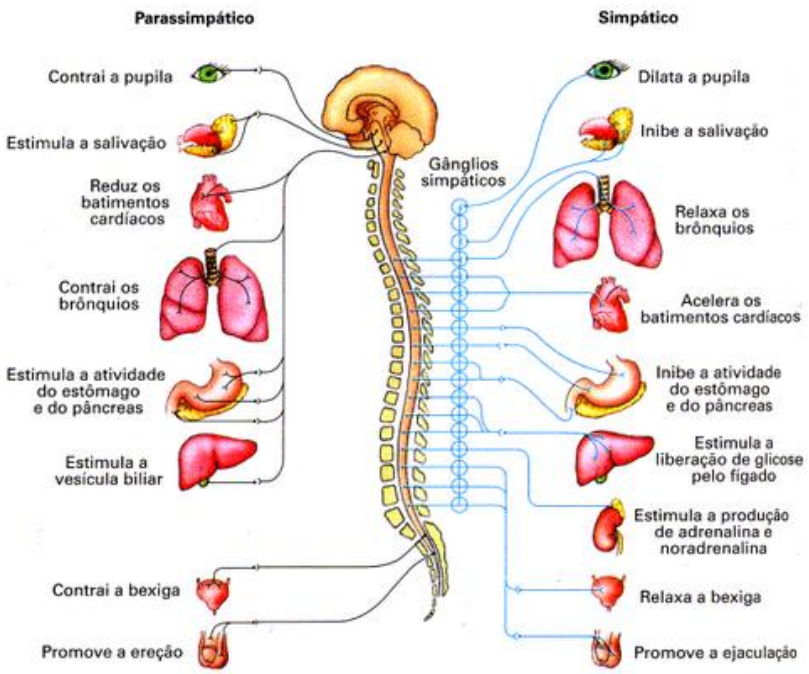
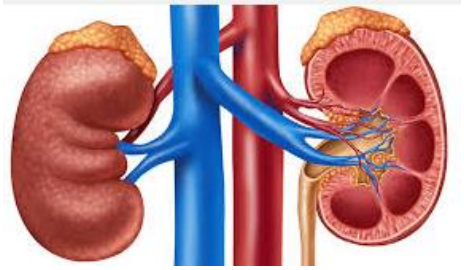
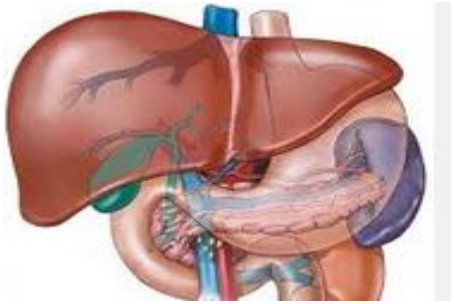
Órgãos e Células do Sistema Imune

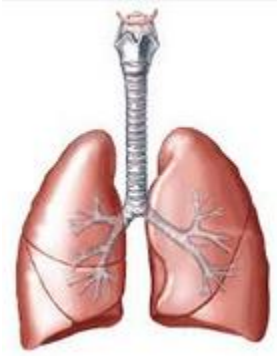
Prof. Jean Pierre

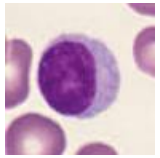
E em Sistemas Biológicos como o Sistema Imune ?
O Sistema Imune É de Defesa, Por Quê ?

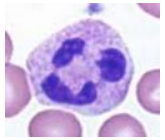


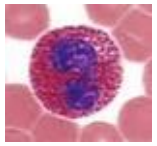


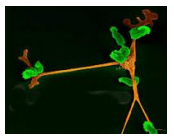


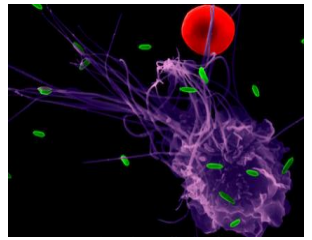


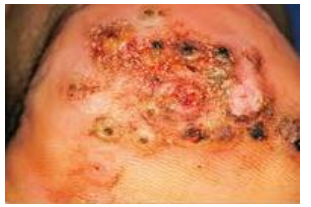


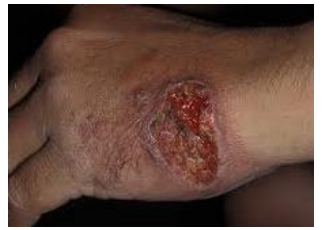




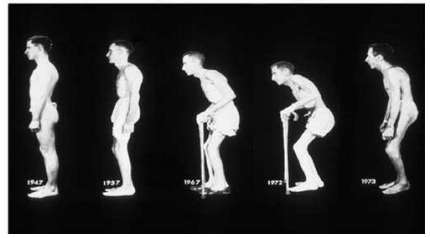


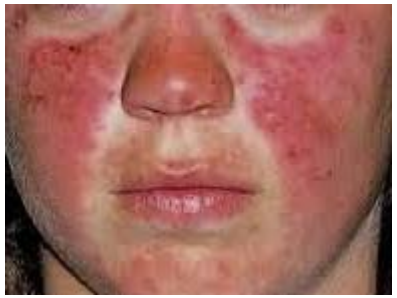


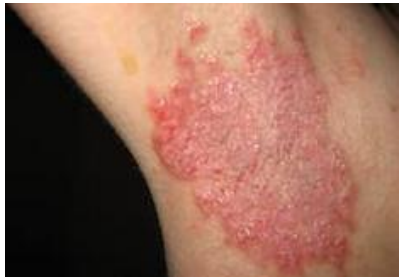




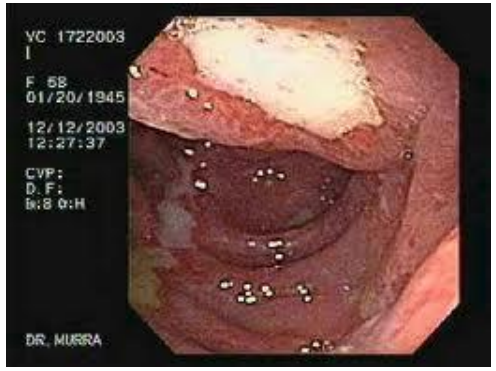
Progressive deformity due to AS over a period of 36 years



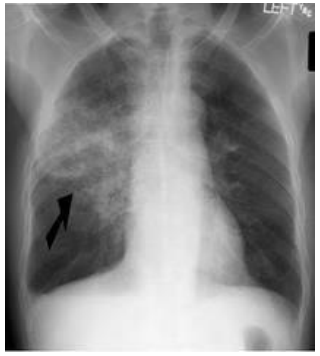




Imunodeficiências – Infecções de Repetição

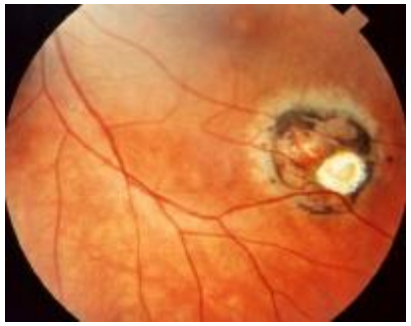


Colite

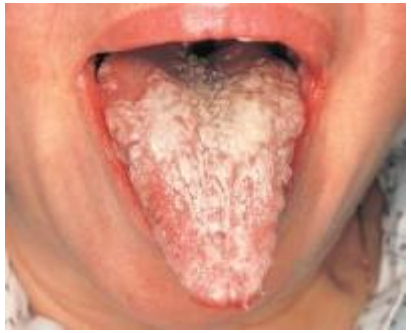


Pneumonia

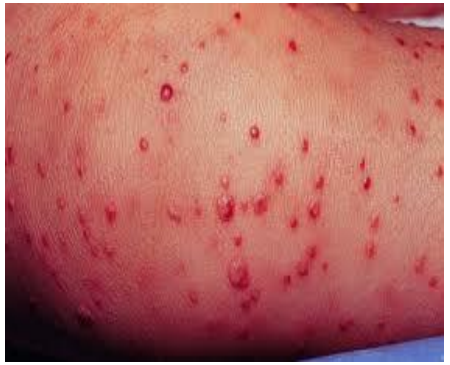
AIDS



Toxoplamose Ocular



Candida



Staphilococcus

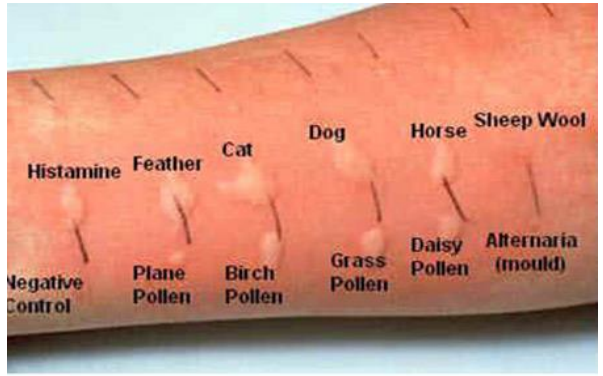
Infecções Múltiplas

Mas será que o sistema imune está tempo todo combatendo algo ?

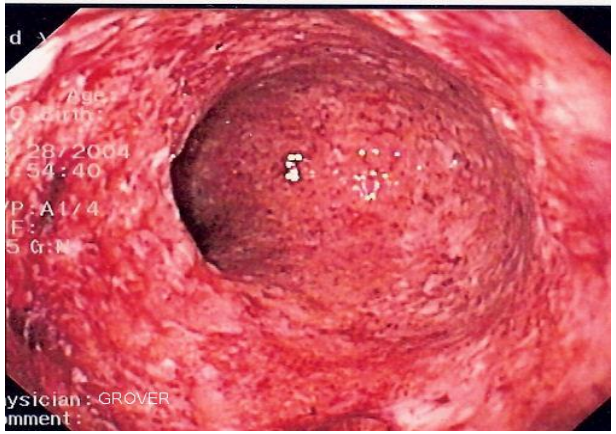
Se não está, então o que ele está fazendo nesse ínterim?

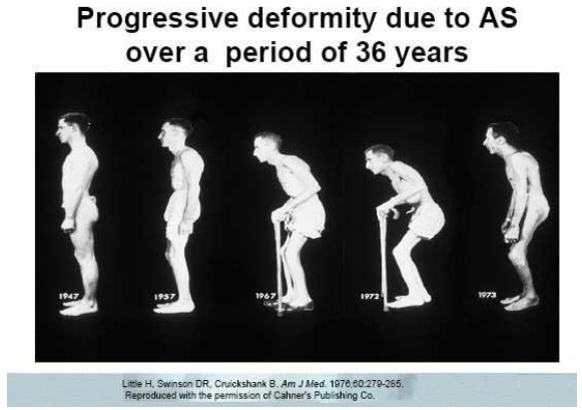
Então, mesmo assim ele é de defesa?

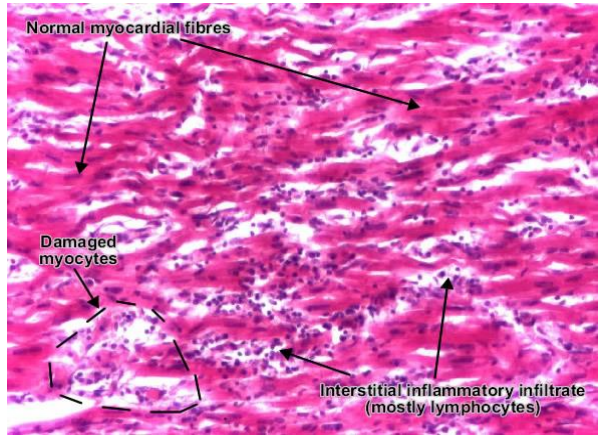
Auto-imunidades e Alergias

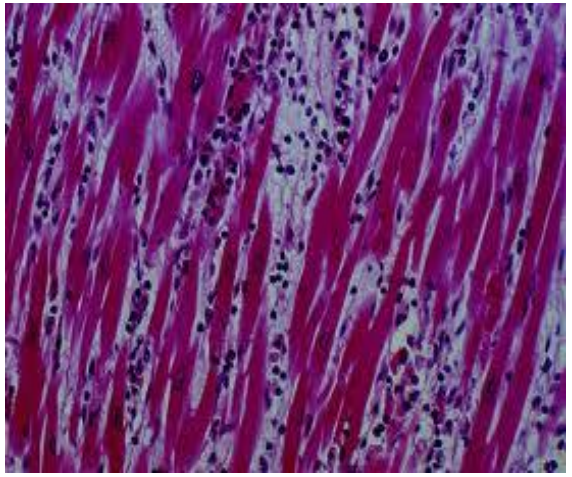


Skin Allergy Test

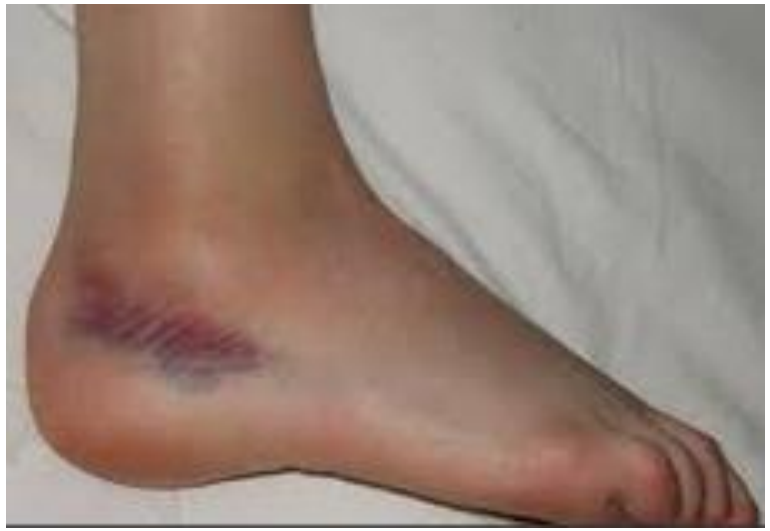


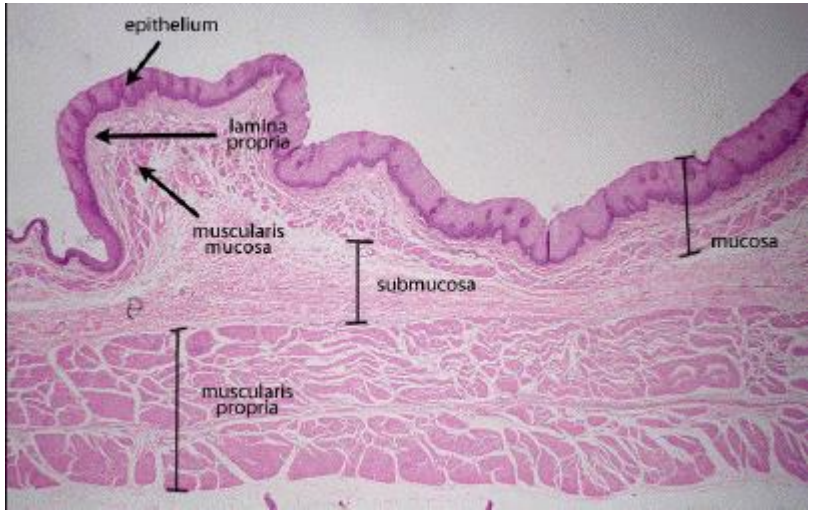


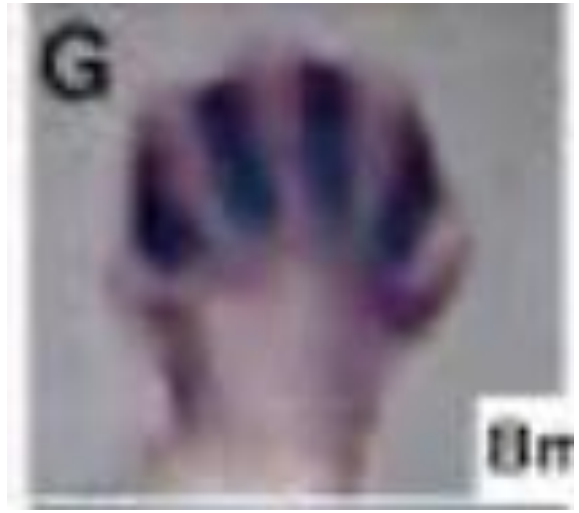




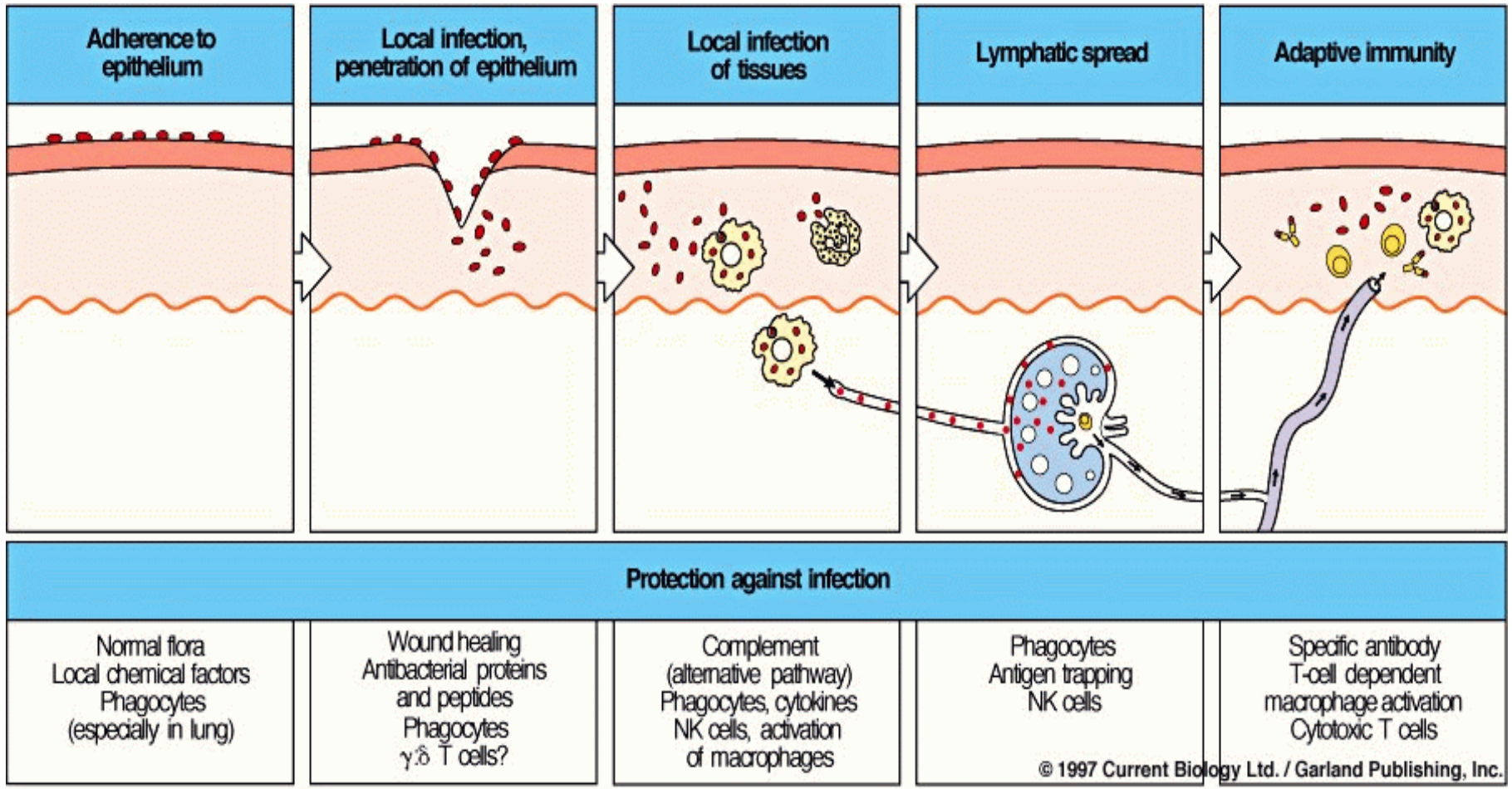
Mas o sistema imune também se relaciona com outras funções que não combater patógenos



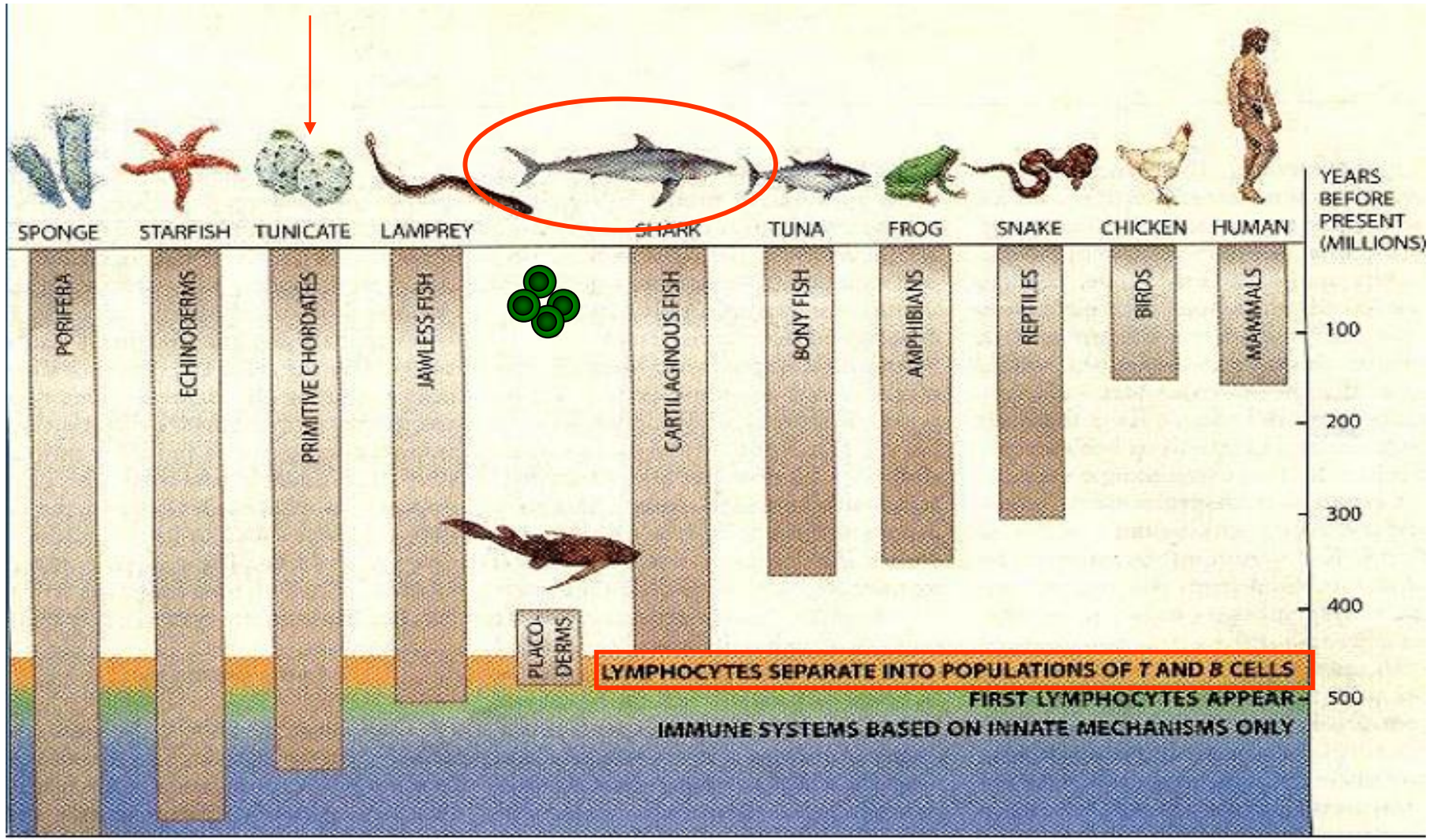


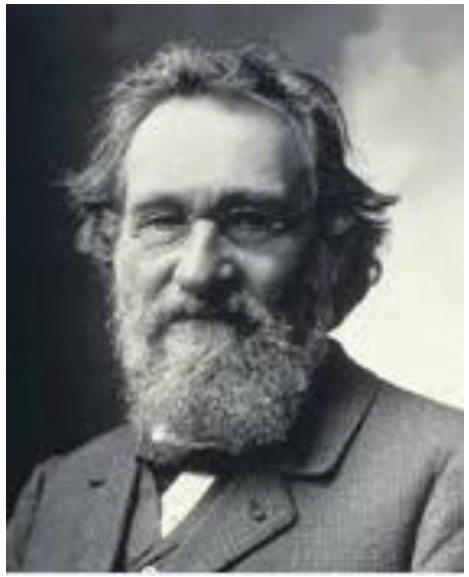


Drenagem Antigênica

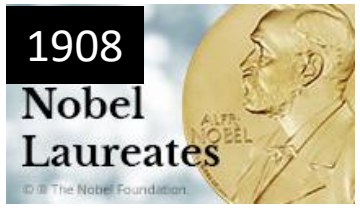


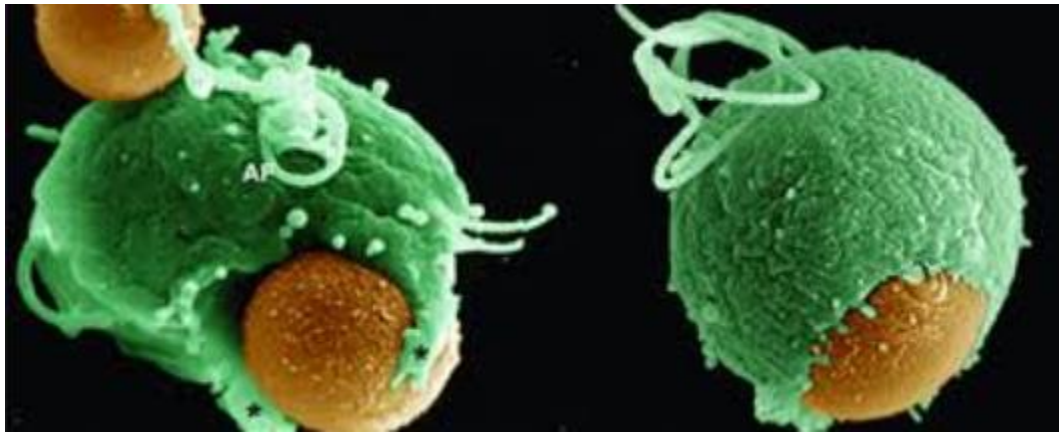
Filogenia Do Sistema Imune





Élie Metchnikoff





Fagócitos

Células que internalizam partículas

Experimento do espinho na estrela-do-mar

O sistema imune se Divide em Imunidade Inata e Adaptativa

- Imunidade Inata
- Sente a presença de determinadas moléculas que obedecem padrões;

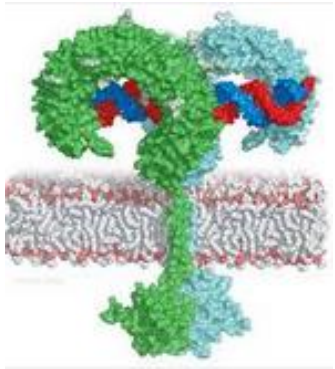
Lipídeos, proteínas, carbohidratos

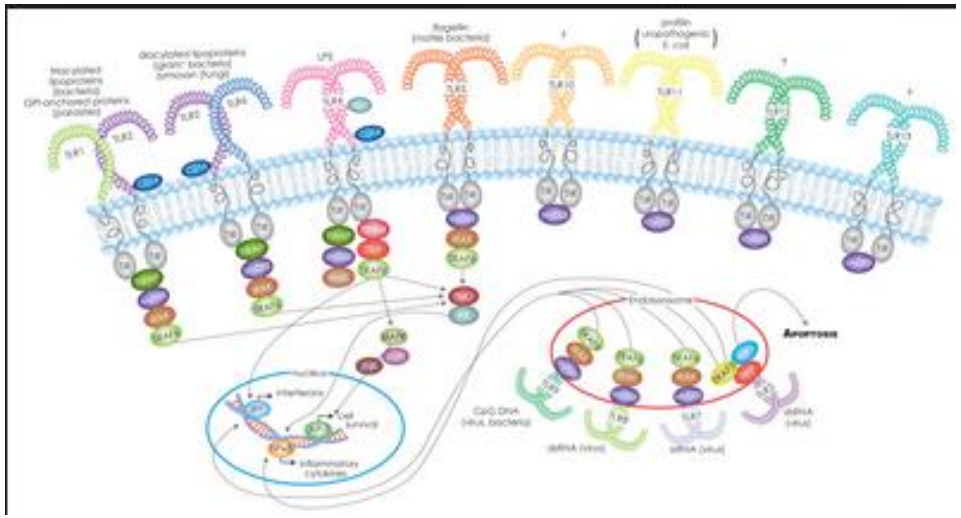
–

endógenas ou exógenas

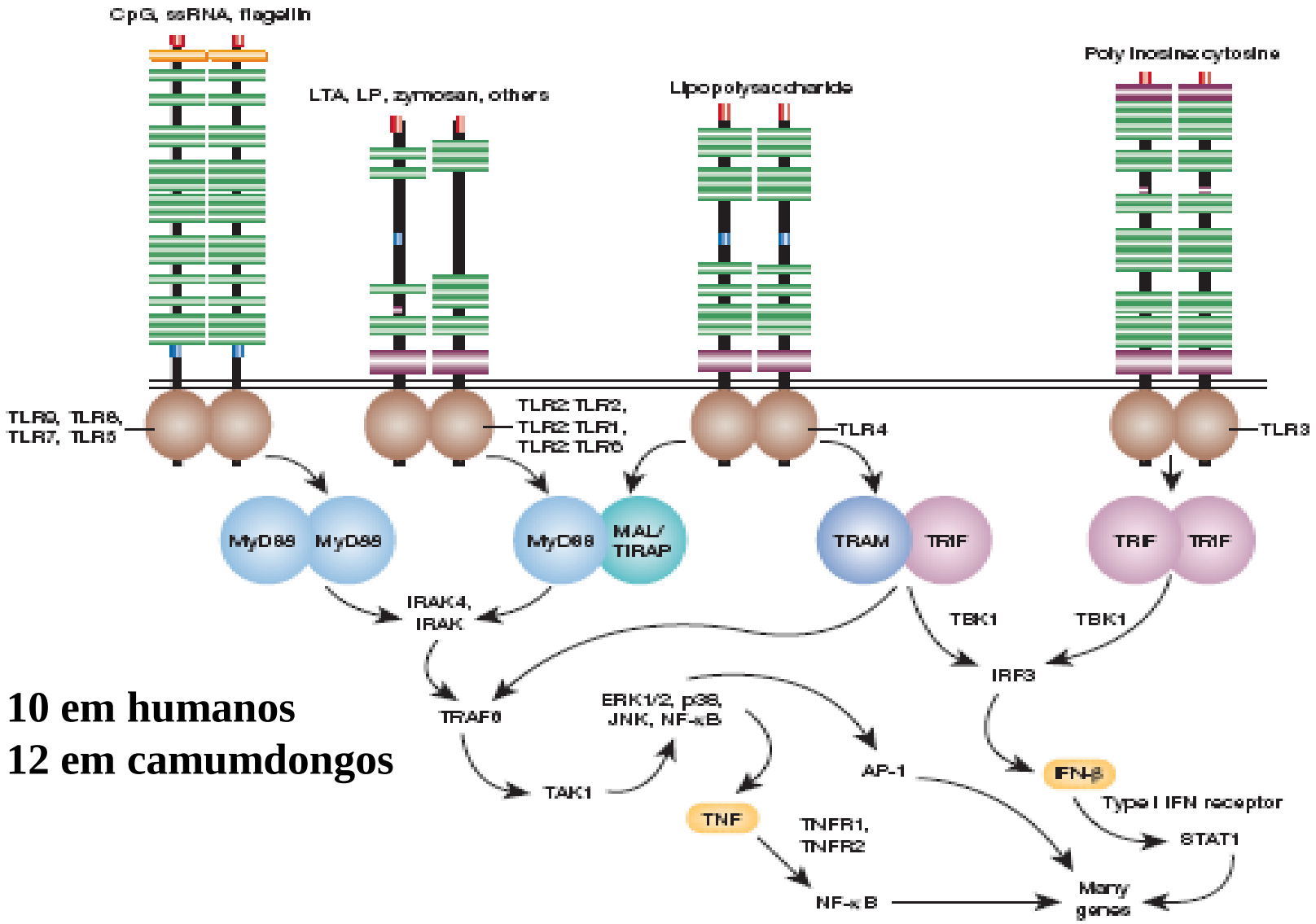
Pattern Recognition Receptors

Toll-like recptors (1-12 em camundongos) – NF-κB
NOD – IRFs
Inflamasoma – IL-1 / IL-18





Ligantes de Toll-like Receptors



10 em humanos
12 em camumdongos

LRR – Repetições Ricas em Leucina

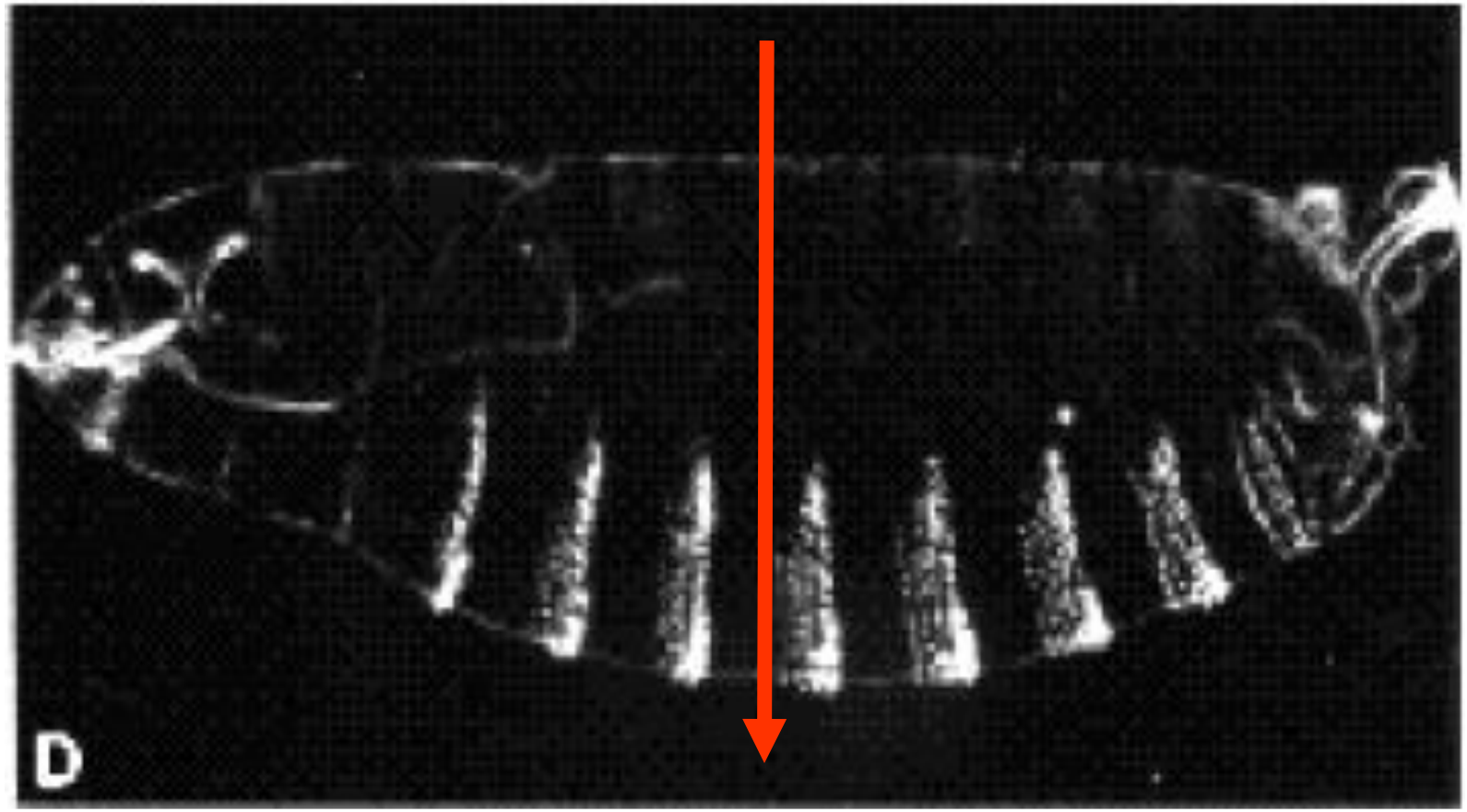
Ligantes Endógenos

HSPs
Poliglicanas
Colágeno
Colesterol

Presentes
na membrana
retículo

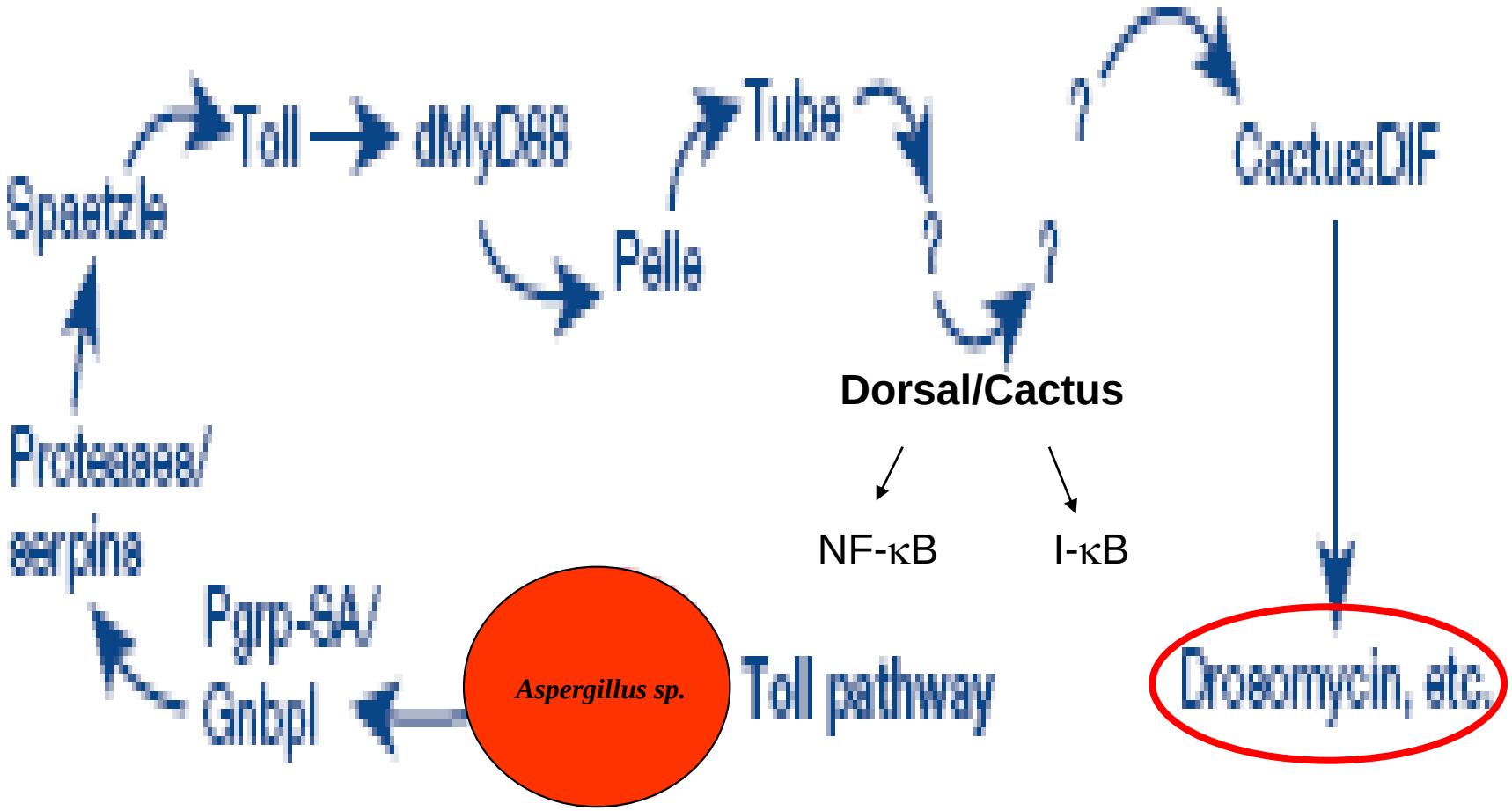
Toll Protein – Muito antigo filogeneticamente

(1985):Orientação dorso-ventral do embrião de Drosófilas.



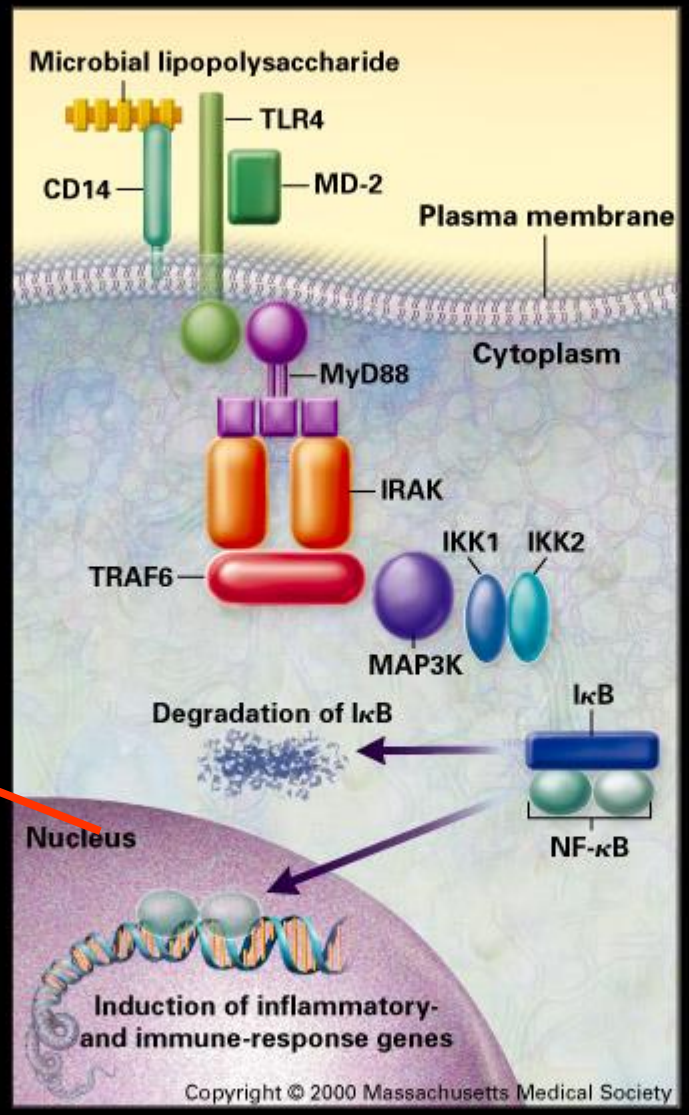
St. Johnston, D AND Nusslein-Volhard.1988. The origin of pattern and polarity in the Drosophila embrio. ***Cell*** 68, 201-219.

(1996): *Resposta a Aspergillus fumigatus*.



Lemaitre, B.*et all.* The dorsoventral regulatory gene cassette spatzle/Toll/cactus controls the potent antifungal response in *Drosophila* adults. ***Cell*** 86**,**973–983 (1996).

Genes Alvo do NF-KB



CITOCINAS PRÓ-INFLAMATÓRIAS

Pró- IL-1β
IL-18
IL-6
IL-12
IL-23
TNF-α

Moléculas de Apresentação Antigênica
MHC I e II
CD80
CD86
CD40

Enzimas
Ciclooxigenase
Lipo-oxigenasse
Mieloperoxidase

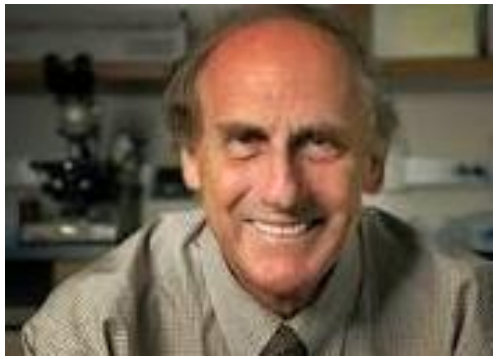
Medzhitov R, Janeway C Jr. Innate Immunity. N Engl J Med 2000;343:338-44.

The New England Journal of Medicine

Bruce A. Beutler

Jules A. Hoffmann,

Ralph M. Steinman



Charles A. Janeway – Ruslan Medzhitov

Inflamasoma

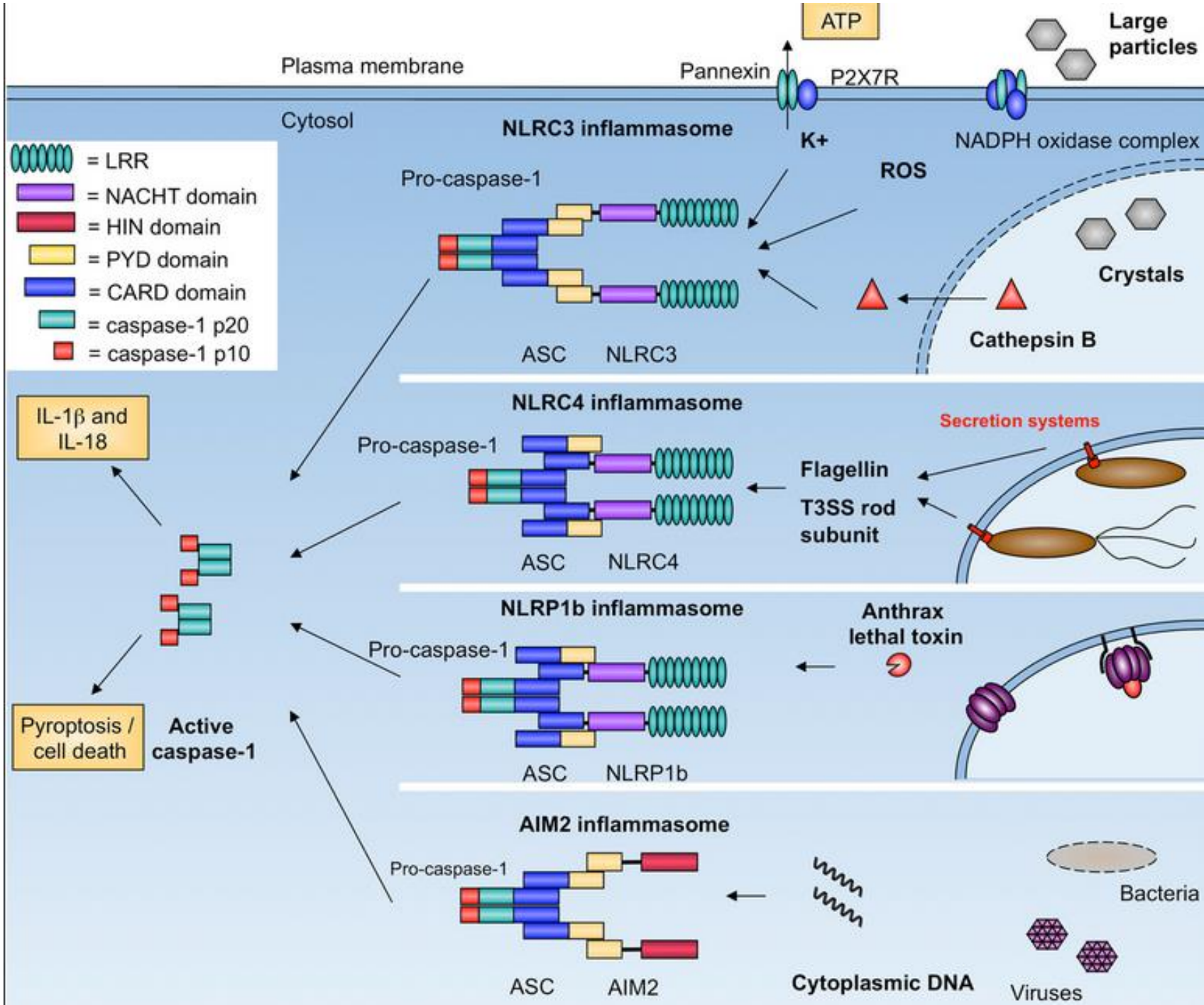
Complexo protéico
Composto de muitas
Proteínas

Ativam

Pró-caspase 1 – Caspase-1

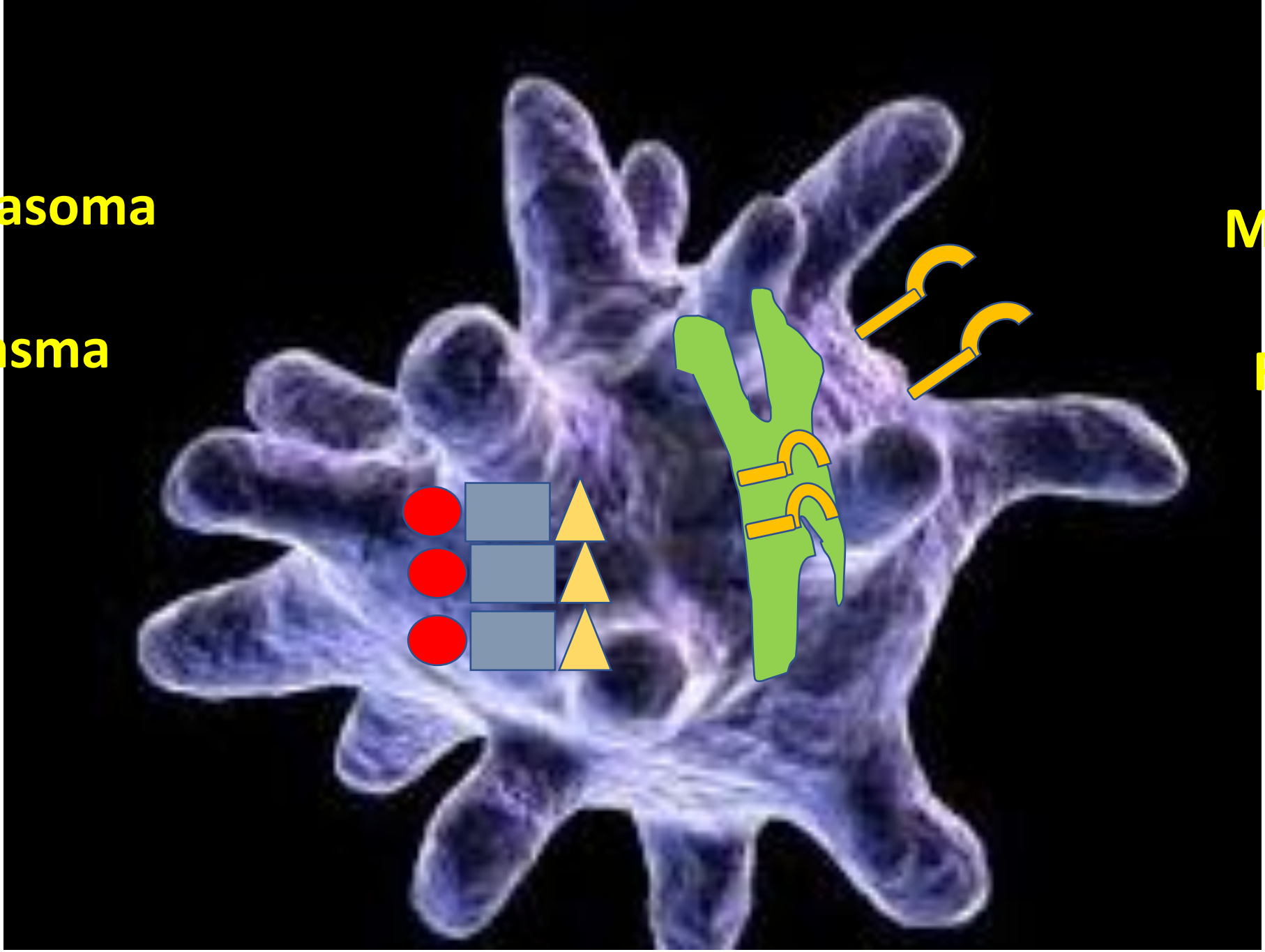
Pró-IL-1β / IL-18

CITOSOL



Inflamasoma

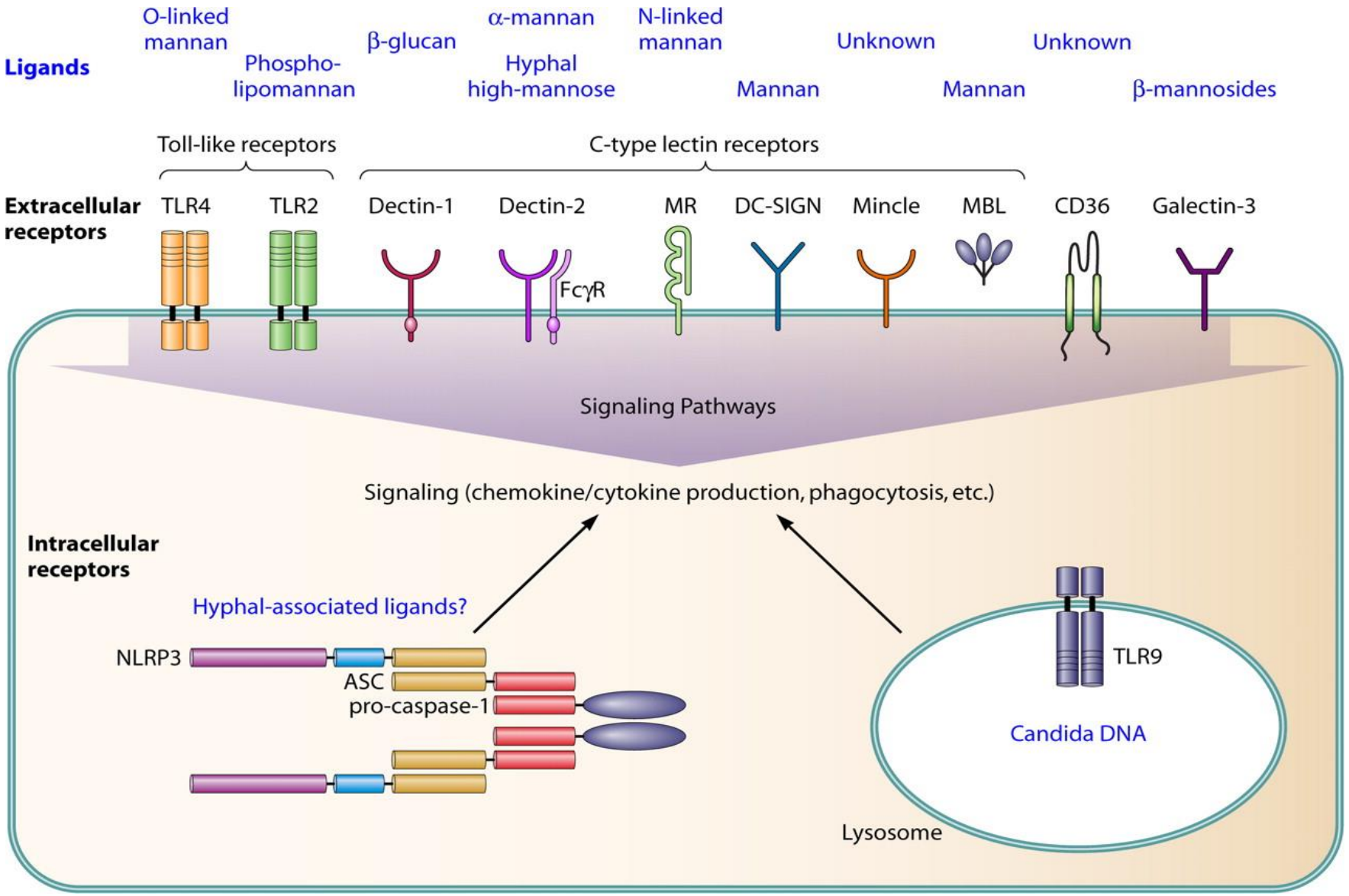
Citoplasma



TLRs

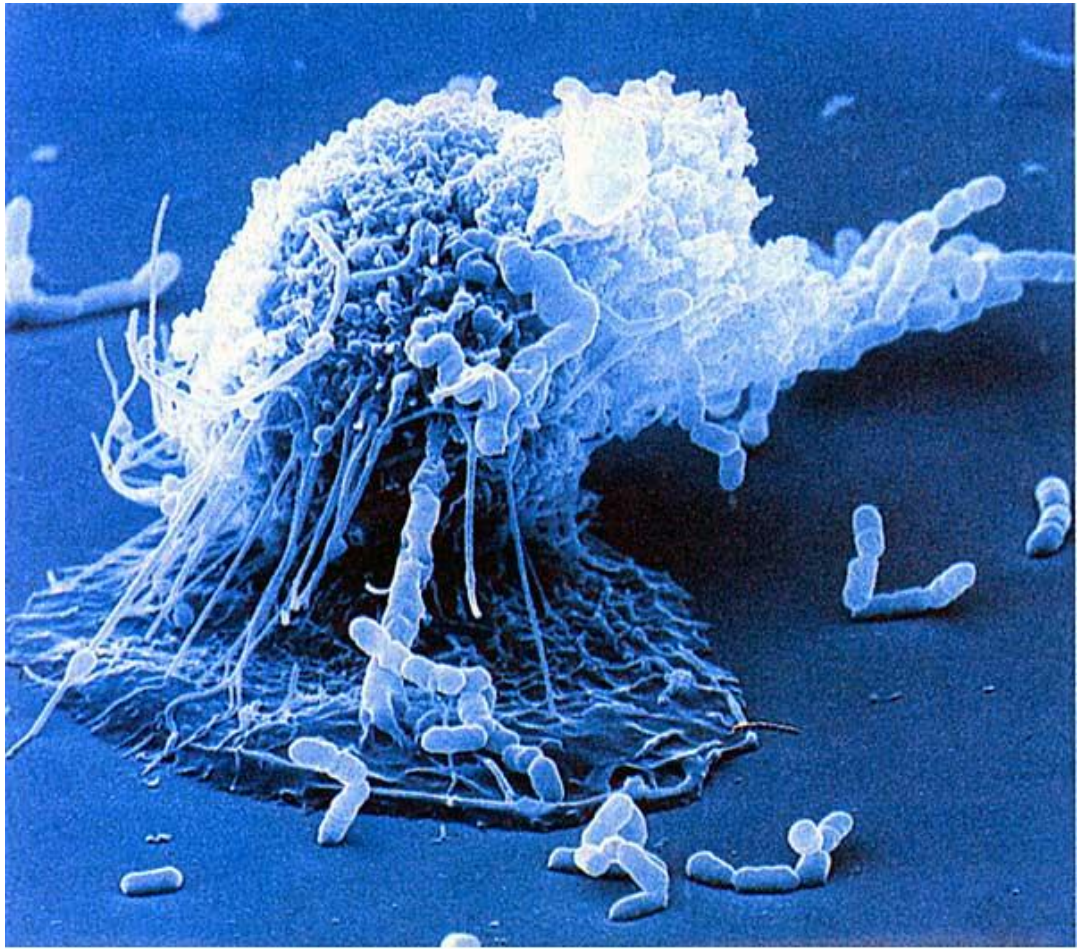
Membrana
Ou
Retículo

Pattern Recognition Receptors



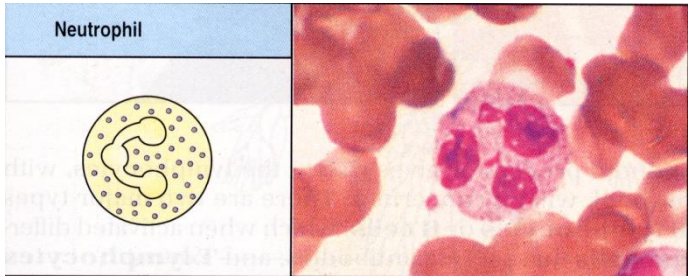
Outros Receptores

- Lectinas;
- *Scavengers;*
- Receptores Fc;
- NOD (**nucleotide-binding oligomerization domain**);
- Receptores de complemento.



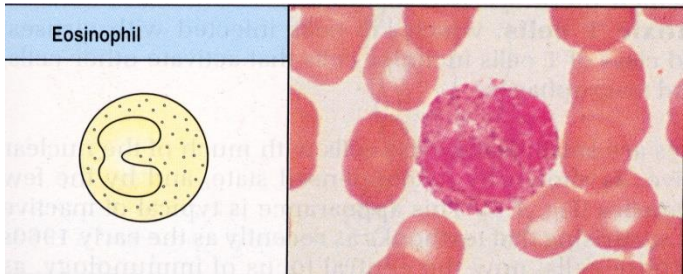
Células do Sistema Imune Inato

- **IMUNIDADE INATA**
- **Primeiras células infiltrantes,**
- **Grande capacidade fagocítica e microbicida:**
- **Mecanismos efetores ROS RNS (SOD, NADPH Oxidase, iNOS, Mieloperoxidase)**



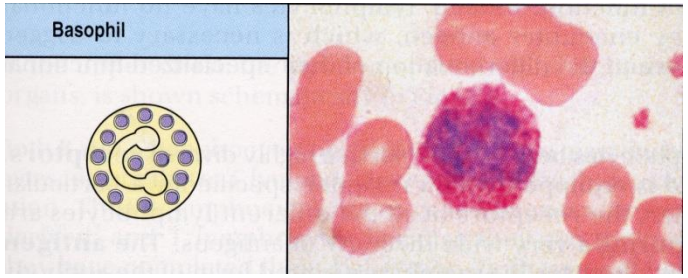
Neutrófilos

- **Importante contra helmintos**
- **Respostas alérgicas (tecidos conectivos das mucosas) (Asma)**
- **Receptores para IgG1(anafilática) e IgE (CD23)**
- **Grânulos: Proteína catiônica eosinofílica, peroxidase, hidrolases, lisofosfolipase**



Eosinófilos

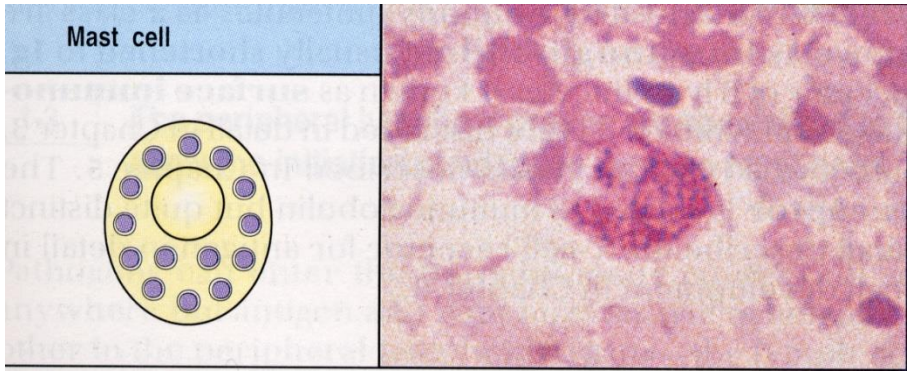
- **Presença de grânulos básicos no citoplasma**
- **Envolvido na proteção de mucosas**
- **Secretam histamina que aumenta a permeabilidade vascular**
- **Raramente encontrados no sangue (0,5%-1%)**



Basófilos

Células do Sistema Imune Inato

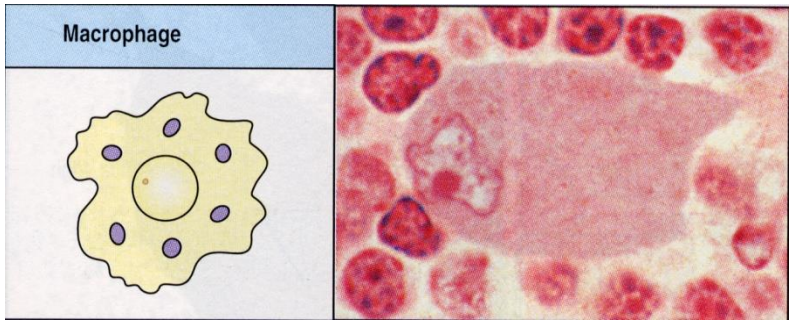
Mastócitos



- **Presente em mucosas**
- **Receptores de alta afinidade para IgE (CD23)**
- **Envolvidos em processos alérgicos**
- **Secretam histamina que aumenta a permeabilidade vascular**
- **Produzem IL-4 (citocina)**

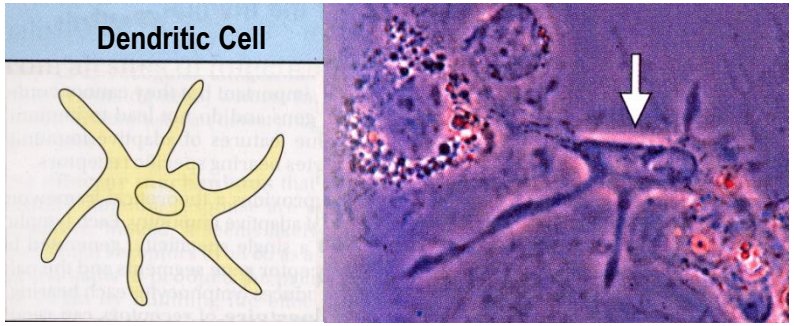
Células do Sistema Imune Inato

- **Receptores para IgG / Complemento (CD11b+)**
- **Receptores tipo TLR (PAMPS)**
- **Capacidade fagocítica e microbicida (= Neutrófilos)**
- **Importantes Células Apresentadoras de Antígeno (APC)**
- ***LINK* com a IMUNIDADE ADAPTATIVA**



Monócitos / Macrófagos

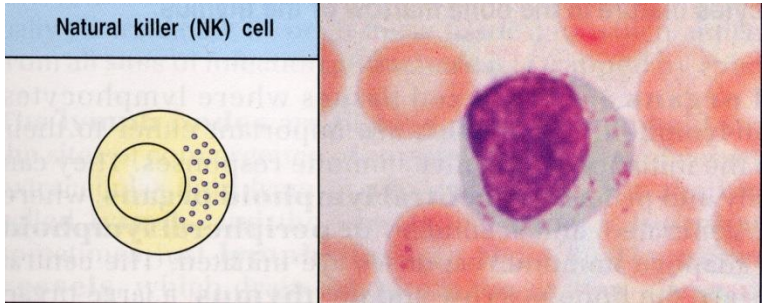
- **Importante para a IMUNIDADE ADAPTATIVA**
- **Progenitor linfóide, $CD8^+$ e produtoras de IL-12**
- **Progenitor mielóide, $CD14^+$ e não-produtoras de IL-12**
- **Células de Langerhans (epitélios de revestimento) – Mielóide**
- **Presentes em vários tecidos**
- **Capacidade fagocítica**
- **MAIS IMPORTANTES APCS**



Células Dendríticas

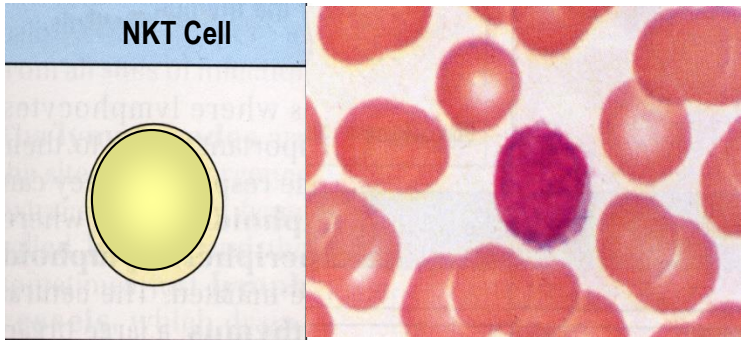
Células do Sistema Imune Inato

- **Destruição de células infectadas com vírus ou células tumorais**
- **Citotoxicidade mediada por anticorpos (ADCC) via CD16 (FcγRIII)**
- **Outros receptores (?):**
  CD2 / integrinas / receptor para MHC I (?): lise das células sem ligantes
- **Grânulos citoplasmáticos (perforina e granzima)**
- **Modulam as IMUNIDADES INATA E ADAPTATIVA (IFN-γ)**



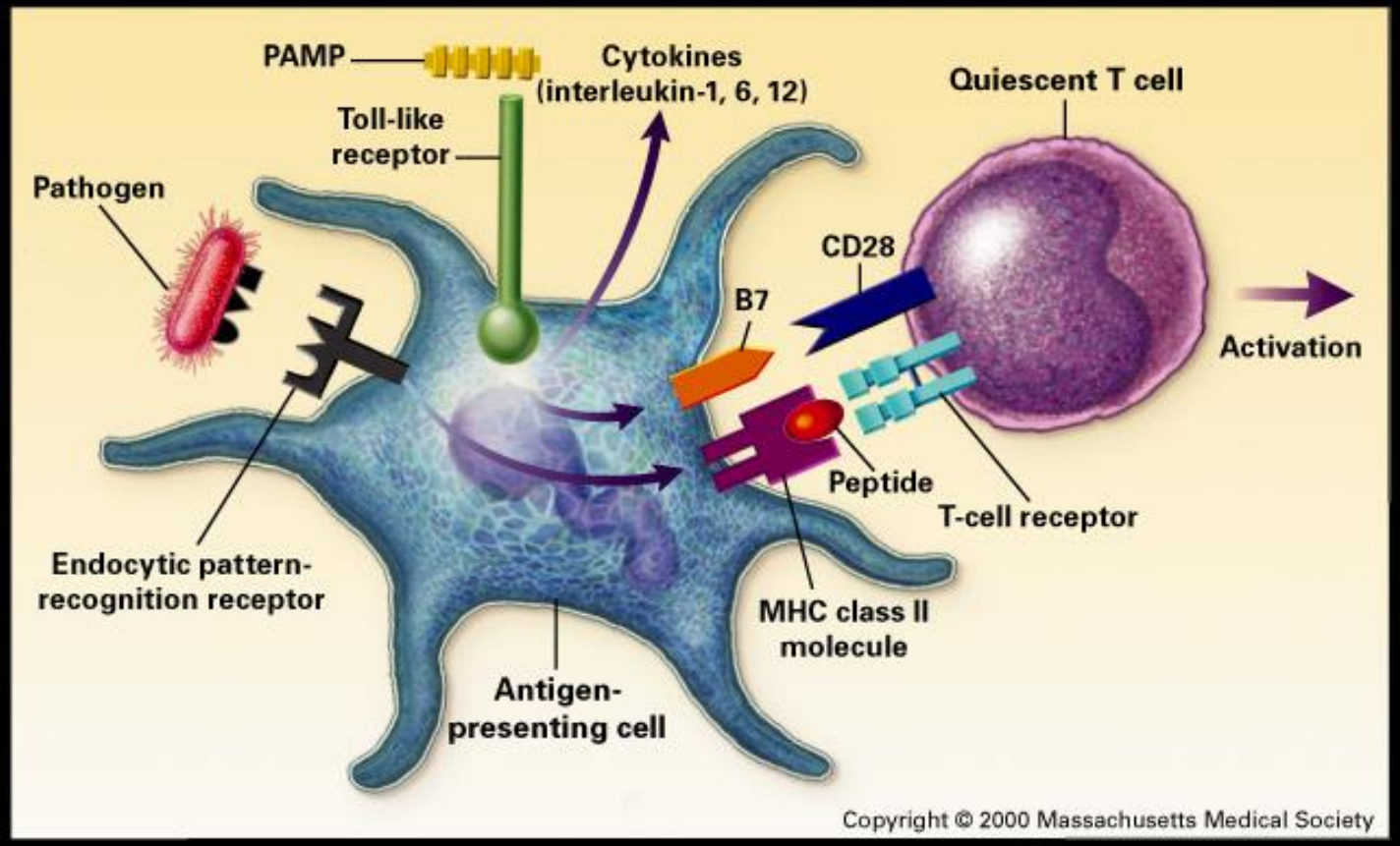
Células NK

- **Reconhecem α-Galactoseramida via CD1(a-d) glicolipídeos**
- **Receptor na membrana: TCR Vβ11Vα24 (humanos)**
  TCR Vβ8Vα14 (camundongos)
- **Podem produzir IL-4 ou IFN-γ e IL-17**



Células NKT

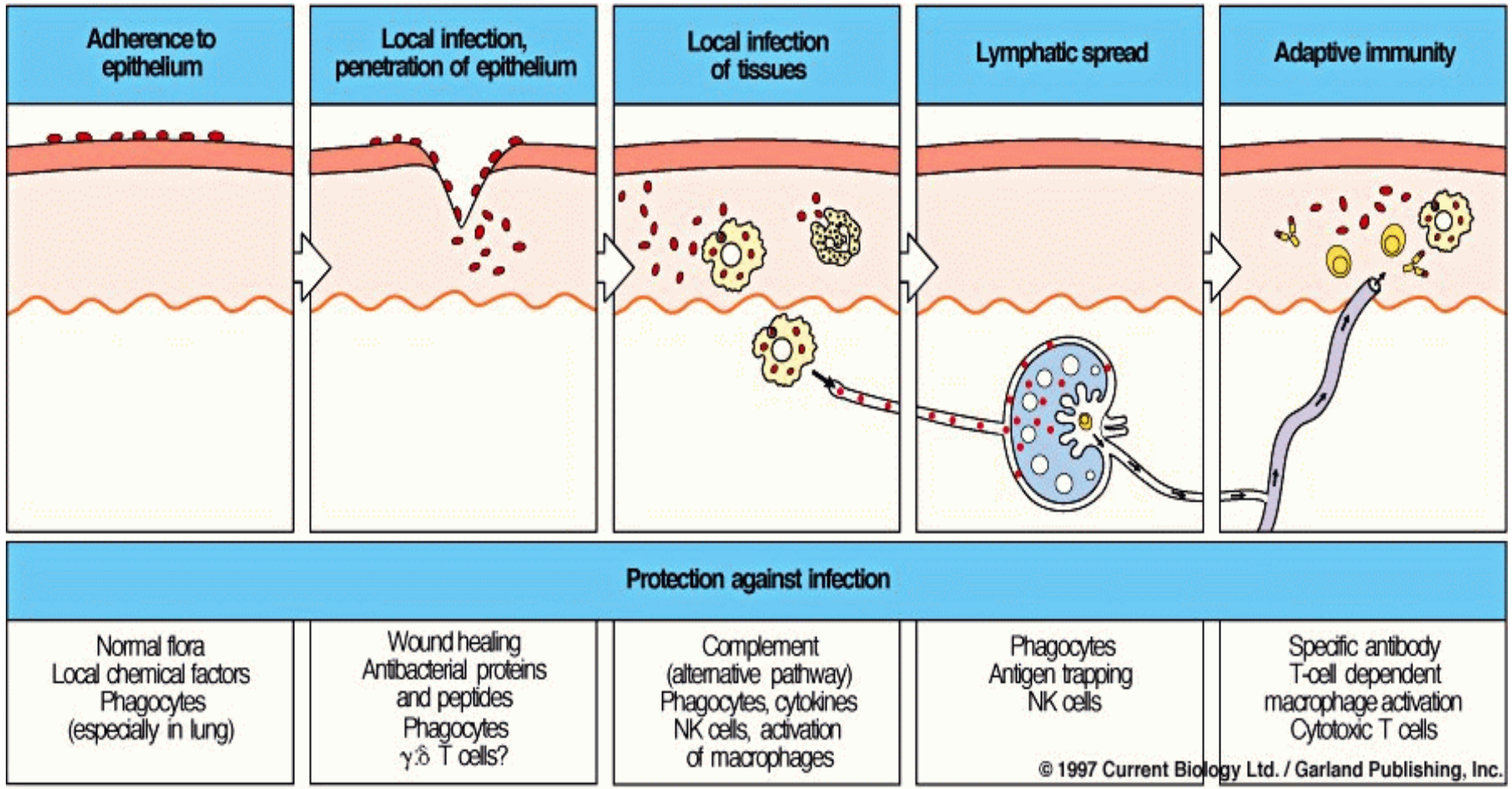
Link Entre a Imunidade Inata e a Adaptativa



Medzhitov R, Janeway C Jr. Innate Immunity.
N Engl J Med 2000;343:338-44.

The New England Journal of Medicine

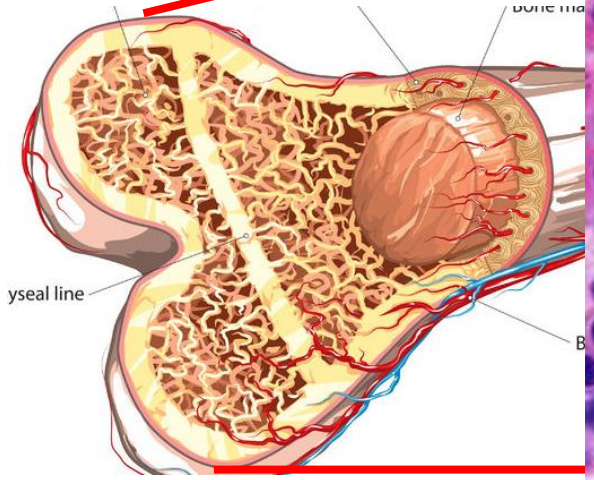
Drenagem Antigênica

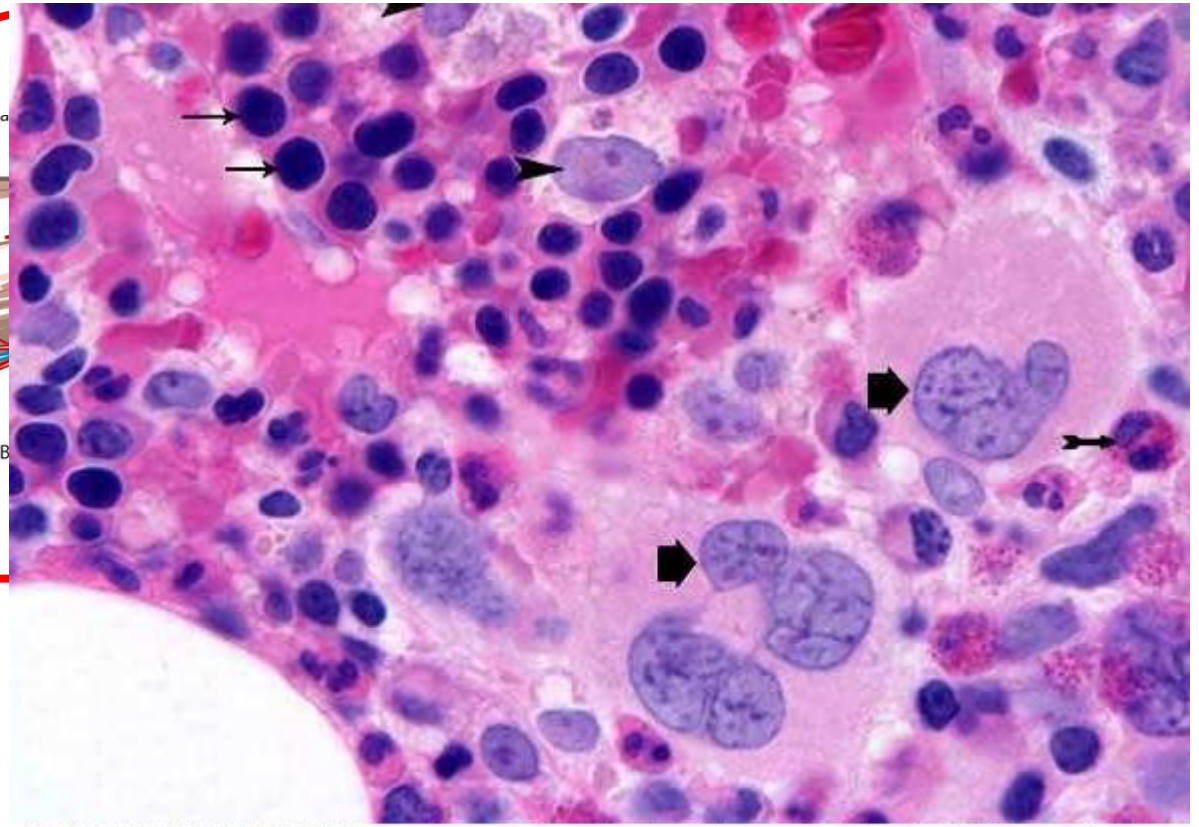


Mas onde acontece a apresentação de antígenos ??????

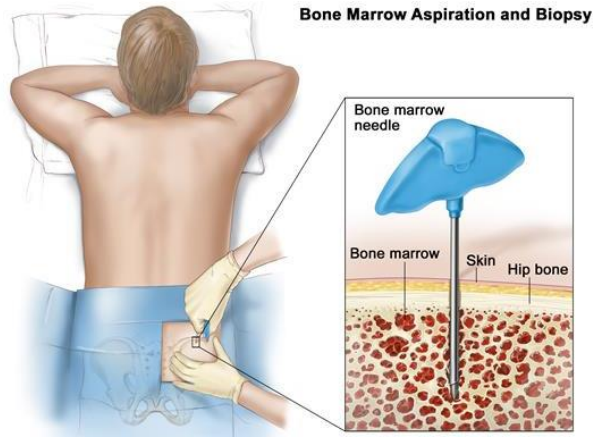
1) Nos linfonodos e baço
2) No órgão alvo.

1os – Medula Óssea – Progenitores Linfóides e Mielóides

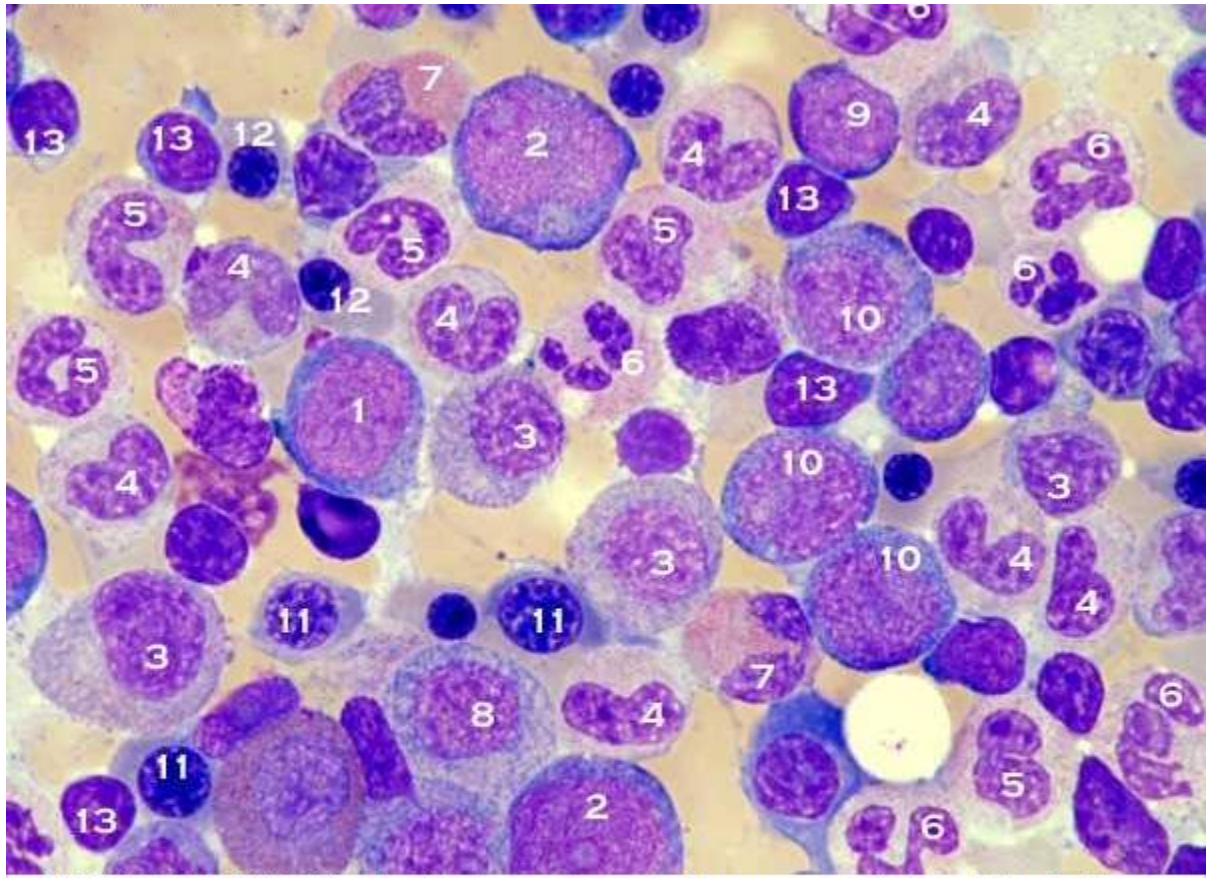




[NORMAL BONE MARROW]. A normal marrow is said to show trilineage hematopoiesis (TLH) meaning that elements of all three major cell lines are represented. These cell lines include myelomonocytic cells, erythroid cells, and megakaryocytic cells. However, other cells types are also present including lymphocytes, plasma cells, connective tissue cells and stromal cells. Two histiocytes are present (arrowheads) engulfing cellular debris. The nucleated erythroid precursors are also dispersed (two long arrows) throughout the marrow. Two normal megakaryocytes are apparent in this field (two big arrows). A binucleated eosinophil is identified with an arrow with tail.

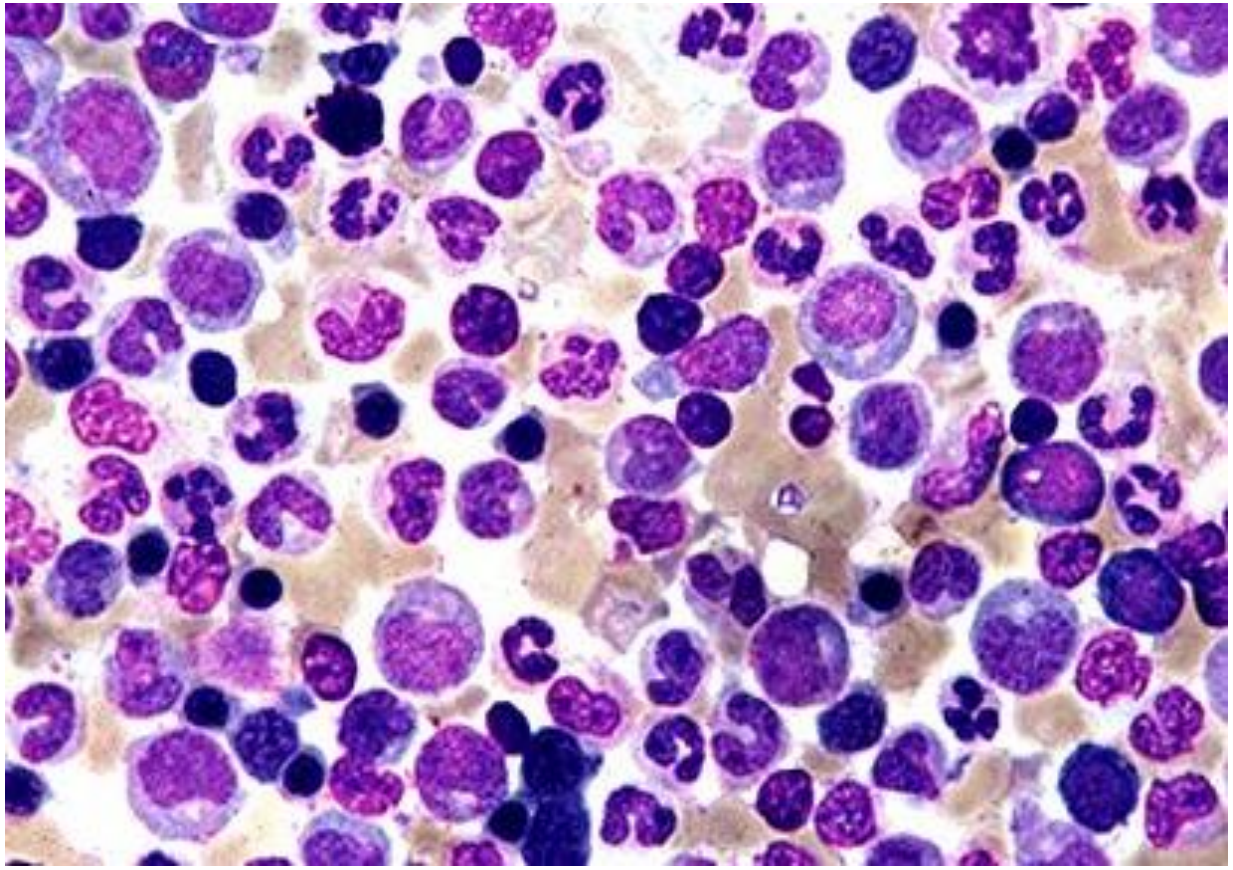


Medula Óssea Normal

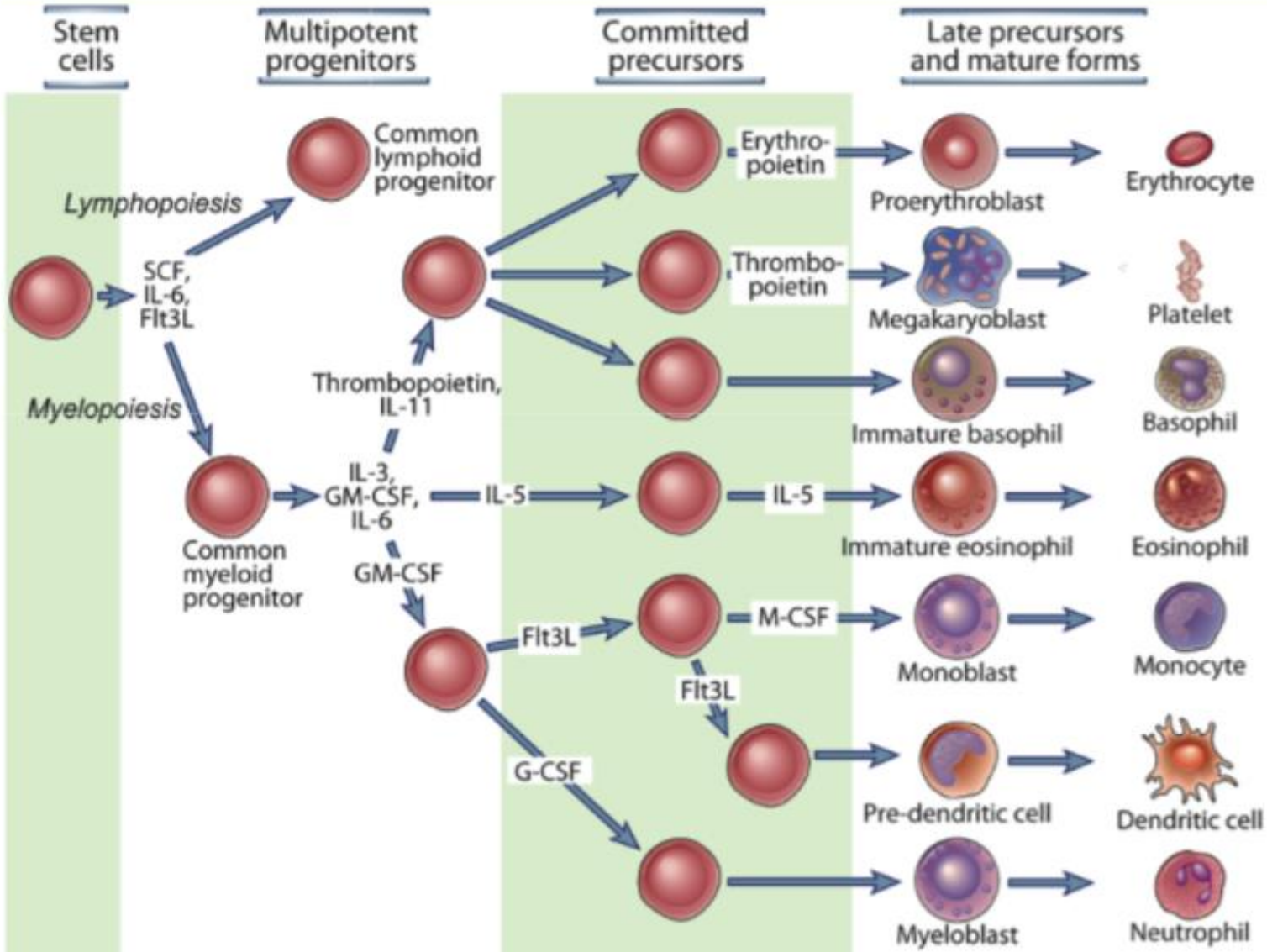


[NORMAL BONE MARROW]. This slide shows various normal bone marrow cells. In myeloid series the cells mature in the following order: Myeloblast >> Promyelocyte >> Myelocyte >> Metamyelocyte >> Band neutrophil >>Segmented neutrophil (or eosinophil or basophil). In the erythroid series the cells mature in the following order: Proerythroblast >> Basophilic erythroblast >> Polychromatic erythroblast >> Orthochromatic erythroblast >> Reticulocyte >> Mature red cell. The various cells are as follows: 1 = Myeloblast, 2 = Promyeloocyte, 3 = Myelocyte, 4 = Metamyelocytes, 5 = Band neutrophil, 6 = Segmented neutrophil, 7 = Eosinophil, 8 = Monocyte, 9 =Proerythroblast, 10 = Basophilic erythroblasts, 11 = Polychromatic erythroblast, 12 = Orthochromatic erythroblast, 13 = Lymphocyte.

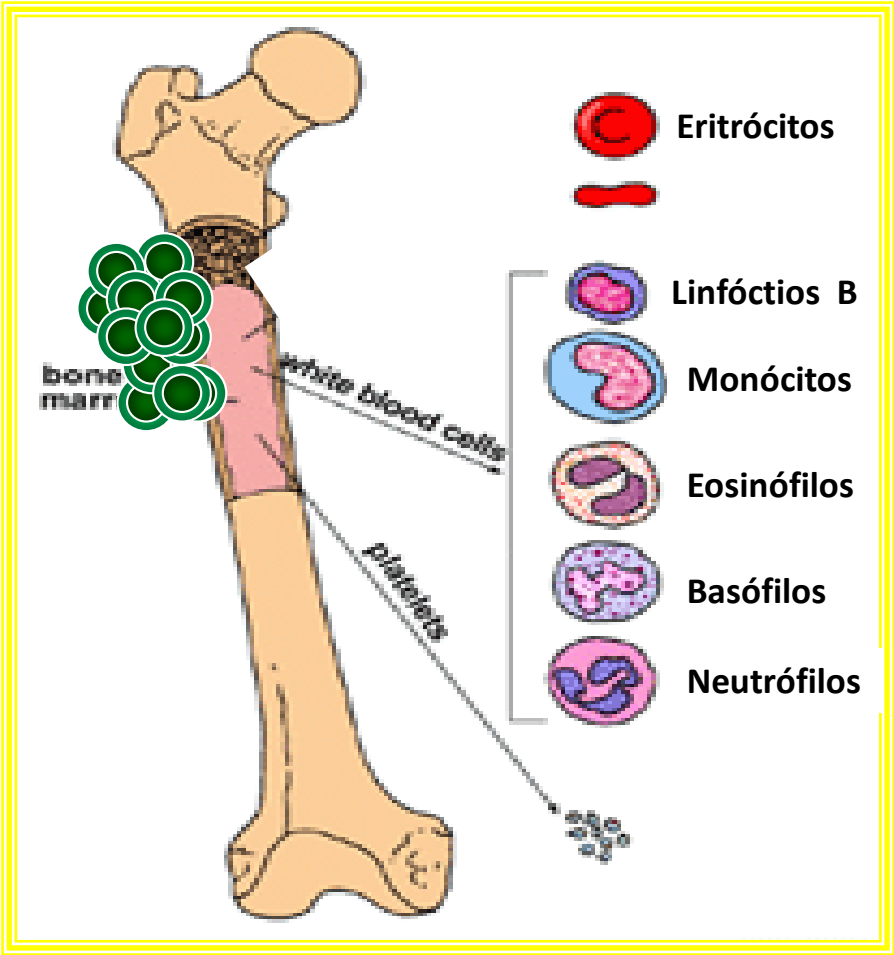
Medula Óssea Leucemia Mielóide Crônica

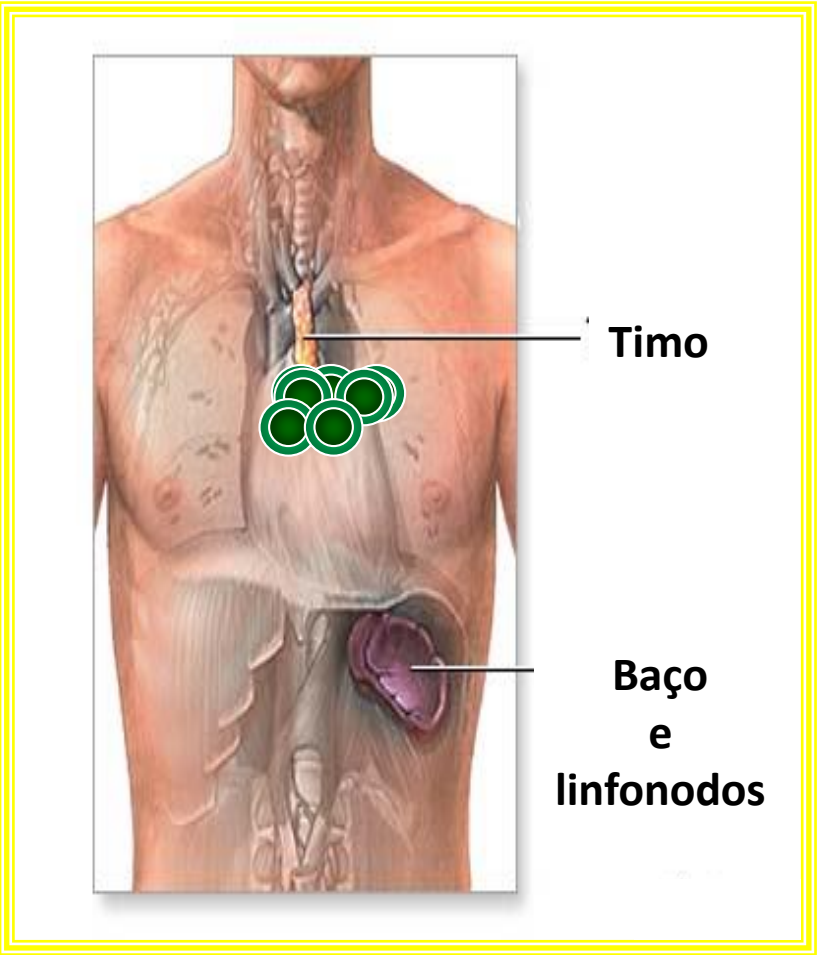


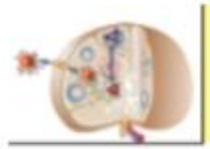
Hematopoiesis



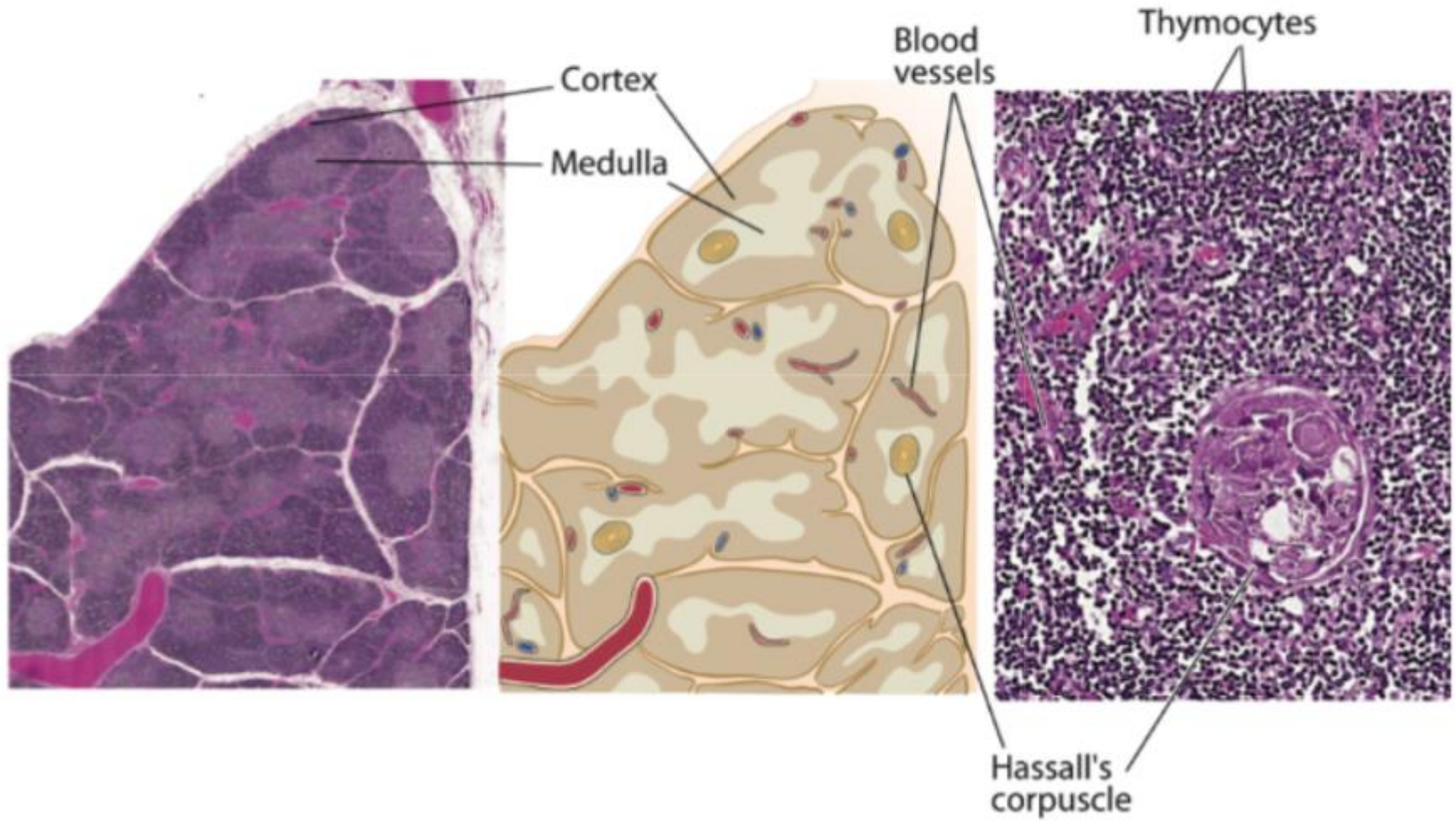
Precursores linfóides migram para o timo para sofrer maturação



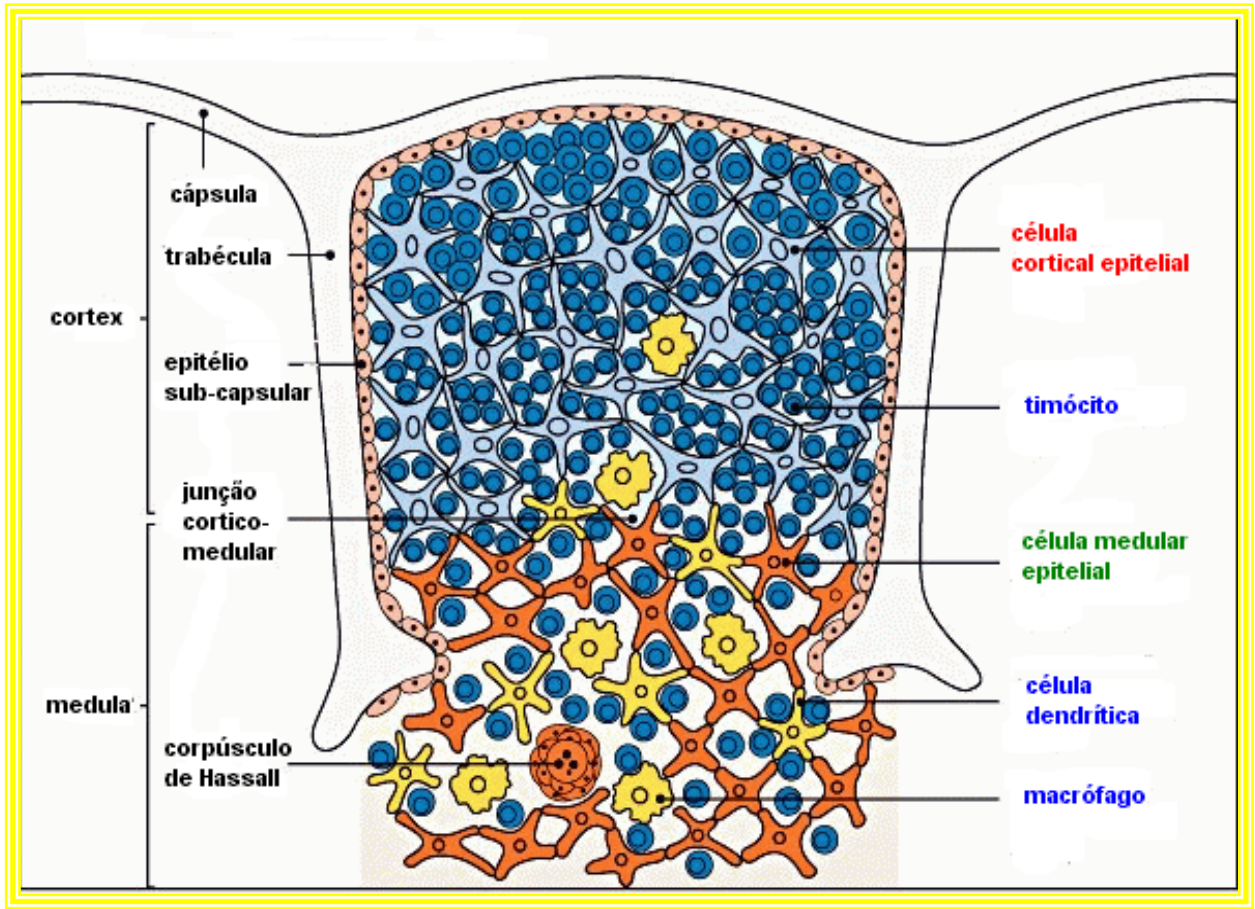


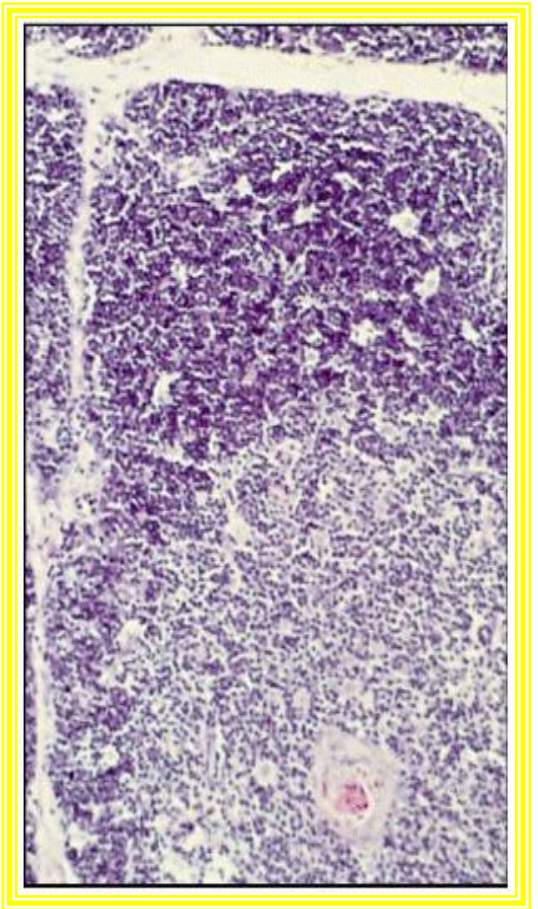


Morphology of the Thymus



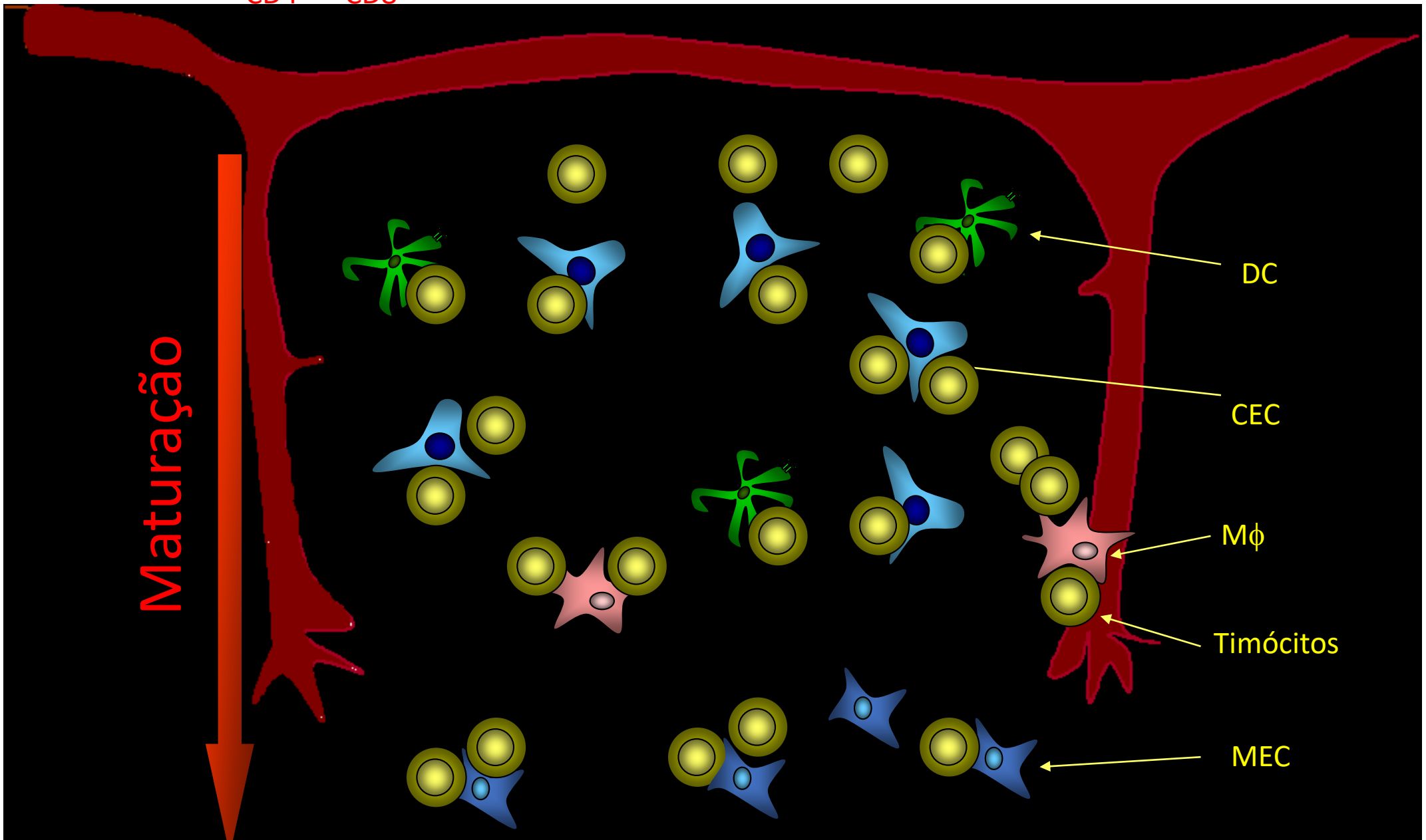
Estrutura Tímica





Precursores linfóides, agora chamados timócitos, migram da CÓRTEX PARA MEDULA e não expressam CD4 nem CD8

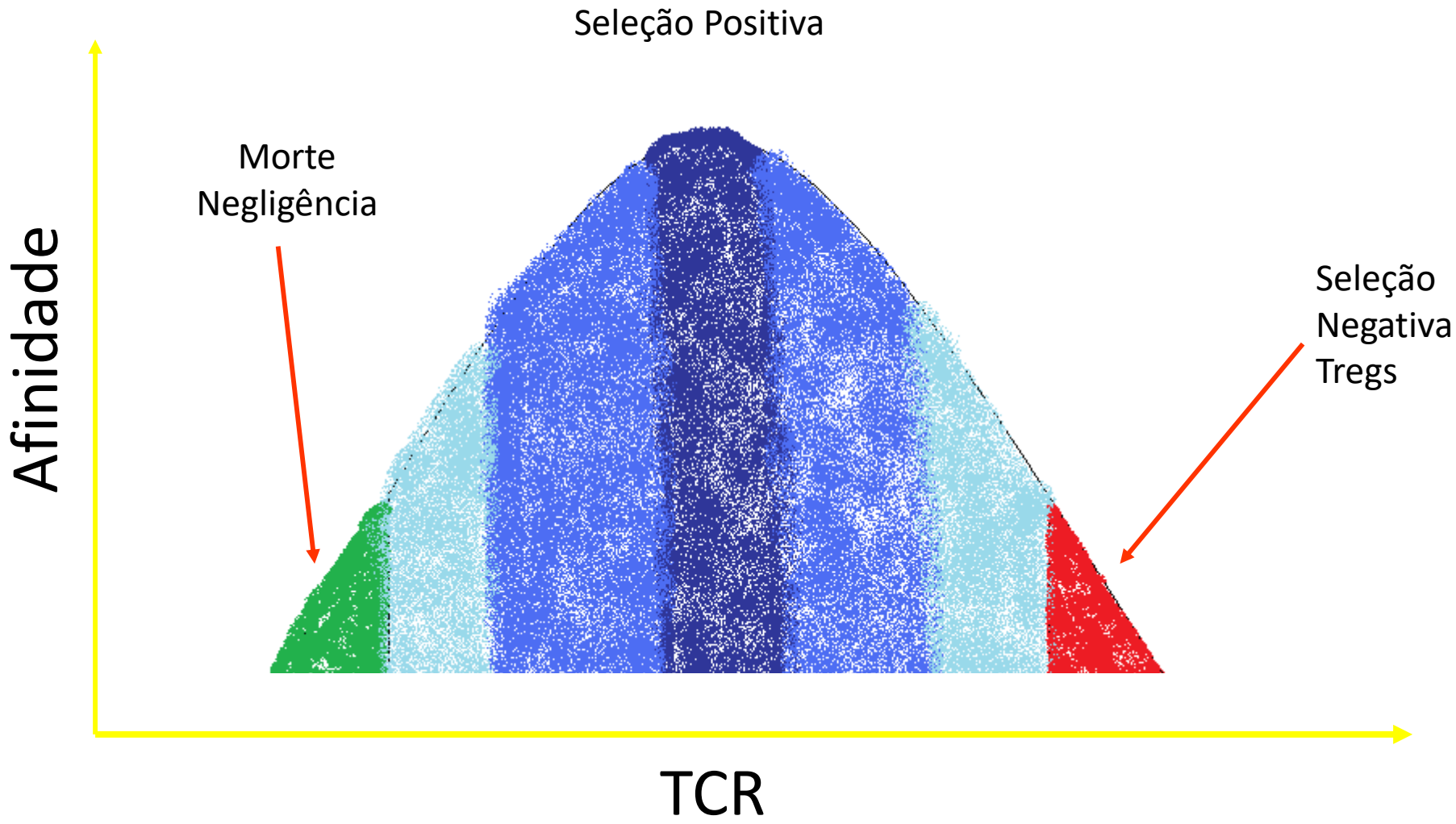
$CD4^{neg}$ $CD8^{pos}$

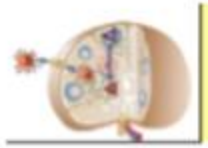


Córtex

Medula

Limiar de Seleção





Lymph Node Morphology (1)

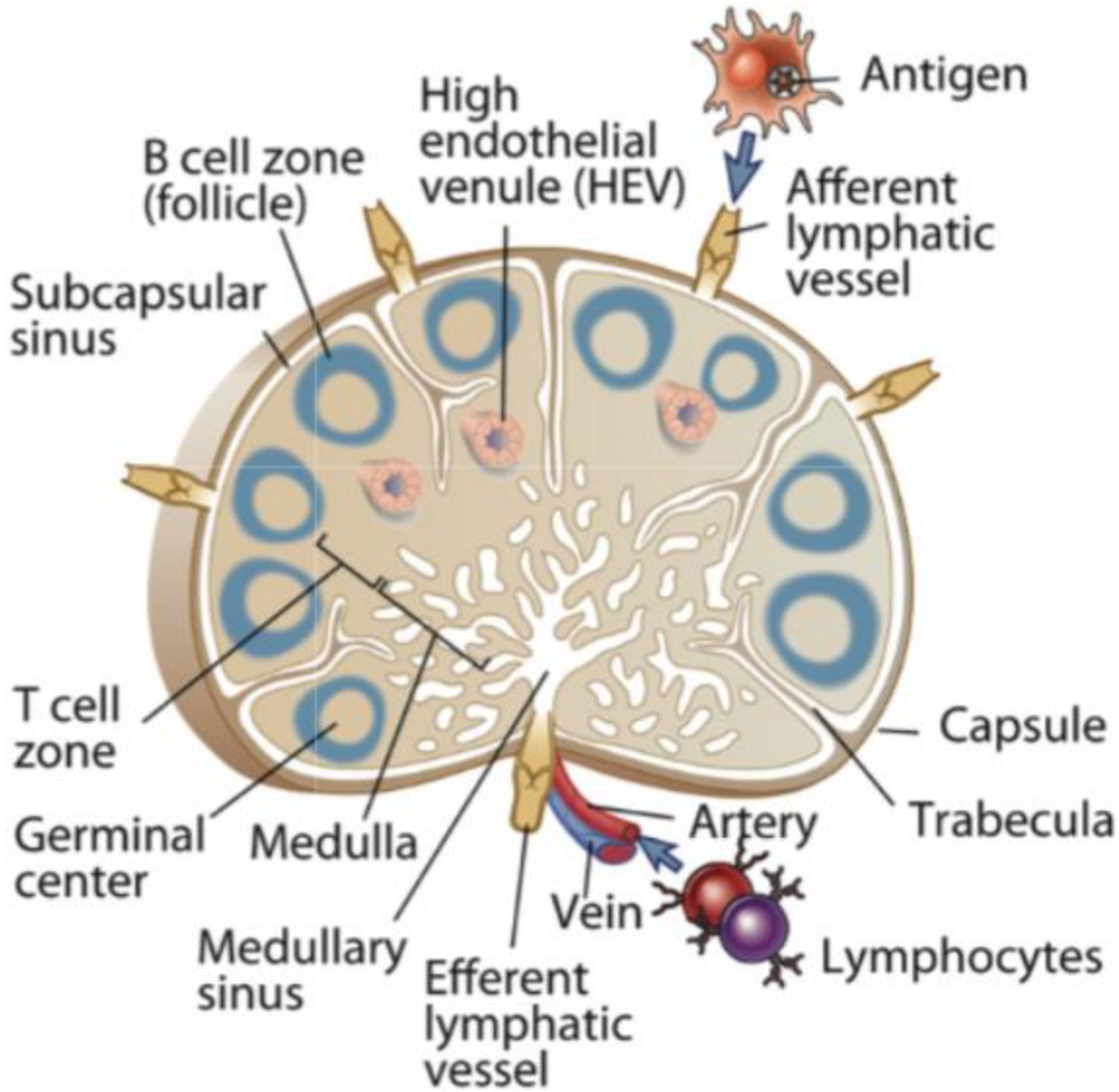
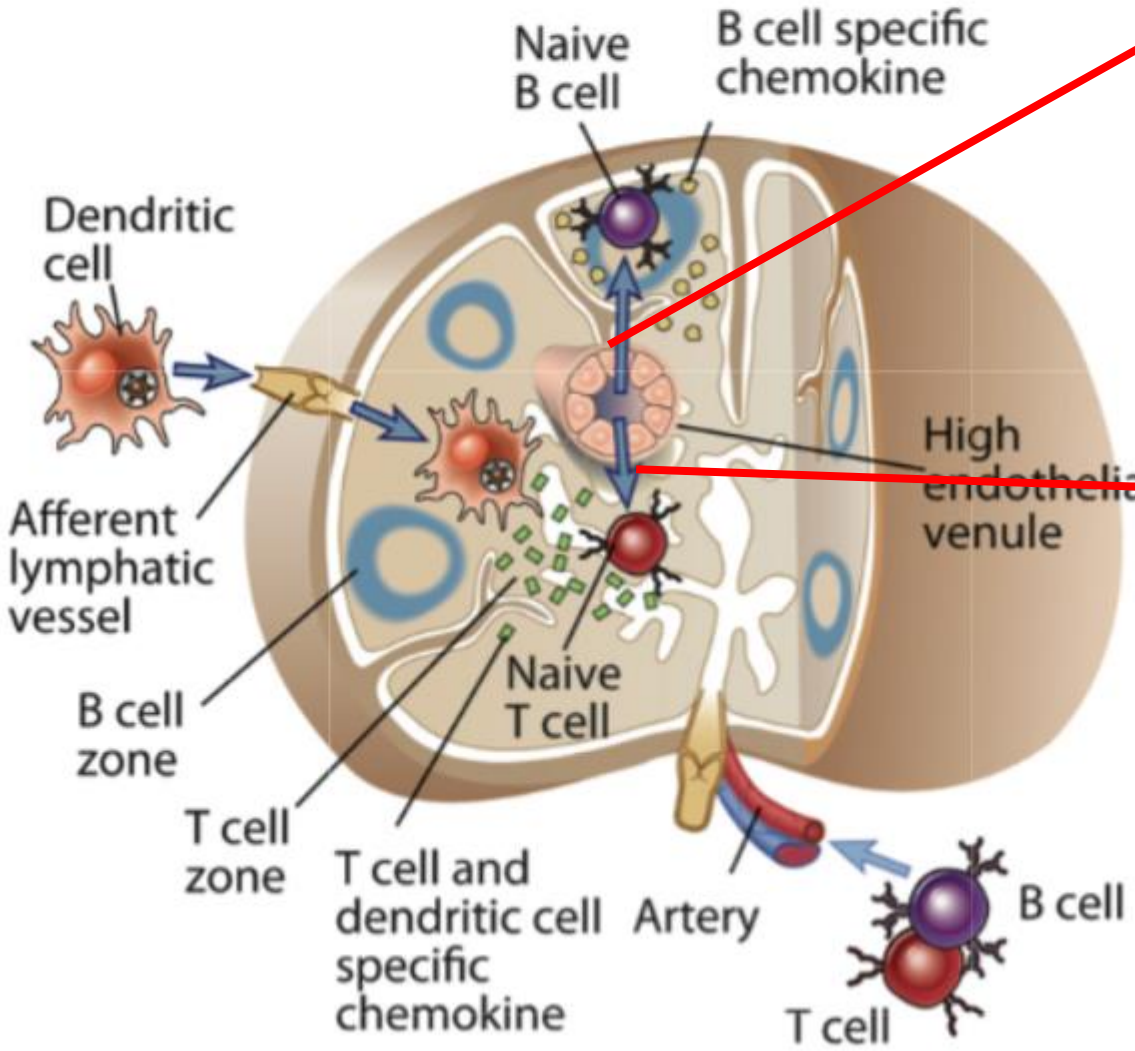


Fig. 2-12 A

B and T Cells Zones in a Lymph Node (1)



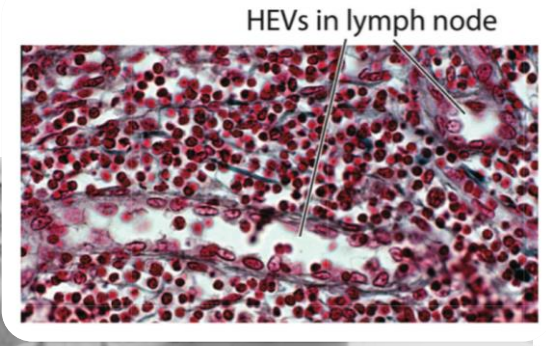
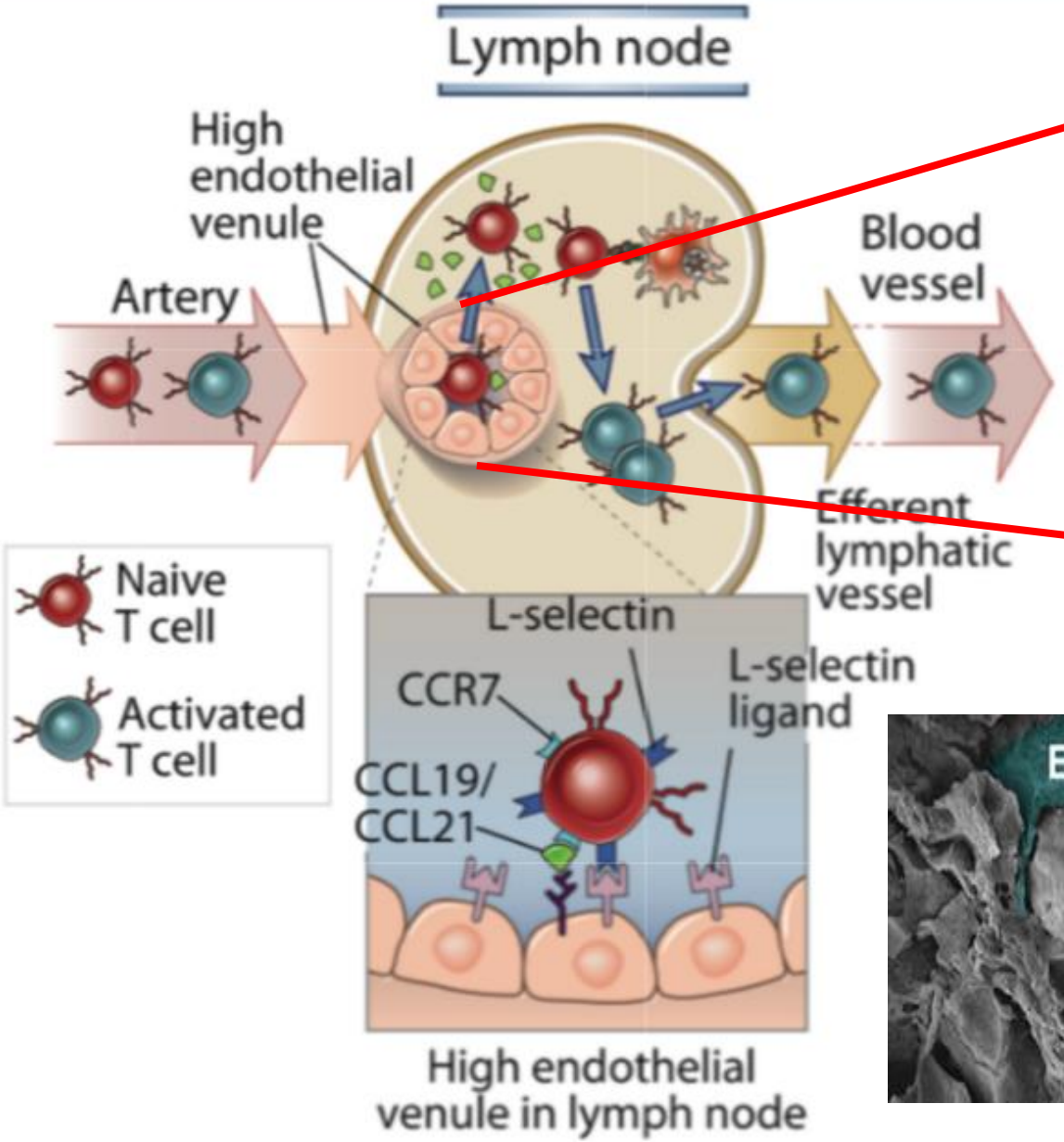
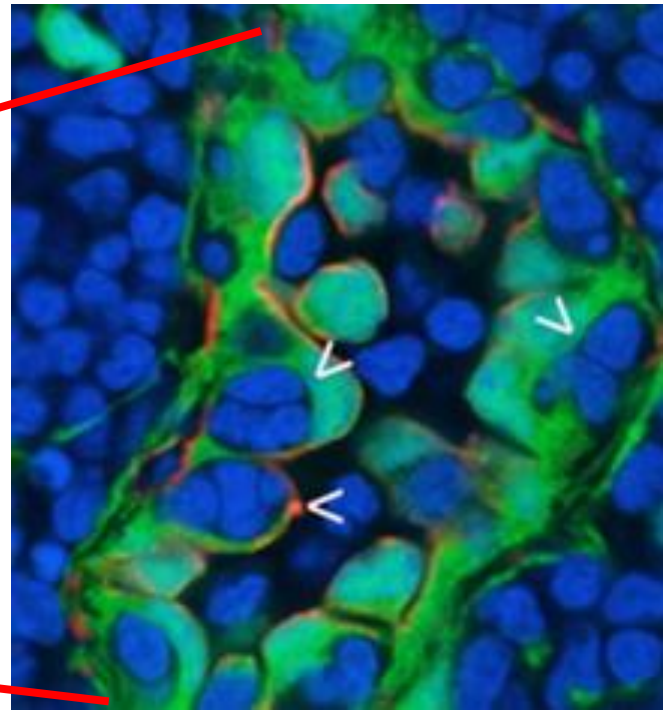


Fig. 2-13 A

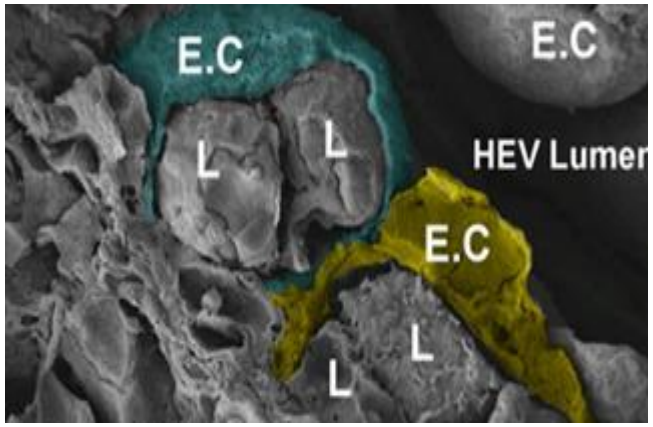
Migration of Naïve T Lymphocytes

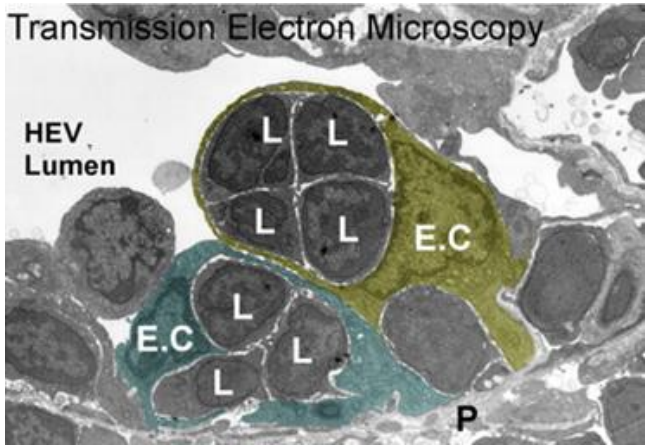


HEV

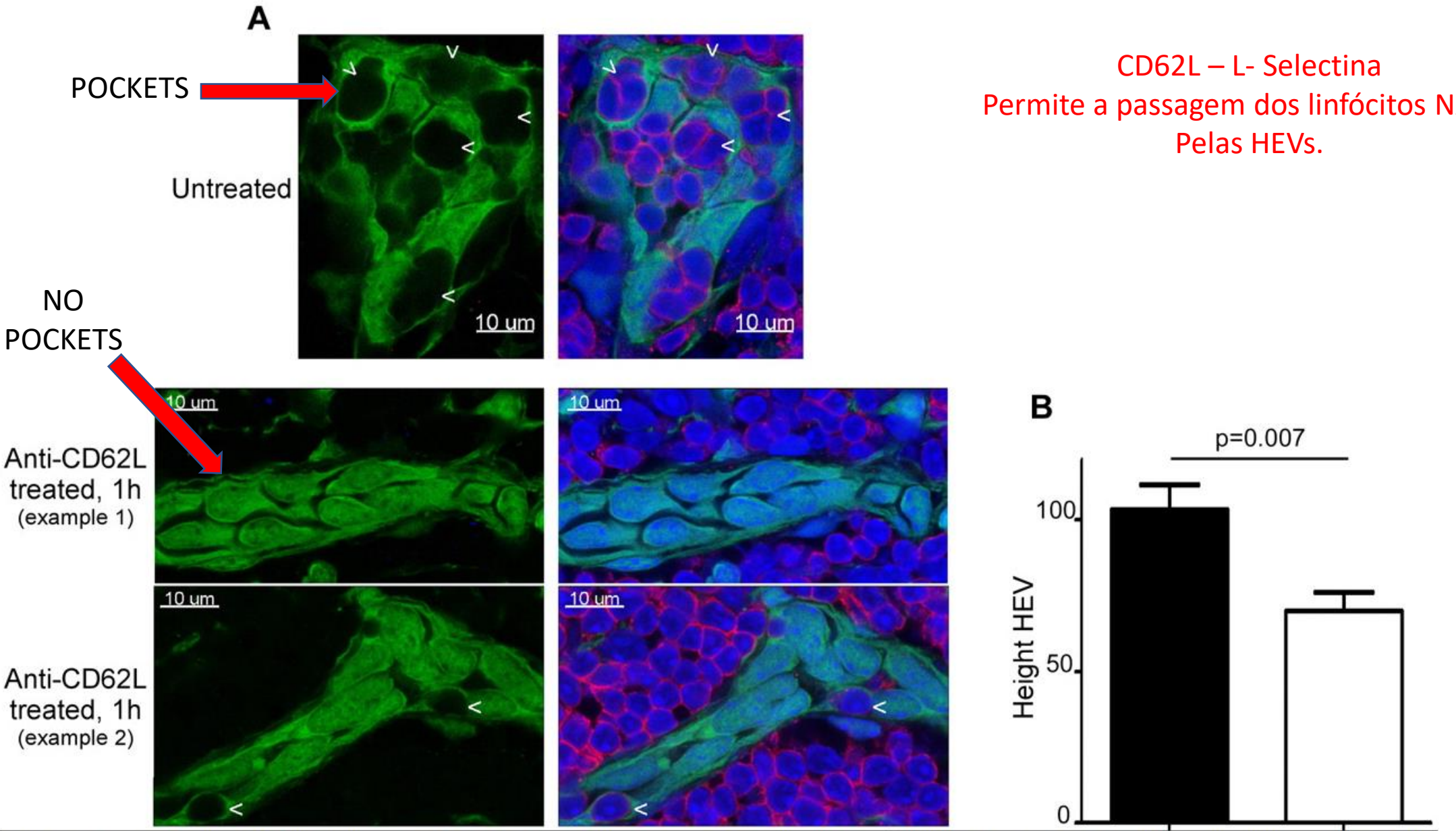


Linfócito

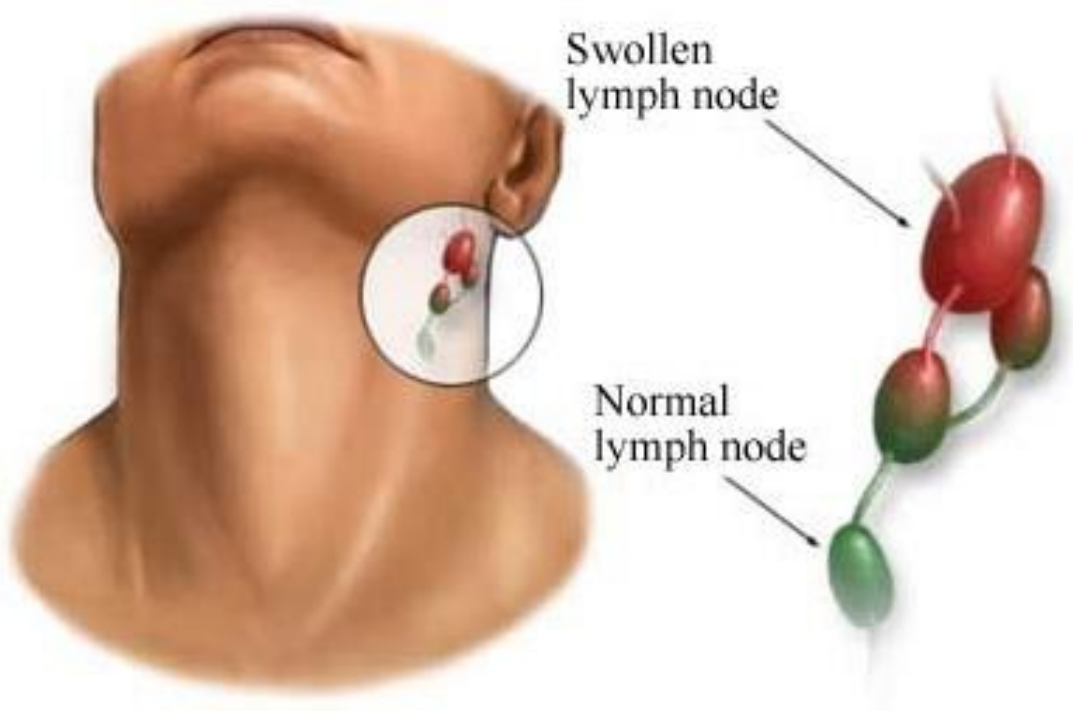




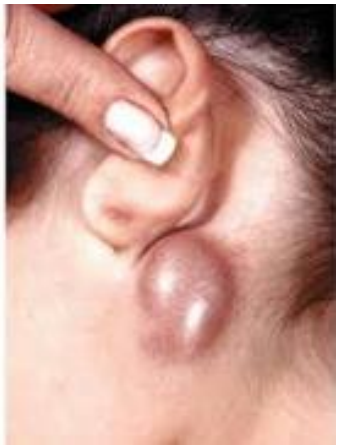
CD62L – L- Selectina
Permite a passagem dos linfócitos NAIVE
Pelas HEVs.

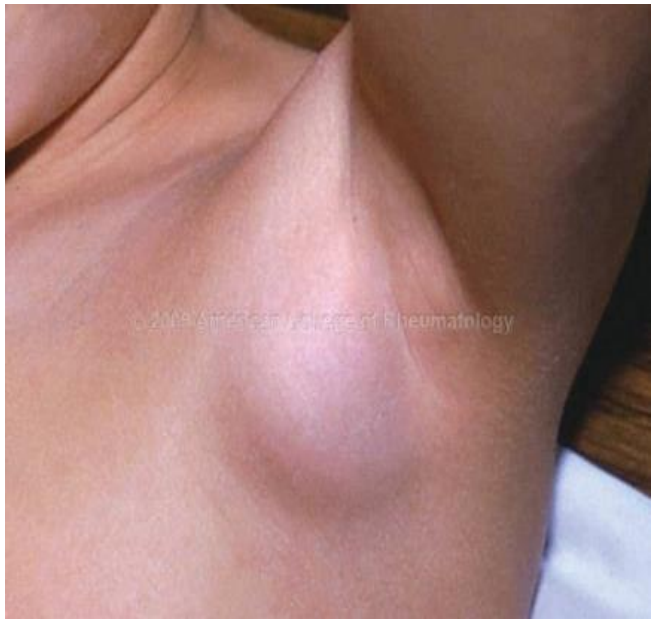


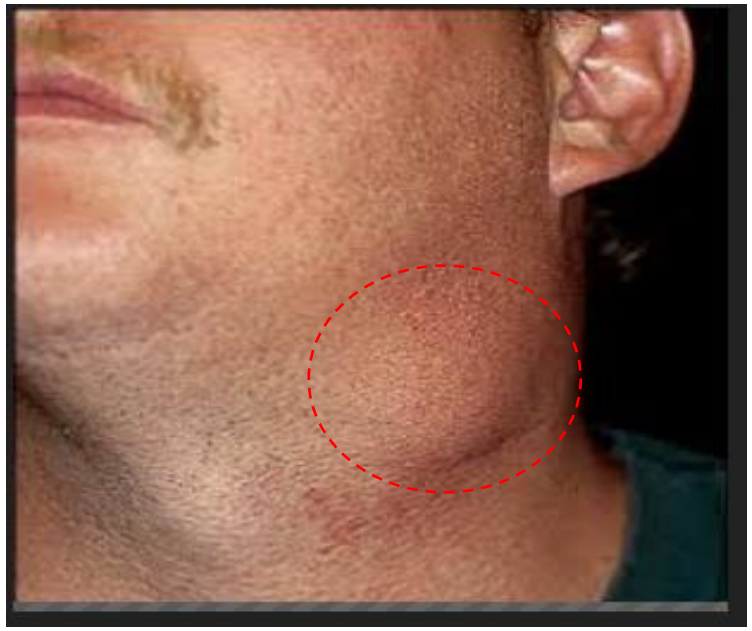
Blockade of lymphocyte homing to LN induces the disappearance of HEV pockets. (A) Confocal images of LNs section from a RAG-2$^{-/-}$ubiquitin-GFP chimera (green) injected or not intravenously for 1 hour with 100 µg of anti-CD62L blocking Ab (MEL-14) and stained for CD3 (red) and sytox 63/nuclei (blue). Arrowheads point to HEV pockets. (B) Height (and standard error) in arbitrary units of LN HEV (see "Morphoretic analysis of HEV"). Data are representative of 2 different experiments (2 mice per experiment, ~ 15 analyzed HEVs for each condition per experiment).



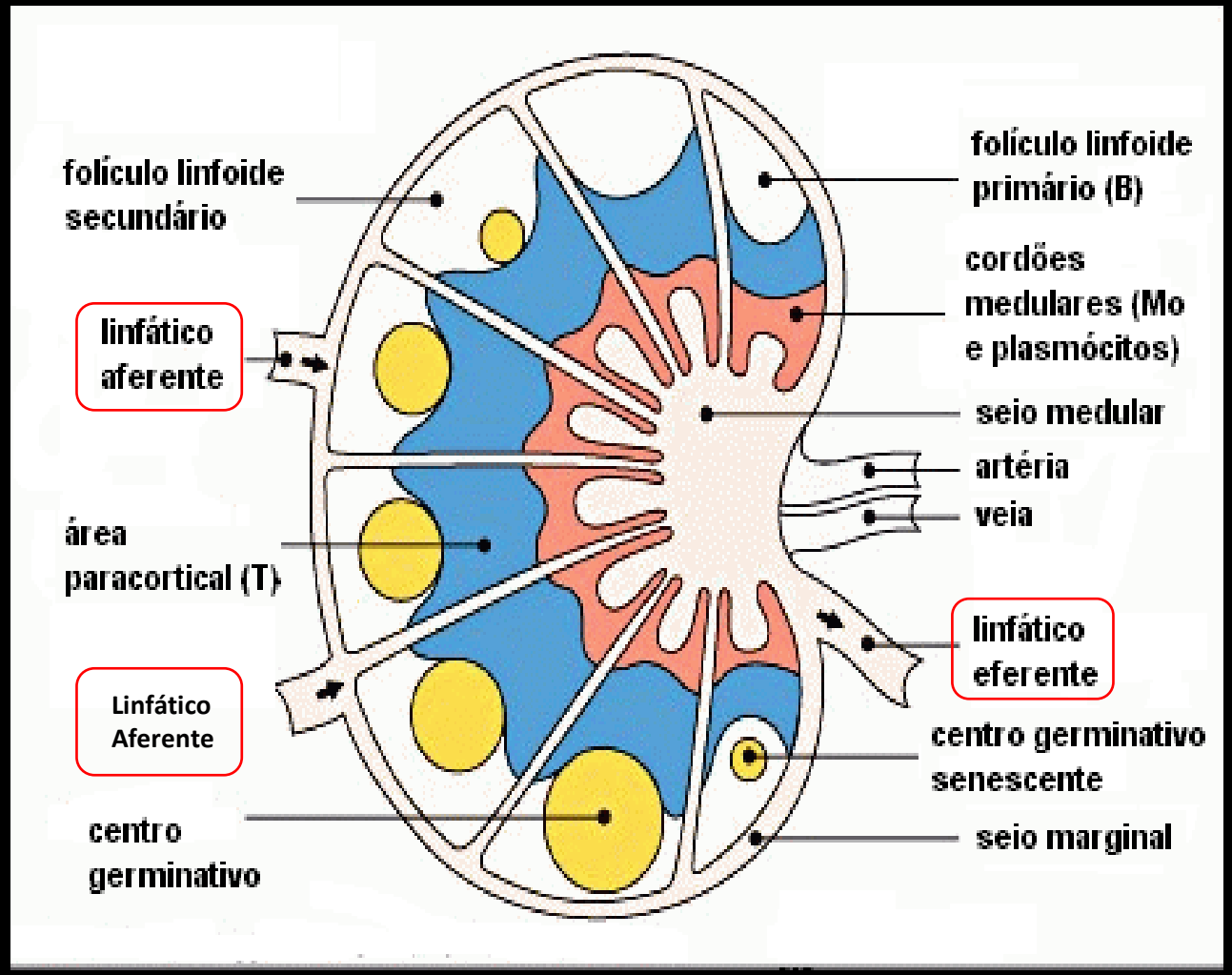
Linfonodos Aumentados

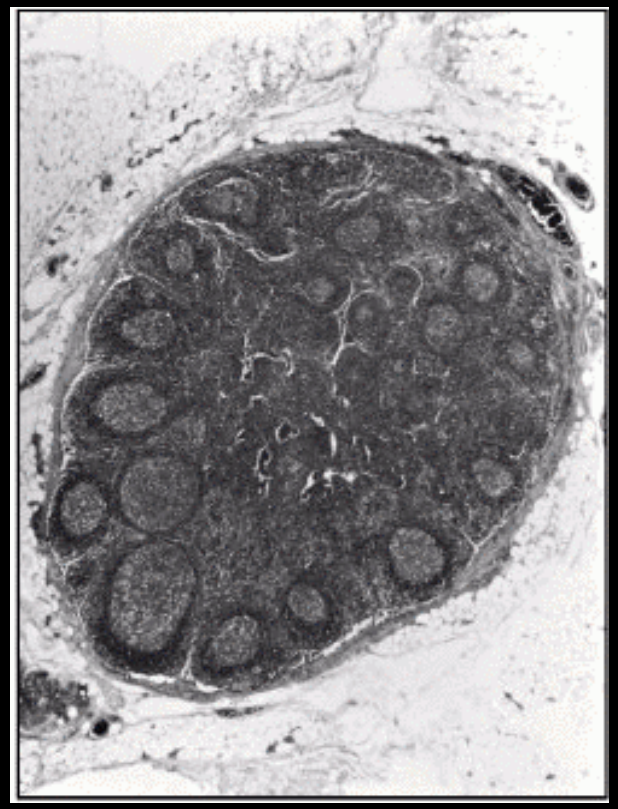






Organização Anatômica dos Linfonodos





Características

High Endothelial Venules

Entrada dos Linfócitos da Circulação

L-Selectina – Ligante de L-selectina

CCL19 – CCL21 Ligam no CCR7

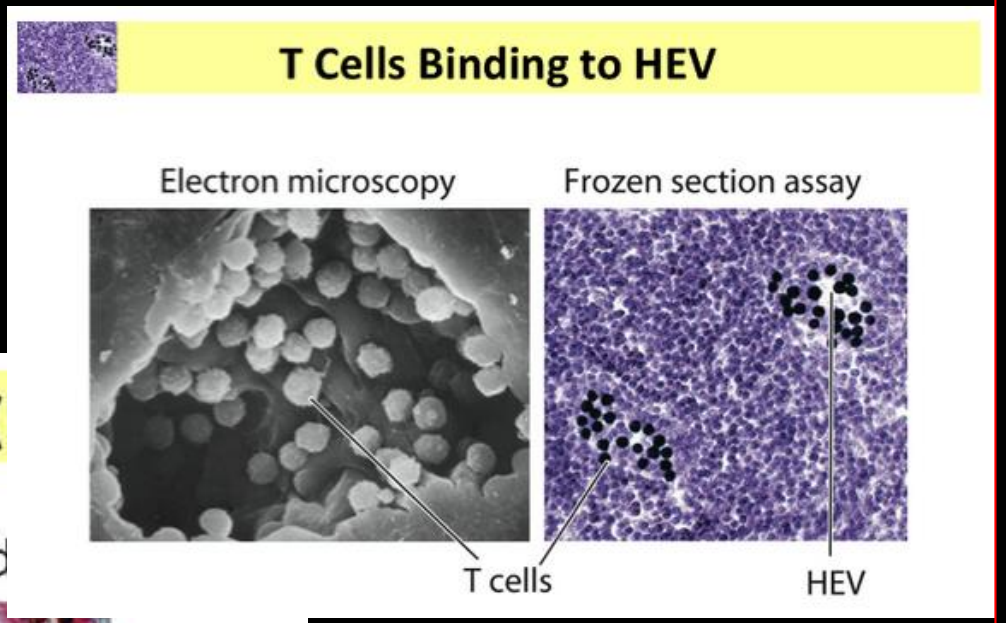
S1P – S1PR – mantém nos linfonodos

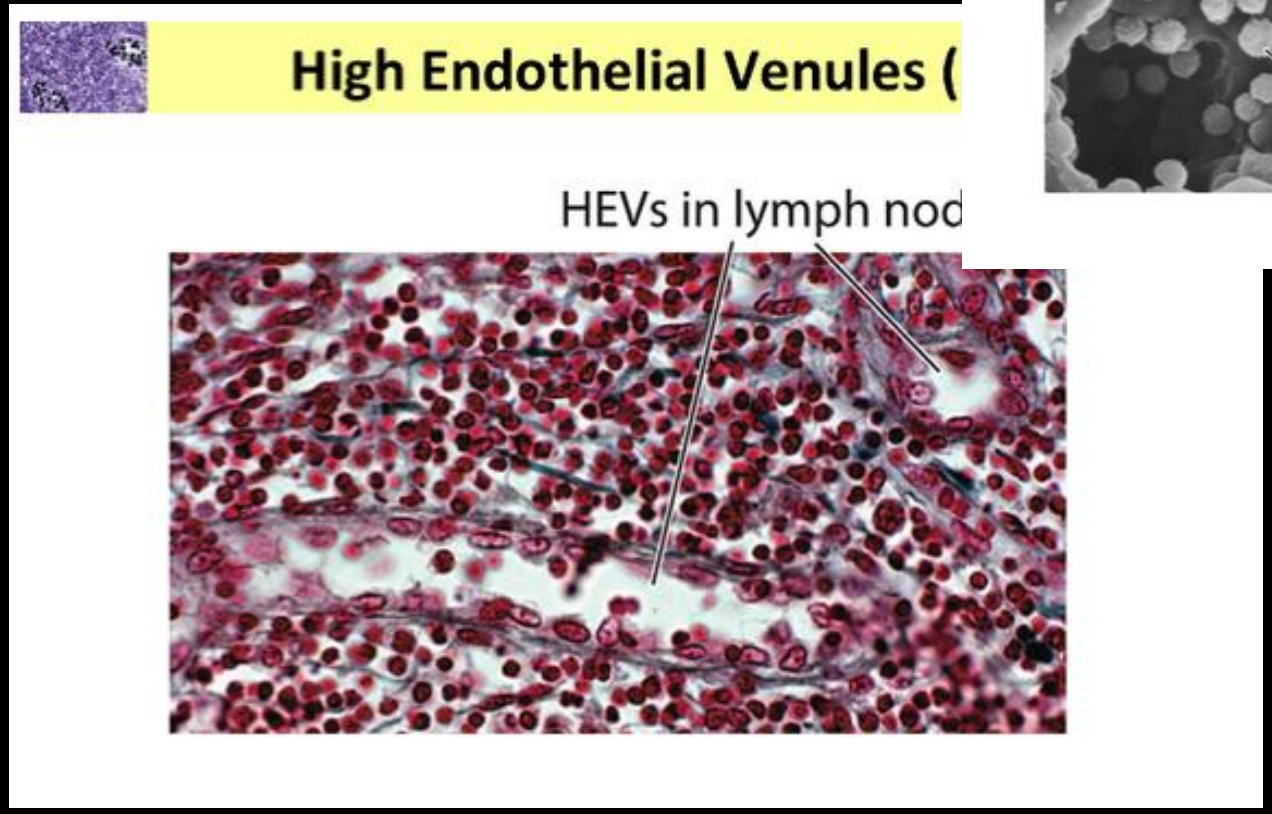
Regiões

Folículo – Linfócitos B e Células dendríticas foliculares

Paracortical – Linfócitos T
70% T CD4
10% T CD8

High endotelial Venules são a porta de entrada dos linfócitos Naive nos linfonodos





Características

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Regiões

Folículo – Linfócitos B e Células dendríticas foliculares

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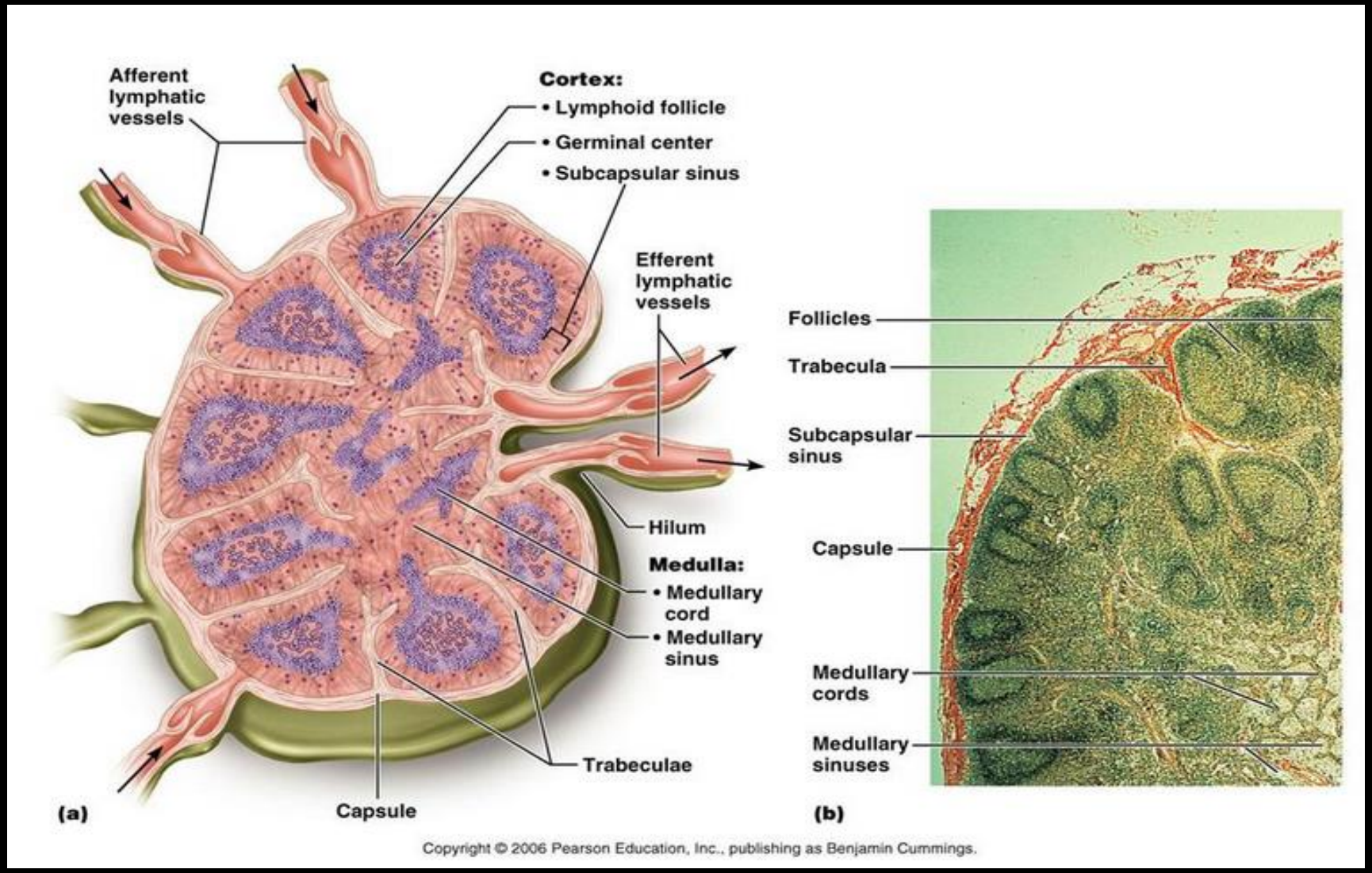
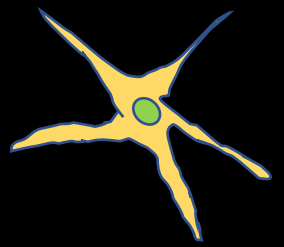
70% T CD4
10% T CD8

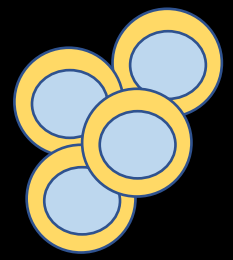
Quais fatores são importantes na manutenção da estrutura dos linfonodos?





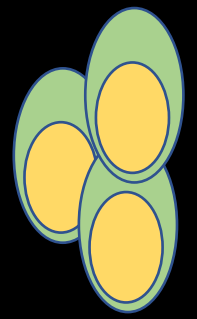
DCs – Carregando Ags

CCR7 – CCL19 e CCL21



T CD4 e T CD8

CCR7 - CCL19 e CCL21



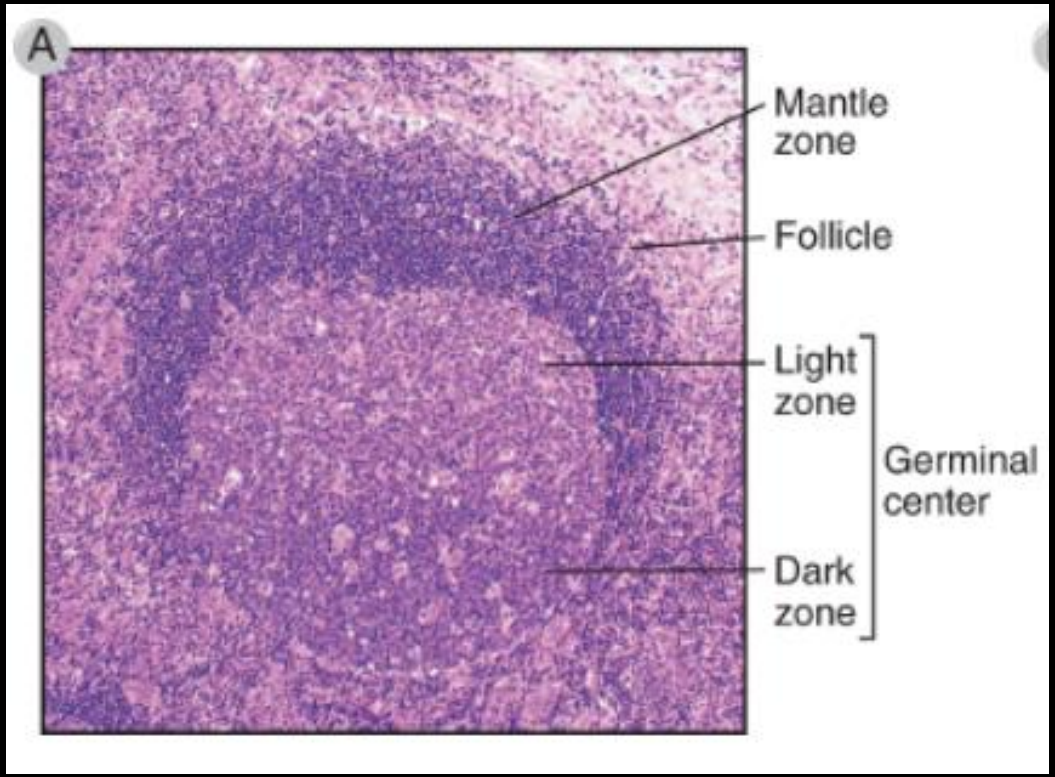
Linfócitos B

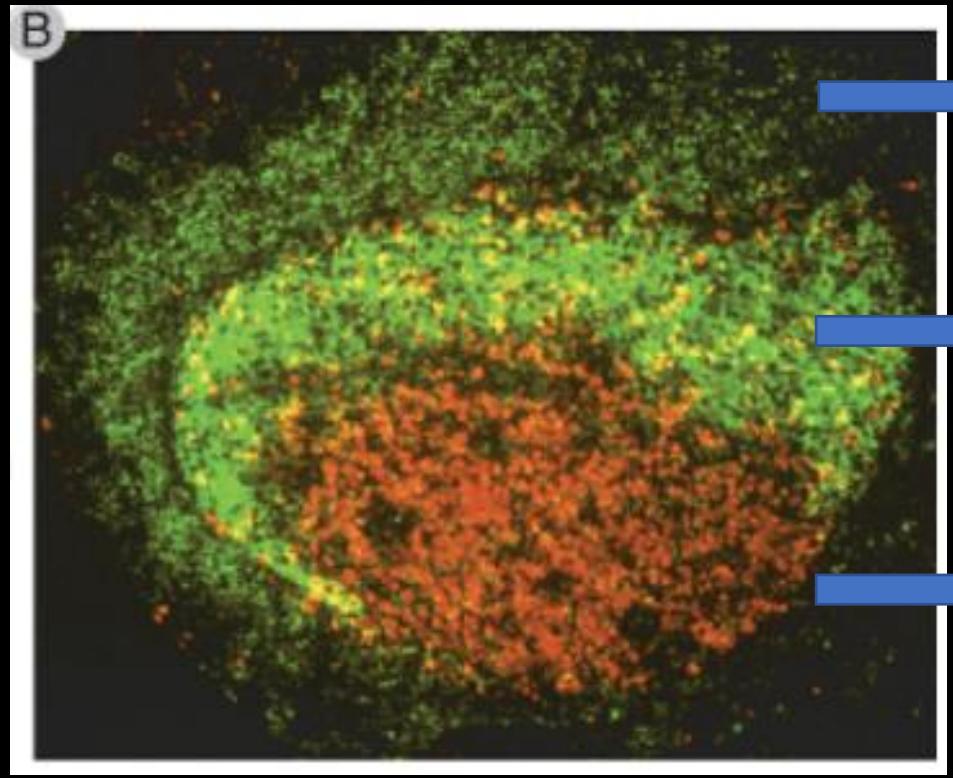
CXCR5 – CXCL13
(DCs foliculares)

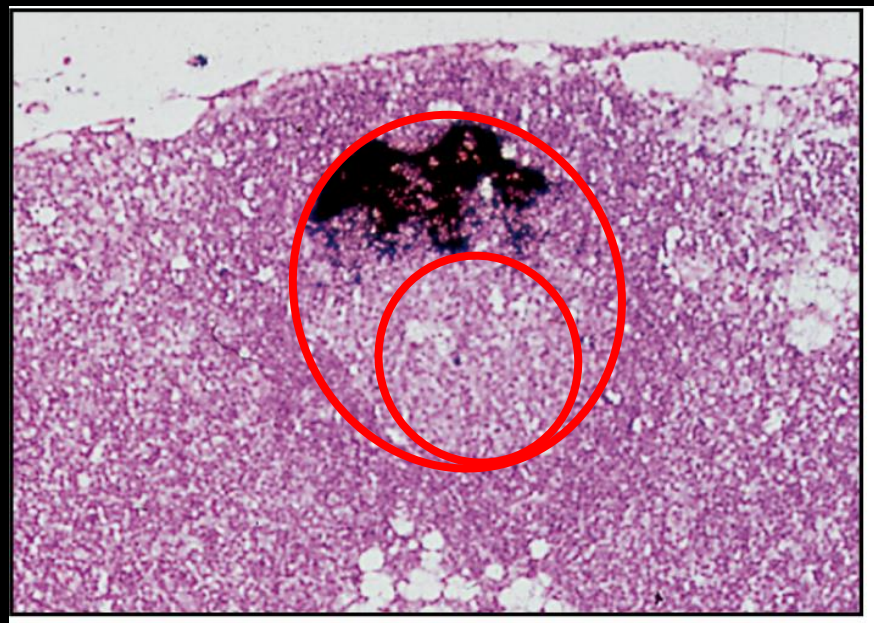
Isso garante que as APCs estejam em contato com os linfócitos apropriados.

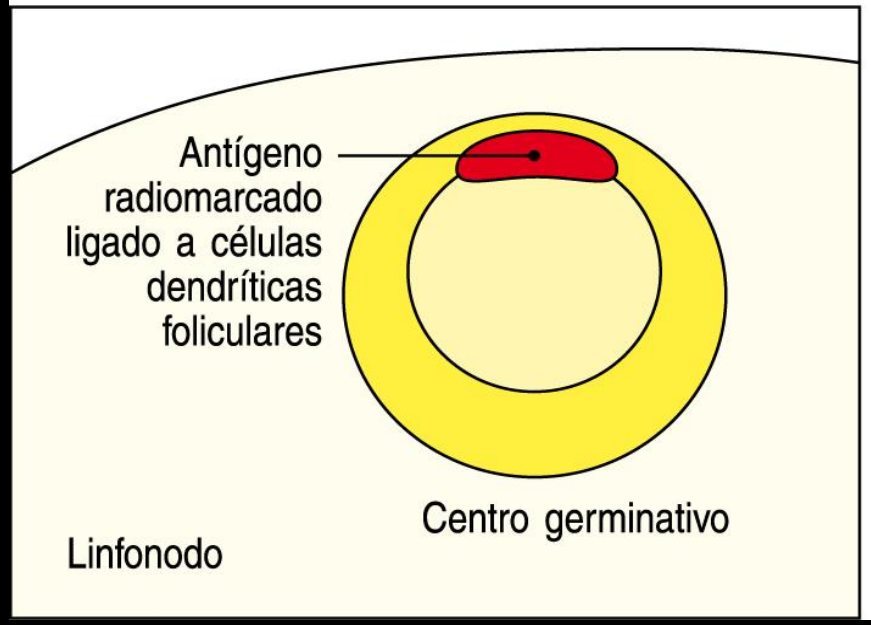
Centros Germinativos – Apresentam 3 regiões distintas

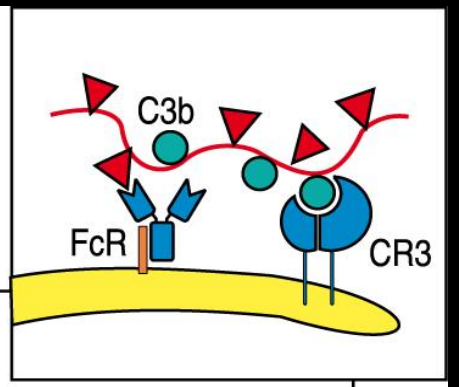
Manto – Linfócitos B não ativados
Zona Clara – Dendríticas foliculares
Zona escura – Linfócitos B ativados e em proliferação

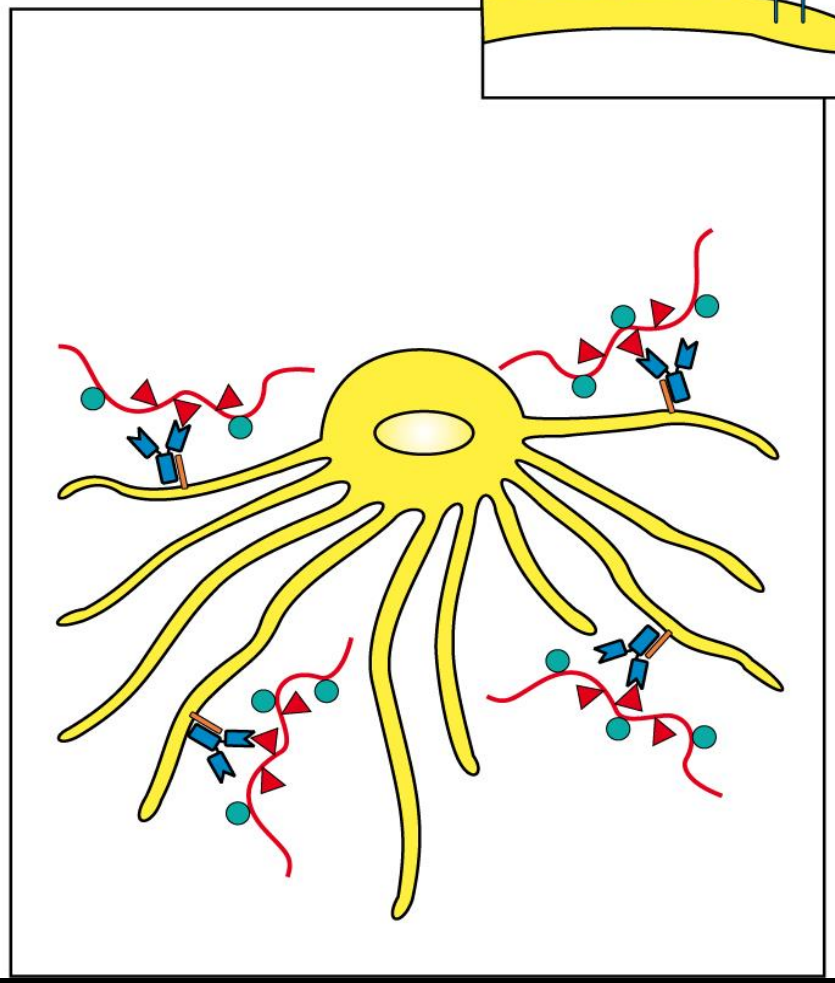












Complexos imunes se ligam à superfície das células dendríticas foliculares.

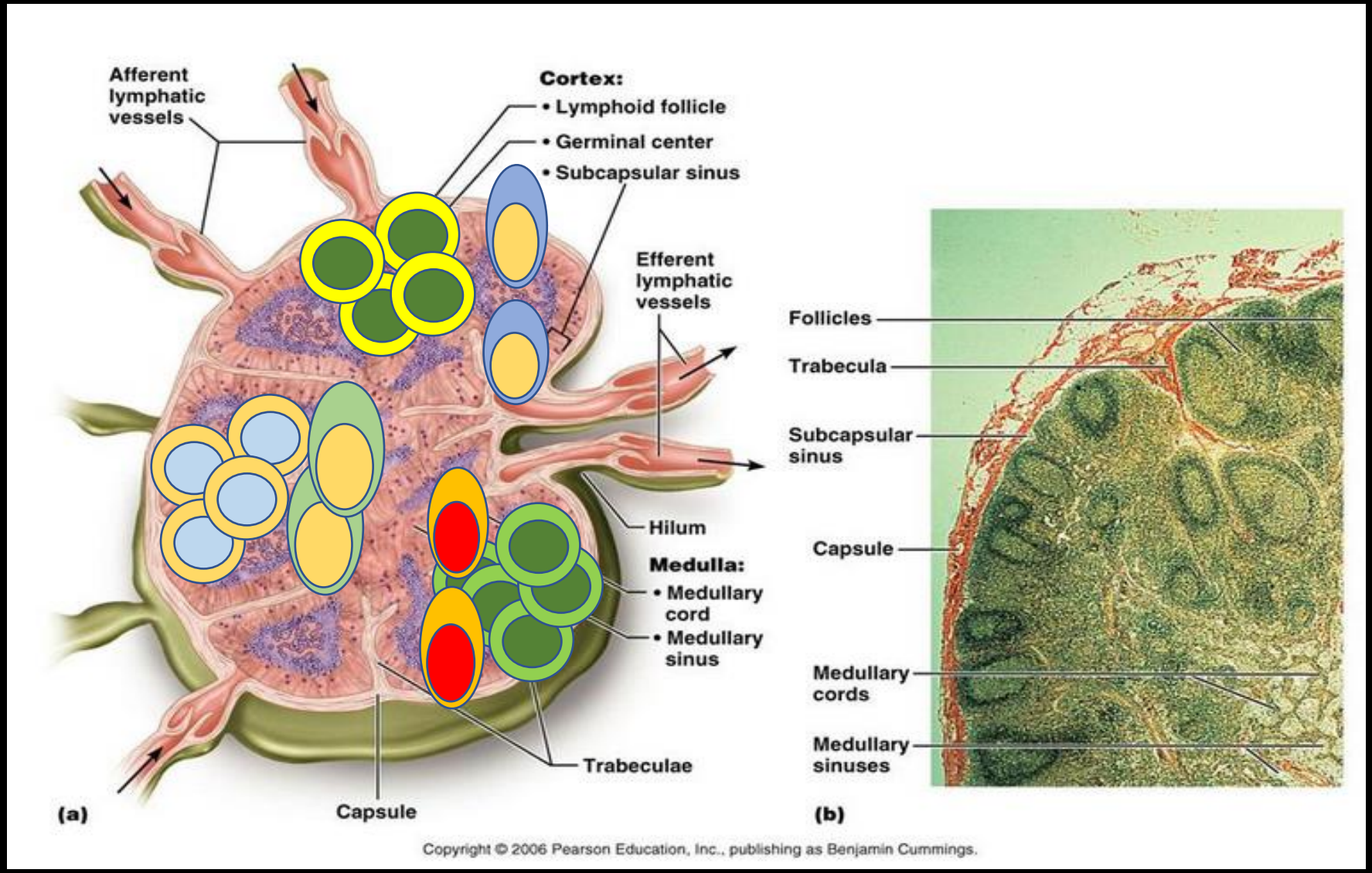
Através de

Receptores de Complemento –

CR2

Receptores FcγR

Estrutura dos Linfonodos



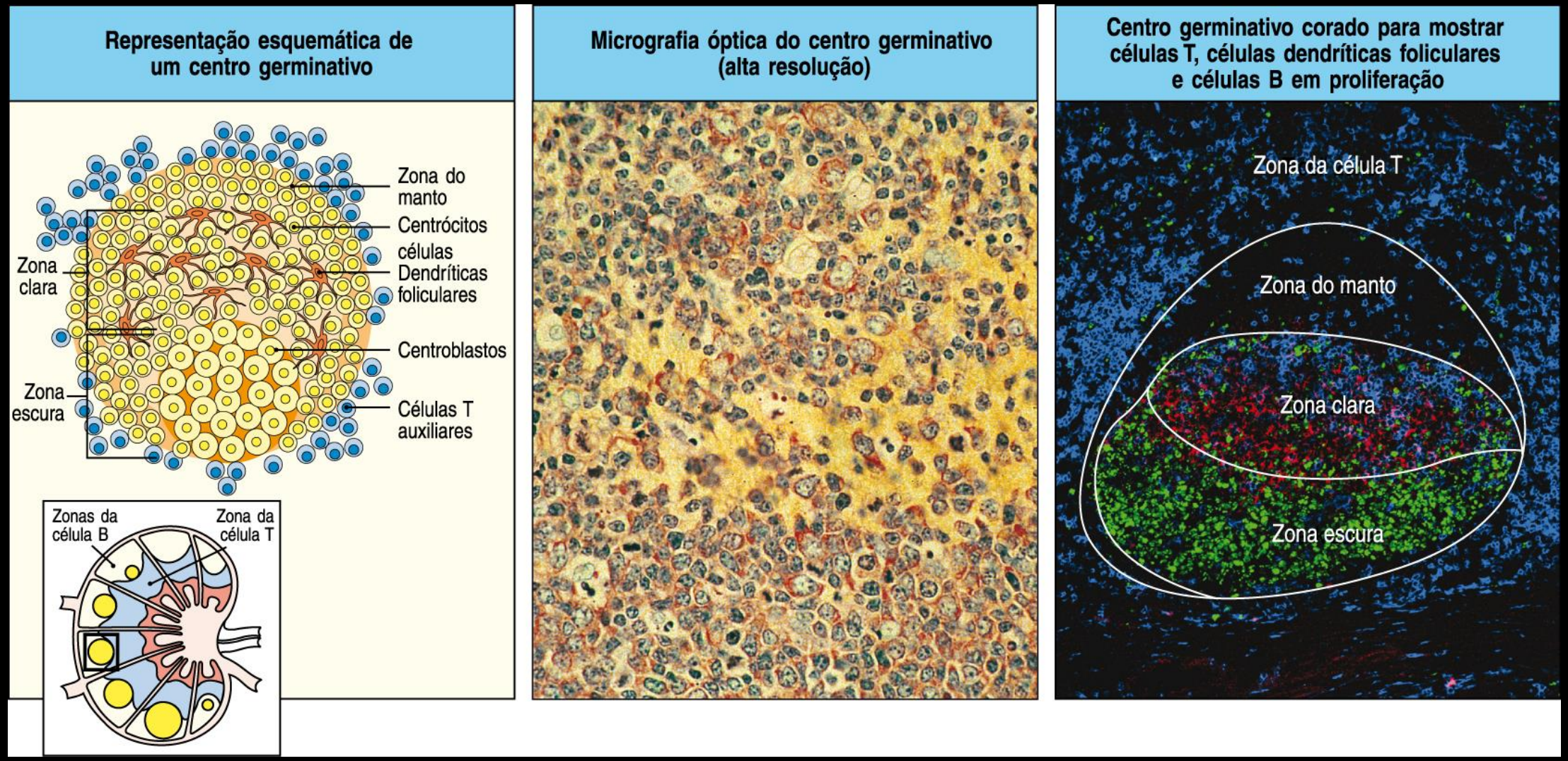


Figura 9.10 Os centros germinativos são formados quando as células B são ativadas nos folículos linfoides.

Mas professor, e no baço, é igual.....??????

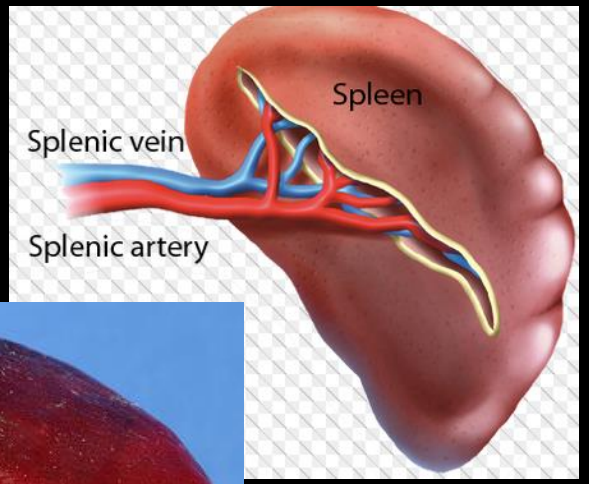
Baço - 150 gramas – Hipocôndrio inferior esquerdo

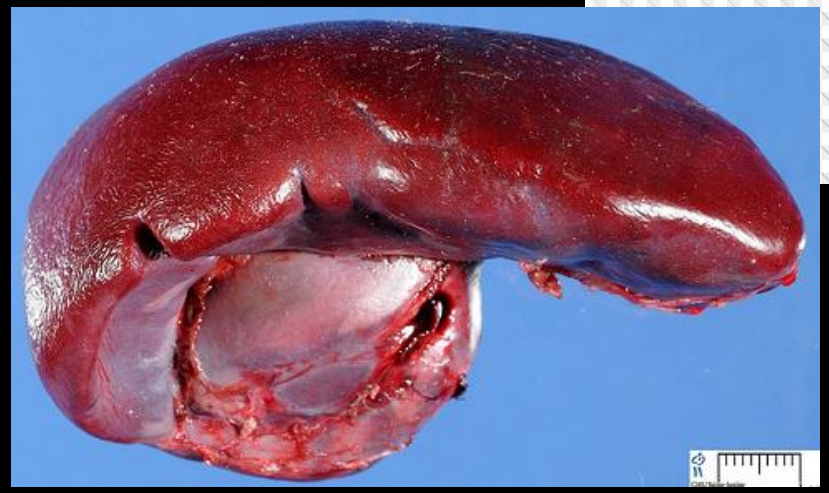
Polpa Branca - Linfócitos

Polpa Vermelha – Macrófagos esplênicos e Eritrócitos

Zona marginal – entre branca e vermelha.
Linfócitos B e Macrófagos

PALs- Bainha Periateriolar
Linfócitos T





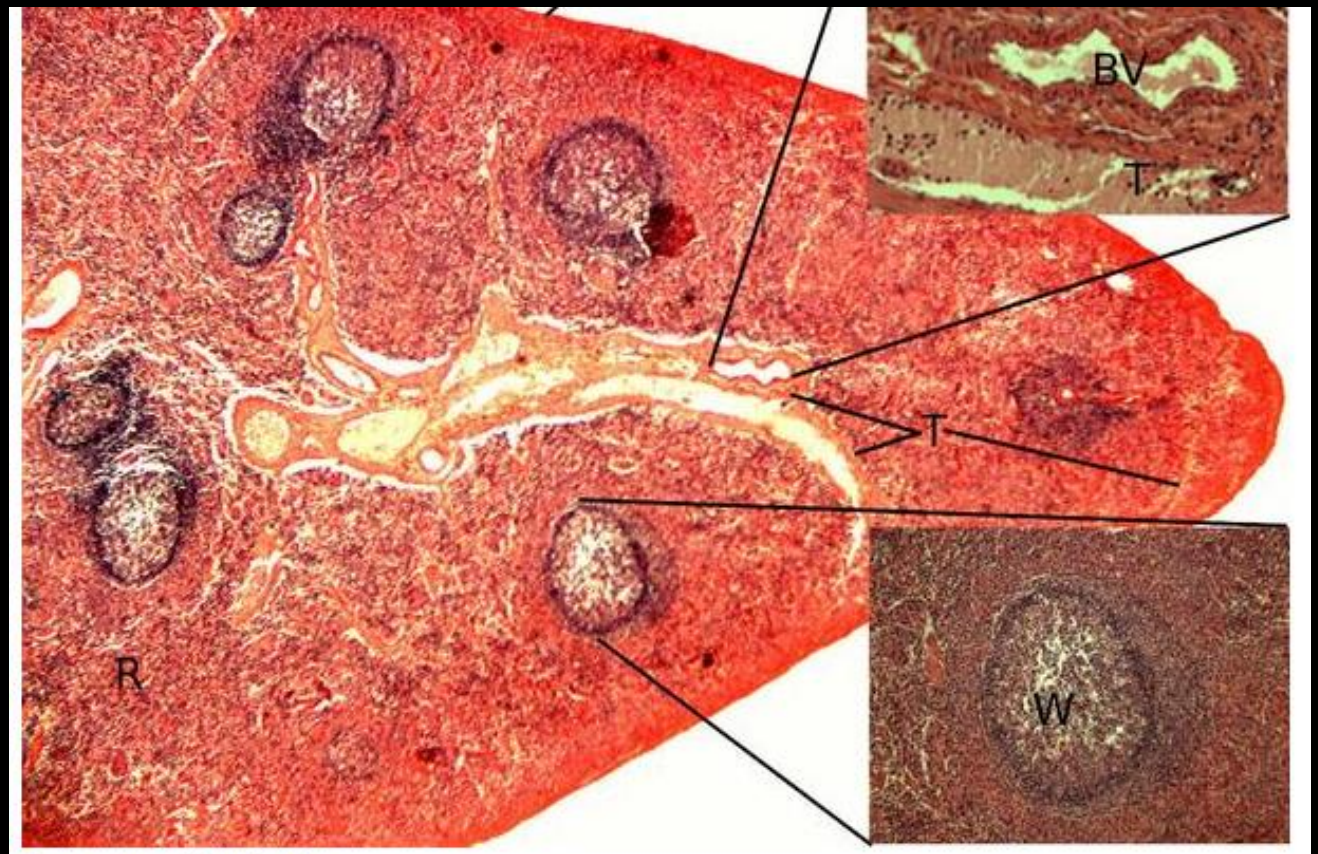
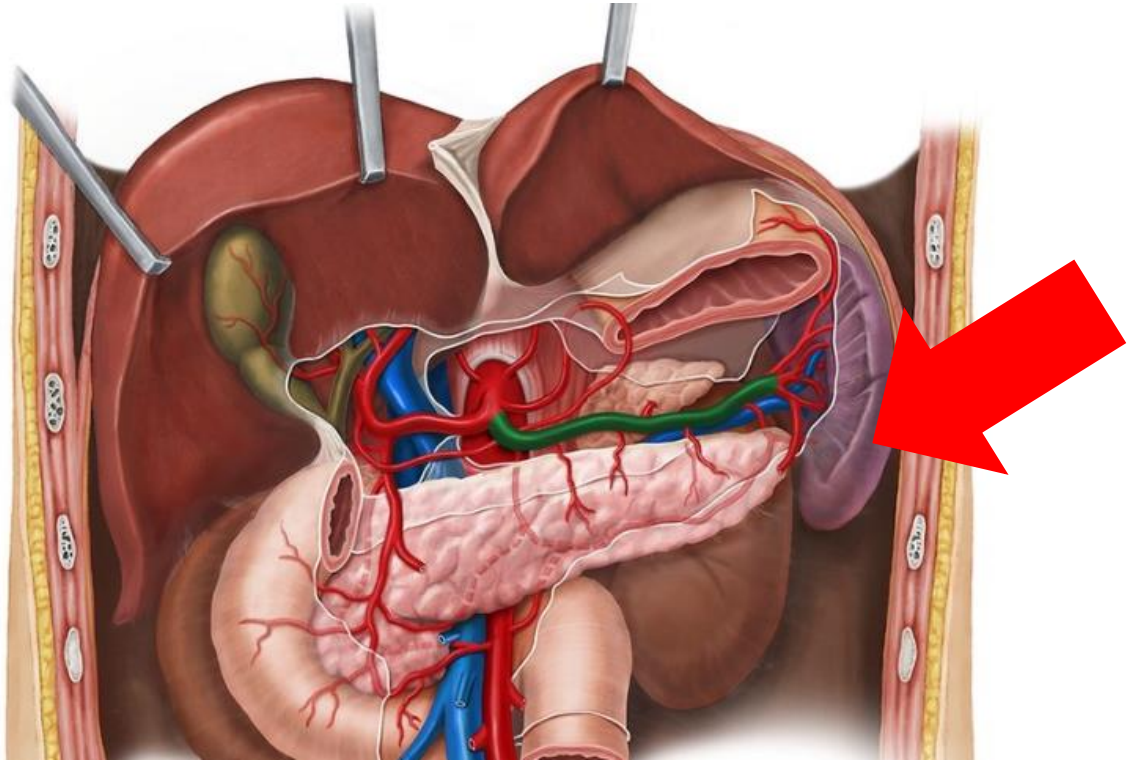
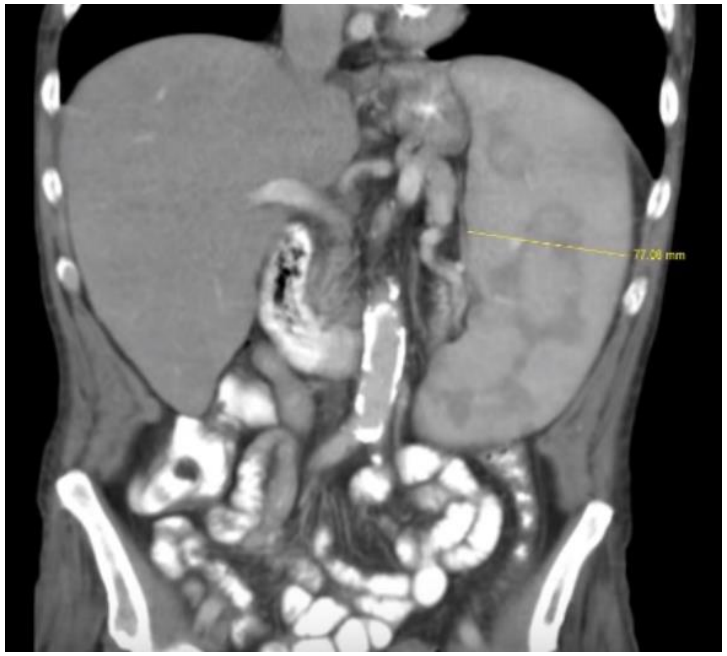


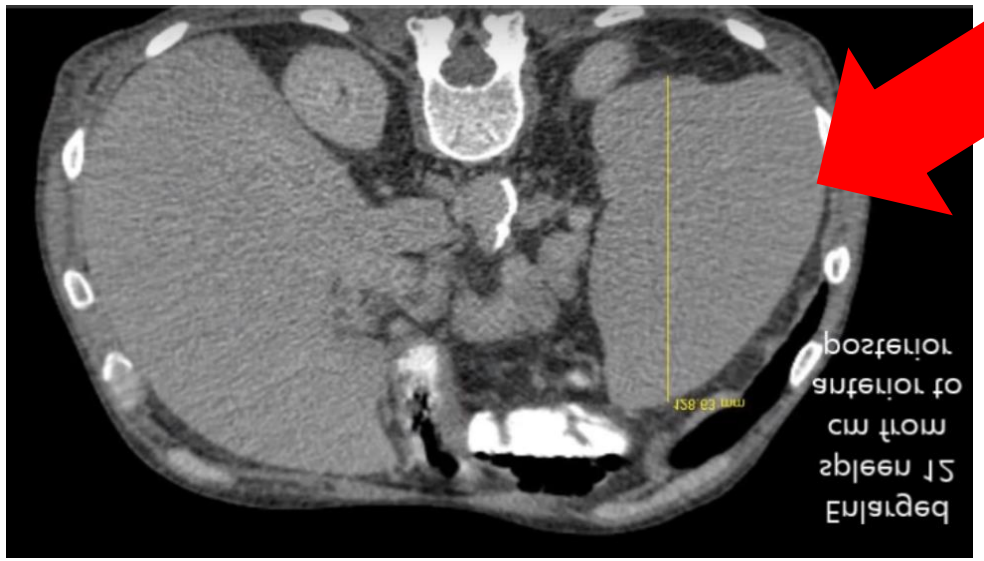
Image magnification 2x
-Top right inset 20x
-Bottom right inset 10x

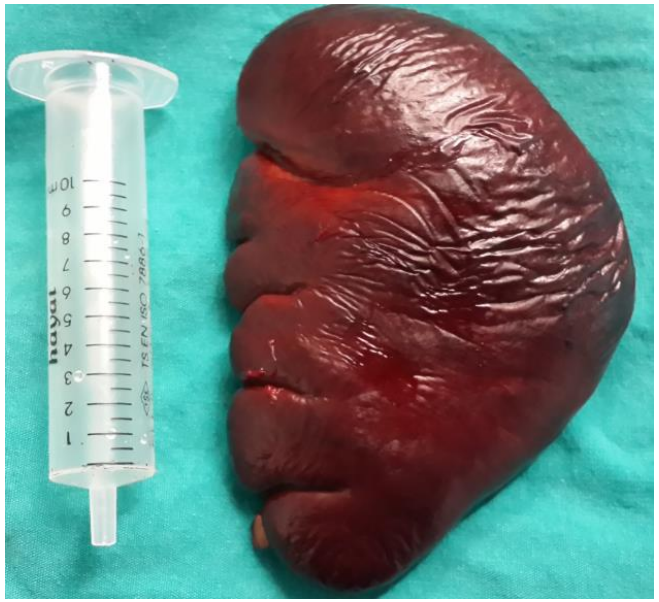
Legend:
C-Capsule
W-White Pulp
R-Red Pulp
BV-Blood Vessel
T-Trabeculae

BAÇO – Filtro do Sangue

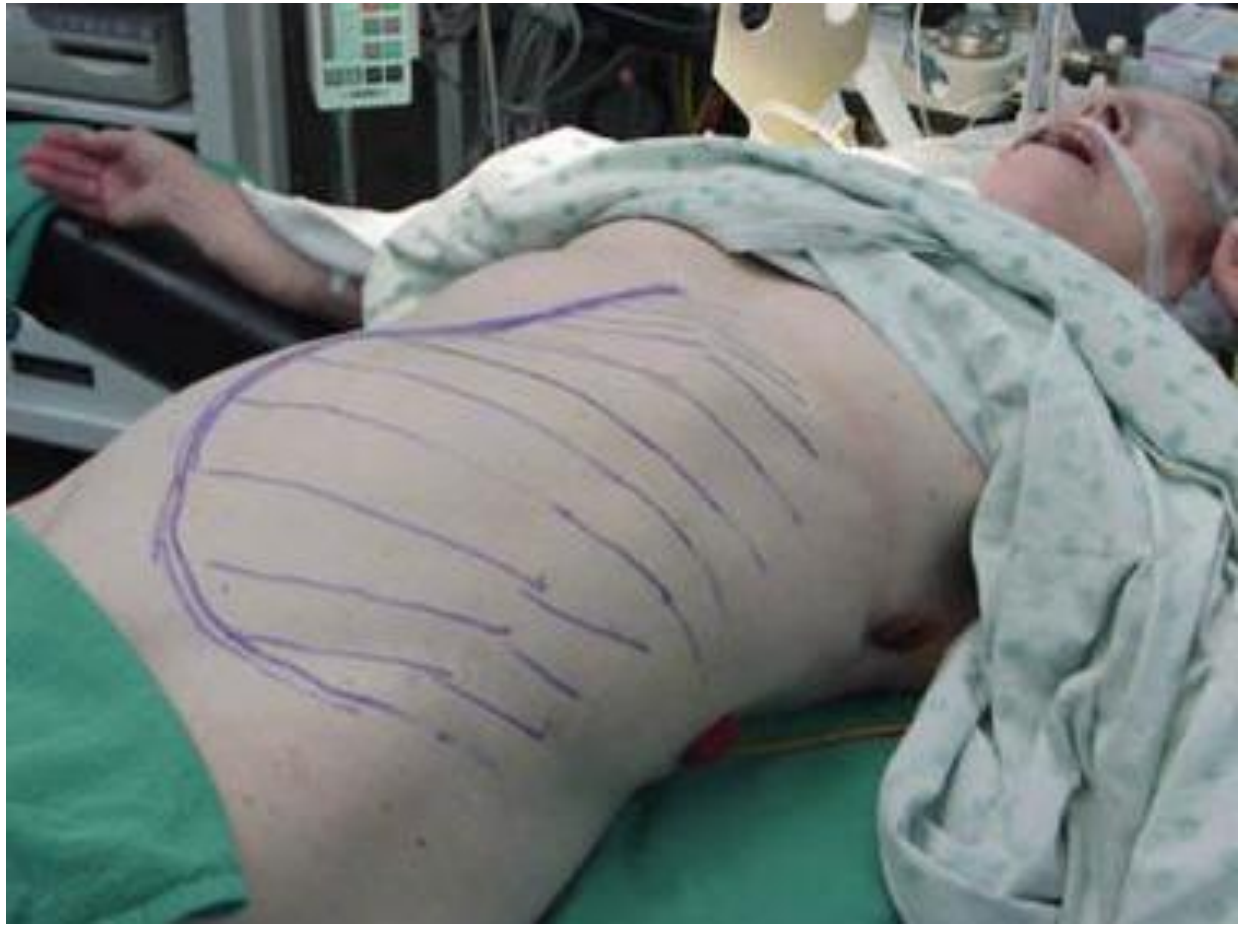


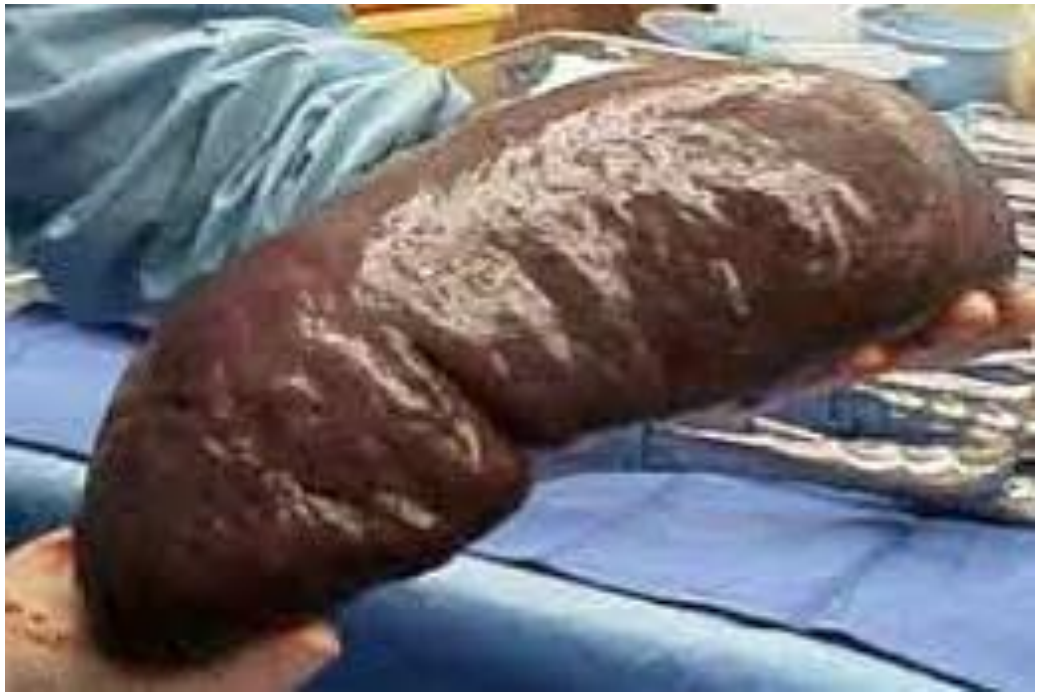


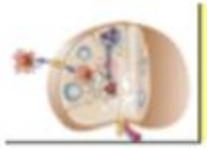




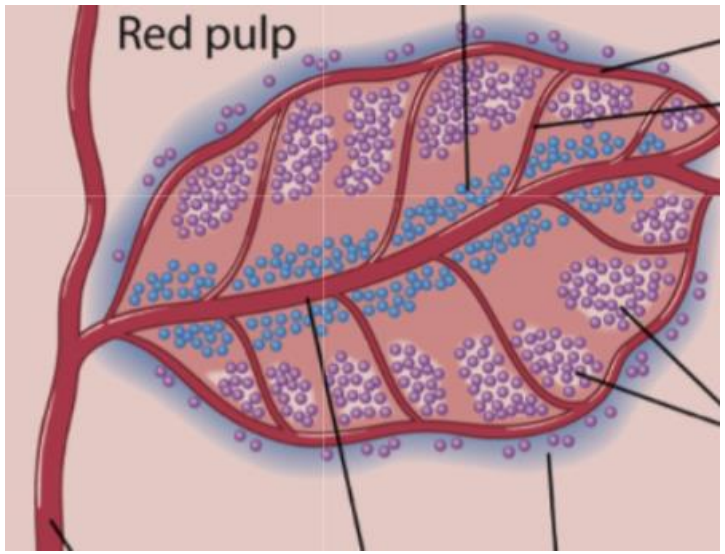
Esplenomegalia – Hiperproliferação de Células Esplênicas

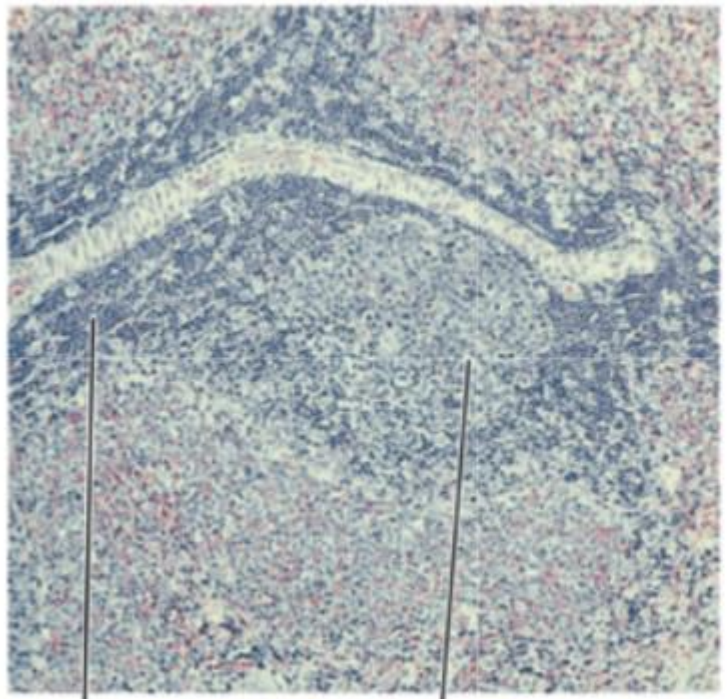






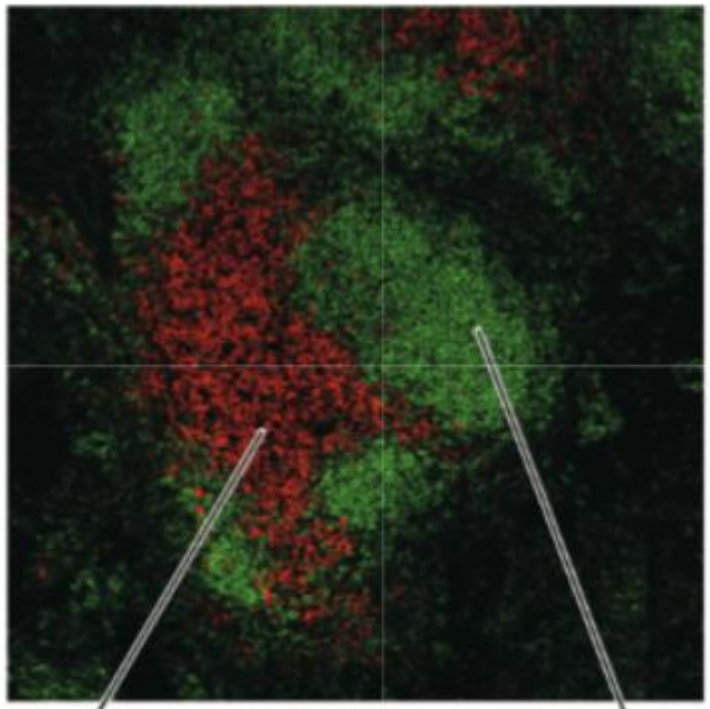
Morphology of the Spleen (2)





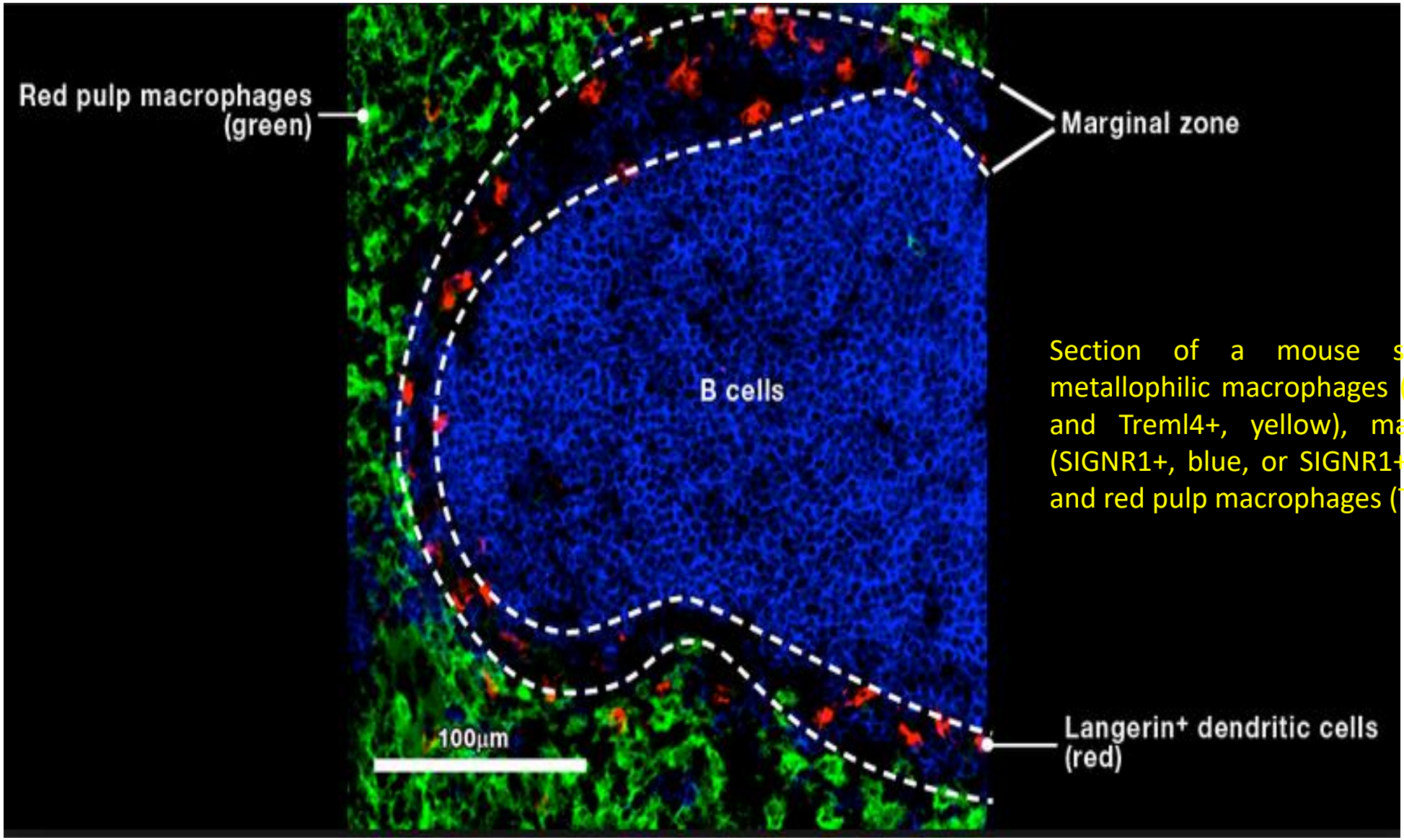
Periarteriolar lymphoid sheath(PALS)

Germinal center of lymphoid follicle



T cell zone (periarteriolar lymphoid sheath)

B cell zone (lymphoid follicle)



Section of a mouse spleen showing marginal metallophilic macrophages (CD169+, green, or CD169+ and Treml4+, yellow), marginal zone macrophages (SIGNR1+, blue, or SIGNR1+ and Treml4v+, light blue), and red pulp macrophages (Treml4

Mas como os linfócitos saem dos linf.....

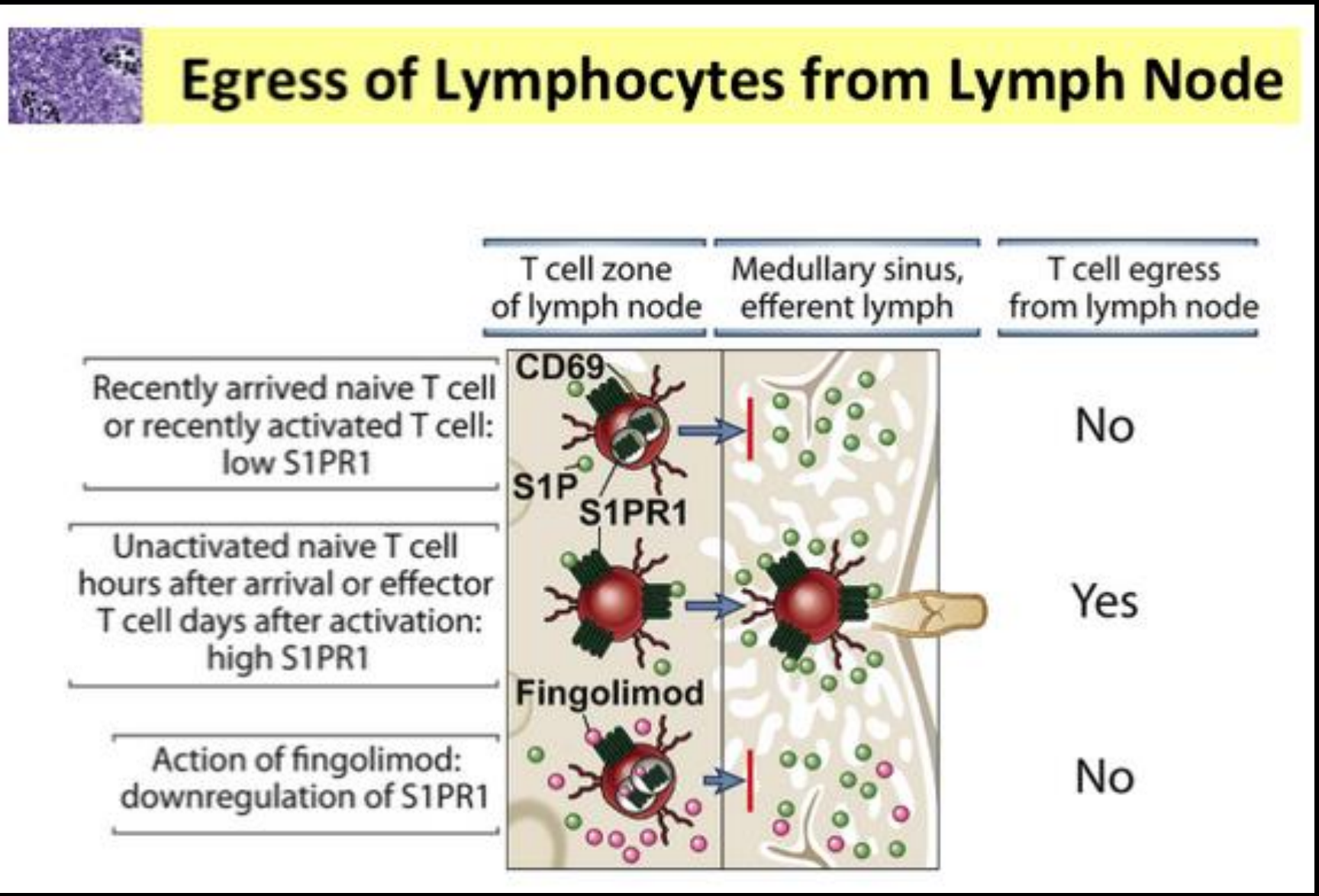
Esfingosina -1- fosfato

Maior concentração na linfa e no sangue
Menor nos tecidos, pois
Estes possuem S1P Liase

Ativação do S1PR induz migração dos linfócitos em direção ao gradiente, ou seja, para fora dos linfonodos.

Linfócitos expressam menos S1PR na circulação, devido ao turnover do receptor

Nos linfonodos porém, essa expressão retorna em algumas horas, permitindo a interação deste com as APCs

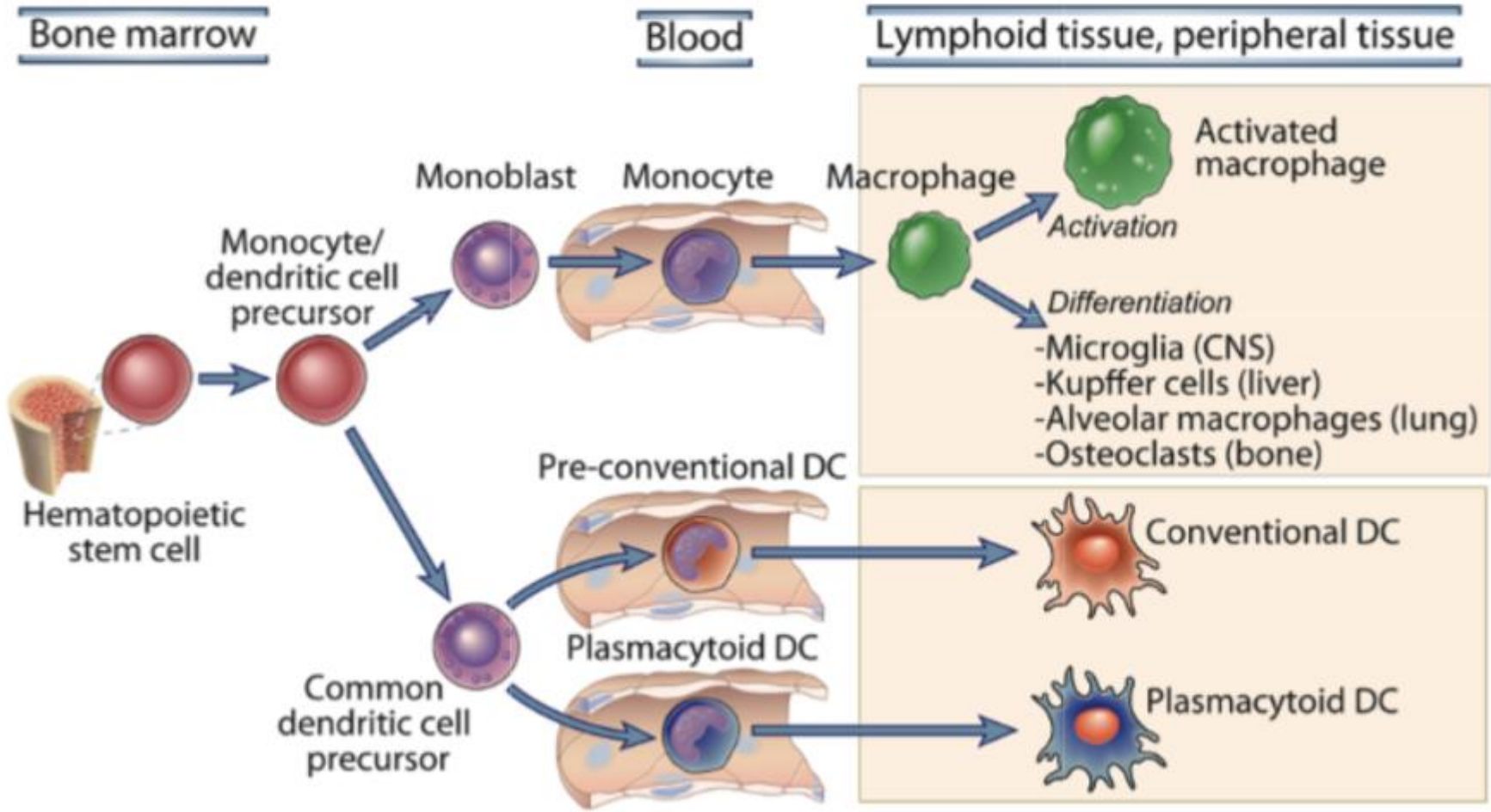


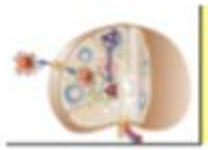
Fingolimod

Liga no S1PR e induz sua internalização
Isso impede sua saída dos linfonodos

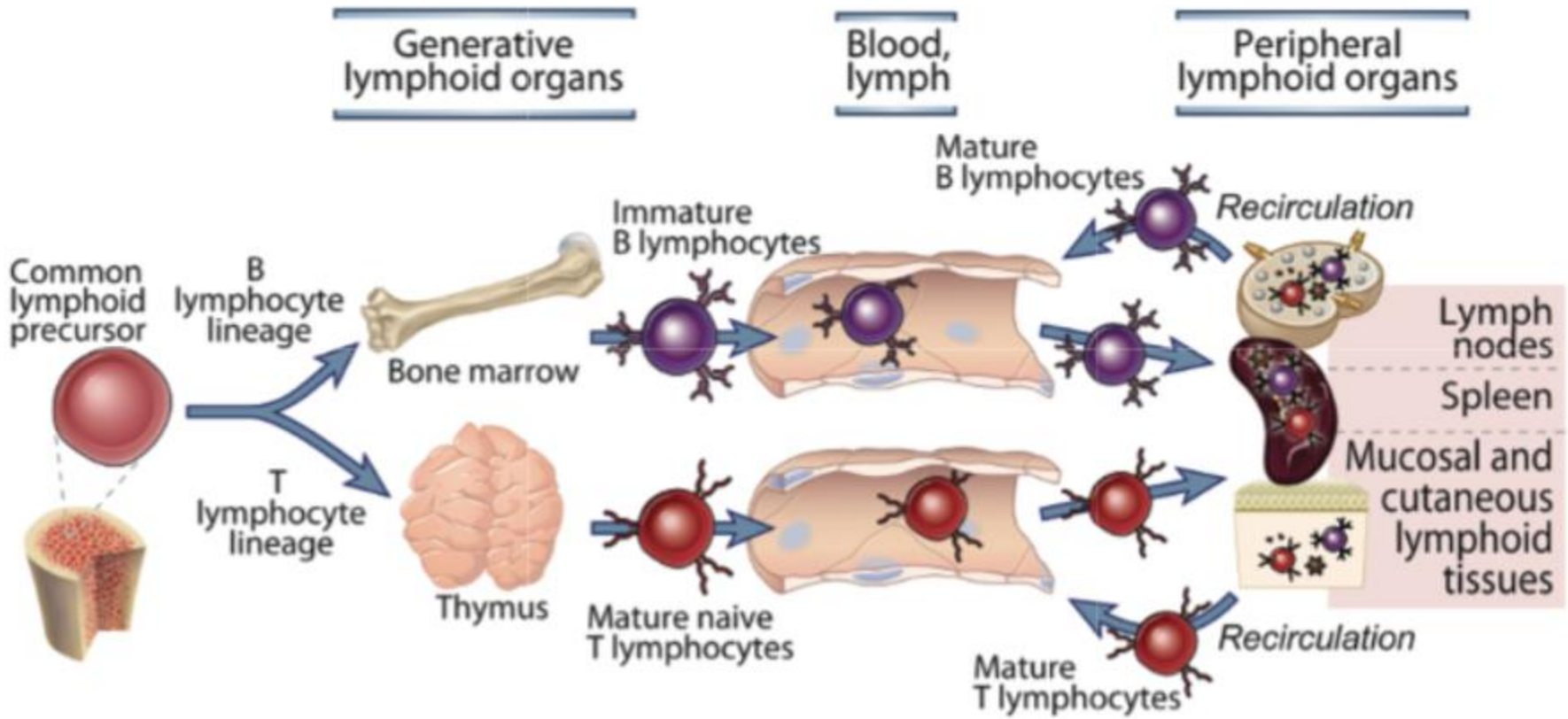
Esclerose ´Múltipla

Maturation of Macrophages and DCs

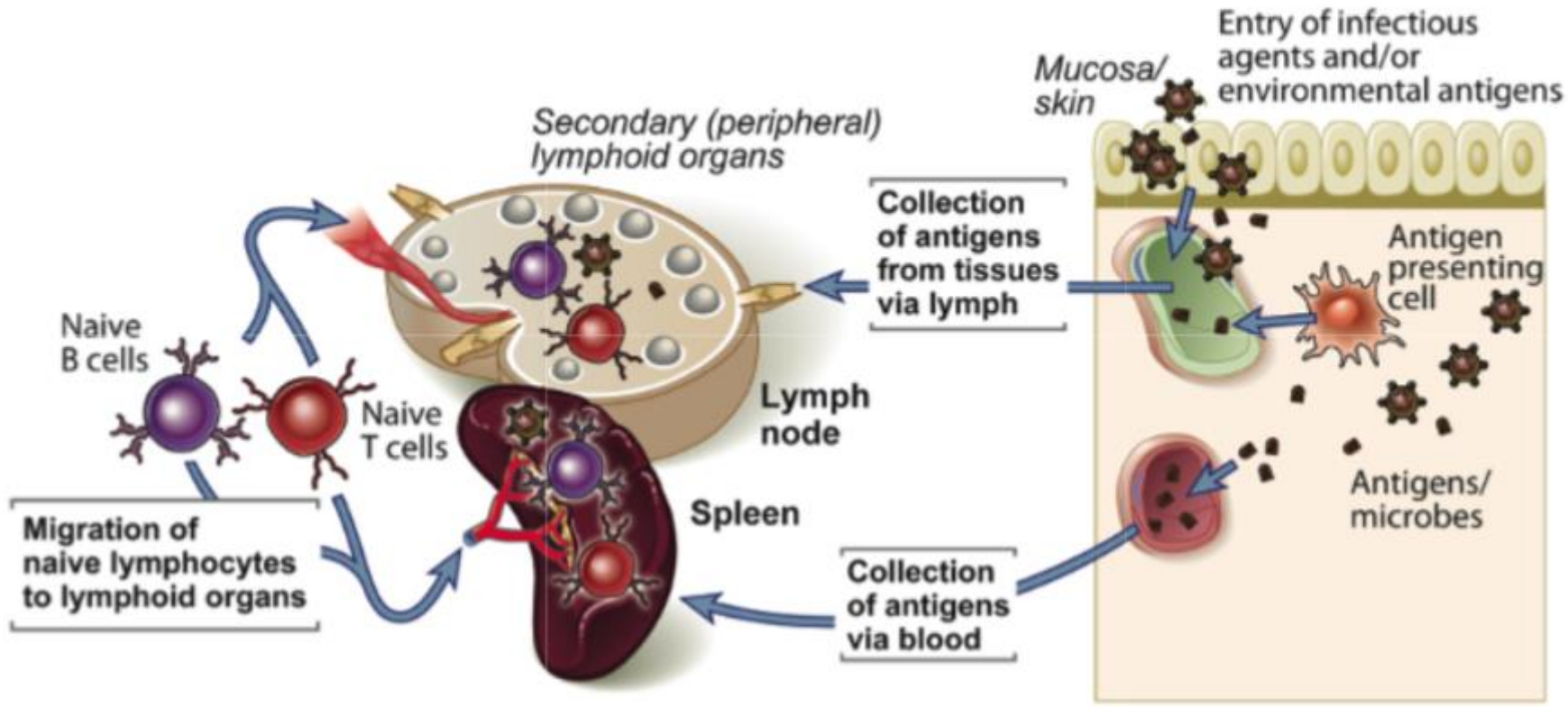


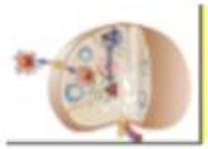


Maturation of Lymphocytes

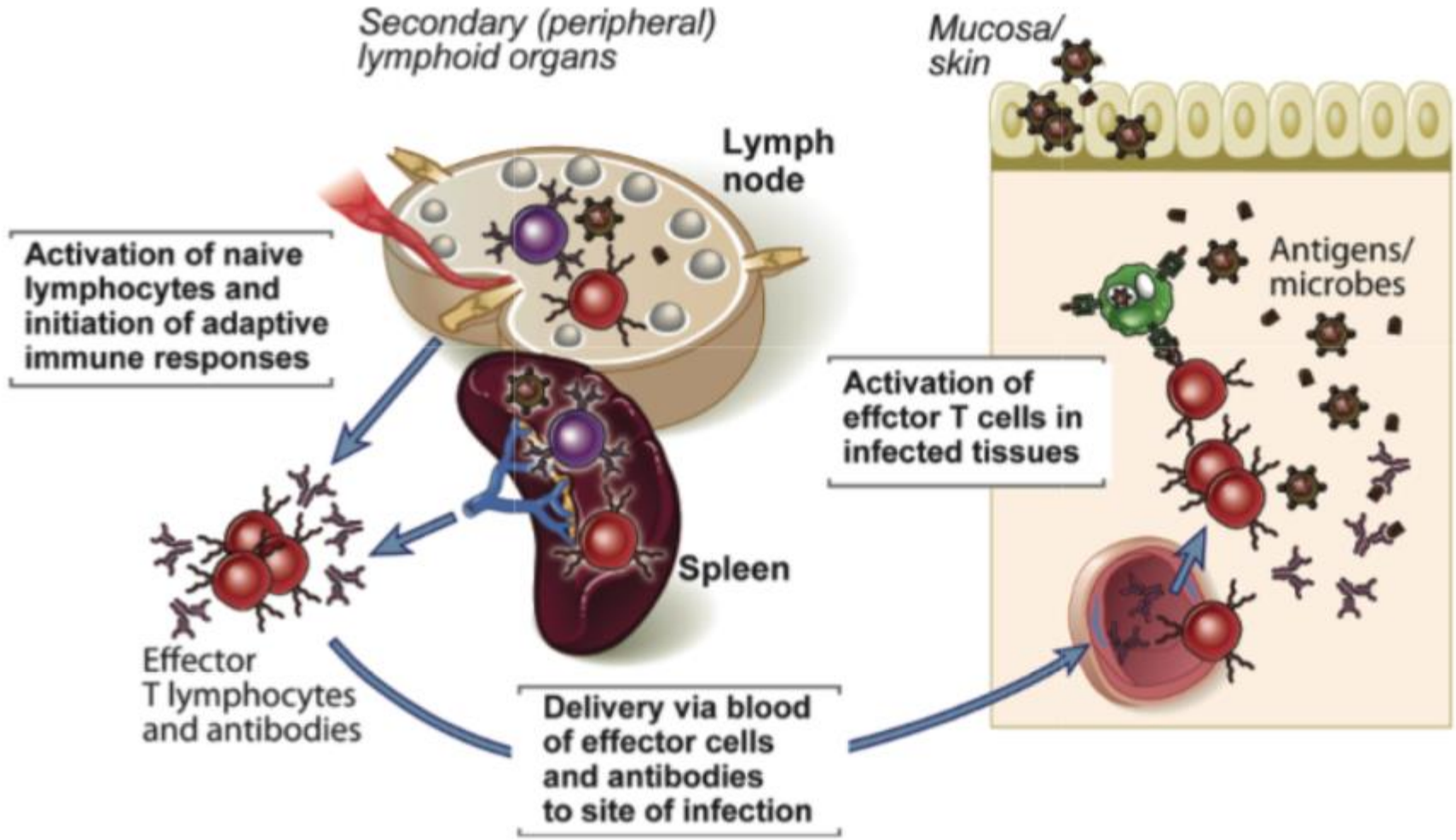


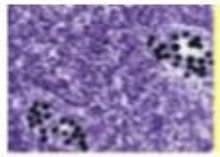
Anatomy of Lymphocyte Activation (1)





Anatomy of Lymphocyte Activation (2)





T lymphocyte Recirculation

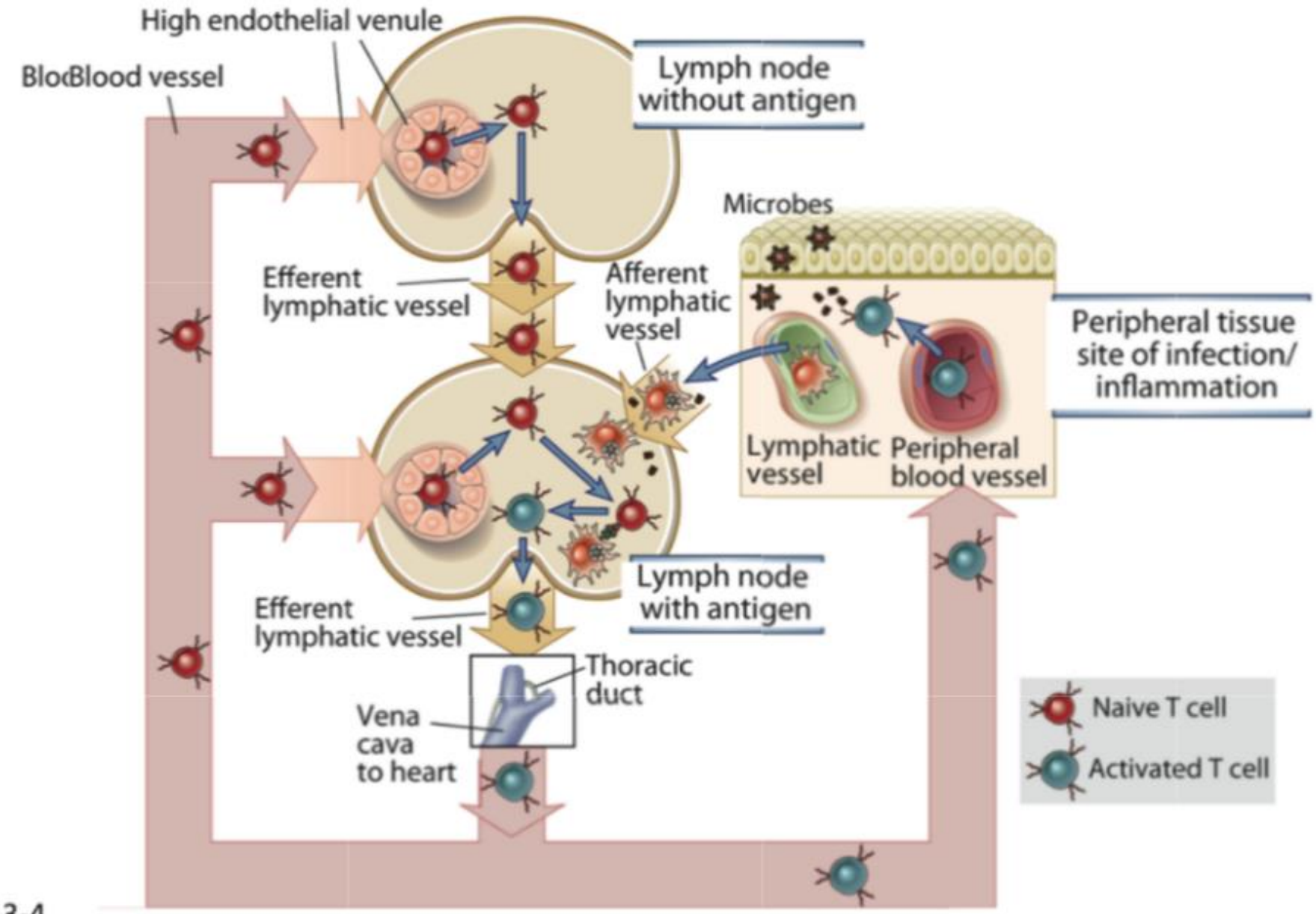
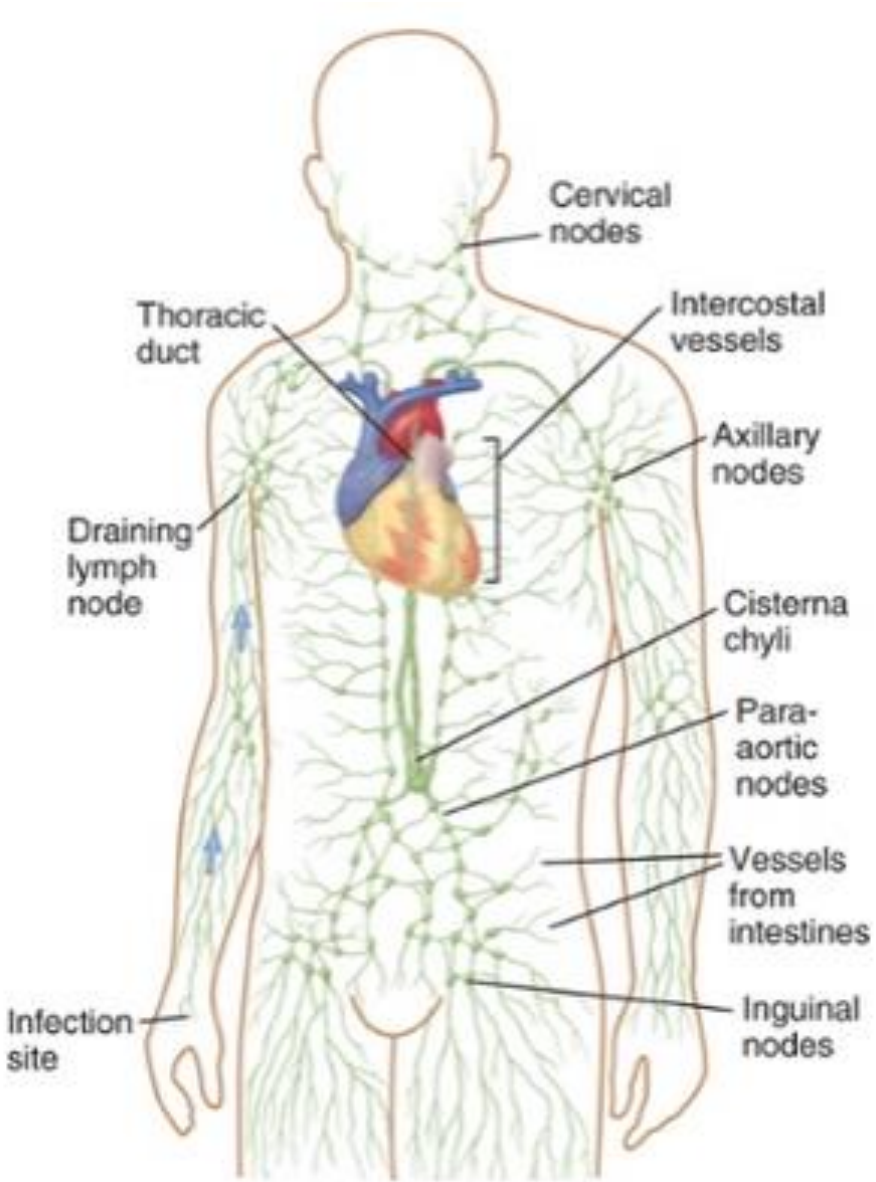
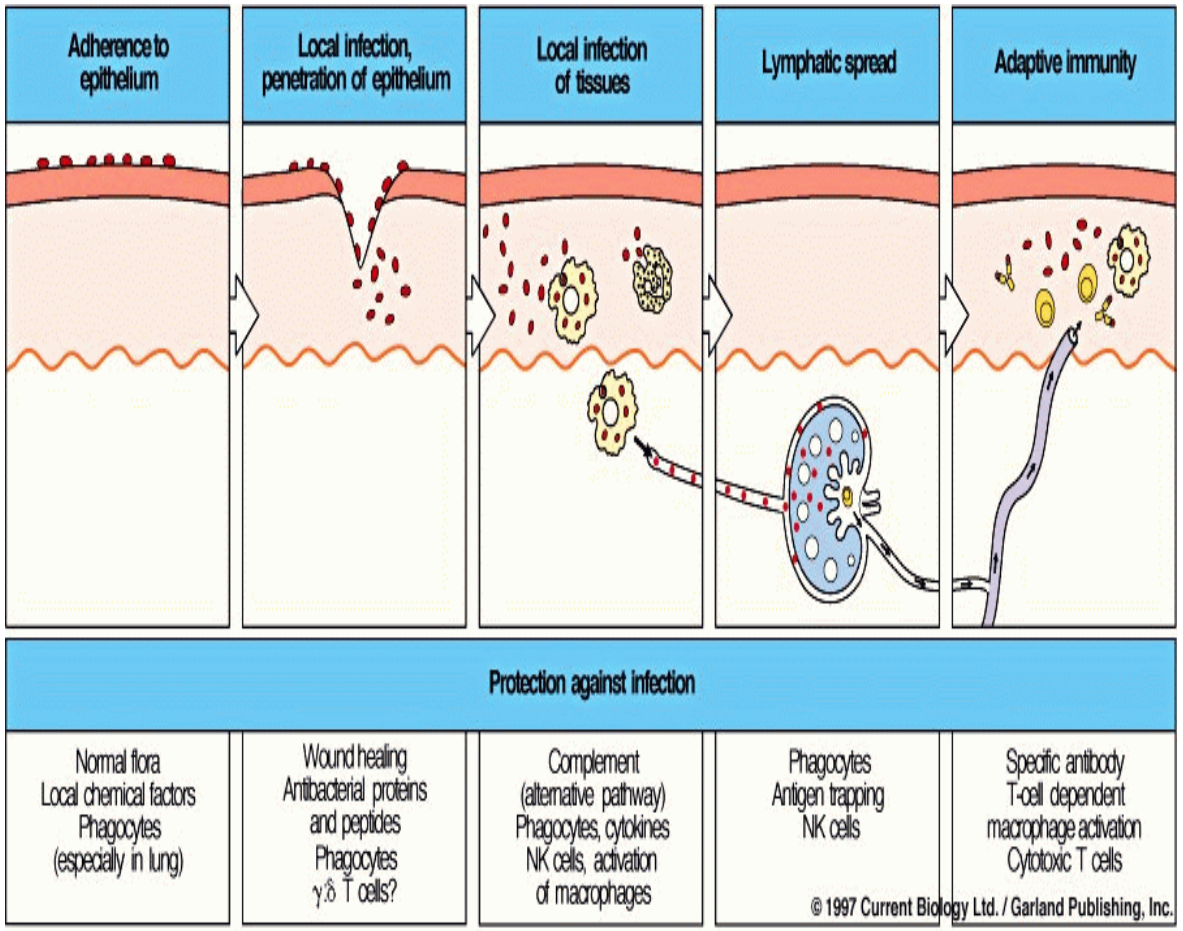


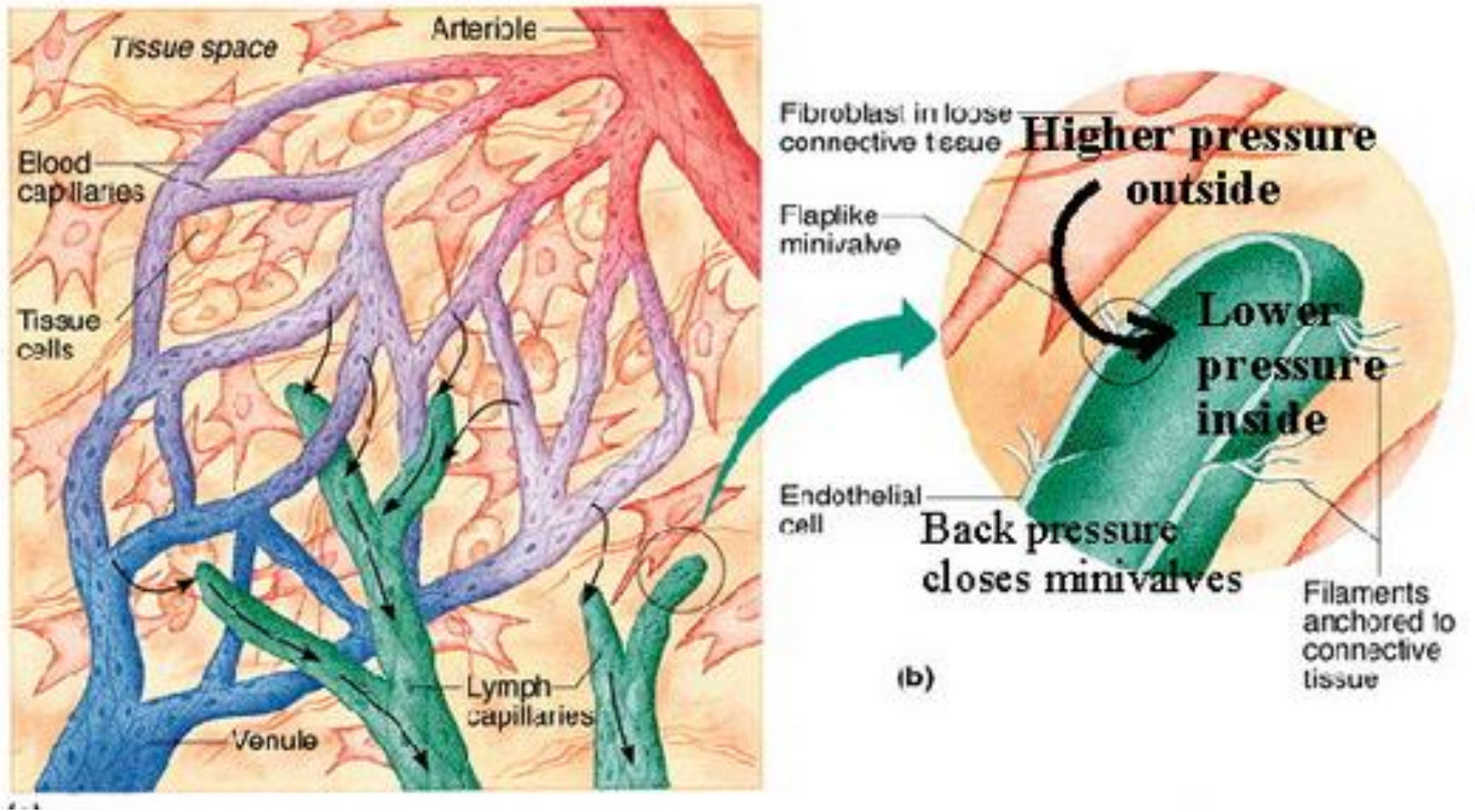
Fig. 3-4

Fisiologia da Resposta Imune

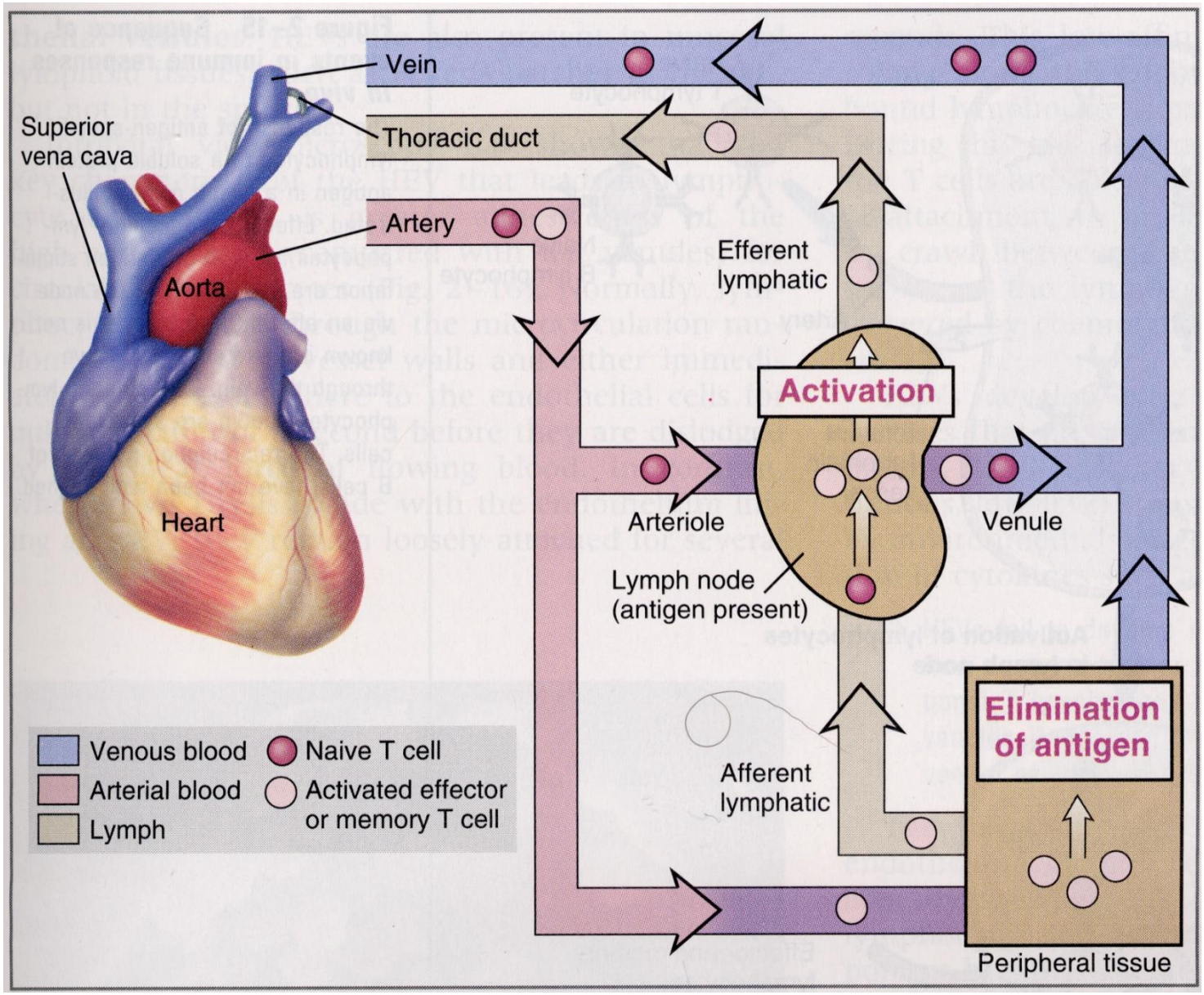




Drenagem do Líquido Intersticial



Recirculação Linfócitária



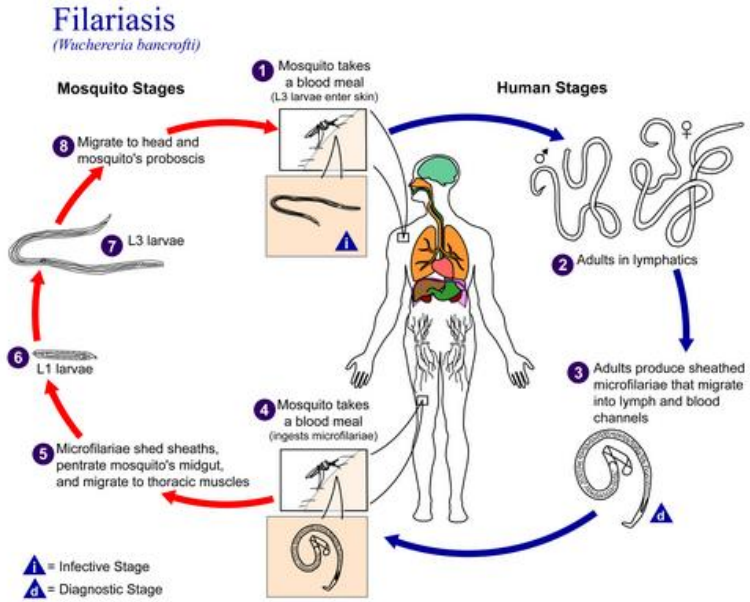
Duto Torácico

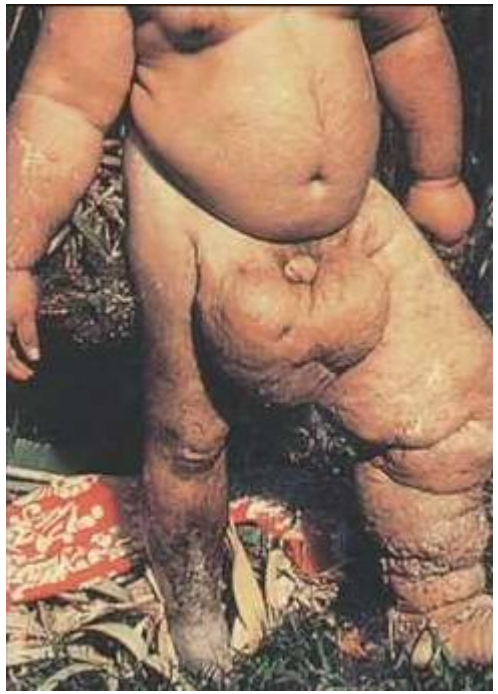
Desemboca da Veia

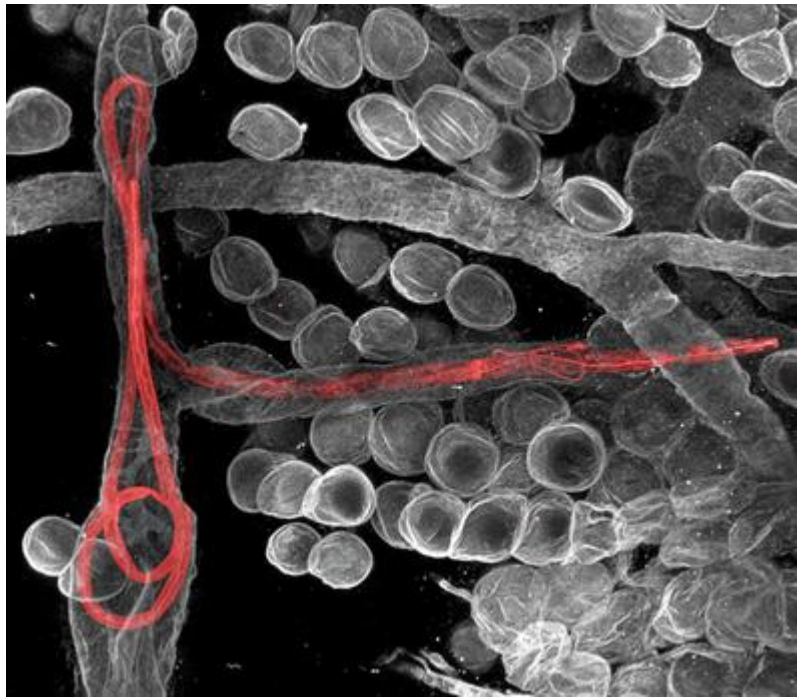
Cava Superior

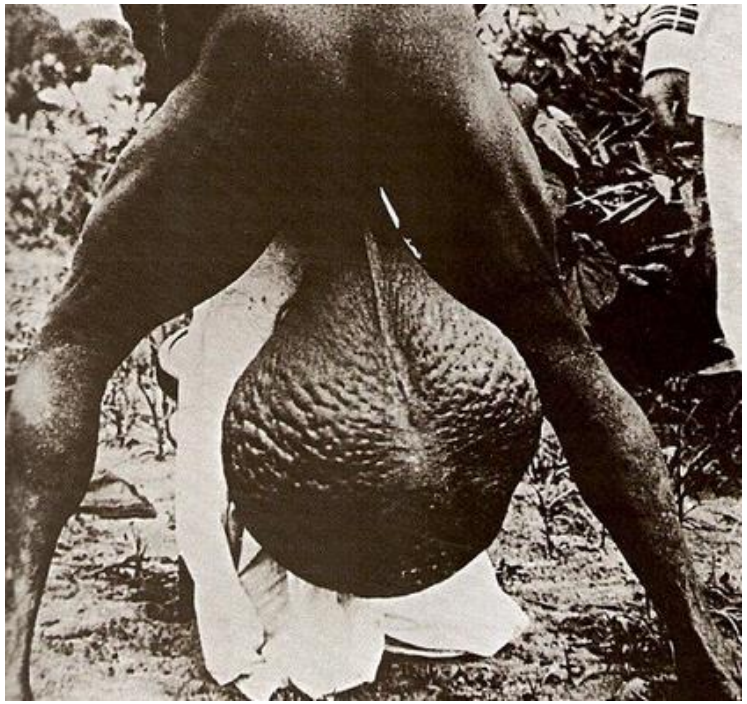
Fechando o Circuito

Filariose
Filárias se acumulam nos linfáticos

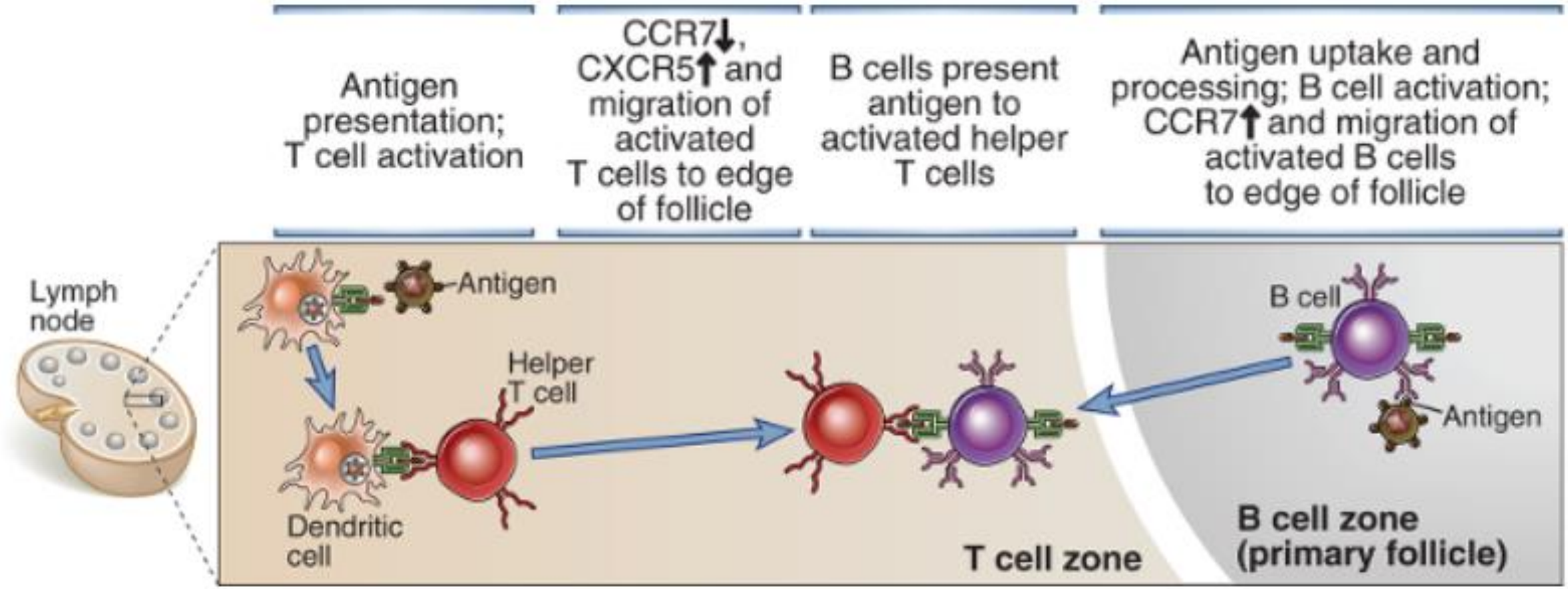


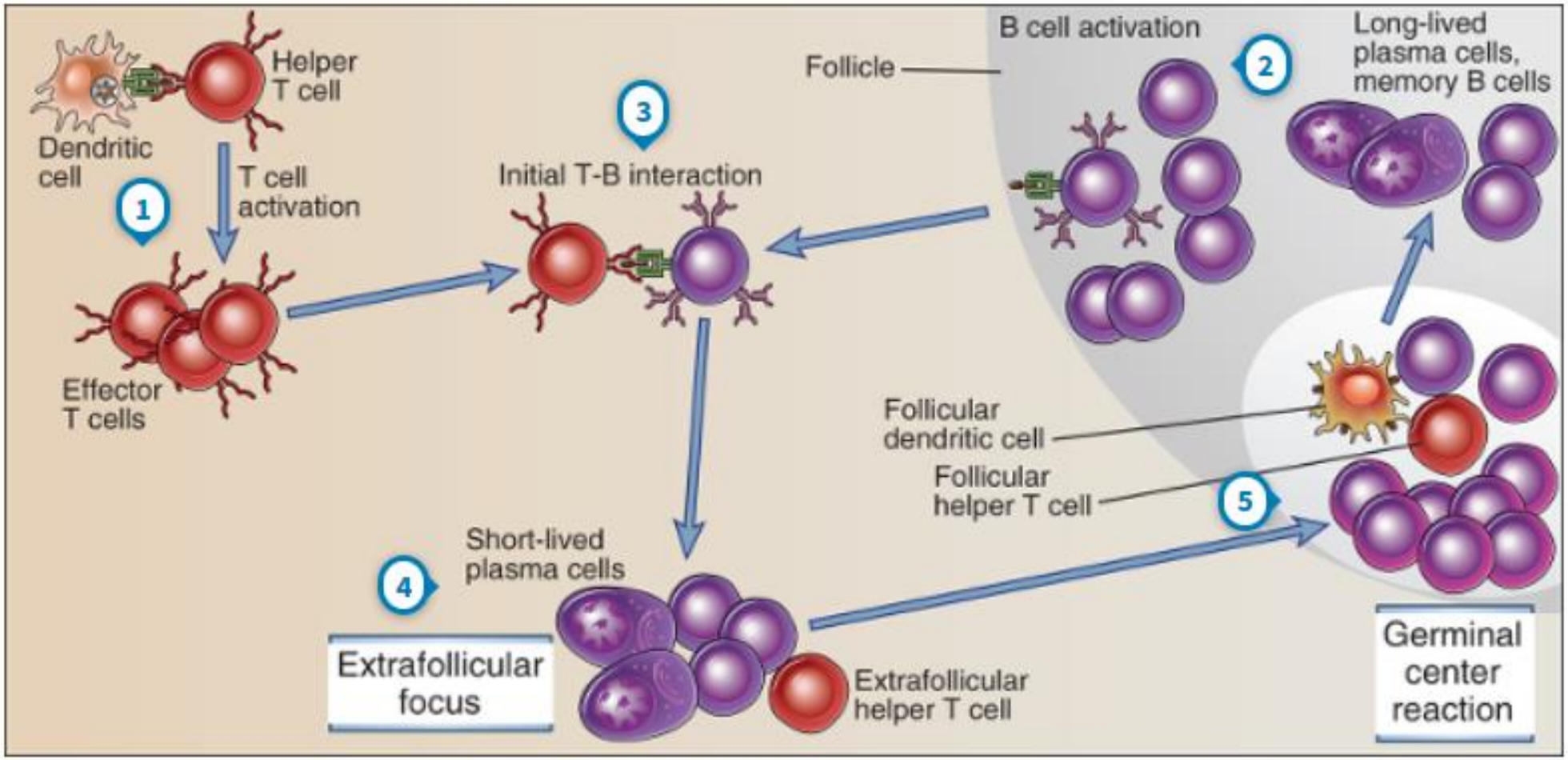


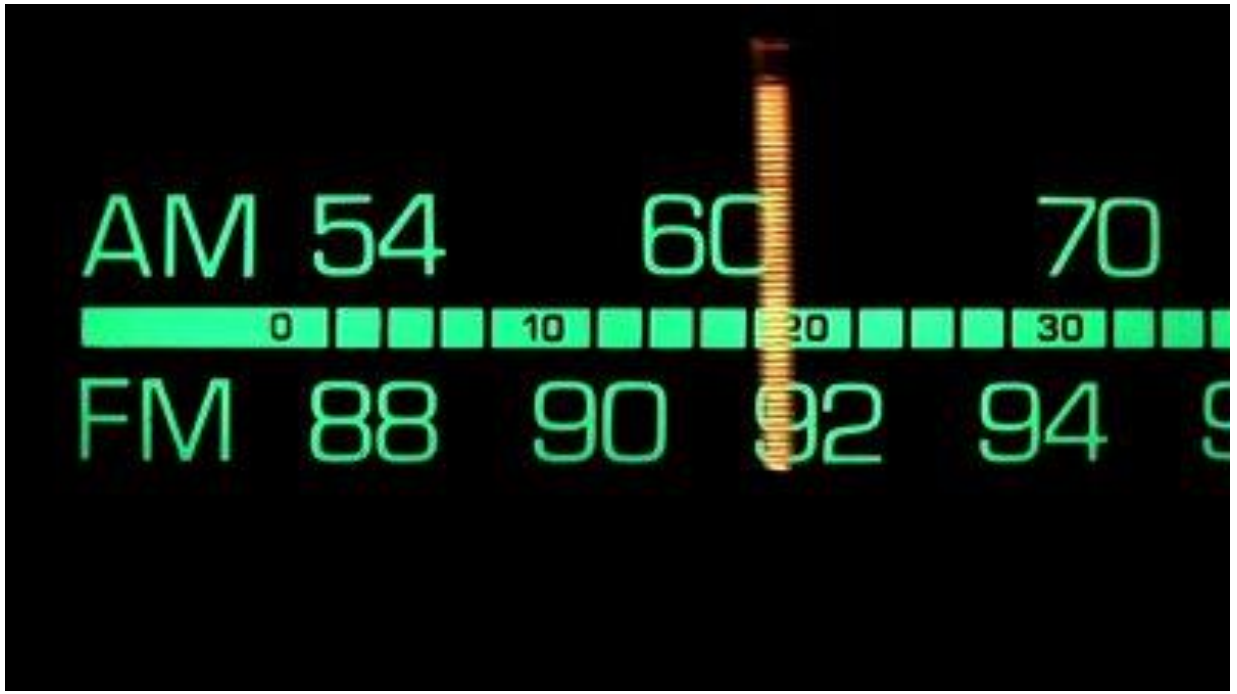




Interação T - B

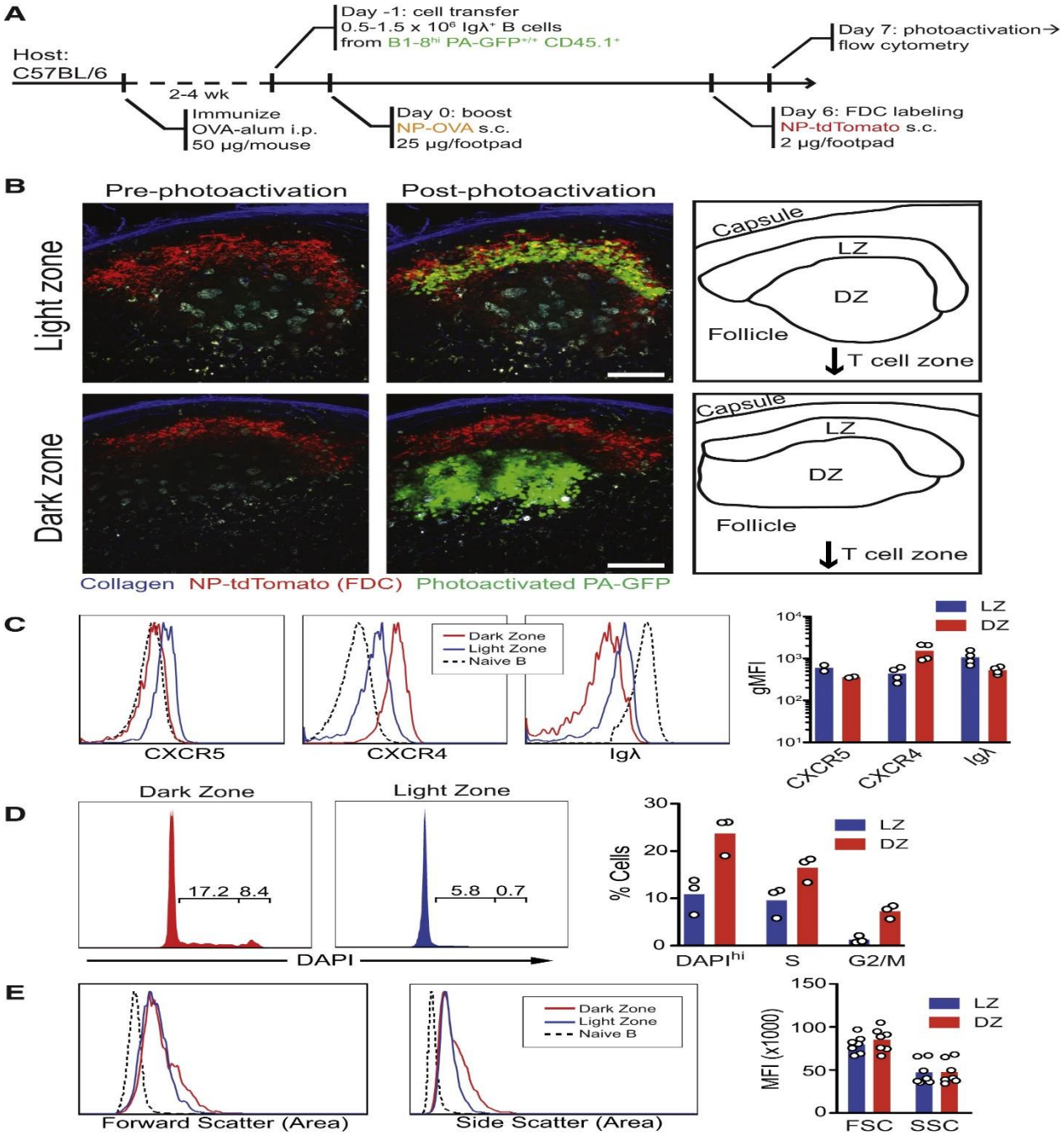


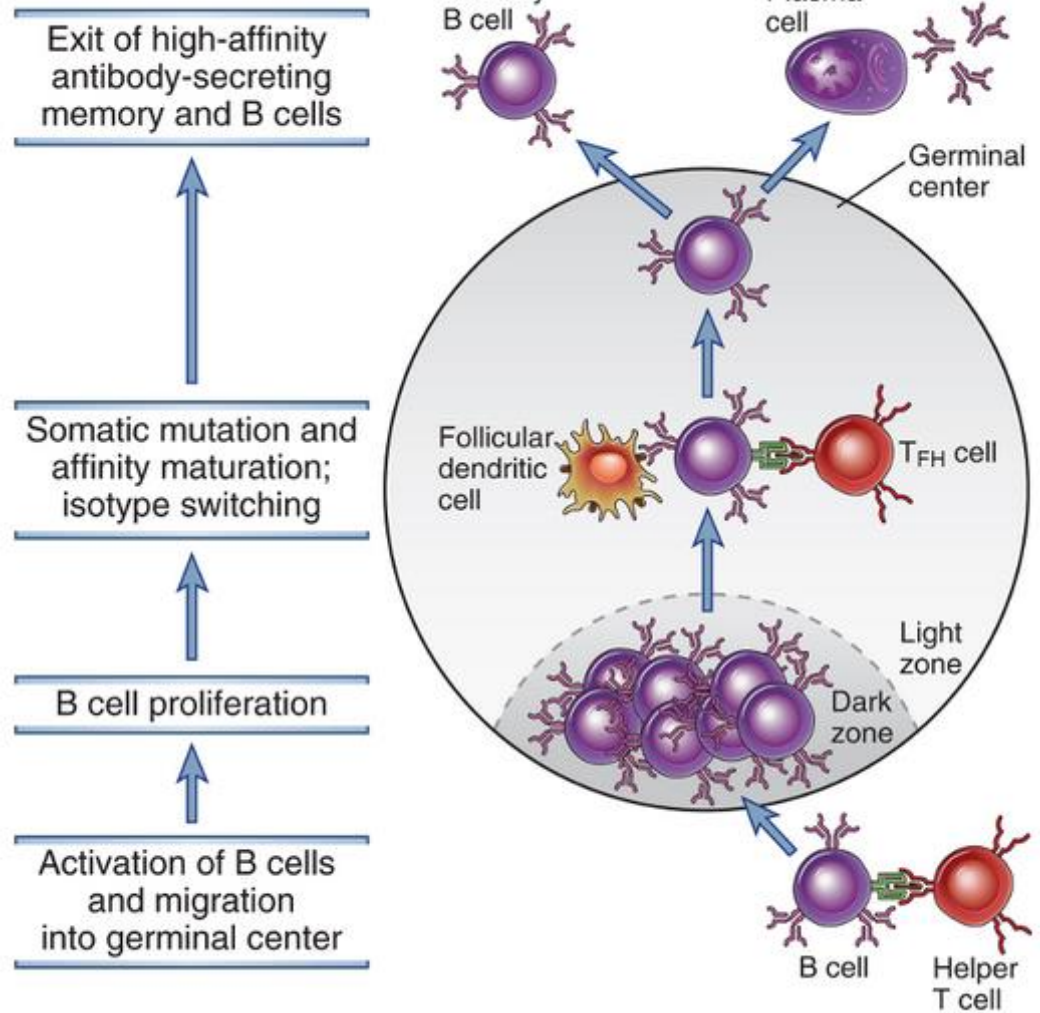

Helper T cell
Dendritic cell
T cell activation
1
Effector T cells
3
Initial T-B interaction
Follicle
B cell activation
2
Long-lived plasma cells, memory B cells
Follicular dendritic cell
Follicular helper T cell
5
Germinal center reaction
4
Short-lived plasma cells
Extrafollicular focus
Extrafollicular helper T cell

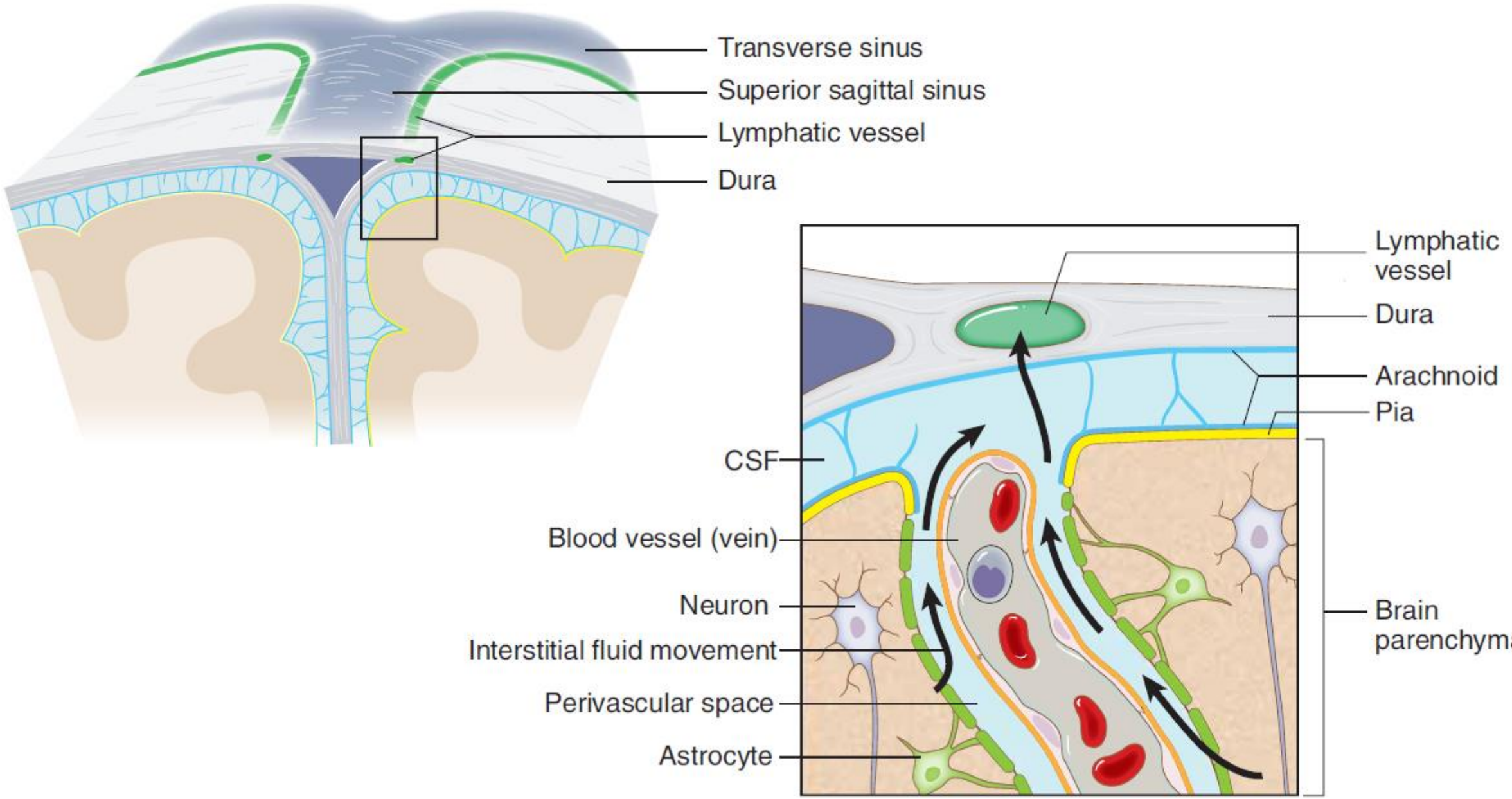


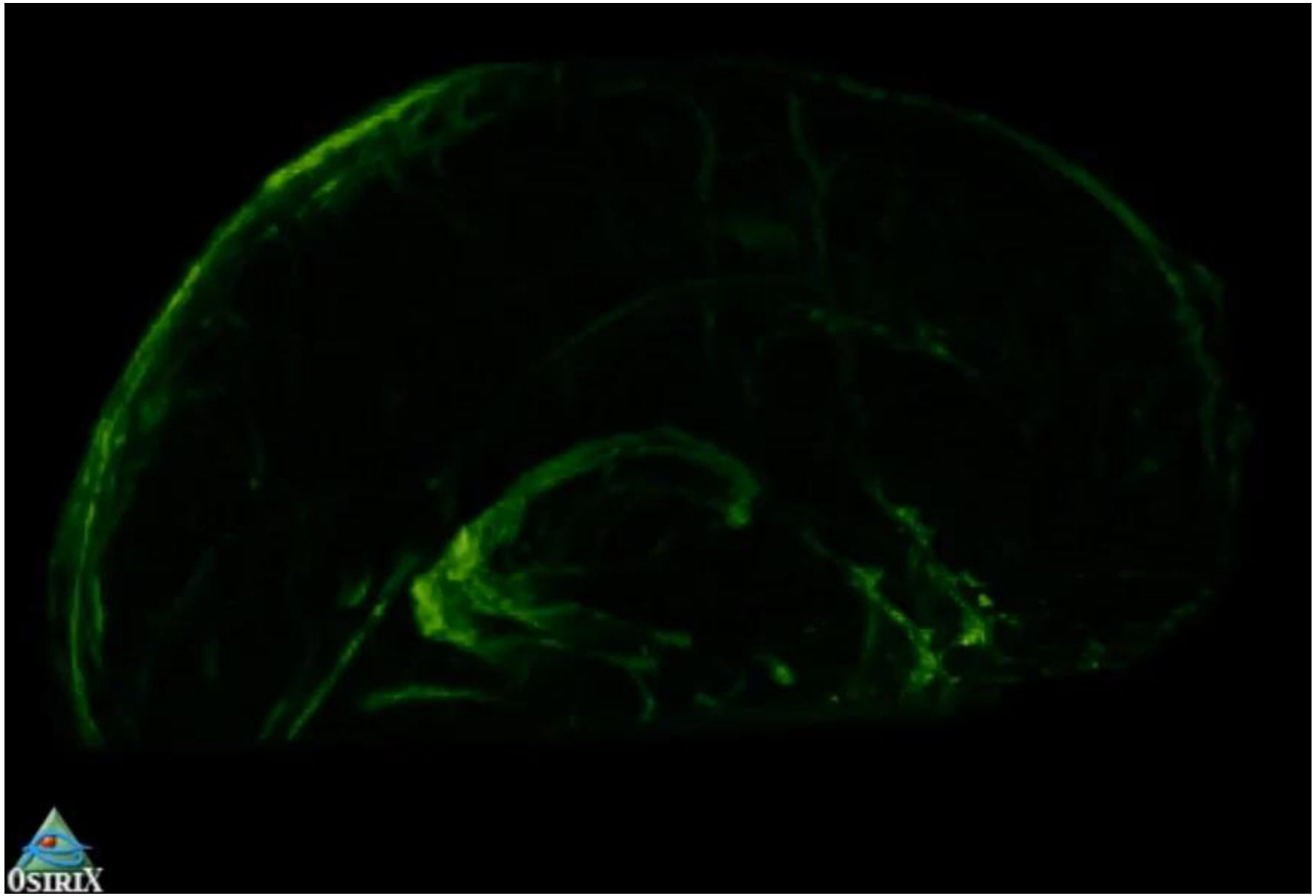
Patógenos Diferentes Requerem Respostas Diferentes

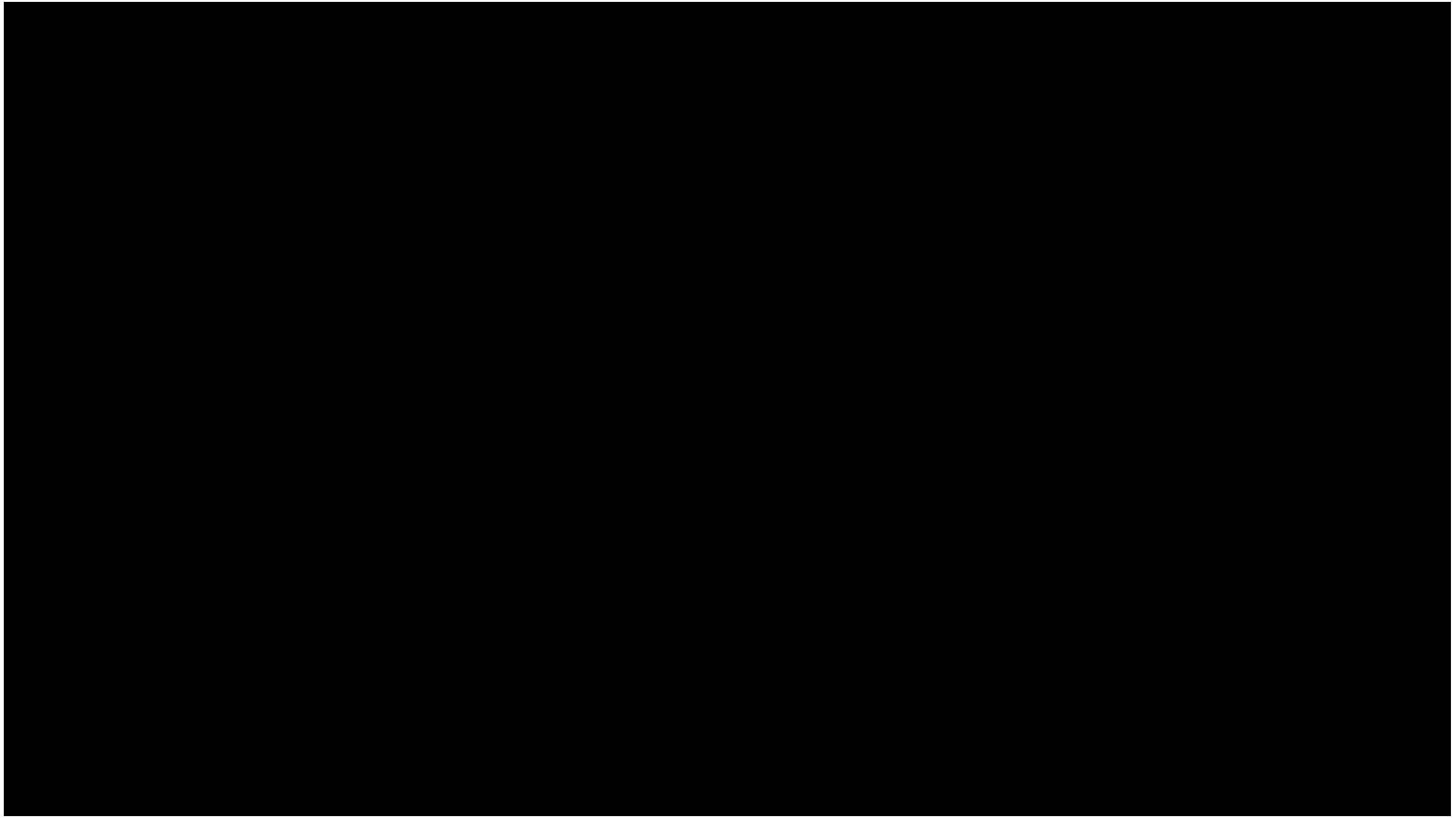
Resposta Imune Adaptativa


A
Host:
C57BL/6
2-4 wk
Immunize
OVA-alum i.p.
50 µg/mouse
Day -1: cell transfer
0.5-1.5 x 10⁶ Igλ⁺ B cells
from B1-8ʰⁱ PA-GFP⁺/⁺ CD45.1⁺
Day 0: boost
NP-OVA s.c.
25 µg/footpad
Day 6: FDC labeling
NP-tdTomato s.c.
2 µg/footpad
Day 7: photoactivation→
flow cytometry
B
Pre-photoactivation
Post-photoactivation
Light zone
Dark zone
Capsule
LZ
DZ
Follicle
T cell zone
Collagen NP-tdTomato (FDC) Photoactivated PA-GFP
C
Dark Zone
Light Zone
Naive B
CXCR5
CXCR4
Igλ
gMFI
LZ
DZ
D
Dark Zone
Light Zone
17.2 8.4
5.8 0.7
DAPI
% Cells
DAPIʰⁱ
S
G2/M
E
Forward Scatter (Area)
Side Scatter (Area)
MFI (x1000)
FSC
SSC

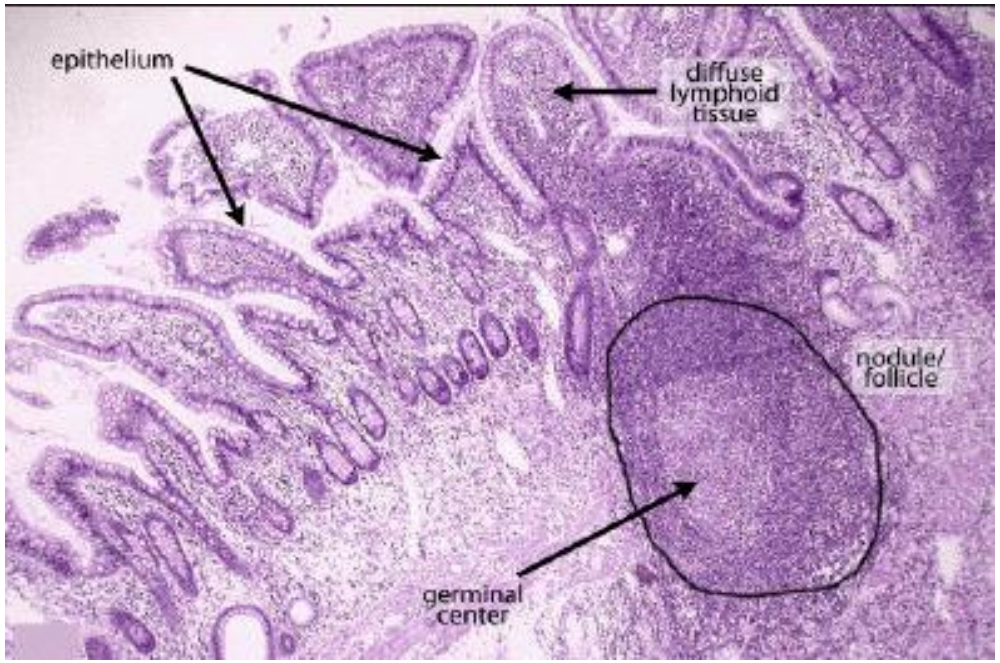

Exit of high-affinity antibody-secreting memory and B cells
Somatic mutation and affinity maturation; isotype switching
B cell proliferation
Activation of B cells and migration into germinal center
Memory B cell
Plasma cell
Germinal center
Follicular dendritic cell
TFH cell
Light zone
Dark zone
B cell
Helper T cell

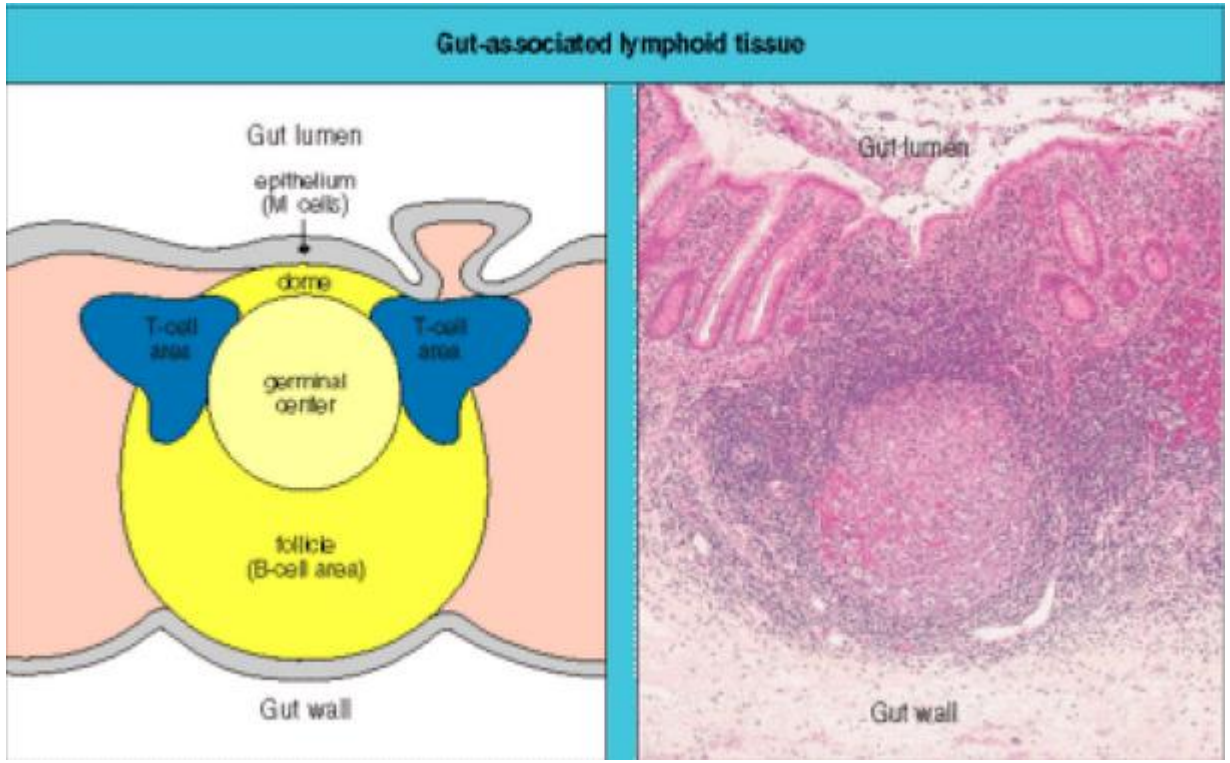

Transverse sinus
Superior sagittal sinus
Lymphatic vessel
Dura
Lymphatic vessel
Dura
Arachnoid
Pia
CSF
Blood vessel (vein)
Neuron
Interstitial fluid movement
Perivascular space
Astrocyte
Brain parenchyma

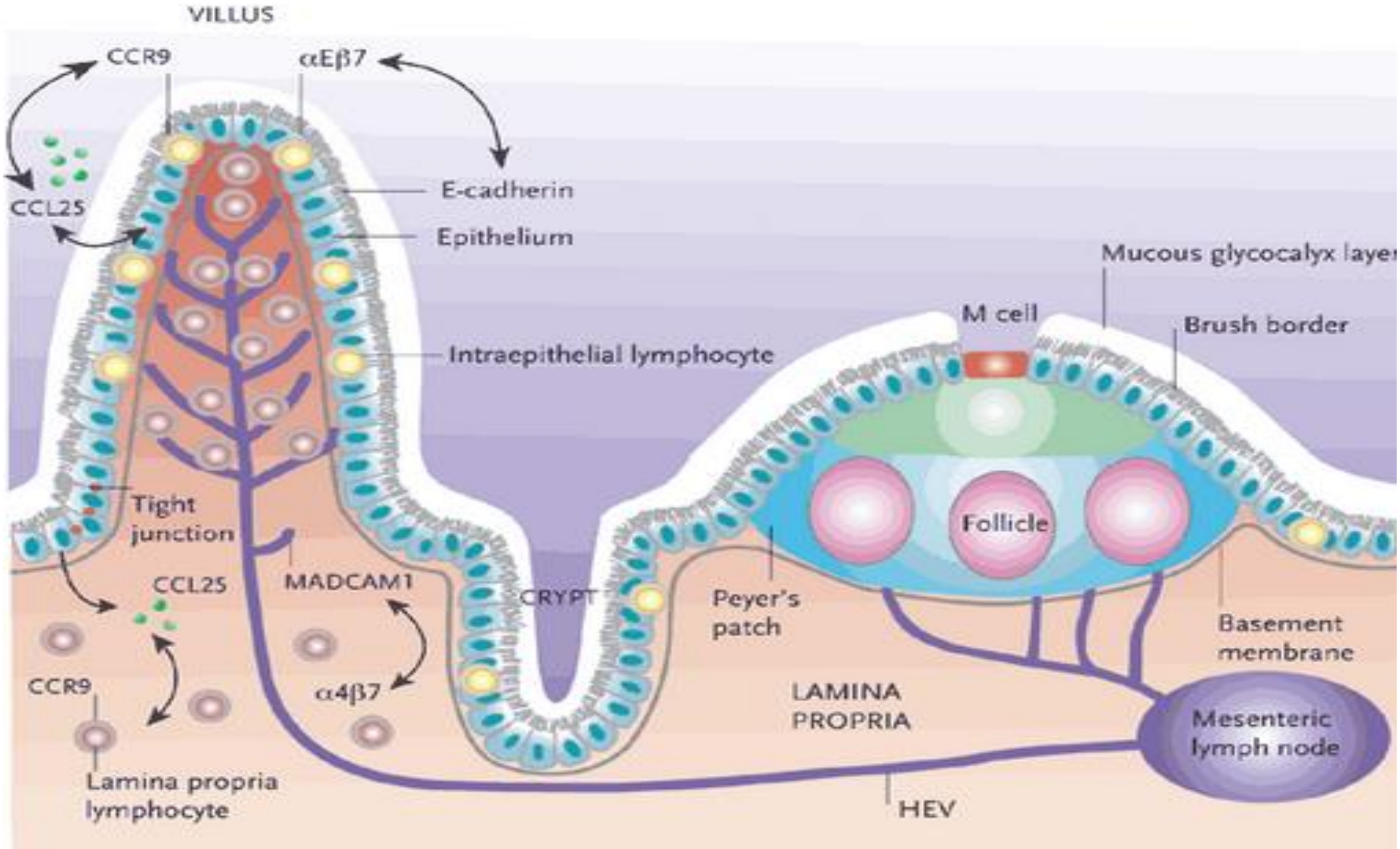

OSIRIX

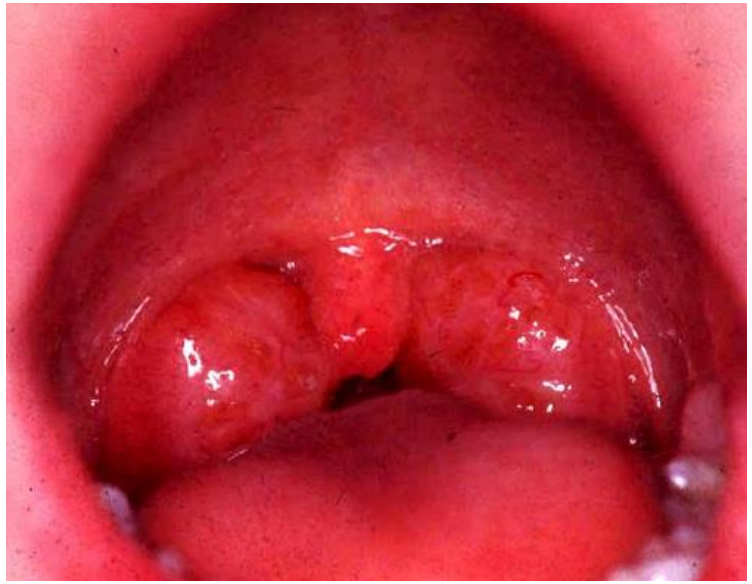


GALT- Gut Associated Lymphoid Tissue

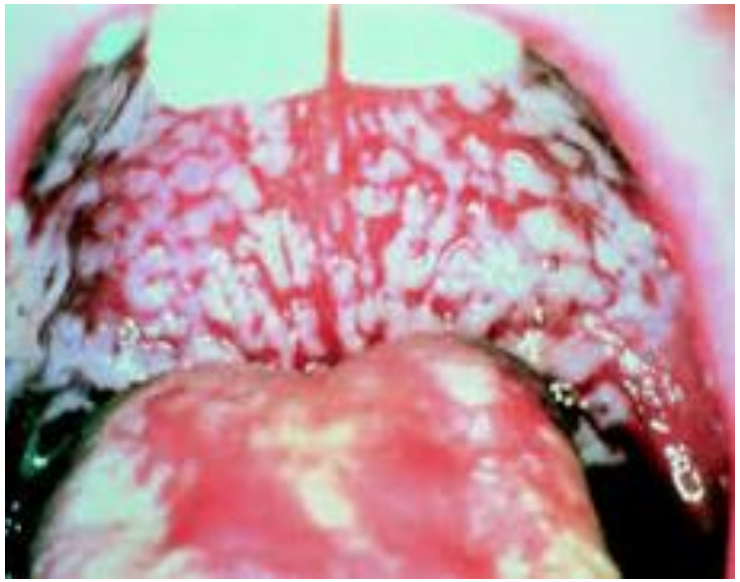




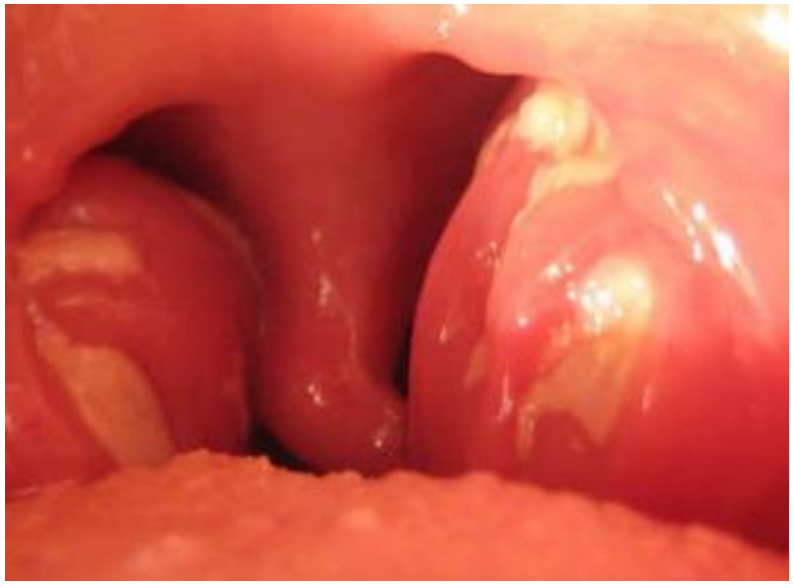

VILLUS
CCR9
αEβ7
CCL25
E-cadherin
Epithelium
Intraepithelial lymphocyte
Tight junction
CCL25
MADCAM1
CRYPT
CCR9
α4β7
Lamina propria lymphocyte
M cell
Mucous glycocalyx layer
Brush border
Follicle
Peyer's patch
Basement membrane
LAMINA PROPRIA
Mesenteric lymph node
HEV



Streptococcus



Candidíase



Ebstein Barr