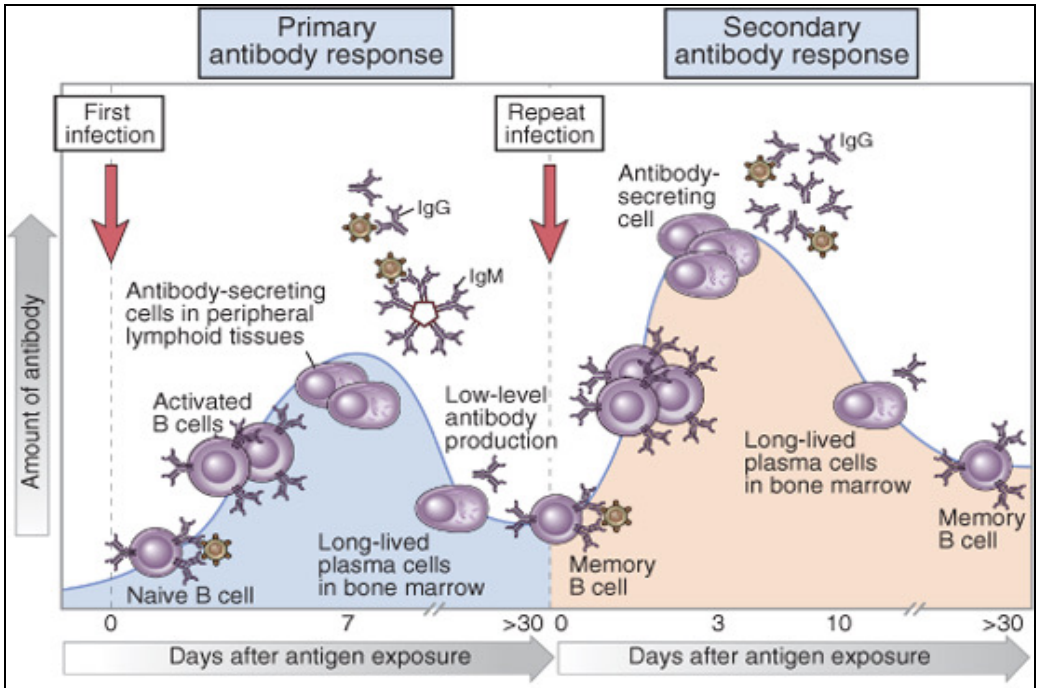
Mecanismos Efetores da Resposta Imune

Parte I- Mecanismos Efetores da Imunidade Humoral

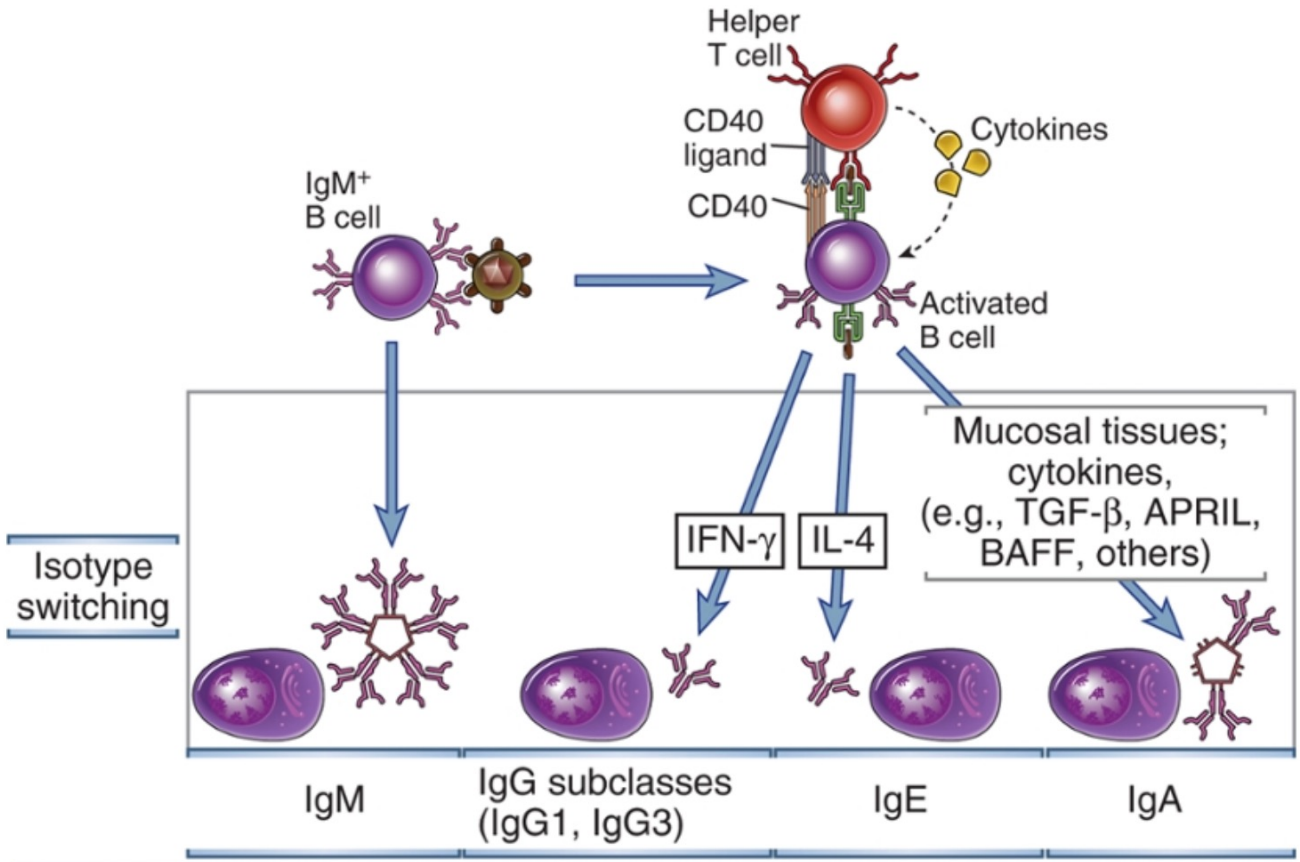
Vera Calich - 2021

Respostas Primária e Secundária da Produção de Anticorpos



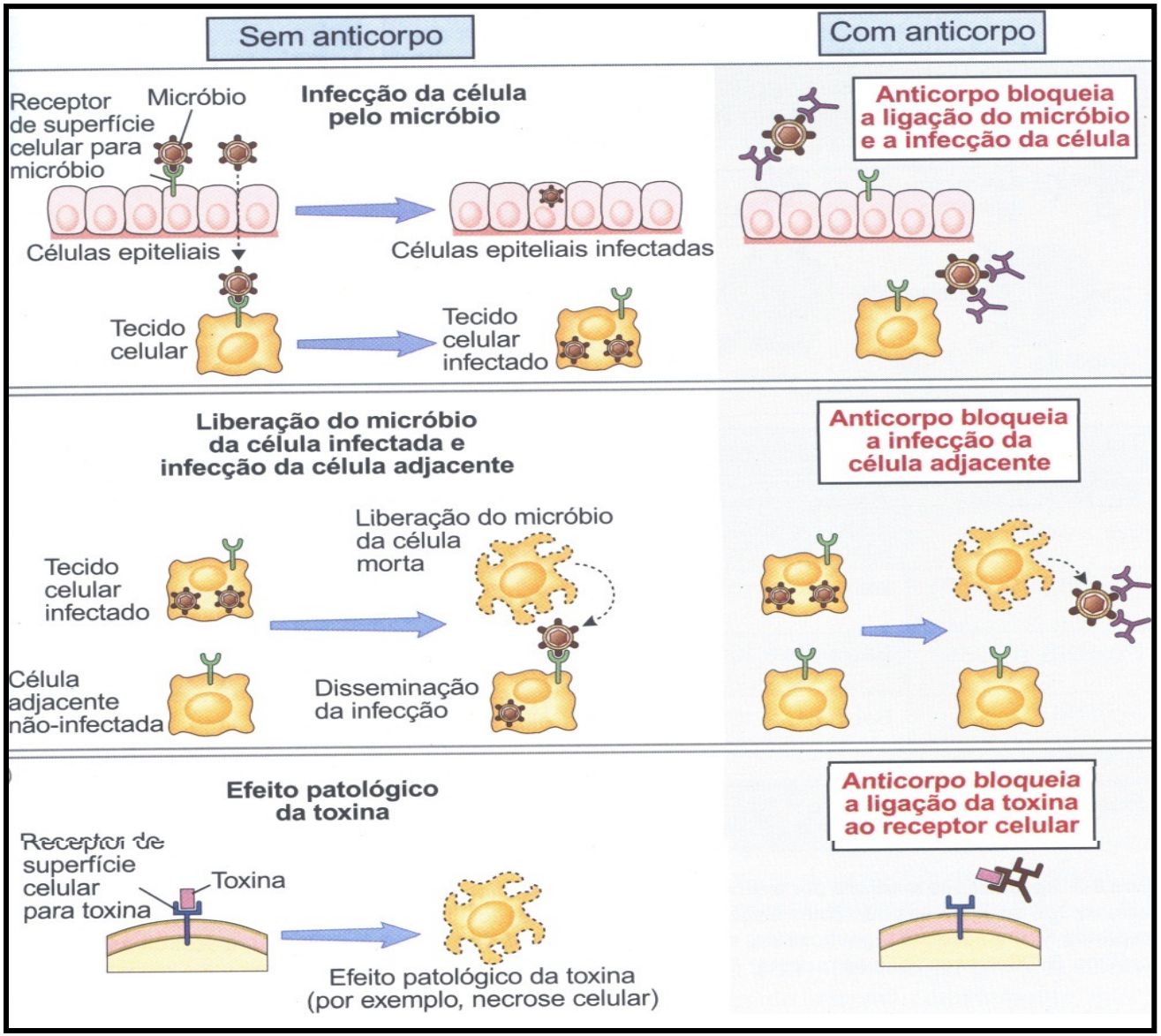
Feature	Primary response	Secondary response
Time lag after immunization	Usually 5–10 days	Usually 1–3 days
Peak response	Smaller	Larger
Antibody isotype	Usually IgM > IgG	Relative increase in IgG and, under certain situations, in IgA or IgE
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)
Induced by	All immunogens	Only protein antigens
Required immunization	Relatively high doses of antigens, optimally with adjuvants (for protein antigens)	Low doses of antigens; adjuvants may not be necessary

Mudança ("switching") de Isótipo ou Classe de Anticorpo
(Influência da Citocina Secretada por Thf)

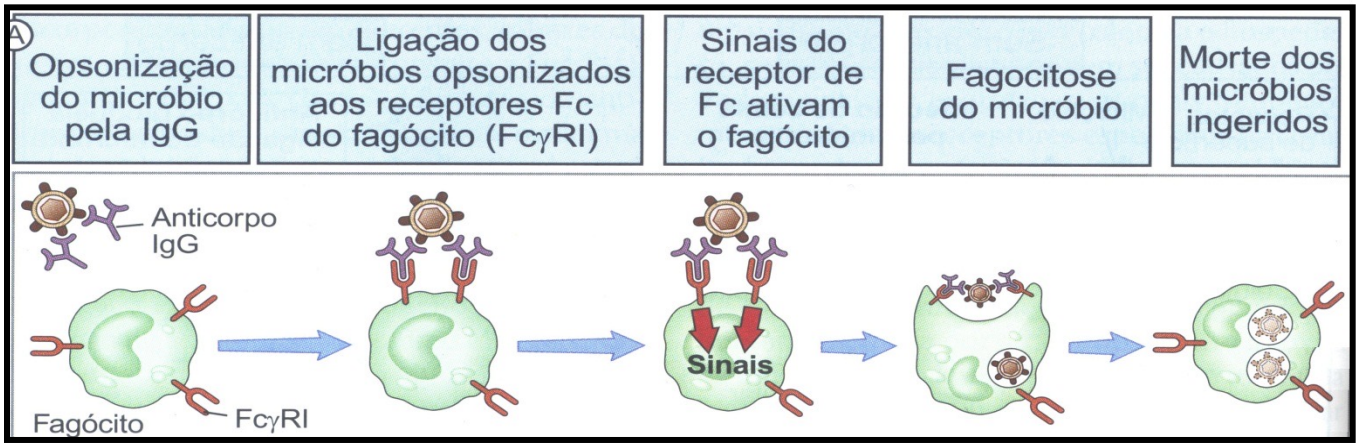


Principal effector functions	Complement activation	Fc receptor-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

Neutralização de micróbios e toxinas pelos anticorpos



Opsonização mediada por Anticorpo e Receptores para Fc em Fagócitos (FcR)



B

Receptor de Fc	Afinidade para Ig	Distribuição celular	Função
FcγRI (CD64)	Alta (K_d ~ 10^{-9} M); liga-se a IgG1 e IgG3; pode-se ligar à IgG monomérica	Macrófagos, neutrófilos; também eosinófilos	Fagocitose; ativação dos fagócitos
FcγRIIA (CD32)	Baixa (K_d > 10^{-7} M)	Macrófagos, neutrófilos; eosinófilos, plaquetas	Fagocitose; ativação celular (ineficiente)
FcγRIIB (CD32)	Baixa (K_d > 10^{-7} M)	Linfócitos B	Inibição por retroalimentação das células B
FcγRIIIA (CD16)	Baixa (K_d > 10^{-6} M)	Células NK	Citotoxicidade celular dependente de anticorpo (ADCC)
FcεRI	Alta (K_d ~ 10^{-10}M); liga-se à IgE monomérica	Mastócitos, basófilos, eosinófilos	Ativação celular (degranulação)

ADCC: “Antibody-Dependent Cellular Cytotoxicity”

- Cels NK: Receptores de baixa afinidade para Fc de IgG

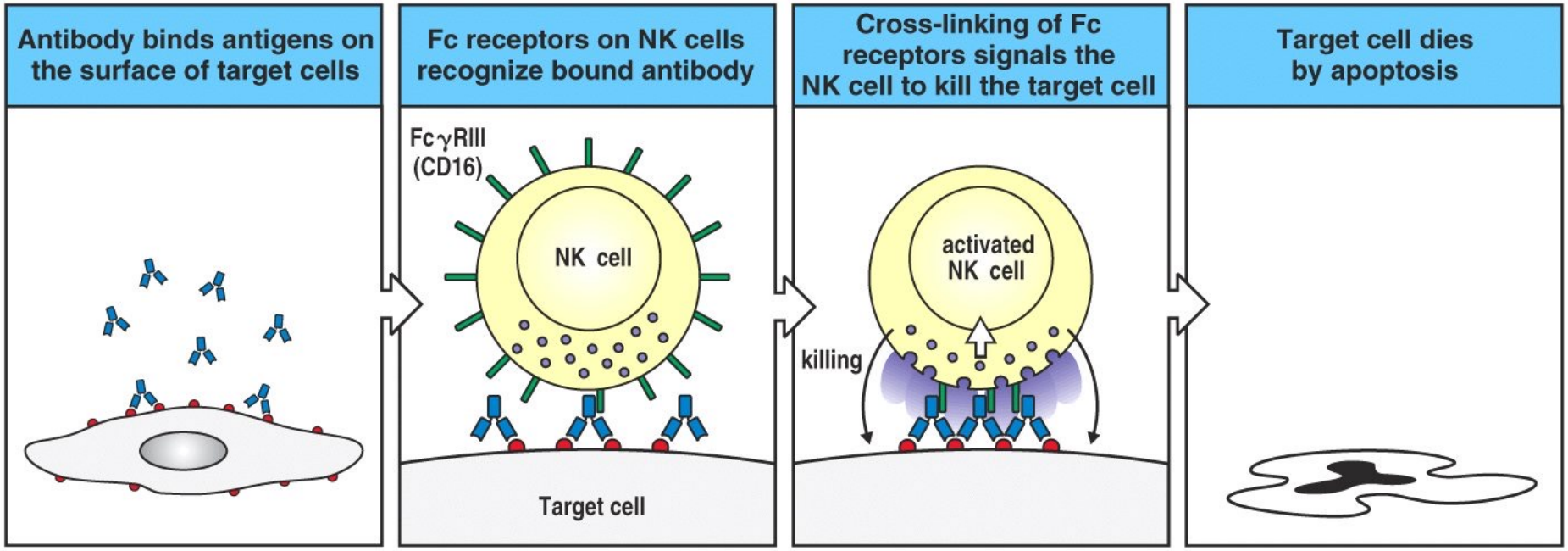
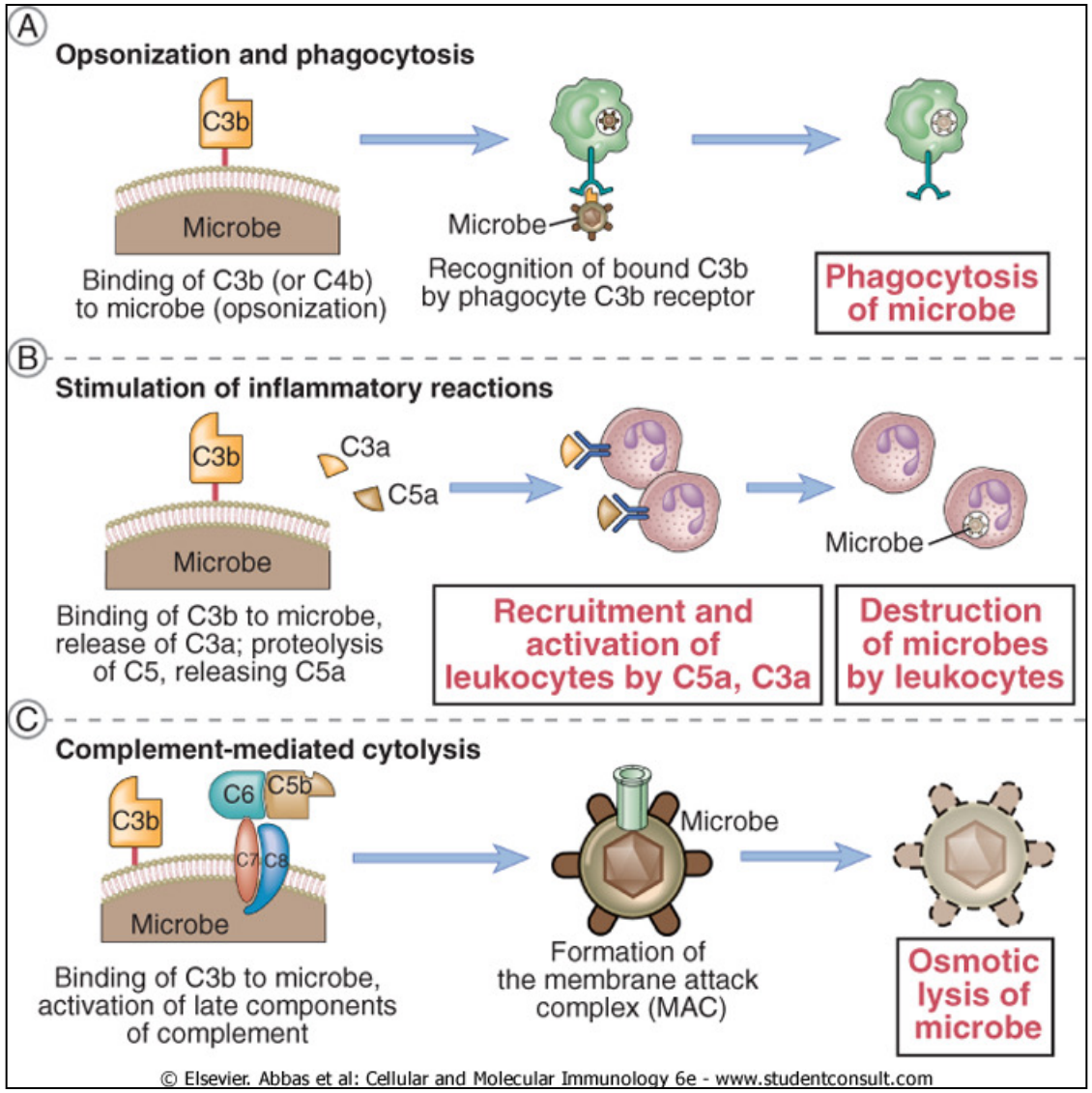


Figure 9-34 Immunobiology, 6/e. (© Garland Science 2005)

A ativação do complemento auxilia na Imunidade Humoral e na eliminação de patógenos extra-celulares



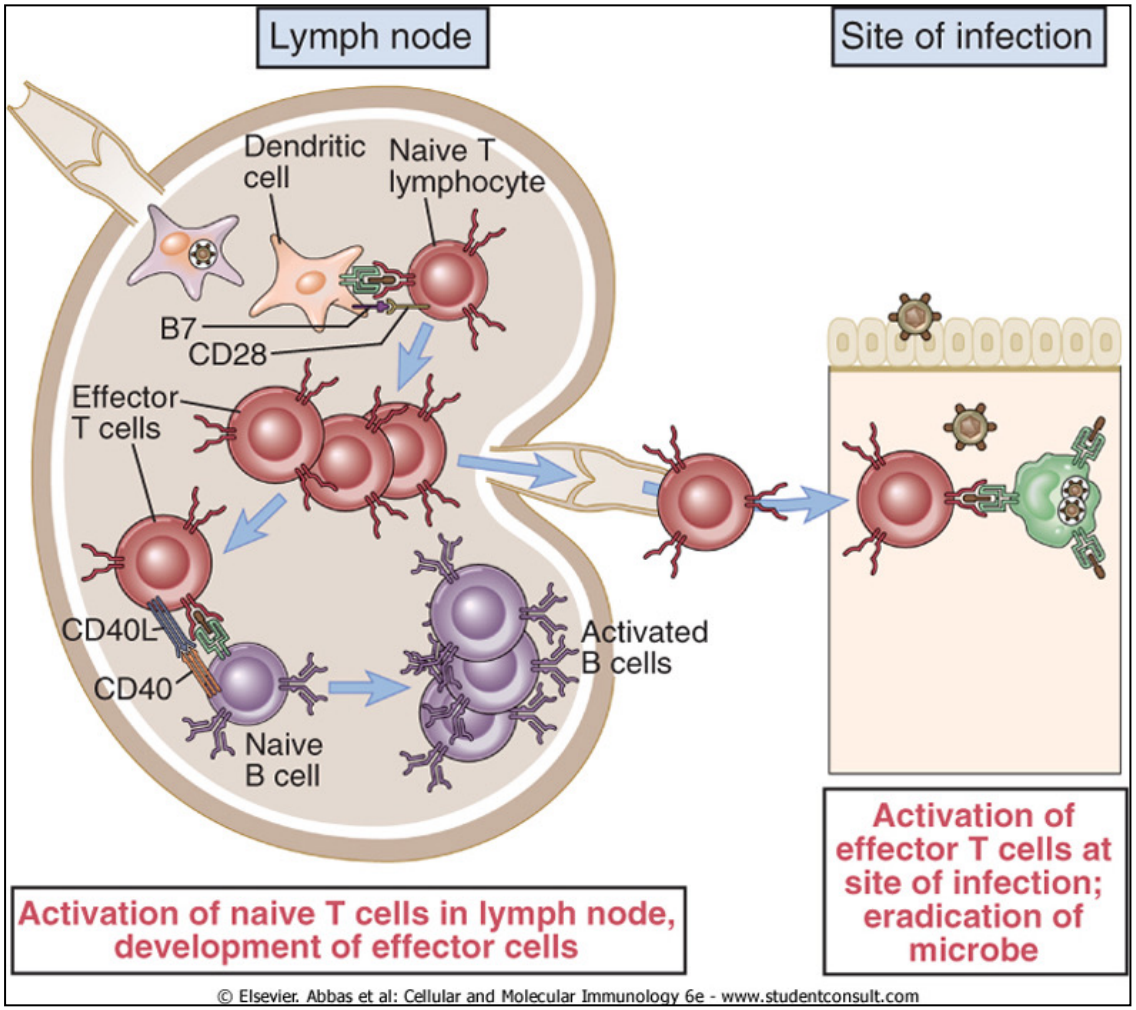
Diferentes Isótipos Têm Diferentes Funções

Antibody Isotope	Isotype-specific effector functions
IgG	Opsonization of antigens for phagocytosis by macrophages and neutrophils Activation of the classical pathway of complement Antibody-dependent cell-mediated cytotoxicity mediated by natural killer cells Neonatal immunity: transfer of maternal antibody across the placenta and gut Feedback inhibition of B cell activation
IgM	Activation of the classical pathway of complement Antigen receptor of naive B lymphocytes*
IgA	Mucosal immunity: secretion of IgA into the lumens of the gastrointestinal and respiratory tracts Activation of complement by the lectin pathway or by the alternative pathway
IgE	Mast cell degranulation (immediate hypersensitivity reactions)
IgD	Antigen receptor of naive B lymphocytes*

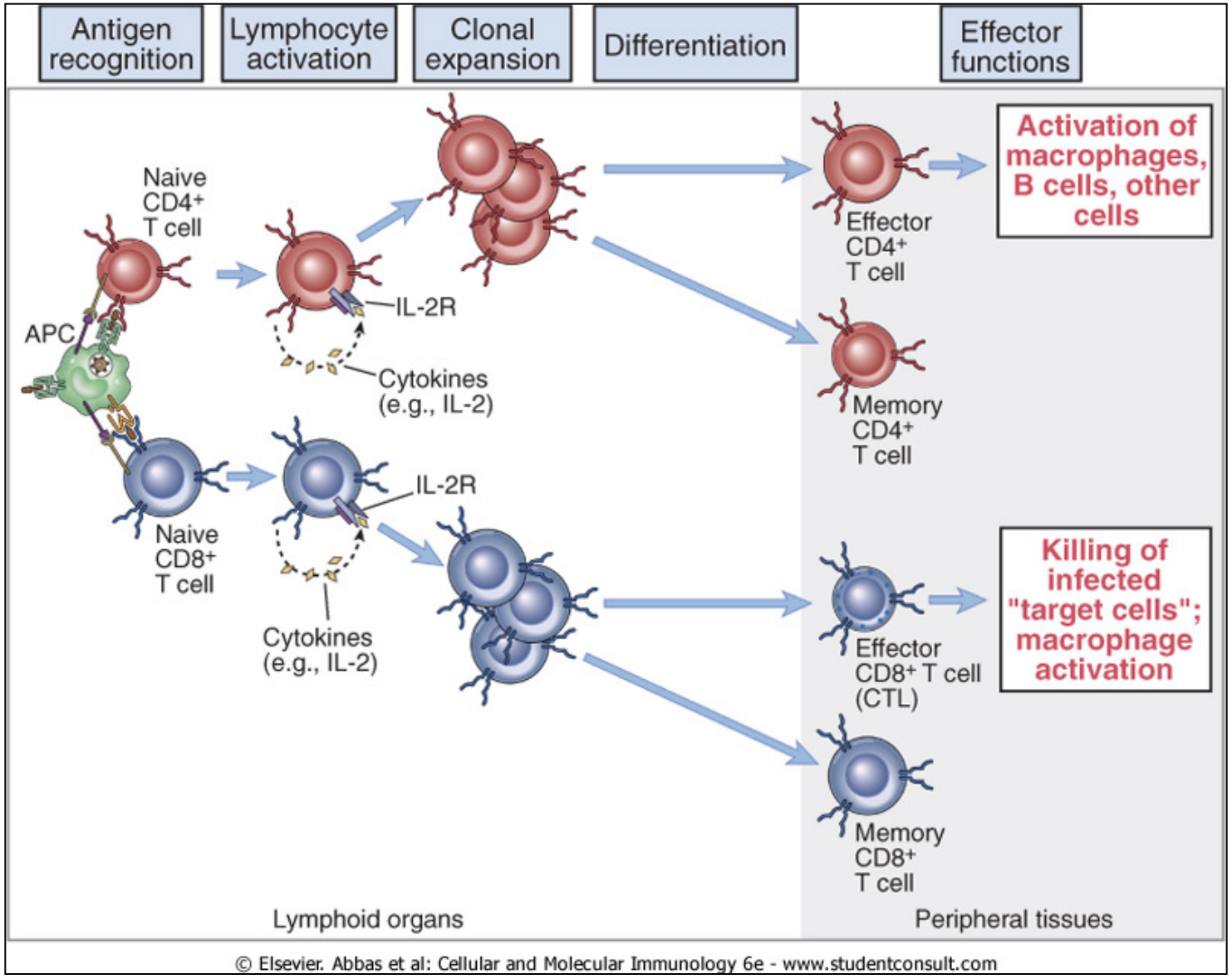
Mecanismos Efetores da Resposta Imune Celular

Vera Calich, 2021

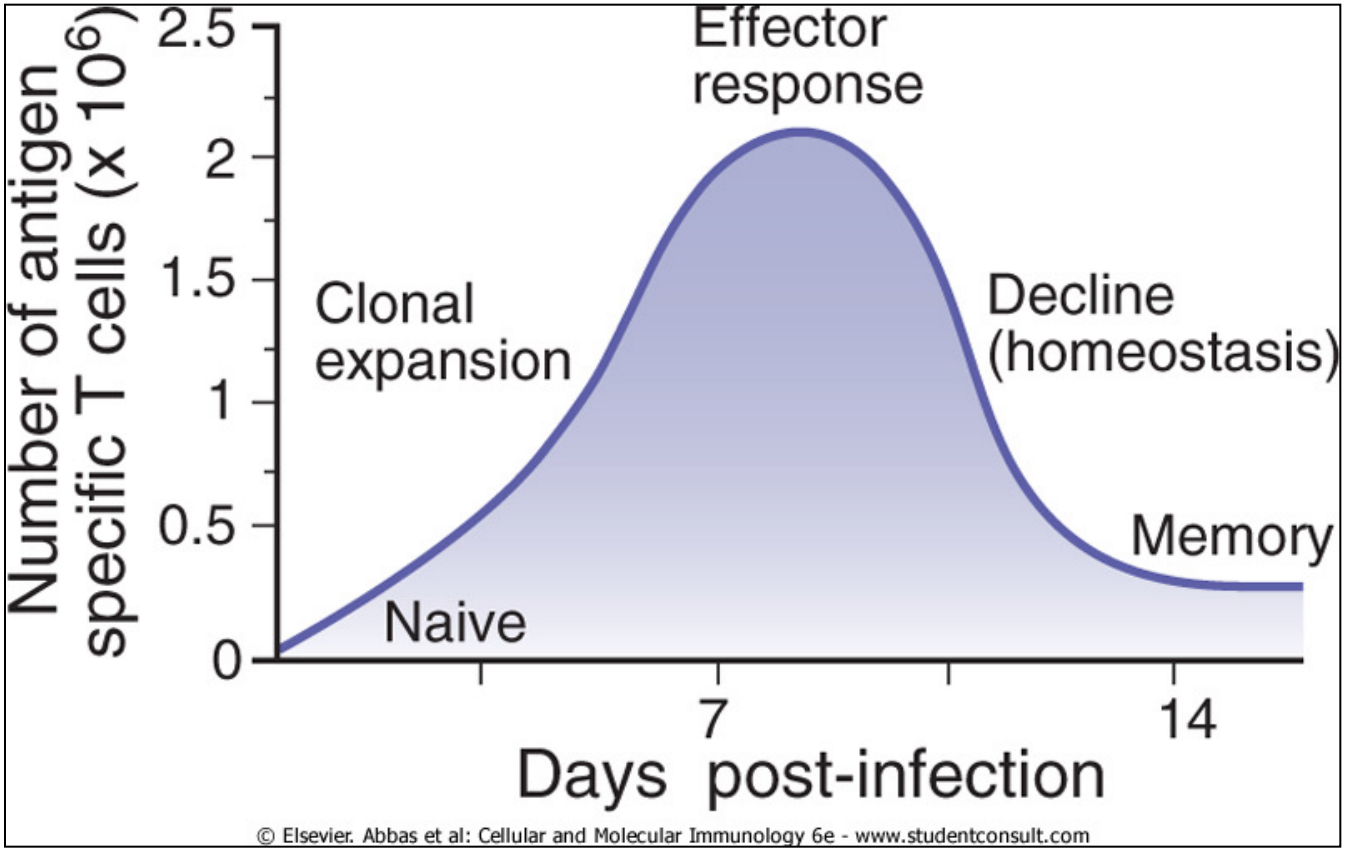
Ativação de linfócitos T virgens e efetores pelo antígeno (peptídeo + APCs)



Fases da resposta de linfócitos T



Expansão clonal de linfócitos T

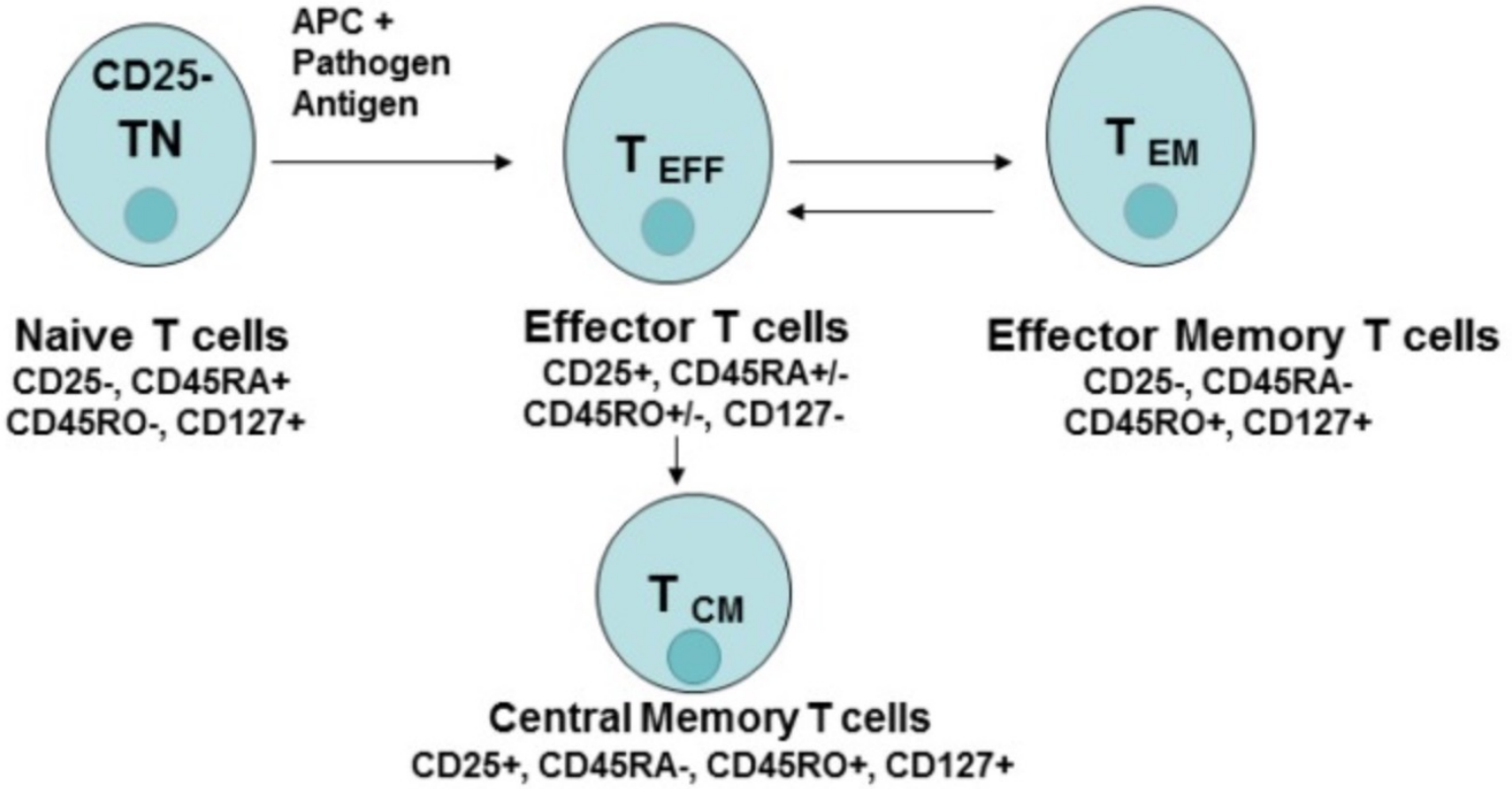


Células T de Memória

Memória Central:
- Recirculam pouco
- Altos níveis de L-selectina CD62L
- Homing em LN (Sialomucinas em Vênulas de Endotélio Alto)
- Altos níveis de CD127 (IL-7R): auto-renovação (~a cels tronco),
- Altos níveis de proteínas anti-apoptóticas (ex: bcl2)

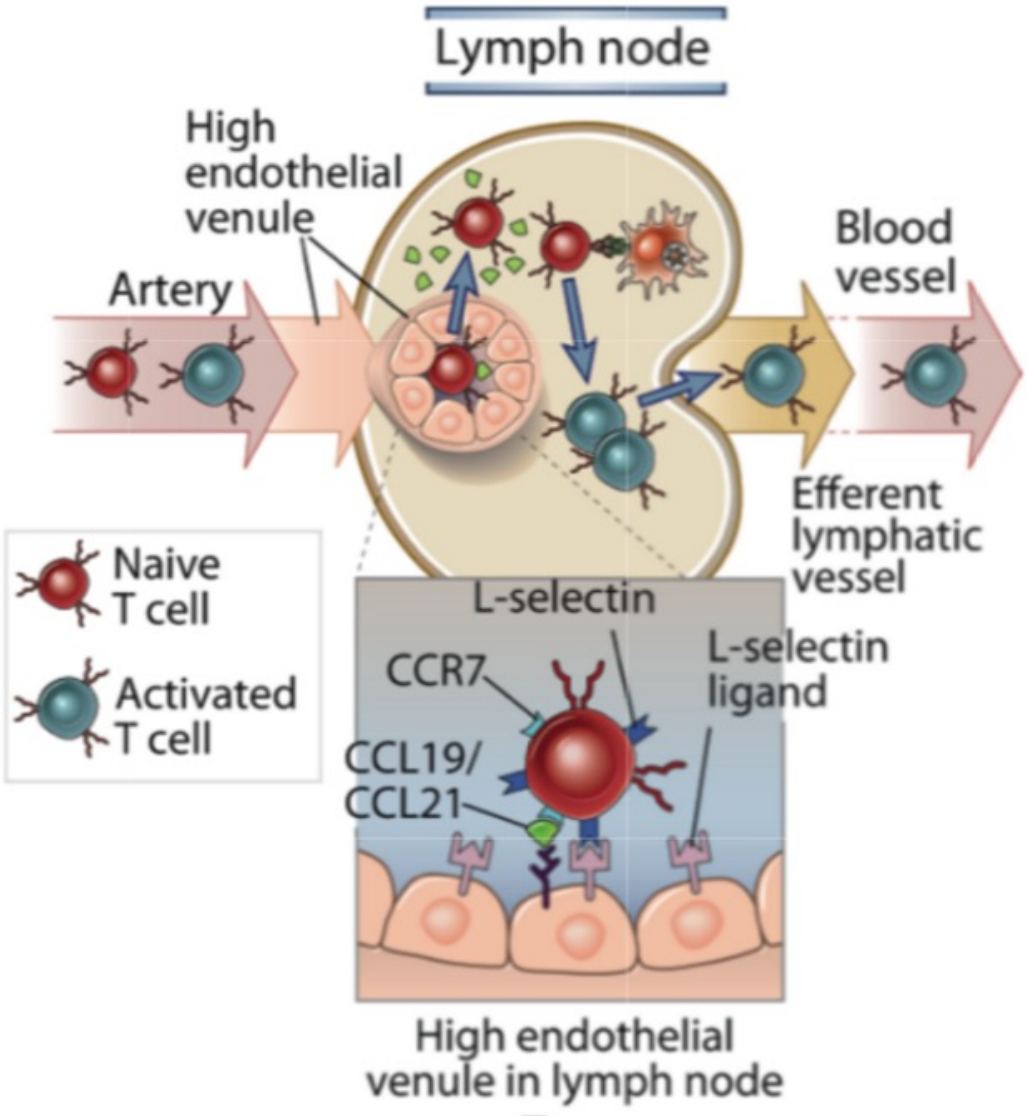
Memória Efetora:
- Cels T de memória que recirculam muito
- Baixos níveis de L-selectina (CD62L) e IL-7R (CD127)
- Altos níveis de receptores de P e E selectinas do endotélio,
- Altos níveis de integrina e ICAMs
- Secretam grandes quantidades de citocinas na reestimulação,
- Baixos os níveis de prots anti-apoptóticos (ex: bcl2)

Diferenças Fenotípicas de Cels T Efetoras, Memória Efetora e Memória Central



CD25=IL-2R CD127=IL-7R
CD45= Glycoprotein expressed on all hematopoietic cells. 8 isoforms
CD45RA is the long isoform expressed on naive T cells.
CD45RO is the shorter isoform expressed on activated T cells

Homing de Cels T naive nos Linfonodos



L-Selectinas=CD62L em cel. T Naive

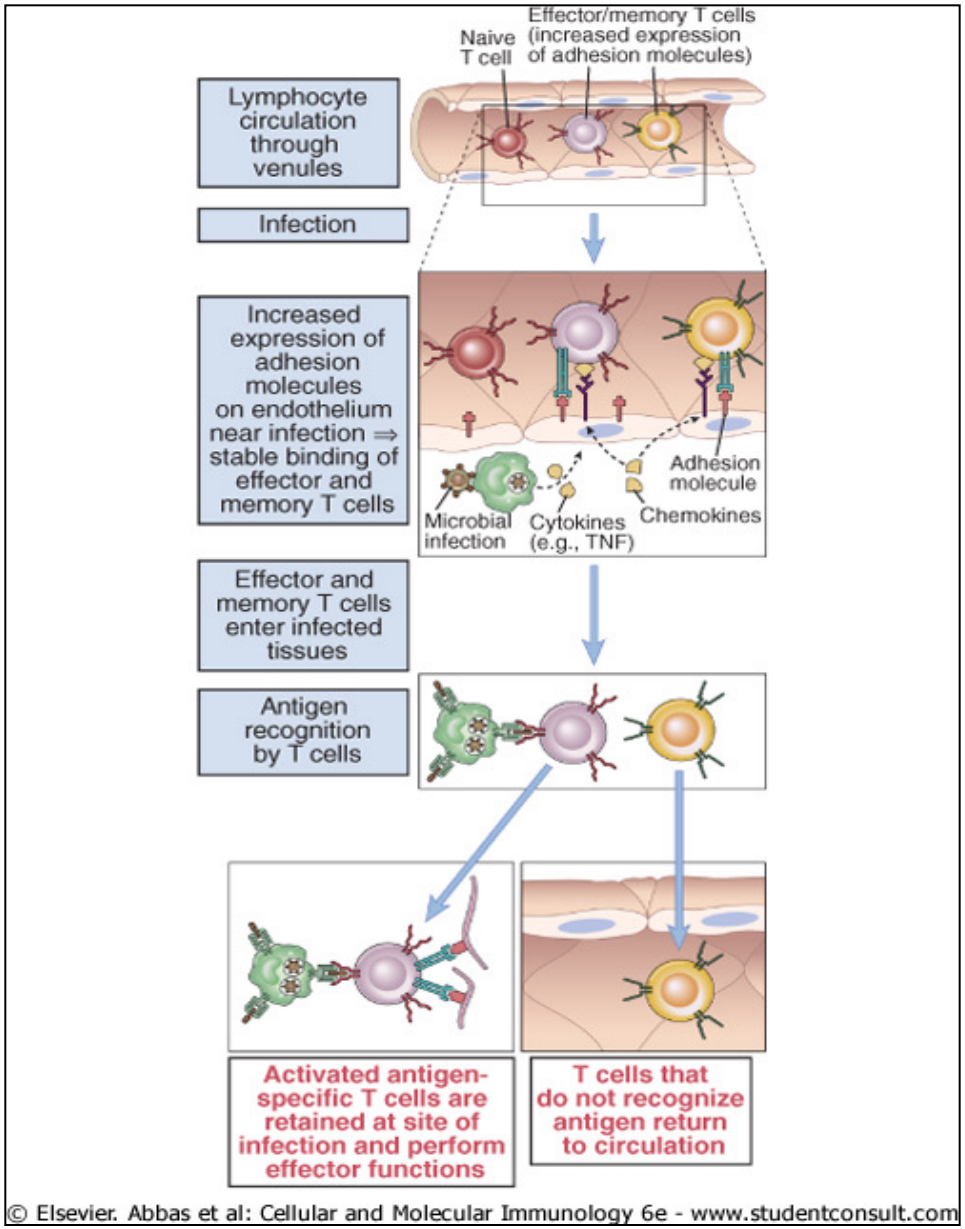
L-Selectina Ligante=Sialomucinas do endotélio

CCR7 em linfs T naives

atraídos por CCL19, CCL21 dos ln

ELSEVIER

Fase Efetora: Migração e retenção de células T efetoras e de memória nos locais da infecção



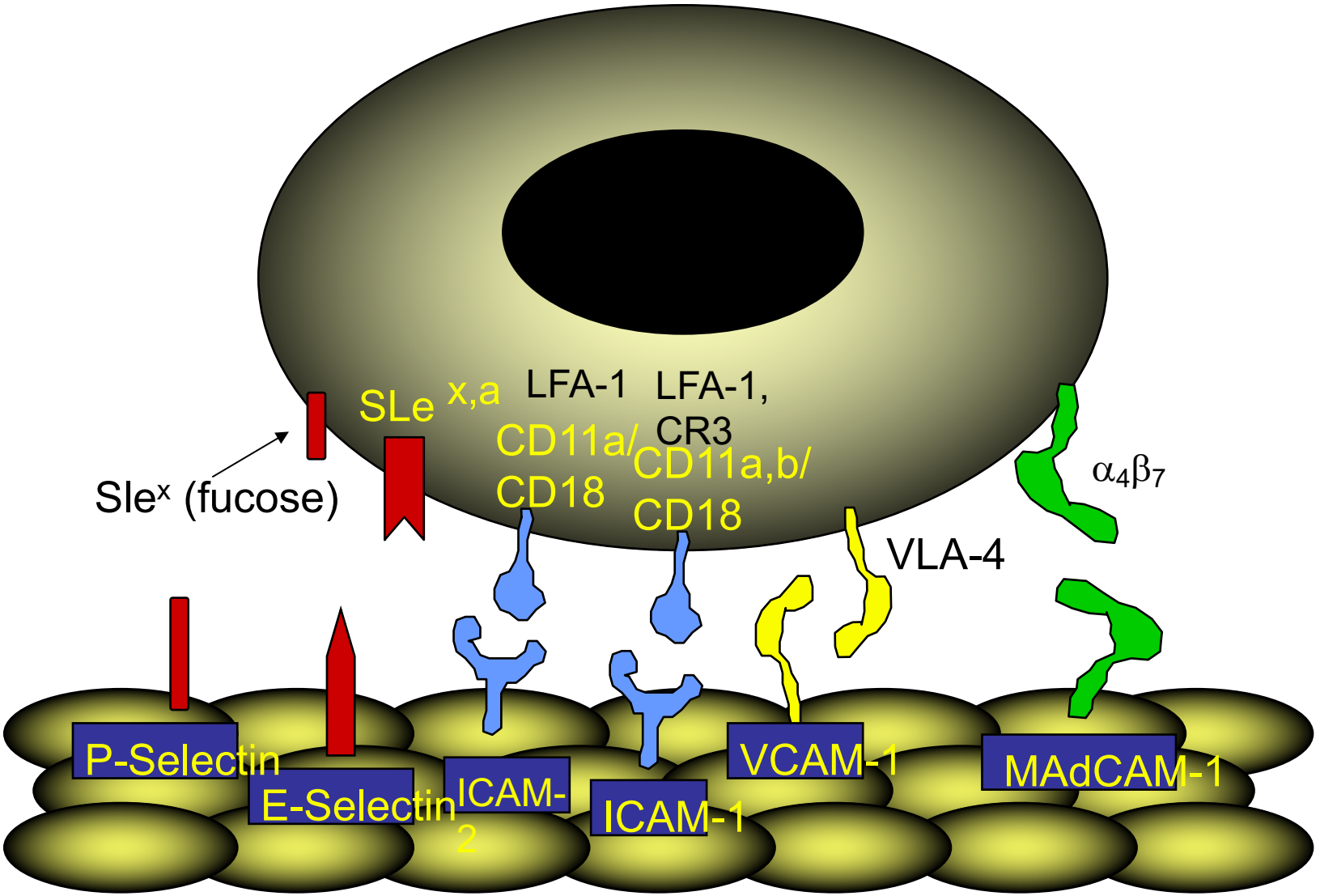
Migração T-Efetora:

Quimioc + Ligante de Quimic

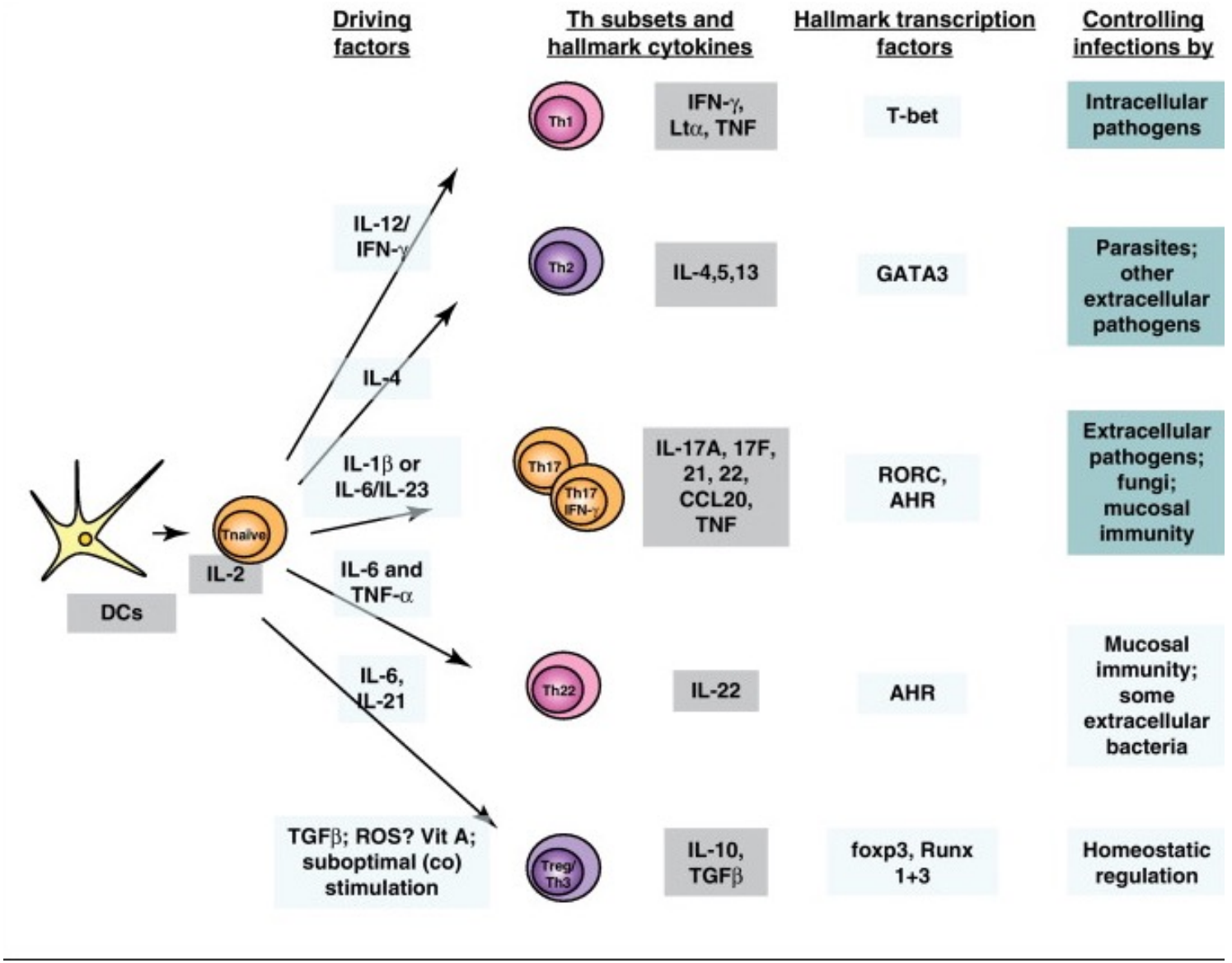
P e E Selectinas do Endot
+ ligantes (CH) dos Linfs

Integrinas
+ S.Fam das Igs (ICAMs)

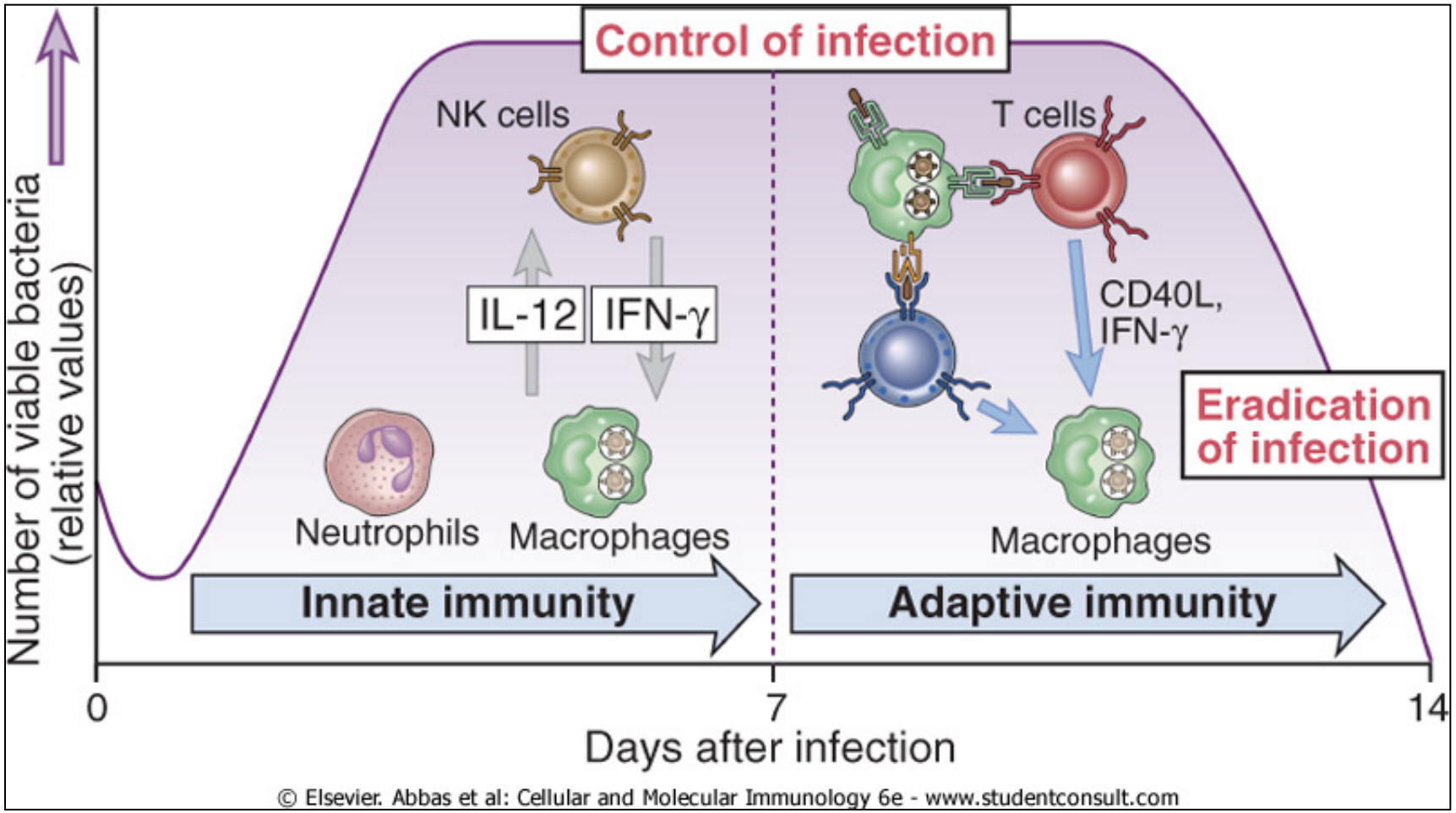
Migração Celular: Moléculas de Adesão do Endotélio e dos Leucócitos



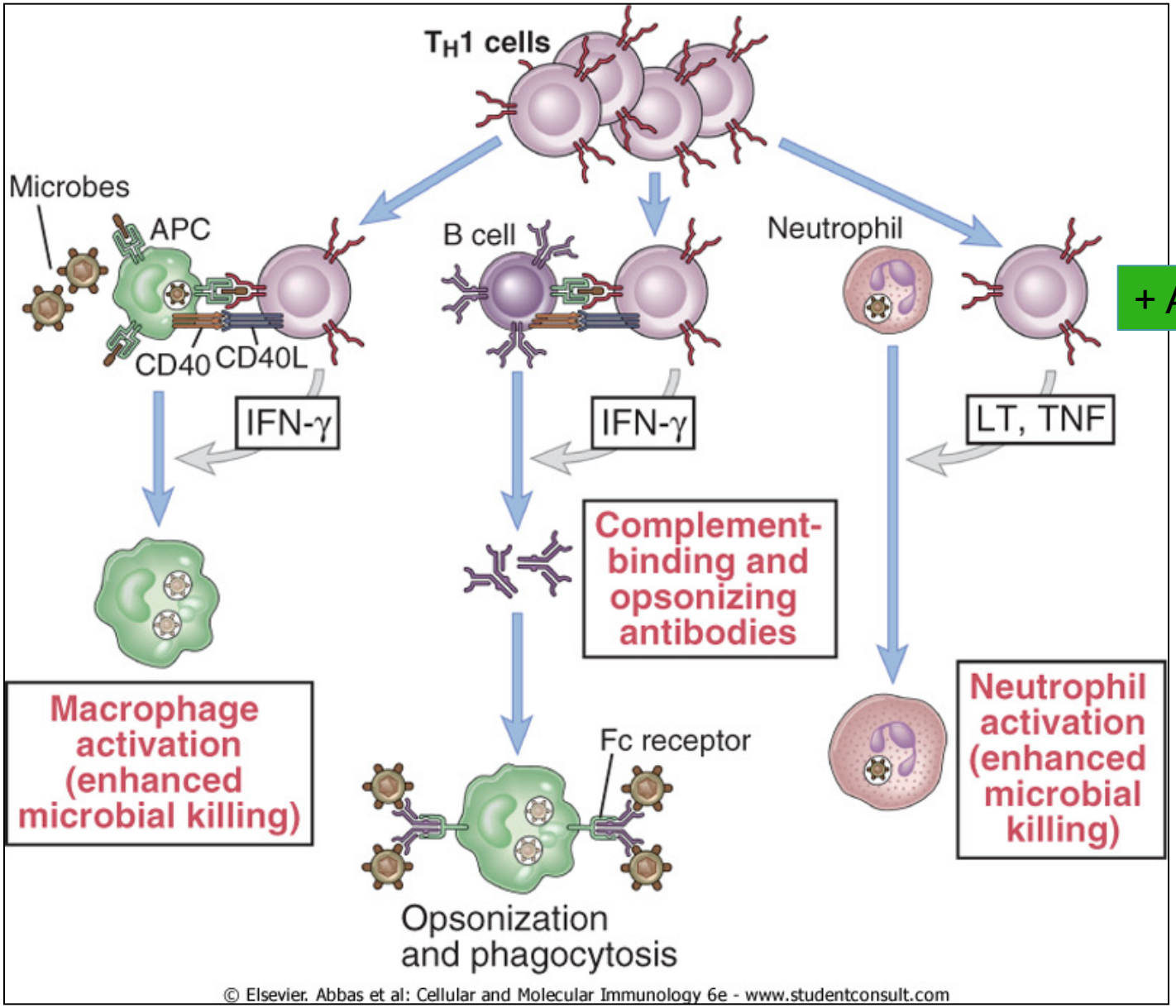
Diferenciação Funcional de Sub-populações de Células T
"Tipos diferentes de resposta imune para proteção contra patógenos diferentes"



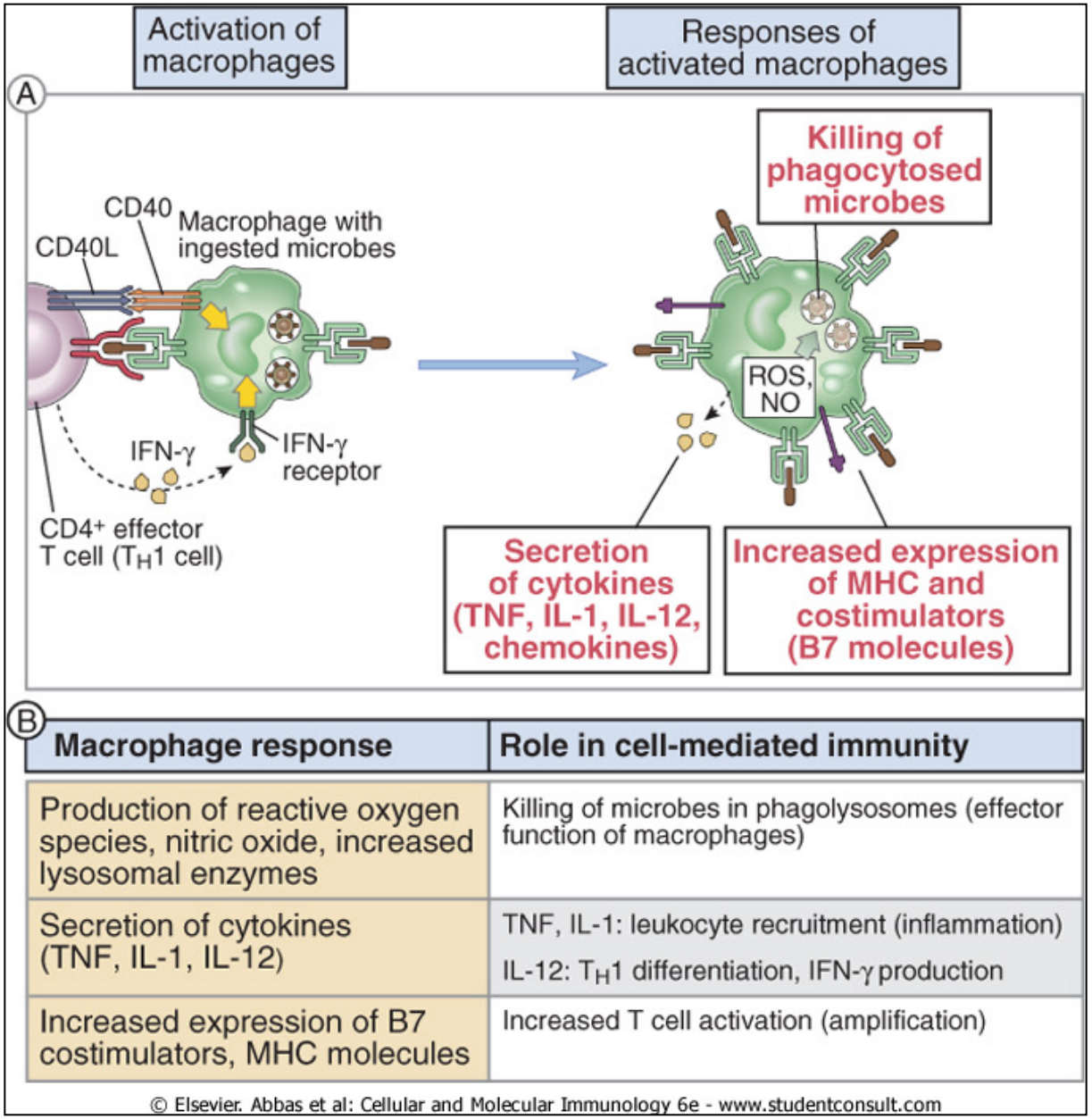
Imunidade Th1: Proteção contra Bactérias Intracelulares



Funções efetoras das células Th1



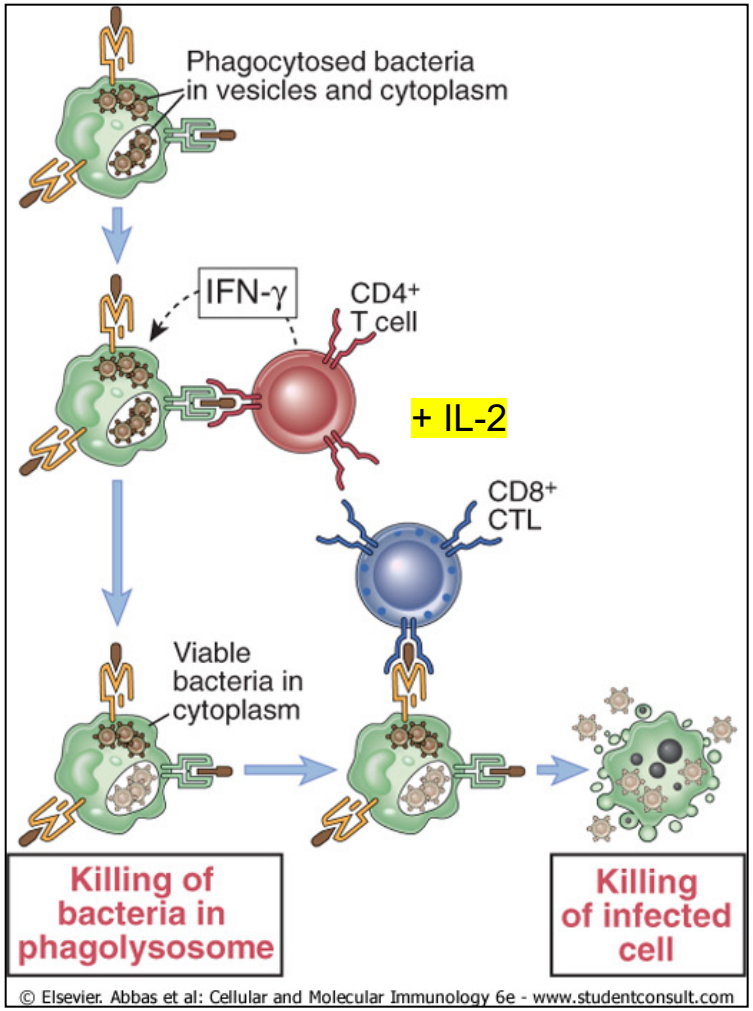
Funções Efetoras das Cels Th1: Ativação dos Macrófagos



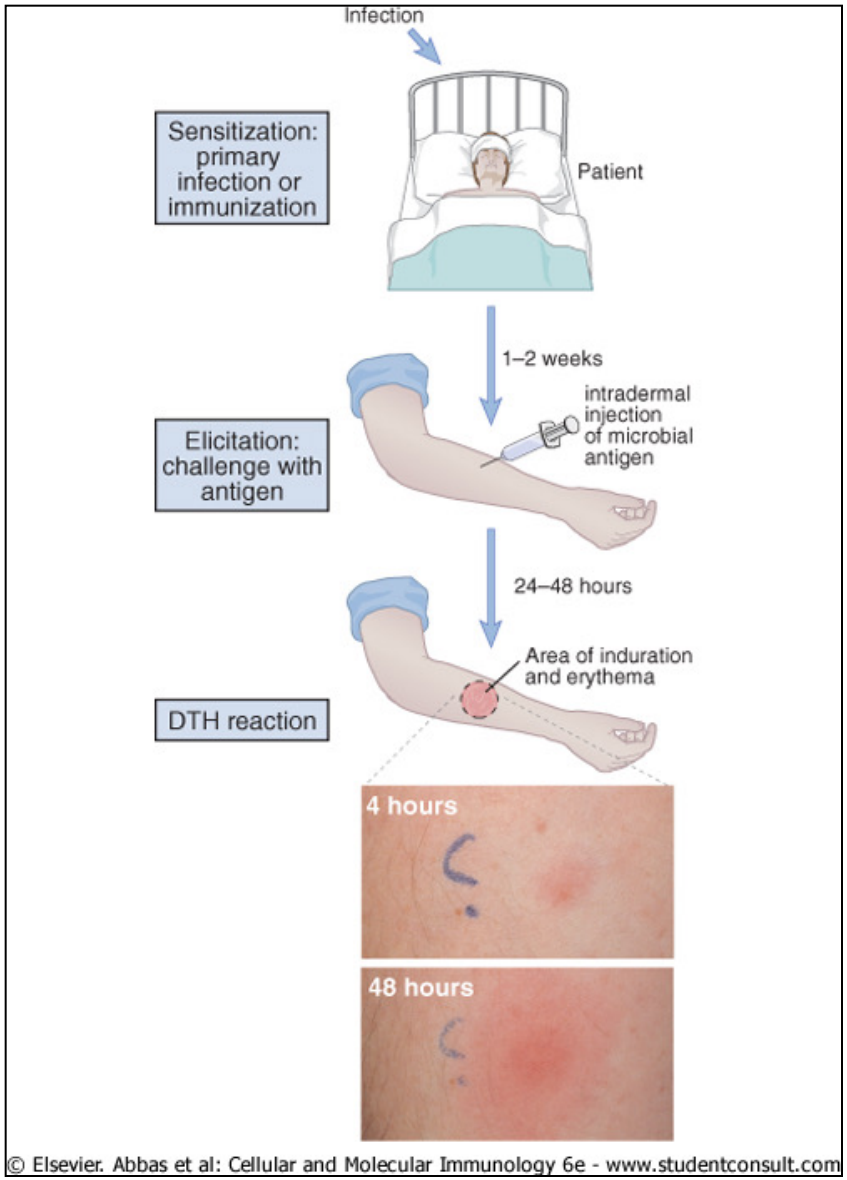
B

Macrophage response	Role in cell-mediated immunity
Production of reactive oxygen species, nitric oxide, increased lysosomal enzymes	Killing of microbes in phagolysosomes (effector function of macrophages)
Secretion of cytokines (TNF, IL-1, IL-12)	TNF, IL-1: leukocyte recruitment (inflammation) IL-12: T_H1 differentiation, IFN-γ production
Increased expression of B7 costimulators, MHC molecules	Increased T cell activation (amplification)

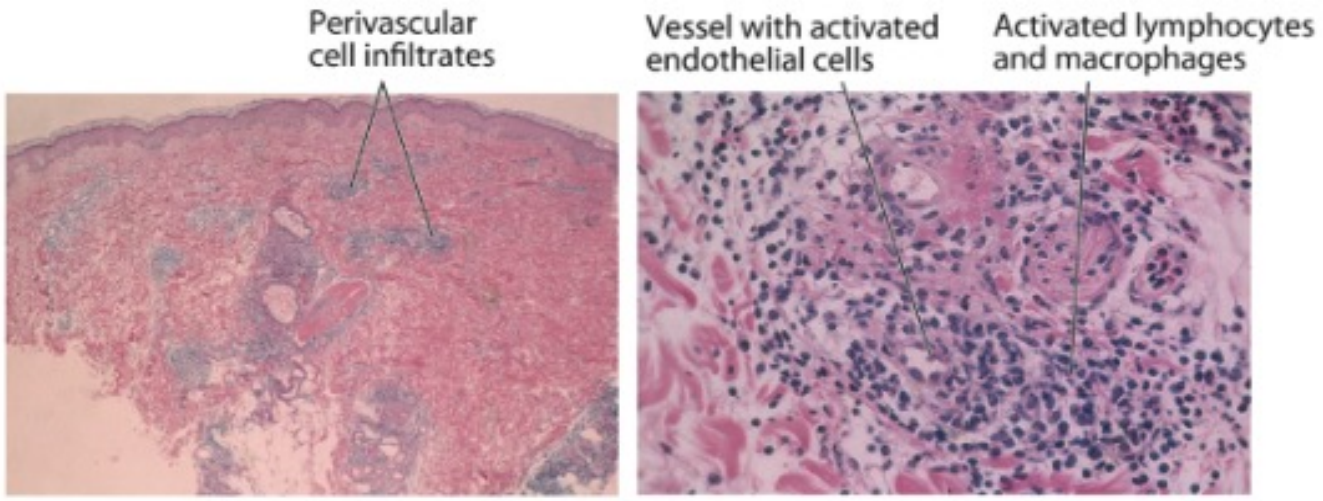
Cooperação entre linfs T CD4+ e CD8+ na defesa contra micróbios intracelulares



Reação de HTT (hipersensibilidade do tipo tardio) para detecção de imunidade celular (Th1) in vivo



Histologia de pele com reação positiva de HTT (acúmulo de linfócitos e macrófagos)



Teste de Mantoux (ppd)– Tuberculose

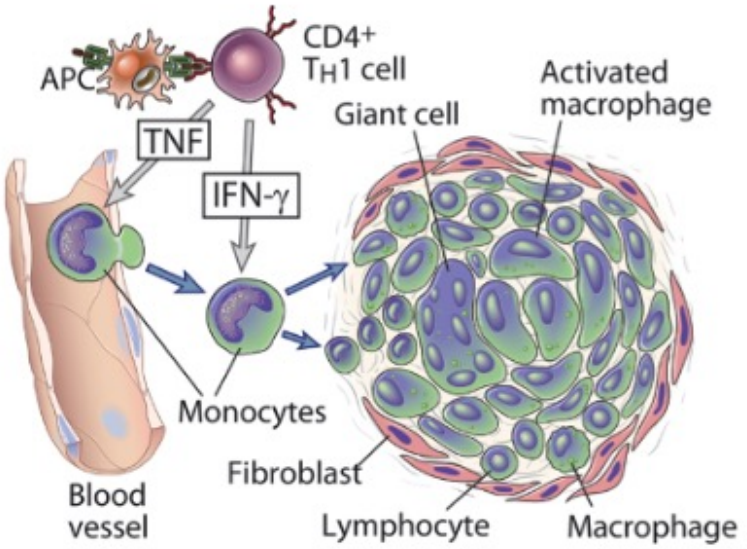
Teste de Machado Guerreiro – Chagas

Teste de Matsuda – Lepra

Teste de Montenegro - Leishmaniose

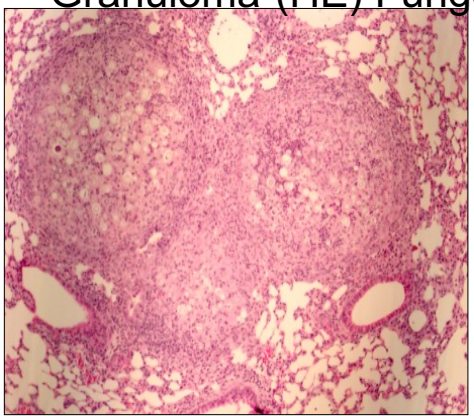
Quantiferon Substitui a Reação de HTT: Leucócitos + Peptideos da *M. tuberc.:* Ativação de Linfs T memória especificos e Produção de IFN-γ Dosado por ELISA

Permanência do Ag: Granuloma com predomínio Th1 em MTB e Fungo Patogênico

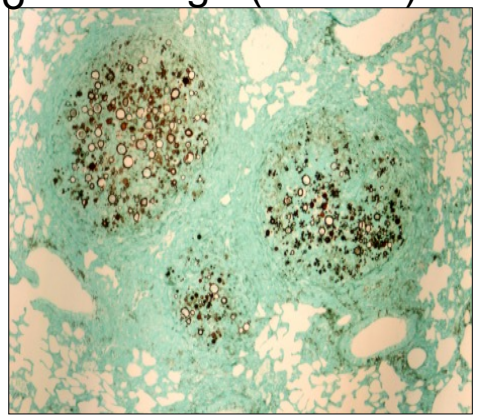


- **Doenças infecciosas com granulomas**
  Bactérias (*Coxiella burnetti, Listeria*…)
  Micobacterias (lepra e tuberculose)
  Fungos (histoplasmose e paracoccidioidomicose)
- **Silicose**: doença pulmonar rara: inalação de sílica, inflamação e dano tecidual – "*industrial lung disease*"

Granuloma-(HE) Fungo

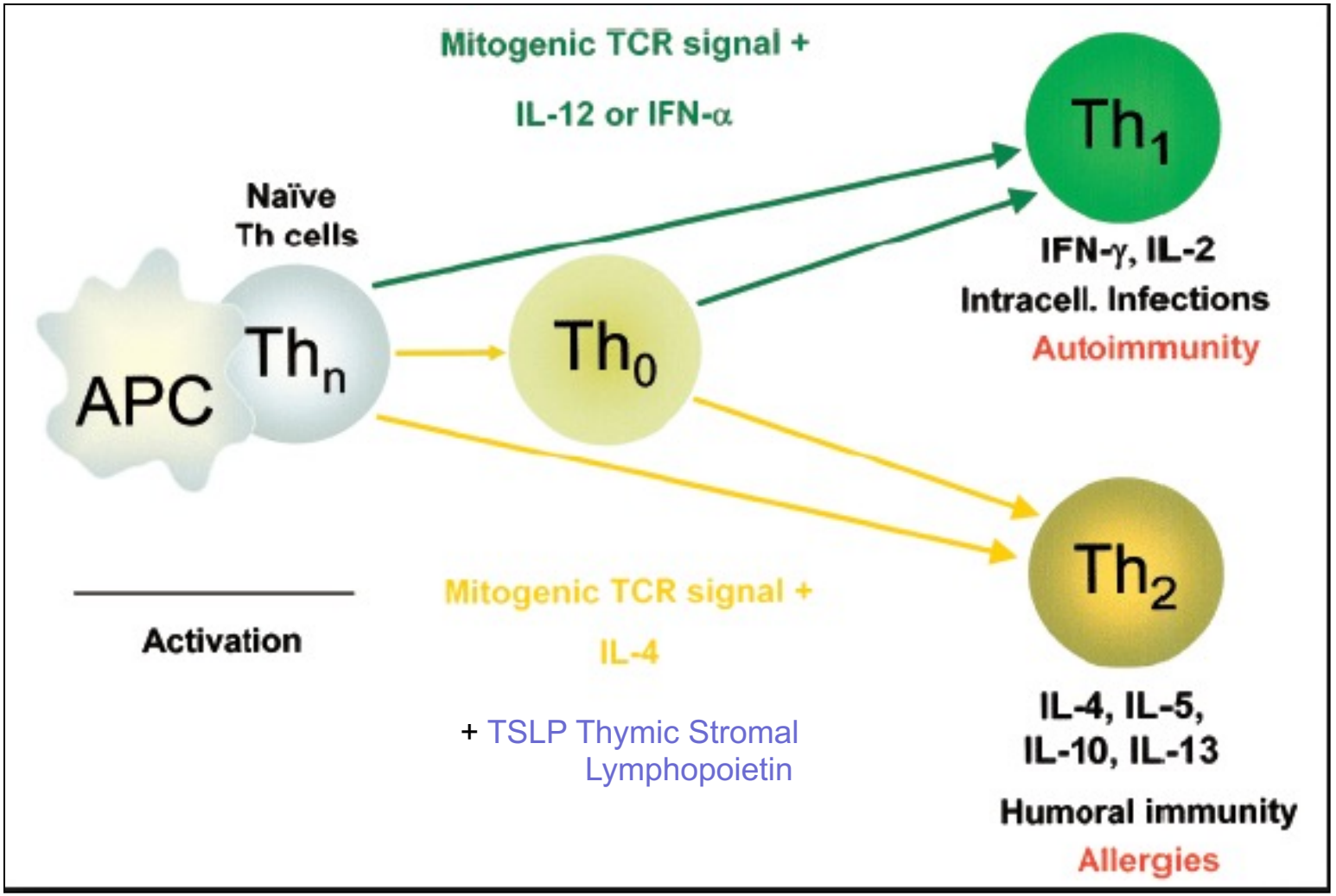


Fungo-(Grocott)

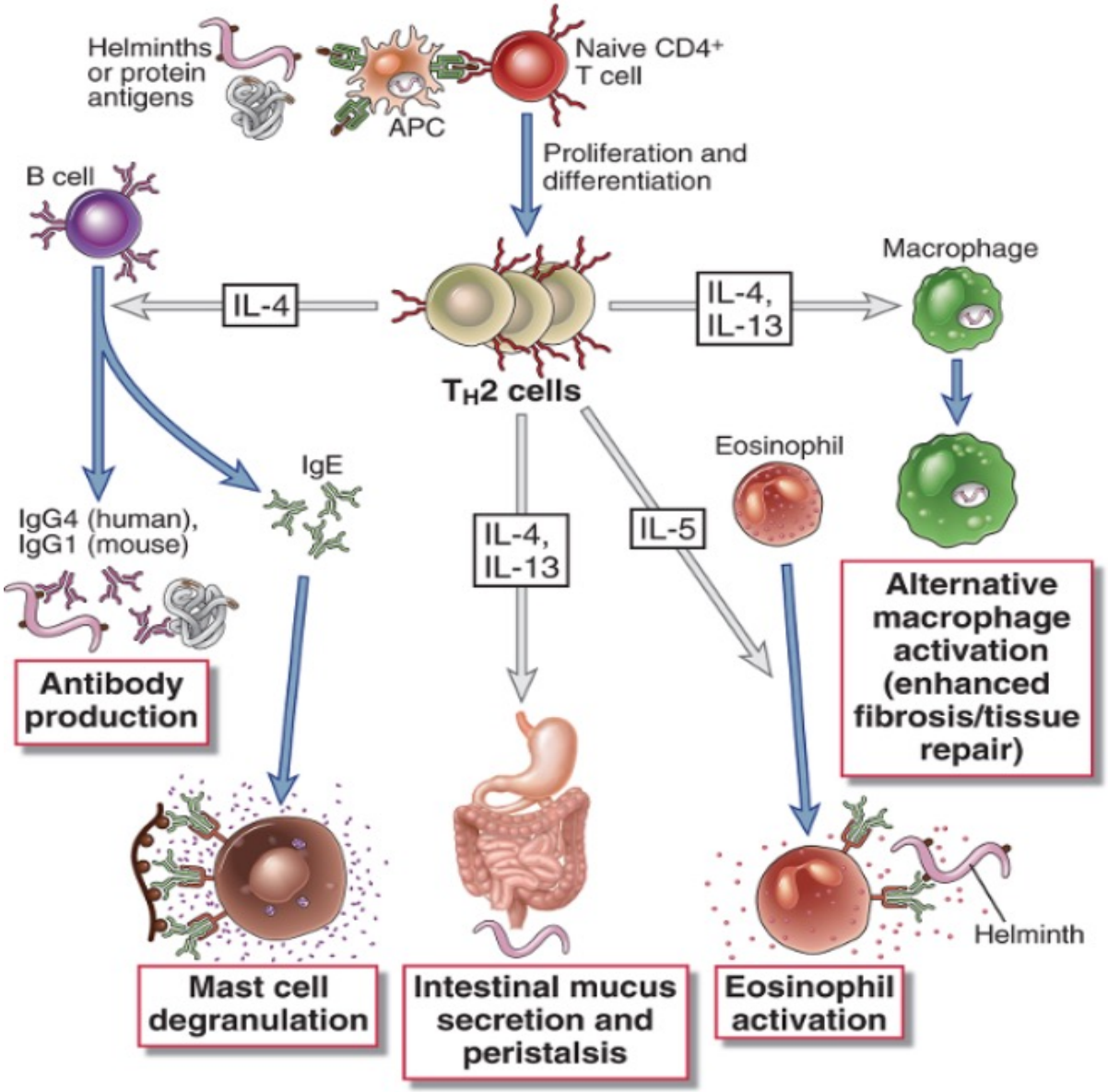


Anti-TNF em DAI =
Desorganização do granuloma
e reativação de Tb

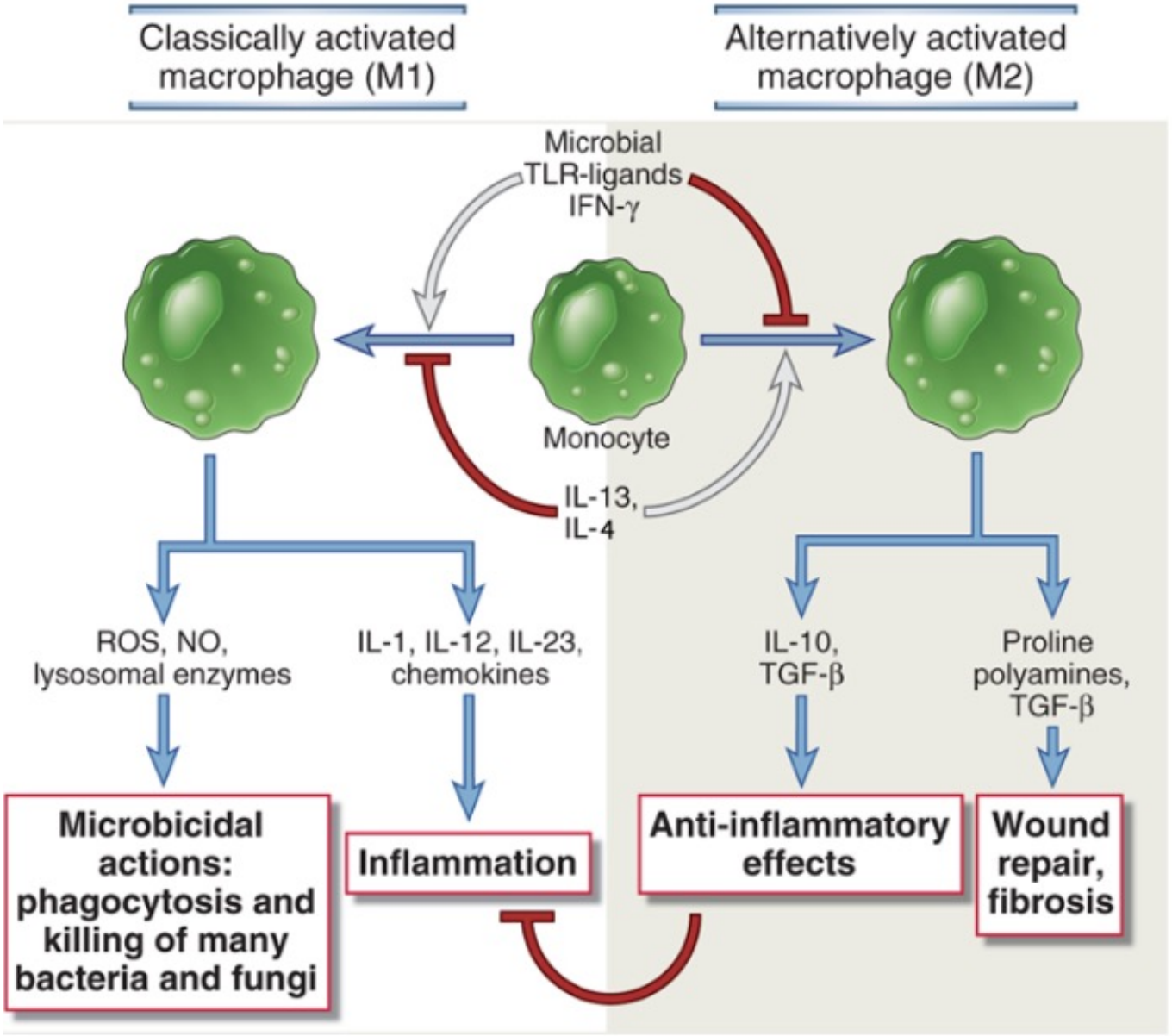
Resposta Th2



Mecanismos Indutores e Efetores Th2: Helmintos e Alergia

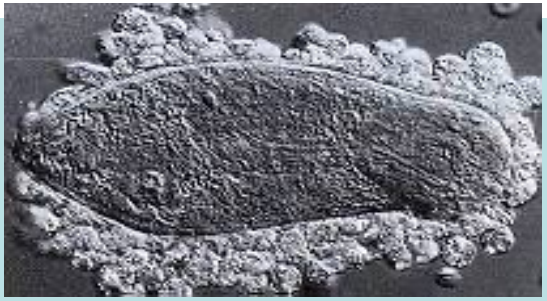


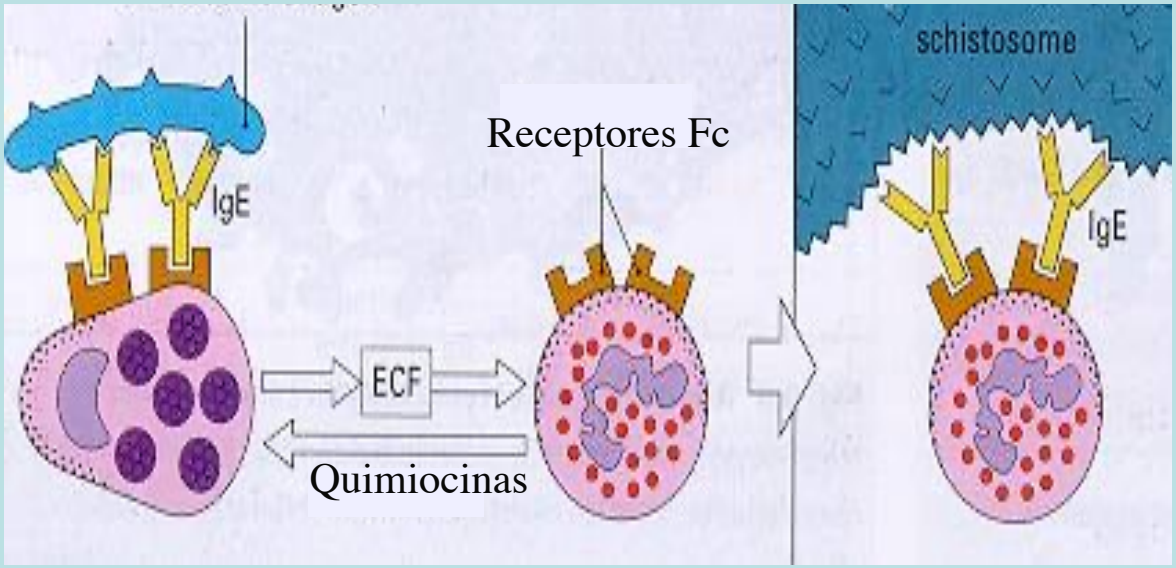
Macrófagos M1 X Macrófagos M2



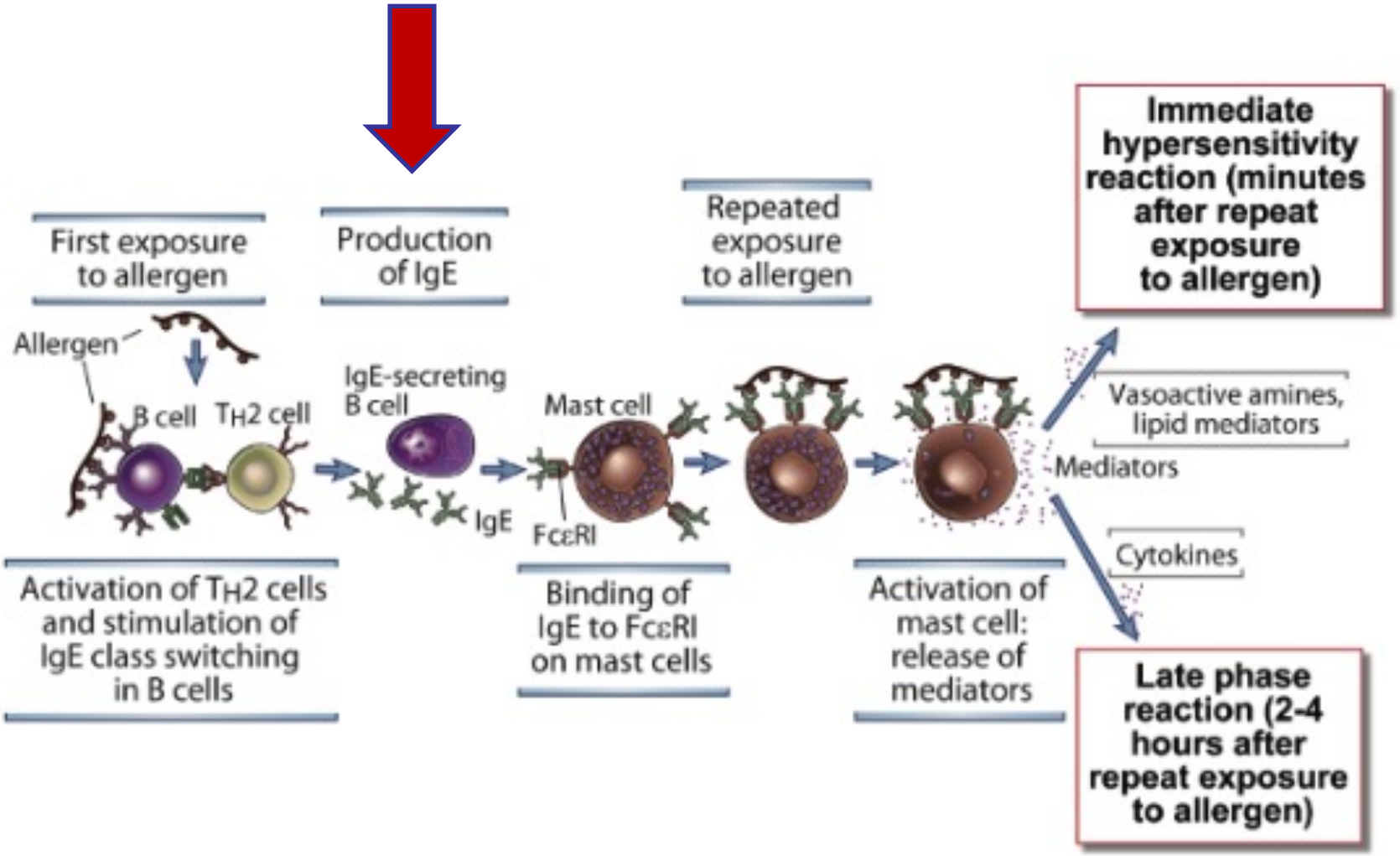
Imunidade Th2: IgE e Eosinófilos são importantes mecanismos de defesa contra Schistosoma

Destruição de esquistossômulos de *S. mansoni*





A resposta Th2 está associada a Hipersensibilidade do Tipo I (Alergia)



Ativação de mastócitos

Fase imediata

Histamina, serotonina, PGs, LTs : vasodilatação, aumento da pemeabilidade capilar, edema e contração da musc. lisa

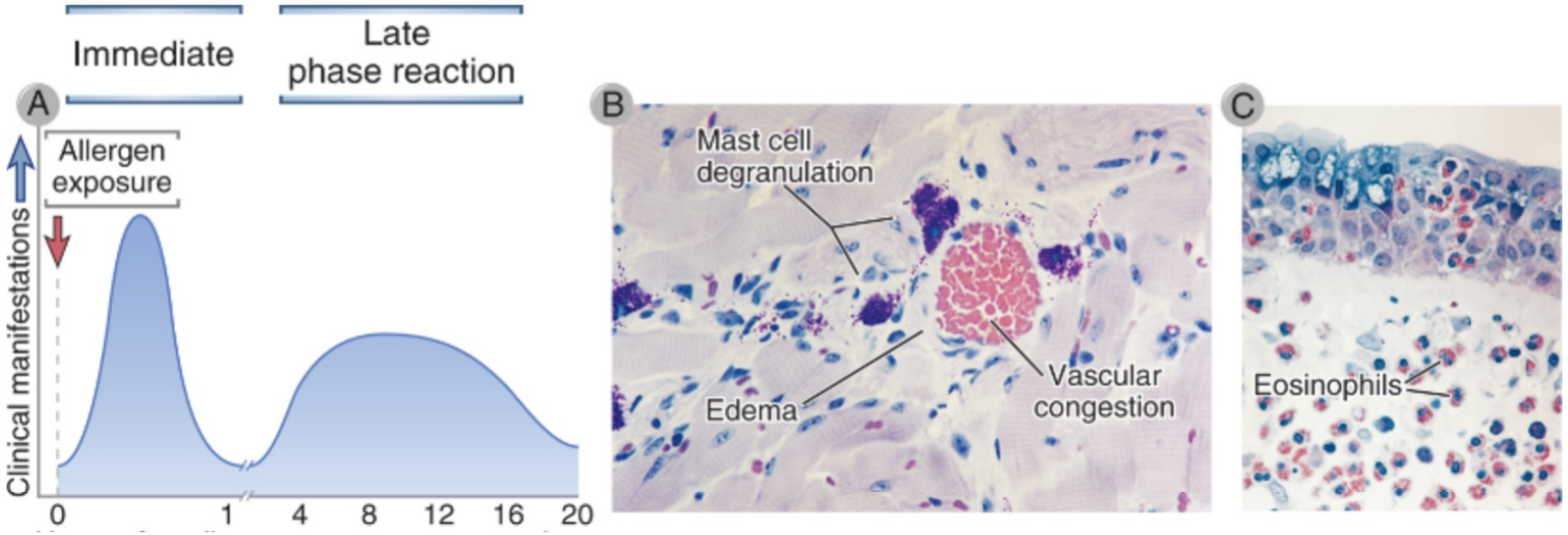
Ativação de mastócitos

Fase tardia

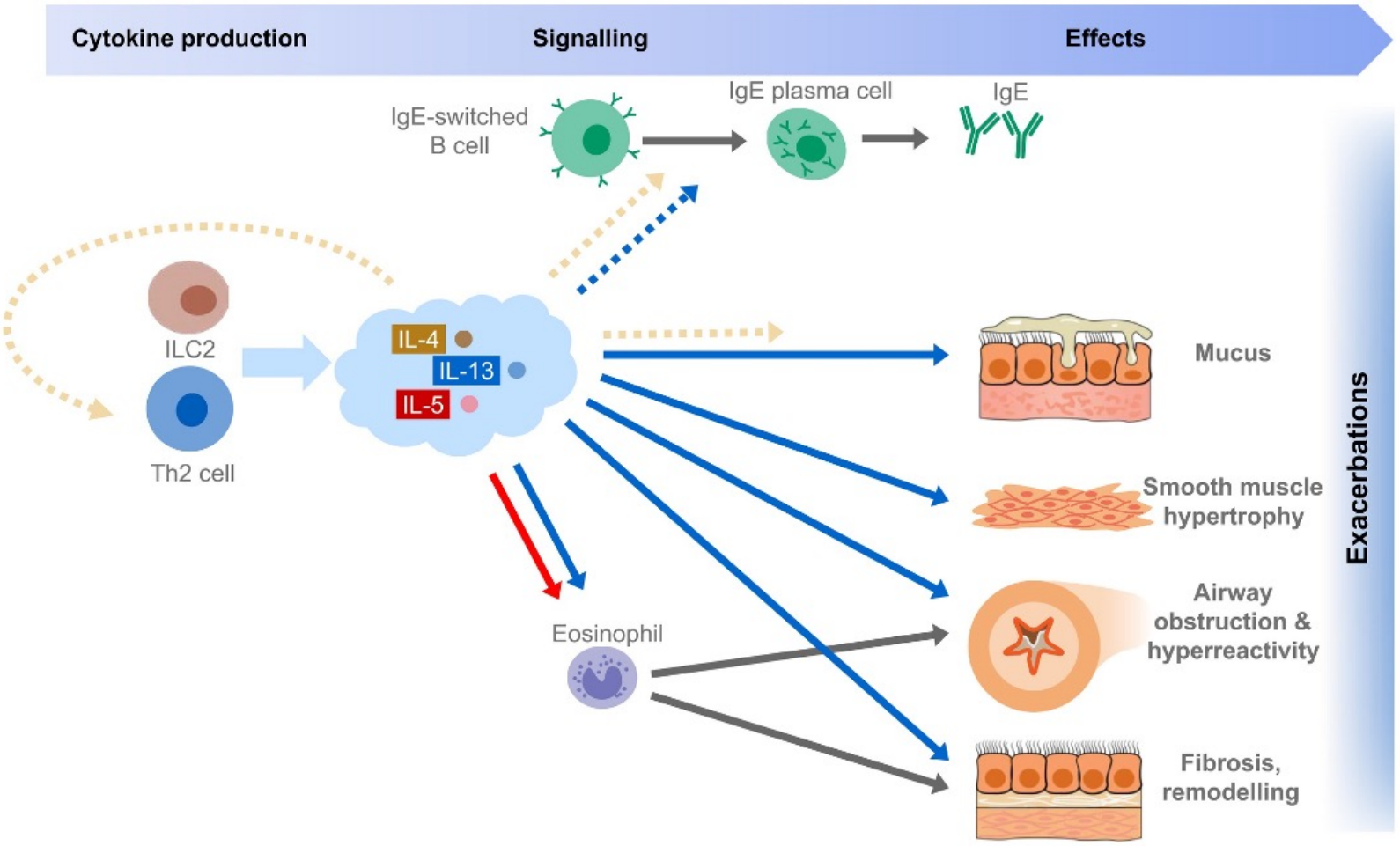
Citocinas e Migração Eosinofílica

IL-4 (mais IgE), IL-13 (muco), IL-5 (eosinofilia e ativação de eosinófilos), Lesão tecidual (Enzimas)

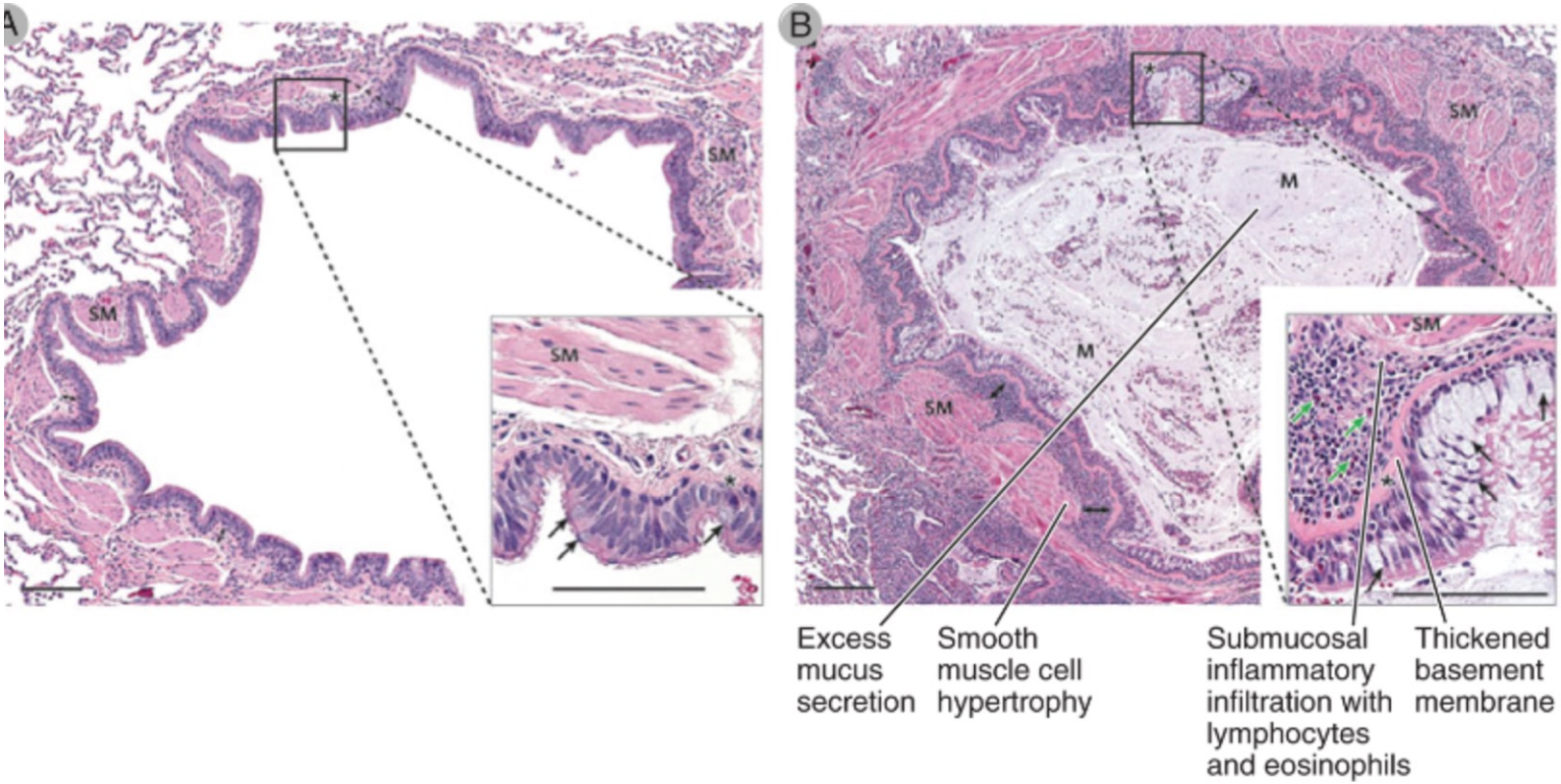
Características das Fases Imediata e Tardia da Imunidade Th2



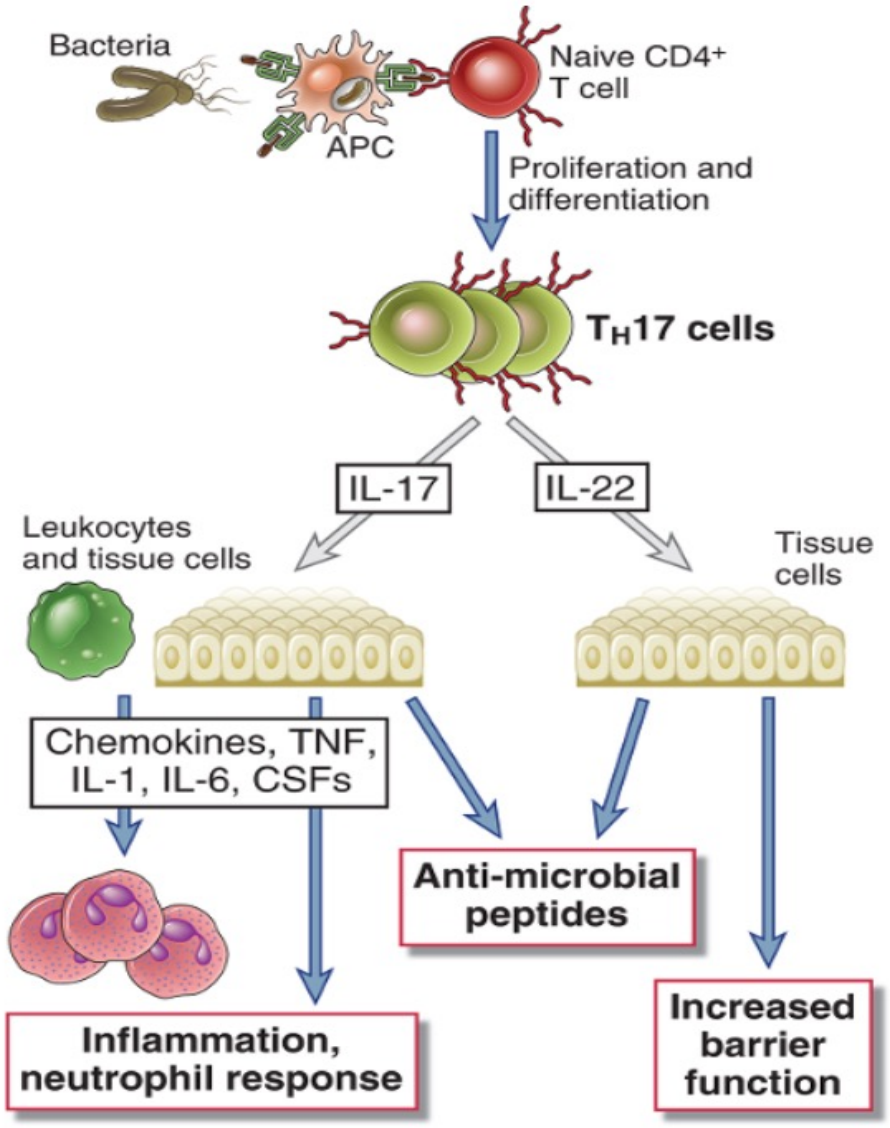
A Resposta Th2 na Asma Brônquica



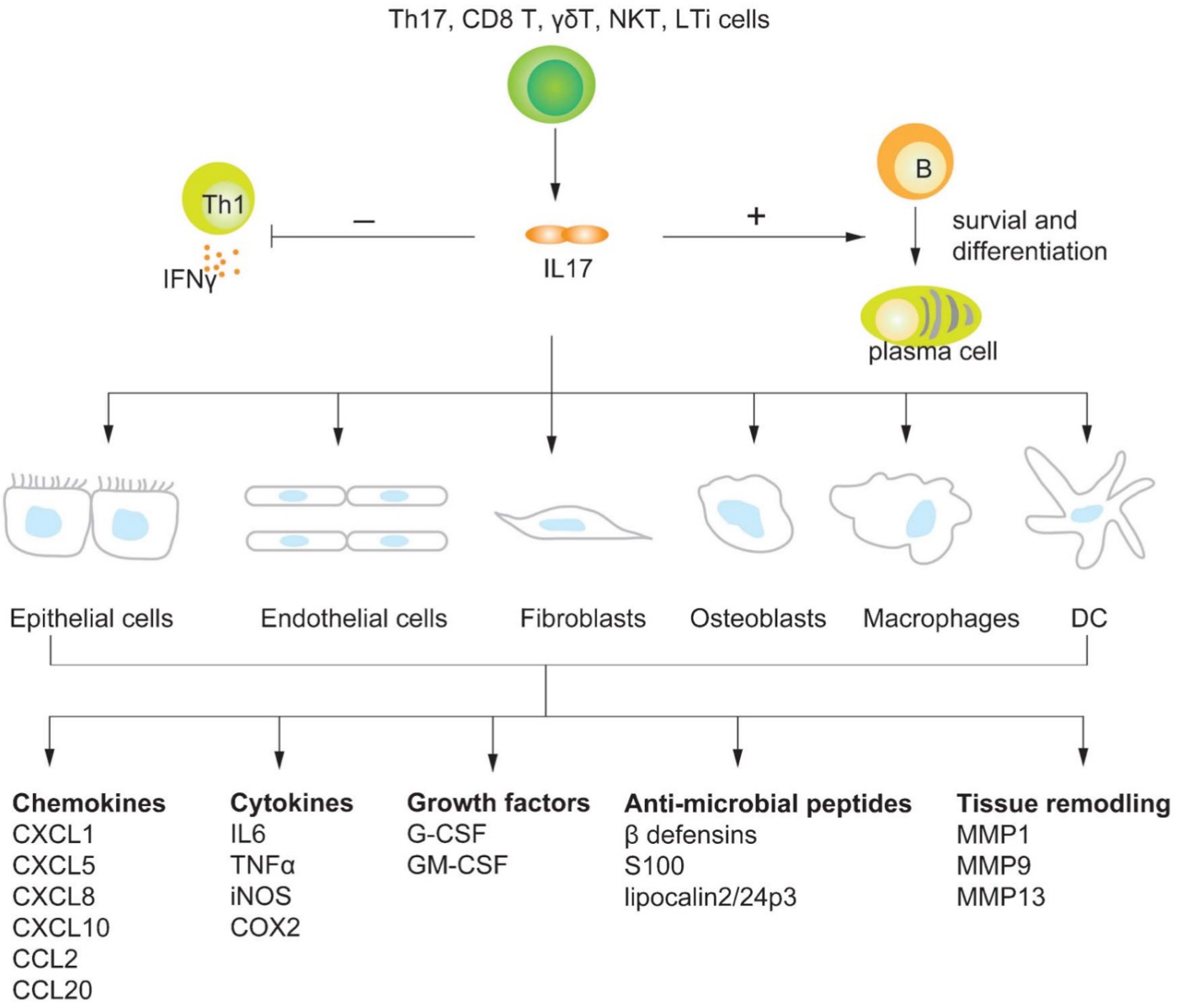
Asma Brônquica como modelo de Patologia Celular Mediada por Resposta Th2



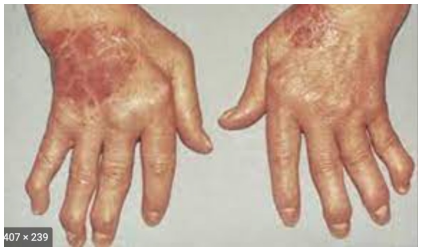
Mecanismos Efetores Mediados por Linfs Th17
Imunidade a Patógenos Extracelulares e Fungos

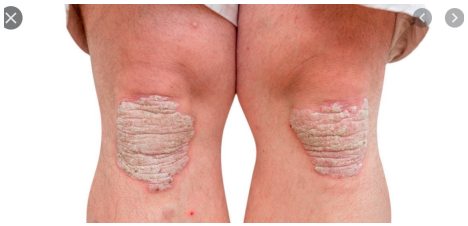


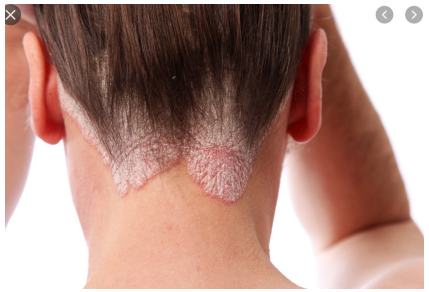
As Muitas Funções Biológicas da IL-17



Patologia Mediada por Cels Th17
Artrite Psoriásica: Cels Th17, Neutrófilos e Macrófagos







AMP=AntiMicrobial Peptides
(cathelicidin peptide modulate psoríasis

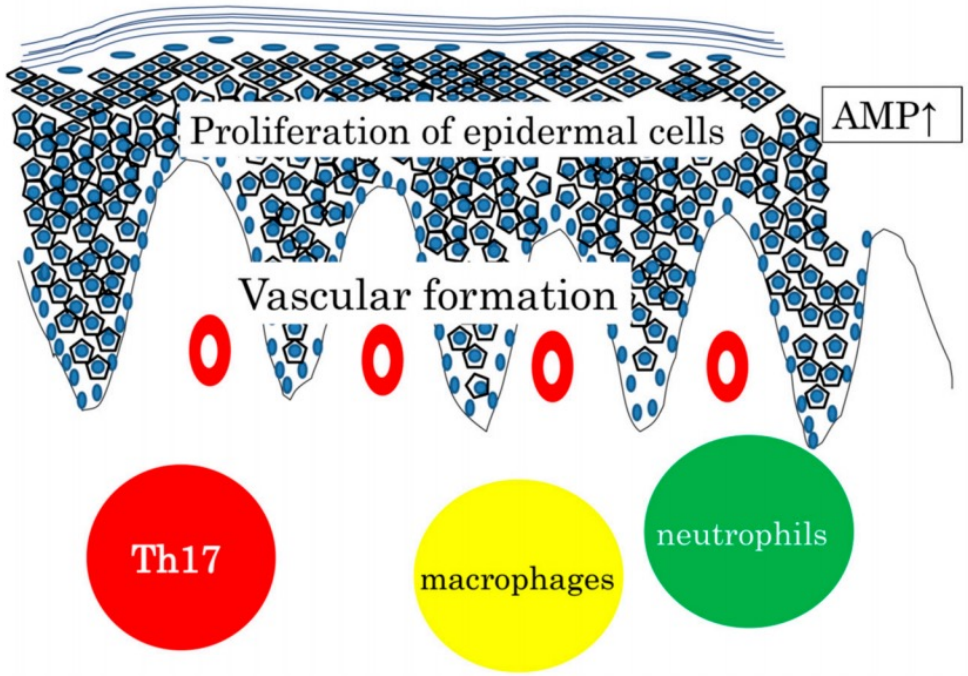
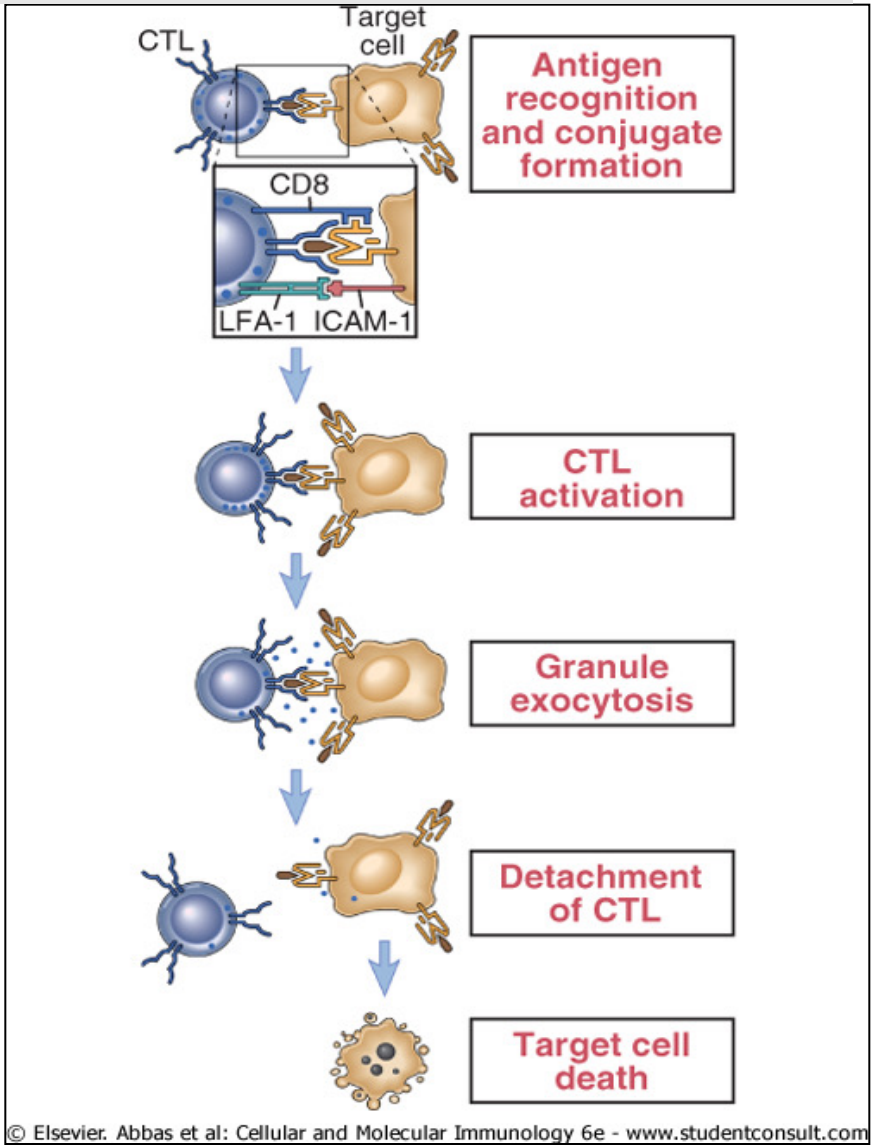


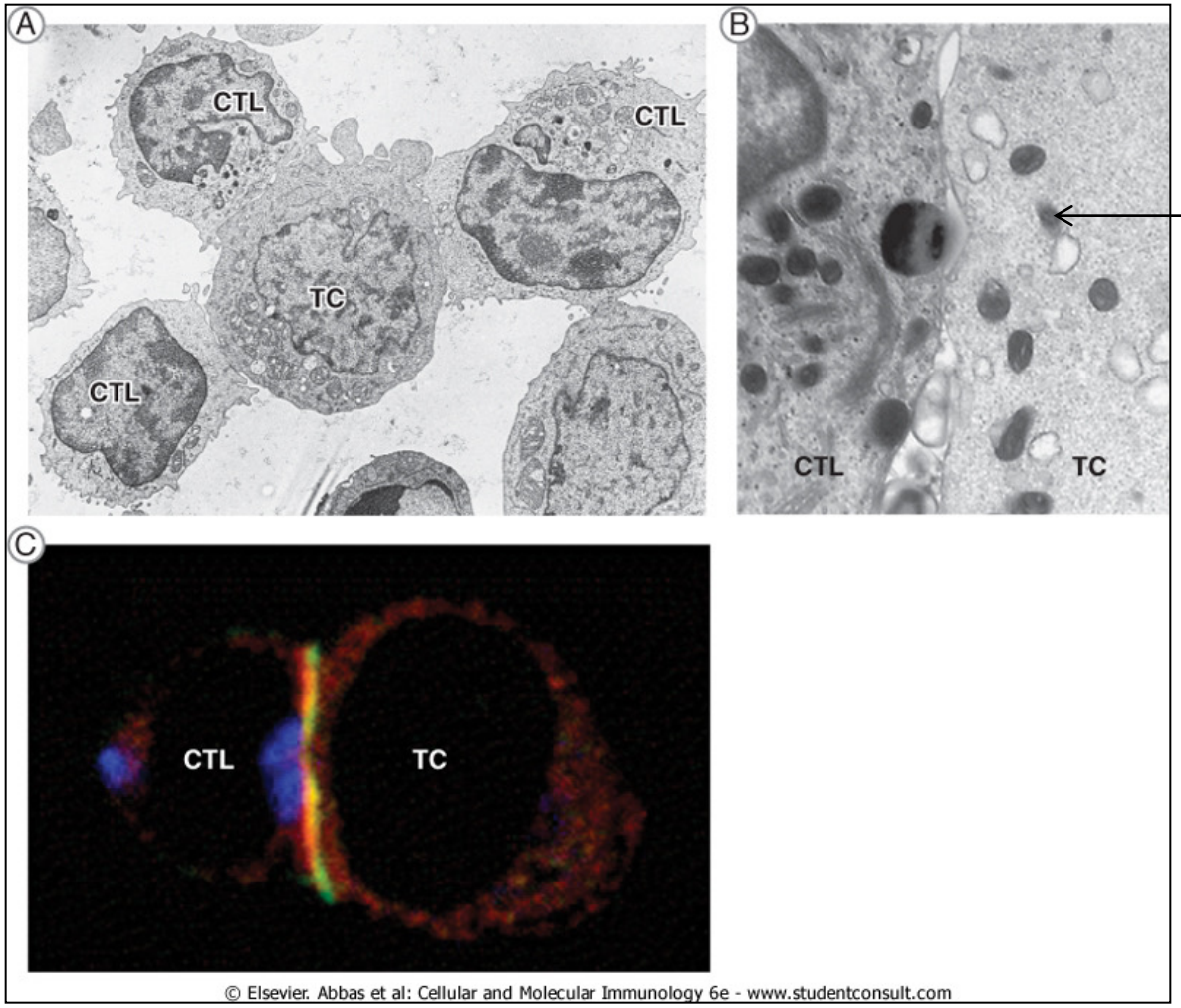
Figure 1. Proliferation of epidermal cells, AMP expression, vascular formation, and infiltration of Th17, neutrophils, and macrophages, commonly seen in wounded skin and in psoriasis skin.

Tratamento com mAb: Cosentix secukimumabe=anti-17A
Stelara ustekinumabe=Anti-IL-23

Linfócitos T Citotóxicos T CD8+
Lise de célula-alvo infectada com vírus

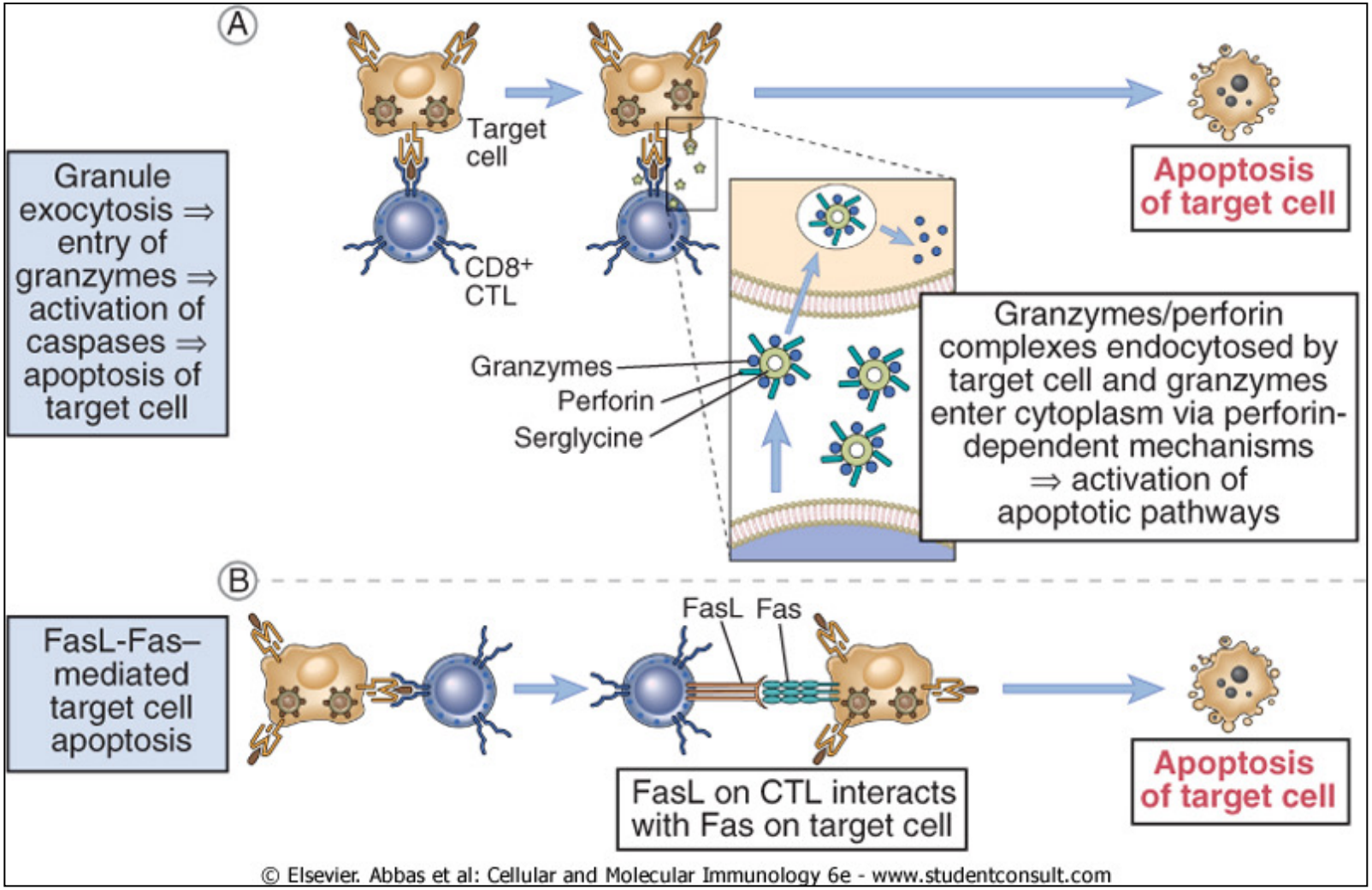


Sinapse Imunológica entre linfócito T CD8 (CTL) e célula-alvo (TC=Target Cell)

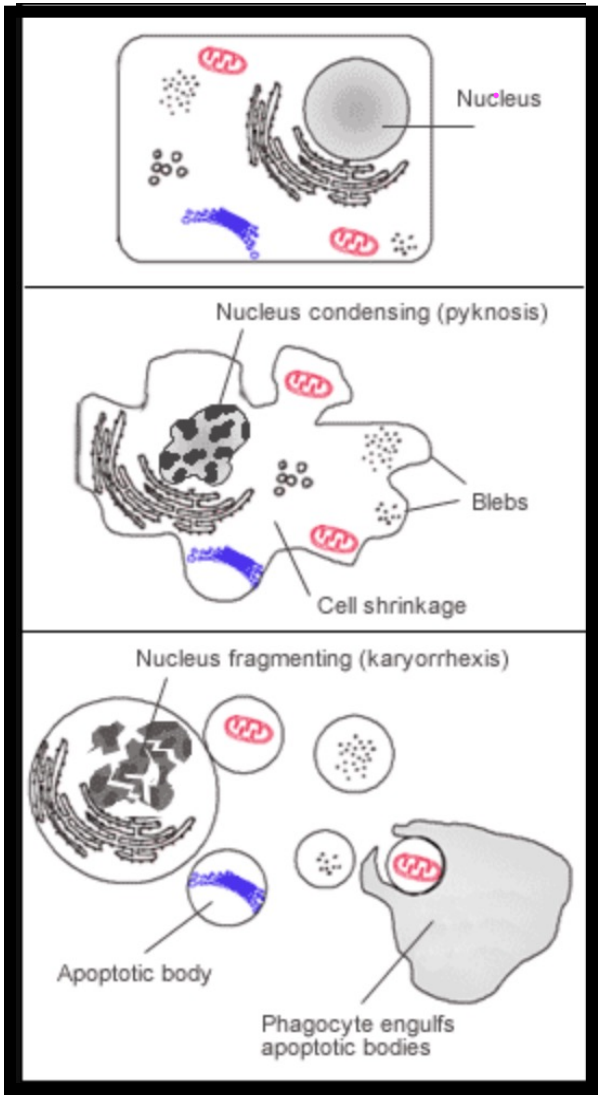


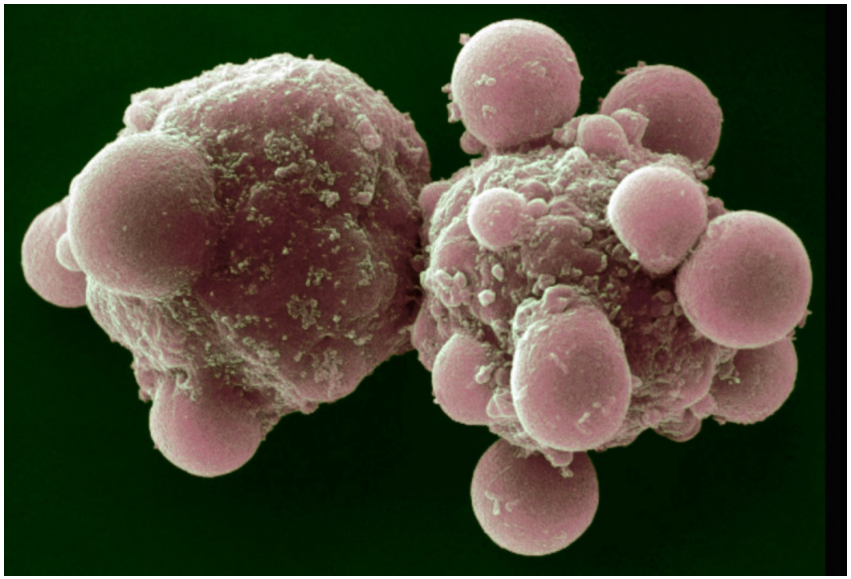
Grânulos dentro da cel. alvo

Mecanismos de lise de célula-alvo por linfócito T CD8+
Apoptose induzida por granzima e perforina e/ou Fas-FasL

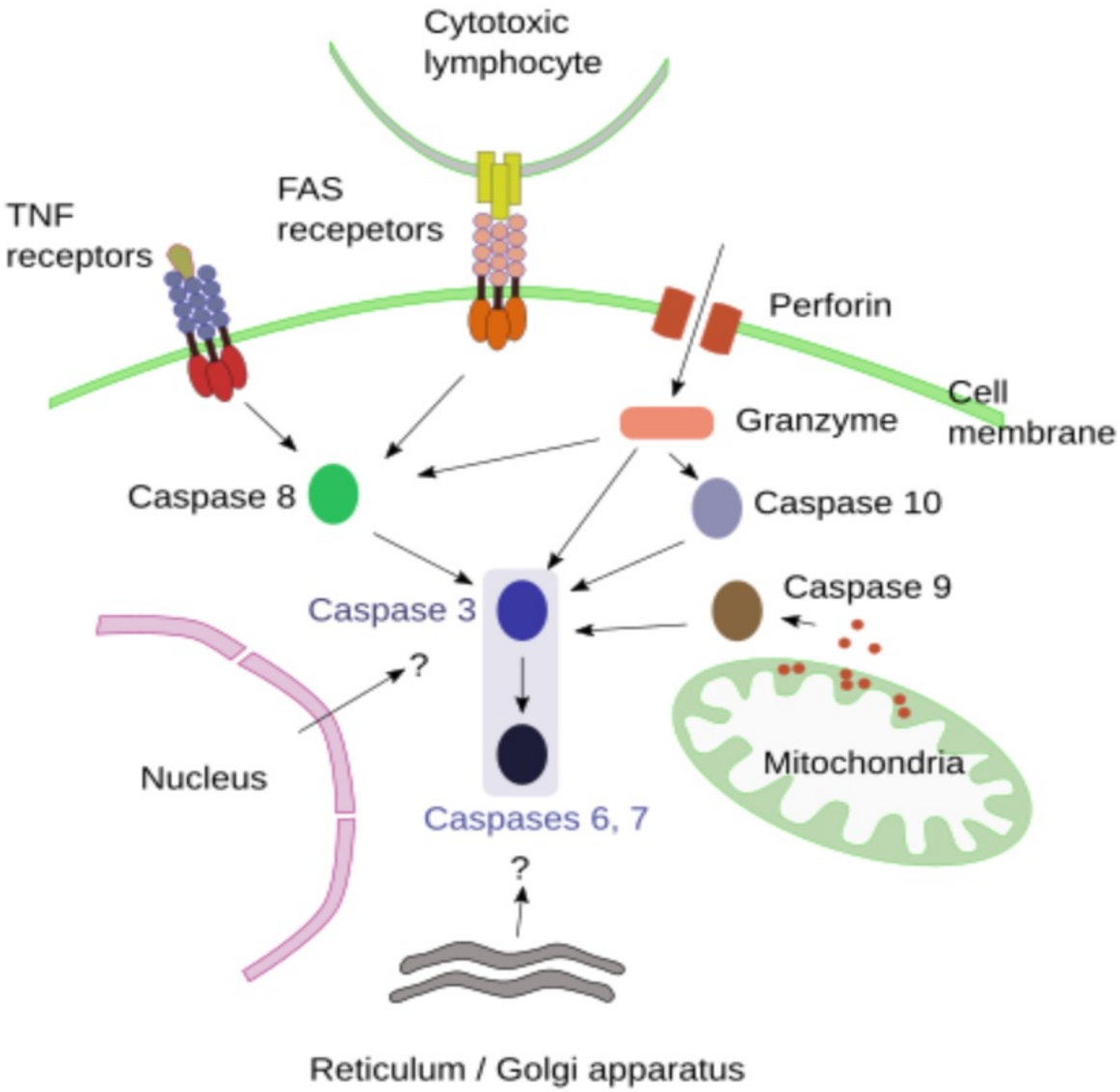


Fases da Apoptose

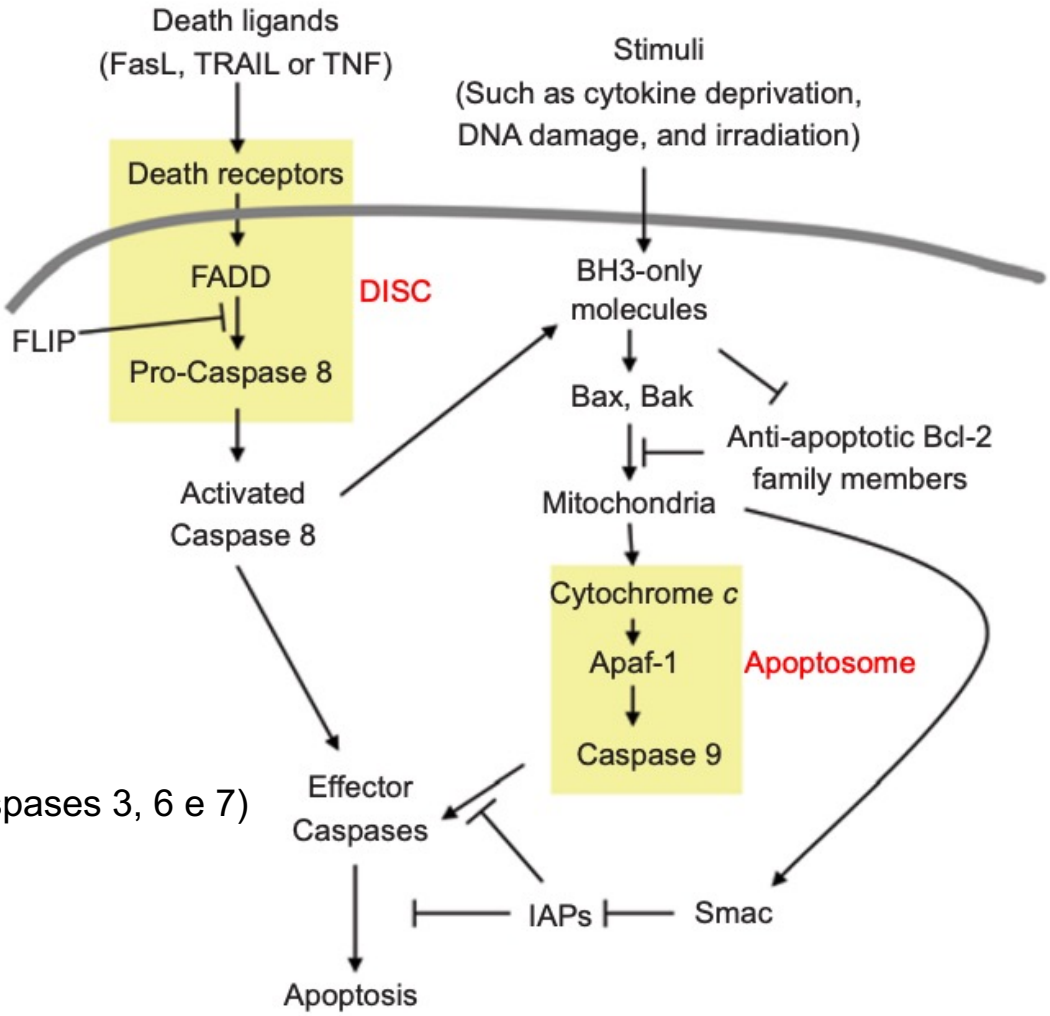




Ativação da Apoptose por Linfócitos T CD8+ Citotóxicos



Mecanismos Intrínsicos e Extrínsicos da Apoptose



(Caspases 3, 6 e 7)

FADD=Fas-Associated Dead Domain
FLIP=Fas Ligand Inhibitory Protein
DISC=Death-Inducing Signaling Complex

BH3-only molecules inhibit the anti-apoptotic proteins (Bcl-2) and activate the pro-apoptotic proteins (Bax, Bak) to cause mitochondrial outer membrane permeabilization (MOMP)

Apaf-1 = Apoptotic protease activating factor-1

IAP= Inhibitory Apoptosis Proteins
Smac= Second mitochondria-derived activator of caspase.

Possíveis Funções de Células T CD8+ em Diversas Doenças Autoimunes

TABLE 1 | The potential role of CD8+ T cells in different autoimmune diseases.

Diseases	Level of CD8+ T cells	Potential role of CD8+ T cells
GD	Decreased	Causes the production of intrathyroidal autoantibodies
MS	Increased	Mediates inflammation
SSc	Increased	Contributes to the skin fibrosis
T1D	Increased	Induces β-cell death
SLE	Increased	Induces autoantibody appearance and causing organ damage
SAA	Increased	Causes hematopoietic cell health
Vitiligo	Increased	Mediates the destruction of melanocytes

GD= Graves Disease MS= Multiple Sclerosis SSc= Systemic Sclerosis T1D= Type-1 Diabetis
SLE= Systemic Lupus Erithematous SAA=Systemic Aplatic Anemia

Front. Immunol. 10:856.
doi: 10.3389/fimmu.2019.00856

Modificações Epigenéticas Induzem Ativação de Cels T CD8+ e Autoimunidade

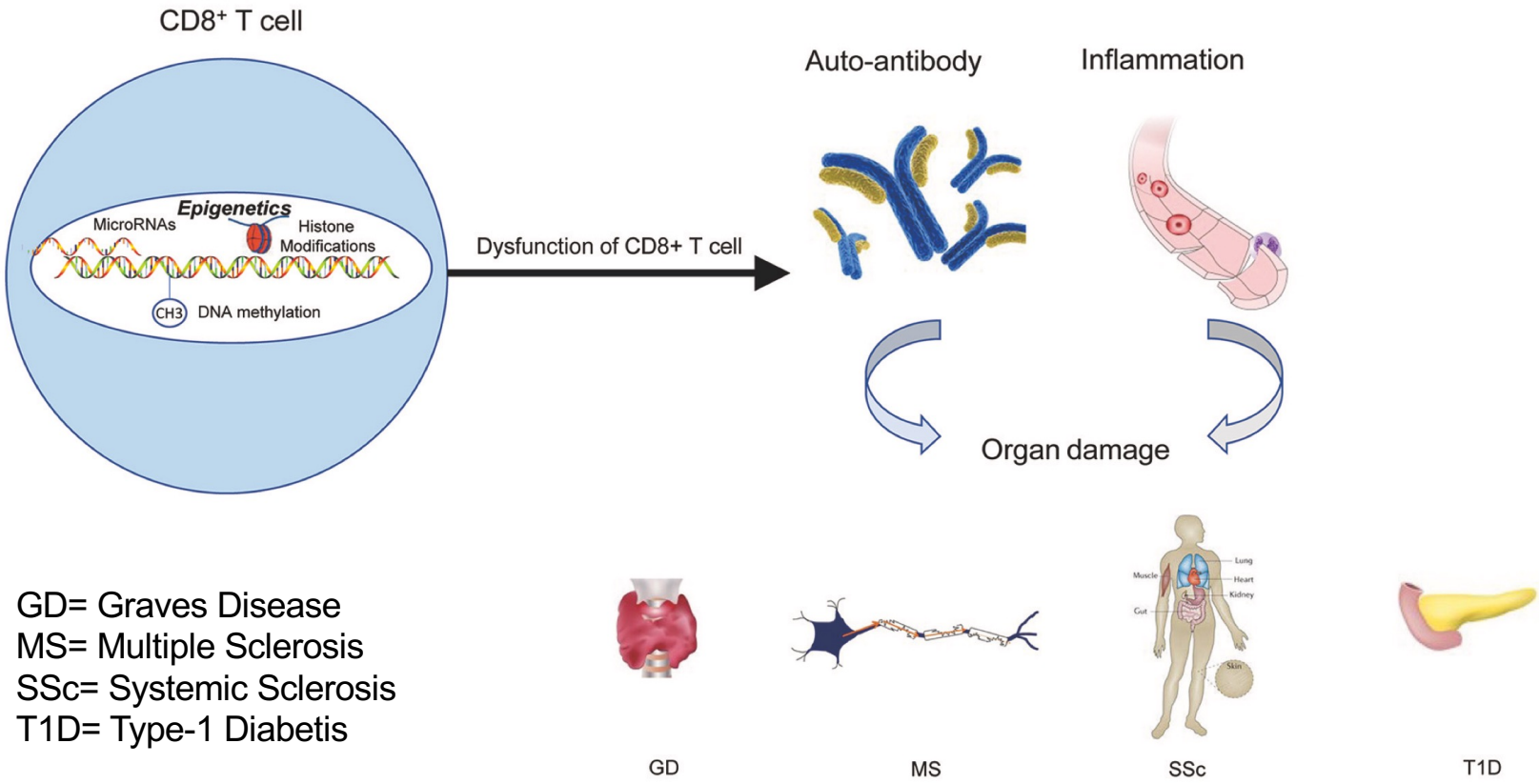


FIGURE 4 | The epigenetic role of CD8+ T cells in autoimmune diseases. Epigenetic mechanisms participate in CD8+ T cells' activation, differentiation, and development, and finally lead to the dysfunction of CD8+ T cells. The results of dysfunction of CD8+ T cells can initiate abnormal CD8+ T-cell responses, thus triggering the production of autoantibodies and inflammation that lead to autoimmune diseases.

Mecanismos Epigenéticos que Levam a Repressão ou Transcrição Gênica

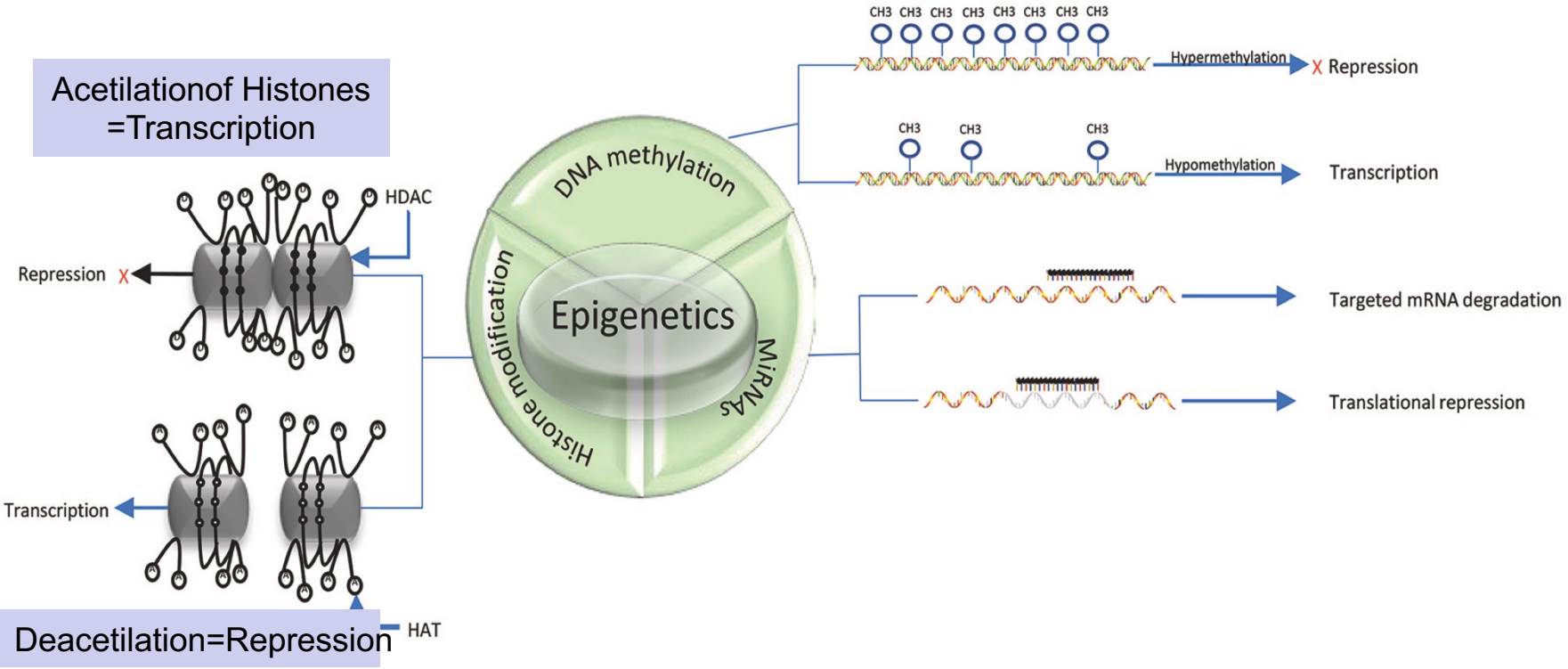
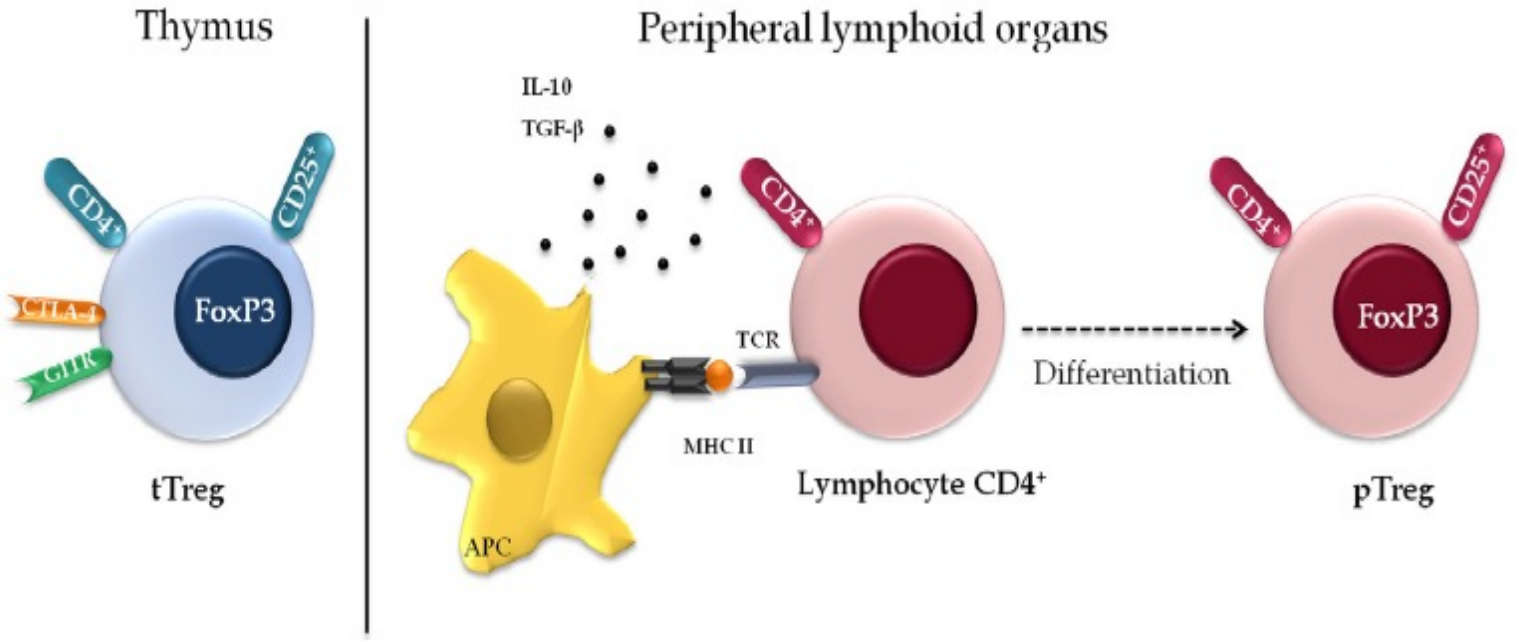


FIGURE 2 | Mechanisms of epigenetics. DNA hypermethylation leads to the repression of gene expression, while DNA hypomethylation promotes gene transcription. Histone deacetylation (D) of histone tails catalyzed by HDACs in association with DNA methylation (black solid circle) represses gene expression; Acetylation of histone tails (A) regulated by HATs in association with DNA demethylation (black hallow circle) promotes gene expression. miRNAs can suppress translation by binding to specific mRNAs. The three epigenetic modifications can interplay with each other.

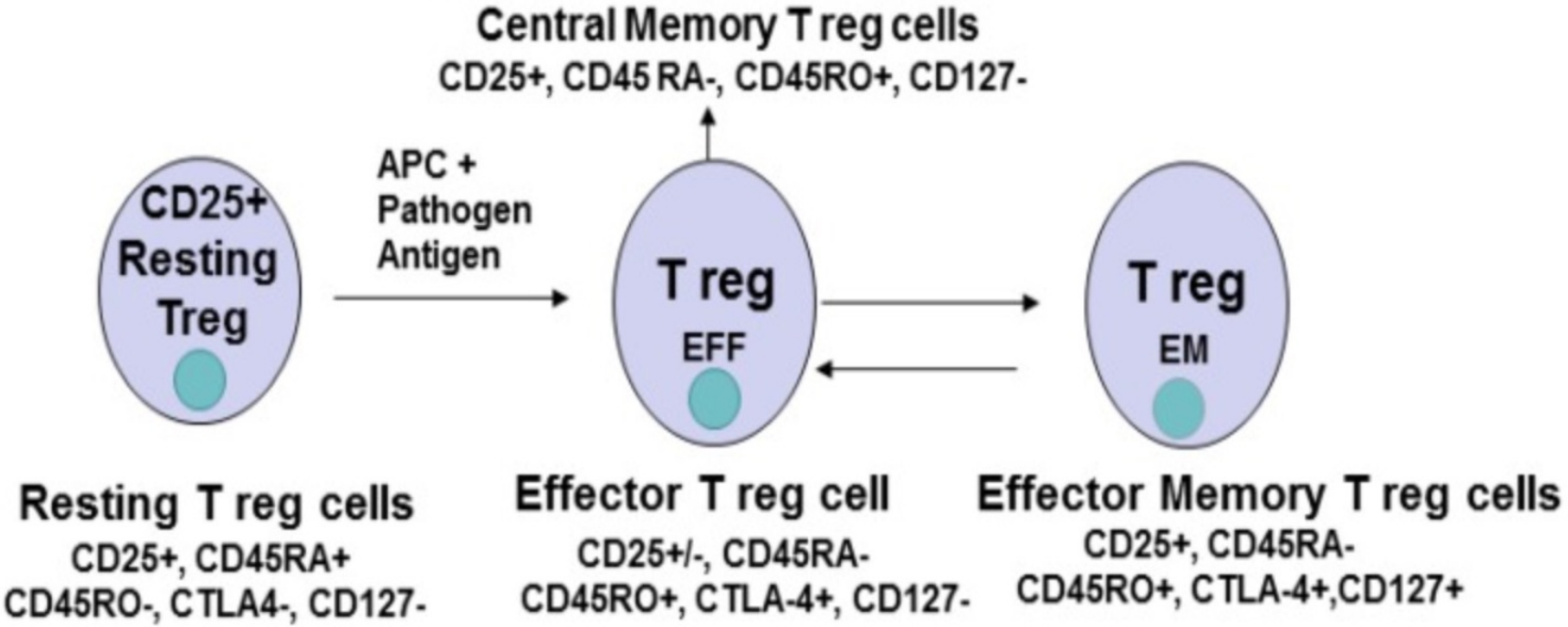
Células Treg Tímicas e Periféricas (naturais ou induzidas)



Alta expressão de PD1, neuropilin1, Helios e CD73 (ectonucleotidase)
TCR anti- AutoAgs

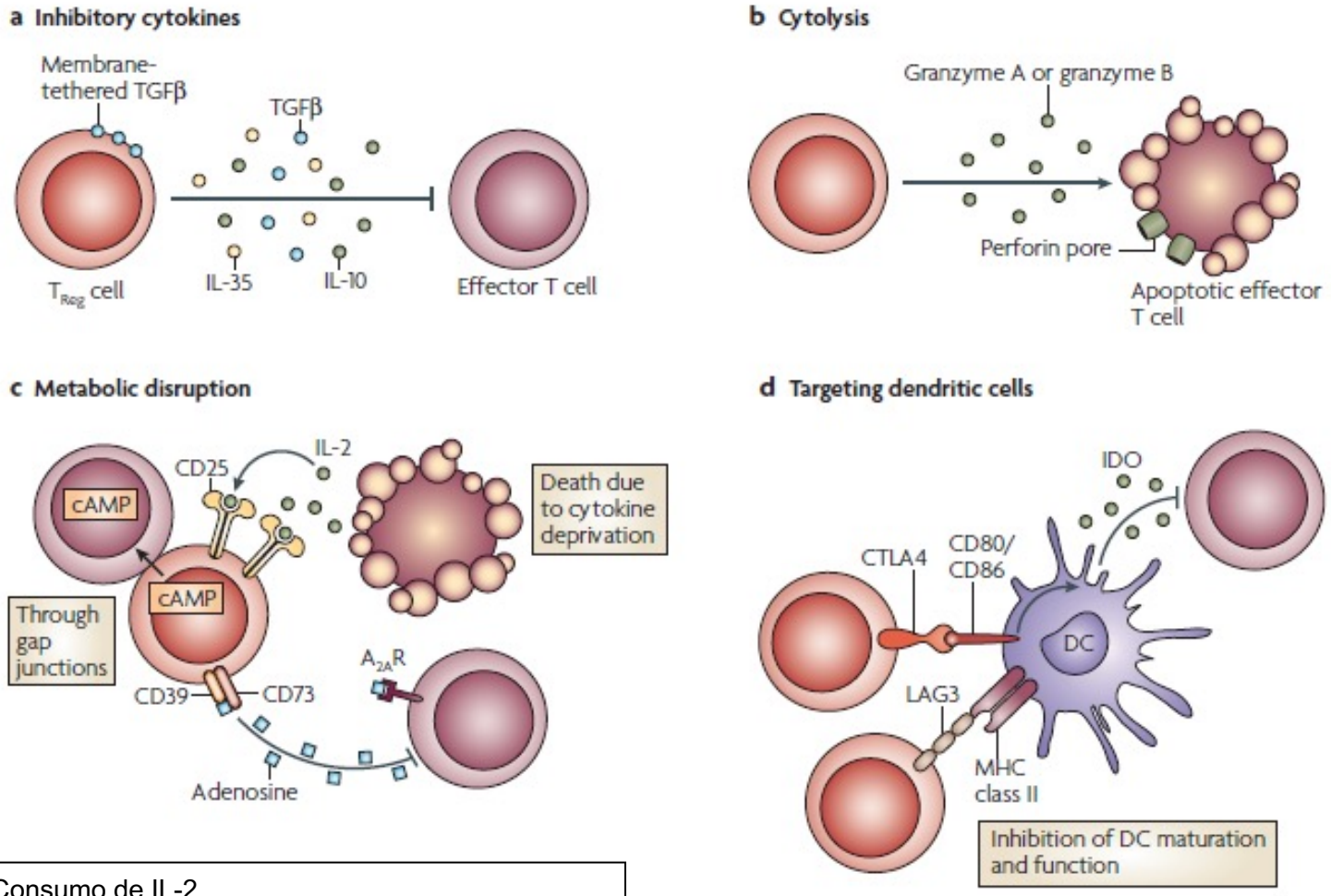
Baixa expressão de PD1, neuropilin1, Helios e CD73
TCR anti-Ags Heterólogos

Sub-Populações de Cels Treg



CD25=IL-2R CD127=IL-7R
CD45= Glycoprotein expressed on all hematopoietic cells. 8 isoforms
CD45RA is the long isoform expressed on naive T cells.
CD45RO is the shorter isoform expressed on activated T cells

Mecanismos de Regulação da RI por Cels Treg (CD4+CD25+ Foxp3+)



Consumo de IL-2
Geração de cAMP ou Adenosina (anti-inflamatória) a partir de ADP/ATP (pró-inflamatórios) pelas Ectonucleotidases CD39/CD73

Indução de IDO via CTLA4/B7,
Depleção de Triptofano
Produção de Kinureninas supressoras

ELSEVIER

As células Treg Podem Inibir ou Induzir Patologia