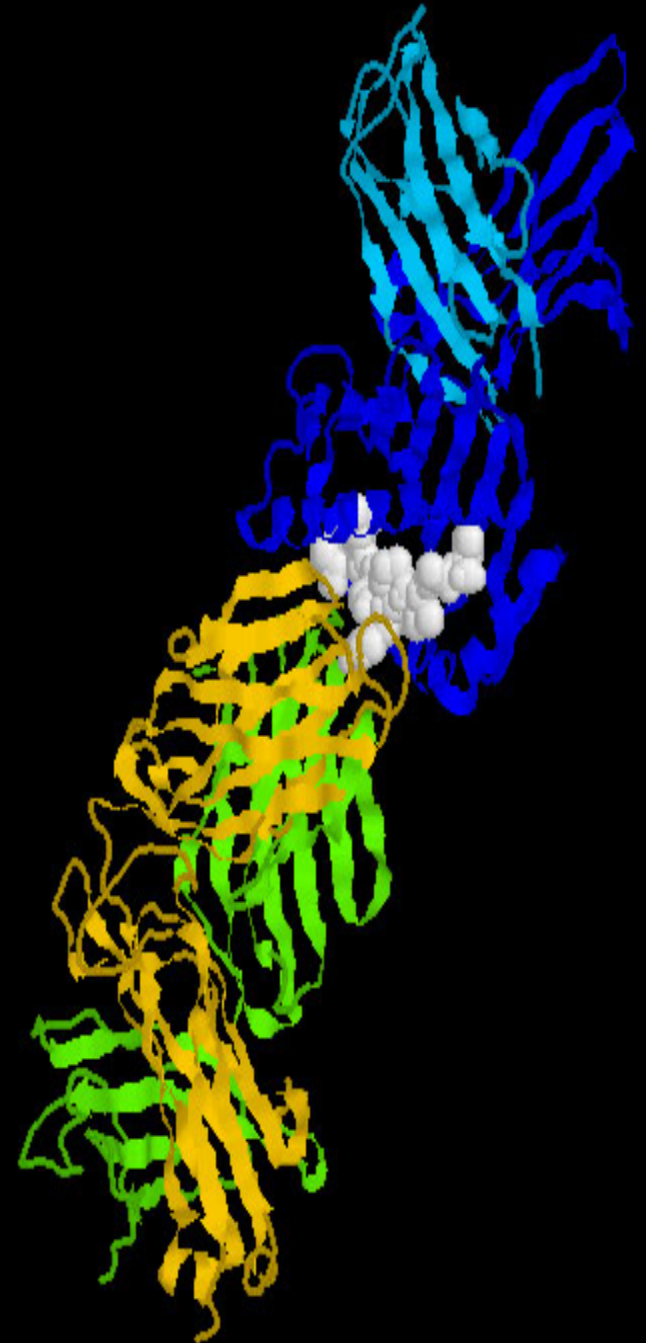
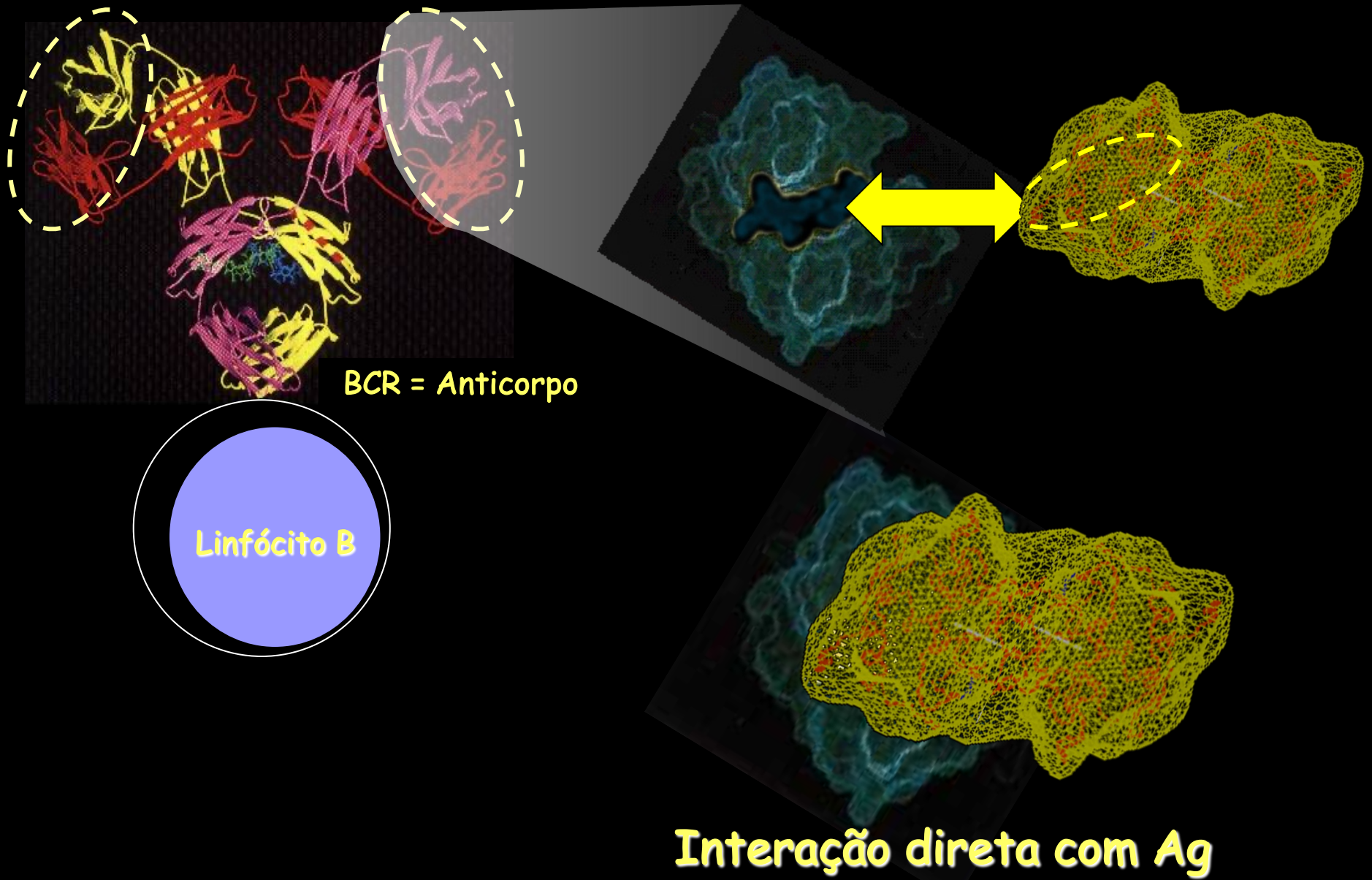


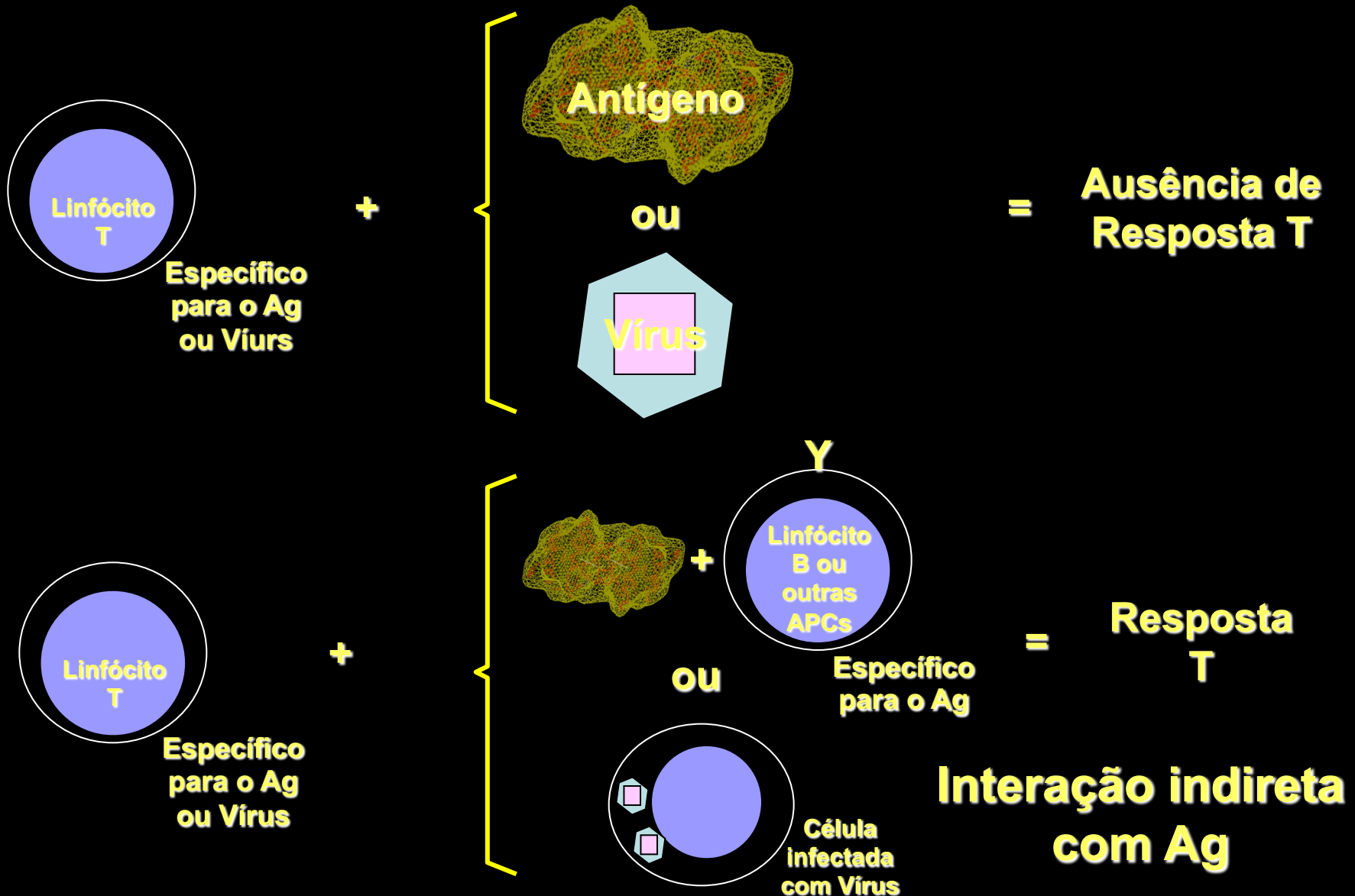
Complexo de  
Histocompatibilidade  
Principal: Estrutura,  
Função, Apresentação  
de Antígenos e  
Implicações Clínicas



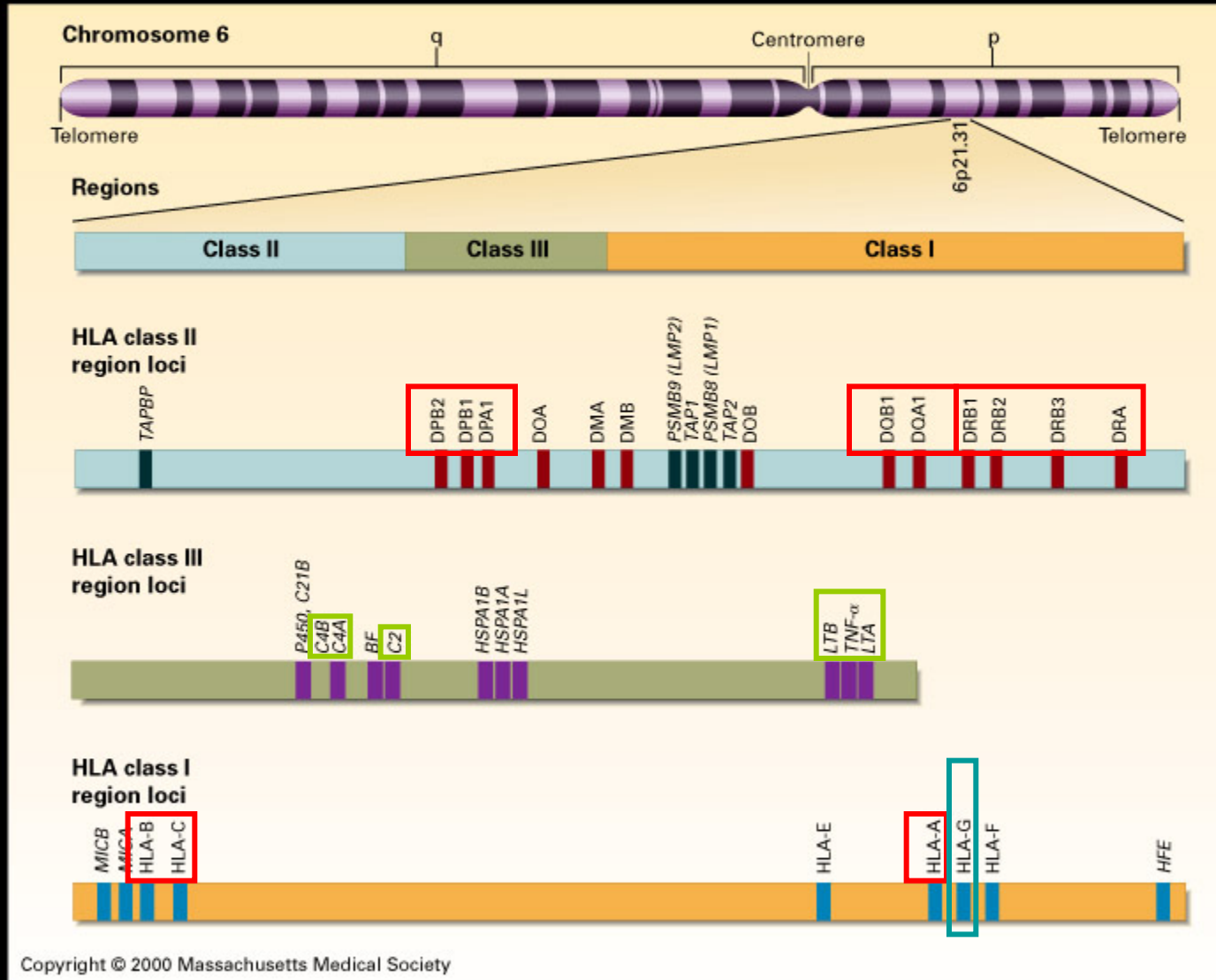
# Reconhecimento Antigênico pela Célula B



# Reconhecimento Antigênico pelas Células T



# Localização no Genoma

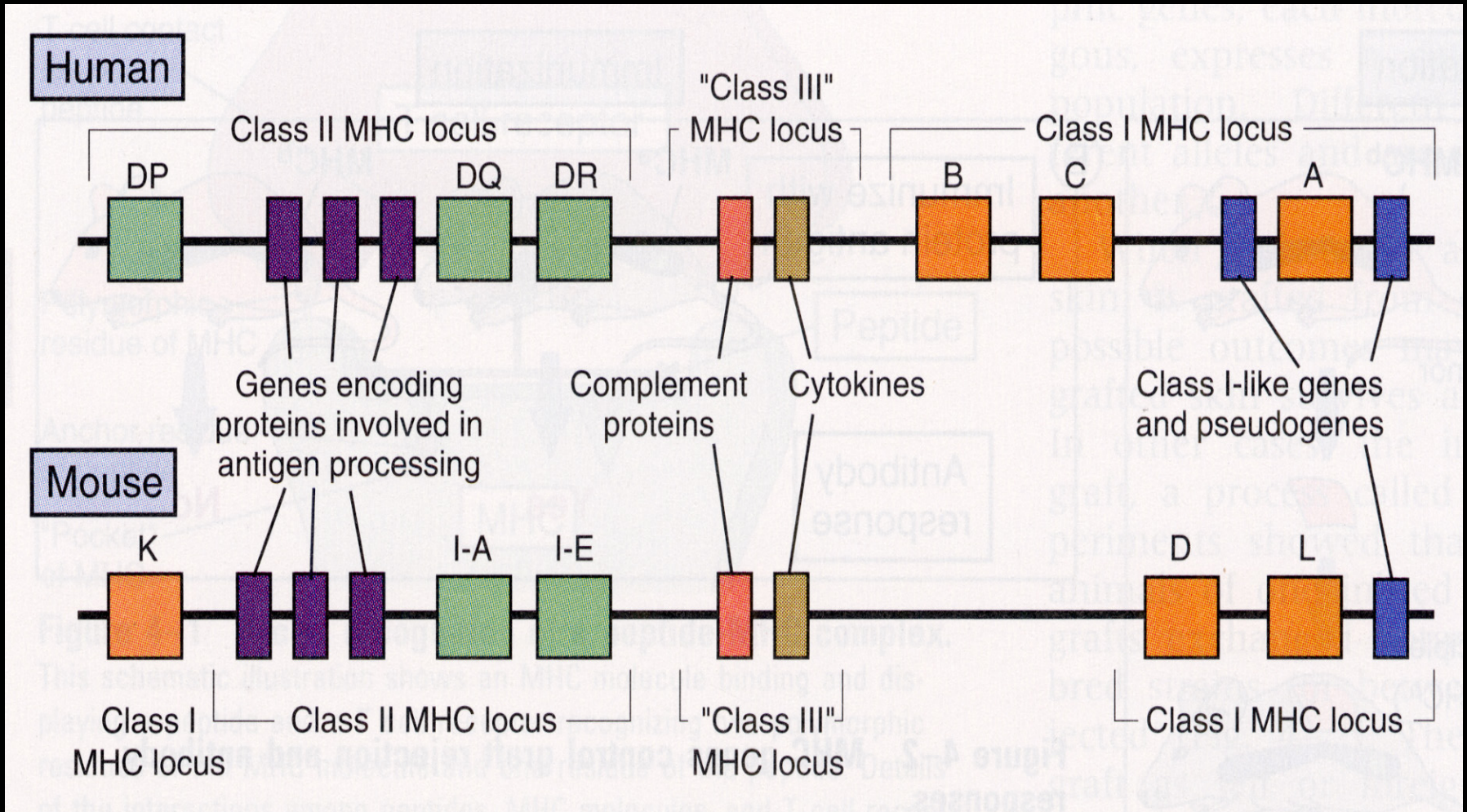


Klein J, Sato A. The HLA System. First of two parts. N Engl J Med 2000;343:702-9.

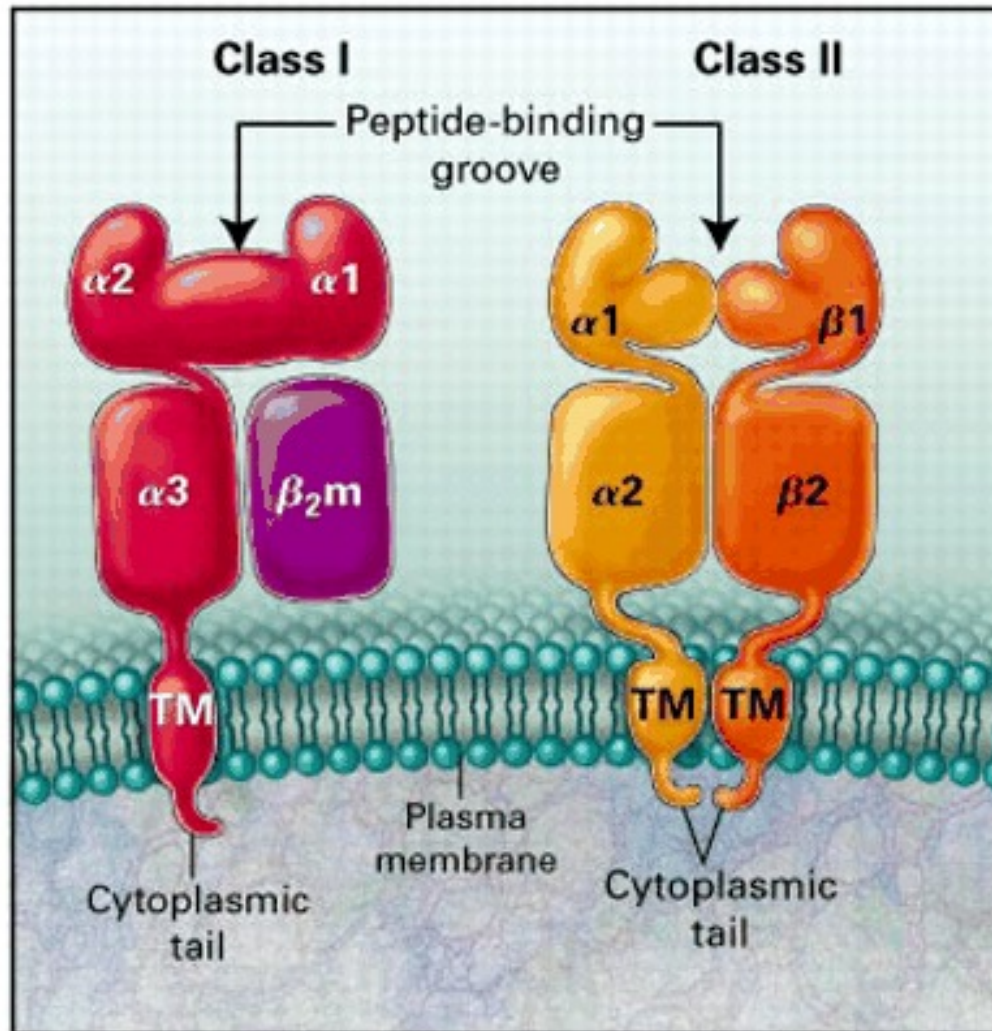


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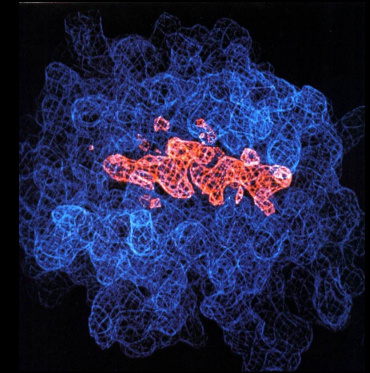
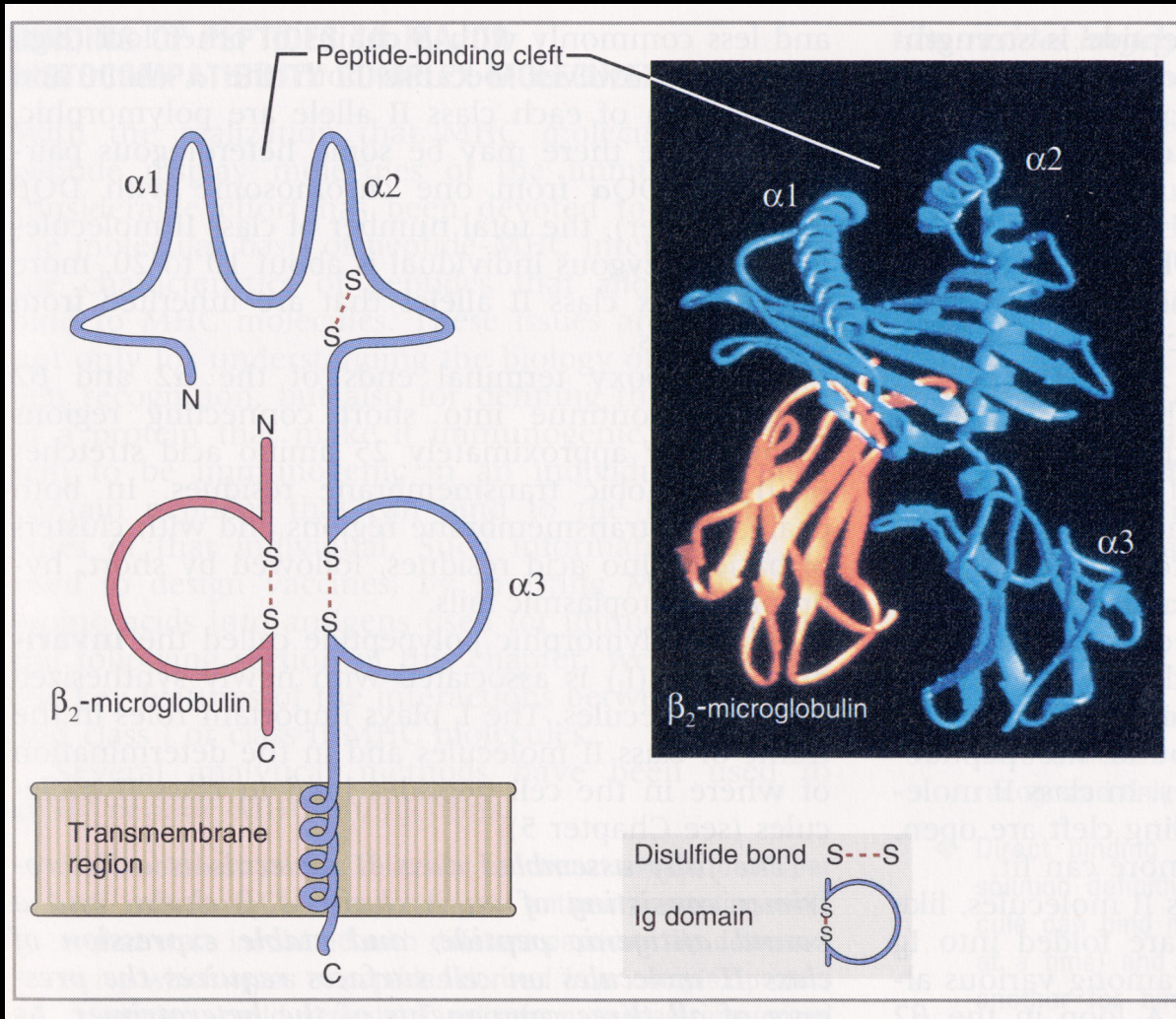
# Locus dos Genes do MHC



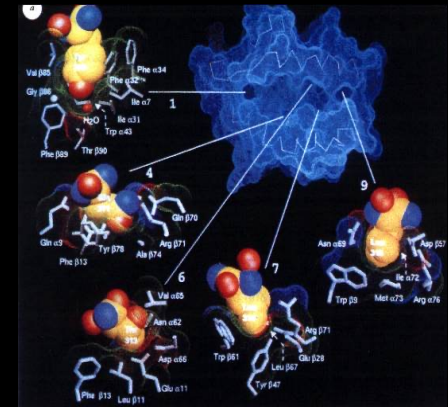
# Estrutura do MHC



# Molécula Classe I

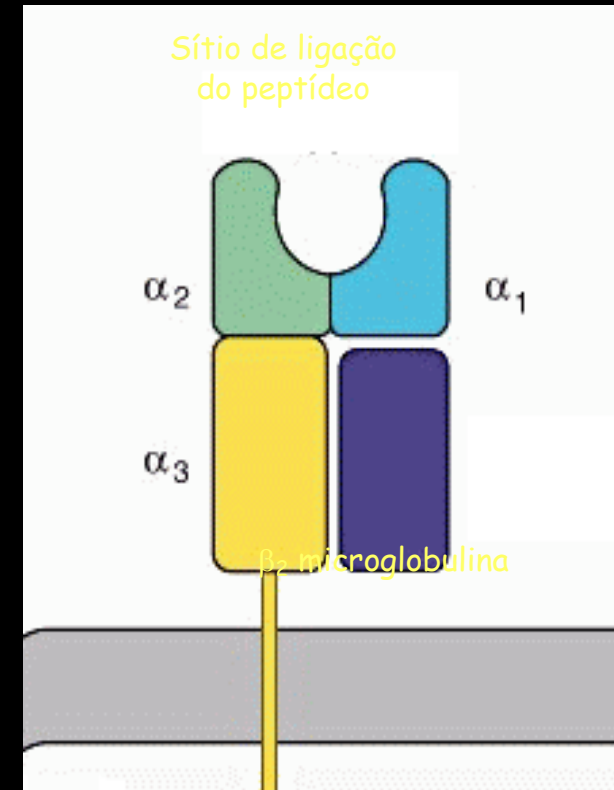
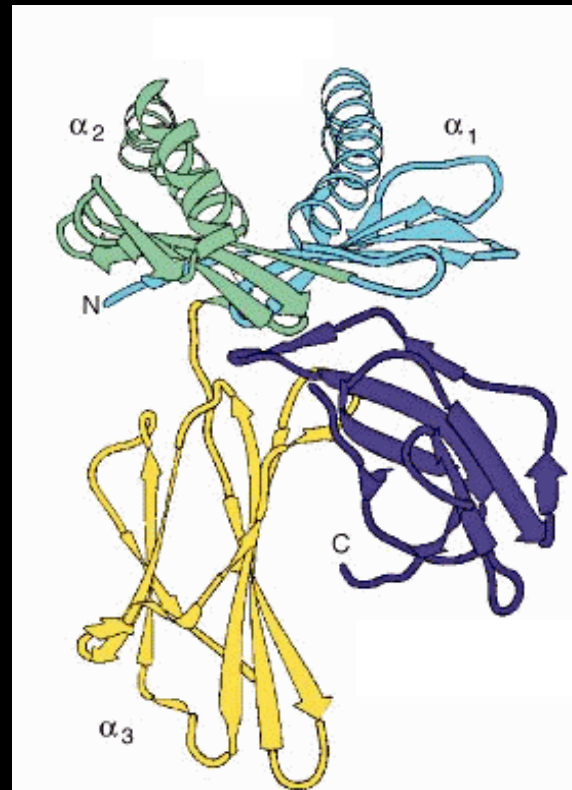
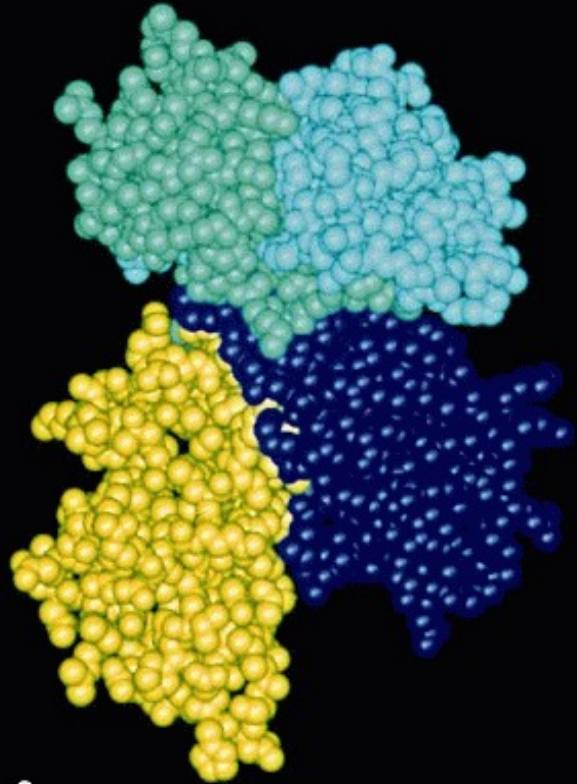


Fenda Fechada



Todas as células nucleadas

# Estrutura da molécula de MHC classe I





# Ligação do peptídeo à molécula de MHC classe I



H <sup>2</sup> N	T	Y	Q	R	T	R	A	L	V	COO
H <sup>2</sup> N	S	Y	F	P	E	I	T	H	I	COO
H <sup>2</sup> N	K	Y	Q	A	V	T	T	T	L	COO
H <sup>2</sup> N	S	Y	I	P	S	A	E	K	I	COO

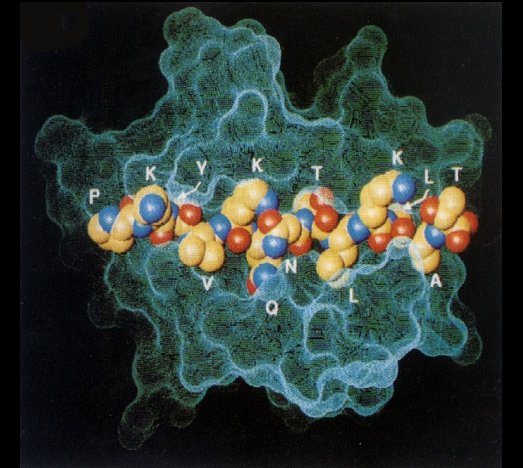
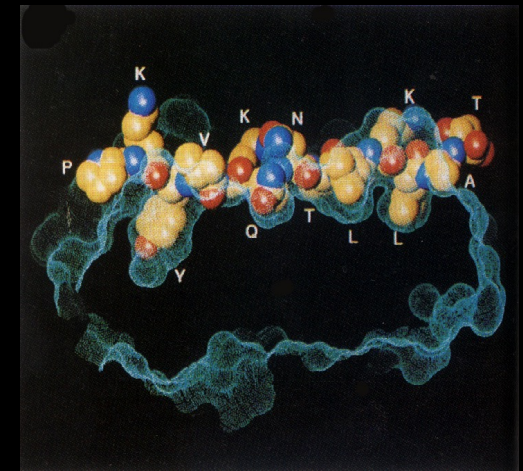
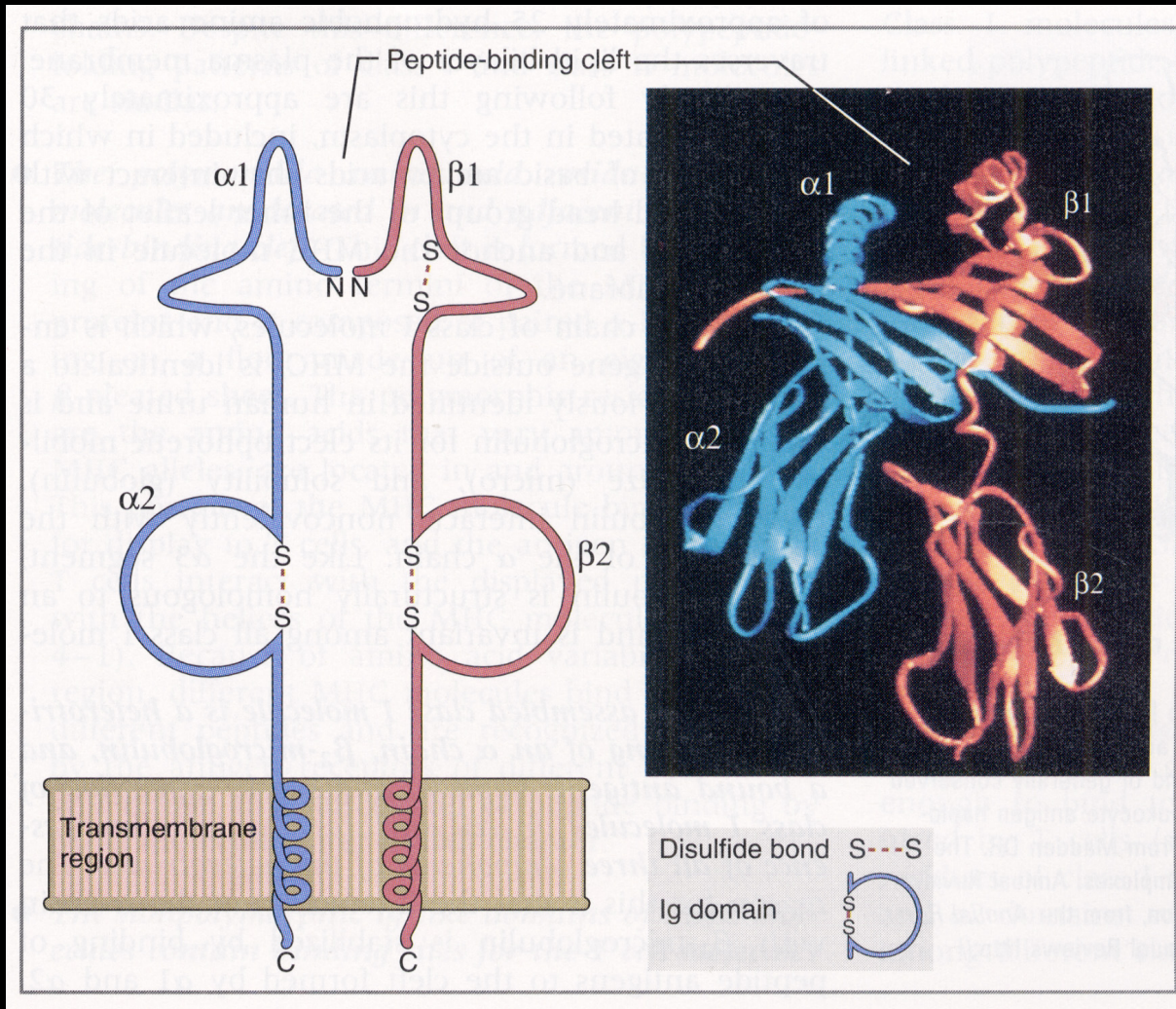
8-10 aa

Ligam ~ 2000 peptídeos

$10^5$  de cada variante alélica por célula

apresentação ~ 100-4000 cópias

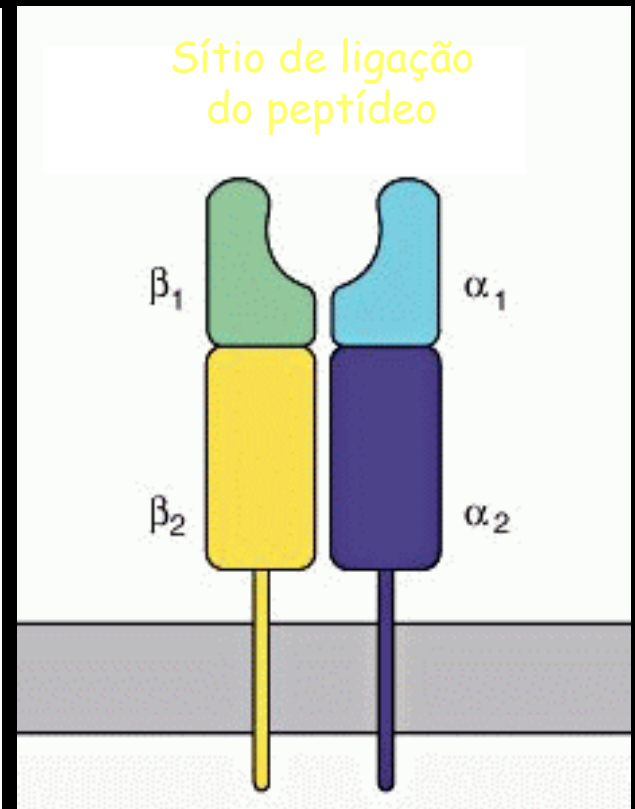
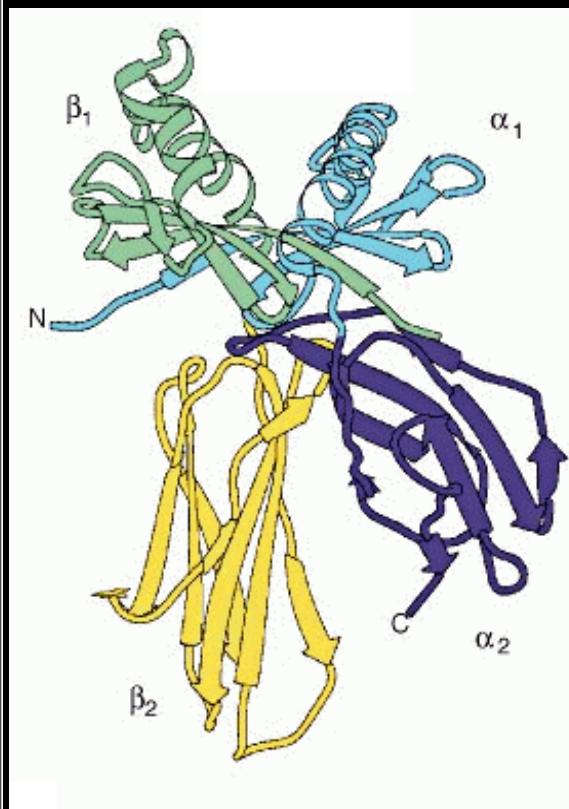
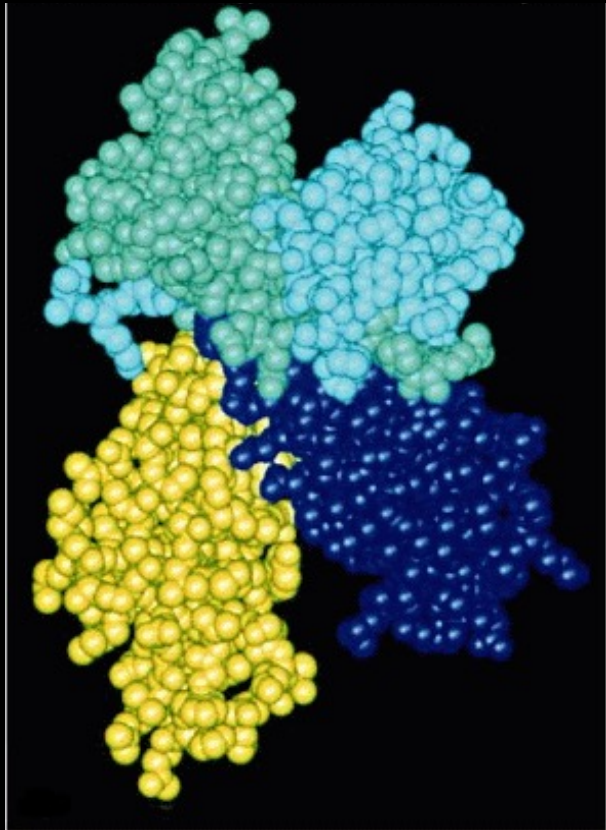
# Molécula Classe II



**Fenda Aberta**

**Todas as Células Apresentadoras de Antígeno**

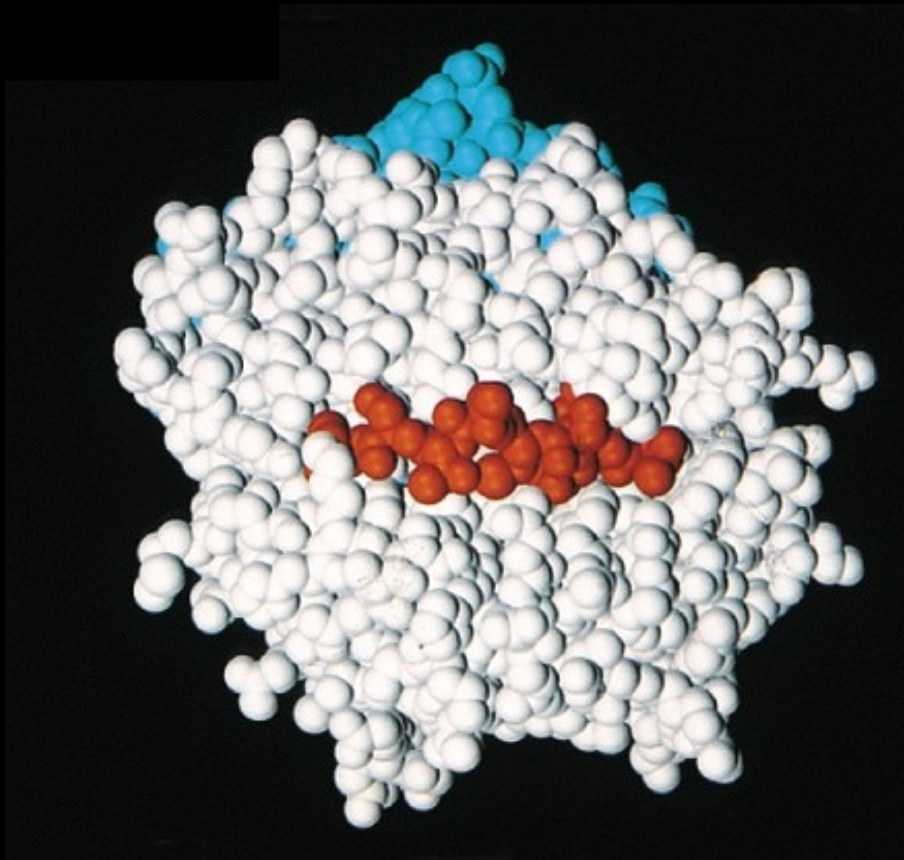
# Estrutura da molécula de MHC classe II



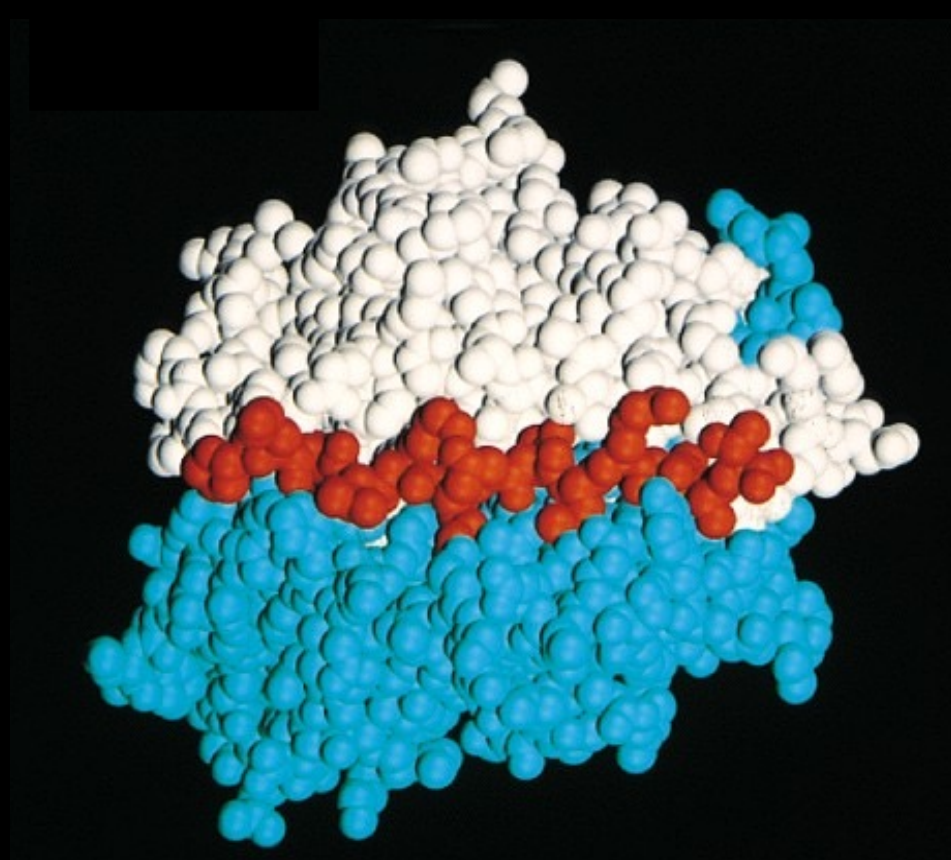


# O Acomodamento do Antígeno na Fenda

MHC Classe I



MHC Classe II



# Prêmio Nobel de Medicina e Fisiologia 1980



George Snell  
Estados Unidos

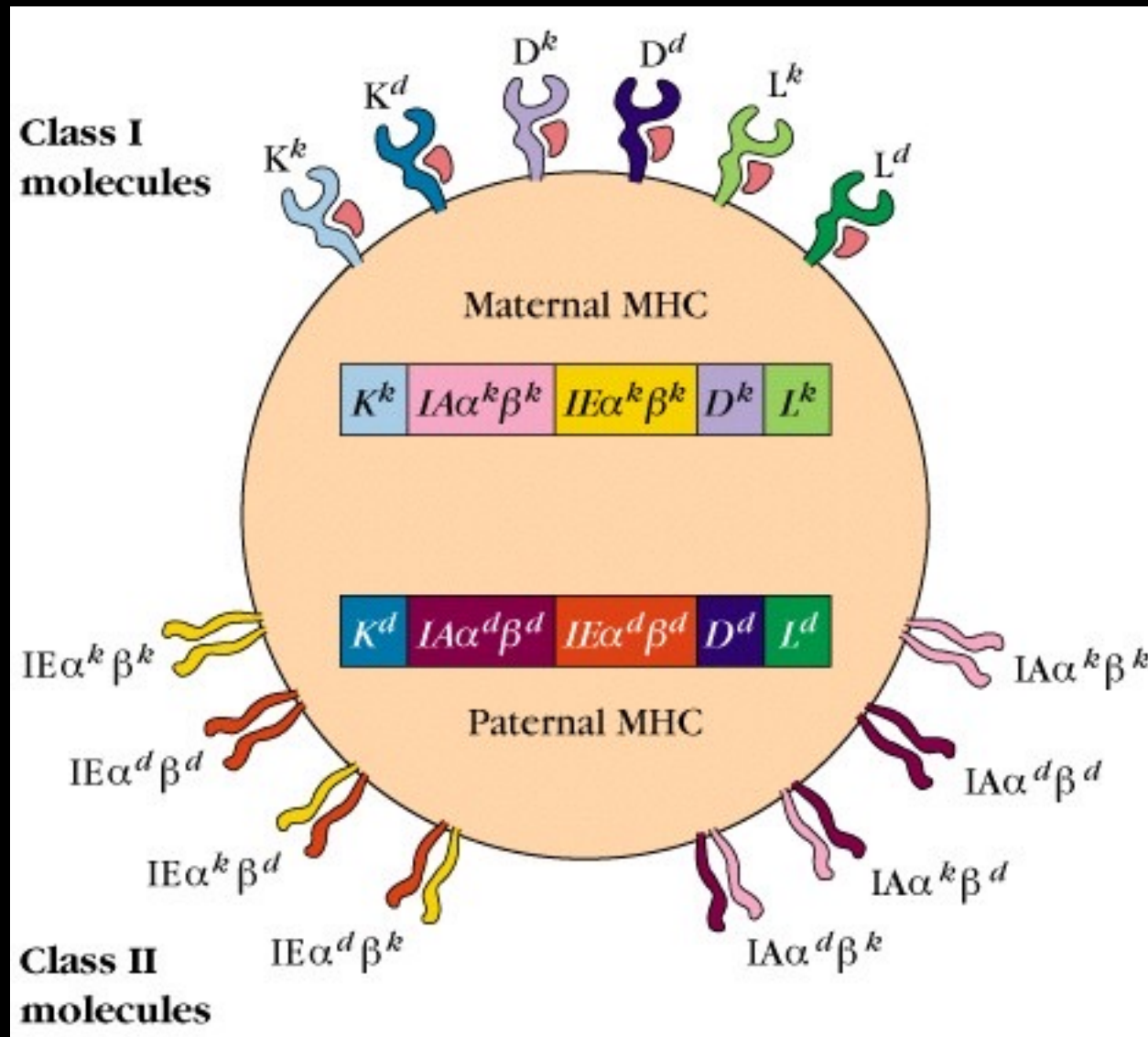


Jean Dausset  
França



Baruj Benacerraf  
Venezuela

# Co-dominância dos Genes do MHC

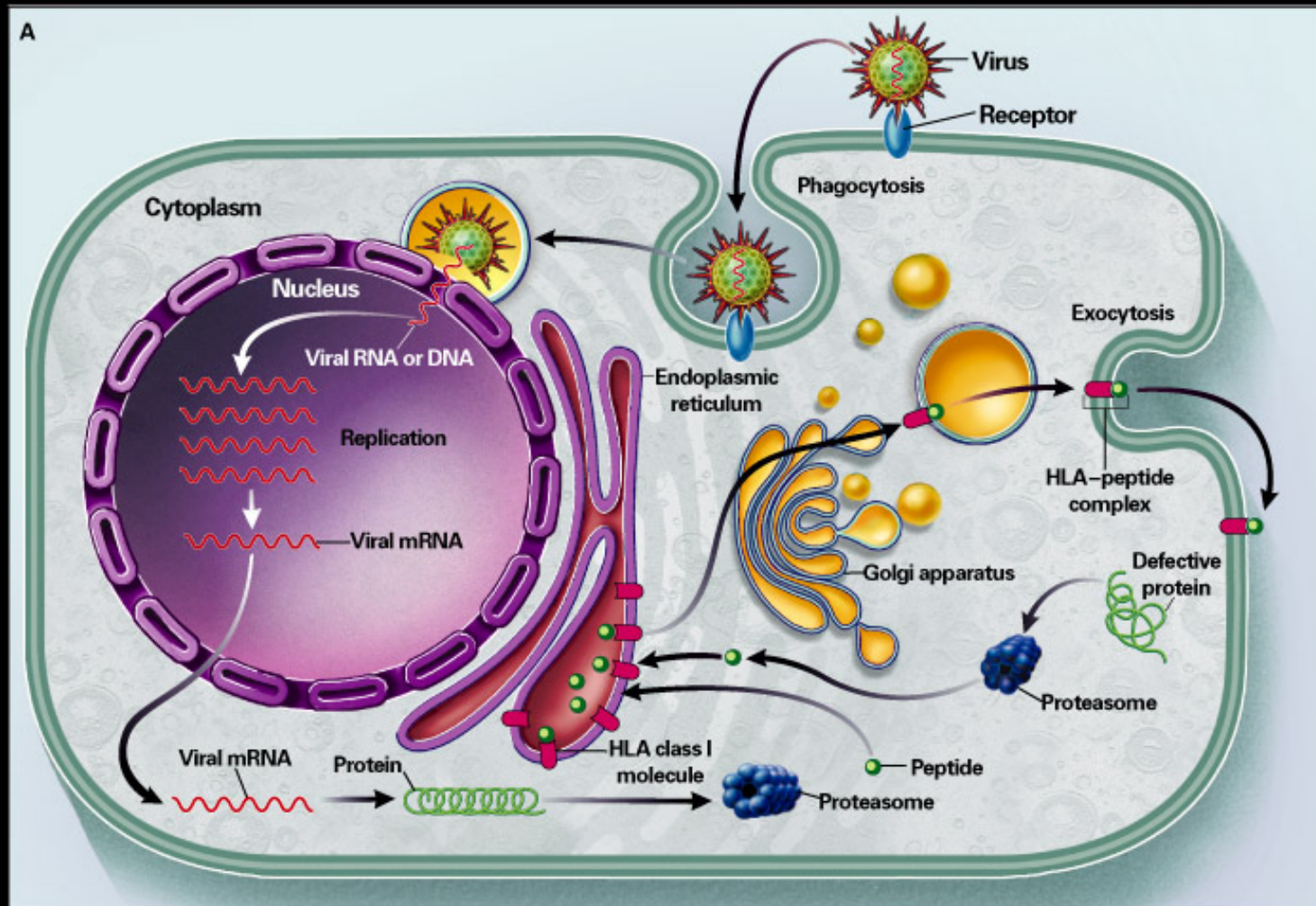


Como se dá o processamento e a apresentação do antígeno ?





# Antigen Processing, Panel A

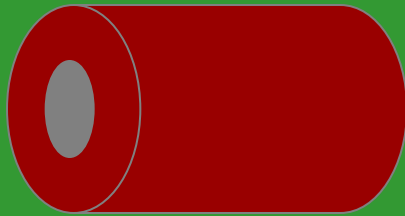
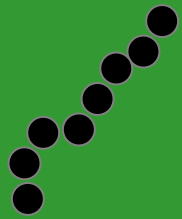


Klein J, Sato A. The HLA System. First of two parts.  
N Engl J Med 2000;343:702-9.

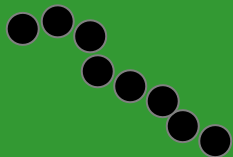
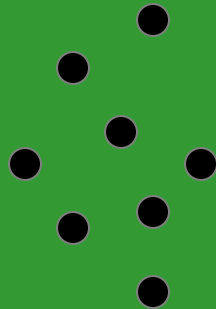


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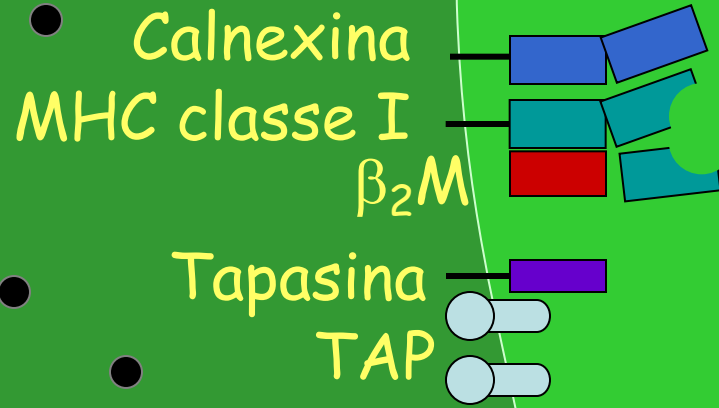
# Degradação de substâncias presentes no citosol



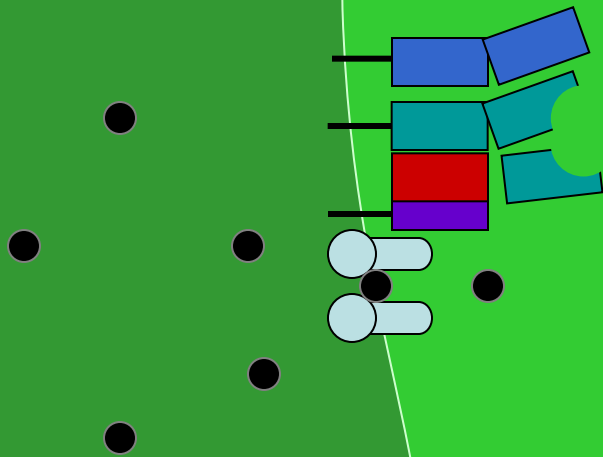
Proteosomas



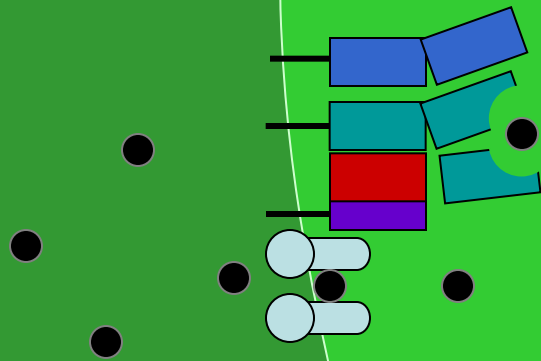
# Tráfego de peptídeos presentes no citosol



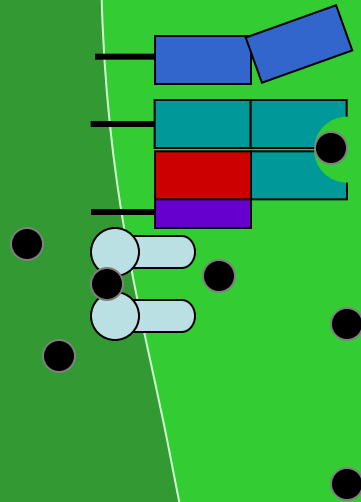
# Tráfego de peptídeos presentes no citosol



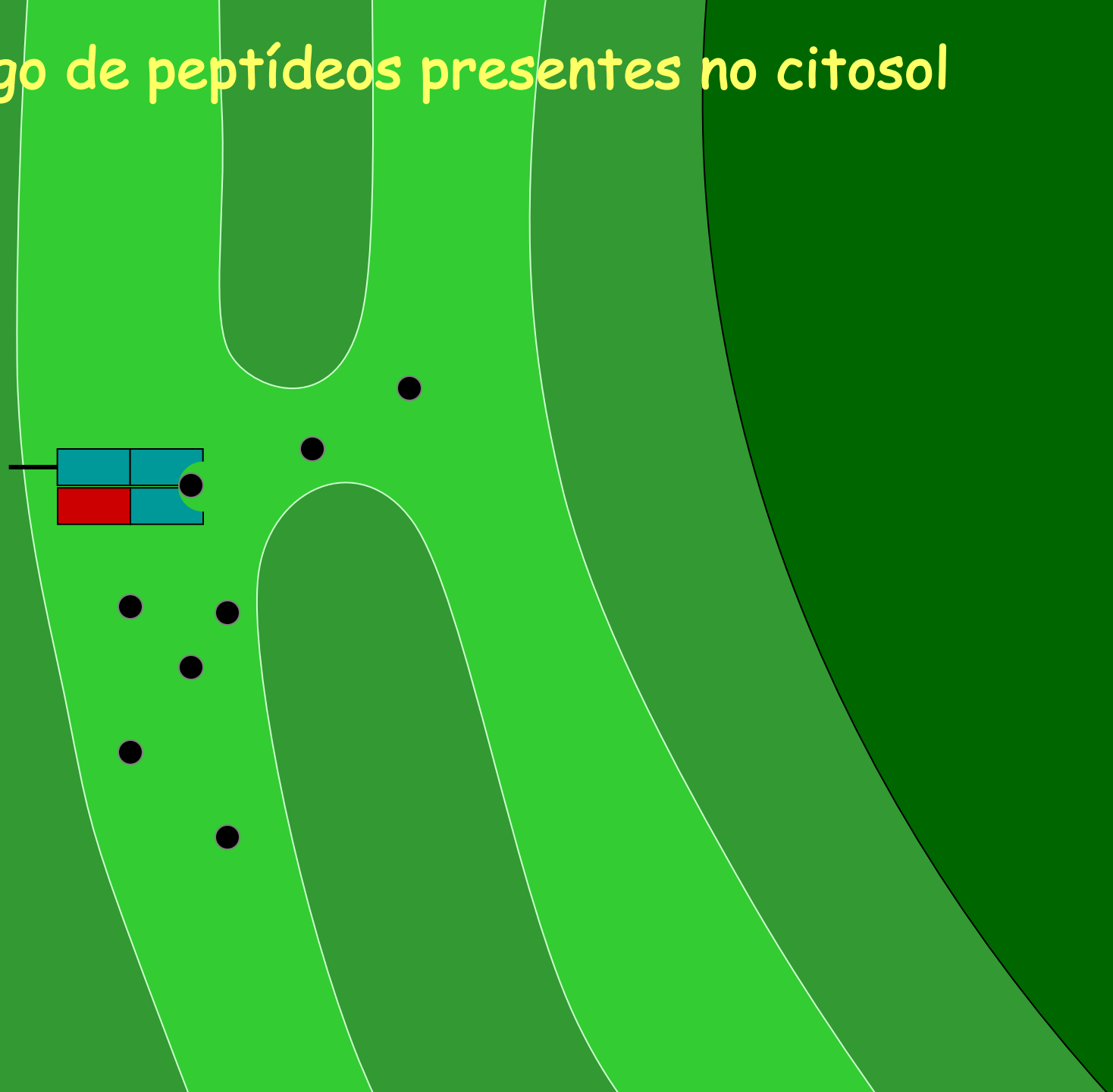
# Tráfego de peptídeos presentes no citosol



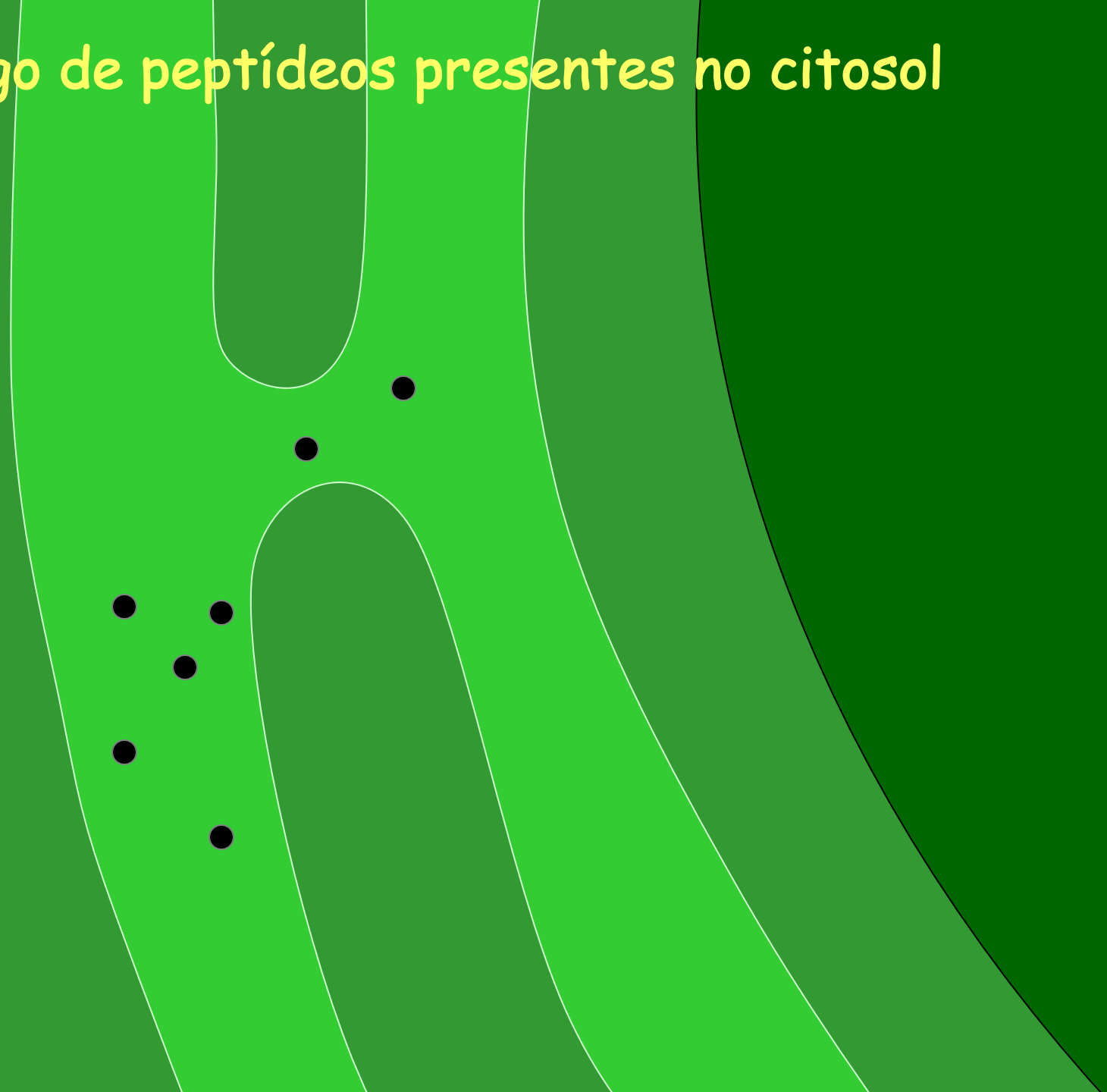
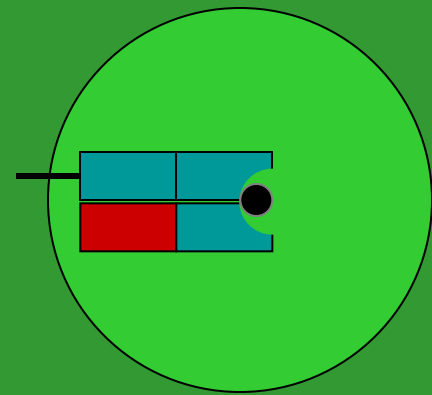
# Tráfego de peptídeos presentes no citosol



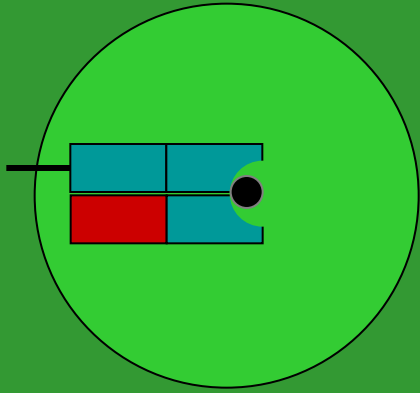
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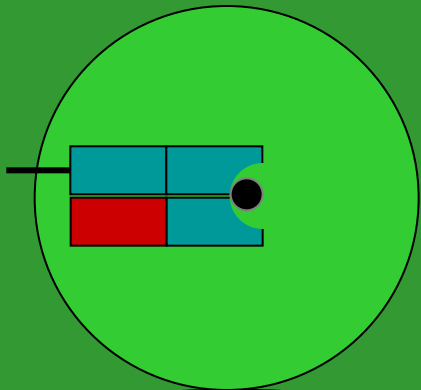


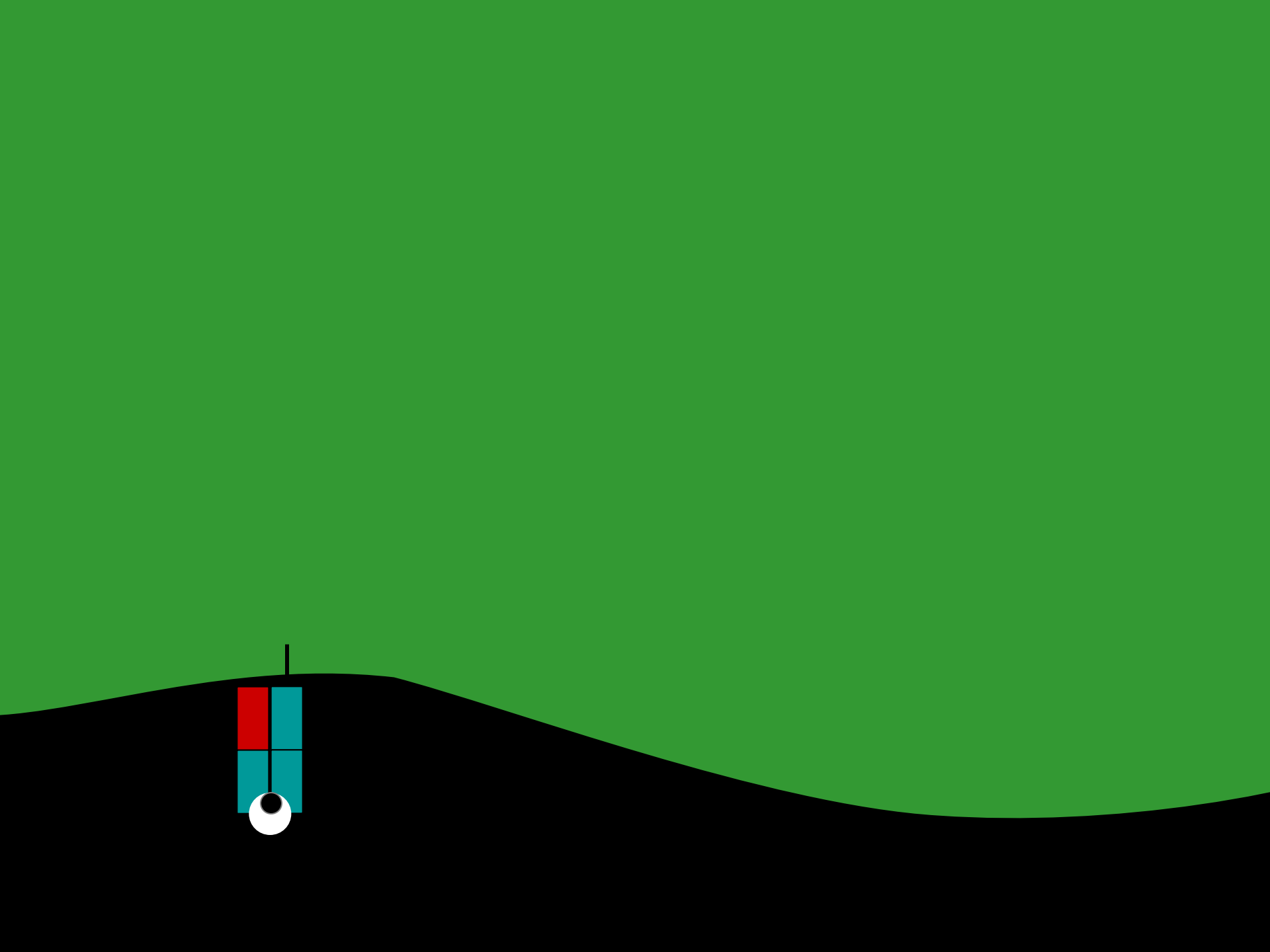
# Tráfego de peptídeos presentes no citosol



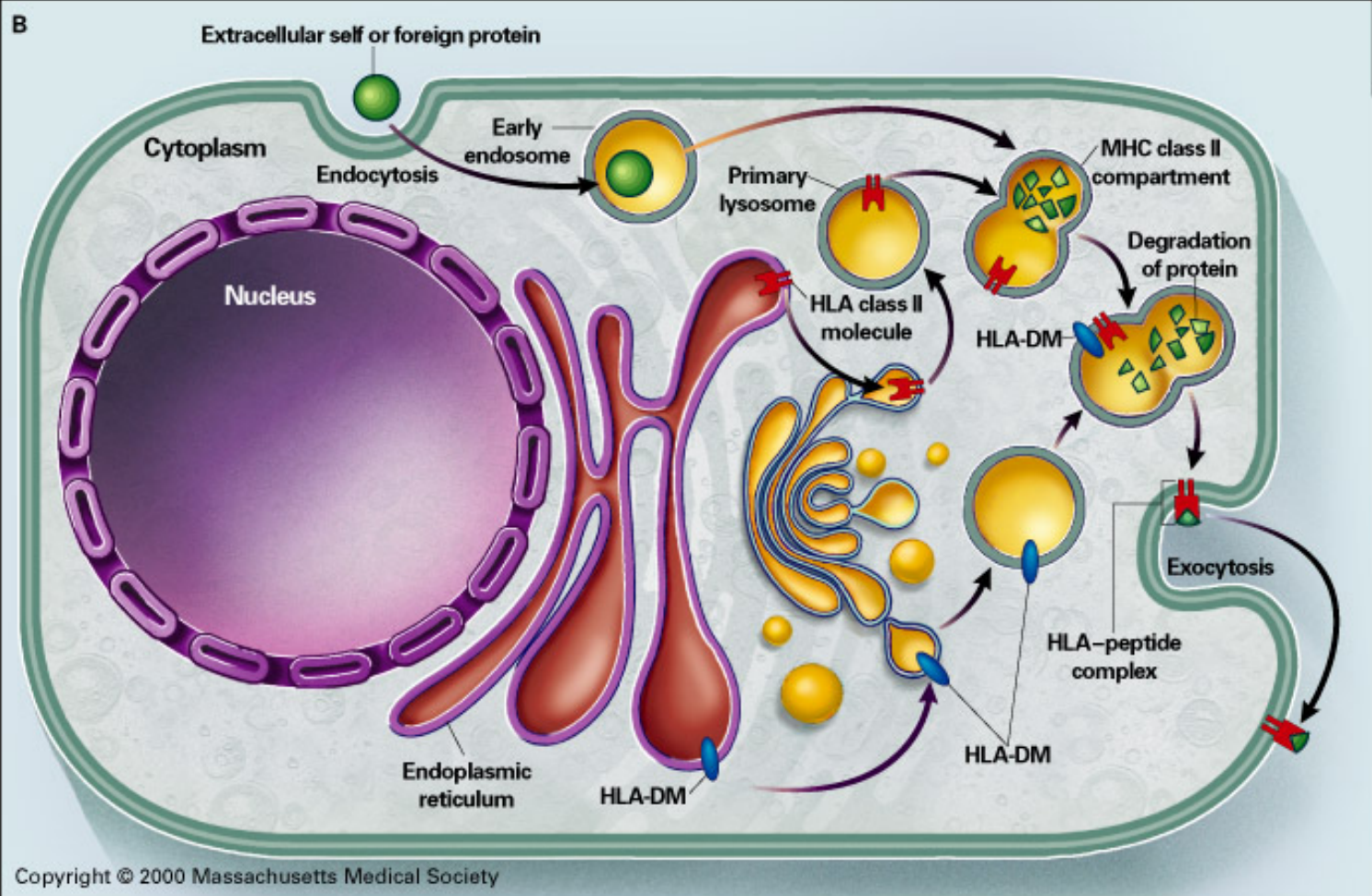








# Antigen Processing, Panel B

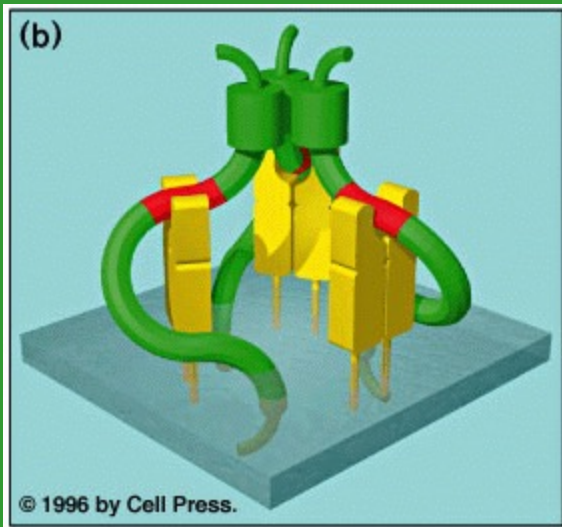


Klein J, Sato A. The HLA System. First of two parts. N Engl J Med 2000;343:702-9.

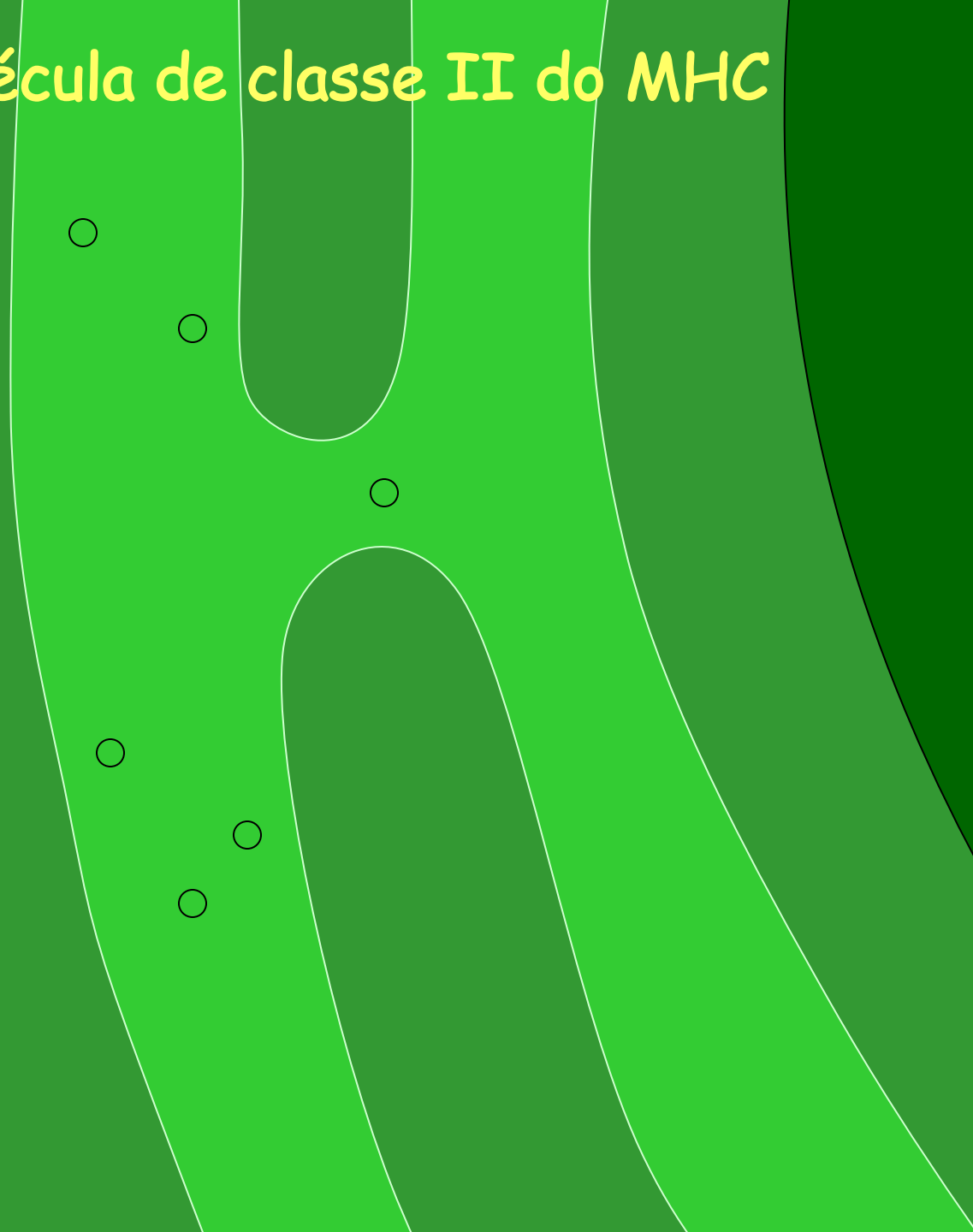
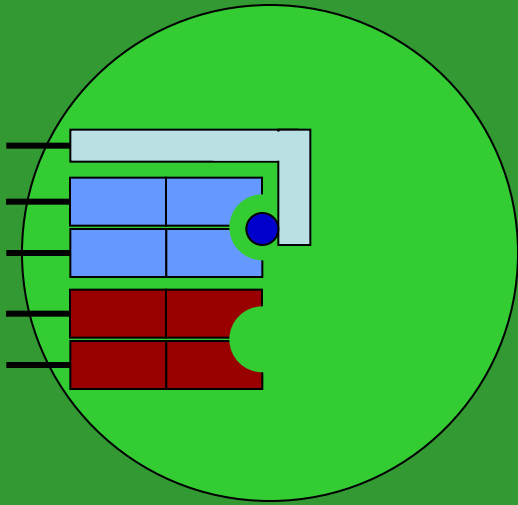


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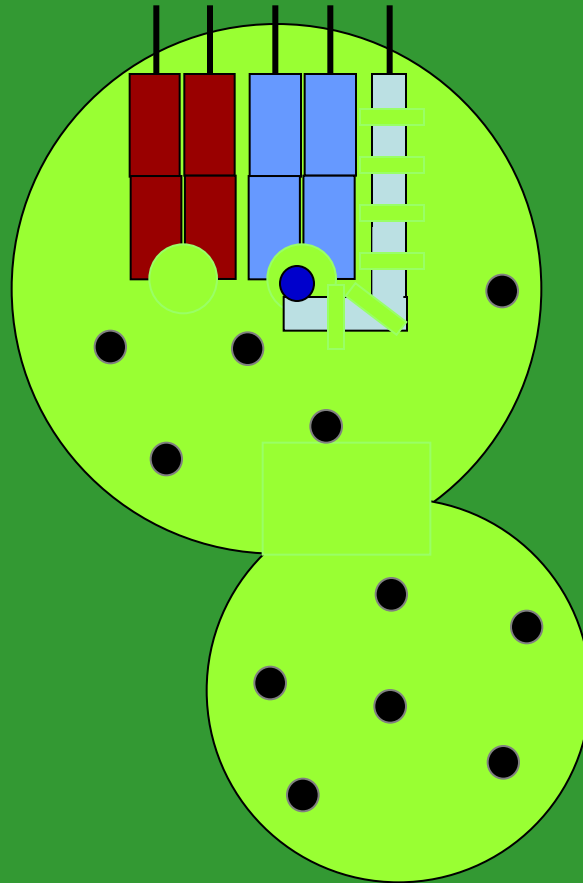
# Síntese da molécula de classe II do MHC



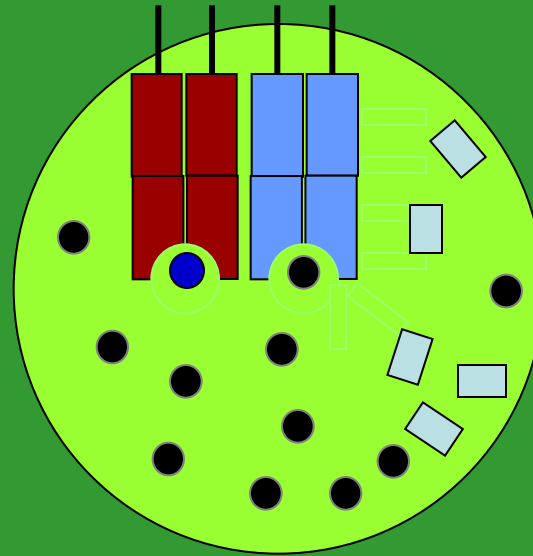
# Síntese da molécula de classe II do MHC



# Degradação da cadeia invariante

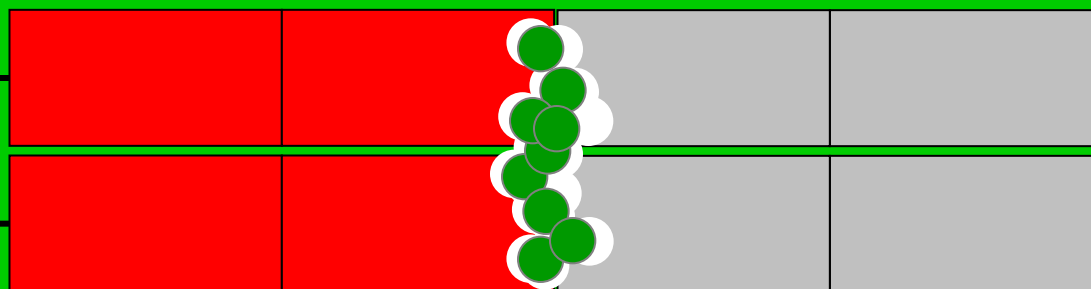


# Apresentação do peptídeo na superfície celular





# Formação do Complexo MHC - Ag - TCR

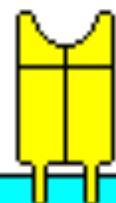


MHC

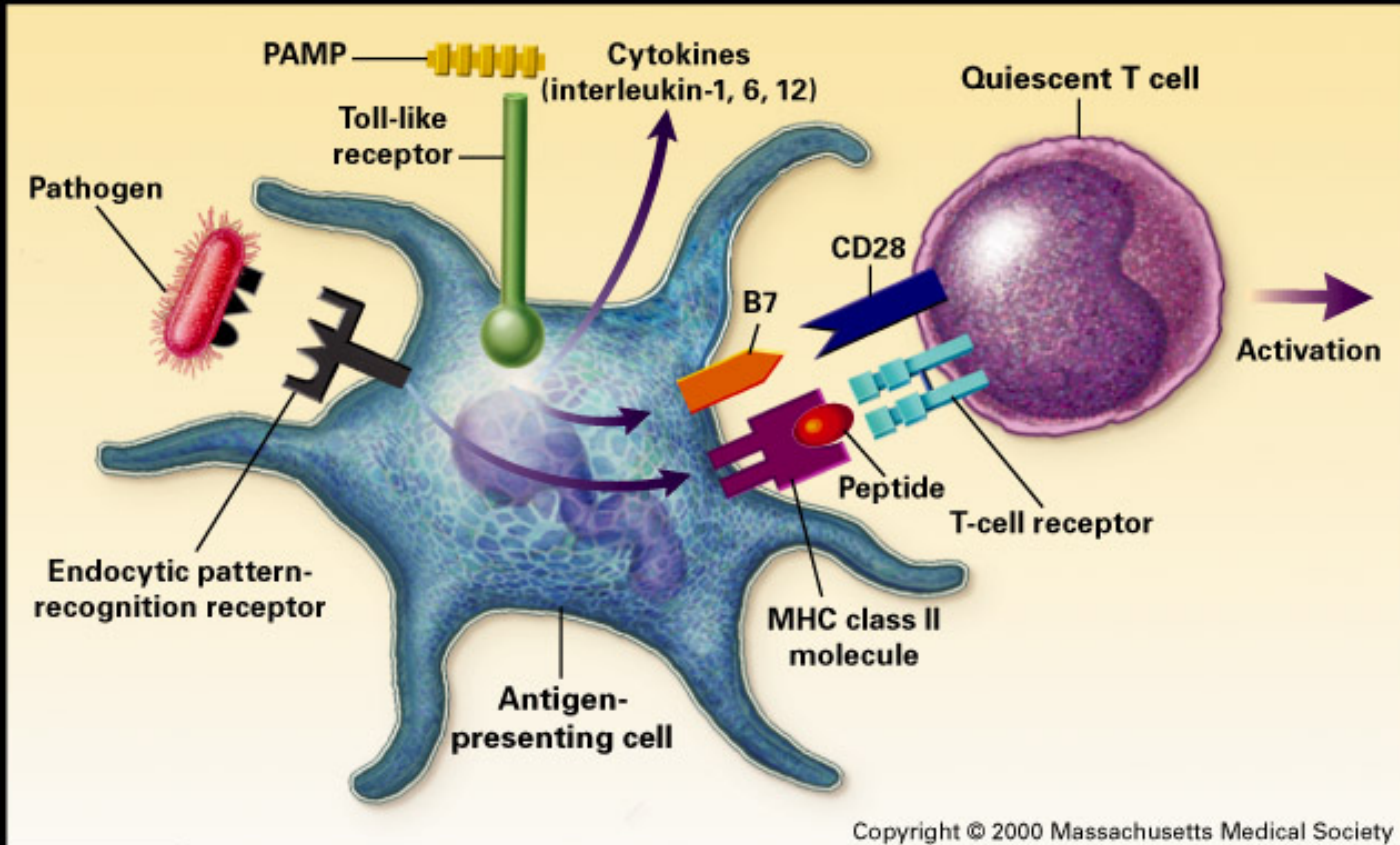
TCR

# *Macrophage*

Endoplasmic  
reticulum



# Interação APC + Célula T

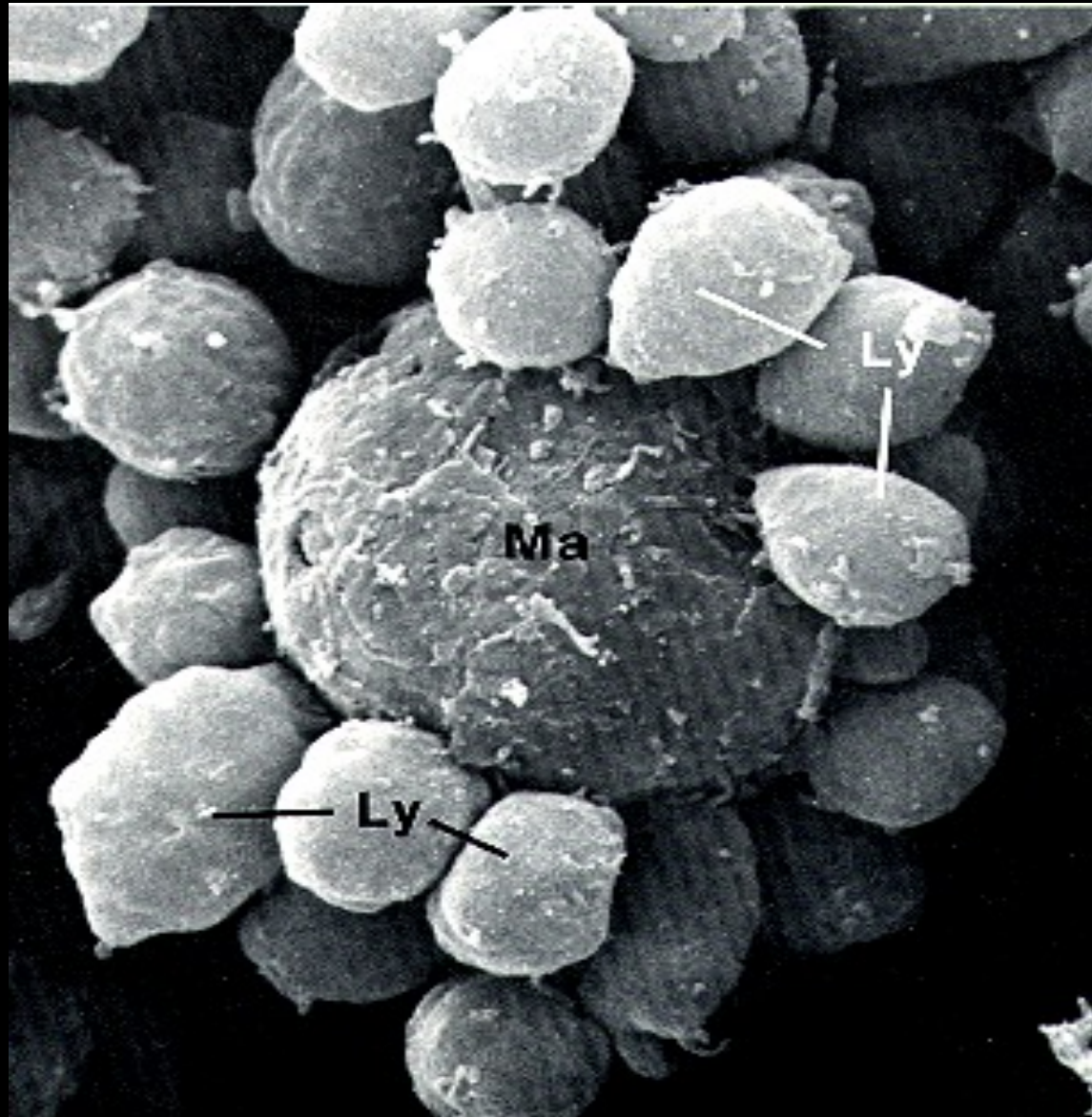


Medzhitov R, Janeway C Jr. Innate Immunity.  
N Engl J Med 2000;343:338-44.



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Journal of Medicine

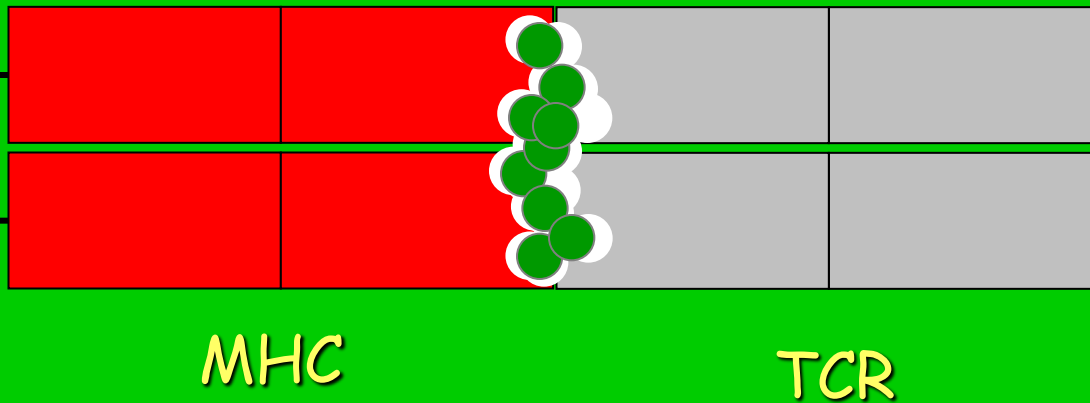
# 1 APC Vs. Várias Células T



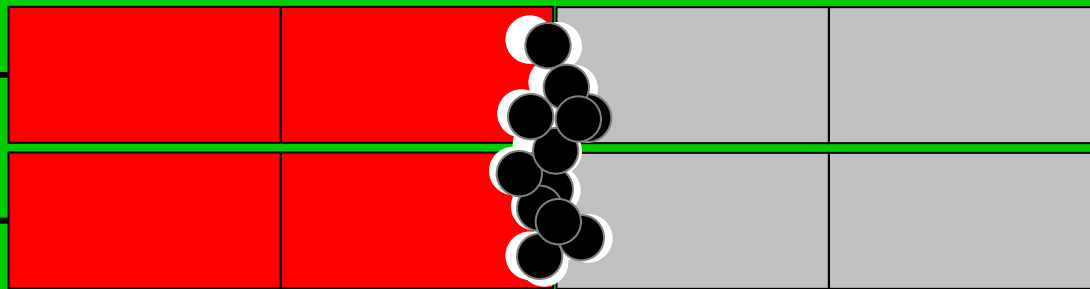
# IMPORTANTE

- MHC I é encontrado em todas as células nucleadas
- MHC II é encontrado em células do sistema imune
  - Linfócitos T CD4 Humanos expressam MHC II
- MHC I apresenta antígenos para células T CD8 (citotóxicas)]
- MHC II apresenta antígenos para células T CD4 (auxiliares)

A afinidade do TCR pelo complexo MHC-peptídeo influencia a resposta das células T maduras

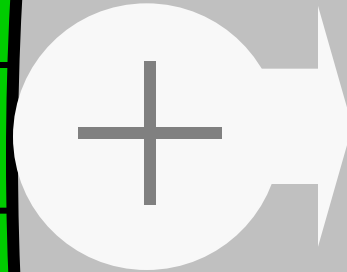


A afinidade do TCR pelo complexo MHC-peptídeo influencia a resposta das células T maduras

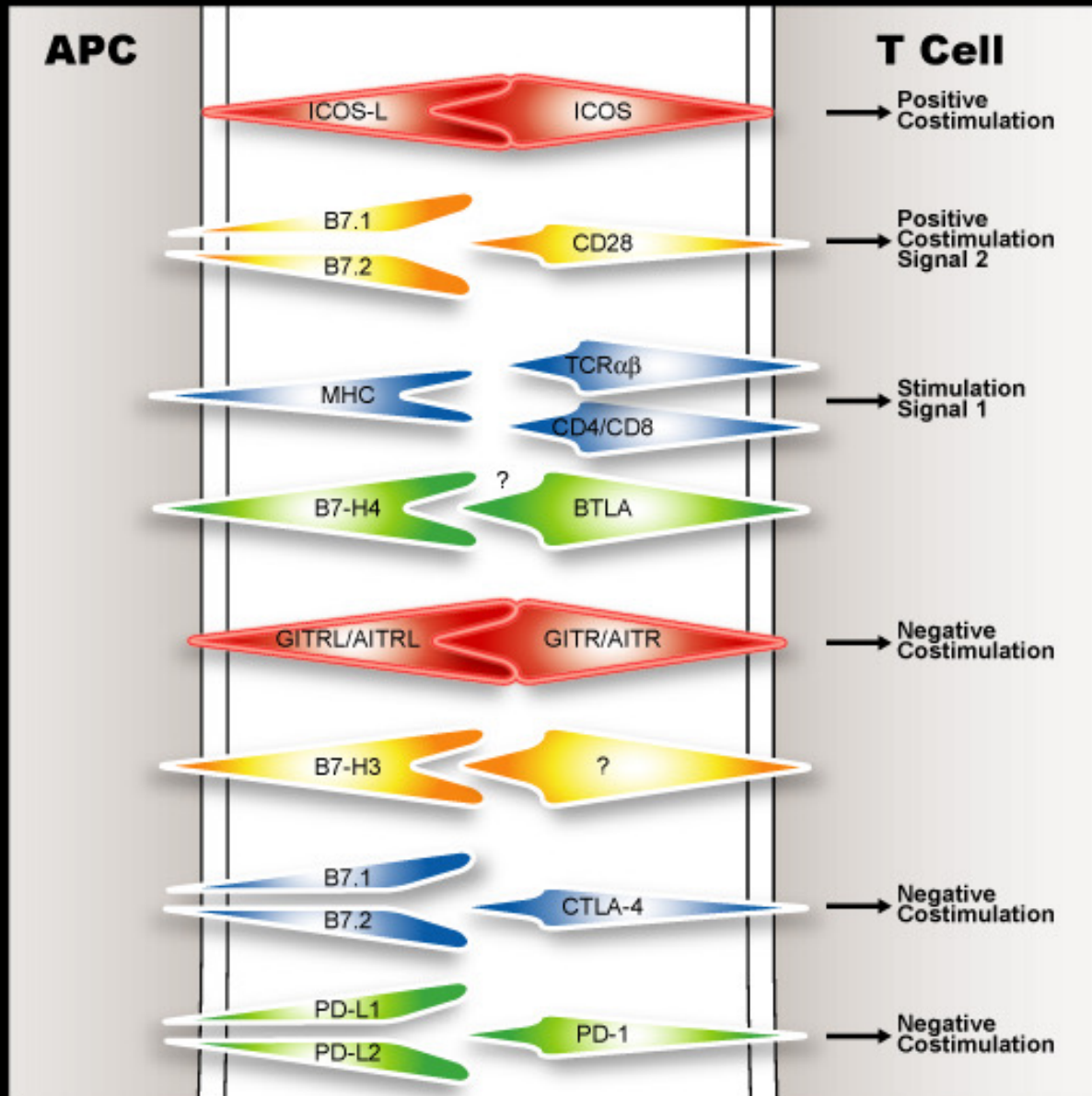


MHC

TCR

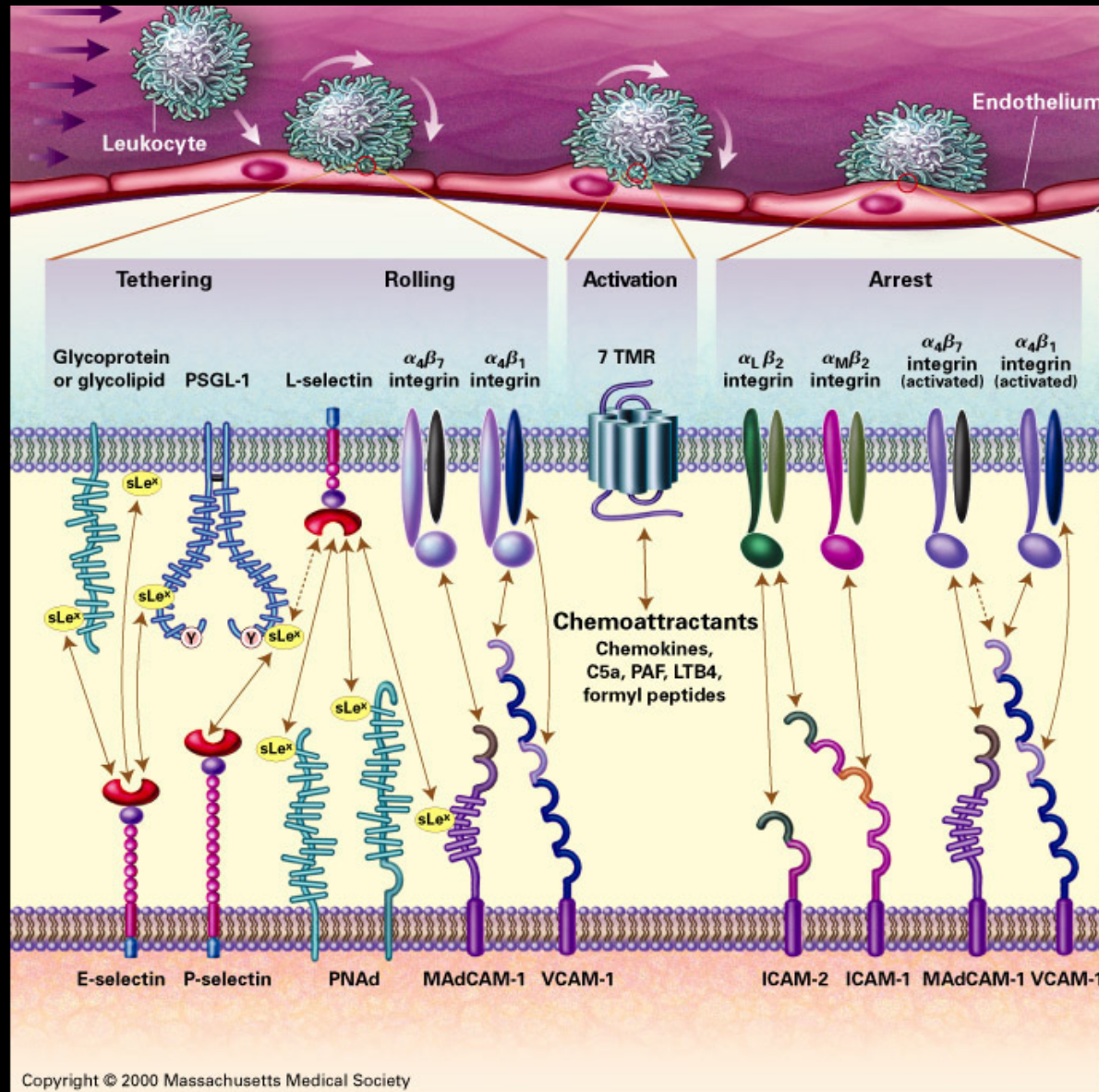


# Outras Moléculas

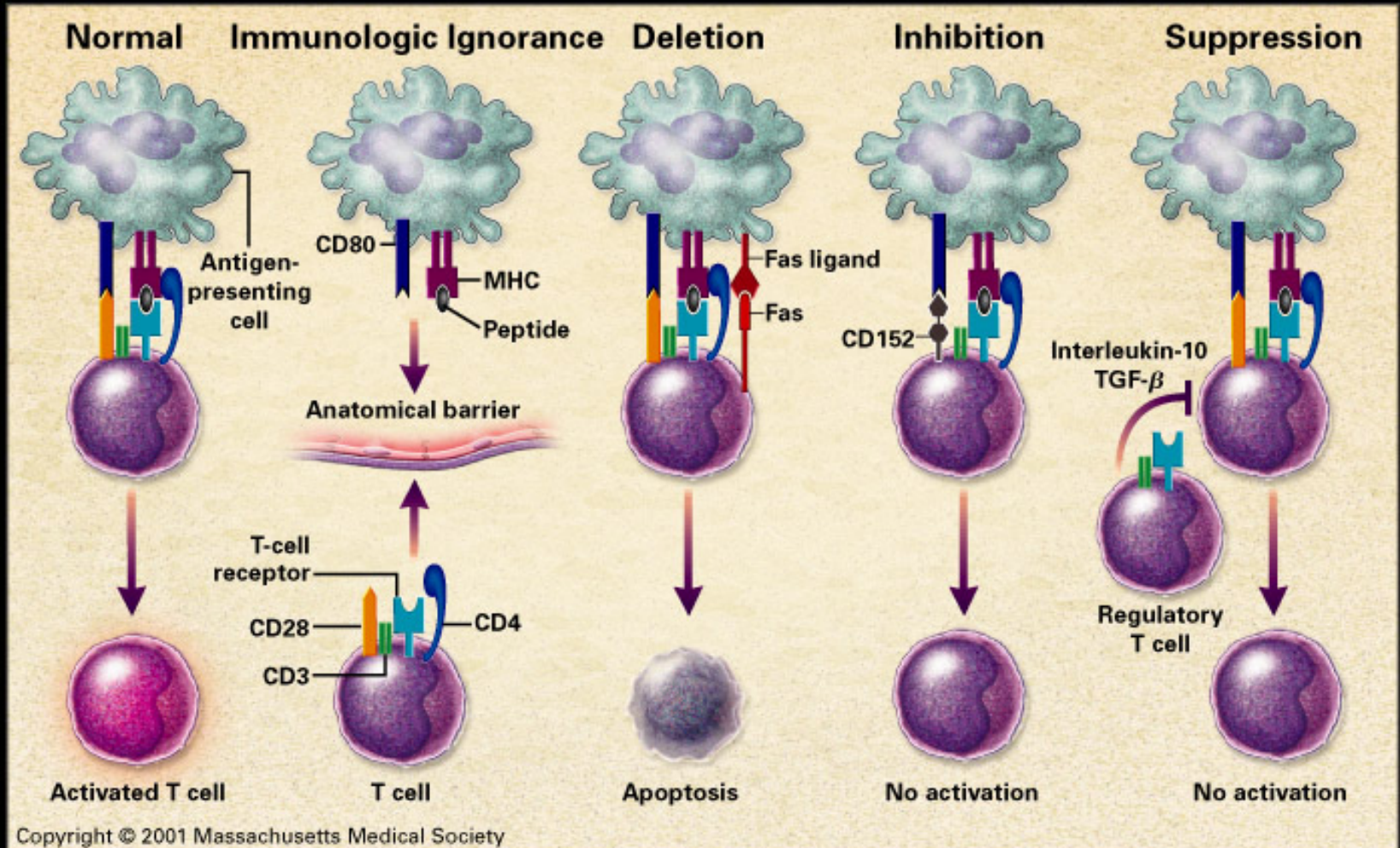




# Moléculas de Adesão e Integrinas

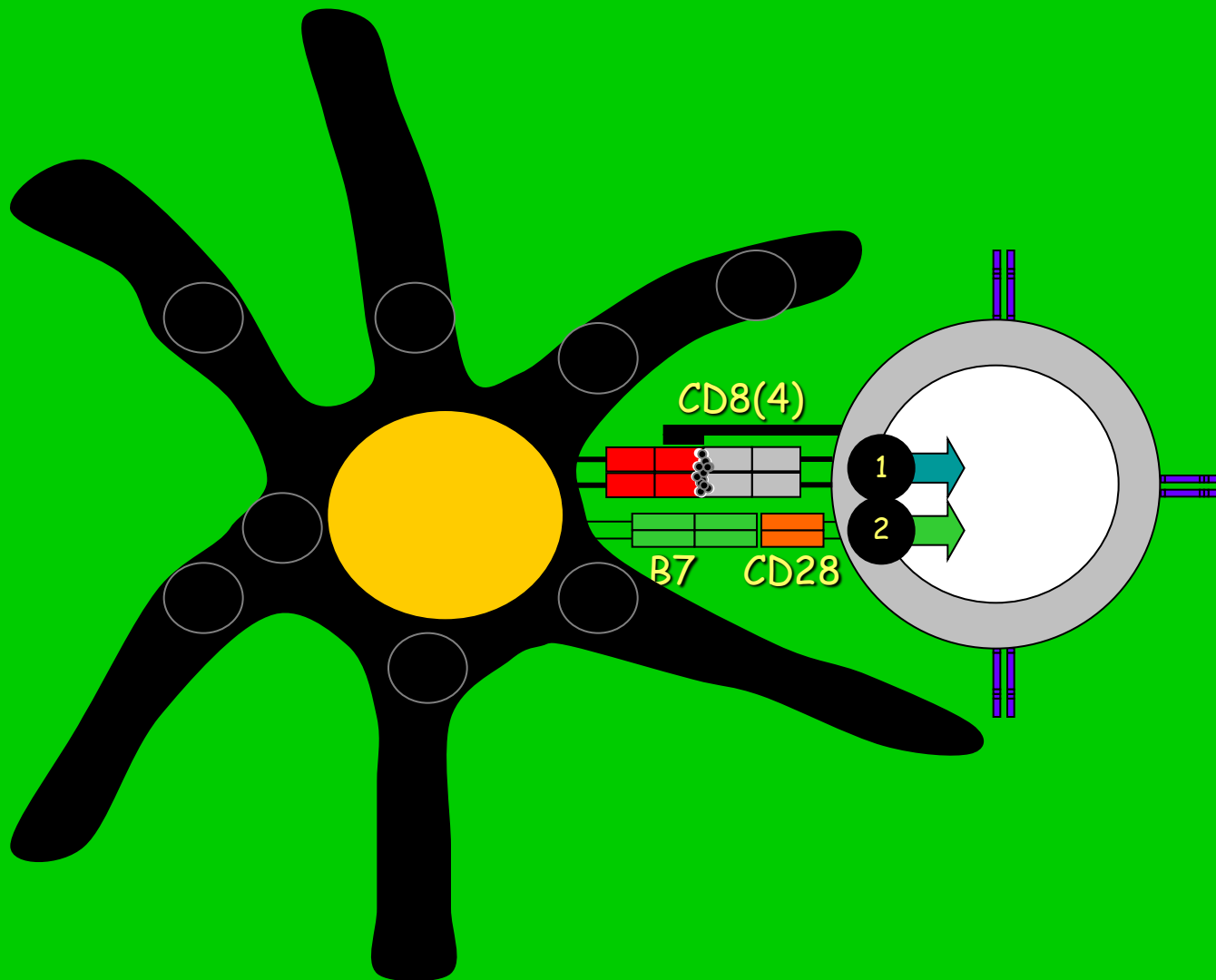


# Ativação ou Desativação ?

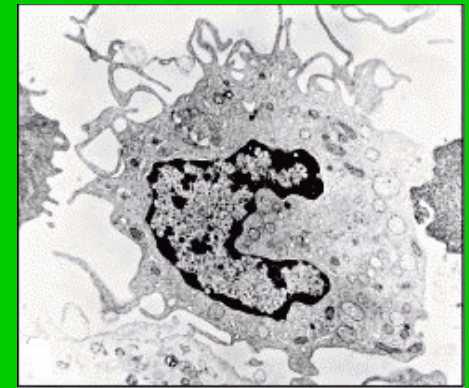
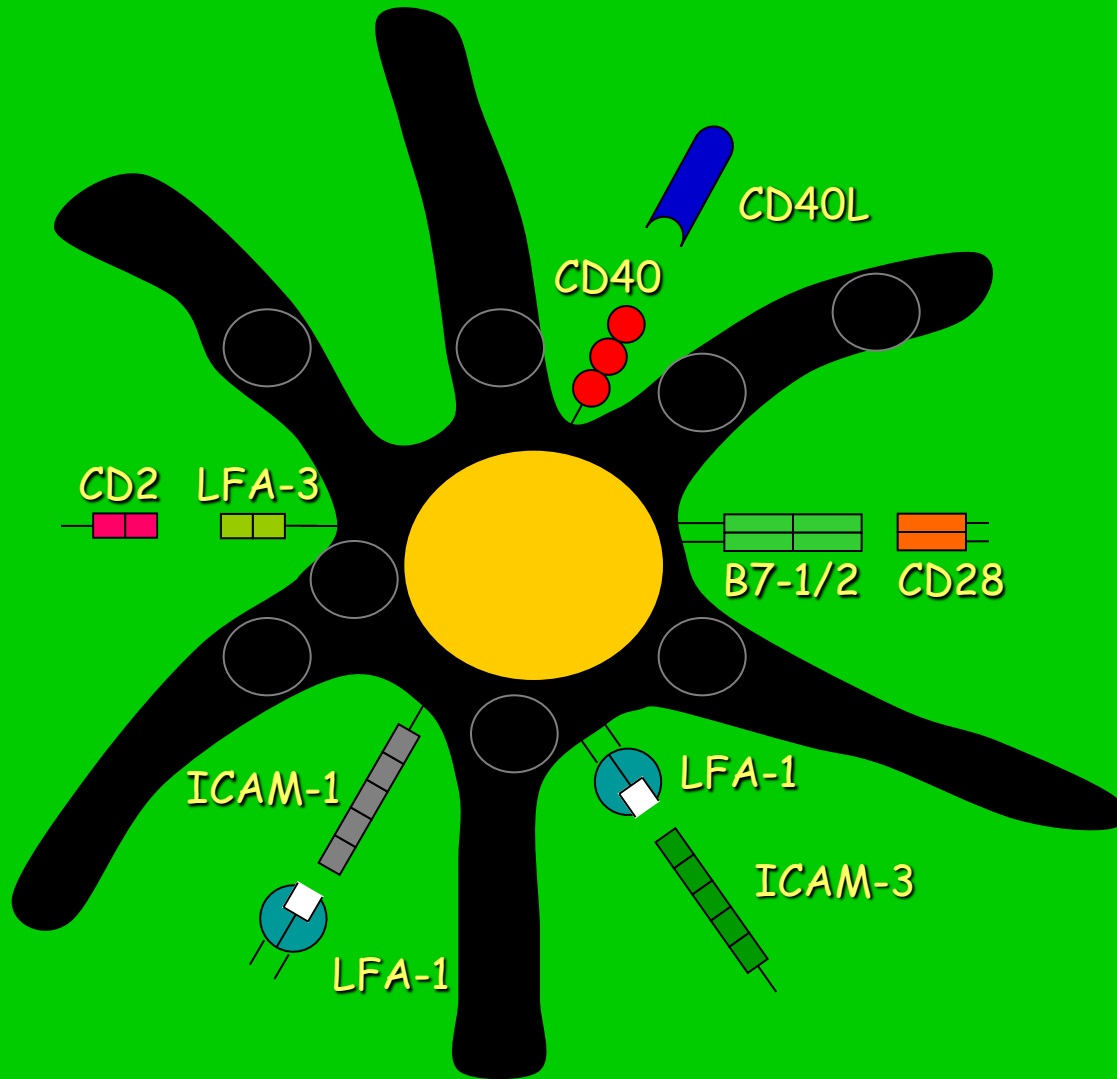


A apresentação de antígenos associada à presença ou não de moléculas co-estimulatórias ou inibitórias regem a ativação das células T

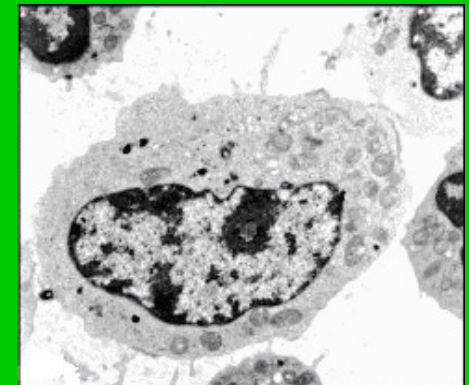
# Sinais para a ativação dos linfócitos T



# APC: moléculas co-estimuladoras e seus ligantes



Célula dendrítica

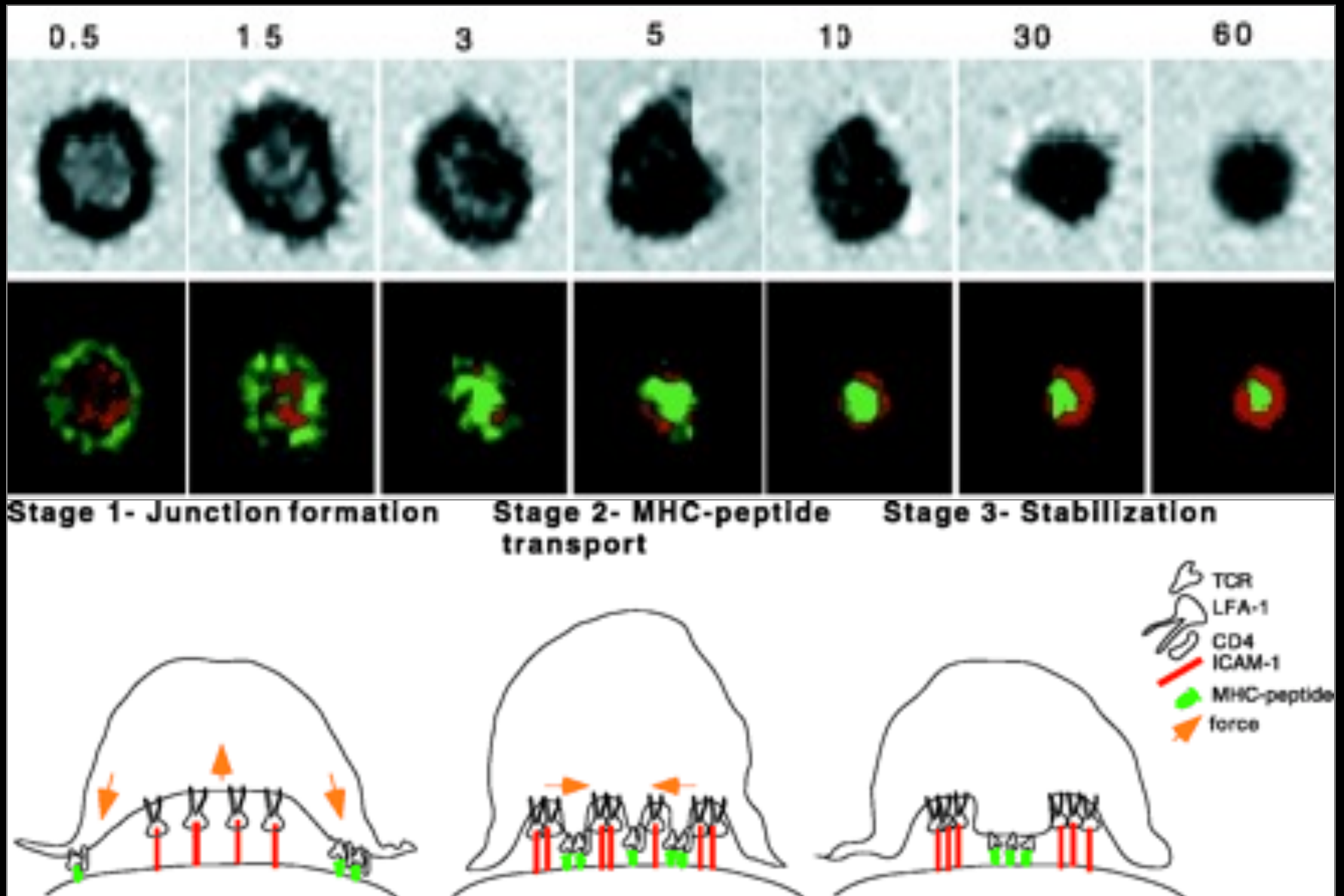


Macrófago



Linfócito B

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

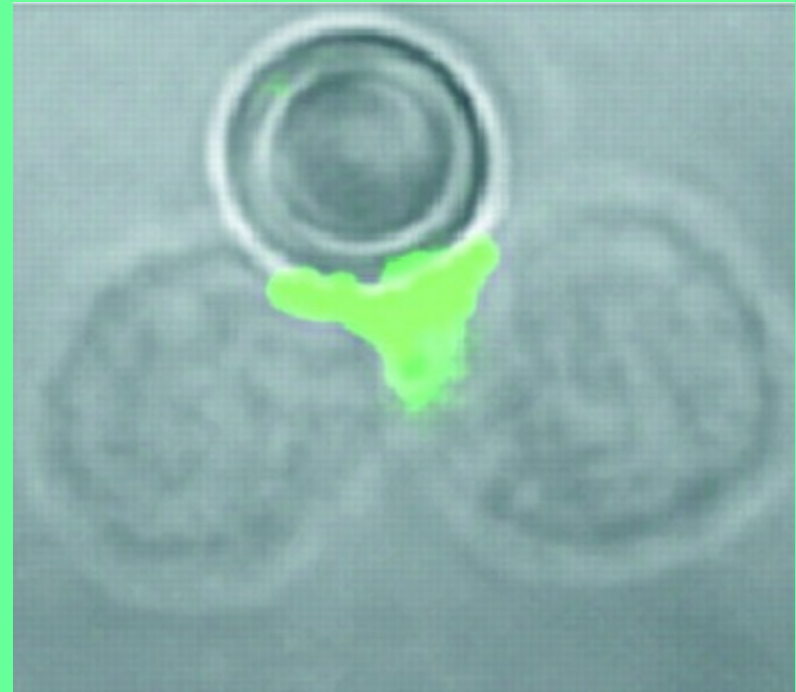
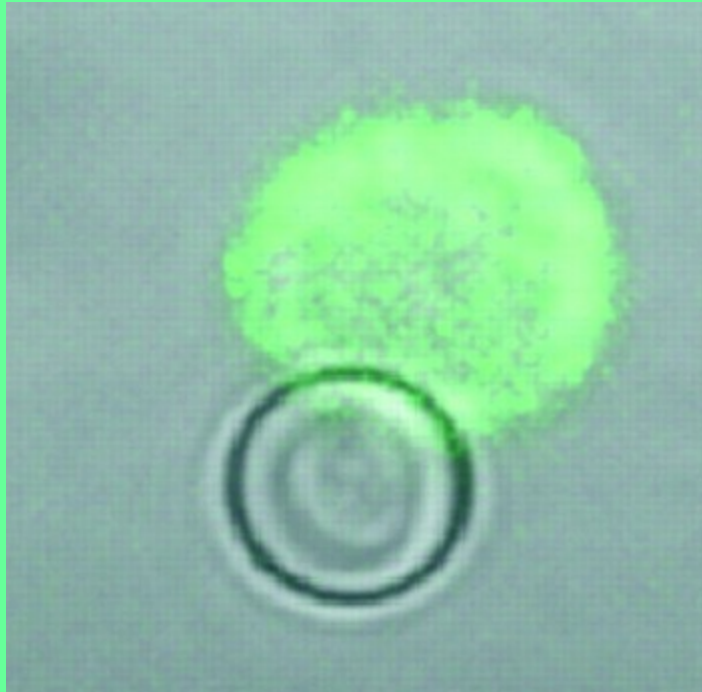


# A co-estimulação promove a polarização "rafts"

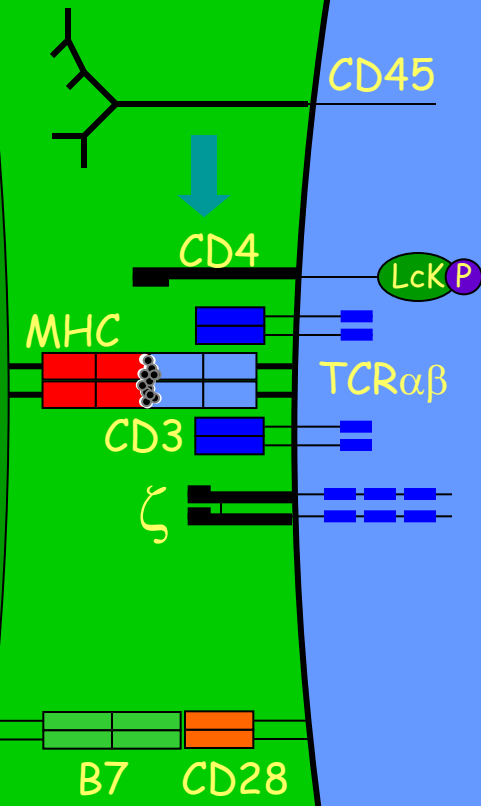
dos

MHC+peptídeo

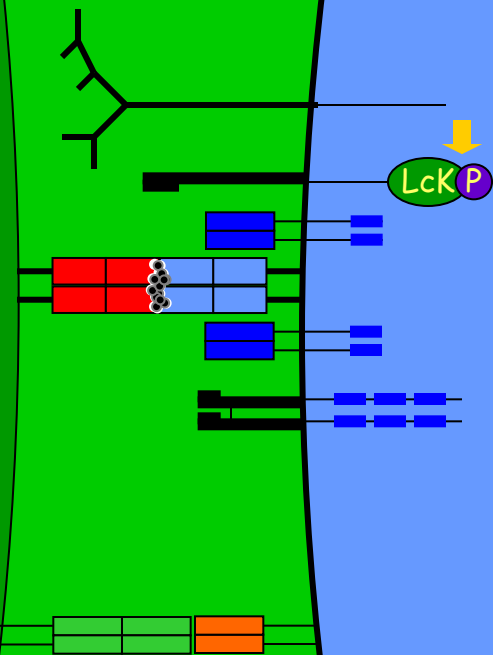
MHC+peptídeo+B7



# Sinalização intracelular durante a ativação dos linfócitos T

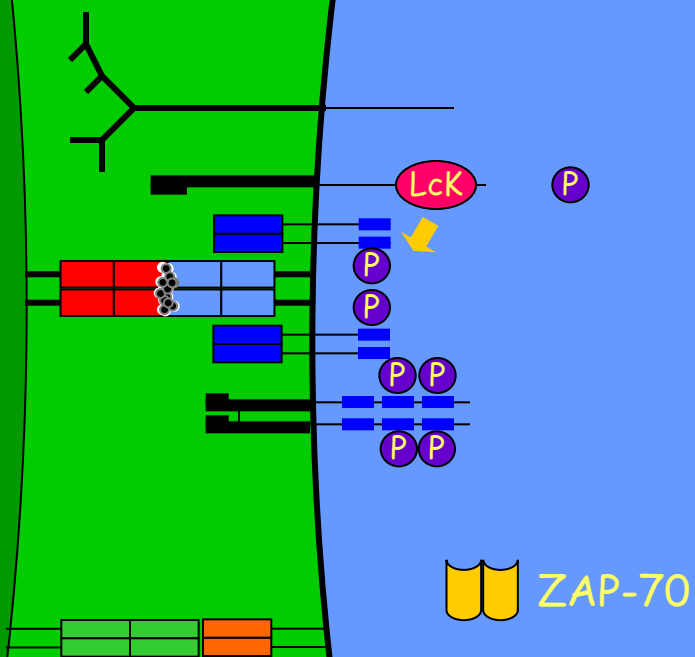


# Sinalização intracelular durante a ativação dos linfócitos T

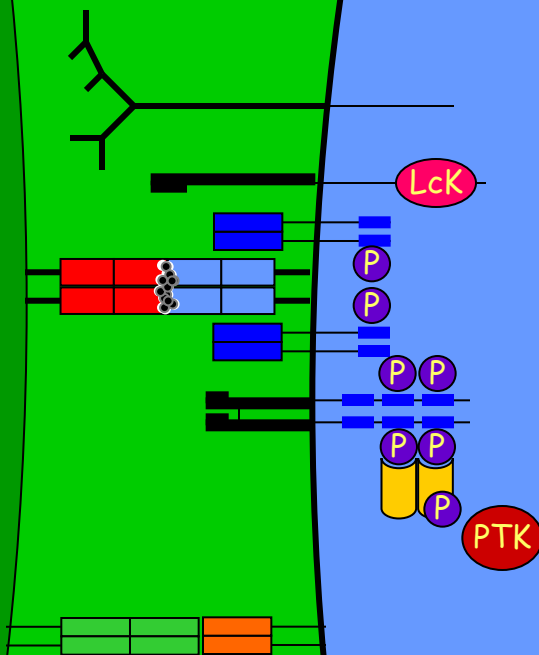




# Sinalização intracelular durante a ativação dos linfócitos T

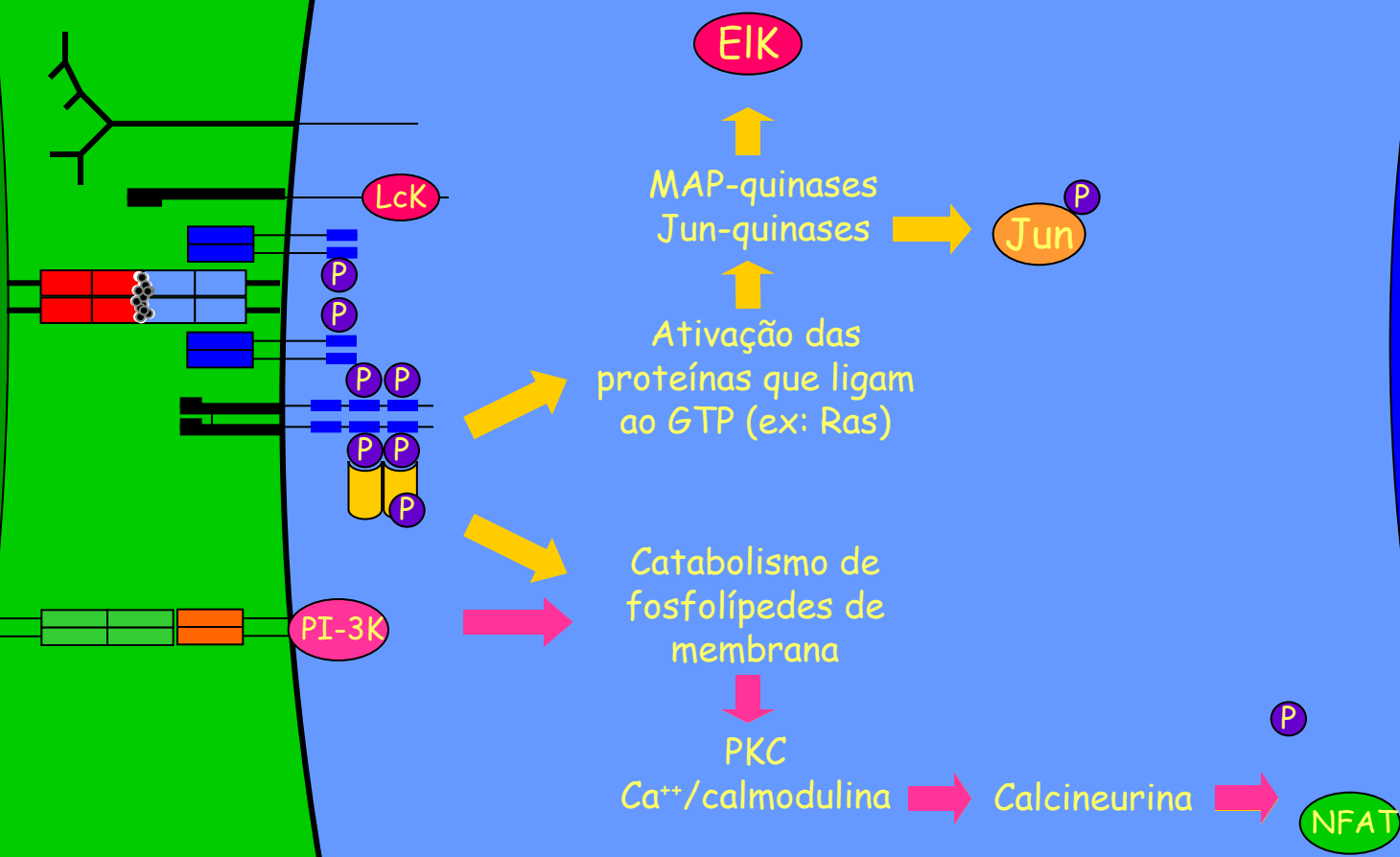


# Sinalização intracelular durante a ativação dos linfócitos T





# Sinalização intracelular durante a ativação dos linfócitos T



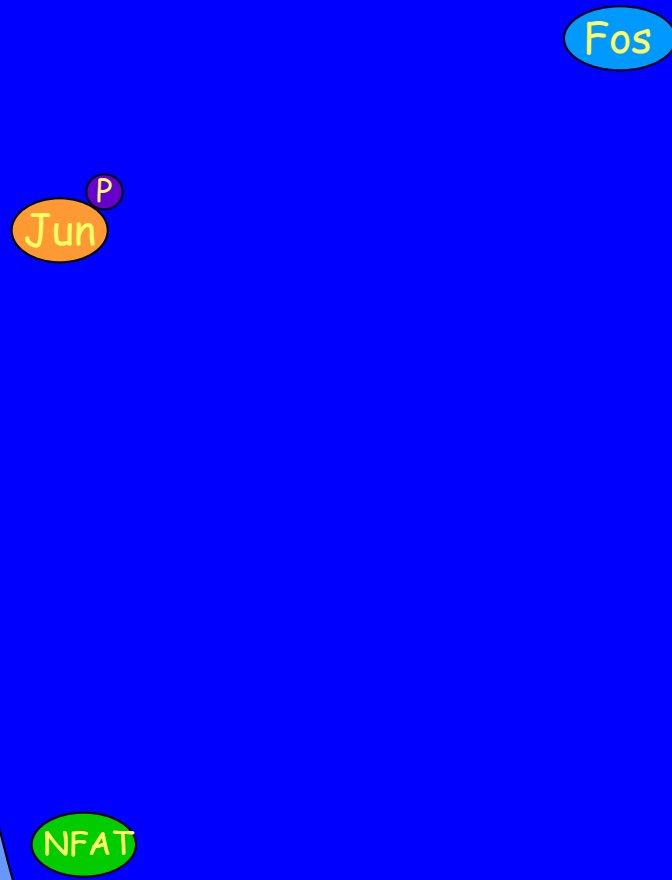
# Ativação dos fatores de transcrição nos linfócitos T

EIK → Transcrição do cFos

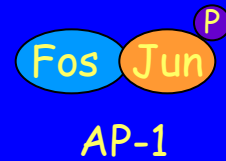
Jun<sup>P</sup>

NFAT

# Ativação dos fatores de transcrição nos linfócitos T

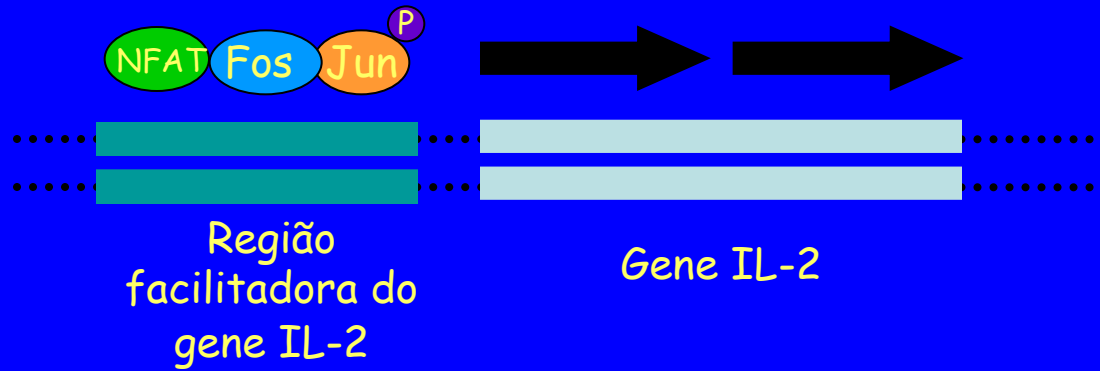


# Ativação dos fatores de transcrição nos linfócitos T



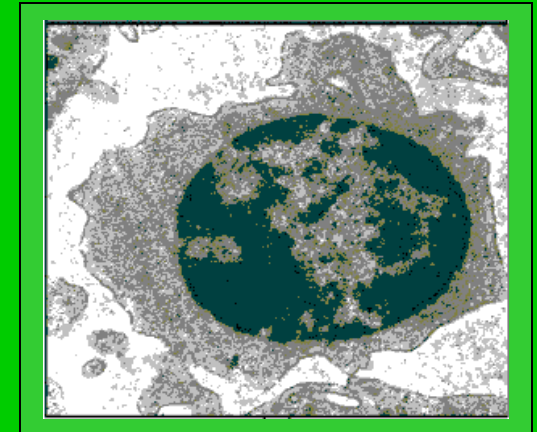
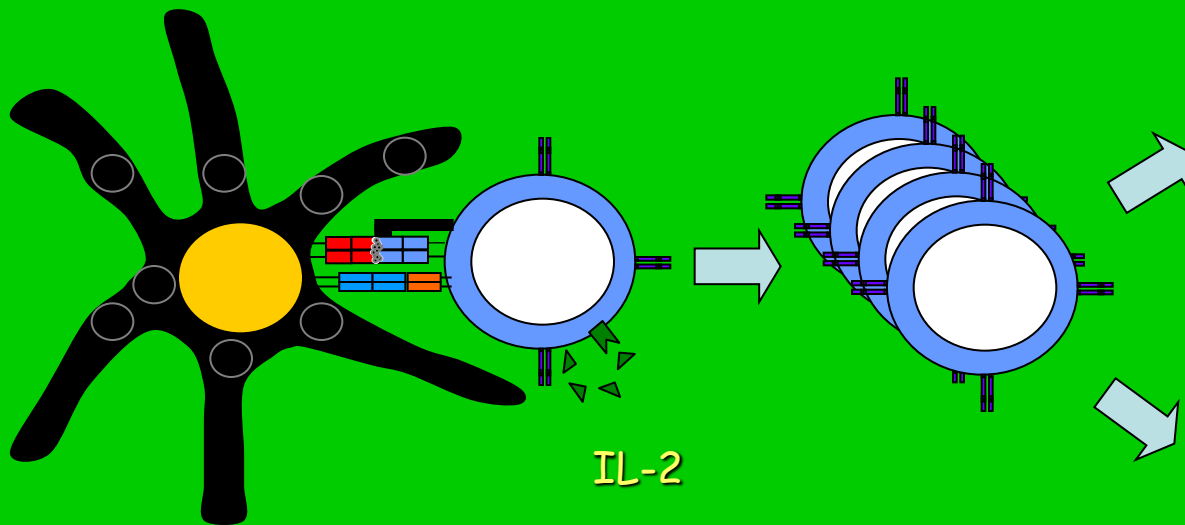
NFAT

# Ativação dos fatores de transcrição nos linfócitos T

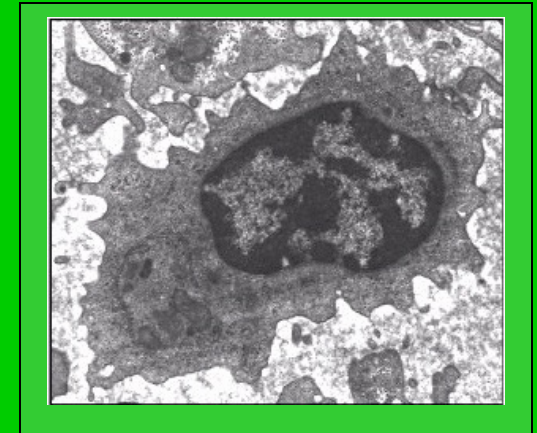




# Proliferação e diferenciação dos linfócitos T

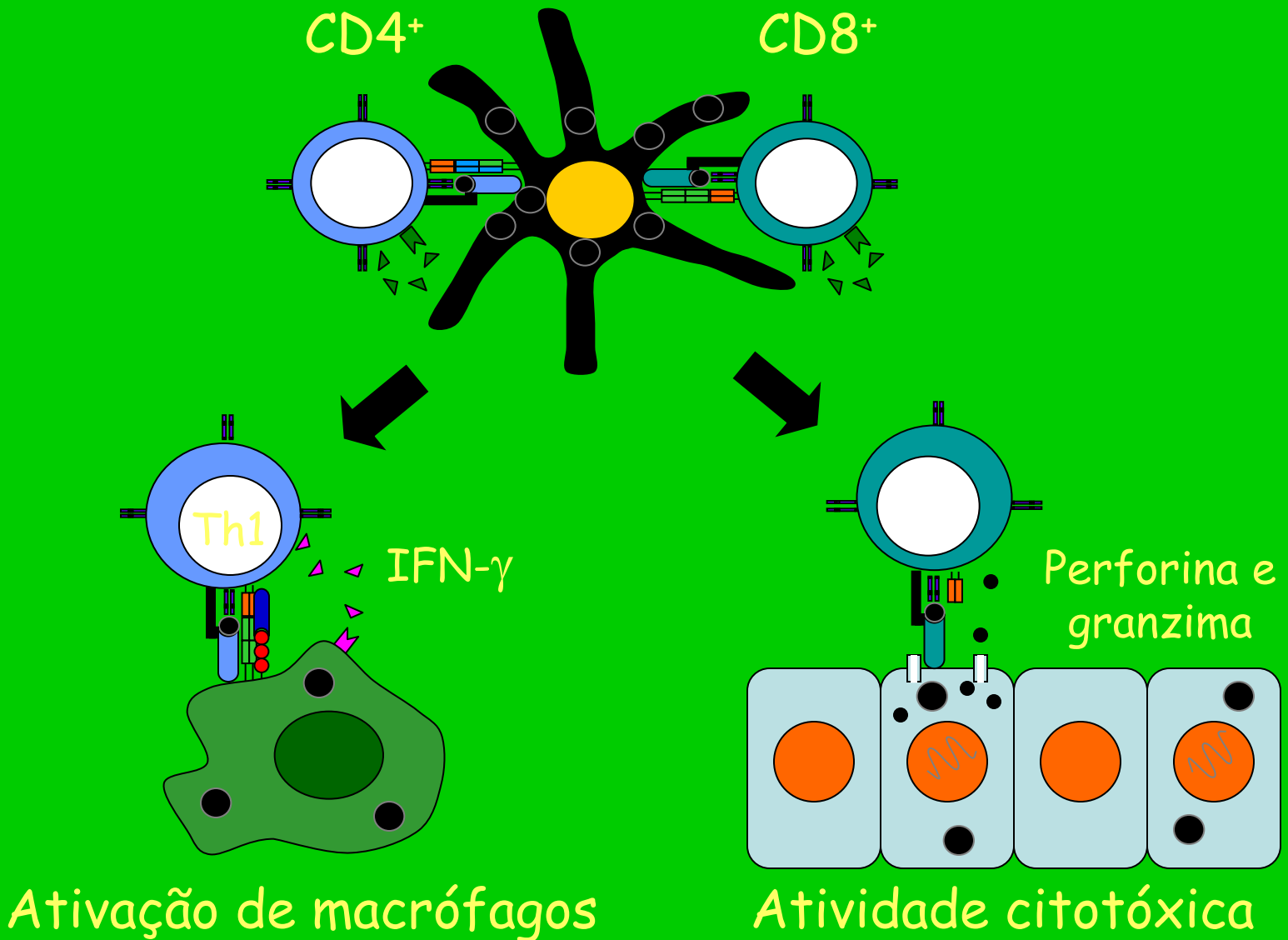


Célula T de memória



Célula T efetora

# Respostas efetoras mediadas por células T

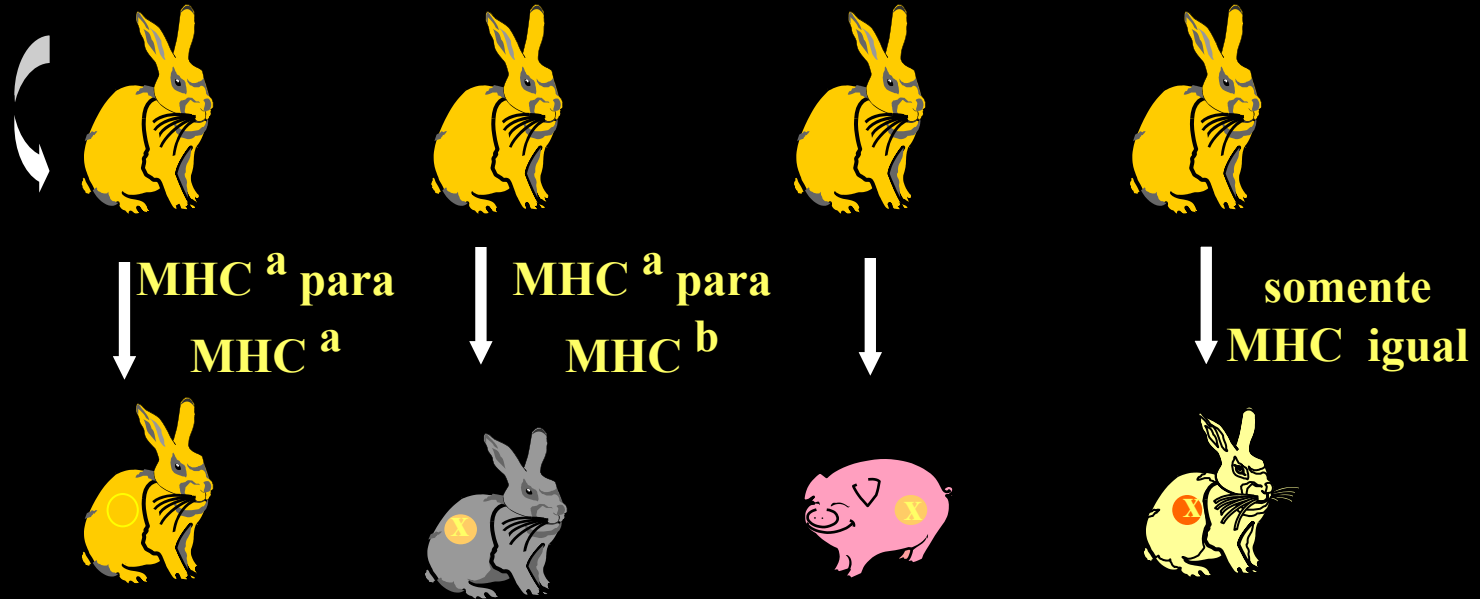


Por quê Complexo Principal de  
Histocompatibilidade ?



# Por quê Complexo Principal de Histocompatibilidade?

auto-  
enxerto



enxerto  
isogênico

enxerto  
alogenico

enxerto  
xenogenico

enxerto  
congenico

Qual a Relação entre HLA e Doenças Auto-  
imunes ?



## Associations of HLA genotype with susceptibility to autoimmune disease

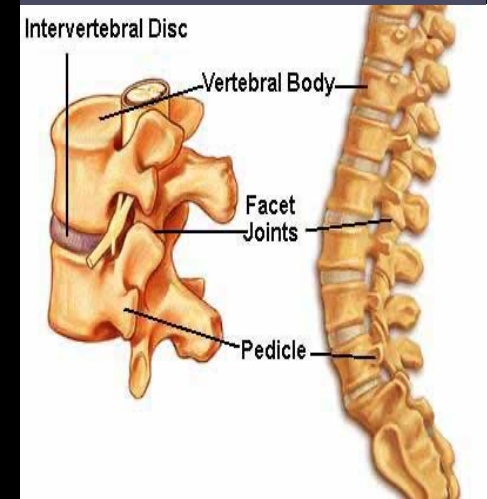
Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10.04	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4-5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10-20
Insulin-dependent diabetes mellitus	DR3 and DR4	3.2	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4-5

# Espondilite Anquilosante

- HLA-B27
- Inflamação crônica da medula espinhal e articulações
- Resposta auto-imune
- Outros genes *ARTS 1* e *IL-23r*



Patient before and after surgery.



# Associação entre infecções e doenças auto-imunes

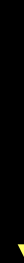
Associations of infection with immune-mediated tissue damage		
Infection	HLA association	Consequence
Group A <i>Streptococcus</i>	?	Rheumatic fever (carditis, polyarthritis)
<i>Chlamydia trachomatis</i>	HLA-B27	Reiter's syndrome (arthritis)
<i>Shigella flexneri</i> , <i>Salmonella typhimurium</i> , <i>Salmonella enteritidis</i> , <i>Yersinia enterocolitica</i> , <i>Campylobacter jejuni</i>	HLA-B27	Reactive arthritis
<i>Borrelia burgdorferi</i>	HLA-DR2, DR4	Chronic arthritis in Lyme disease



# Especificidades HLA detectadas sorologicamente

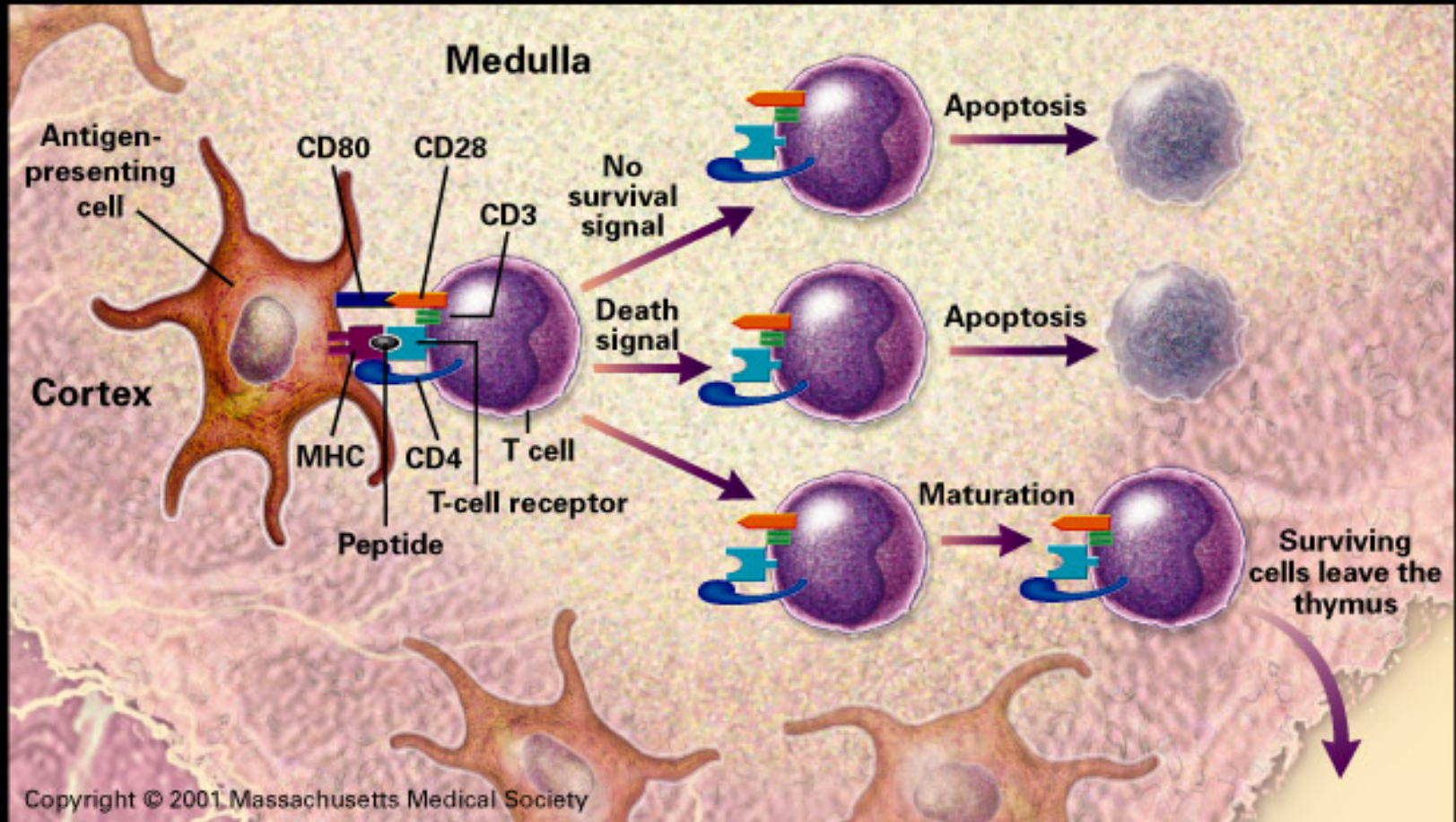
locos	classe I			classe II			
	A	B	C	DR	DQ	DP	
antígenos	1	5	w50	w1	1	w1	w1
	2	7	51	w2	2	w2	w2
	3	8	w52	w3	3	w3	w3
	9	12	w53	w4	4	w4	w4
	10	13	w54	w5	5	w5	w5
	11	14	w55	w6	w6	w6	w6
	w19	15	w56	w7	7	w7	
	23	16	w57	w8	w8	w8	
	24	17	w58	w9	w9	w9	
	25	18	w59	w10	w10		
	26	21	w60	w11	w11		
	28	w22	w61		w12		
	29	27	w62		w13		
	30	35	w63		w14		
	31	37	w64		w15		
	32	38	w65		w16		
	w33	39	w67		w17		
	w34	40	w70		w18		
	w36	w41	w71		w52		
	w43	w42	w72		w53		
	w66	44	w73				
	w68	45	w75				
	w68	w46	w76				
	w69	w47	w4				
		w48	w6				

Será por isso que é tão difícil desenvolvermos vacinas ?



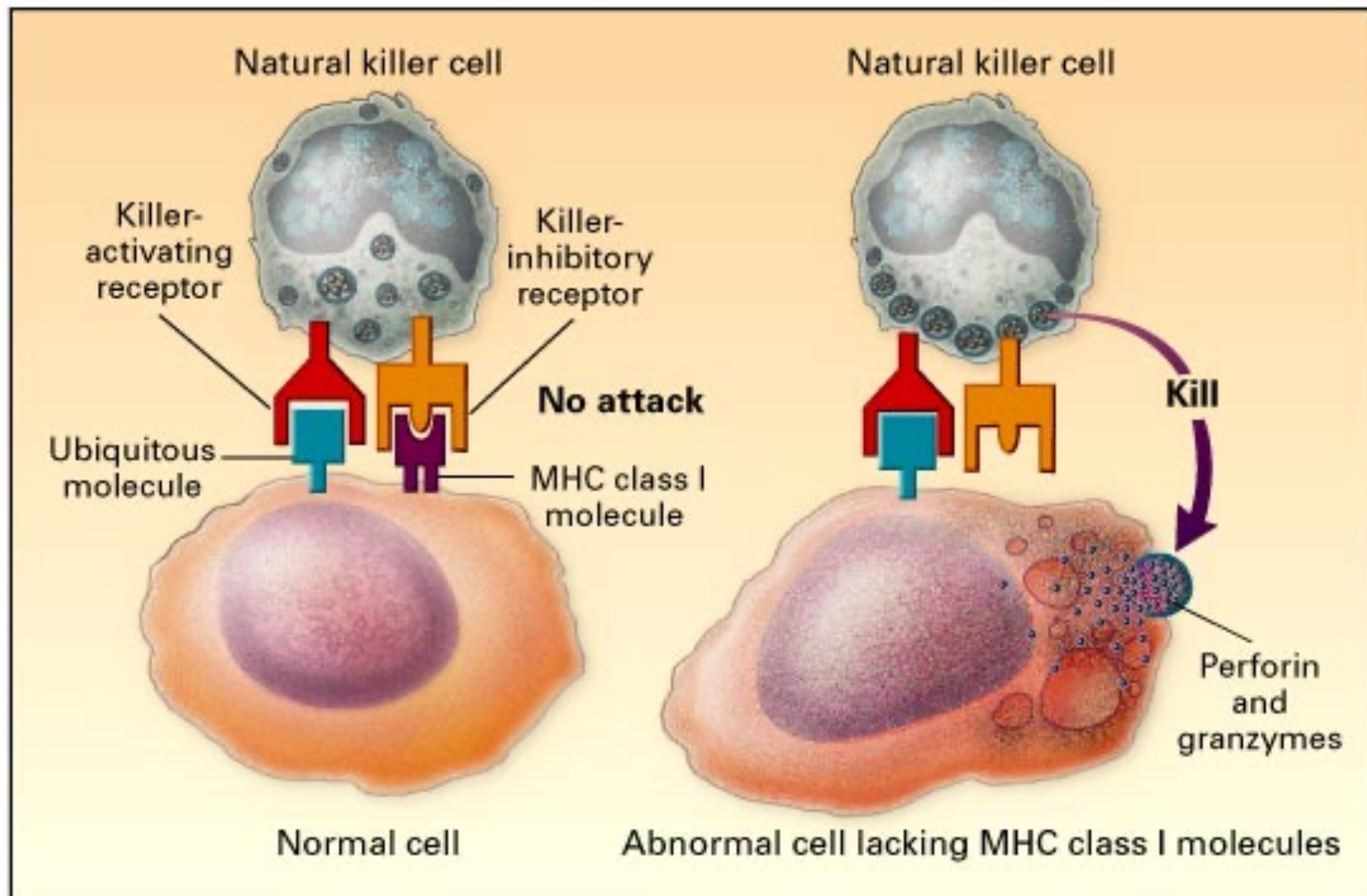
Imunodominância

# Mecanismos Centrais de Tolerância

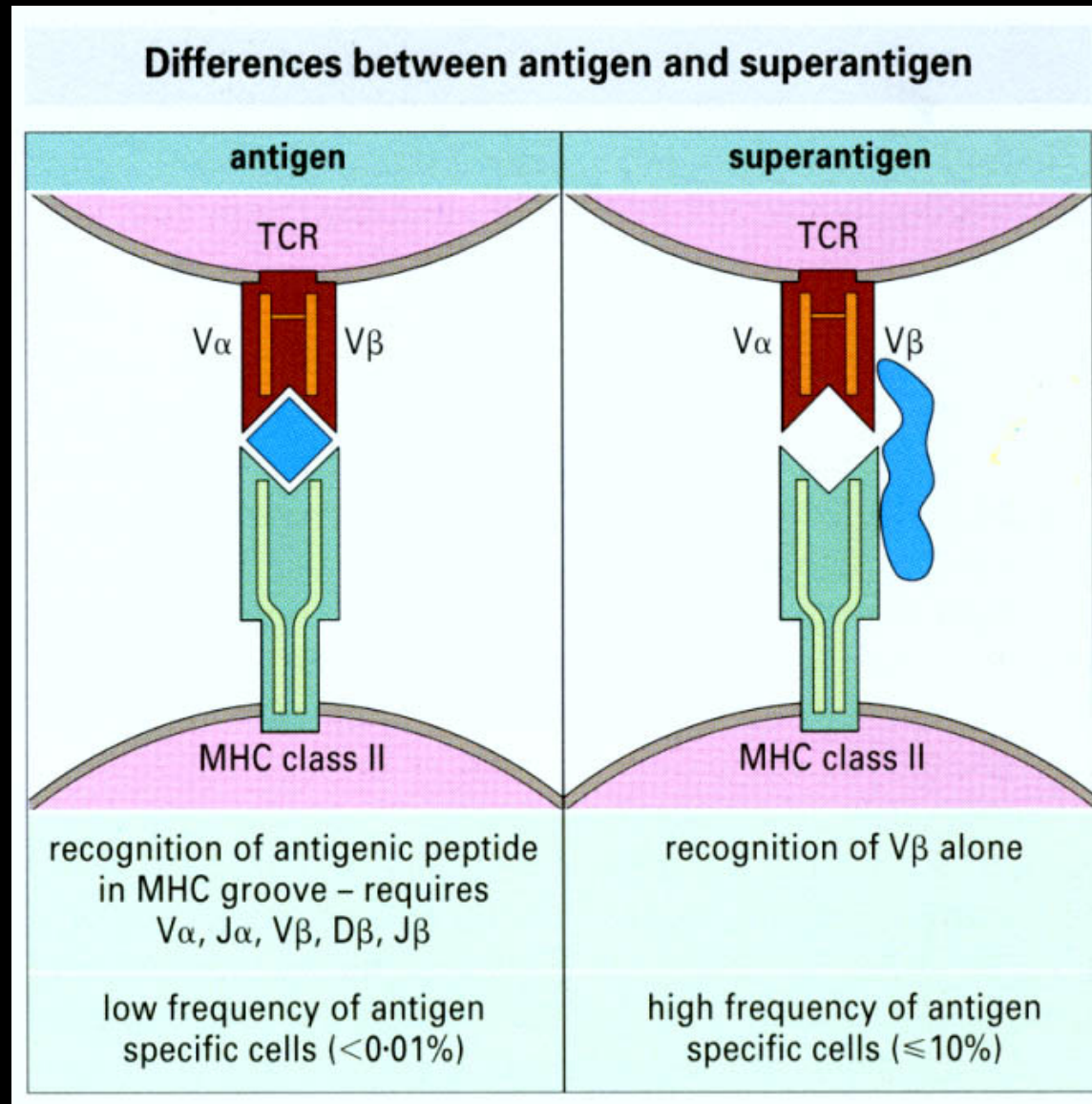


Comprometimento na Apresentação do Antígeno, Possibilita o Escape de Células Auto-reativas - Ativação na Periferia

# Células com Baixa Expressão de MHC I São Alvos de Lise por Células NK



# Alguns Patógenos Apresentam Moléculas Chamadas Superantígenos - Ativação Policlinal



# Resumindo

- MHC I e II codificam moléculas de superfície capazes de apresentar Ags para CD8 e CD4 respectivamente,
- HLA - A,B,C (Classe I) HLA-DP, DQ DR (Classe II)
- Importantes na apresentação de Ag
- Geração de Tolerância
- Relação com Doenças Auto-imunes.