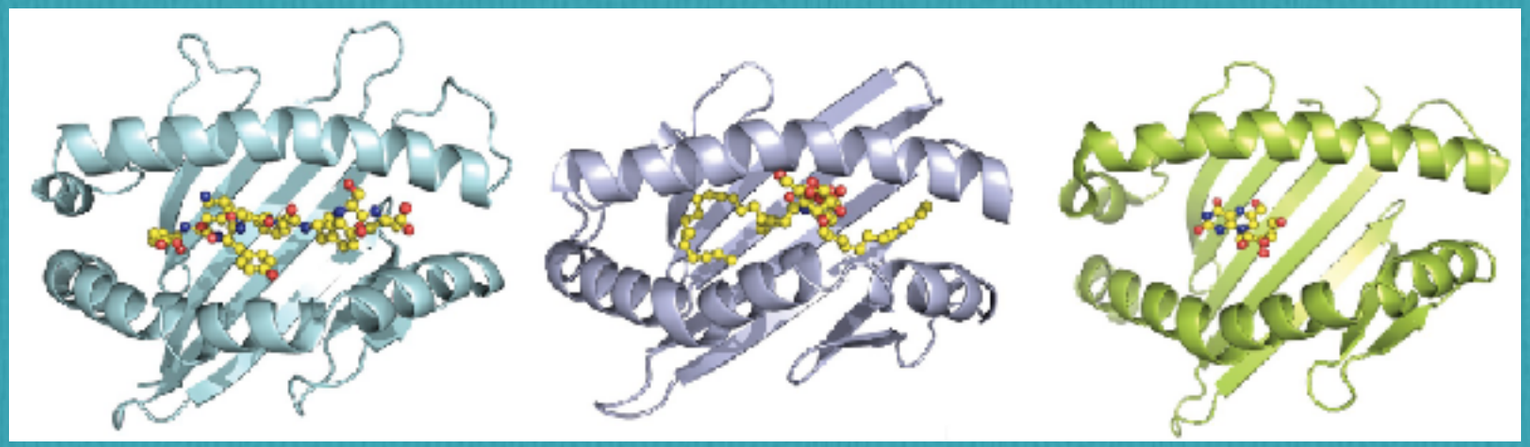
Programa de Pôs-graduação em Imunologia ICB/USP

Disciplina BMI 5904
Reconhecimento no Sistema Imune



Aula 7 - MHC/HLA

Alessandra Pontillo

Lab. Imunogenetica/Dep.Imunologia/ICB/USP

Reconhecimento

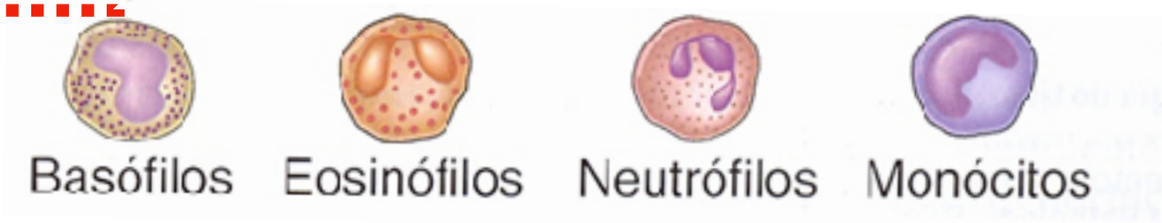
SISTEMA IMUNE

“SELF” ALTERADO

NK Rec

PADRÕES MOLECULARES (MAMPs, PAMPs, NAMPs, DAMPs, HAMPs, VAMPs….)

PRRs

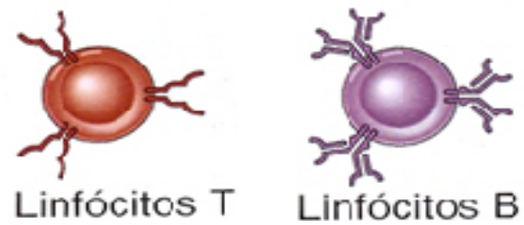


&….todas as outras células

20-40 genes para reconhecer um limitado numero de pattern “mais prevalentes e conservados”

ANTIGENOS ESPECIFICOS

TCR, BCR, Ig



Rec com potencial de reconhecer um amplo leque de antígenos (recombinação somática randômica)

MHC/HLA

- ◇ Glico-proteinas (super familia das Ig) da superficie celular
- ◇ Codificadas pelos genes MHC (humanos: HLA no chr 6)
- ◇ Tipo: **MHC-I e MHC-II, e MHC-I non-classica, MHC-I like**

MHC-I, MHC-II	elevado polimorfismo
MHC-I non classicas MHC-I like	baixo polimorfismo monomorfico

MHC/HLA

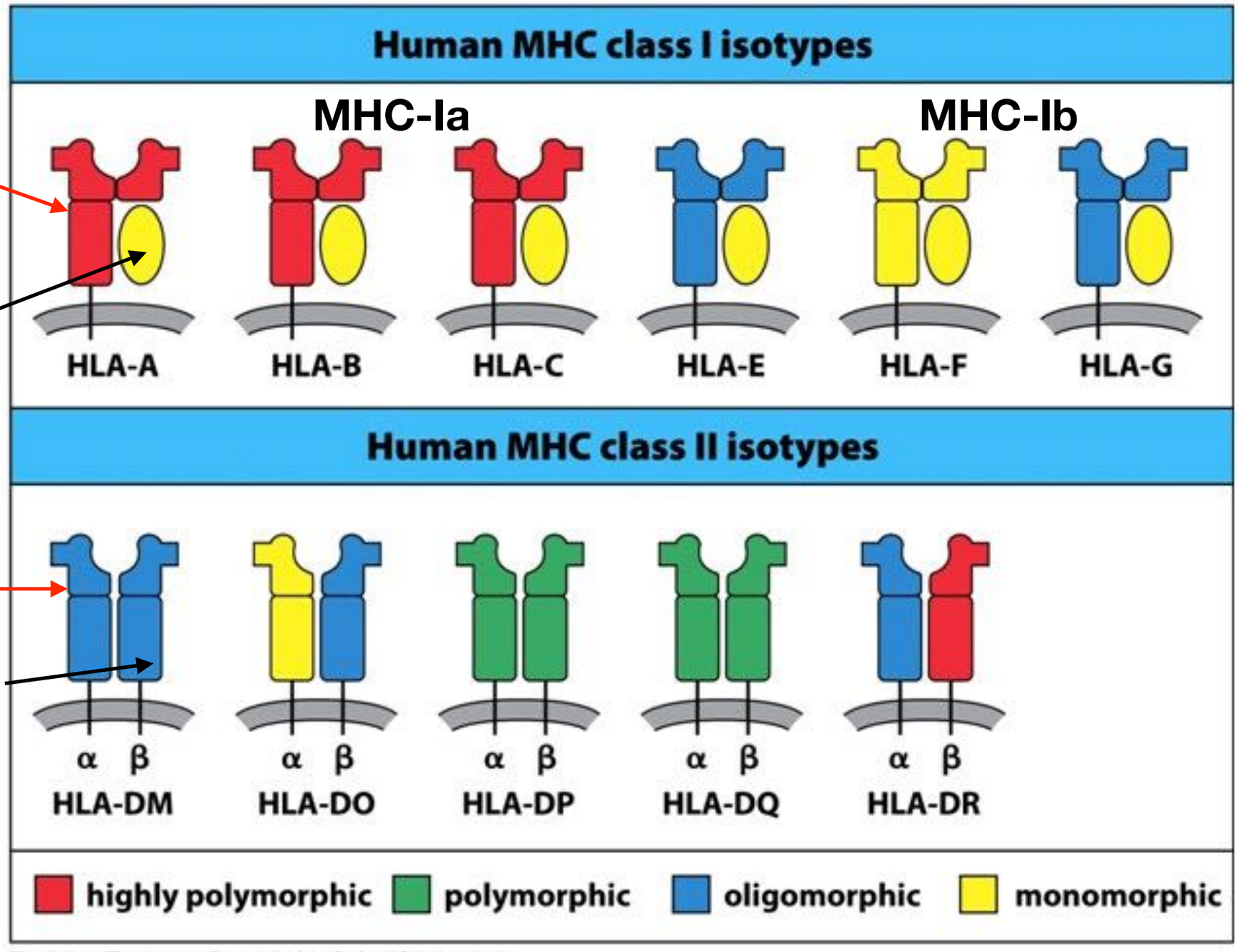
Glico-proteinas (super familia das Ig)

cadeia **α**

ß2-micro glubulina (B2M)

cadeia **α**

cadeia ß



MHC-I like

C1D, MR1

MICA
MICB
ULBP

Figure 5.24 The Immune System, 3ed. (© Garland Science 2009)

MHC/HLA

Chr6

Chr6

MHC I	Immune function	ligand binding between the α1 and α2 domains	TCR binding	NKR binding	β_2m-associated
Classical MHC I molecules					
HLA-A	Yes	Peptide	Yes	LCR/ LIR, KIR*	Yes
HLA-B	Yes	Peptide	Yes	LIR, KIR*	Yes
HLA-C	Yes	Peptide	Yes	LIR, KIR	Yes
Non-classical MHC I molecules					
HLA-E	Yes	Peptide	Yes	CD94/NKG2A/C, LIR	Yes
HLA-G	Yes	Peptide	Yes	LIR, KIR2DL4[165]	Yes
HLA-F	Yes[b]	No[c]		LIR	Yes
CD1	Yes	Lipids	Yes		Yes
MICA	Yes	No	Yes (γδ lineage[167])	NKG2D	No
MICB	Yes	No	Yes (γδ lineage[167])	NKG2D	No
ULBPs	Yes	No	ULBP4 (γδ lineage[168])	NKG2D	No
FcRn[169]	Yes	No	No		Yes
HFE[170]	No	No	No		Yes
MR1[171]	Yes	Vitamin B metabolites	Yes (MAIT cells)		Yes
EPCR[172]	Yes	Phospholipid	Yes (γδ lineage[173])		No
ZAG[174]	No	Fatty acids			No
HCMV-encoded MHC I-like molecules					
UL18	Yes	Peptide	No	LIR1	Yes
UL142	Yes				
UL37					

Halenius et al. Cellular & Molecular Immunology 2015

MHC/HLA

MHC-I

1 cadeia variavel (**α**)

1 cadeia invariavel (ß2-microglobulina)

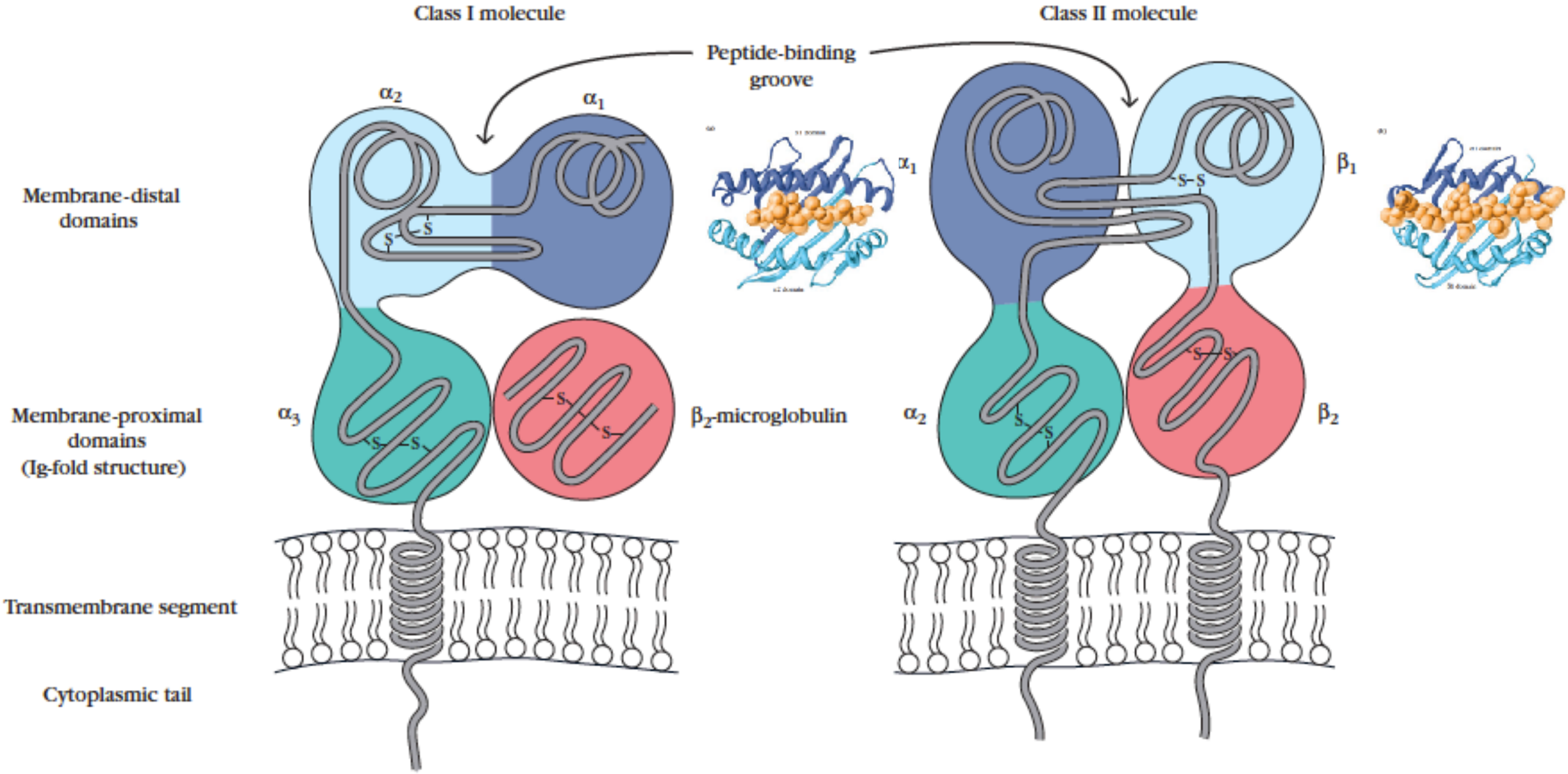
Sitio de ligaçao do Ag (α_1+ α_2): **8-10 AA**

MHC-II

1 cadeia variavel (**α**)

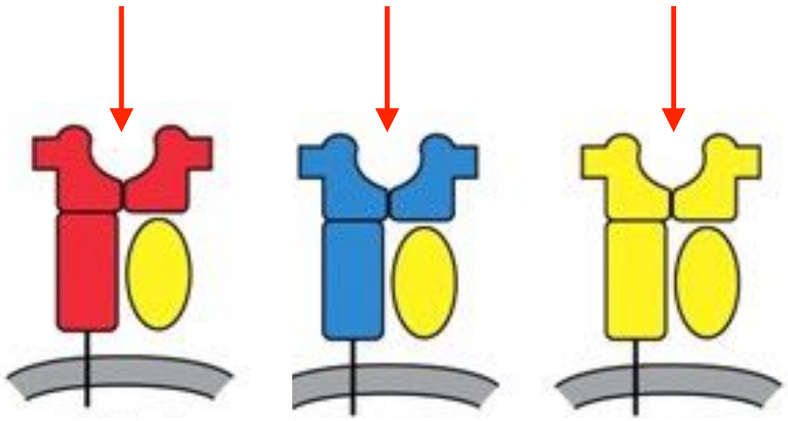
1 cadeia variavel (**ß**)

Sitio de ligaçao do Ag (α_1+ $ß_1$): **13-18 AA**

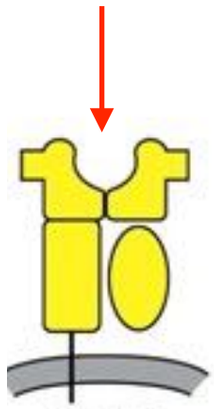


Classical & Non-classical MHC-I

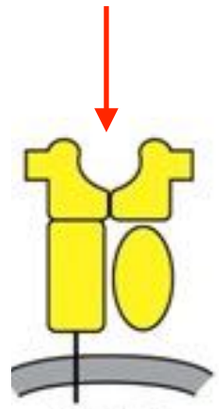
Broadly similar structure and binding groove



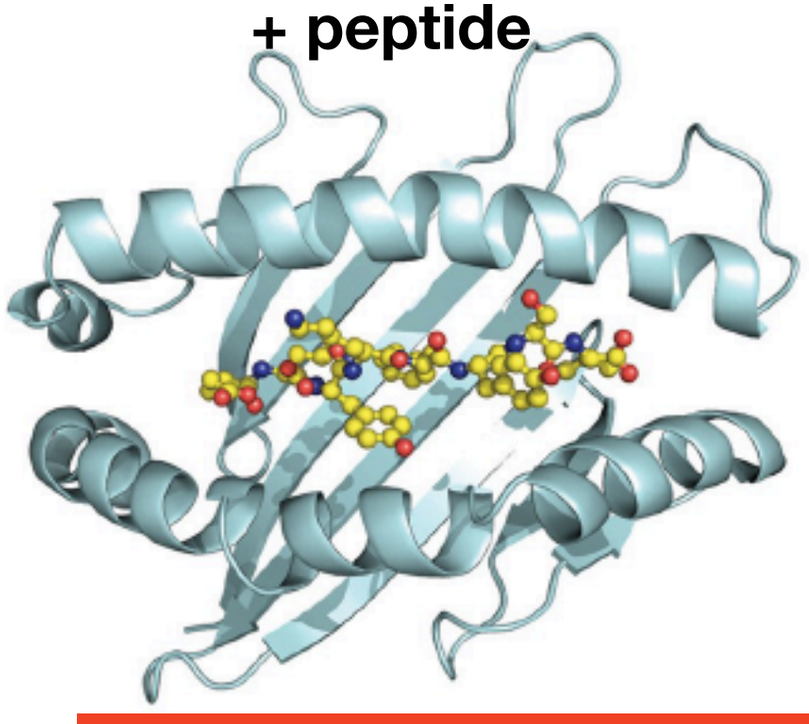
MHC-I
+ peptide

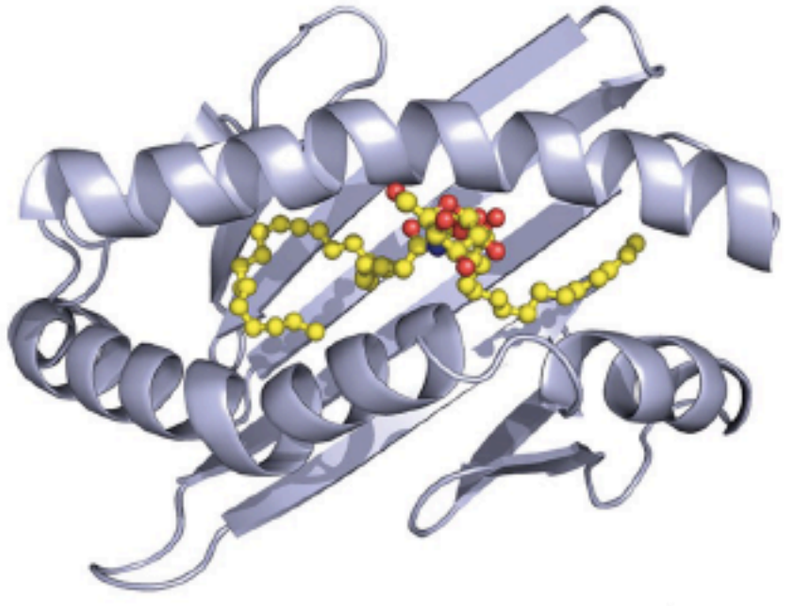


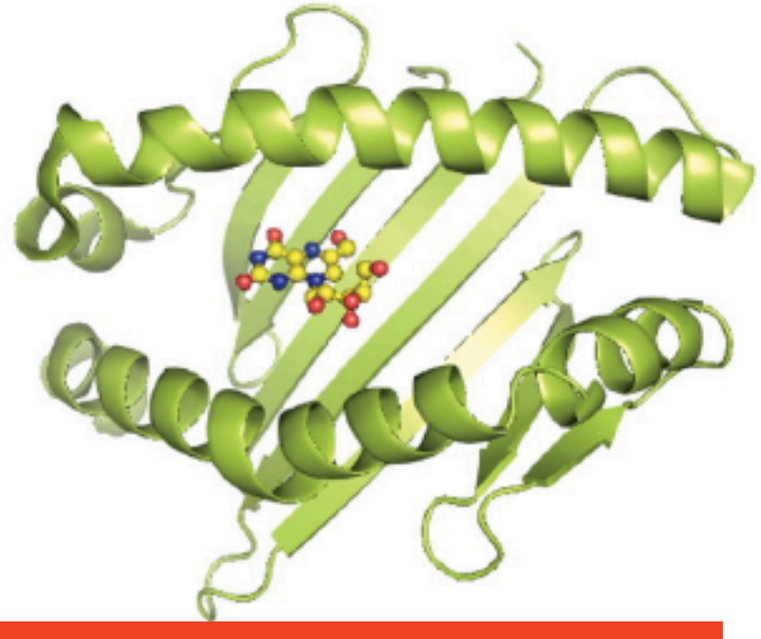
CD1
+ lipid



MR1
+ small metabolite







Endogenous molecules

D'Souza et al. PLoS Pathog 2019

Apresentação de Ag via MHC-I

MHC presente em todas as celulas!

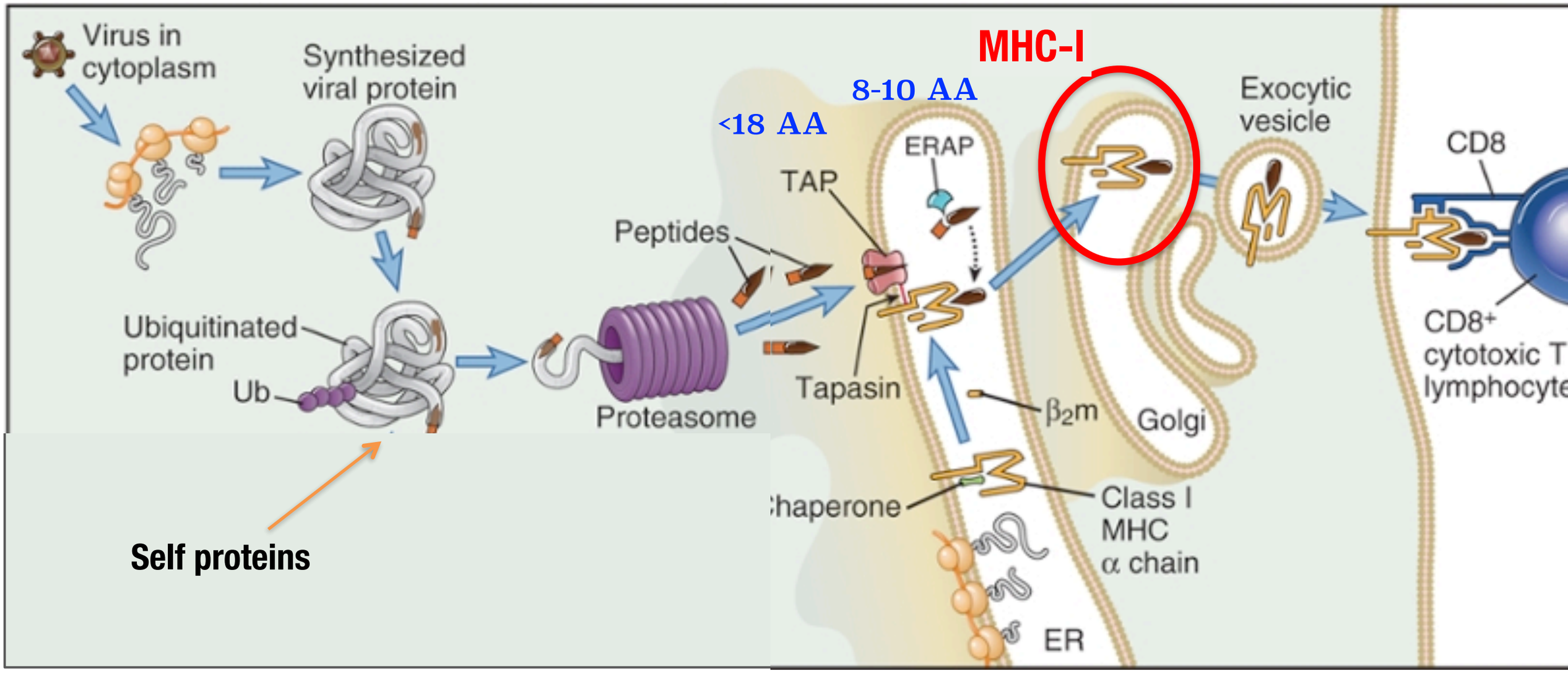
- no citosol de qualquer celula
- turn over de proteinas endogenas
- infecçao viral
  → sintese de proteinas virais

→ Digestao no PROTEASOMA →peptideos de ate 18 AA

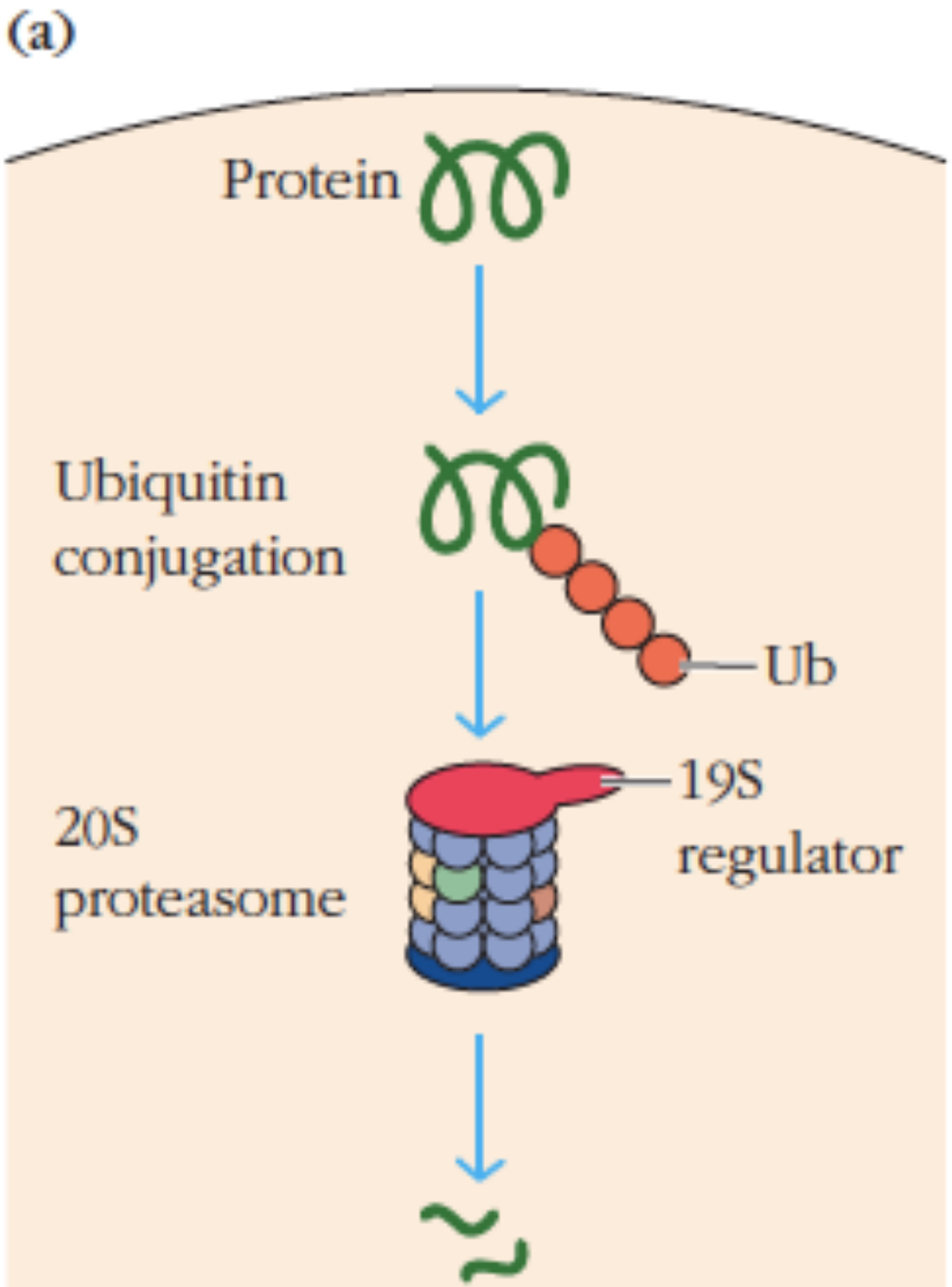
→ Peptideos transportados no ER (TAP) ERAP1/2: 8-10 AA

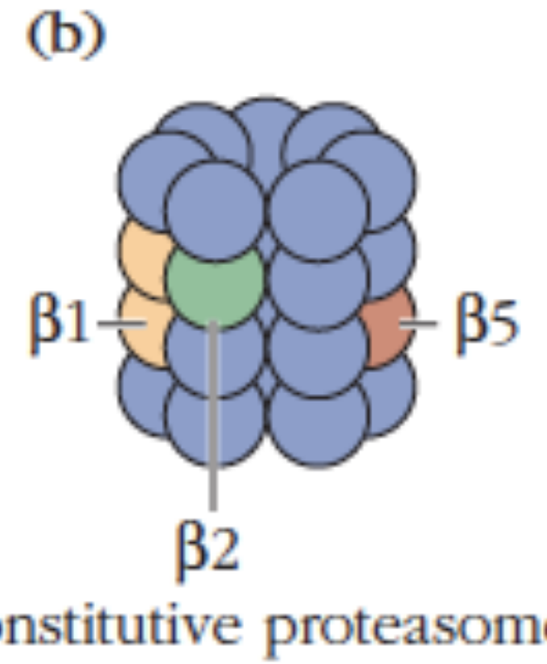
→ Peptideos encaixas no MHC-I

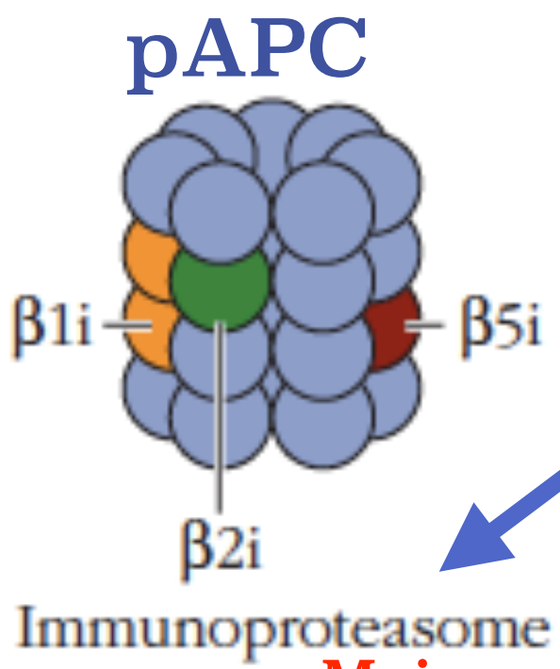
→ Complexos MHC-I/peptideo apresentados na S (via Golgi)



Proteassoma e Imunoproteassoma





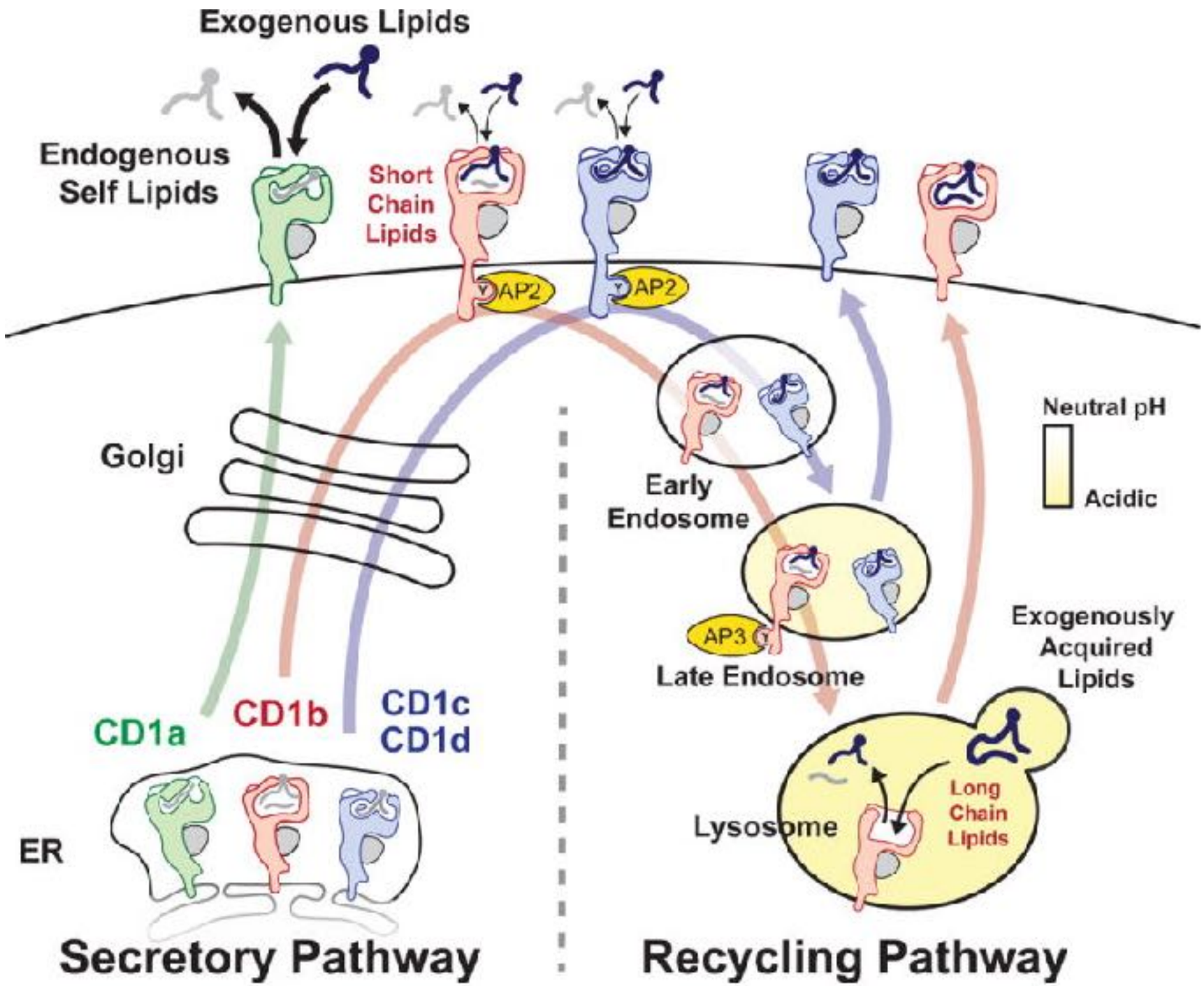


IFN-g, TNF

LMP-2, LMP-7

Maior geração de peptídeos que podem ligar MHC-I

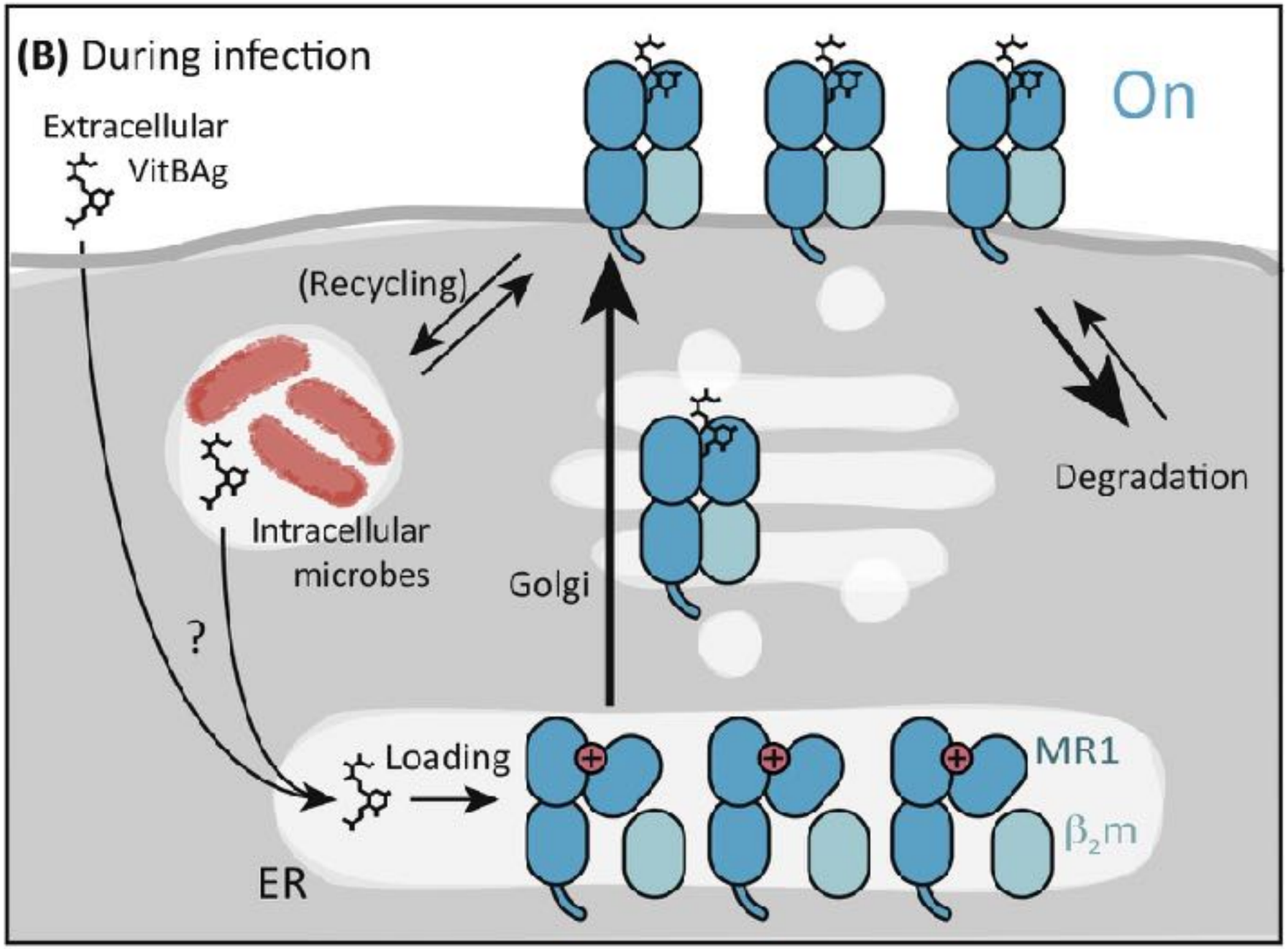
Apresentação de lipídios via CD1



Moody et al. Curr Op Immunol 2017

Apresentação de metabólitos via MR1

metabolites derived from the synthesis of vitamin B2 (riboflavin)



McWilliam & Villadangos. Trends in Immunol 2017

Apresentação de Ag via MHC-II

MHC presente nas APC profissionais

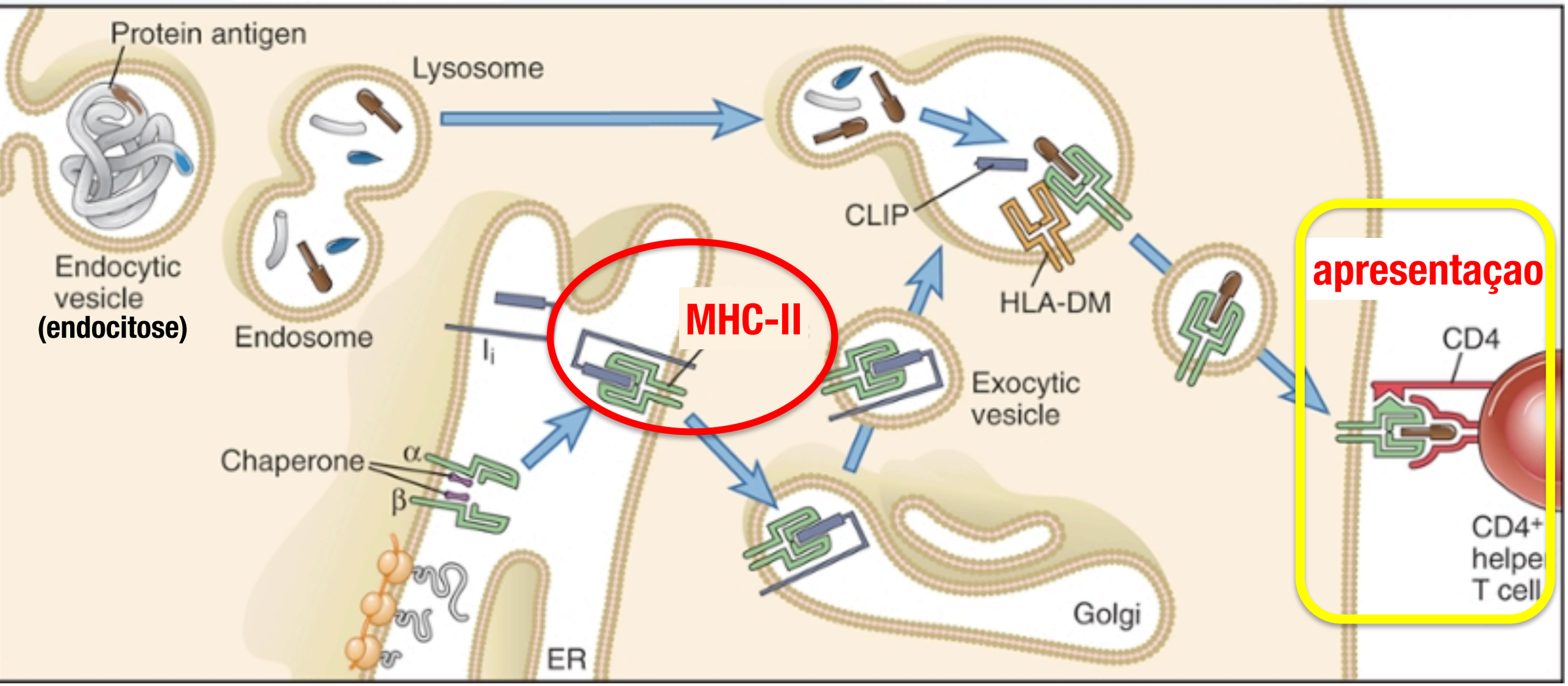
Captaçao de proteinas extracelulares em compartamentos vesiculares

Digestao das proteinas

Biosintese e transporte do MHC-II aos endosomas (via Golgi)

Associaçao dos peptideos originados com MHC-II

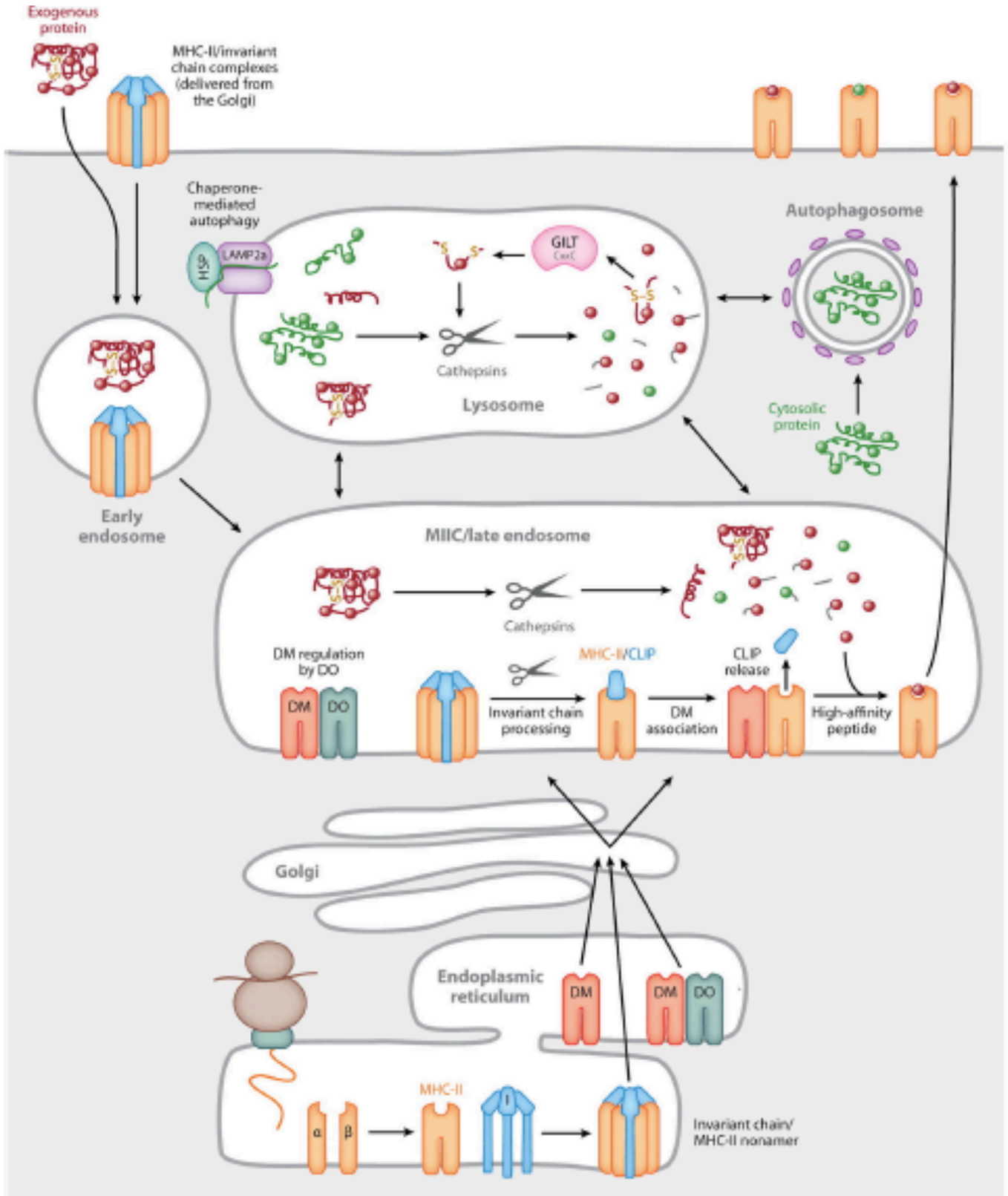
Expressao dos complexos peptideos-MHC na superficie da APC



Abbas Cellular and Molecular Immunology 8ed

Apresentação de Ag via MHC-II

Not only phagocytes or endocyted molecules but also “self” proteins (autophagy)

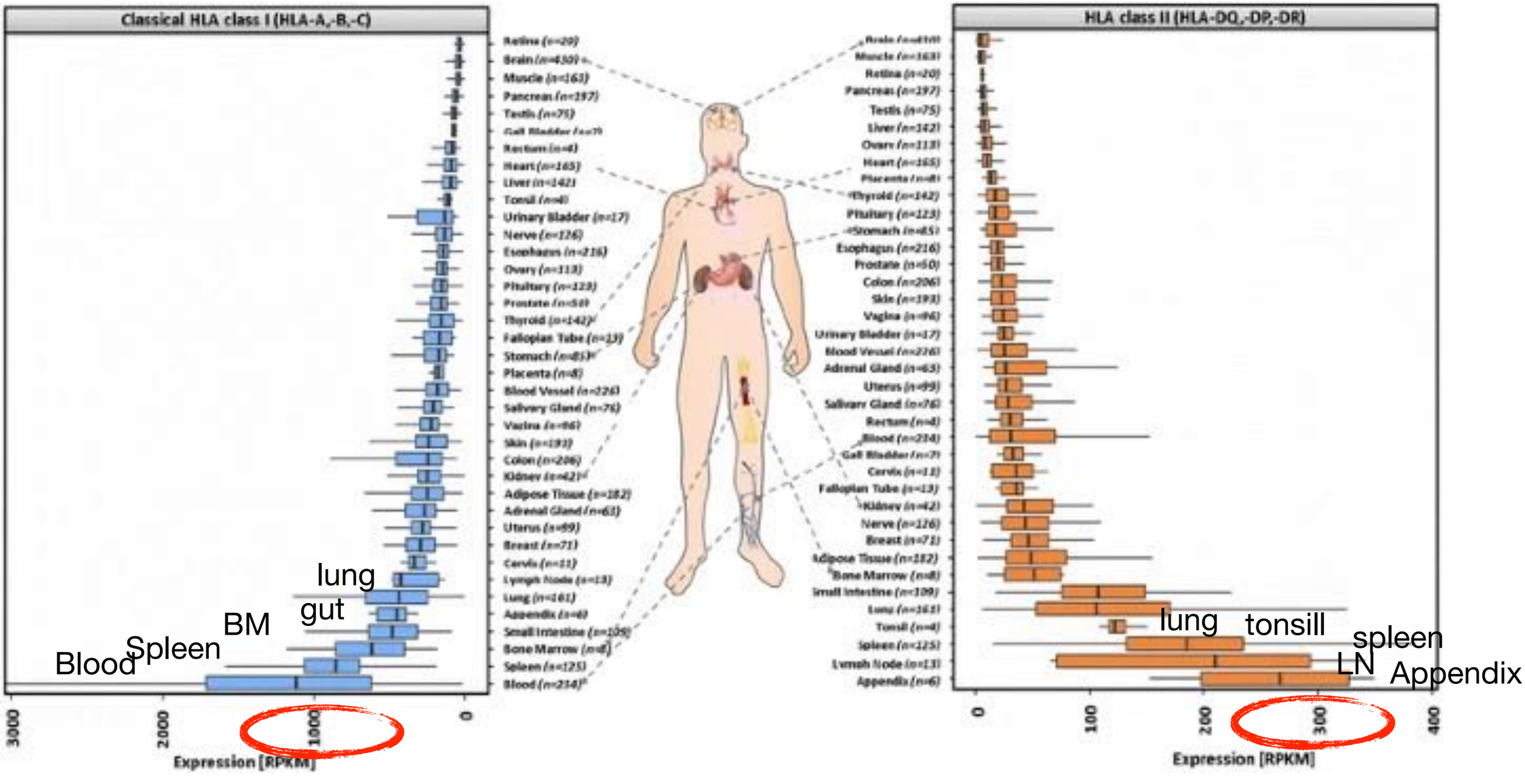


Cresswell Immunogenetics 2019

Classical MHC genes expression

MHC-I
(ubiquitous)

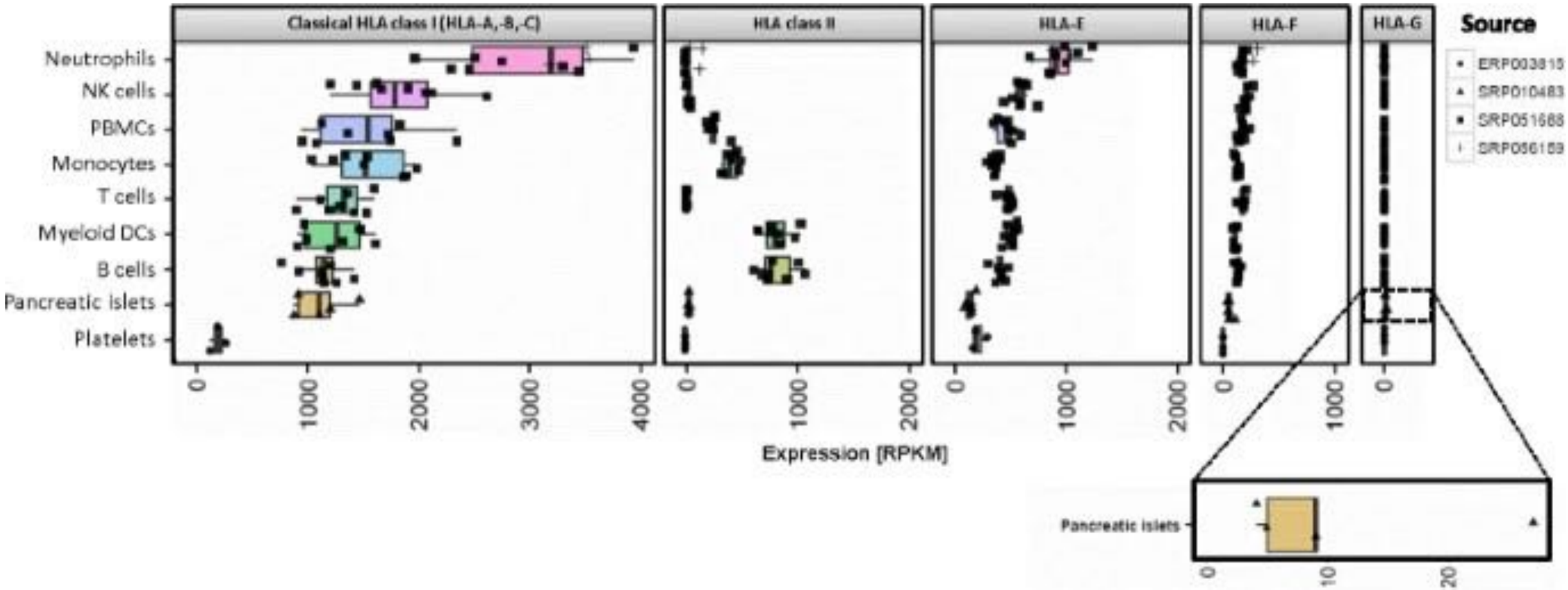
MHC-II
(mainly APCs)



Boeget et al. BMC Med Genomics 2018

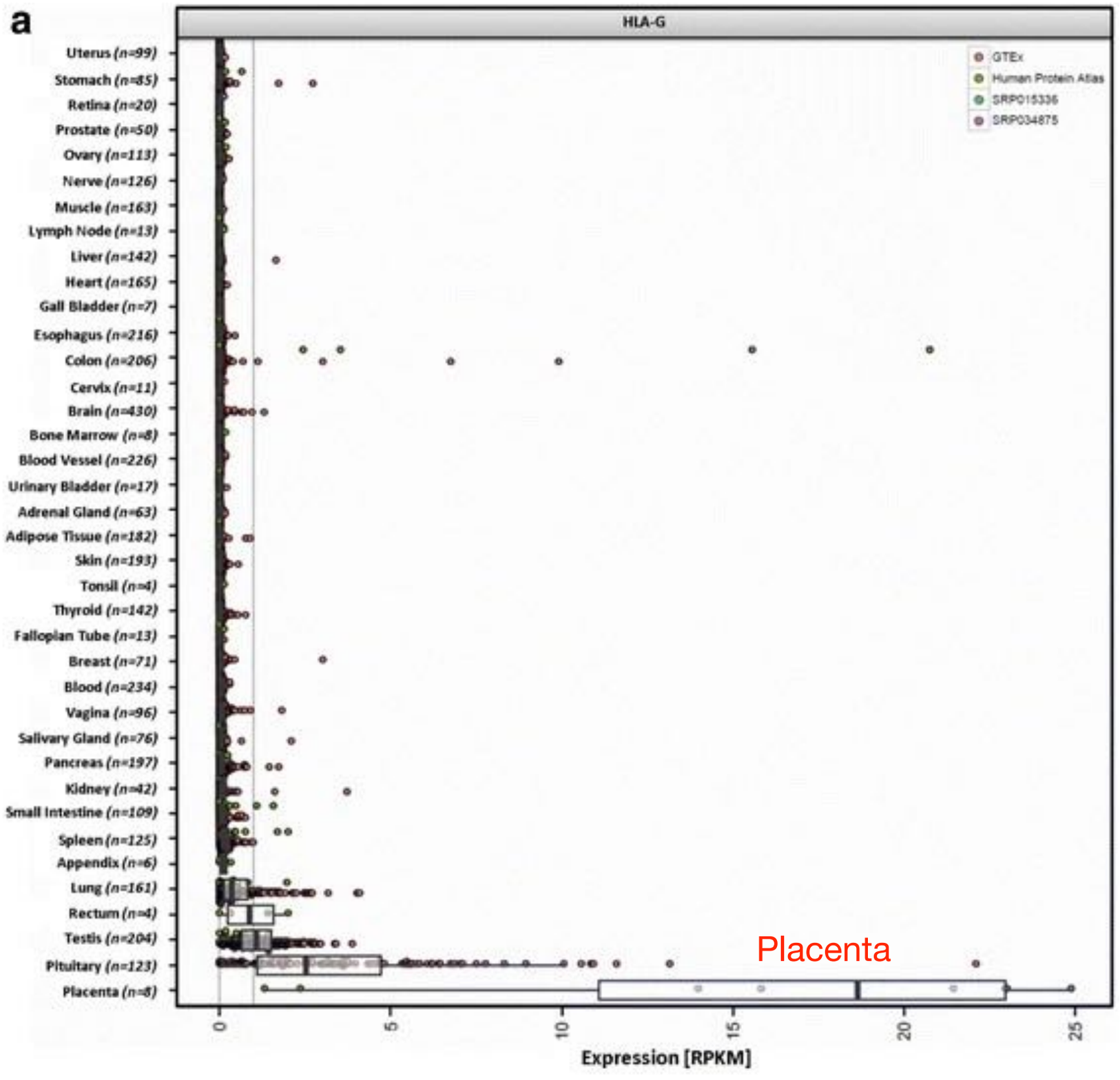
MHC genes expression

MHC-I (ubiquitous) **MHC-II (mainly APCs)** **HLA-E (ubiquitous)** **HLA-G (restricted)**



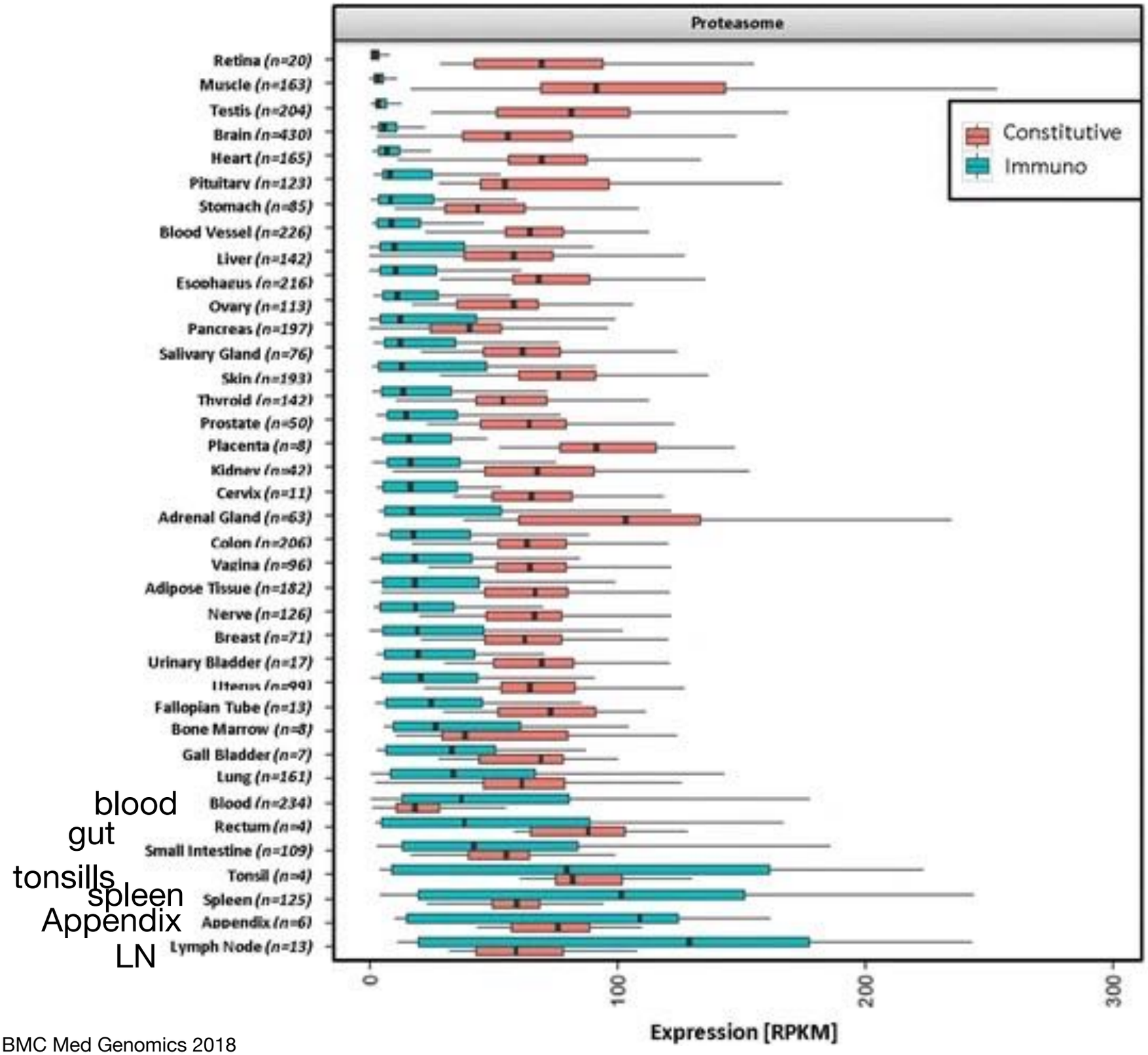
Boeget et al. BMC Med Genomics 2018

HLA-G expression



Boeget et al. BMC Med Genomics 2018

Proteasome expression

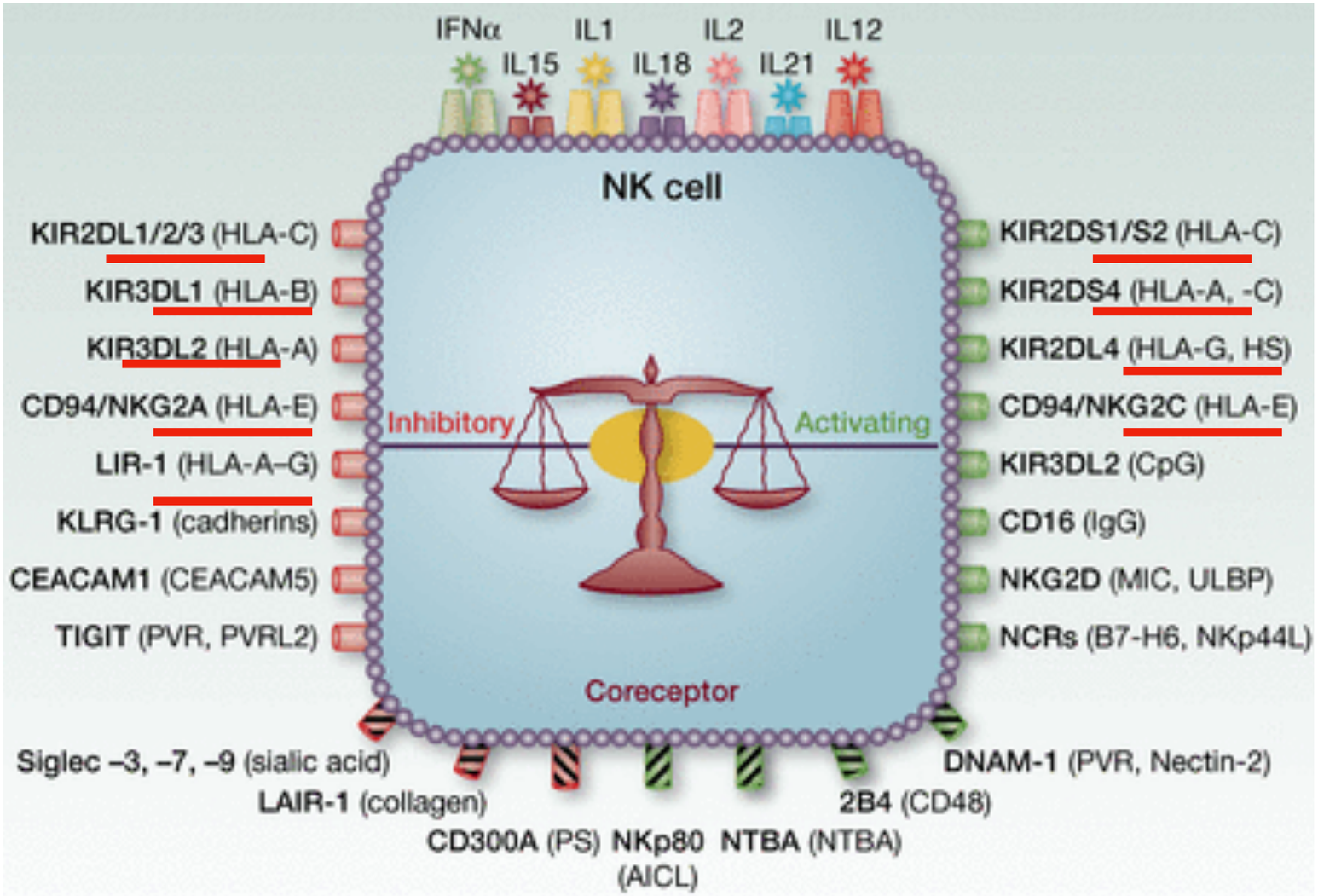


Boeget et al. BMC Med Genomics 2018

Funções dos MHC

- ligandos de Receptores NK cells (**imunovigilancia**)

ex: HLA-E + NKG2A/CD94 = inibição
HLA-E + NKG2C/CD94 = ativação
HLA-A + KIR3DL2 = inibição
HLA-A + KIR2DS4 = ativação

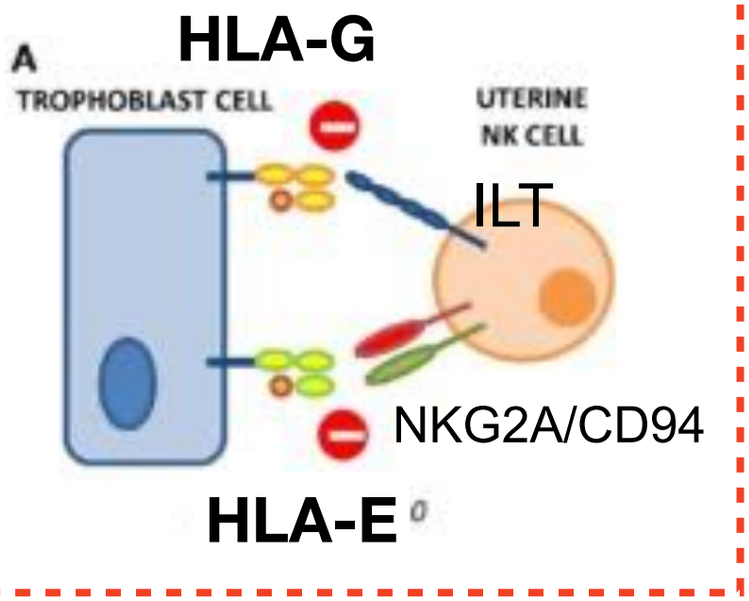


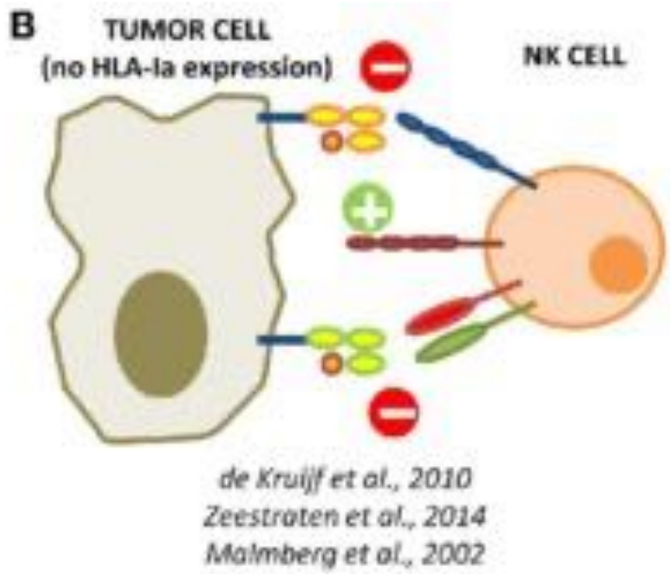
Wing Leung 2014

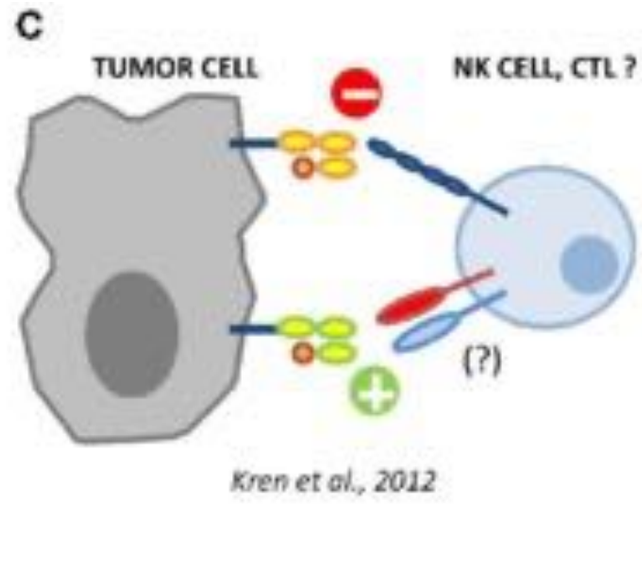
Funções dos MHC

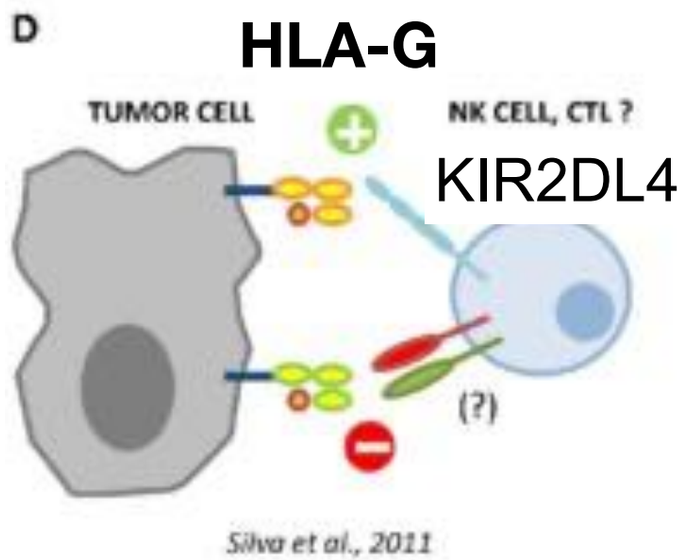
- **imunoregulação**

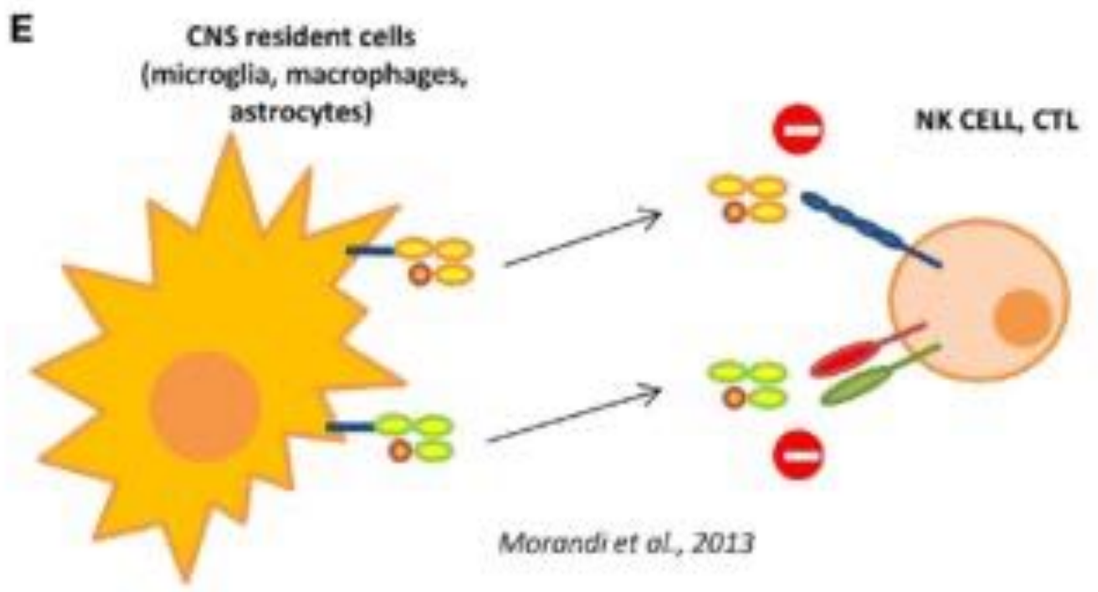
placenta







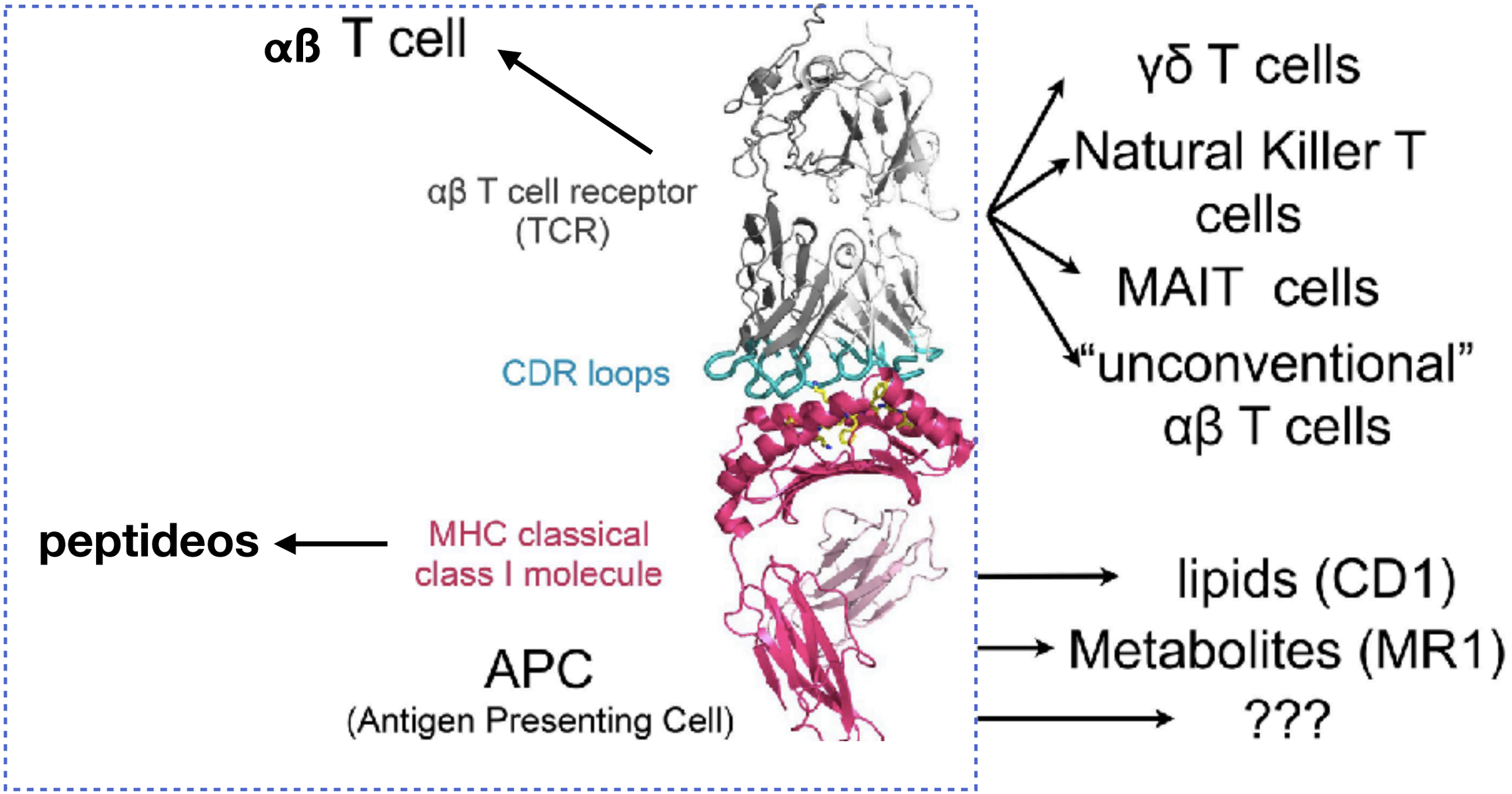




Morandi & Pistoia. Front. Immunol. 2014

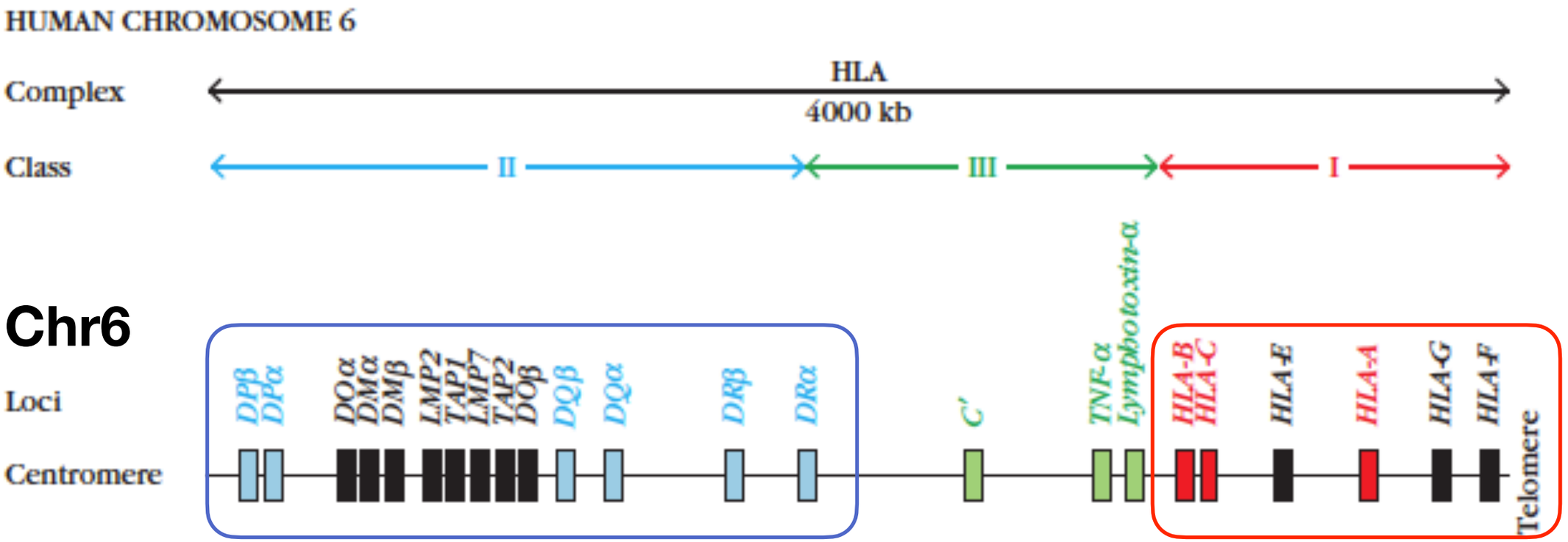
Funções dos MHC

- apresentação de antígenos aos linfócitos T (**ligando do TCR;** ativação imunidade adquirida)



D'Souza et al. PLoS Pathog 2019

Organização do locus MHC

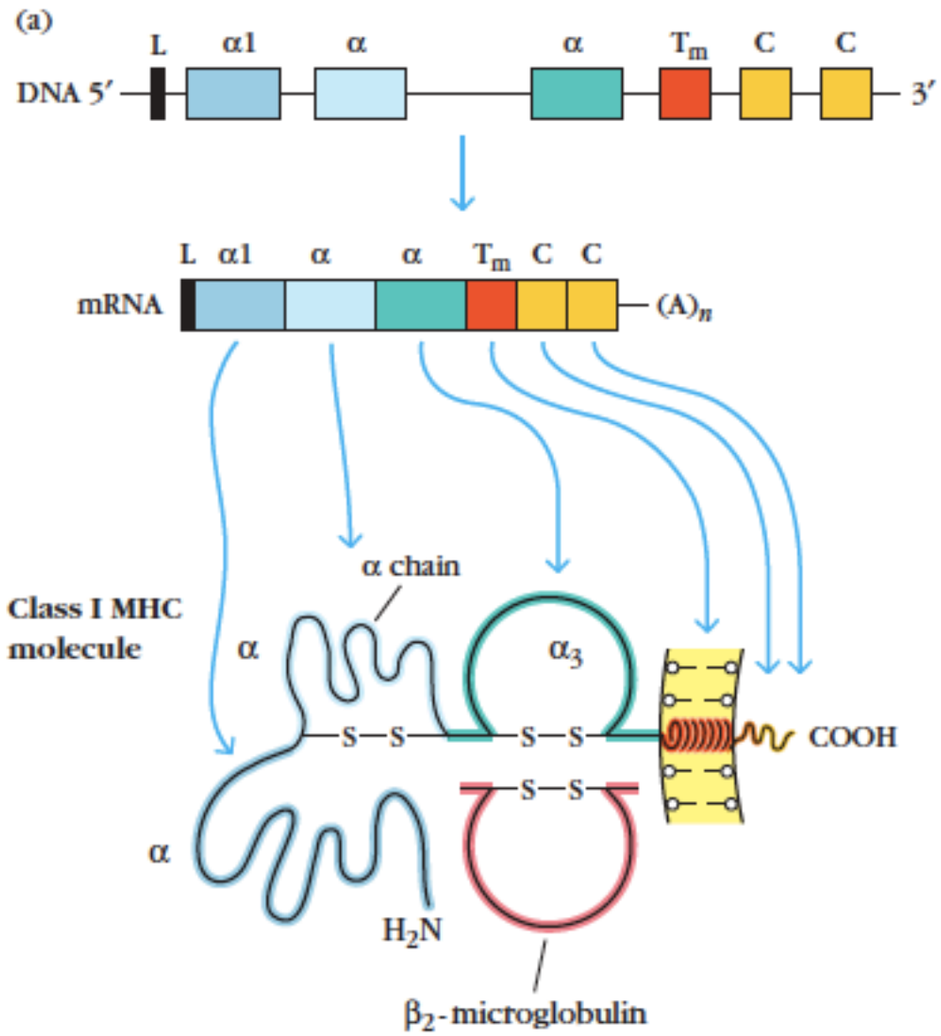


Human HLA complex

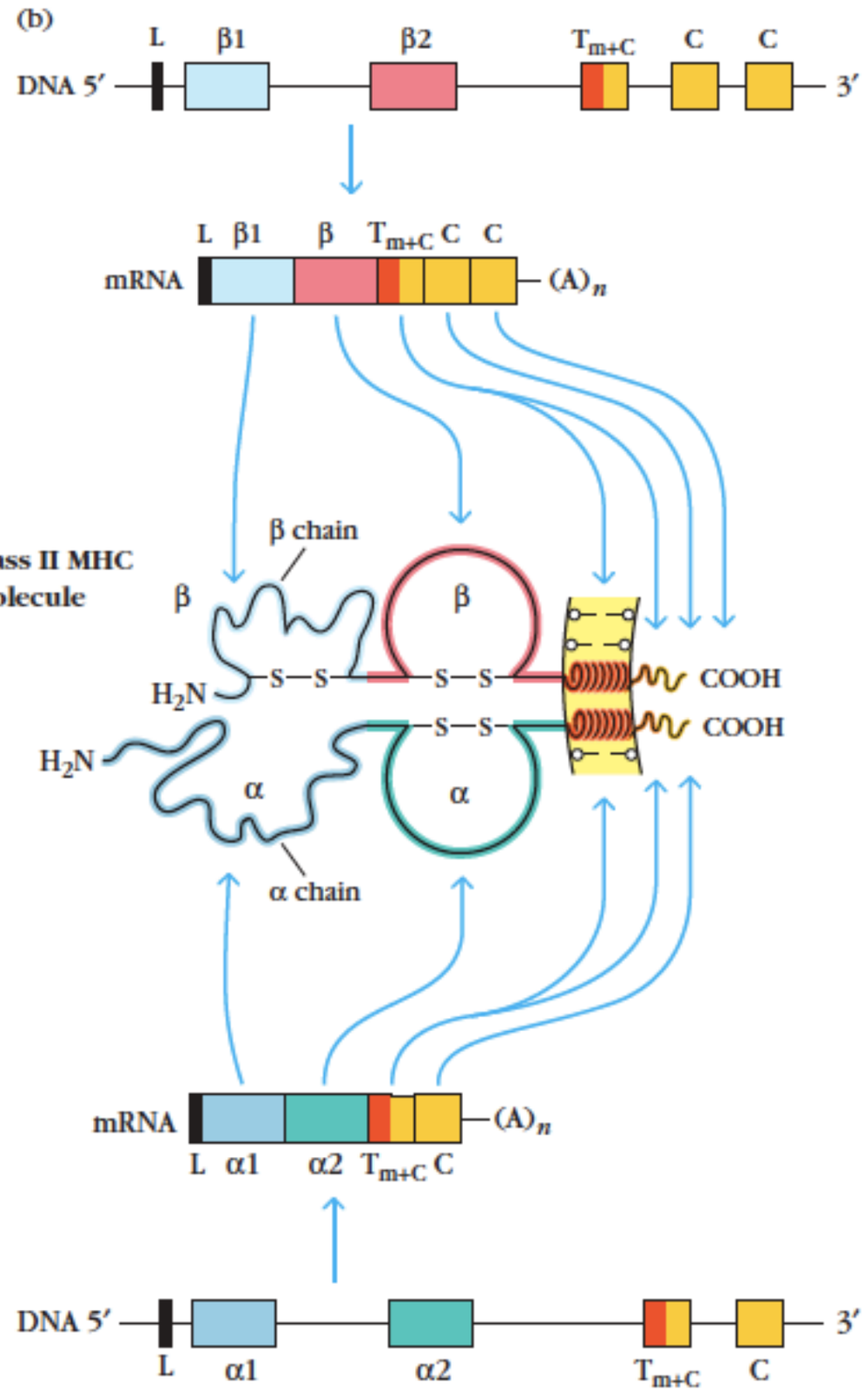
Complex	HLA								
MHC class	II			III		I			
Region	DP	DQ	DR	C4, C2, BF		B	C	A	
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α Lymphotoxin-α	HLA-B	HLA-C	HLA-A	

MHC/HLA

MHC-I



MHC-II



Variabilidade do MHC

Several hundred different allelic variants of class I and II MHC molecules

Regioes variaveis no sitio de ligaçao para o peptideo

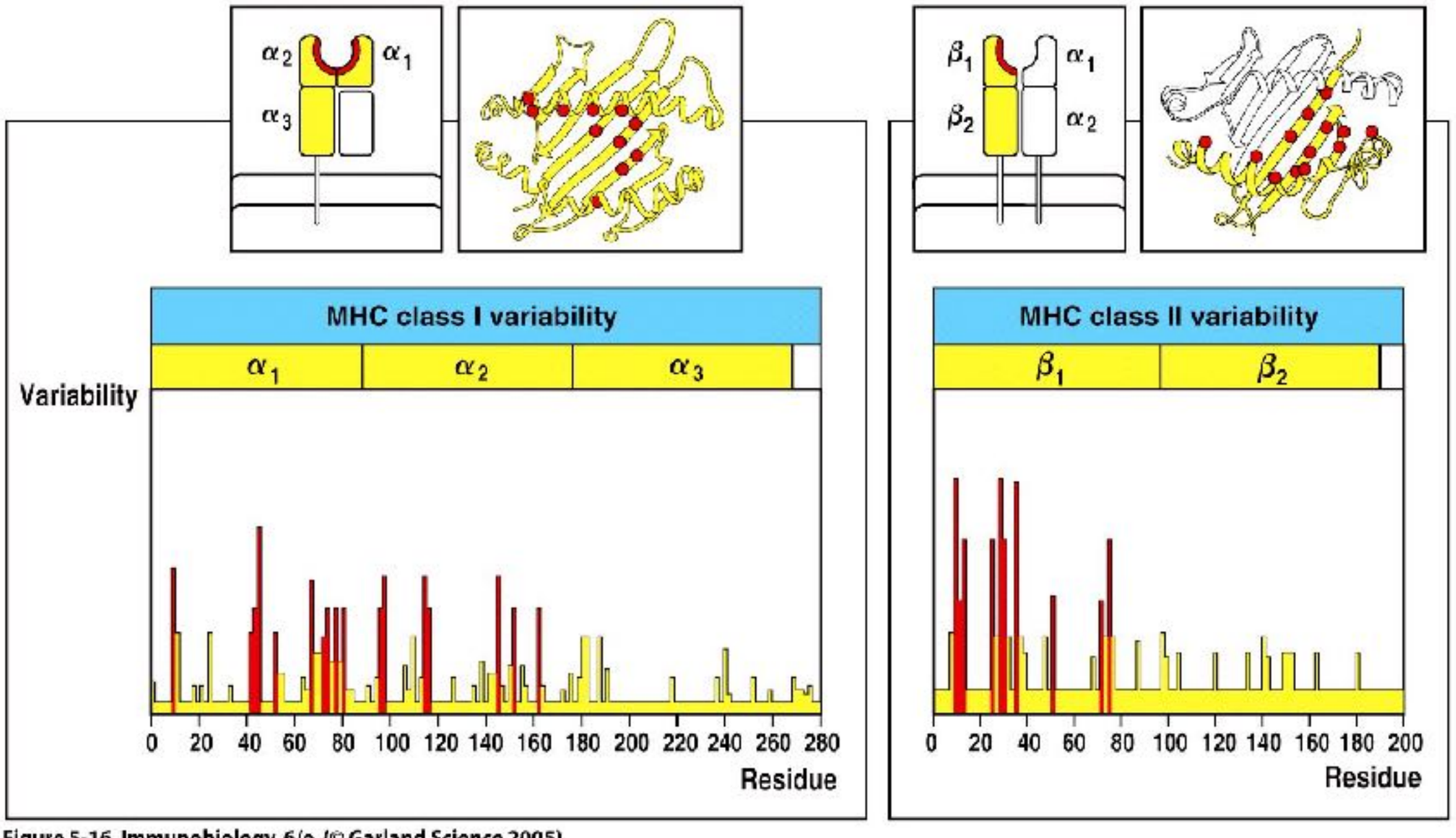


Figure 5-16 Immunobiology, 6/e. (© Garland Science 2005)

Variabilidade do MHC

- Genes MHC sao muito polimorficos e muitos alelos existem para cada gene
- Muito raro 2 individuos compartilhar os 2 sets de genes HLA (problemas transplante!)

TABLE 8-3 Genetic diversity of MHC loci in the human population

MHC CLASS I

HLA locus	Number of allotypes (proteins)
A	1448
B	1988
C	1119
E	3
F	4
G	16

MHC CLASS II

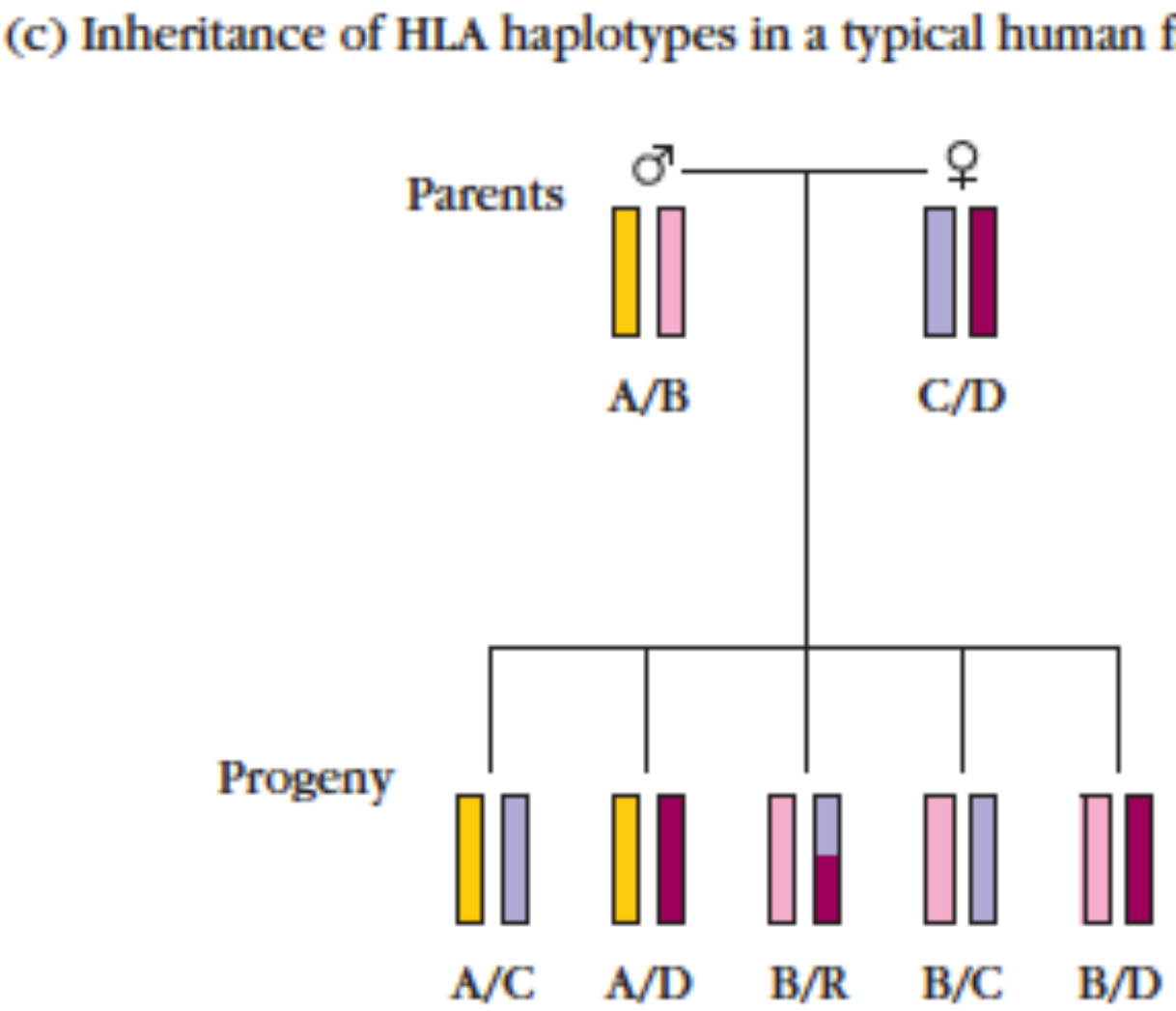
HLA locus	Number of allotypes (proteins)
DMA	4
DMB	7
DOA	3
DOB	5
DPA1	17
DPB1	134
DQA1	47
DQB1	126
DRA	2
DRB1	860
DRB3	46
DRB4	8
DRB5	17

Source: Data obtained from http://hla.alleles.org, a Web site maintained by the HLA Informatics Group based at the Anthony Nolan Trust in the United Kingdom, with up to date information on the numbers of HLA alleles and proteins.

DQ Serotype	DR-DQ haplotype	DR B1	DQ A1	DQ B1	Freq %[5]
DQ2	DR17-DQ2	0301	0501	0201	13.1
	DR7-DQ2	0701	0201	0202	11.1
DQ4	DR8-DQ4	0801	0401	0402	2.2
DQ5	DR1-DQ5	0101	0101	0501	9.1
		0102	0101	0501	1.4
		0103	0101	0501	0.5
	DR10-DQ5	1001	0104	0501	0.7
	DR16-DQ5	1601	0102	0502	1.0
	DR14-DQ5	1401	0104	0503	2.0
DQ6	DR15-DQ6	1502	0103	0601	0.7
		1501	0102	0602	14.2
	DR13-DQ6	1301	0103	0603	5.6
		1302	0102	0604	0.7
		1302	0102	0609	3.4
DQ7	DR11-DQ7	1101	0505	0301	5.6
		1104	0505	0301	2.7
	DR12-DQ7	1201	0505	0301	1.1
	DR13-DQ7	1303	0505	0301	0.7
	DR4-DQ7	0401	0303	0301	5.3
		0407	0303	0301	0.9
DQ8	DR4-DQ8	0402	0301	0302	1.0
		0404	0301	0302	4.2
		0401	0302	0302	0.7
DQ9	DR7-DQ9	0701	0201	0303	3.7
	DR9-DQ9	0901	0302	0303	0.8

Genetica do MHC

- Cada individuo è geralmente heterozigoto para cada locus (materno/paterno=
- Diferentes genes vizinhos (haplotipos; LD)
- Apesar da baixa taxa de recombinaçao, essa contribue pela diversidade dos loci



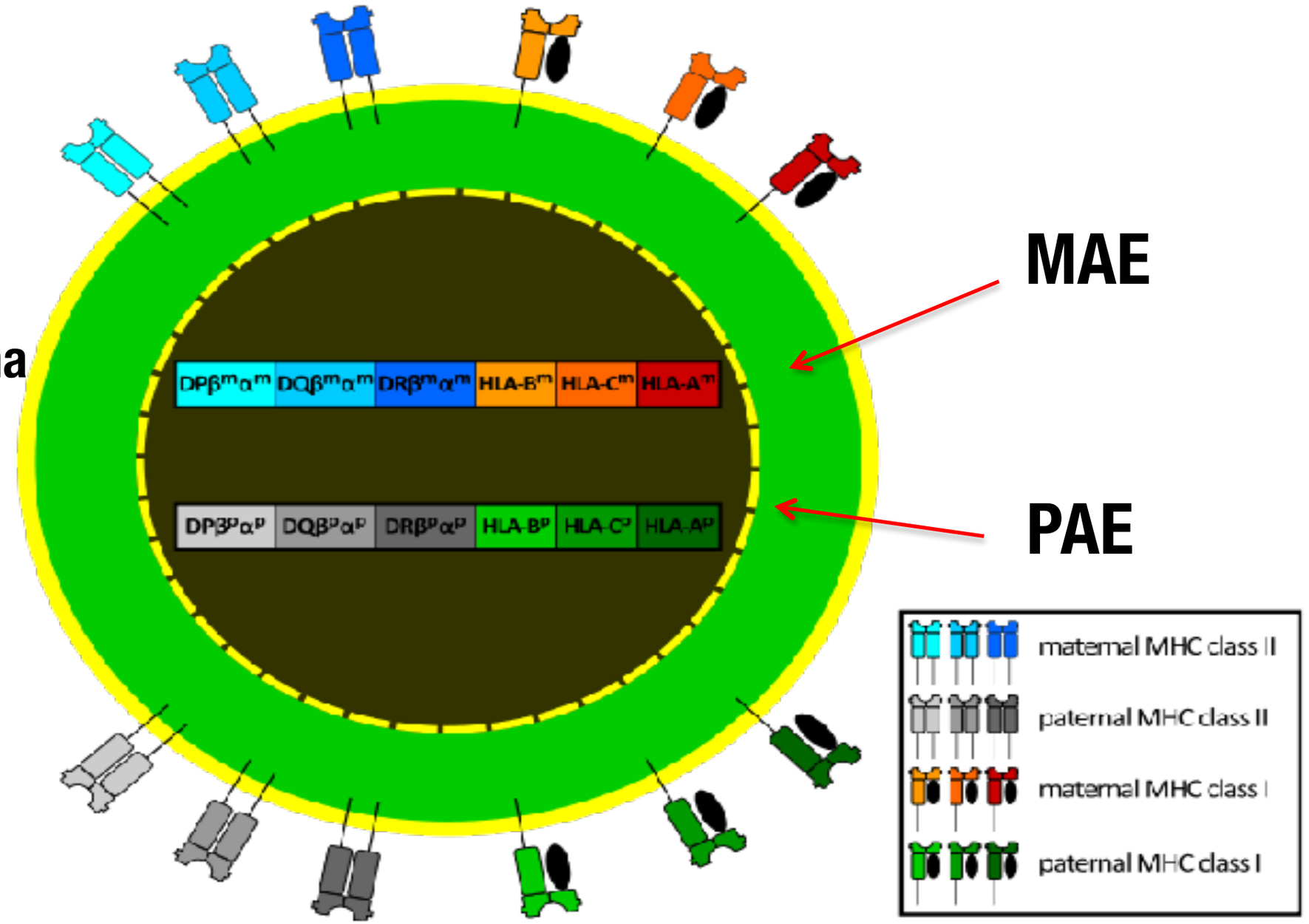
- *Genitor e filho compartilha apenas um haplotipo*
- *Ha uma chance de 25% que 2 irmaos herdem haplotipos compativeis de HLA*

Genetica do MHC

➢ Cada celula expressas diferentes genes MHC de modo co-dominante

Celula com HLA de origem materna e paterna

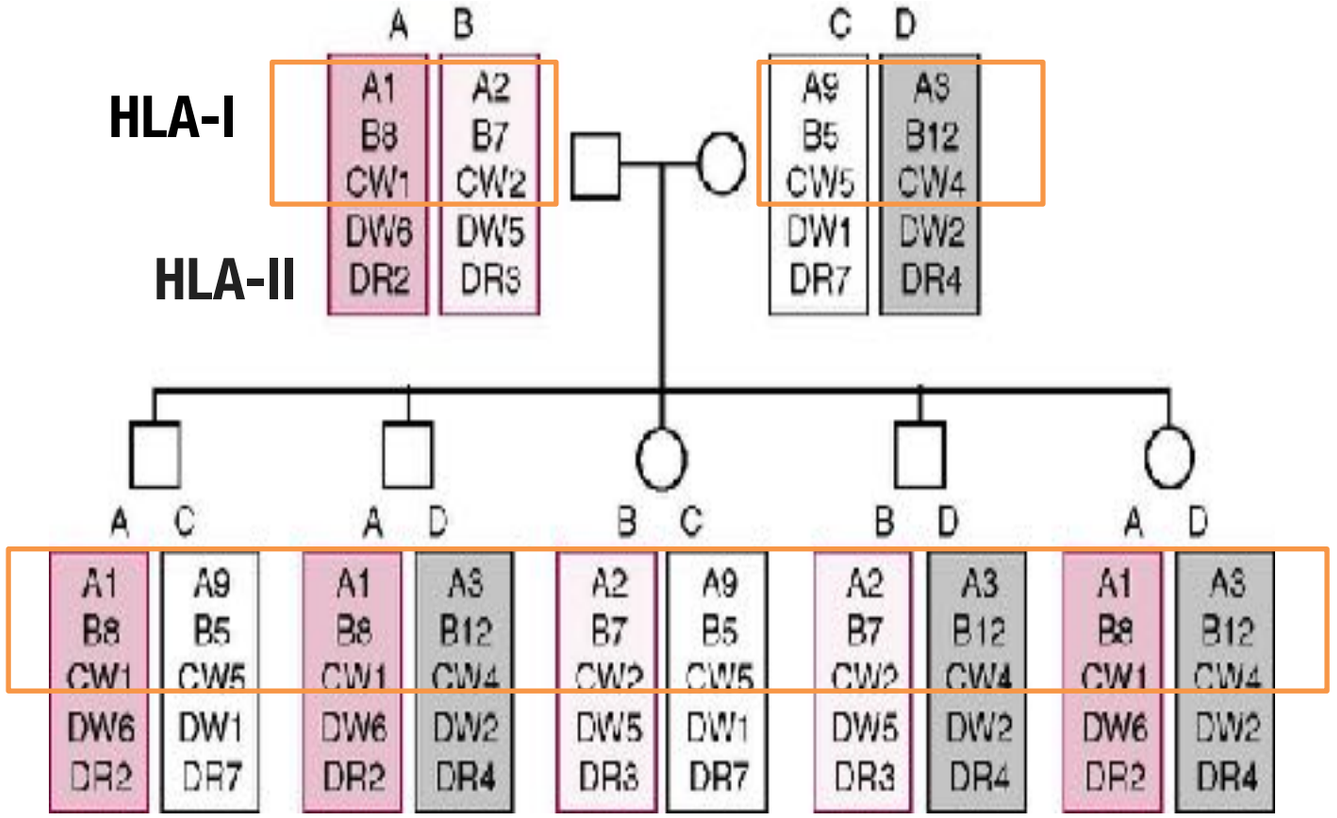
Para MHC-II combinaçao de cadeia α e ß de chr diferentes



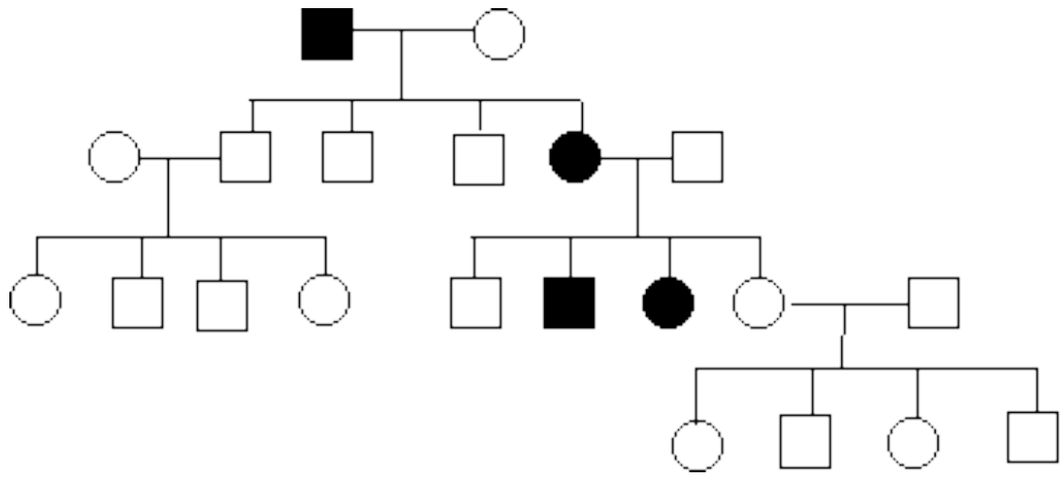
Genetica do MHC

muitos genes codominantes x polimorfismo alelico x possibilidade de recombinaçao

MUITA VARIABILIDADE



Herança de tipo mendeliano



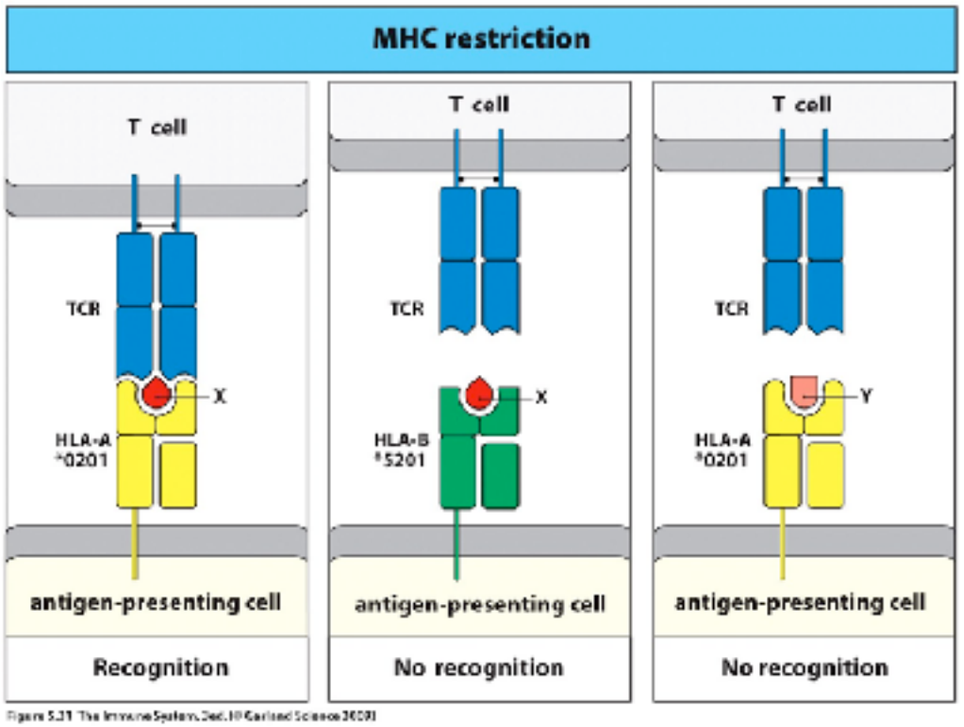
Genetica do MHC

- ◇ possibilidade de ter diferentes combinaçoes alelicas para apresentar de modo otimal um maior numero possivel de Ag aos varios linfocitos T → **Vantagem seletivo**

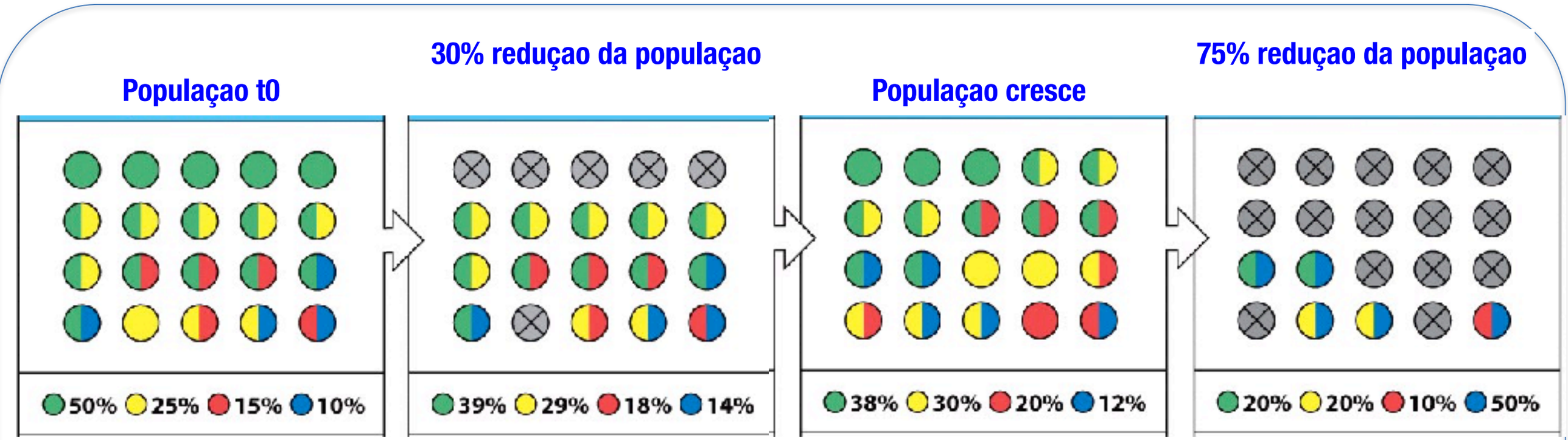
- ◇ A maioria dos alelos sao presentes com frequencia diferente nas populaçoes
- ◇ Isso indica que as mutaçoes nao sao “neutras” mas que aconteceu alguma “seleçao” favorecendo alguns alelo

HLA-A*0201 representa:

- 95% dos alelos A2 na popolaçao caucasiana
- 25% dos alelos A2 na populaçao chinesa Han
- 3% dos alelos A2 populaçao indiana



Genetica do MHC



→ Epidemias sucessivas
Seleçao forte a favor dos HZ

Epoca de paz e prosperidade
Medicina eficaz

→ Epidemia de novos patogenos
Apenas individuos com blue MHC sobrevivem
→ forte seleçao

Os 4 haplotipos sao presentes na populaçao sobrevivente

MHC

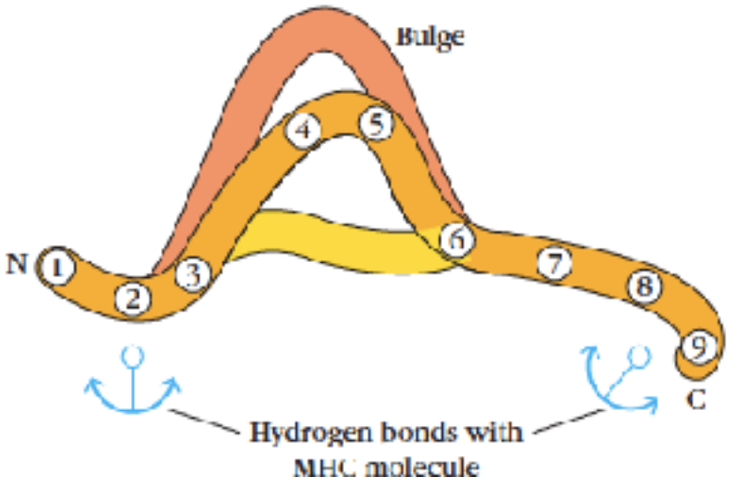
Several hundred different allelic variants of class I and II MHC molecules

Any one individual express only a small number of these molecules
- up to 6 different class I molecules
- 12 or more different class II molecules

Such a limited number of molecules for an enormous array of antigen peptides

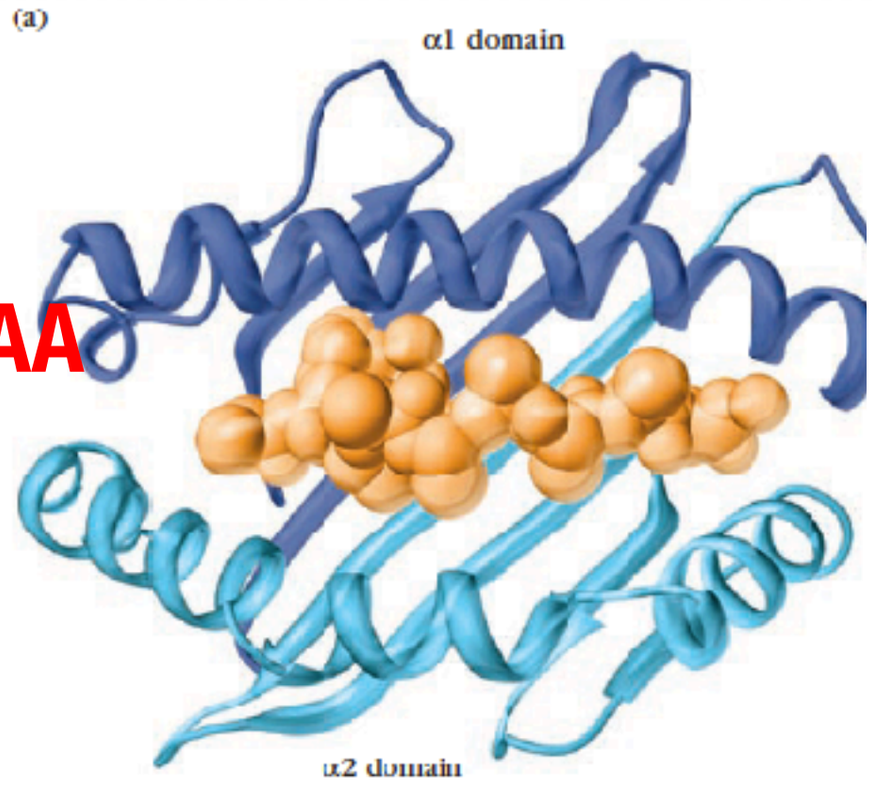
The peptide binding of MHC-I and -II molecules does not exhibits the specificity characteristic of antigen-binding by antibodies and TCR

A given MHC molecule can bind numerous different peptides, and some peptides can bind to several different MHC (promiscuous binding)

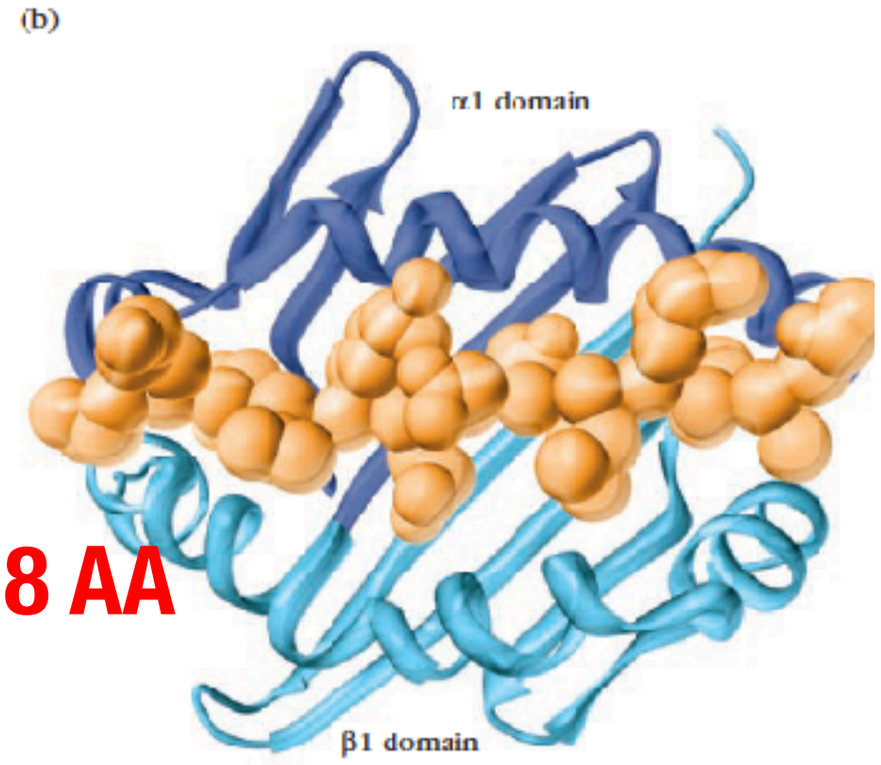


MHC

8-10 AA



13-18 AA

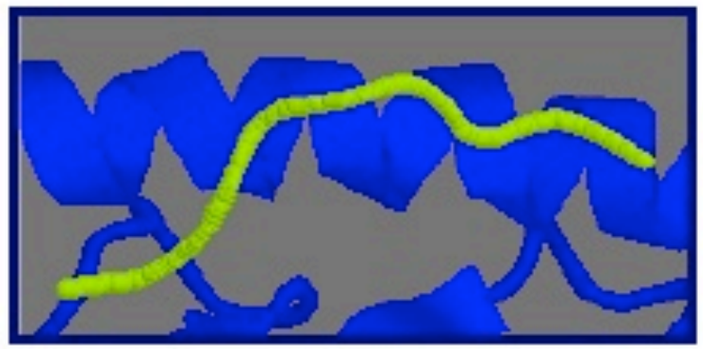


Residuos ancora

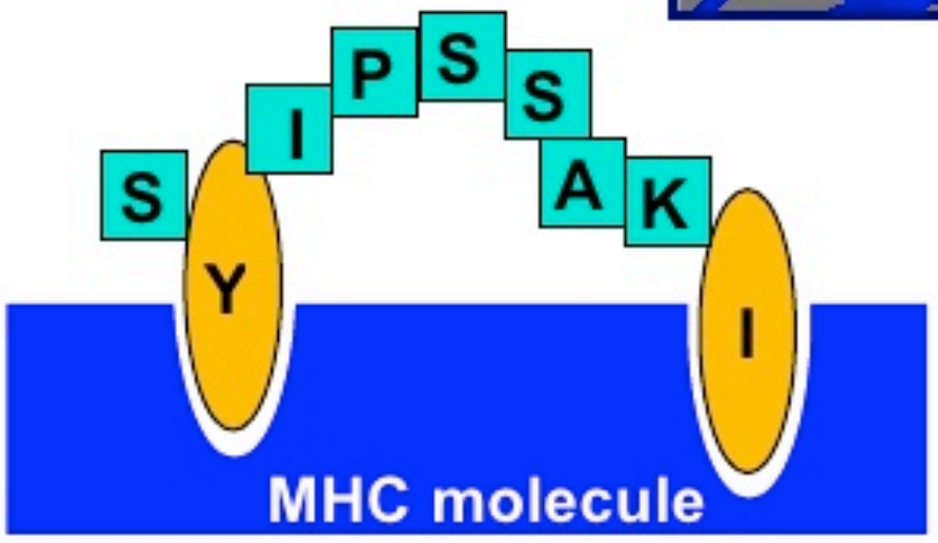
A = alanine	K = lysine	R = arginine
E = glutamic acid	L = leucine	S = serine
F = phenylalanine	N = asparagine	T = threonine
G = glycine	P = proline	V = valine
H = histidine	Q = glutamine	Y = tyrosine
I = isoleucine		

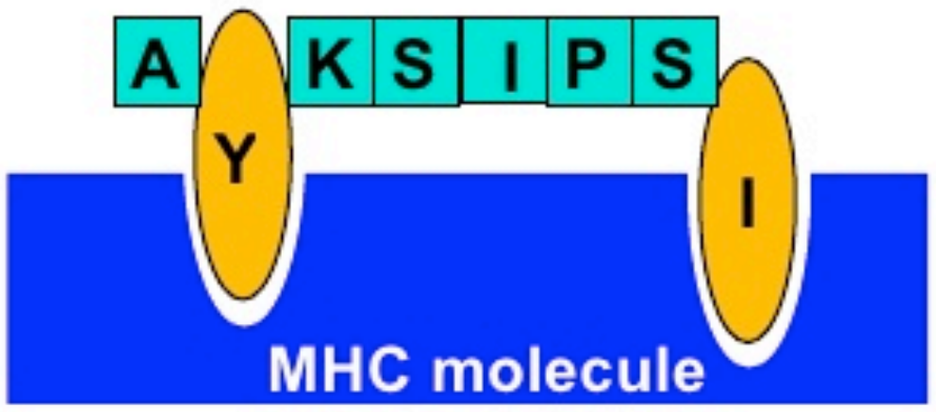
MHC

MHC molecules can bind peptides of different length



Arched peptide



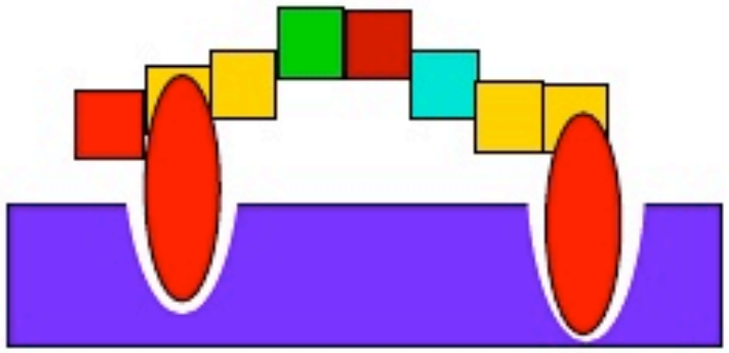


Complementary anchor residues & pockets provide the broad specificity of a particular type of MHC molecule for peptides

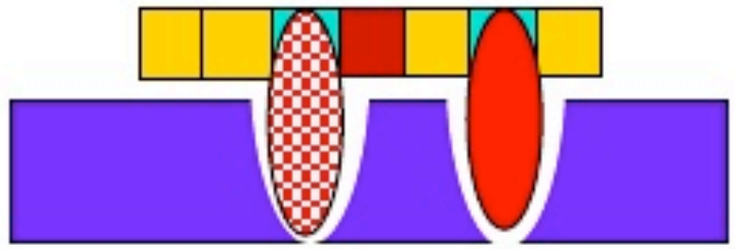
Peptide sequence between anchors can vary
Number of amino acids between anchors can vary

MHC

Polymorphism in the MHC affects peptide antigen binding



MHC allele A



MHC allele B

Changes in the pockets, walls and floor of the peptide binding cleft alter peptide MHC interactions and determine which peptides bind.

MHC allele A

MHC allele B

Products of different MHC alleles bind a different repertoire of peptides