



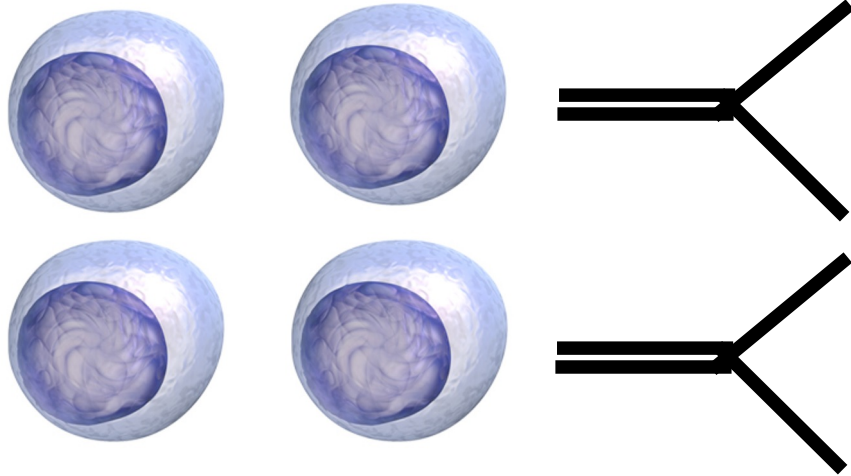
Montando o Sistema Imune

Laboratório de Interações Neuroimunes

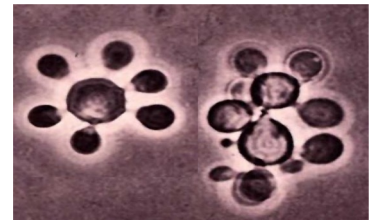
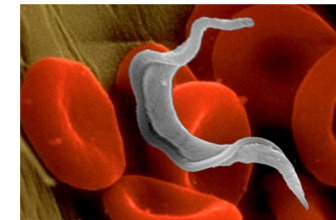
Prof. Dr. Jean Pierre Schatzmann Peron



# E o sistema imune?



DEFESA  
?  
ou  
não?

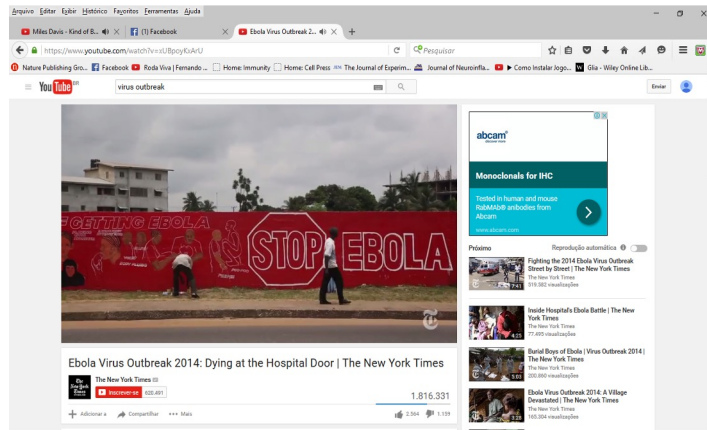




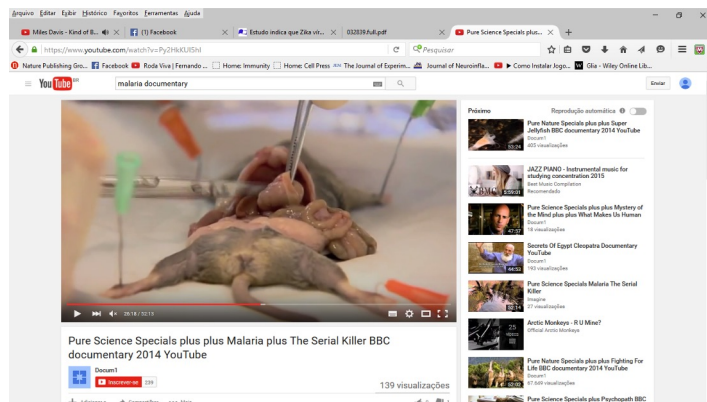
# Grandes Mazelas da Humanidade - Infecções

EBOLA

<https://www.youtube.com/watch?v=xUBpoyKxArU>



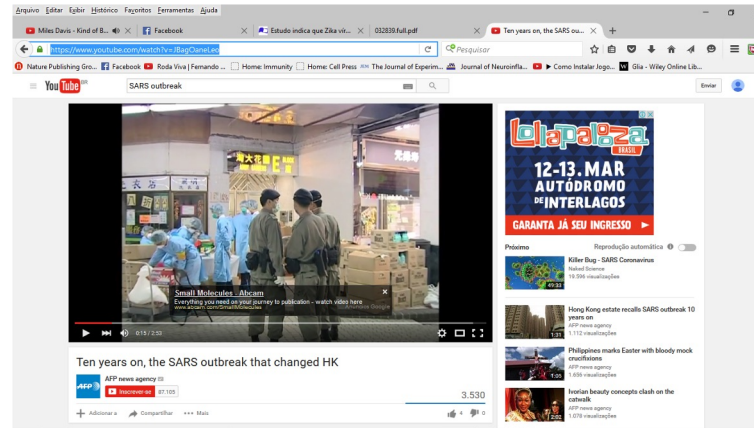
<https://www.youtube.com/watch?v=Py2HkKUI5hI>



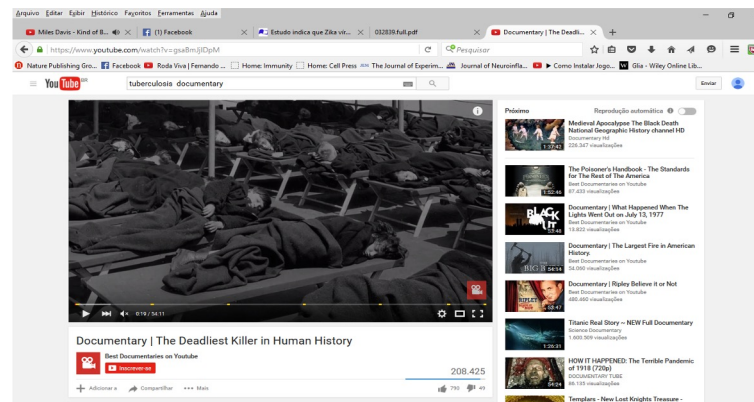
Malária

SARS

<https://www.youtube.com/watch?v=JBagOaneLeo>



<https://www.youtube.com/watch?v=gsaBmjIDpM>

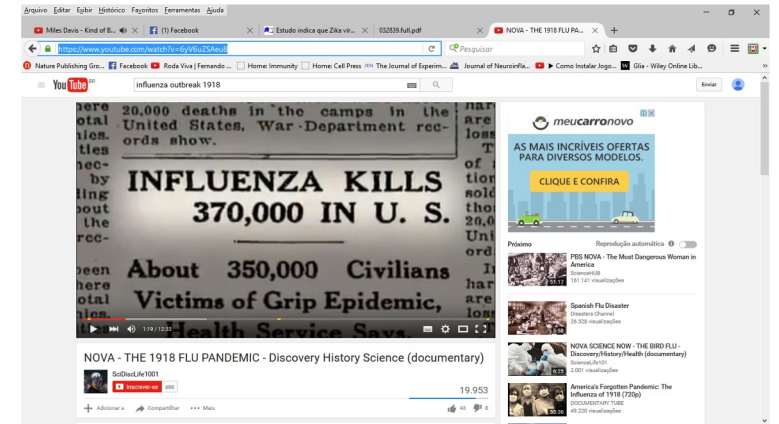


Tuberculos

e

Influenza

<https://www.youtube.com/watch?v=6yV6uZSAeu8>



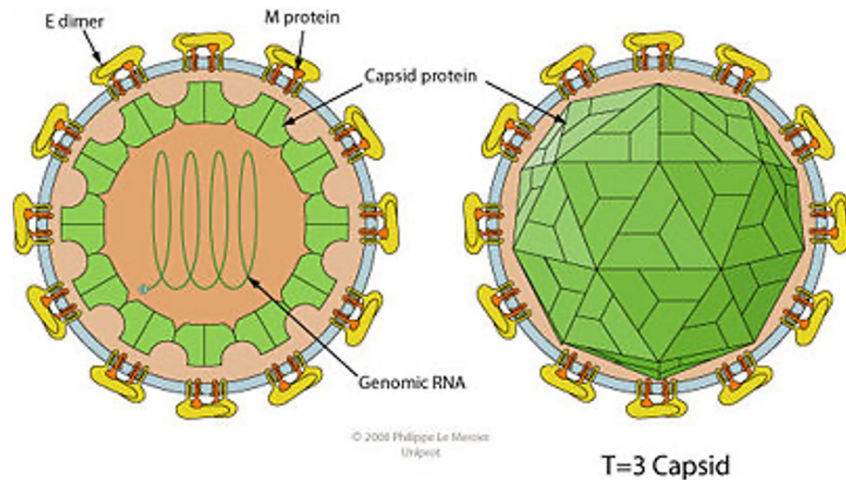
<https://www.youtube.com/watch?v=ugdPBvT5YPQ>



HIV

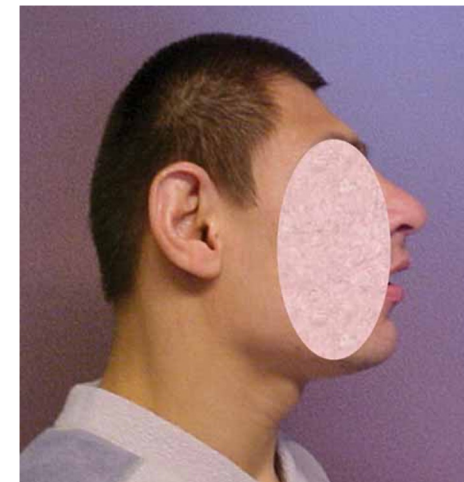


# Zika Vírus – 1947 Floresta de Zika



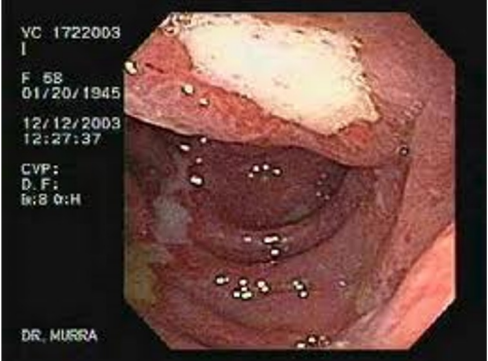
Relatório do Ministério da Saúde 09 Jan 2016

*“há 3.530 casos suspeitos de microcefalia relacionada ao vírus Zika no país. Os casos são computados desde o início das investigações (em 22 de outubro de 2015) até 9 de janeiro deste ano e ocorreram em 724 municípios de 21 unidades da federação. Também estão em investigação 46 óbitos de bebês com microcefalia possivelmente relacionados ao vírus Zika, todos na região nordeste”*





# Imunodeficiências – Infecções de Repetição



**Colite**



**Pneumonia**



**Toxoplasmose Ocular**



**Candida**



**Staphilococcus**



**Infecções Múltiplas**

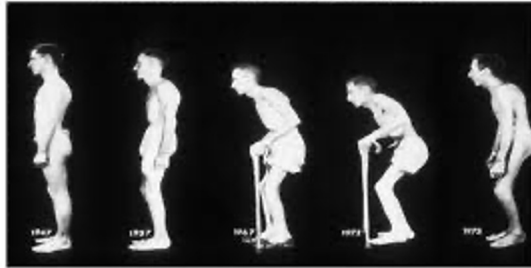


# Autoimunidade

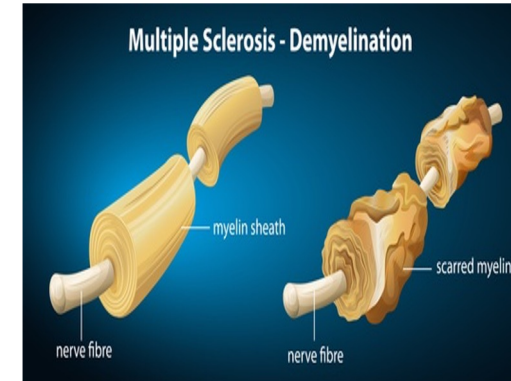


**LUPUS**

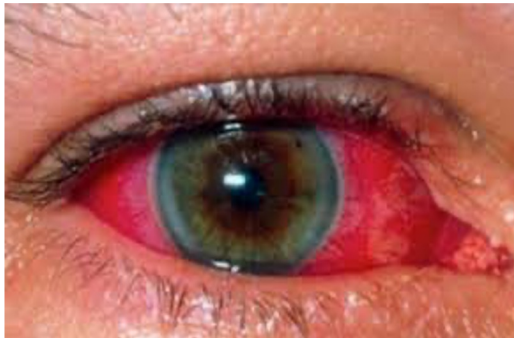
Progressive deformity due to AS  
over a period of 36 years



**Spondilite Anquilosante**



**Esclerose Múltipla**



**Uveíte**

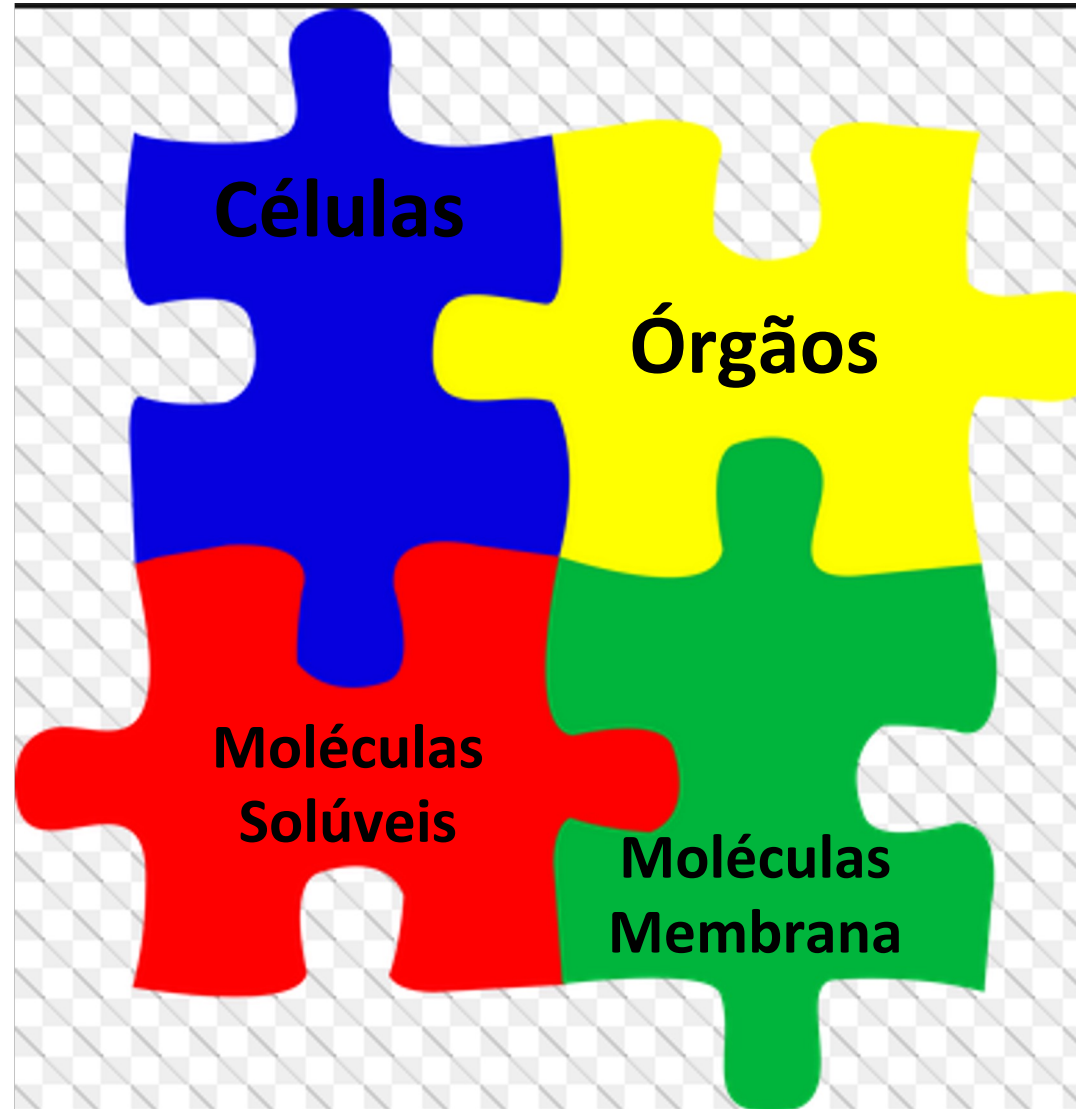


**Doença de Graves**



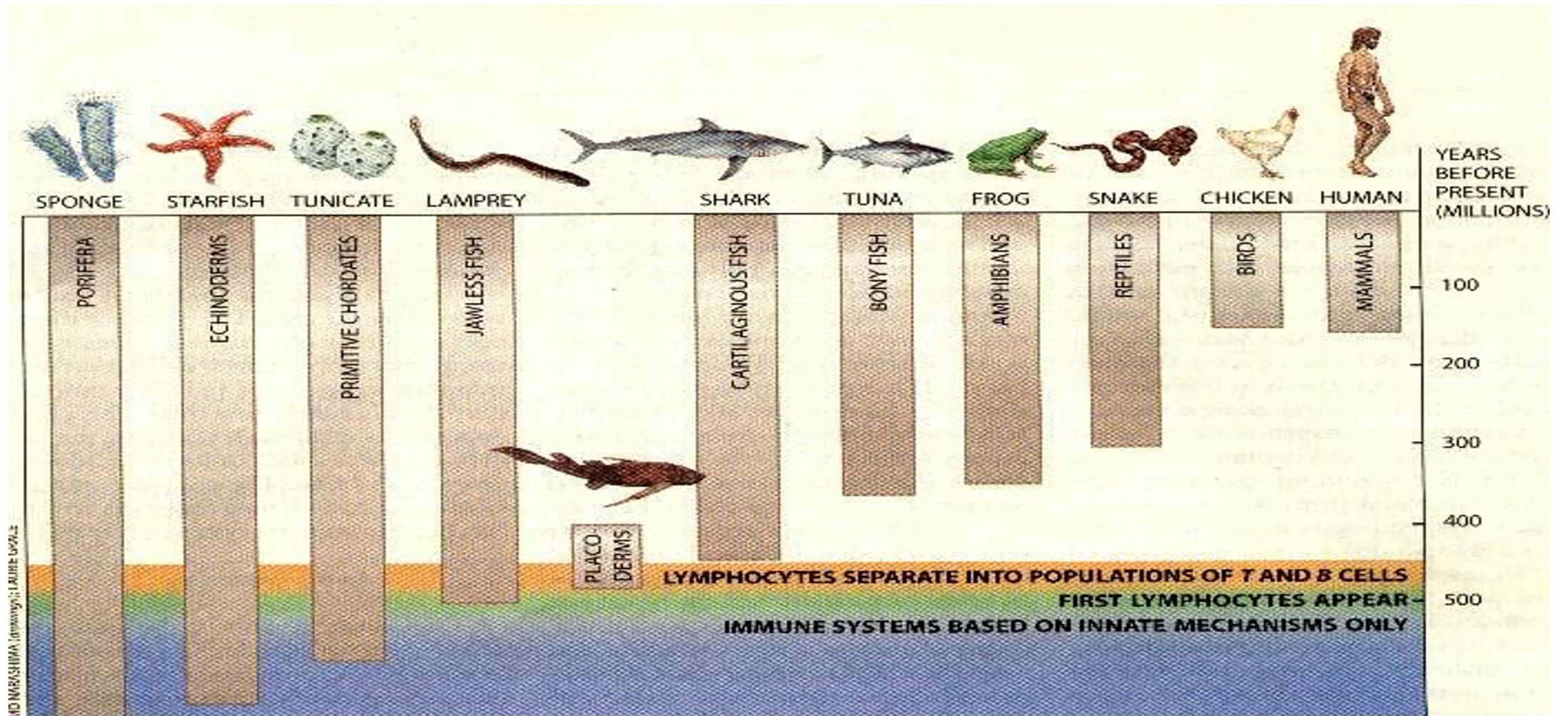
**Psoríase**

# Montando o Sistema Imune



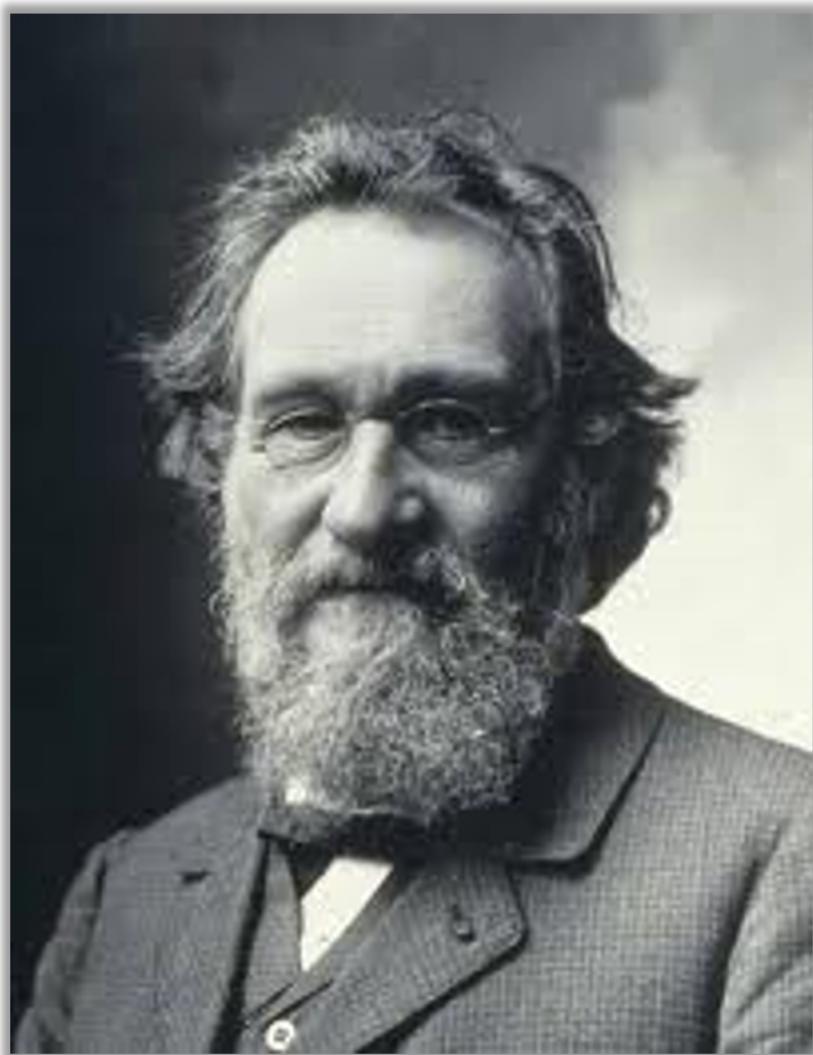


# Evolução do Sistema Imune





**Elie *Metchnikoff*: Pai da Imunidade Natural**  
**Nobel: 1908**



**Fagócitos de larvas de estrelas-do-mar.**



# Imunidade Inata

- **1ª linha de defesa contra infecções**

- **Existe antes da infecção:**
  - **Age *de pronto***
  - **Eliminar patógenos instantaneamente;**
  - **Não possuem memória imunológica;**
- *Reconhecem Padrões Moleculares Associados a Patógenos (PAMPs)*
  - *Padrões Moleculares Associados ao Perigo (DAMPs)*

- **Mecanismos efetores:**

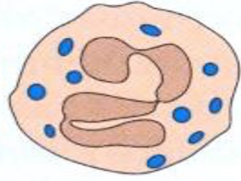
- **Fagocitos: neutrófilos e macrófagos**
- **Células NK**
- **Citocinas**
- **Sistema Complemento - Via alternativa/lectinas**

**Imprescindível para a Ativação da Imunidade Adaptativa**





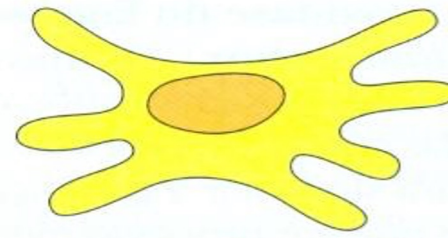
Tipo celular



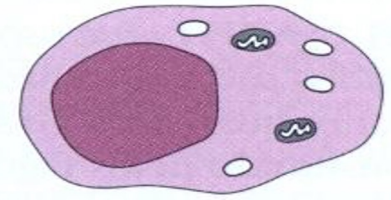
Neutrófilo



Macrófago



Células dendríticas



Célula *natural killer*

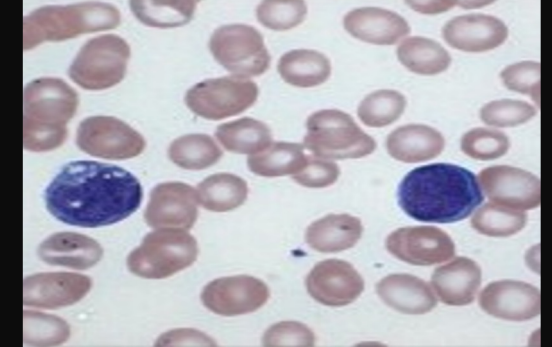
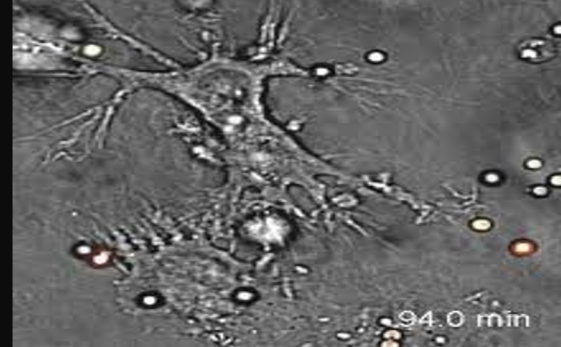
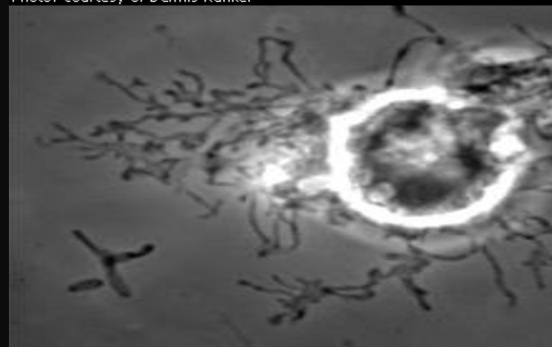
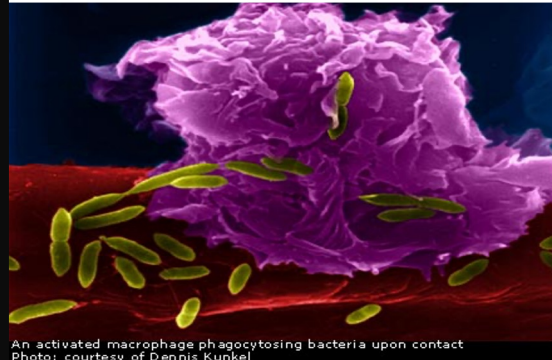
Função

Fagocitose  
Espécies reativas de oxigênio e nitrogênio  
Peptídeos antimicrobianos

Fagocitose  
Mediadores inflamatórios  
Apresentação de antígenos  
Espécies reativas de oxigênio e nitrogênio  
Citocinas  
Proteínas do complemento

Apresentação de antígeno  
Sinais co-estimuladores  
Espécies reativas de oxigênio  
Interferon  
Citocinas

Lise da célula infectada por vírus  
Interferon  
Ativação de macrófagos





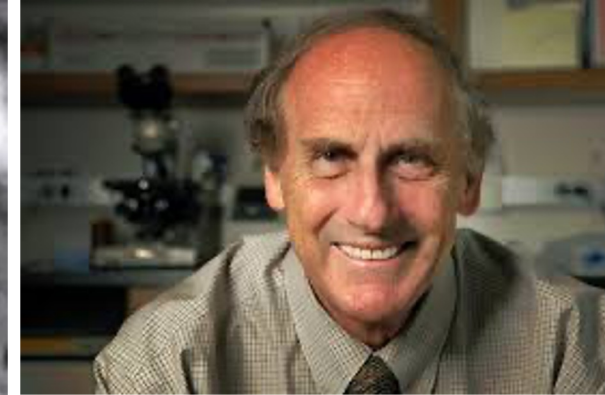
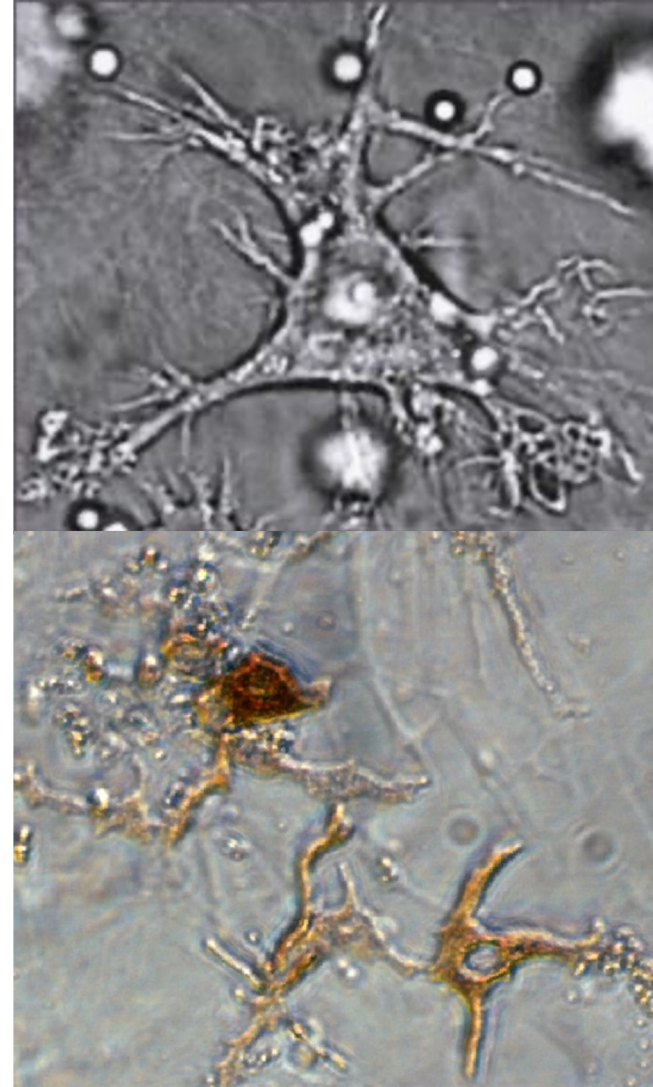
# Neutrófilos

- **Grande quantidade no sangue / primeiras células no infiltrado**
- **Receptores para IgG (CD16b) / Complemento (C5R)**
- **Vida média curta ( $\pm$  6h)**
- **Capacidade fagocítica e microbicida:**
  1. **Grânulos primários: lisozima, hidrolases lácticas, proteases, mieloperoxidase (HOCl) e proteínas catiônicas**
  2. **Grânulos secundários: lisozima, lactoferrina (quelante de  $Fe^{++}$ ), colagenase, cininogenase e ativador do plasminogênio**
  3. **Metabólitos tóxicos do oxigênio e nitrogênio**
- **Não possuem superóxido desmutase: acúmulo de  $O_2^-$**
- **Deficiência: infecções bacterianas**



# Células Dendríticas

- **Importante para a IMUNIDADE ADAPTATIVA**
- **Progenitor linfóide, CD8<sup>+</sup> e produtoras de IL-12**
- **Progenitor mielóide, CD14<sup>+</sup> e não-produtoras de IL-12**
- **Plasmocitóides Resposta viral (TLR-9 e IFN- $\alpha$ ) e escape de tumores**
- **Células de Langerhans (epitélios de revestimento) – Mielóide**
- **Presentes em vários tecidos**
- **Células Apresentadoras de Antígeno (APC)**
- ***Toll-like* receptors**



**Ralph Steinman**

**Nobel 2011**



# Macrófagos

- **Sangue: Monócitos**
- **Receptores para IgG / Complemento e PAMPs (*Toll-like receptors*) / *NLRs***
- **Kupfer, microglia, osteoclastos, macrófagos alveolares...**
- **Capacidade fagocítica e microbicida (= Neutrófilos)**
- **Essenciais para reparação tecidual**
- **Células Apresentadoras de Antígeno (APC)**
- **Importantes para geração/modulação da IMUNIDADE ADAPTATIVA**



# Qual a função principal dessas células ?

Eliminar

O

Patógeno ?



Reparo

Tecidual

Depuração

Debris ?



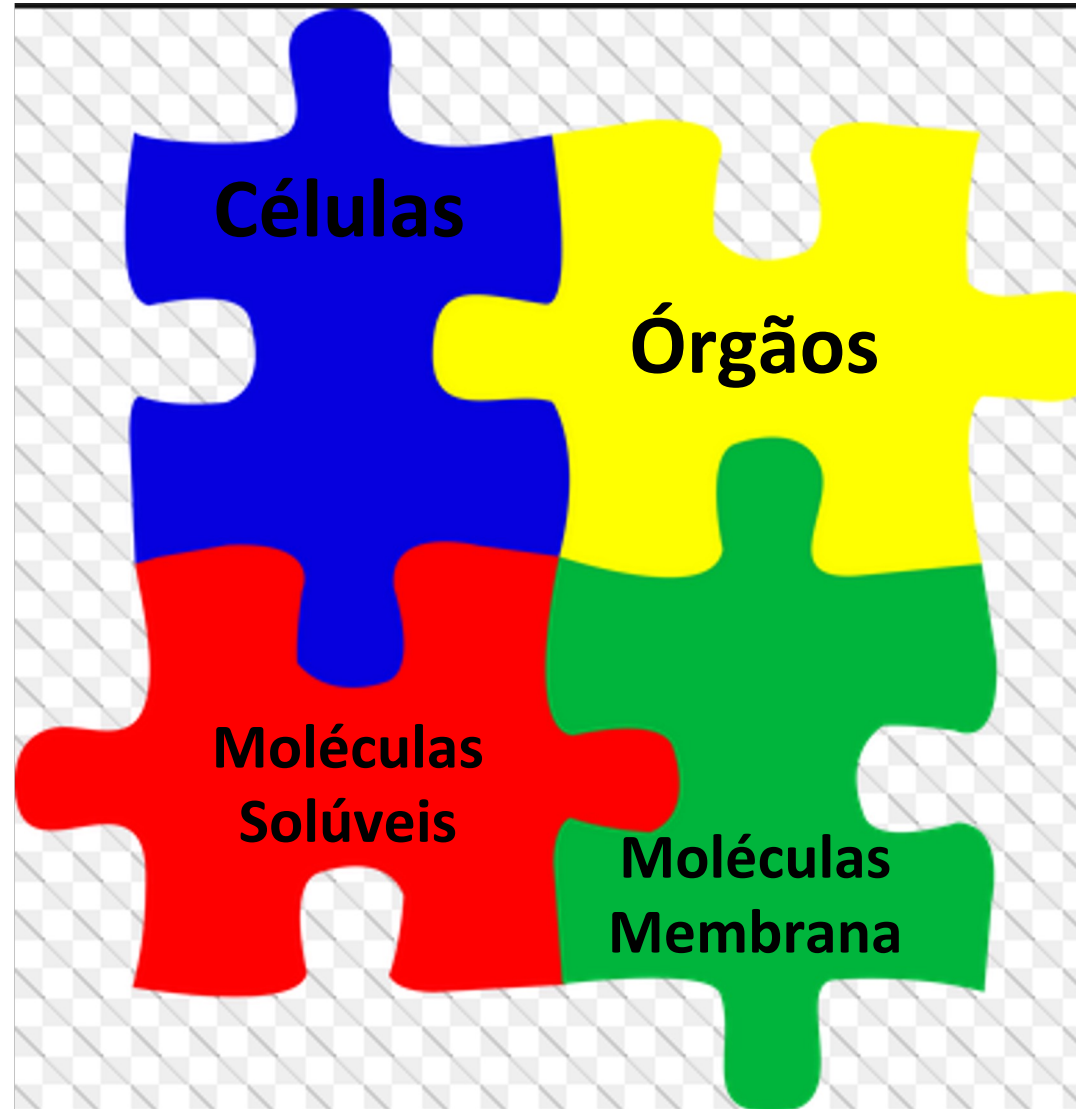








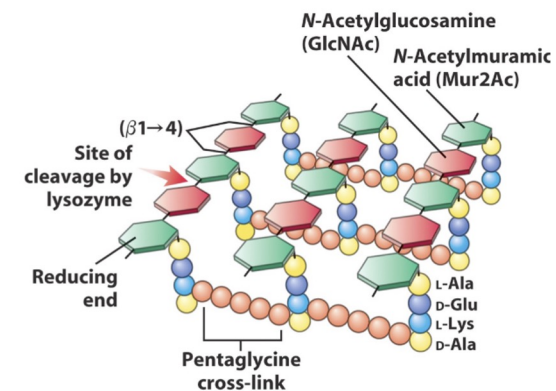
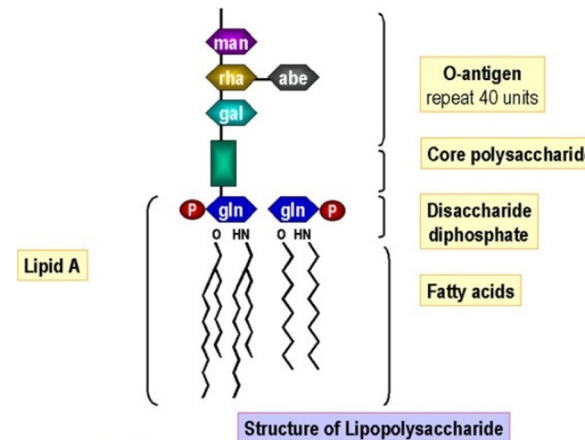
# Montando o Sistema Imune



# Receptores para Reconhecimento de Padrões

- TLRs 1-13 em humanos
  - Padrões Endógenos ( Matrix extracelular, cristais urato, cristais colesterol)
  - Padrões Exógenos ( Bactérias Gram + ou -, retrovírus, fungos,...)

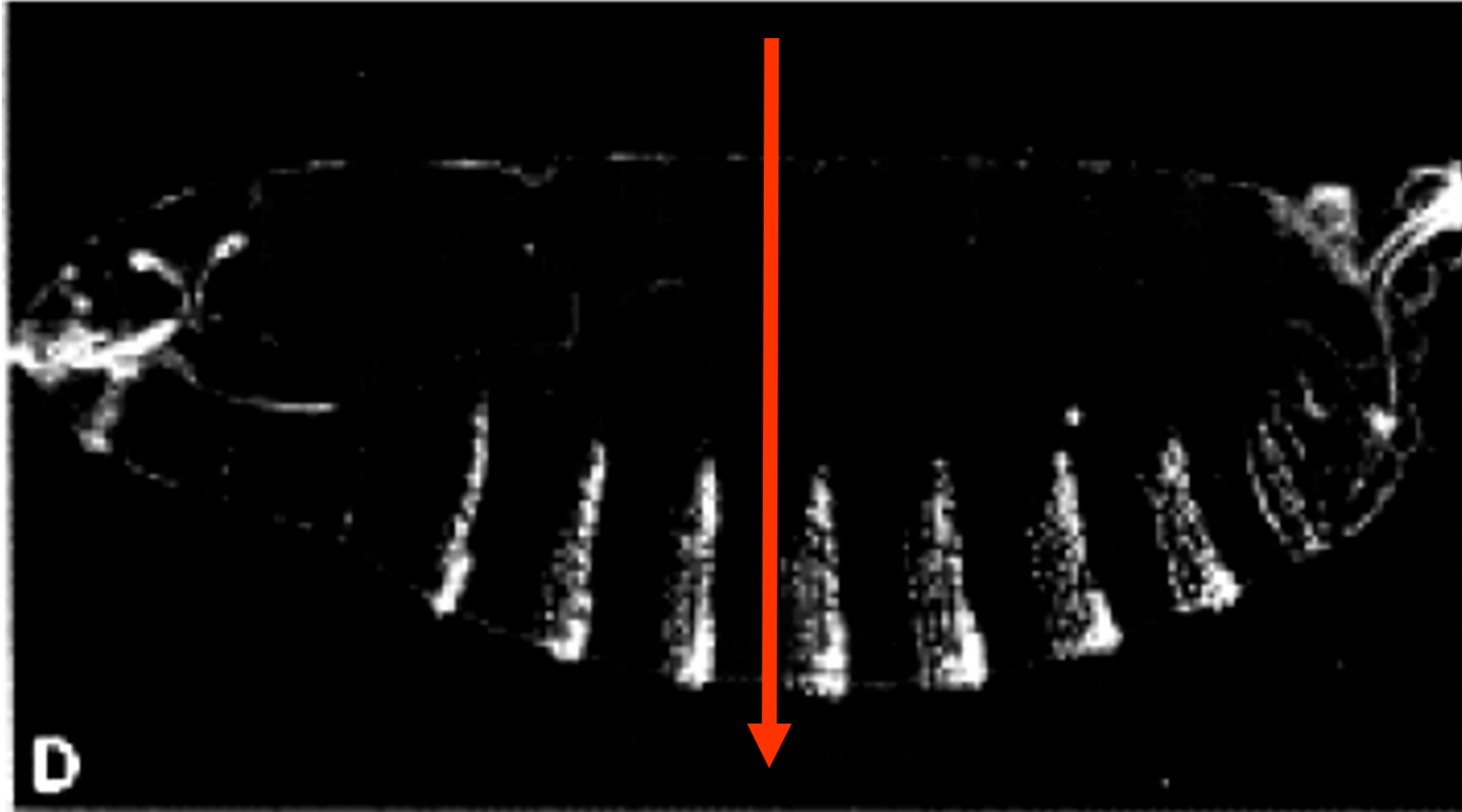
- Inflamasoma
  - NOD 1 e 2
  - IPAF
  - NAIP
  - NALP 1, 2, 3.





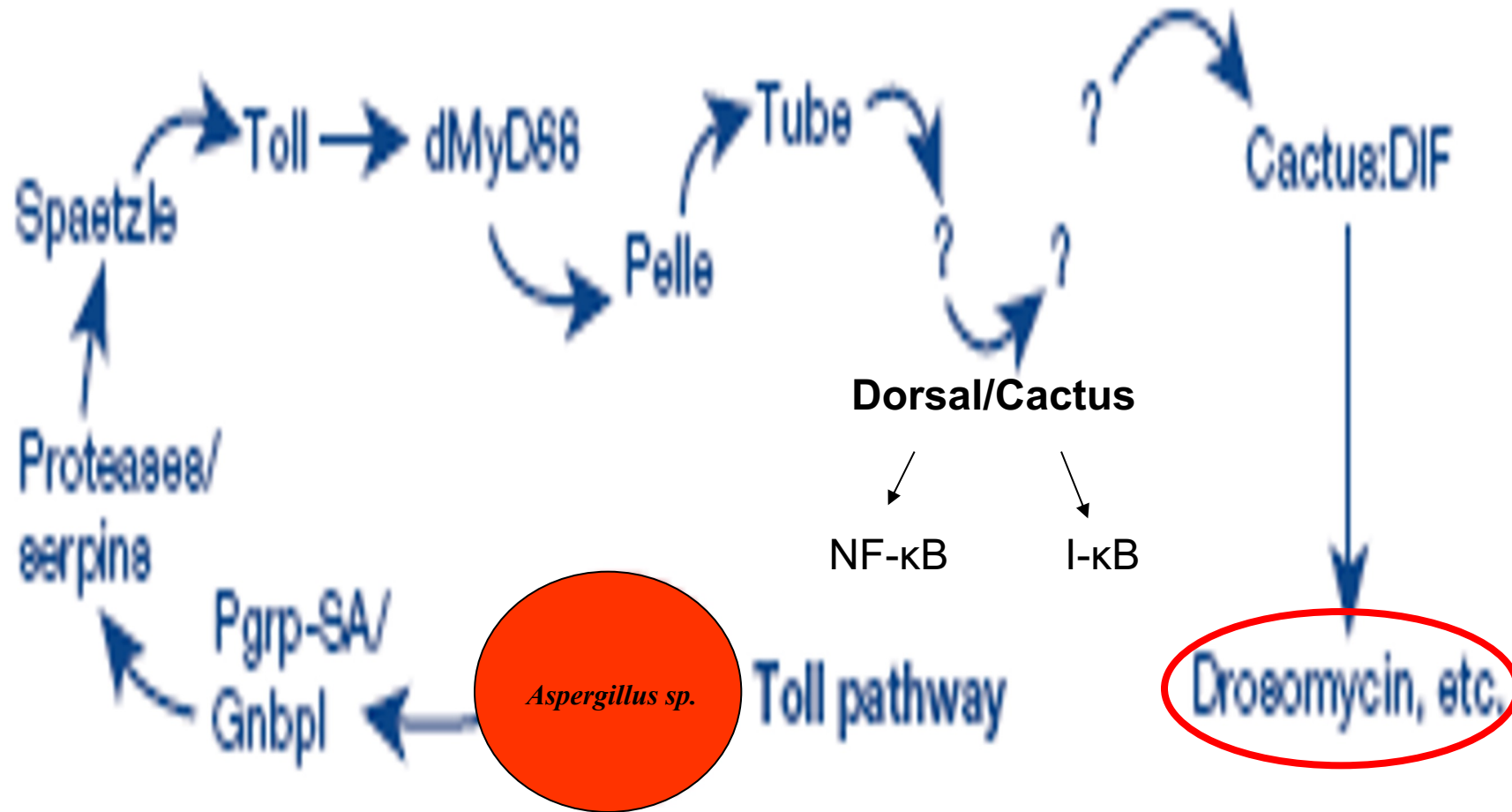
# Toll Protein

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



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

(1996): *Resposta a Aspergillus fumigatus*.



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



# Charles A. Janeway – Ruslan Medzhitov



Photo: The Scripps Research Institute

**Bruce A. Beutler**



Photo: CNRS Photo Library/Pascal Disdier

**Jules A. Hoffmann**



Photo: Rockefeller University Press

**Ralph M. Steinman**

The Nobel Prize in Physiology or Medicine 2011 was divided, one half jointly to Bruce A. Beutler and Jules A. Hoffmann *"for their discoveries concerning the activation of innate immunity"* and the other half to Ralph M. Steinman *"for his discovery of the dendritic cell and its role in adaptive immunity"*.

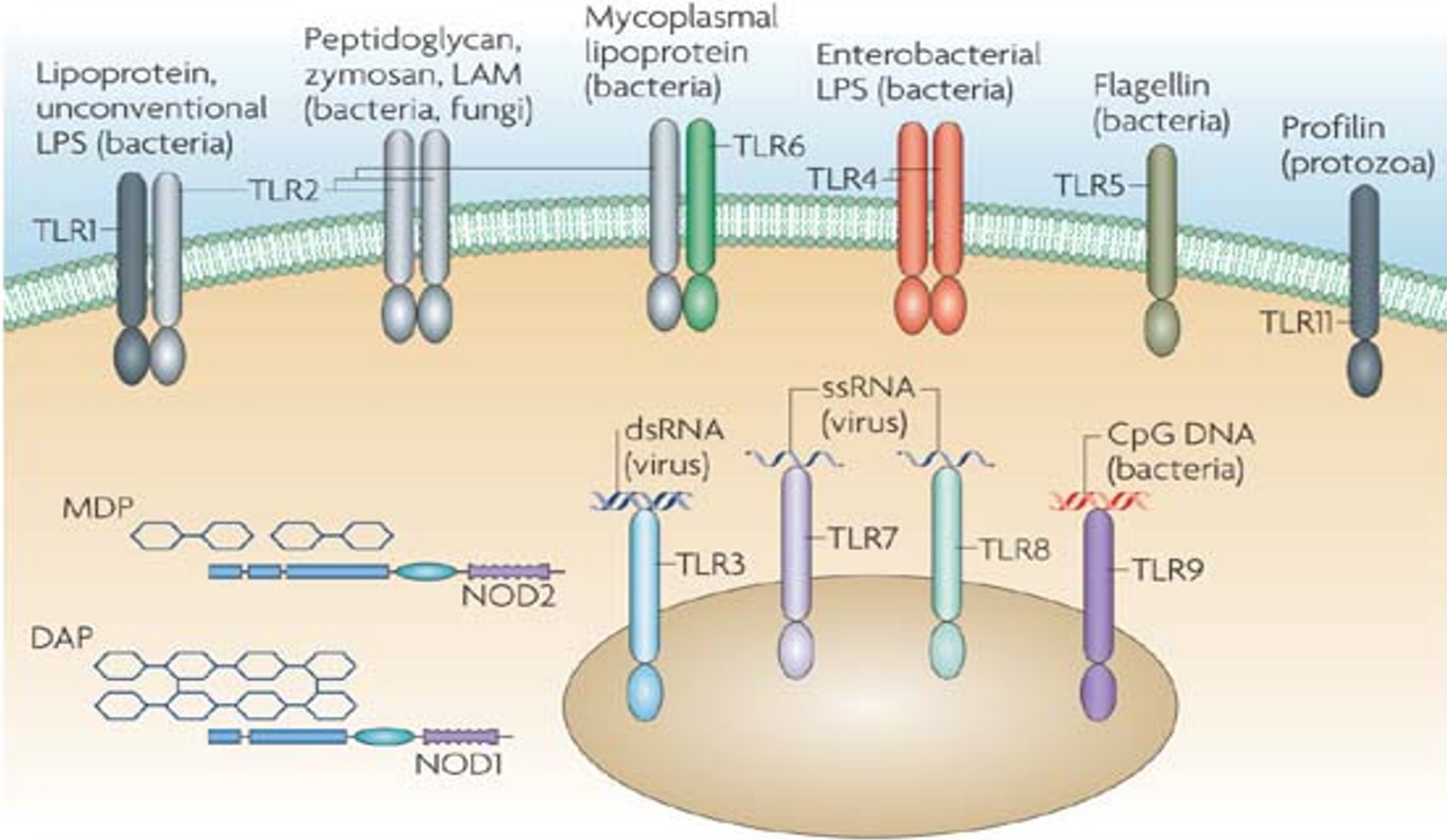
**Charles Janeway**

**Ruslan Medzhitov**



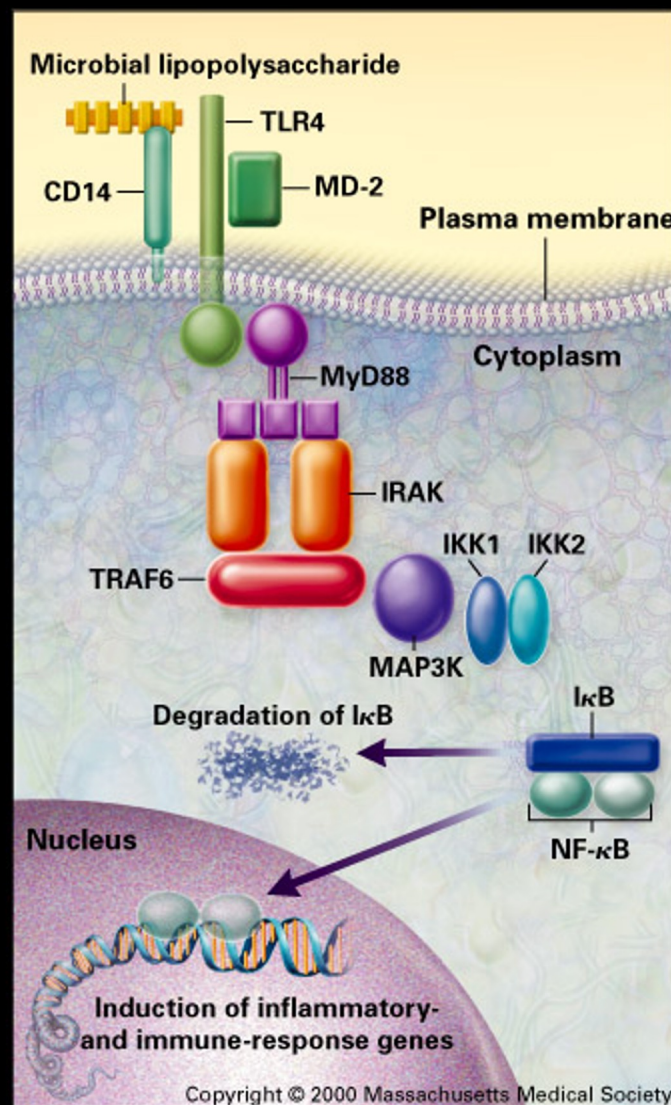
**"for their discoveries concerning the activation of innate immunity"**

# Receptores Toll-like





# Sinalização e Ativação do NF- $\kappa$ B ou IRFs

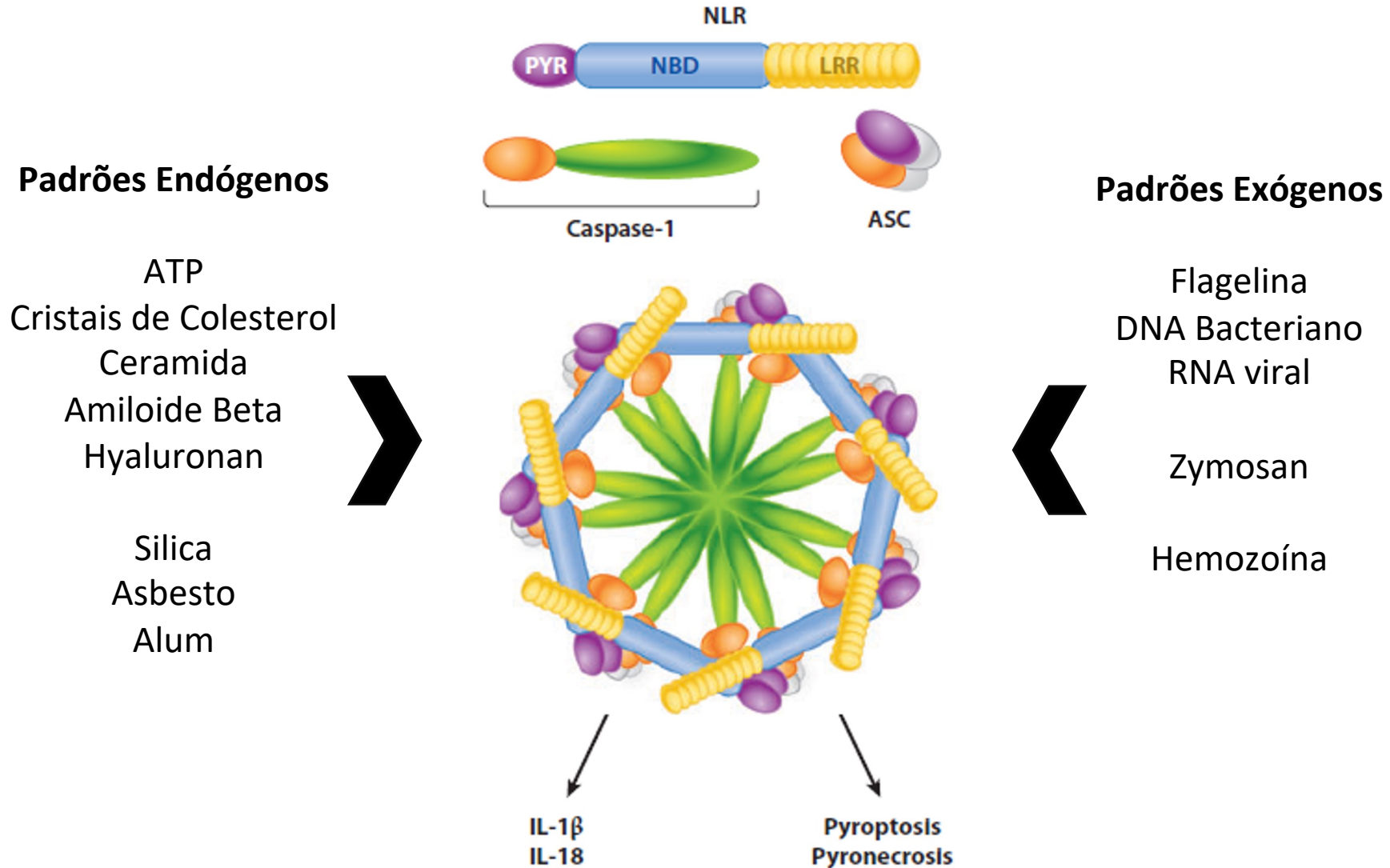


## Genes pro-inflamatórios

- Citocinas  
Pró-IL-1, IL-6, IL-12, IL-15,  
IL-23, TNF- $\alpha$ , etc...
- Quimicinas  
CCL1, CCL2, CCL3, CXCL
- Ag Presentation  
MHC I e II, CD80, CD86
- Enzimas  
COX, 5-LO, iNOS, NADPH

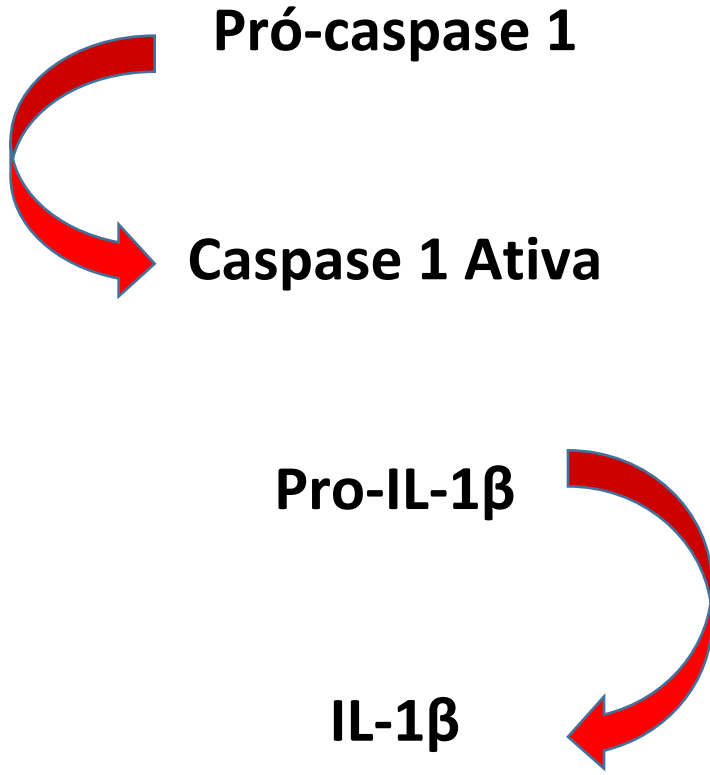
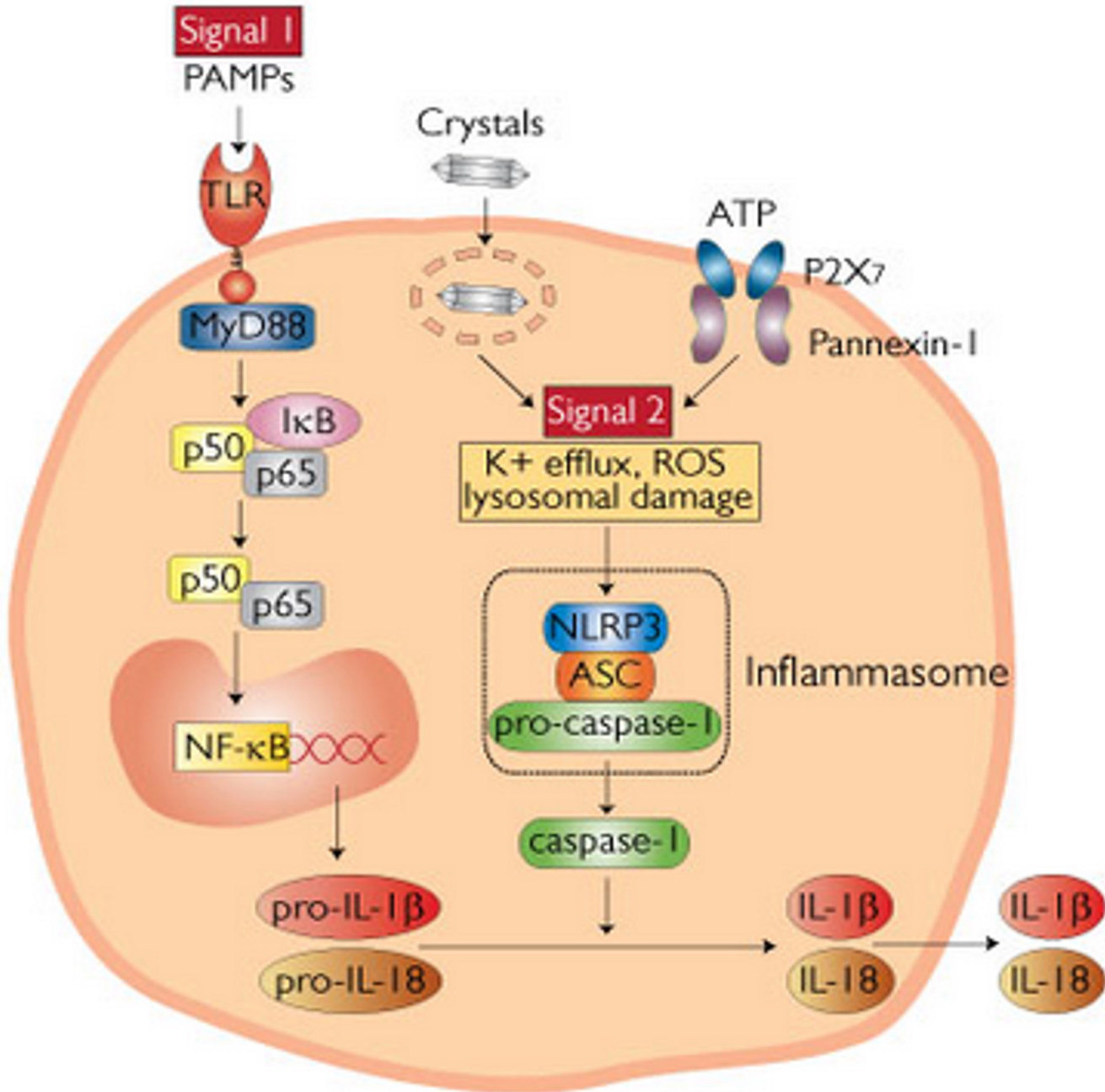
# Inflamasoma

## Receptores NOD, NLRs, IPAF, AIM, NAIP...





# Ativação dos Inflamasomas

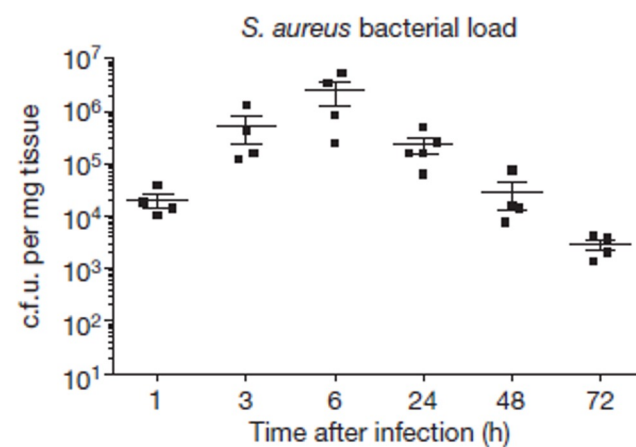
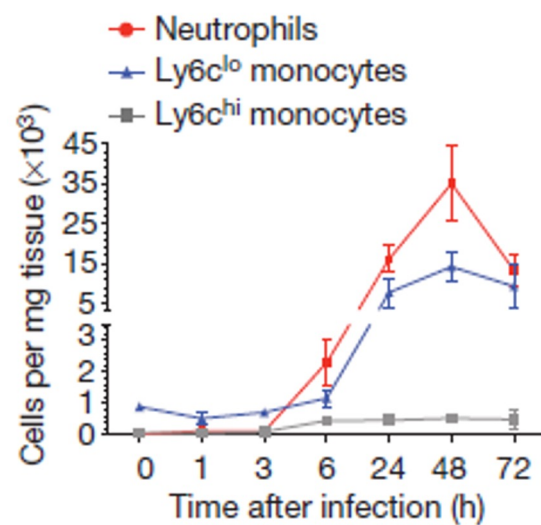
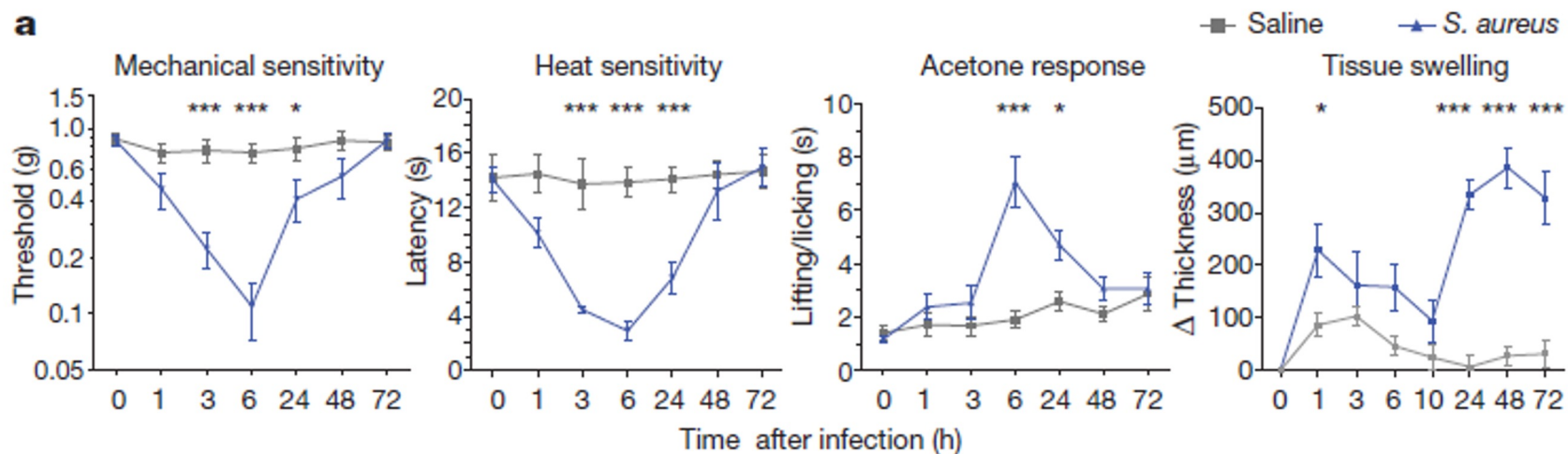


## Bacteria activate sensory neurons that modulate pain and inflammation

Isaac M. Chiu<sup>1</sup>, Balthasar A. Heesters<sup>2,3</sup>, Nader Ghasemlou<sup>1</sup>, Christian A. Von Hehn<sup>1</sup>, Fan Zhao<sup>4</sup>, Johnathan Tran<sup>1</sup>, Brian Wainger<sup>1</sup>, Amanda Strominger<sup>1</sup>, Sriya Muralidharan<sup>1</sup>, Alexander R. Horswill<sup>5</sup>, Juliane Bubeck Wardenburg<sup>6</sup>, Sun Wook Hwang<sup>1,7</sup>, Michael C. Carroll<sup>2</sup> & Clifford J. Woolf<sup>1</sup>



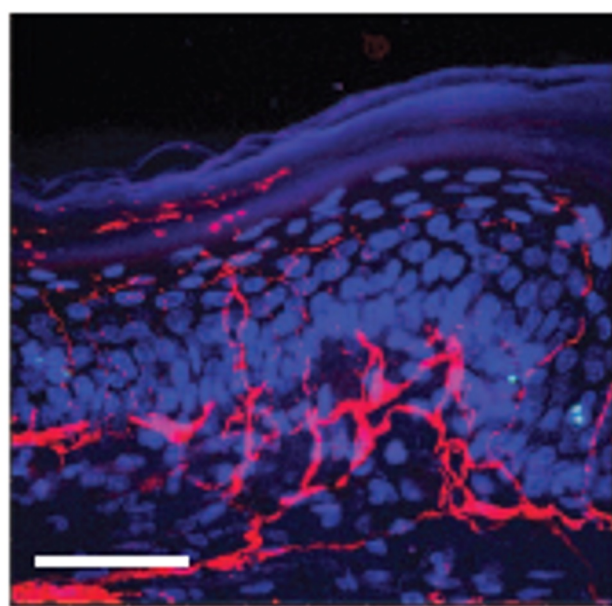




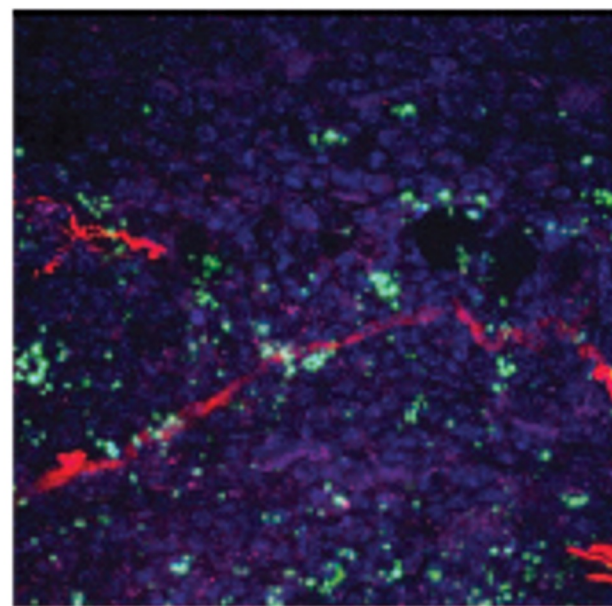
e

Nav1.8-Cre/TdTomato/GFP-*S. aureus*/DAPI

Epidermis

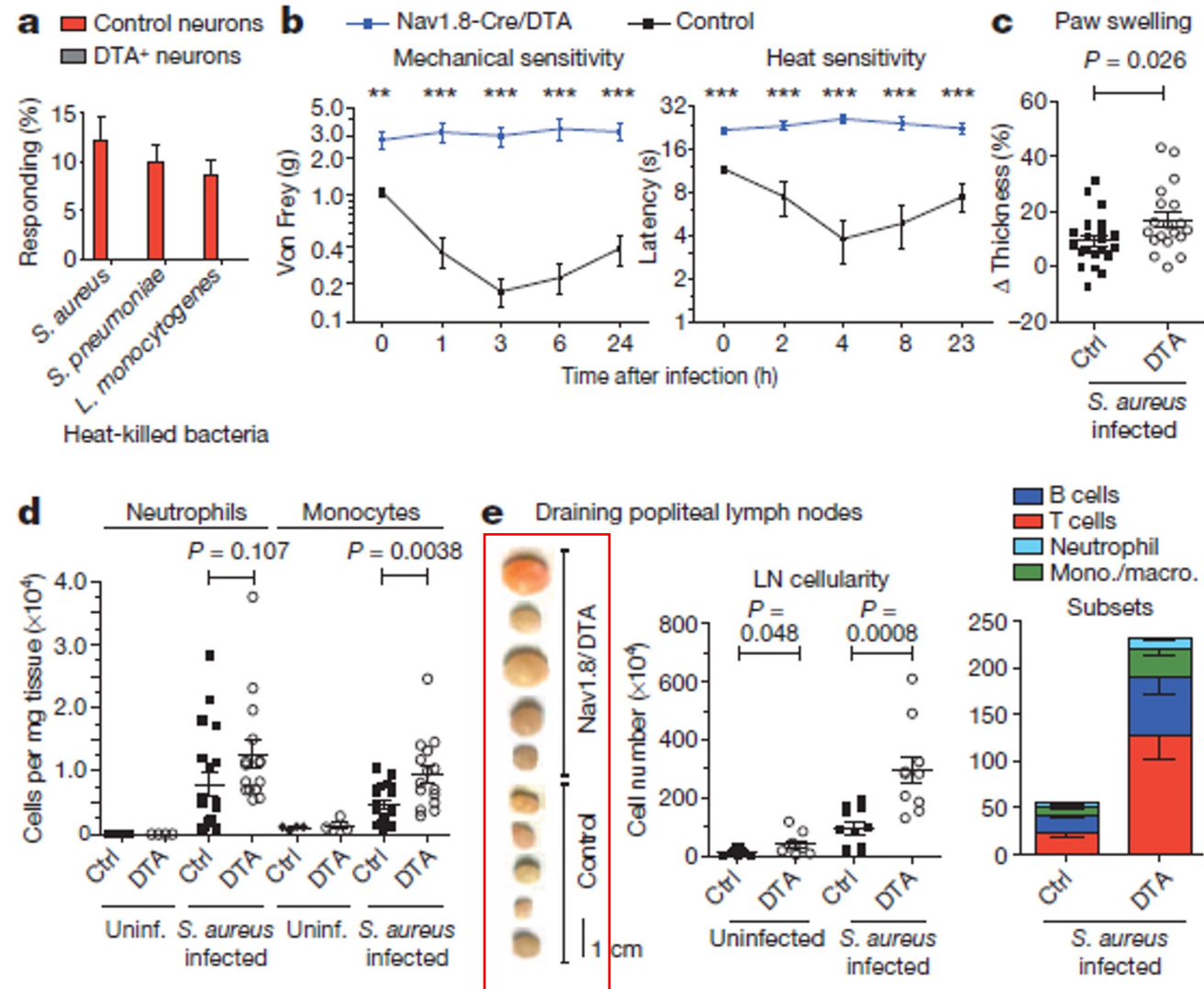


Dermis

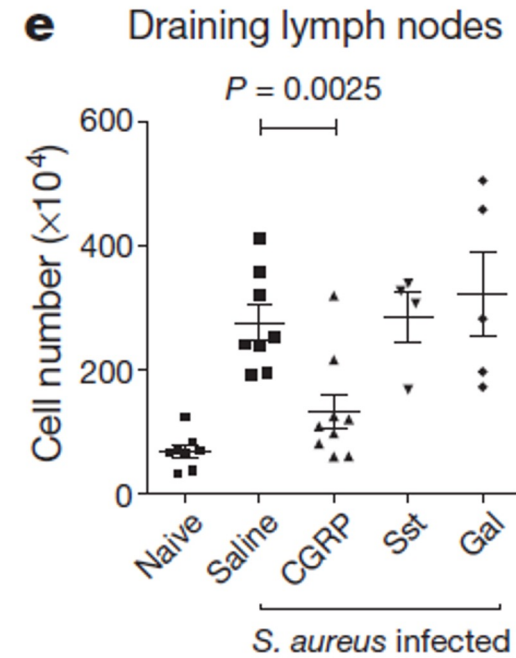
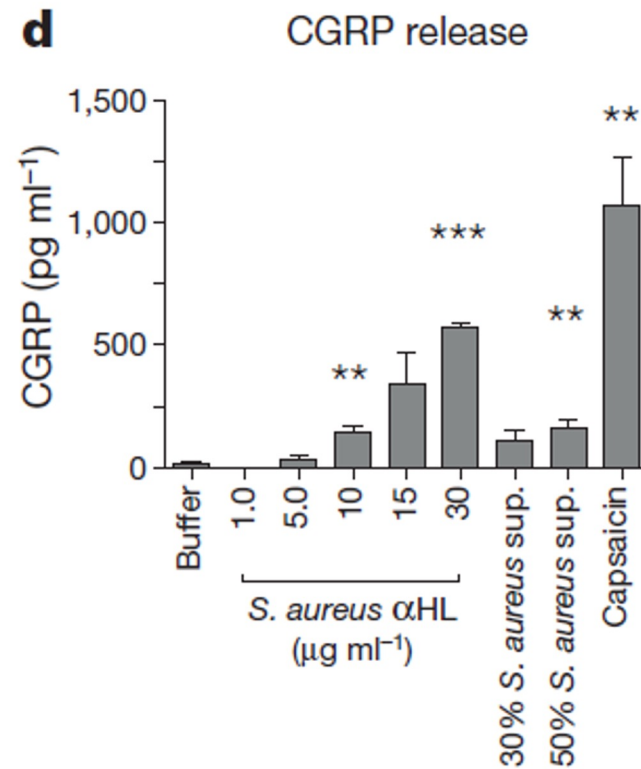
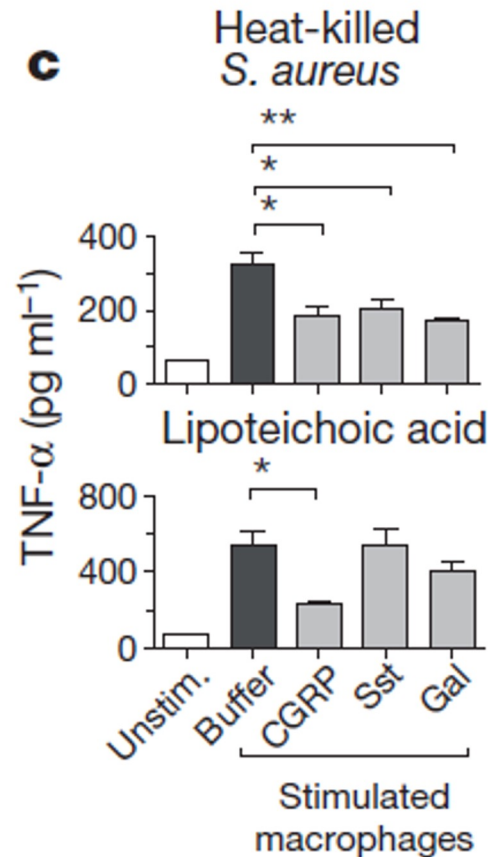




# Dépleção Neurônios Nav1.8 Aumenta a Resposta Inflamatória Local



# Sst, Gal e CGRP Suprimem a Resposta Inflamatória Local





# Qual a função principal dessas células ?

Eliminar

O

Patógeno ?



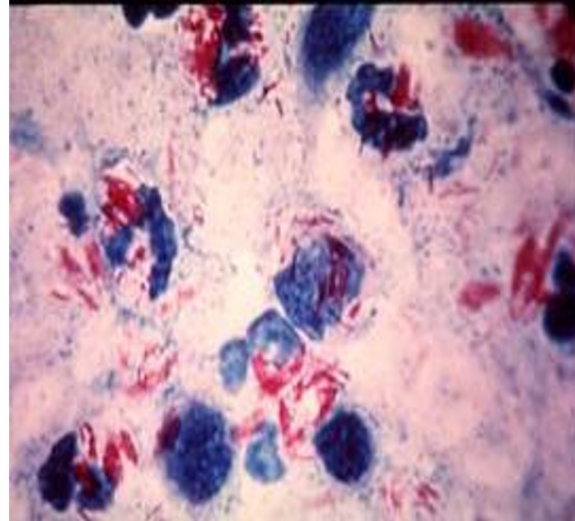
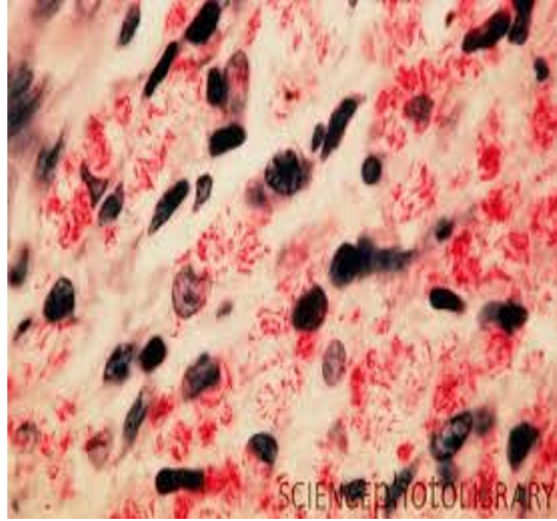
Reparo

Tecidual

Depuração

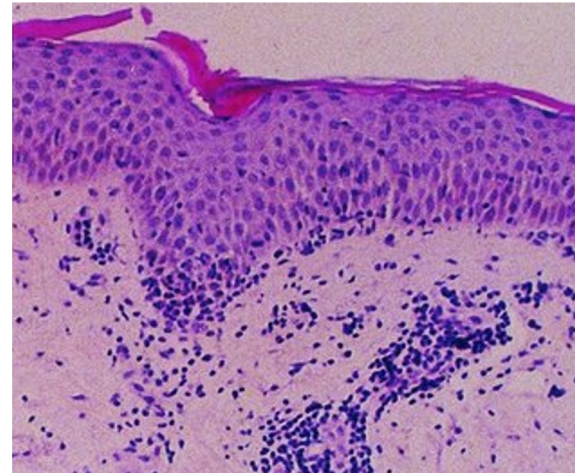
Debris ?

## Lepra



Então é um Sistema  
De

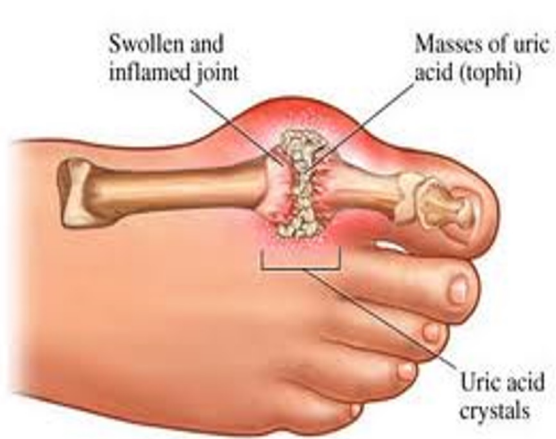
## *Staphylococcus aureus*



Defesa?



## Gota Úrica



...coisas endógenas

Também

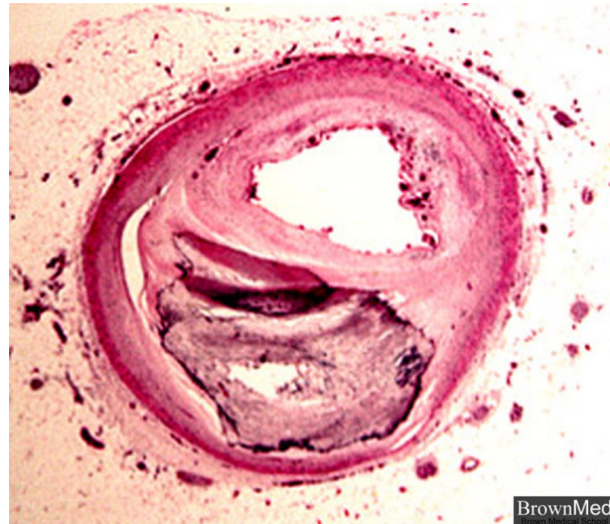
Ativam

Essas vias

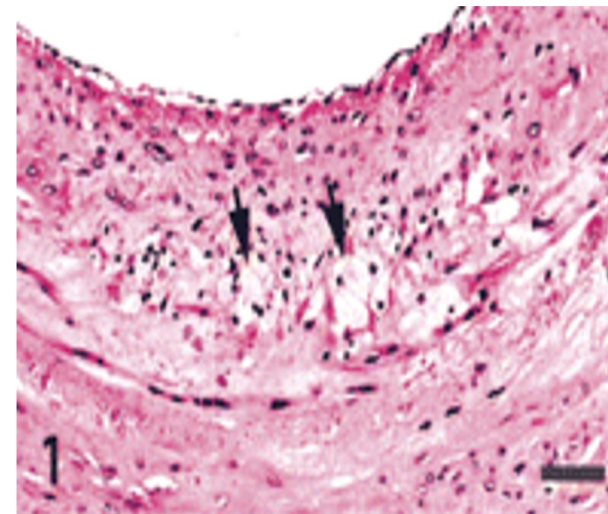
Não é de Defesa.

??????????

## Aterosclerose

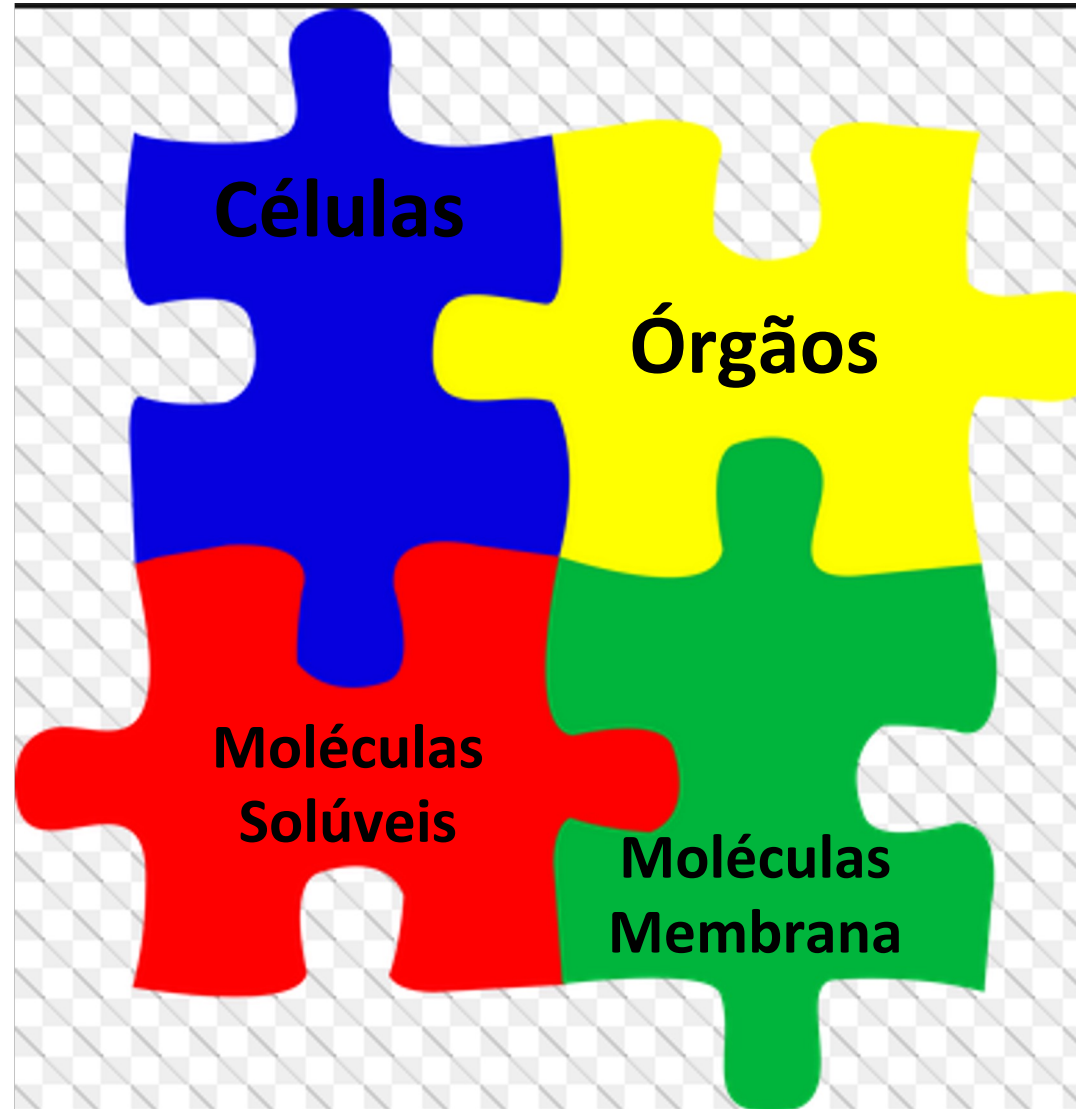


Placa de Ateroma



Células Espumosas

# Montando o Sistema Imune

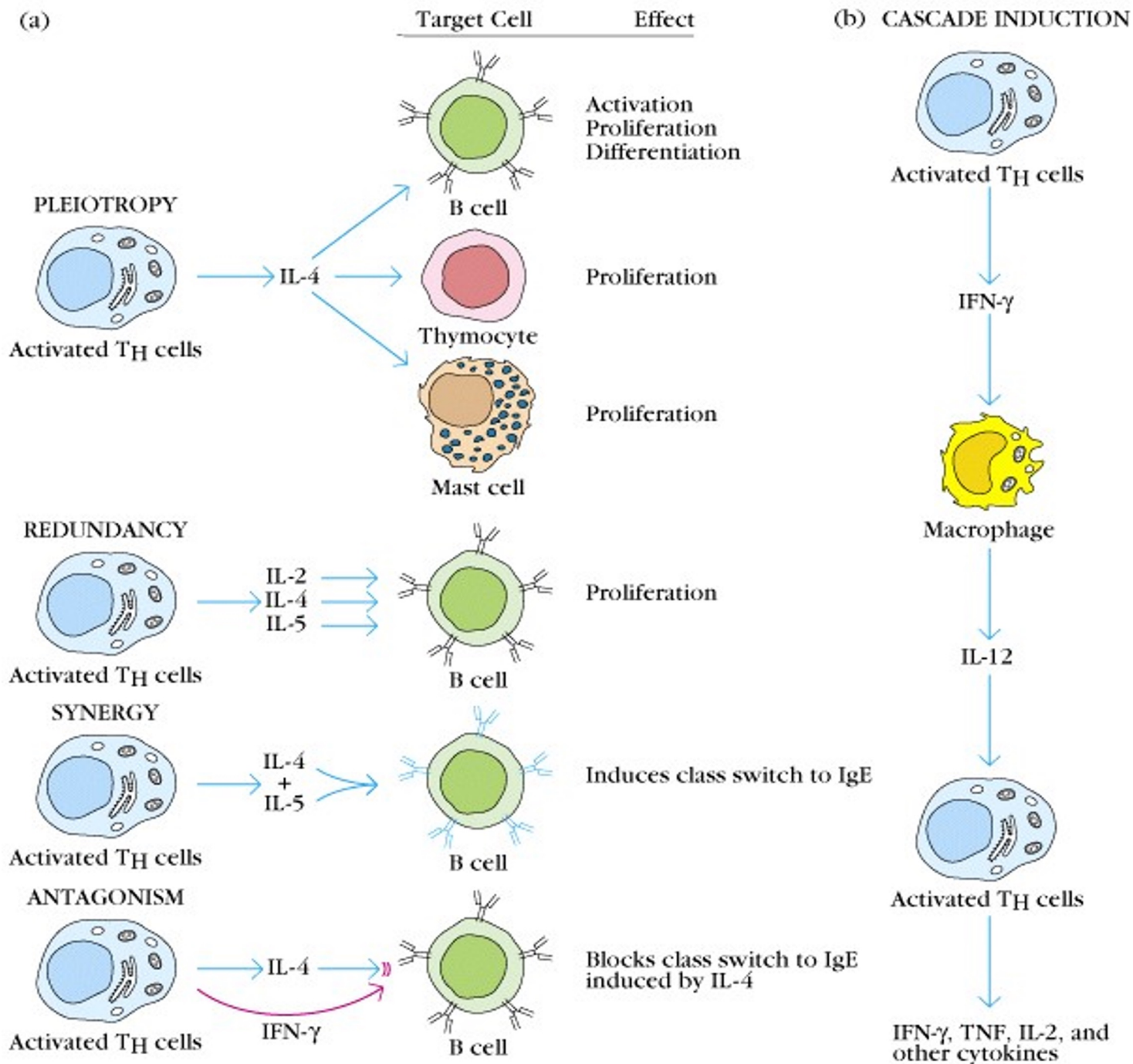




# Características

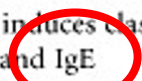
## Das

## Citocinas



**TABLE 12-1** SELECTED FUNCTIONS OF SOME CYTOKINES

Cytokine	Secreted by*	Major biological functions	
		Target cells/tissues	Activity
Interleukin 1 (IL-1 $\alpha$ , IL-1 $\beta$ )	Monocytes, macrophages, B cells, dendritic cells, endothelial cells, other cell types	T <sub>H</sub> cells B cells  NK cells Vascular endothelial cells Macrophages and neutrophils Hepatocytes  Hypothalamus	Co-stimulates activation Promotes maturation and clonal expansion Enhances activity Increases expression of ICAMs <sup>†</sup>  Chemotactically attracts  Induces synthesis of acute- phase proteins Induces fever
Interleukin 2 (IL-2)	T <sub>H</sub> 1 cells	Antigen-primed T <sub>H</sub> and T <sub>C</sub> cells Antigen-specific T-cell clones NK cells (some) and T <sub>C</sub> cells	Induces proliferation Supports long-term growth  Enhances activity
Interleukin 3 (IL-3)	T <sub>H</sub> cells, NK cells, mast cells	Hematopoietic cells Mast cells	Supports growth and differentiation Stimulates growth and histamine secretion
Interleukin 4 (IL-4)	T <sub>H</sub> 2 cells, mast cells, NK cells	Antigen-primed B cells Activated B cells  Resting B cells  Thymocytes and T cells Macrophages  Mast cells	Co-stimulates activation Stimulates proliferation and differentiation; induces class switch to IgG1 and IgE Up-regulates class II MHC expression Induces proliferation Up-regulates class II MHC expression; increases phagocytic activity Stimulates growth





**TABLE 12-1** SELECTED FUNCTIONS OF SOME CYTOKINES

Cytokine	Secreted by*	Major biological functions	
		Target cells/tissues	Activity
Interleukin 5 (IL-5)	T <sub>H</sub> 2 cells, mast cells	Activated B cells  Eosinophils	Stimulates proliferation and differentiation; induces class switch to IgA Promotes growth and differentiation
Interleukin 6 (IL-6)	Monocytes, macrophages, T <sub>H</sub> 2 cells, bone-marrow stromal cells	Proliferating B cells Plasma cells Myeloid stem cells Hepatocytes	Promotes terminal differentiation into plasma cells Stimulates antibody secretion Helps promote differentiation Induces synthesis of acute-phase proteins
Interleukin 7 (IL-7)	Bone-marrow, thymic stromal cells	Lymphoid stem cells  Resting T cells	Induces differentiation into progenitor B and T cells Increases expression of IL-2 and its receptor
Interleukin 8 (IL-8)	Macrophages, endothelial cells	Neutrophils	Chemokine; chemotactically attracts; induces adherence to vascular endothelium and extravasation into tissues
Interleukin 9 (IL-9)	T <sub>H</sub> cells	Some T <sub>H</sub> cells	Acts as mitogen, supporting proliferation in absence of antigen
Interleukin 10 (IL-10)	T <sub>H</sub> 2 cells	Macrophages  Antigen-presenting cells	Suppresses cytokine production and thus indirectly reduces cytokine production by T <sub>H</sub> 1 cells Down-regulates class II MHC expression

Th17

**TABLE 12-1** SELECTED FUNCTIONS OF SOME CYTOKINES

Cytokine	Secreted by*	Major biological functions	
		Target cells/tissues	Activity
Interleukin 11 (IL-11)	Bone-marrow stromal cells	Plasmacytomas Progenitor B cells Megakaryocytes Hepatocytes	Supports growth Promotes differentiation Promotes differentiation Induces synthesis of acute-phase proteins
Interleukin 12 (IL-12)	Macrophages, B cells	Activated T <sub>C</sub> cells  NK and LAK cells and activated T <sub>H1</sub> cells	Acts synergistically with IL-2 to induce differentiation into CTLs Stimulates proliferation
Interleukin 13 (IL-13)	T <sub>H</sub> cells	Macrophages	Inhibits activation and release of inflammatory cytokines; important regulator of inflammatory response
Interleukin 15 (IL-15)	T cells	T cells, intestinal epithelium NK Activated B cells	Stimulates growth of intestinal epithelium, T-cell proliferation Supports proliferation Co-mitogen for proliferation and differentiation
Interleukin 16 (IL-16)	T cells (primarily CD8 <sup>+</sup> ) and eosinophils	CD4 <sup>+</sup> T cells  Monocytes Eosinophils	Chemotaxis; induces expression of class II MHC; induces synthesis of cytokines; suppresses antigen-induced proliferation Chemotaxis; induces class II MHC Chemotaxis; induces cell adhesion
Interleukin 17 (IL-17)	T cells	Macrophages	Initiates and maintains inflammation
Interleukin 18 (IL-18)	Activated macrophages	T cells NK cells	Induces IFN- $\gamma$ production Enhances NK cell cytotoxicity
Interferon alpha (IFN- $\alpha$ )	Leukocytes	Uninfected cells	Inhibits viral replication
Interferon beta (IFN- $\beta$ )	Fibroblasts	Uninfected cells	Inhibits viral replication

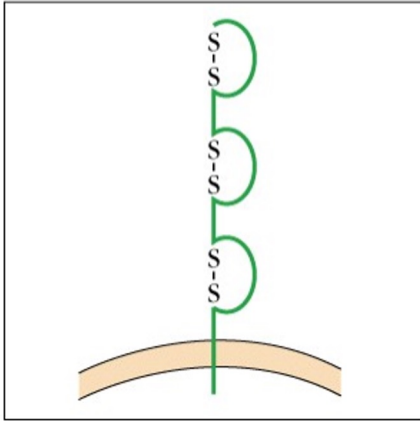
Th1



**TABLE 12-1** SELECTED FUNCTIONS OF SOME CYTOKINES

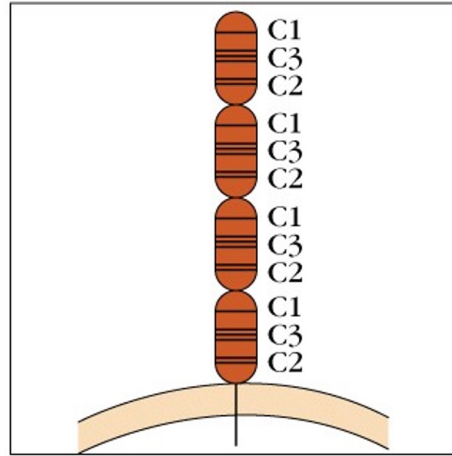
Cytokine	Secreted by*	Major biological functions	
		Target cells/tissues	Activity
Interferon gamma (IFN- $\gamma$ )	T <sub>H</sub> 1, T <sub>C</sub> , NK cells	Uninfected cells Macrophages Many cell types  Proliferating B cells  T <sub>H</sub> 2 cells Inflammatory cells	Inhibits viral replication Enhances activity Increases expression of class I and class II MHC molecules Induces class switch to IgG2a; blocks IL-4–induced class switch to IgE and IgG1 Inhibits proliferation Mediates various effects important in delayed-type hypersensitivity
Leukemia-inhibitory factor (LIF)	Thymic epithelial cells, bone-marrow stromal cells	Hepatocytes  Embryonic stem (ES) cells	Induces synthesis of acute-phase proteins Supports proliferation and differentiation
Oncostatin M (OSM)	Macrophages, T cells	Tumor cells Hepatocytes  Kaposi's sarcoma	Inhibits growth Induces synthesis of acute-phase proteins Stimulates growth
Transforming growth factor $\beta$ (TGF- $\beta$ )	Platelets, macrophages, lymphocytes, mast cells	Monocytes and macrophages Activated macrophages Epithelial, endothelial, lymphoid, and hematopoietic cells Proliferating B cells	Chemotactically attracts  Induces increased IL-1 production Inhibits proliferation, thus limiting inflammatory response and promoting wound healing Induces class switch to IgA
Tumor necrosis factor $\alpha$ (TNF- $\alpha$ )	Macrophages, mast cells	Tumor cells Inflammatory cells	Has cytotoxic effect Induces cytokine secretion and is responsible for extensive weight loss (cachexia) associated with chronic inflammation
Tumor necrosis factor $\beta$ (TNF- $\beta$ )	T <sub>H</sub> 1 and T <sub>C</sub> cells	Tumor cells  Macrophages and neutrophils	Has cytotoxic and other effects similar to TNF- $\alpha$ Enhances phagocytic activity

(a) Immunoglobulin superfamily receptors



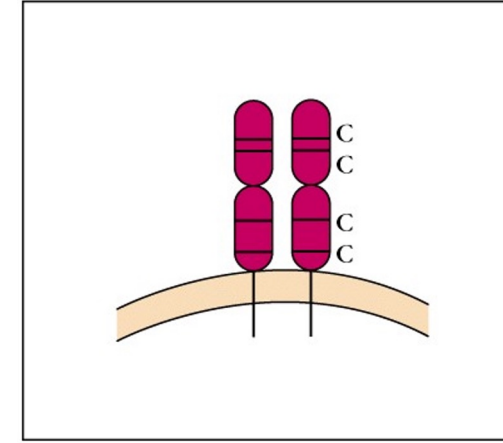
IL-1  
M-CSF  
C-Kit

(d) TNF receptors



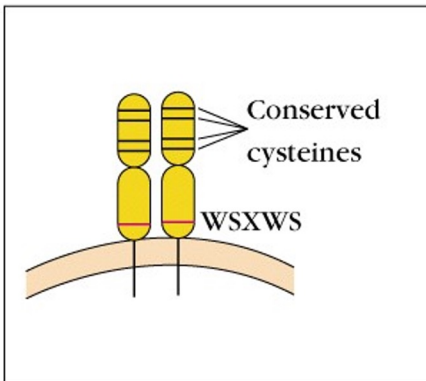
TNF- $\alpha$   
TNF- $\beta$   
CD40  
Nerve growth factor (NGF)  
FAS

(c) Class II cytokine receptors (interferon)



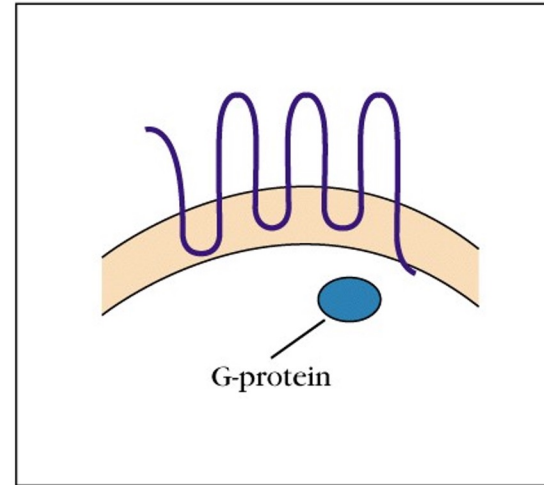
IFN- $\alpha$   
IFN- $\beta$   
IFN- $\gamma$   
IL-10

(b) Class I cytokine receptors (hematopoietin)



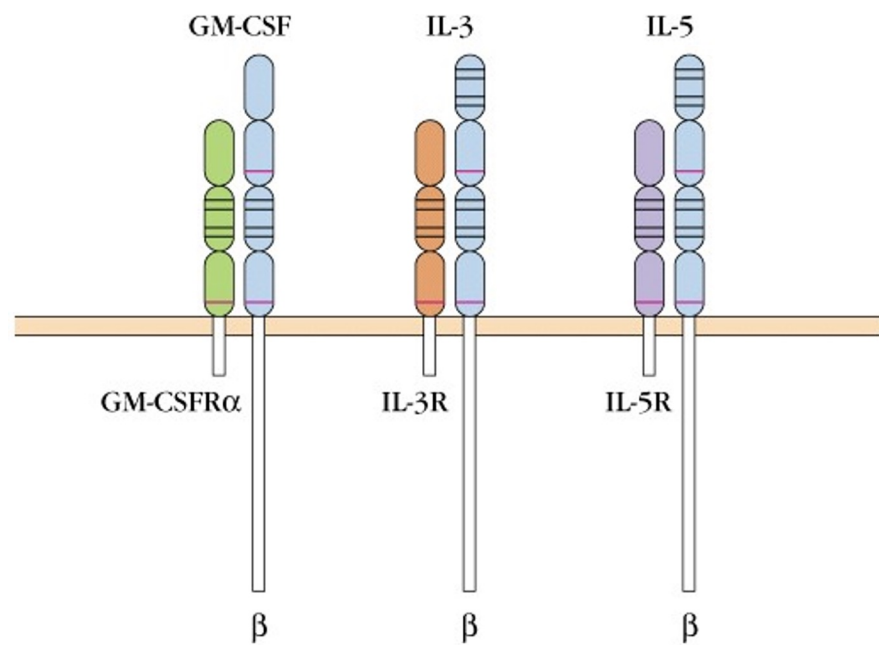
IL-2	IL-13
IL-3	IL-15
IL-4	GM-CSF
IL-5	G-CSF
IL-6	OSM
IL-7	LIF
IL-9	CNTF
IL-11	Growth hormone
IL-12	Prolactin

(e) Chemokine receptors

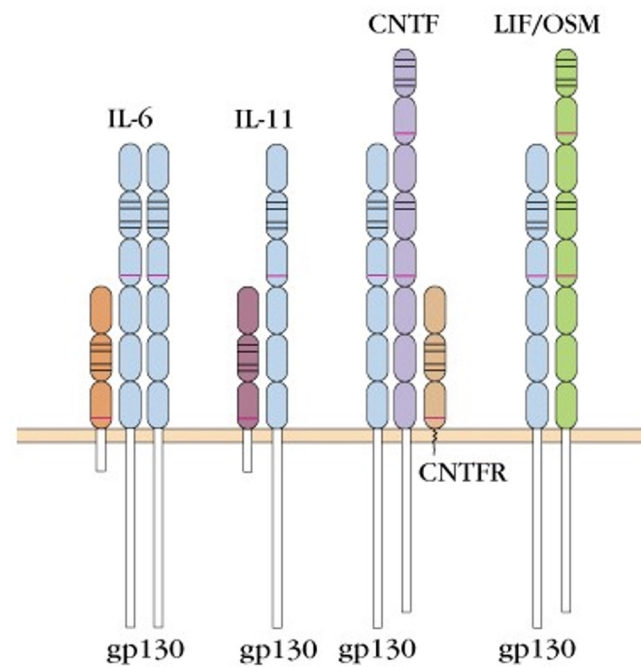


IL-8  
RANTES  
MIP-1  
PF4  
MCAF  
NAP-2

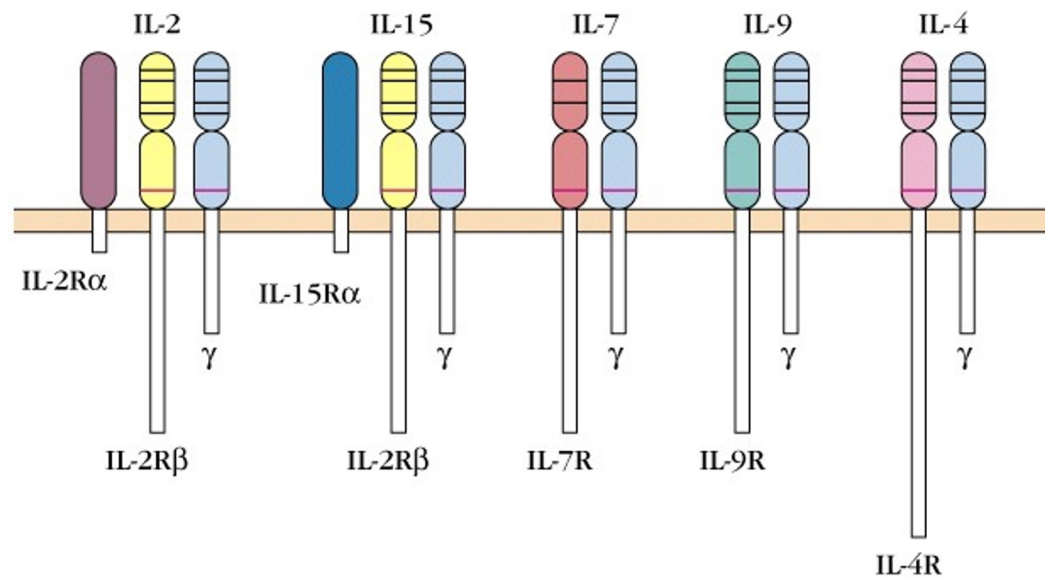
(a) GM-CSF receptor subfamily (common  $\beta$  subunit)



(b) IL-6 Receptor subfamily (common gp130 subunit)



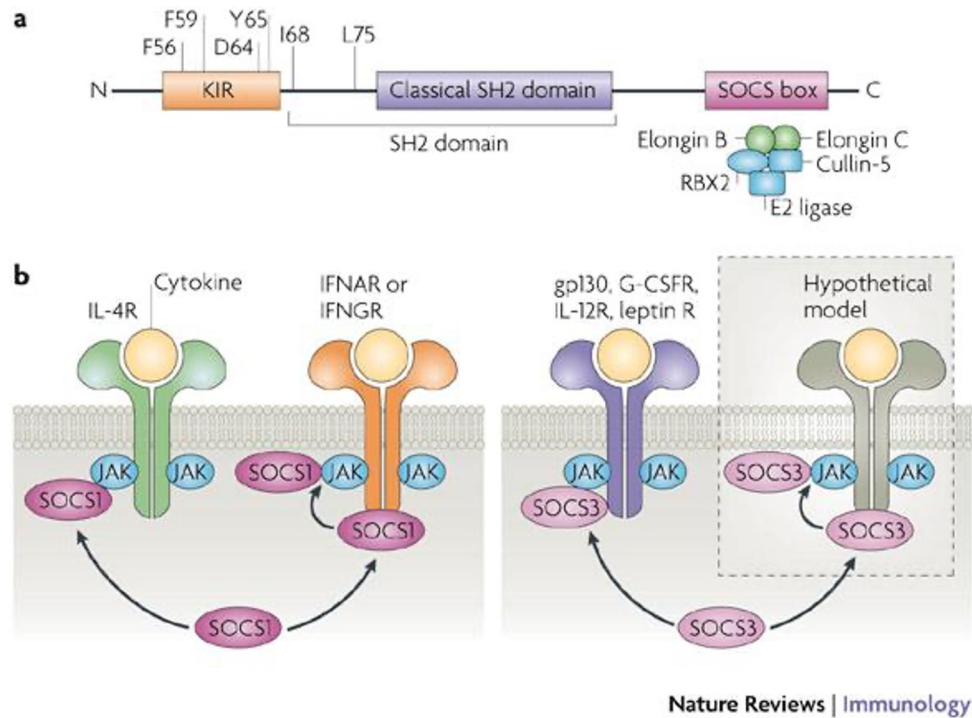
(c) IL-2 receptor subfamily (common  $\gamma$  subunit)



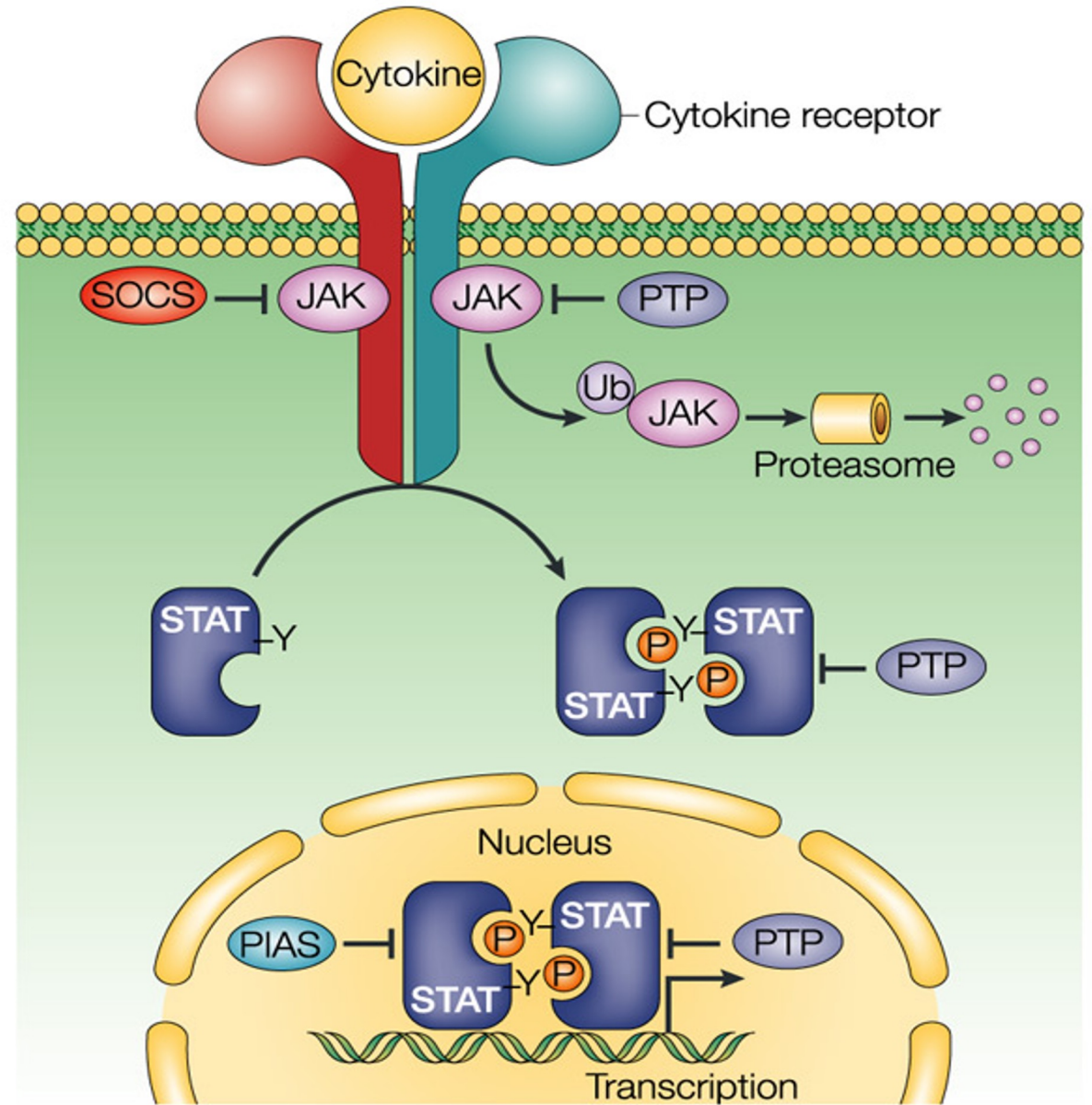


# Vias de Sinalização

## JAK - STAT



Inibida por SOCS



Nature Reviews | Immunology

Fatores de Crescimento

Apresentação de Ag

Moléculas Costimuladoras

Moléculas microbidas

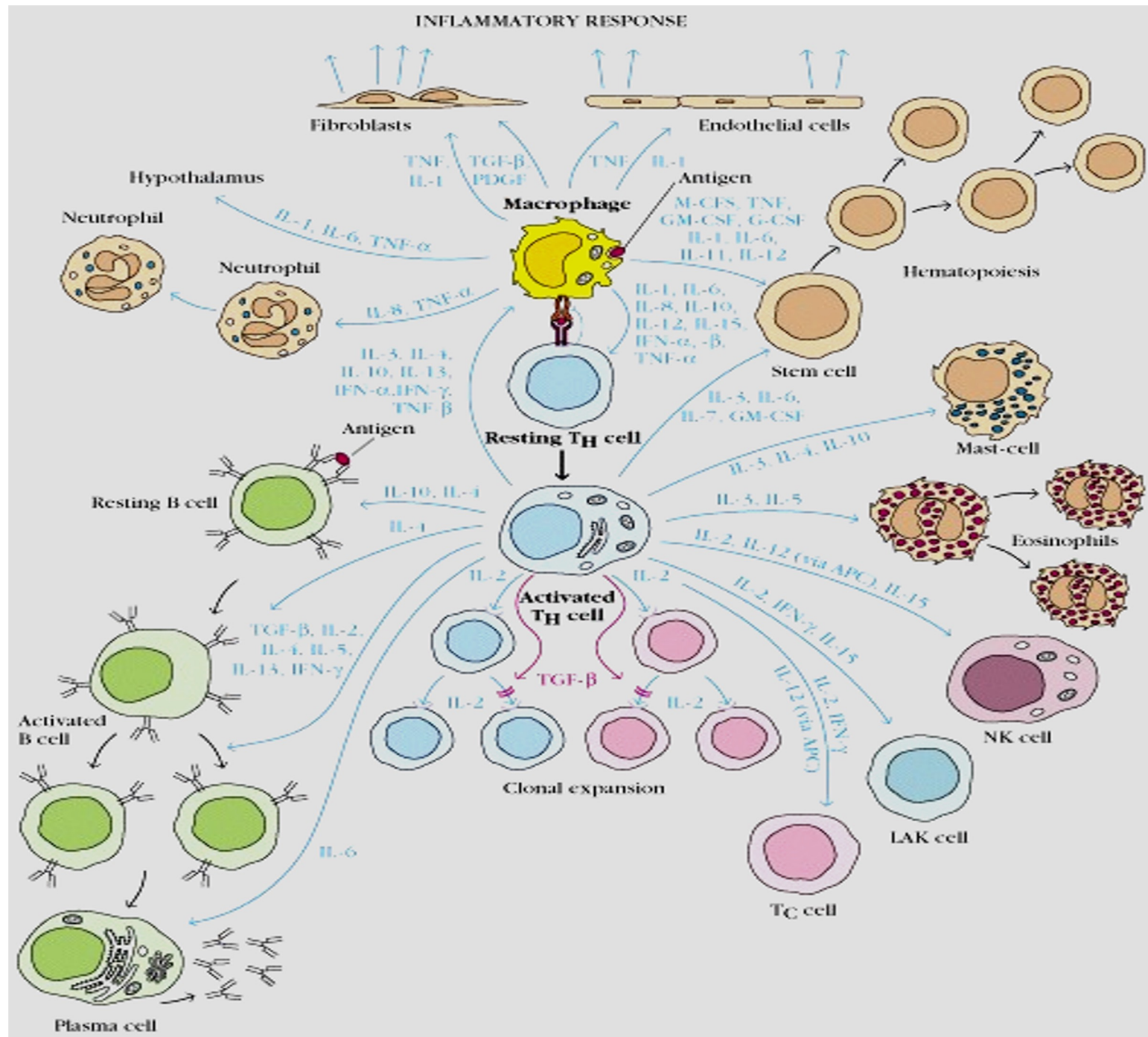
Quimiotraentes

Febre

Estado anti-viral

Fibrose

Morte Celular

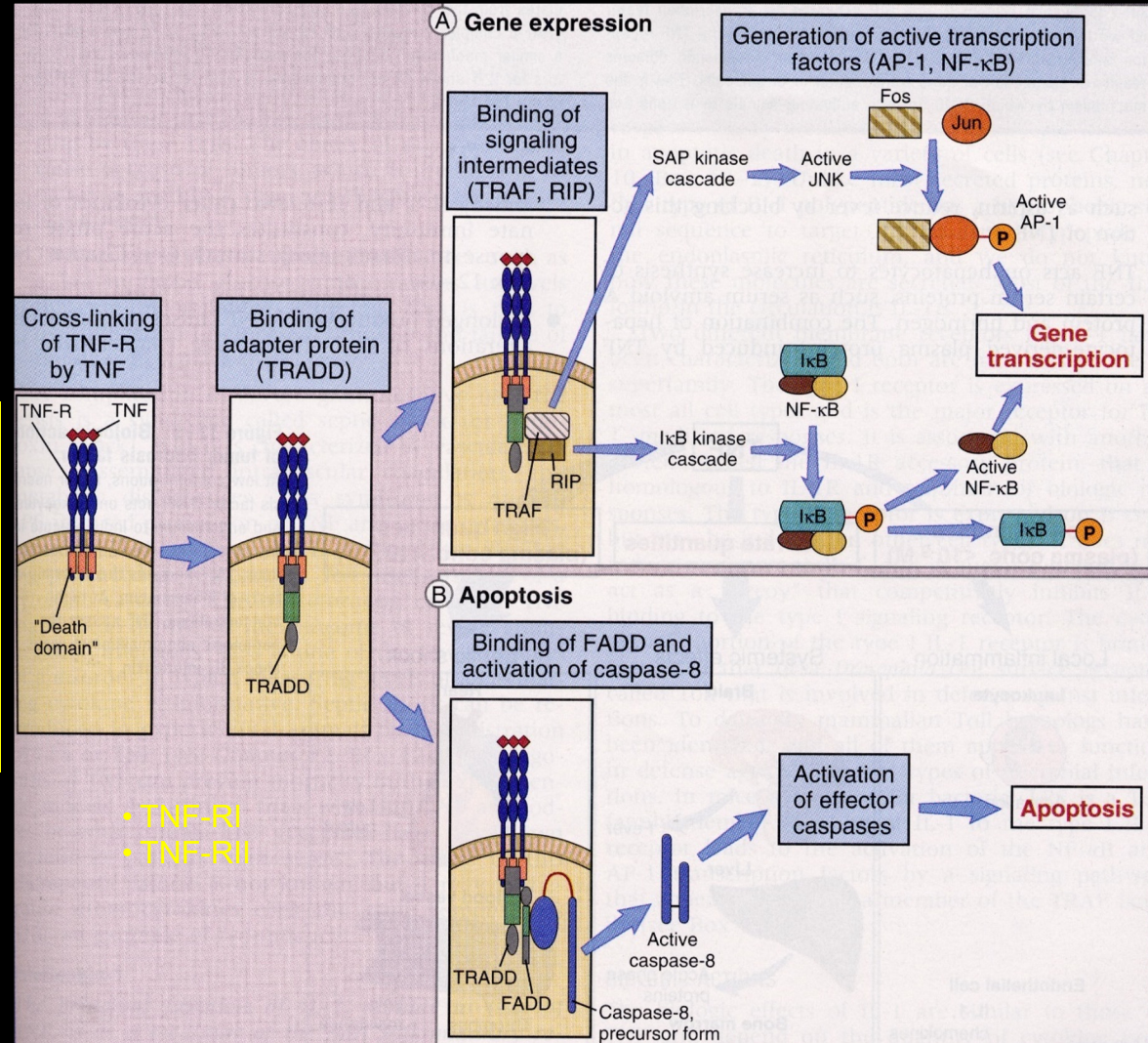
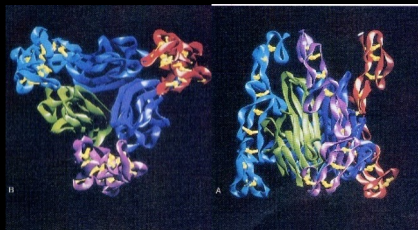
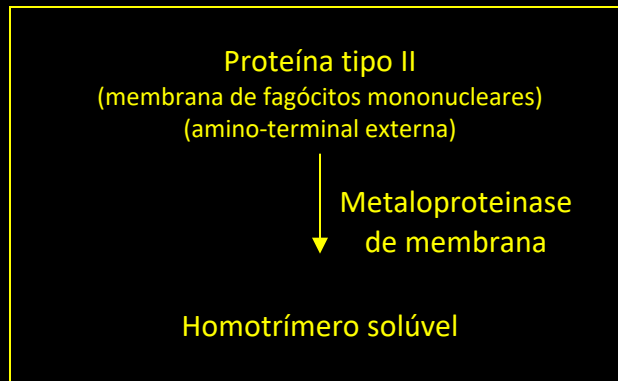




# Citocinas na Imunidade Inata

## TNF- $\alpha$ - Produção, Estrutura e Receptores

- Substância no soro de animais com LPS que causava necrose de tumores
- FAGÓCITOS MONONUCLEARES, Células T, NK e mastócitos
- LPS em MACRÓFAGOS: forte estímulo
- IFN- $\gamma$ : adjuvante para estímulo com LPS



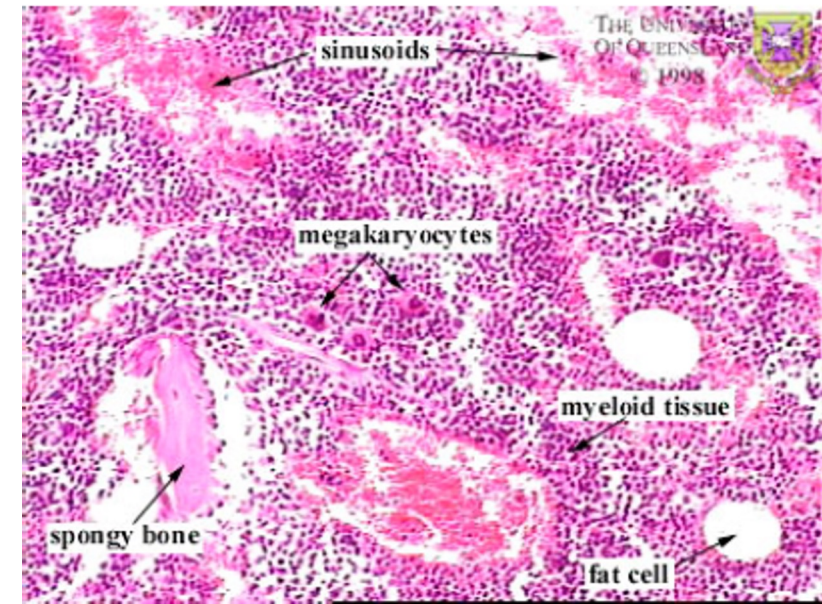
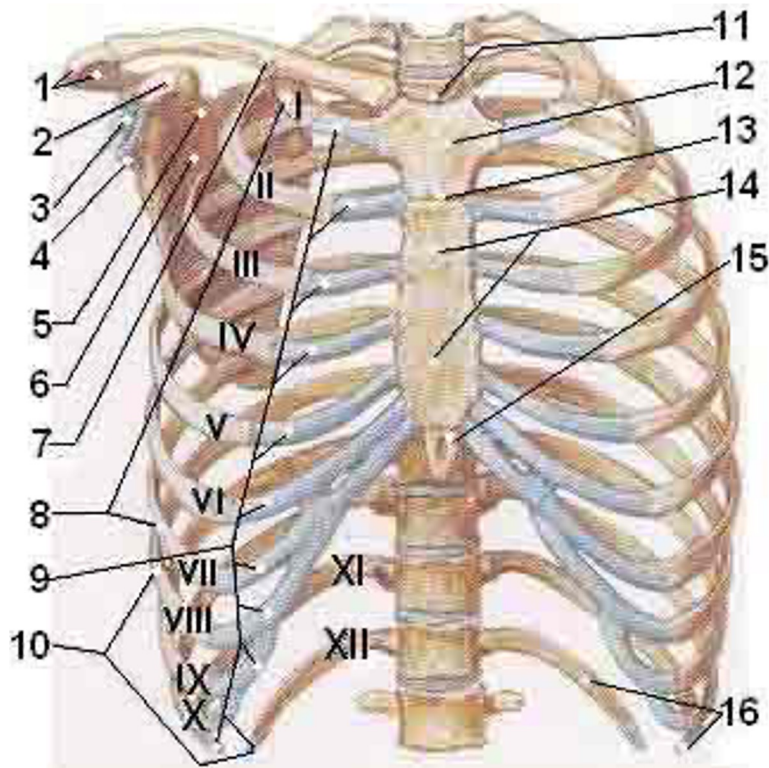


Quais são e onde ficam os órgãos linfóides ?



# Órgãos Linfóides Primários

## Ossos Achatados

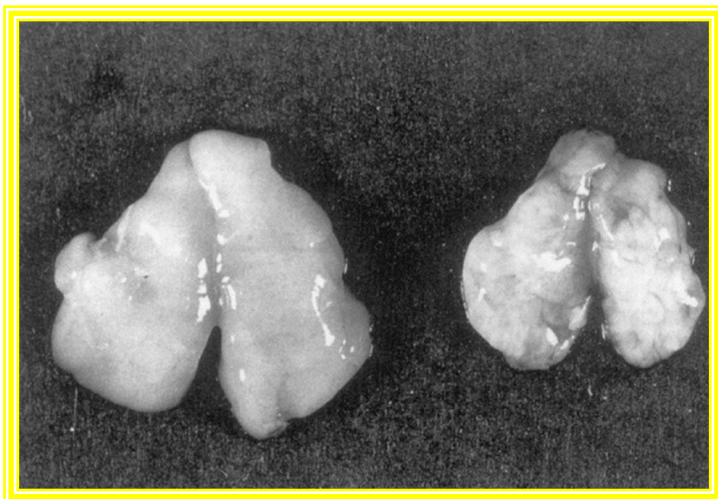


- **Hematopoiese**  
saco vitelino → fígado → baço → medula óssea
- **Ossos achatados**
- **Arcabouço reticular ósseo**
- **Células adiposas, fibroblastos e precursores celulares**
- **Células precursoras: CD34<sup>+</sup> Sca-1<sup>+</sup>**
- **Produção de Fatores Estimuladores de Colônias (CSF)**
- **CFS: células do estroma e macrófagos**
- **Plasmócitos**

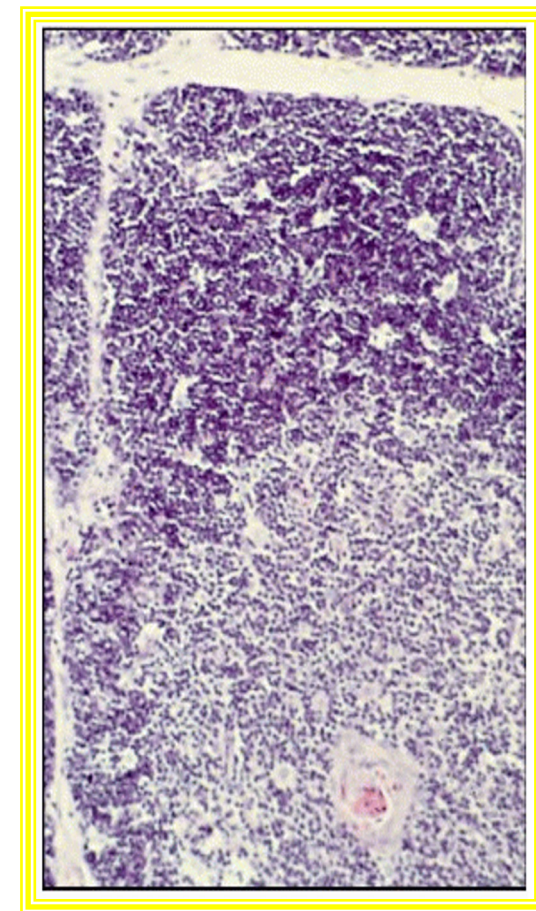
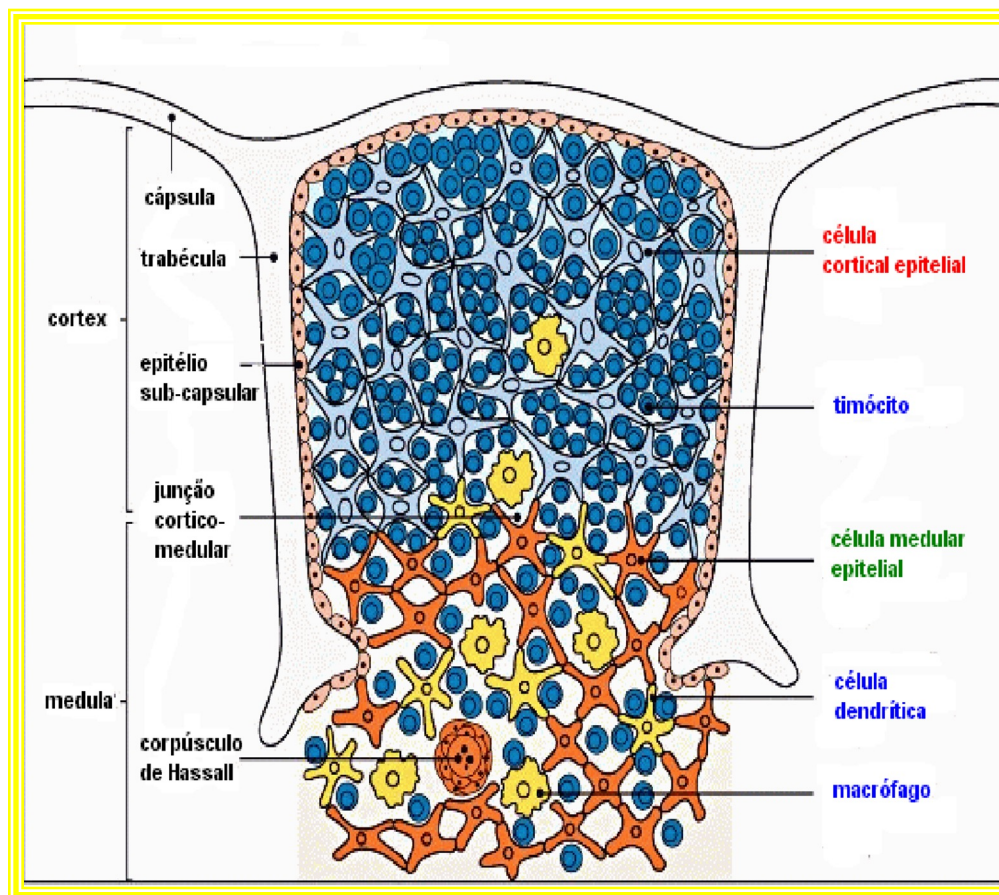


# Órgãos Linfóides Primários

## Timo



- Bilobado
- Ectoderme (arcos branquiais)
- NUDE: sem pelos e timo  
(homem: Síndrome de DiGeorge)
- Maturação de Linfócitos T CD4<sup>+</sup> ou CD8<sup>+</sup>



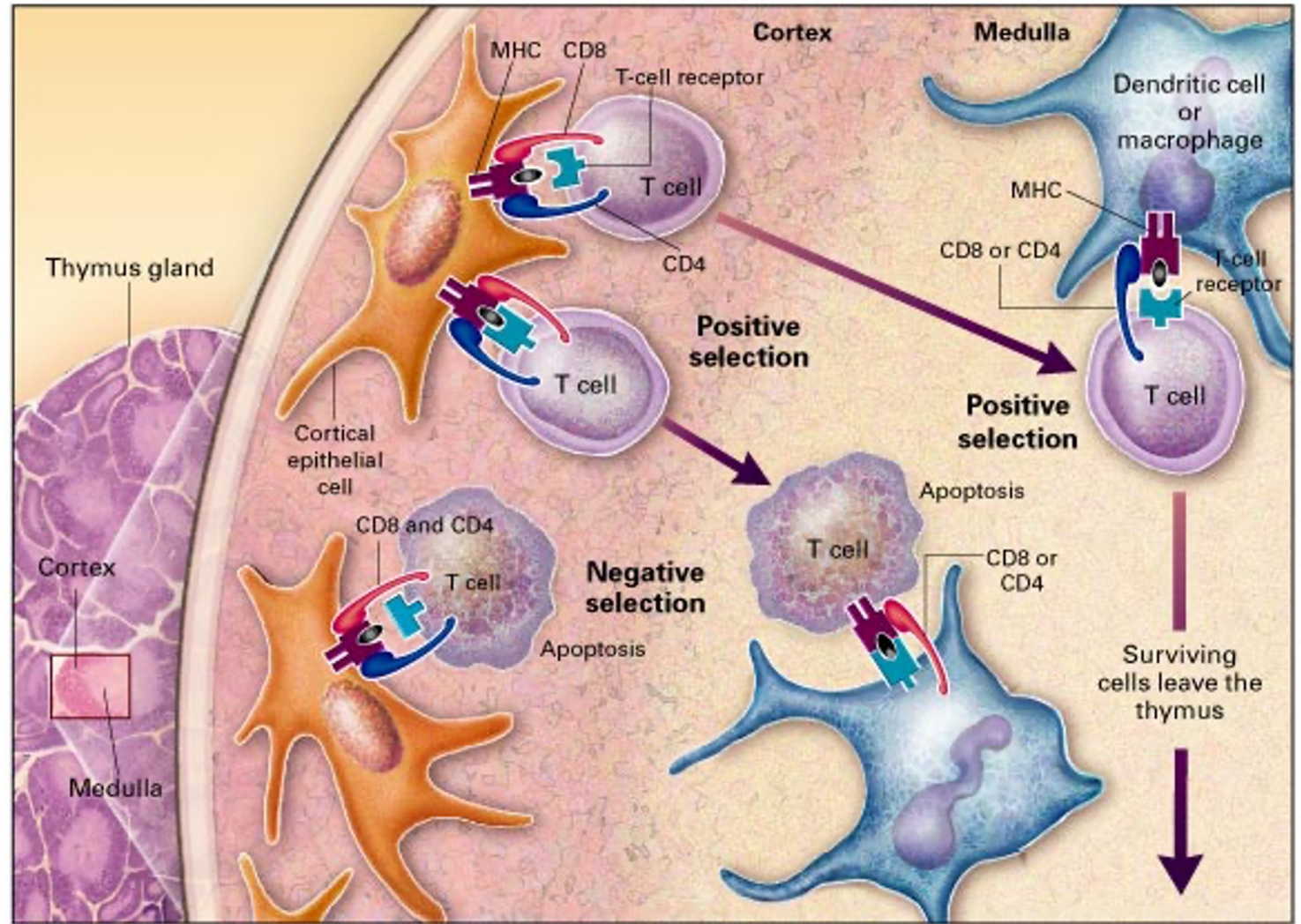


## Tolerância Central

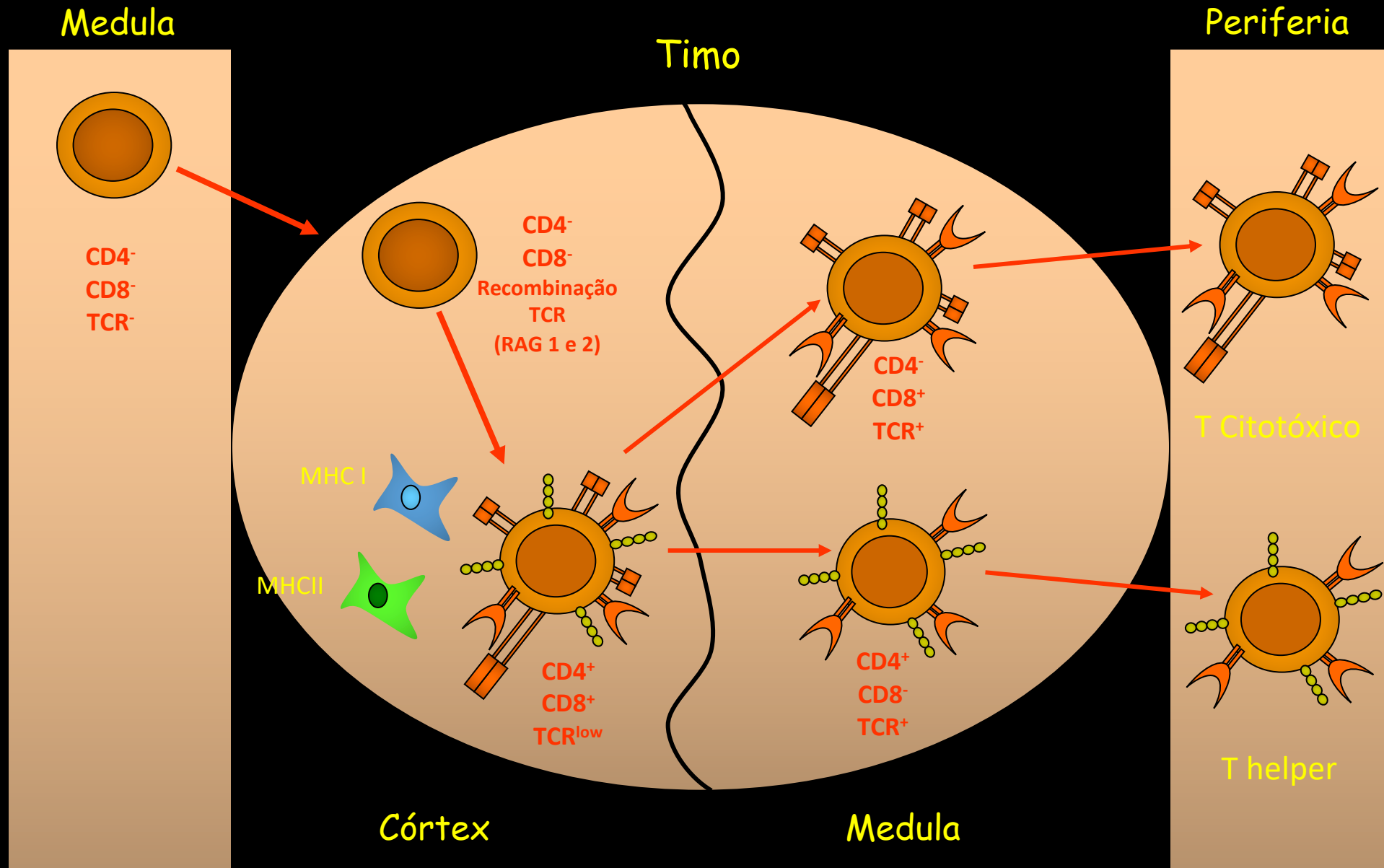
Linfócitos T Reconhecem  
Peptídeos + MHC

Precisam aprender  
Quais são as nossas  
Proteínas

# AIRE



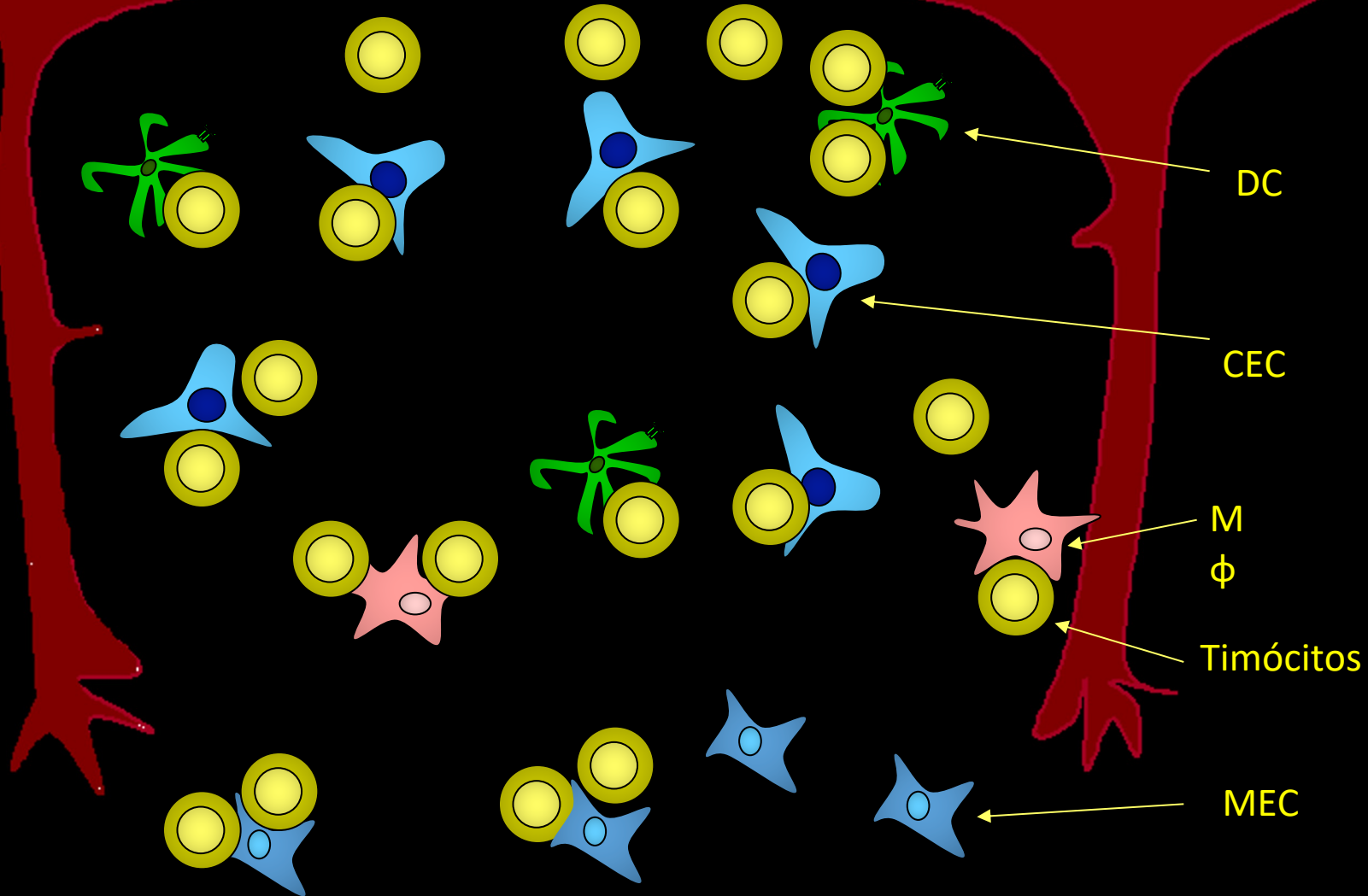
# Ao adentrar o timo, timócitos passam a expressar CD4<sup>pos</sup> CD8<sup>pos</sup>





# Migração Intra-Tímica

Maturação



DC

CEC

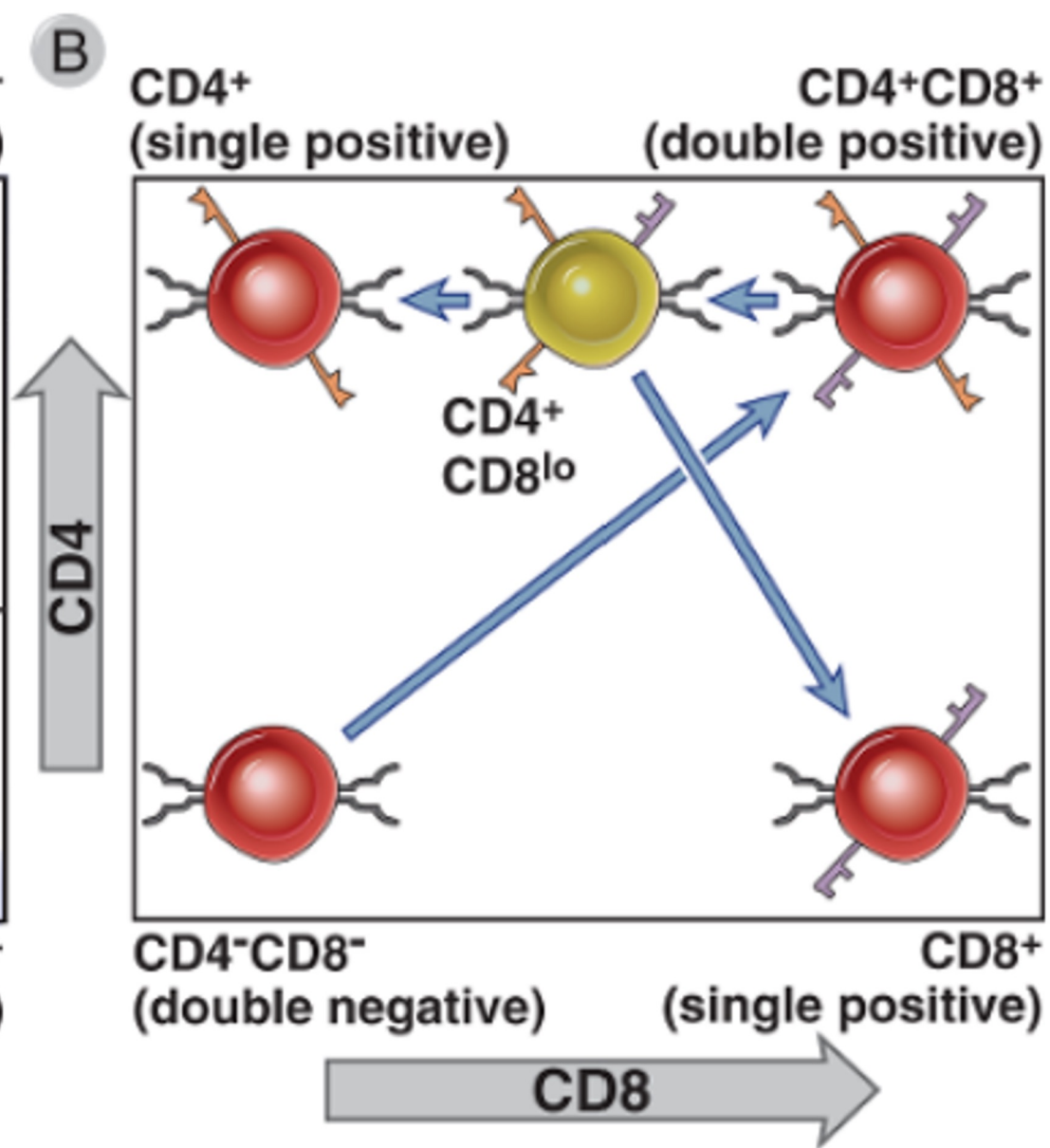
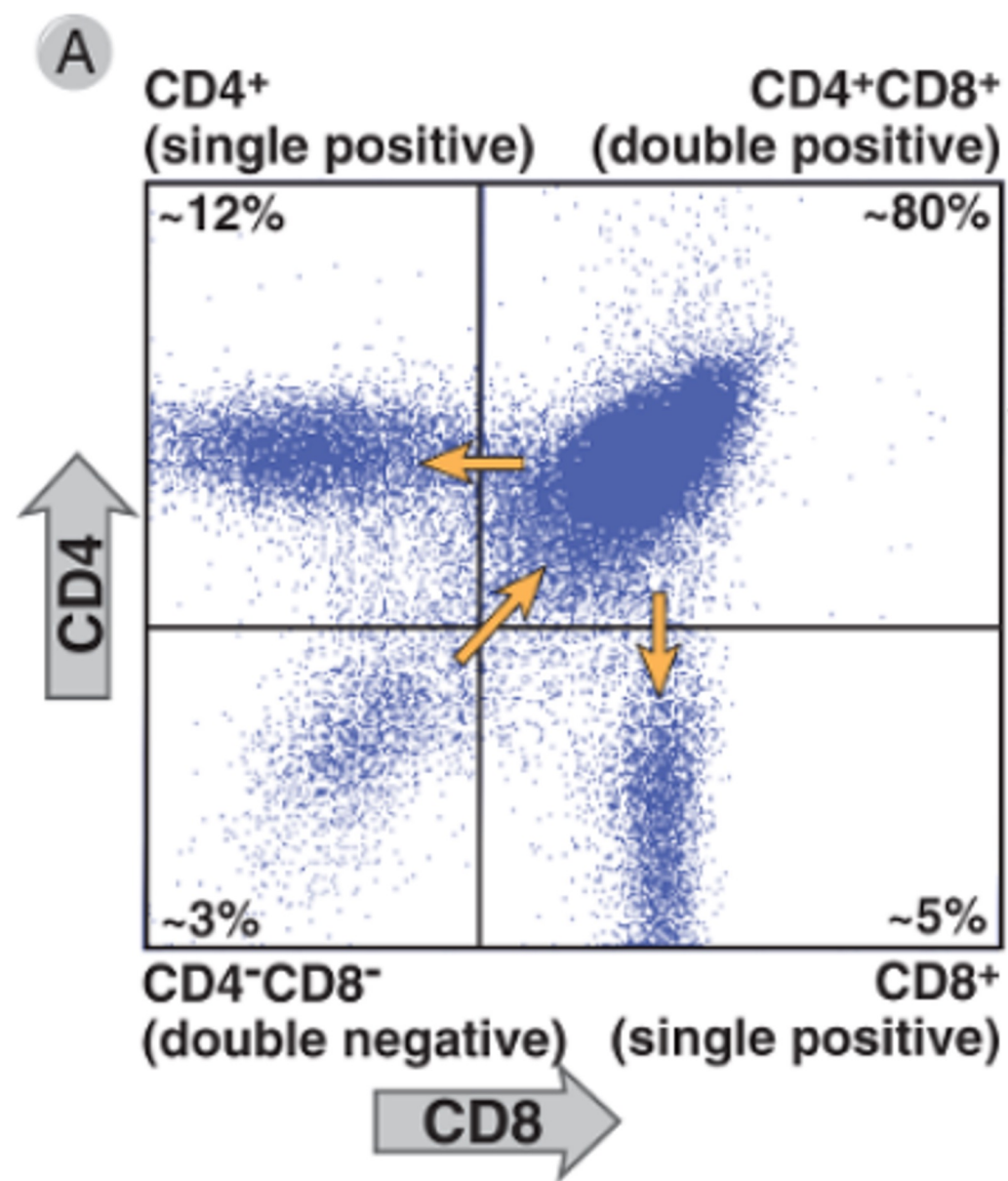
M  
φ

Timóцитos

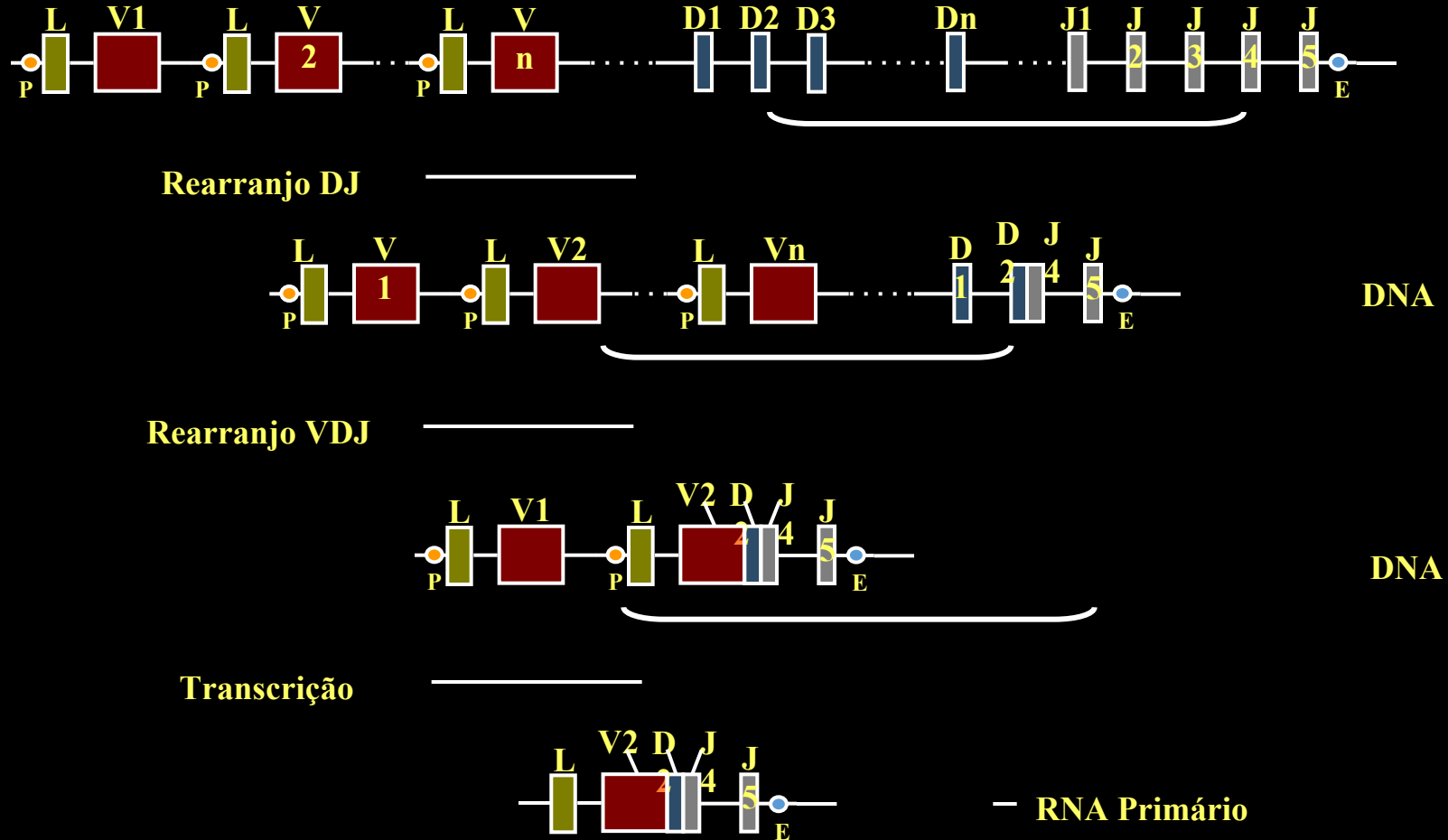
MEC







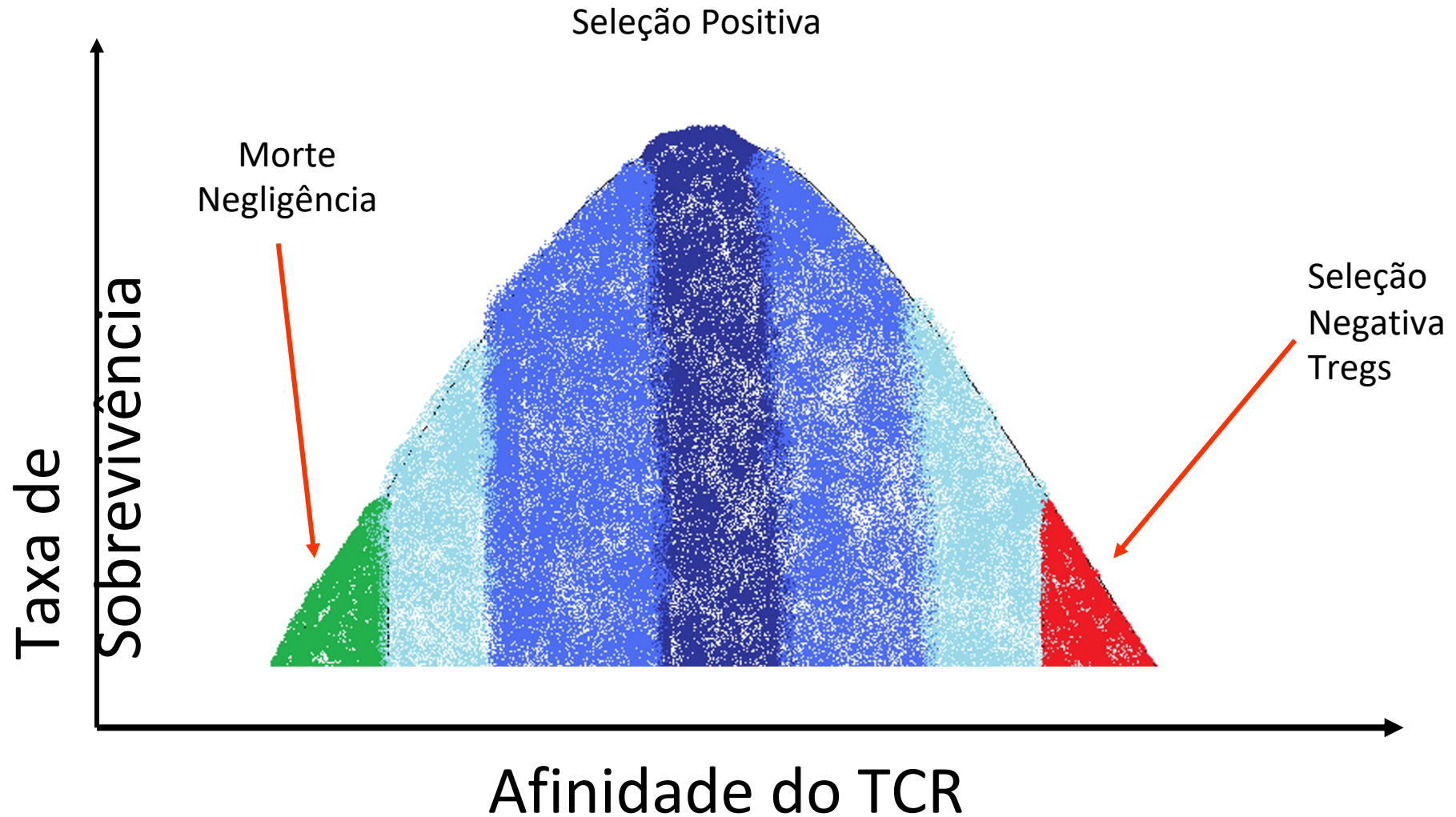
# Rearranjo V(D)J do TCR – Enzimas RAG



Especificidade da Célula T



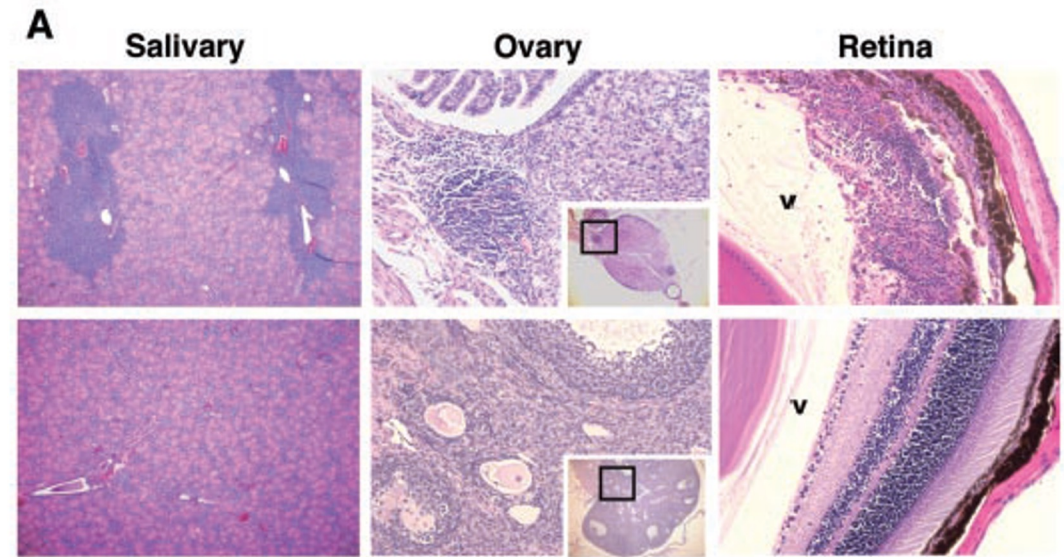
Limiar de Seleção  
Regido pela Força de Interação Entre os Linfócitos e Antígenos Próprios



# Projection of an Immunological Self Shadow Within the Thymus by the Aire Protein

Mark S. Anderson,<sup>1</sup> Emily S. Venanzi,<sup>1</sup> Ludger Klein,<sup>2</sup>  
 Zhibin Chen,<sup>1</sup> Stuart P. Berzins,<sup>1</sup> Shannon J. Turley,<sup>1</sup>  
 Harald von Boehmer,<sup>2</sup> Roderick Bronson,<sup>3</sup> Andrée Dierich,<sup>4</sup>  
 Christophe Benoist,<sup>1\*</sup> Diane Mathis<sup>1\*</sup>

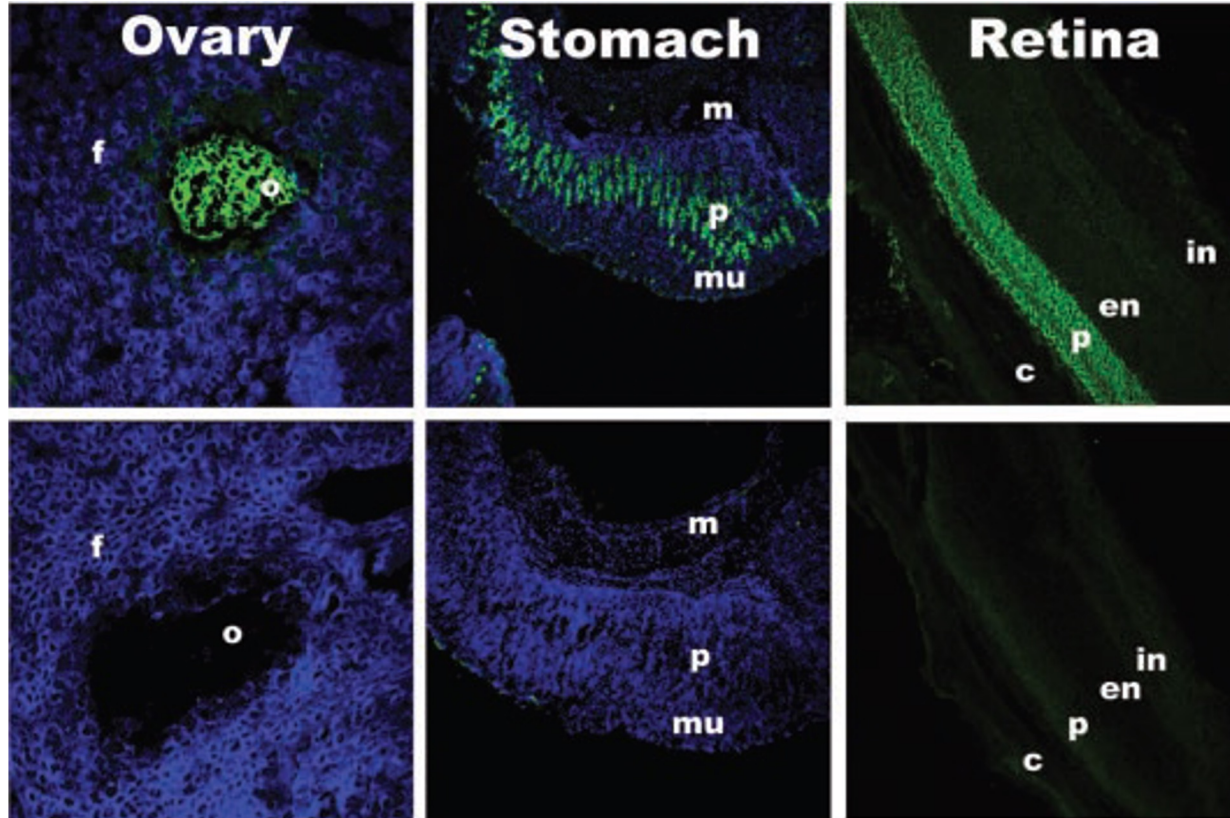
Humans expressing a defective form of the transcription factor AIRE (autoimmune regulator) develop multiorgan autoimmune disease. We used *aire*-deficient mice to test the hypothesis that this transcription factor regulates autoimmunity by promoting the ectopic expression of peripheral tissue-restricted antigens in medullary epithelial cells of the thymus. This hypothesis proved correct. The mutant animals exhibited a defined profile of autoimmune diseases that depended on the absence of *aire* in stromal cells of the thymus. *Aire*-deficient thymic medullary epithelial cells showed a specific reduction in ectopic transcription of genes encoding peripheral antigens. These findings highlight the importance of thymically imposed “central” tolerance in controlling autoimmunity.



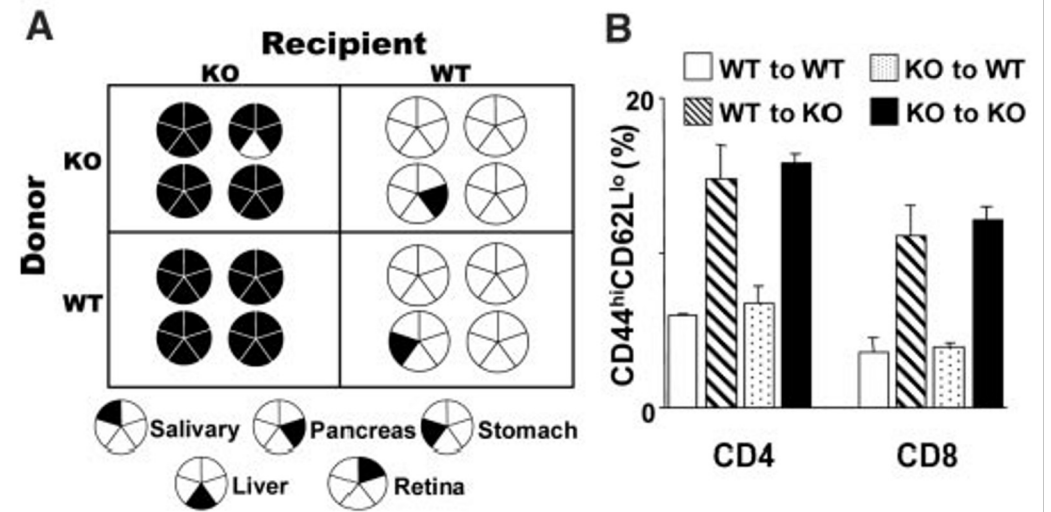
<u>Sex</u>	<u>Age</u>	<u>Salivary</u>	<u>Reproduc.</u>	<u>Thyroid</u>	<u>Retina</u>	<u>Liver</u>	<u>Stomach</u>
F	3	-	-	+	ND	-	-
M	4	-	-	-	ND	-	-
M	4	-	-	-	ND	-	-
F	9	+	-	-	ND	-	-
F	9	+	-	ND	ND	ND	ND
M	9	-	-	ND	-	ND	ND
M	10	tr	-	ND	+	ND	ND
M	15	+	-	-	ND	-	-
F	15	+	+	+	+	tr	-
F	15	+	-	-	-	tr	-
F	22	+	-	NA	+	tr	-
M	30	+	+	NA	-	+	+
F	31	+	tr	-	++	+	+
M	35	+	+	NA	+	+	-



# AIRE KO Animals Have Serum Auto-antibodies



Transference of BM to WT or AIRE KO





# Tissue Specific Genes Orchestrated by AIRE

Human

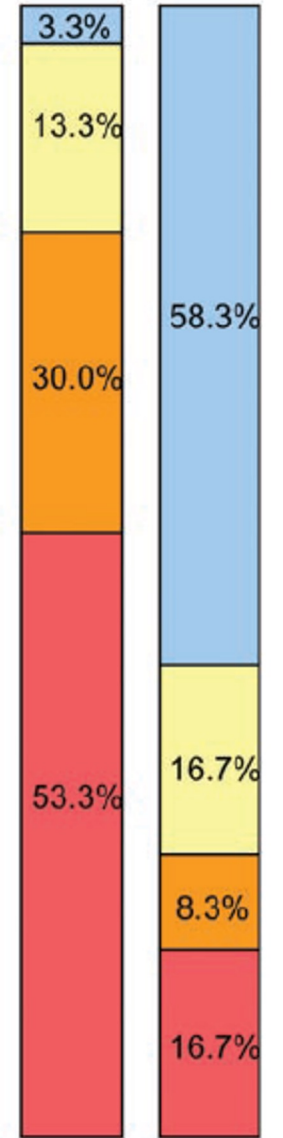
APECED

AIRE Mutation

Probe name	Gene name	Tissue(s)	WT signal	KO signal	KO/WT	t-test p-val	FPR Quad	FPR SAM
96030_at	casein alpha	mammary	75.82	1	0.013	0.0417	0.043	0.014
97180_f_at	hemoglobin y, beta-like embryonic chain	fetal erythrocytes	87.36	1.29	0.015	0.0803	0.279	0.014
100106_at	intestinal trefoil factor	intestinal goblet cells	74.59	1.99	0.027	0.0504	< 0.02	0.014
101820_at	neurotoxin homologue	granulocytes, monocytes	29.50	1	0.034	0.1105	< 0.02	0.014
94738_s_at	cryptdin, related sequence 2	Paneth cells	100.47	3.85	0.038	0.2561	0.164	-
101682_f_at	major urinary protein IV	lachrymal gland, parotid gland	26.49	1.2	0.045	0.0392	0.063	0.014
94153_g_at	salivary protein 1	salivary gland	22.82	1.06	0.047	0.0712	0.131	0.014
102998_at	cytochrome P450 1a2	liver, lung, duodenum	20.99	1.01	0.048	0.0868	0.043	0.014
101115_at	lactotransferrin	mammary gland, uterus	19.78	1	0.051	0.0320	0.043	0.014
92353_at	serine protease (BSSP)	hair follicles, brain	18.77	1	0.053	0.1070	1	-
100463_at	gamma-casein precursor	mammary gland	21.93	1.17	0.053	0.0596	0.071	0.014
92546_r_at	prostaglandin D	brain, epididymis	22.82	1.26	0.055	0.0001	0.063	0.014
96153_at	neutrophilic granule	granulocytes	28.46	1.72	0.060	0.0246	0.063	0.014
160899_at	Purkinje cell protein 4	brain, eye (lens)	32.87	2.09	0.064	0.0327	< 0.02	0.014
161815_f_at	major urinary protein I	liver	31.23	2.04	0.065	0.0704	0.043	0.014
98858_at	glucose dependent insulinotropic polypeptide	K cells of small intestine	27.16	1.78	0.066	0.0517	< 0.02	0.014
101910_f_at	major urinary protein 3	liver	21.02	1.47	0.070	0.0328	0.164	0.014
94775_at	oxytocin	brain	26.59	1.92	0.072	0.0334	1	-
101636_at	salivary protein 2	salivary gland	16.80	1.23	0.073	0.0382	1	-
98623_g_at	insulin-like growth factor II	embryo, choroid plexus and leptomeninges in adult	94.85	6.96	0.073	0.1179	< 0.02	0.014
99958_at	mast cell protease-2	mast cells	13.70	1.01	0.074	0.0248	0.043	0.014
94707_s_at	amelogenin	ameloblast cells	34.89	2.57	0.074	0.0328	< 0.02	0.014
103235_at	preproneuropeptide y	brain	19.54	1.47	0.075	0.0143	0.043	0.014
103887_at	S100 calcium binding protein A9	immature BM myeloid cells, monocytes, neutrophils	68.93	5.26	0.076	0.1529	0.279	0.014
162341_r_at	aldose reductase	many	19.37	1.48	0.076	0.0121	0.279	-
97889_at	fatty acid binding protein	intestine	37.46	3.04	0.081	0.0254	0.043	0.014
94045_at	α-1-microglobulin/bikunin precursor	liver	12.74	1.04	0.082	0.0781	0.279	0.014
100150_f_at	preproinsulin II	pancreatic islet beta cells	19.70	1.62	0.082	0.1692	< 0.02	0.014
100002_at	inter-alpha-inhibitor H3 chain	liver, brain	12.07	1	0.083	0.0266	0.043	0.014
98830_at	spermine binding protein	prostate	13.56	1.13	0.083	0.1047	0.131	-

one specific tissue  
several specific tissues

hematopoietic cells  
housekeeping



“top 30” random set

Se o sistema imune é cunhado para  
“ignorar” o próprio,

Isso não torna mais fácil reconhecer o não  
próprio ?

Defesa ?



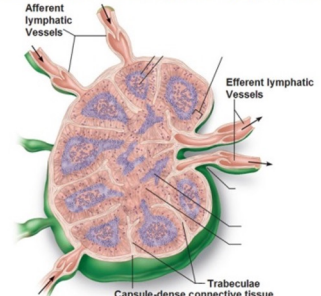


ESCAPE

He finally did it!

Anti-Insulina  
Anti-Mielina  
anti-Colágeno  
Anti Fator  
Extrínseco

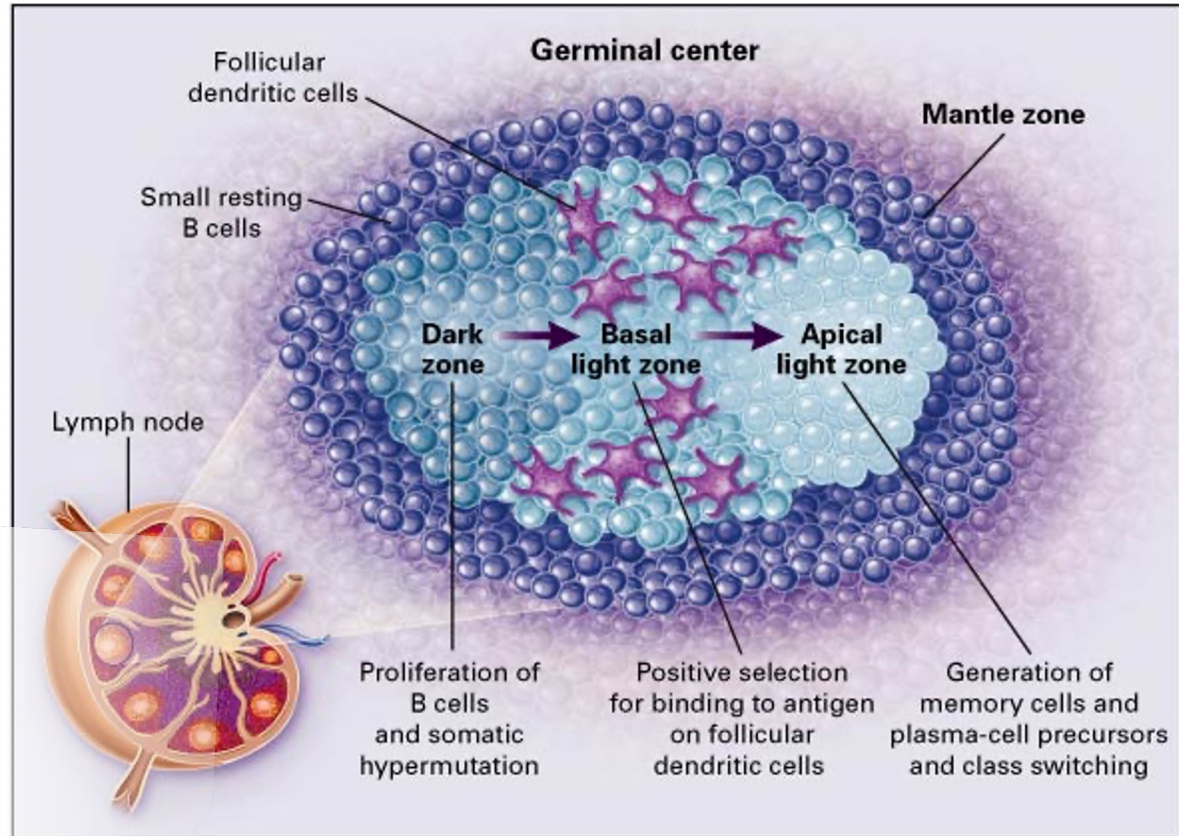
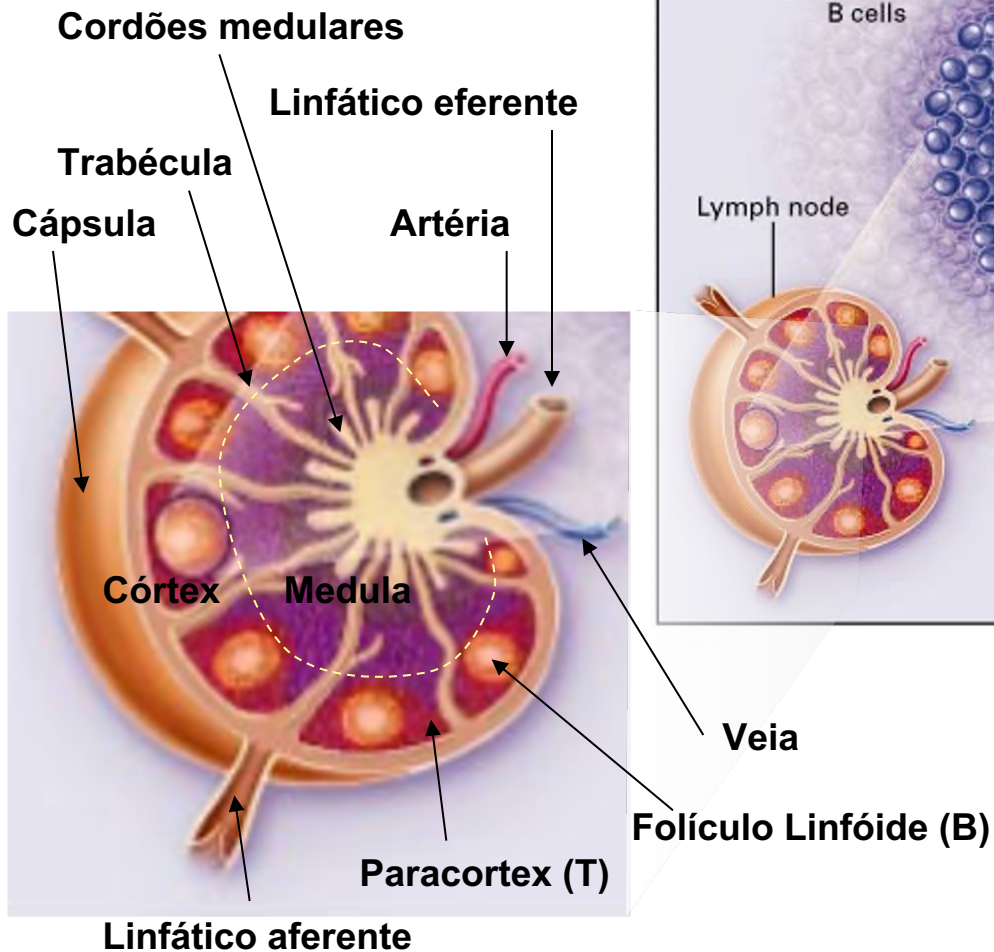
Microscopic Anatomy of a Lymph Node



Longitudinal view of the internal structure of a lymph node and associated lymphatics

# Órgãos Linfóides Secundários

## Linfonodos

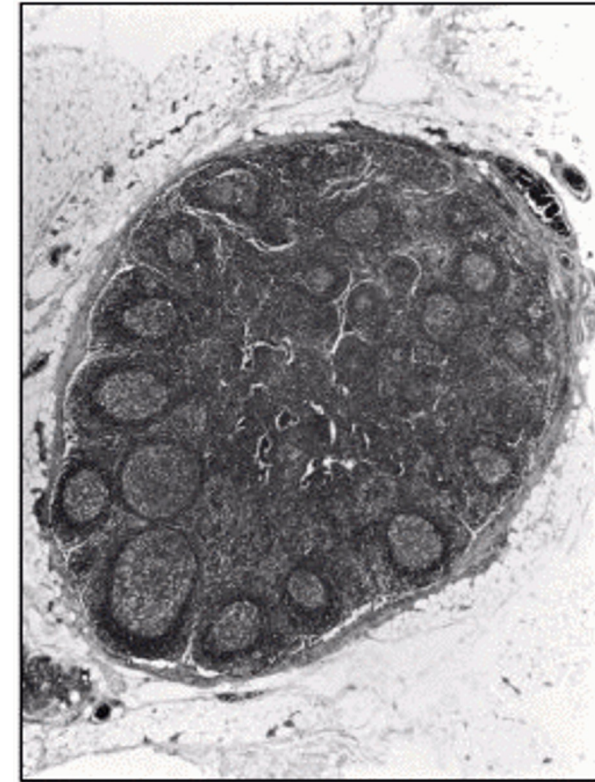
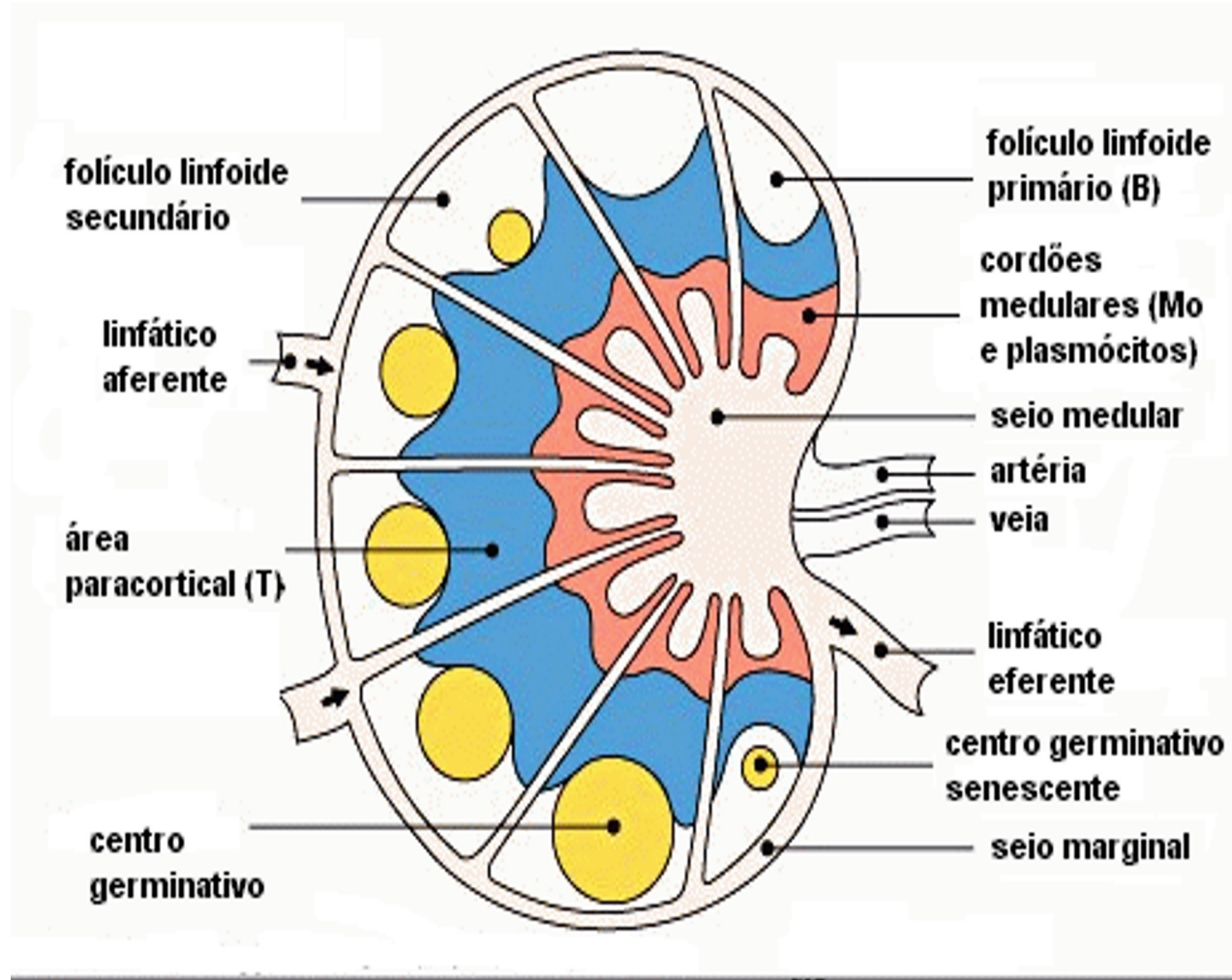


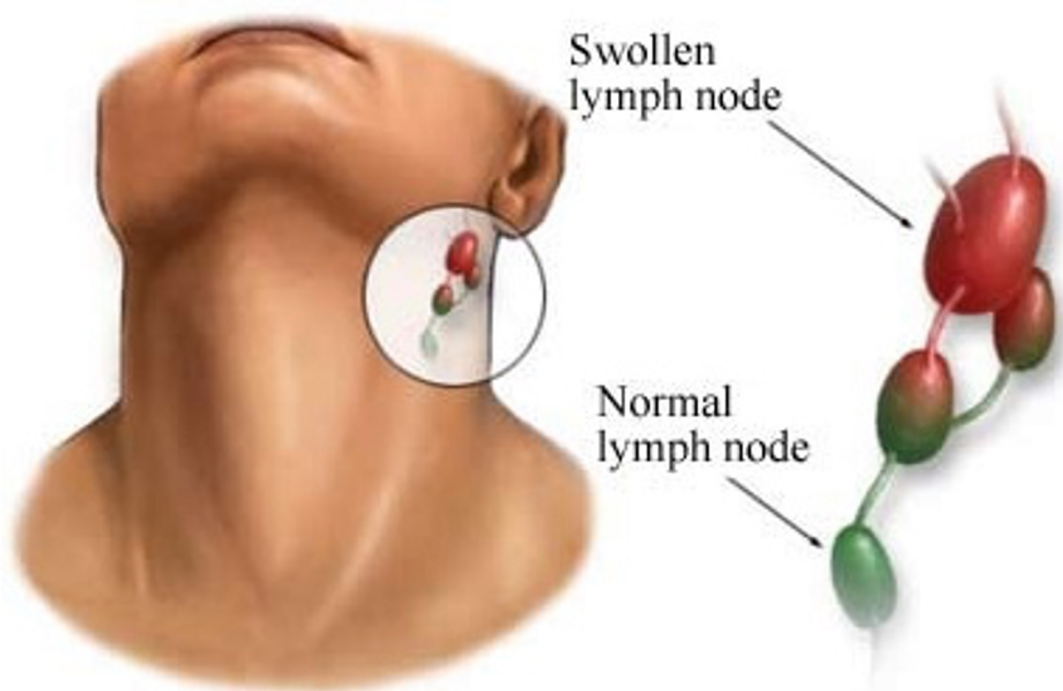
- **Vênulas: Células Endoteliais “Altas” (HEV)** (entrada das células circulantes)
- **Folículos Primários**
- **Folículos Secundários (Centros germinativos)**





# Estrutura do linfonodo



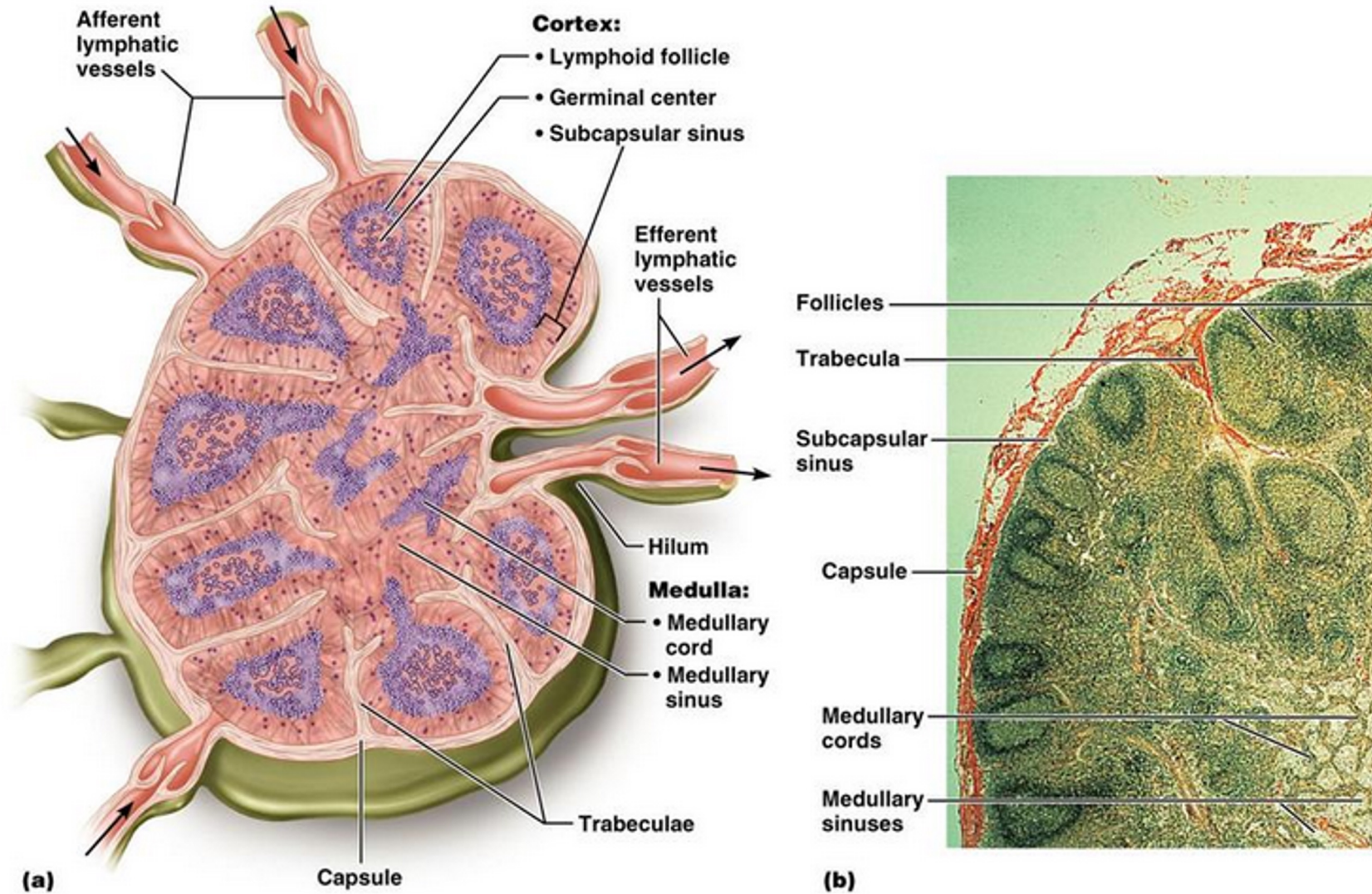


Linfonodo Aumentado



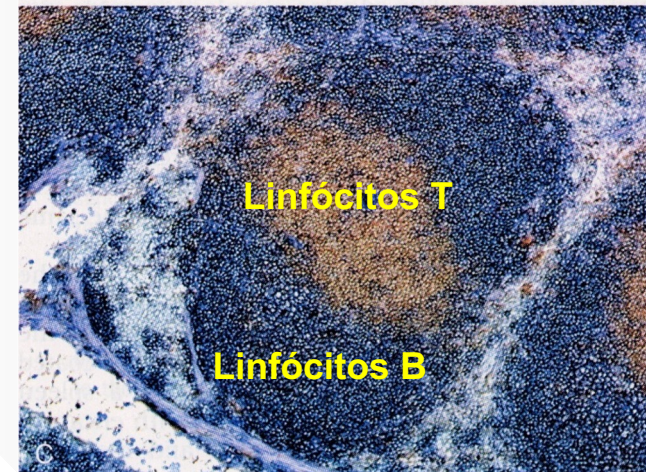
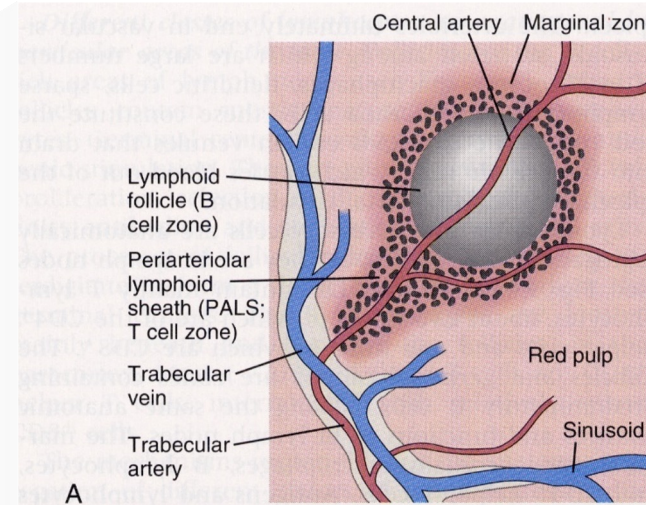
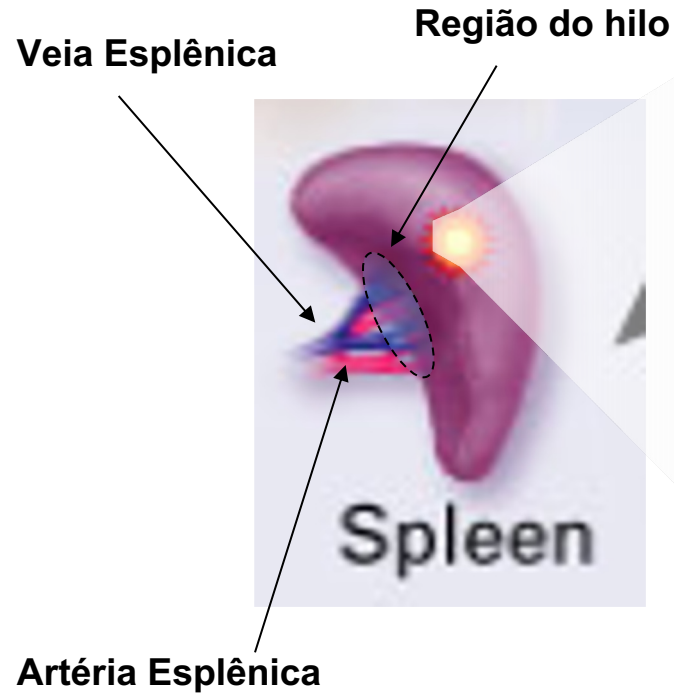


# Linfonodos



# Órgãos Linfóides Secundários

## Baço



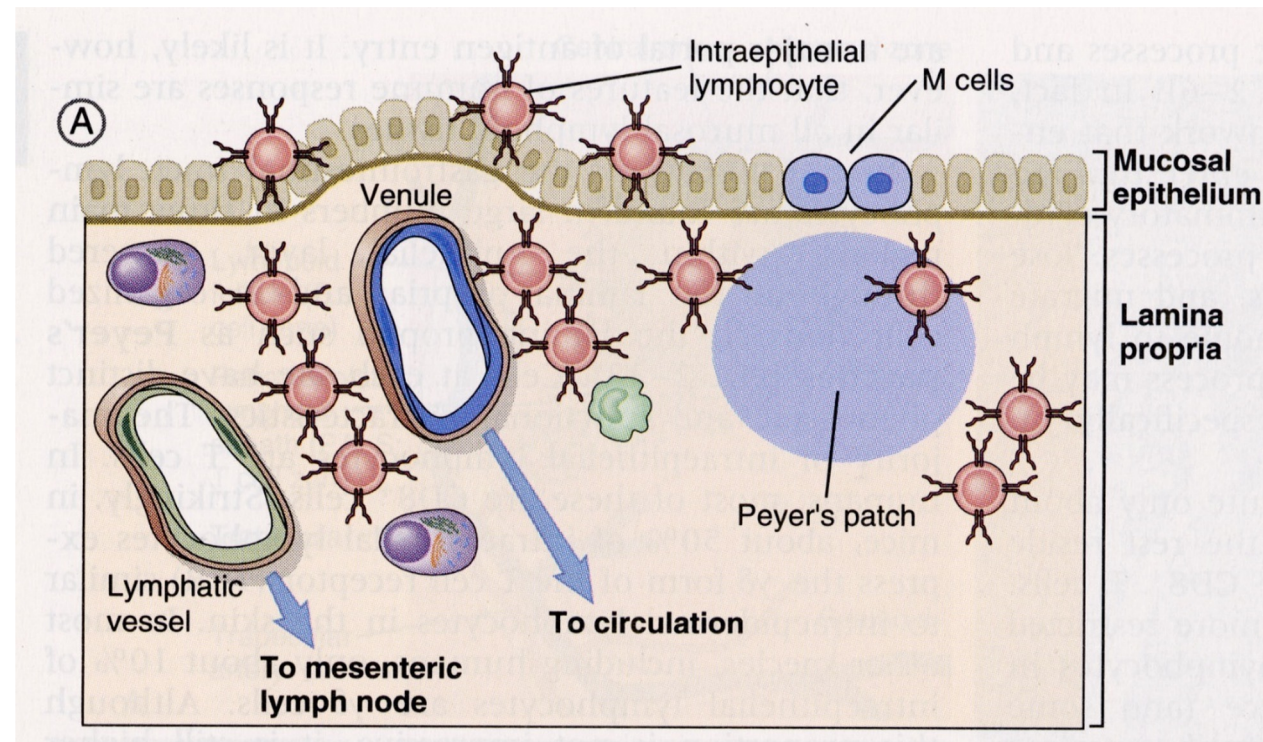
- Sinusóides vasculares (Entrada do Antígeno)
- Não possuem HEV
- “Filtro” sangüíneo para remoção de células danificadas antígenos circulantes



# Órgãos Linfóides Secundários

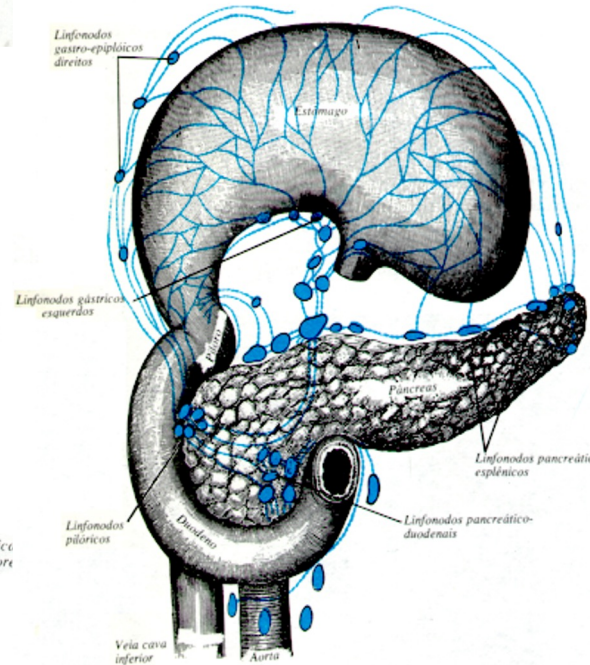
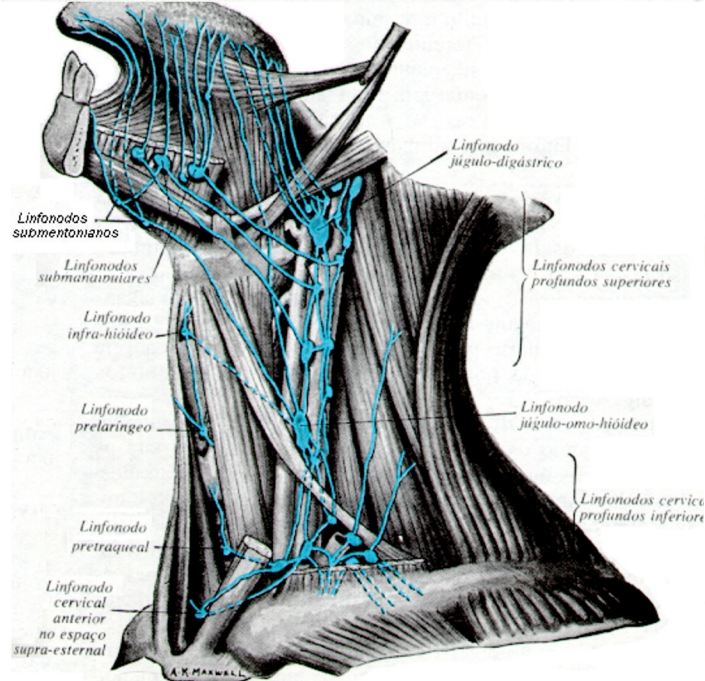
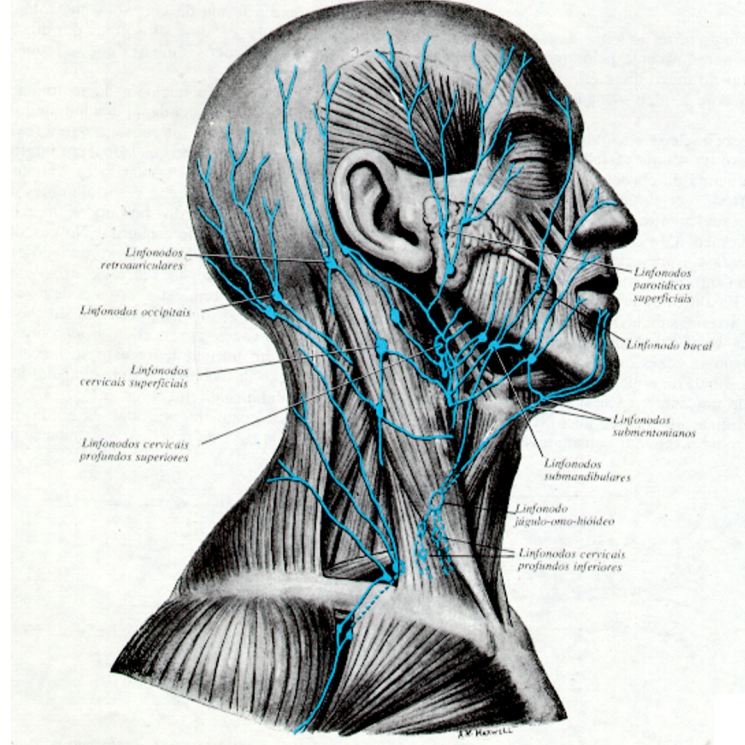
- Primeira barreira aos antígenos externos
- Maior área exposta do organismo
- Linfócitos Intraepiteliais: TCR $\alpha\beta$  CD8<sup>+</sup> (homem) / TCR $\gamma\delta$  (camundongo)
- Lâmina própria: CD4<sup>+</sup> ativados / Macrófagos / DCs / Eosinófilos / Mastócitos
- Folículos linfóides de mucosa: Células B (R. Central) / Células T CD4<sup>+</sup>(R. interfolicular)
- Células M: transporte de antígenos
- Alta produção de IgA
- Imunização oral: Tolerância

## Sistema Imune de Mucosas

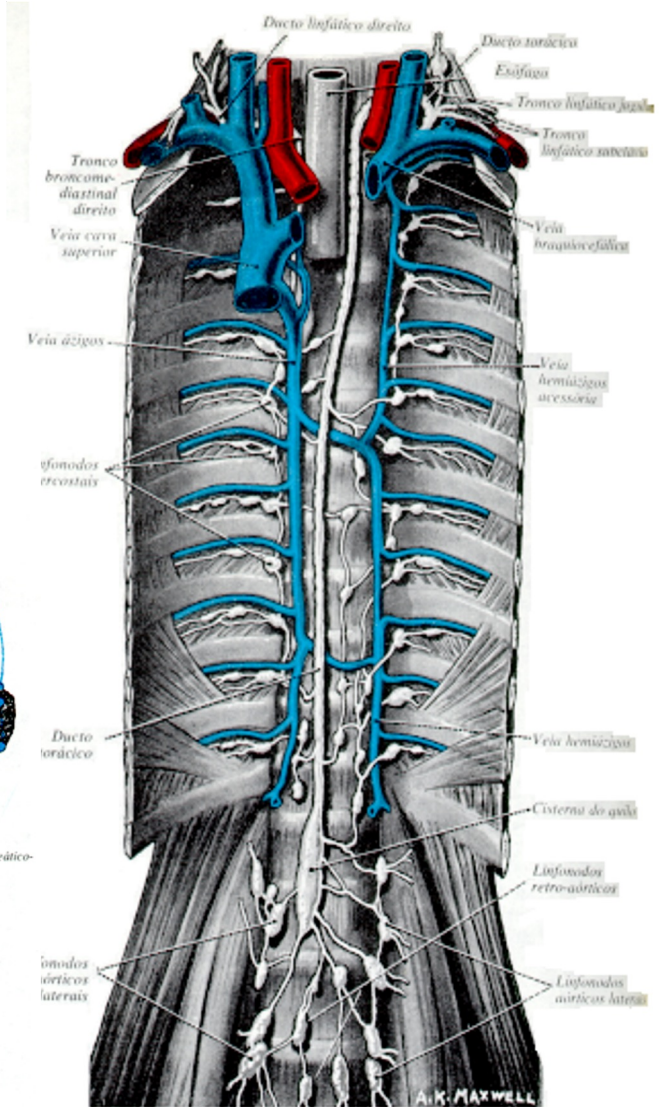




# LINFONODOS

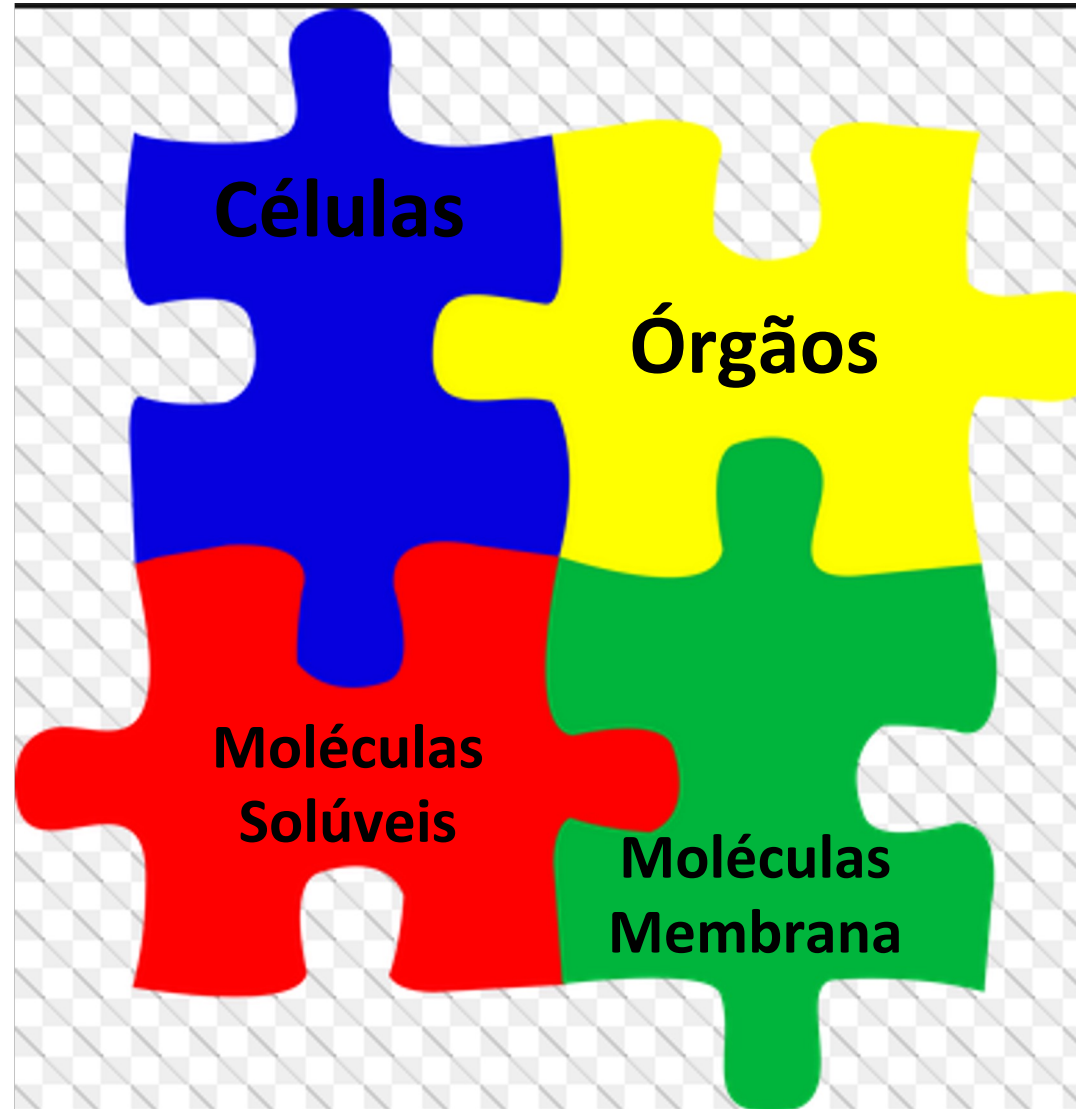


Linfonodos e vasos linfáticos do estômago, duodeno e pâncreas. O estômago está virado para cima. (Segundo Jamieson e Dobson.)





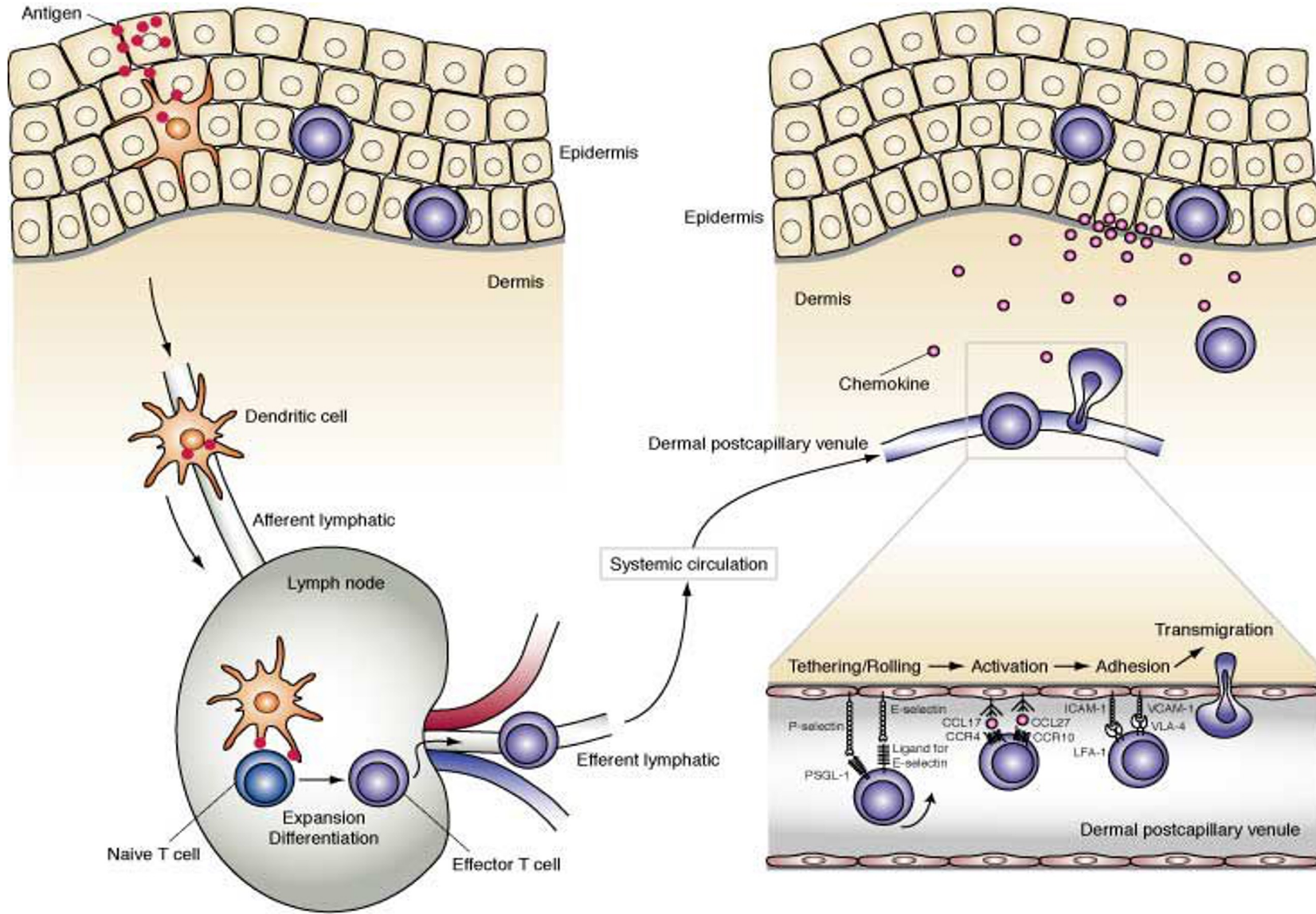
# Montando o Sistema Imune



Mas como essas células e tecidos de integram ?







**Antígenos**

**São**

**Drenados**

**Aos**

**Linfonodos**

**E**

**Apresentados**

**Aos linfócitos**

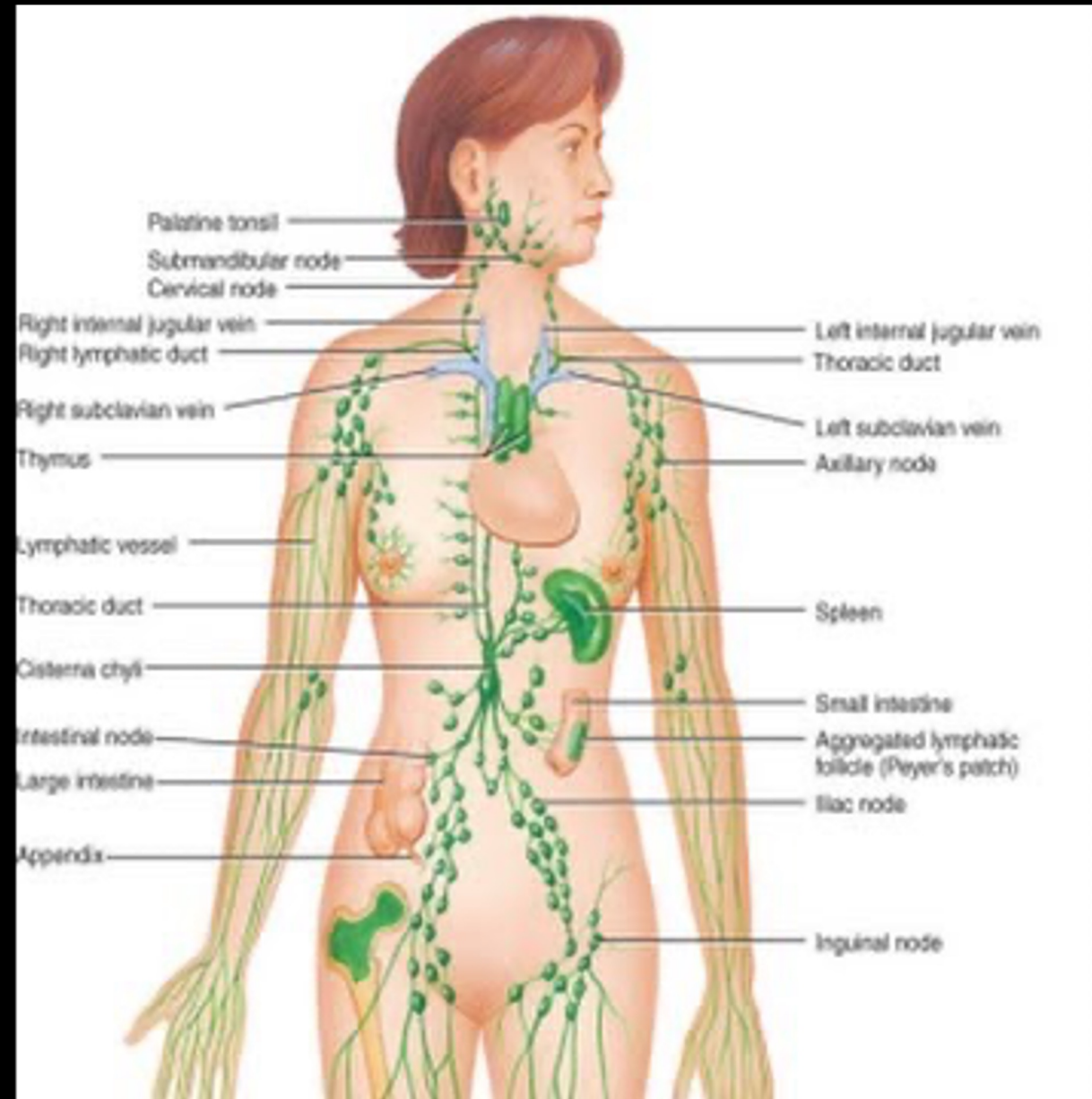
**T e B**

# Sistema Linfático

## Drenagem dos

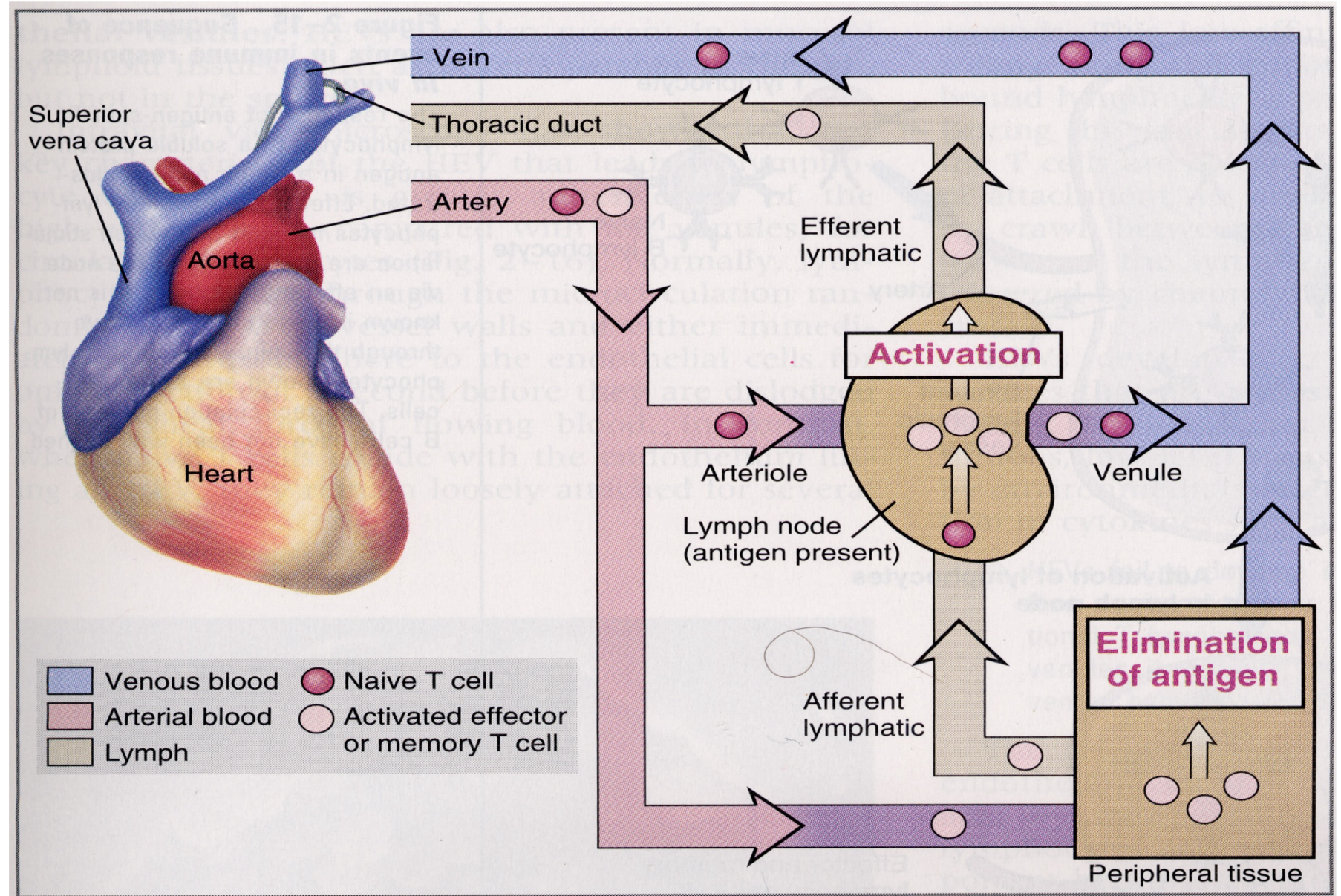
## Antígenos e Debris

## Presentes nos Tecidos



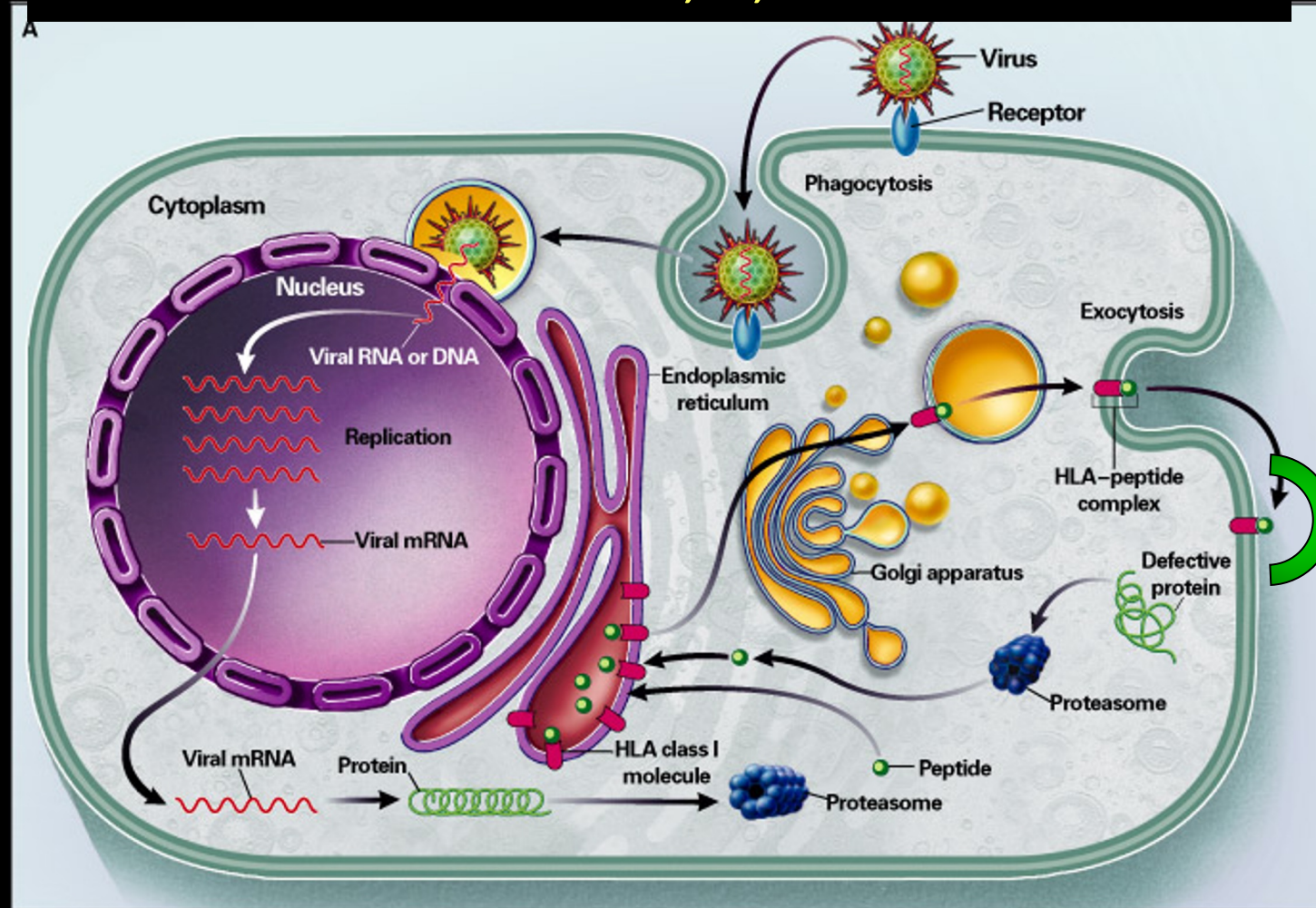


# Recirculação Leucocitária





# Apresentação de Antígenos via MHC Classe I HLA- A, B, C



Klein J, Sato A. The HLA System. First of two parts.  
N Engl J Med 2000;343:702-9.

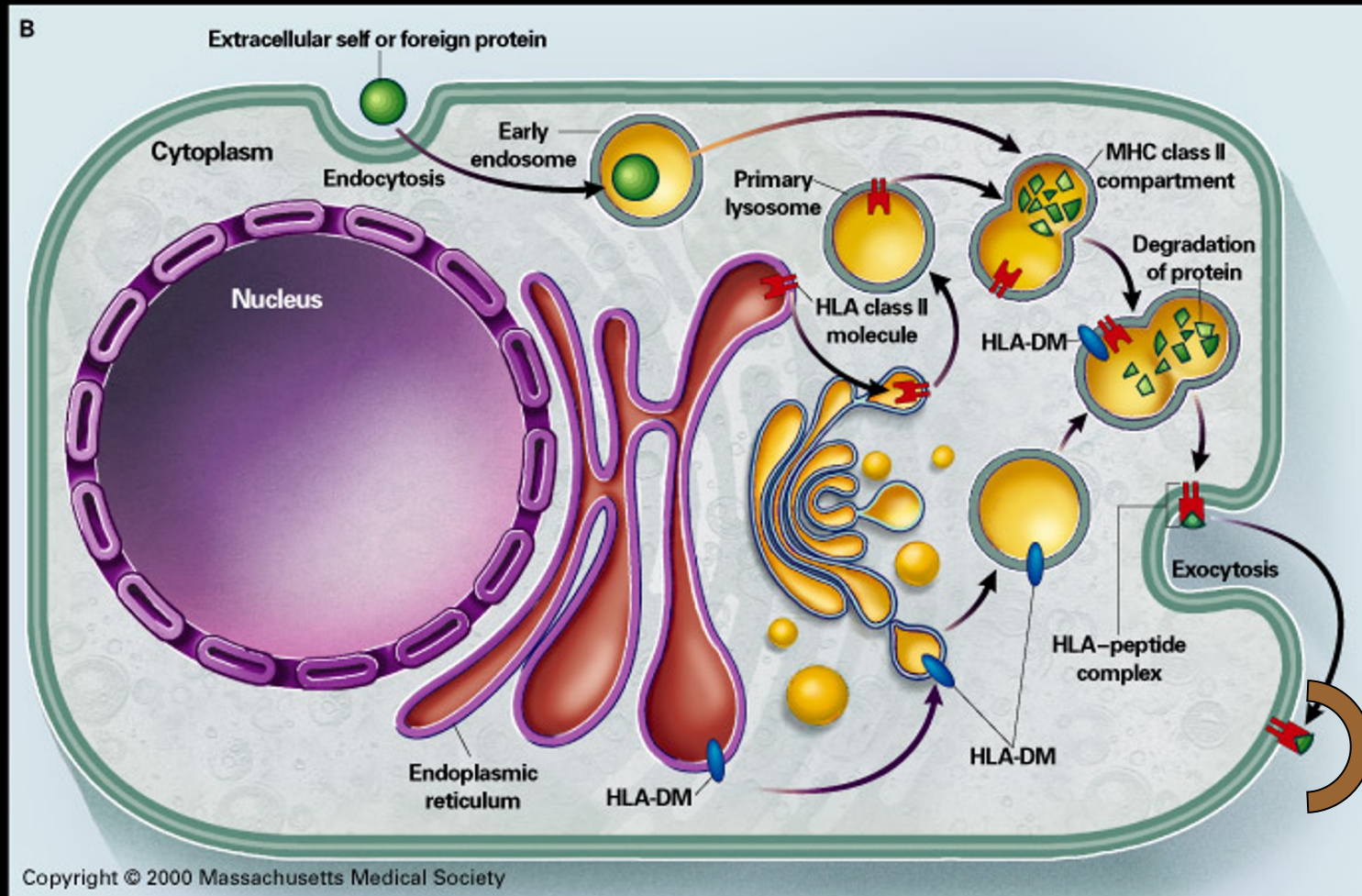


The New England  
Journal of Medicine

T CD8



# Apresentação via MHC Classe II HLA-DP, DQ, DR



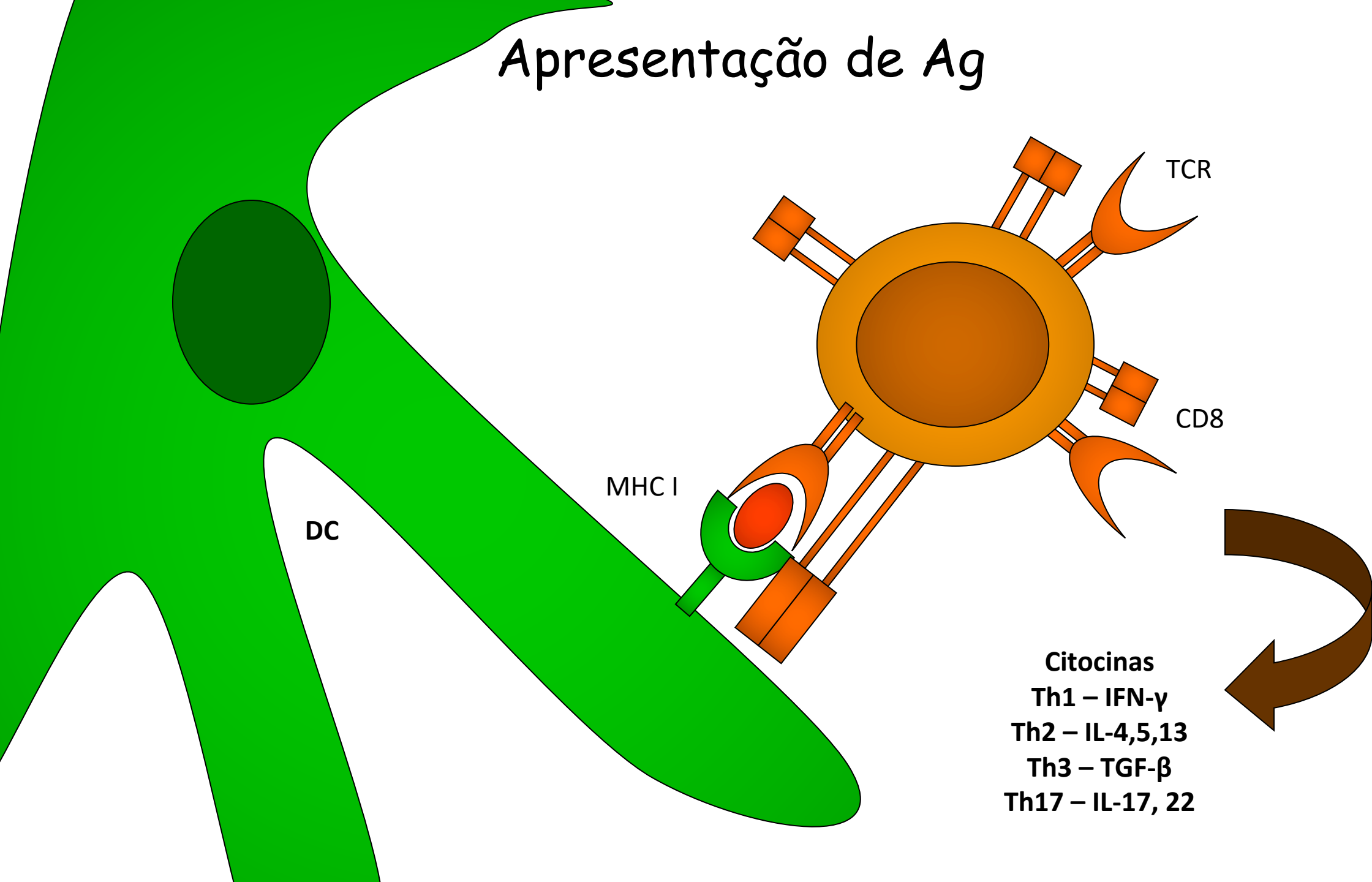
Klein J, Sato A. The HLA System. First of two parts.  
N Engl J Med 2000;343:702-9.



The New England  
Journal of Medicine

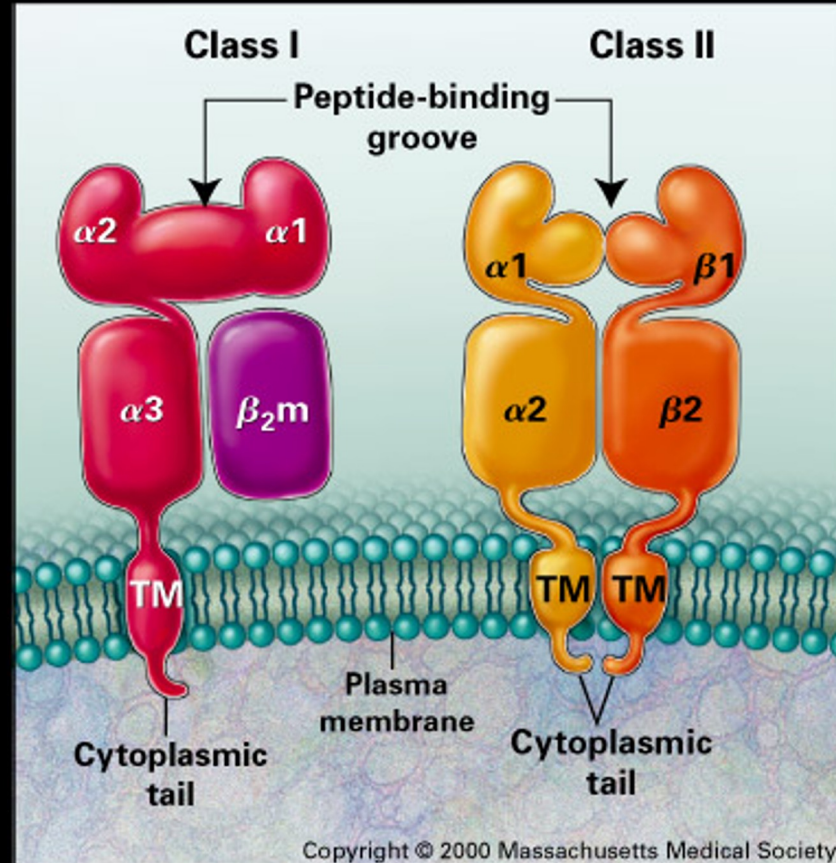
T CD4

# Apresentação de Ag





# Estrutura das Moléculas de MHC I e II



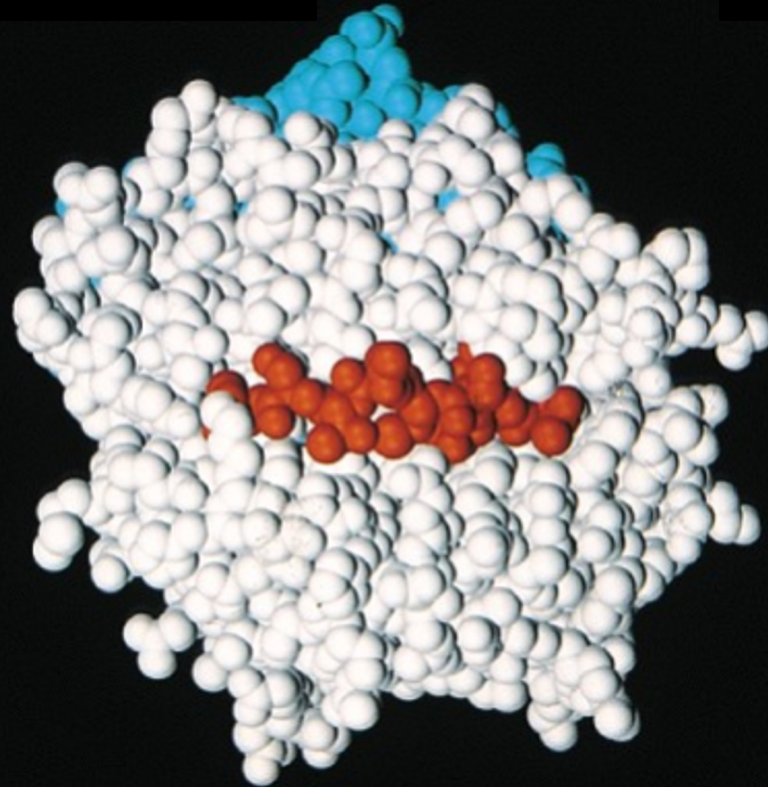
Klein J, Sato A. The HLA System. First of two parts. N Engl J Med 2000;343:702-9.



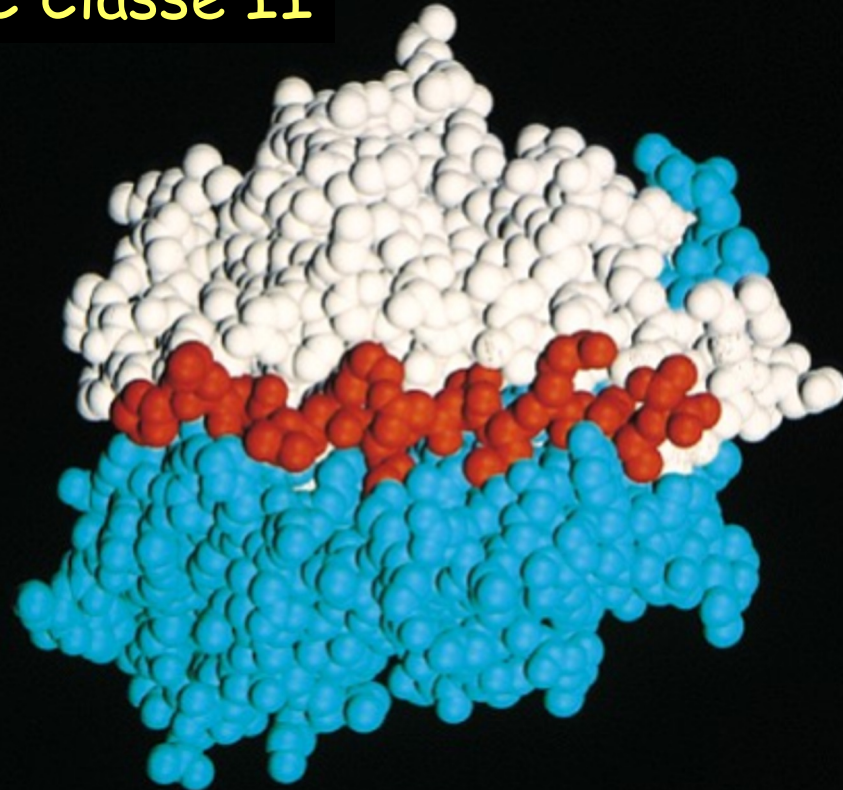
The New England  
Journal of Medicine

# Estrutura das Moléculas de MHC I e II

MHC Classe I

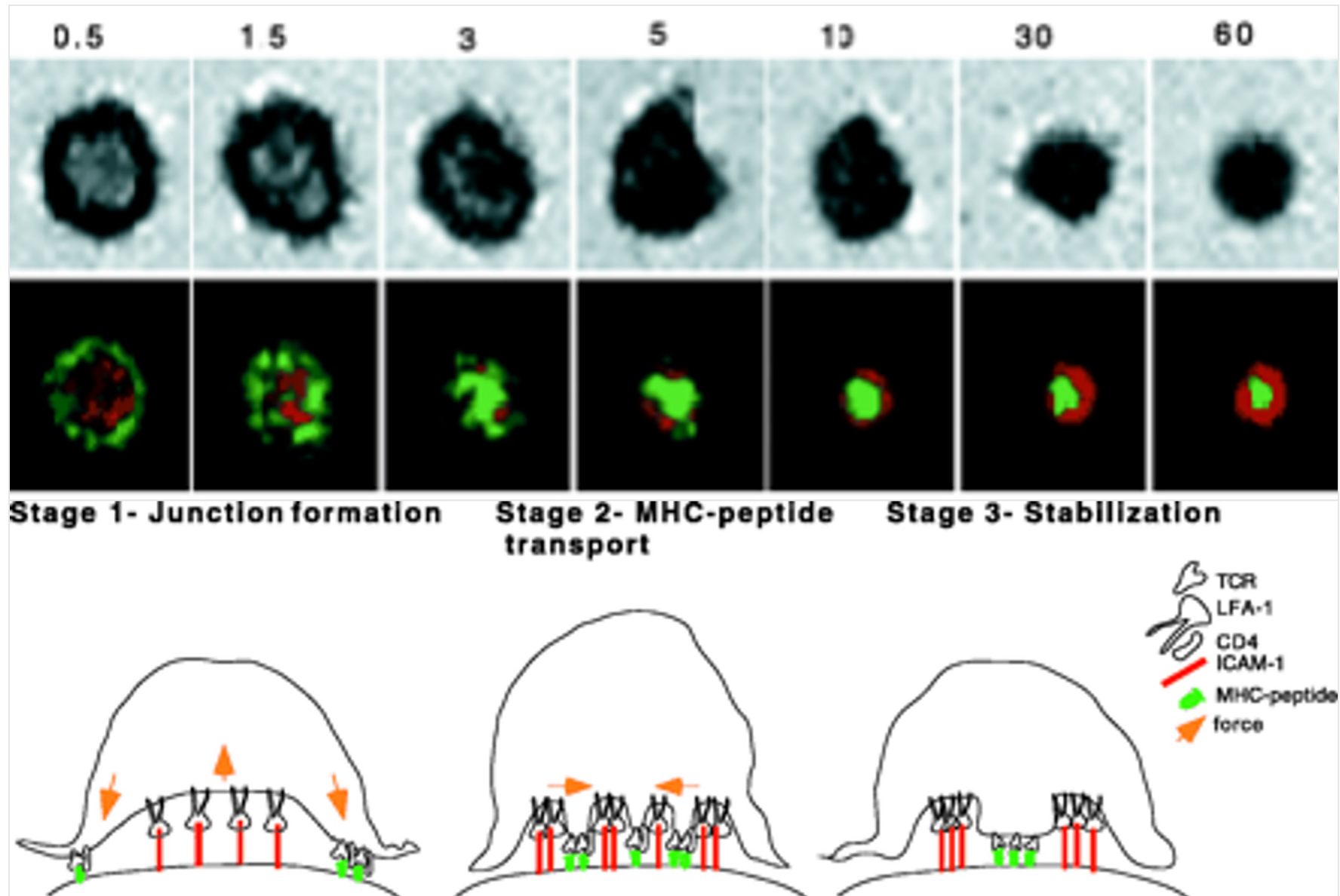


MHC Classe II

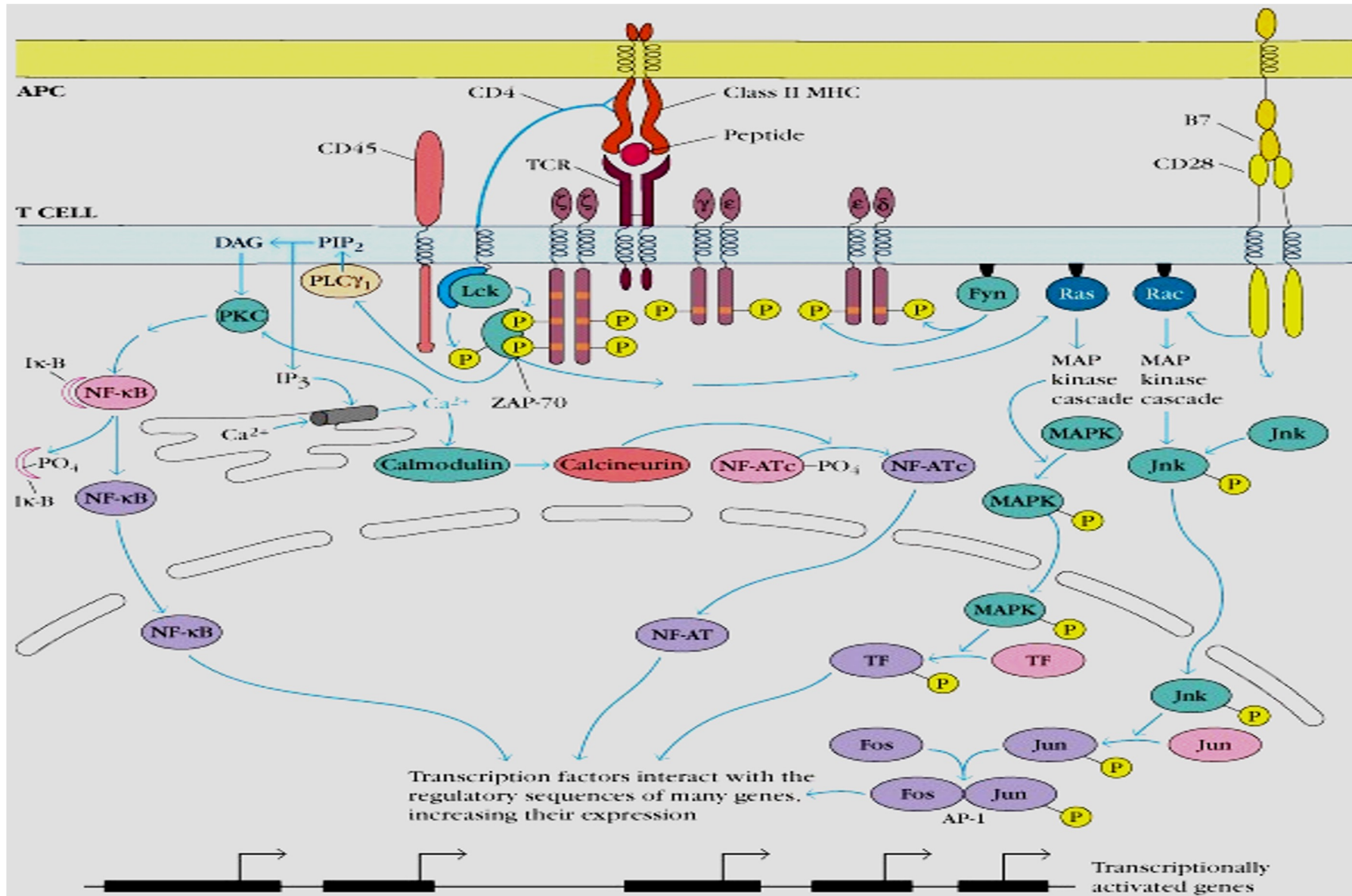




# A ligação com o complexo MHC-peptídeo promove a formação de sinapses imunológicas

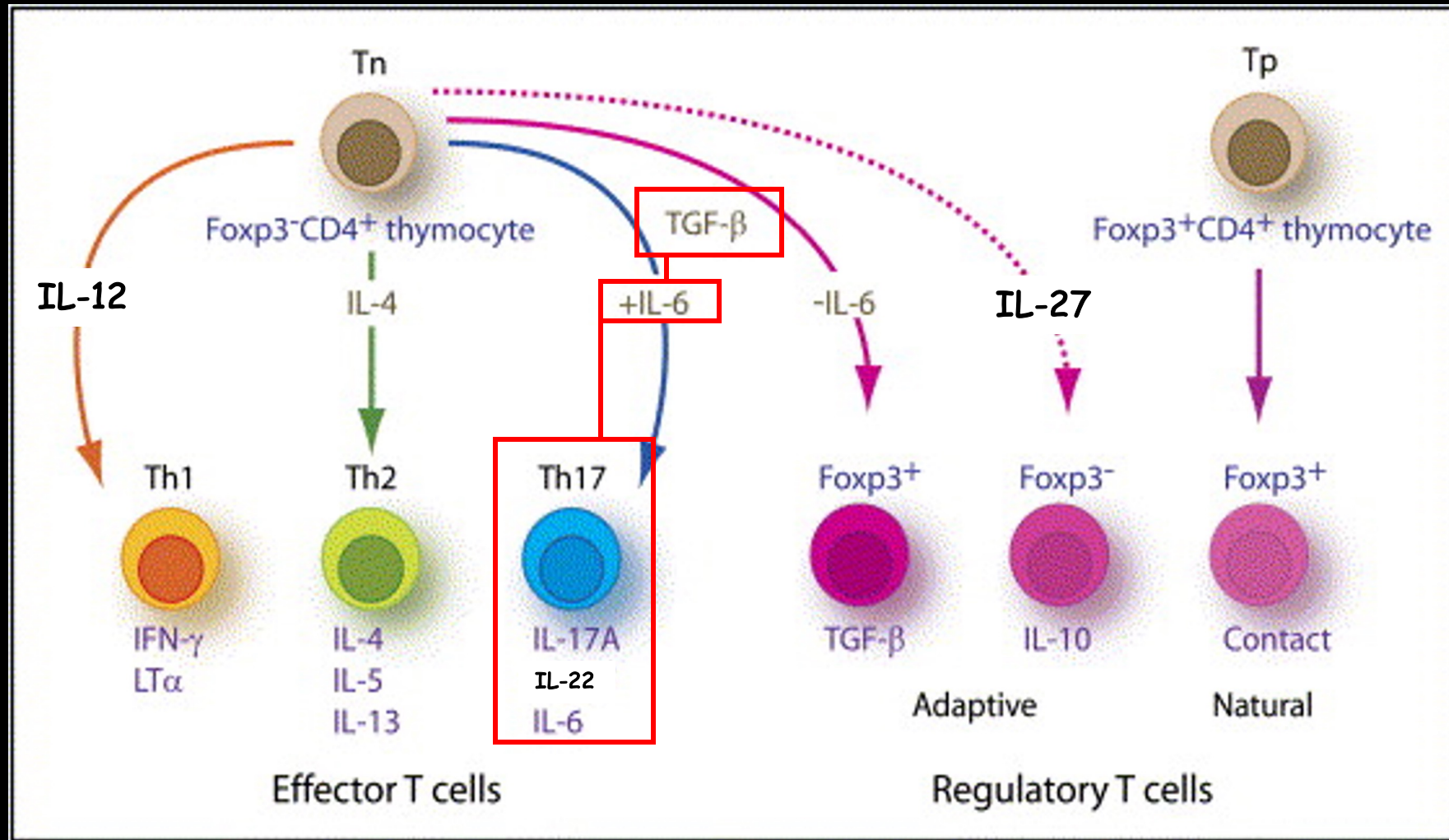


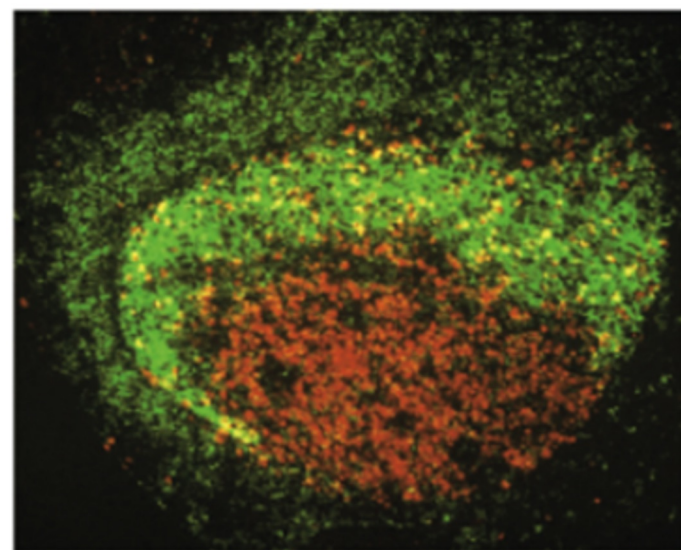
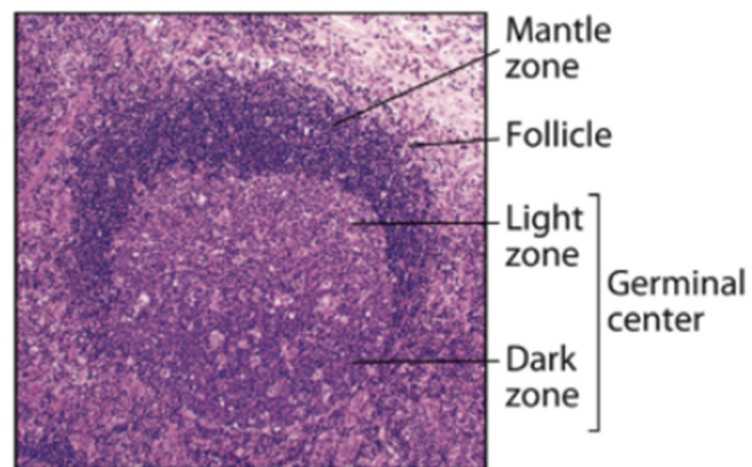
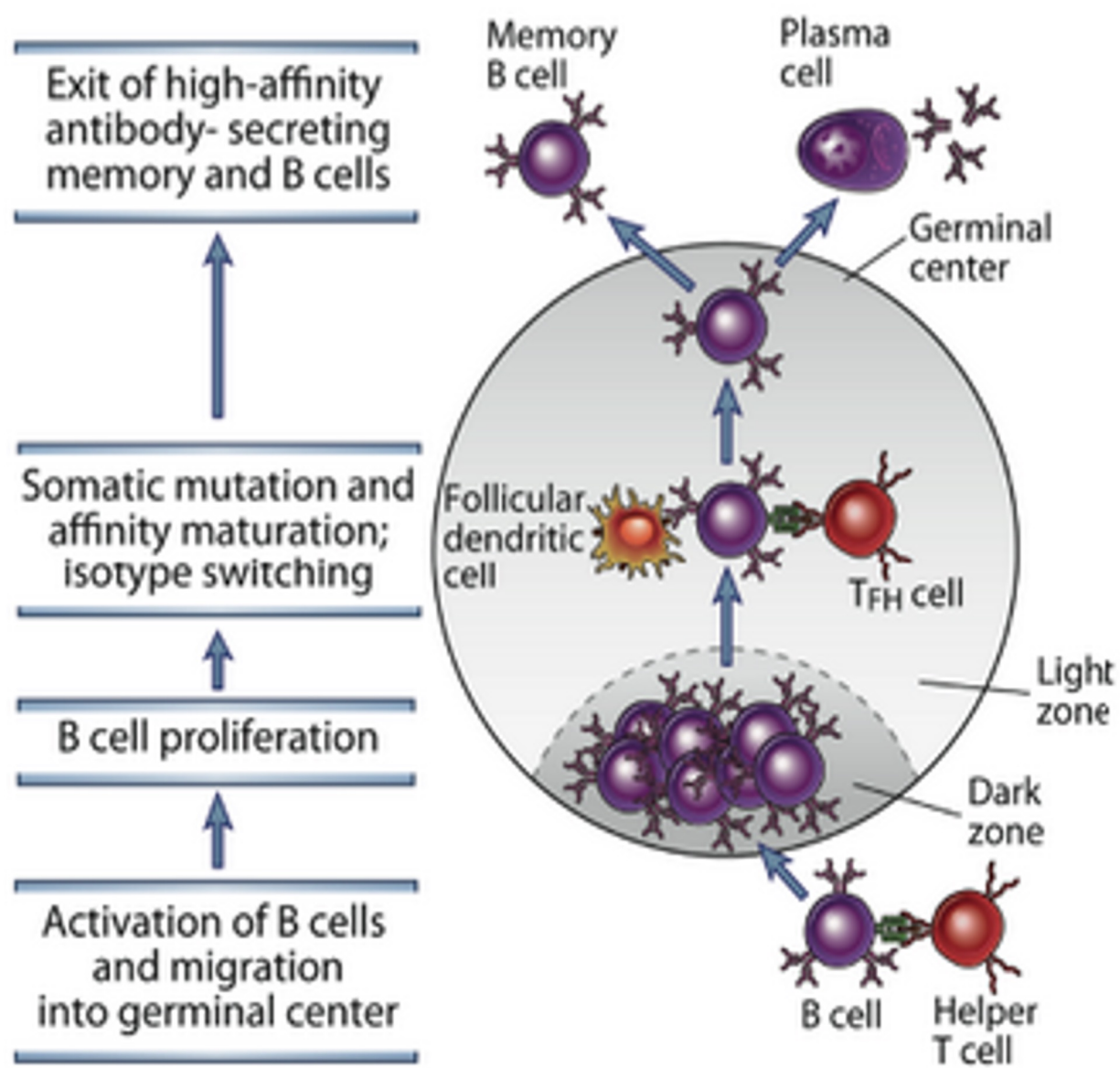
# Vias de Sinalização do TCR





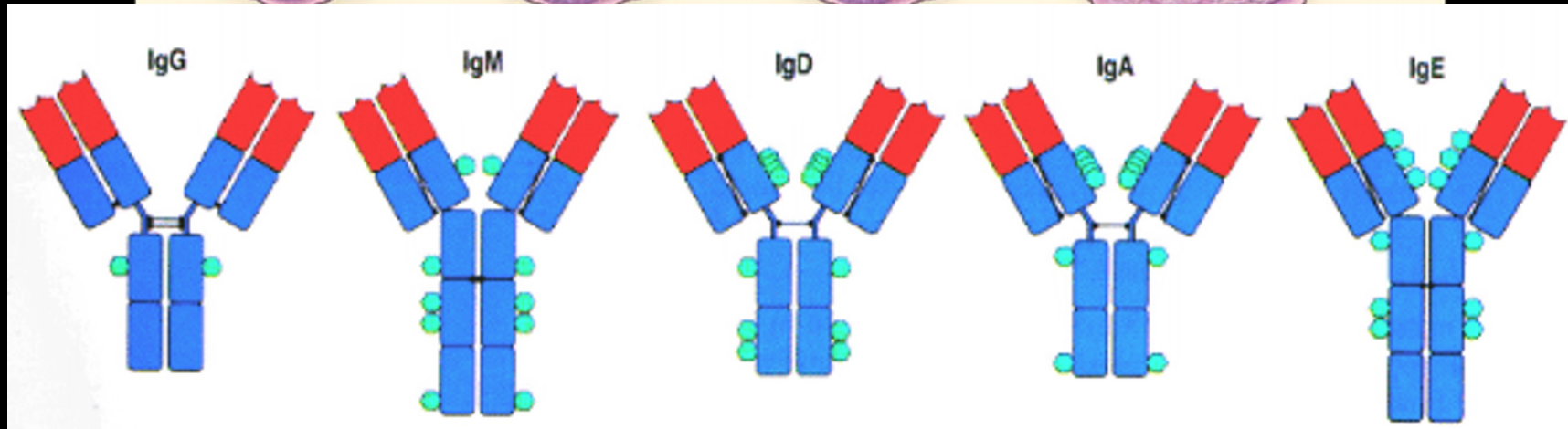
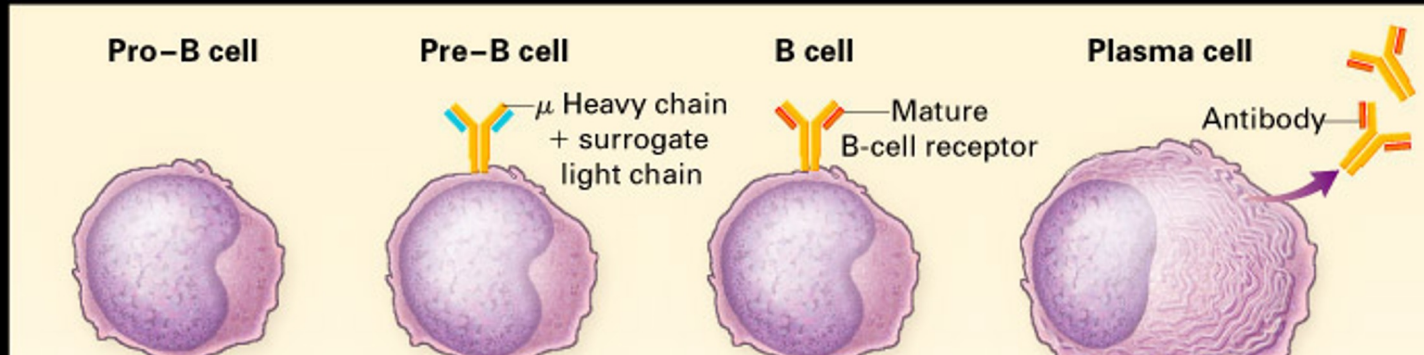
# Populações de Células T







# Receptores de Células B

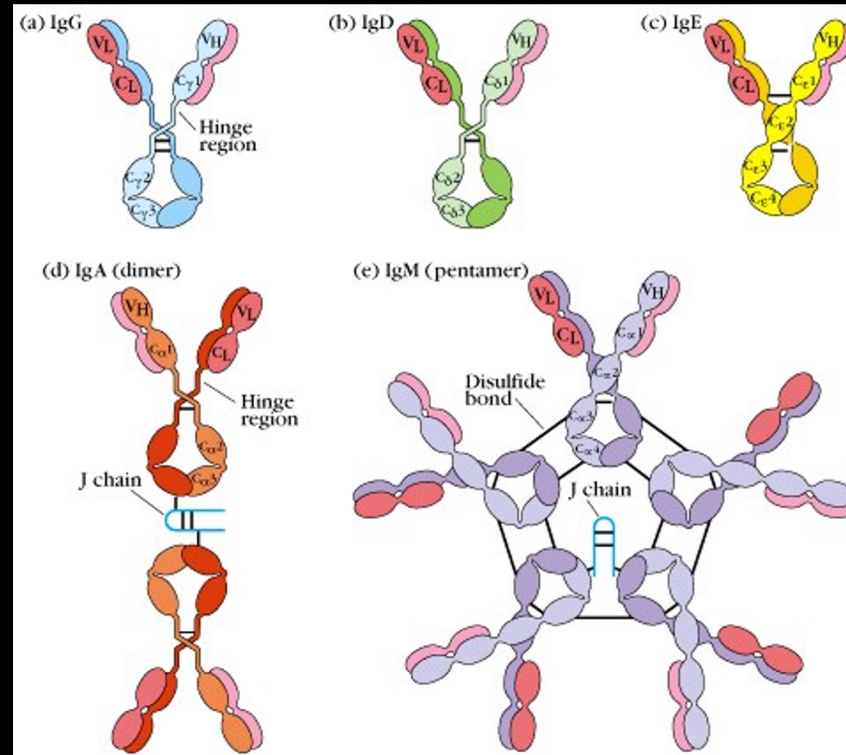
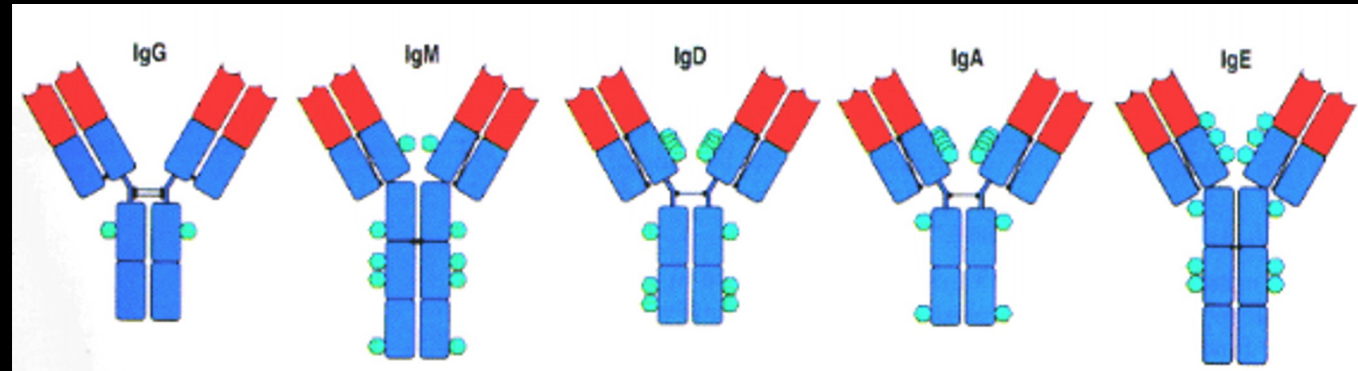


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Delves PJ, Roitt IM. The Immune System (Part1).  
N Engl J Med 2000;343:37-49.

 The New England  
Journal of Medicine

# Anticorpos ou Imunoglobulinas





# Comprovação da Recombinação Somática

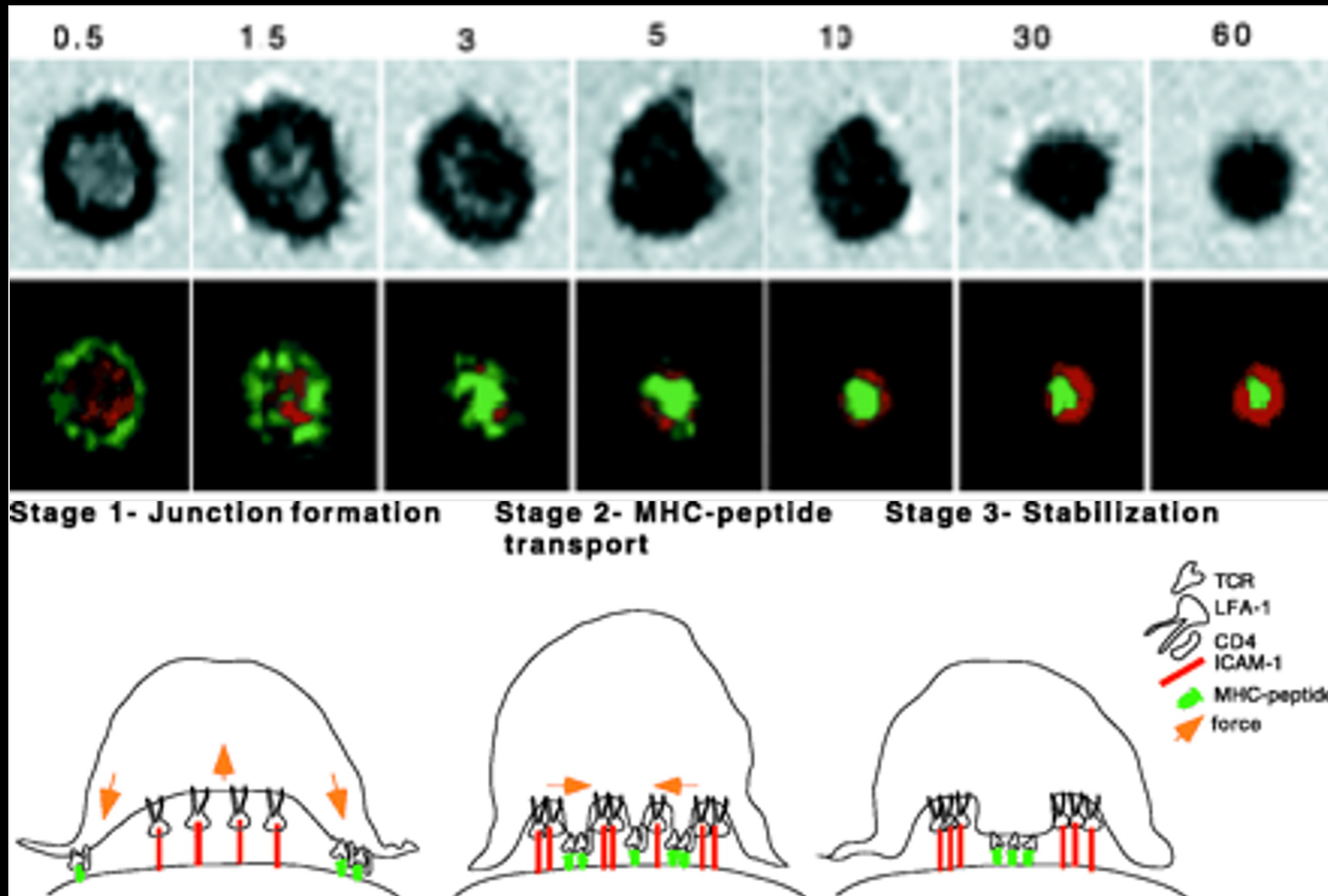


***Susumo Tonegawa***

**1975: DNA de fibroblastos não rearranjado;  
DNA de células B rearranjado**

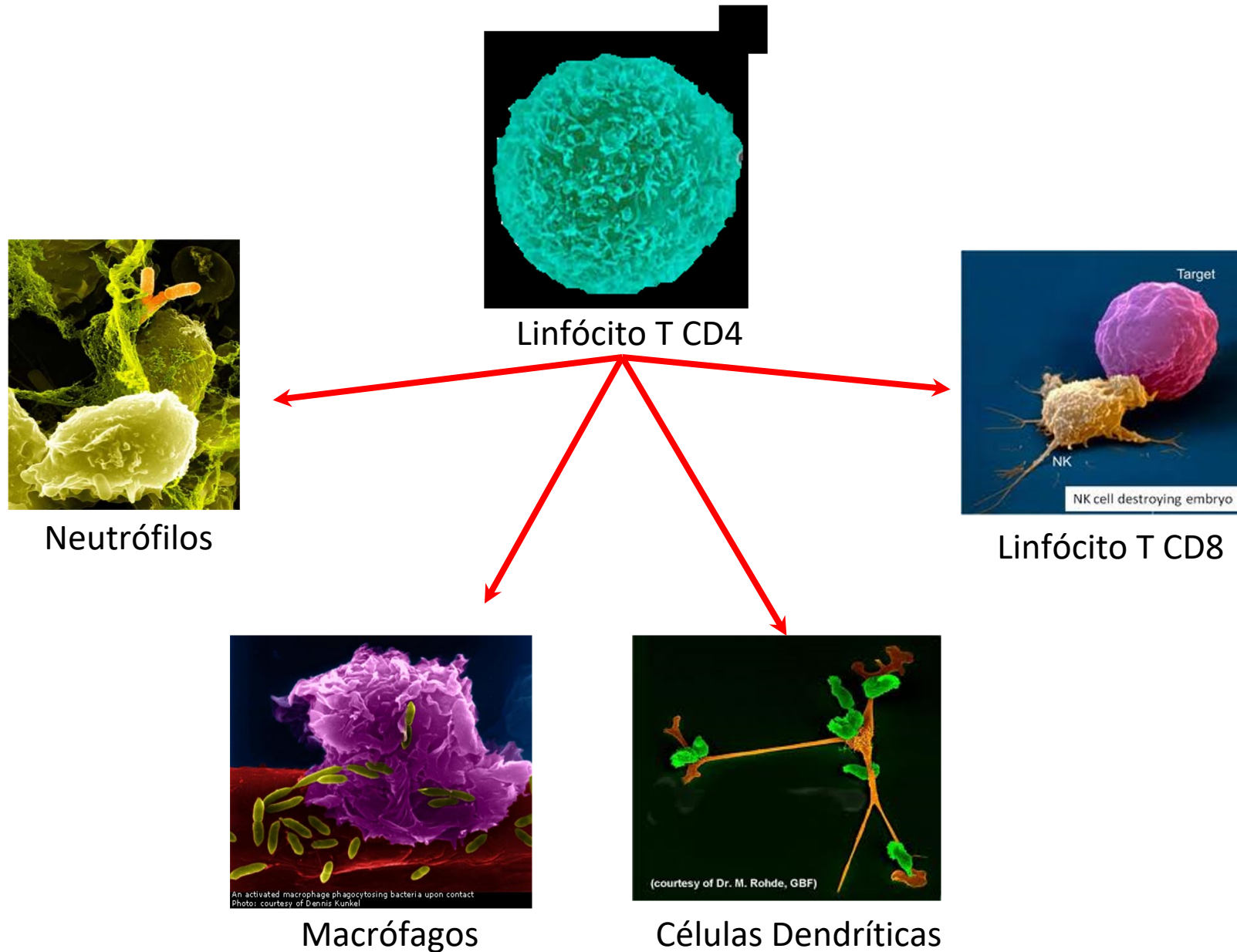
- **DNA de Fibroblastos (digerido)**
- **DNA de Hybridomas de Células B (digerido)**
- **Sondas de DNA**

A ligação com o complexo MHC-peptídeo promove a formação de sinapses imunológicas

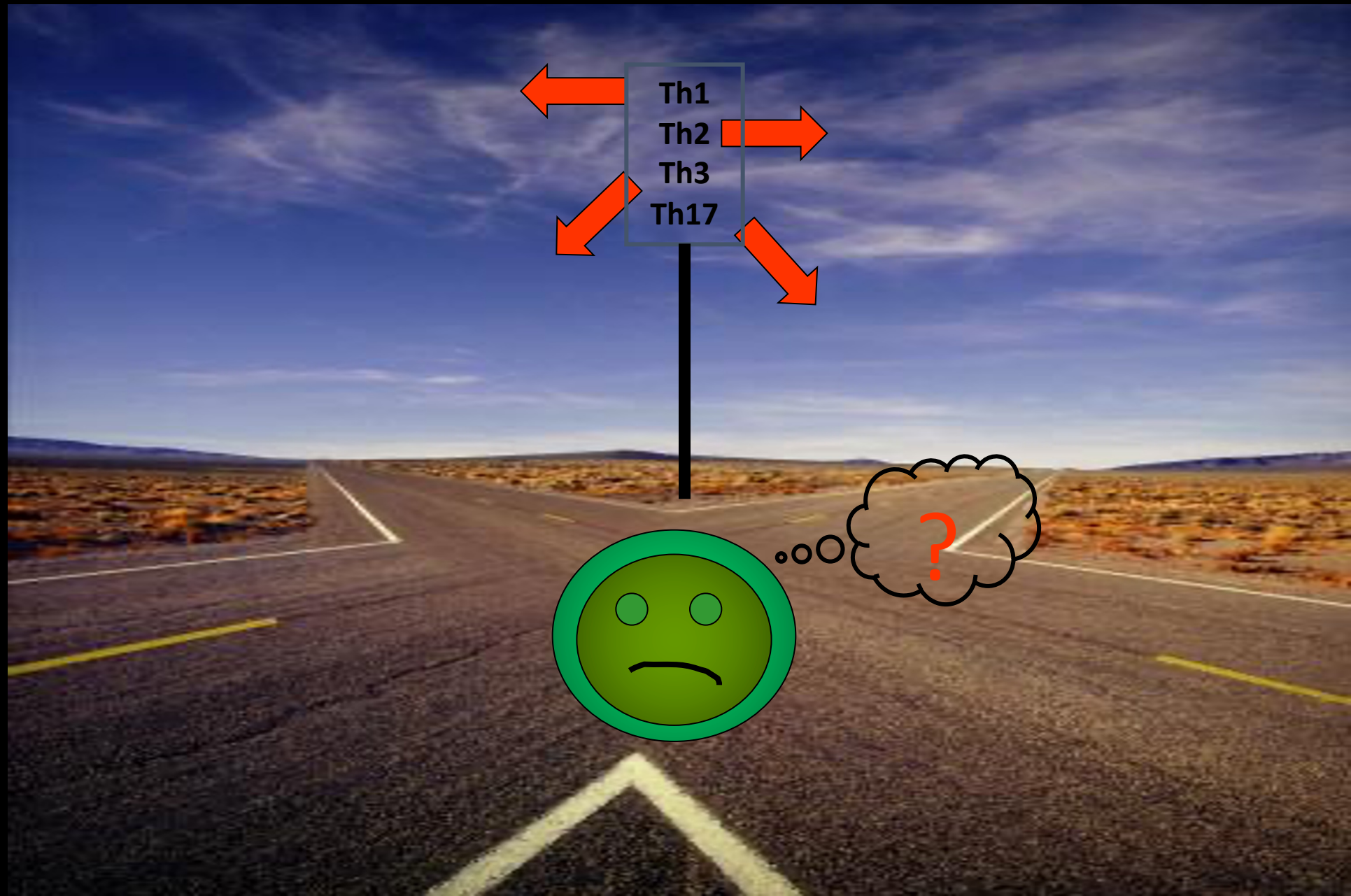




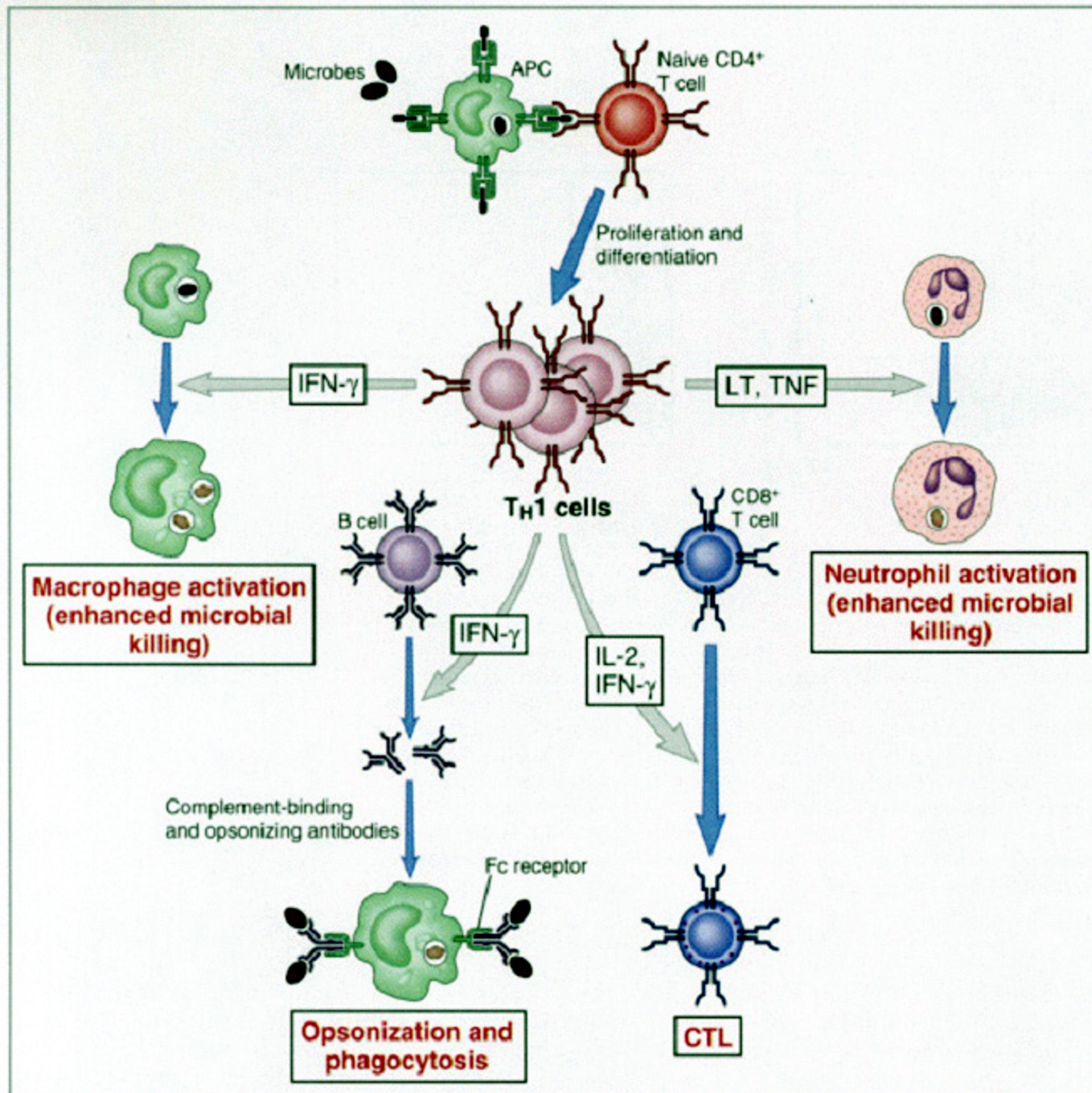
# Linfócitos T CD4 são os regentes da “orquestra” chamada Sistema Imune



# Comprometimento das Células T







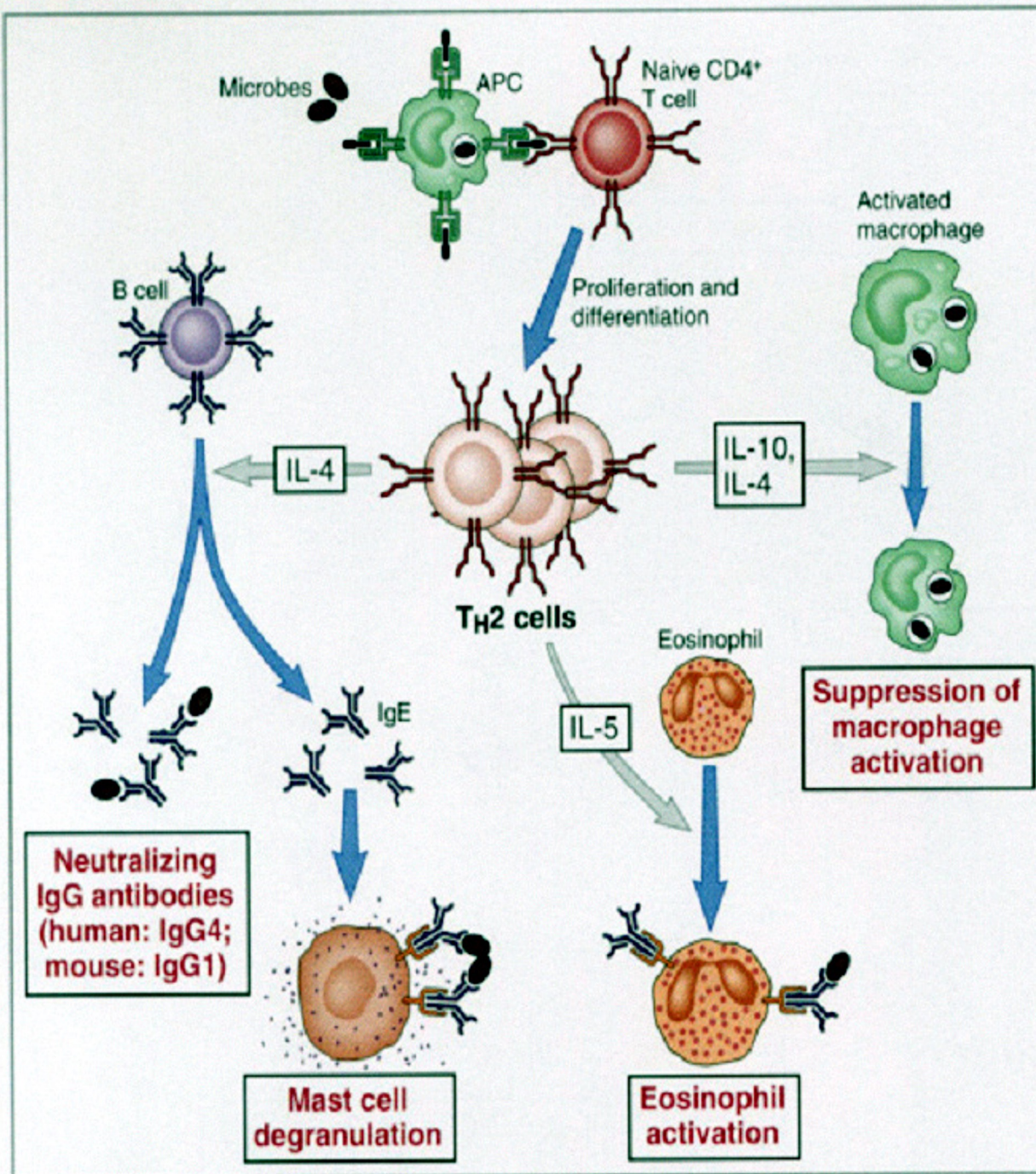
Células Th1 são geradas na presença de IL-12 e ausência de IL-4

e orquestram a resposta imune a patógenos intracelulares

Vírus e bactérias

Secretam Interferon -  $\gamma$



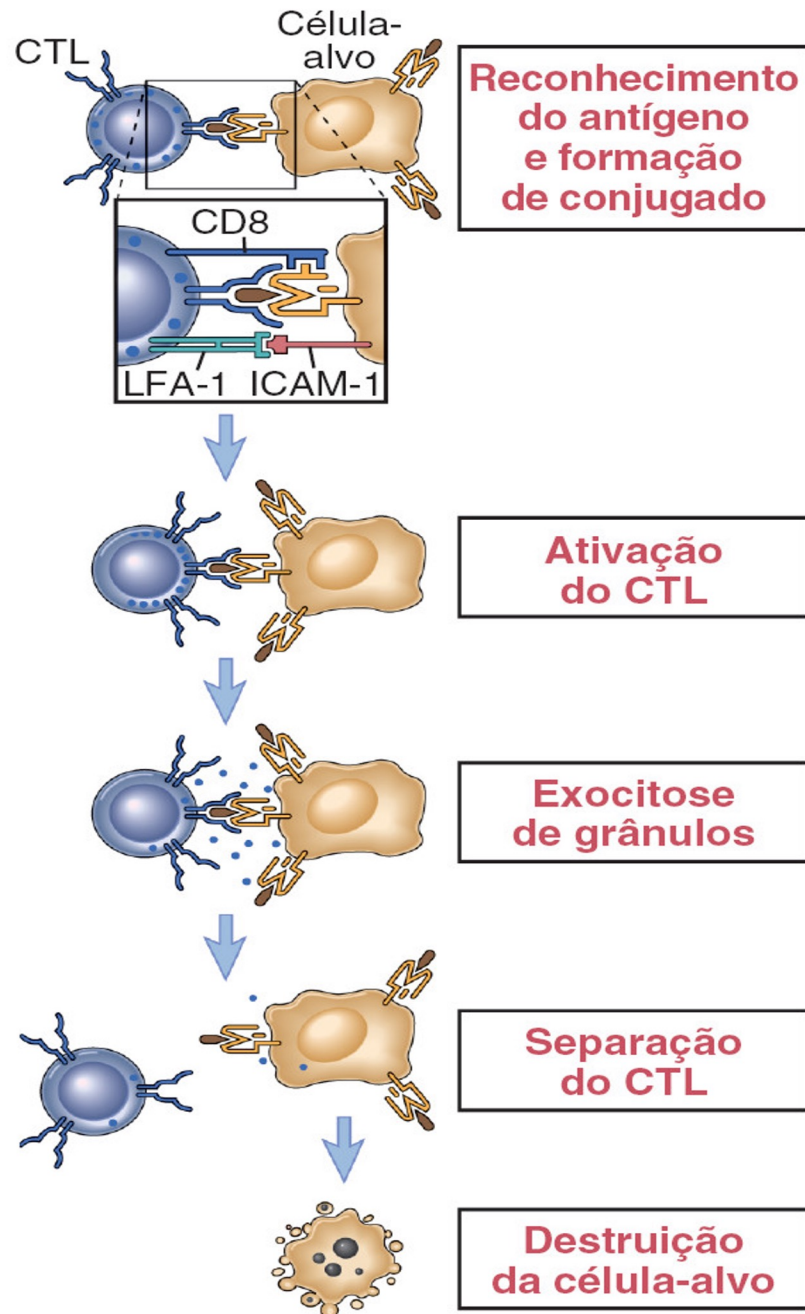


Células Th2 são geradas na presença de IL-4 e ausência de IL-12 e orquestram a resposta imune a patógenos extracelulares

Vermes  
E bactérias

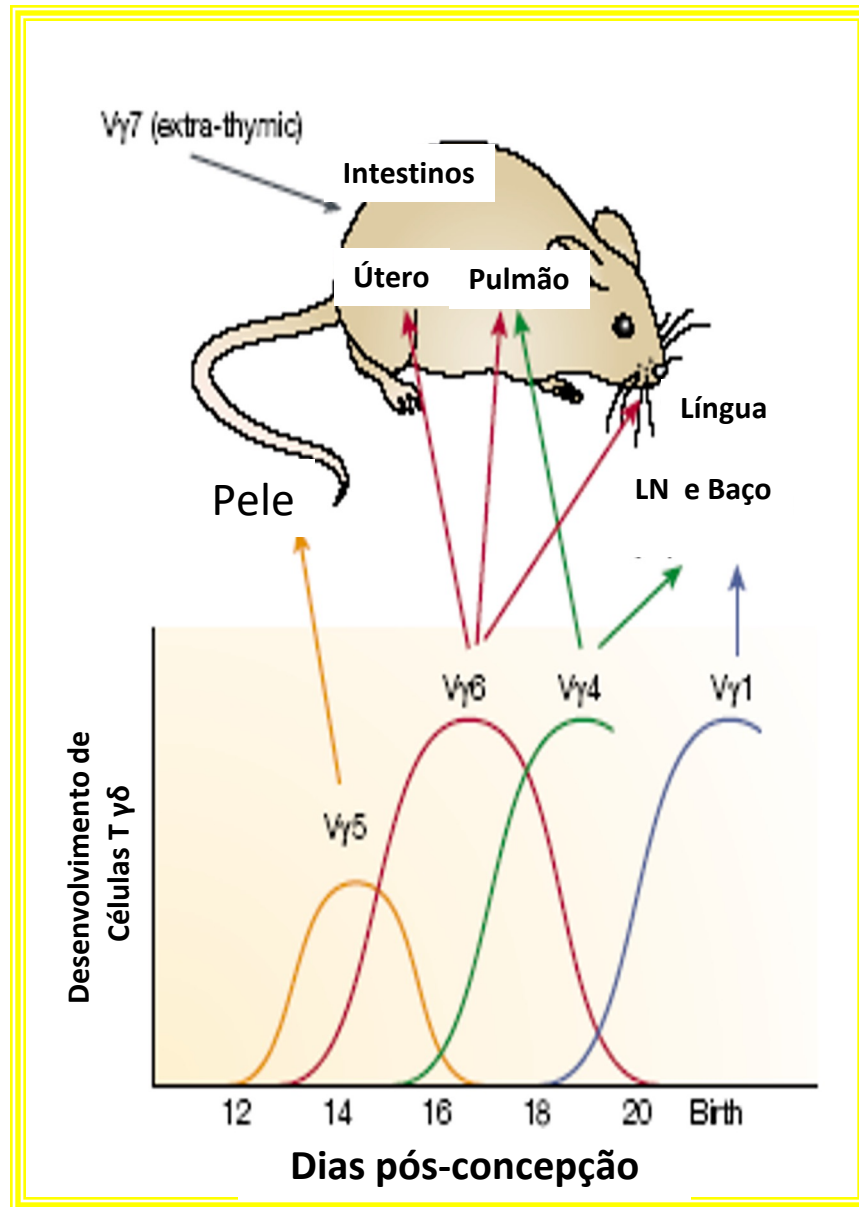
Secretam  
IL-4, IL-5 e IL-13





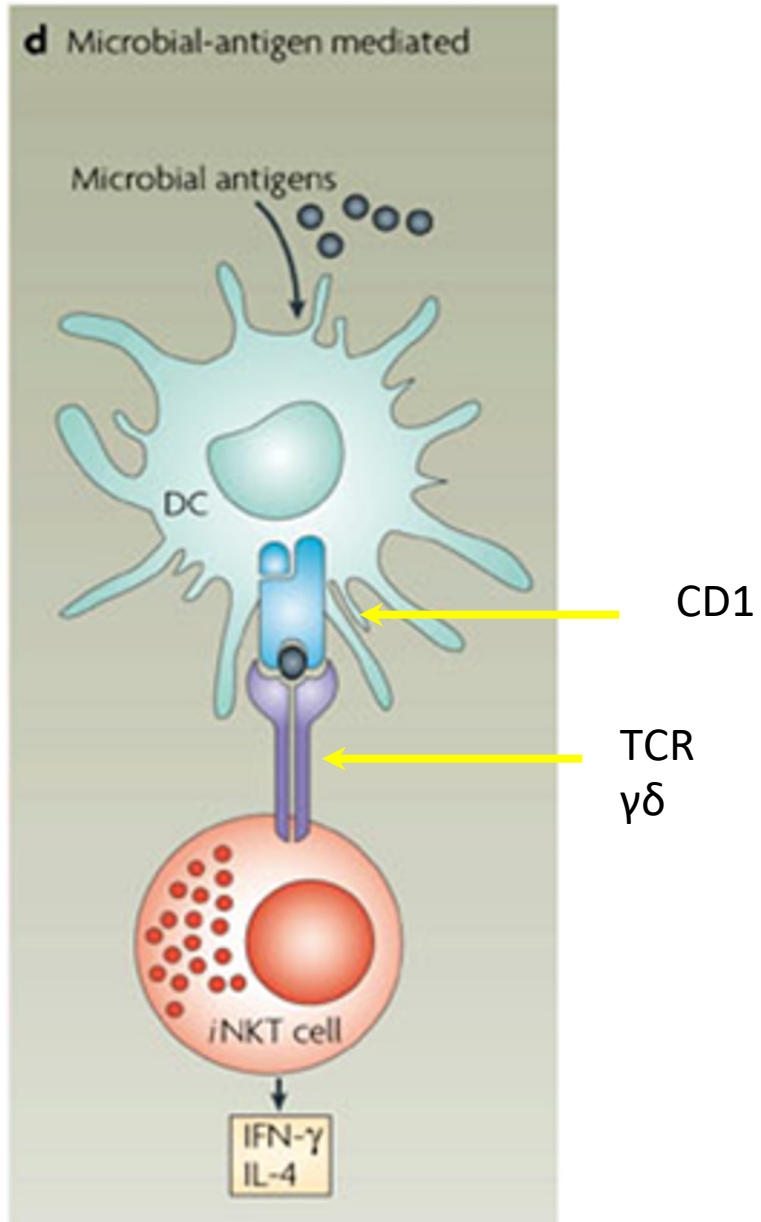
**Linfócitos T  
CD8  
eliminam  
células  
infectadas  
por vírus ou  
células  
Tumorais.  
Secretam  
IFN- $\gamma$**

# Linfócitos T $\gamma\delta$



- Linfócitos Intra-epiteliais
- $\alpha\beta$  /  $\gamma\delta$  - 50:1 Linfonodos
- $\alpha\beta$  /  $\gamma\delta$  - 5:1 Lâmina própria
- CD8 $\alpha$  ou DN
- Distribuição tecidual específica
- Homeostase local e proteção local



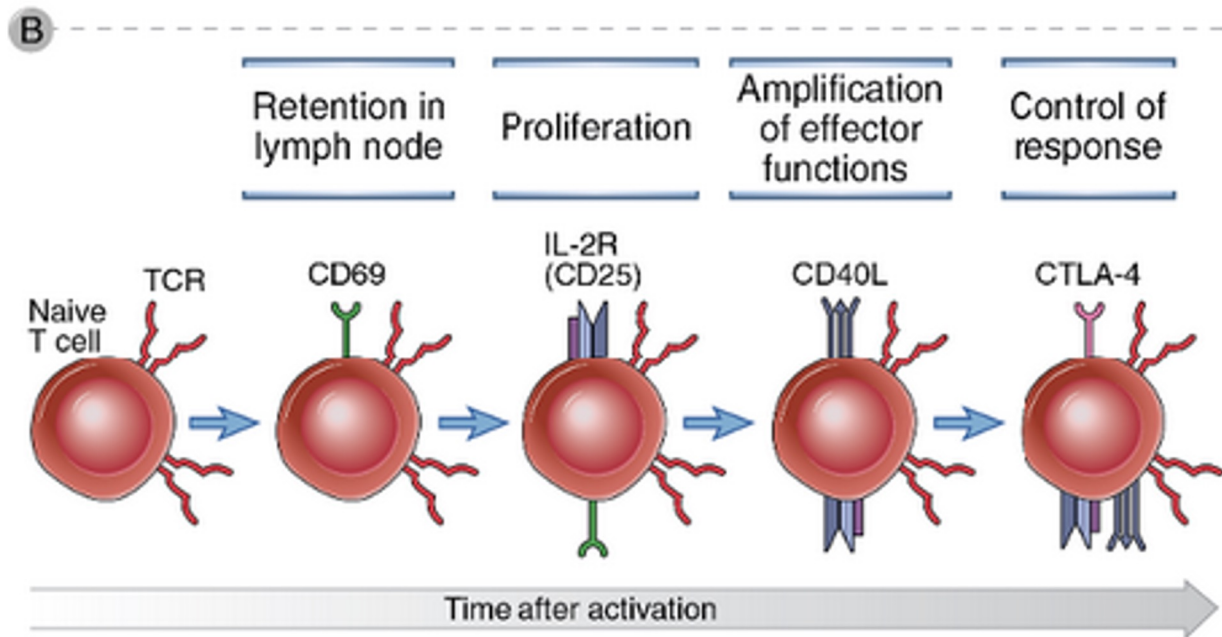
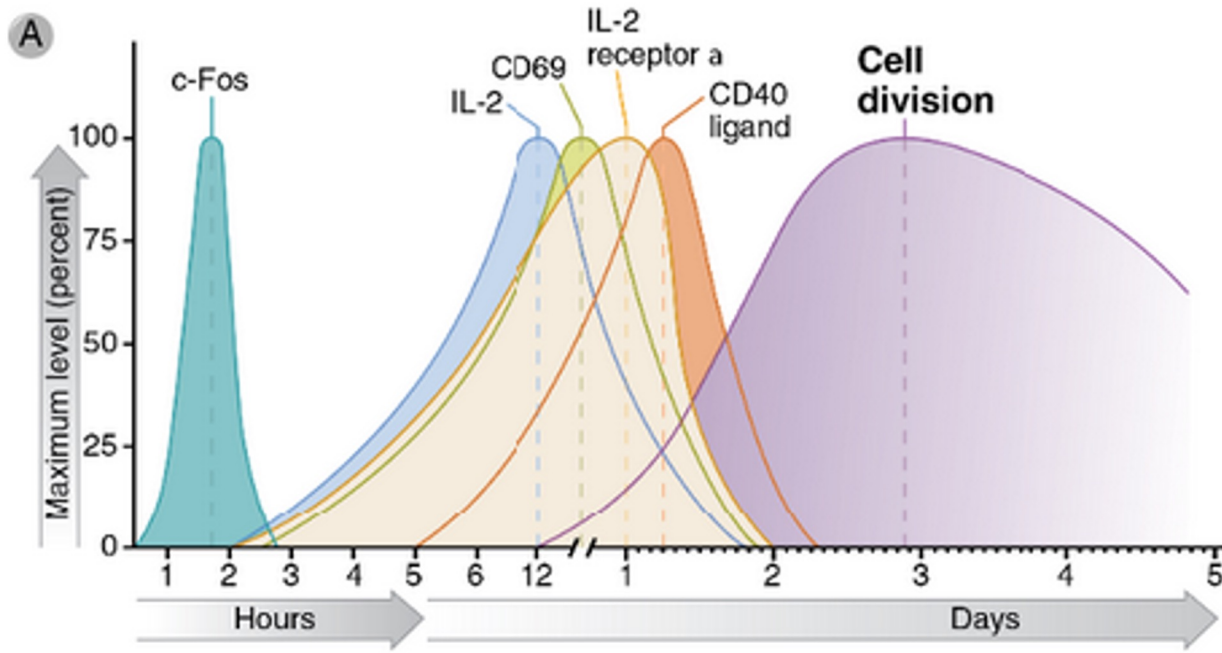


Células NKT são Células T que apresentam o TCR com baixa variabilidade ou invariável

Reconhecem antígeno apresentados por moléculas de CD1

Amplamente encontradas no Fígado

Podem secretar IL-4 e IFN- $\gamma$



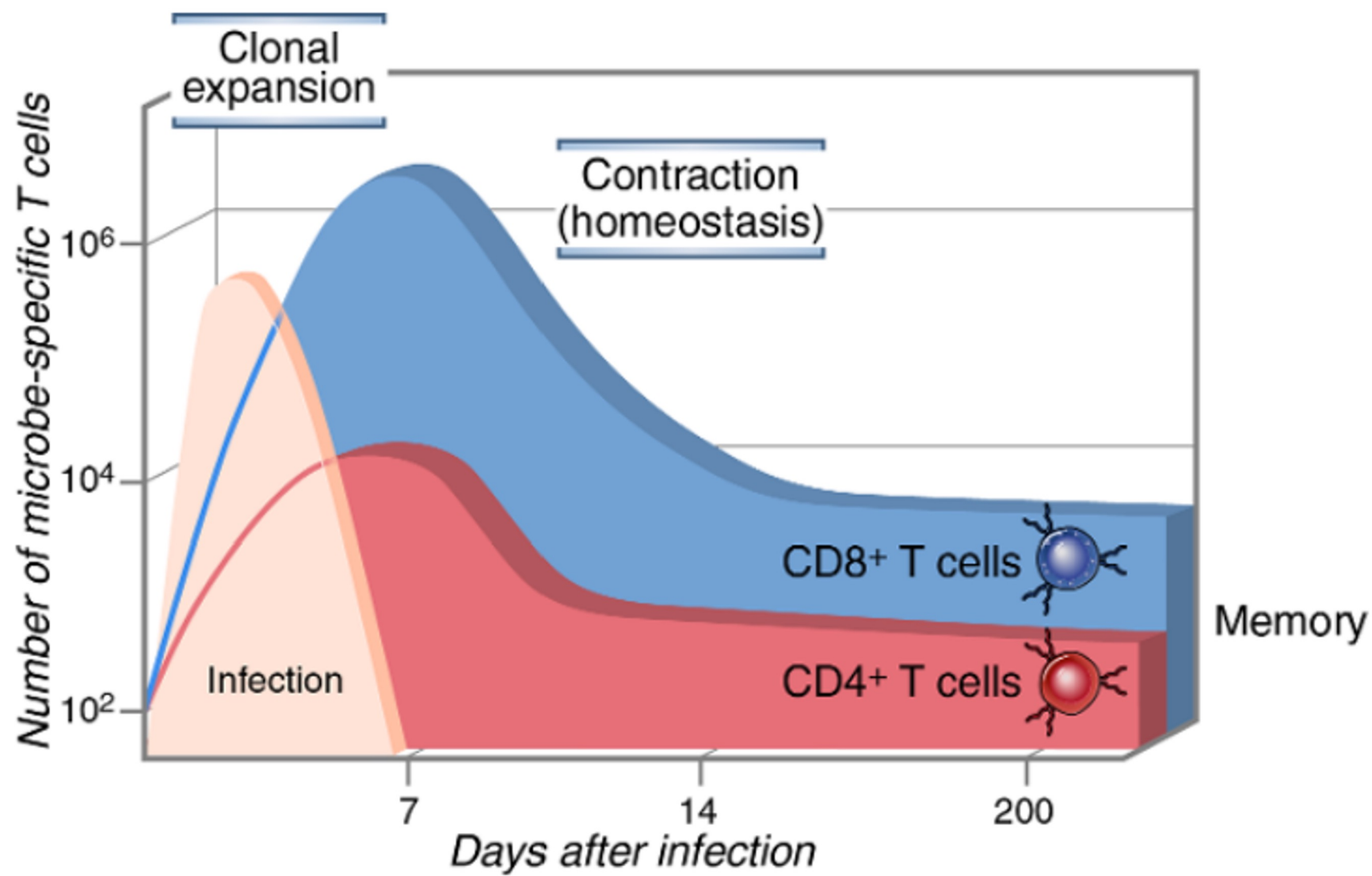
**Cinética**

**Ativação da  
resposta imune  
Obedece uma  
certa ordem  
Cronológica**

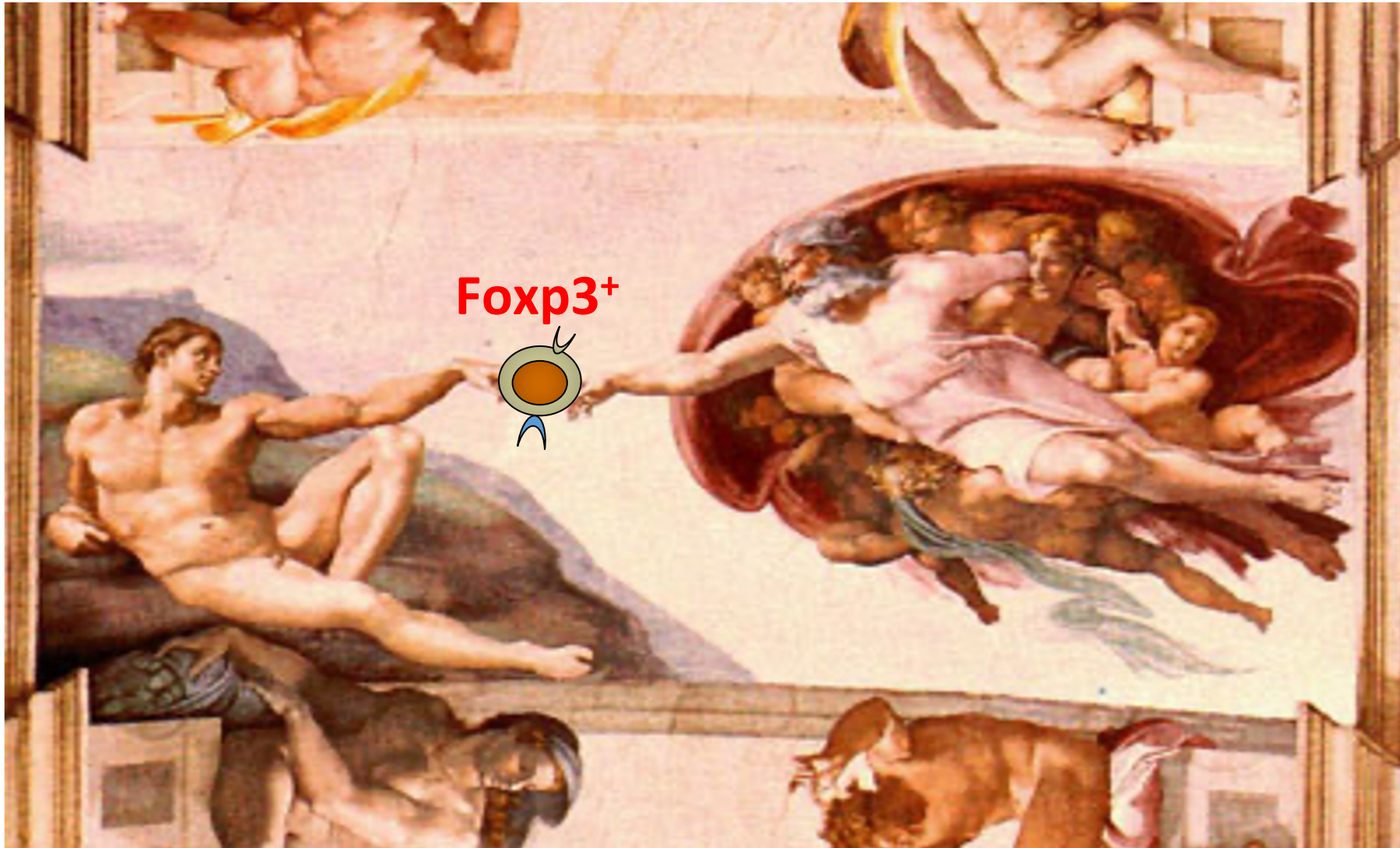
**Fatores Precoces**

**Fatores Tardios**

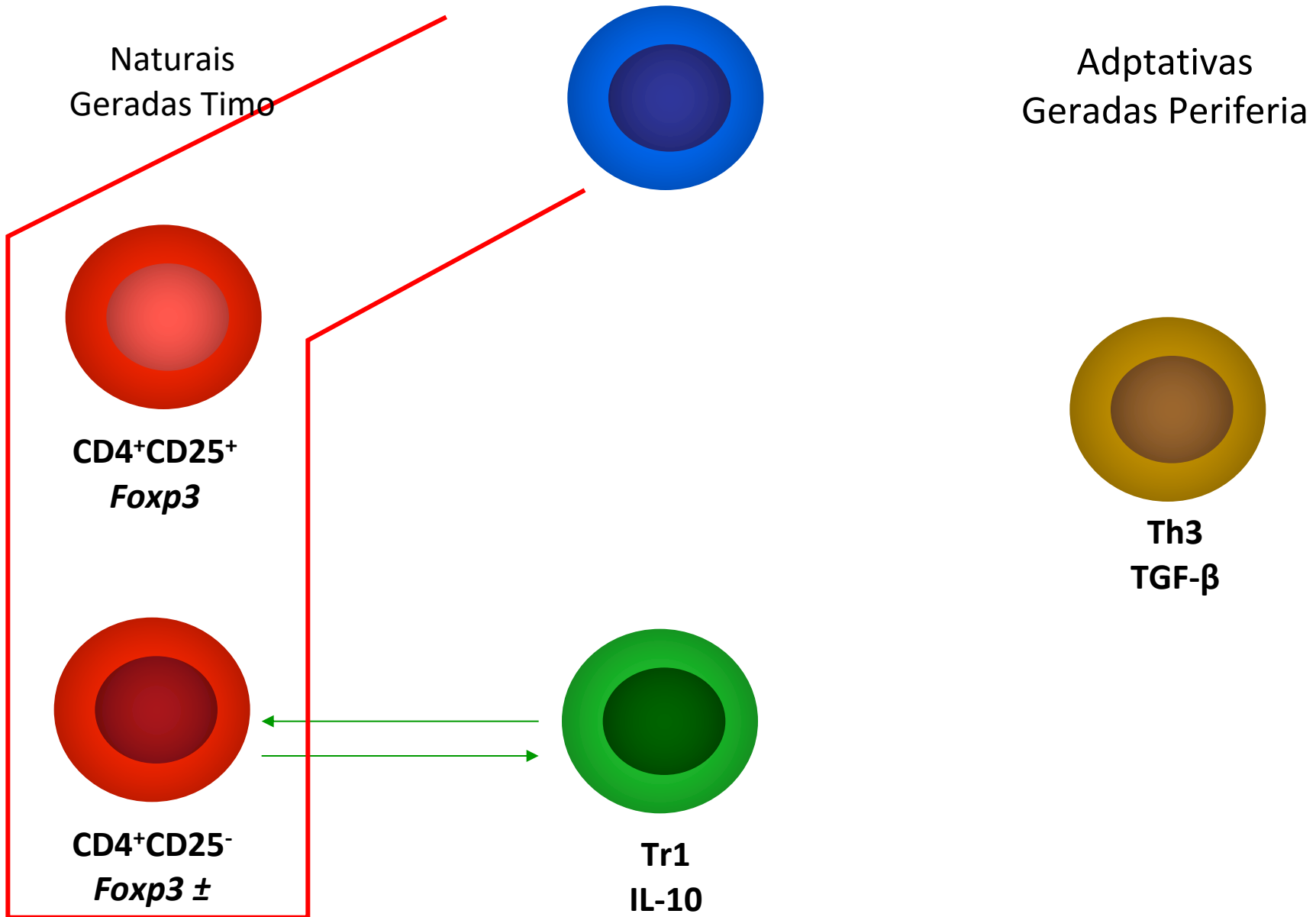




# 1995 Renascimento das células T reguladoras

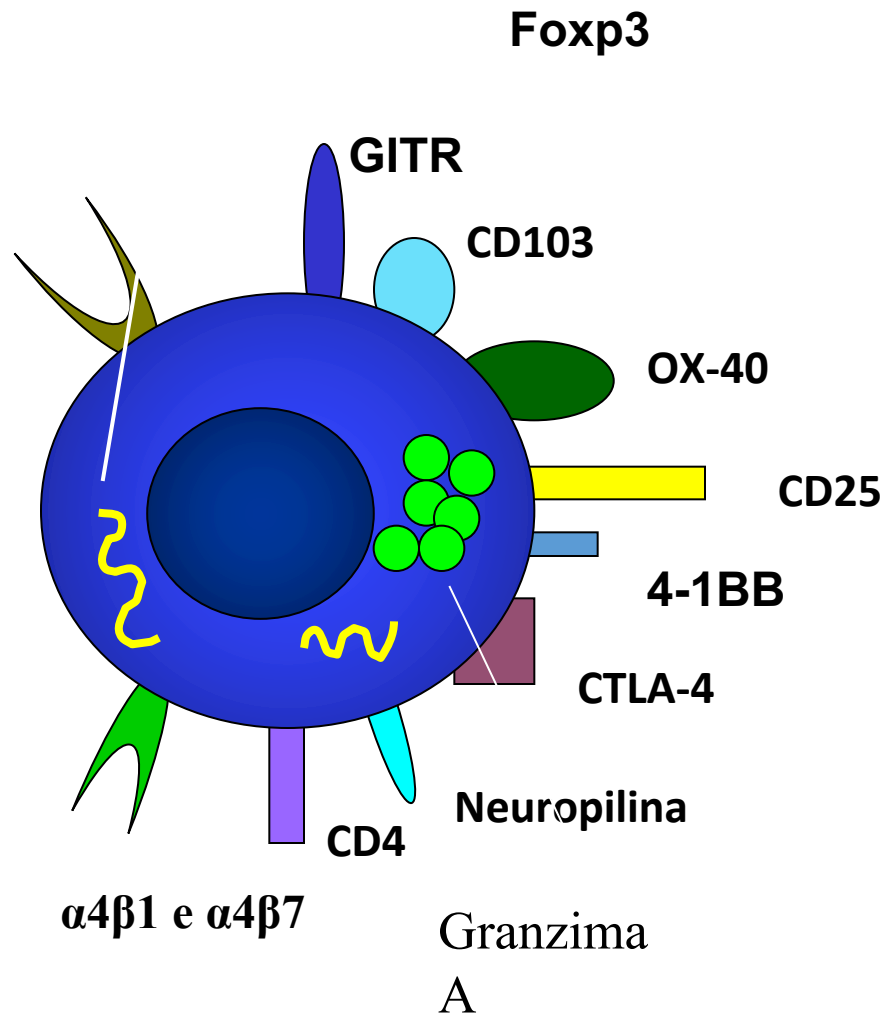


# Tipos de Tregs





# Tregs Naturais



Ação por contato;  
IL-2;  
Geradas no timo;  
GITR  
*Foxp3*  
Granzima A

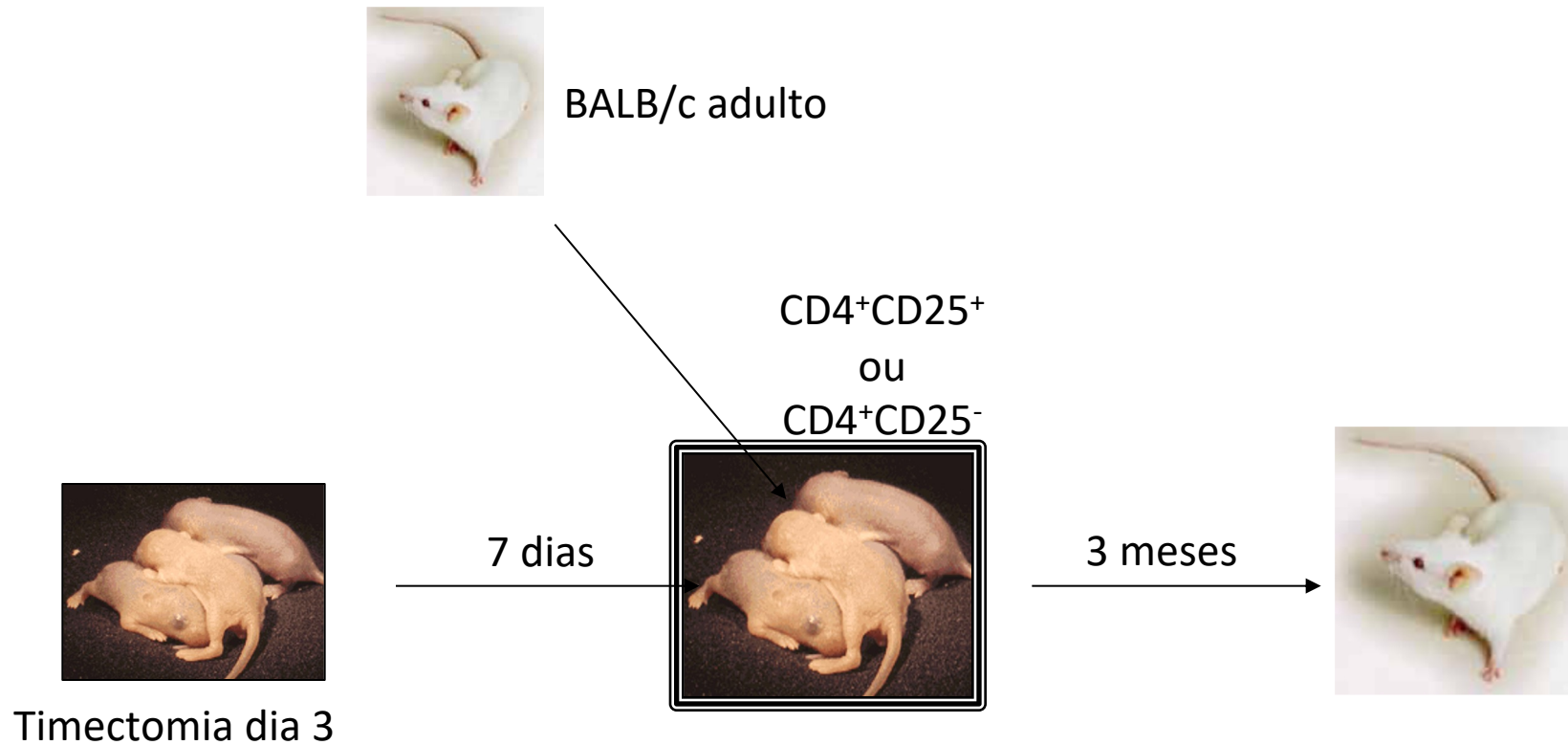
# Mecanismos Regulatórios

- Anergia clonal
- Citocinas supressoras
- Down-regulation de moléculas apresentadoras
- Indoleamina, 2,3-dioxigenase
- Citotoxicidade
- Fosfatases, ubiquitina ligases, SOCS
- miRNA

Células T Reguladoras



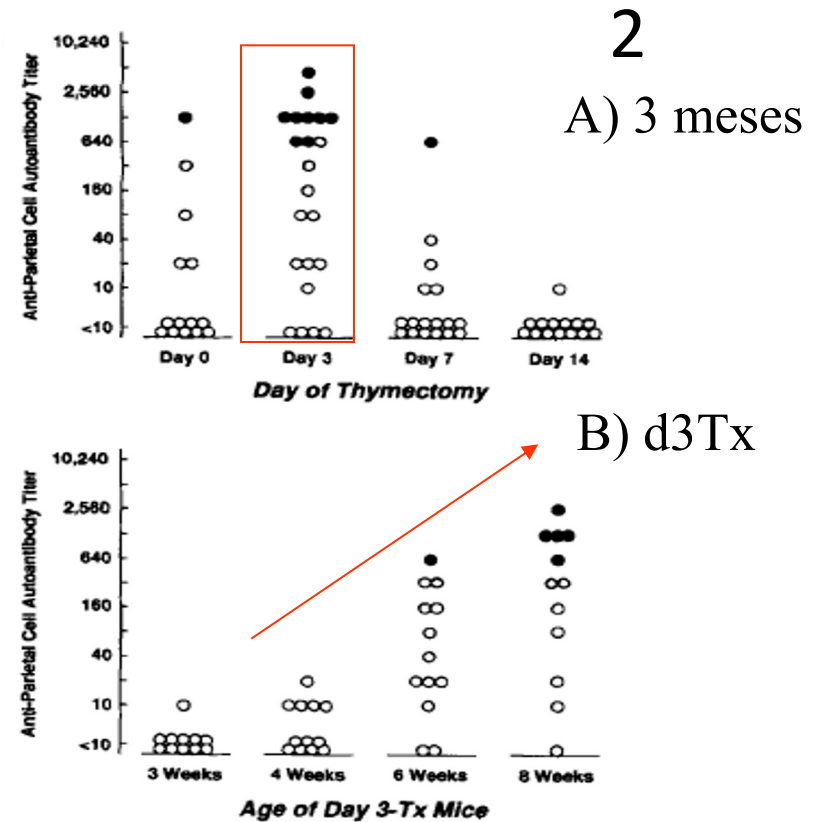
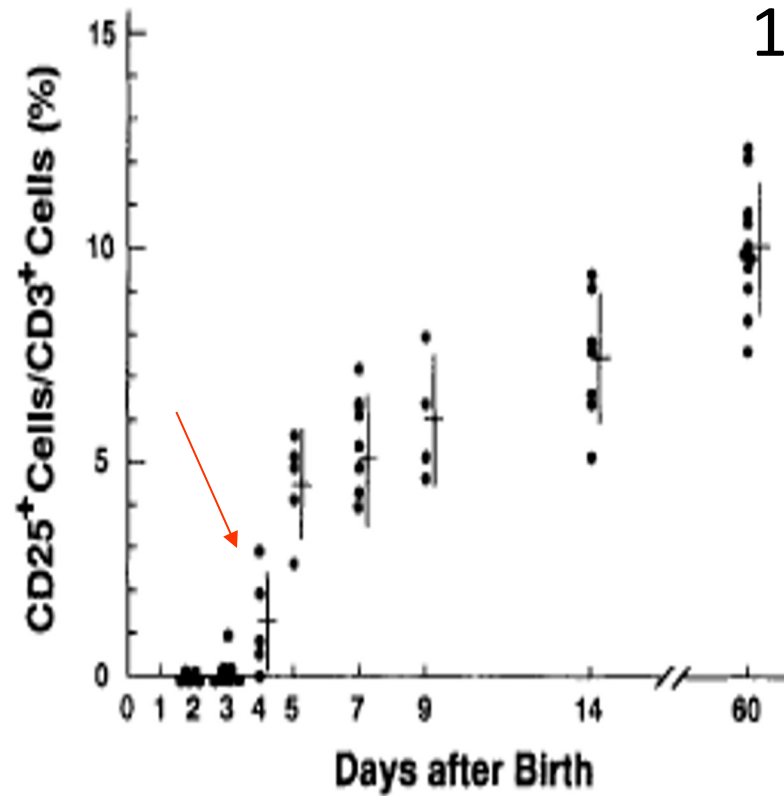
# Timectomia



Asano, M.; Toda, M.; Sakaguchi, N. and Sakaguchi, S. Autoimmune disease as a consequence of developmental abnormality of a T cell subpopulation. *J Exp Med* 184: 387, 1996.

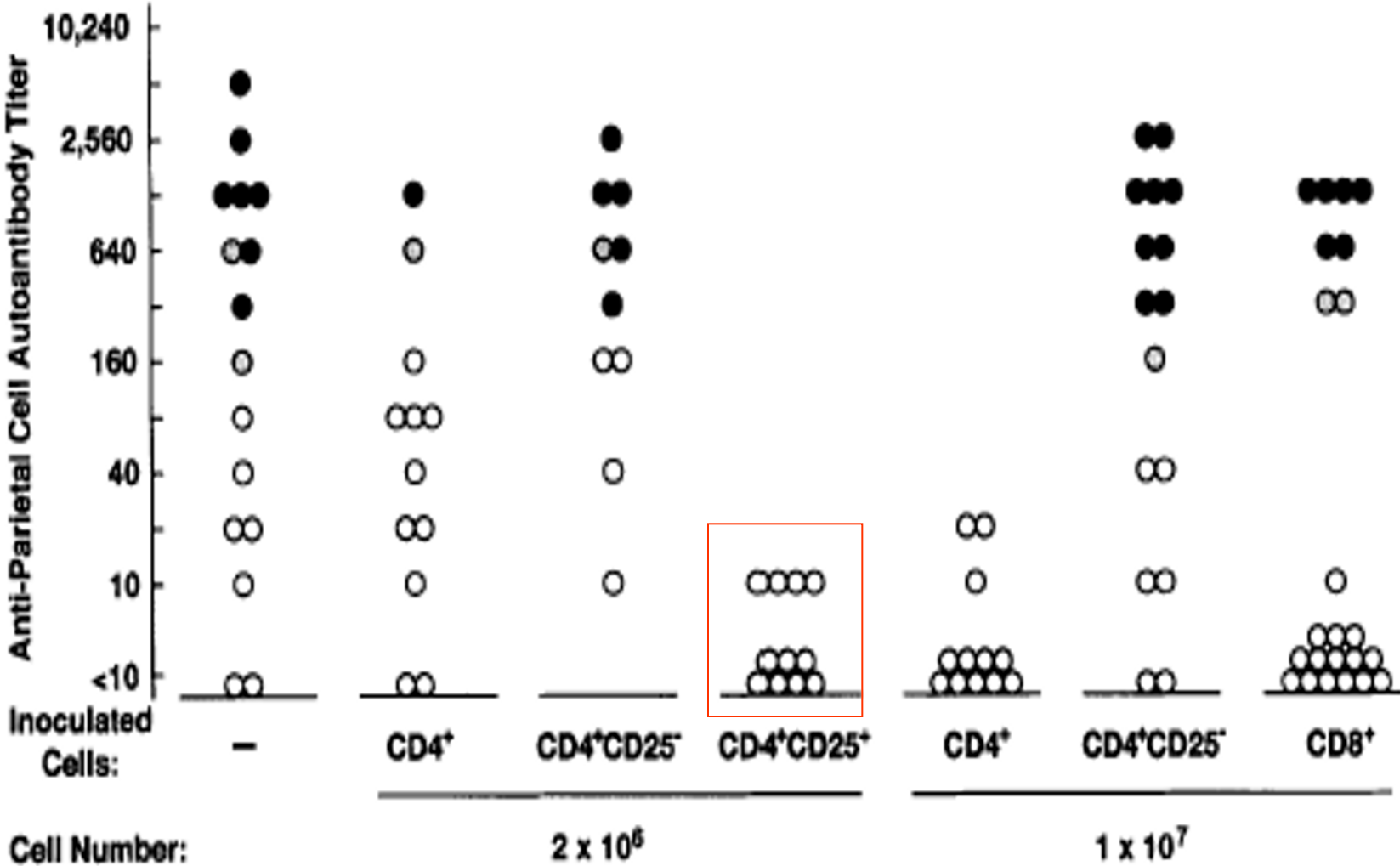


# Resultados



- 1) Número de células T CD4<sup>+</sup>CD25<sup>+</sup> no baço de camundongos BALB/c nos dias 1-60.
- 2) Auto-anticorpos em camundongos que receberam células CD4<sup>+</sup>CD25<sup>+</sup> ou CD4<sup>+</sup>CD25<sup>-</sup>.

# Gastrite Auto-immune



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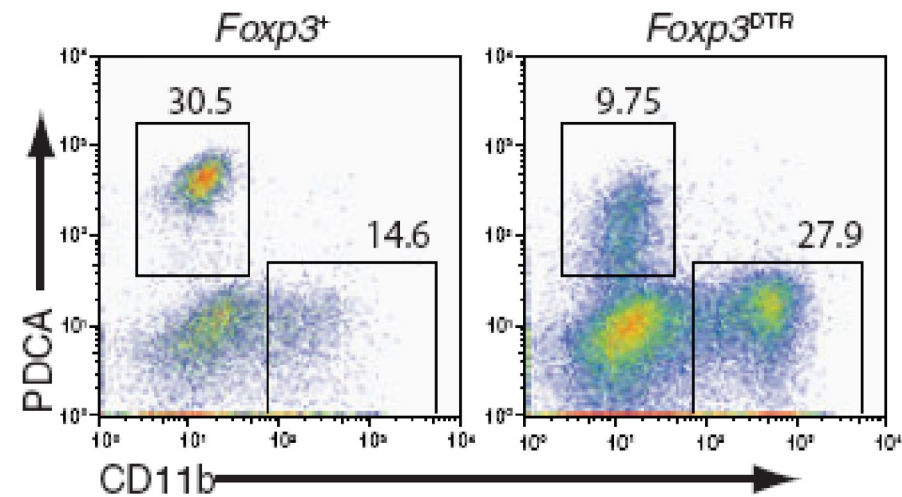
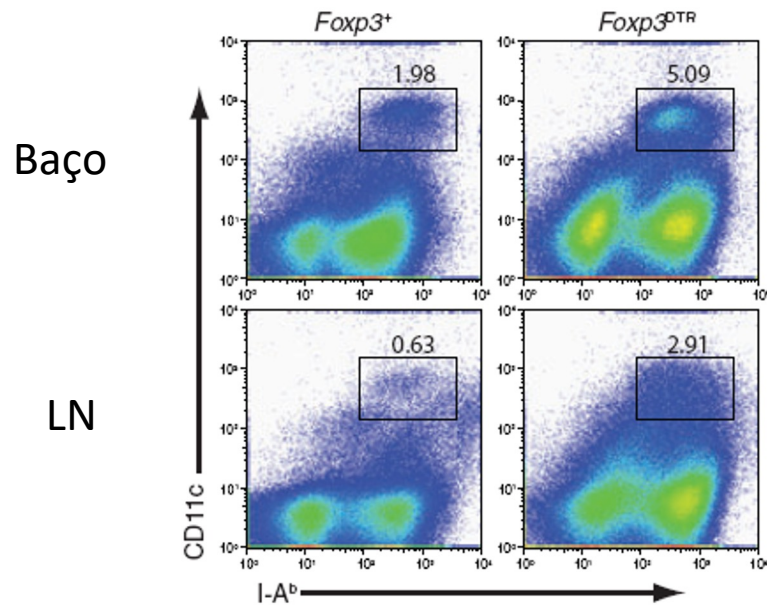
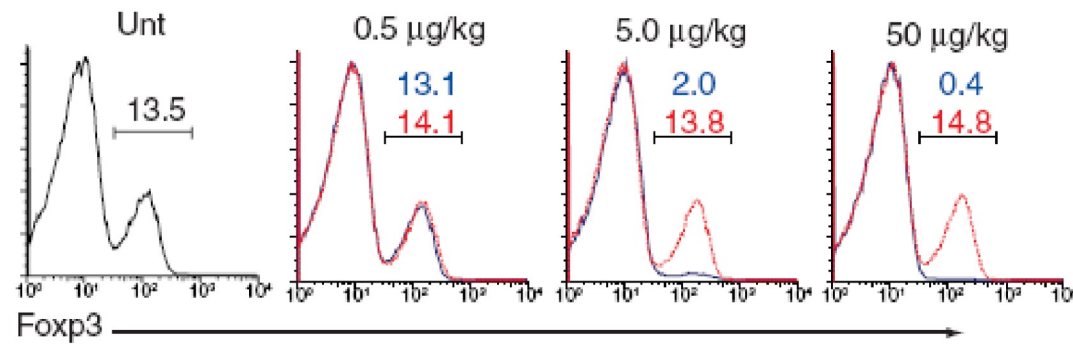
# Regulatory T cells prevent catastrophic autoimmunity throughout the lifespan of mice

Jeong M Kim<sup>1</sup>, Jeffrey P Rasmussen<sup>1</sup> & Alexander Y Rudensky<sup>1,2</sup>

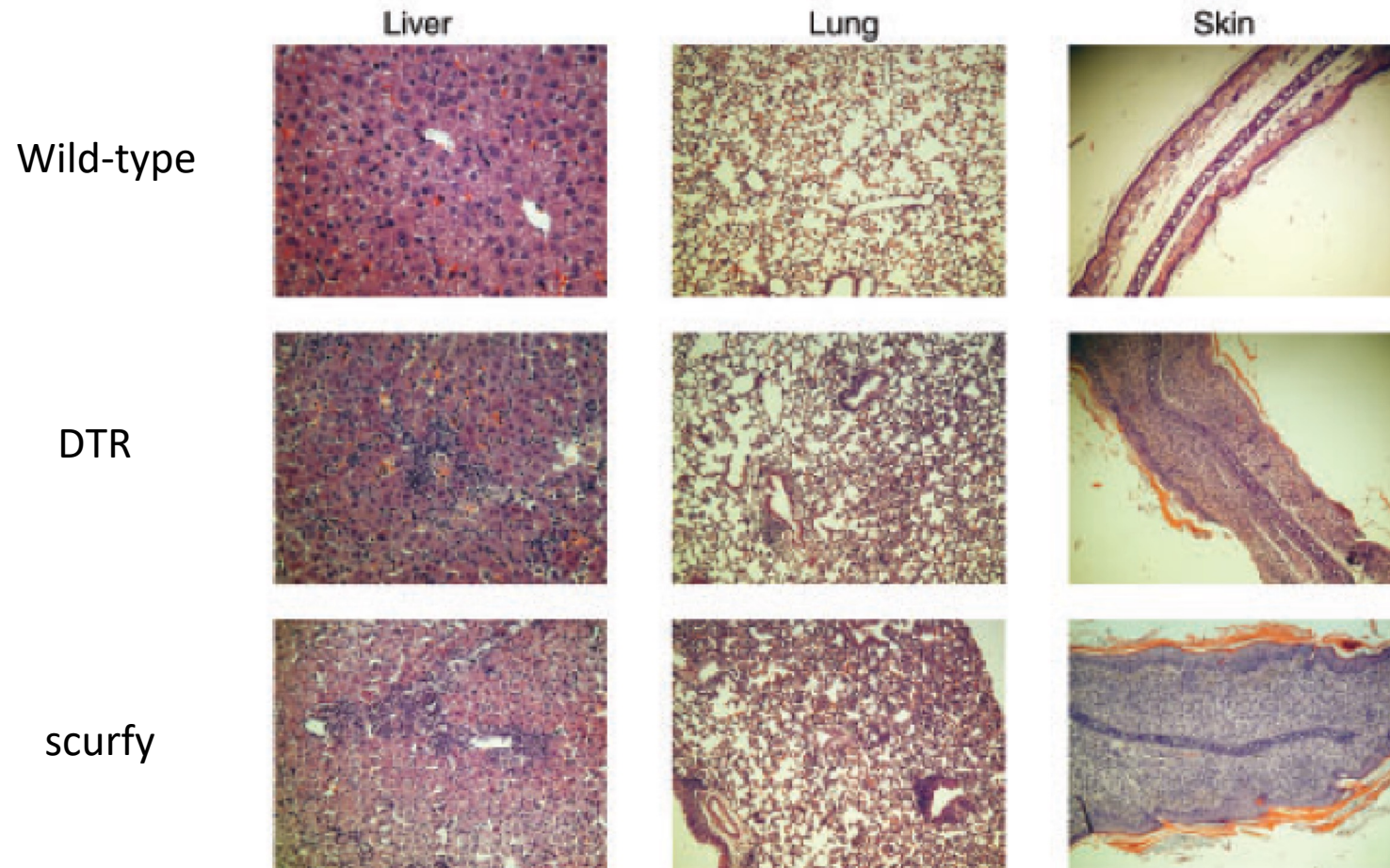
Mice lacking the transcription factor *Foxp3* (*Foxp3*<sup>-</sup>) lack regulatory T (T<sub>reg</sub>) cells and develop fatal autoimmune pathology. In *Foxp3*<sup>-</sup> mice, many activated effector T cells express self-reactive T cell receptors that are expressed in T<sub>reg</sub> cells in wild-type mice. Thus, in wild-type mice, most self-reactive thymocytes escaping negative selection are diverted into the T<sub>reg</sub> lineage, and whether T<sub>reg</sub> cells are critical in self-tolerance in wild-type mice remains unknown. Here, acute *in vivo* ablation of T<sub>reg</sub> cells demonstrated a vital function for T<sub>reg</sub> cells in neonatal and adult mice. We suggest that self-reactive T cells are continuously suppressed by T<sub>reg</sub> cells and that when suppression is relieved, self-reactive T cells become activated and facilitate accelerated maturation of dendritic cells.



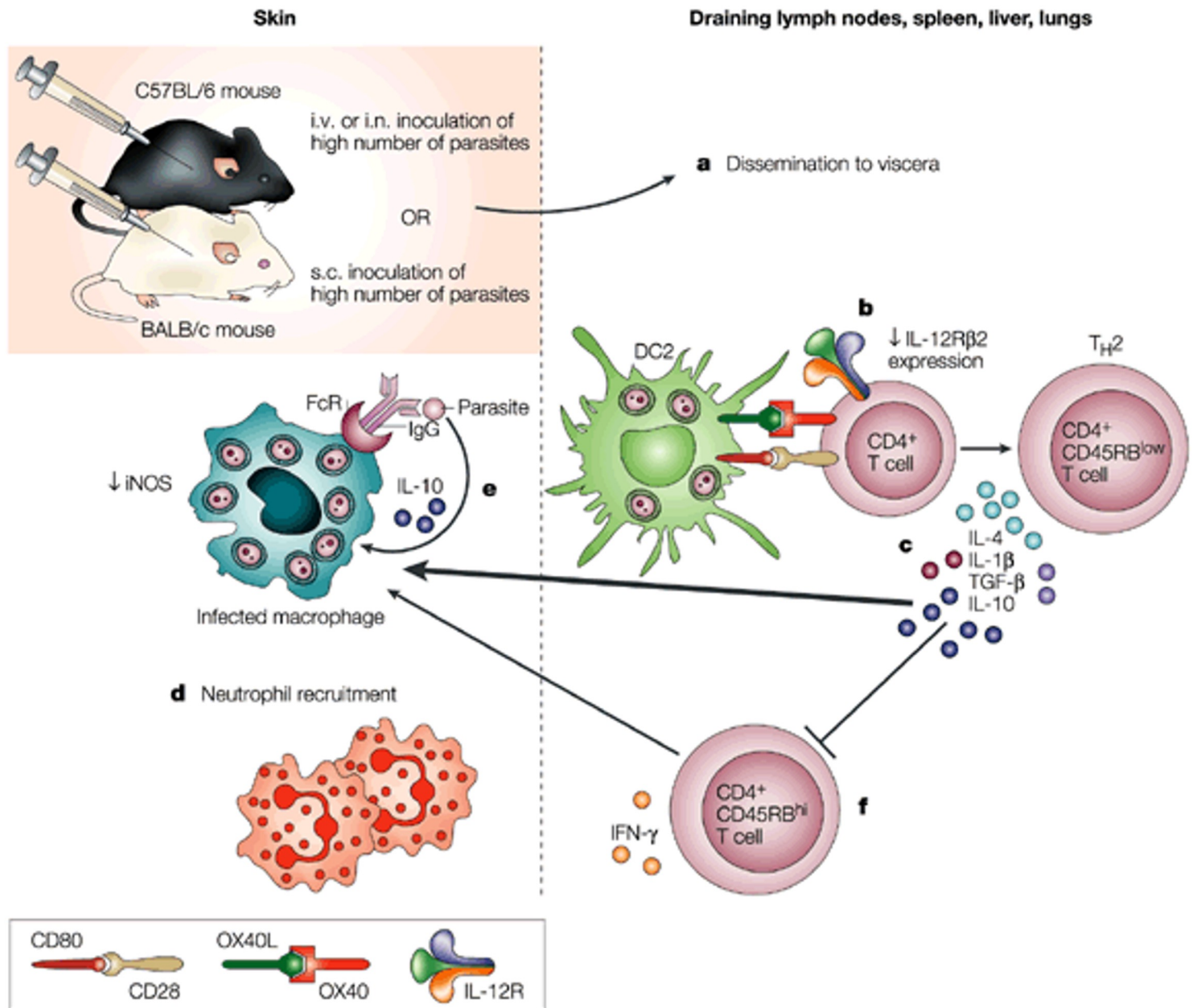
# Depleção de Tregs



# Depleção de Tregs leva a infiltrado inflamatório espontâneo





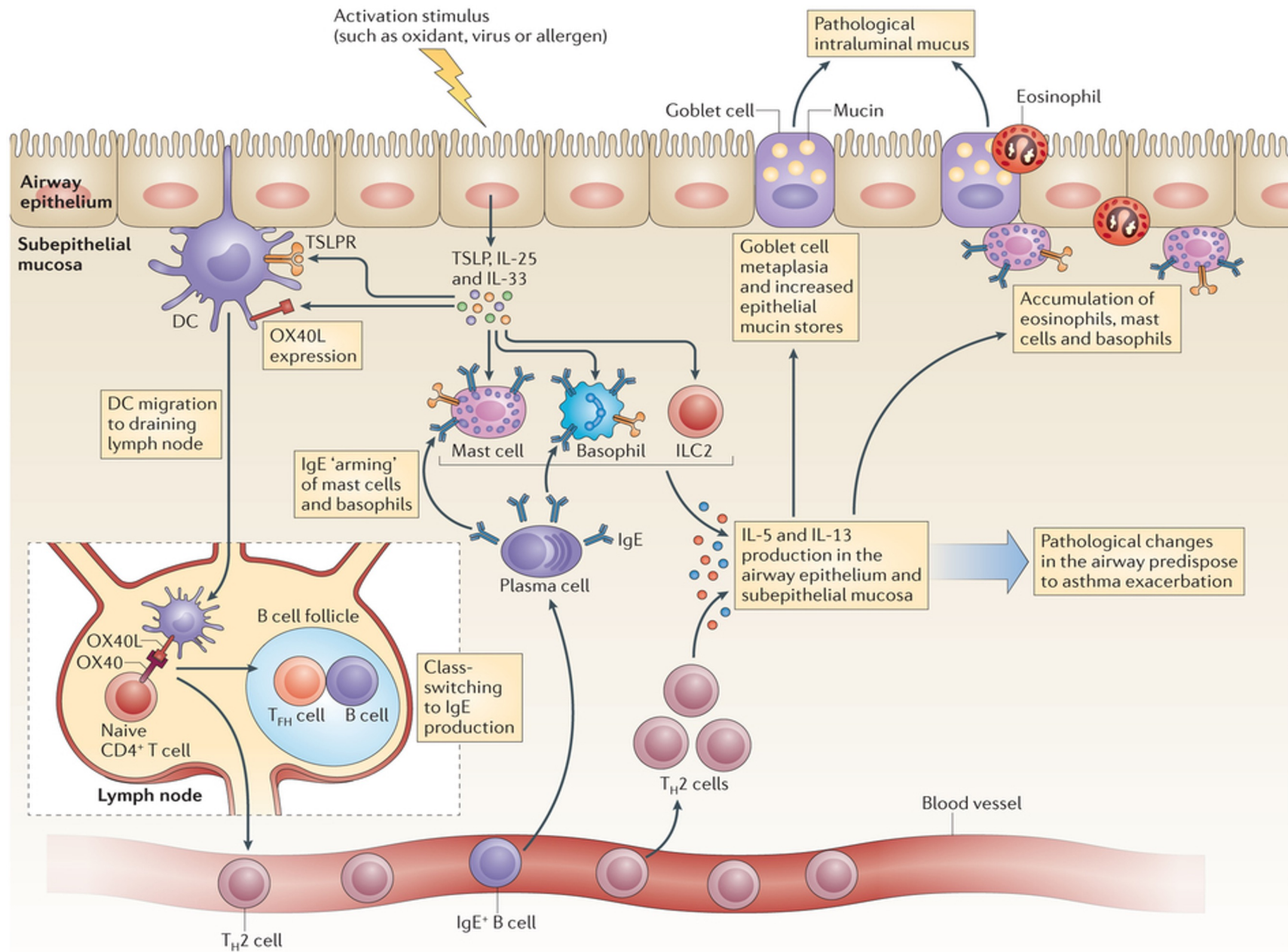


# Leishmaniose

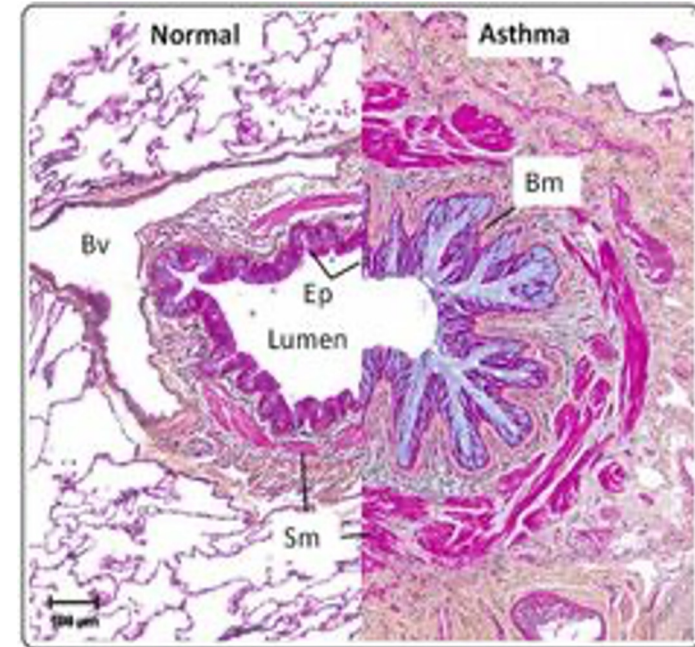
## Cutânea







# Asma



# Qual a função principal dessas células ?

Eliminar

O

Patógeno ?



Reparo

Tecidual

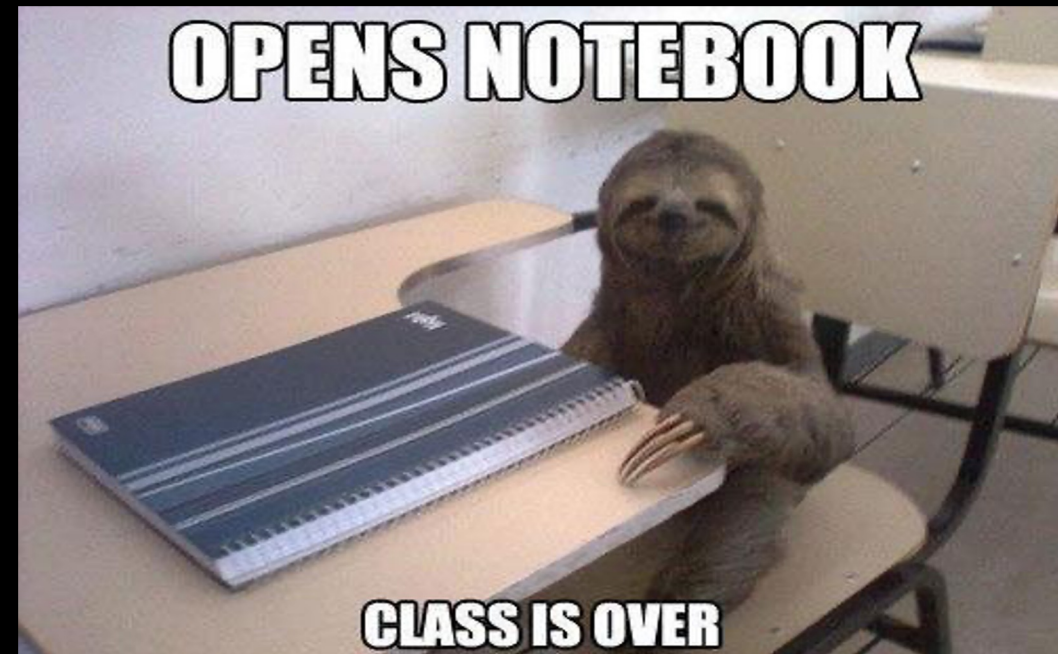
Depuração

Debris ?



Defesa ou Não?

Ambos !!







Jovem  
Pesquisador  
2011/18703-2

Cristiano  
Doctorat  
e

Carla  
Doctorat  
e

Isabell  
a  
Master

Wesley  
Doctorat  
e

David  
Post-doc

Jean  
Pierre  
Head

Carol  
Master  
s

