

# Eventos celulares e moleculares da inflamação

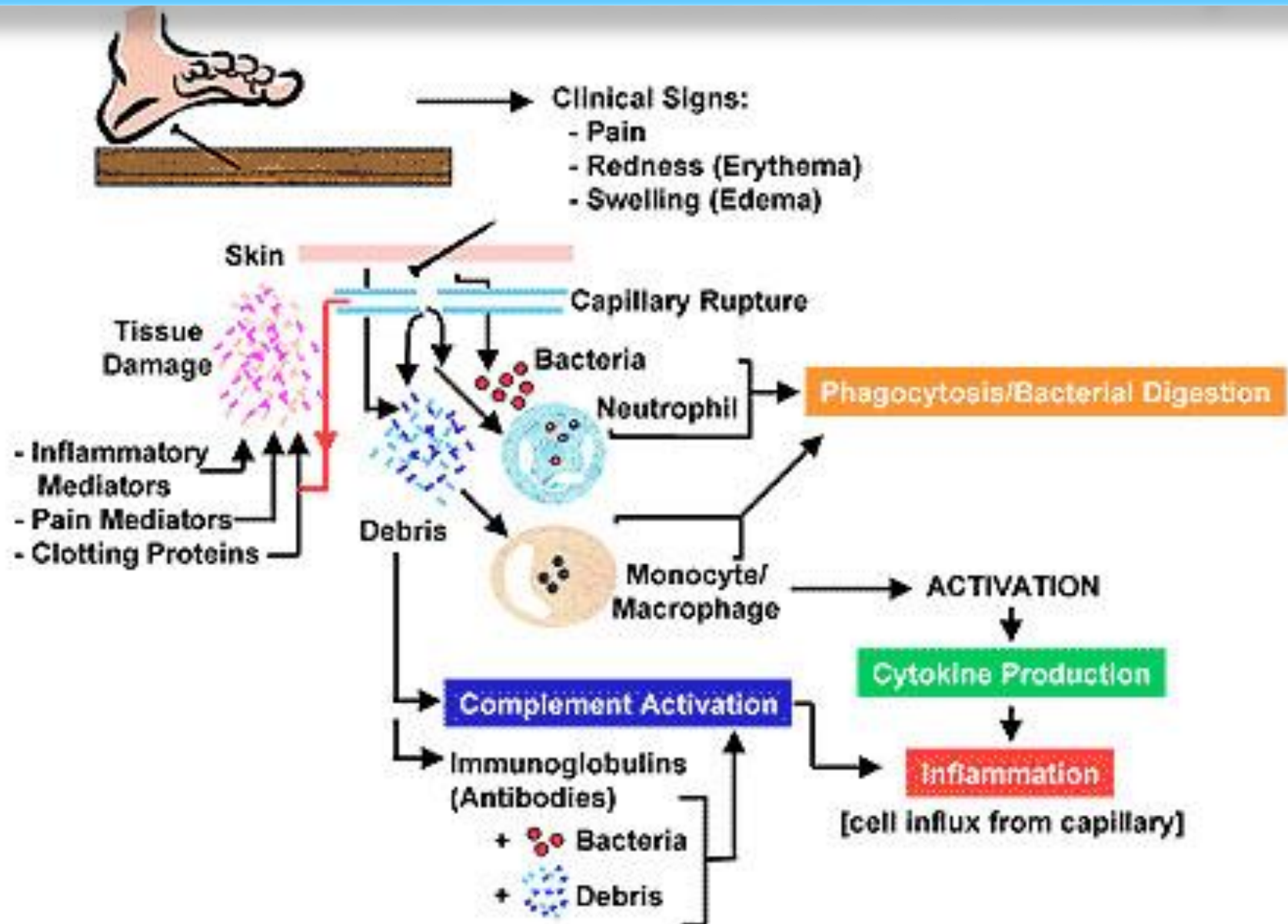
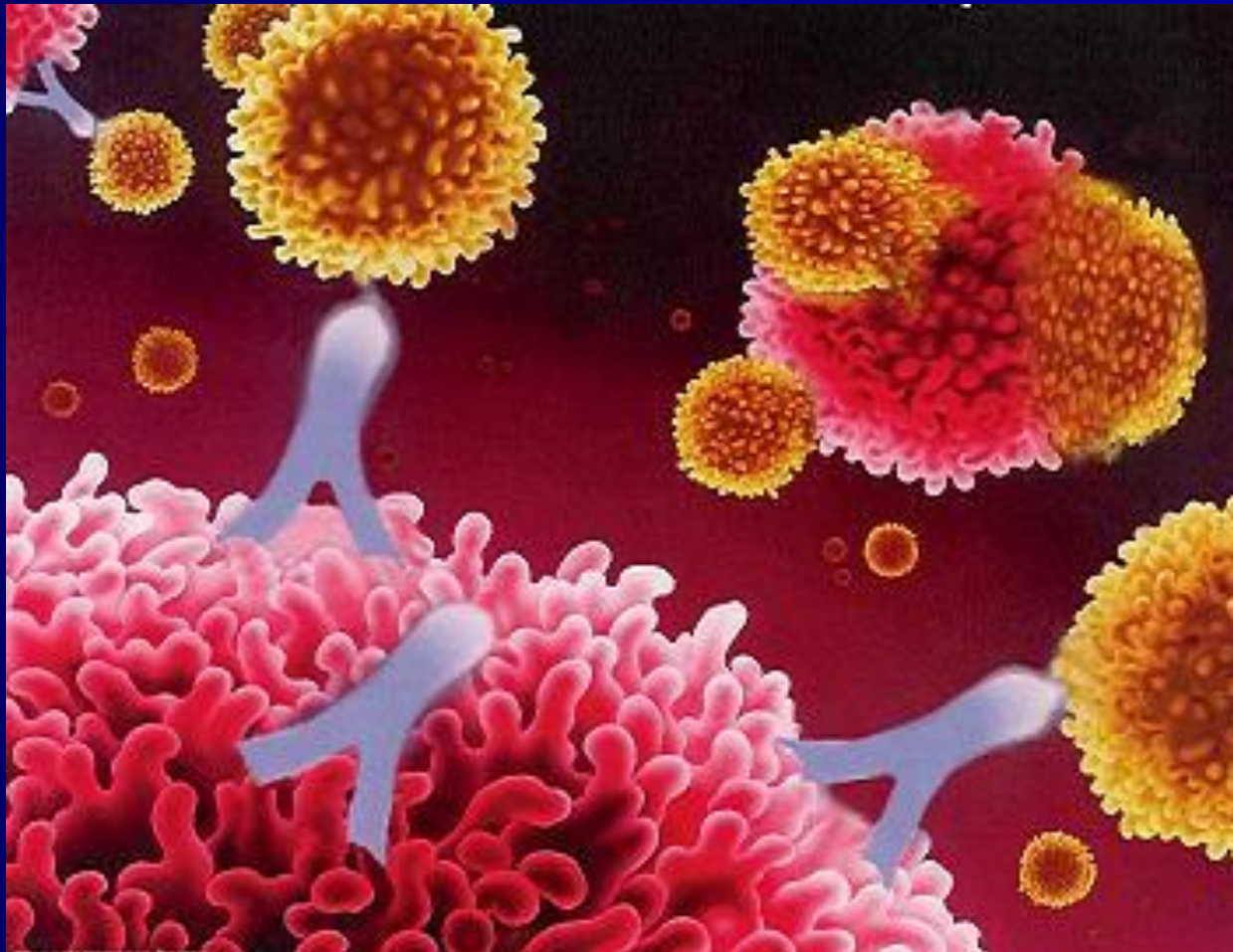


Figure 8. Innate immunity and inflammation.

# ONTOGENIA DOS LINFÓCITOS B



# ONTOGENIA:

desenvolvimento e a sobrevivência dos linfócitos

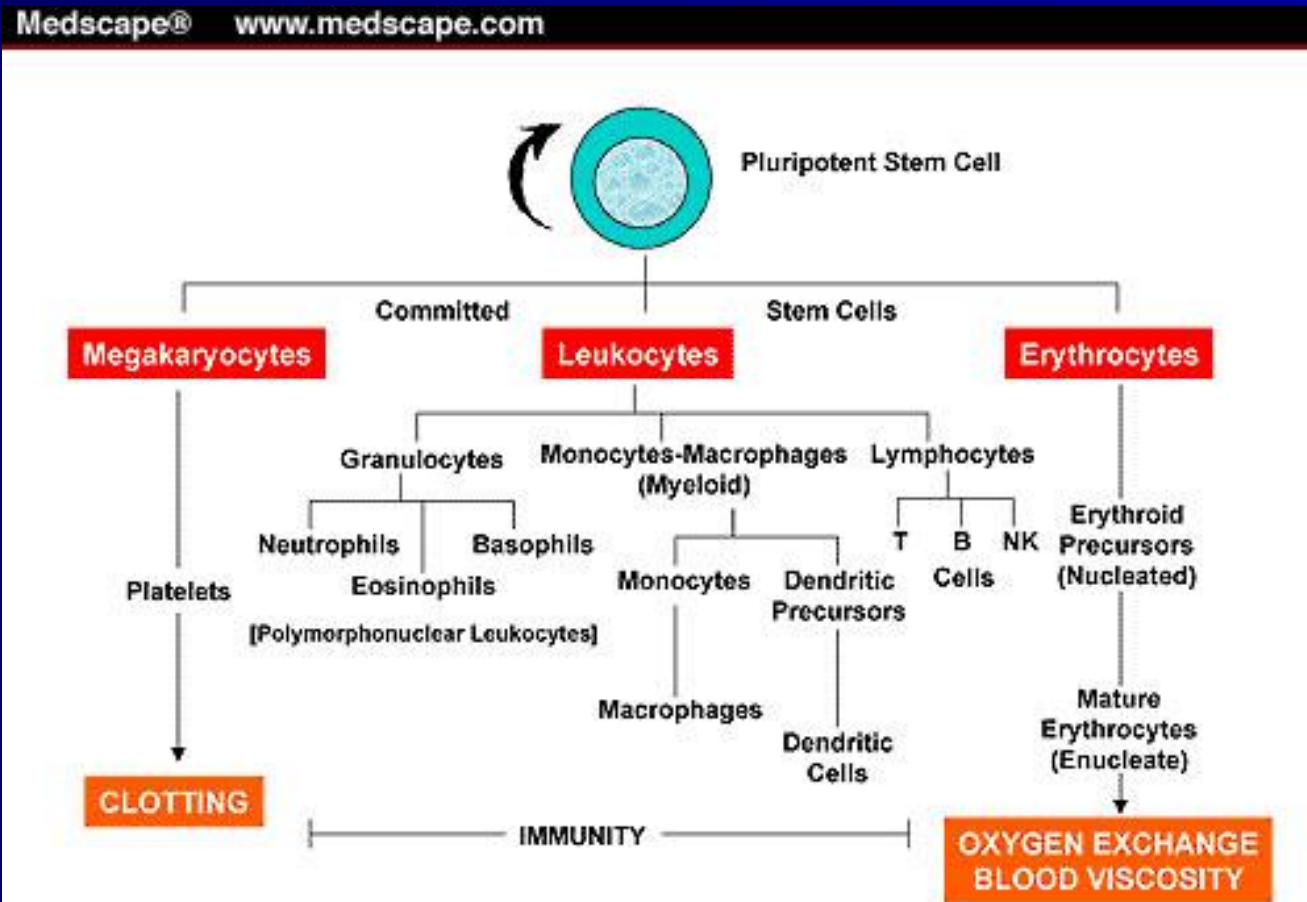
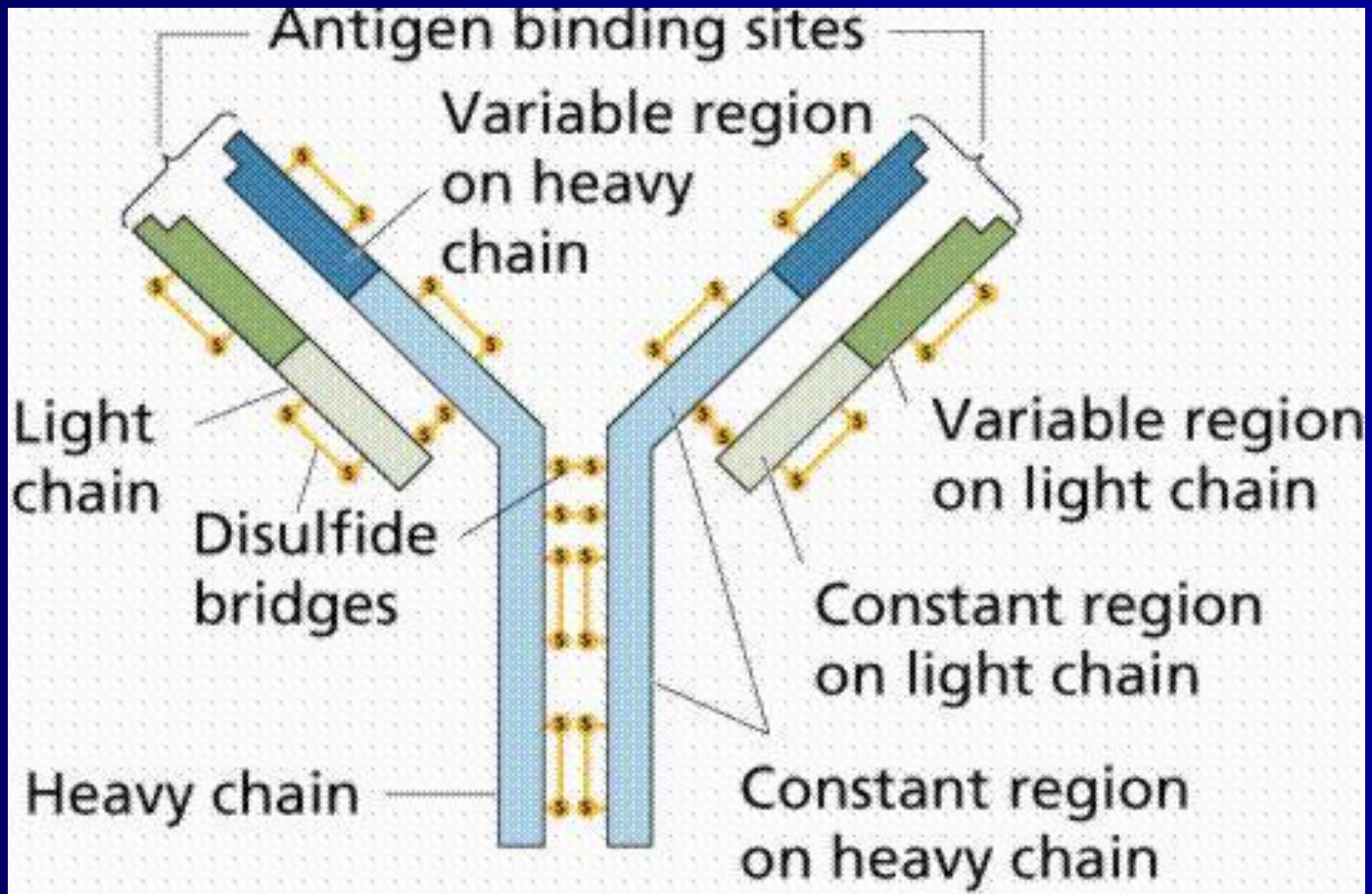


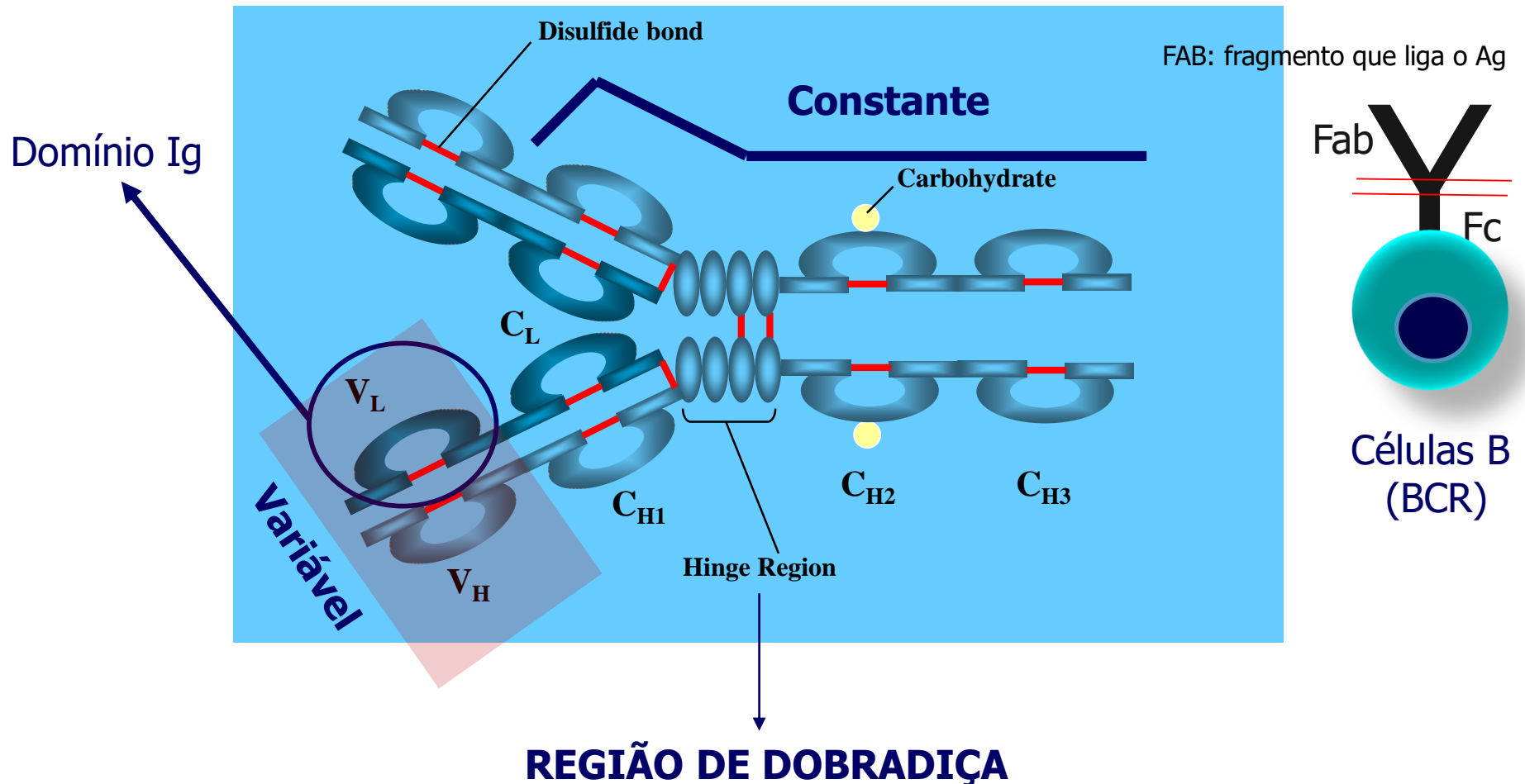
Figure 4. Hemopoiesis in the bone marrow.



**BCR:** receptor de antígeno expresso sobre as células B

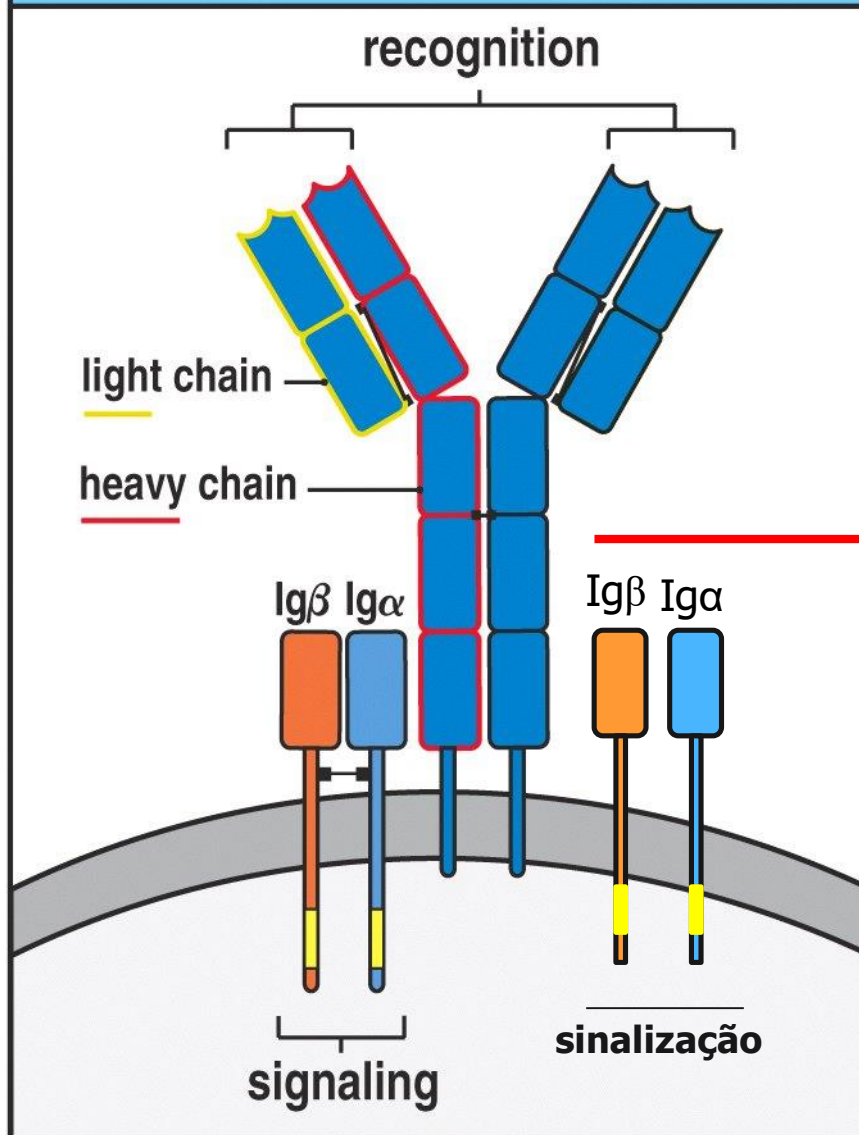


# ESTRUTURA DA MOLÉCULA DE IMUNOGLOBULINA



**Classes de anticorpos: IgA, IgD, IgE, IgG e IgM**

## Membrane-bound IgM (mIgM)



Primeiro tipo de BCR formando é da classe IgM

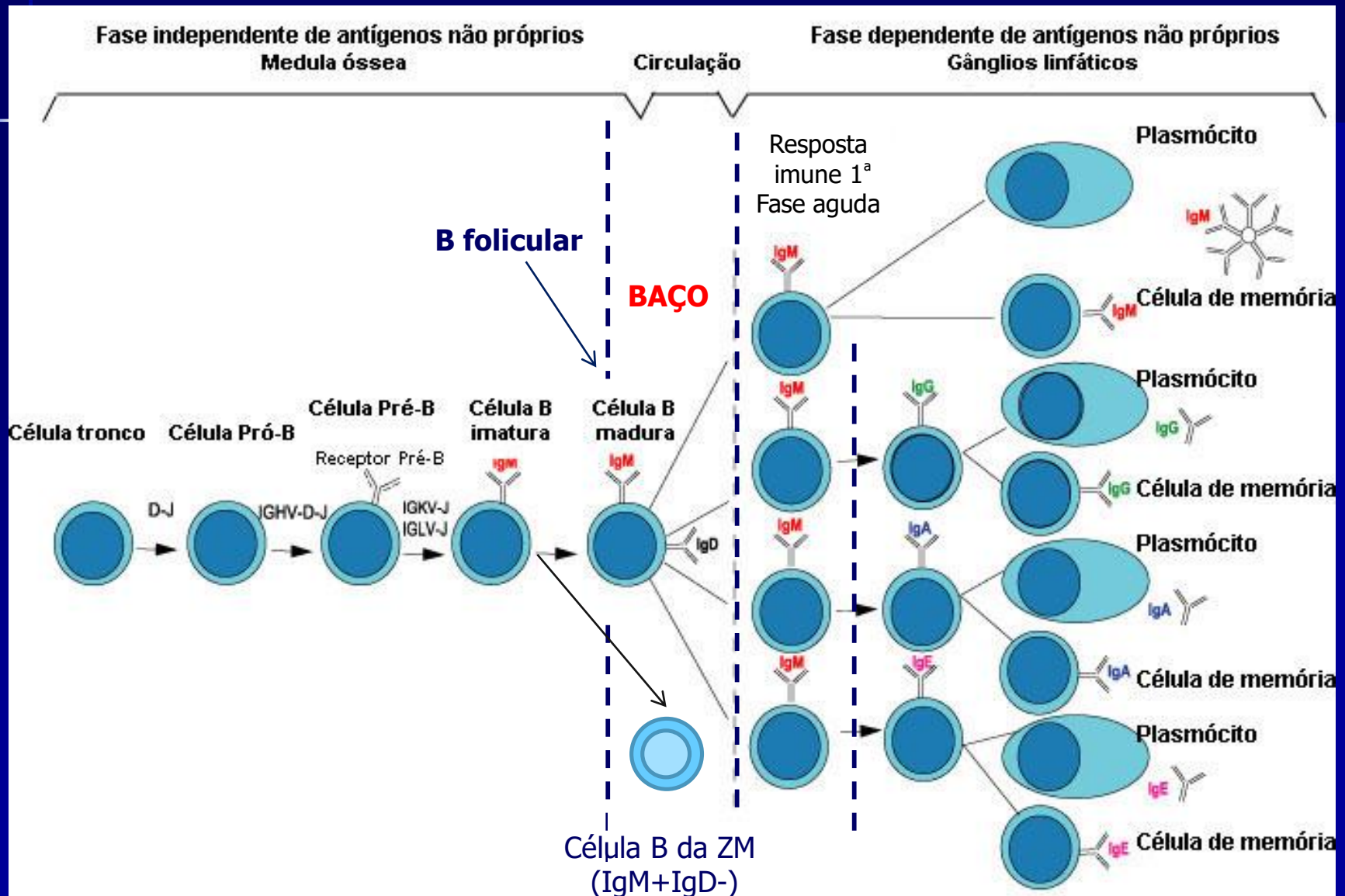
Figure 6-8 Immunobiology, 6/e. (© Garland Science 2005)

# Tipos de células B

Fígado fetal e peritônio em adultos: Células B-1 que são  $\text{IgM}^+$  e reconhecem antígenos T-independentes (polissacarídeo, glicolipídeos, DNA e RNA)

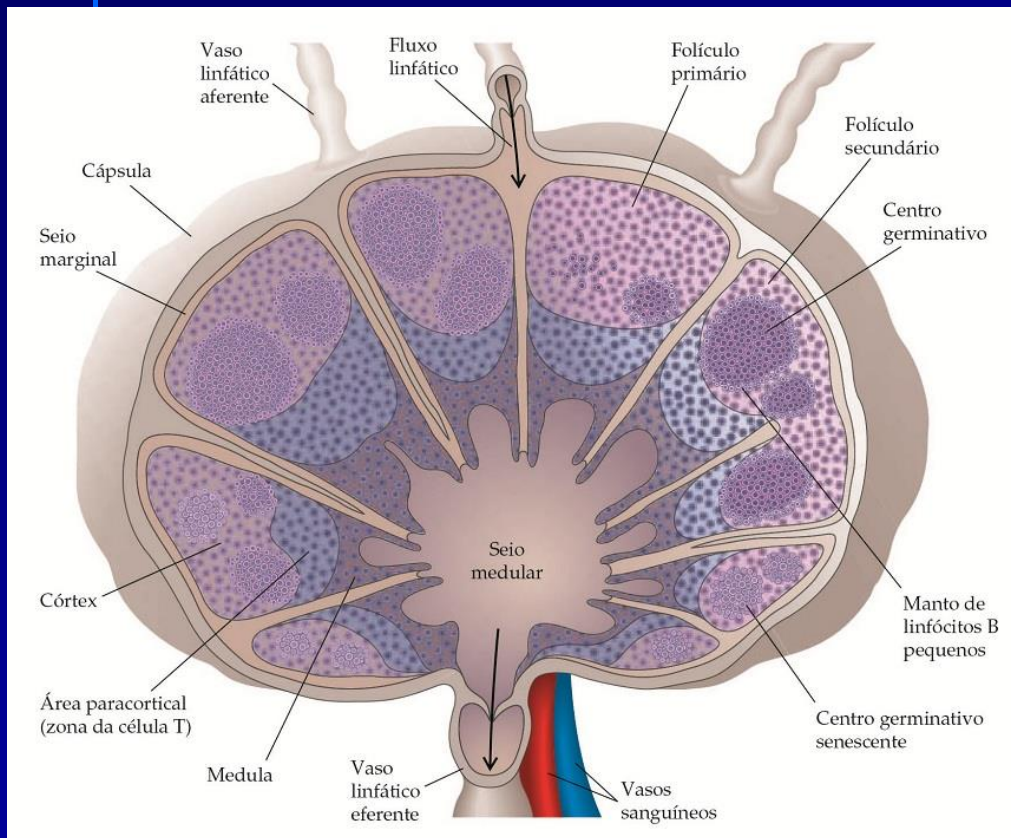
Medula-óssea: Células B-2 (foliculares e são  $\text{IgM}^+$  e  $\text{IgD}^+$  x Ags proteicos) e células B da zona marginal ( $\text{IgM}^+$  e reconhecem Ags polissacarídeos e lipídeos)

# VISÃO GERAL DAS ETAPAS DE DESENVOLVIMENTO DOS LINFÓCITOS B-2 folicular/Zona Marginal

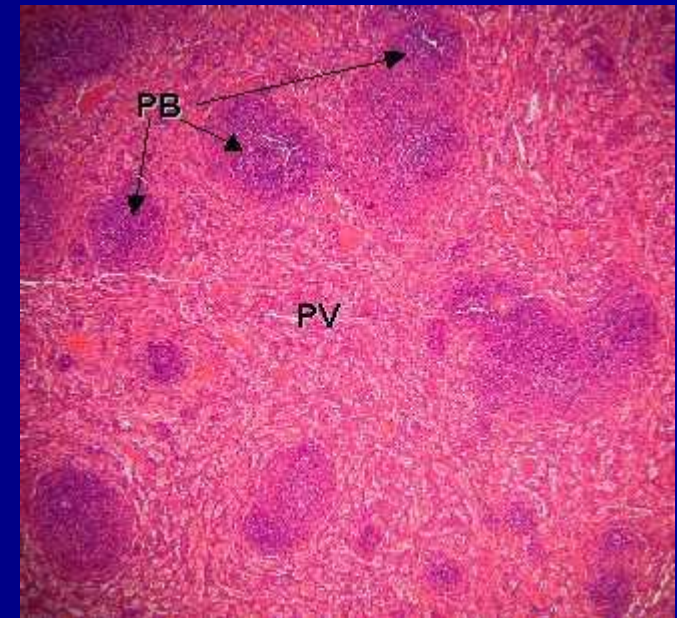




# Linfonodo



# Baço



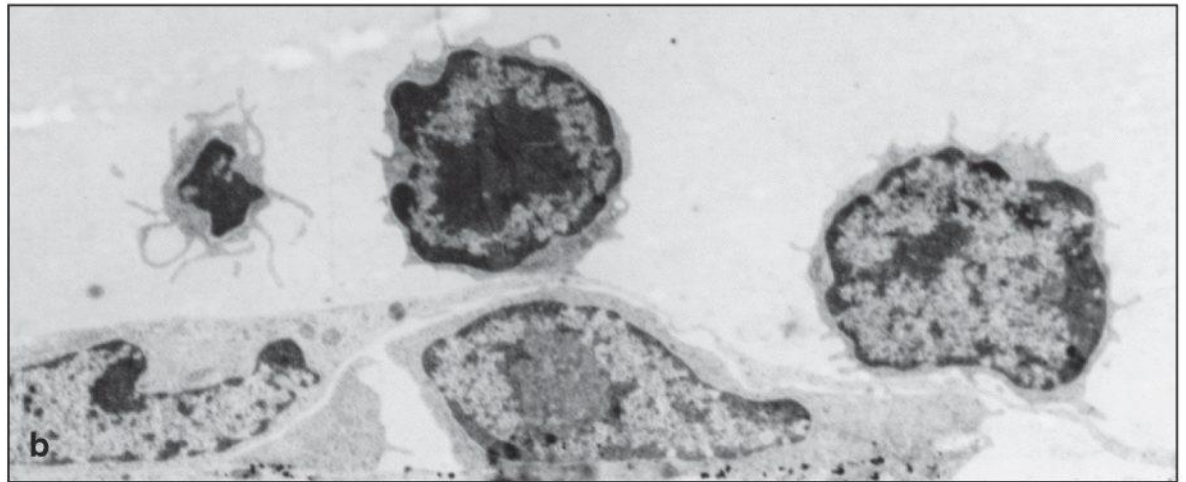
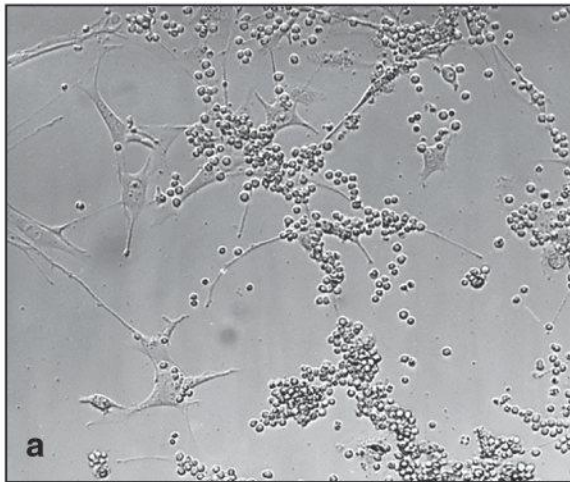
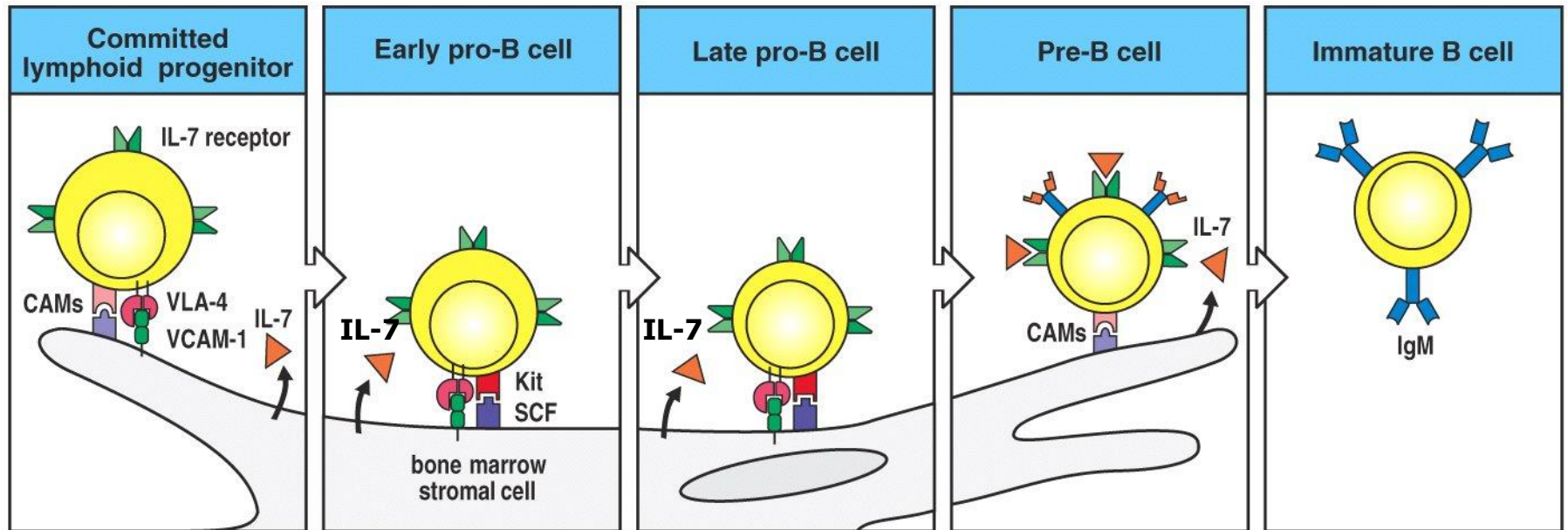
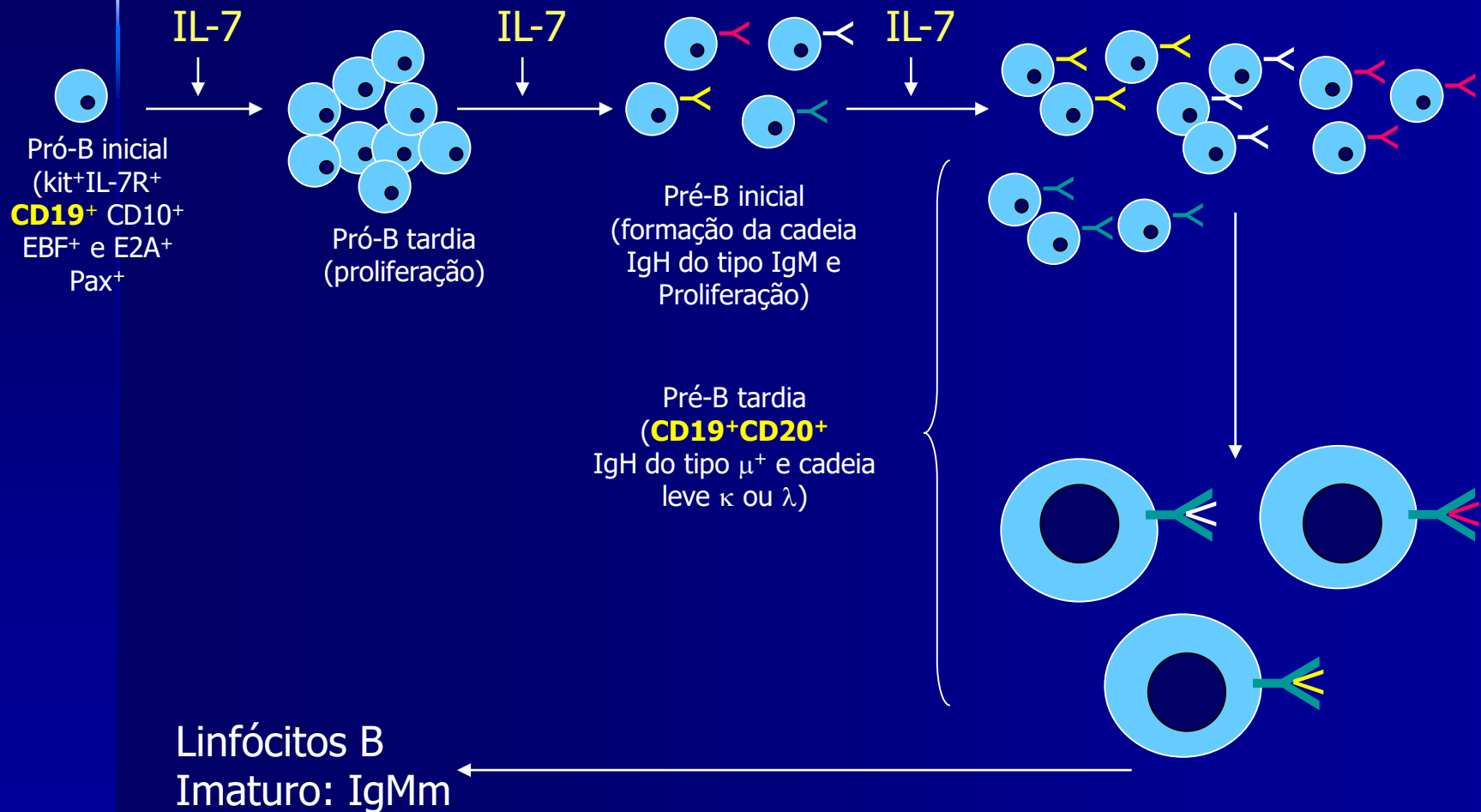


Figure 7-4 Immunobiology, 6/e. (© Garland Science 2005)

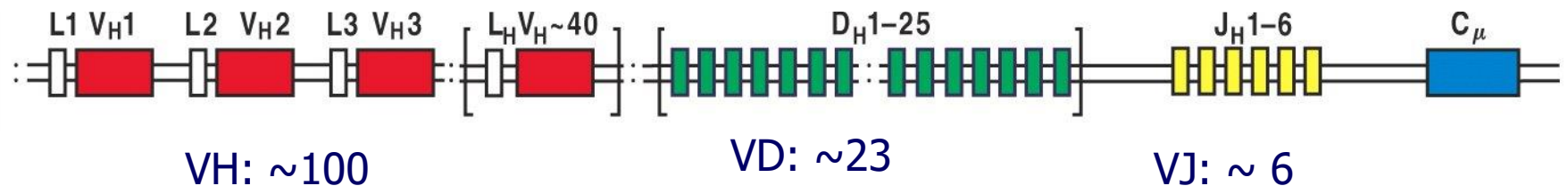
Fatores de transcrição para maturação das células B: EBF/E2A/Pax5/BTK

# Estágios da maturação dos linfócitos B na medula-óssea



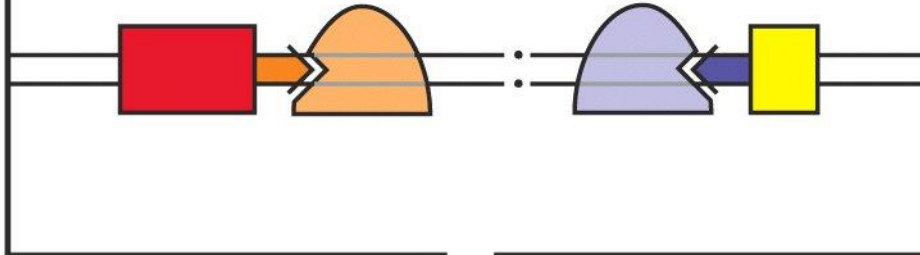
# RECOMBINAÇÃO GÊNICA DAS REGIÕES VARIÁVEIS DO BCR: cadeia pesada (H)

Locus IgH, c14





**RAG protein complexes bind to 12 and 23 bp spaced recombination signal sequences (RSSs)**



**The protein complexes bind to each other, bringing together the segments to be joined**

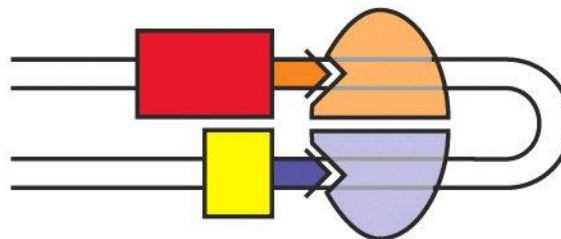
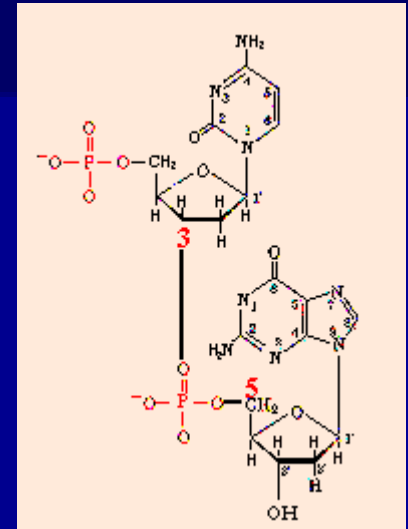
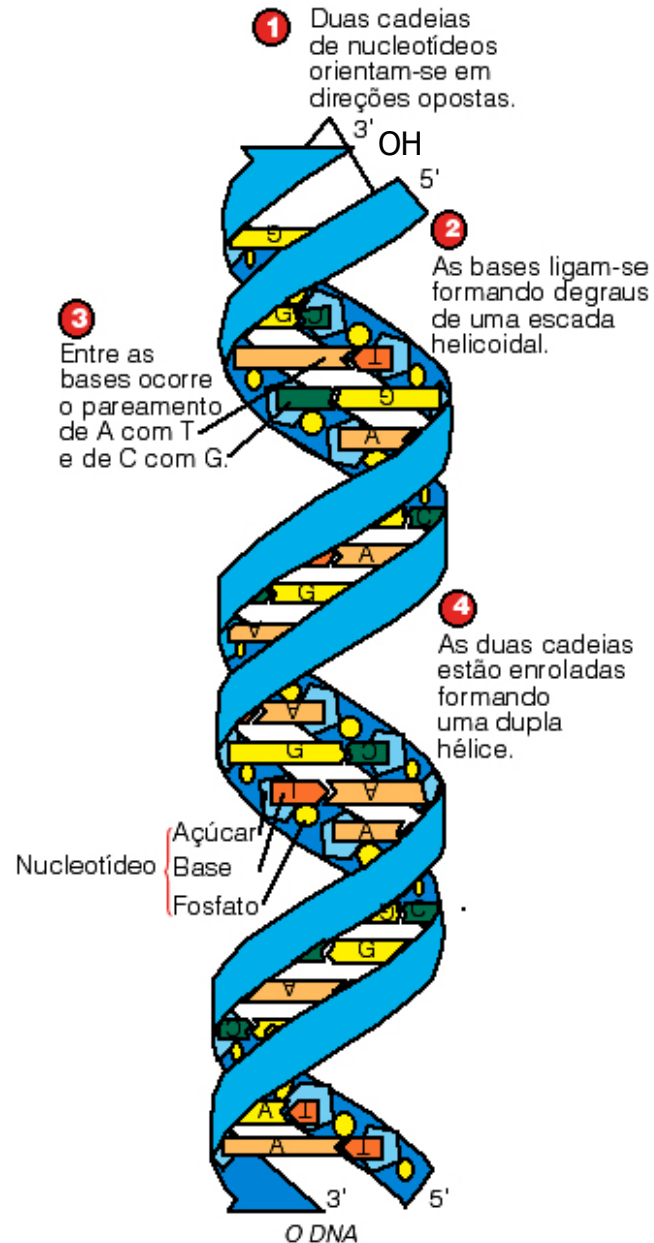
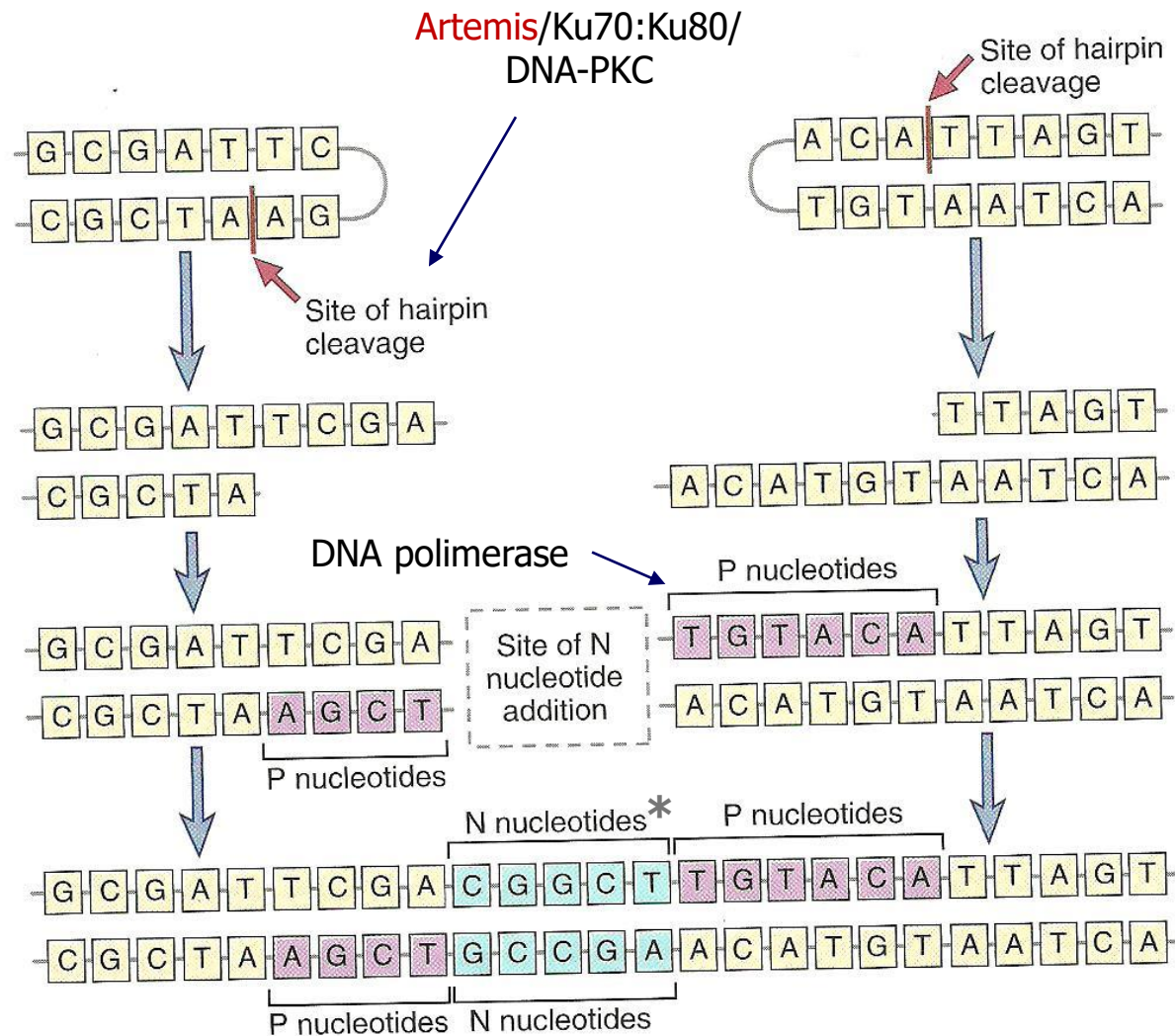


Figure 4-7 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)



# Formação do grampo Nos terminais cortados Pelas RAGs

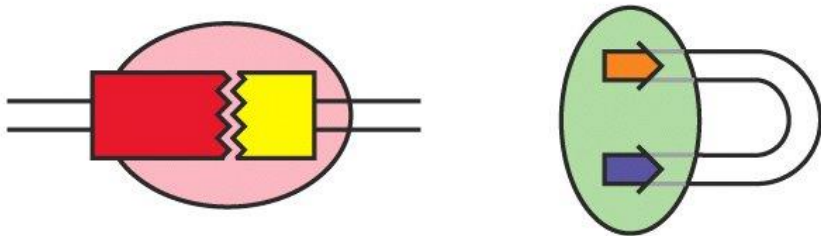




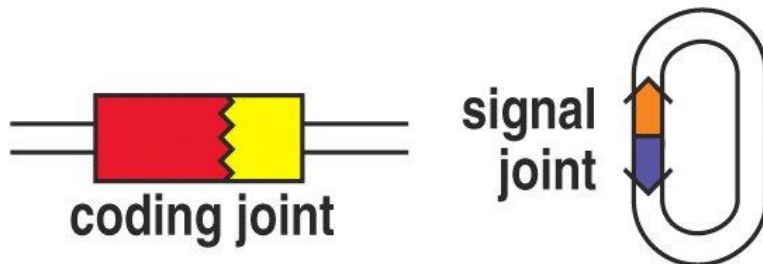
\* TdT (desoxyribonucleotidyl terminal transferase)

**FIGURE 8-13 Junctional diversity.** During the joining of different gene segments, addition or removal of nucleotides may lead to the generation of novel nucleotide and amino acid sequences at the junction. Nucleotides (P sequences) may be added to asymmetrically cleaved hairpins in a templated manner. Other nucleotides (N regions) may be added to the sites of VD, VJ, or DJ junctions in a nontemplated manner by the action of the enzyme TdT. These additions generate new sequences that are not present in the germline.

The DNA hairpins are cleaved at random. Additional bases may be added by terminal deoxynucleotidyl transferase (TdT) or subtracted by exonuclease to generate imprecise ends



DNA ligase IV, along with XRCC4, joins the ends of the gene segments to form the coding joint and the RSS ends to



## Geração de diversidade

1- As RAGs 1 e 2 escolhem ao acaso um segmento V, D e J (função tipo endonuclease): formação do grampo

2- Abertura do grampo (Artemis/Ku70:Ku80/DNA-PKC);

2- DNA polimerase;

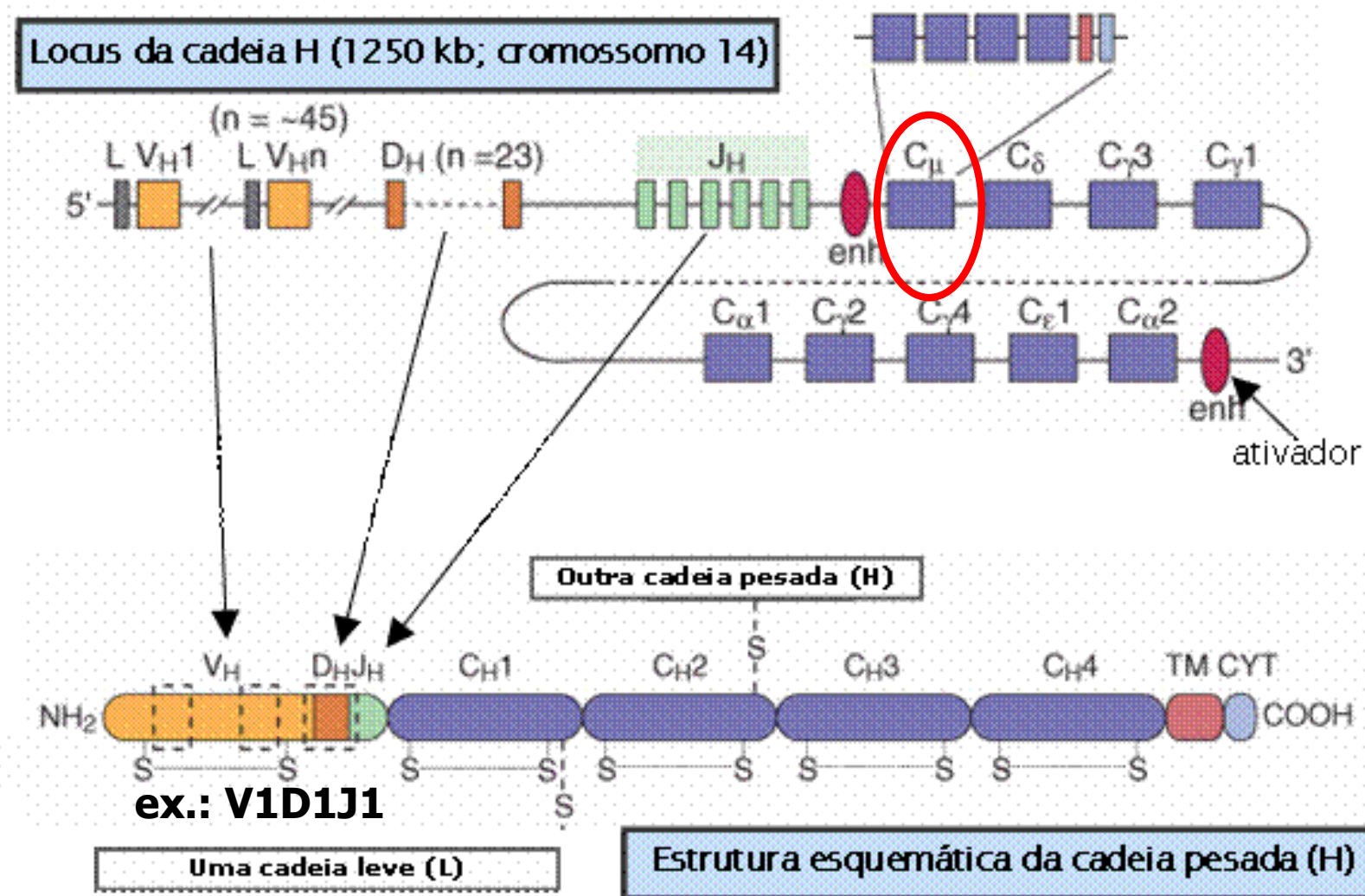
3- Adição de nucleotídeos (sem molde): TdT;

4- DNA polimerase;

4- Ligase IV.

# Diversidade de anticorpos

- Os genes para as imunoglobulinas e a geração da diversidade de anticorpos



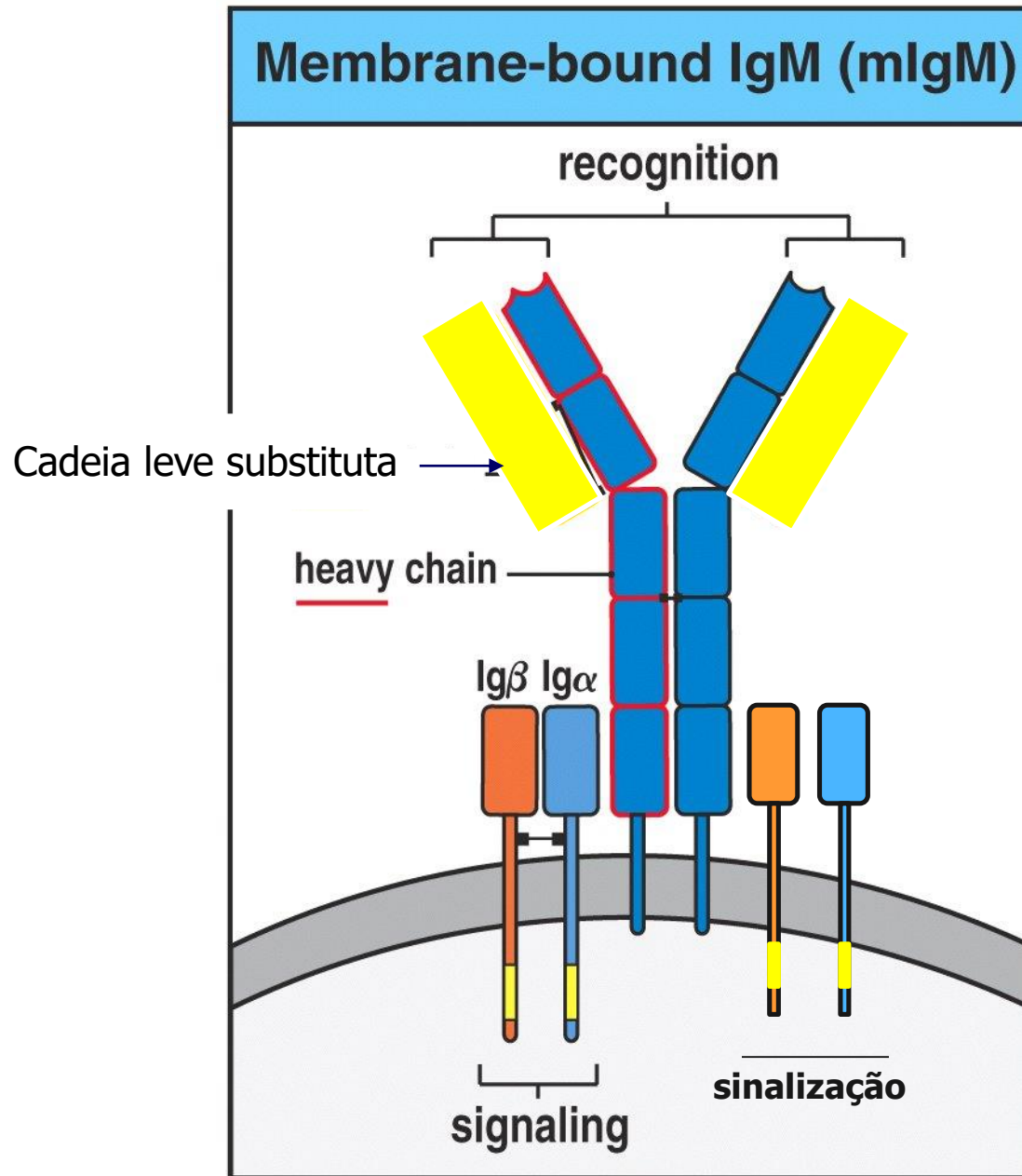
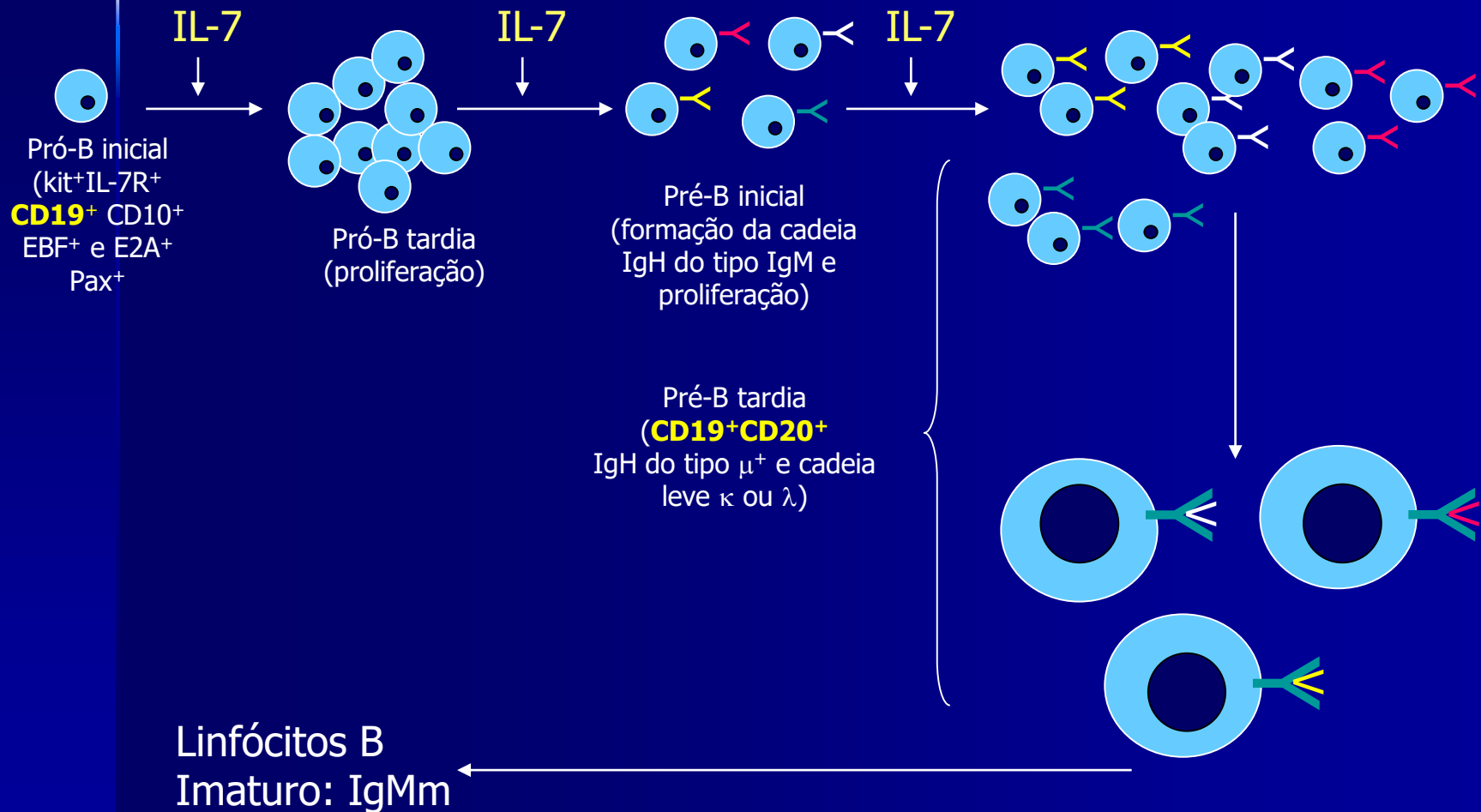


Figure 6-8 Immunobiology, 6/e. (© Garland Science 2005)

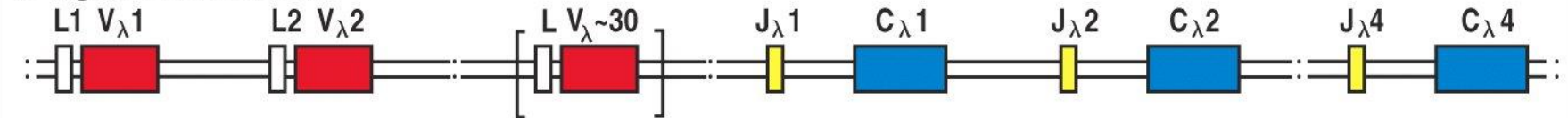


# Estágios da maturação dos linfócitos B na medula-óssea

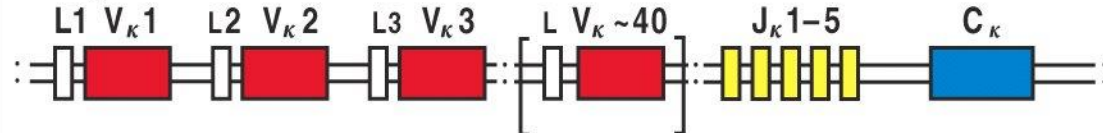


# RECOMBINAÇÃO GÊNICA DAS REGIÕES VARIÁVEIS DO BCR: cadeia L

## $\lambda$ light-chain locus



## $\kappa$ light-chain locus



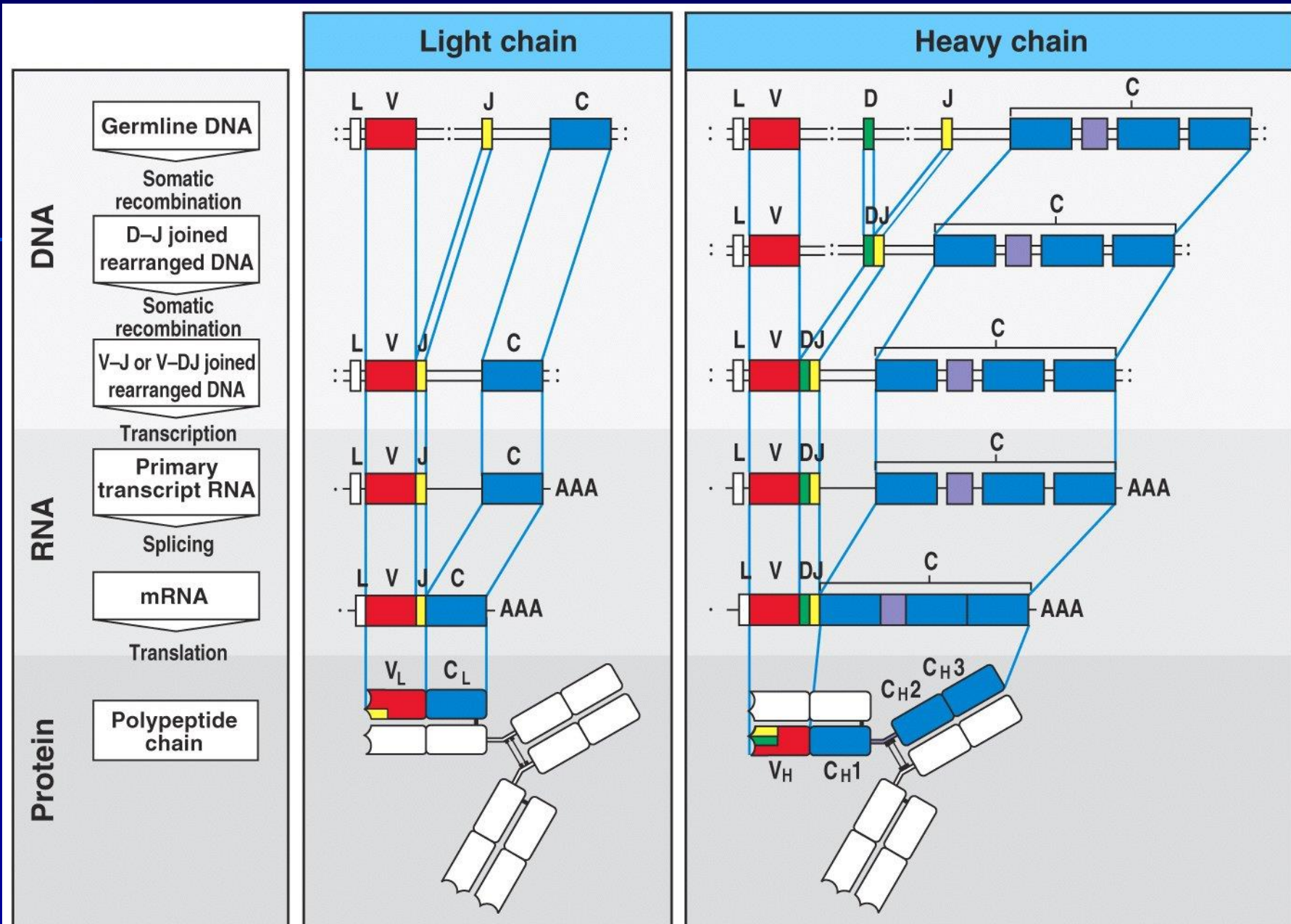
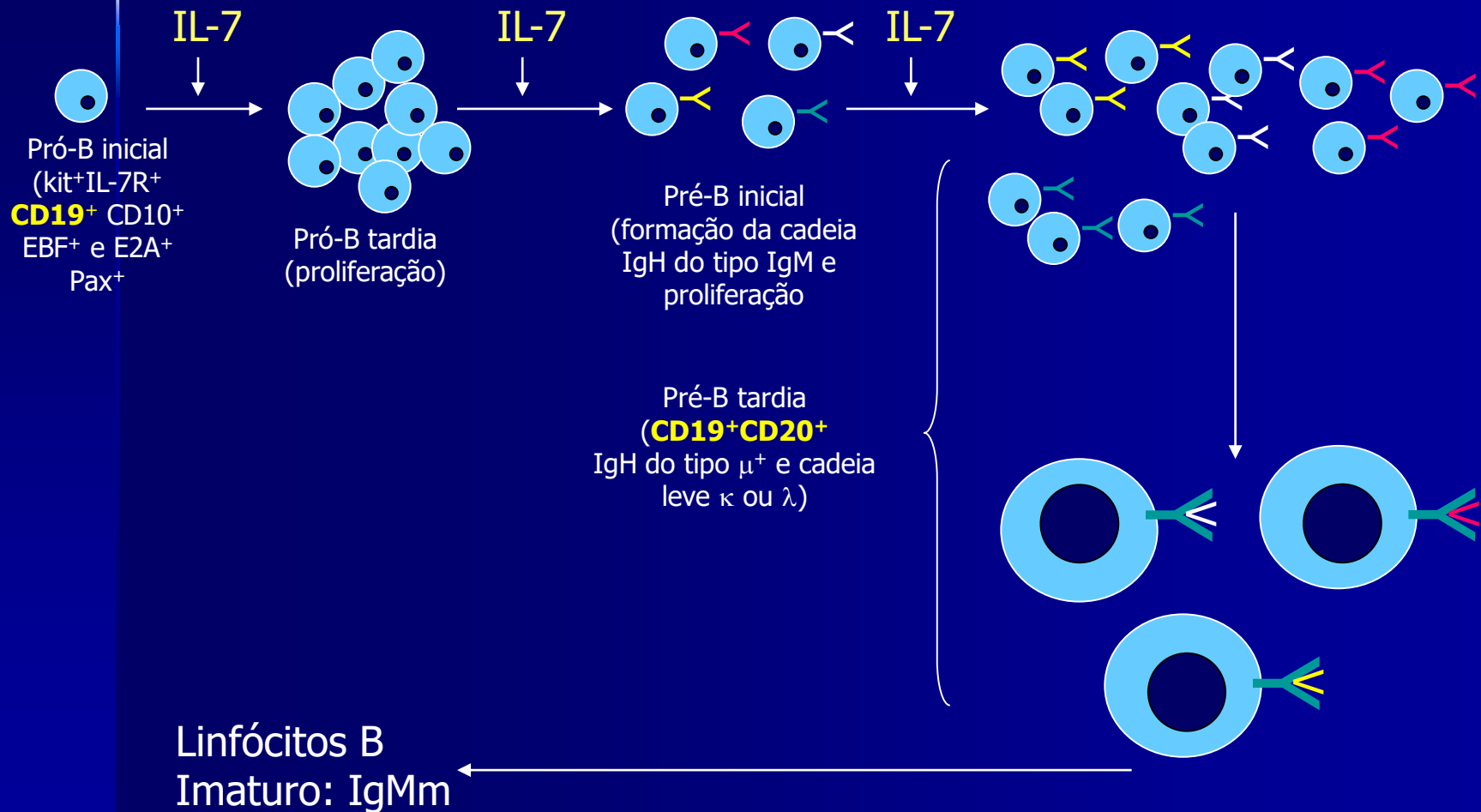
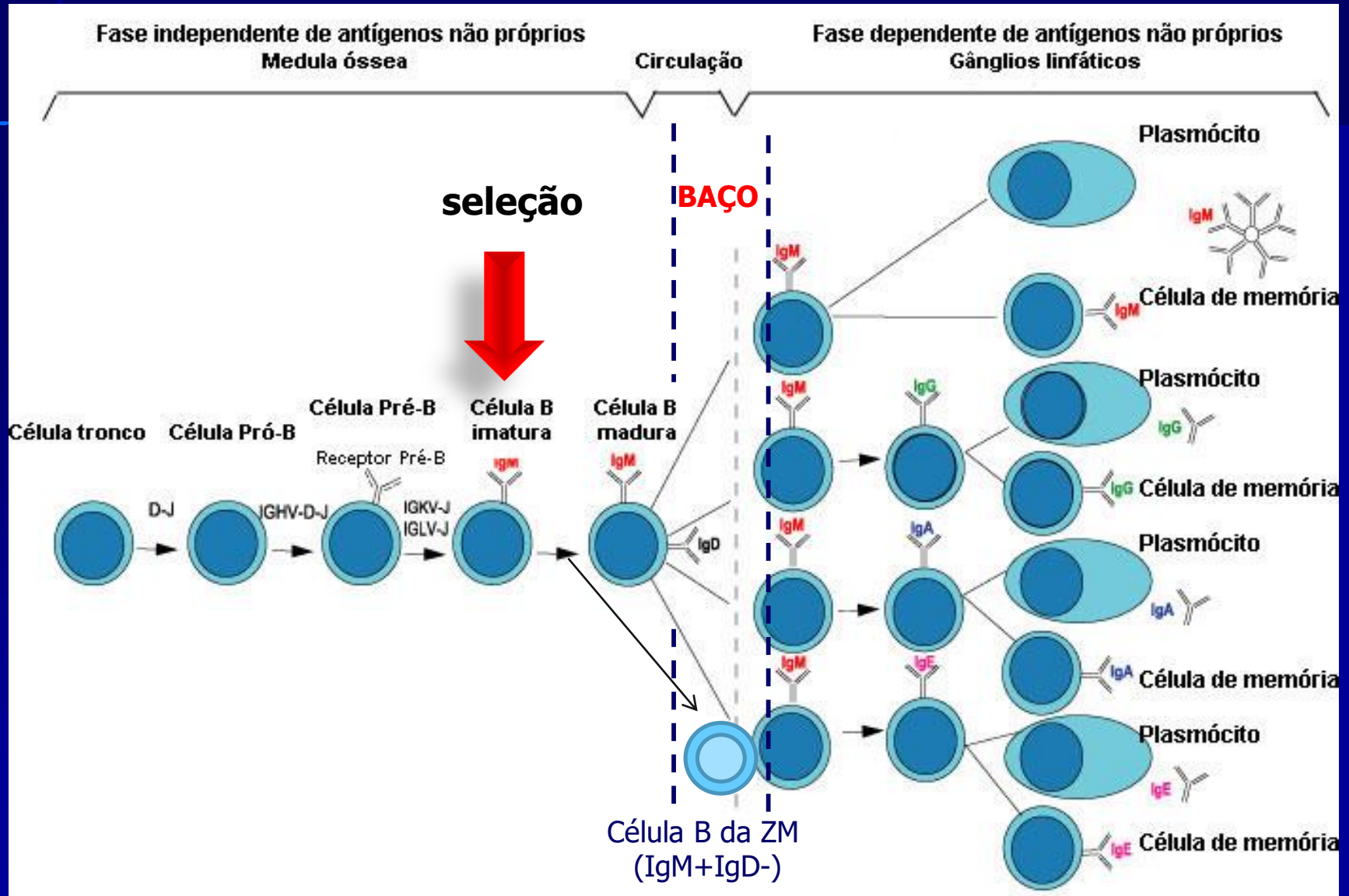


Figure 4-2 Immunobiology, 6/e. (© Garland Science 2005)

# Estágios da maturação dos linfócitos B na medula-óssea



# VISÃO GERAL DAS ETAPAS DE DESENVOLVIMENTO DOS LINFÓCITOS B-2 folicular/Zona Marginal





# EVENTOS MOLECULARES ENVOLVIDOS NA SELEÇÃO DOS LINFÓCITOS B

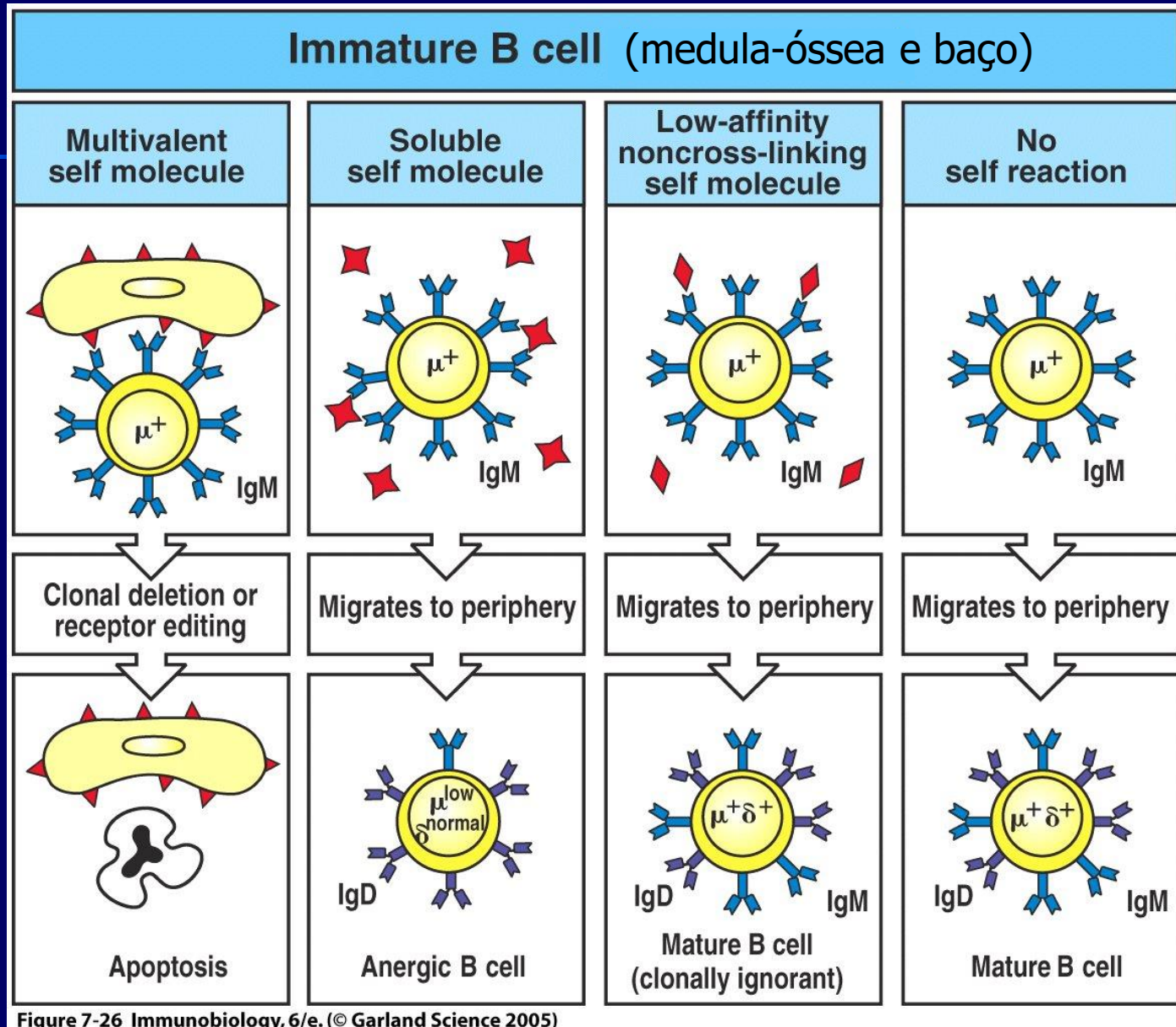


Figure 7-26 Immunobiology, 6/e. (© Garland Science 2005)

# RE-EDIÇÃO DO BCR

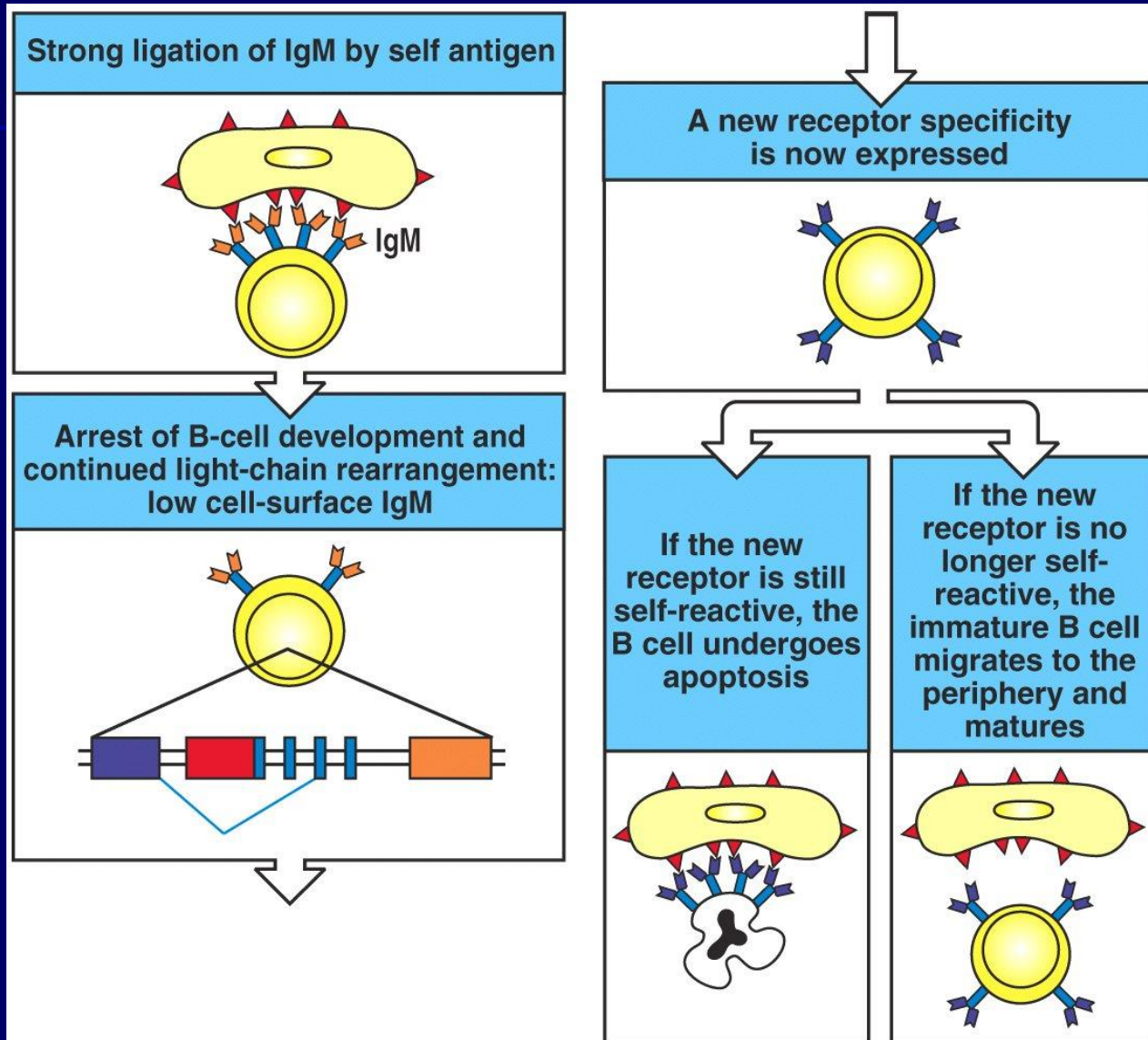


Figure 7-27 Immunobiology, 6/e. (© Garland Science 2005)

# EXCLUSÃO ALÉLICA E ISOTÍPICA NA FORMAÇÃO DO BCR

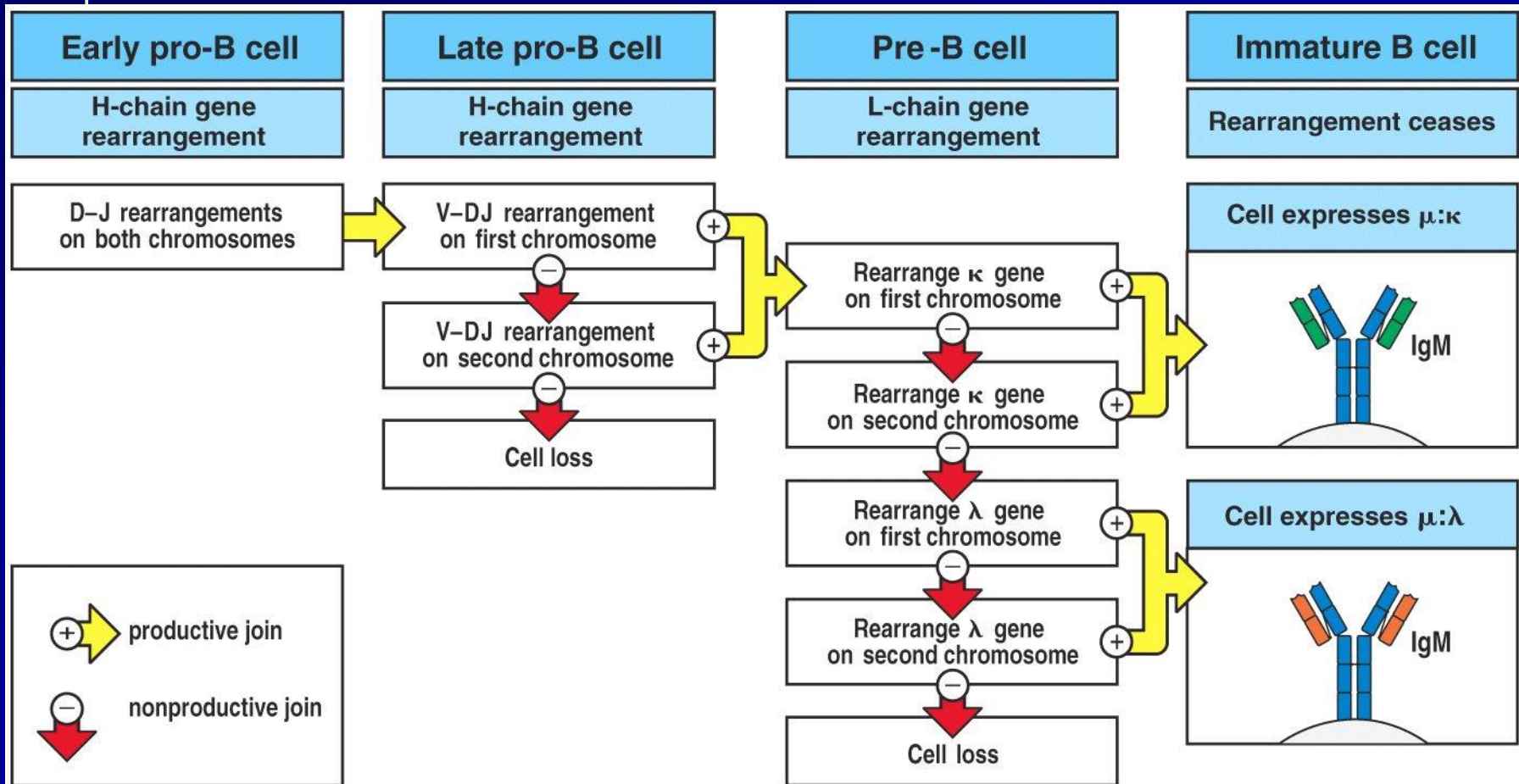
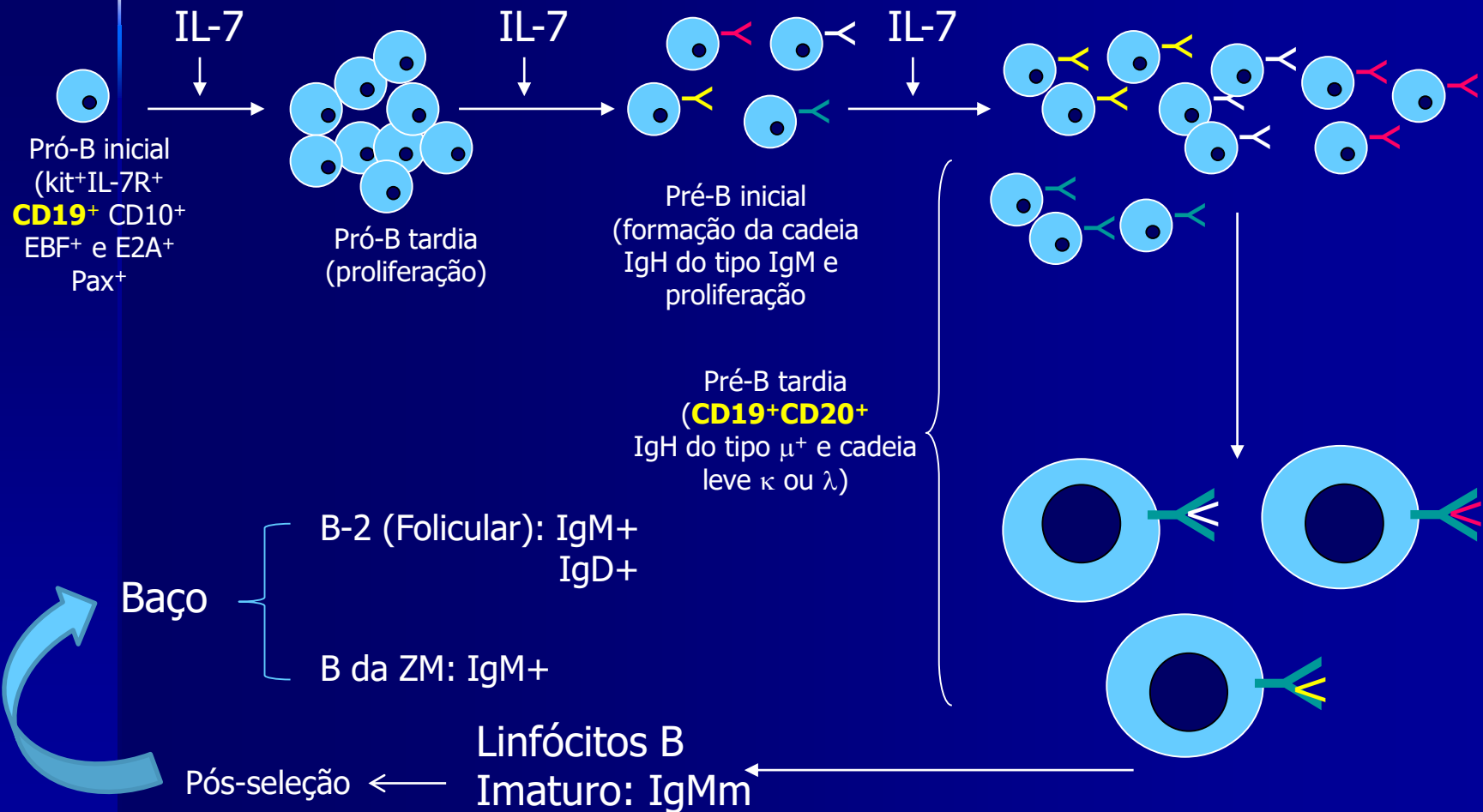


Figure 7-15 Immunobiology, 6/e. (© Garland Science 2005)

# Estágios da maturação dos linfócitos B na medula-óssea





# CO-EXPRESSÃO DE IgM e IgD

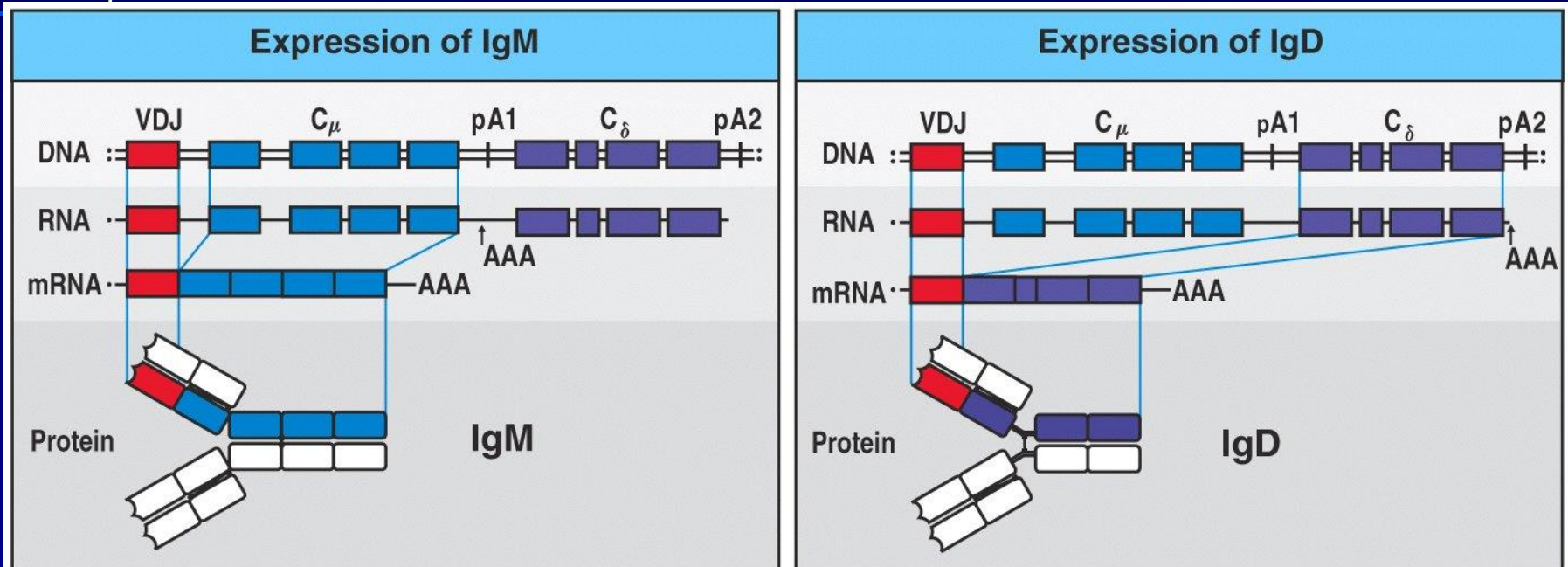


Figure 4-20 Immunobiology, 6/e. (© Garland Science 2005)

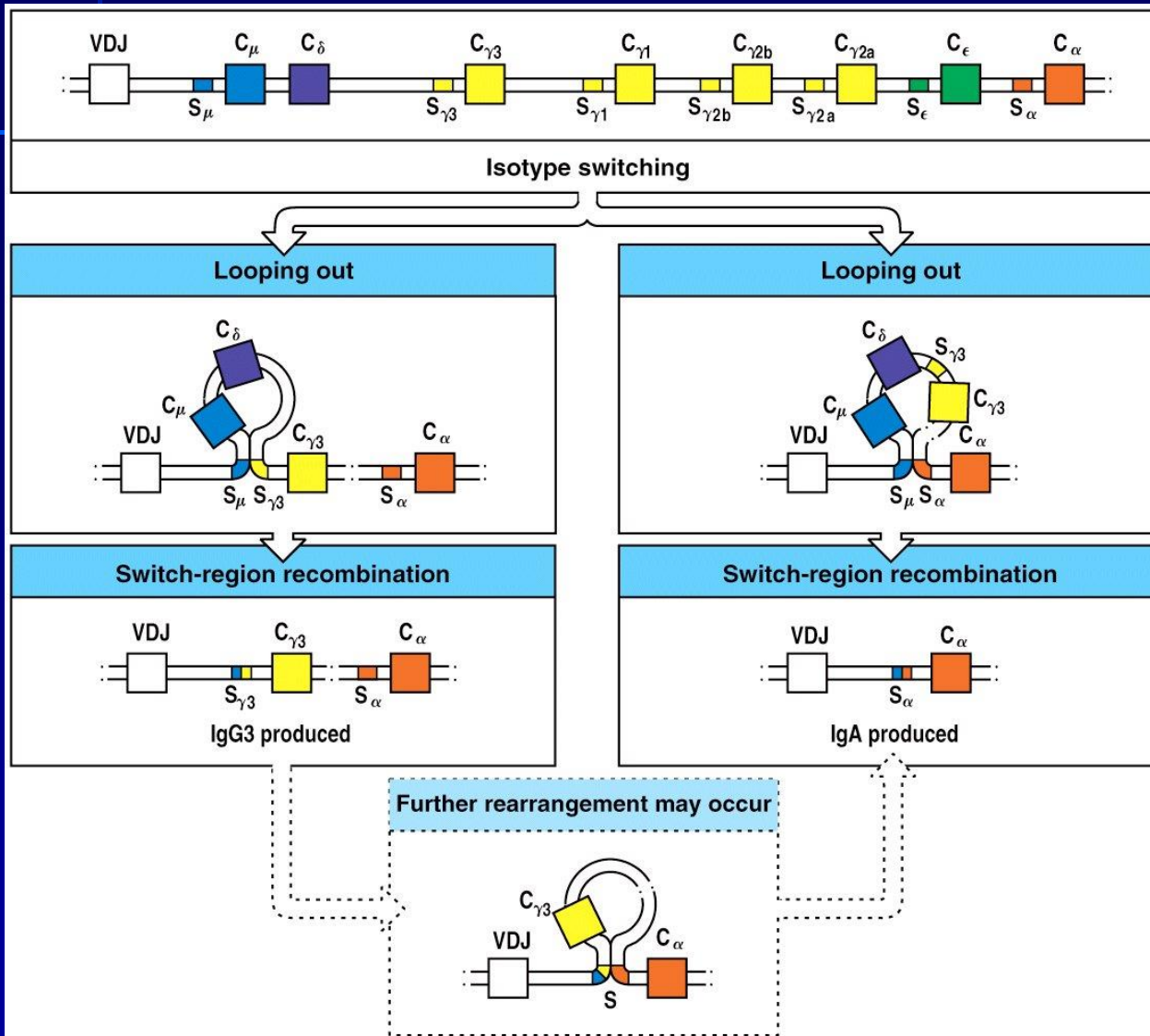
Região variável (V): regiões hipervariáveis

CDR1 e CDR2= dentro do gene V original

CDR3= diversidade juncional entre V e J (cadeia leve) e VDJ (cadeia pesada)



# TROCA DE CADEIA PESADA: EVENTO TARDIO NA DIFERENCIAÇÃO DOS LINFÓCITOS B



$\text{IgM} = \mu$   
 $\text{IgG} = \gamma$   
 $\text{IgA} = \alpha$   
 $\text{IgE} = \epsilon$

Figure 4-21 Immunobiology, 6/e. (© Garland Science 2005)

	Immunoglobulin								
	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Heavy chain	$\gamma_1$	$\gamma_2$	$\gamma_3$	$\gamma_4$	$\mu$	$\alpha_1$	$\alpha_2$	$\delta$	$\epsilon$
Molecular weight (kDa)	146	146	165	146	970	160	160	184	188
Serum level (mean adult mg ml <sup>-1</sup> )	9	3	1	0.5	1.5	3.0	0.5	0.03	$5 \times 10^{-5}$
Half-life in serum (days)	21	20	7	21	10	6	6	3	2

Figure 4-17 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Element	Immunoglobulin		$\alpha$ : $\beta$ T-cell receptors	
	H	$\kappa + \lambda$	$\beta$	$\alpha$
Variable segments (V)	40	70	52	~70
Diversity segments (D)	25	0	2	0
D segments read in three frames	rarely	—	often	—
Joining segments (J)	6	5( $\kappa$ ) 4( $\lambda$ )	13	61
Joints with N- and P-nucleotides	2	50% of joints	2	1
Number of V gene pairs	$1.9 \times 10^6$		$5.8 \times 10^6$	
Junctional diversity	$\sim 3 \times 10^7$		$\sim 2 \times 10^{11}$	
Total diversity	$\sim 5 \times 10^{13}$		$\sim 10^{18}$	

Figure 4-13 Immunobiology, 6/e. (© Garland Science 2005)

# Maturação das células B-1

- Fígado (feto) e peritônio e mucosas;
- Repertório VDJ e VJ limitado e TdT negativas;
- São CD19<sup>+</sup>mIgM<sup>+</sup>mIgD<sup>-</sup>;
- Reconhecem antígenos Timo-independentes (não-protéicos);
- Produzem os anticorpos “naturais” (IgM e IgA em **mucosa**).
- Plasmócitos de vida curta