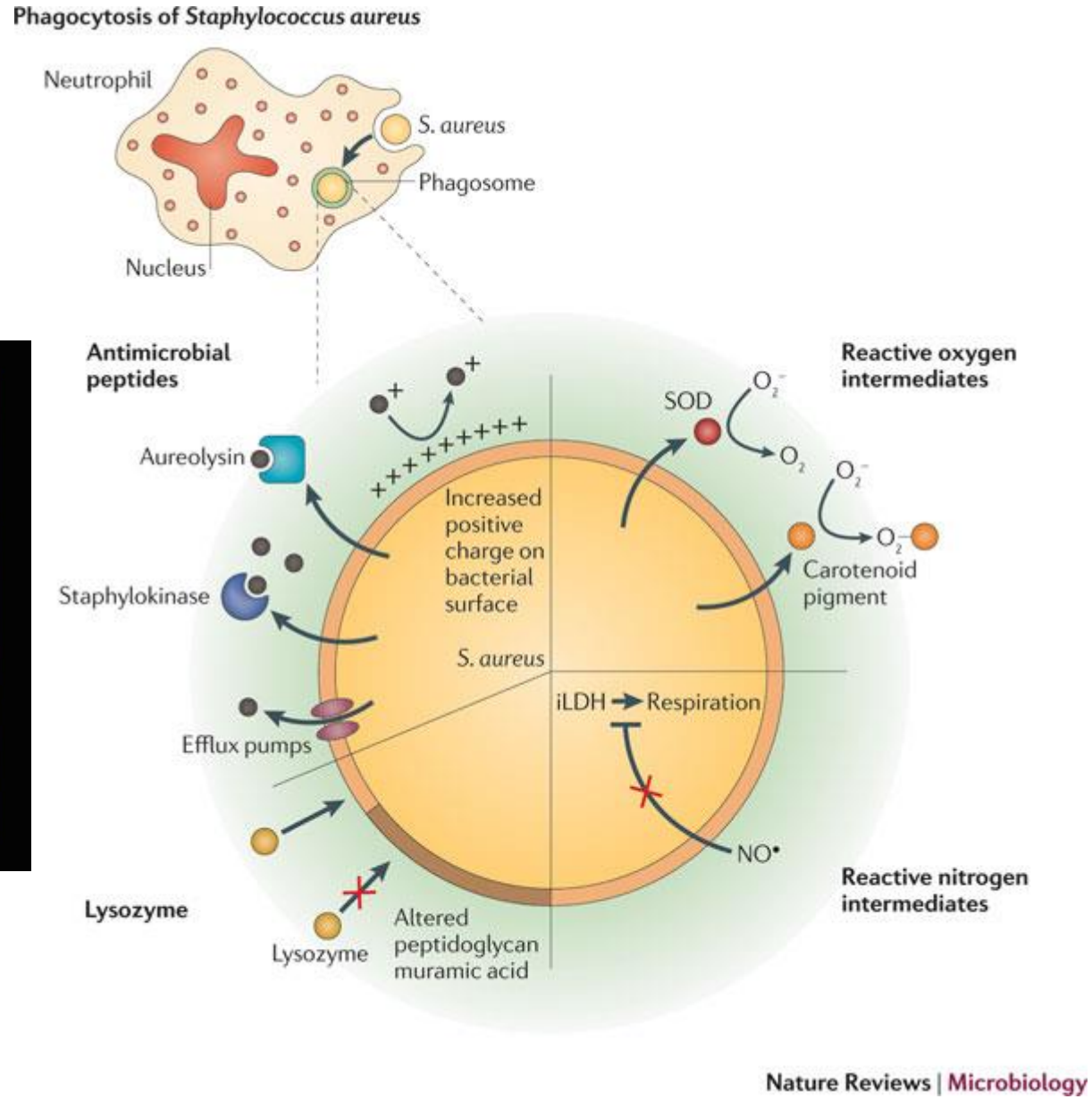
Três etapas: fixação: ativação e digestão

O fagossomo mata pela liberação de espécies reativas de oxigênio

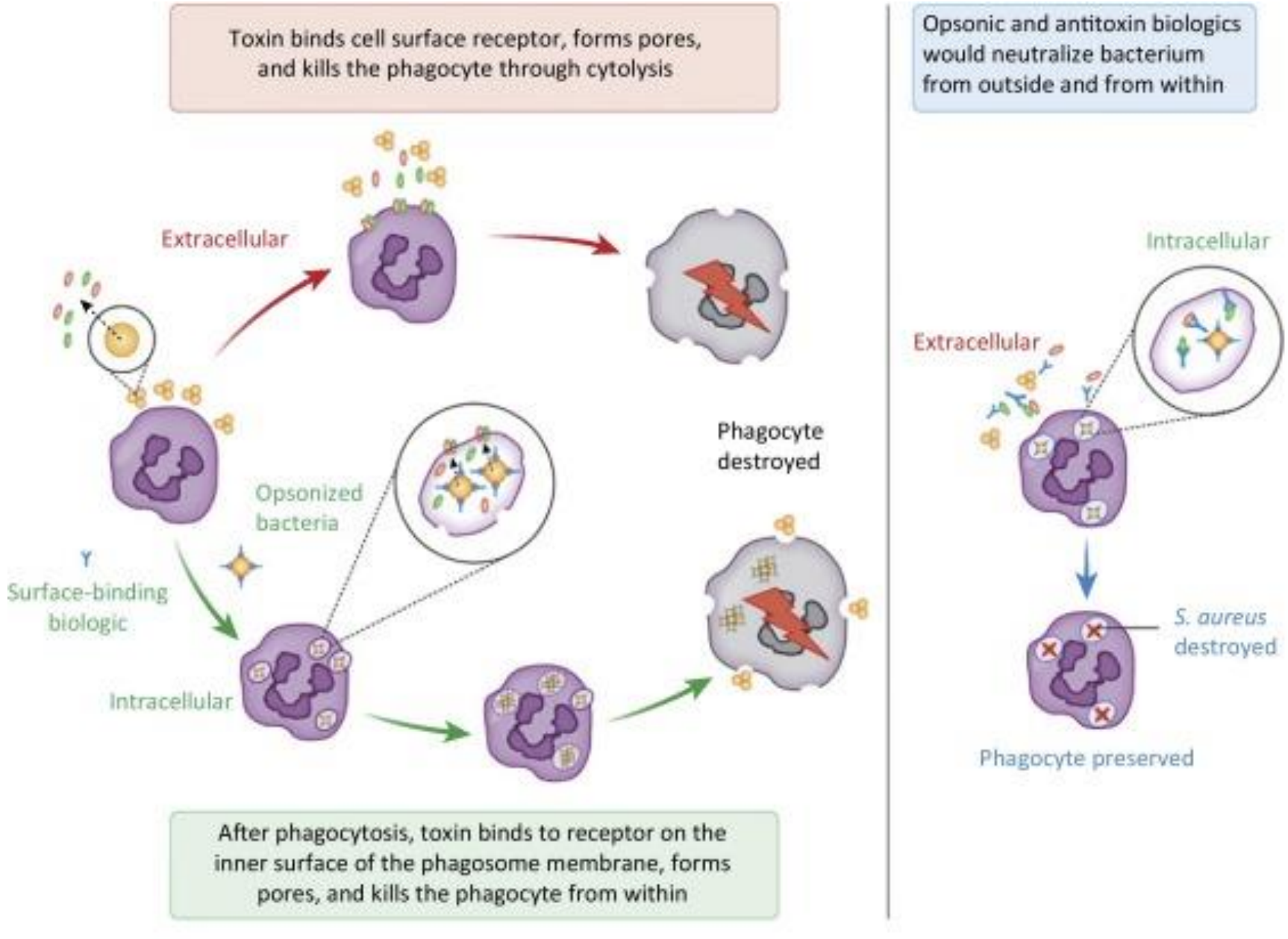


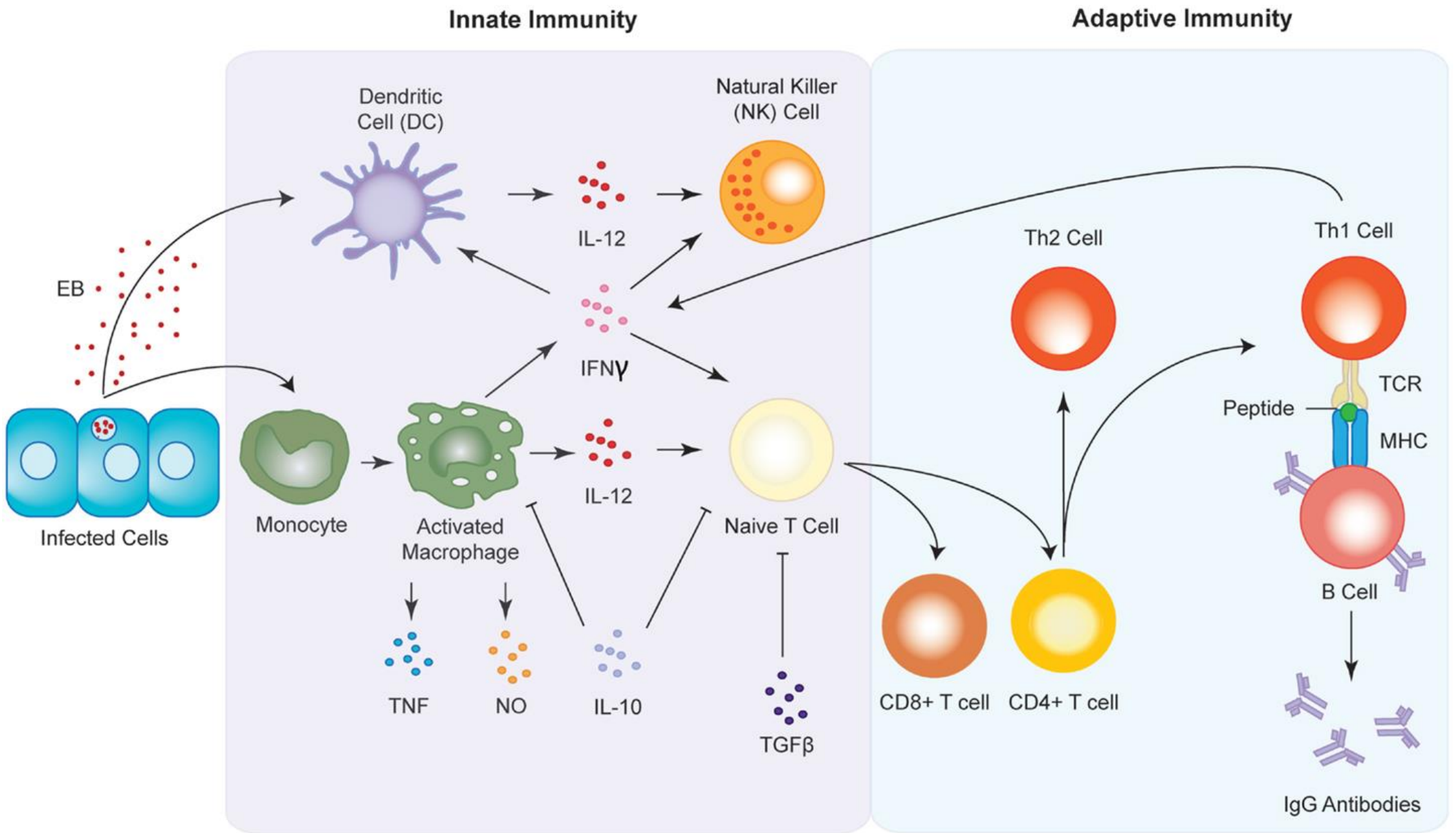
Inibição do fagossomo:

Staphylococcus aureus



Leucocidinas





Receptores de peptidoglicano citoplasmáticos NOD1, NOD2 e criopirina ativa a liberação de IL-1, IL6 e TNF

Respostas imunes aos agentes infecciosos