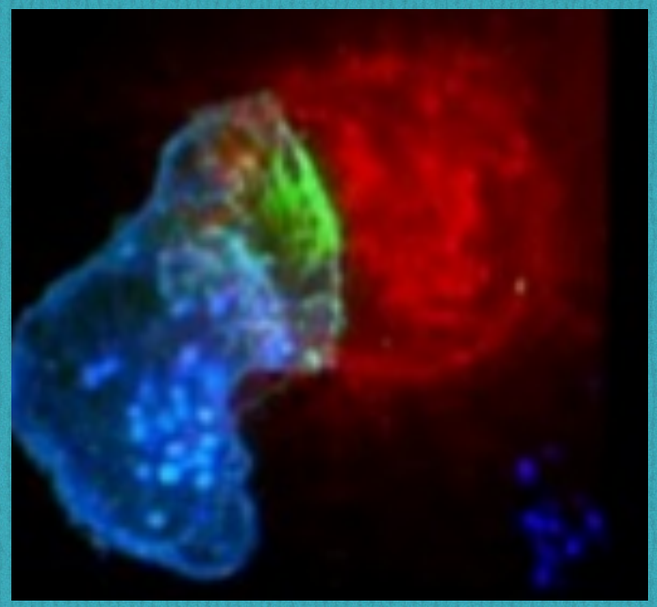
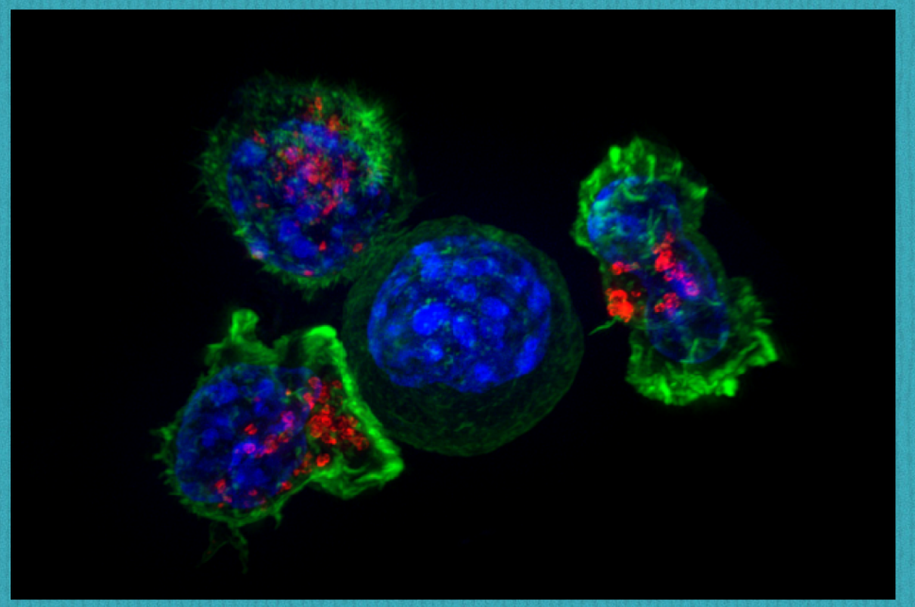
Curso de Ciencias Biologicas
Disciplina BMI-296 – Imunologia basica





Aula 9 – Geraçao e ativaçao dos linfócitos B

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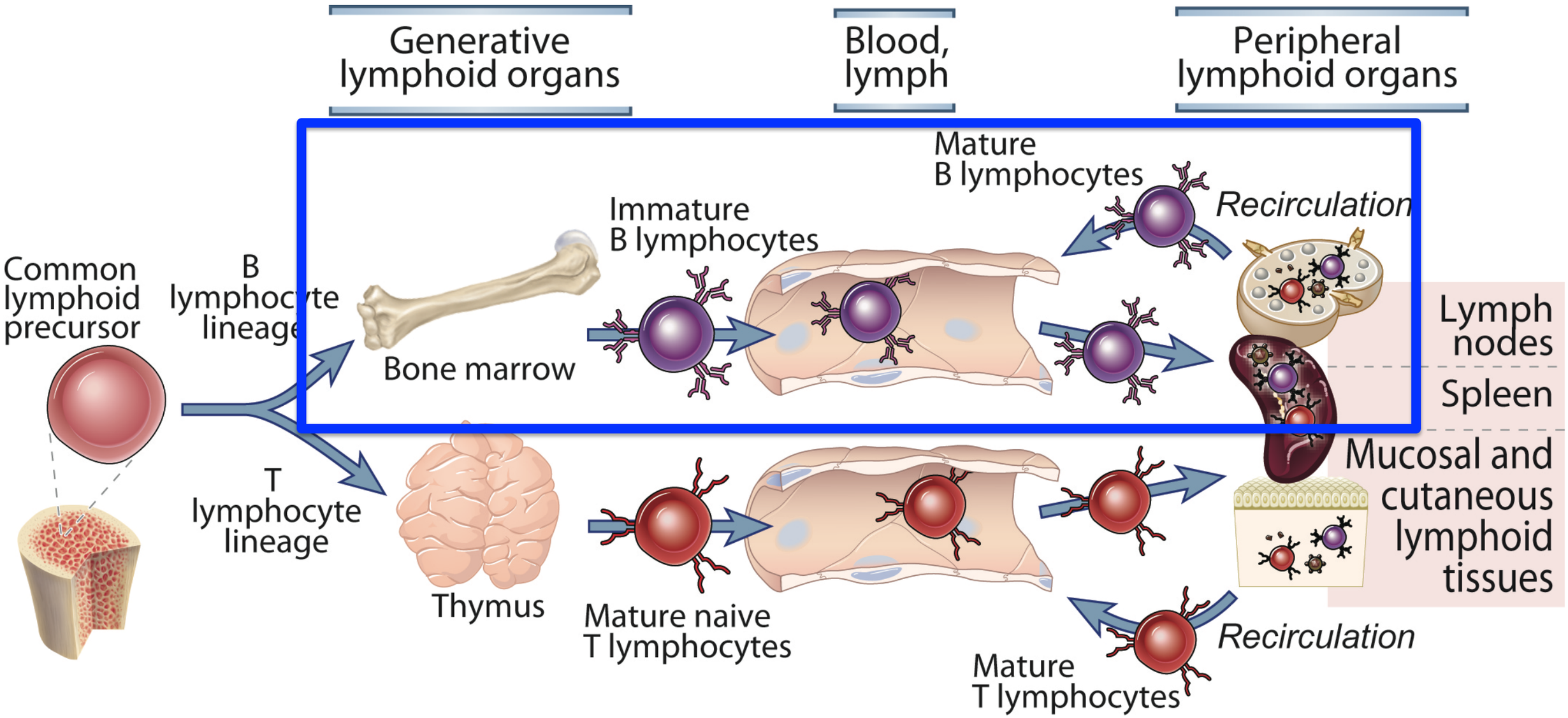
Linfocitos B

Producao de anticorpos
Imunidade adquirida humoral

AC produzidos por um L.B tem todos a mesma especificidade (V) que é identica aquela do proprio BCR

Reconhecem Ag e medeiam varias funçoes efetoras

Desenvolvimento Linfocitos B



Formaçao do receptor
→elevada especificidade de cada clone
→tolerancia a "self"

Desenvolvimento Linfocitos B

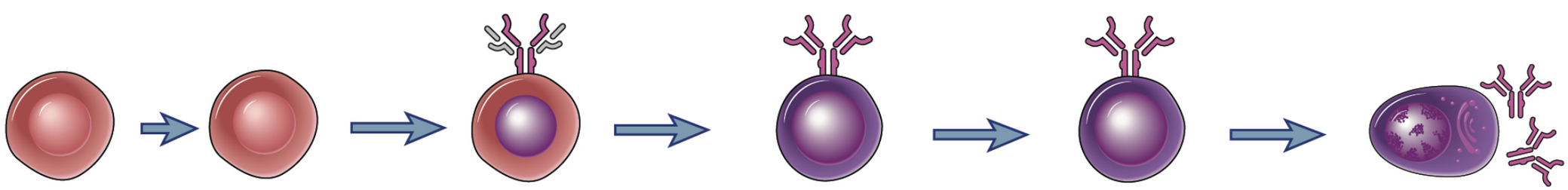
BCR IgM

BCR IgM&IgD

RAG-1/-2 **RAG-1/-2**

Cadeia H D-J V-D-J Cadeia H (μ) Cadeia H (μ) Cadeia H (μ e ∂)

Cadeia L V-J Cadeia L (λ ou κ) Cadeia L (λ ou κ)



Stage of Maturation	Stem cell	Pro-lymphocyte	Pre-lymphocyte	Immature lymphocyte	Mature lymphocyte	Differentiated effector lymphocyte
Major Events	**Growth factor mediated commitment, expansion; initiation of antigen receptor gene rearrangement**		**Selection of cells that express pre-antigen receptors**	**Selection of repertoire and acquisition of functional competence**	**Initial responders**	**Performance of effector functions**
Anatomic Site		Generative organ (bone marrow or thymus)			Peripheral lymphoid organ or tissue	
Antigen Dependence		No		Self antigen	Foreign antigen	

Desenvolvimento Linfocitos B

Construçao do BCR

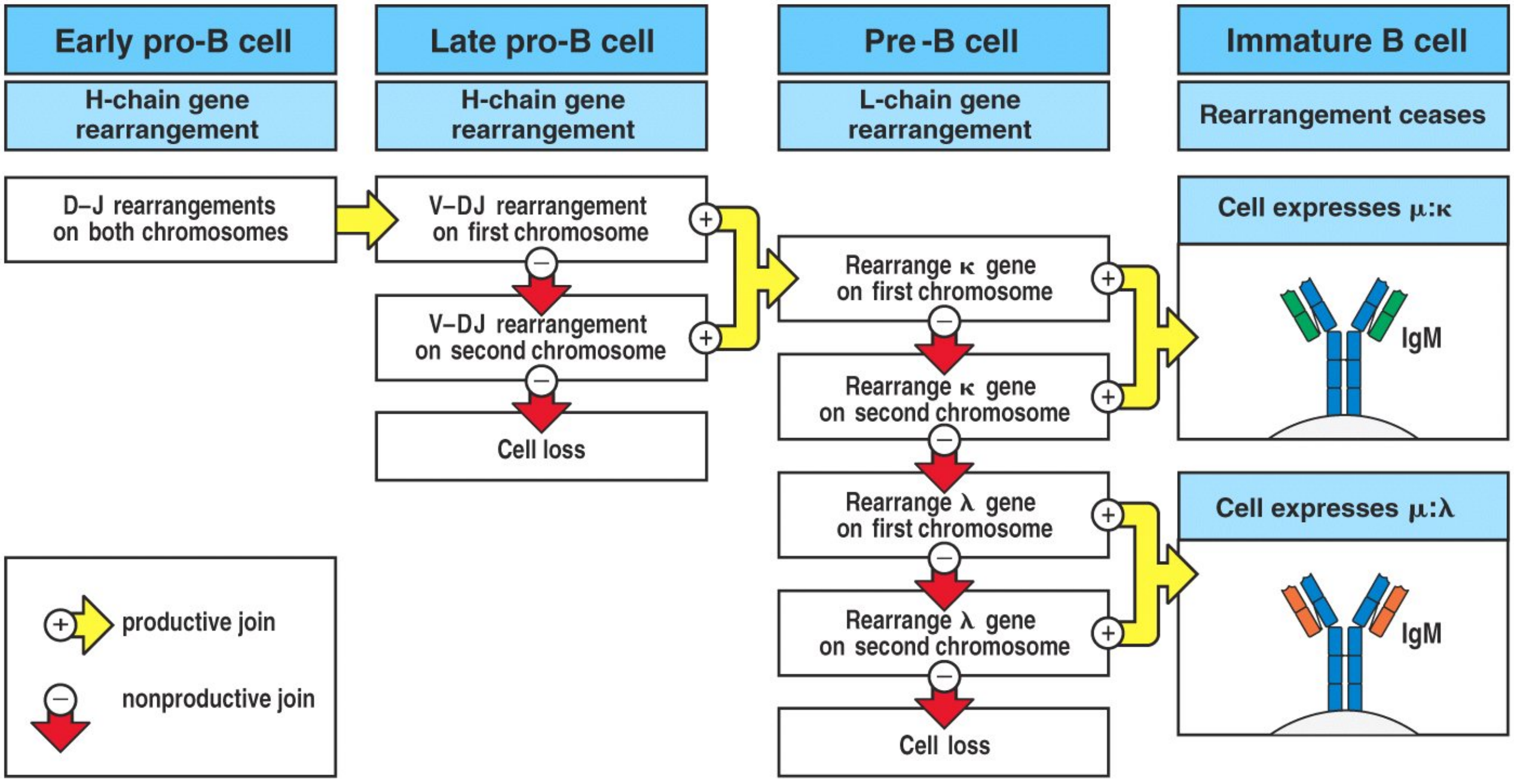


Figure 7-15 Immunobiology, 6/e. (© Garland Science 2005)

Desenvolvimento Linfocitos B

Seleçao do BCR

Proliferation | Pre-B/T antigen receptor expression | Proliferation | Antigen receptor expression | Positive and negative selection

Ag-dependente

Ag-independente

Linfocito Pre B expressa a cadeia H μ

Linfocito B Imaduro expressa o BCR

BCR/Ag fraca

Positive selection

Mature T/B cell

Pro-B/T cell

BCR/Ag forte

Negative selection

falha na expressao da cadeia H μ

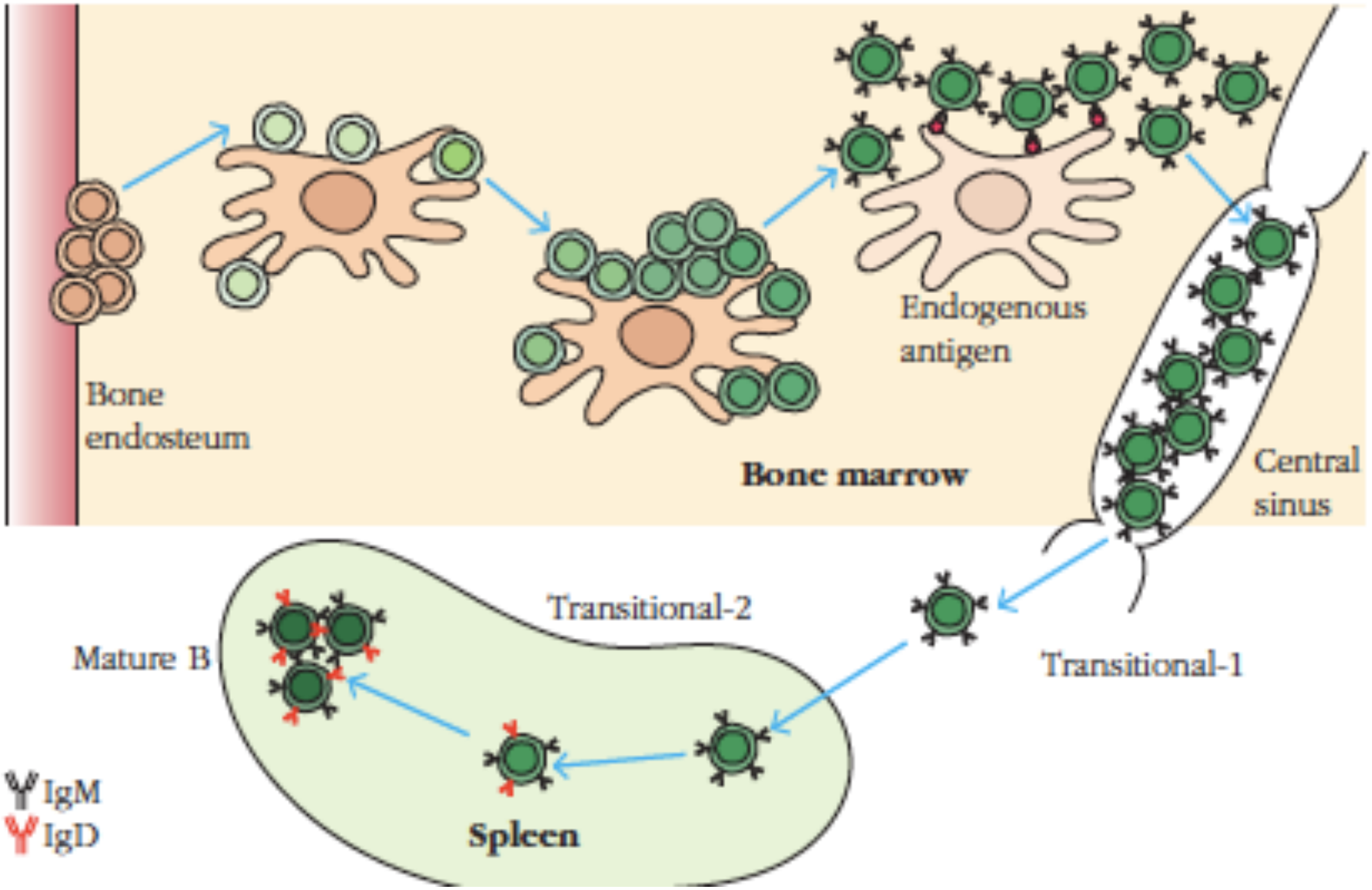
Falha na construçao do BCR

Desenvolvimento Linfocitos B

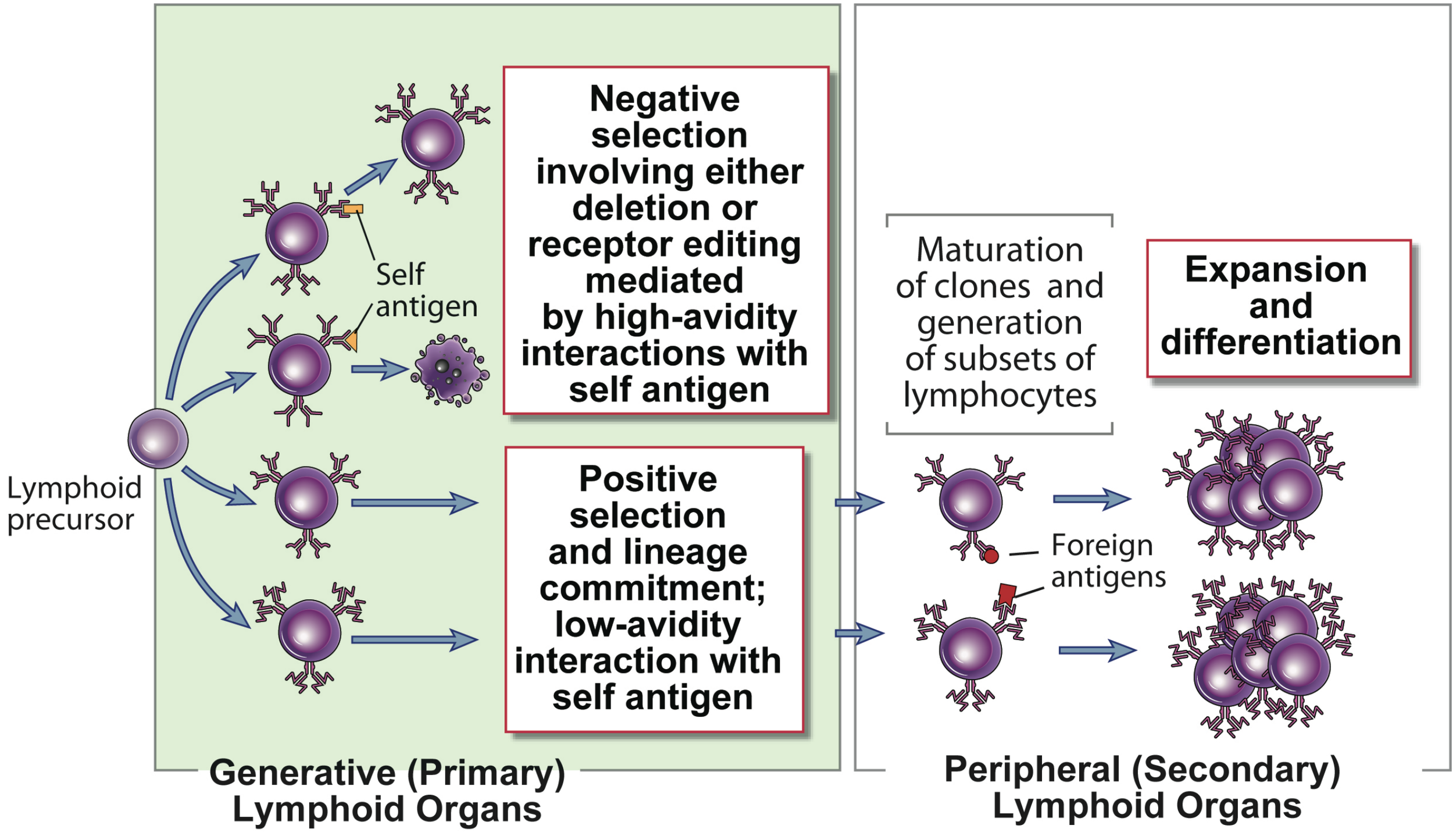
Early ProB	ProB or preB	Immature B
• DJ H chain recombination • Start of VDJ H chain recombination	• Complete VDJ H chain recombination • Clonal expansion • VJ L chain recombination	

Seleçao negativa:

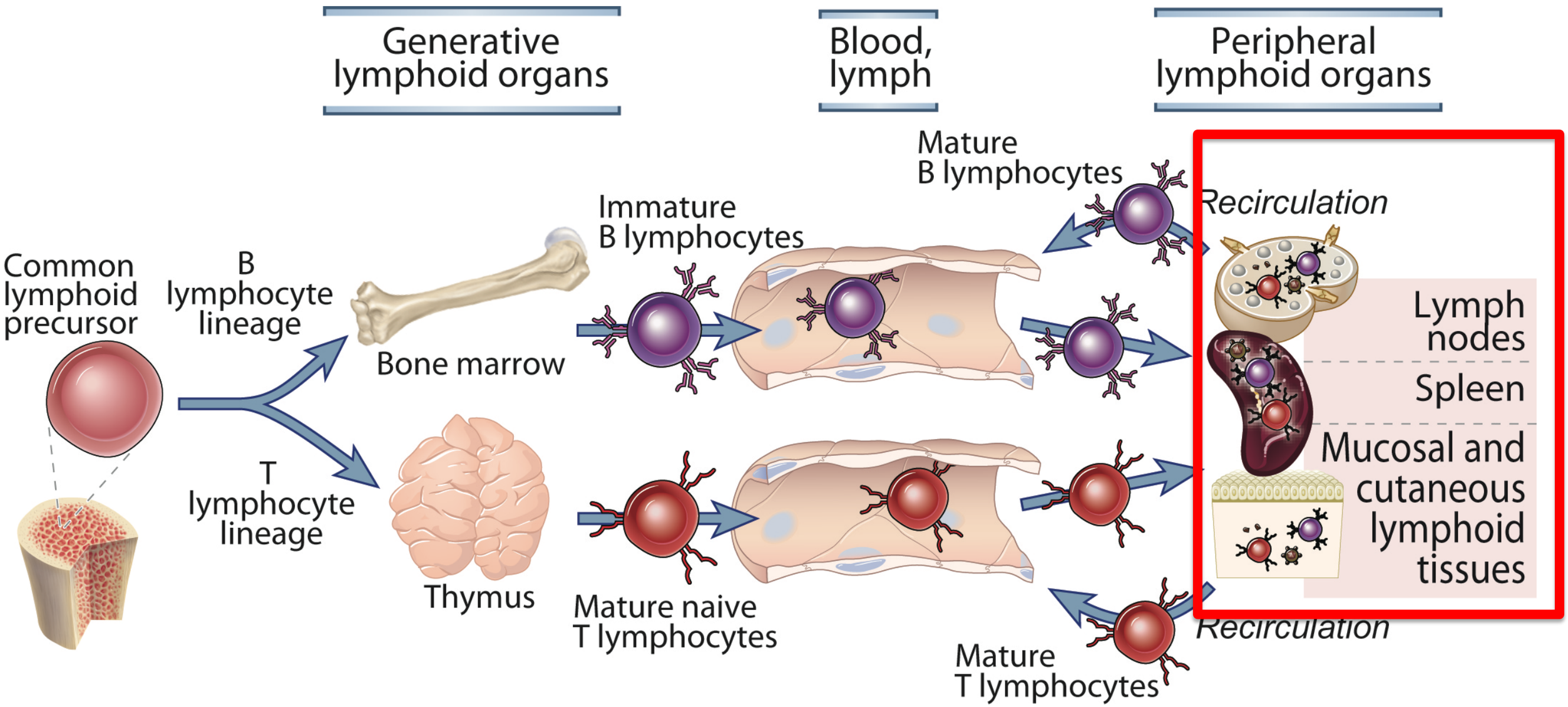
- **sinal de morte** aos LB com BCR com elevada afinidade aos peptideos proprios → *tolerança ao "proprio" (T. central)*
- **Edicao do receptor**



Ativaçao dos Linfocitos B



Ativaçao Linfocitos B

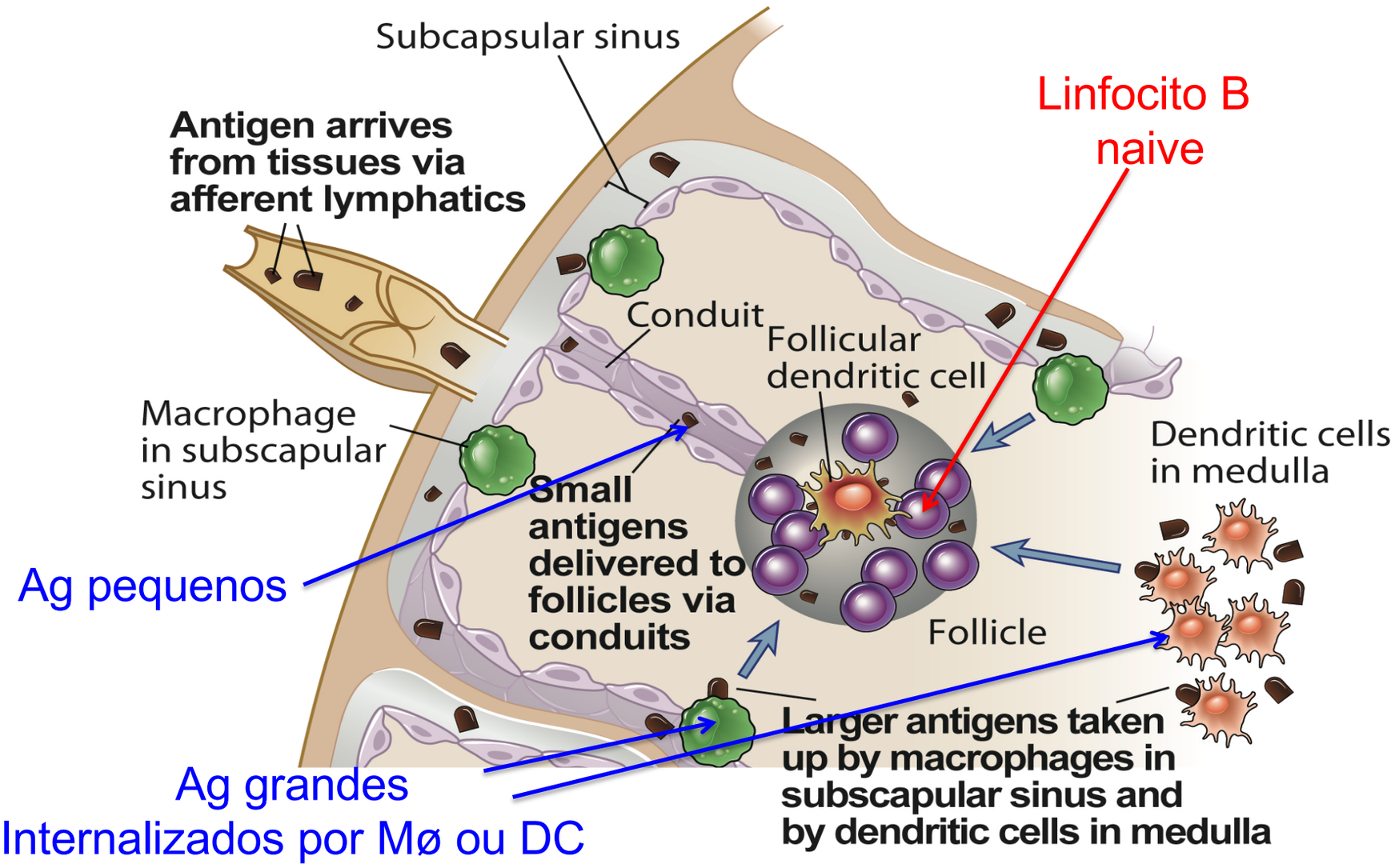


Recirculaçao dos linfocitos "naive"
Encontro com Ag
→ Ativaçao do linfocito
→ Resposta ao Ag
→ Geraçao de memoria

Ativaçao Linfocitos B

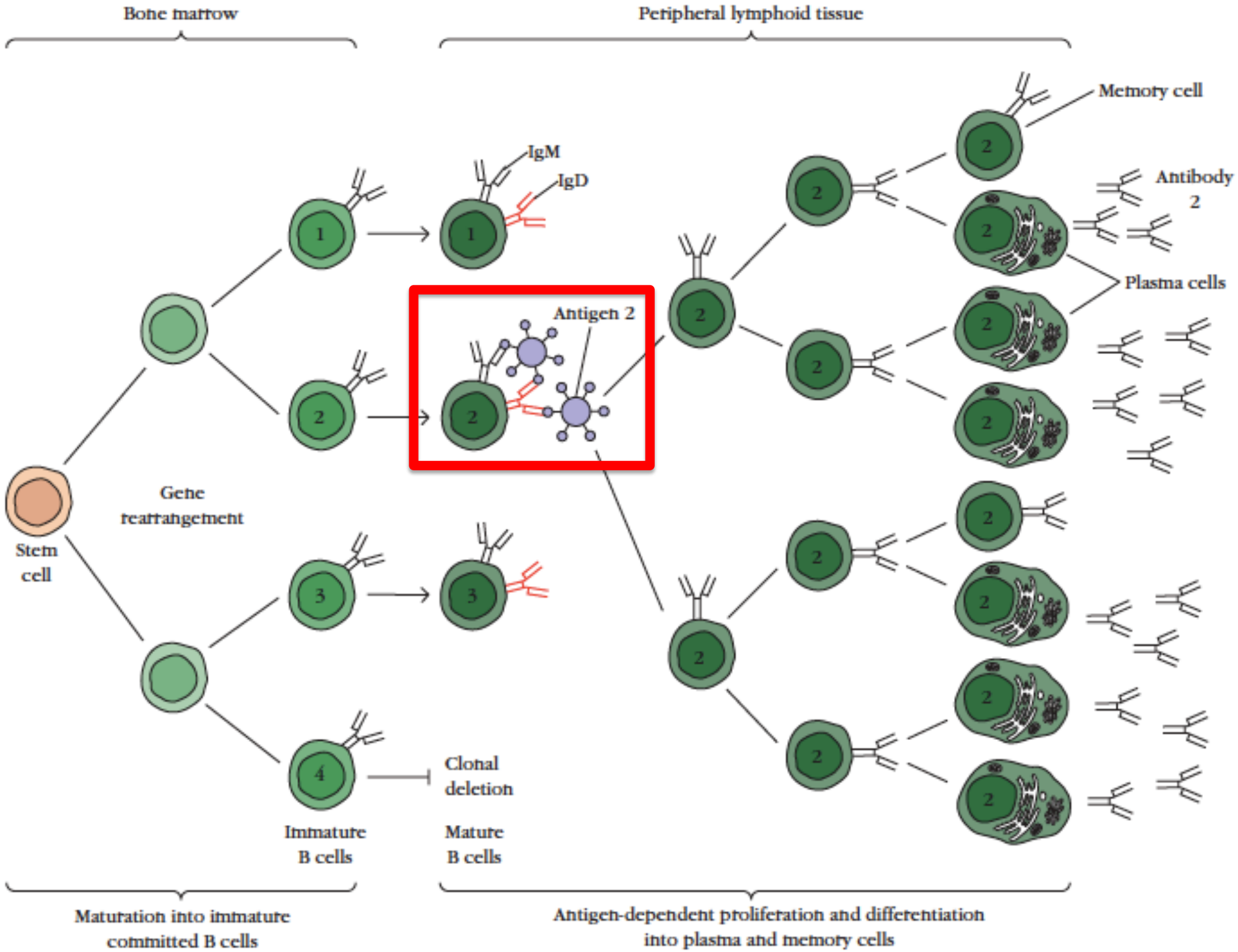
RECONHECIMENTO DO Ag

* Ag soluveis <70kDa chegam a zona de B pelos condutos e interagem diretamente com os B
* Mø subcapsular e DC medullar capturam Ag maiores ou microrganismos inteiro e podem ativar os B
* Complexos Ag/Ac+complemento liga Rec (CR2)



Ativaçao Linfocitos B

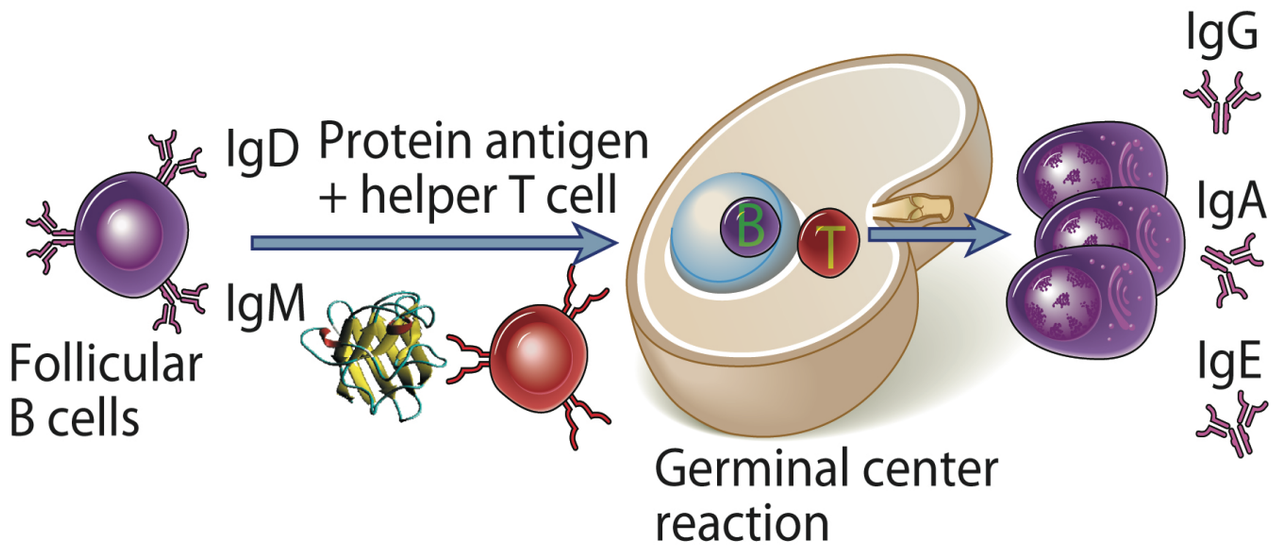
EXPANSAO CLONAL



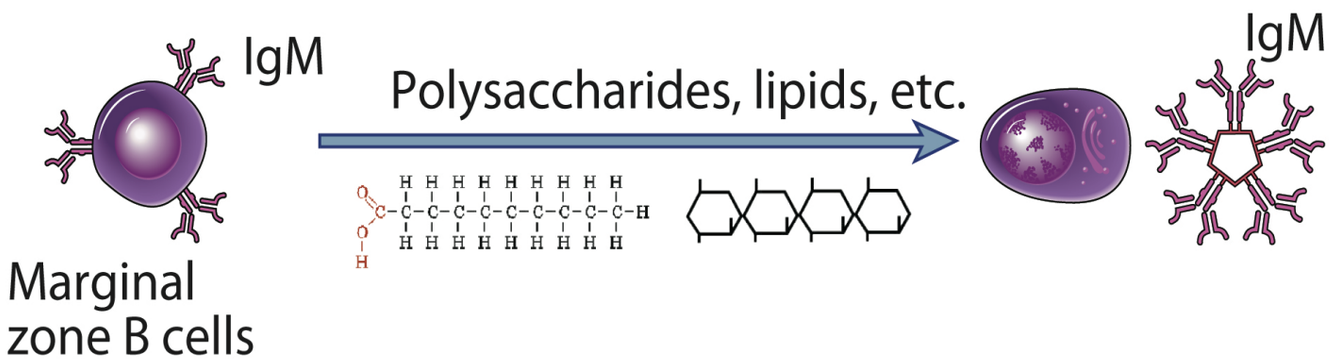
Ativaçao Linfocitos B

Diferentes tipos de sinal do Ag

Baço e outros OL

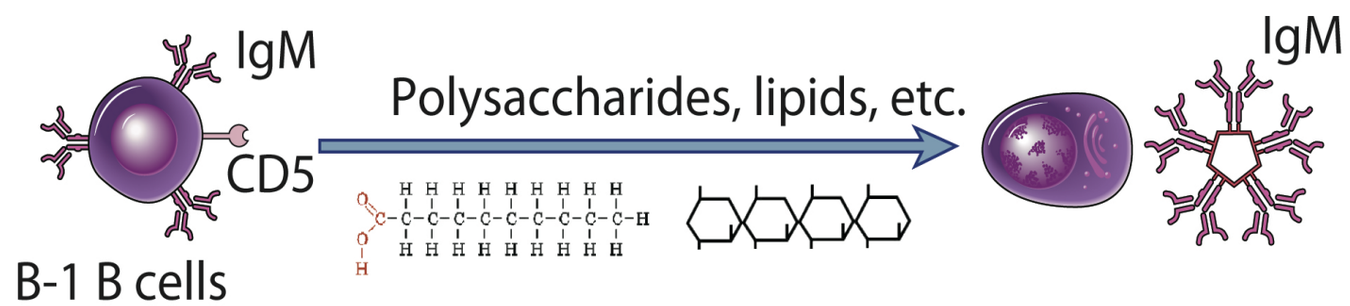


T-dependente: plasmacell de vida longa, isotipo switchado, Ac de elevada afinidade



T-independente: plasmacell de vida curta, **IgM**

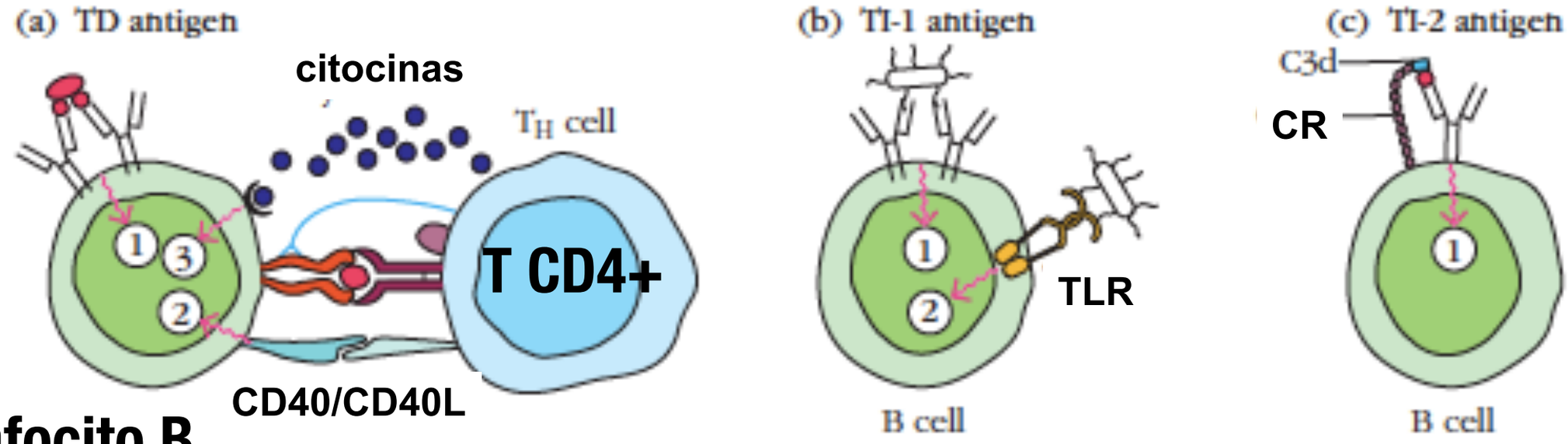
Mucosas, cavidade peritoneal



T-independente: plasmacell de vida curta, **IgM**

Ativaçao Linfocitos B

Diferentes tipos de sinal do Ag

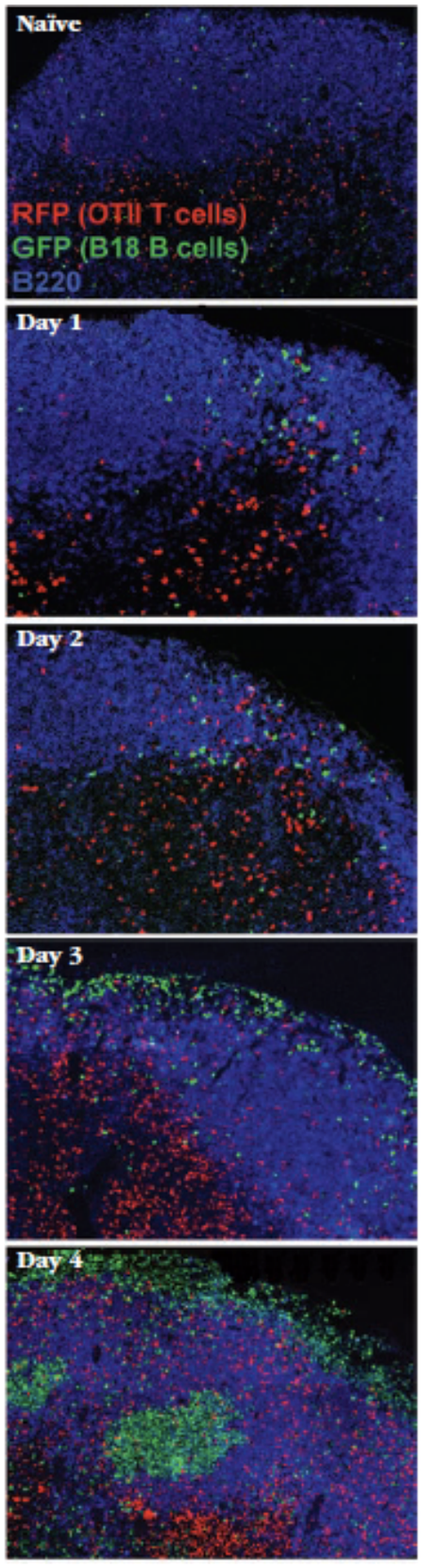


T-independente (TLRs, CRs):
plasmacell de vida curta, IgM

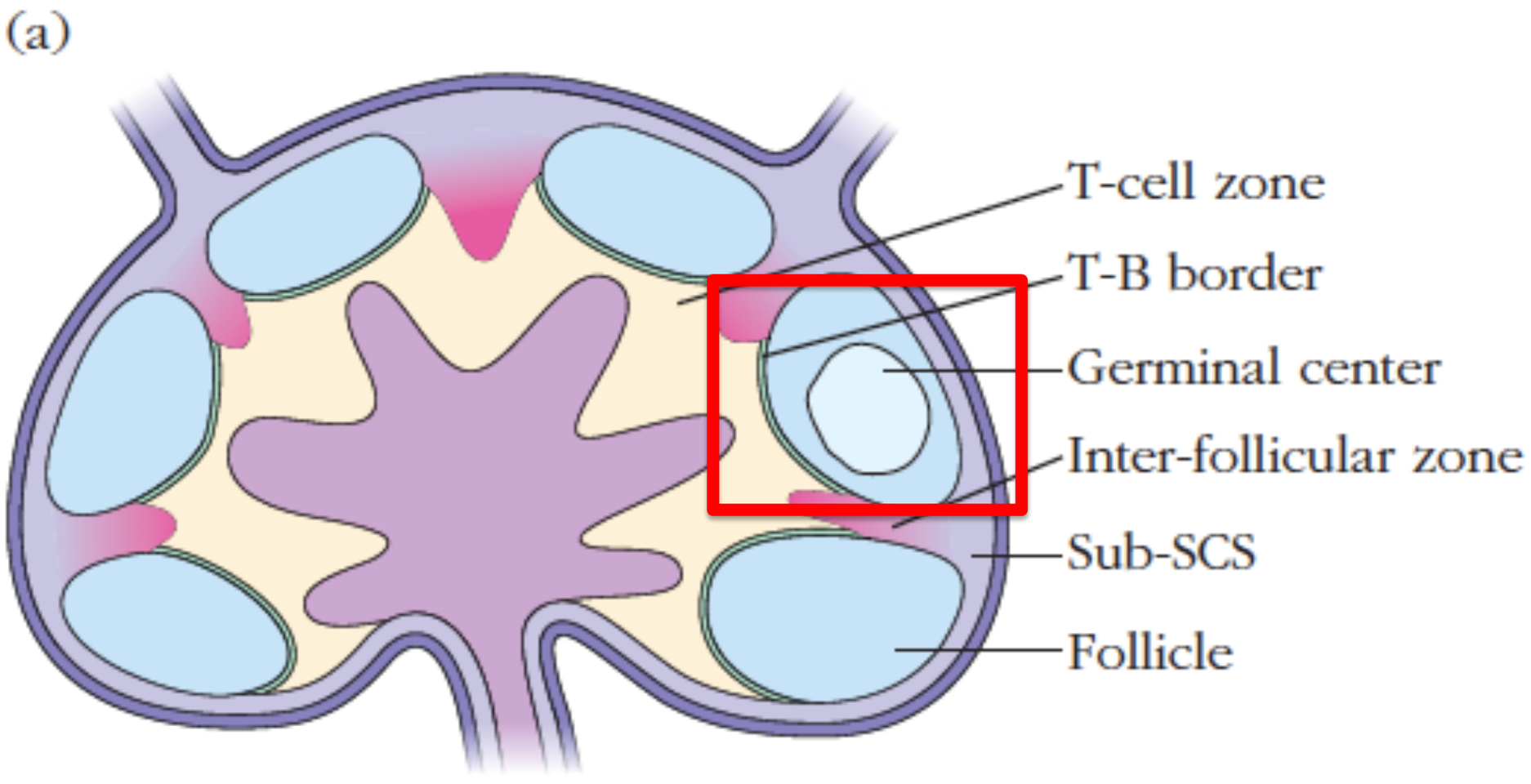
T-dependente:

- ✓ CD4+ativado e diferenciado ajuda a ativaçao do LB
- ✓ estimulam troca de isotipo, maduraçao de afinidade e geraçao de plasmacel de vida longa e cel de memoria → mais “sofisticada” resposta humoral
- ✓ Ag proteicos! (Ag/MHC-II)

Ativaçao Linfocitos B



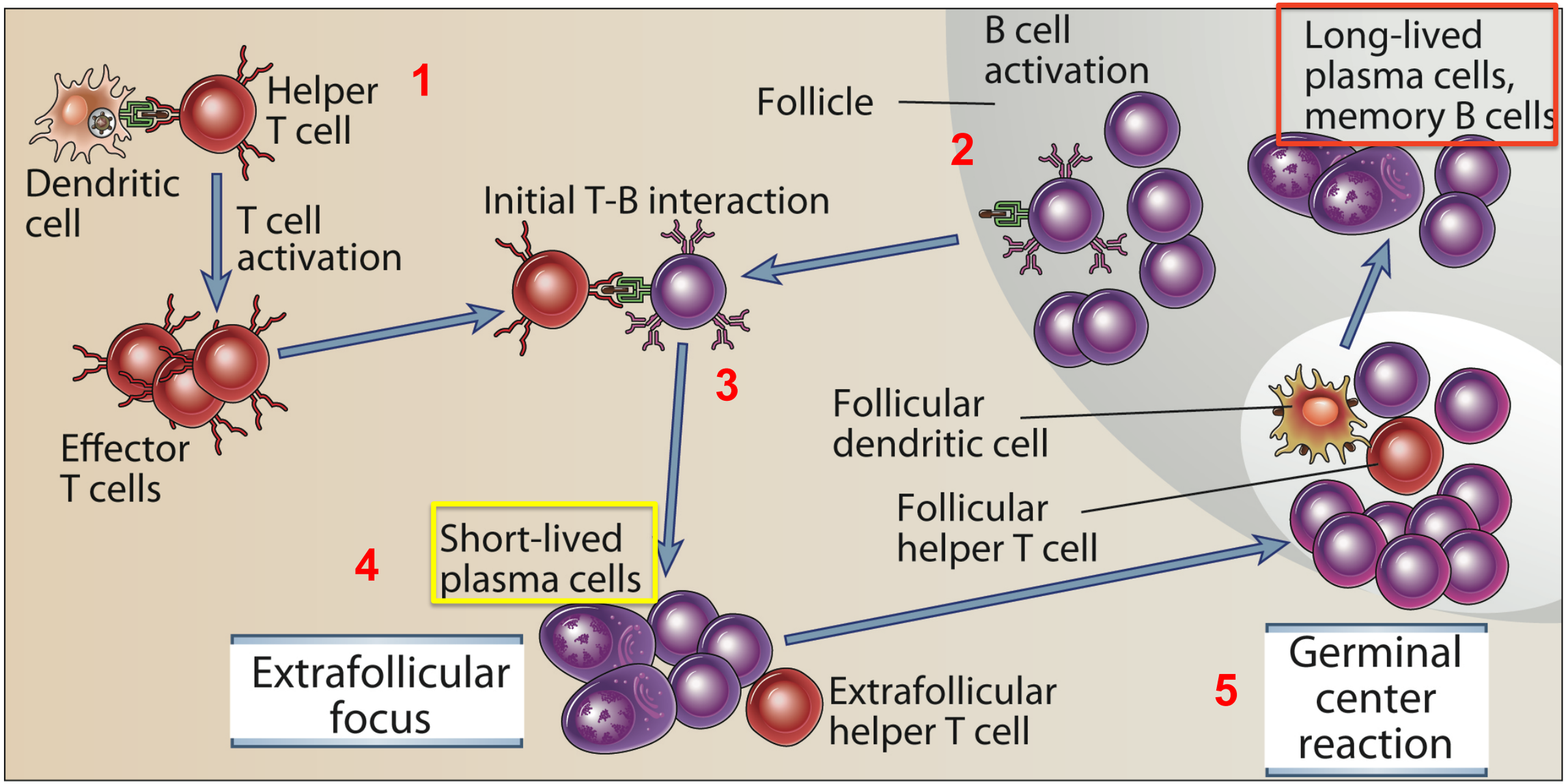
Ativaçao T-dependente…tem lugar



Ativaçao Linfocitos B

ATIVAÇAO EXTRA-FOLICULO (3-4 dd)

CENTRO GERMINAL (6-10 dd)



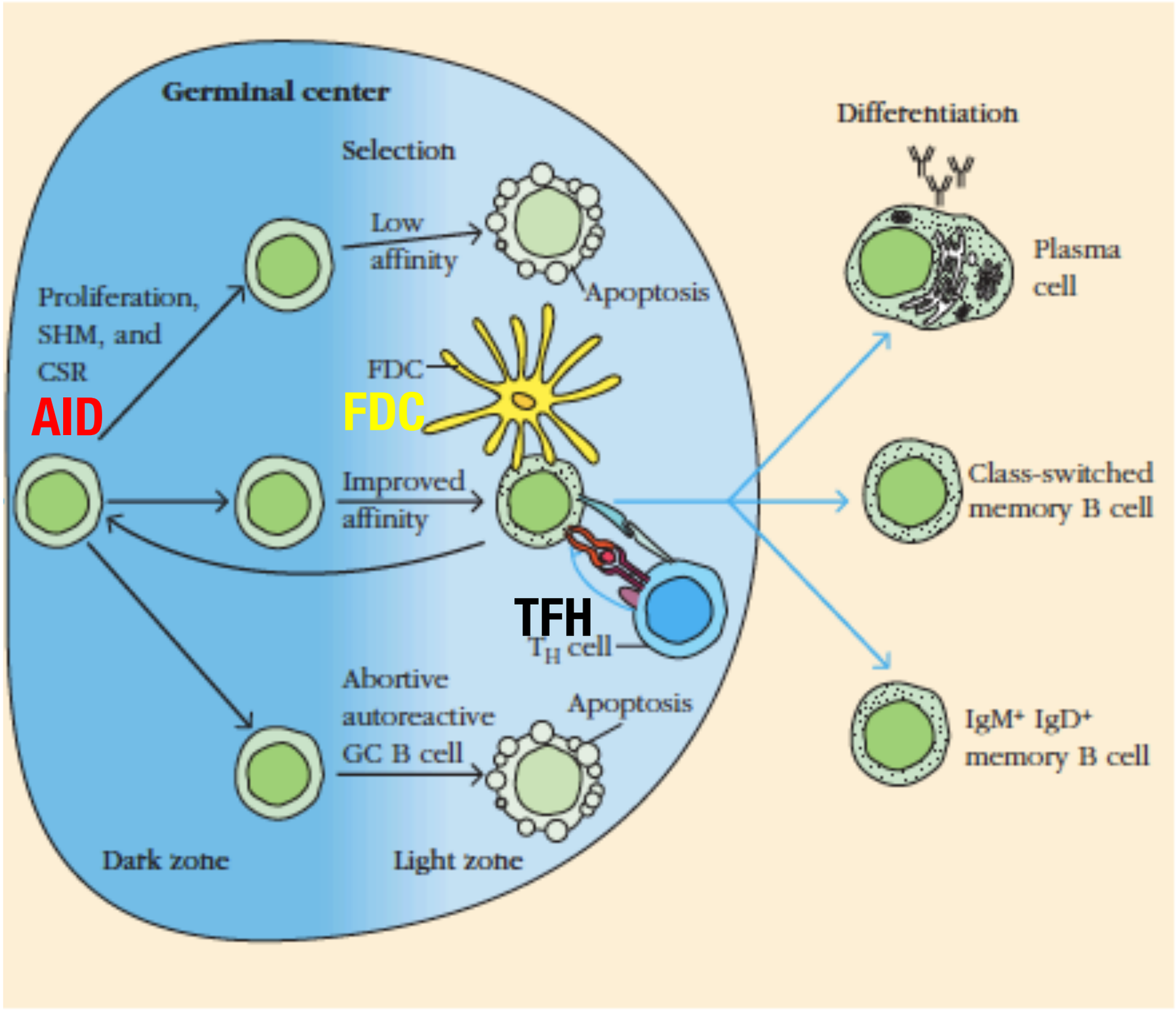
Mudança de isotipo; Hipermutaçao somatica limitada; Afinidade de AC baixa; Plasmocitos de vida curta (3d)	Mudança de isotipo; Hipermutaçao somatica elevada; Maturaçao da afinidade → AC com alta afinidade Plasmocitos de vida longa & Cel B memoria

Ativaçao Linfocitos B

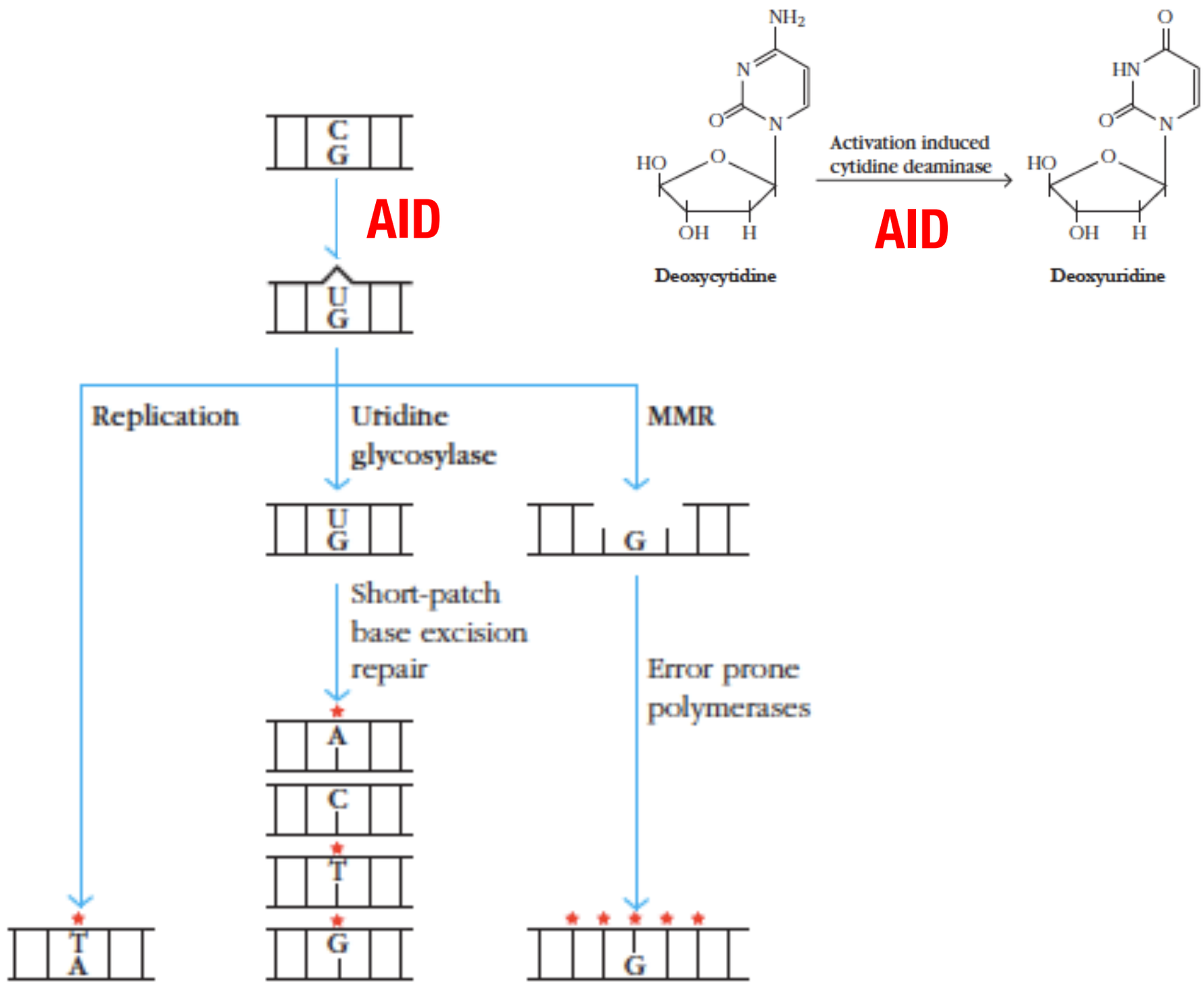
CENTRO GERMINAL

L.B.

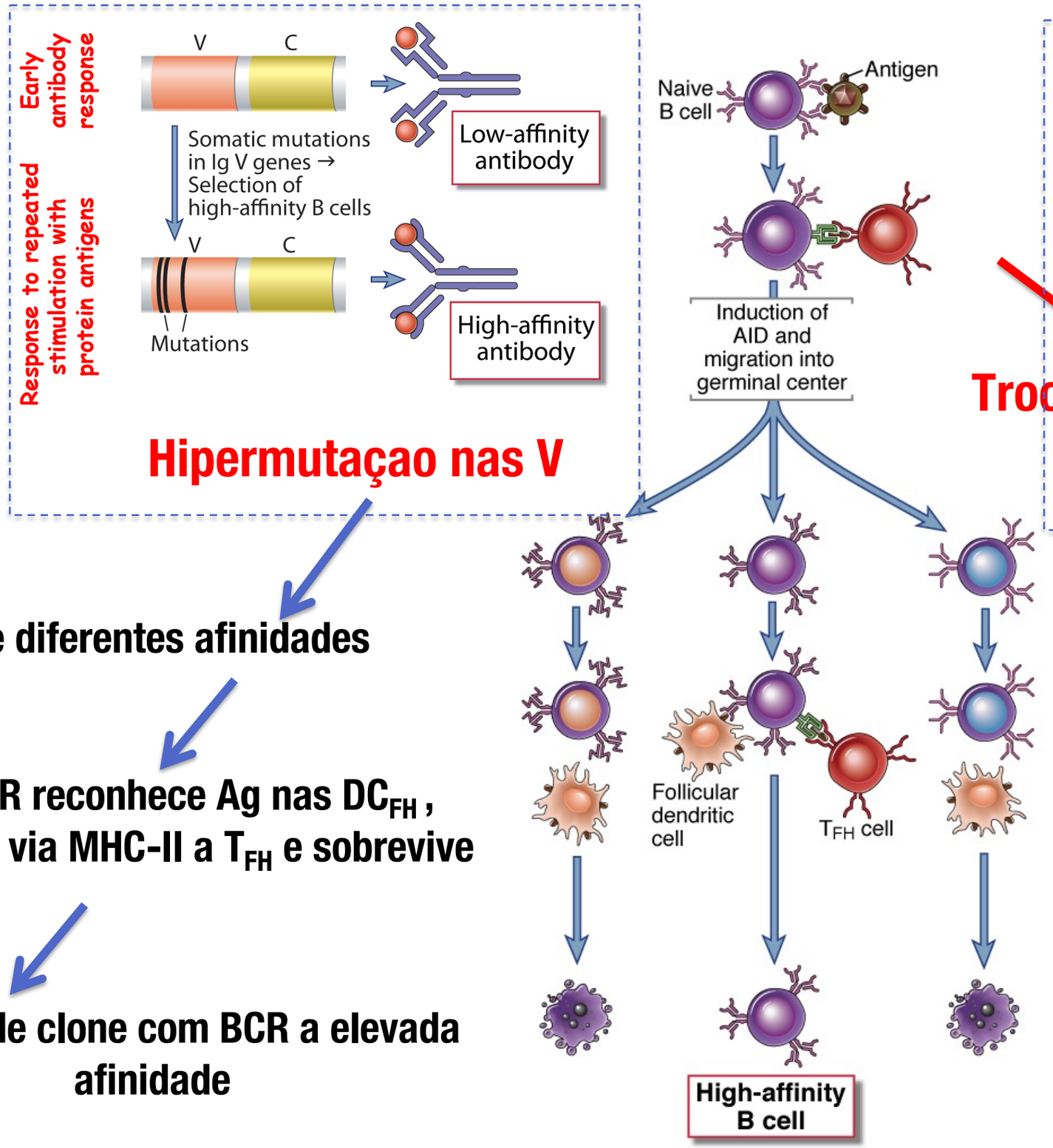
- ✓ Proliferaçao
- ✓ Hipermutacao somatica (→ BCR testado pelas FDC)
- ✓ Switch isotipico (→classe depende do tipo de patogeno)

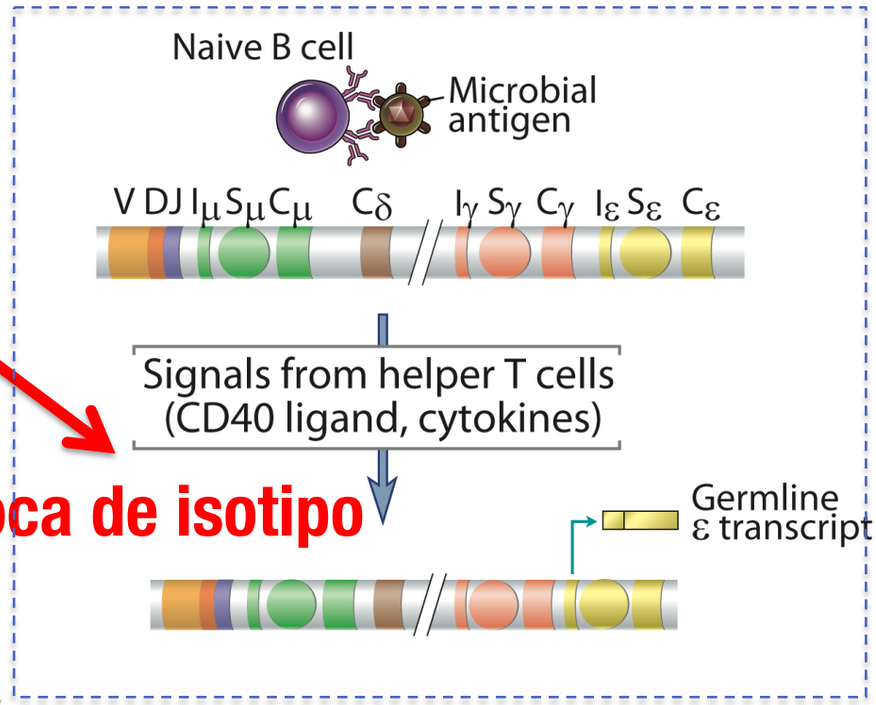


Ativaçao AID e hipermutaçao



Hipermutaçao & Switch isotipico





Switch isotipico

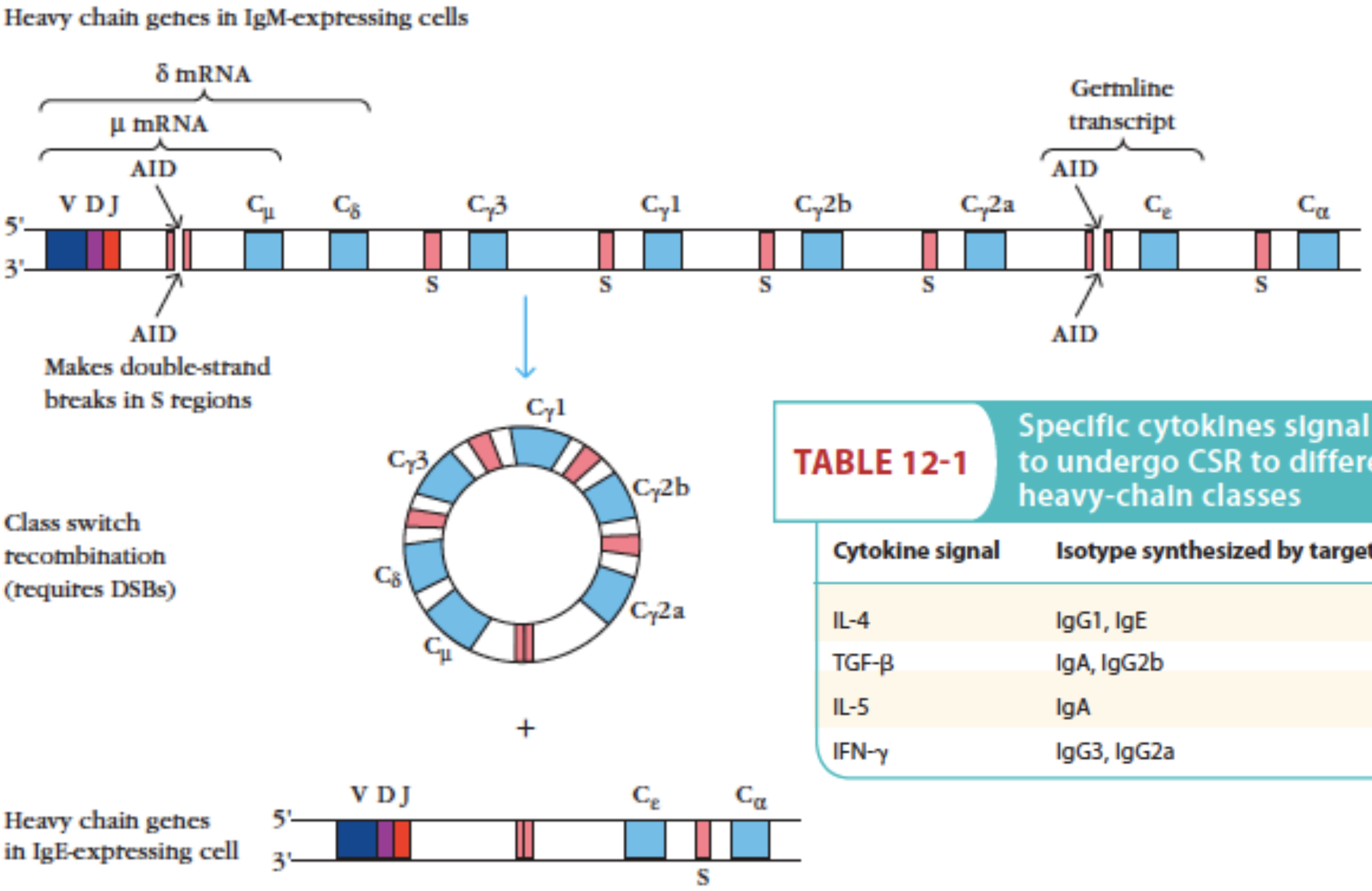


TABLE 12-1 Specific cytokines signal B cells to undergo CSR to different heavy-chain classes

Cytokine signal	Isotype synthesized by target B cell
IL-4	IgG1, IgE
TGF-β	IgA, IgG2b
IL-5	IgA
IFN-γ	IgG3, IgG2a

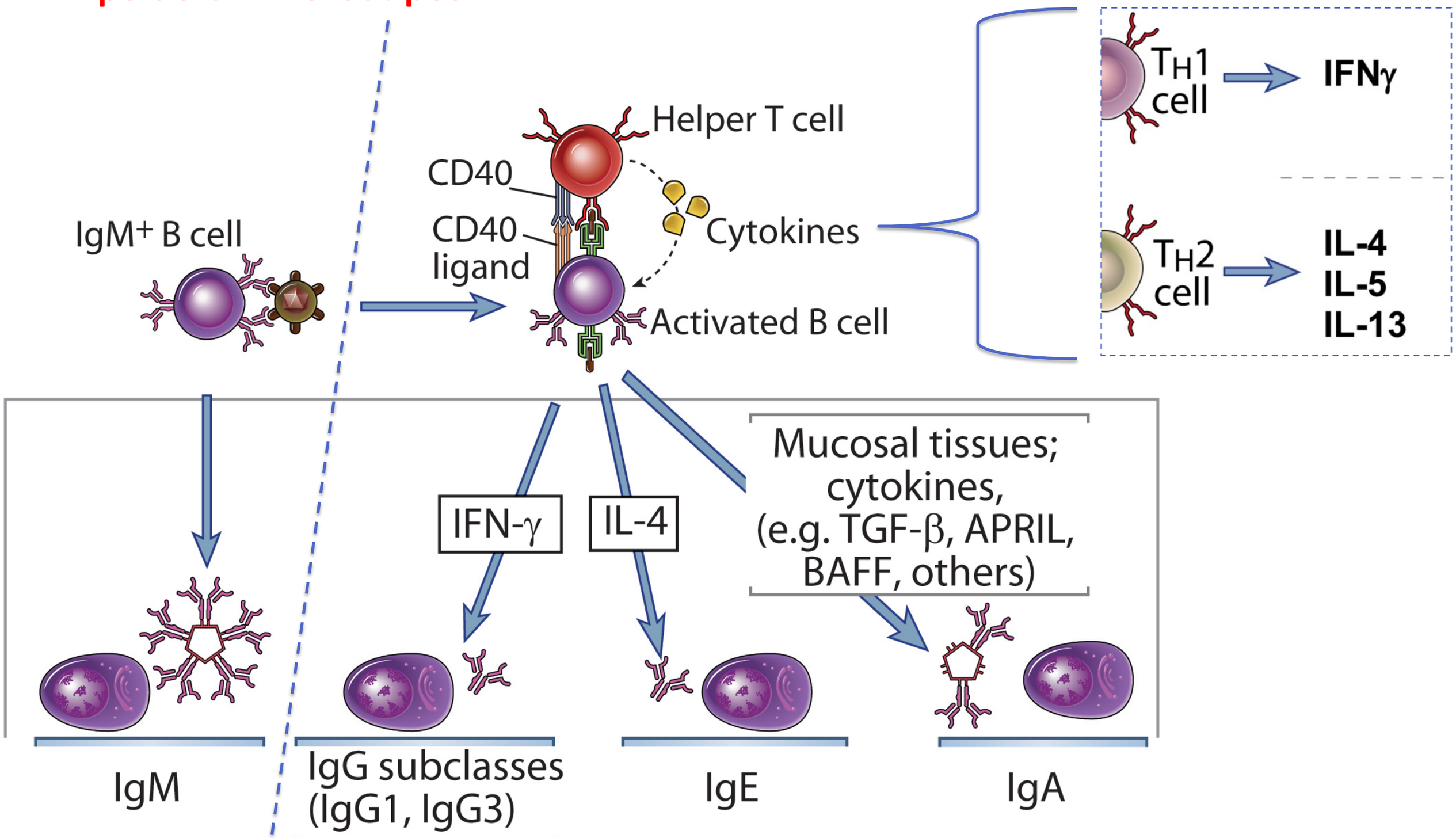
Ativaçao Linfocitos B TD e TI

TABLE 12-4 Functional differences among mature B-cell subsets

Attribute	Conventional B2 B cells	B-1 B cells	Marginal zone B cells
Major sites	Secondary lymphoid organs	Pleural and peritoneal cavity; also spleen	Marginal zones of spleen in mice; primates also have MZ cells in other locations
V region diversity	Highly diverse	More restricted diversity	Moderate diversity
Rapidity of antibody response	Slow; plasma cells appear 7–10 days post stimulation	Rapid; plasma cells appear as early as 3 days after stimulation	Rapid; plasma cells appear as early as 3 days after stimulation
Surface IgD?	High levels of IgD	Low levels of IgD	Low levels of IgD
Somatic hypermutation	Yes	No	Yes in primates; possibly in rodents
Requirements for help from other cell types	Provided by T cells	No, although T and other cells can enhance response	Dendritic cells and neutrophils can enhance response (see Box 12-2)
Participate in germinal center reaction?	Yes	No	Possibly, although with slower kinetics than follicular B cells
Isotypes produced	All isotypes	Predominantly IgM	Predominantly IgM
Immunological memory	Yes	Very little	Yes; source of IgM-producing memory cells

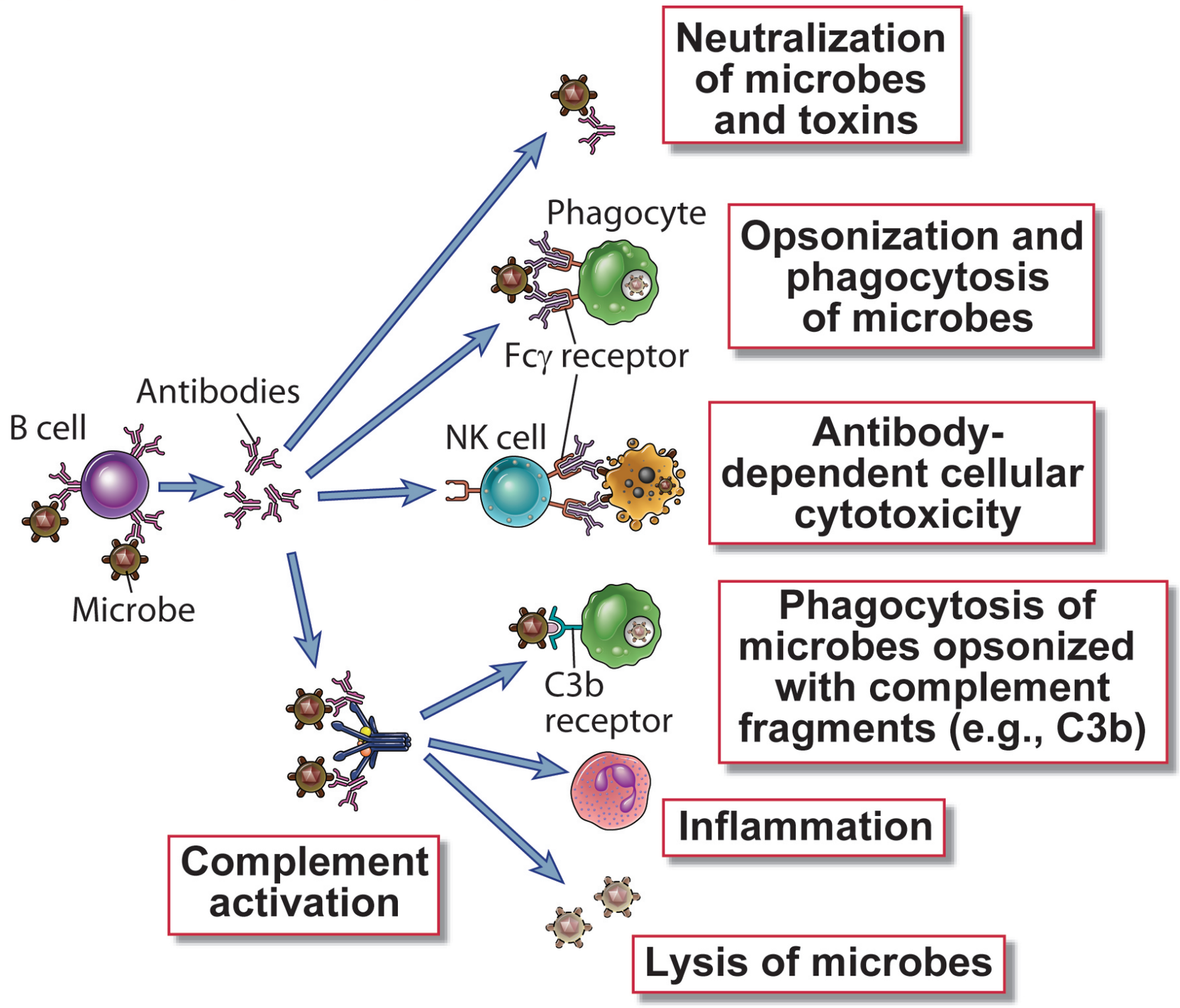
Ativaçao Linfocitos B e AC

Tipo de CD4+ e isotipos

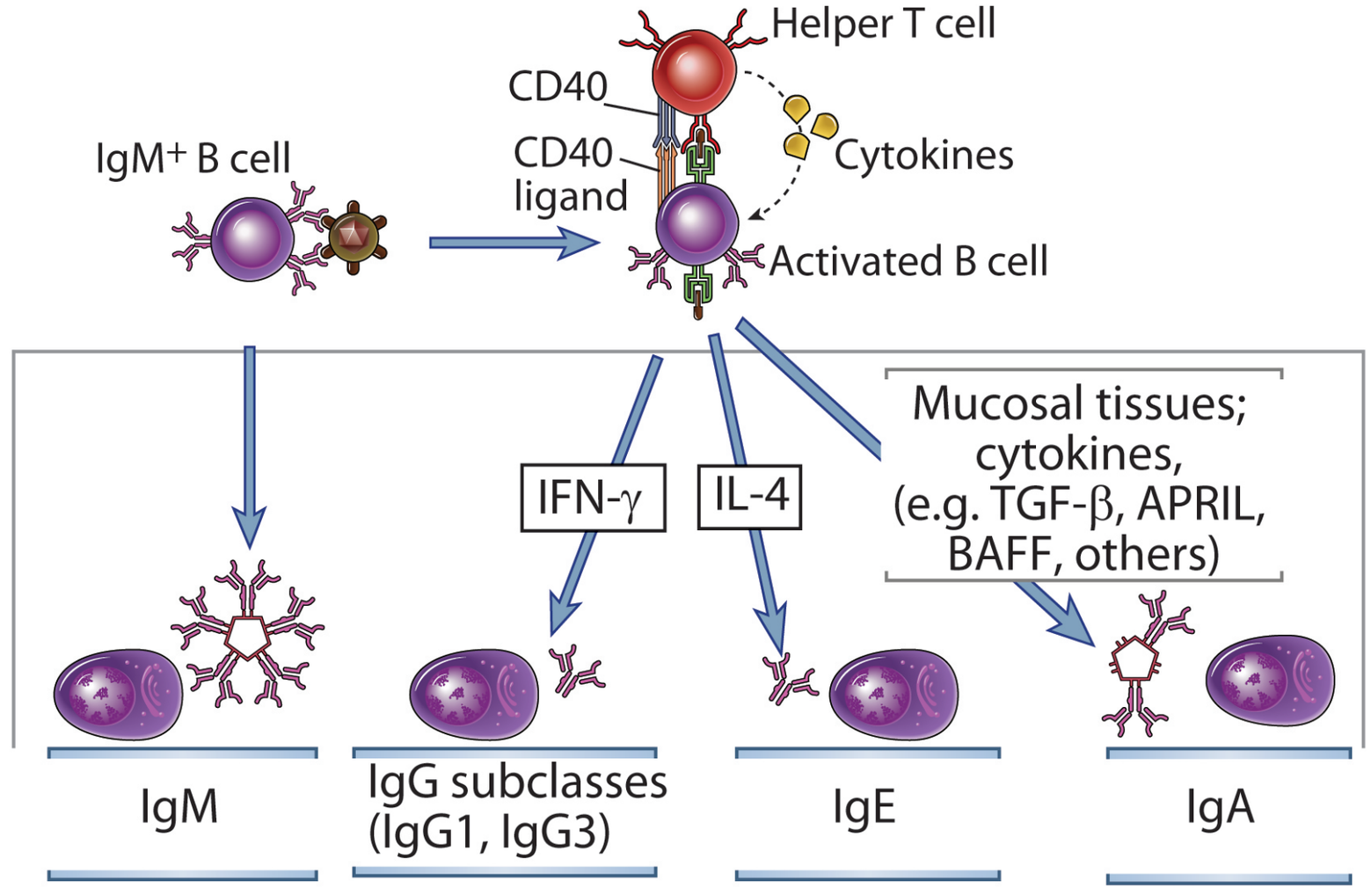


Funcao efetora dos Linfocitos B

= FUNCAO EFETORA DOS AC

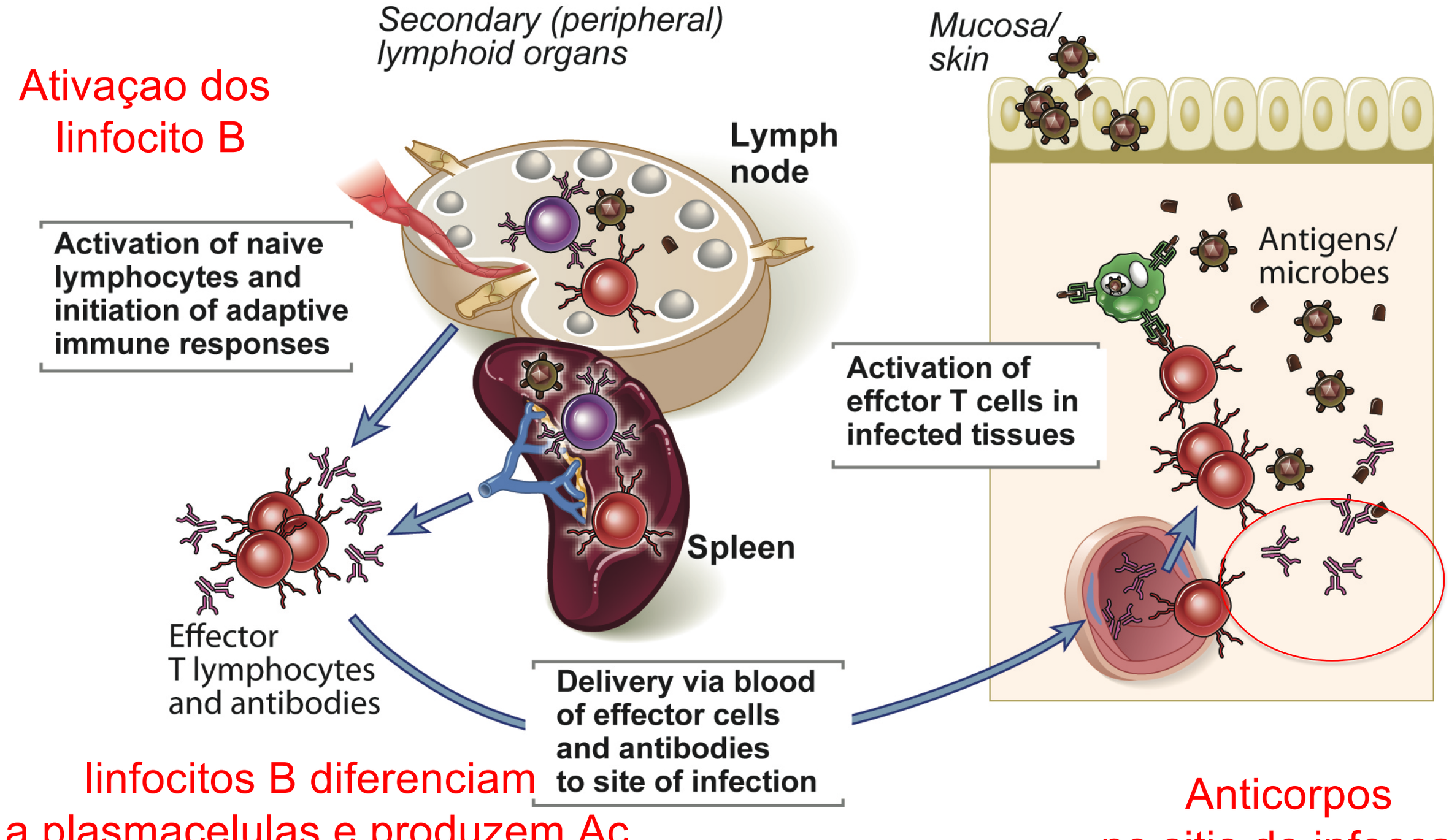


Funcao efetora dos Linfocitos B



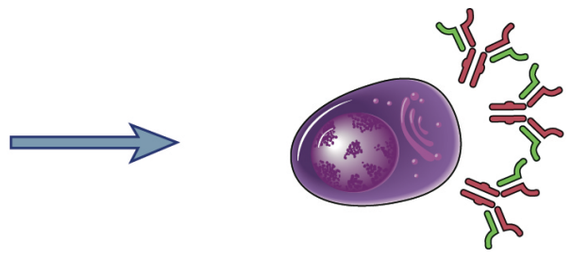
Complement activation	FcR-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

Ativaçao dos linfocito B

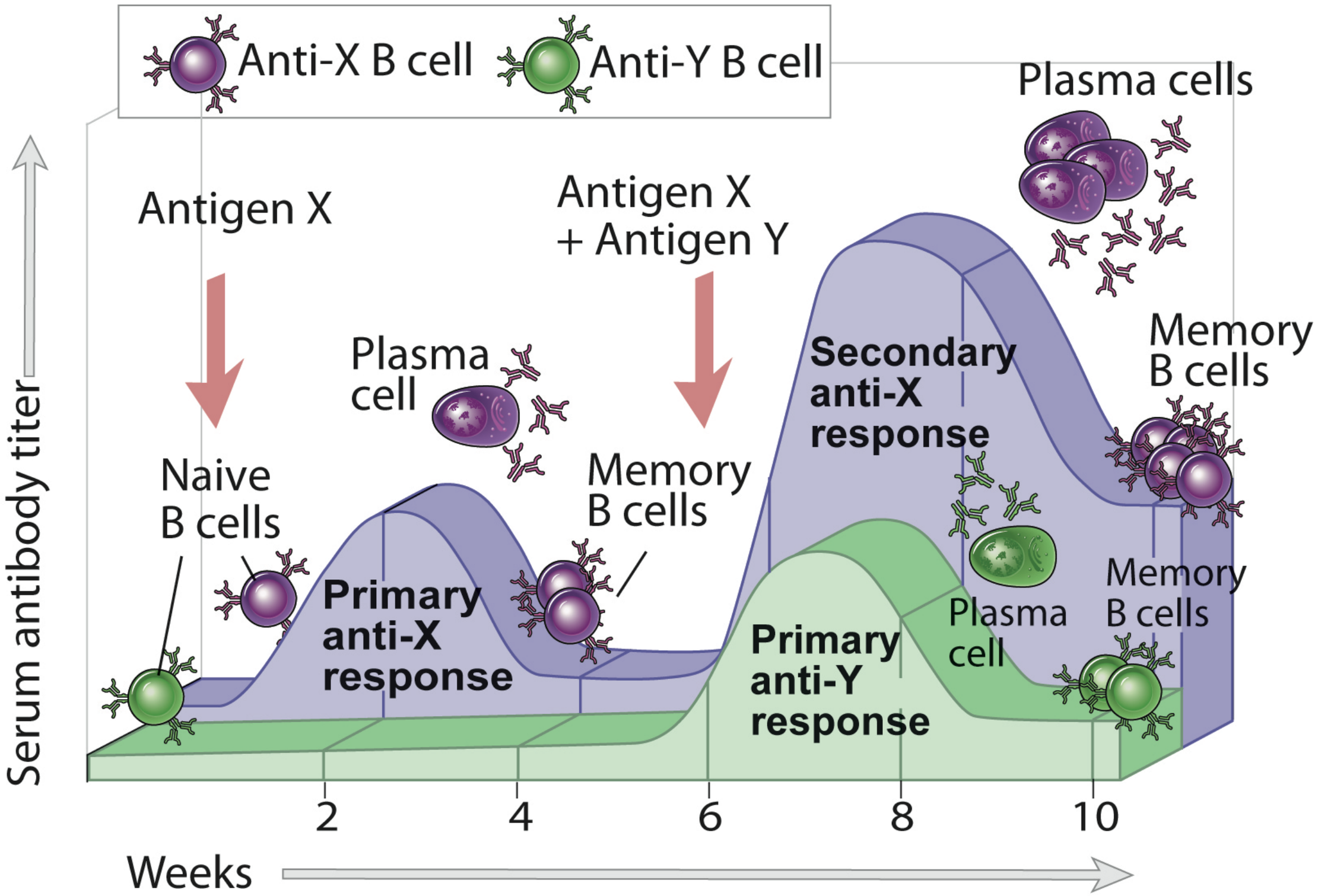


linfocitos B diferenciam a plasmacelulas e produzem Ac

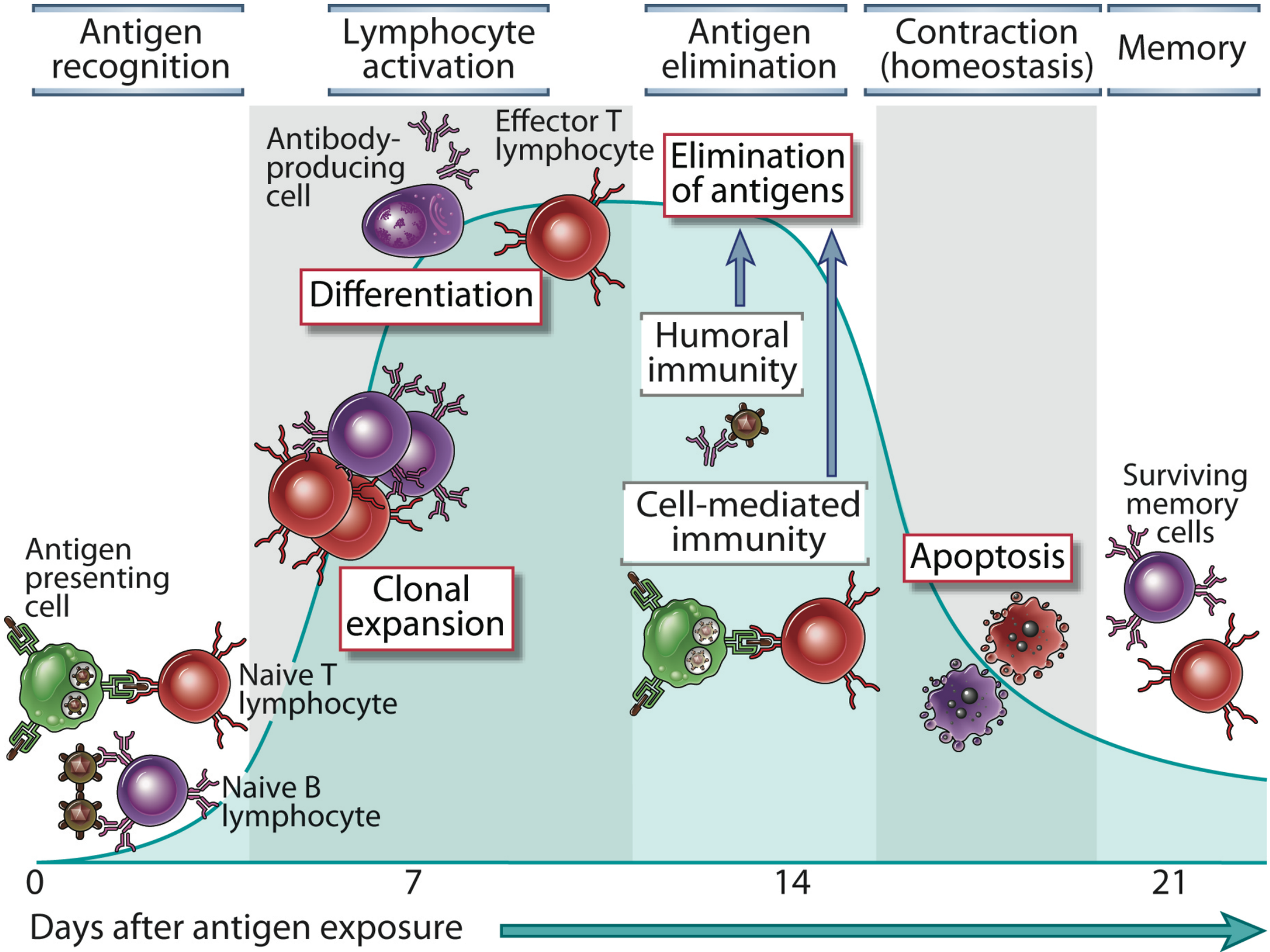
Anticorpos no sitio de infecçao



Cinetica da ativaçao Linfocitos B



Resposta mediada por Linfocitos B



Linfocitos B & AC & idade