# Curso de Ciencias Biologicas
# Disciplina BMI-296 – Imunologia basica

# Aula 10 – Resposta aos patogenos

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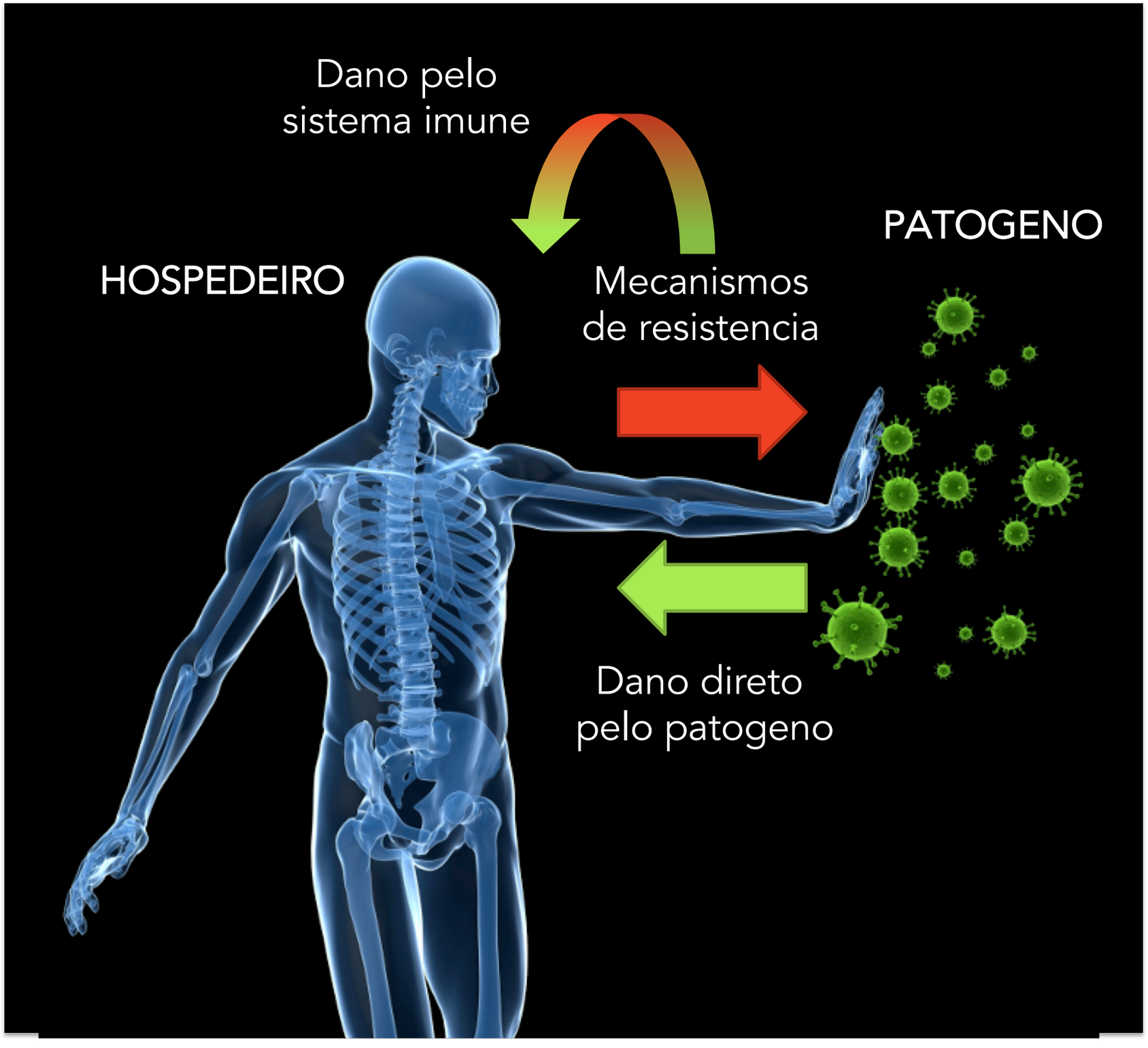
# Interação patógeno/hospedeiro




Eventos:

- Entrada
- Invasao e colonizaçao
- Lesao tecidual/dano

**PAMPs/DAMPs**
**Ag**

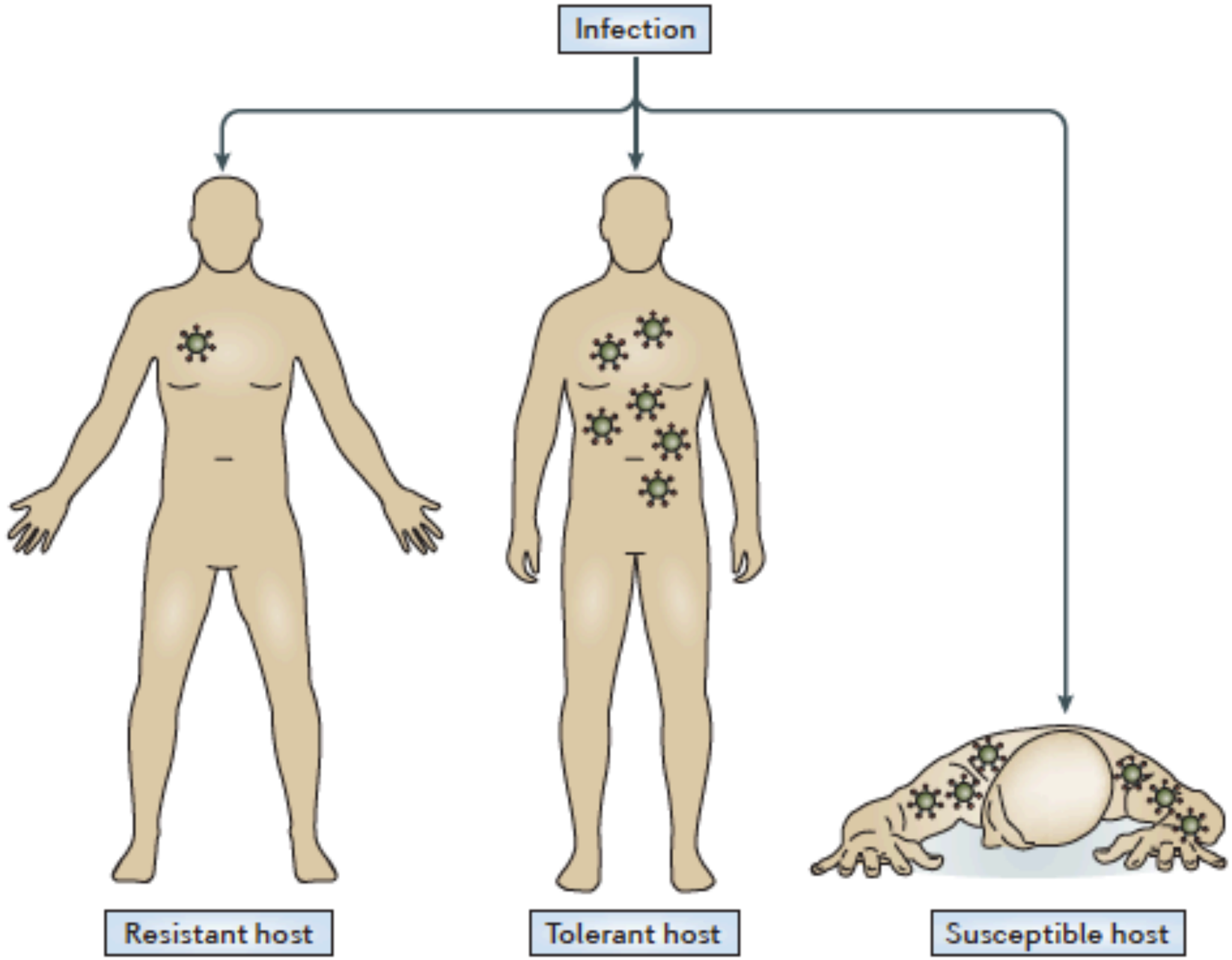
patogenicidade
vs resposta imune

Evasão
do sistema imune

# Interação patógeno/hospedeiro

- Imunidade inata e adaptativa
- Resposta é diferenciada dependo do patógeno (*resposta imune protetora*)
- Infecção aguda ou crônica (latência, evasão)
- Lesão tecidual como dano direto do patógeno MAS tbm como resposta “exagerada” às infecções
- 2 estratégias de resposta: resistência/eliminação ou limitação do dano/tolerância
- Imunocompetencia vs imunodeficiência do hospedeiro

# Interação patógeno/hospedeiro




**Resposta imune**

**Desfecho**

Eliminaçao do patogeno

Reduçao do dano produzido pelo patogeno

Incapacidade de
- conter/eliminar o patogeno
- tolerar as consequencias da resposta imune a infecçao

# Infecção por bactérias extracel

- Replicam fora das células do hospedeiro (sangue, tecidos conjuntivos, espaços teciduais como lúmen do tratos respiratório e gastrointestinal)
- 2 principais mecanismos de patogenicidade

- Inflamação → destruição tecidual no sitio da infecção *(ex. Streptococcus, Staphylococcus)*

- Toxinas *(ex. Clostridium tetani,Vibrio cholerae)*
  - exotoxinas → citotóxicas, interferência nas funções cel, indução CK
  - endotoxinas (ex:LPS)→ potente ativador de Mø e DC (elevada produção de CK inflamatórias)

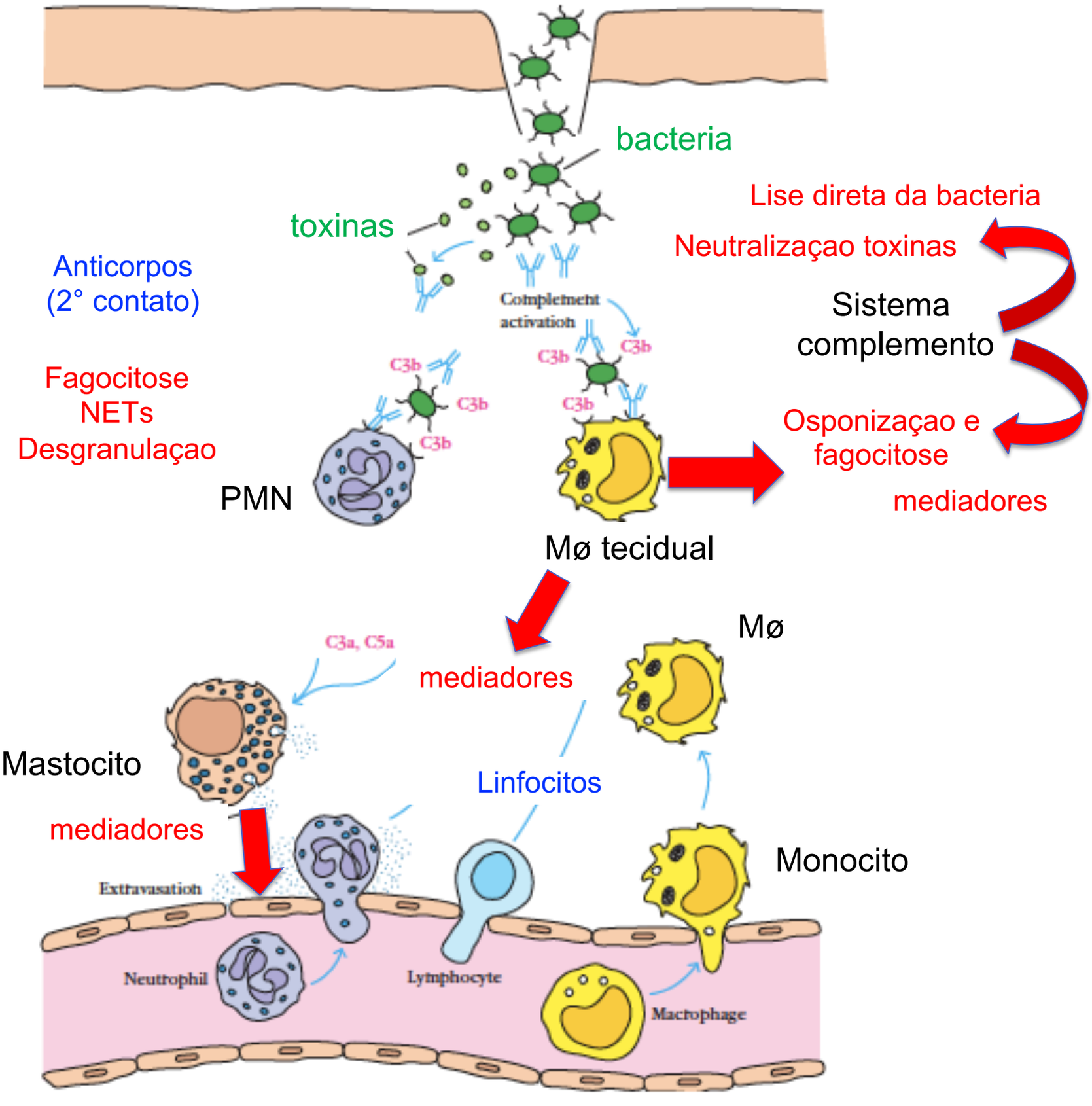
- Super Ag *(ex. Staphylococcus)*
  - exotoxinas → ativação DIRETA de linfócitos Th → produção sistêmica de CK → shock

- Pequeno inoculo e baixa virulência –> resposta inata é suficiente
- Maior inoculo e/ou elevada virulência –> resposta adaptativa é induzida

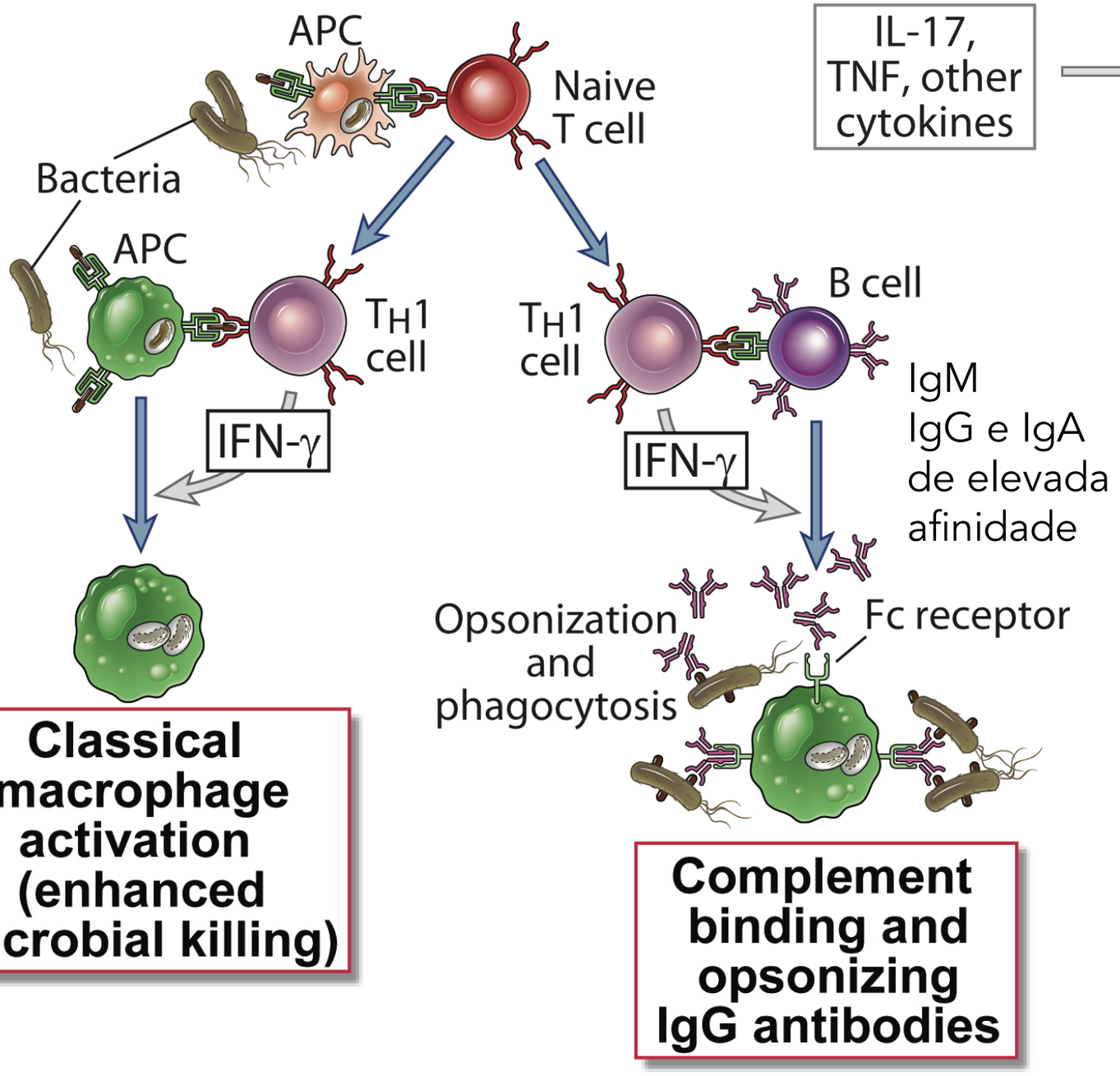
# Infecção por bactérias extracel

| Microbe | Examples of Human Diseases | Mechanisms of Pathogenicity |
|---|---|---|
| **Extracellular bacteria** | | |
| *Staphylococcus aureus* | Skin and soft tissue infections, lung abscess<br>Systemic: toxic shock syndrome, food poisoning | Skin infections: acute inflammation induced by toxins; cell death caused by pore-forming toxins<br>Systemic: enterotoxin ("superantigen")-induced cytokine production by T cells causing skin necrosis, shock, diarrhea |
| *Streptococcus pyogenes* (group A) | Pharyngitis<br>Skin infections: impetigo, erysipelas; cellulitis<br>Systemic: scarlet fever | Acute inflammation induced by various toxins, e.g., streptolysin O damages cell membranes |
| *Streptococcus pyogenes* (pneumococcus) | Pneumonia, meningitis | Acute inflammation induced by cell wall constituents; pneumolysin is similar to streptolysin O |
| *Escherichia coli* | Urinary tract infections, gastroenteritis, septic shock | Toxins act on intestinal epithelium chloride and water secretion; endotoxin (LPS) stimulates cytokine secretion by macrophages |
| *Vibrio cholerae* | Diarrhea (cholera) | Cholera toxin ADP ribosylates G protein subunit, which leads to increased cyclic AMP in intestinal epithelial cells and results in chloride secretion and water loss |
| *Clostridium tetani* | Tetanus | Tetanus toxin binds to the motor end plate at neuromuscular junctions and causes irreversible muscle contraction |
| *Neisseria meningitidis* (meningococcus) | Meningitis | Acute inflammation and systemic disease caused by potent endotoxin |
| *Corynebacterium diphtheriae* | Diphtheria | Diphtheria toxin ADP ribosylates elongation factor 2 and inhibits protein synthesis |

# Resposta a bactérias extracel



# Resposta a bactérias extracel

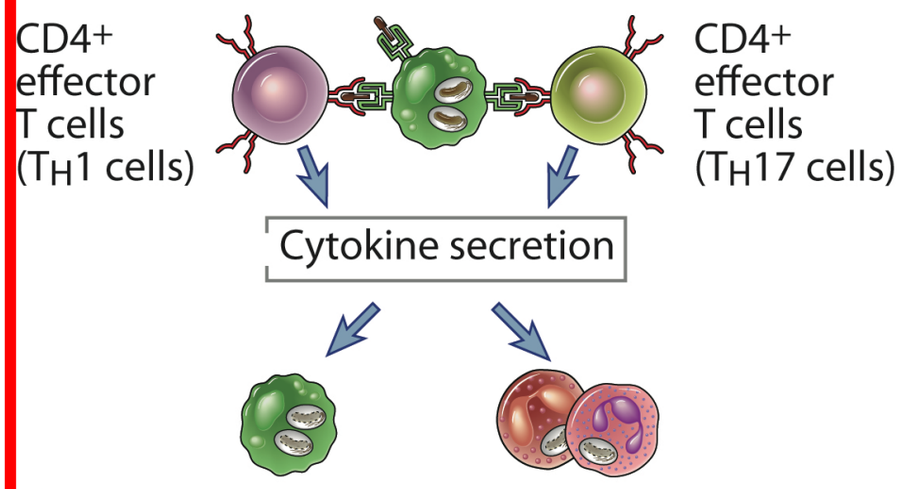



IL-17, TNF, other cytokines → **Inflammation**

**Classical macrophage activation (enhanced microbial killing)**

**Complement binding and opsonizing IgG antibodies**

**Phagocytes with ingested microbes in vesicles**

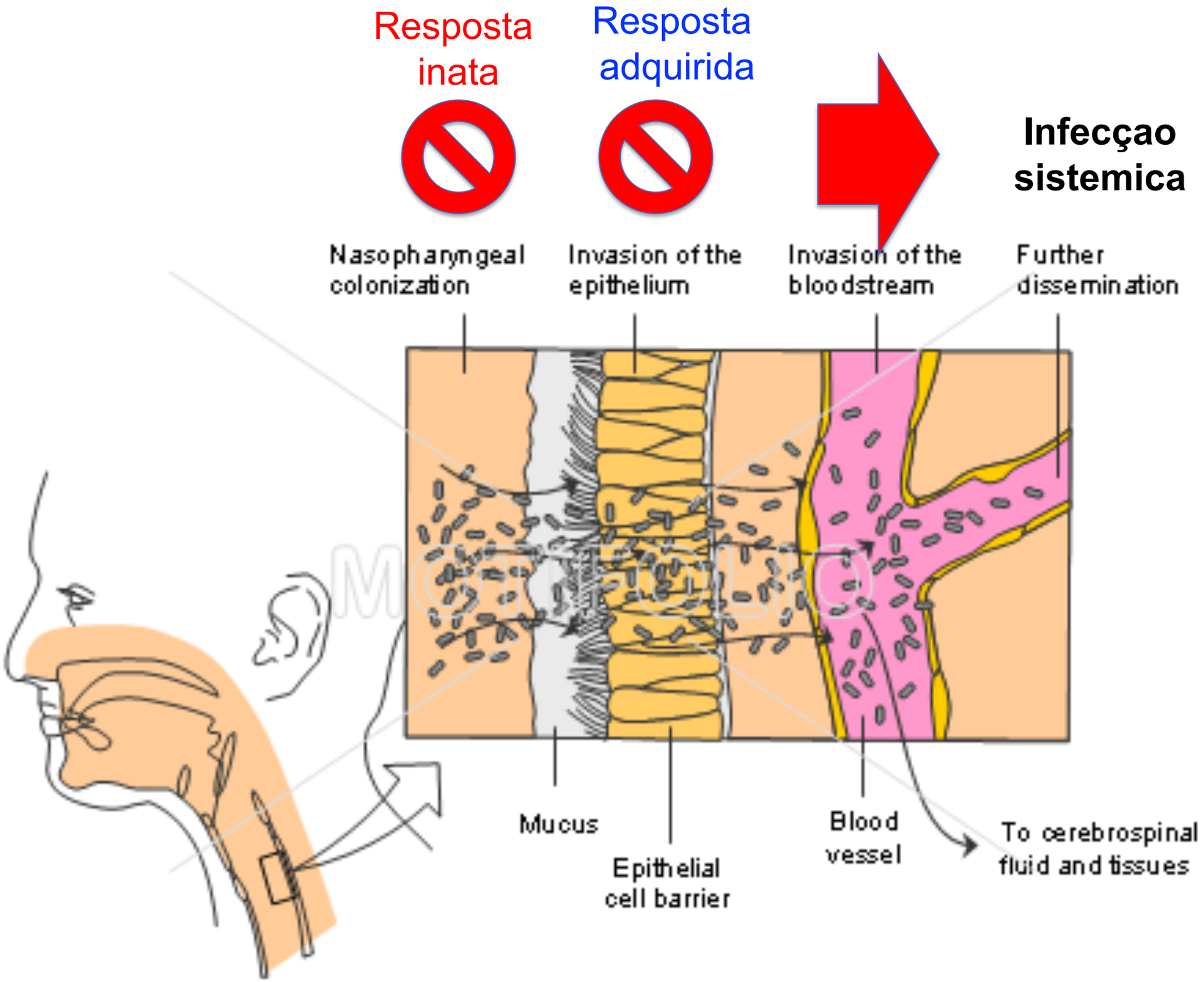



**Macrophage activation ⇢ killing of ingested microbes**

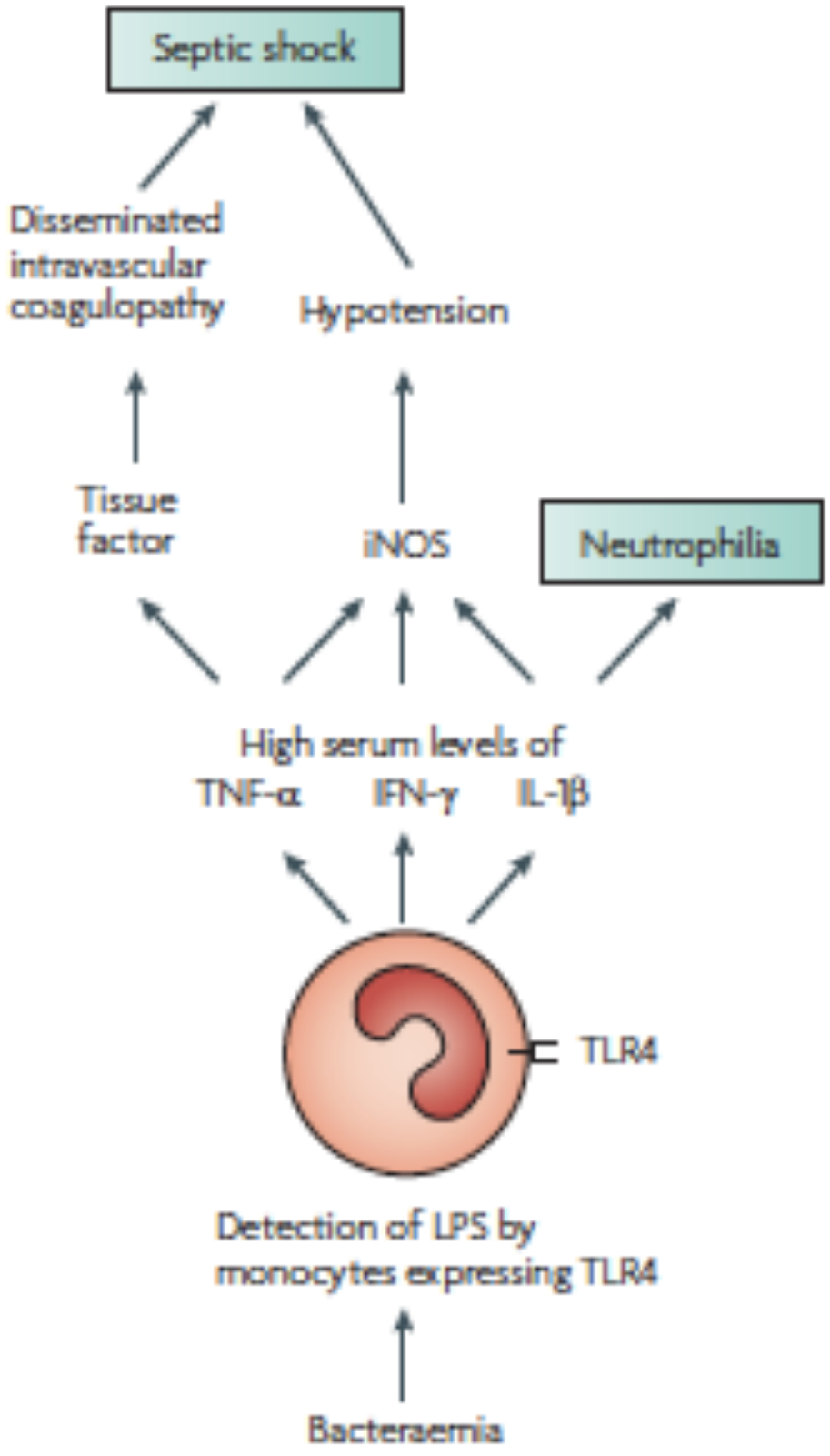
**Inflammation, killing of microbes**

**imunidade mediada por AC è PROTETORA**

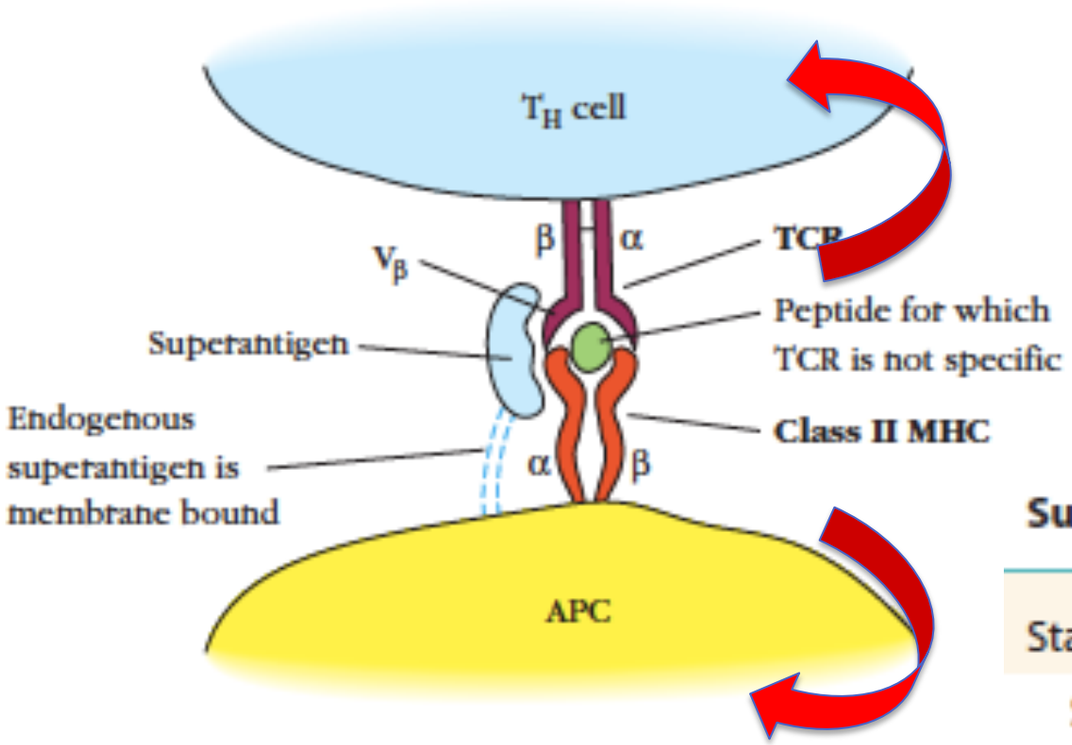
# Resposta a bactérias extracel



# Shock septico



# Resposta a bactérias extracel




Es are a major cause of food poisoning, which typically occurs after ingestion of different foods, particularly processed meat and dairy products, contaminated with *S. aureus* by improper handling and subsequent storage at elevated temperatures. Symptoms are of rapid onset and include nausea and violent vomiting, with or without diarrhea. The illness is usually self-limiting and only occasionally it is severe enough to warrant hospitalization.

## Super Ag

| Superantigen | Disease* |
|---|---|
| Staphylococcal enterotoxins | |
| SEA | Food poisoning |
| SEB | Food poisoning |
| SEC1 | Food poisoning |
| SEC2 | Food poisoning |
| SEC3 | Food poisoning |
| SED | Food poisoning |
| SEE | Food poisoning |
| Toxic shock syndrome toxin (TSST1) | Toxic shock syndrome |
| Exfoliative dermatitis toxin (ExFT) | Scalded skin syndrome |
| *Mycoplasma arthritidis* supernatant (MAS) | Arthritis, shock |
| Streptococcal pyrogenic exotoxins (SPE-A, B, C, D) | Rheumatic fever, shock |

# Imunodeficiências

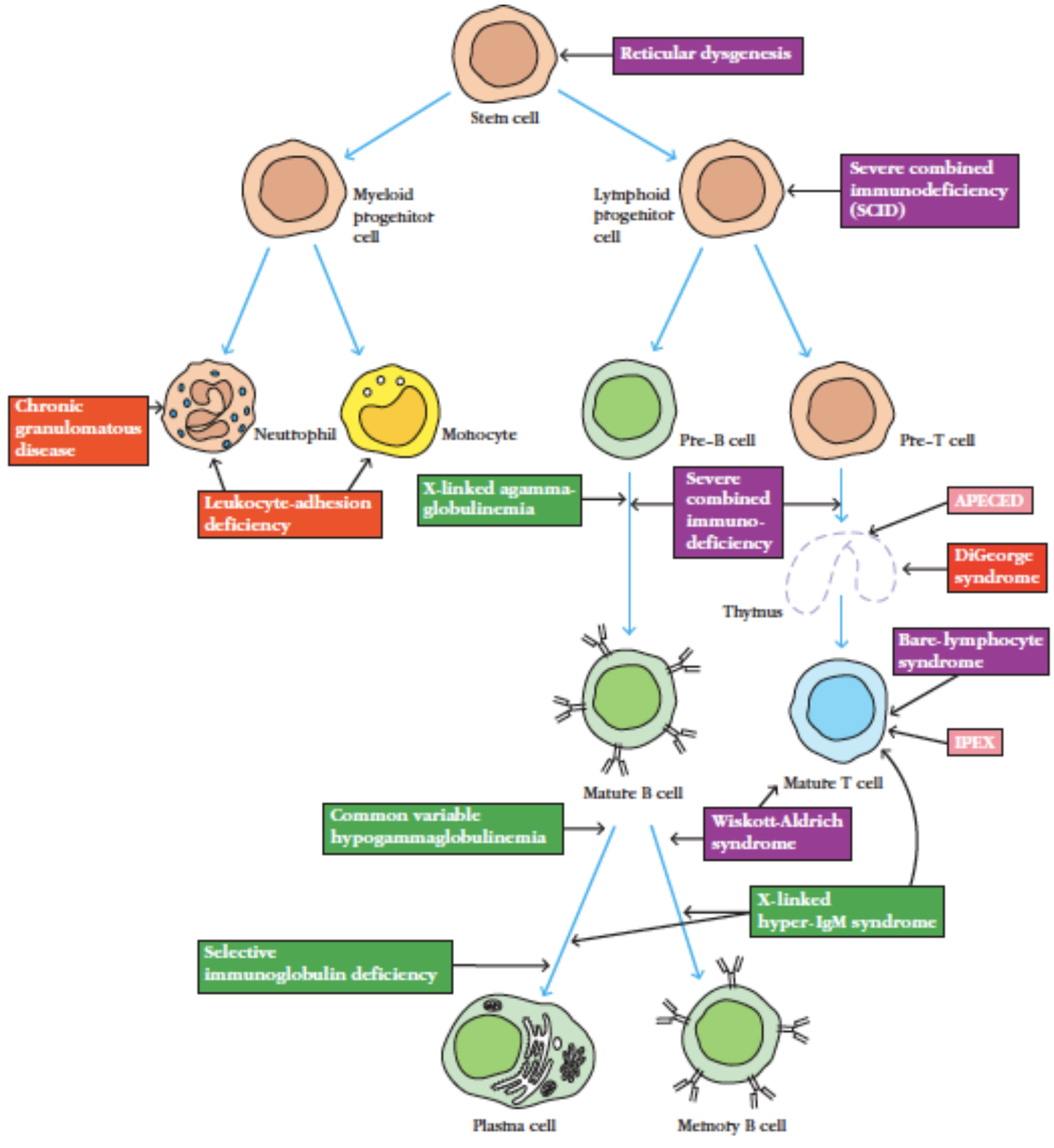
defeito em 1 ou mais componentes do sistema imune

defeito na (1) maturação ou (2) ativação das células ou no (3) mecanismo efetor da imunidade inata ou adaptativa.

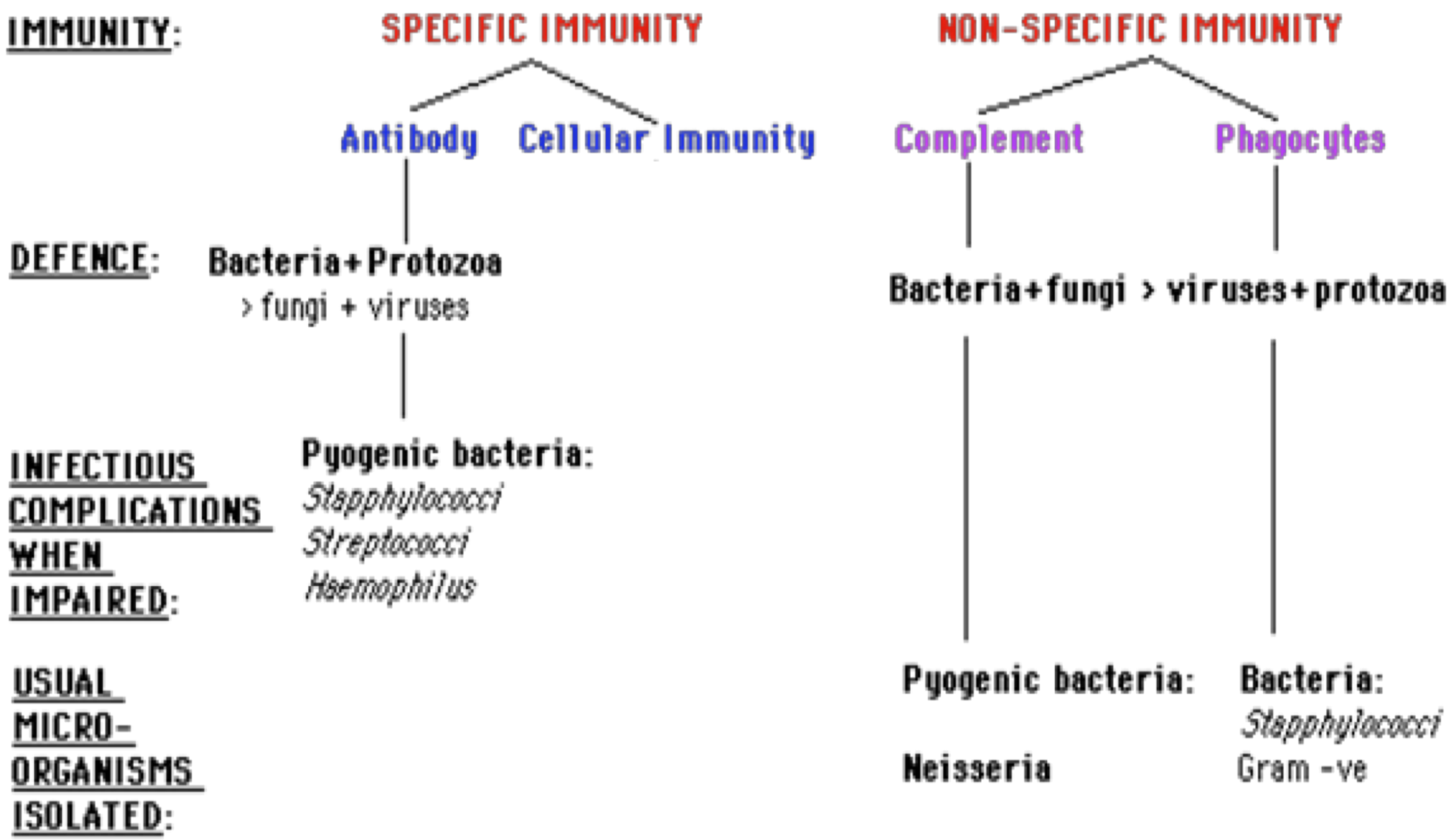
resposta imune comprometida

classificadas em

- primarias ou congênitas (PID)
- secundarias ou adquiridas

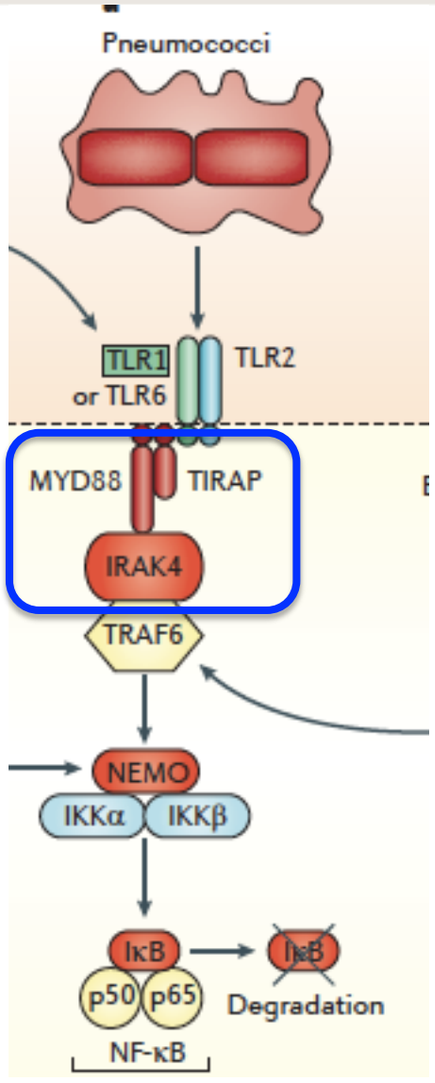


# PID e bactérias extracel



# Genes & susceptibilidade a Bactérias extracel

| Pathogen | Phenotype | Probable mechanism | Gene or genes |
|---|---|---|---|
| *Streptococcus pneumoniae* | Susceptibility to invasive disease | Impaired TLR–IL-1R signalling | *IRAK4* |
| | | | *MYD88* |
| *Neisseria meningitidis* | Susceptibility to invasive disease | Membrane attack complex deficiency | *C5-C9* |
| | | Properdin deficiency | *CFP* |
| | | Factor D deficiency | *CFD* |
| Encapsulated bacteria (for example, *S. pneumoniae*, *N. meningitidis* and *Haemophilus influenzae*) | Susceptibility to invasive disease | Classical complement pathway deficiency | *C2*, *C1Q*, *C1R*, *C1S*, *C4* |




*Chapman and Hill, 2012*

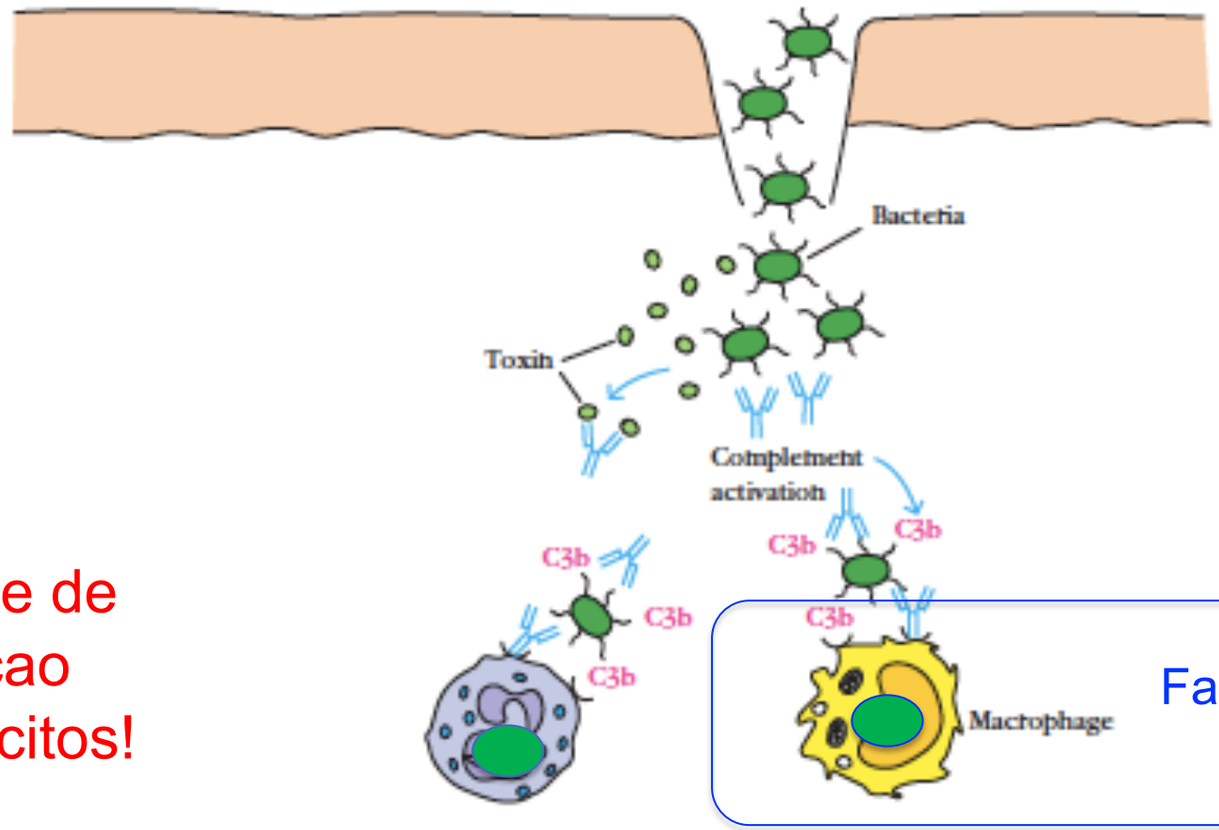
# Infecção por bactérias intracel

- Sobrevivem e replicam dentro de fagocitos
- Nao sao citoliticos
- Nicho no qual sao inacessiveis a mecanismos extraceluares (AC)
- Patogenicidade:

- ativaçao de Mø→ inflamaçao granulomatosa e destruiçao tecidual (Mycobacteria)
- toxinas citoliticas e/ou inflamatorias (Listeria monpcytogenes, Legionella pneumophila)

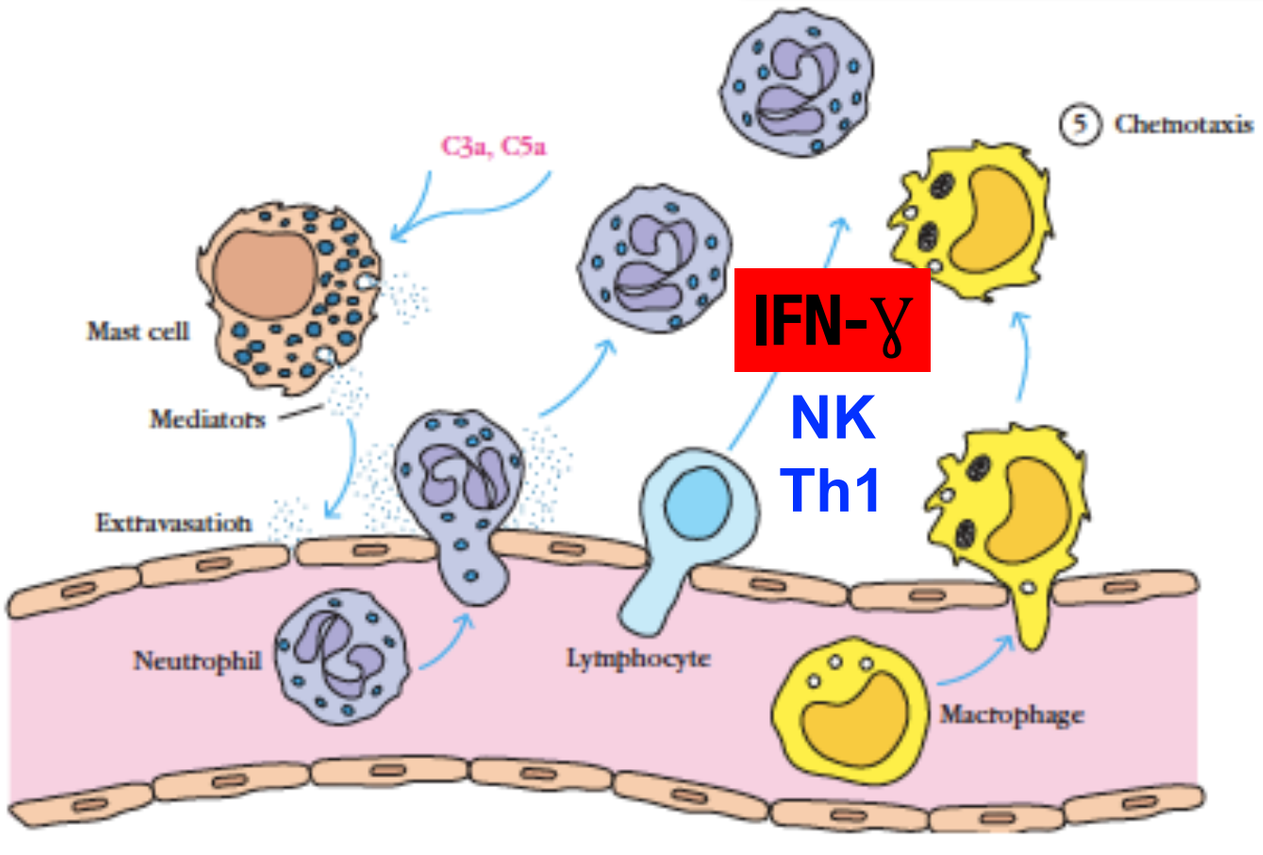
| Microbe | Human Diseases | Pathogenicity |
|---|---|---|
| *Mycobacteria species* | Tuberculosis, Leprosy | Macrophage activation, granulomatous inflammation, tissue destruction |
| *Listeria monocytogenes* | Listeriosis | Listeriolysin damages cell membrane |
| *Legionella pneumophila* | *Legionnaires' disease* | Cytotoxin lyses cells |

# Resposta a bactérias intracel




Dificuldade de eliminaçao pelos fagocitos!

Fagocitos infectados “alvo” de celulas citotoxicas

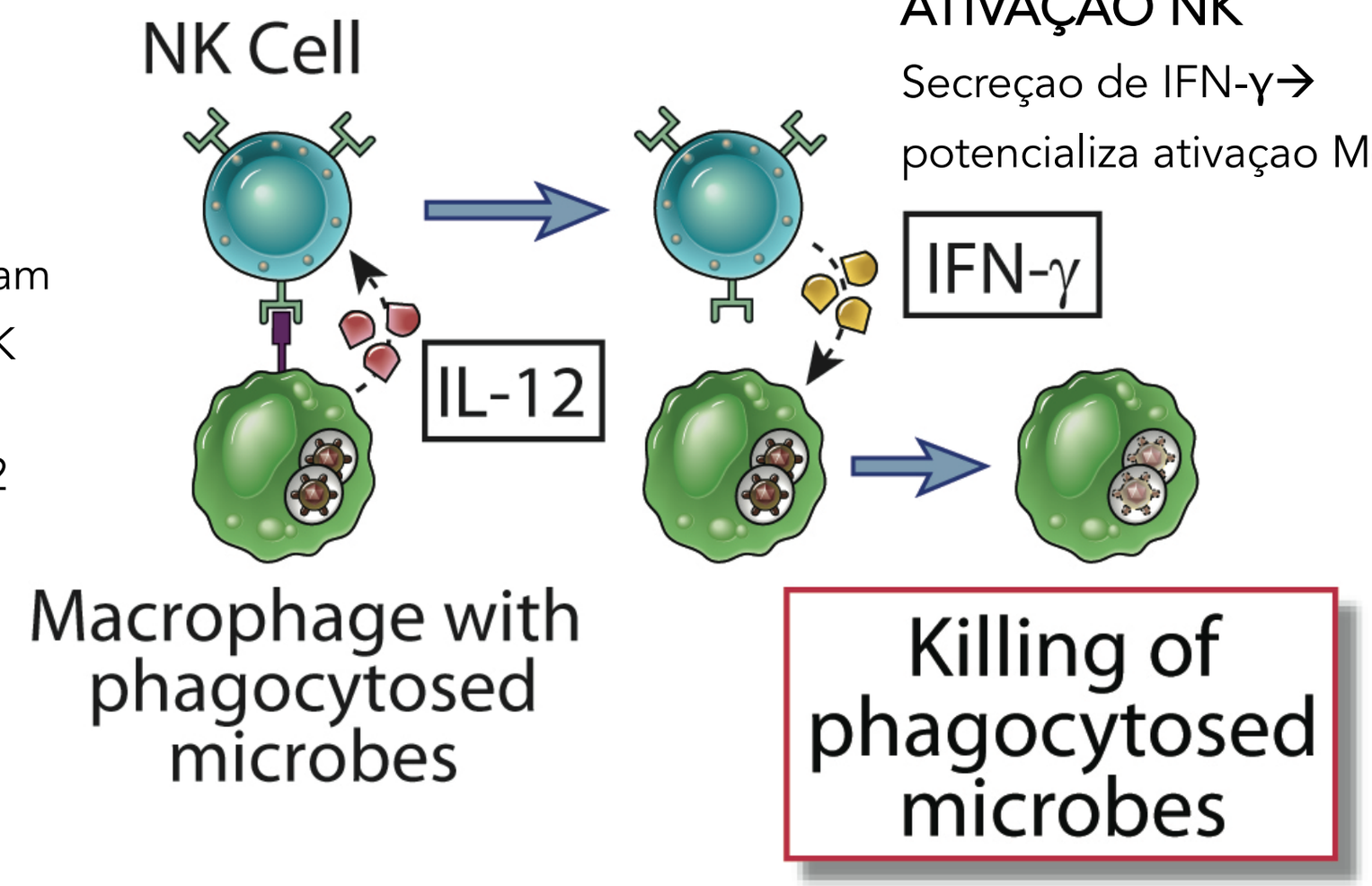


# Resposta a bactérias intracel

- células NK → IFN-**γ** ajuda os Mø a matar

Celulas infectadas expressam ligantes ativadores para NK

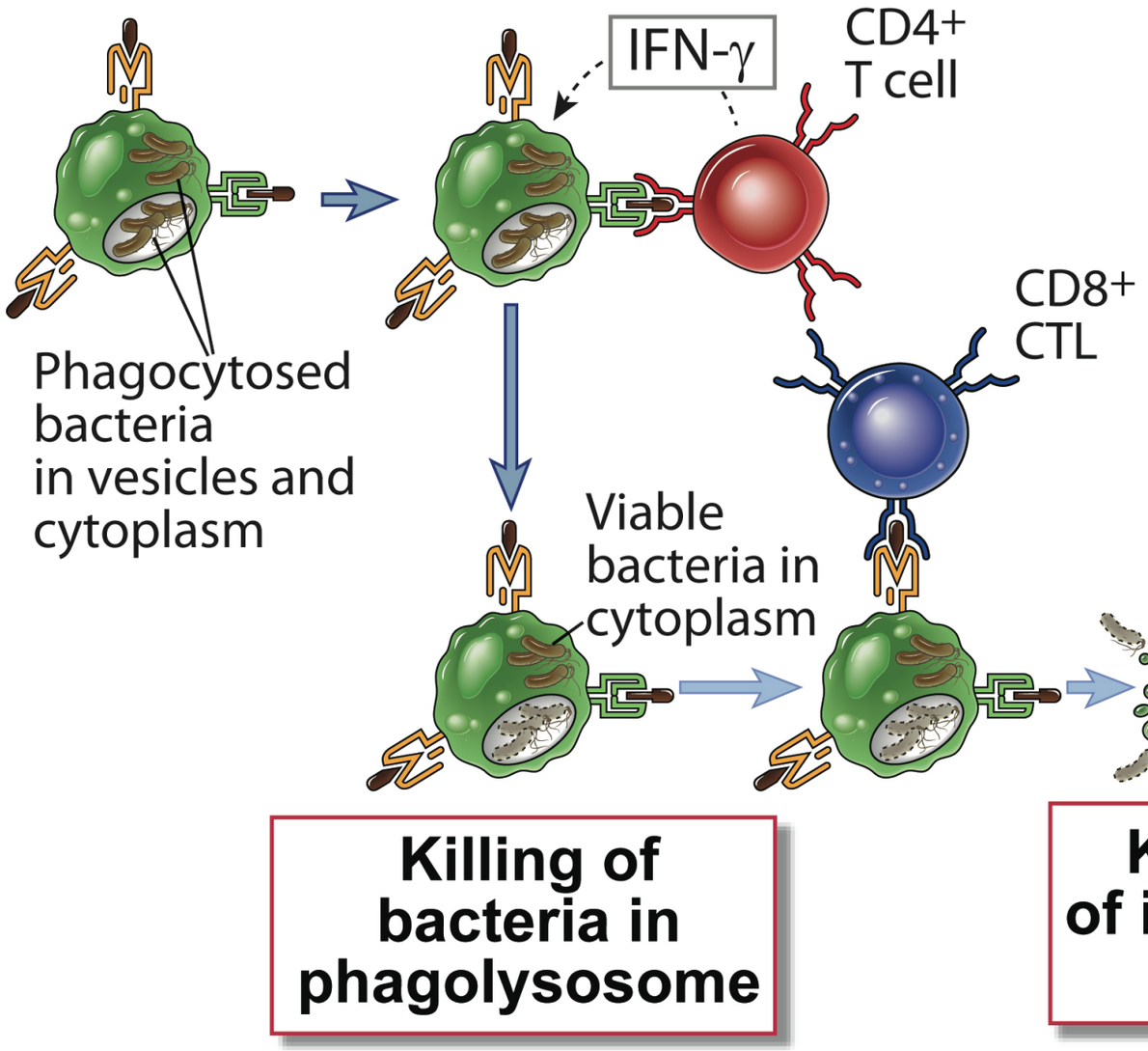
Mø ativado produz IL-12




ATIVAÇAO NK

Secreçao de IFN-γ→ potencializa ativaçao Mø

# Resposta a bactérias intracel




## TH1

ATIVAÇAO Mø

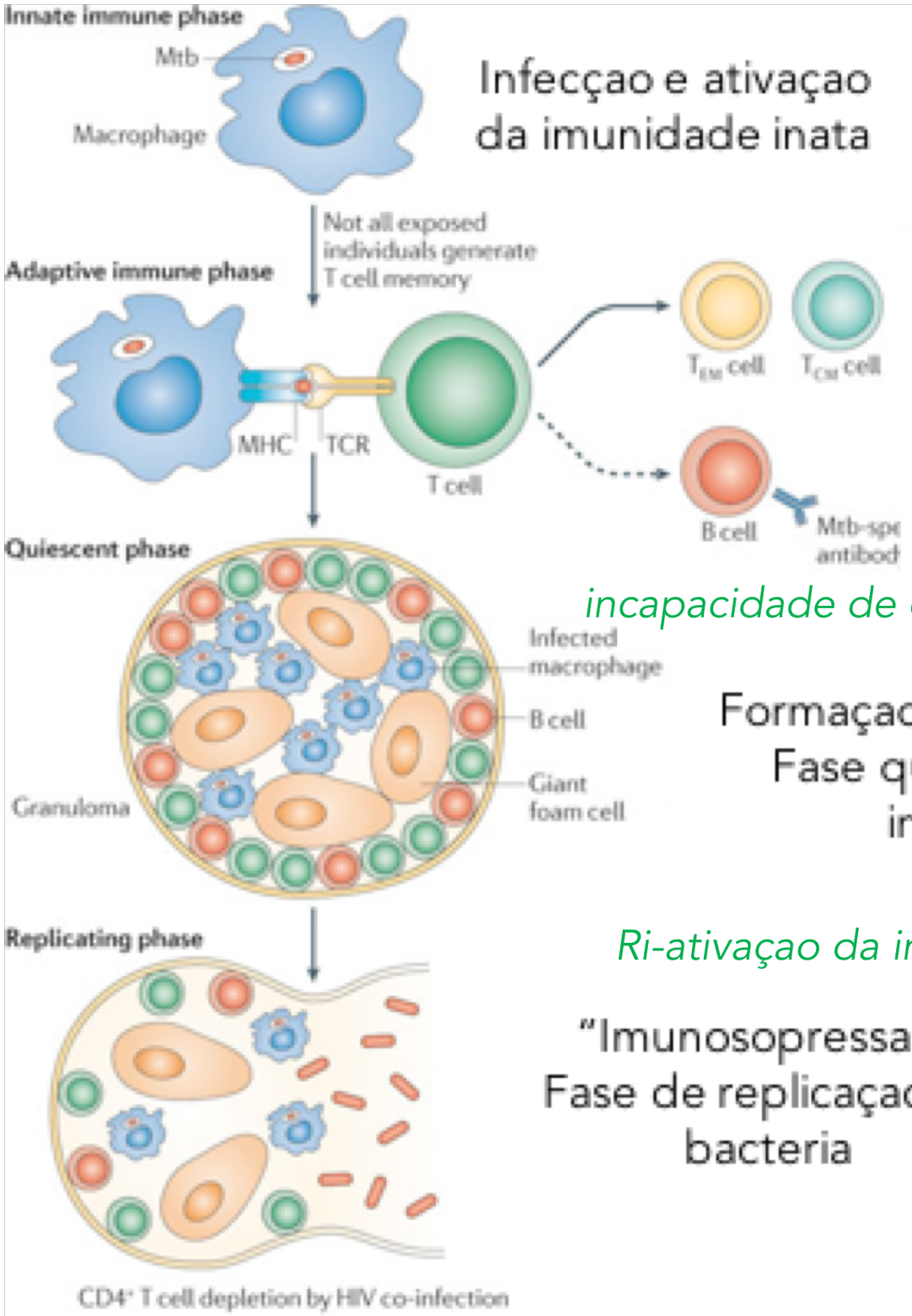
Secreçao de IFN-γ

ATIVAÇAO CTL

perforina, granzima B e granulisina

imunidade mediada por celulas T è PROTETORA

# Resposta a bactérias intracel




Infecçao e ativaçao da imunidade inata

Induçao da imunidade adquirida (Th1):
IFN-ɣ
Linfocitos B→AC

**ELIMINCAO DAS BACTERIAS "RESISTENCIA"**

*incapacidade de eliminar a bacteria, infecçao cronica*

Formaçao do granuloma
Fase quiescente da infecçao

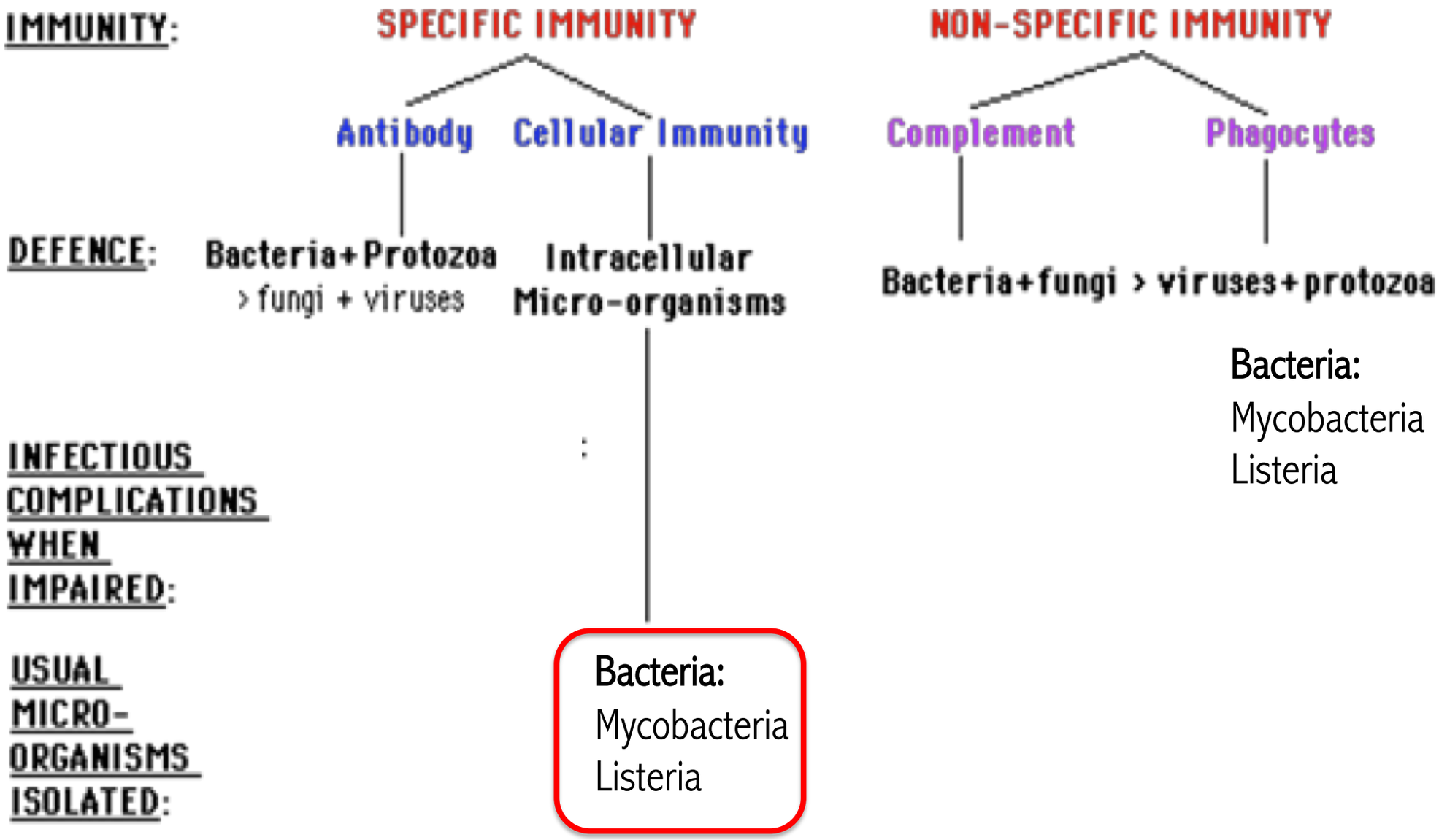
**"TOLERANCIA" AS BACTERIAS**

*Ri-ativaçao da infecçao e dano tecidual importante*

"Imunosopressao"
Fase de replicaçao da bacteria

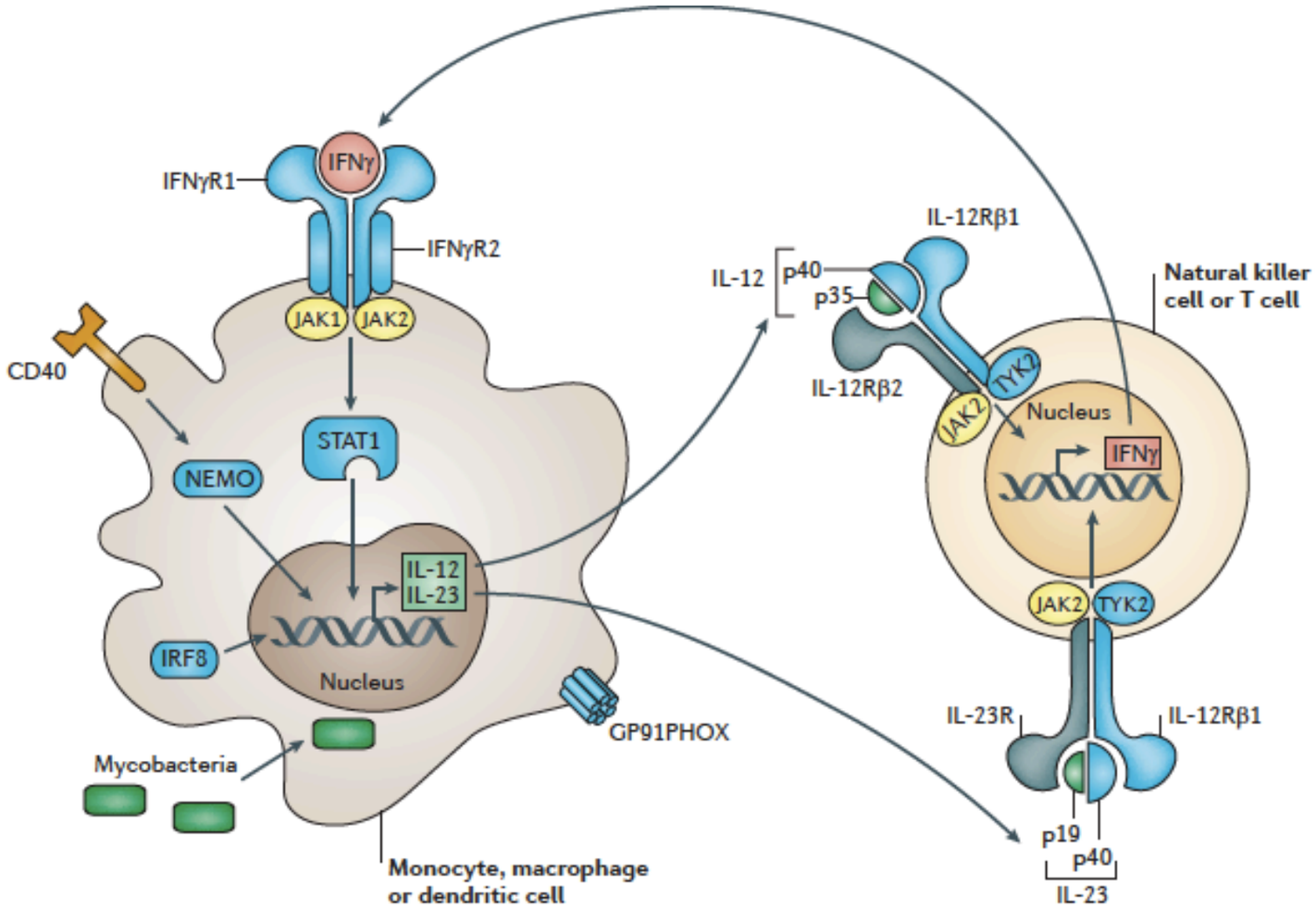
**NECROSE DANO TECIDUAL GRAVE**

# PID e bactérias intracel



# Genes & susceptibilidade a Bactérias intracel

| | | | |
|---|---|---|---|
| Mycobacteria | Susceptibility (MSMD) | Impaired IFNγ response | *IFNGR1, IFNGR2, STAT1* |
| | | Impaired IFNγ production | *IL12B, IL12RB1, NEMO* |
| | | Impaired macrophage respiratory burst | *CYBB* |
| | | Impaired differentiation of dendritic cell subgroups | *IRF8* |




*Chapman and Hill, 2012*

# Infecção por parasitas

- ✓ Protozoarios (Leishmania, Plasmodium, Trypanossoma)
- ✓ Helmintas (Schistossoma, Tenia)
- ✓ Adaptados para conviver o hospedeiro (estratégias de evasão da resposta imunológica)
- ✓ Resposta Imunes Variáveis – dependendo do tipo do parasita, e de sua localização.
- ✓ Maioria das infecçoes è cronica (fraca imunidade inata; parasita escapa da imunidade adaptativa)
- ✓ P. intracelulares, podendo estar hospedados no citoplasma da célula ou em vesículas especializadas
- ✓ *Coincidentemente, não existem vacinas atualmente que apresentem boa eficácia no combate a NENHUM parasita.*

# Resposta a helmintos

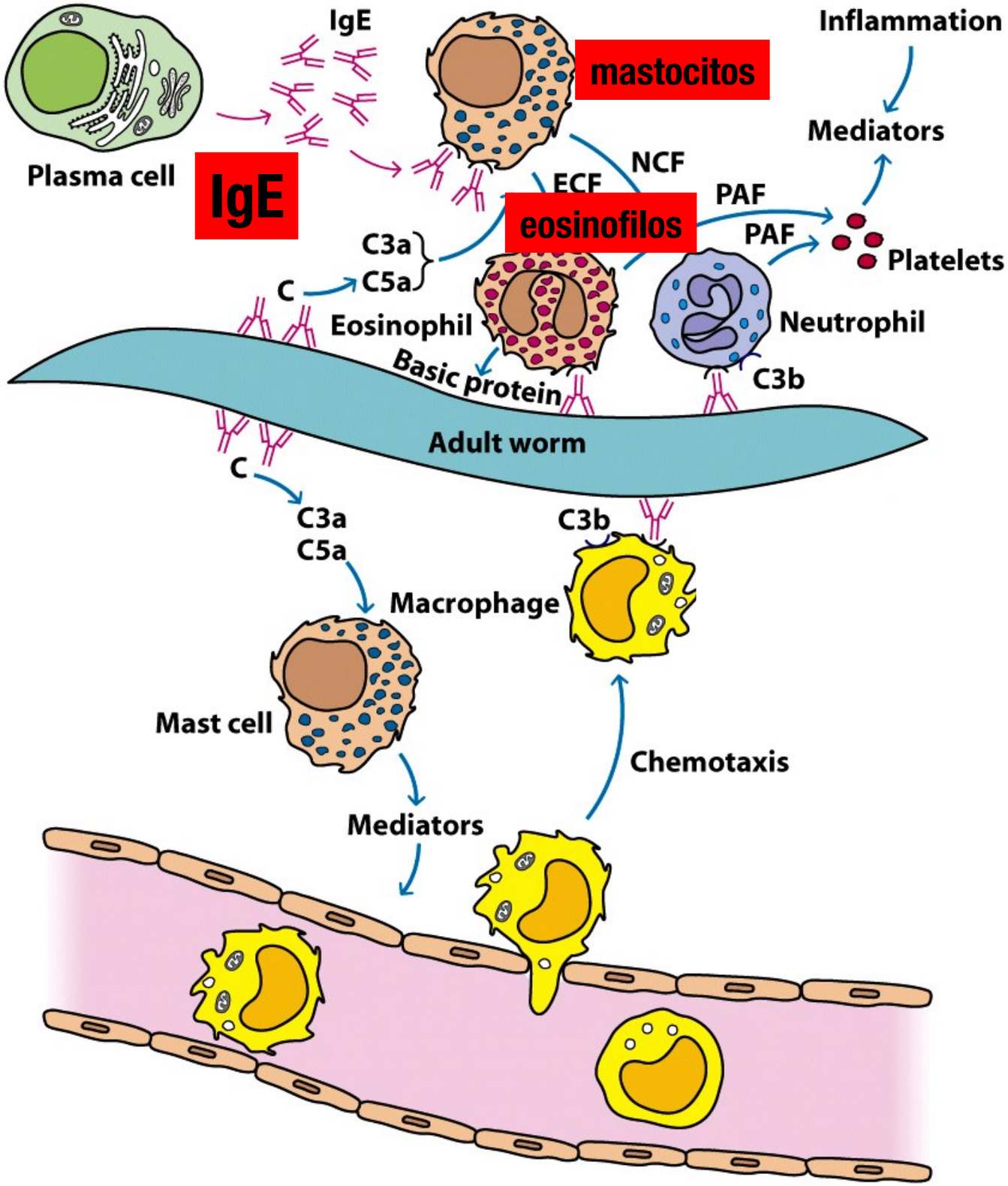
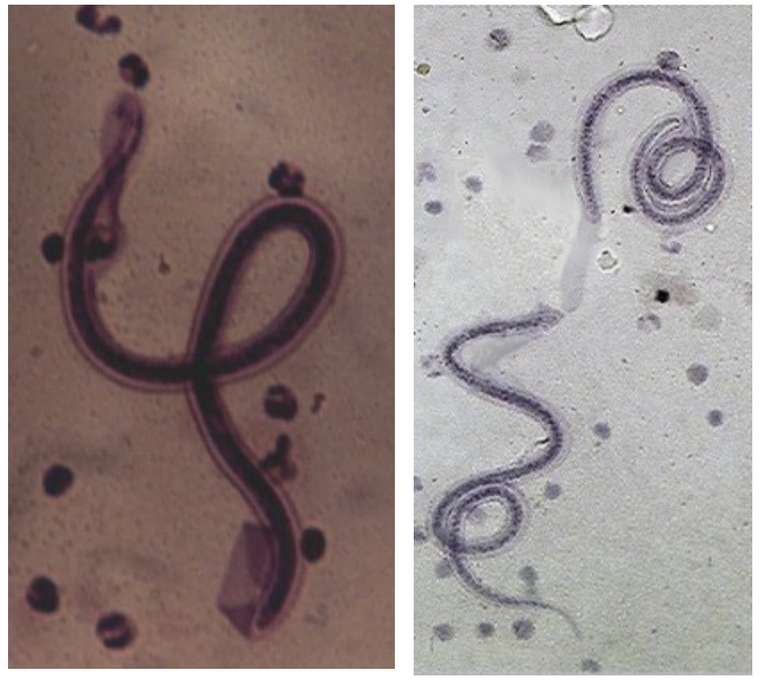
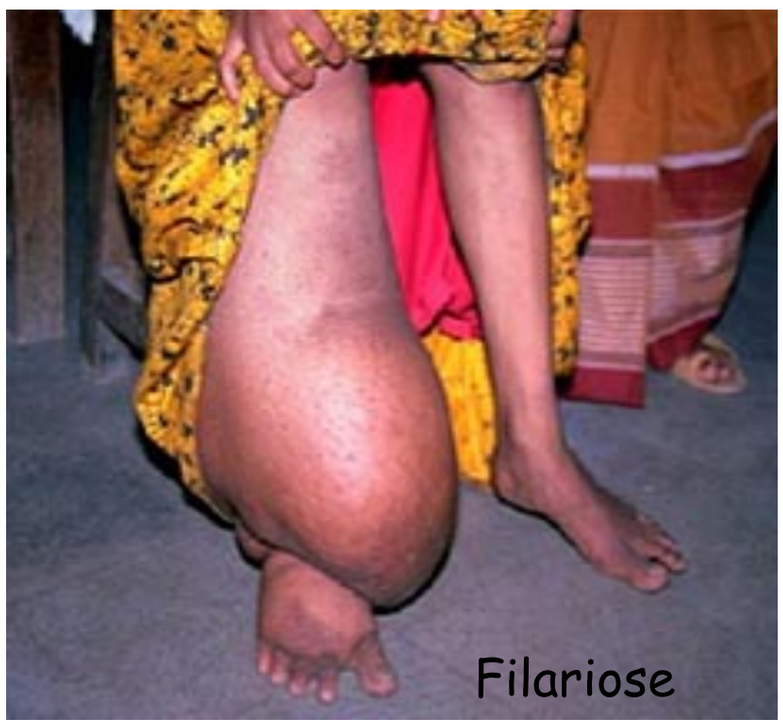



**Figure 18-13**
***Kuby IMMUNOLOGY, Sixth Edition***

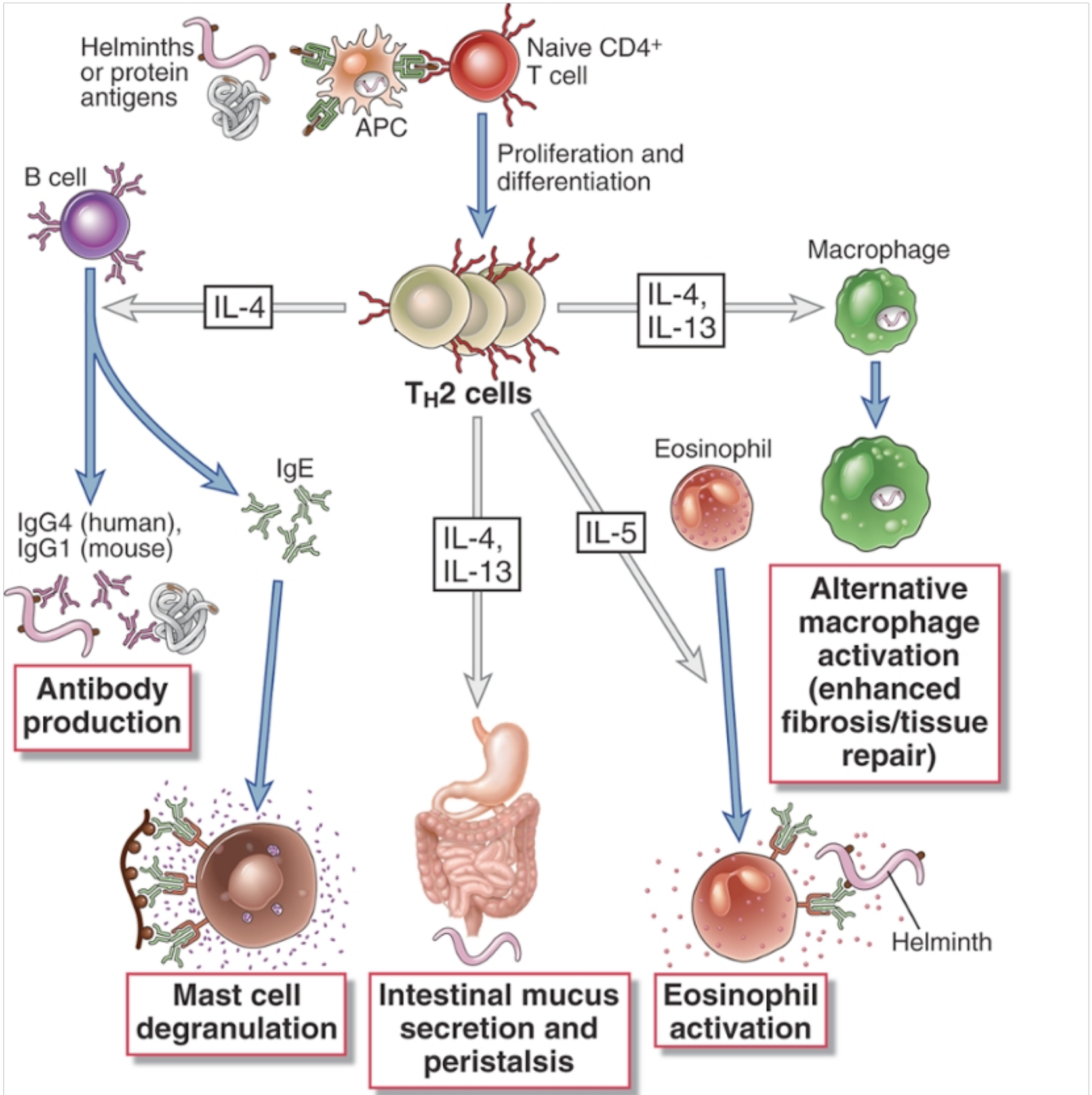



Wuchereria bancrofti



Filariose

# Resposta a helmintos




## Fase Aguda

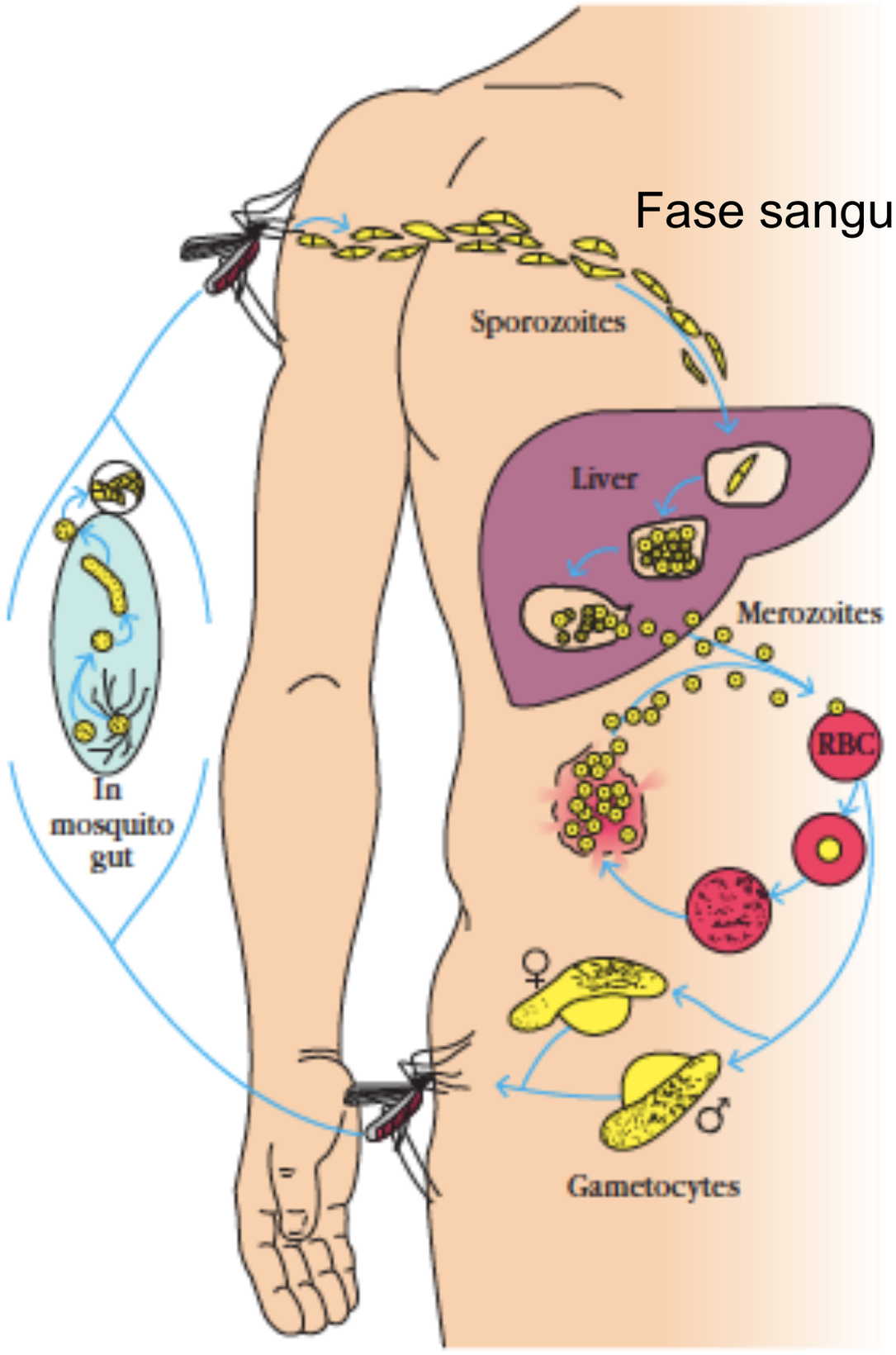
Th2: IgE & eosinófilos mediam inflamação sistêmica
→expulsão do parasito

## Exposição crônica

- Th1 / ativação de macrófagos → granulomas
- Th2 / Aumento da produção de IgE, do número de mastócitos e eosinófilos ativados → inflamação

# Resposta a protozoarios

*P. falciparum*

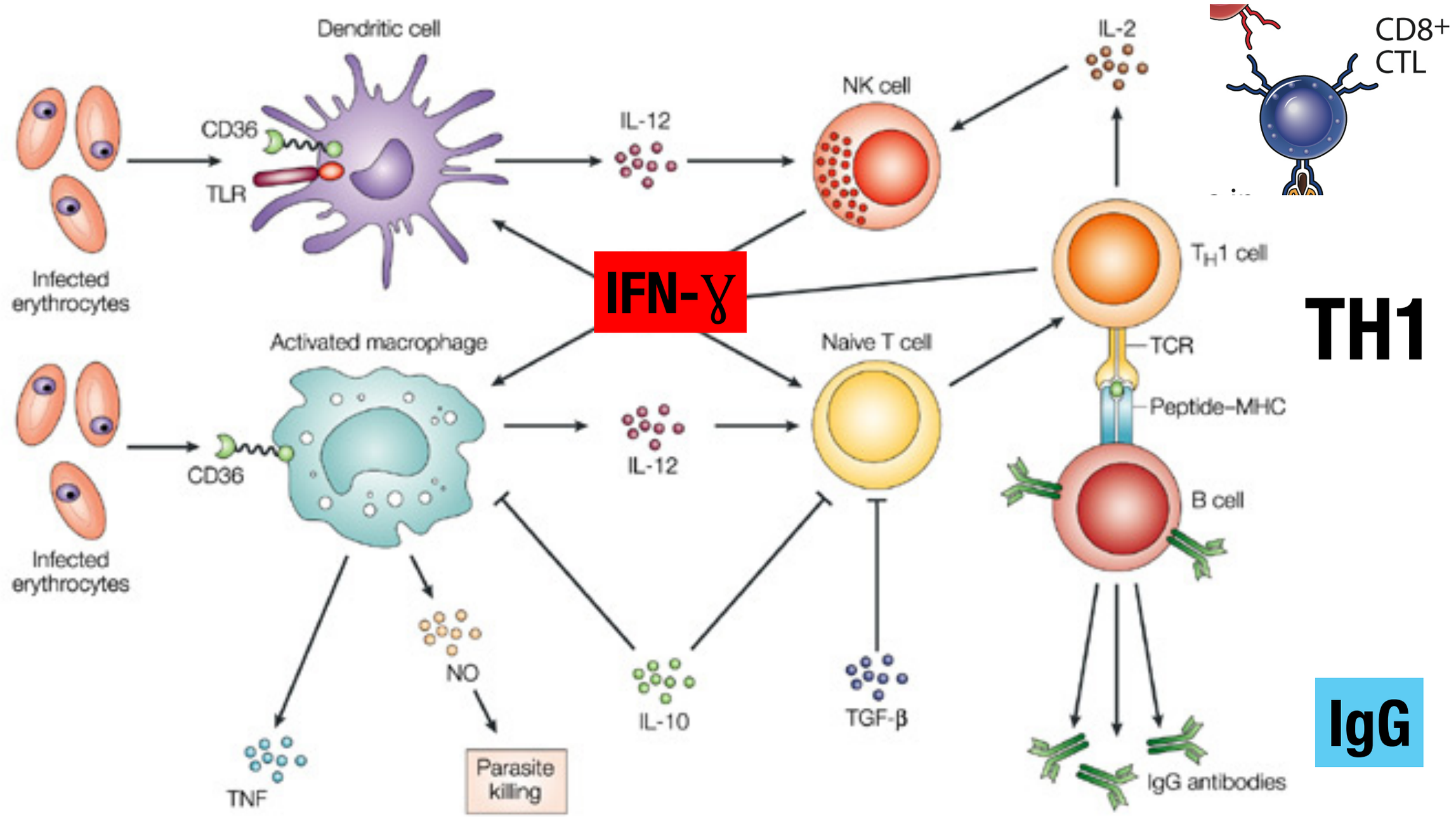



Fase sanguinea

Fase hepatica

Fase eritroblasto

# Resposta a *P.falciparum*

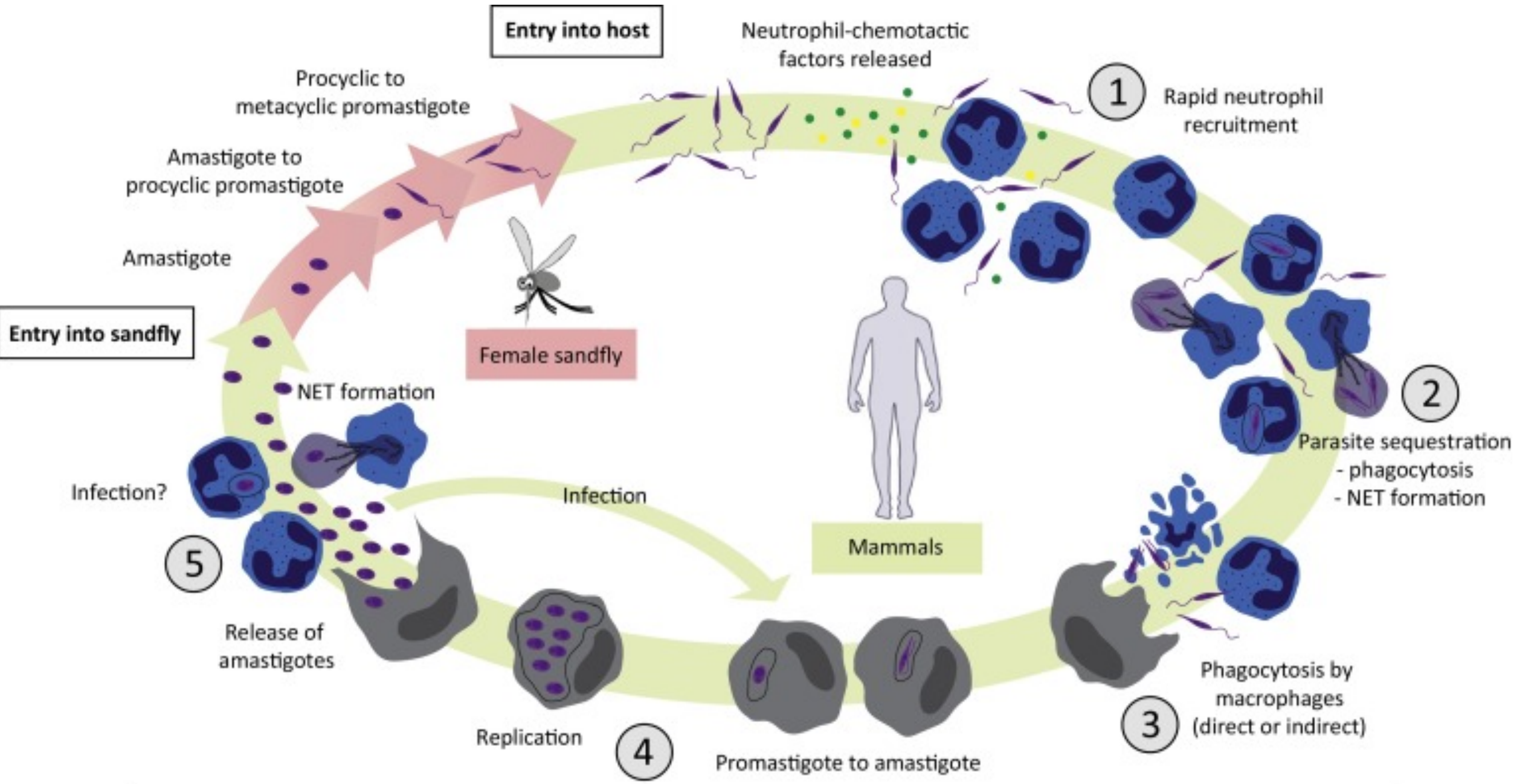



Inibiçao infeccao eritrocitos
Clearance eritrocitos infectados

# Resposta a protozoarios

*Leishmania spp*

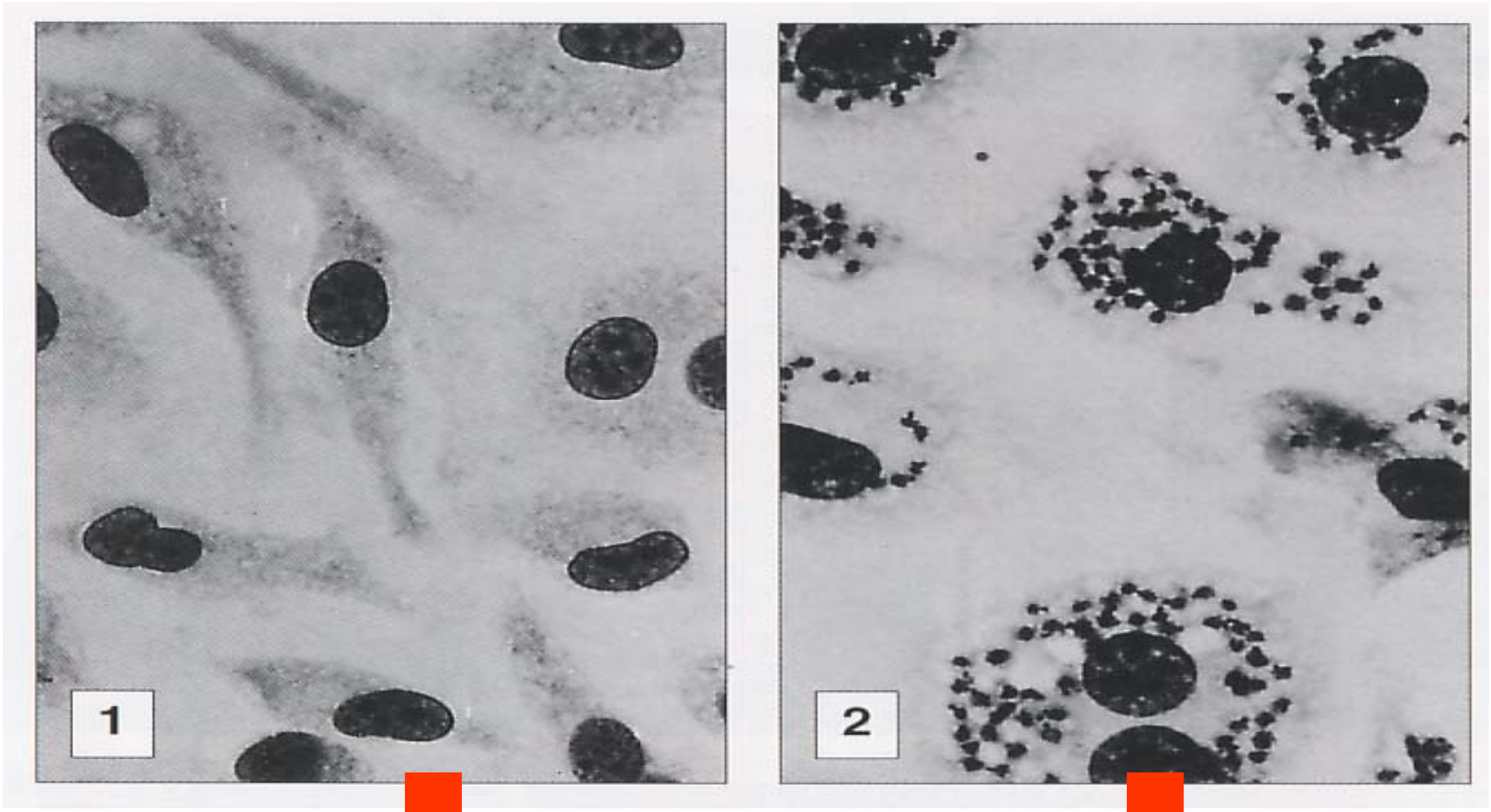
Fase sanguinea




Fase intracelular (fagocitos)

# Resposta a *Leishmania spp*

## Parasitas intracelulares: imunidade celular (TH1)



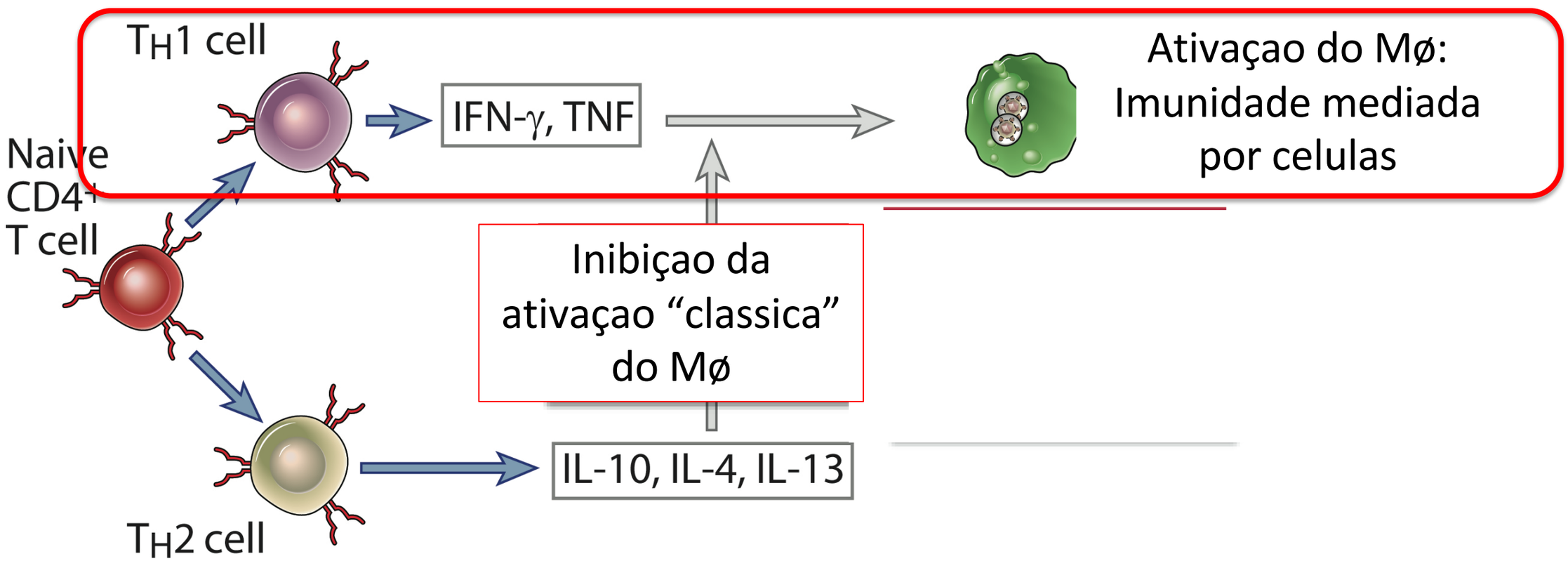

*Macrófagos infectados com L. Donovani e tratados* com IFN-γ

Macrófagos crescem *L. Donovani em* meio sem IFN-γ

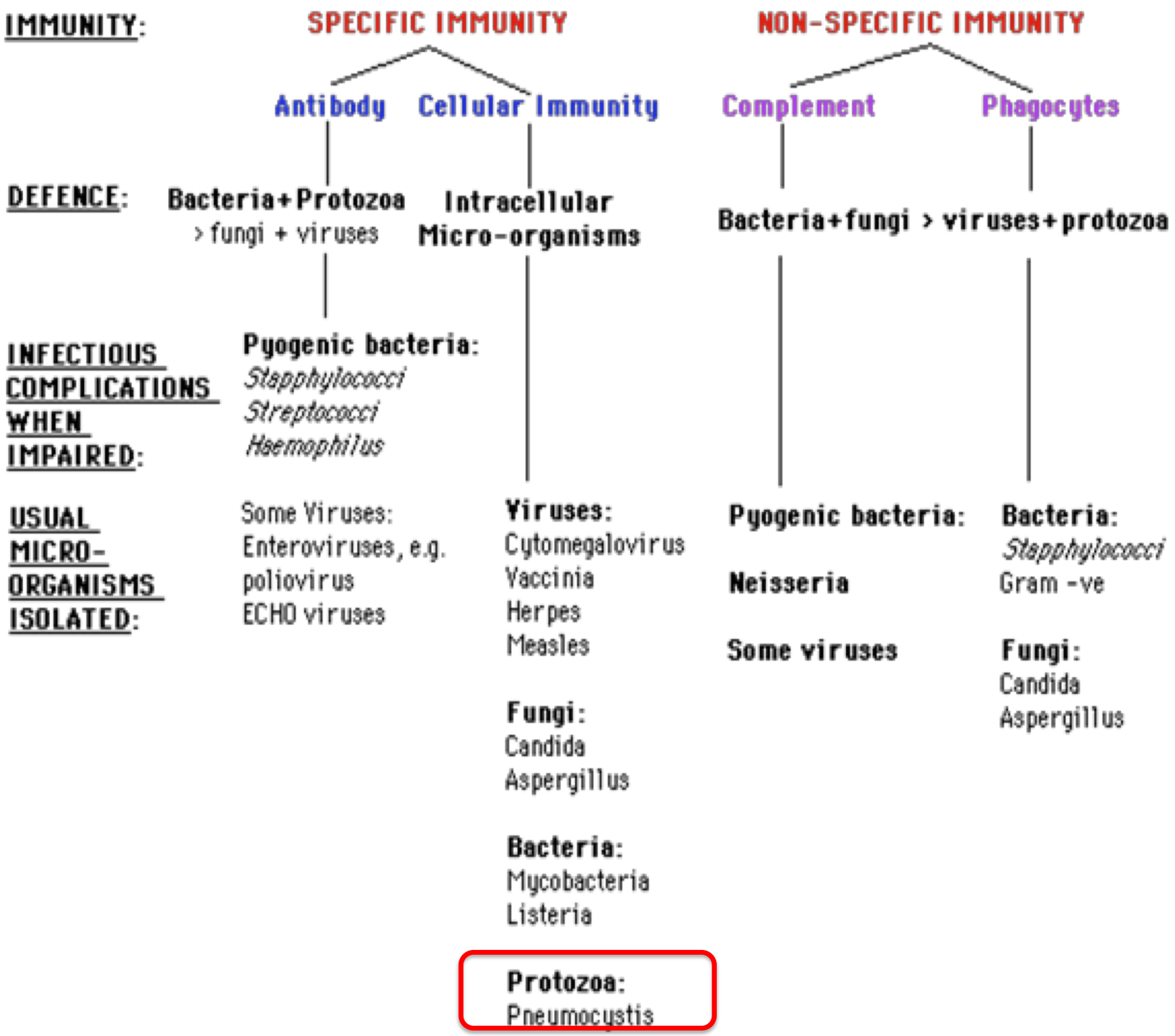
# Resposta a patogenos intracel

Desfecho depende da cepa mas tbm do hospedeiro!!

| Infection | Response | | Outcome |
|---|---|---|---|
| Leishmania major | Most mouse strains: $T_H1$ | ⇒ | Recovery |
| | BALB/c mice: $T_H2$ | ⇒ | Disseminated infection |
| Mycobacterium leprae | Some patients: $T_H1$ | ⇒ | Tuberculoid leprosy |
| | Some patients: Defective $T_H1$ or dominant $T_H2$ | ⇒ | Lepromatous leprosy (high bacterial count) |



# PID e Protozoario



# Infecção por Virus

- Intracelulares obrigatorios que utilizam componentes do hospedeiro para replicar e disseminar-se
- Utilizam receptores celulares para infetar (geralmente celula-especificos)

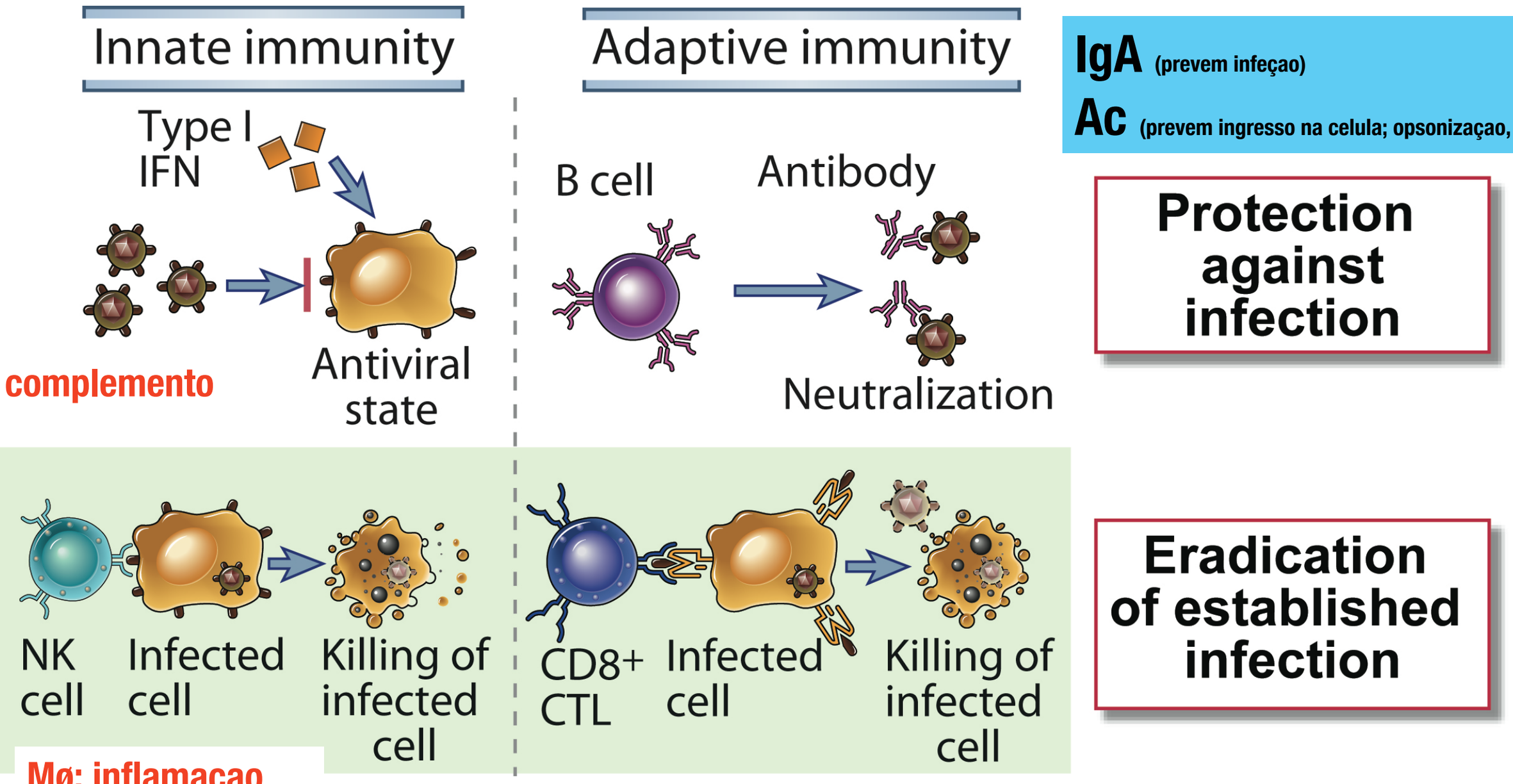
Patogenicidade:

-Citoliticos → lesao tecidual (…)

-Subversao da funçao celular (…)

| Microbe | Examples of Human Diseases | Mechanisms of Pathogenicity |
|---|---|---|
| **Viruses** | | |
| Polio | Poliomyelitis | Inhibits host cell protein synthesis (tropism for motor neurons in the anterior horn of the spinal cord) |
| Influenza | Influenza pneumonia | Inhibits host cell protein synthesis (tropism for peripheral nerves) |
| Rabies | Rabies encephalitis | Inhibits host cell protein synthesis (tropism for ciliated peripheral nerves) |
| Herpes simplex | Various herpes infections (skin, systemic) | Inhibits host cell protein synthesis; functional impairment of immune cells |
| Hepatitis B | Viral hepatitis | Host CTL response to infected hepatocytes |
| Epstein-Barr virus | Infectious mononucleosis; B cell proliferation, lymphomas | Acute infection: cell lysis (tropism for B lymphocytes)<br>Latent infection: stimulates B cell proliferation |
| Human immunodeficiency virus (HIV) | Acquired immunodeficiency syndrome (AIDS) | Multiple: killing of $CD4^+$ T cells, functional impairment of immune cells (see Chapter 20) |

# Resposta a Virus



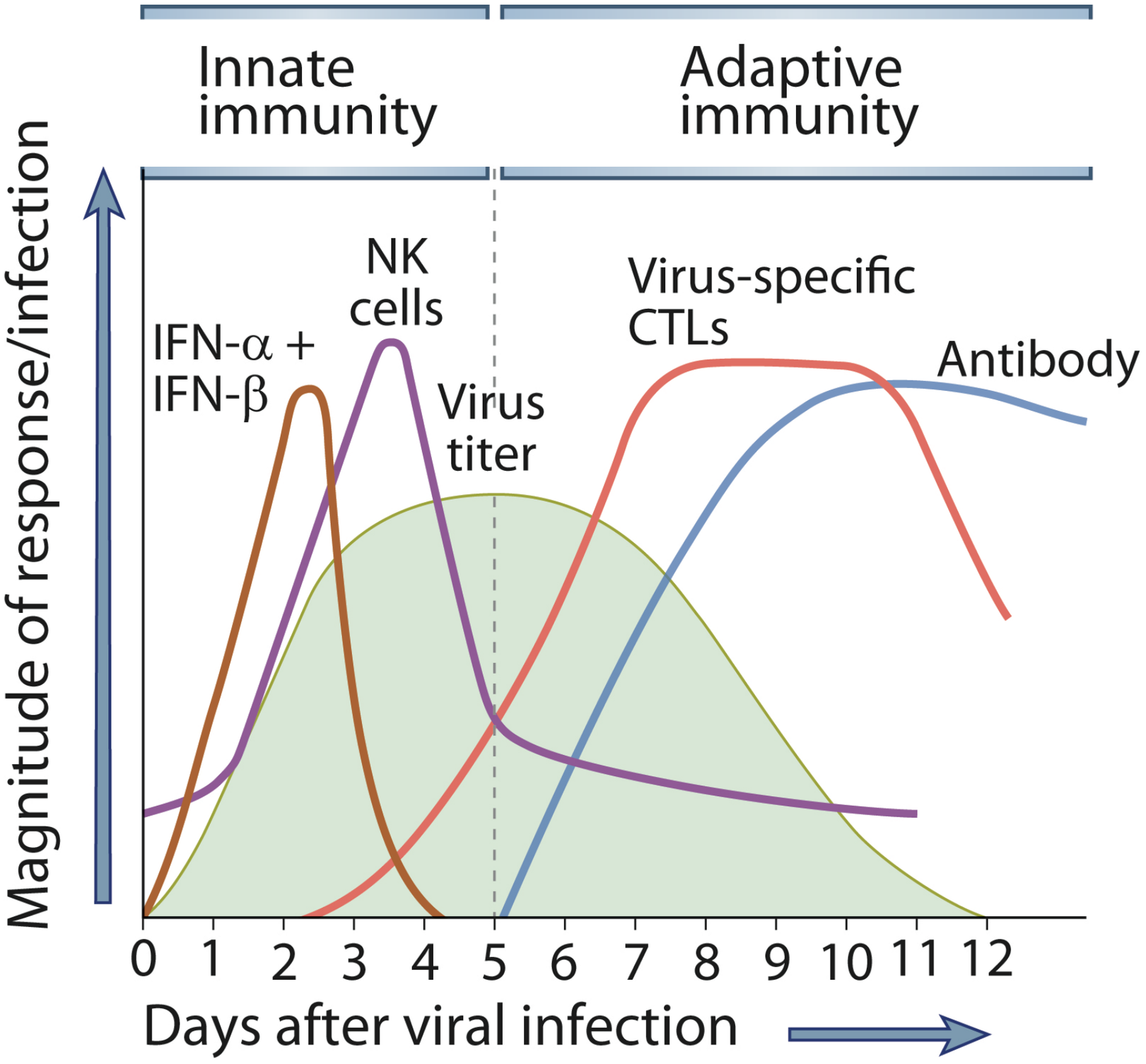

**IgA** (prevem infeçao)

**Ac** (prevem ingresso na celula; opsonizaçao, ADCC)

**Protection against infection**

**Eradication of established infection**

# Resposta a Virus



# Virus e vacina

Quase sempre a imunidade protetora è humoral

| Doença | Vacina | Mecanismo de imunidade protetora |
|---|---|---|
| Polio | Poliovirus atenuado oral | Neutralizaçao do virus por IgA de mucosa |
| Hepatite A ou B | Proteinas recombinantes do envelope viral | Neutralizaçao do virus por IgG sistemicos |
| Influenza | Virus inativado | Neutralizaçao do virus por IgA |
| HPV-16/18/45 | DNA recombinante | Neutralizaçao do virus por IgA |
| HIV-1 | ?????? | Humoral e celulo-mediado (CTL)? |

# PID e Virus

**IMMUNITY:**

**SPECIFIC IMMUNITY**

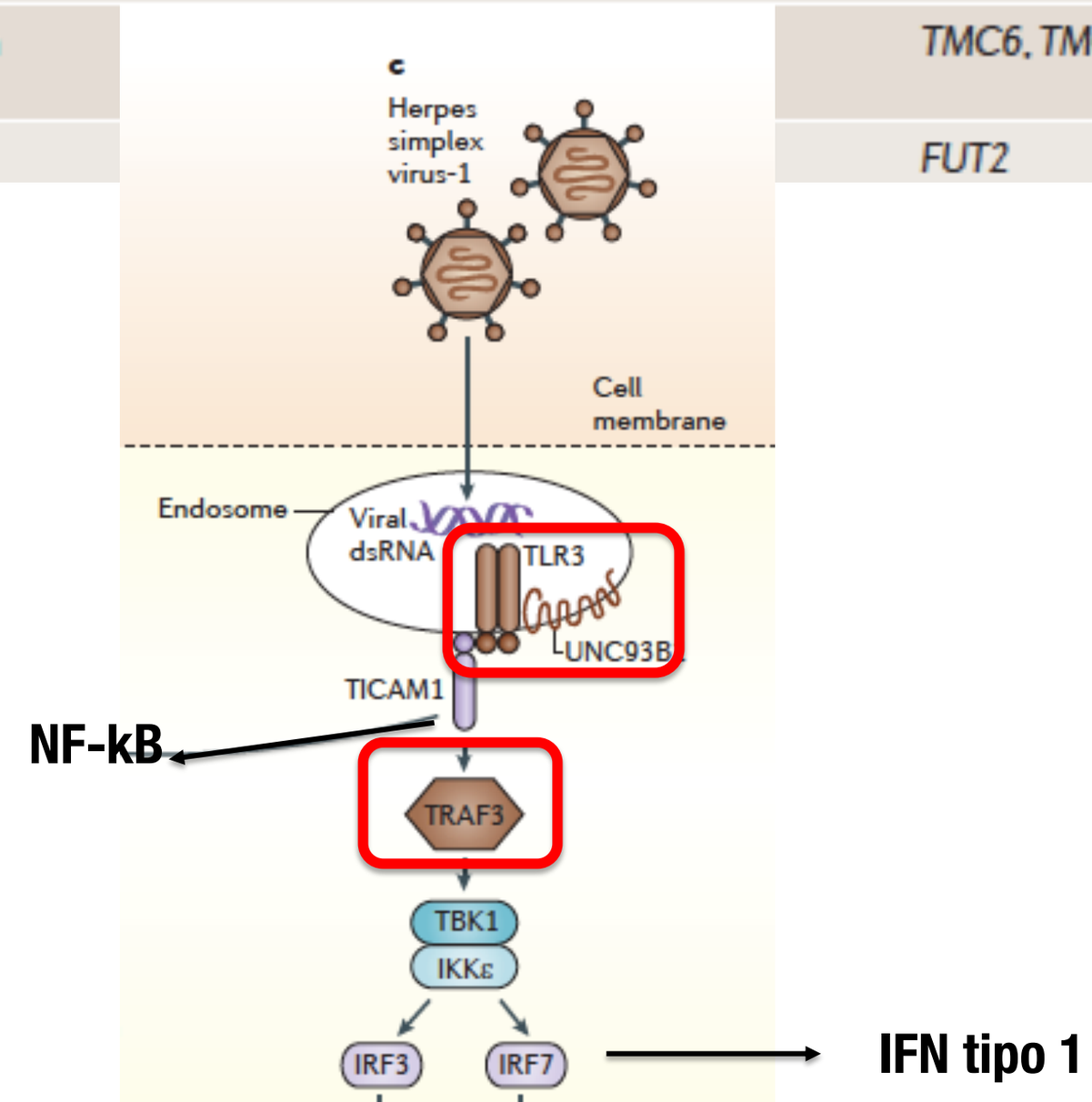
- **Antibody**
  - **DEFENCE:** Bacteria+Protozoa > fungi + viruses
  - **INFECTIOUS COMPLICATIONS WHEN IMPAIRED:** Pyogenic bacteria: *Staphylococci* *Streptococci* *Haemophilus*
  - **USUAL MICRO-ORGANISMS ISOLATED:** Some Viruses: Enteroviruses, e.g. poliovirus ECHO viruses
- **Cellular Immunity**
  - **DEFENCE:** Intracellular Micro-organisms
  - **USUAL MICRO-ORGANISMS ISOLATED:**
    - **Viruses:** Cytomegalovirus Vaccinia Herpes Measles
    - **Fungi:** Candida Aspergillus
    - **Bacteria:** Mycobacteria Listeria
    - **Protozoa:** Pneumocystis

**NON-SPECIFIC IMMUNITY**

- **Complement**
- **Phagocytes**
  - **DEFENCE:** Bacteria+fungi > viruses+protozoa
  - **USUAL MICRO-ORGANISMS ISOLATED:**
    - **Pyogenic bacteria:** **Neisseria** **Some viruses**
    - **Bacteria:** *Staphylococci* Gram -ve
    - **Fungi:** Candida Aspergillus

# Genes & susceptibilidade a Virus

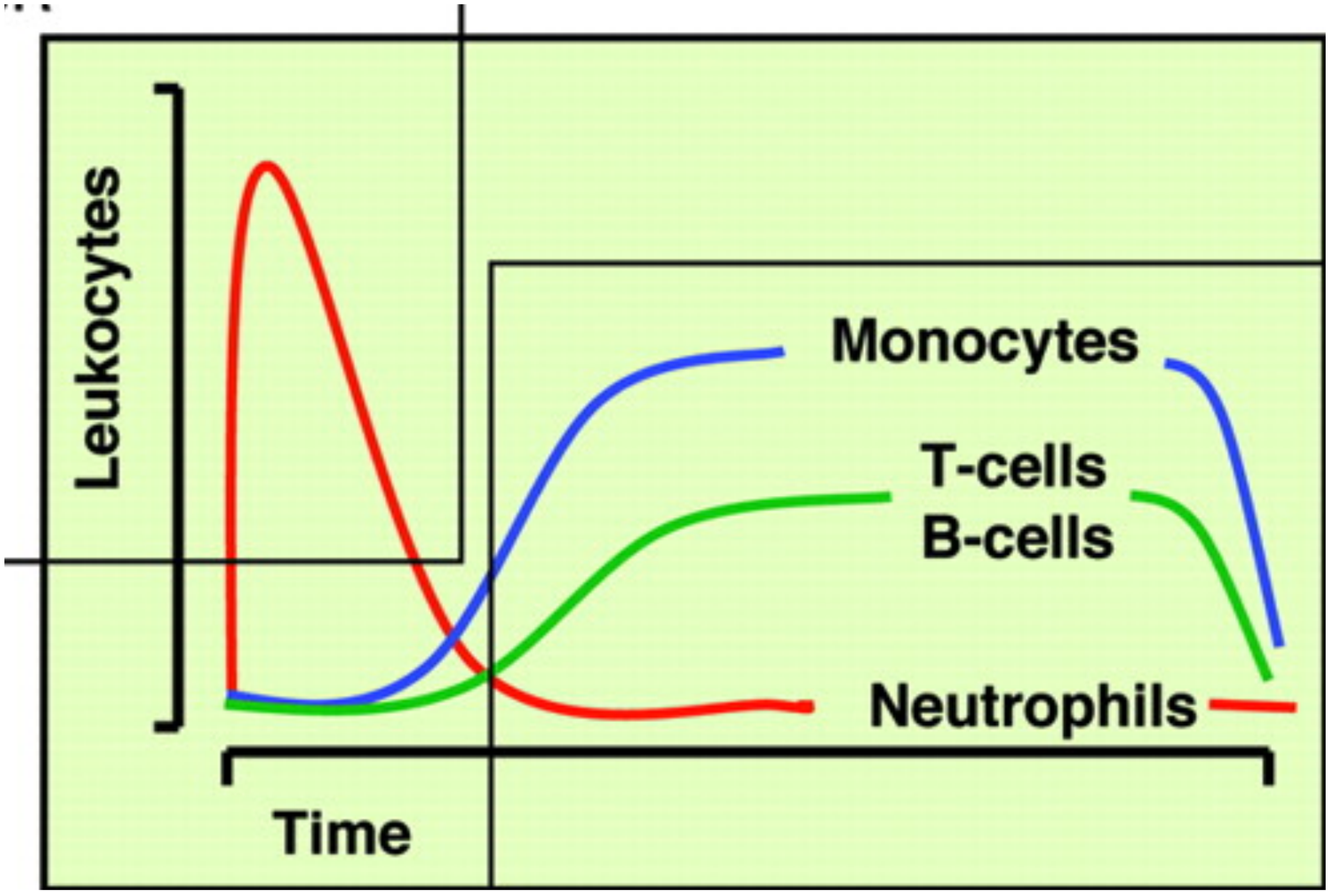
| | | | |
|---|---|---|---|
| HIV-1 | Resistance | Absence of coreceptor for pathogen | *CCR5* |
| HSV-1 | Susceptibility to HSV encephalitis | Impaired production of IFNα, IFNβ and/or IFNλ | *UNC93B1* |
| | | | *TLR3* |
| | | | *TRAF3* |
| Human herpesvirus-8 | Classic Kaposi's sarcoma | T cell deficiency | *STIM1* |
| Human papillomaviruses | Epidermodysplasia verruciformis | | *TMC6, TMC8* |
| Norovirus | Resistance | | *FUT2* |




*Chapman and Hill, 2012*

# Resoluçao da resposta imune

Resoluçao da
imunidade inata




Resoluçao da
imunidade
adaptativa

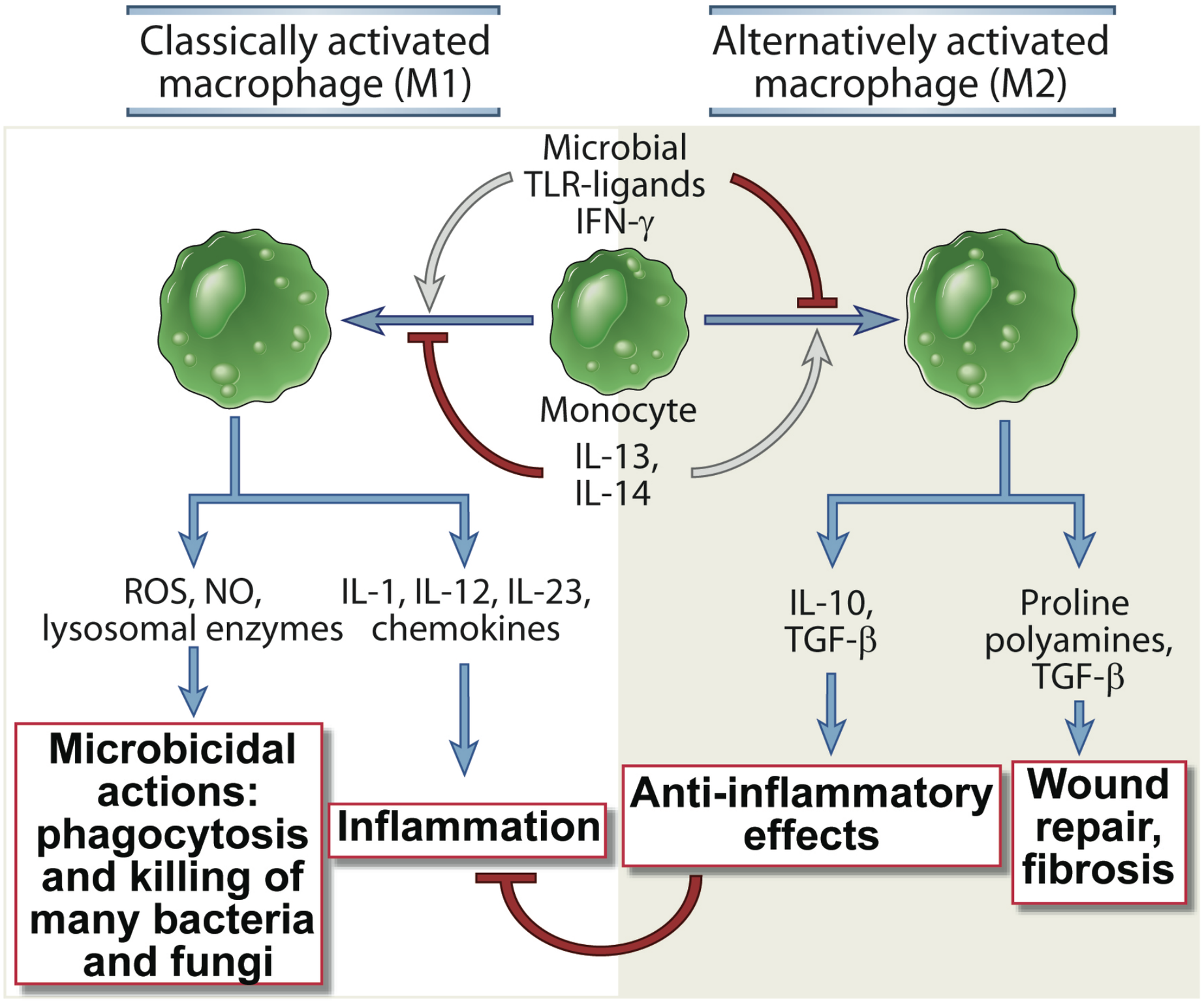
Reparaçao do tecido
e dos vasos

# Resoluçao da resposta imune

**Diferentes mecanismos contribuem pela resoluçao da resposta imune**

1. Eliminaçao do estimulo
2. Supressao ativa atraves da produçao de mediadores anti-inflamatorios (p.ex.: IL-10, TGF-ß, IL-4, NO) ou inibidores dos mediadores pro-inflamatorios (p.ex.:ILRa; sTNFR)
3. Ativaçao e proliferaçao de linfocitos Treg
4. Variaçao das moleculas co-estimul. (↓ CD28, ↑ CTLA-4)
5. Apoptose

# Macrofagos M2 (anti-inflamatorio)

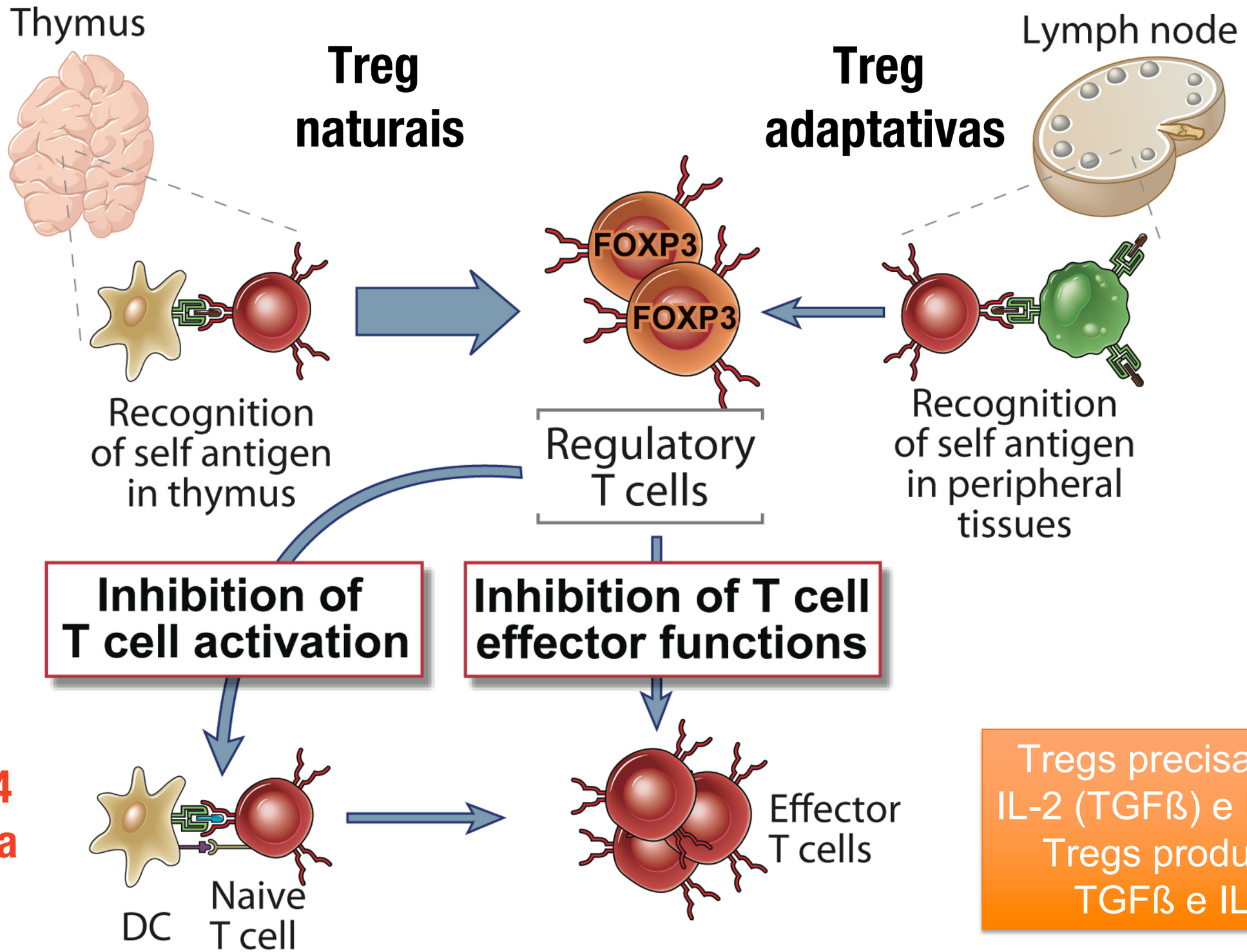



Eliminaçao do estimulo
+ mediadores anti-inflamatorios

M1→M2

Mediadores anti-inflamatorios + fatores de reparo do tecido e dos vasos

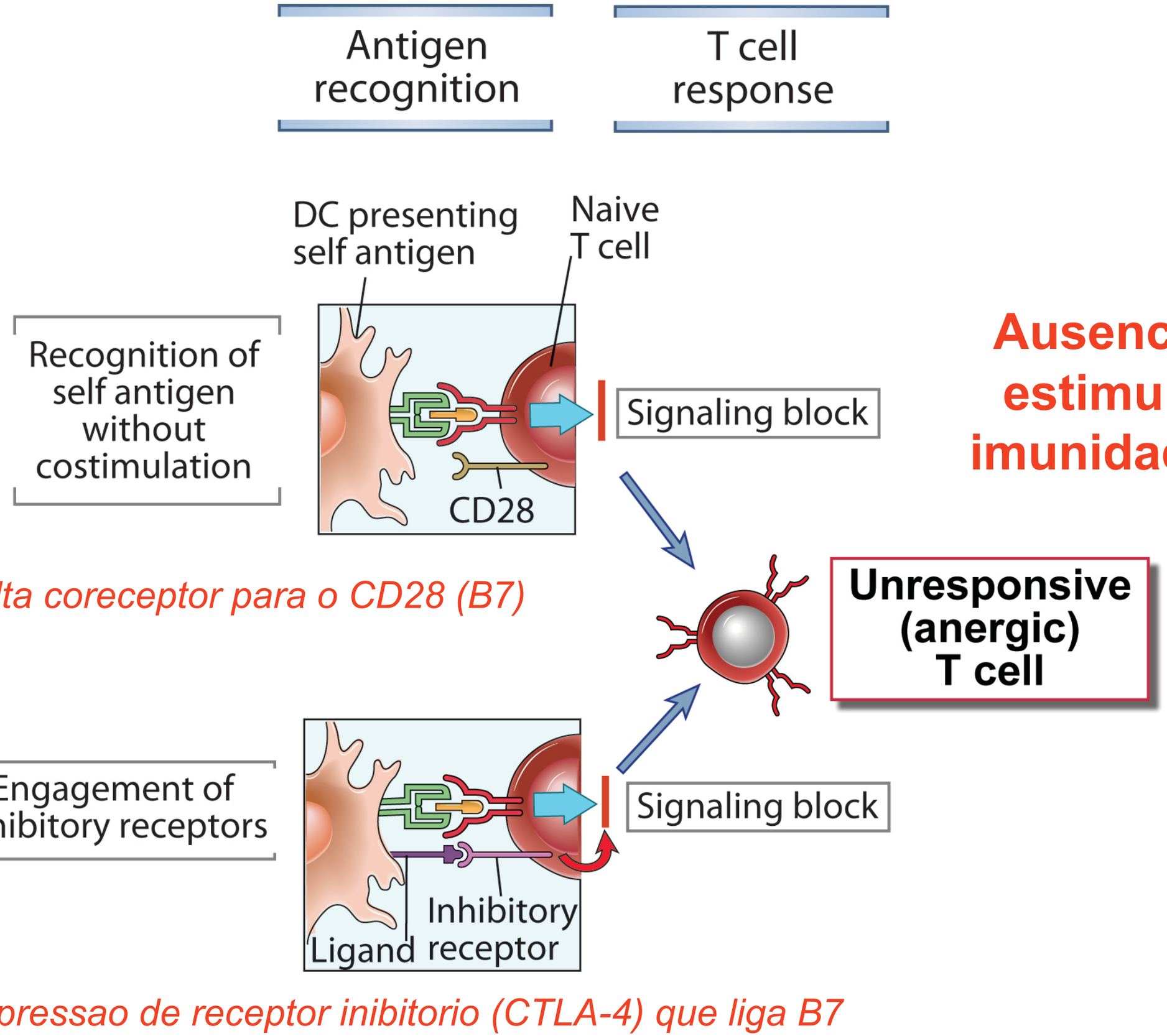
# Linfocitos T reg




**Via CTLA-4 Interfere na sinapse**

Tregs precisam de IL-2 (TGFß) e FOXP3
Tregs produzem TGFß e IL10

# Variaçao de moleculas coestimulatorias



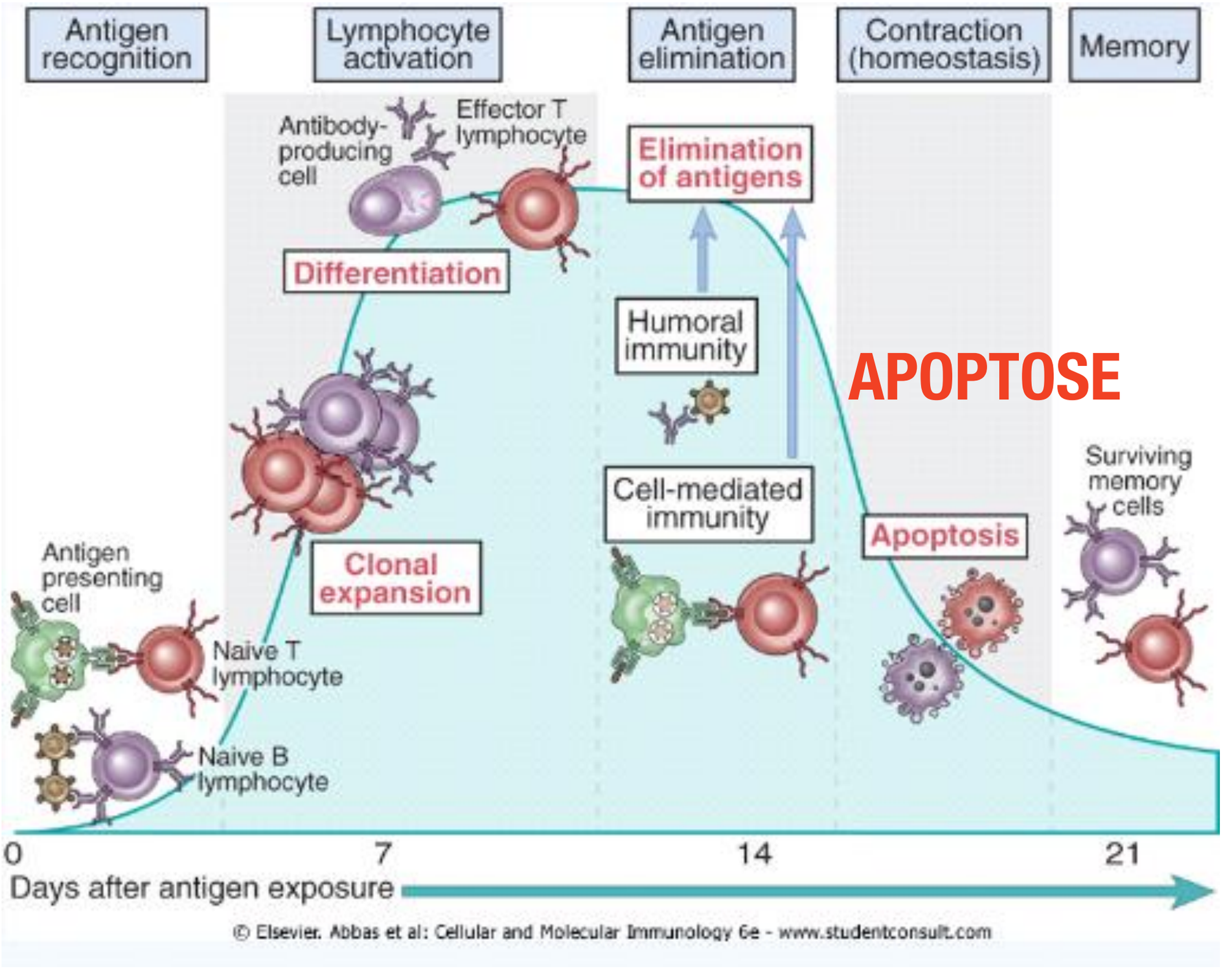

**Ausencia de co-estimulaçao ou imunidade natural**

*Falta coreceptor para o CD28 (B7)*

*Expressao de receptor inibitorio (CTLA-4) que liga B7*

# Contraçao clonal da imunidade adaptativa

**ELIMINAÇAO do Ag**




**APOPTOSE**