ATIVAÇÃO DE LINFÓCITOS

- Histórico
- Ativação de linfócitos T: bases da imunidade
- Reconhecimento de antígenos por TCR
- Apresentação de antígenos por APC
- Restrição de ativação de linfócitos T (controle)
- Diferenciação de linfócitos (T cell populations)
- Sinapse imunológica
- Controle da ativação de T
- Ativação de linfócitos B

Profº. João Santana FMRP-USP, 2023

History of Vaccination: Smallpox

Smallpox killed or maimed 10% of humankind.

Killed > 300,000,000 people in the 20th century alone

Ancient Chinese history: a once in a lifetime disease.

11th century China and India: "Variolation"

Scratch a healthy person with pus from infected person

If they don't die, they are immune for life

FIGURES SHOWING VACCINATION PUSTULES

From a Chinese work on Vaccination

May 14, 1796, Edward Jenner

AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

LONDON:

PRINTED FOR THE AUTHOR,

AND SOLD BY LAW, ST. PAUL'S CHURCH-YARD; AND MURRAY AND HIGHLEY, FLEET STREET.

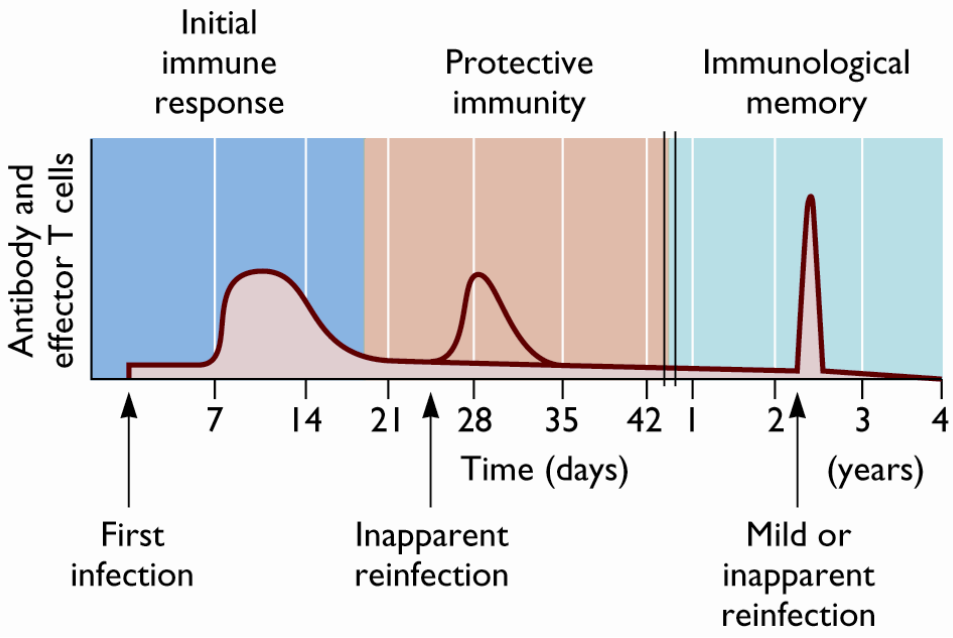
1798.

History of Vaccination

- Despite Jenner's success, it took 100 years til the next vaccine.
- 1881, Louis Pasteur: coined the word Vaccine.
  - Used dried spinal cord from rabid rabbit to create a rabies vaccine.
  - Also developed vaccines to fowl cholera and anthrax

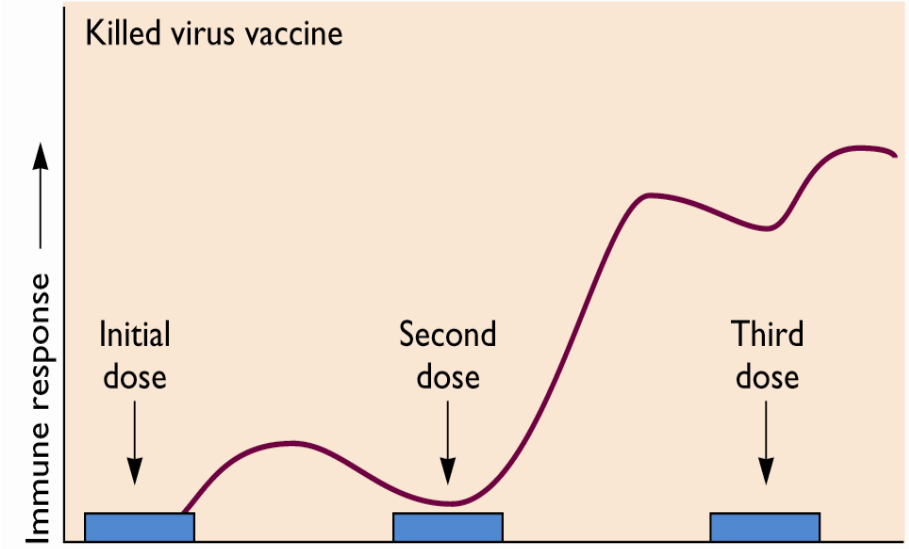
- July 6, 1885: 9 year old Joseph Meister who was badly bitten by a rabid dog.
- Although Pasteur was not a licensed physician and faced legal risks, the boy would most certainly have died without treatment like many before him.
- Pasteur decided to treat the boy nevertheless and inoculated Joseph with rabies vaccine that had been tested only on dogs previously.
- The risk paid off and the boy recovered dramatically.

Antibody and effector T-cells are the basis of protective immunity

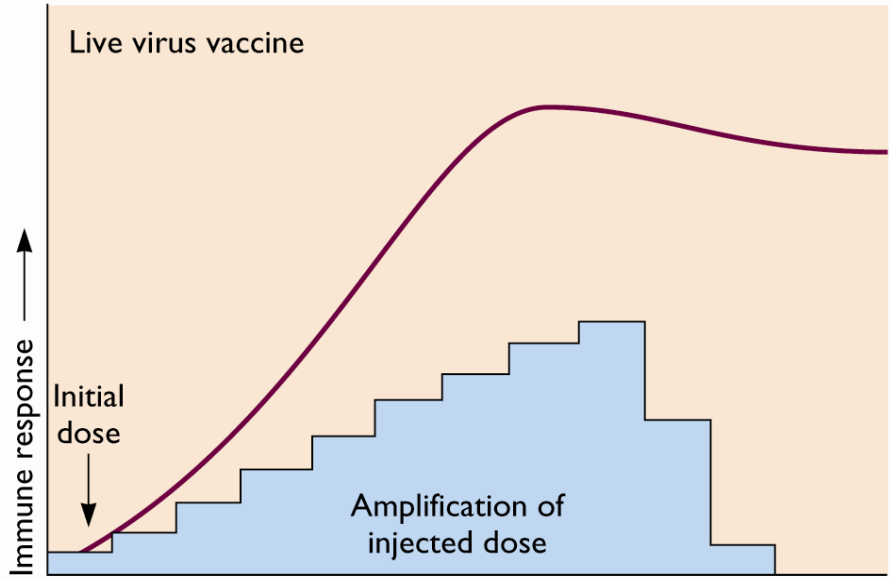


- Primary infection stimulates an initial immune response.
- A second infection is “inapparant” because it provokes no symptoms.
- However, it does re-stimulate and fine tune the immune response.
- Years later, memory B- and T-cells can become reactivated upon infection, protecting the individual from disease

Vaccines stimulate immune memory



•Killed virus vaccine requires multiple doses (booster shots) to adequately stimulate a protective immune response



•Live virus vaccines replicate in the host.
•No requirement for boosters.

Estágios de maturação do linfócito T

1- Proliferação de células imaturas;
2- Expressão de genes dos receptores de antígenos;
3- Seleção dos linfócitos que expressam receptores de antígenos funcionais ;

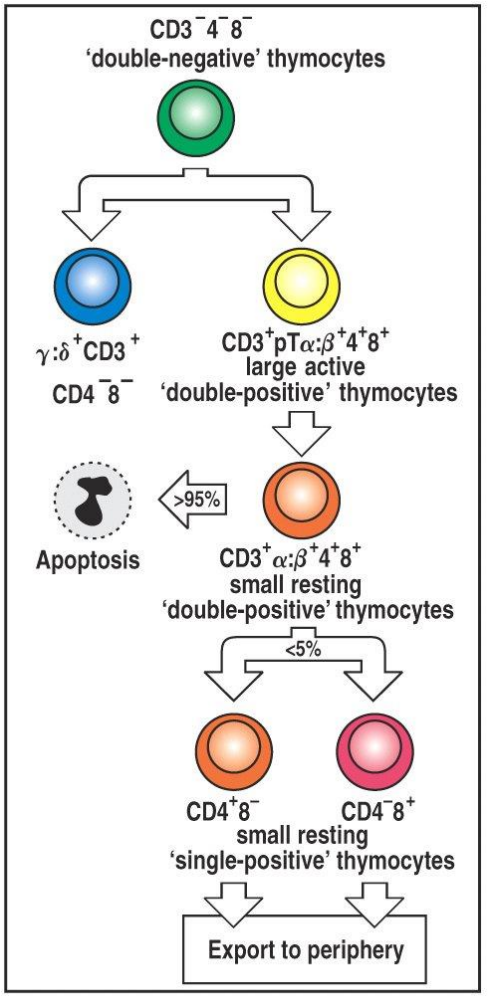


Figure 7-12 Immunobiology, 6/e. (© Garland Science

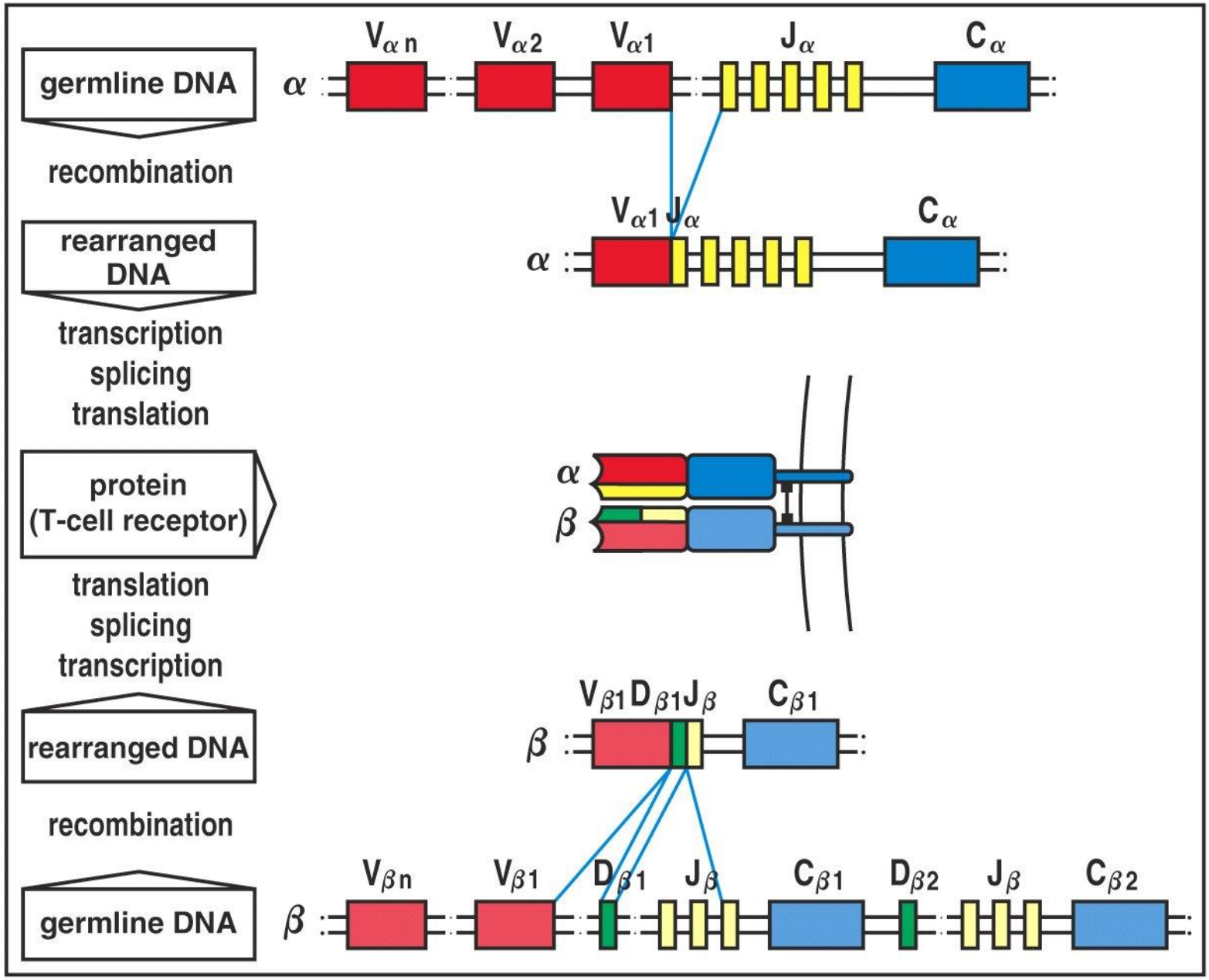


Figure 4-12 Immunobiology, 6/e. (© Garland Science 2005)

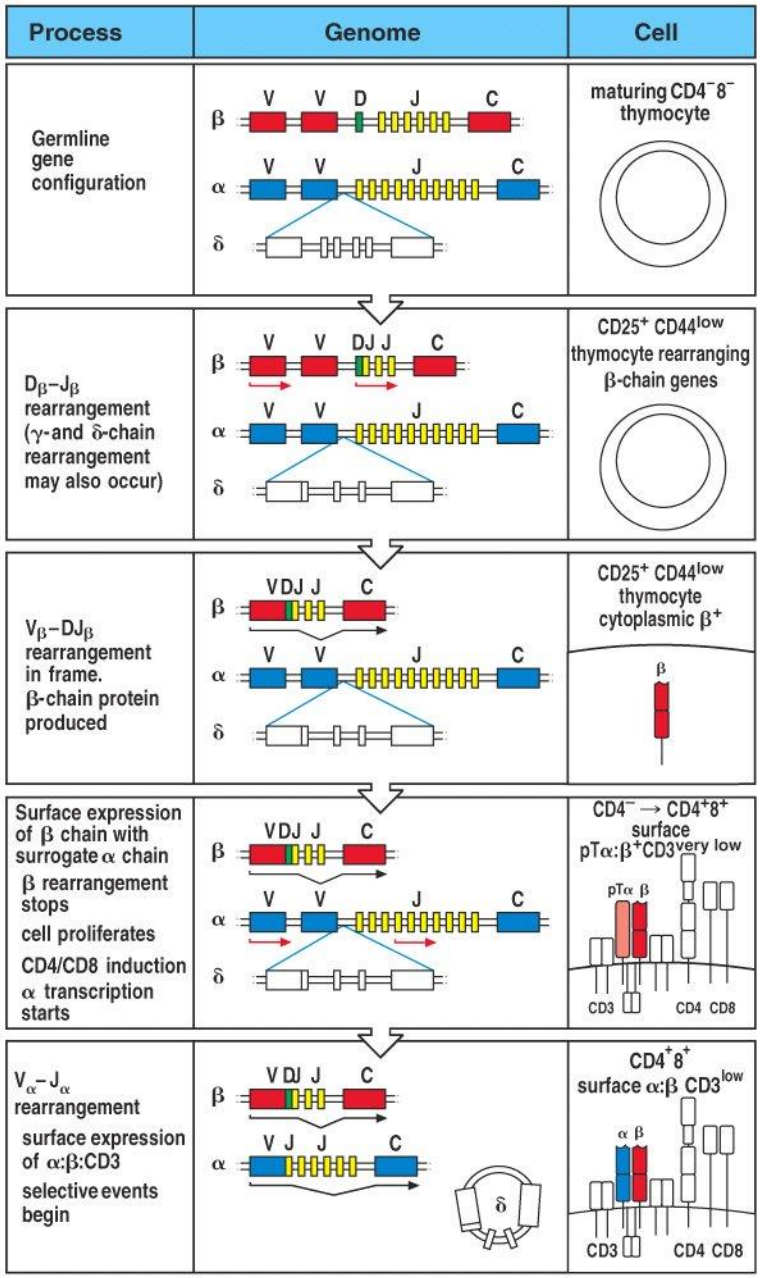
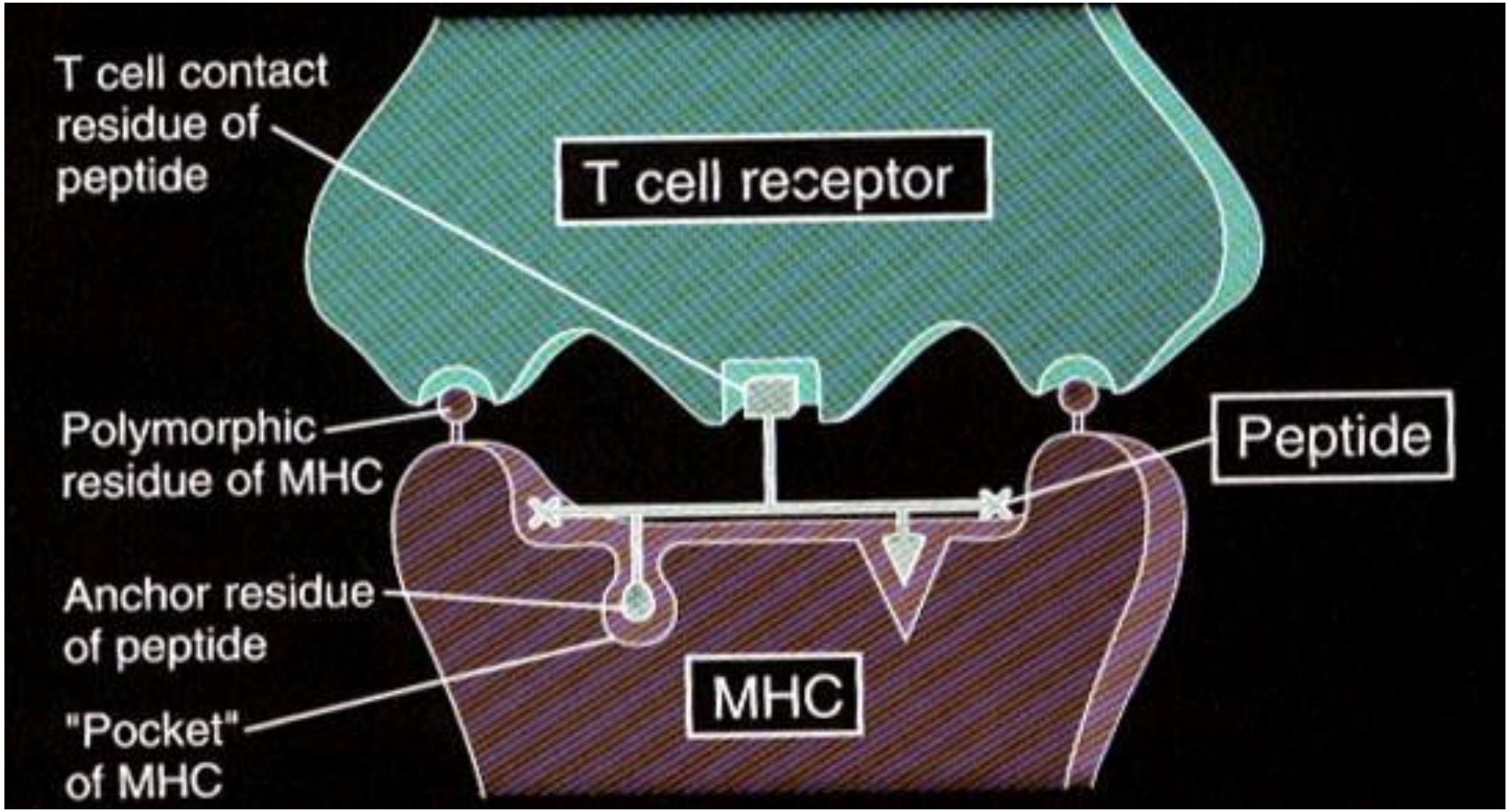
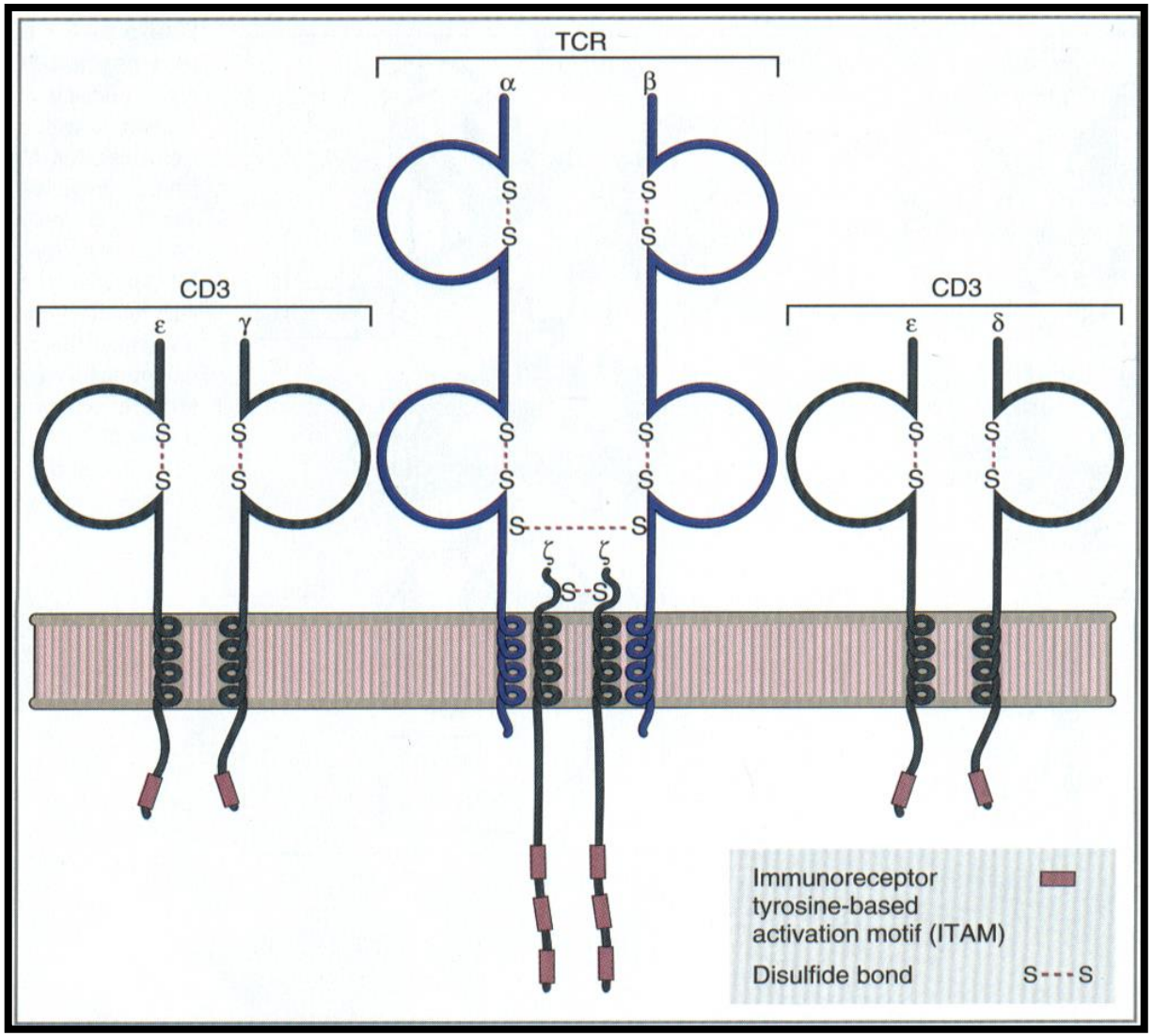


Figure 7-21 Immunobiology, 6/e. (© Garland Science 2005)

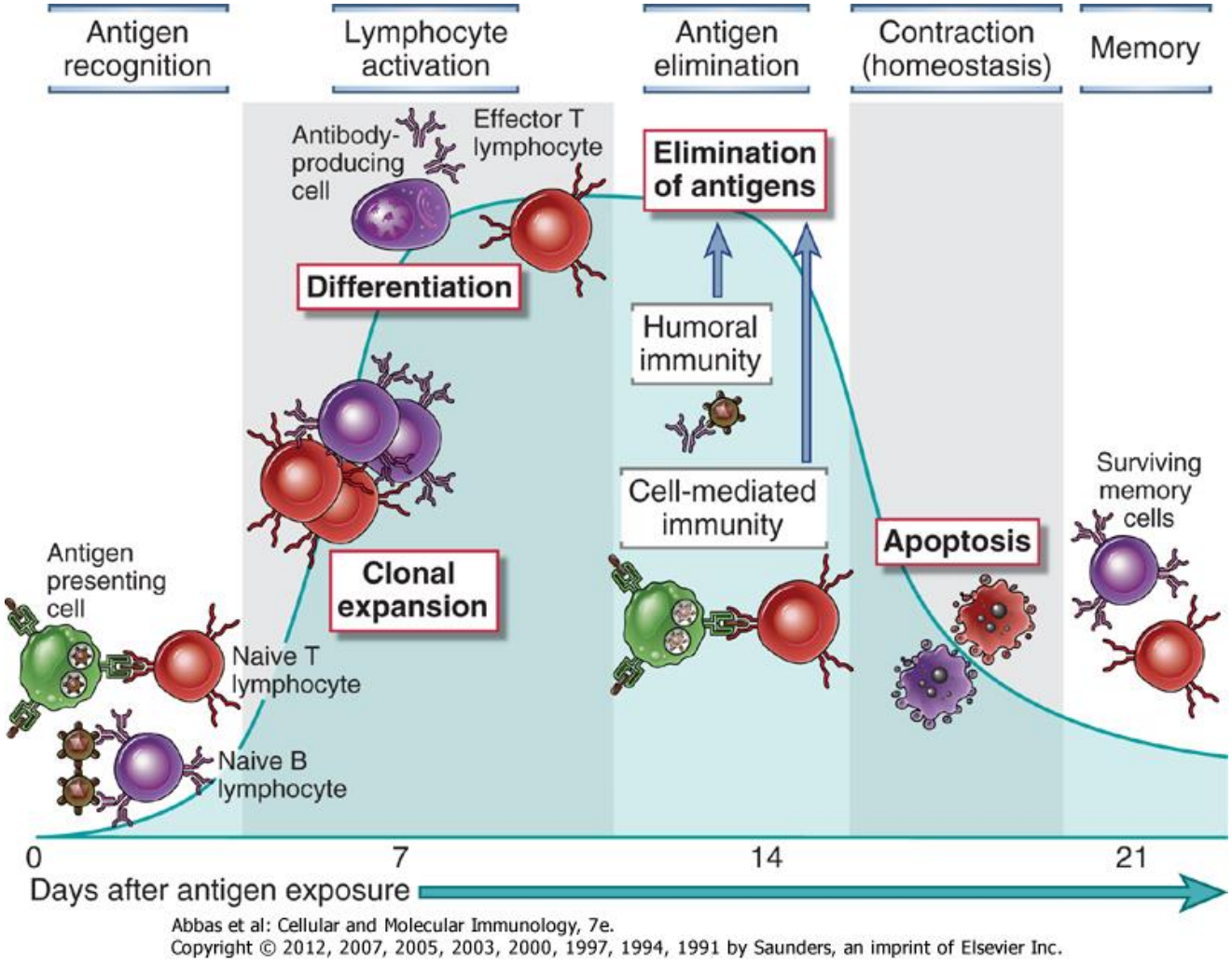
TCR & MHC/Pept


T cell contact residue of peptide
T cell receptor
Polymorphic residue of MHC
Peptide
Anchor residue of peptide
MHC
"Pocket" of MHC

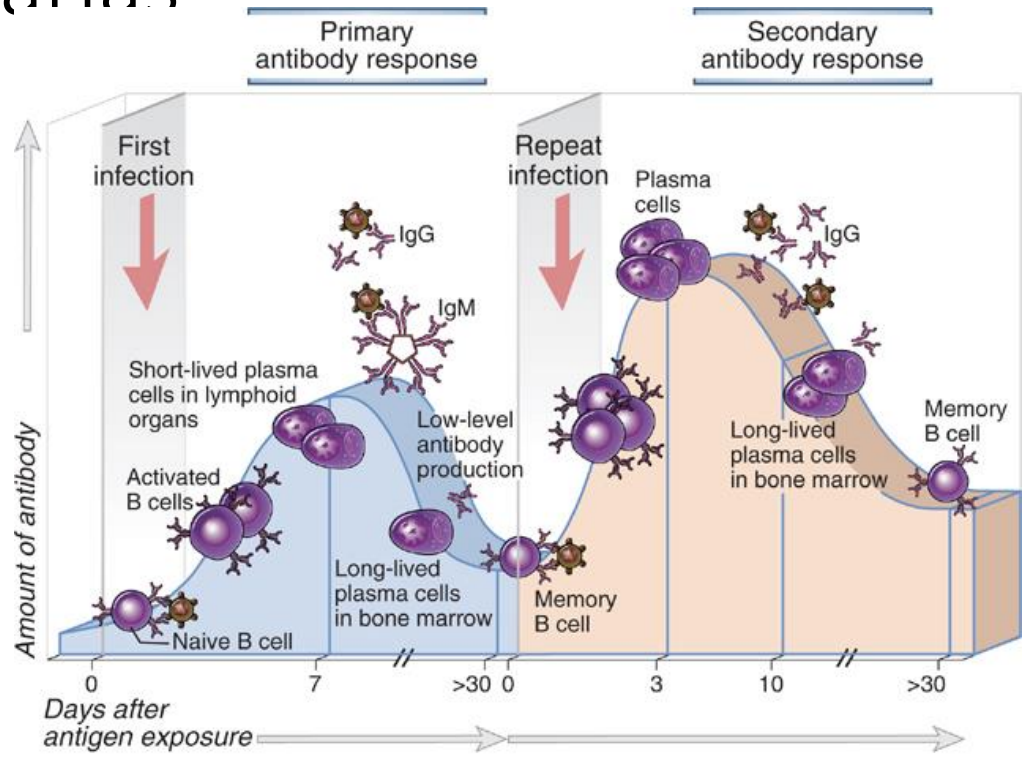
COMPLEXO TCR



Fases das Respostas de Células T



Respostas Imunes Primárias e Secundárias



Feature	Primary response	Secondary response
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

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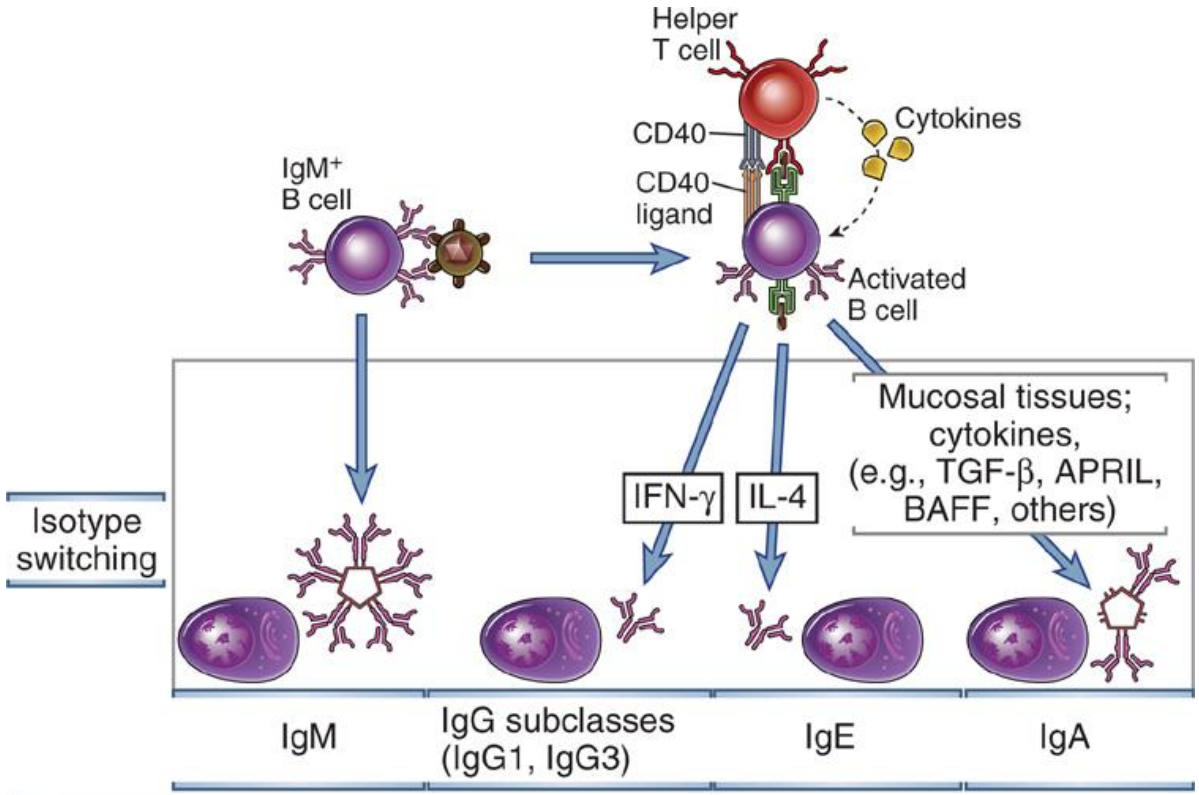
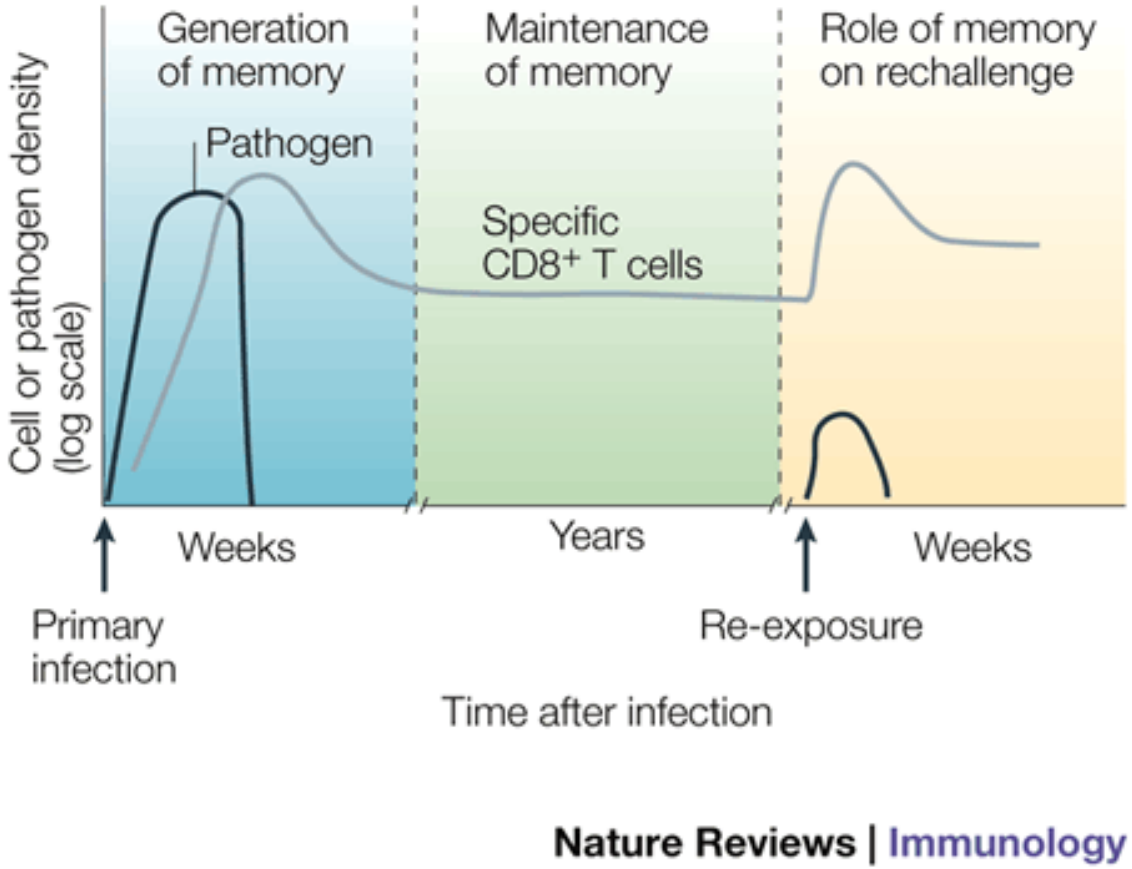
Mudança de Isotipo de cadeia pesada

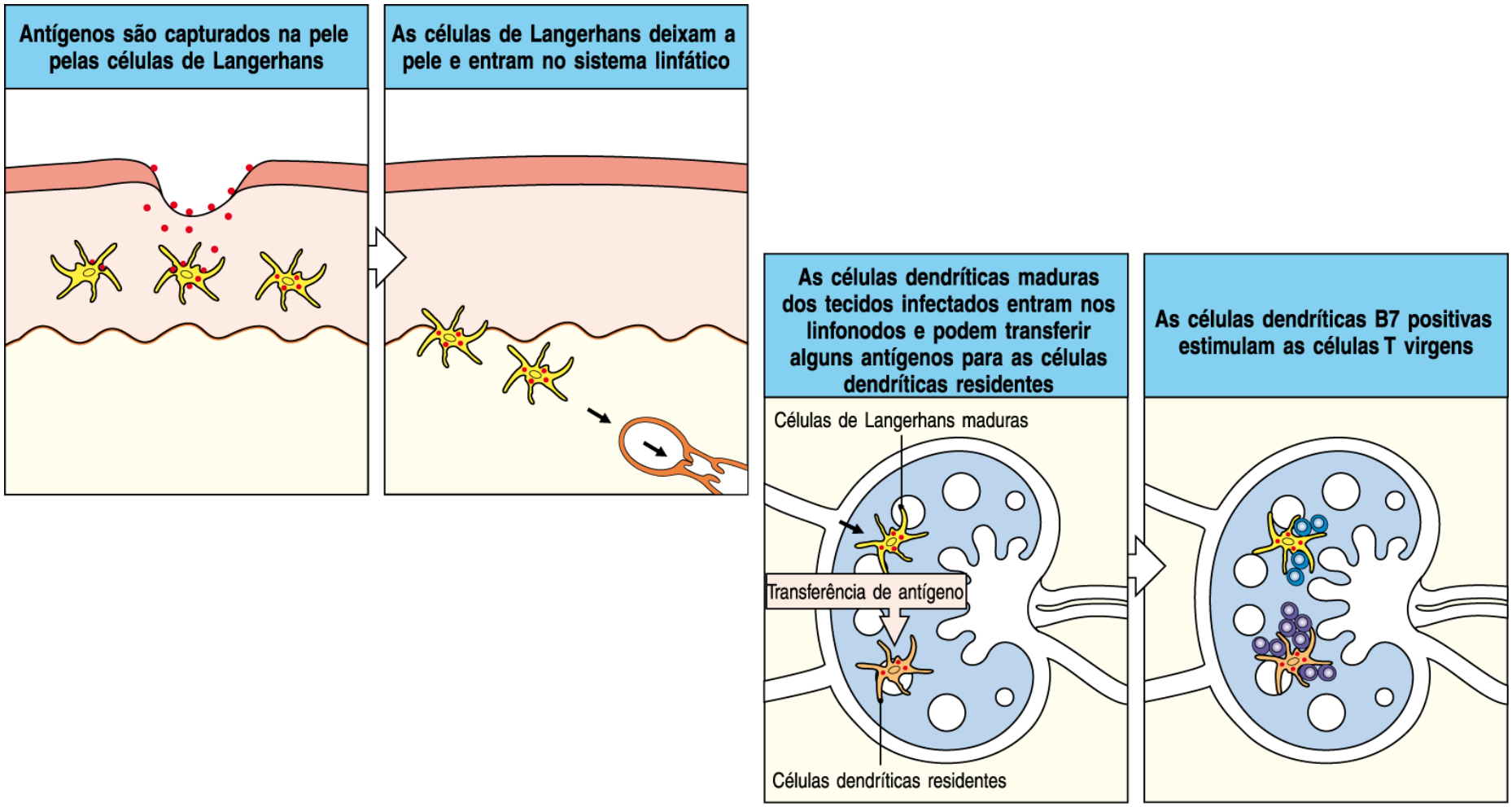


Principal effector functions	Complement activation	Fc receptor-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

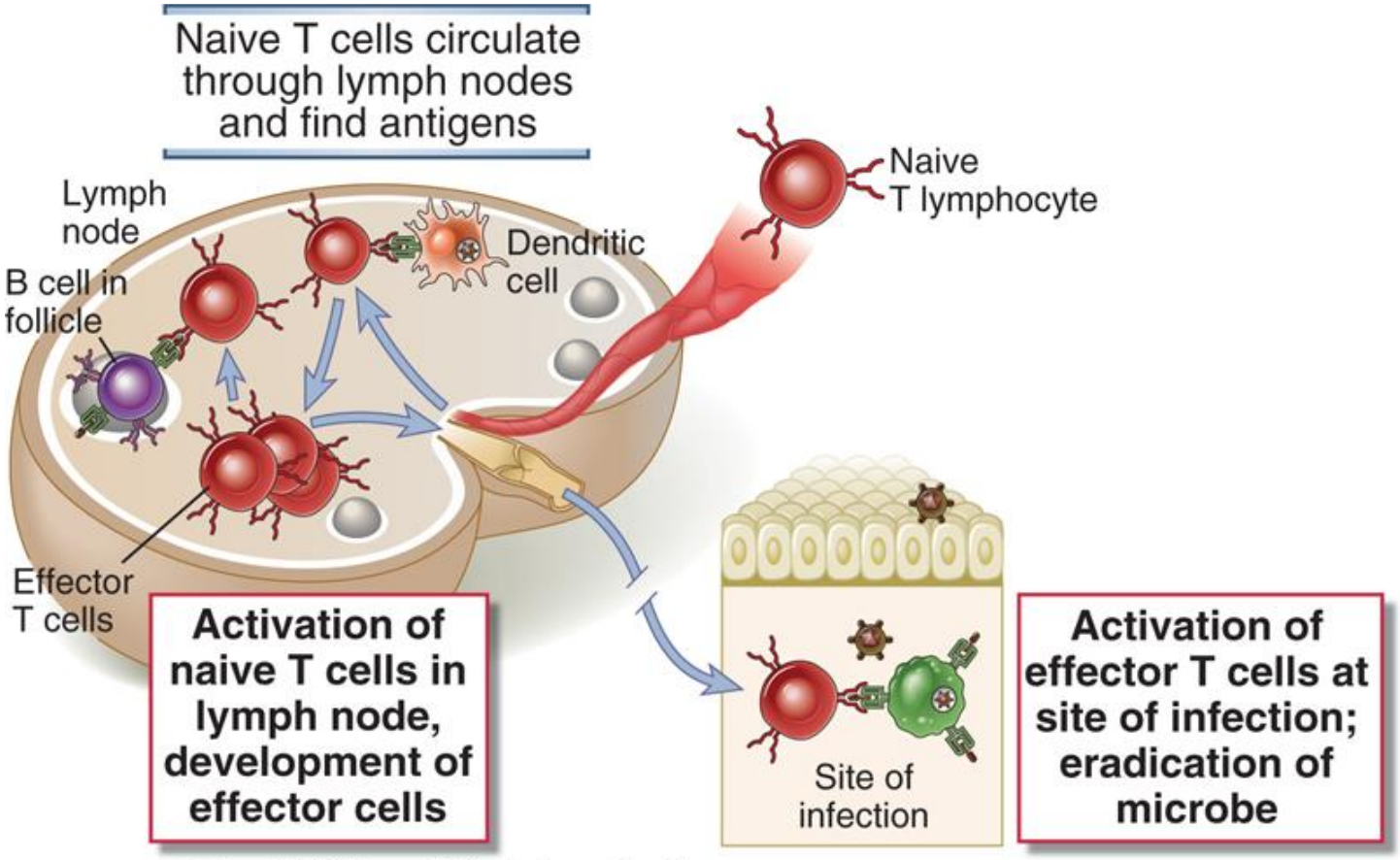
Células T CD8^{+} de memória



DC: apresentação de Ag nos LNs

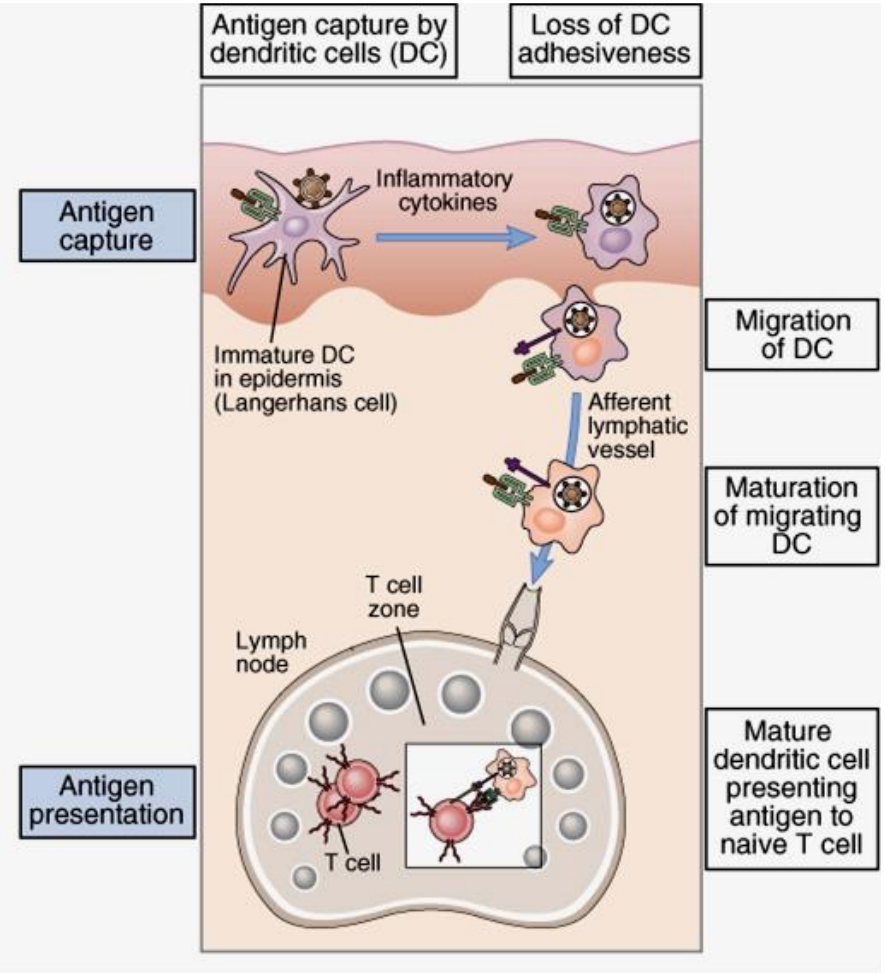


Recirculação dos Linfócitos T virgens



Fase 1: Reconhecimento do Antígeno

Captura e Apresentação



Moléculas de Adesão

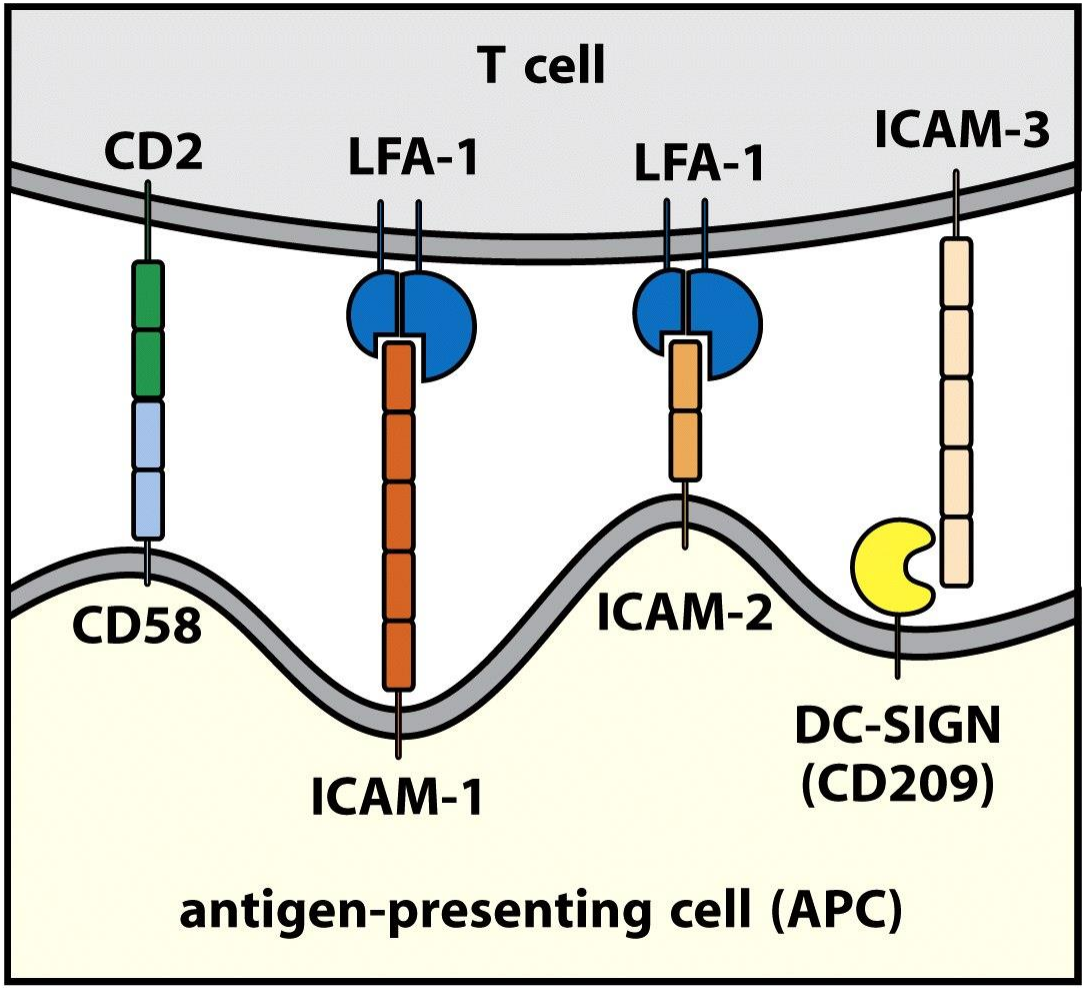
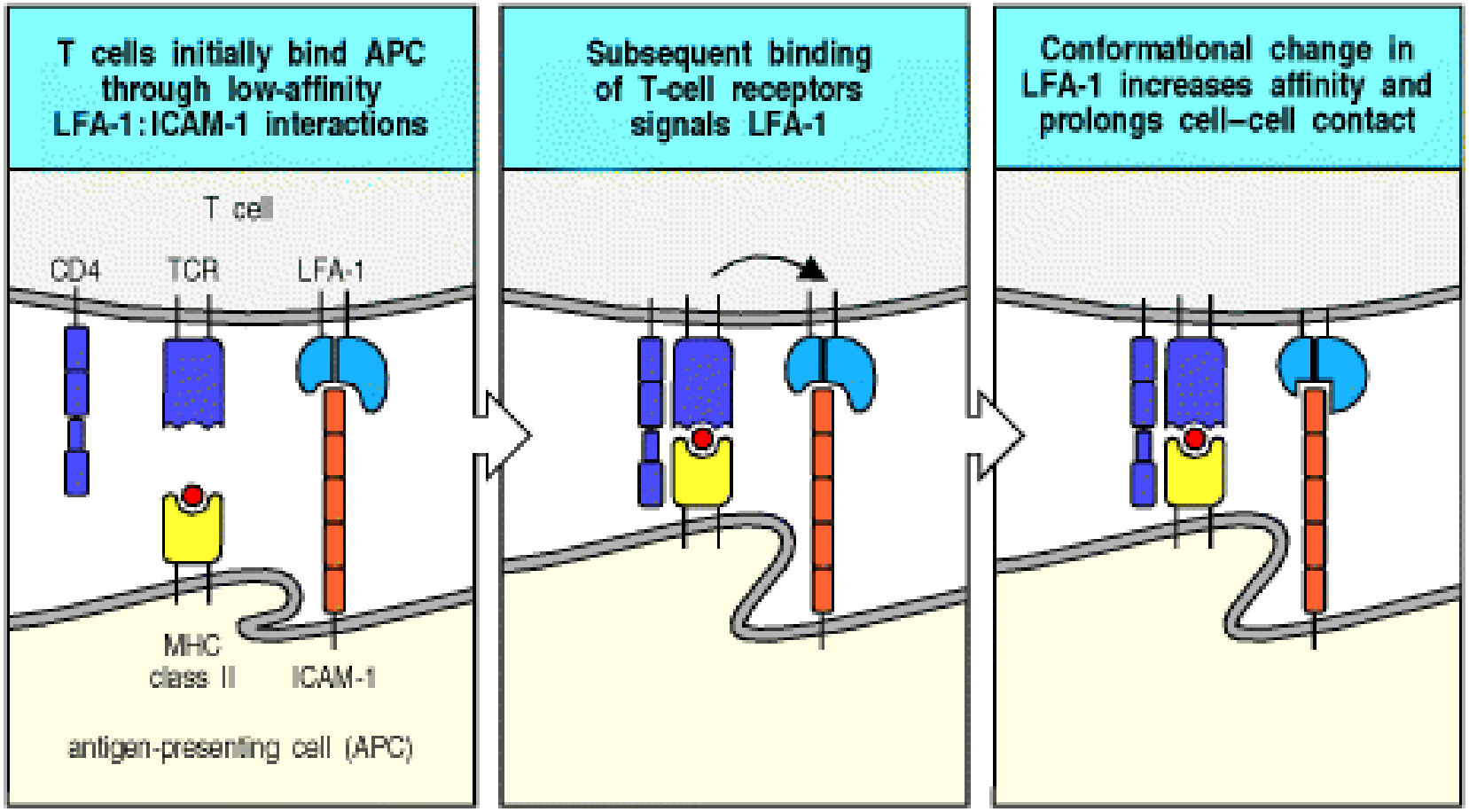


Figure 8-17 Immunobiology, 7ed. (© Garland Science 2008)


T cells initially bind APC through low-affinity LFA-1:ICAM-1 interactions
Subsequent binding of T-cell receptors signals LFA-1
Conformational change in LFA-1 increases affinity and prolongs cell–cell contact
T cell
CD4
TCR
LFA-1
MHC class II
ICAM-1
antigen-presenting cell (APC)

Entrada de Linfócitos T virgens em órgãos Linfóides

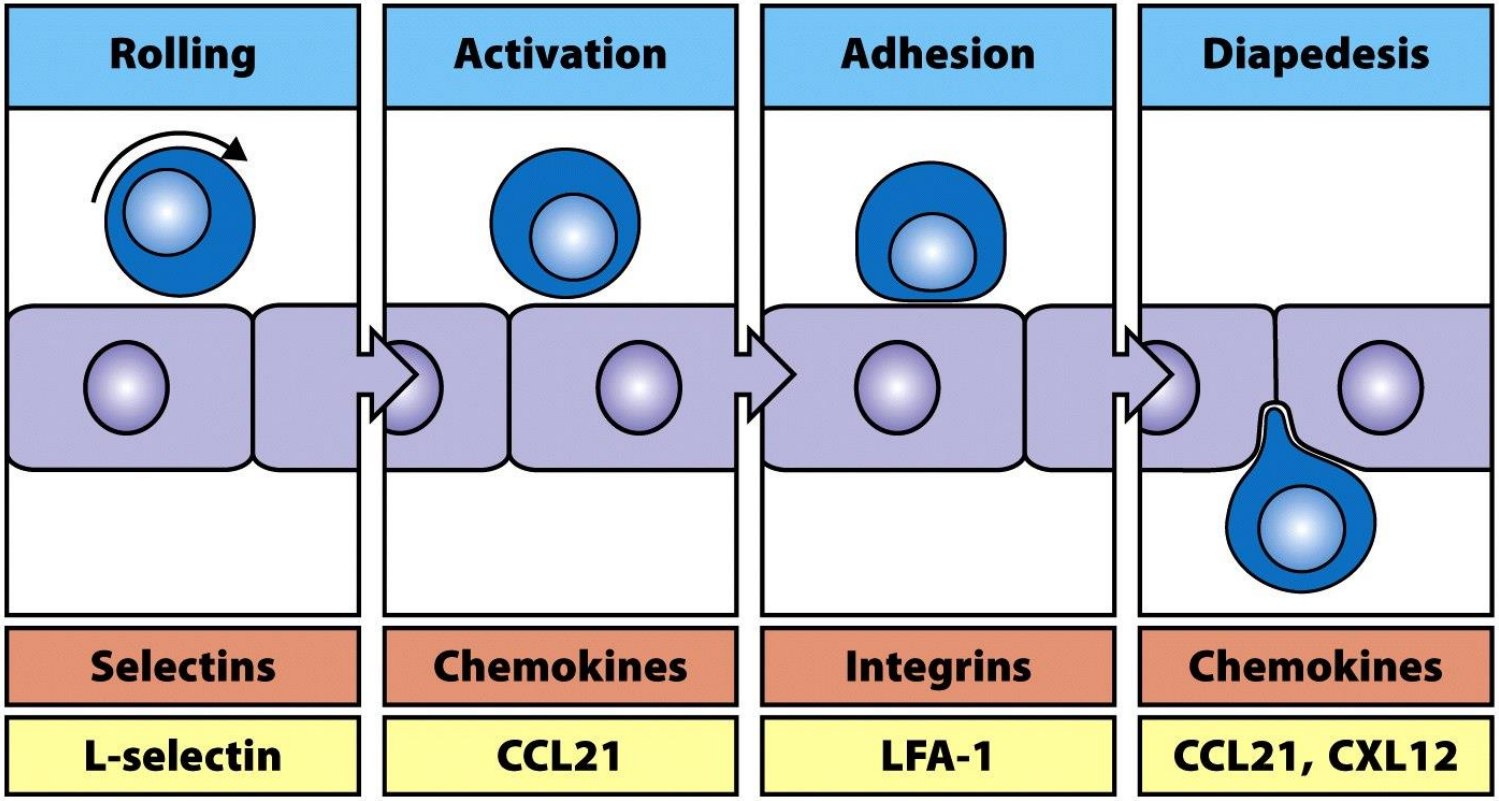


Figure 8-4 Immunobiology, 7ed. (© Garland Science 2008)

Entrada de Linfócitos T virgens em órgãos Linfóides

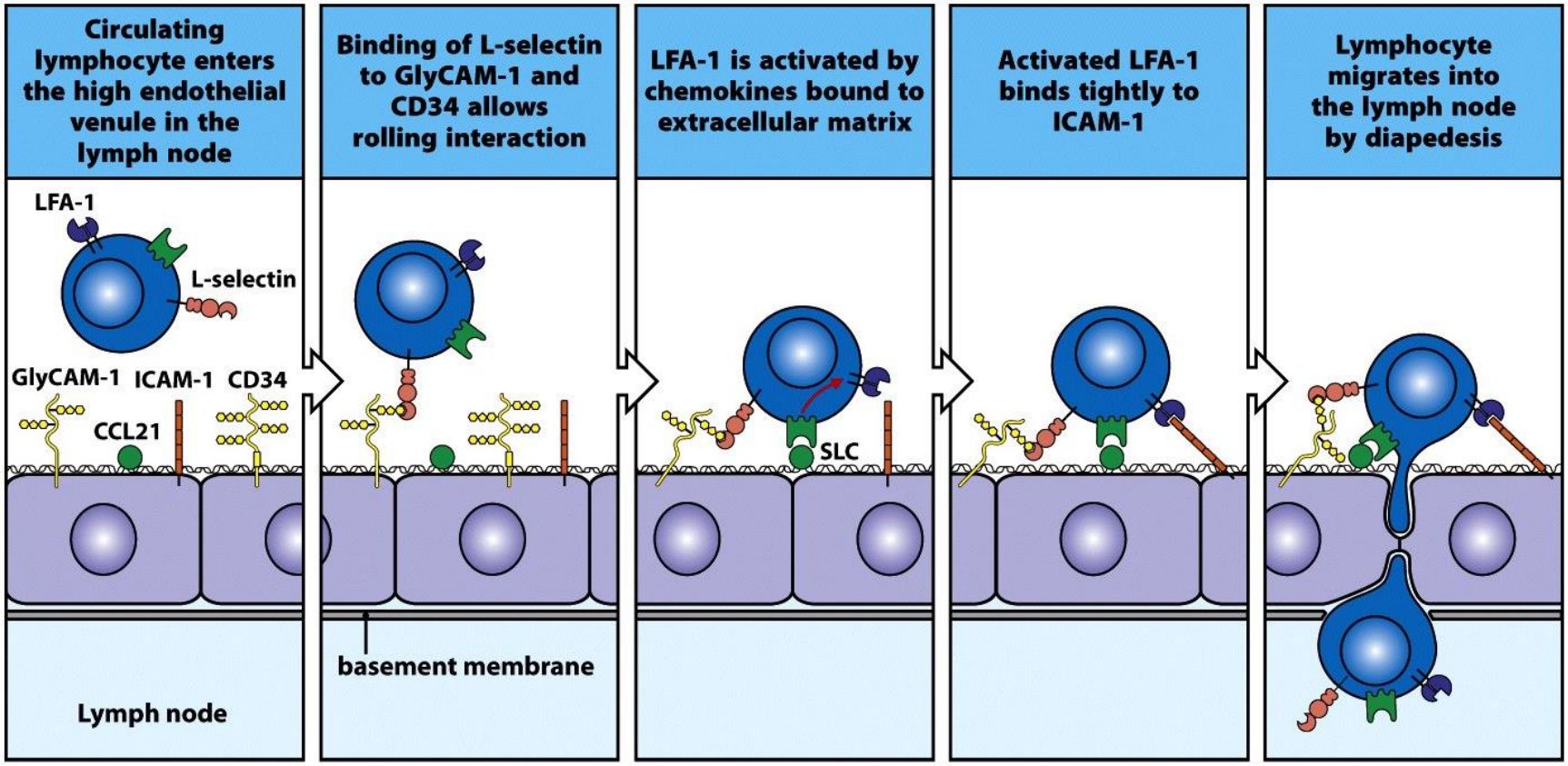
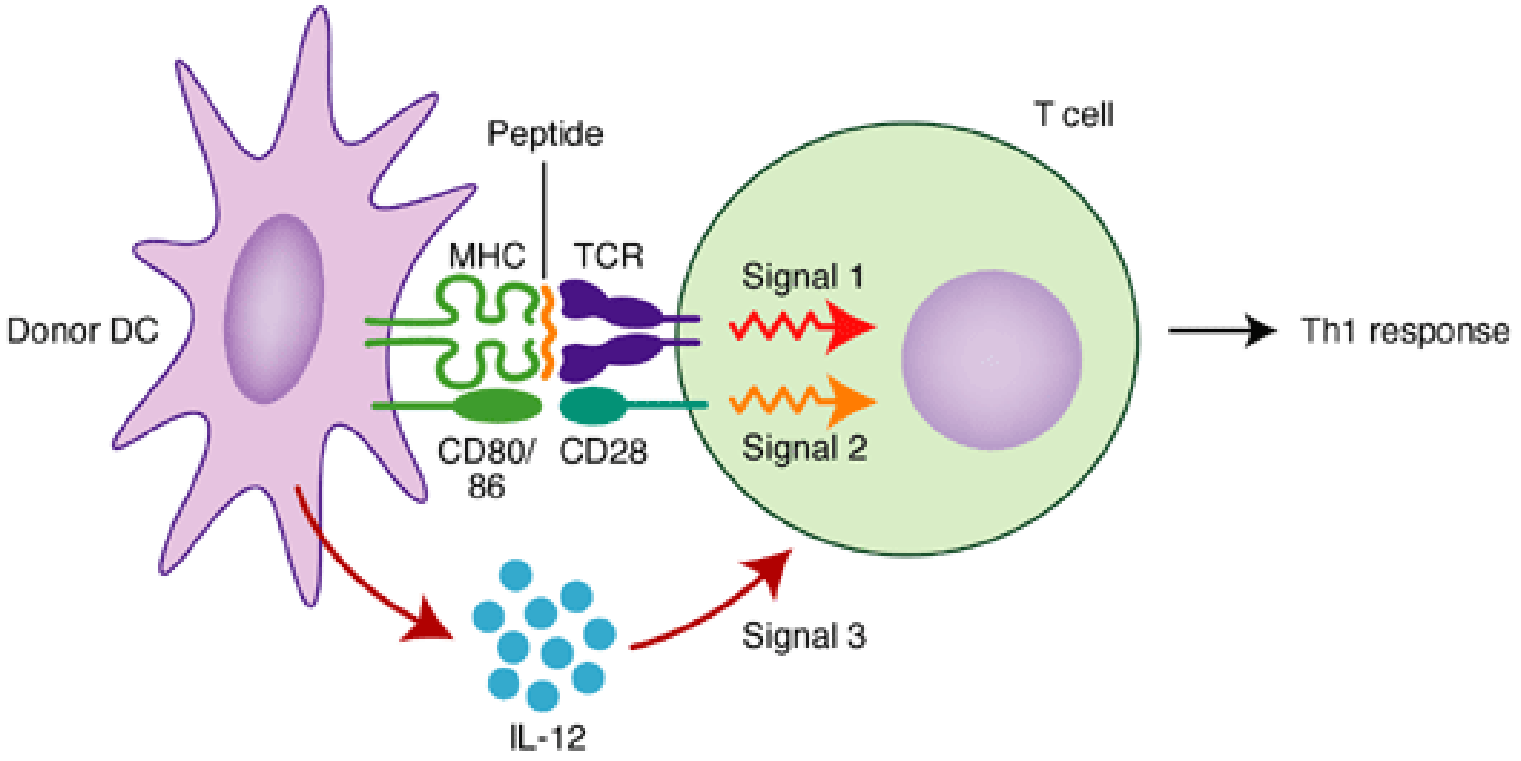


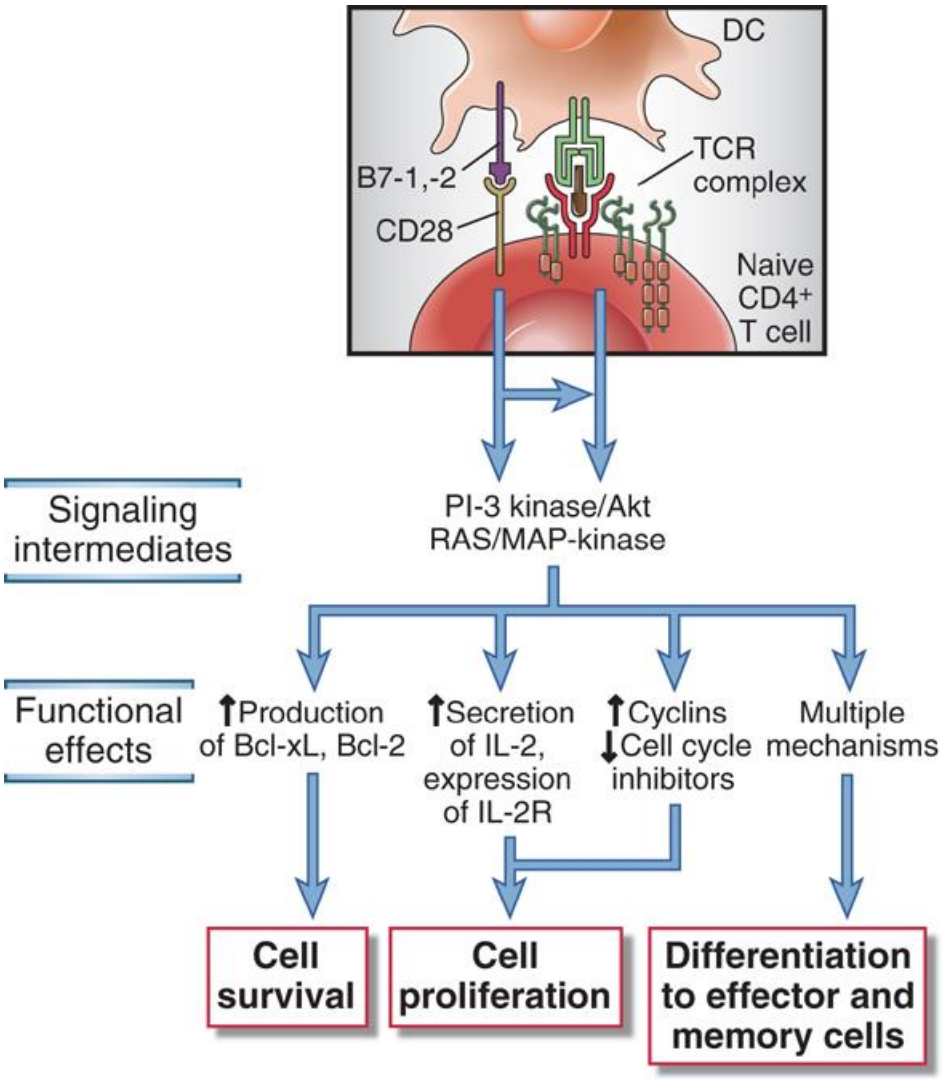
Figure 8-8 Immunobiology, 7ed. (© Garland Science 2008)

Fase 2: Ativação de Linfócitos

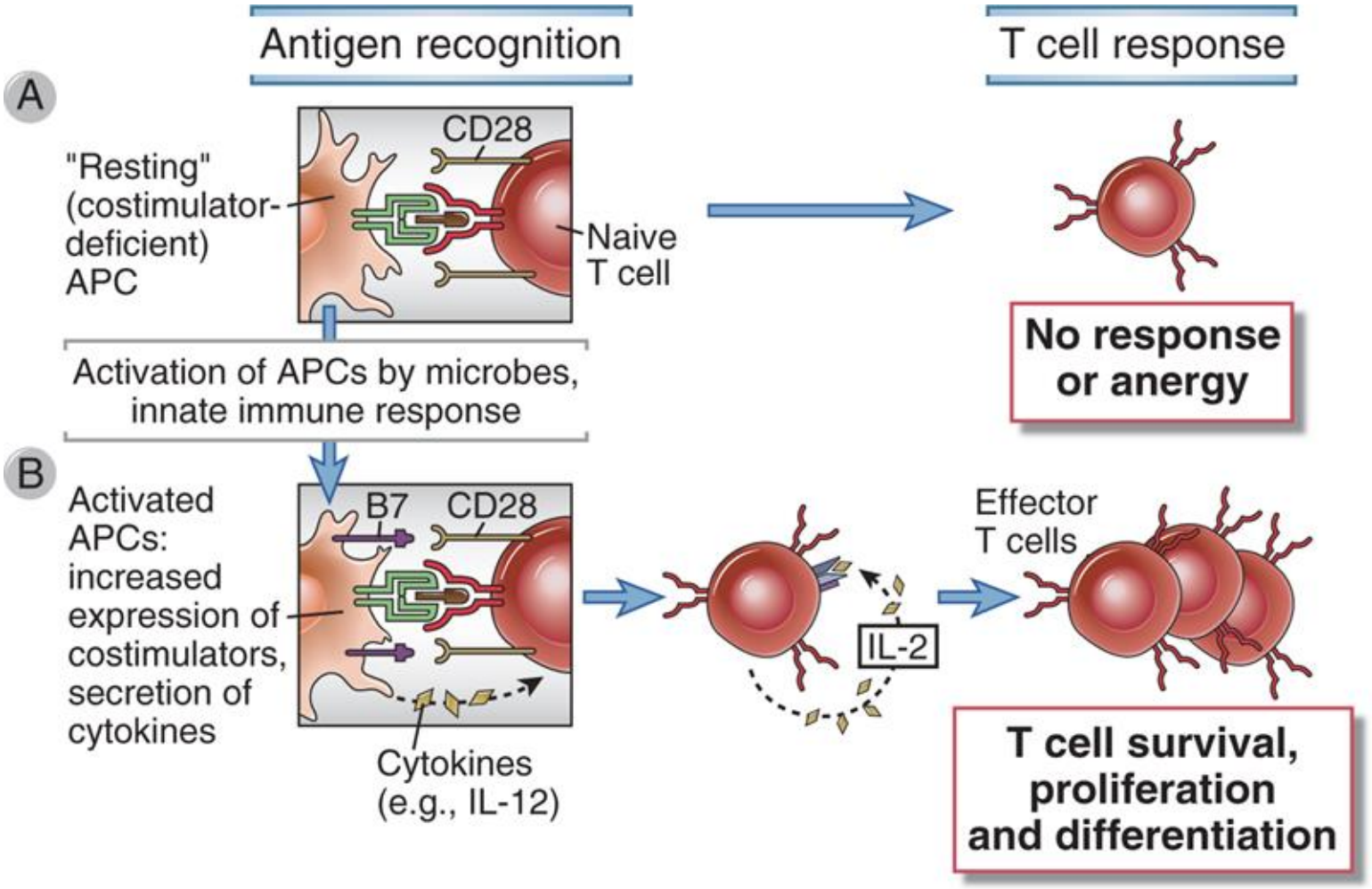


The interaction between dendritic cells (DCs) and T cells involves three signals

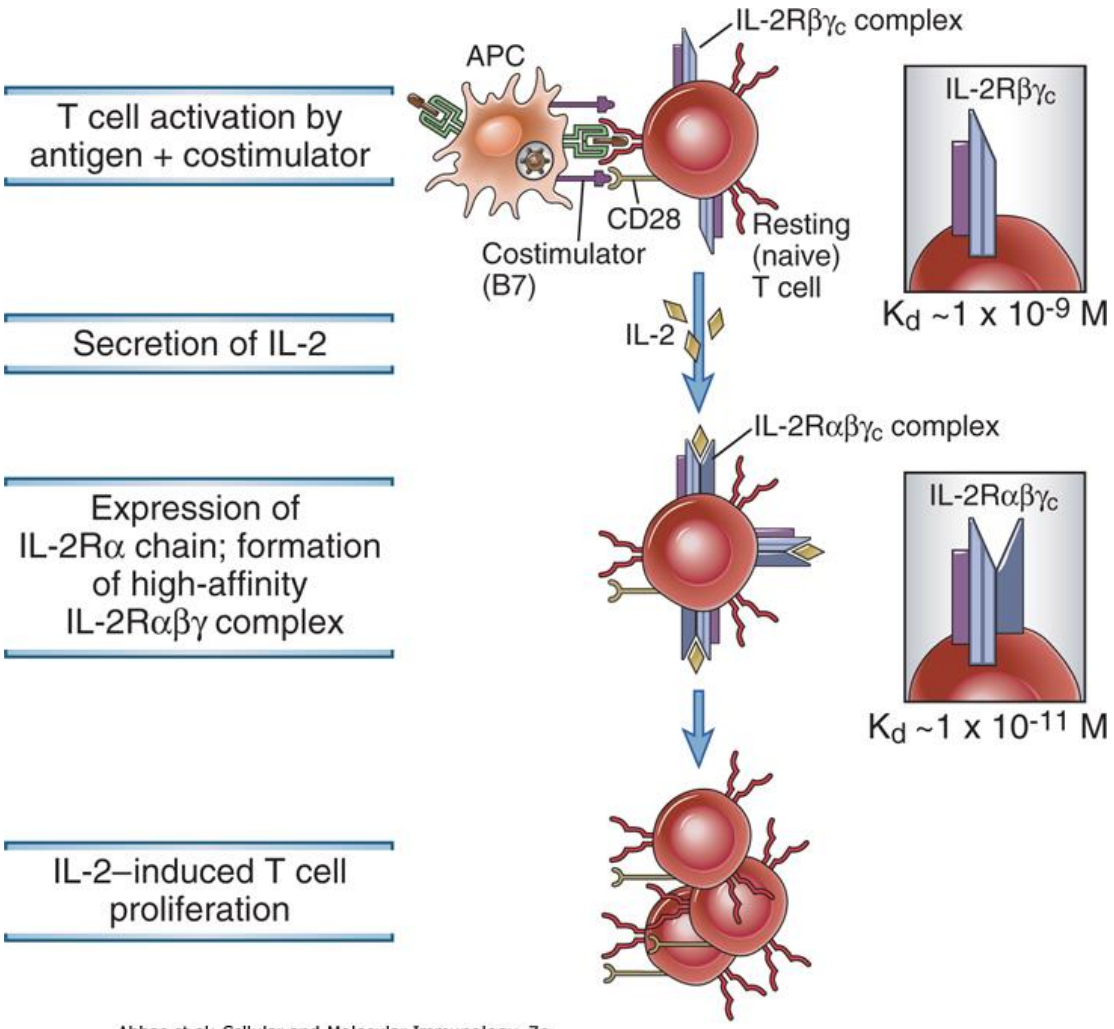
Molécula Coestimuladora: CD28



Fase 2: Ativação de Linfócitos
Papel de Moléculas Coestimuladoras



IL-2 e IL2R



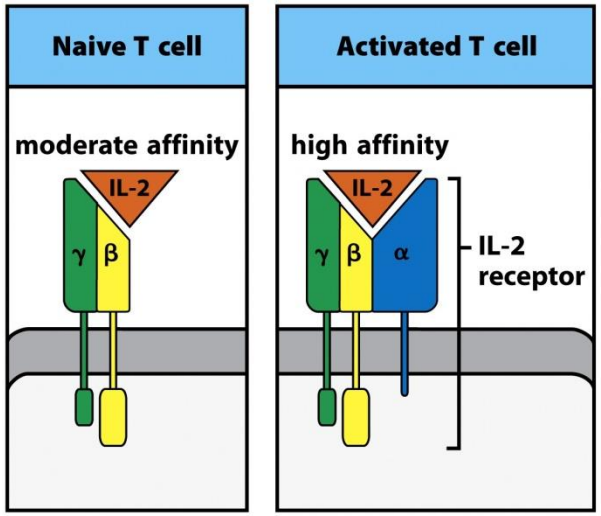
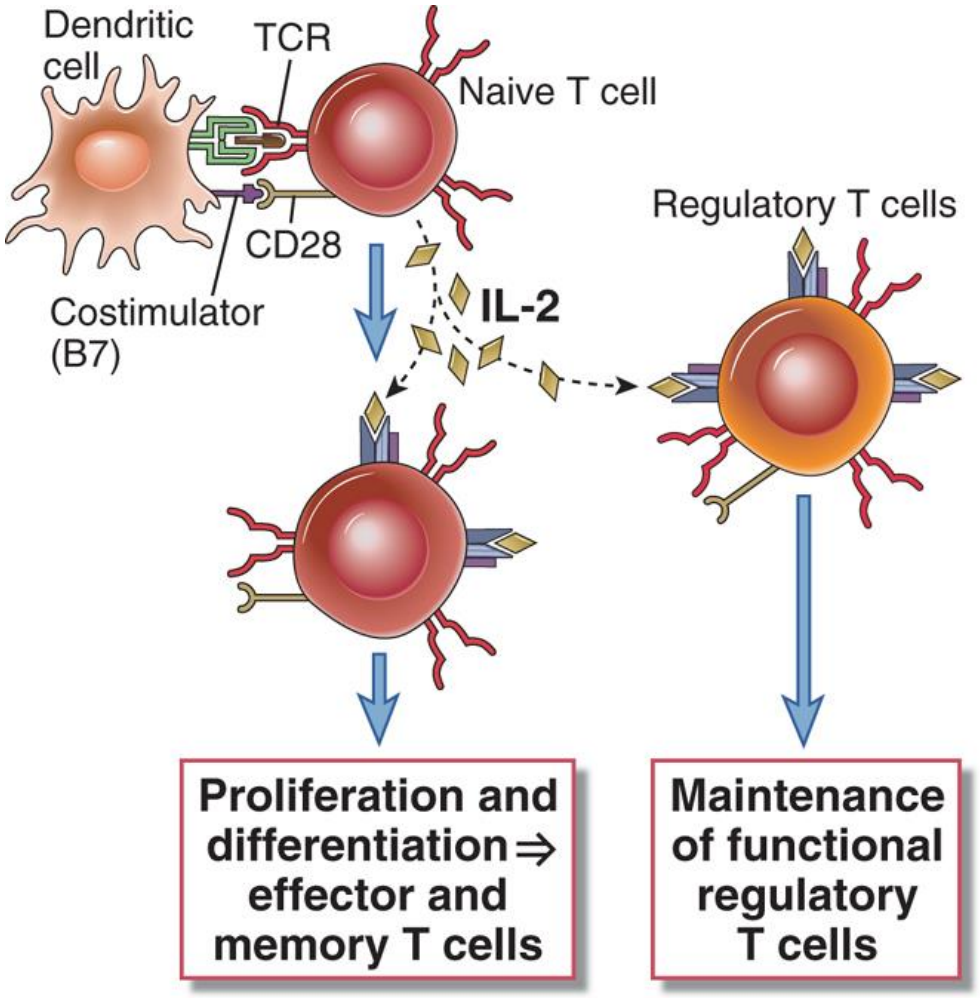


Figure 8-20 Immunobiology, 7ed. (© Garland Science 2008)

Papel Biológico da IL-2
Fase 3: Expansão Clonal



Sinal 3: Citocinas
Diferenciação de Linfócitos T (Fase 4)

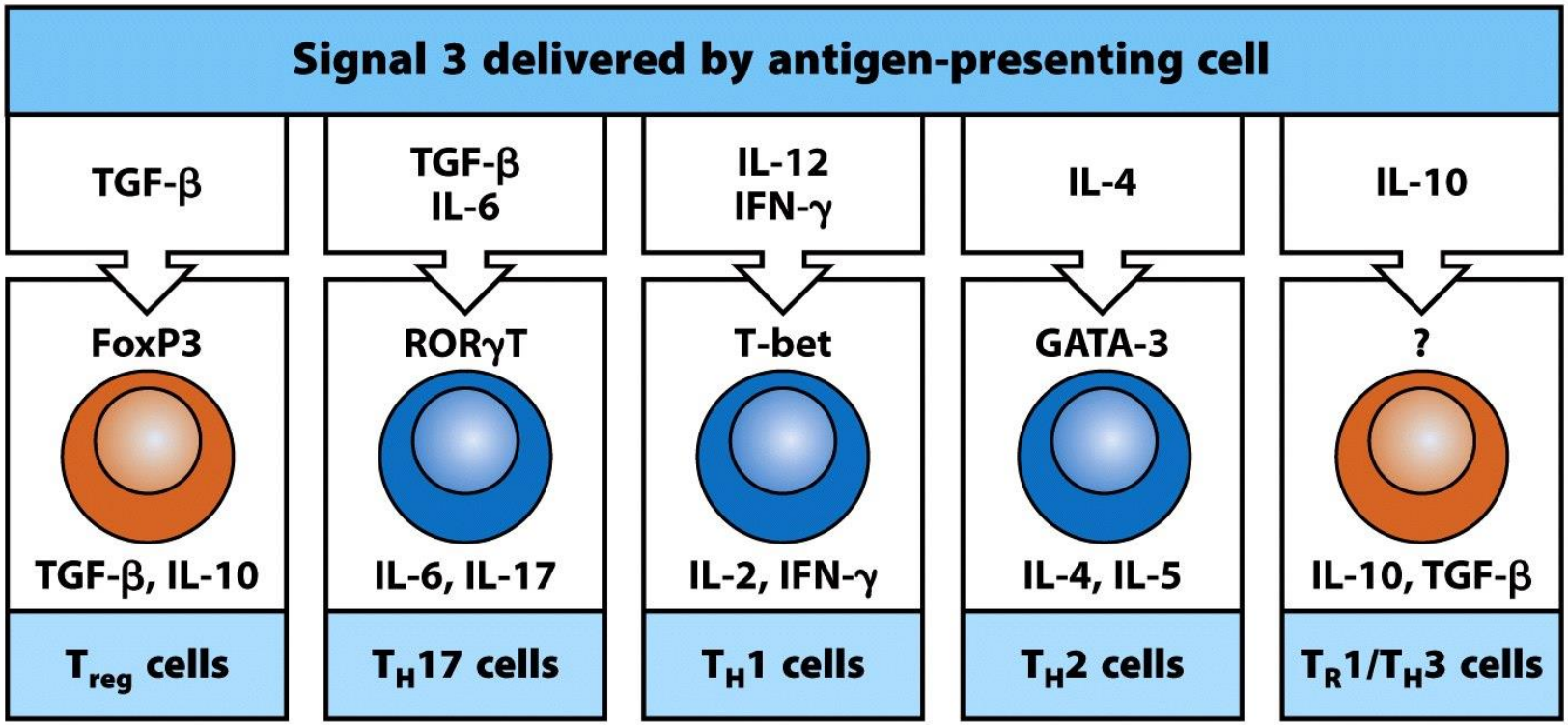
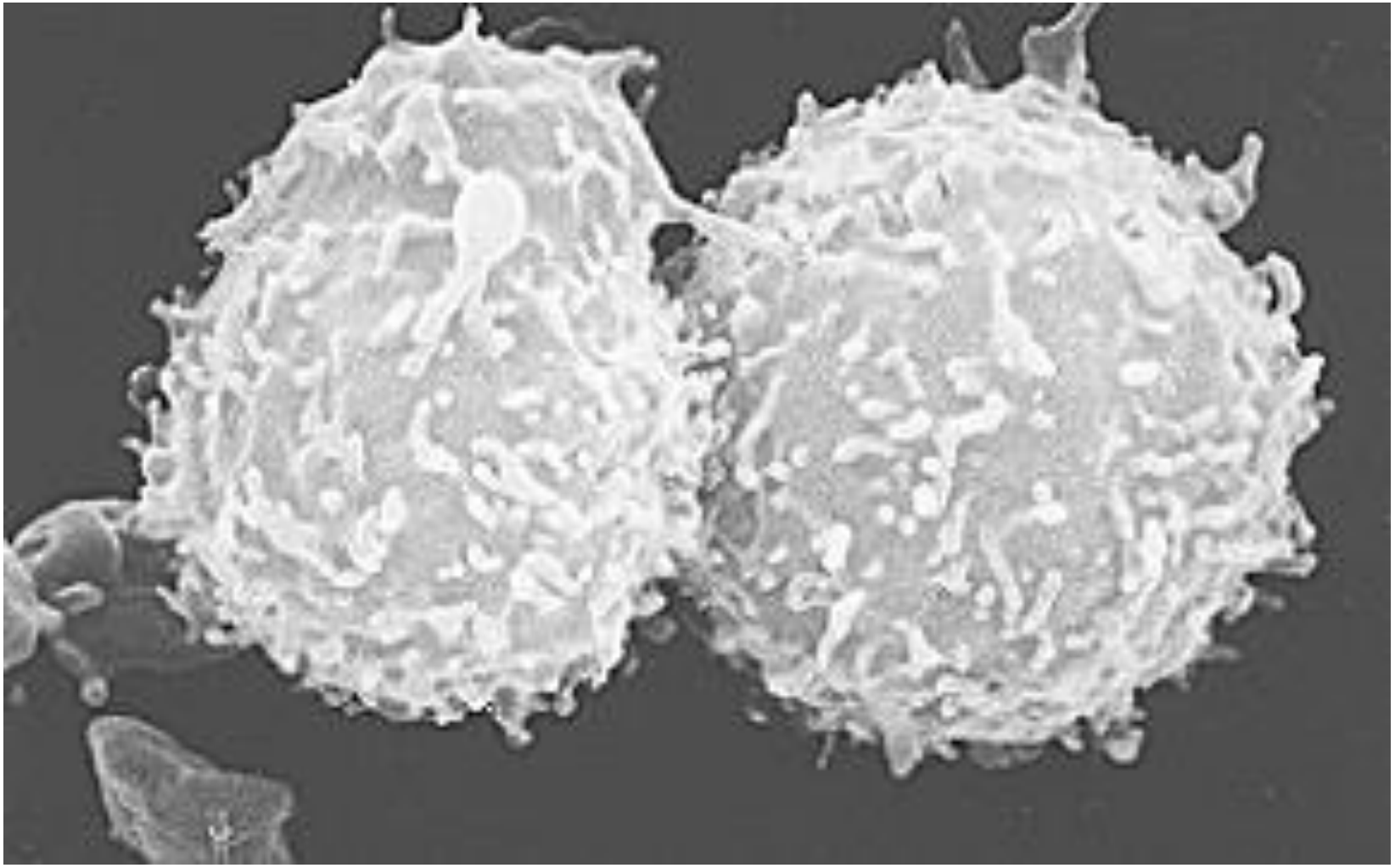
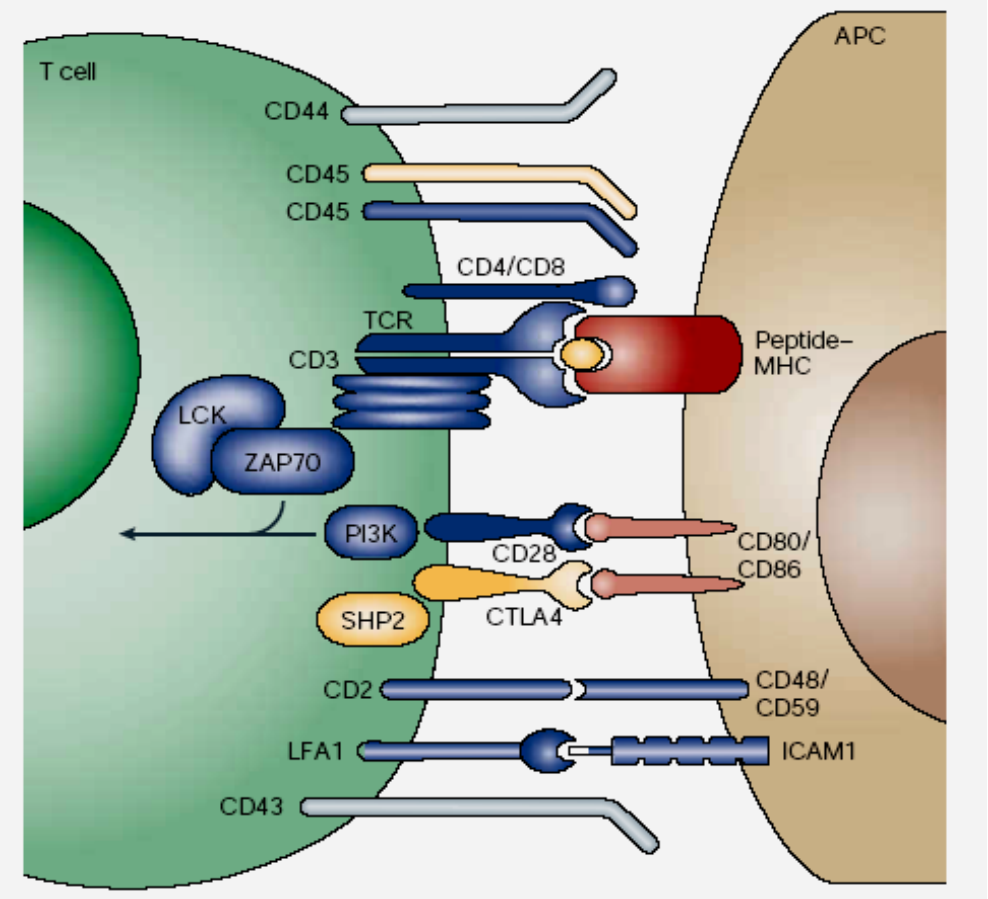


Figure 8-29 Immunobiology, 7ed. (© Garland Science 2008)

Sinapse Imunológica

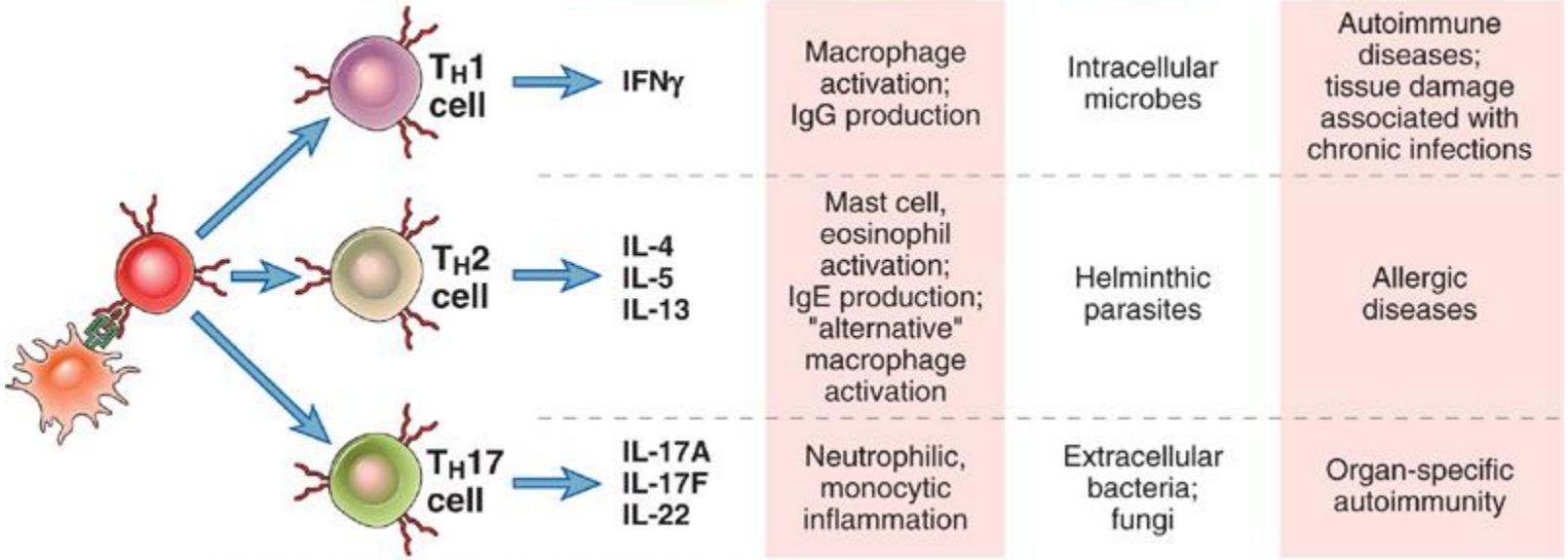


Sinapse Imunológica



NATURE REVIEWS | IMMUNOLOGY VOLUME 3 | DECEMBER 2003

Propriedades Gerais dos Subtipos Th1, Th2 e Th17



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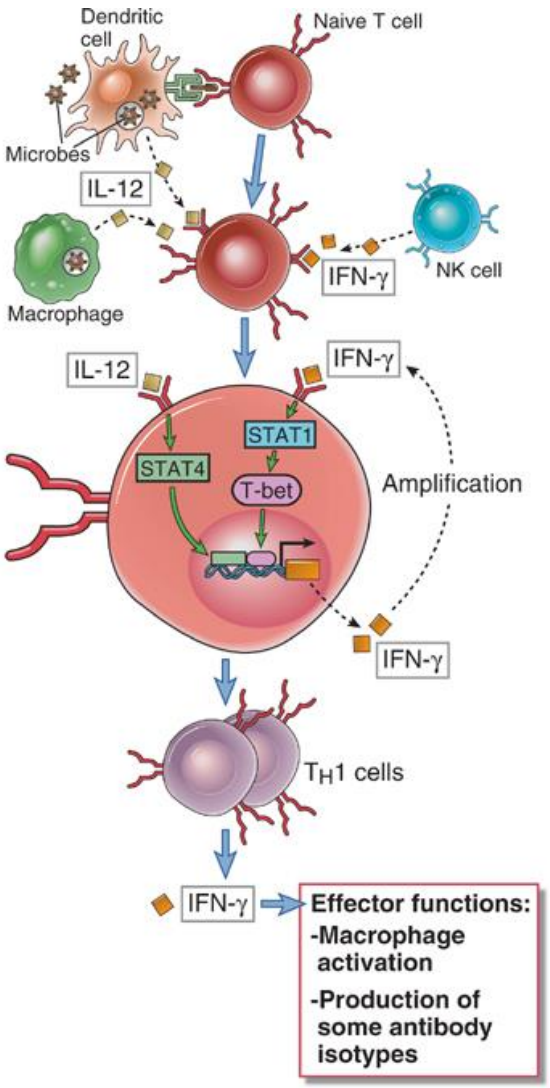
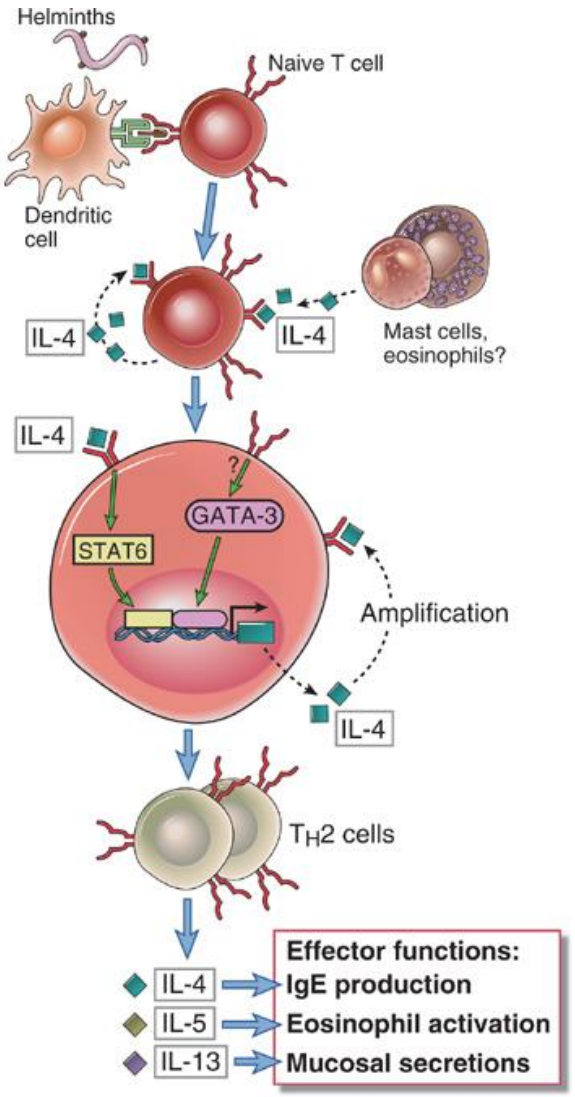
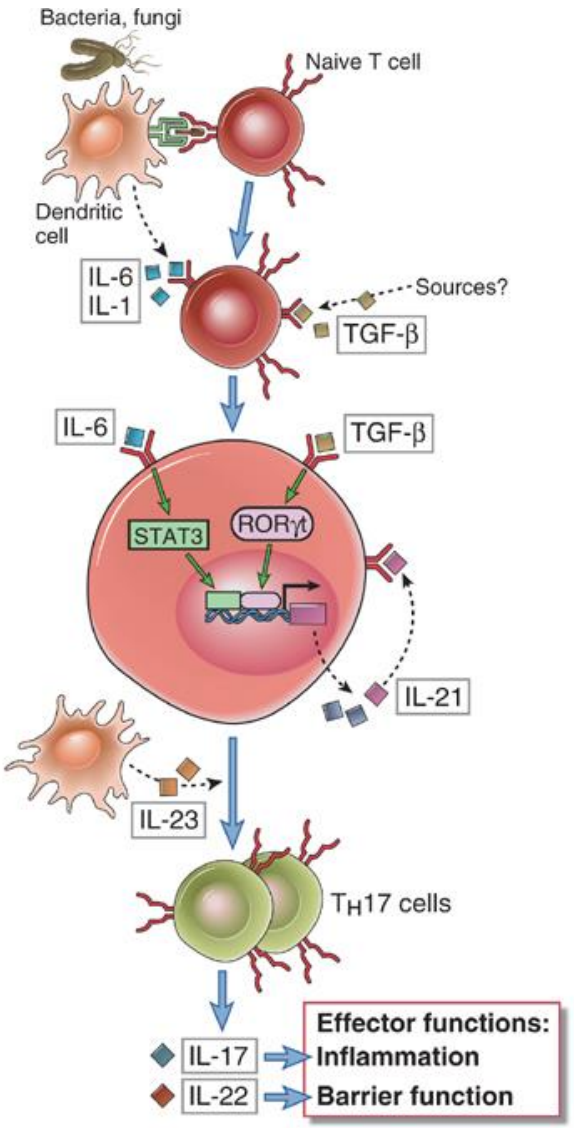
Diferenciação de Th1



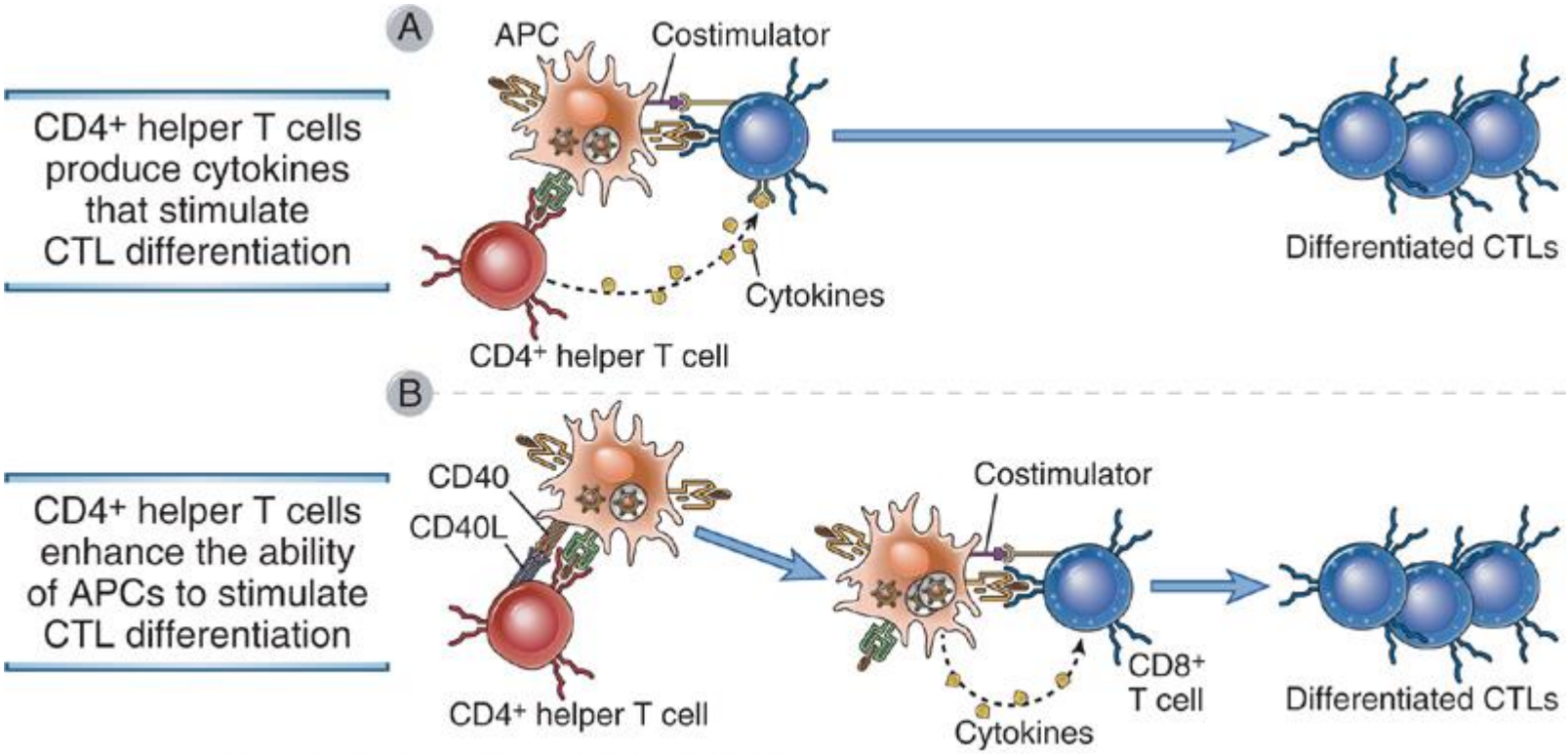
Diferenciação de Th2



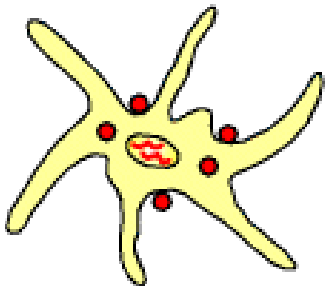
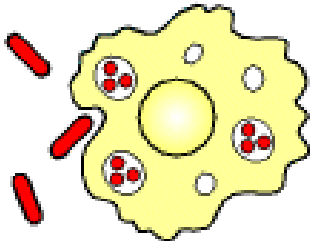
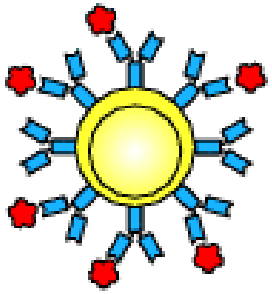
Diferenciação de Th17

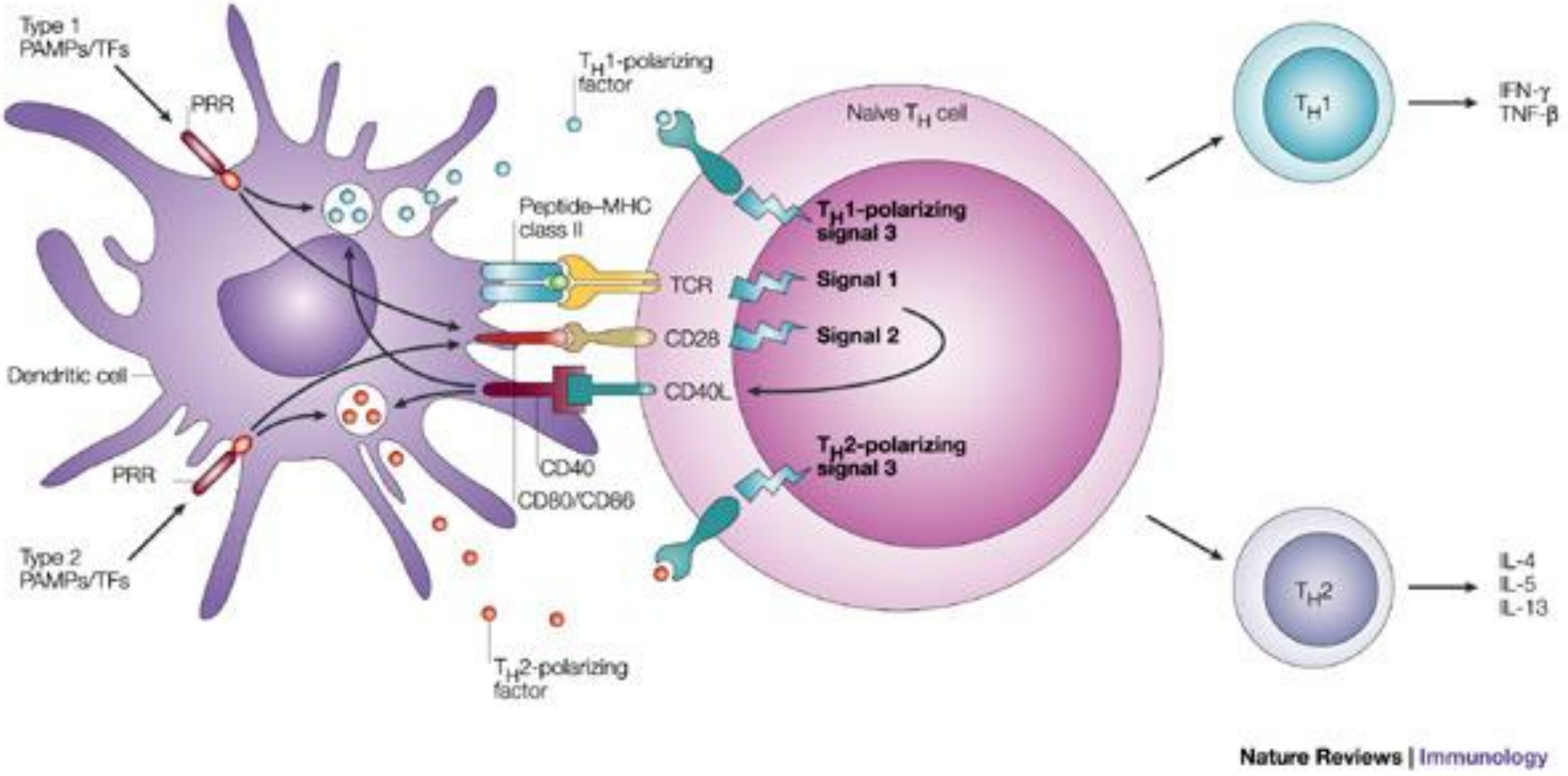


Papel de Th na diferenciação de TCD8



	Cell-mediated immunity		Humoral immunity
Typical pathogens	Vaccinia virus Influenza virus Rabies virus *Listeria*	*Mycobacterium tuberculosis* *Mycobacterium leprae* *Leishmania donovani* *Pneumocystis carinii*	*Clostridium tetani* *Staphylococcus aureus* *Streptococcus pneumoniae* Polio virus *Pneumocystis carinii*
Location	Cytosol	Macrophage vesicles	Extracellular fluid
Effector T cell	Cytotoxic CD8 T cell	T_H1 cell	T_H2/T_H1 cell
Antigen recognition	Peptide:MHC class I on infected cell	Peptide:MHC class II on infected macrophage	Peptide:MHC class II on antigen-specific B cell
Effector action	Killing of infected cell	Activation of infected macrophages	Activation of specific B cell to make antibody

	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	Lymphoid tissue Connective tissue Epithelia	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood



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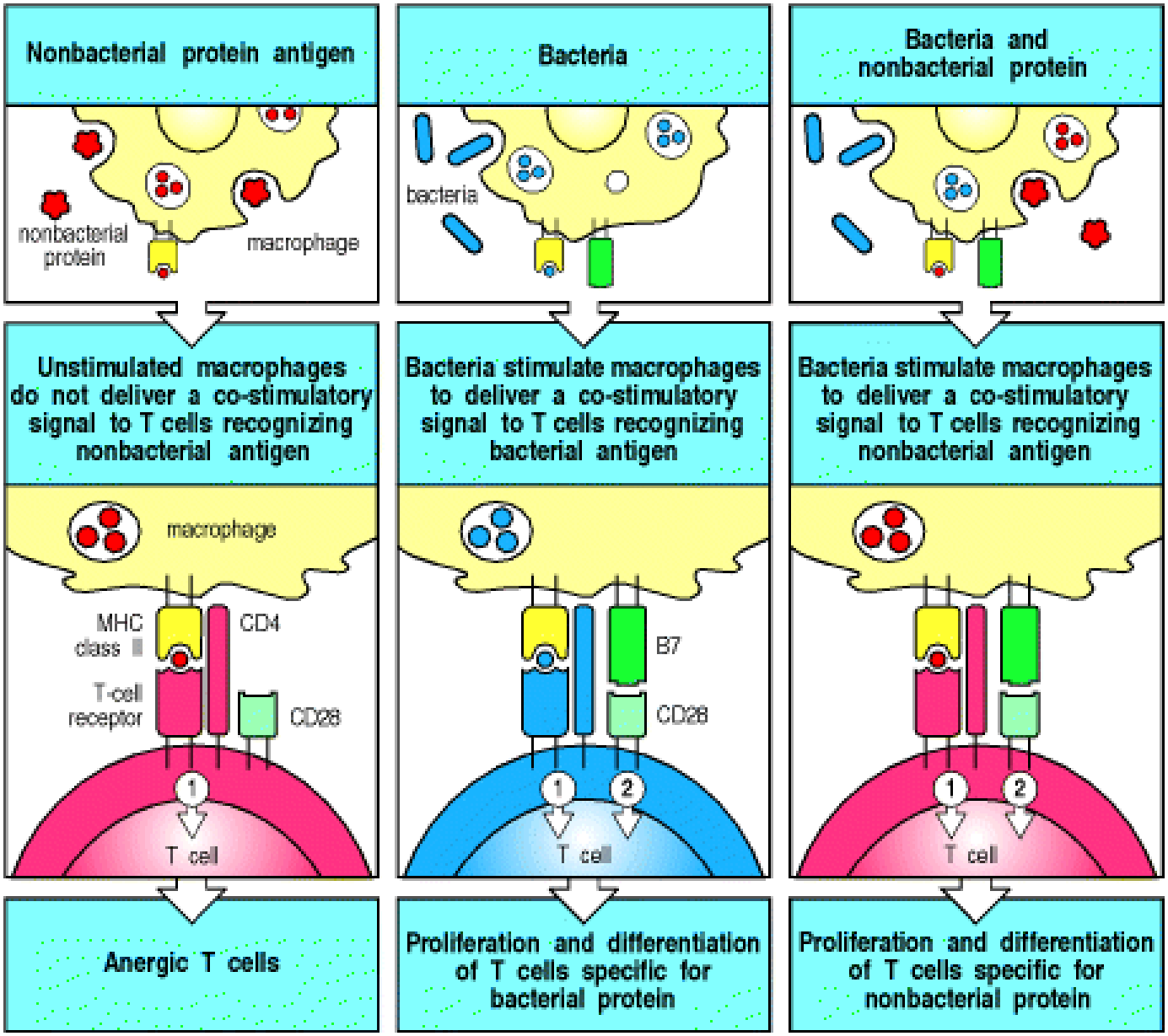
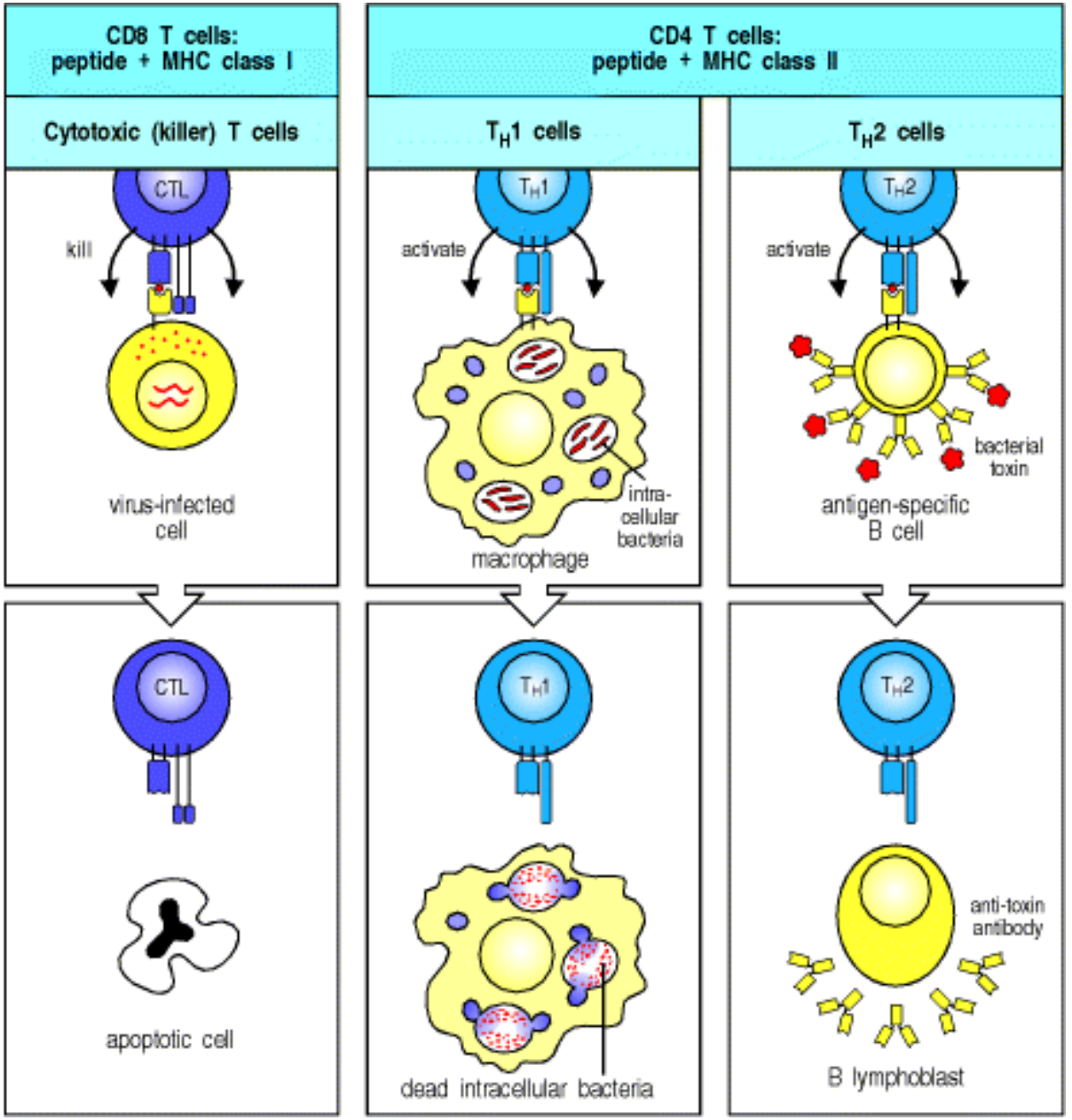
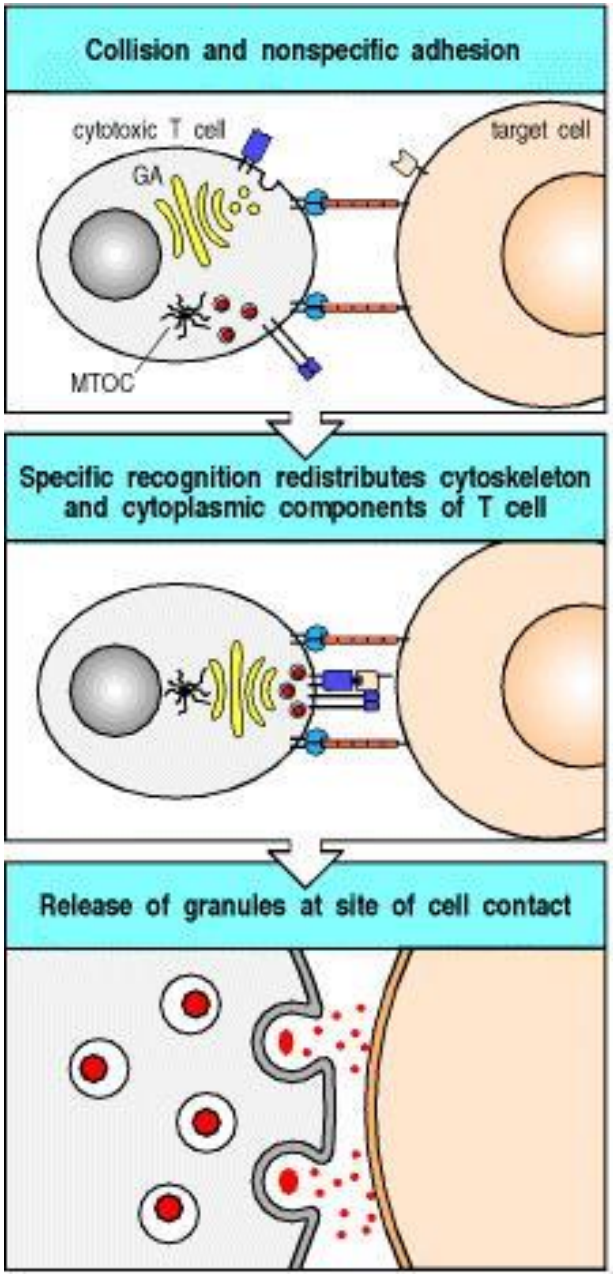
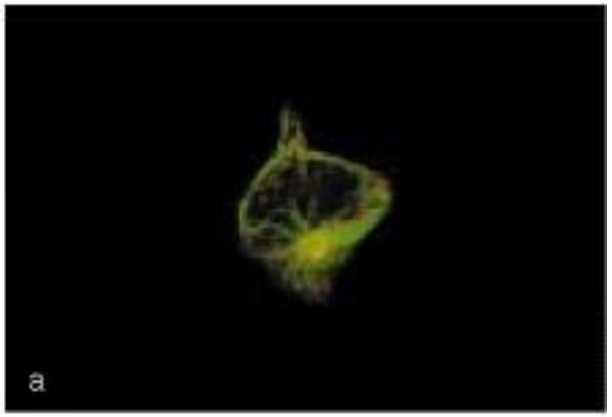
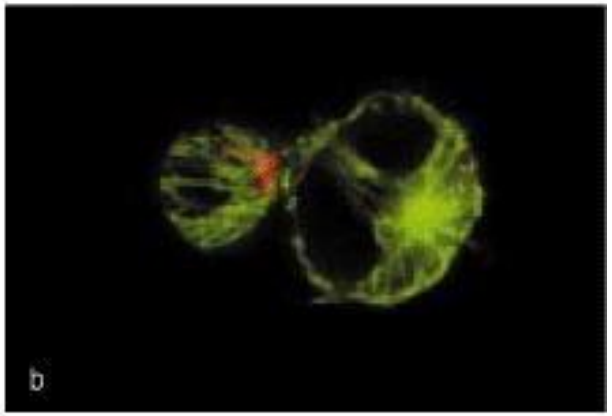
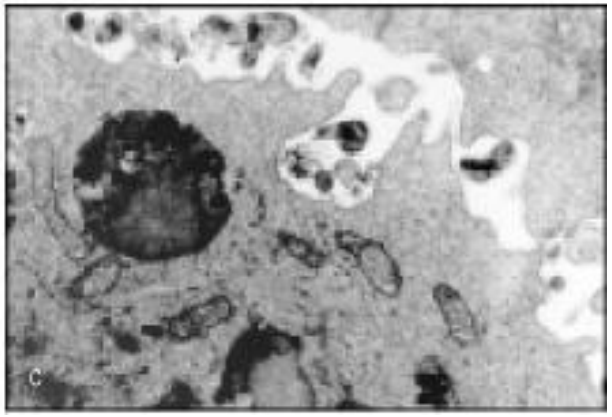

Nonbacterial protein antigen
nonbacterial protein
macrophage
Bacteria
bacteria
Bacteria and nonbacterial protein
Unstimulated macrophages do not deliver a co-stimulatory signal to T cells recognizing nonbacterial antigen
Bacteria stimulate macrophages to deliver a co-stimulatory signal to T cells recognizing bacterial antigen
Bacteria stimulate macrophages to deliver a co-stimulatory signal to T cells recognizing nonbacterial antigen
macrophage
MHC class II
CD4
T-cell receptor
CD28
B7
1
2
T cell
Anergic T cells
Proliferation and differentiation of T cells specific for bacterial protein
Proliferation and differentiation of T cells specific for nonbacterial protein


CD8 T cells:
peptide + MHC class I
CD4 T cells:
peptide + MHC class II
Cytotoxic (killer) T cells
TH1 cells
TH2 cells
CTL
kill
virus-infected cell
TH1
activate
intra-cellular bacteria
macrophage
TH2
activate
bacterial toxin
antigen-specific B cell
CTL
apoptotic cell
TH1
dead intracellular bacteria
TH2
anti-toxin antibody
B lymphoblast


Collision and nonspecific adhesion
cytotoxic T cell
target cell
GA
MTOC
Specific recognition redistributes cytoskeleton and cytoplasmic components of T cell
Release of granules at site of cell contact


a


b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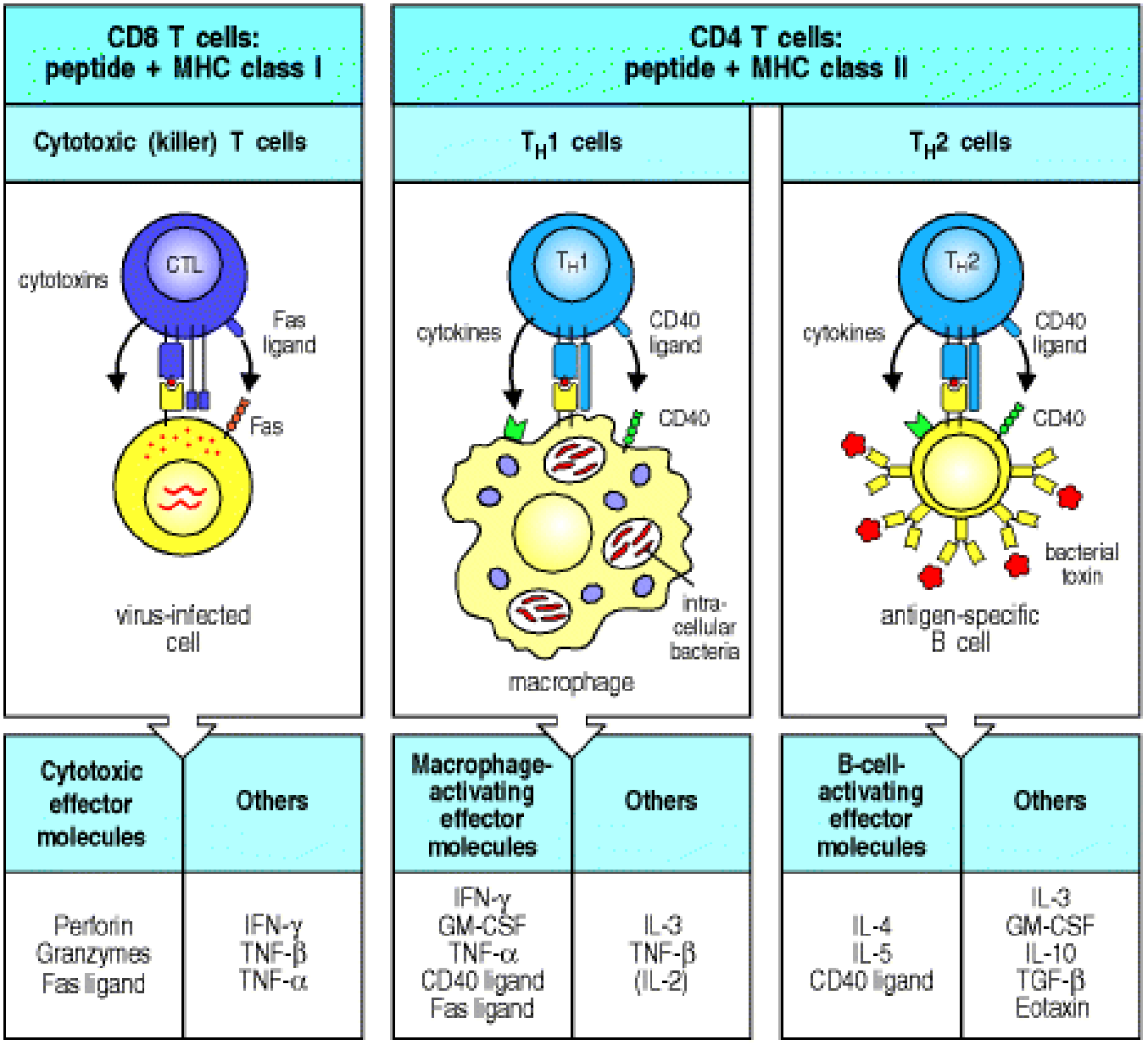
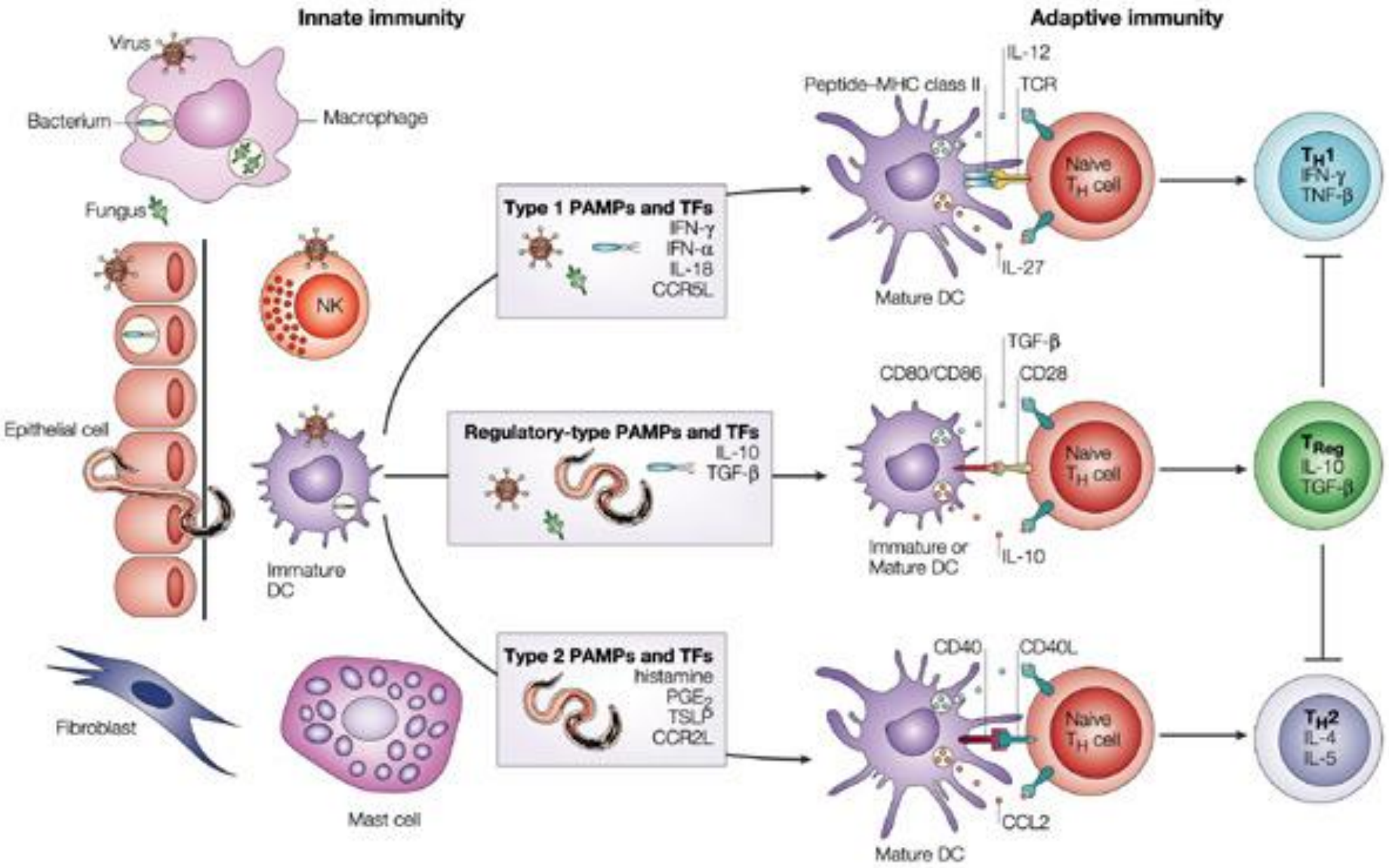
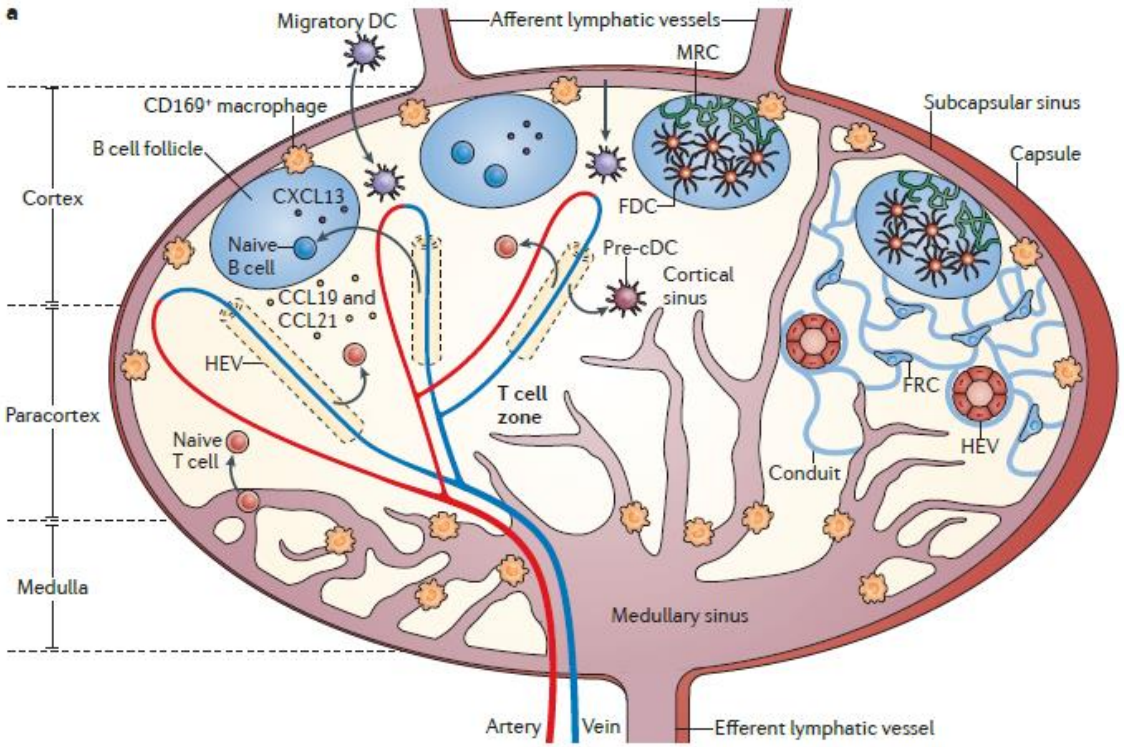
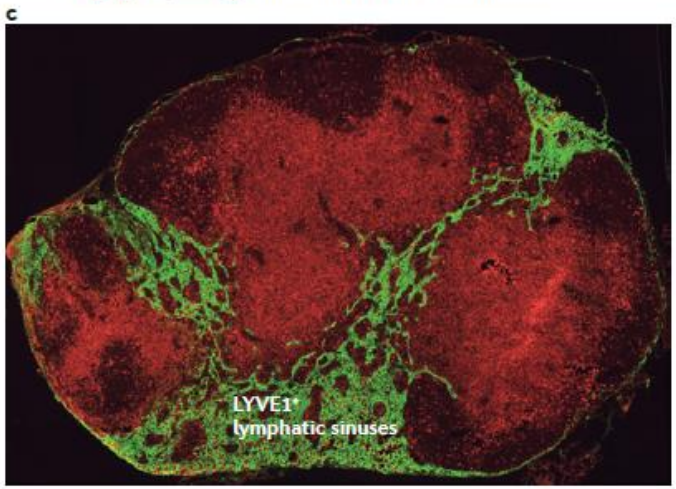

CD8 T cells:
peptide + MHC class I
CD4 T cells:
peptide + MHC class II
Cytotoxic (killer) T cells
TH1 cells
TH2 cells
cytotoxins
CTL
Fas ligand
Fas
virus-infected cell
TH1
cytokines
CD40 ligand
CD40
intra-cellular bacteria
macrophage
TH2
cytokines
CD40 ligand
CD40
bacterial toxin
antigen-specific B cell
Cytotoxic effector molecules
Others
Perforin
Granzymes
Fas ligand
IFN-γ
TNF-β
TNF-α
Macrophage-activating effector molecules
Others
IFN-γ
GM-CSF
TNF-α
CD40 ligand
Fas ligand
IL-3
TNF-β
(IL-2)
B-cell-activating effector molecules
Others
IL-4
IL-5
CD40 ligand
IL-3
GM-CSF
IL-10
TGF-β
Eotaxin


Innate immunity
Adaptive immunity
Virus
Bacterium
Macrophage
Fungus
Epithelial cell
NK
Immature DC
Fibroblast
Mast cell
Type 1 PAMPs and TFs
IFN-γ
IFN-α
IL-18
CCR5L
Regulatory-type PAMPs and TFs
IL-10
TGF-β
Type 2 PAMPs and TFs
histamine
PGE2
TSLP
CCR2L
Peptide–MHC class II
IL-12
TCR
Naive TH cell
IL-27
Mature DC
TH1
IFN-γ
TNF-β
CD80/CD86
TGF-β
CD28
Immature or Mature DC
IL-10
TReg
IL-10
TGF-β
CD40
CD40L
CCL2
TH2
IL-4
IL-5

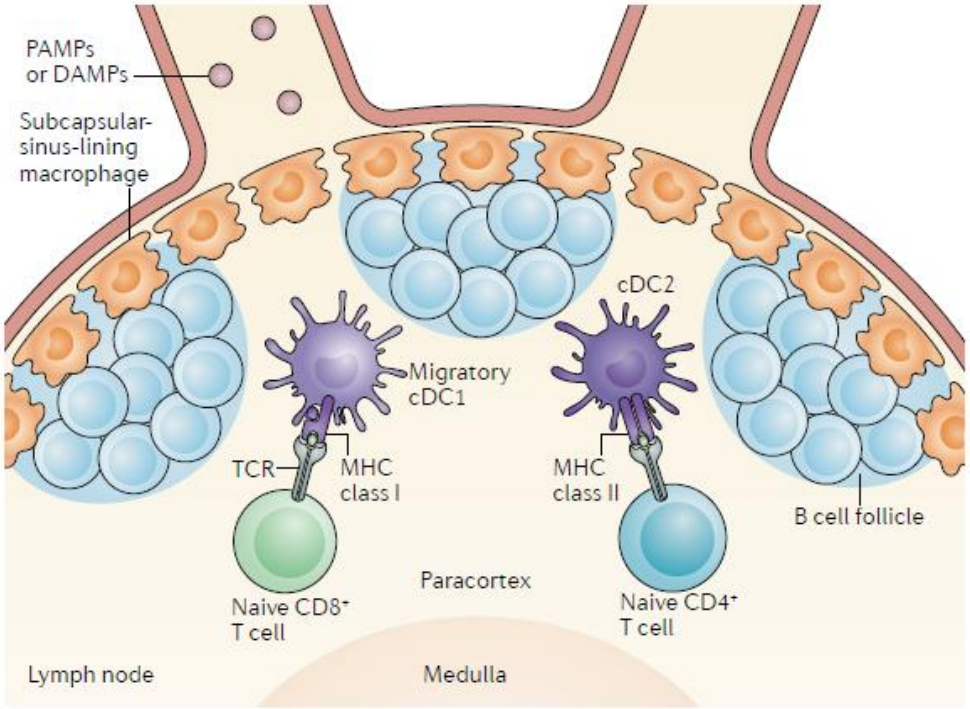
Estrutura do linfonodo e circulação de células

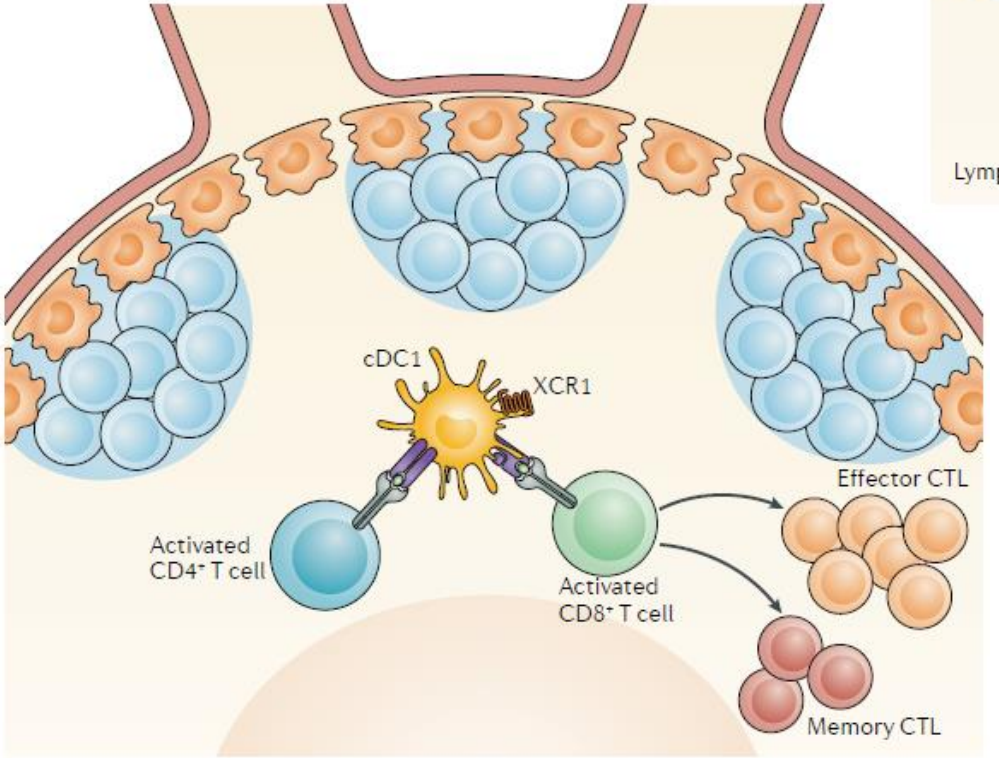




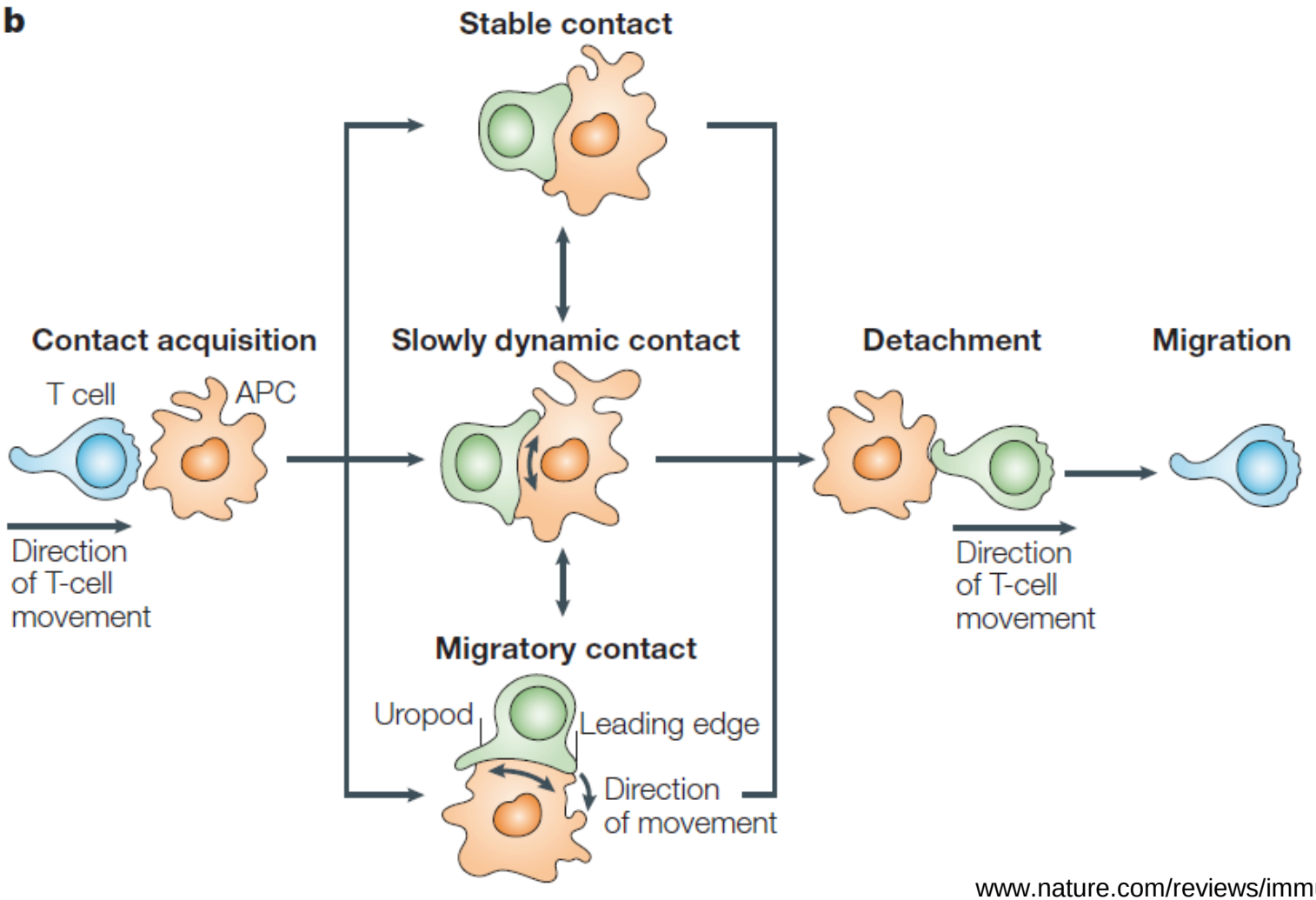
www.nature.com/reviews/immunol.

Interações celulares no linfonodo



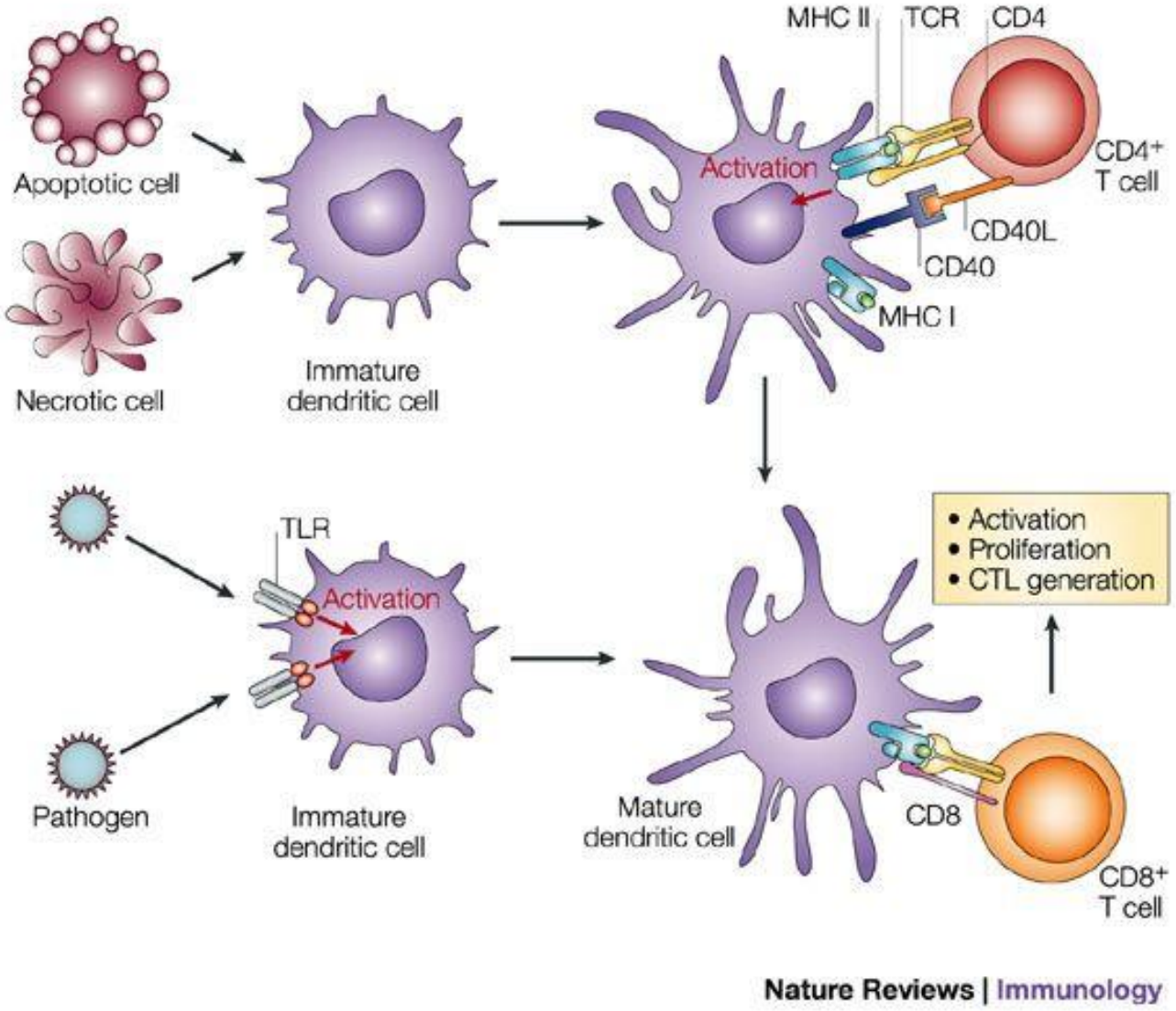


Fases da interação entre APCs e linfócitos T

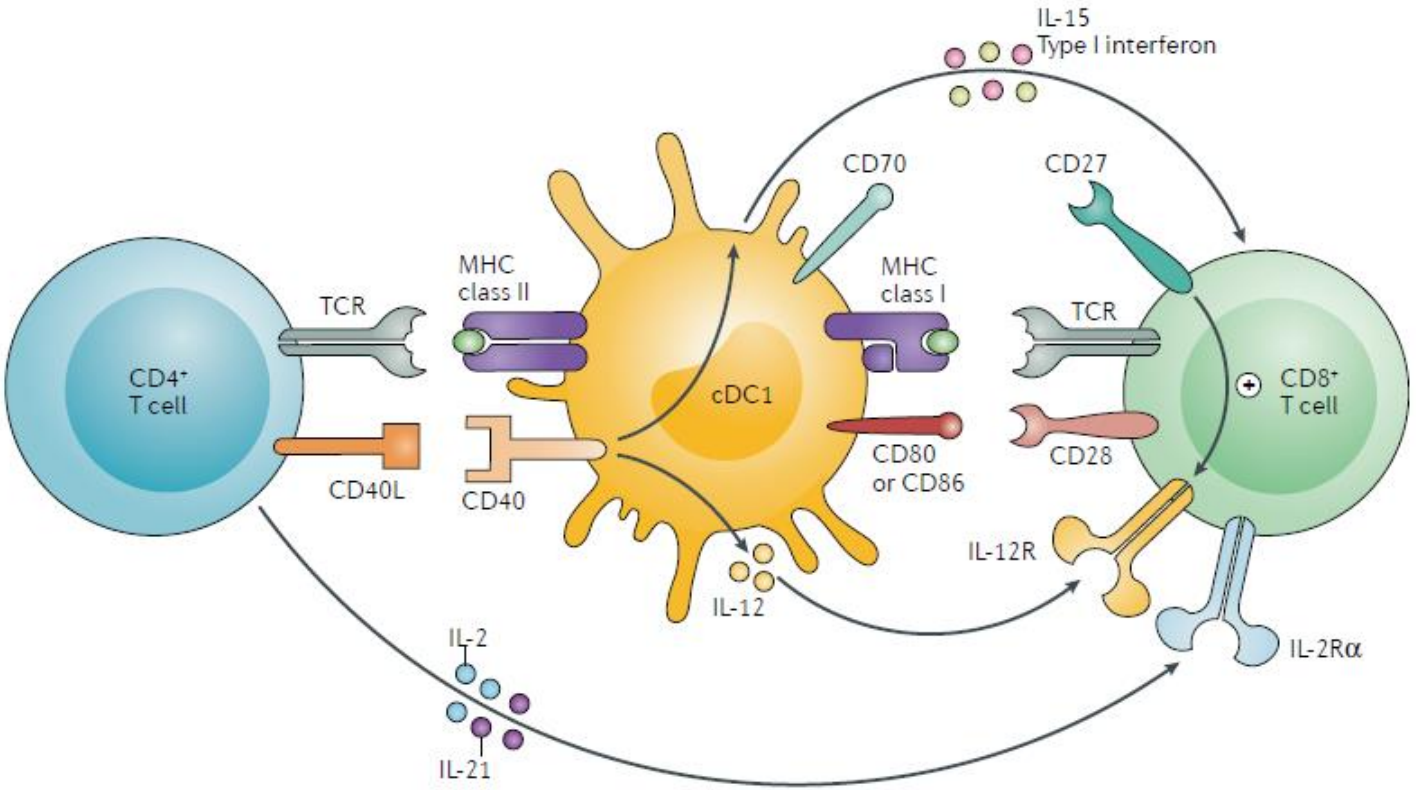


www.nature.com/reviews/immunol.

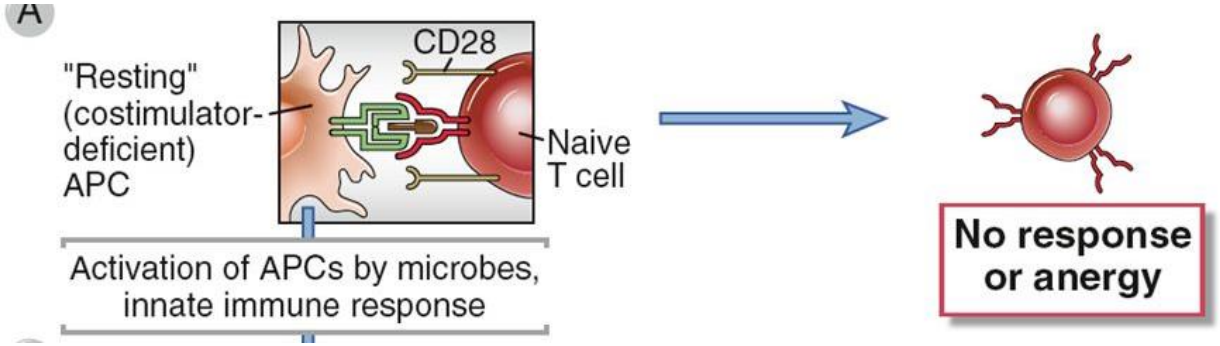
Ativação de DCs e expressão de moléculas co-estimuladoras



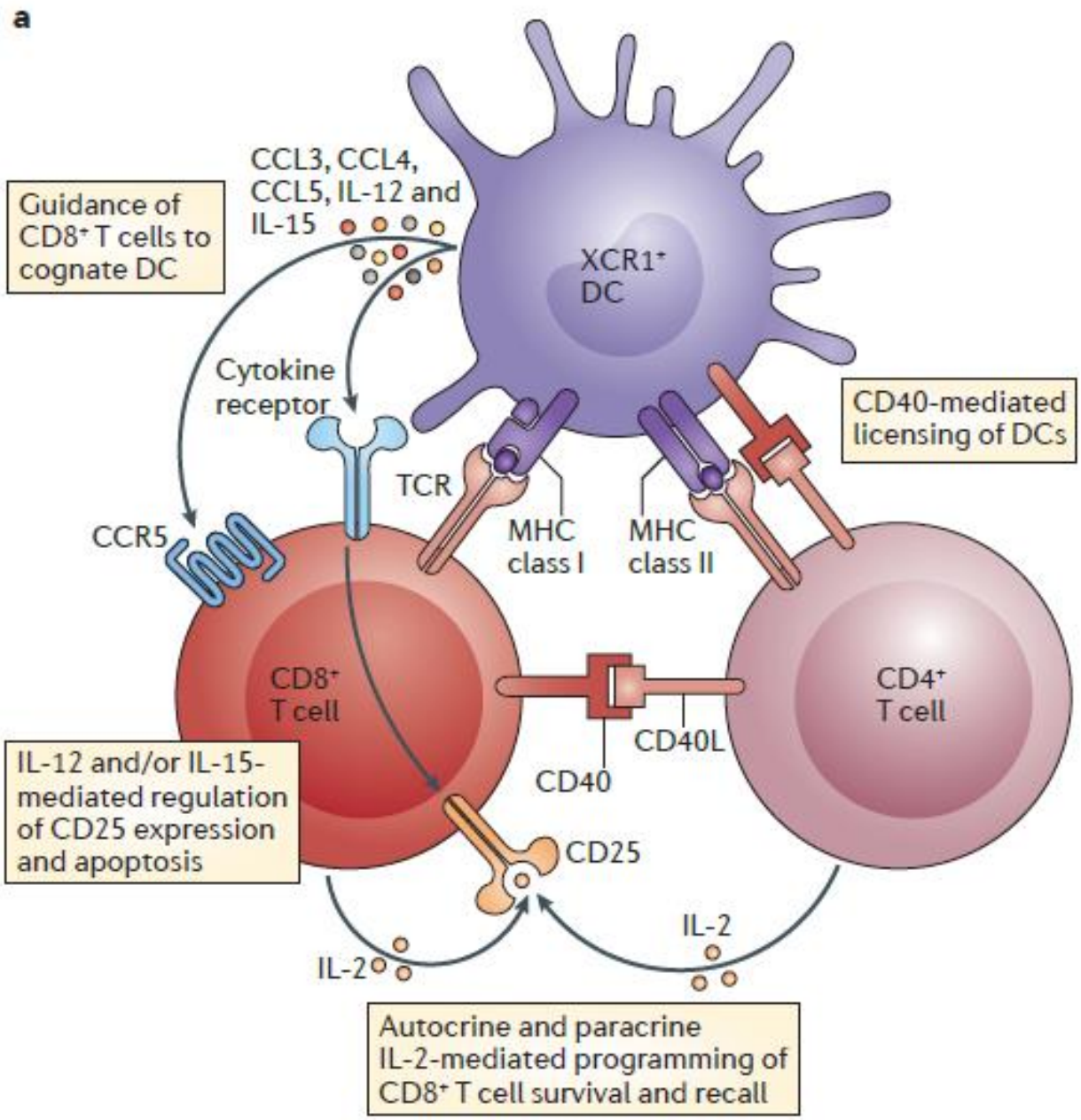
Moléculas co-estimuladoras na ativação de linfócitos T



www.nature.com/reviews/immunol.

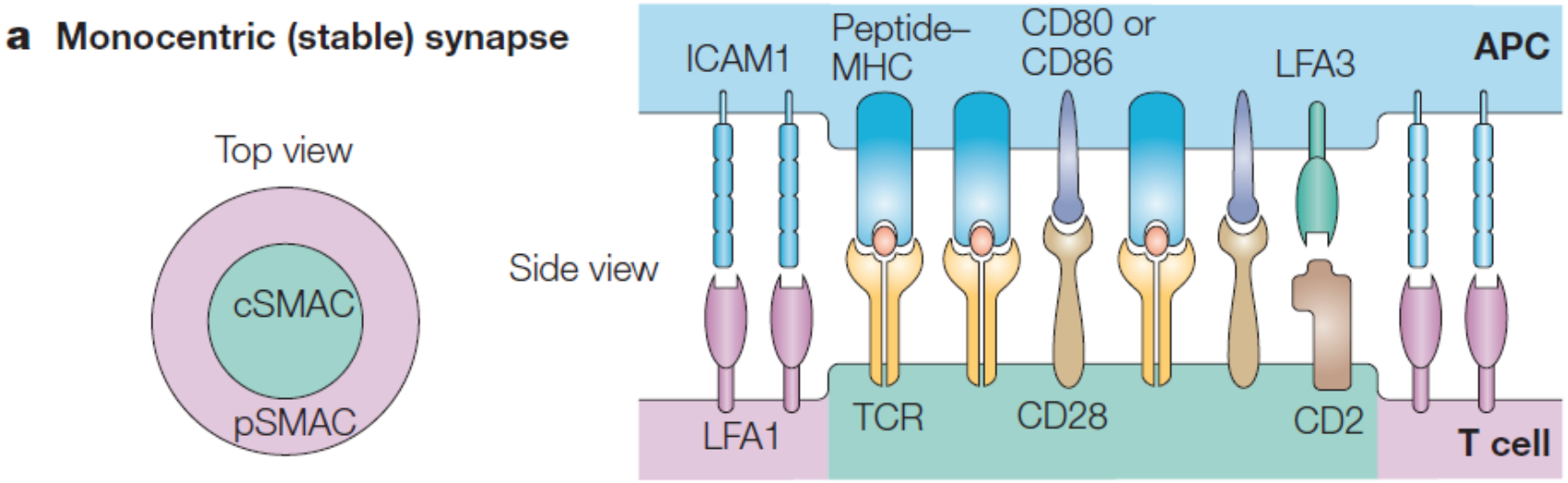


O papel do linfócito T CD4+ helper na diferenciação de T CD8+



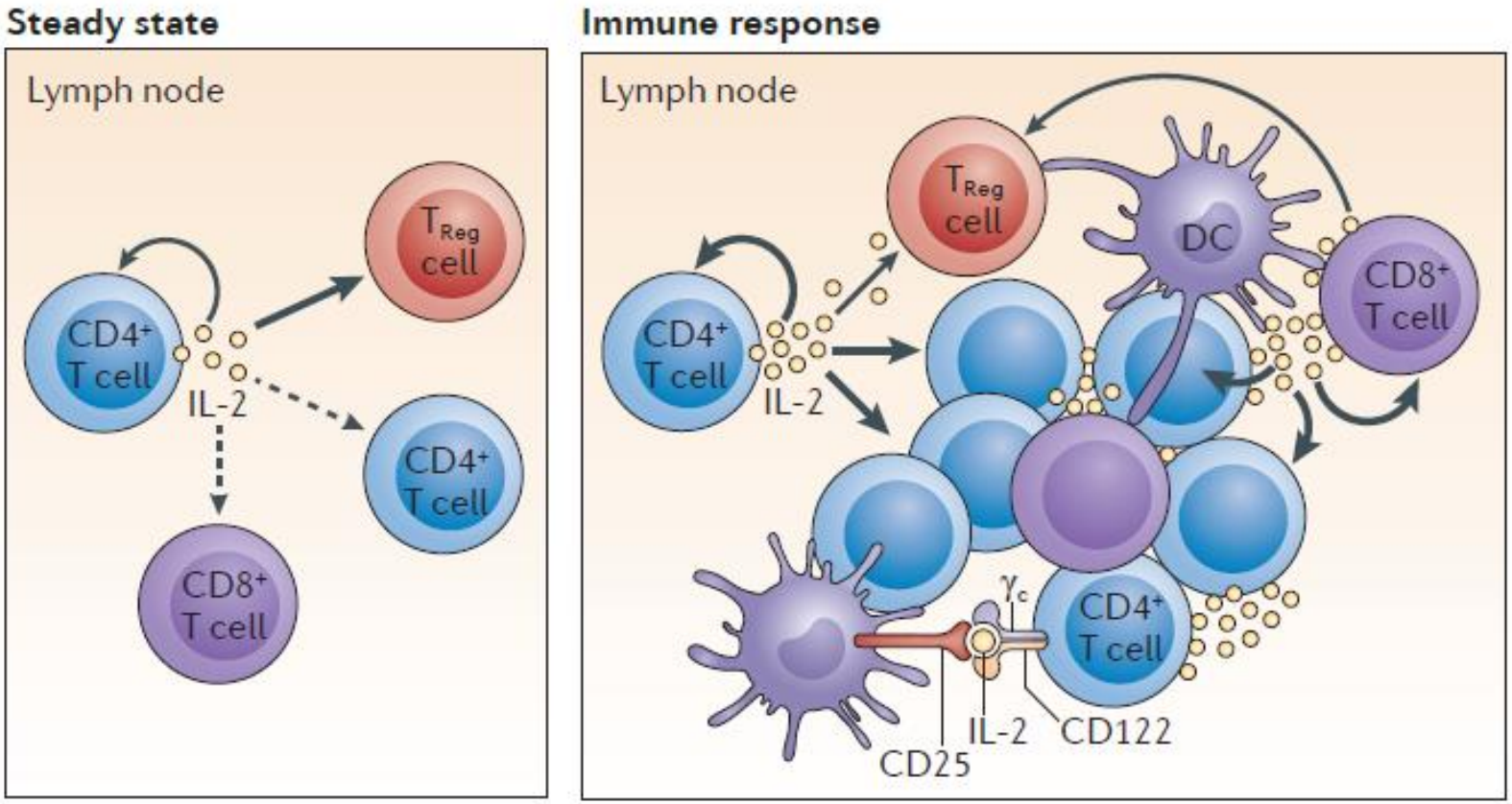
www.nature.com/nri

Interações moleculares na sinapse imunológica



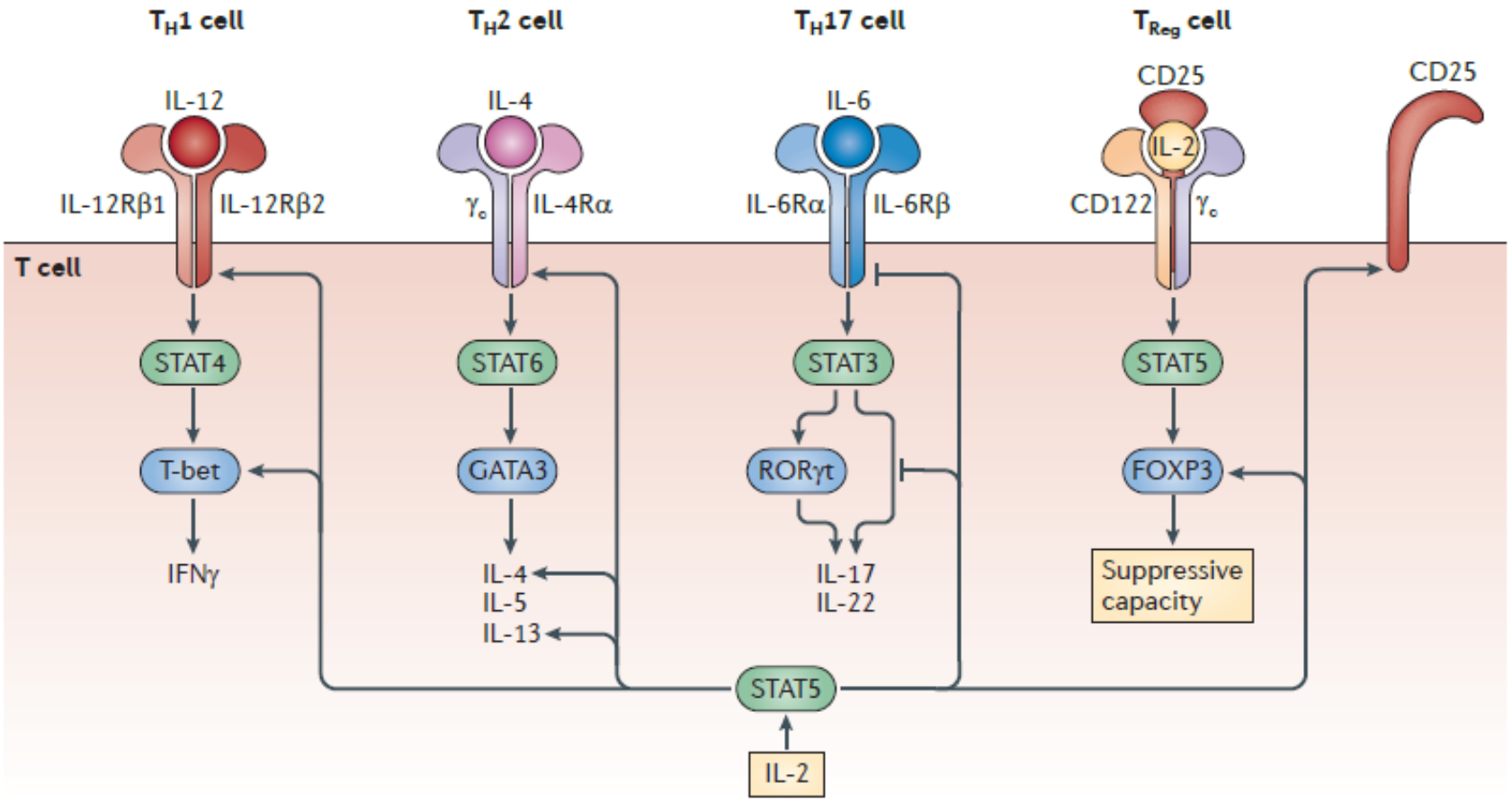
www.nature.com/reviews/immunol.

A importância da IL-2 na proliferação de linfócitos T



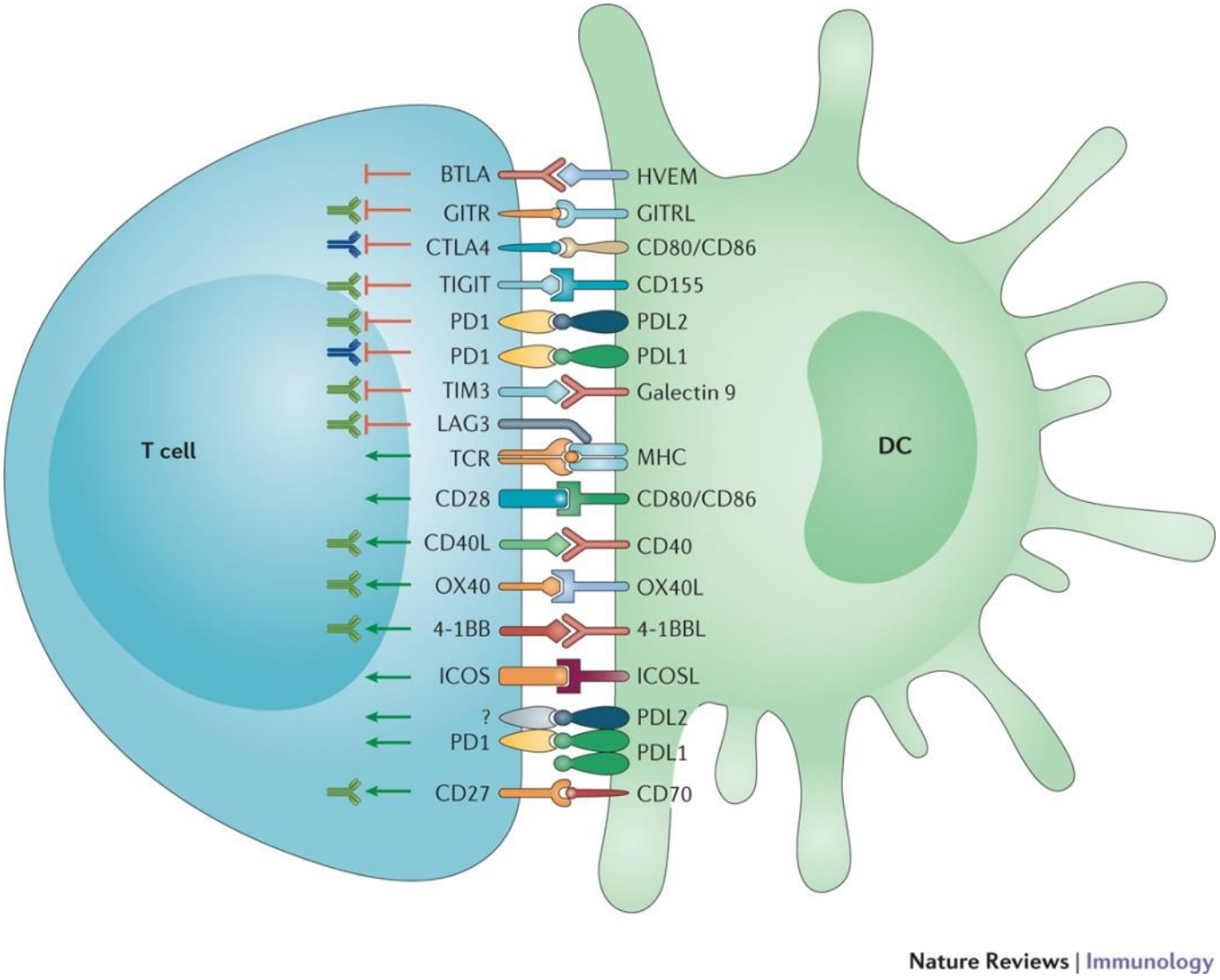
www.nature.com/reviews/immunol.

A importância da IL-2 na diferenciação de linfócitos T

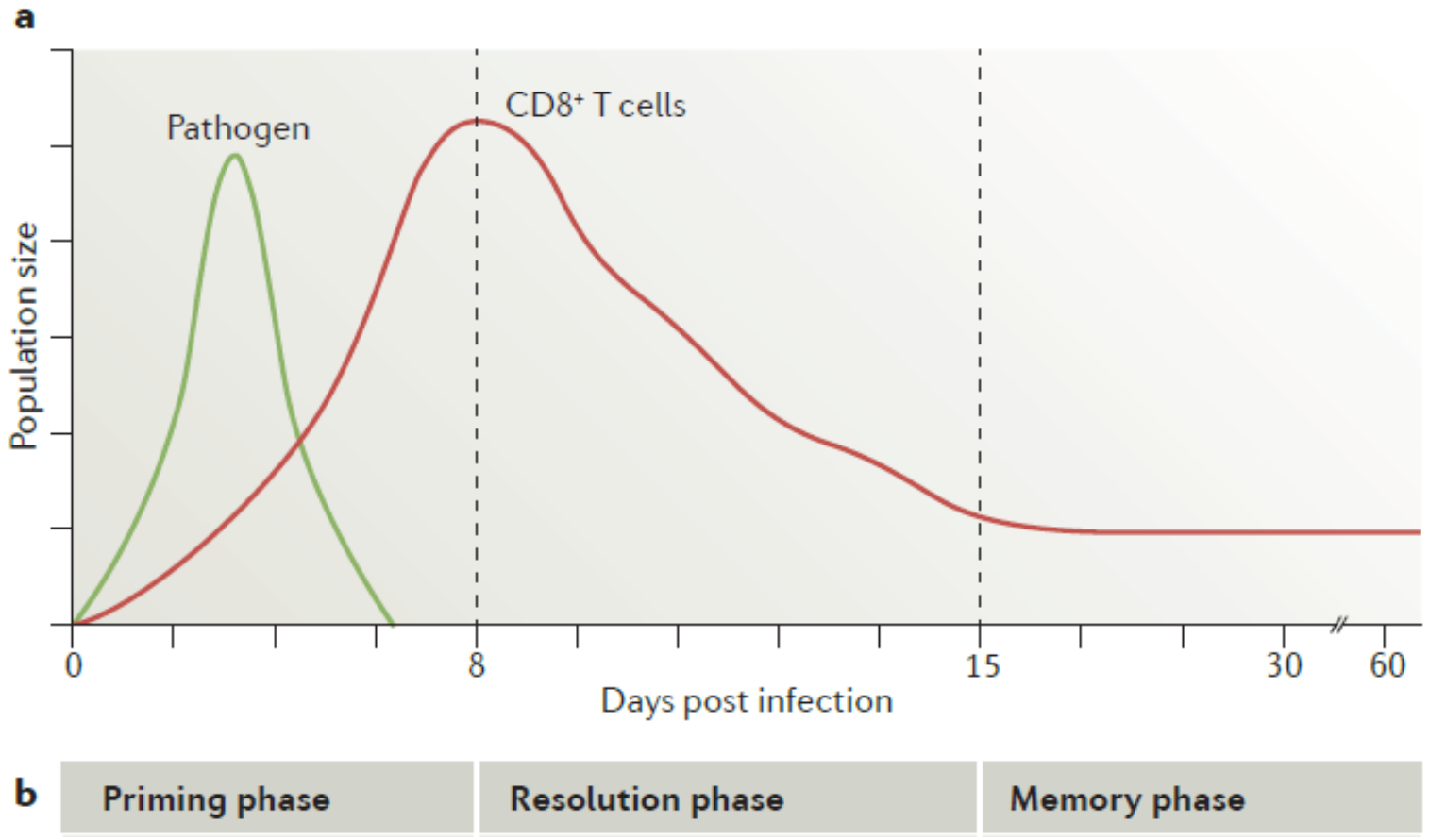


www.nature.com/reviews/immunol.

Co-estimulação e regulação negativa da ativação de linfócitos



Modelo temporal de linfócitos T CD8^{+} durante uma infecção



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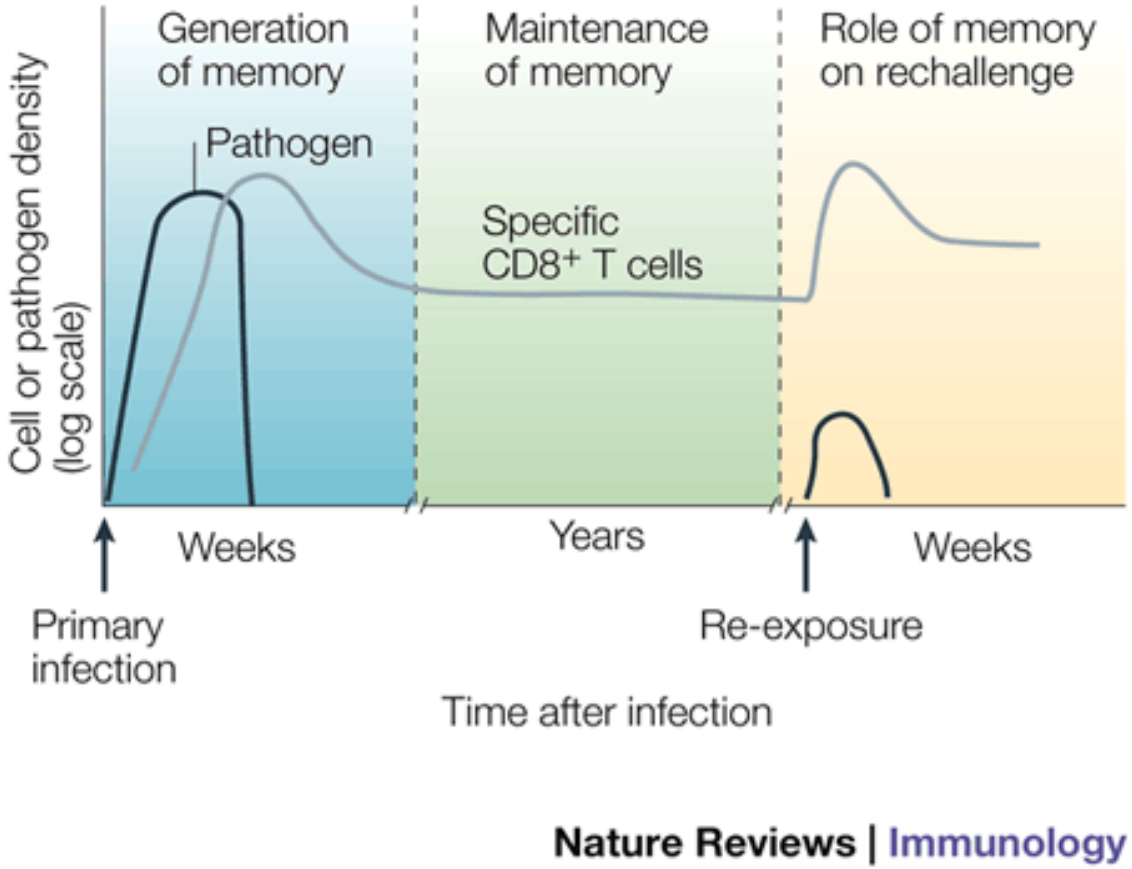
Células T CD8^{+} de memória



Como a resposta humoral protege o nosso corpo ?