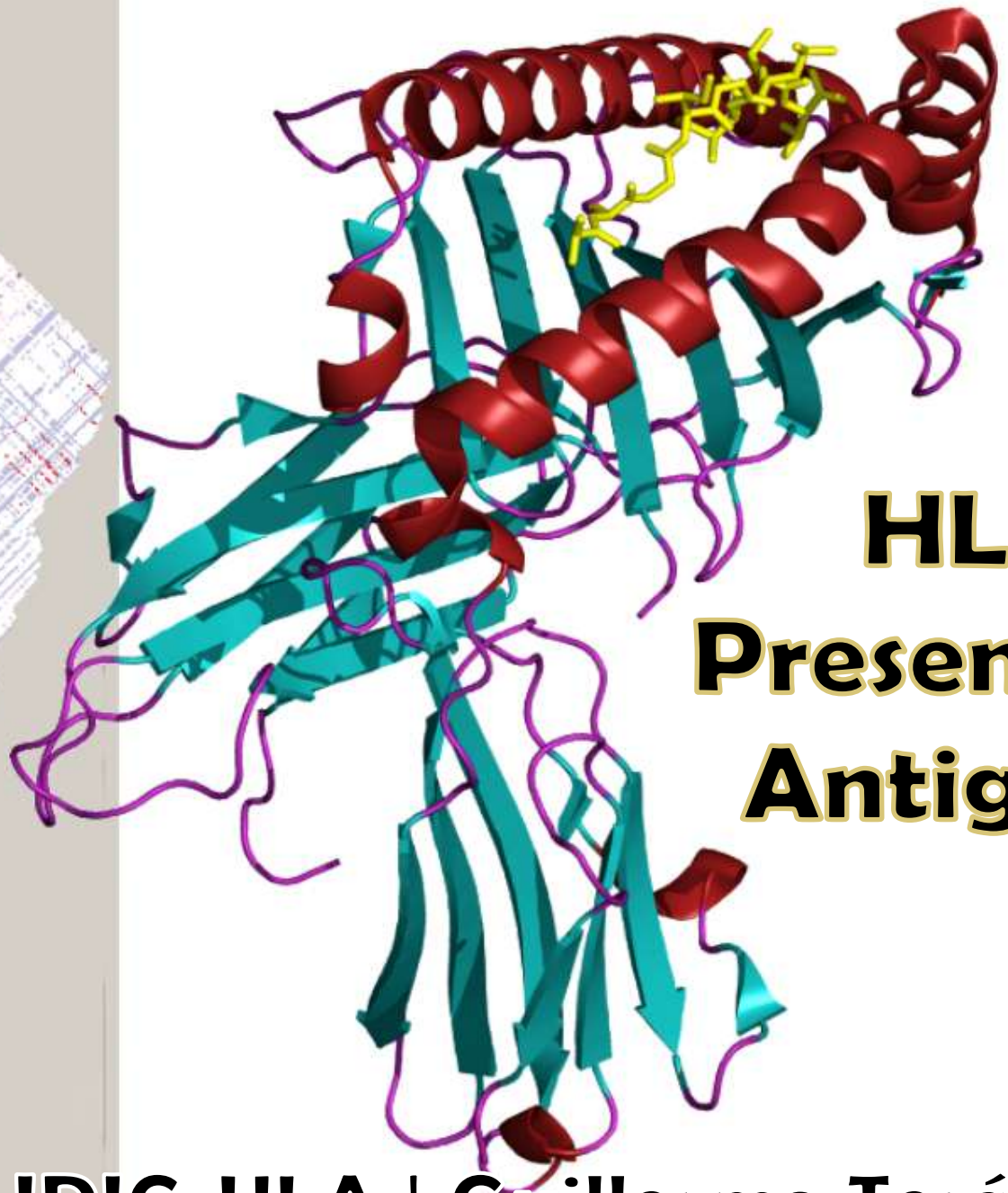


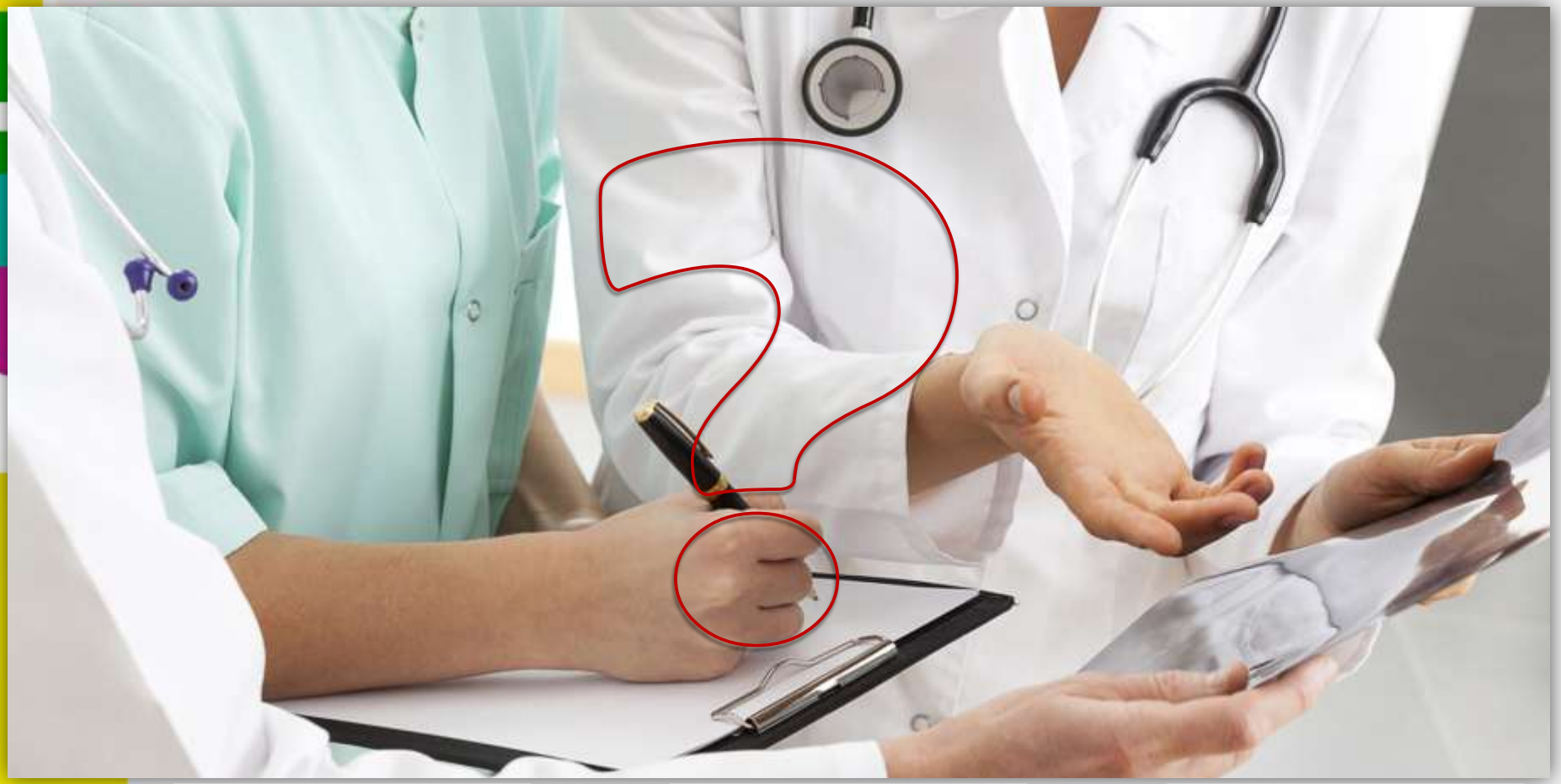
HLA y Presentación Antigénica

IDIC-ULA | Guillermo Terán-Angel

Temario


HLA
Complejo mayor de histocompatibilidad
Moléculas
Inmunogenetica
Aspectos genéticos
Papel en la respuesta inmune
Mecanismos de presentación antigénica
Bioquímica
Funciones biológicas
Estructura

Interconsulta



Paciente:

HLA- A*0201
B*0702
Cw*0401
DRB1*0101
DQB1*0501

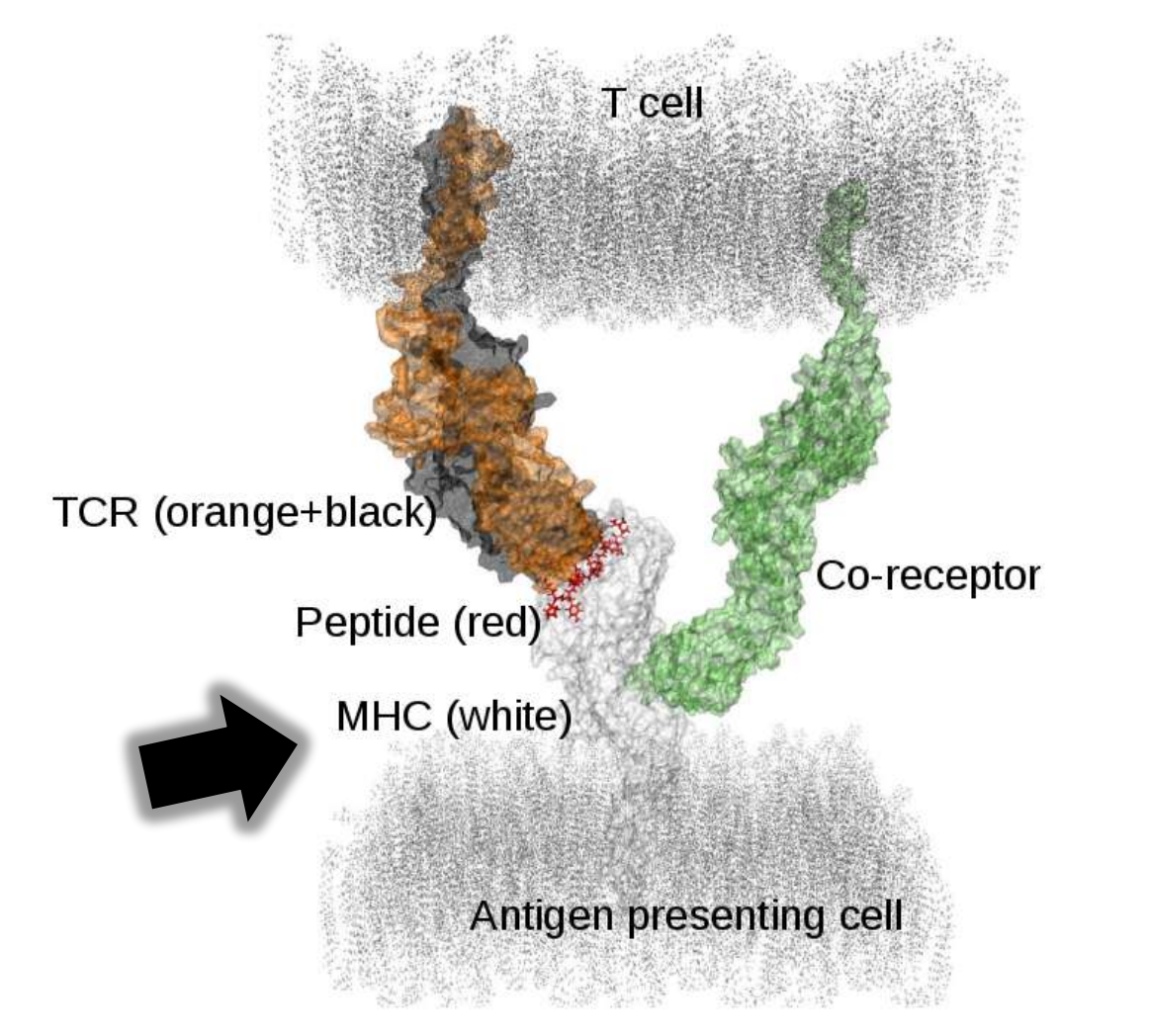
Donante 1:

HLA- A*0202
B*0702
Cw*0401
DRB1*0104
DQB1*1206

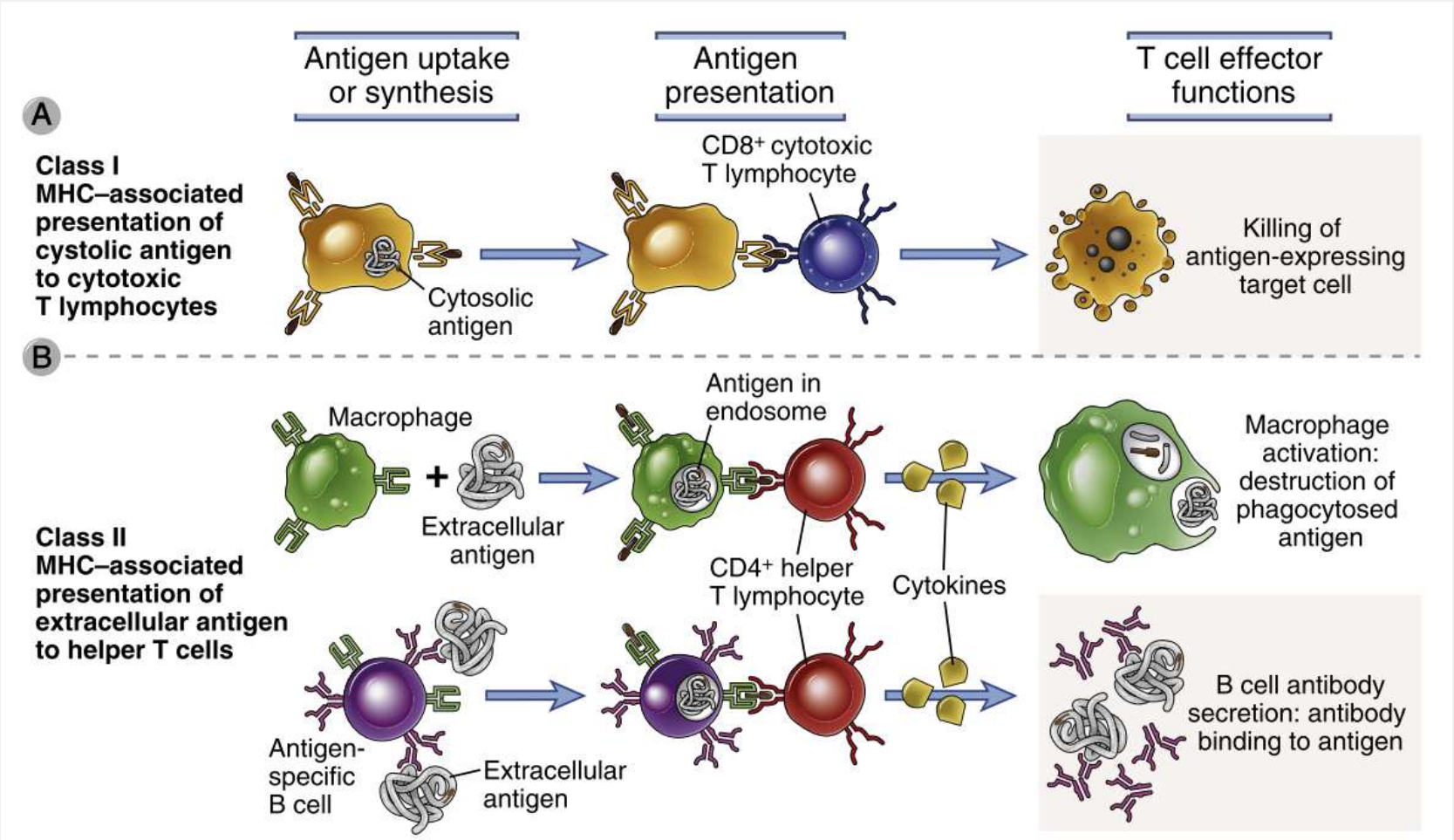
Donante 2:

HLA- A*0201
B*1602
Cw*0401
DRB1*0101
DQB1*0501

La piedra angular



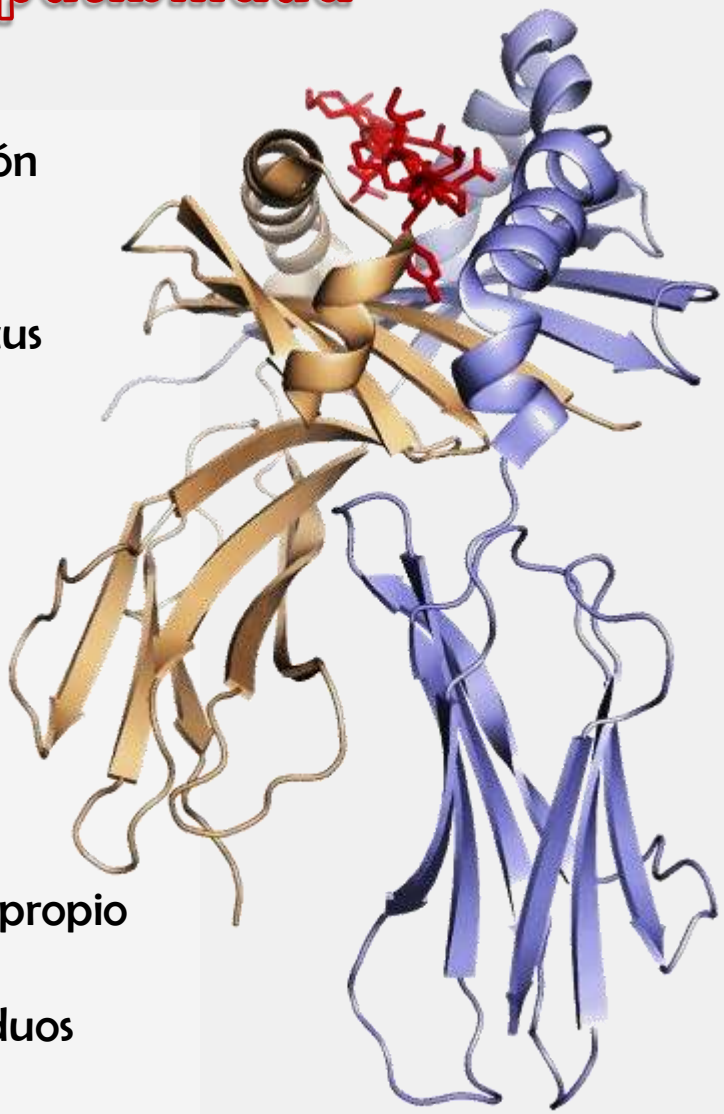
Ubicándonos



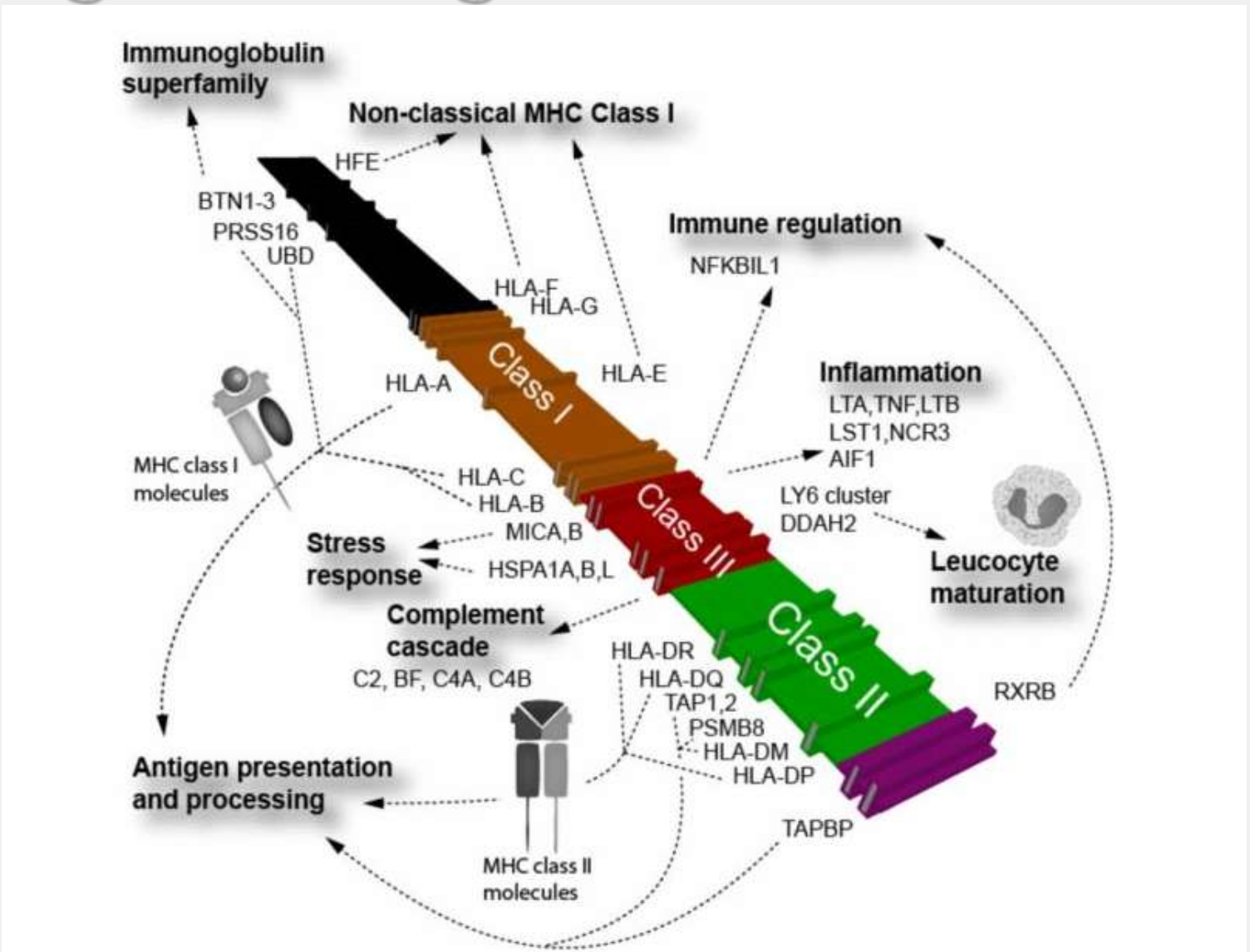
Comencemos por el HLA

Complejo mayor de histocompatibilidad

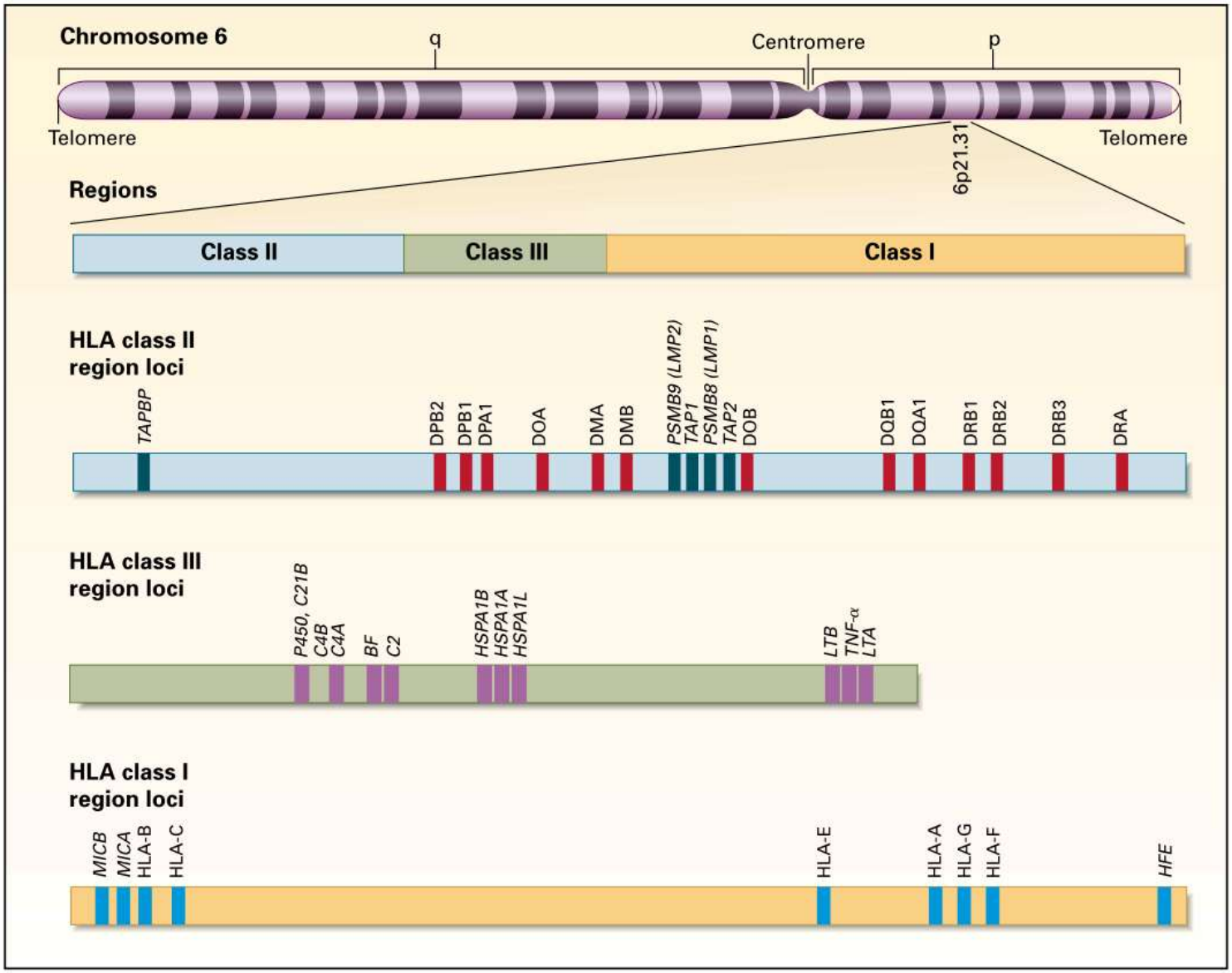
- Proteínas especializadas en la presentación antigénica
- Codificadas por genes presentes en un locus denominado complejo principal de histocompatibilidad (CPH)
- Genes altamente polimórficos
- Participan en:
  - ✓ Reconocimiento intercelular
  - ✓ Discriminación de lo propio y no propio
  - ✓ Trasplante de tejido entre individuos
  - ✓ Presentación de péptidos a los linfocitos T



El mega combo genético



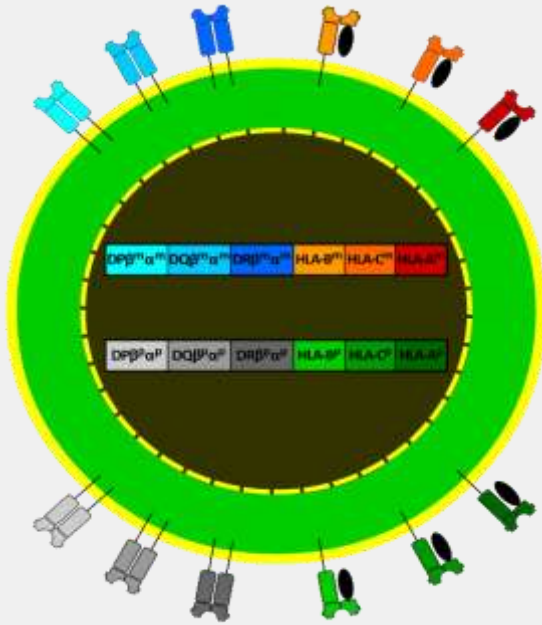
Estructura génica

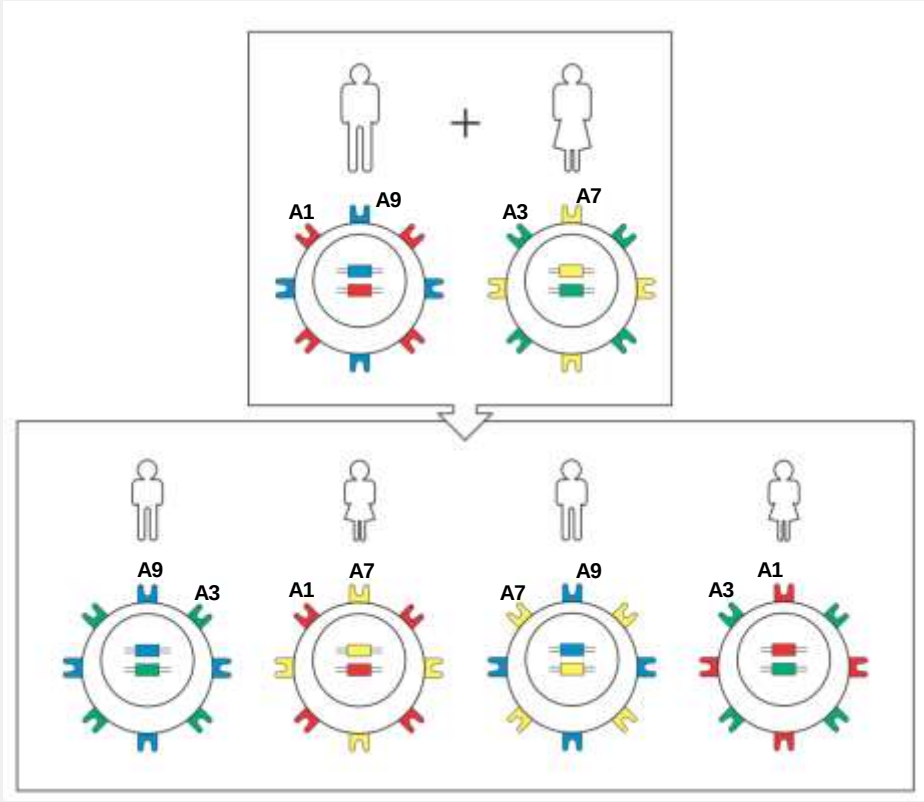


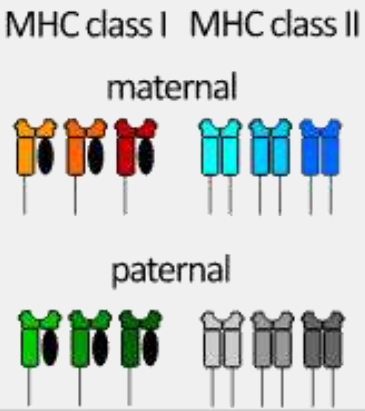
N Engl J Med 2000; 343:702-709

Herencia

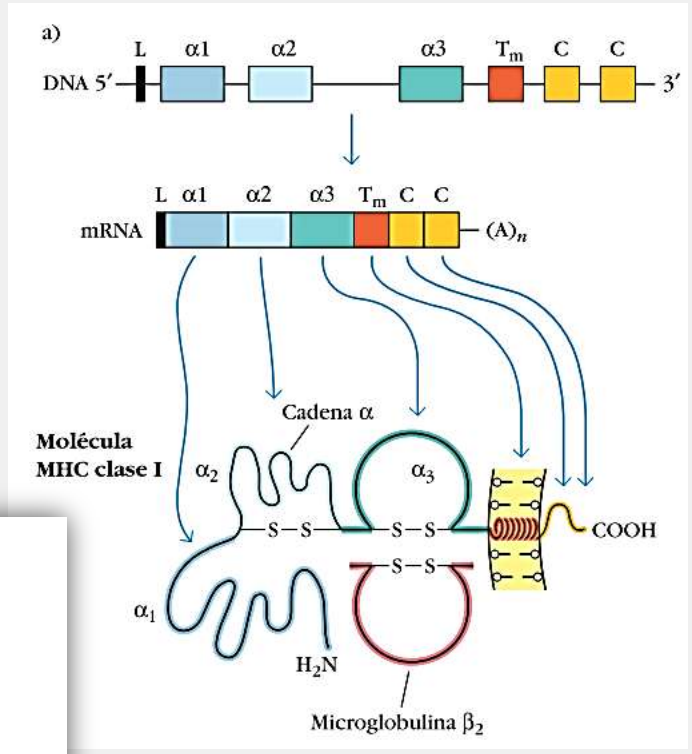
Codominancia

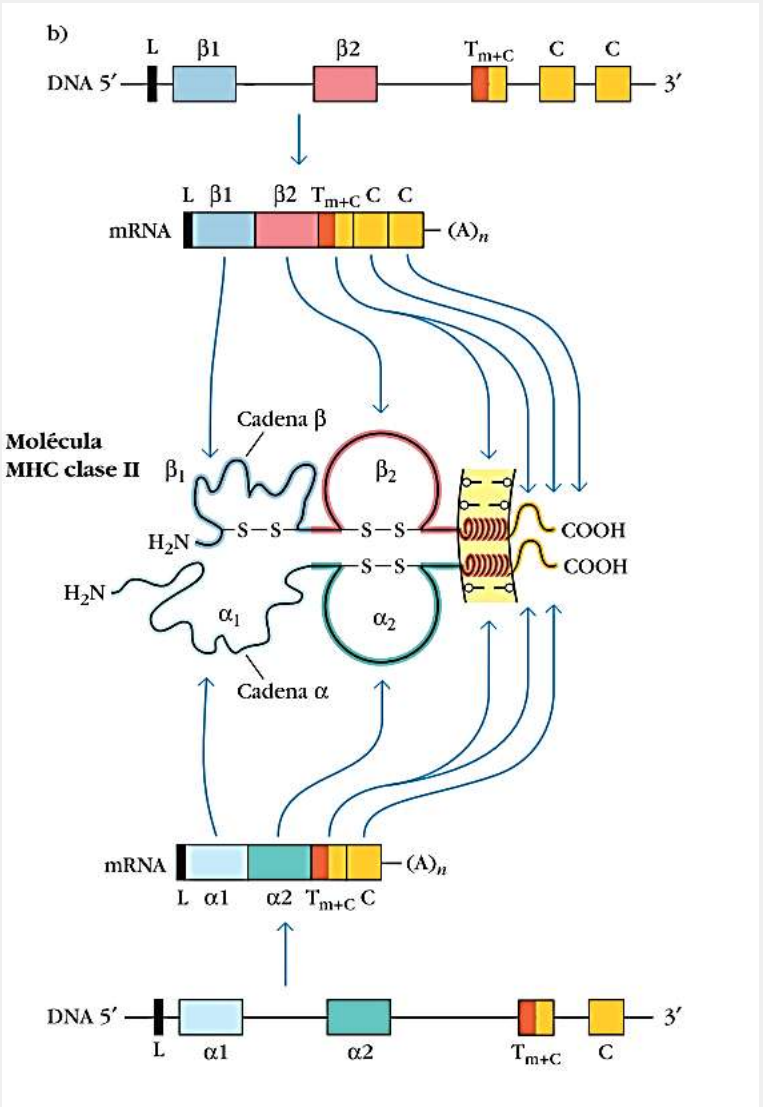


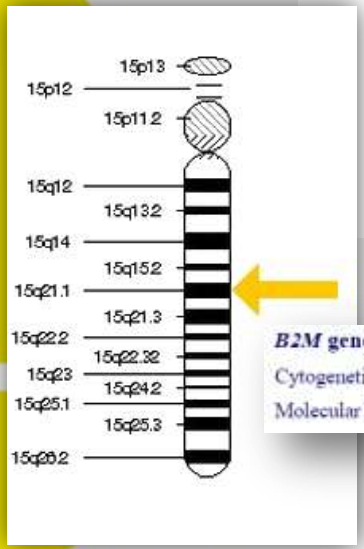




Expresión génica





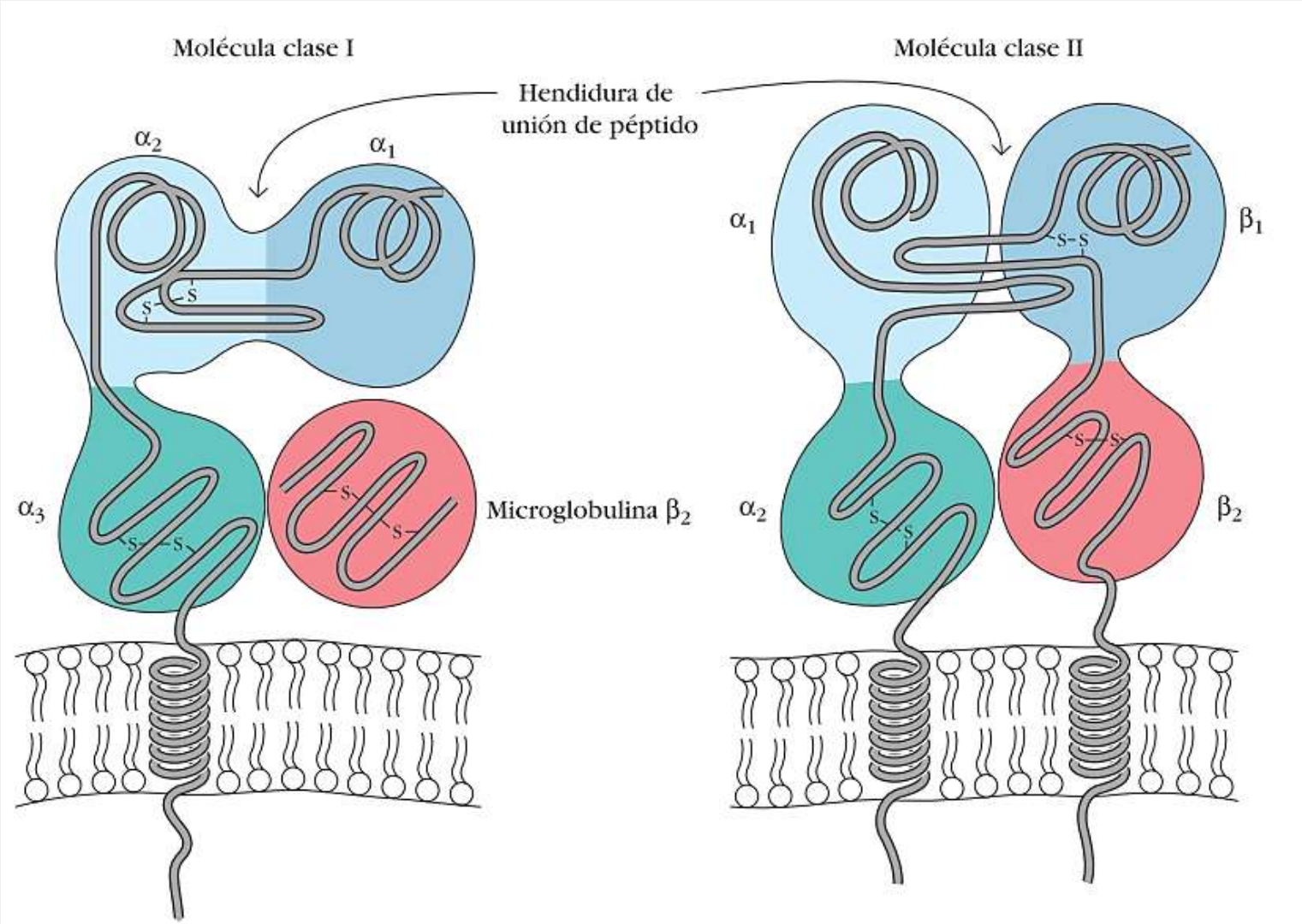


***B2M* gene**

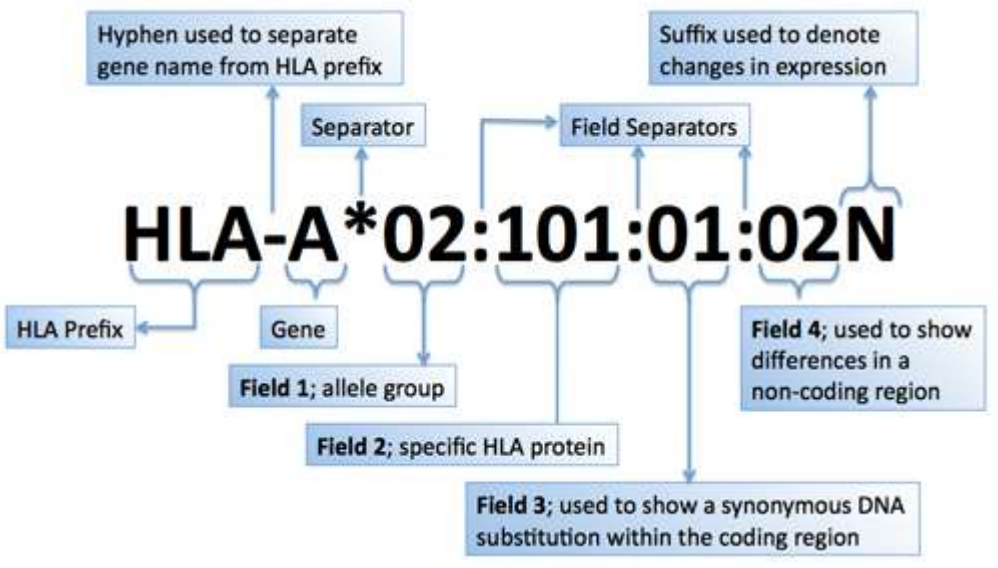
Cytogenetic Location: 15q21.1

Molecular Location on chromosome 15: base pairs 44,711,486 to 44,718,158

Entendamos las moléculas

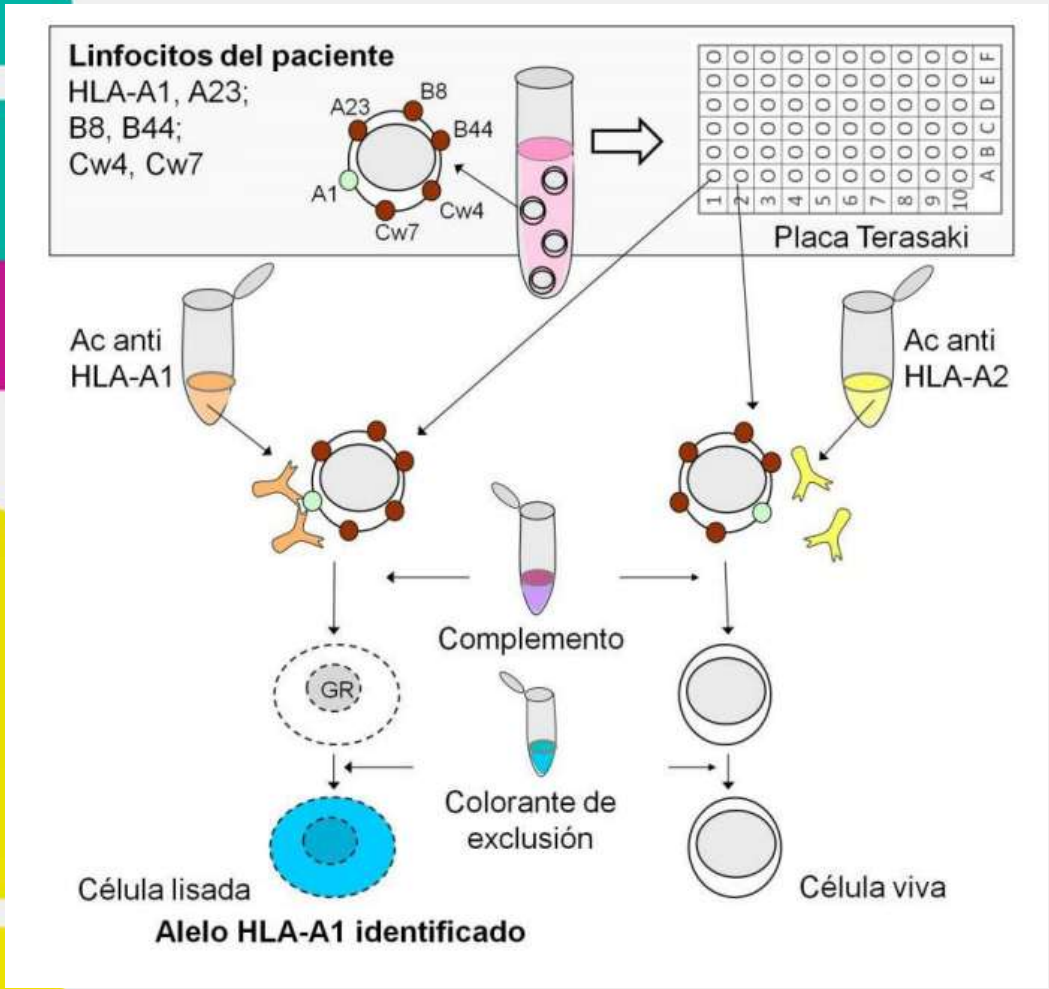


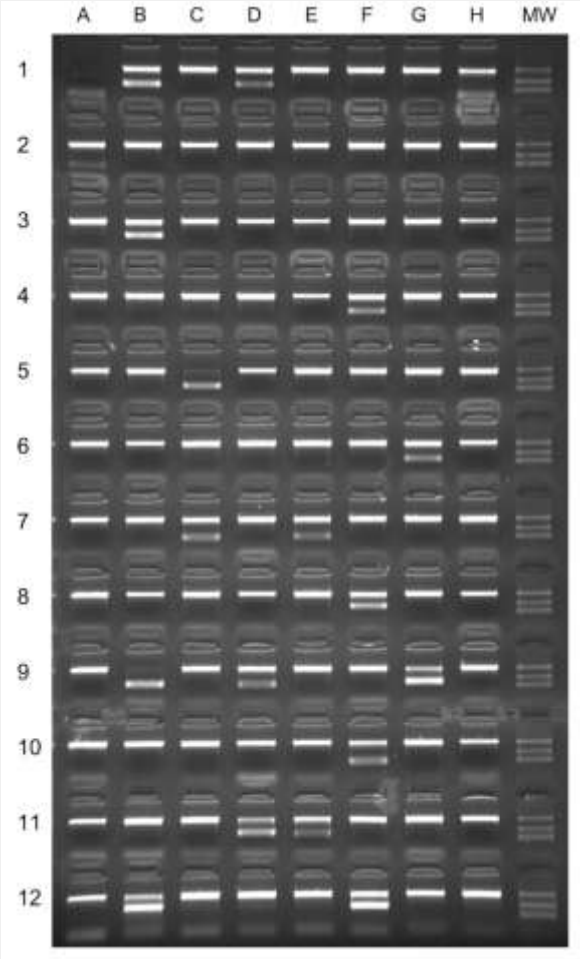
Nomenclatura



Letter	Significance
N	Null allele (produces a non-functional protein)
L	Lower than normal cell surface expression
S	Soluble protein not found on cell surface
Q	Questionable (allele may affect normal expression)
C	Protein that is present in cytoplasm but not cell surface
A	Aberrant expression (uncertain if protein is expressed)

Tipificación

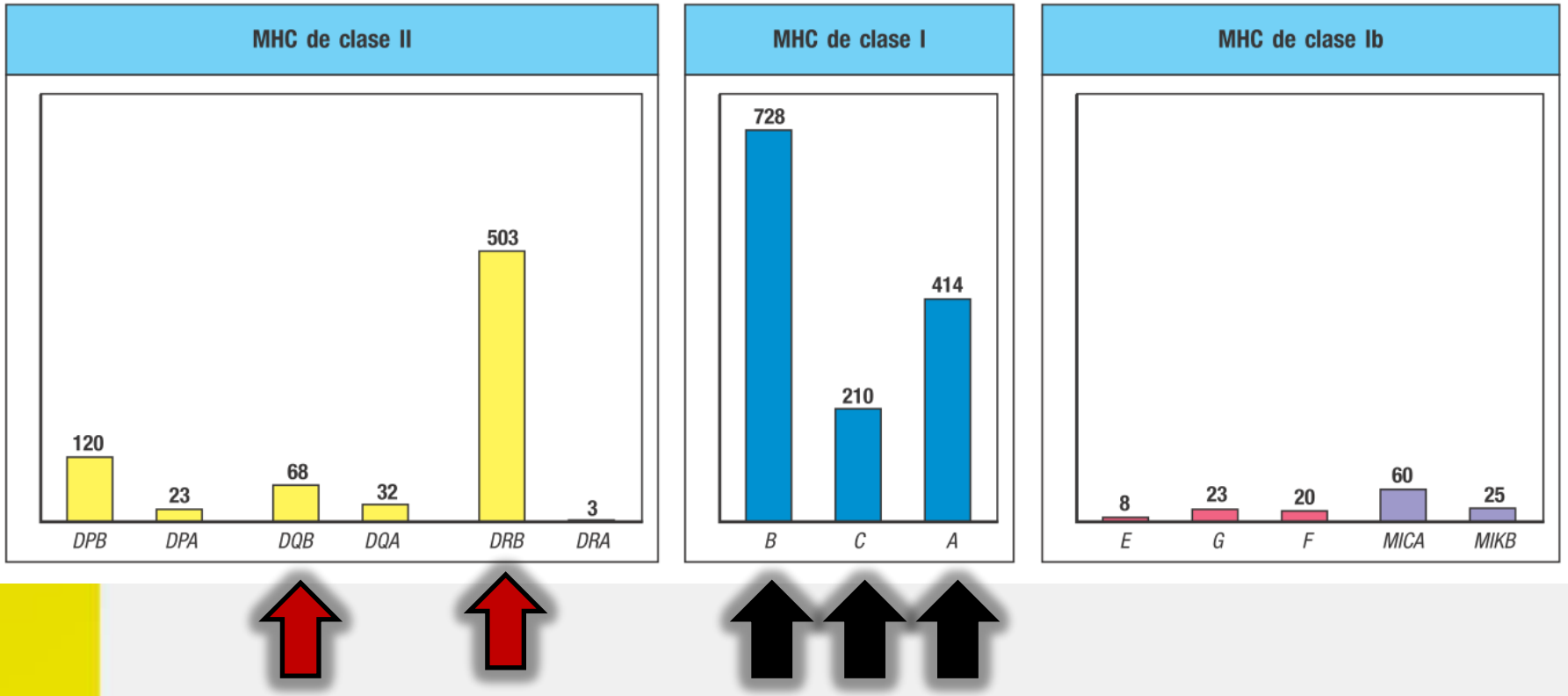




Prueba de microlinfocitotoxicidad
Prueba de Terasaki

PCR-SSP

Variabilidad

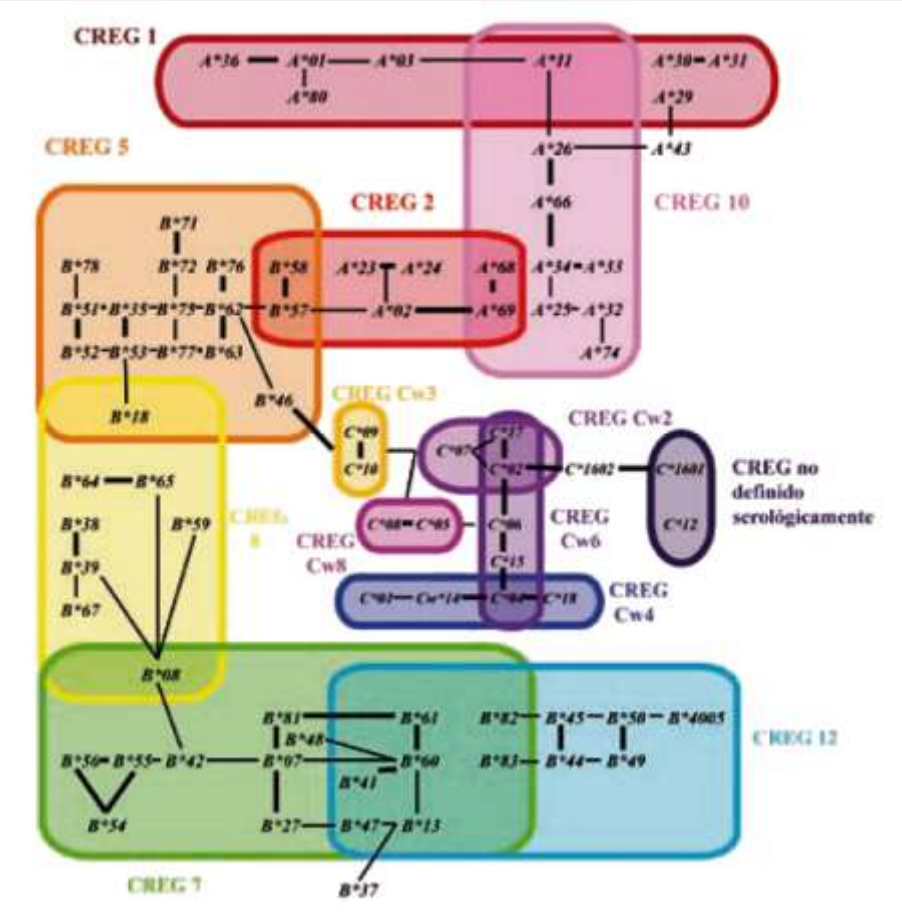


- Una incompatibilidad menor en HLA-A y -B se define como 2 antígenos que pertenecen al mismo CREG.
- Una incompatibilidad menor en DR se define como un par de alelos DRB1 que codifican la misma especificidad DR serológica, por ejemplo DRB1*0401 vs. DRB1*0404.
- Hoy en día se acepta que la compatibilidad para los alelos DRB1 y DQB1 tiene una relevancia significativa en el riesgo de desarrollar un GVHD.

Blood. 2015 Feb 12;125(7):1058-9. BLOOD, 12 FEBRUARY 2015 x VOLUME 125, NUMBER 7 1189

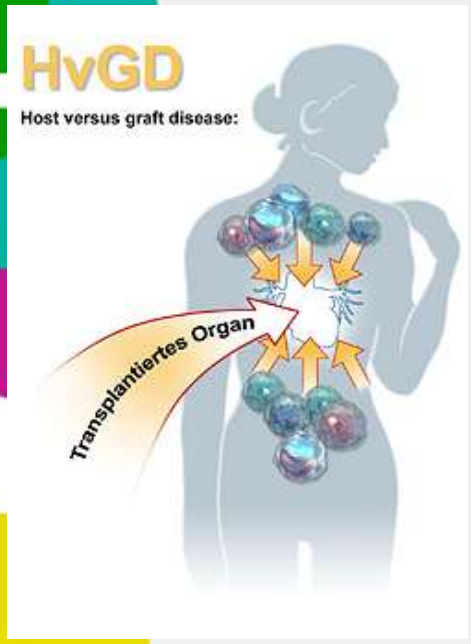
CREGs

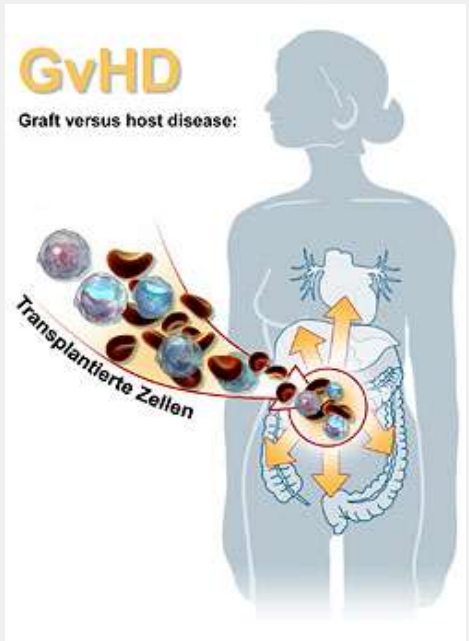
CREG*	CREG present†		CREG match status‡
	Donor	Recipient	
1C	+	+	Match
10C	−	+	Major mismatch
2C	+	+	Match
5C	+	+	Match
7C	+	+	Match
8C	+	+	Match
12C	−	−	Match
Bw4	+	−	Major mismatch
Bw6	+	+	Match

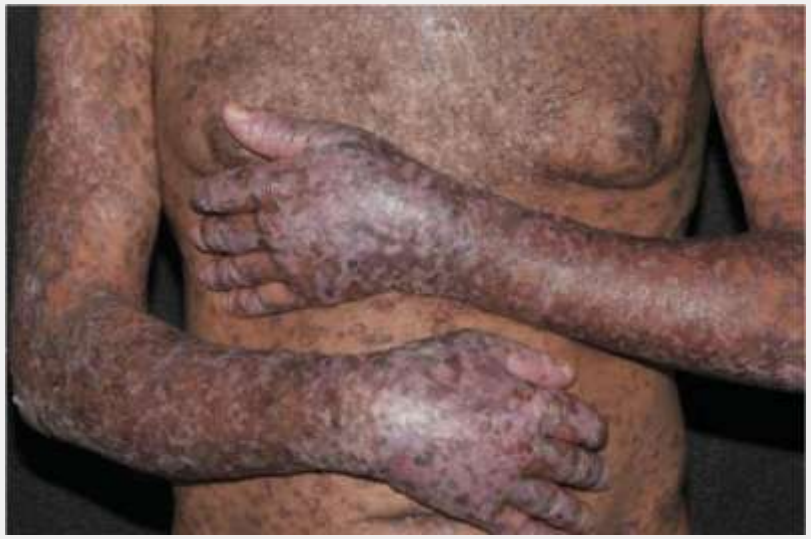


BLOOD, 1 MAY 2007 ▯ VOLUME 109, NUMBER 9

GVHD

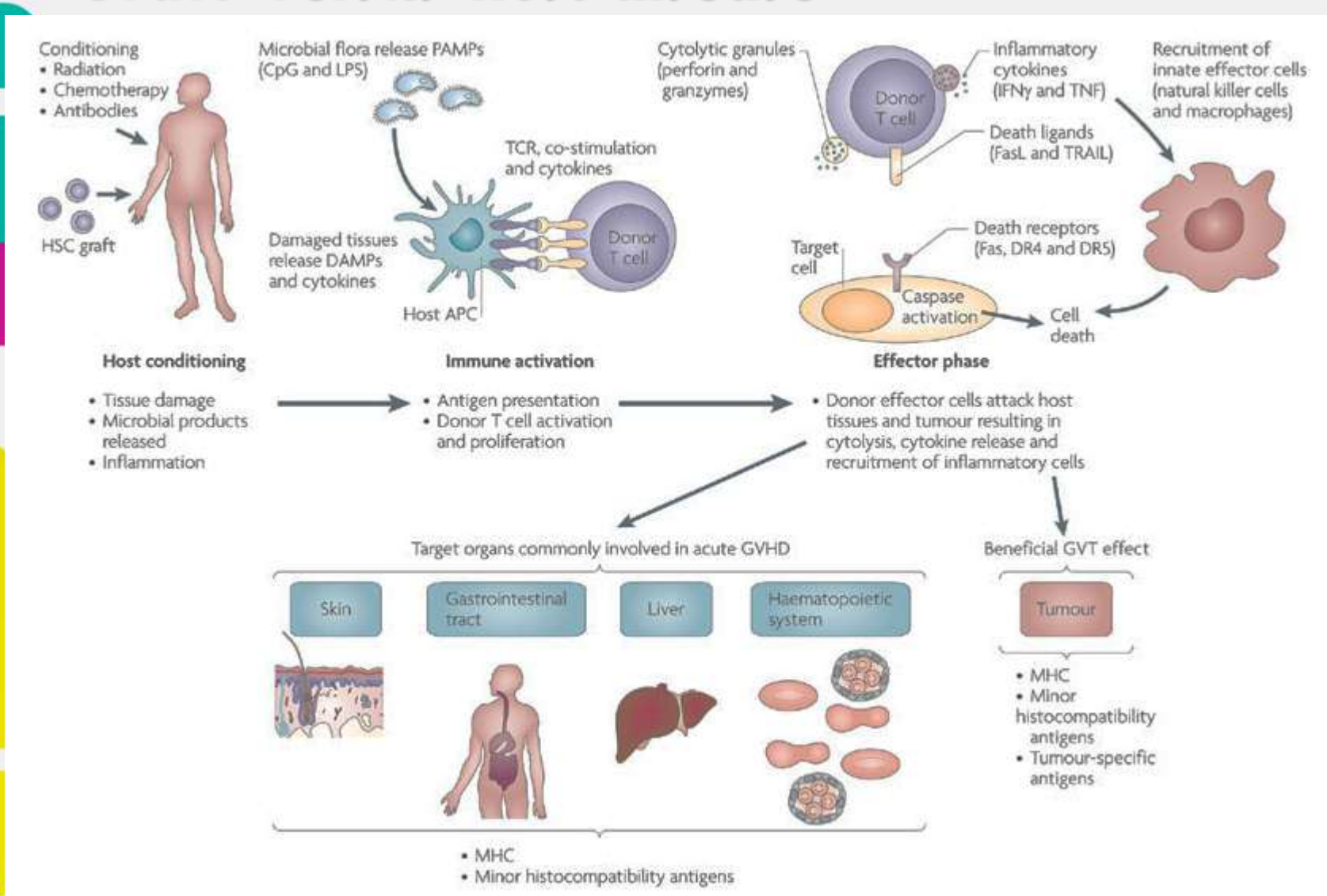






- La piel es el blanco mas frecuente, seguido por la mucosa oral, higado, ojo y tracto GI, no obstante, todos los organos puedes ser afectados

Graft-versus-host disease



Nature Reviews Cancer 10, 213-221 (March 2010)

Graft-versus-host disease

HLA	Match or mismatch*	N	Acute GVHD (Grade III-IV)† RR	95% CI	P	Acute GVHD (Grade II-IV)† RR	95% CI	P	N	Chronic GVHD‡ RR	95% CI	P
A	Match	7048	1.00		.001	1.00		.002	5892	1.00		.328
	Mismatch		1.29	1.10-1.51		1.18	1.06-1.32		636	1.06	0.94-1.21	
B	Match	7475	1.00		.001	1.00		.001	6217	1.00		.235
	Mismatch		1.42	1.16-1.73		1.28	1.11-1.48		311	1.10	0.94-1.30	
C	Match	5365	1.00		<.001	1.00		<.001	4716	1.00		<.001
	Mismatch		1.63	1.45-1.83		1.27	1.17-1.37			1.24	1.13-1.35	
DRB1	Match	5878	1.00		.022	1.00		<.001	4936	1.00		.262
	Mismatch		1.21	1.03-1.43		1.24	1.11-1.39		1592	0.93	0.82-1.05	
DQB1	Match	5681	1.00		.336	1.00		.126	4758	1.00		.018
	Mismatch	2217	1.08	0.92-1.27		1.09	0.98-1.22		1770	1.15	1.03-1.30	
DPB1	Match	2604	1.00		.001	1.00		<.001	2223	1.00		.367
	Mismatch	5294	1.23	1.09-1.38		1.36	1.26-1.47		4305	1.04	0.96-1.12	

HLA matching*	N	Acute GVHD (Grade III-IV)† RR	95% CI	P	Acute GVHD (Grade II-IV)† RR	95% CI	P	Mortality† RR	95% CI	P
DRB1 match and DQB1 match	5356	1.00			1.00			1.00		
DRB1 mismatch and DQB1 match	325	0.98	0.74-1.28	.866	1.19	1.00-1.42	.046	1.04	0.88-1.22	.662
DRB1 match and DQB1 mismatch	522	0.92	0.73-1.16	.482	1.05	0.91-1.21	.517	1.04	0.92-1.19	.532
DRB1 mismatch and DQB1 mismatch	169	1.32	1.16-1.50	<.001	1.34	1.23-1.46	<.001	1.17	1.08-1.27	<.001

BLOOD, 12 FEBRUARY 2015 x VOLUME 125, NUMBER 7

Inmunogenética

TABLE 7-4 Some significant associations of HLA alleles with increased risk for various diseases

Disease	Associated HLA allele	Relative risk*
Ankylosing spondylitis	*B27*	90
Goodpasture's syndrome	*DR2*	16
Gluten-sensitive enteropathy	*DR3*	12
Hereditary hemochromatosis	*A3*	9.3
	B14	2.3
	A3/B14	90
Insulin-dependent diabetes mellitus	*DR4/DR3*	20
Multiple sclerosis	*DR2*	5
Myasthenia gravis	*DR3*	10
Narcolepsy	*DR2*	130
Reactive arthritis (*Yersinia, Salmonella, Gonococcus*)	*B27*	18
Reiter's syndrome	*B27*	37
Rheumatoid arthritis	*DR4*	10
Sjogren's syndrome	*Dw3*	6
Systemic lupus erythematosus	*DR3*	5

*Relative risk is calculated by dividing the frequency of the HLA allele in the patient population by the frequency in the general population:

$$RR = \frac{(Ag^{+}/Ag^{-})\ \text{disease}}{(Ag^{+}/Ag^{-})\ \text{control}}$$

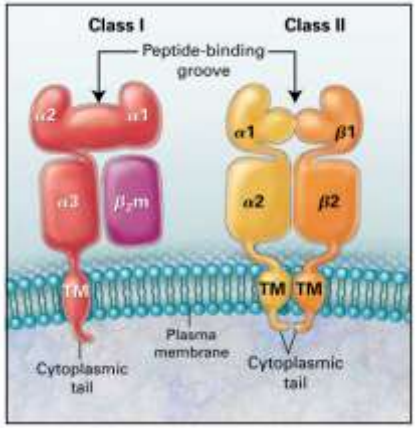
SOURCE: Data from *SAM CD: A Comprehensive Knowledge Base of Internal Medicine*, D. C. Dale and D. D. Federman, eds., 1997, Scientific American, New York.

Mi opinión

- Debe establecerse una relación de la presencia del marcador con una modificación funcional que condicione o favorezca la enfermedad
- El hallazgo *per se* no significa mayor cosa


Veamos las moléculas

Características



CUADRO 8-2 Unión de péptidos por moléculas MHC clase I y clase II

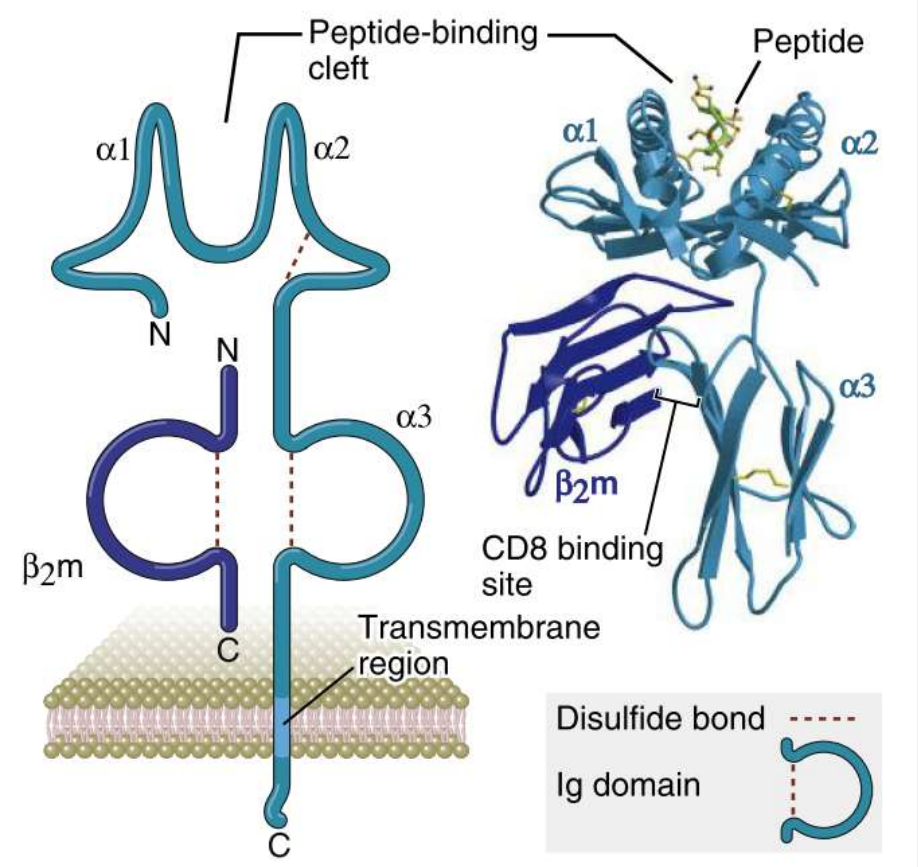
	Moléculas clase I	Moléculas clase II
Dominio de unión de péptido	α1/α2	α1/β1
Naturaleza de la hendidura de unión de péptido	Cerrada en ambos extremos	Abierta en ambos extremos
Tamaño general de los péptidos unidos	8 a 10 aminoácidos	13 a 18 aminoácidos
Elementos peptídicos que participan en la unión a la molécula MHC	Residuos de fijación en ambos extremos del péptido; por lo general ancla hidrófoba en el extremo carboxilo terminal	Residuos de fijación distribuidos a todo lo largo del péptido
Naturaleza del péptido unido	Estructura extendida en la que ambos extremos interactúan con la hendidura de MHC pero la parte media se arquea alejándose de la molécula MHC	Estructura extendida que se mantiene a una elevación constante arriba del piso de la hendidura del MHC

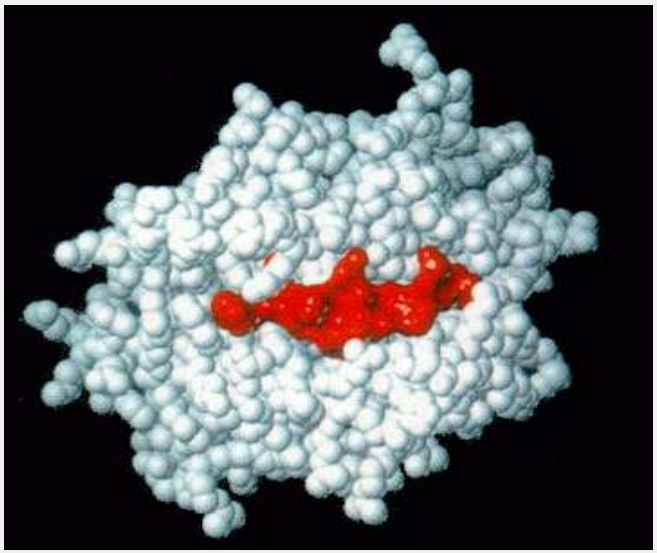
TABLE 6-4 Features of Class I and Class II MHC Molecules

Feature	Class I MHC	Class II MHC
Polypeptide chains	α β_2-microglobulin	α and β
Locations of polymorphic residues	α1 and α2 domains	α1 and β1 domains
Binding site for T cell coreceptor	CD8 binds mainly to the α3 domain	CD4 binds to a pocket created by parts of α2 and β2 domains
Size of peptide-binding cleft	Accommodates peptides of 8-11 residues	Accommodates peptides of 10-30 residues or more
Nomenclature		
Human	HLA-A, HLA-B, HLA-C	HLA-DR, HLA-DQ, HLA-DP
Mouse	H-2K, H-2D, H-2L	I-A, I-E

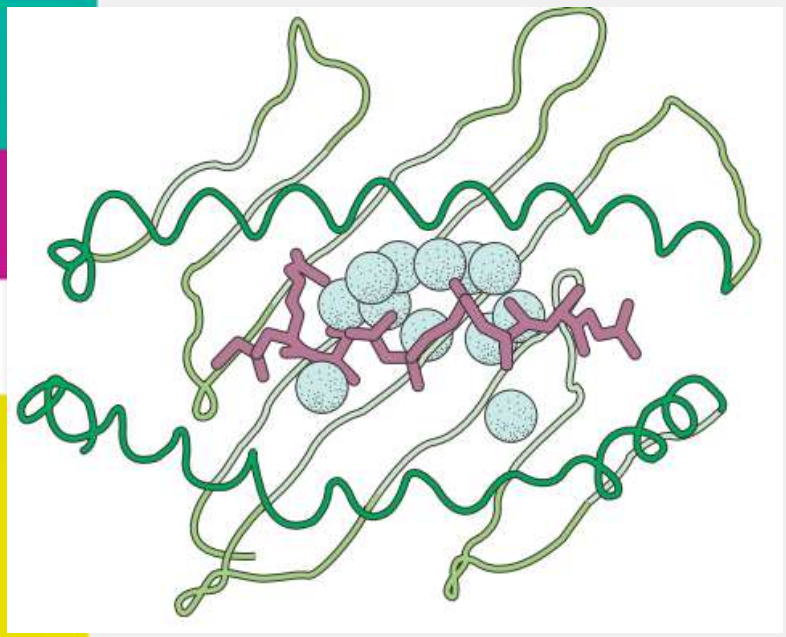
N Engl J Med 2000; 343:702-709

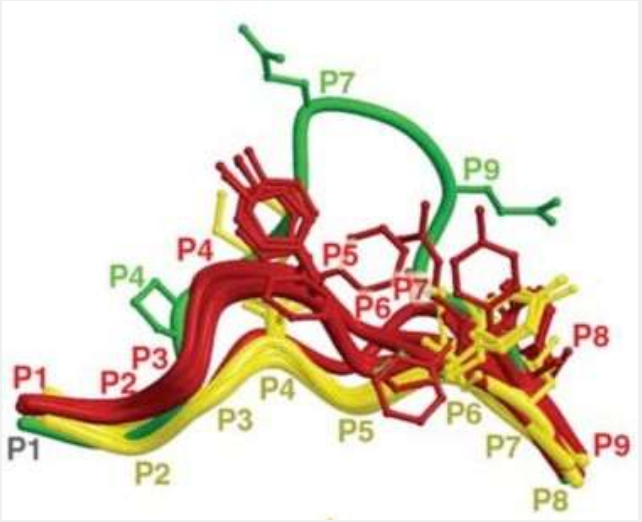
HLA clase I


Peptide-binding cleft
Peptide
α1
α2
α3
N
N
C
C
β2m
β2m
CD8 binding site
Transmembrane region
Disulfide bond
Ig domain



Embolsillamiento tipo I

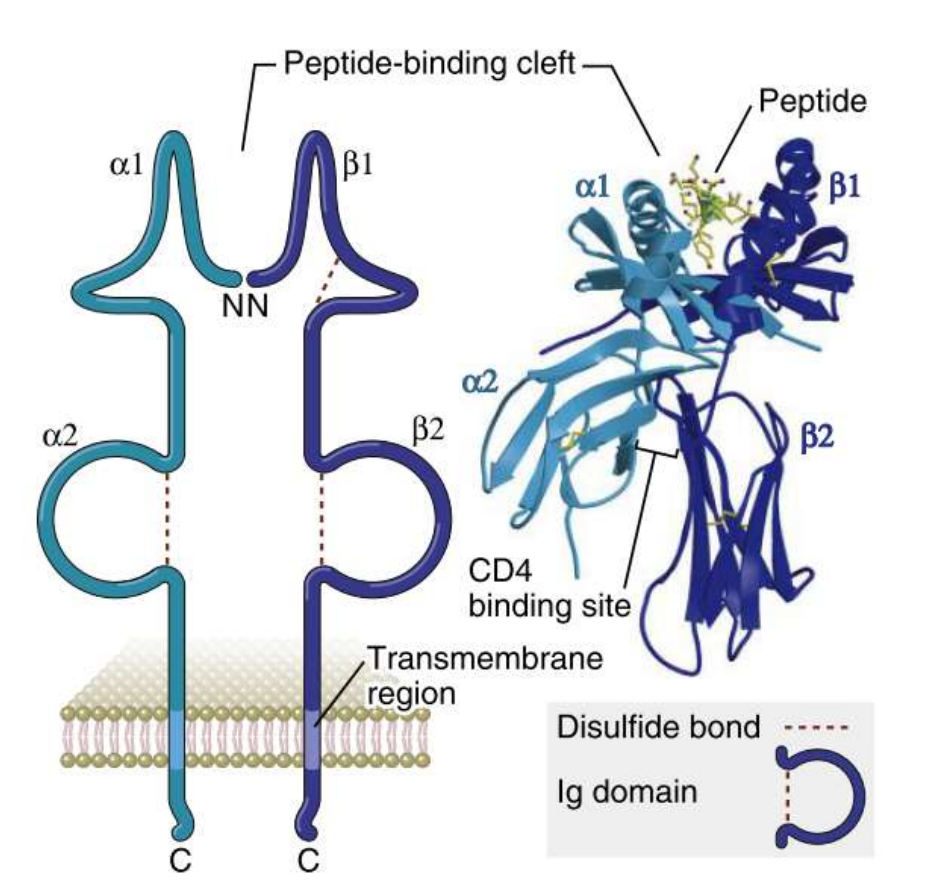


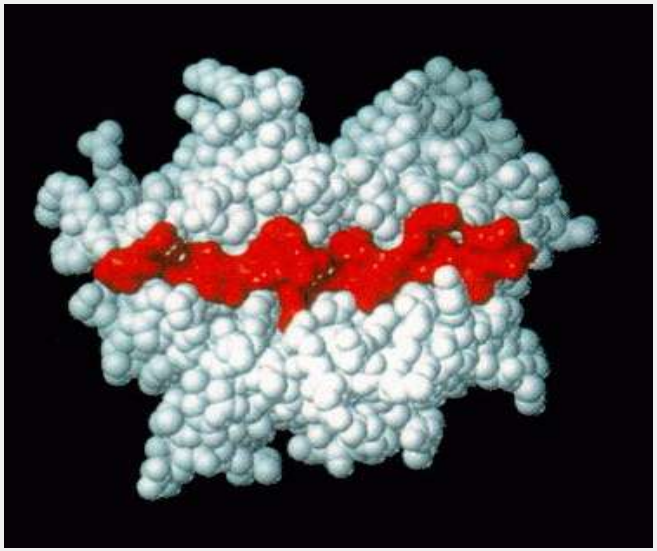


	1	2	3	4	5	6	7	8	9	
H_3N	V	G	P	Q	K	N	E	N	L	COO^-
H_3N	S	G	P	R	K	A	I	A	L	COO^-
H_3N	V	G	P	S	G	K	Y	F	I	COO^-
H_3N	S	G	P	E	R	I	L	S	L	COO^-
H_3N	S	Y	F	P	E	I	T	H	I	COO^-
H_3N	T	Y	Q	R	T	R	A	L	V	COO^-
H_3N	S	Y	I	G	S	I	N	N	I	COO^-

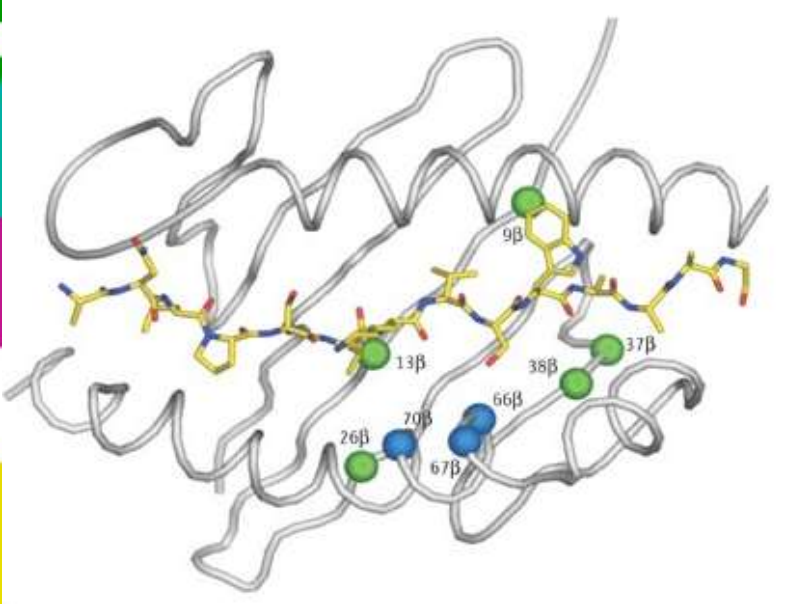
Annu Rev Immunol 24: 419, 2006

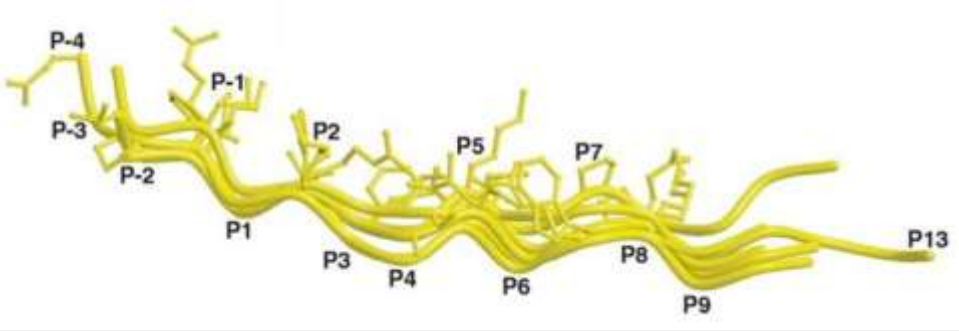
HLA clase II


Peptide-binding cleft
Peptide
α1
β1
NN
α2
β2
CD4
binding site
Transmembrane
region
C
C
Disulfide bond
Ig domain



Embolsillamiento tipo II

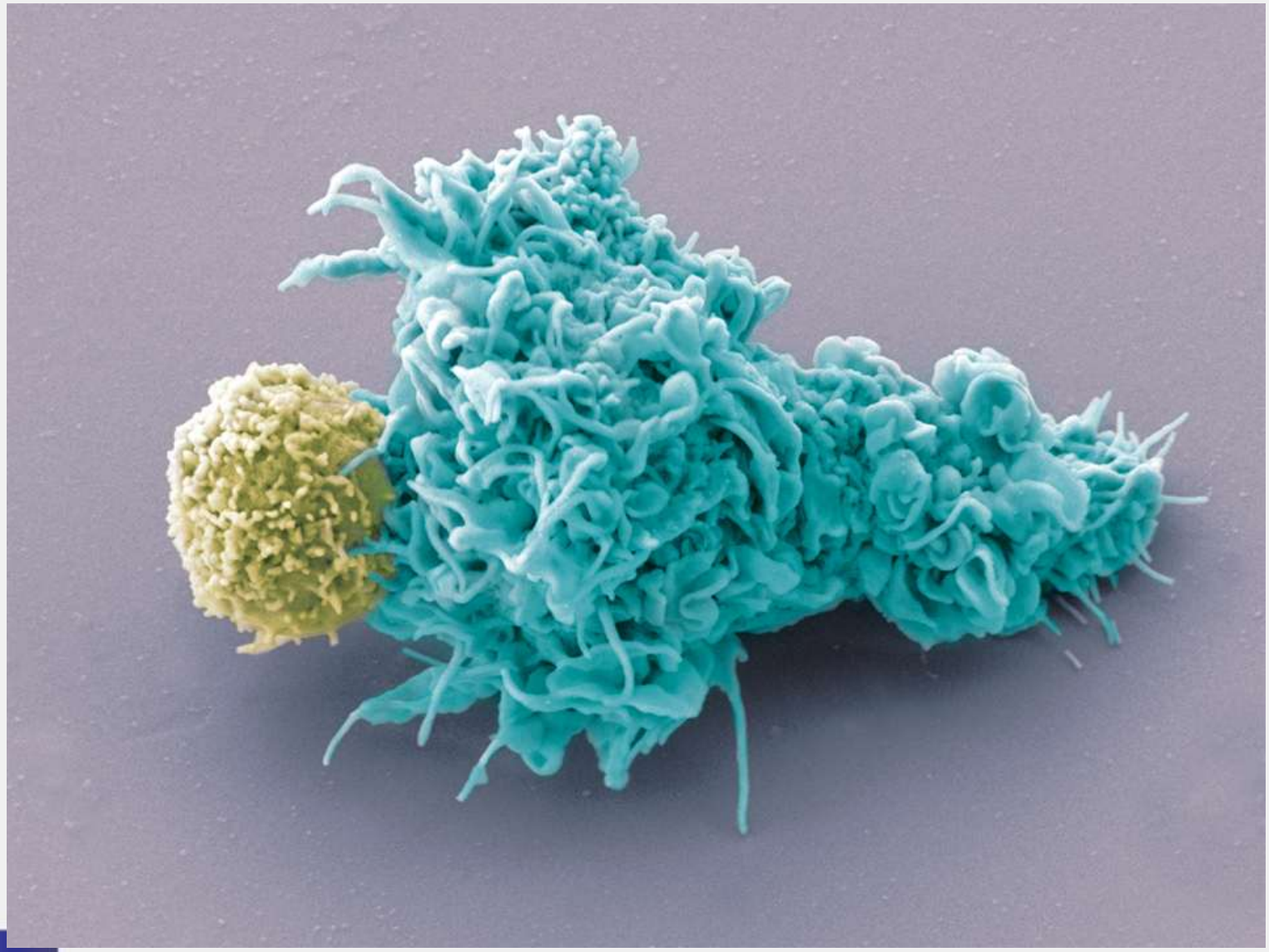




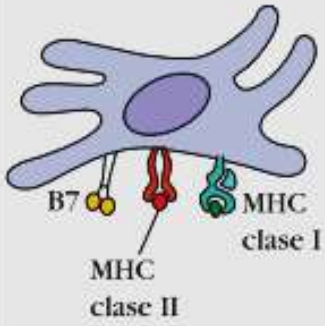
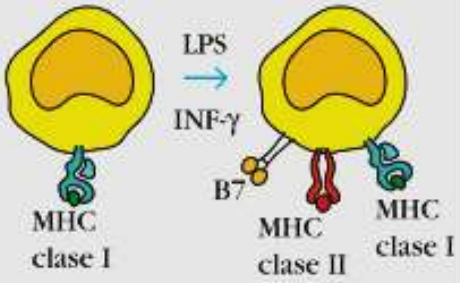
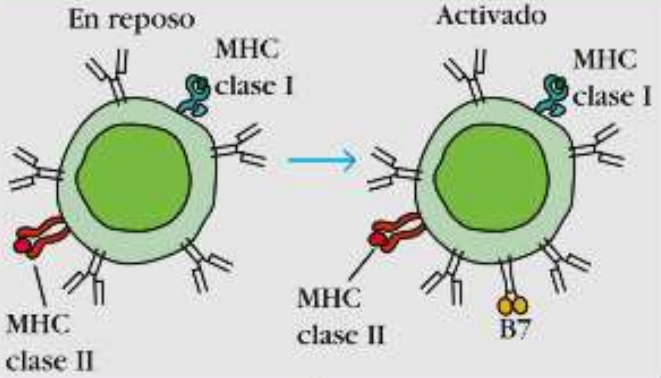
Annu Rev Immunol 24: 419, 2006


Ahora si:
Presentación antigénica

Pero quien realiza la presentación????



Células presentadoras de Antígenos

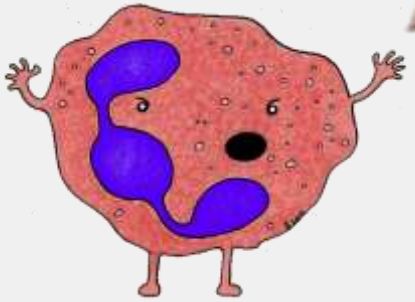
	Célula dendrítica	Macrófago		Linfocito B	
					
Captación de antígeno	Endocitosis, fagocitosis (por células de Langerhans)	Fagocitosis	Fagocitosis	Endocitosis mediada por receptor	Endocitosis mediada por receptor
Expresión de MHC clase II	Constitutiva (+++)	Inducible (−)	Inducible (++)	Constitutiva (++)	Constitutiva (+++)
Actividad coestimuladora	Constitutiva B7 (+++)	Inducible por B7 (−)	Inducible por B7 (++)	Inducible por B7 (−)	Inducible por B7 (++)
Activación de célula T	Células T vírgenes Células T efectoras Células T de memoria	(−)	Células T efectoras Células T de memoria	Células T efectoras Células T de memoria	Células T vírgenes Células T efectoras Células T de memoria

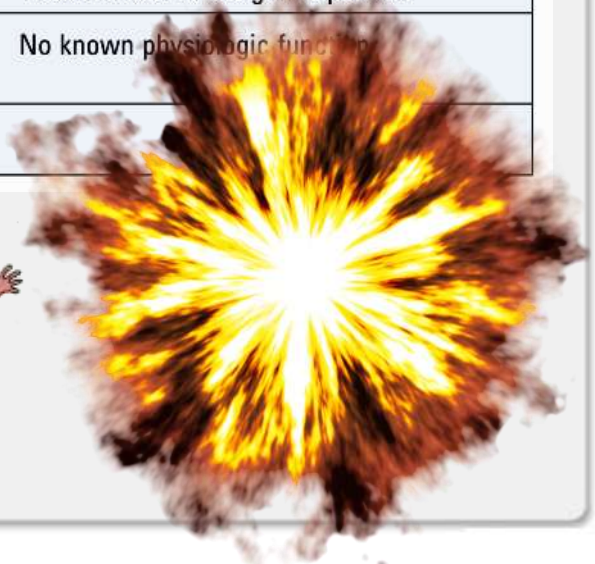
Propiedades y funciones de las APCs

TABLE 6–2 Properties and Functions of Antigen-Presenting Cells

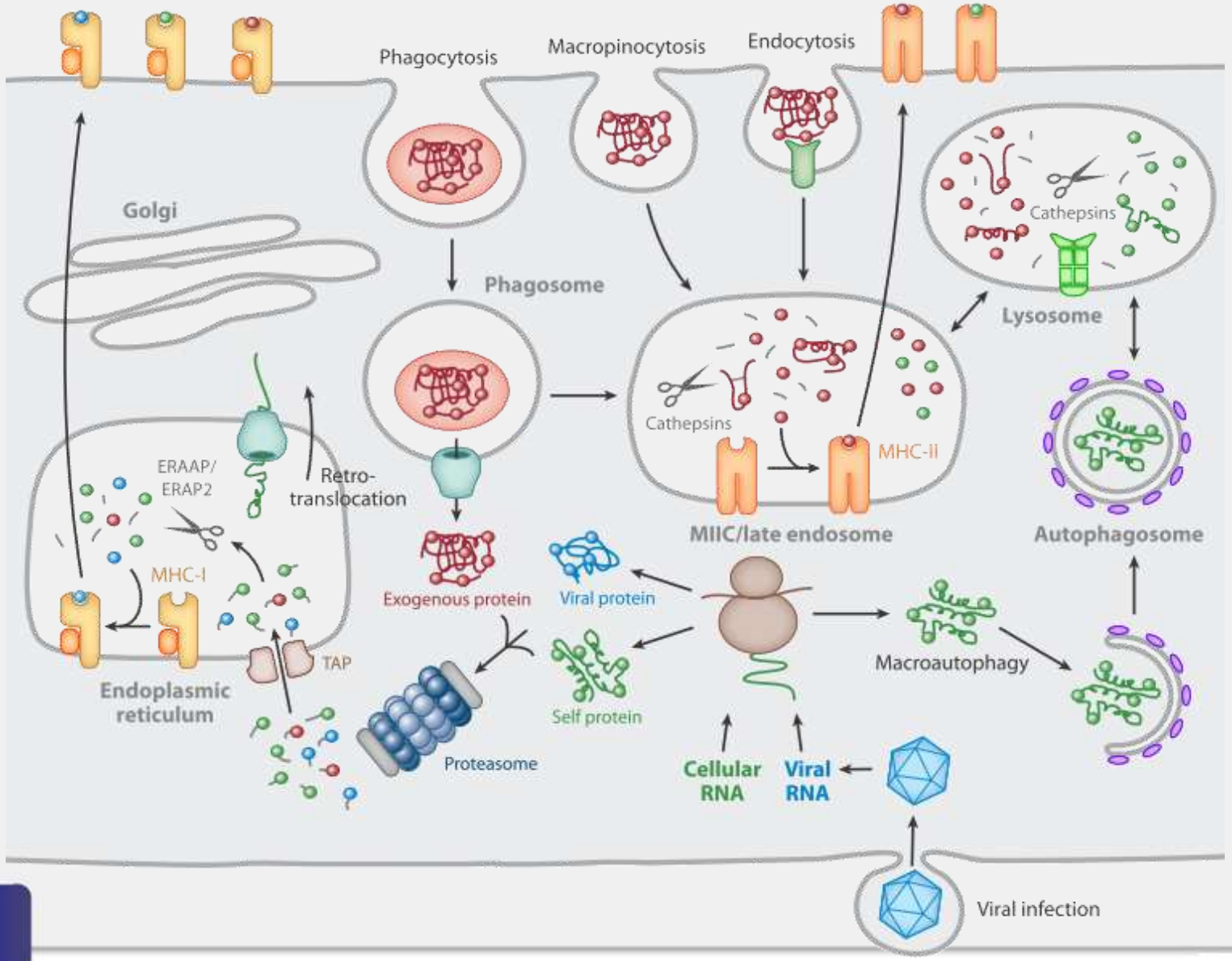
Cell Type	Expression of: Class II MHC	Expression of: Costimulators	Principal Function
Dendritic cells	Constitutive; increases with maturation; increased by IFN-γ	Constitutive; increases with maturation; inducible by IFN-γ, CD40-CD40L interactions	Initiation of T cell responses to protein antigens (priming)
Macrophages	Low or negative; inducible by IFN-γ	Inducible by LPS, IFN-γ, CD40-CD40L interactions	Effector phase of cell-mediated immune responses (T cell–enhanced killing of phagocytosed microbes)
B lymphocytes	Constitutive; increased by IL-4	Induced by T cells (CD40-CD40L interactions), antigen receptor cross-linking	Antigen presentation to $CD4^+$ helper T cells in humoral immune responses (cognate T cell–B cell interactions)
Vascular endothelial cells	Inducible by IFN-γ; constitutive in humans	Constitutive (inducible in mice)	May promote activation of antigen-specific T cells at site of antigen exposure
Various epithelial and mesenchymal cells	Inducible by IFN-γ	Probably none	No known physiologic function

IFN-γ, interferon-γ; IL-4, interleukin-4; LPS, lipopolysaccharide.



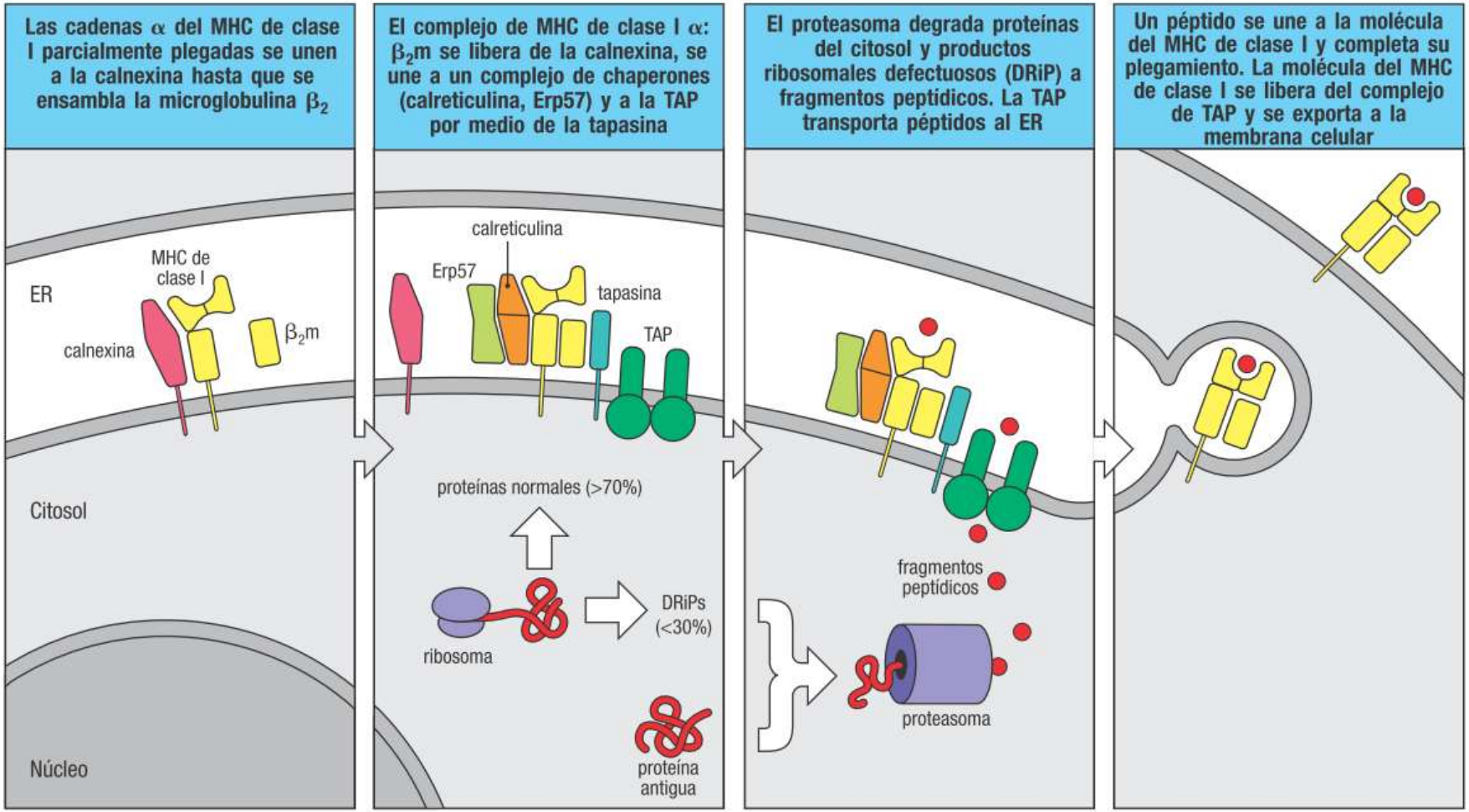


Vías de procesamiento. Generalidades



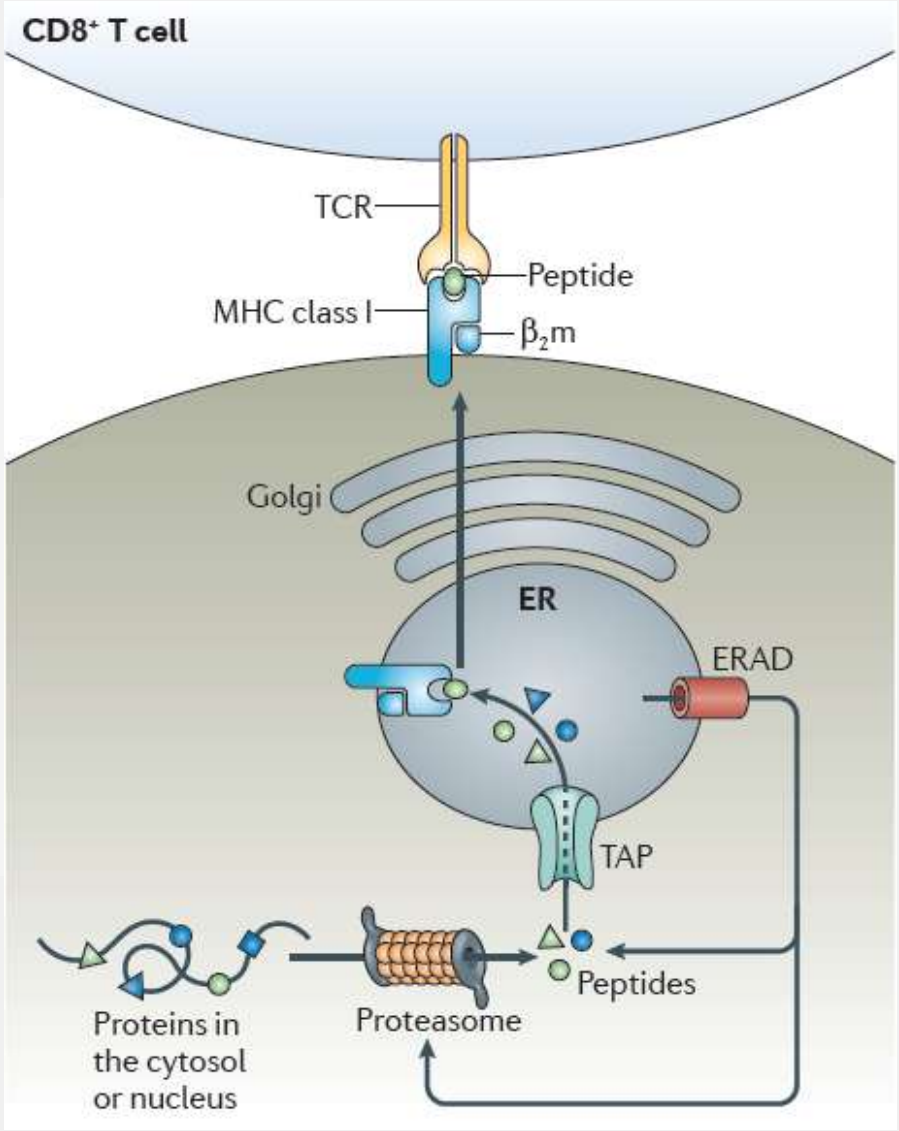
Annu. Rev. Immunol. 2013. 31:443

Presentación asociada al MHC I



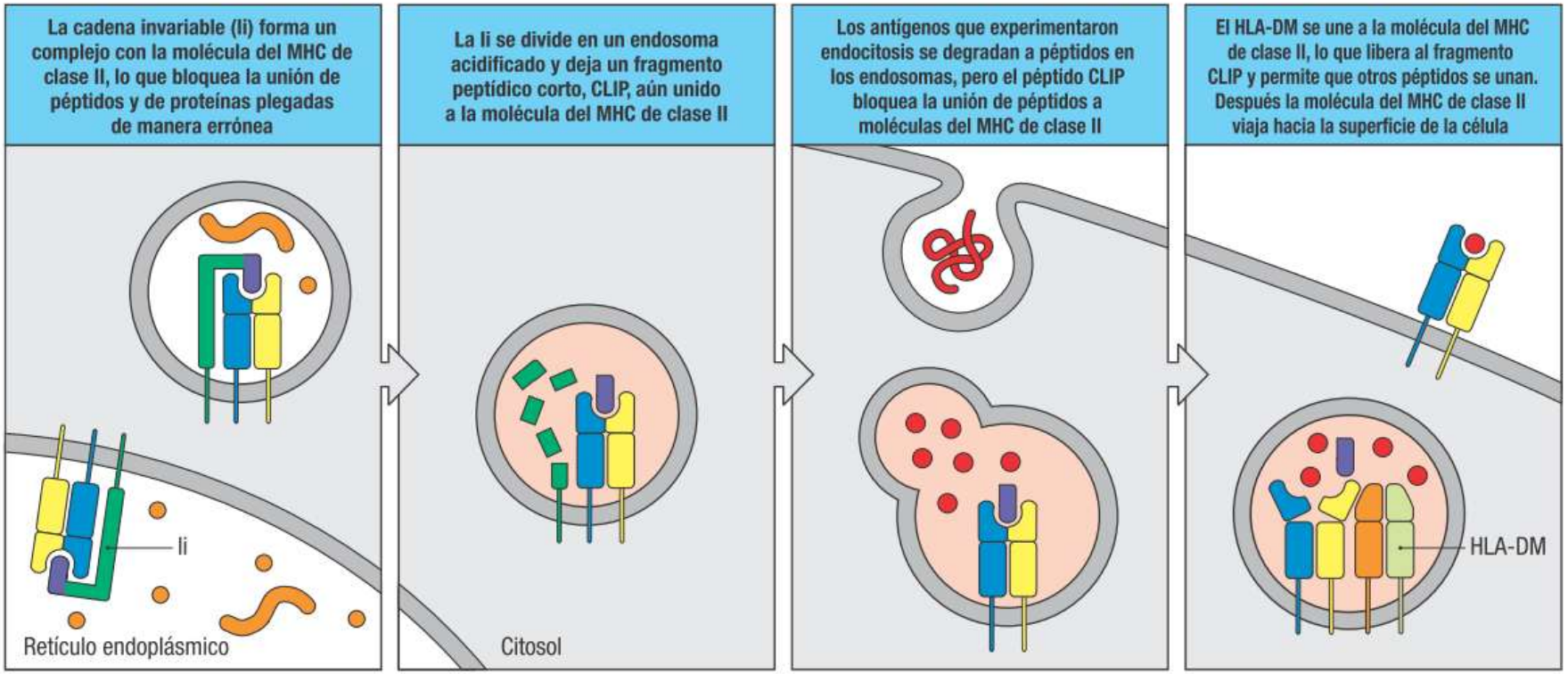
Presentación asociada al MHC I

- Proteínas citosólicas
- Patógenos intracelulares
- Células tumorales
- Antígenos exógenos (presentación cruzada)
- Presentación de Ag a linfocitos T CD8



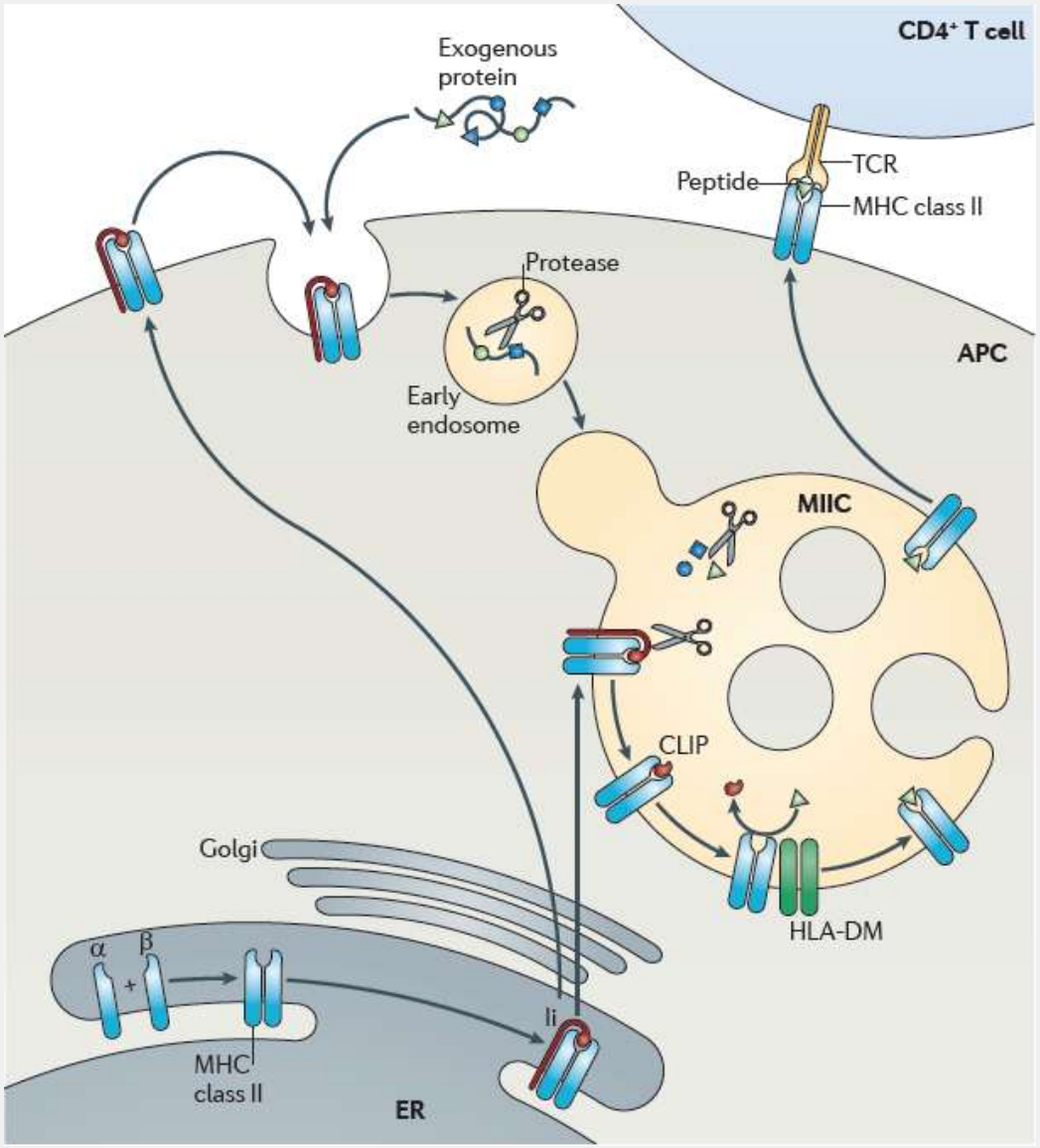
Nat Rev Immunol 2010; 10: 73. Nat Rev Immunol 2011; 11: 823

Presentación asociada al MHC II



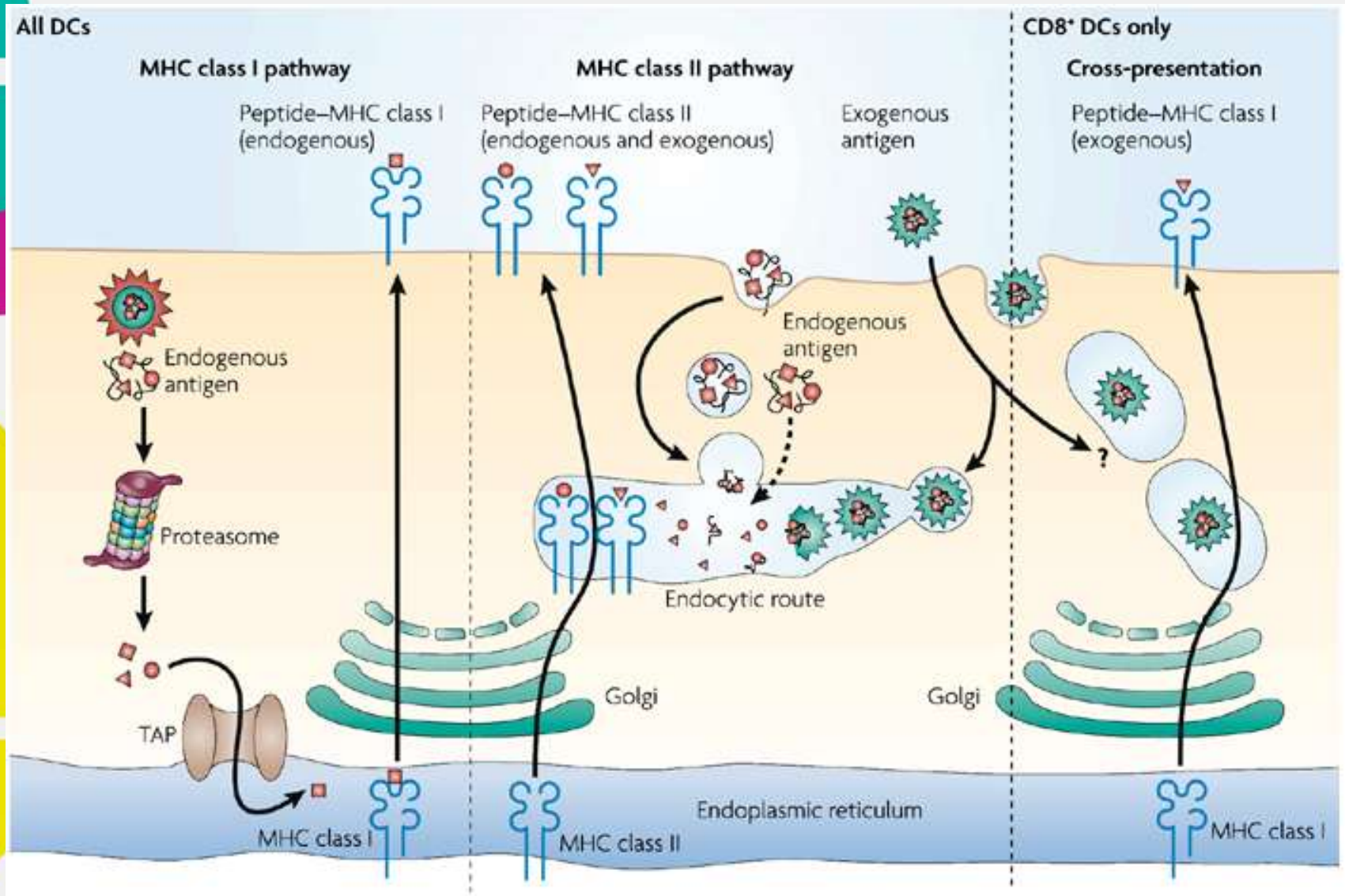
Presentación asociada al MHC II

- Antígenos exógenos
  - ✓ Receptores Fc
  - ✓ Receptores de C3b
  - ✓ BCR
  - ✓ DEC205
- Vía endocítica
- Microbios particulados
  - ✓ Fagosoma
  - ✓ Fusión con lisosomas
- Presentación a células CD4+



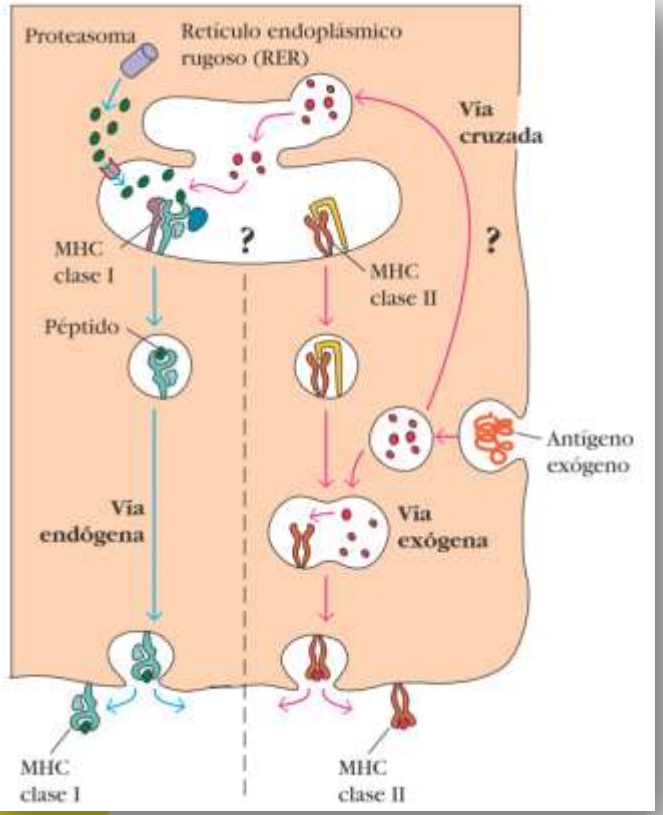
Curr Opin Immunol.2006; 18: 64. Nat Rev Immunol 2008; 8(8):607. Nat Rev Immunol 2011; 11: 823

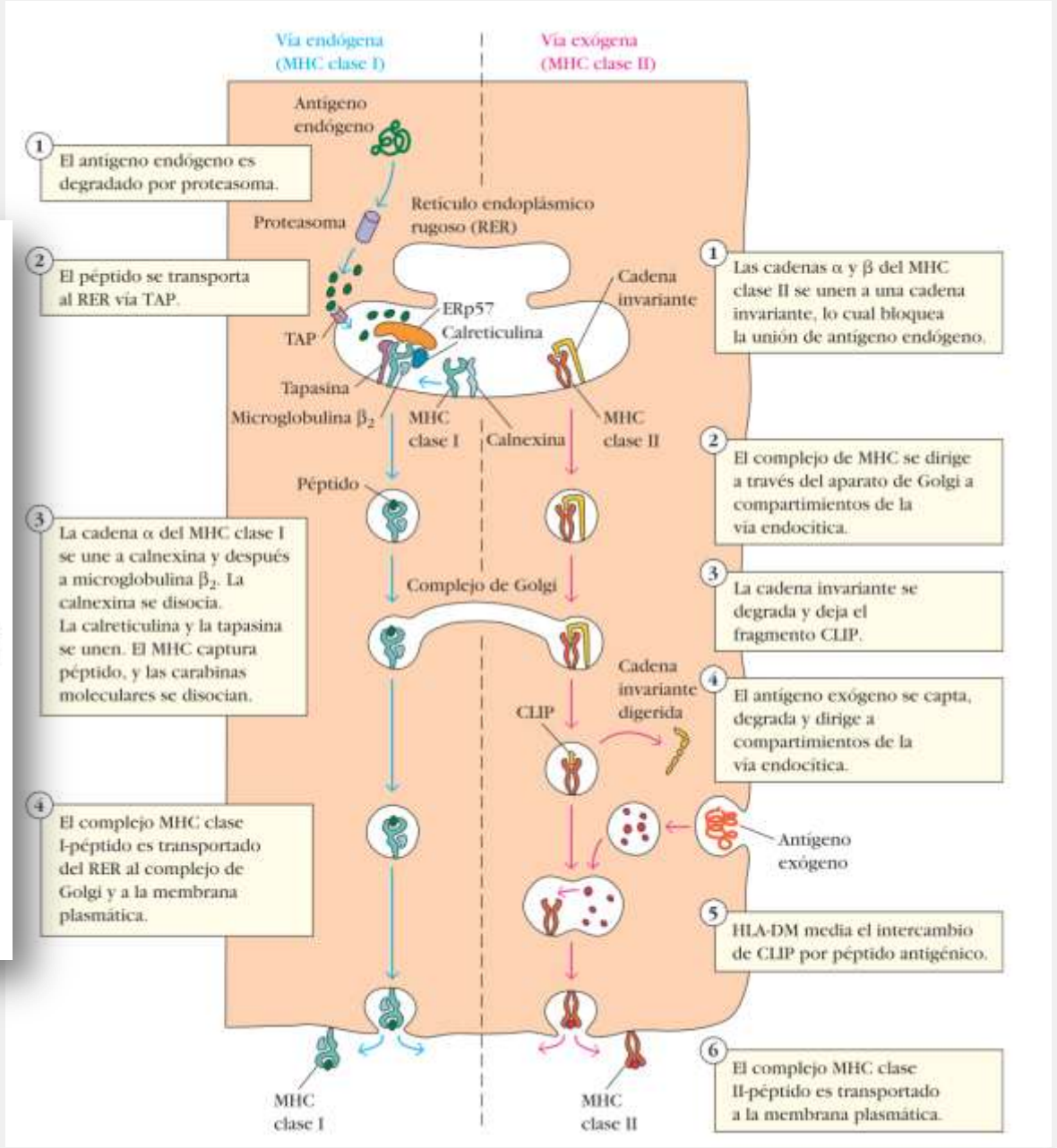
Presentación cruzada



Villadangos J, Schnorrer P. Nat Rev Immunol 2007; 7: 543

Otra vez todo





Moléculas no clásicas

Clase I

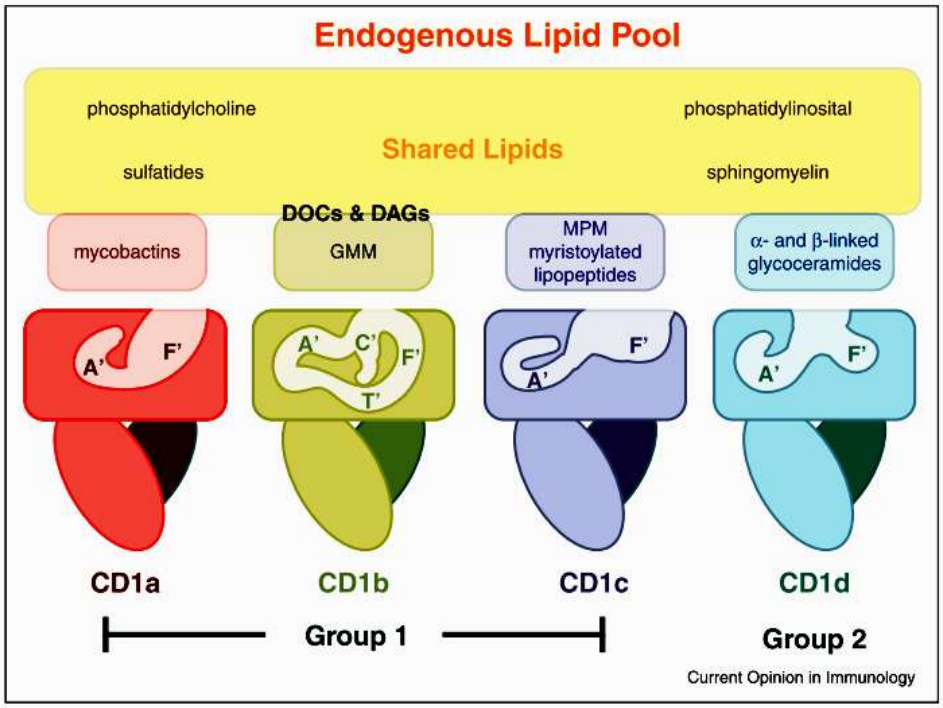
- En su mayoría son pseudogenes
- Polimorfismo escaso o nulo
- Pueden presentar péptidos a células T
- HLA-E-HLA-H, HLA-J, HLA-X
- Ligandos de NKG2D
- Familia MIC (MICA, MICE)
- CD1

Clase II

- Limitado polimorfismo
- Unión del péptido a moléculas clase II
- Regulación de la presentación de antígenos mediada por el MHC II
  - ✓ HLA-DM
  - ✓ HLA-DO

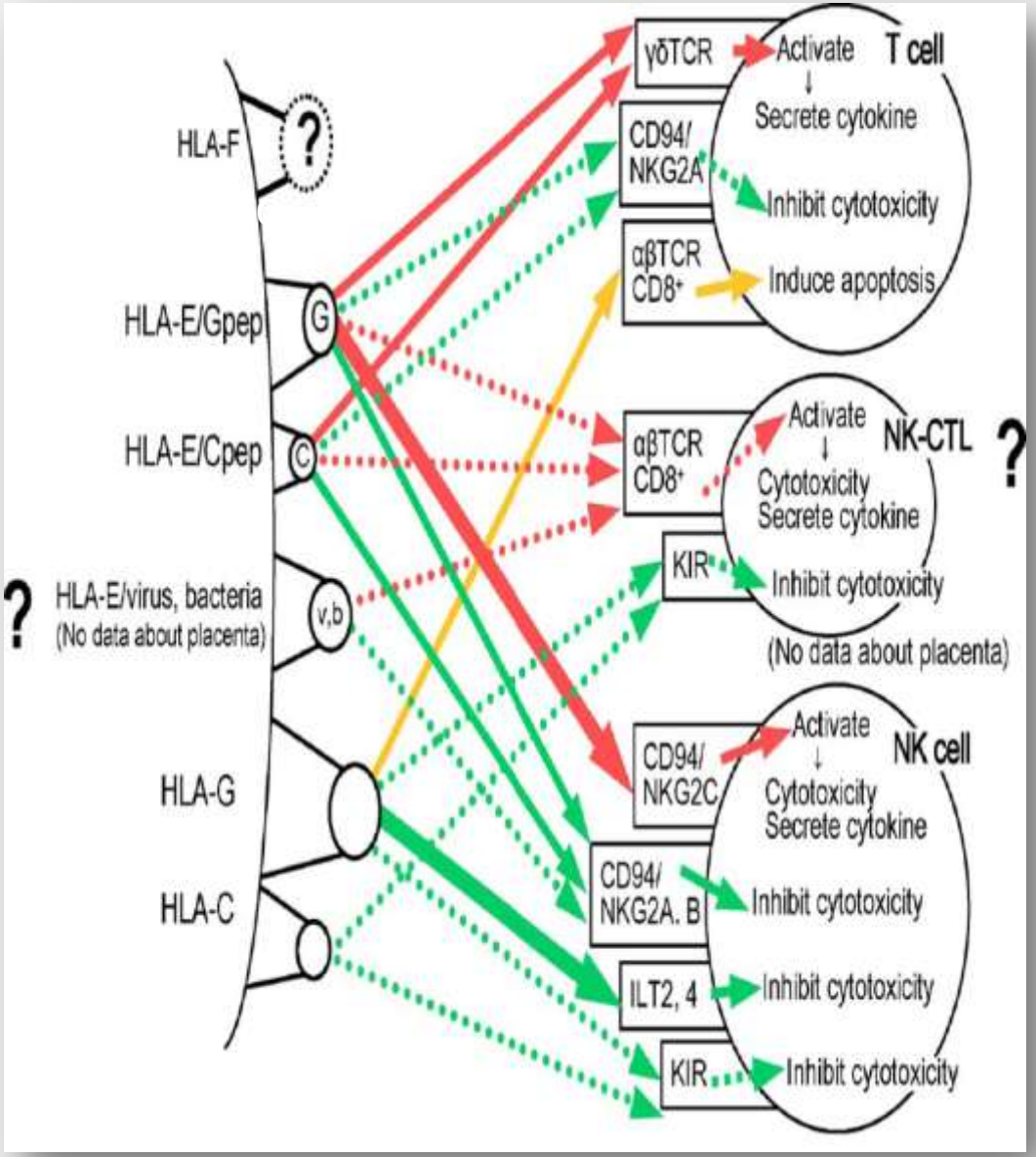
Vias et al. Nat Rev Immunol 2008, 8: 607. Netea. Nat Med 2010; 16:28

CD1

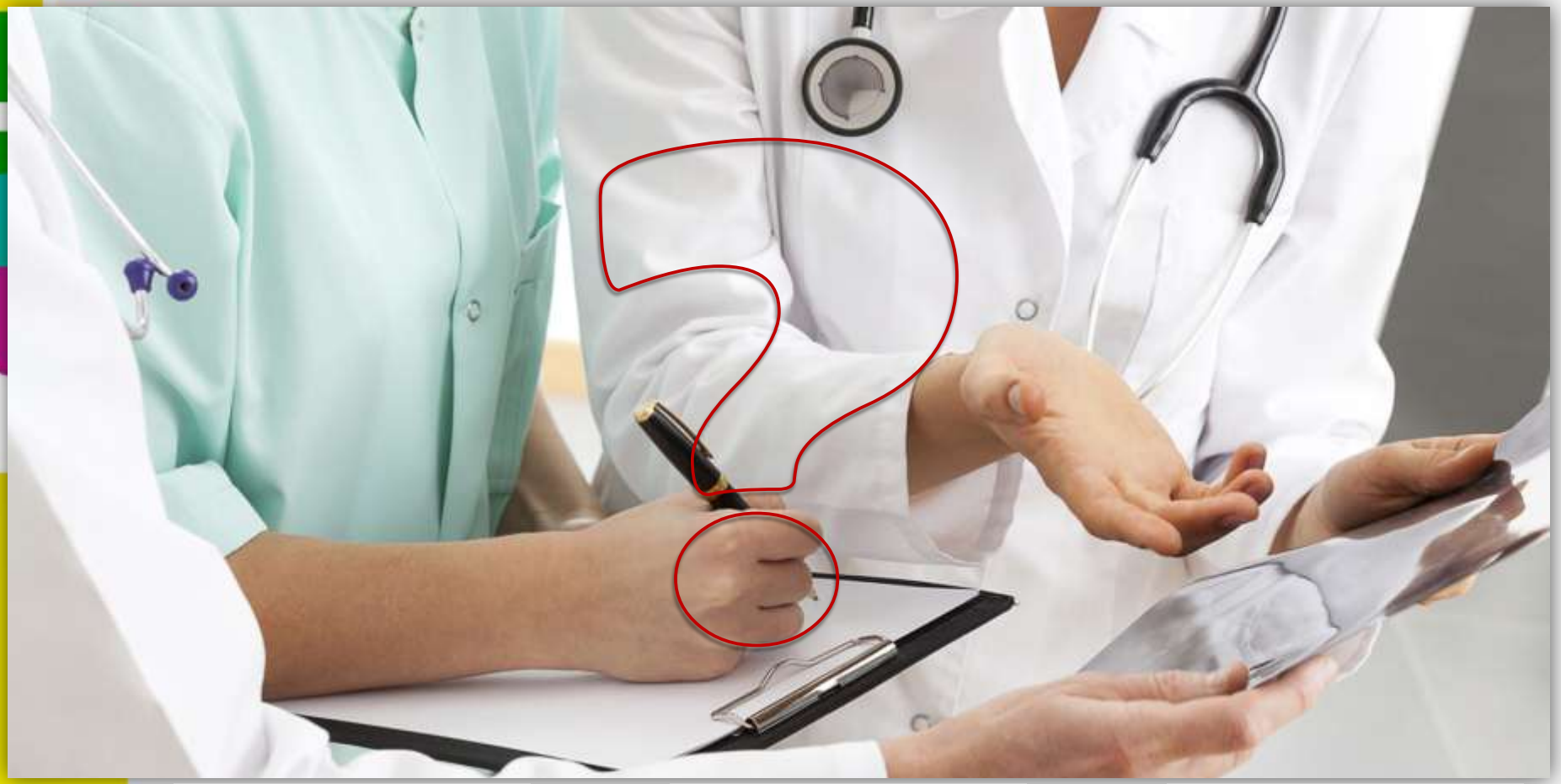


- Presente en compartimientos endosomales
- Glicolípidos microbiales
- Tolerancia central a lípidos propios
- CD1 a pesar de ser parecido a MHC-I, se comporta como MHC-II
- Los antígenos son lípidos y glucolípidos (micobacterias)
- Activa linfocitos T γδ y NKT

Tolerancia materno fetal



Interconsulta



Paciente:

HLA- A*0201
B*0702
Cw*0401
DRB1*0101
DQB1*0501

Donante 1:

HLA- A*0202
B*0702
Cw*0401
DRB1*0104
DQB1*1206

Donante 2:

HLA- A*0201
B*1602
Cw*0401
DRB1*0101
DQB1*0501

¡Pregunten Ahora o Callen Para Siempre!

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http://guillermo.vv.si


¡Gracias por la atención!