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IDIC-ULA

**HLA, procesamiento y
presentación antigénica**

Interconsulta



Paciente:

HLA- A*0201
B*0702
Cw*0401
DRB1*0101
DQA1*0501

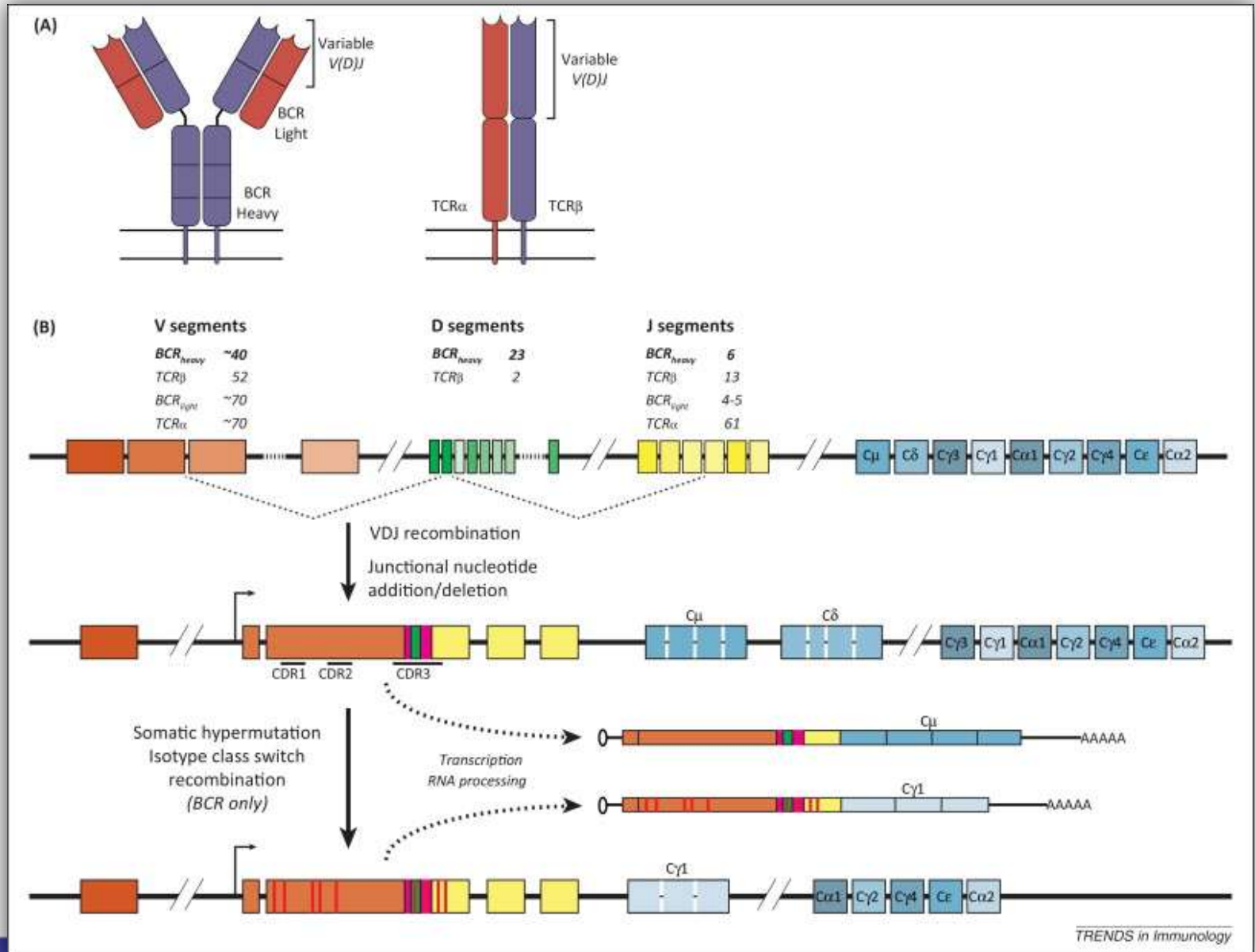
Donante 1:

HLA- A*0202
B*0702
Cw*0401
DRB1*0104
DQA1*1206

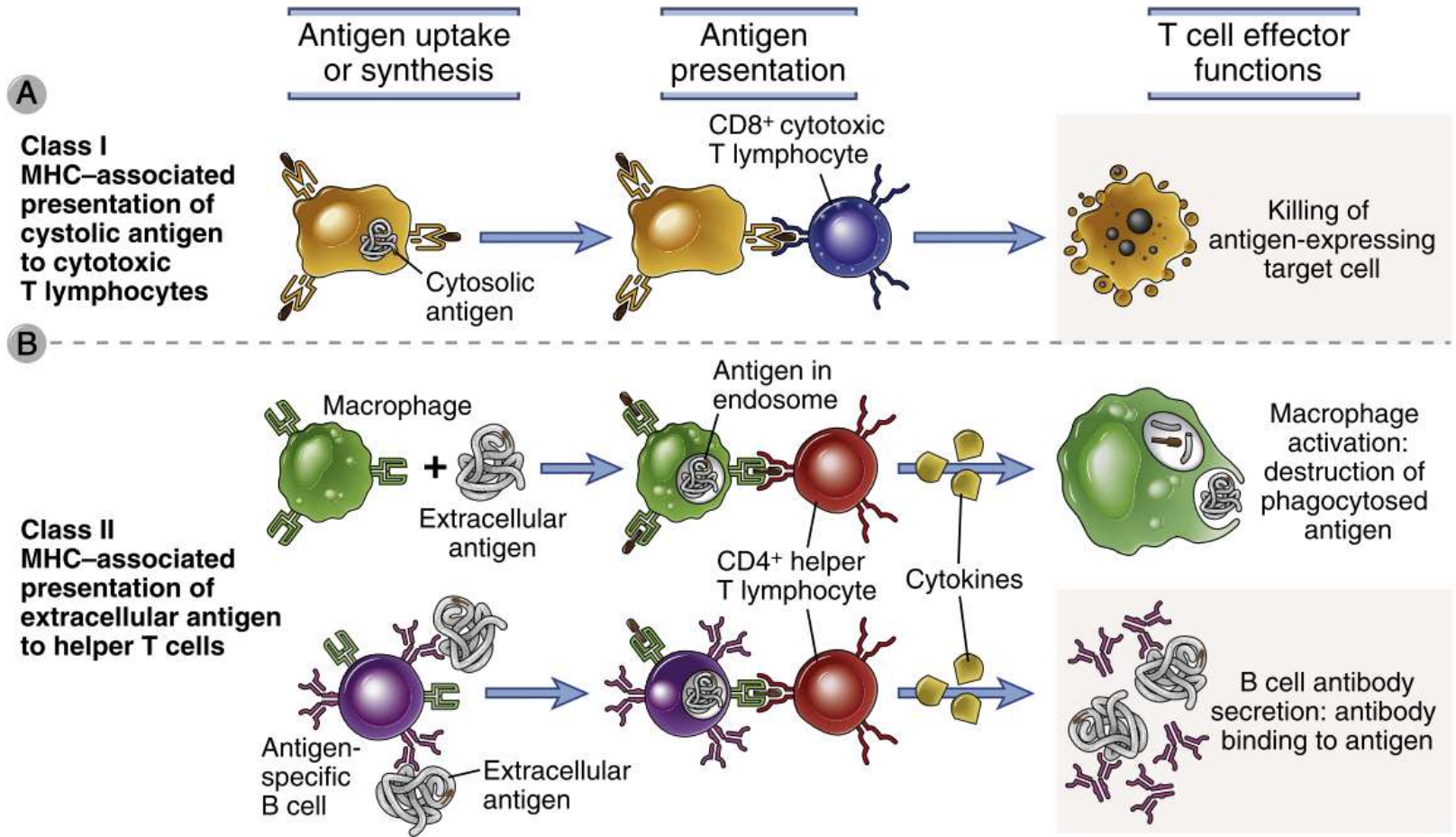
Donante 2:

HLA- A*0201
B*1602
Cw*0401
DRB1*0101
DQA1*0501

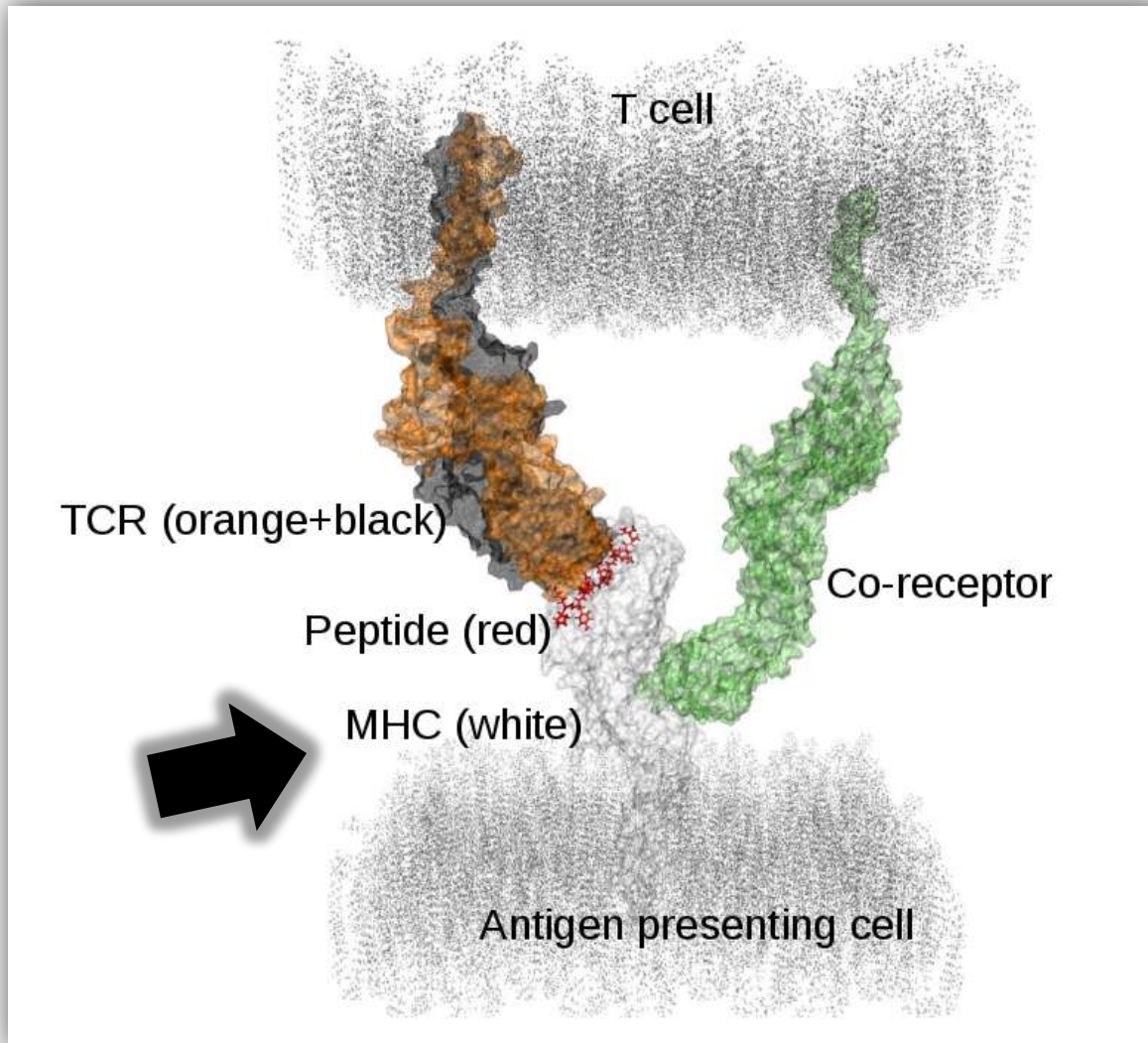
Ubicándonos



Ubicándonos

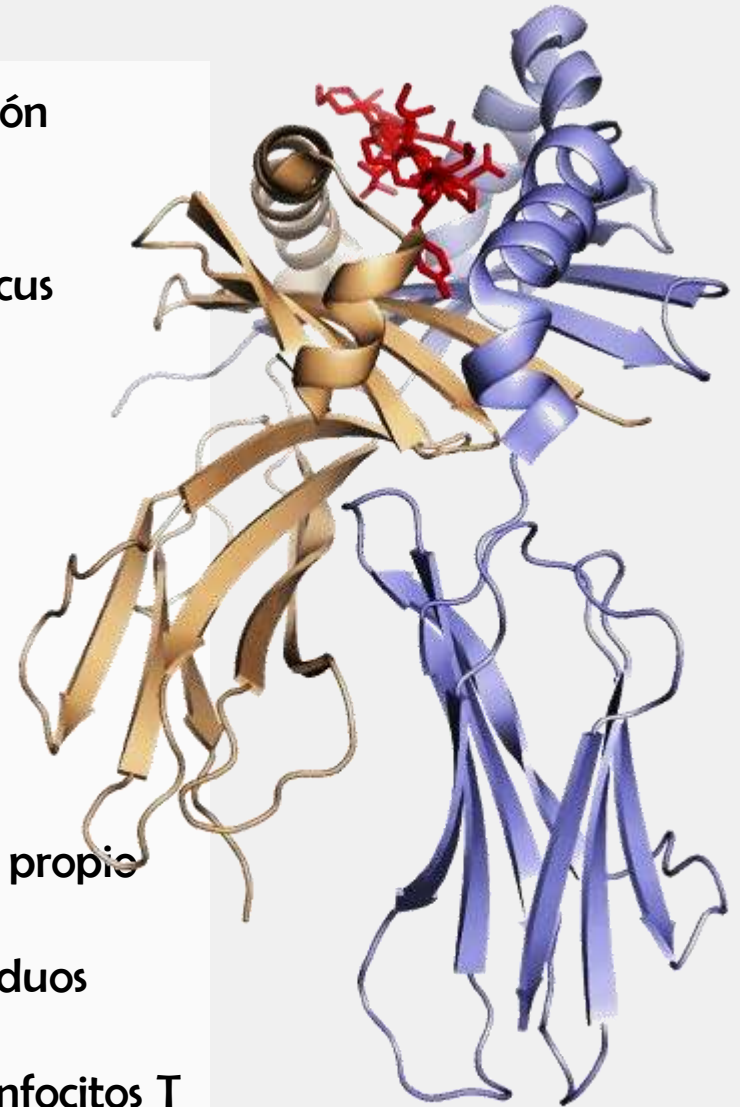


La piedra angular de la RI

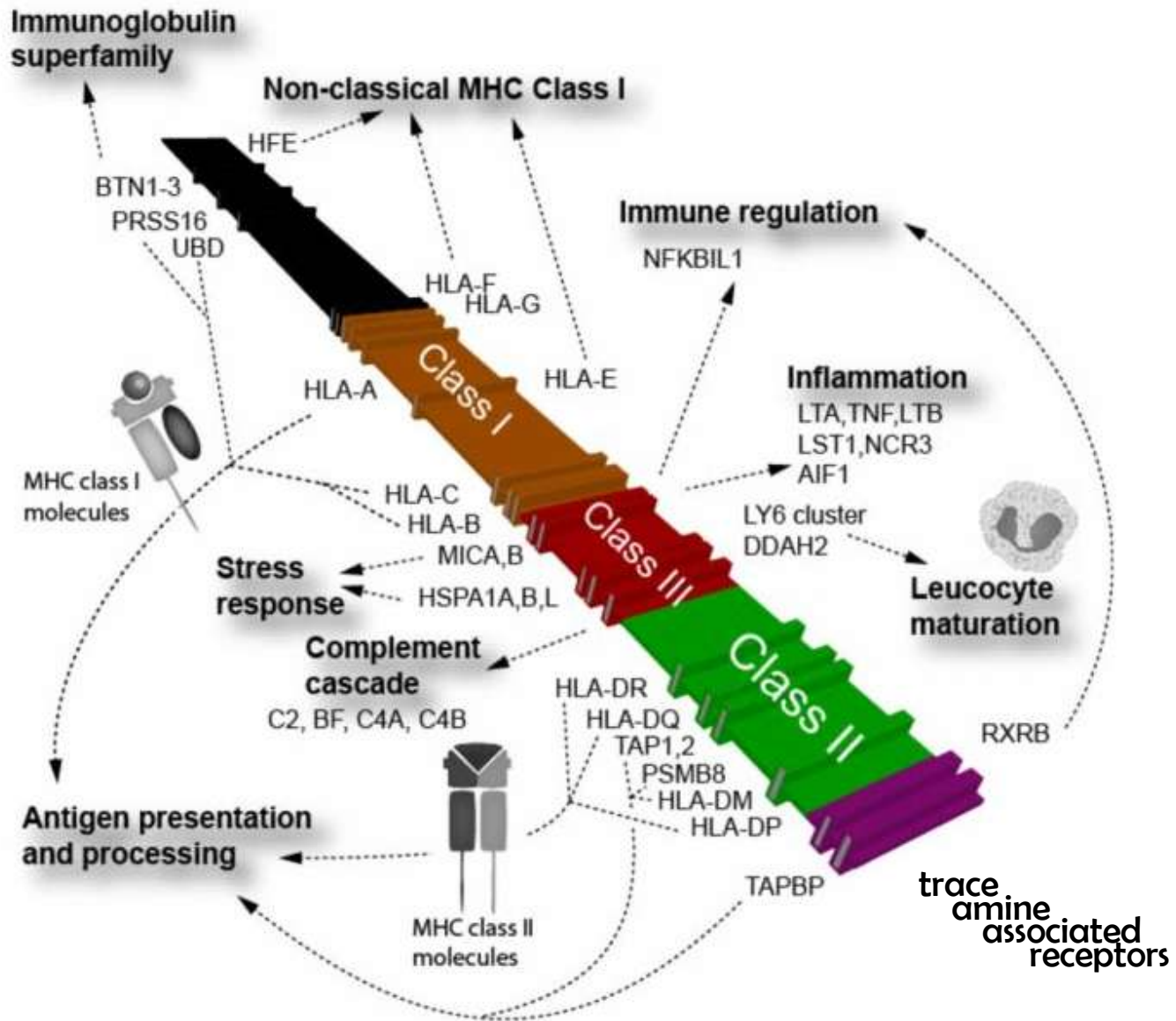


Comencemos por el HLA o MHC

- Proteínas especializadas en la presentación antigénica
- Codificadas por genes presentes en un locus denominado complejo mayor de histocompatibilidad (MHC)
- 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

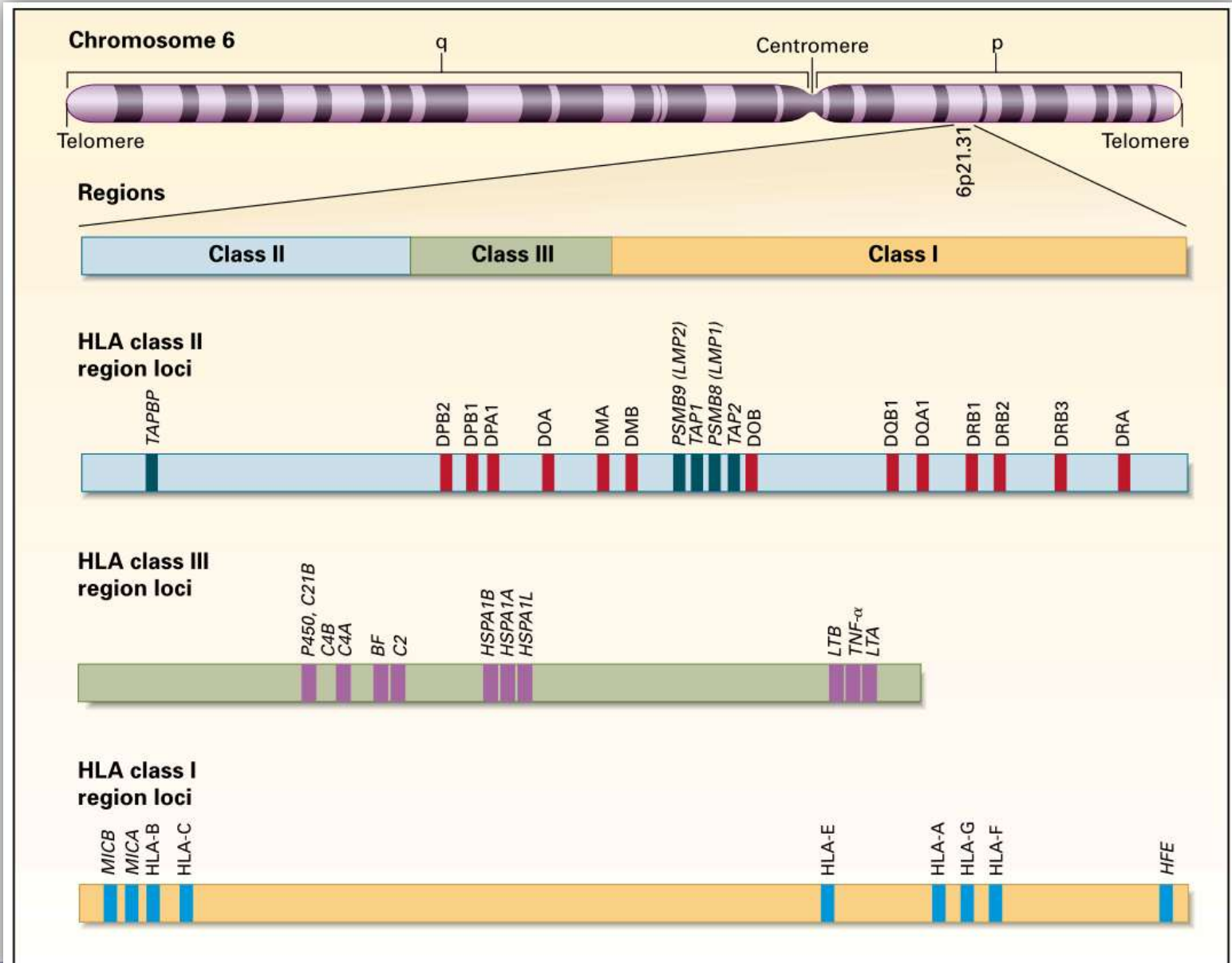


Genetic matchmaking



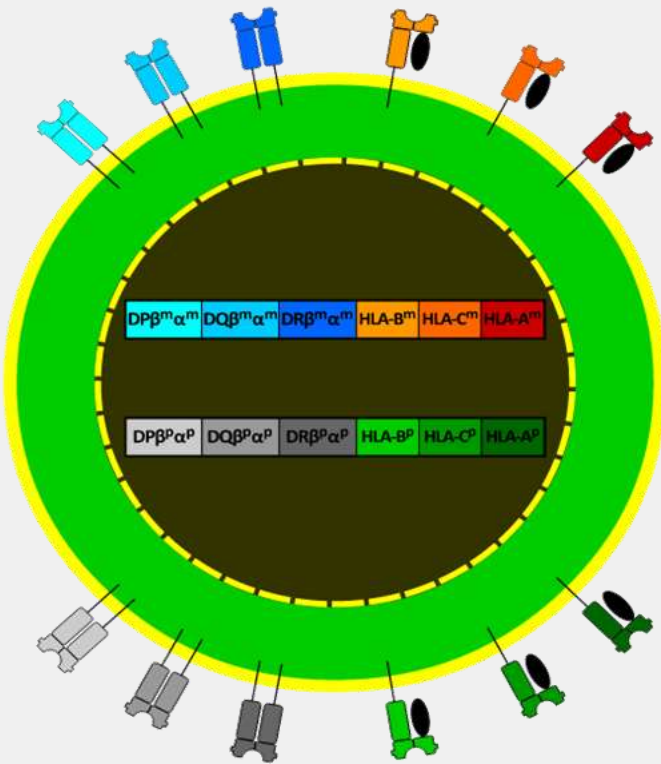
- MHC-dependent mate choice is linked to a trace-amine-associated receptor gene
- Garantizar variabilidad

Estructura génica

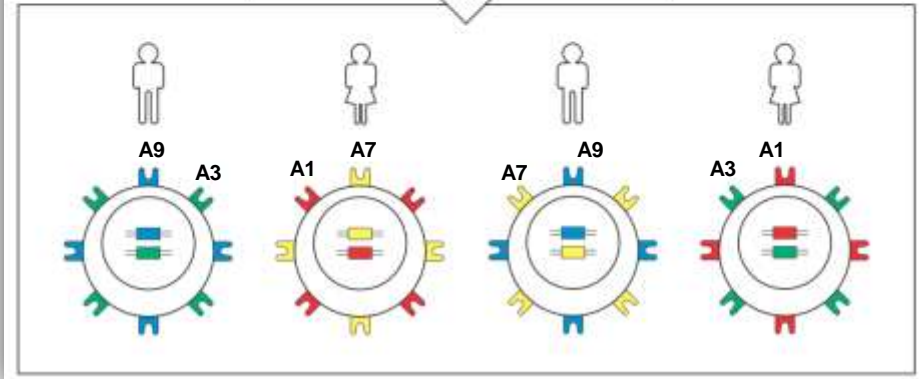
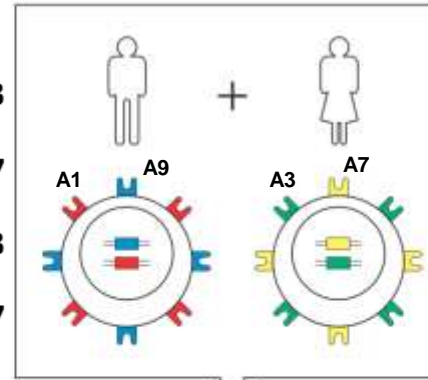


Herencia

Codominancia



- A3 — A1A3
- A1 — A1A7
- A3 — A9A3
- A9 — A9A7



MHC class I MHC class II

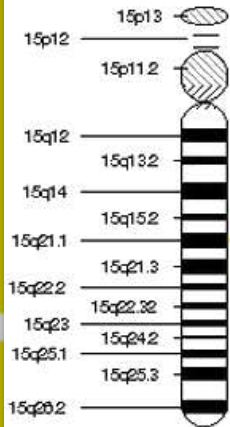
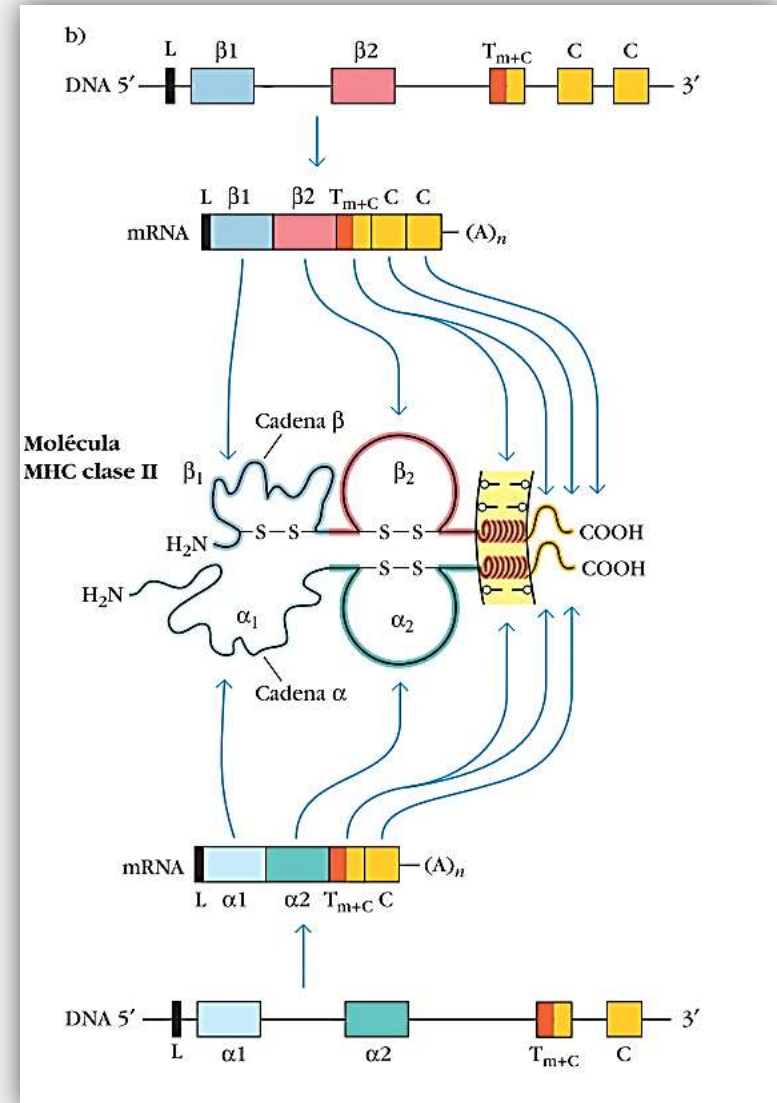
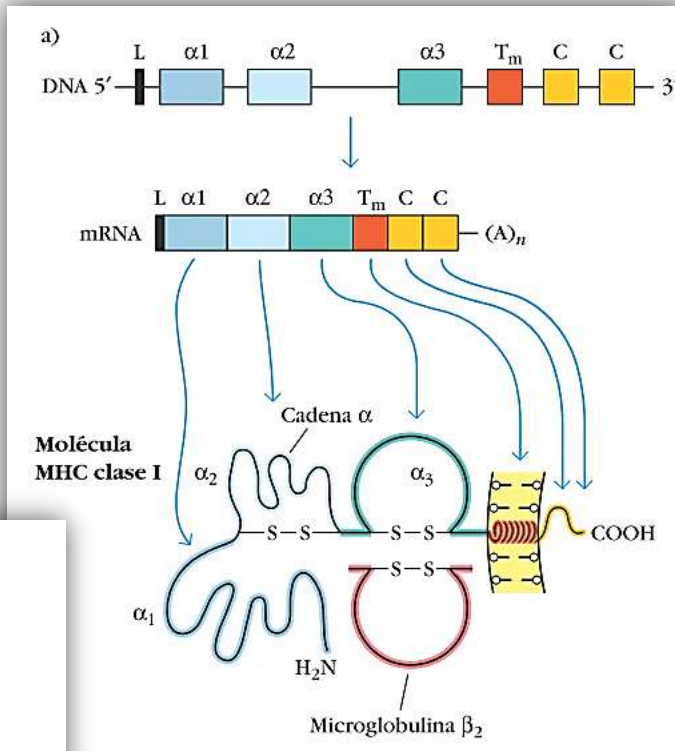
maternal



paternal



Expresión génica



B2M gene

Cytogenetic Location: 15q21.1

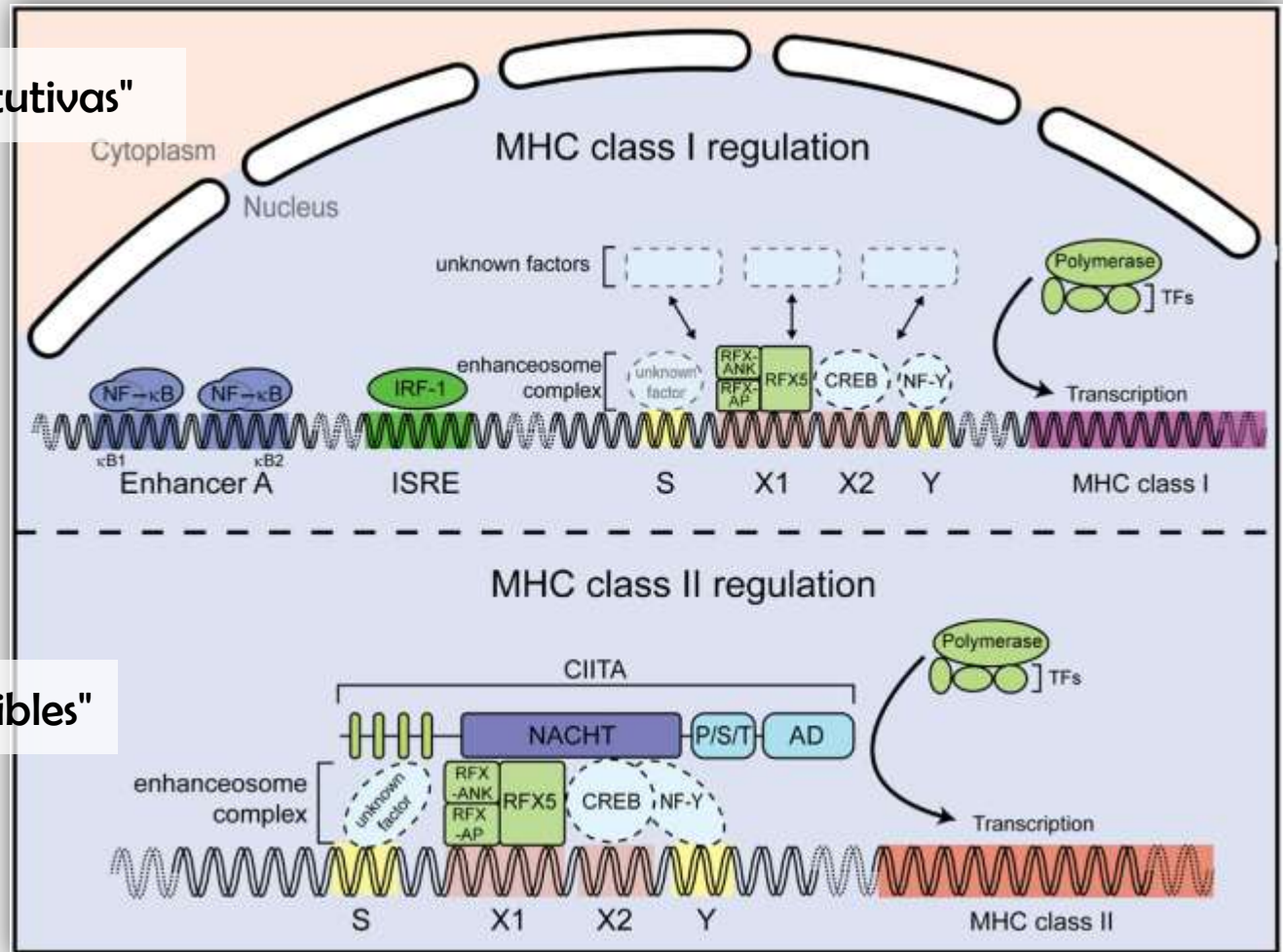
Molecular Location on chromosome 15: base pairs 44,711,486 to 44,718,158

Regulación génica

- "pseudo Constitutivas"

- CIITA deficiency: Bare lymphocyte syndrome, clinically similar to severe combined immunodeficiency

- "pseudo Inducibles"



- Los pacientes con ICS cursan con infecciones severas que se manifiestan en la edad neonatal asociadas a sepsis, neumonías, meningitis, entre otras

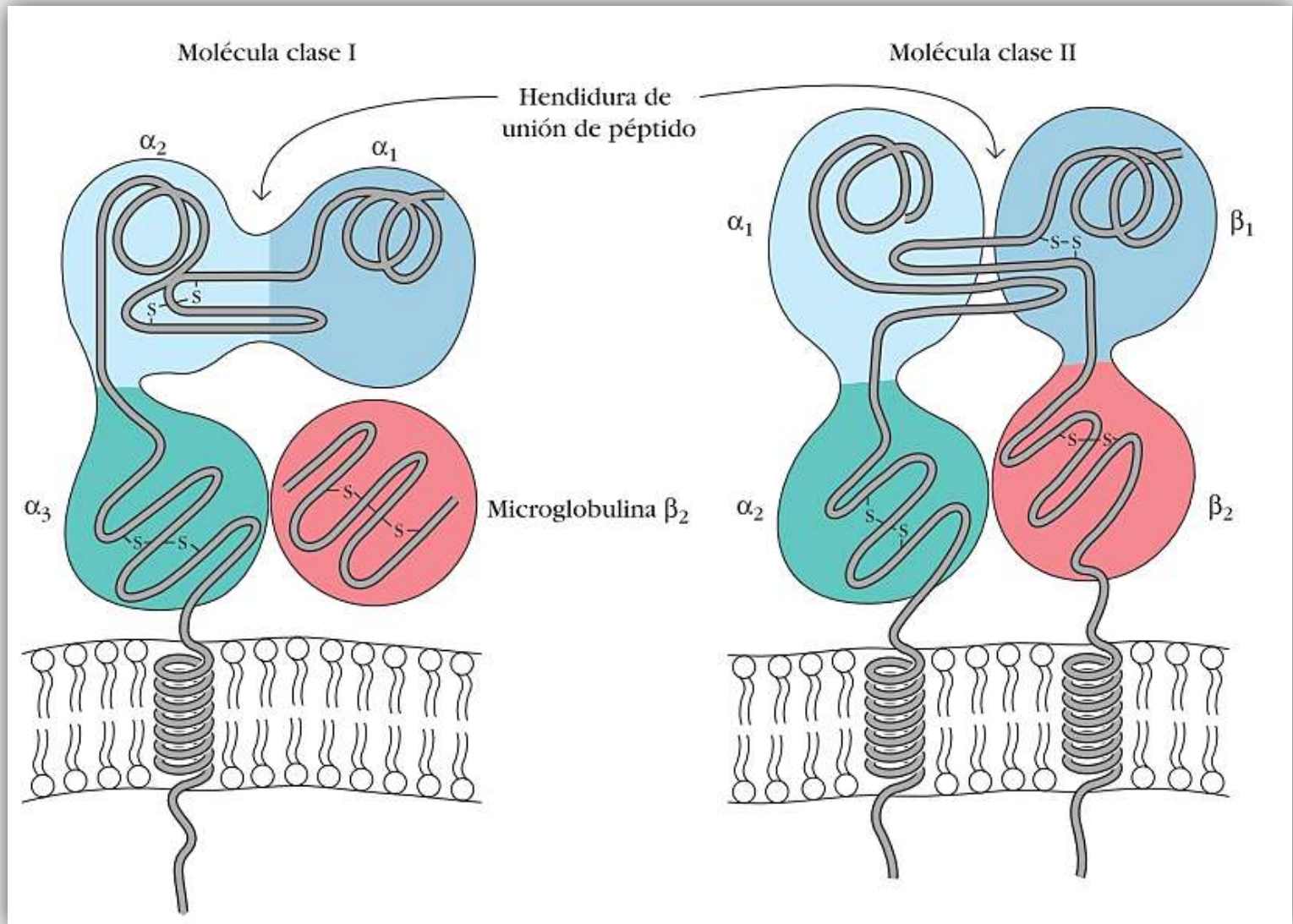
Tabla 2. Expresión fenotípica de las ICS según el defecto genético presente.

Tipo de ICS	Localización Cromosómica
T-B+NK+	
Deficiencia de la cadena α del receptor de IL-7	5p13
Deficiencia de la cadena δ de CD3	11q23
Deficiencia de la cadena ϵ de CD3	11q23
T-B+NK-	
SCID ligada al cromosoma X (Deficiencia de γc)	Xq13.1
Deficiencia de CD45	1q31-1q32
Deficiencia de JAK3	19p13.1
T-B-NK+	
Deficiencia del producto del gen Artemis	10p13
Deficiencia de RAG1 y RAG2	11p13
T-B-NK-	
Deficiencia de Adenosin Deaminasa	20q13.11

Adaptado de (21)



Entendamos las moléculas



Características

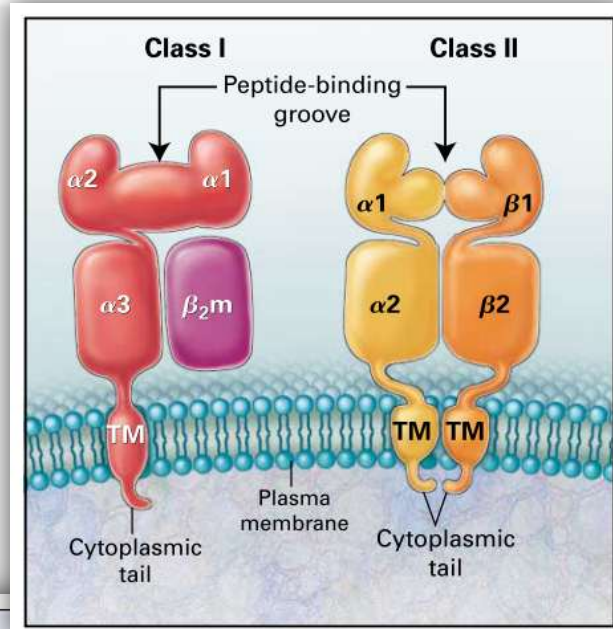
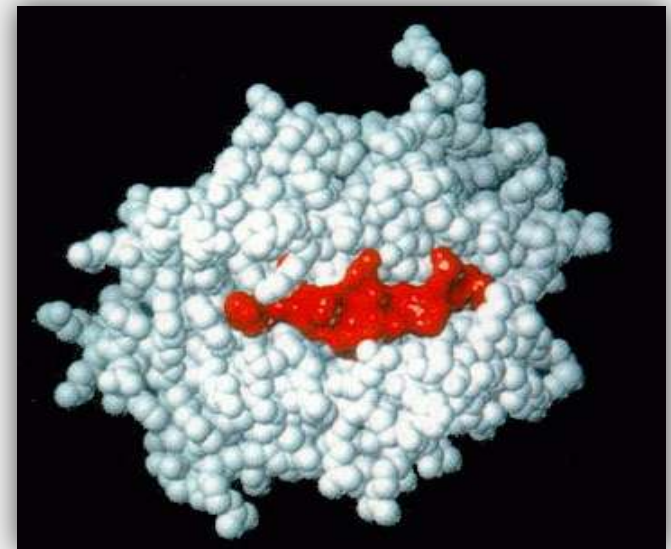
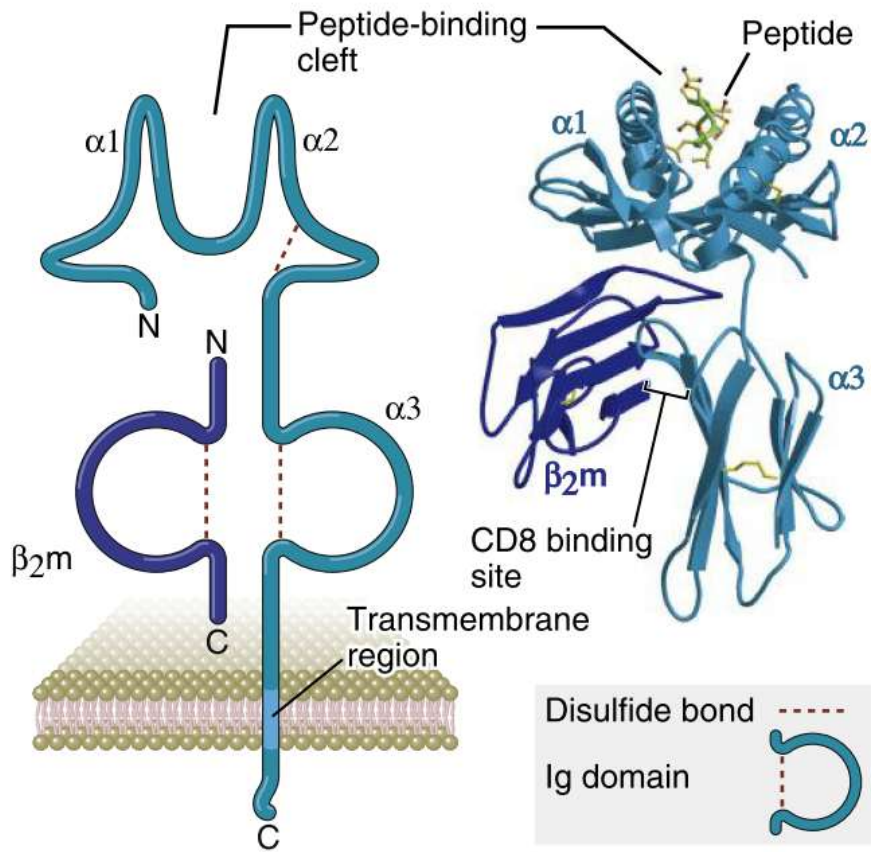


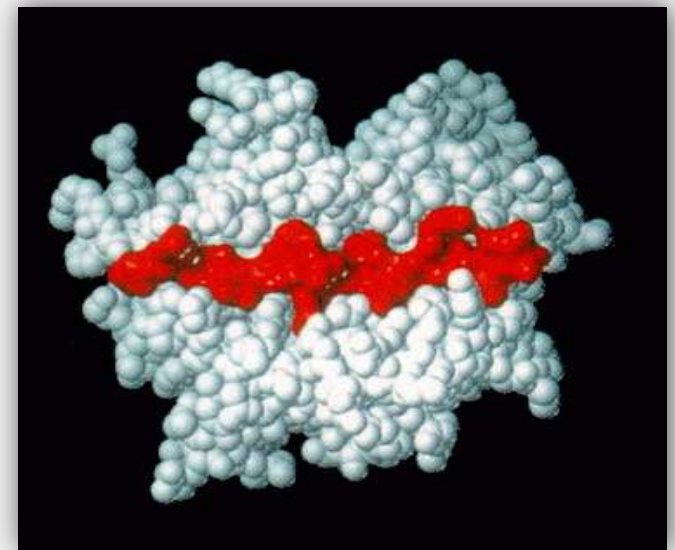
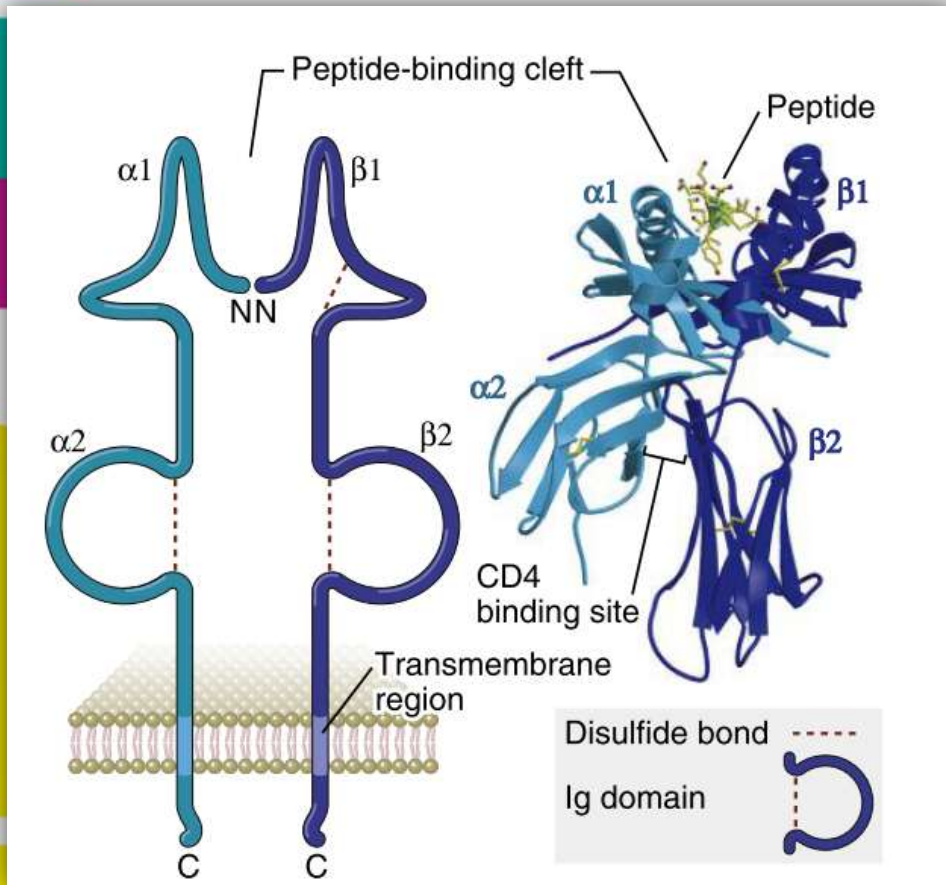
TABLE 6-4 Features of Class I and Class II MHC Molecules

Feature	Class I MHC	Class II MHC
Polypeptide chains	α β_2 -microglobulin	α and β
Locations of polymorphic residues	$\alpha 1$ and $\alpha 2$ domains	$\alpha 1$ and $\beta 1$ domains
Binding site for T cell coreceptor	CD8 binds mainly to the $\alpha 3$ domain	CD4 binds to a pocket created by parts of $\alpha 2$ and $\beta 2$ 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

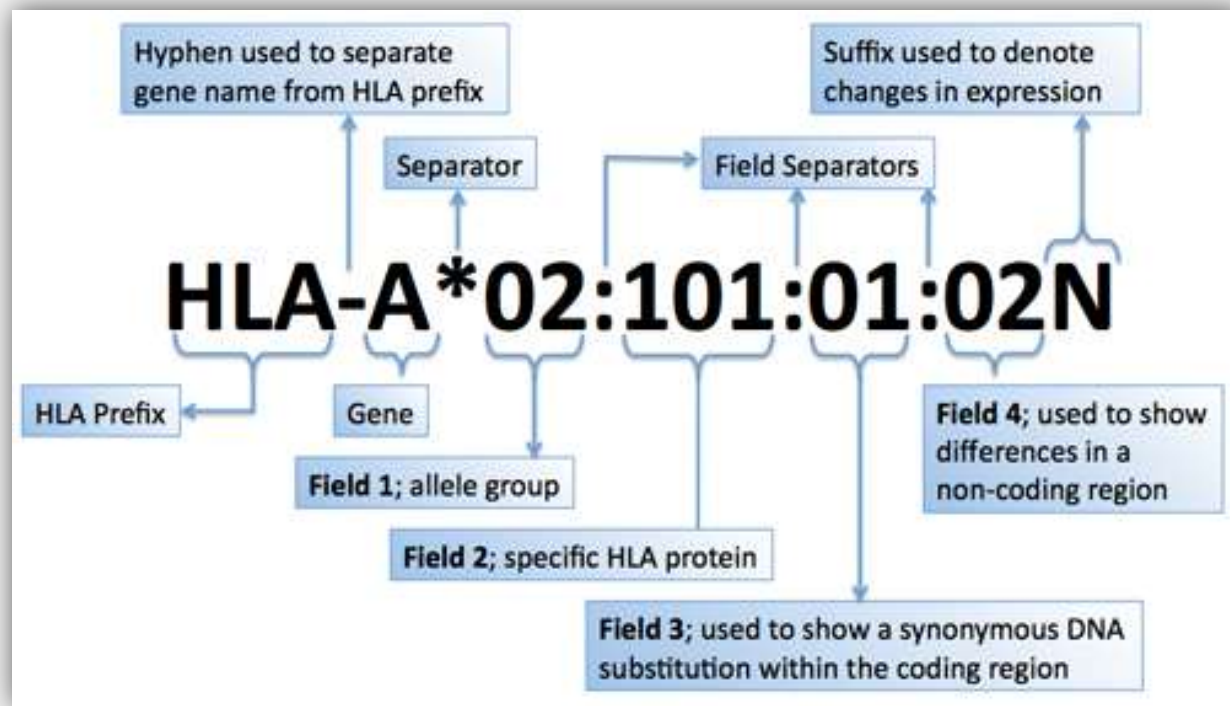
HLA class I



HLA class II

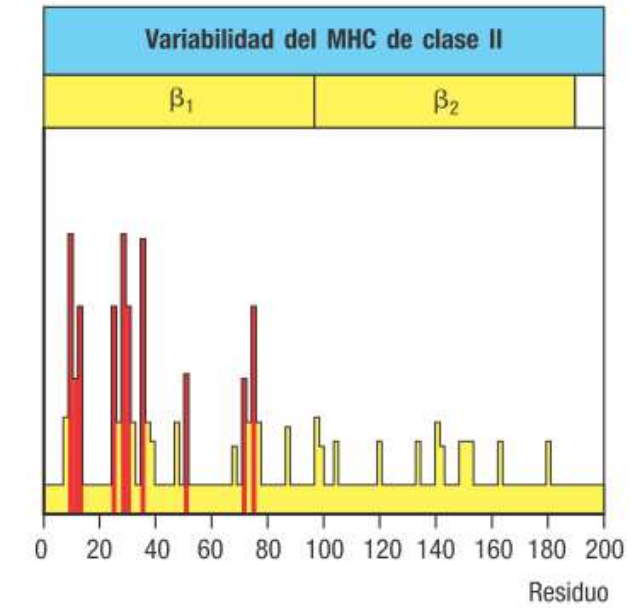
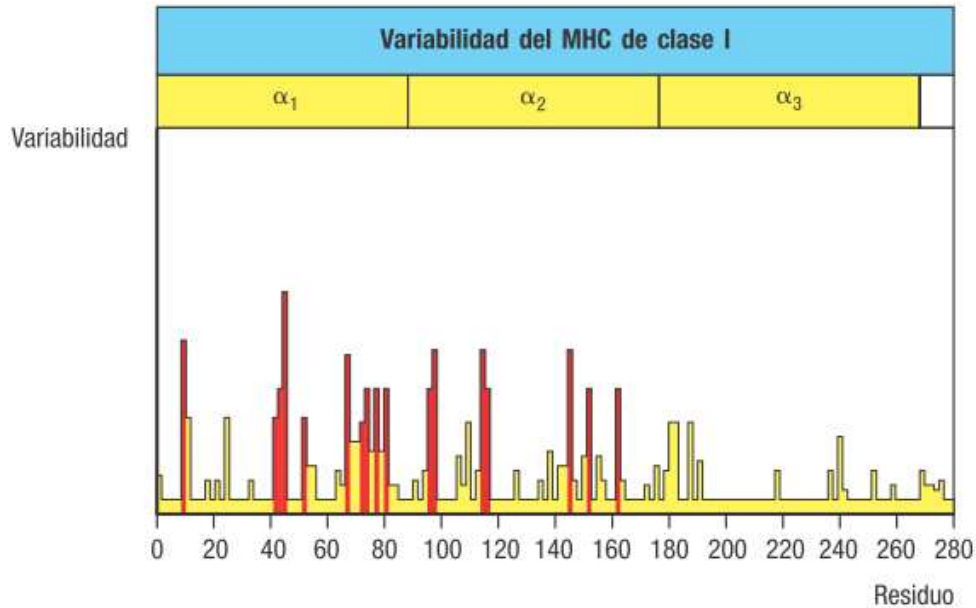
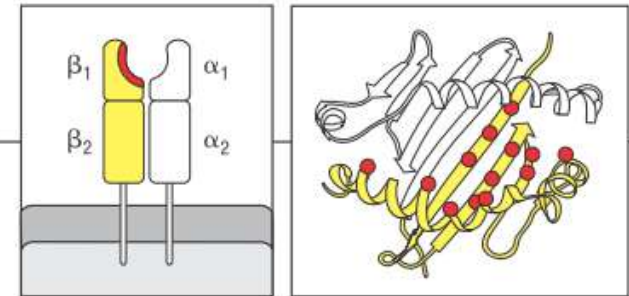
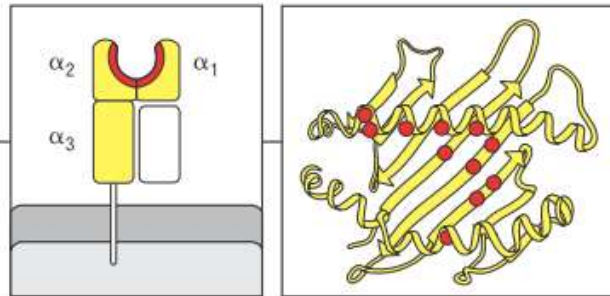


Nomenclatura



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)

Variabilidad específica



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 (<i>Yersinia</i> , <i>Salmonella</i> , <i>Gonococcus</i>)	B27	18
Reiter's syndrome	B27	37
Rheumatoid arthritis	DR4	10
Sjogren's syndrome	Dw3	6
Systemic lupus erythematosus	DR3	5

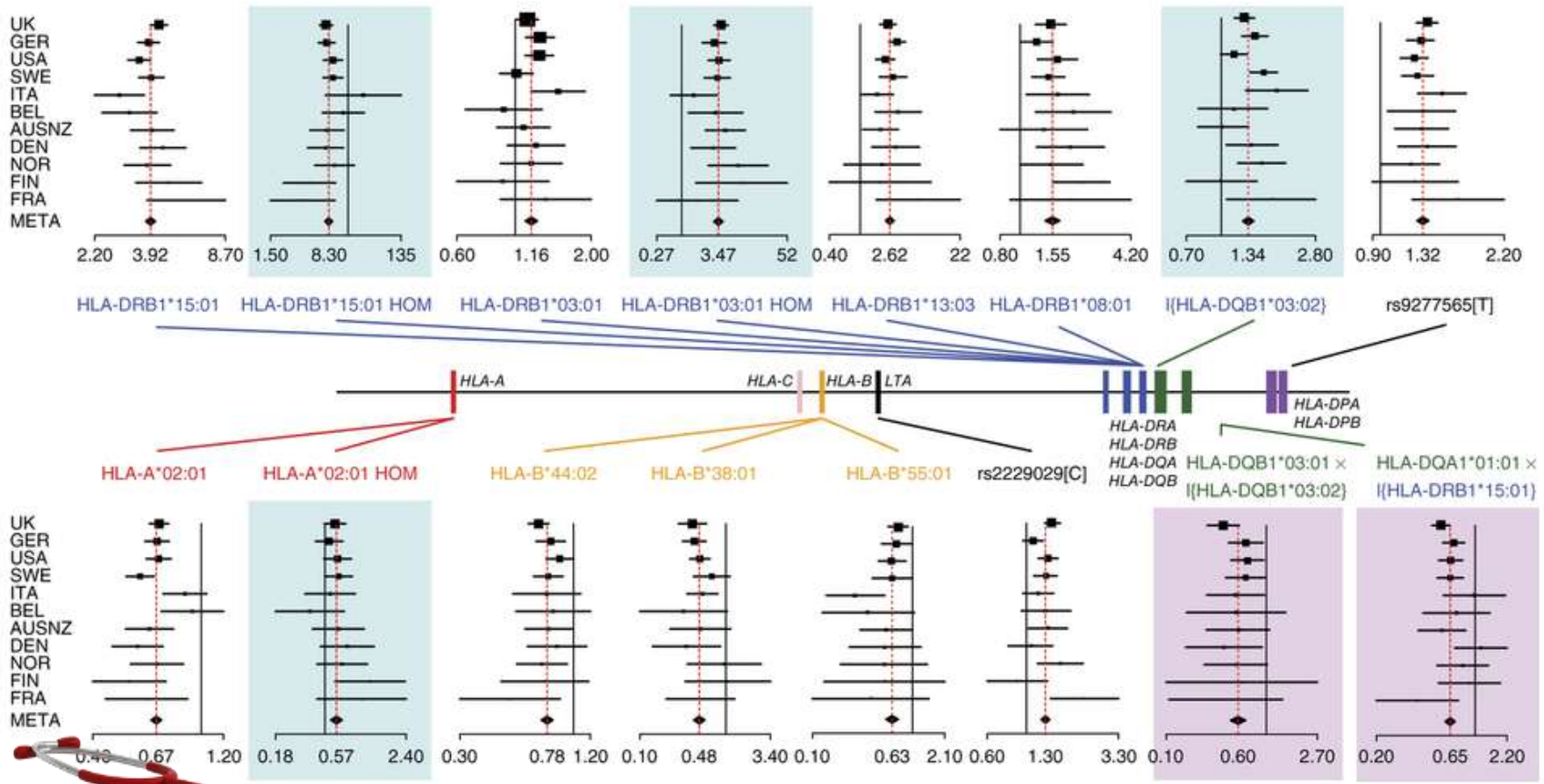
*Relative risk is calculated by dividing the frequency of the HLA allele in the patient population by the frequency in the general population:

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

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.



Un ejemplo: EM

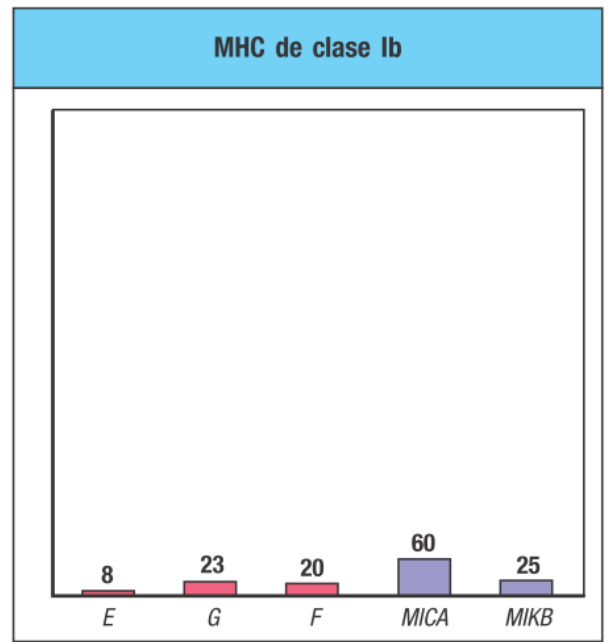
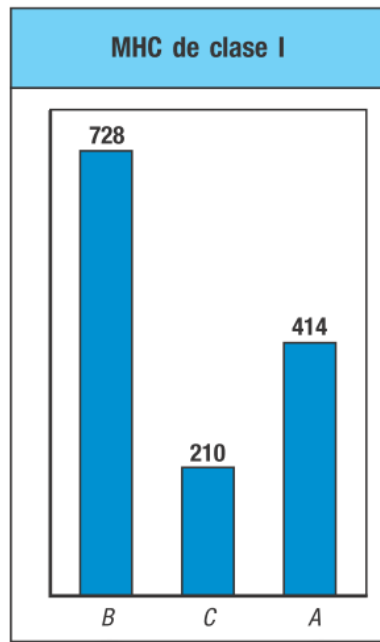
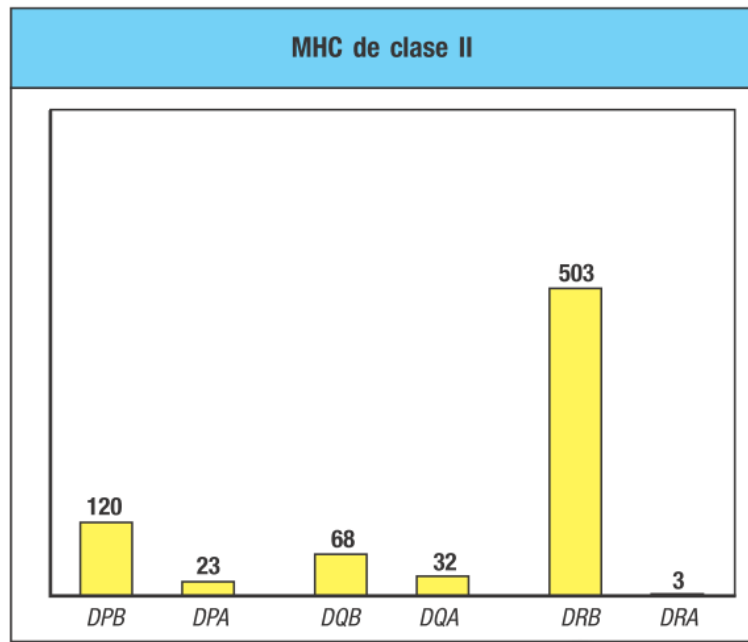


Mi opinión

- 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



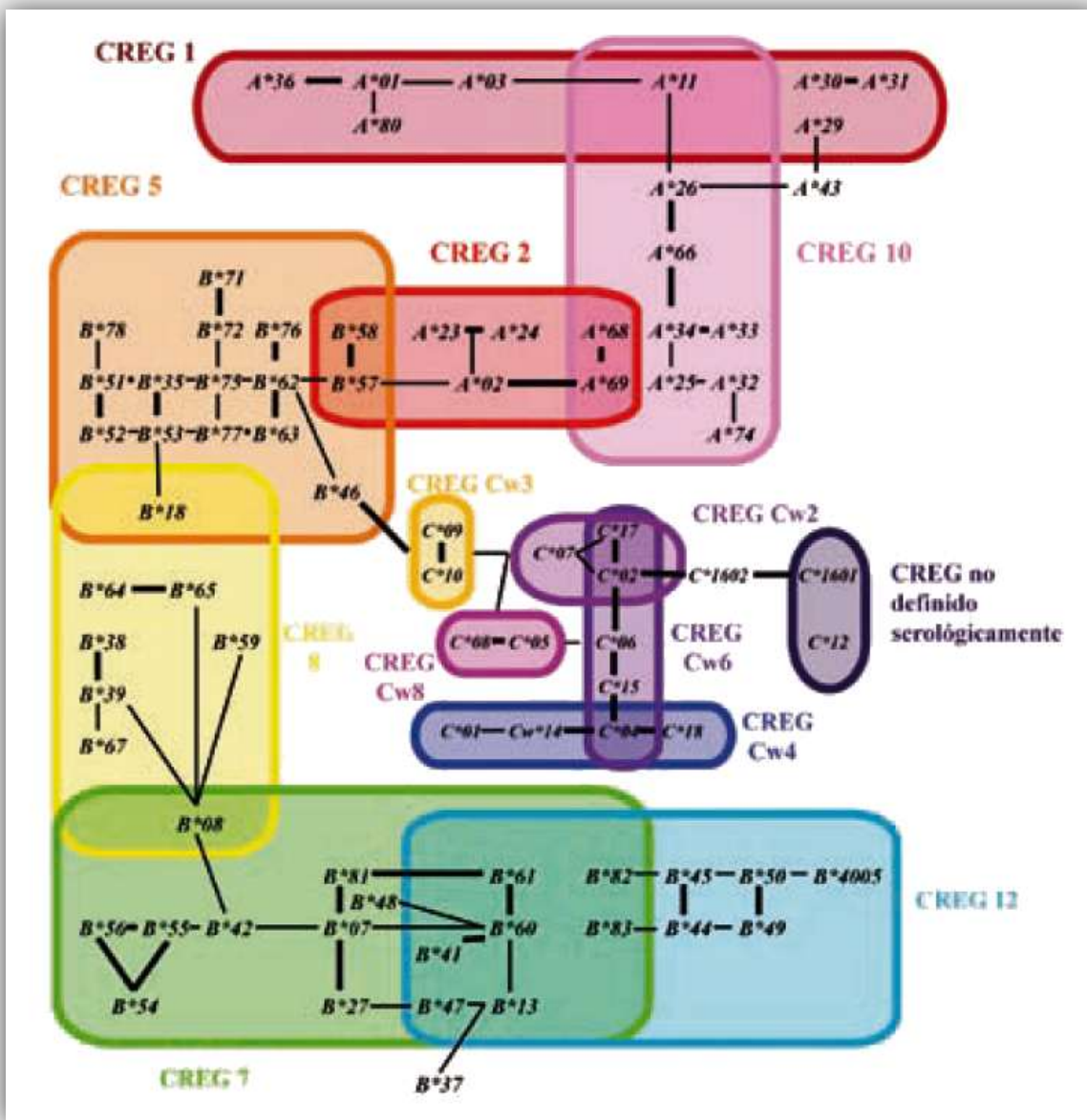
Variabilidad



- 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.



CREGs

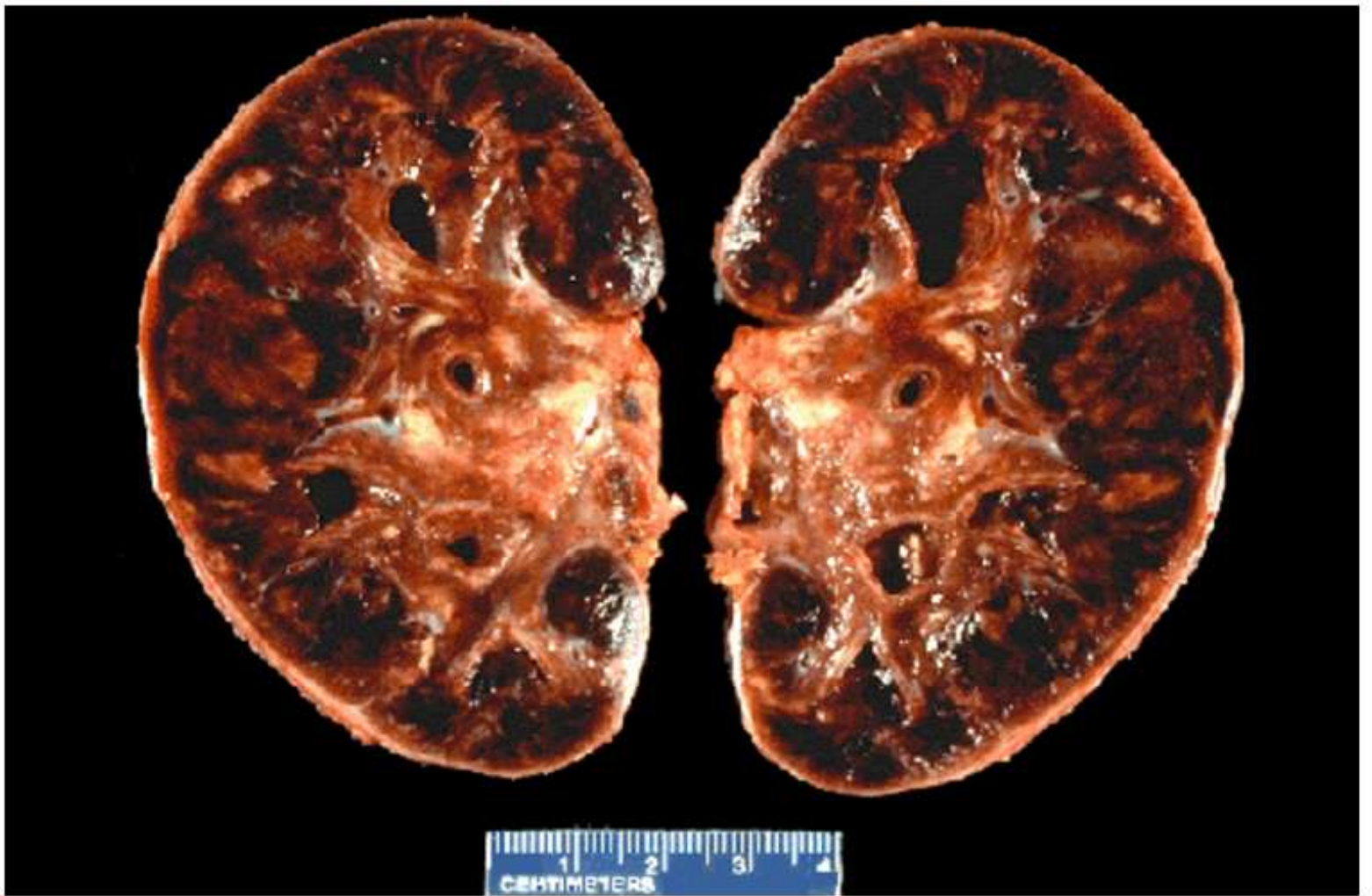


Typing Methods

Method	About method	Pros	Cons
Serotyping	Non-sequencing based typing method where antibodies specific to HLA proteins are used to identify the proteins on the cell surface.	<ul style="list-style-type: none">- Low Cost- Rapid- Traditional	<ul style="list-style-type: none">- Crude Method- Protein based detection- Inaccurate typing- Protein binding to more than one serotype
Sequence Specific Oligonucleotide Hybridization (SSO)	Typing method where specific oligos are first designed for genes of interest and then hybridized to patient or donor DNA to check for hybridization.	<ul style="list-style-type: none">- Checking of specific target- Efficient	<ul style="list-style-type: none">- Cannot account for unrecorded alleles- Hybridization errors- Need to know target sequence- Cannot phase
Sanger Sequencing	Sanger sequencing or Sequencing by Termination (SBT) is a classical method used for sequencing specific regions of the MHC.	<ul style="list-style-type: none">- Used to sequence regions of interest- Fast- Base pair resolution- Coverage only 2x	<ul style="list-style-type: none">- Different HLA alleles share similar sequences, difficulty aligning.- Cannot phase
Next-Gen Seq	Performing long range PCR to amplify HLA genes in MHC region, fragmenting the amplified genes and then performing deep sequencing.	<ul style="list-style-type: none">- Deep coverage (1000x)- Total MHC coverage- Rapid high throughput- Accurate and efficient- Phasing	<ul style="list-style-type: none">- Data Analysis



Implicaciones



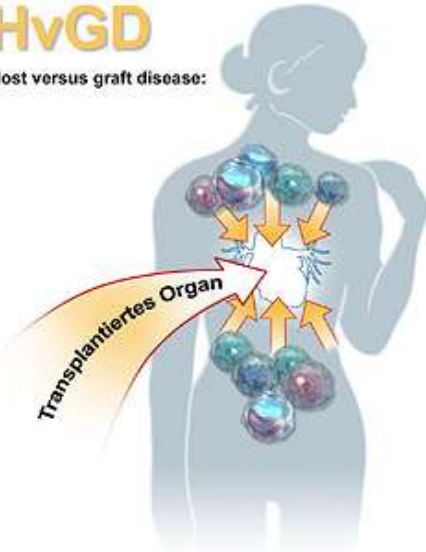
This kidney was removed because of acute transplant rejection. Note the swollen and hemorrhagic appearance of this entire kidney



GVHD

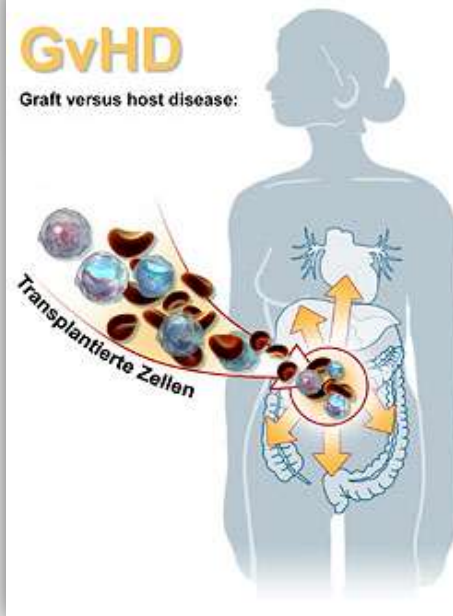
HvGD

Host versus graft disease:



GvHD

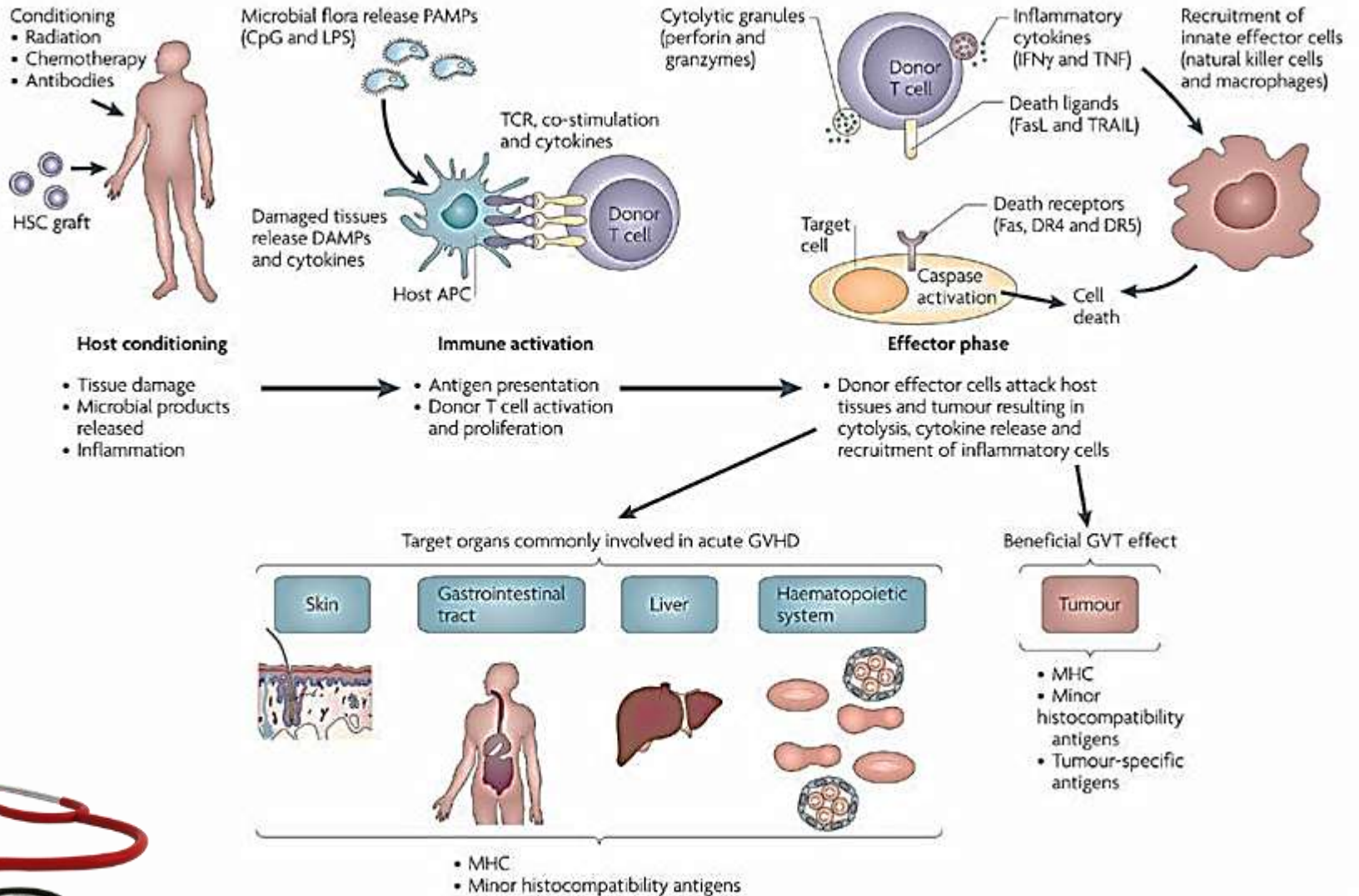
Graft versus host disease:



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



Graft-versus-host disease



Graft-versus-host disease

HLA	Match or mismatch*	N	Acute GVHD (Grade III-IV)†			Acute GVHD (Grade II-IV)†			N	Chronic GVHD‡		
			RR	95% CI	P	RR	95% CI	P		RR	95% CI	P
A	Match	7048	1.00		.001	1.00		.002	5892	1.00		.328
	Mismatch	636	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	311	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	4716	1.63	1.45-1.83		1.27	1.17-1.37		4716	1.24	1.13-1.35	
DRB1	Match	5878	1.00		.022	1.00		<.001	4936	1.00		.262
	Mismatch	1592	1.21	1.03-1.43		1.24	1.11-1.39		1592	0.93	0.82-1.05	
DQB1	Match	5881	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)†			Acute GVHD (Grade II-IV)†			Mortality‡		
		RR	95% CI	P	RR	95% CI	P	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

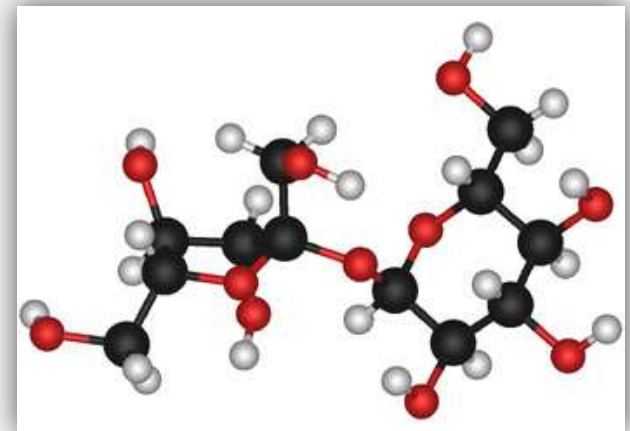
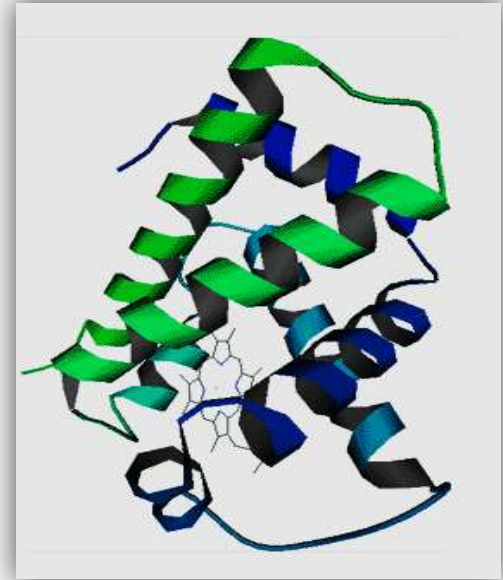


Ahora si: Presentación antigénica



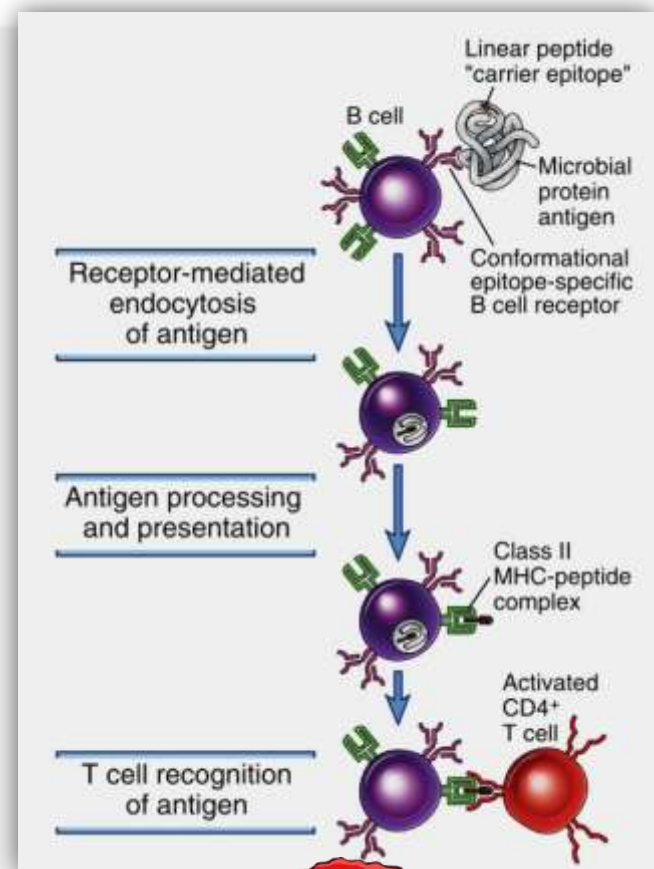
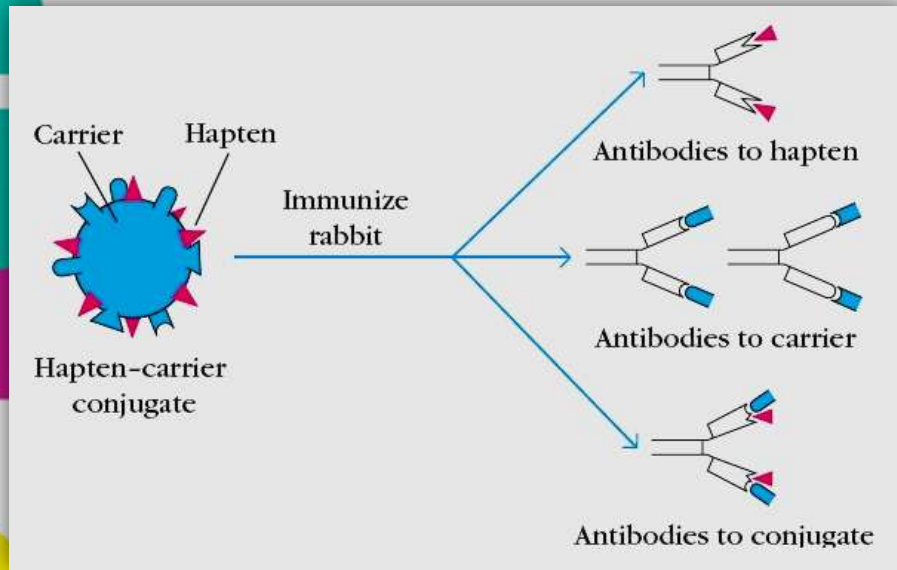
Pero ya va!!!! Antígenos???

- **Antígeno:** Sustancia extraña capaz de ser reconocida por el sistema inmune, específicamente por el TCR o BCR
- **Inmunógeno:** es un antígeno que es capaz de provocar una respuesta inmune incluyendo la producción de anticuerpos
- **Antigenicidad:** es la capacidad de una sustancia para combinarse específicamente con los productos de la respuesta inmune (anticuerpos, TCR)
- **Inmunogenicidad:** Es la capacidad de una sustancia para inducir una respuesta inmune celular u humoral



Antigénico no siempre inmunogénico

Haptenos



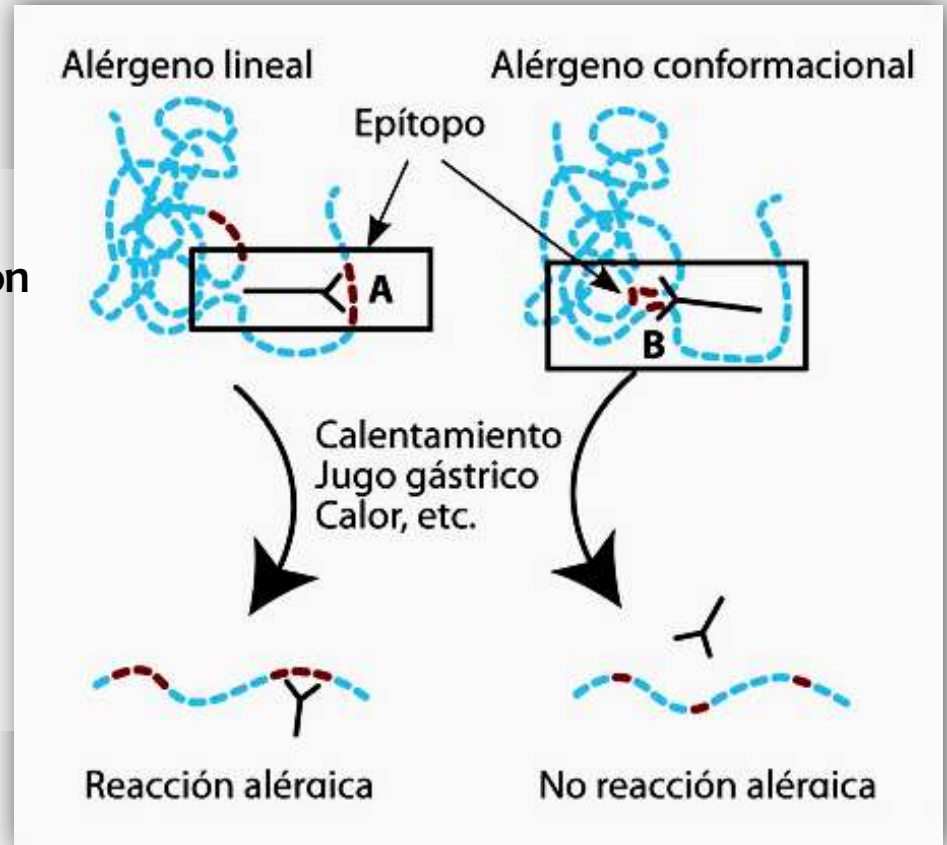
- Hapteno: Sustancia de bajo peso molecular que no es capaz de inducir una respuesta inmune por sí misma, pero que es capaz de reaccionar con los productos de una respuesta inmune específica (anticuerpos).
- Pueden comportarse como inmunógenos cuando se unen a una molécula portadora (Portador o Carrier)



Epítopes

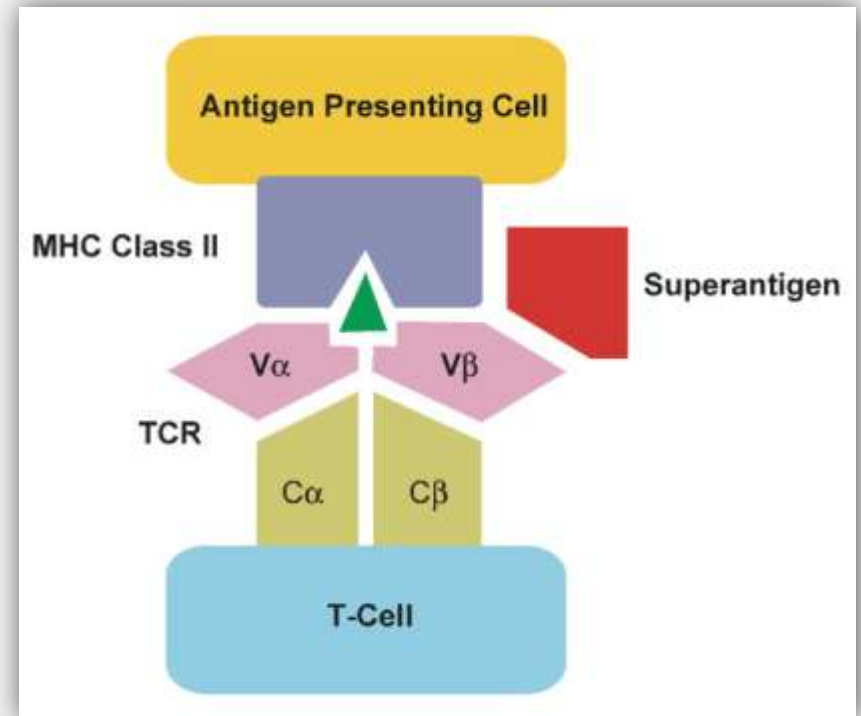
- Epítipo o determinante antigénico: Porción del antígeno que interactúa con el TCR, BCR o con los anticuerpos secretados

- ✓ Lineales
- ✓ Conformacionales



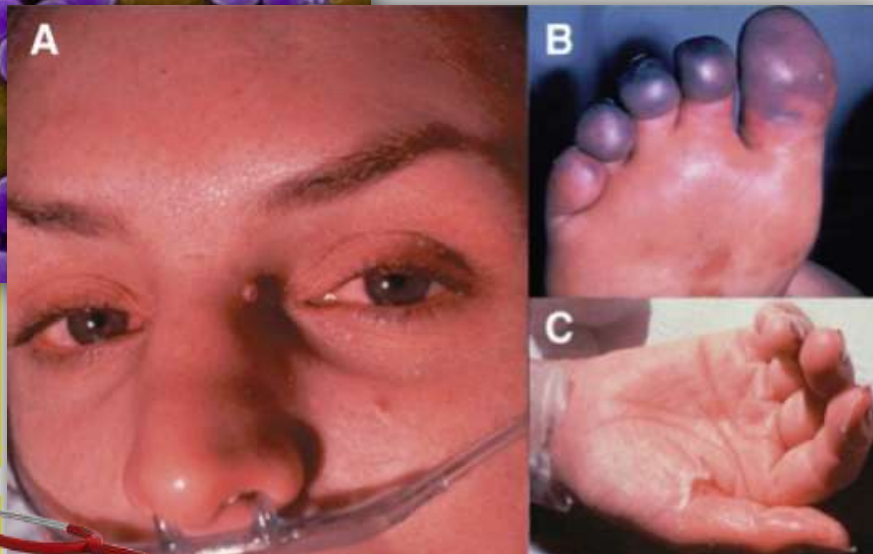
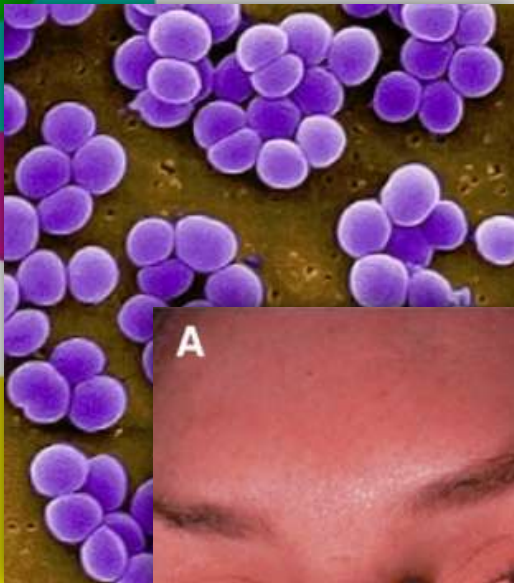
Superantígenos

- Endógenos, provienen principalmente de virus (EBV)
- Exógenos, provienen principalmente de microorganismos: staphylococcal enterotoxins A, B, C1 to C3, streptococcal pyrogenic exotoxins A1 to A4, C.
- Superantígenos de células B (staphylococcal protein A and protein Fv)



Superantígenos

- Staphylococcal enterotoxins A, B, C1 to C3
- Toxic shock syndrome



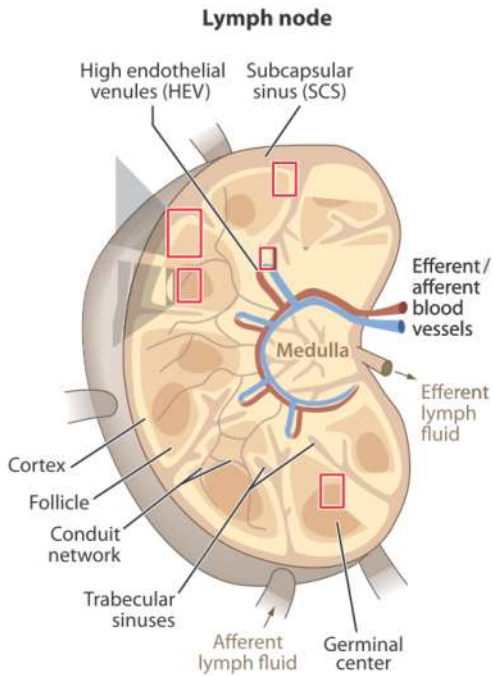
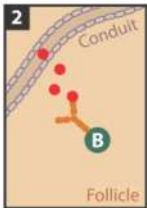
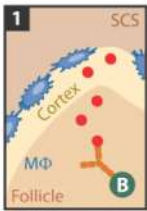
Front Immunol. 2016; 7: 23.

TABLE 2 | Common differentially expressed genes induced by superantigens *in vitro* and *in vivo*.

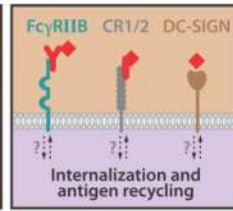
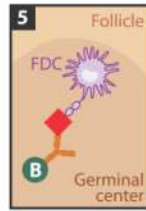
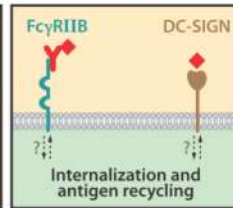
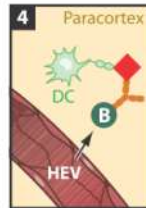
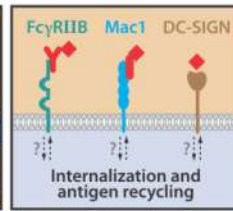
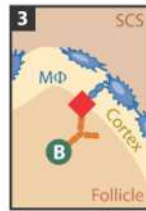
Pathway/network	Gene	Major function	
Innate response	IL6, TNF α , LTA, IL17A, IL22	Host defense, inflammation	
	IFN γ	Host defense, antimicrobial	
	CXCL11, CXXC5, OCL7, XCL1	Host defense, cell migration	
	CISH, CIITA, GBP2, TRAF1, RGS16	Signal transduction	
	PDE4DIP, PDE4B, PTGER3, P2RY14	Signal transduction	
	NEDD9, GNAS, CSF1R	Signal transduction	
	STAT1, STAT2, STAT3, IRF7	Transcription factor (TF)	
	BATF, BATF2	IFN-inducible TF	
	SOCS1, SOCS2, SOCS3	JAK/STAT counter-regulator	
	CD69, CD74, ICAM	Immune regulation	
	NRP2	Vascular signaling	
	Rel A, Rel, NF κ B α	NF κ B regulator	
	DNA damage response	RIPK2	DNA sensor interactor
		CTPS, UPP1	Nucleic acid synthesis
PIM1, PIM2		DNA repair/assembly	
GADD45G		DNA repair adaptor	
ER stress/oxidative stress	SIAH2	Ubiquitin E3 ligase	
	KCNE4	Membrane integrity	
	JunB	Stress response TF	
	MGST1	Cell protection	
Metabolic stress	IL2, IL2RA, MACF1	Cell proliferation regulator	
	FABP4, CD36	Fatty acid metabolism	
	HK1, PDK4, PGS1	Cell metabolism	
	TARS, NDST2	Synthetase	
Apoptosis	PLSCR1, NR4A1	Membrane integrity	
	CD40, TNFRSF9	TNFRSF, death receptor	
	Casp 4, CFLAR	Caspase regulator	
	VCAN, LMNB1	Cell matrix breakdown	
	BCL2, BCL6	Anti-apoptotic regulator	
	CCND2	Cell cycle regulator	
	PLA2G7	Cardiovascular damage	
Others	ARID5A, ZBTB32, NDST2		

Fuente de Antígenos

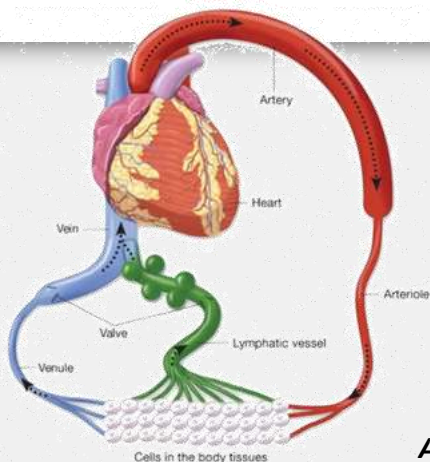
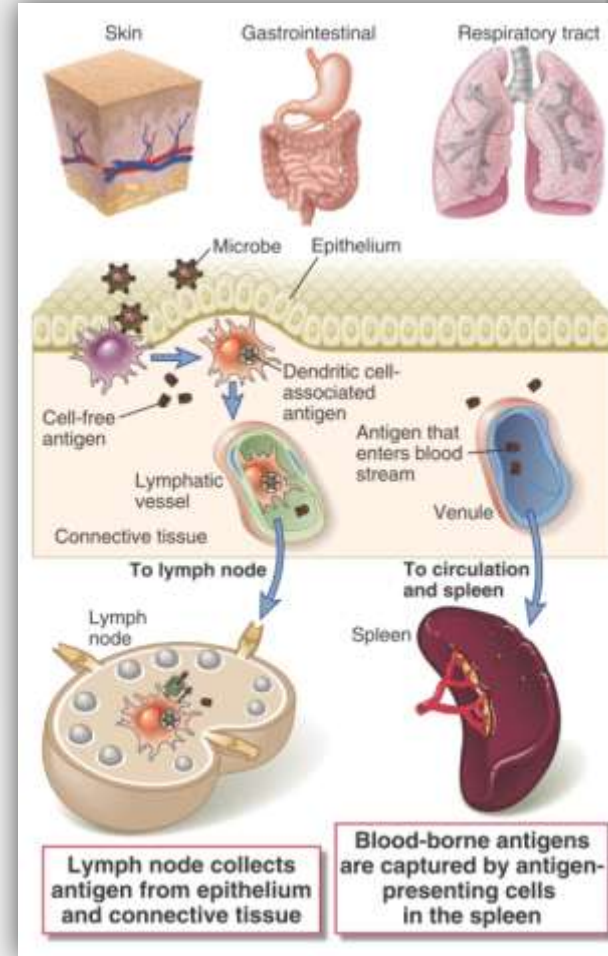
Small antigen
(<70 kDa)



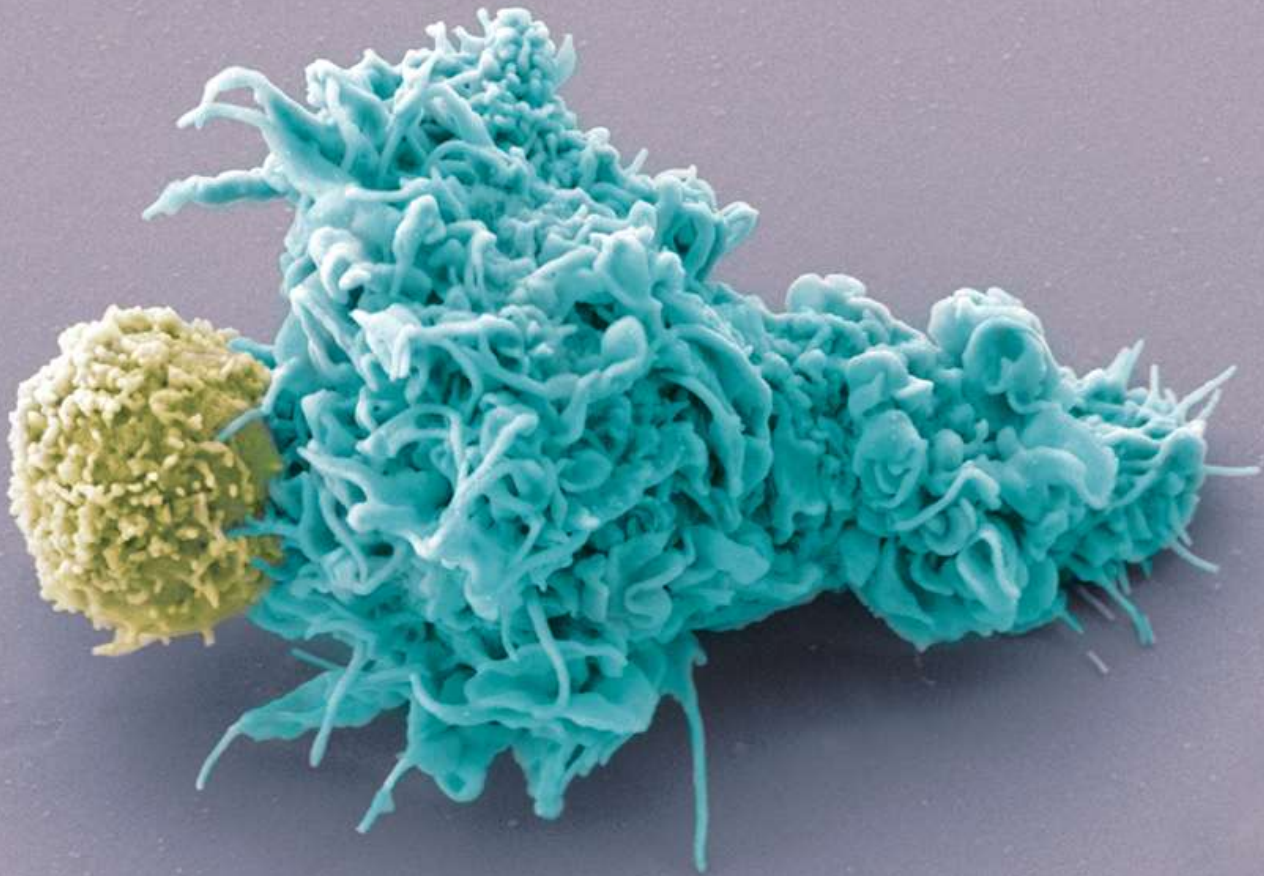
Larger antigen
(>70 kDa)



Cell surface receptors



Y quien presenta???



Tipos de APC

Profesionales vs no profesionales

Profesionales

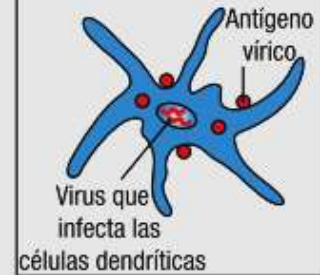
- **Células dendríticas**
- Macrófagos
- Células B

No profesionales

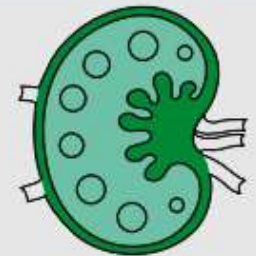
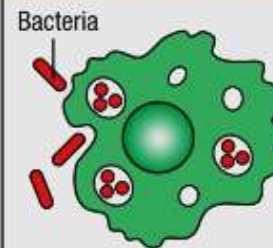
- Células endoteliales
- Fibroblastos
- Células epiteliales del timo

Y las otras...

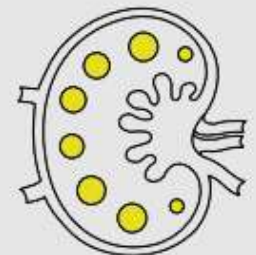
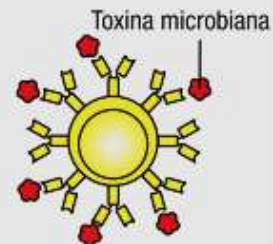
Células dendríticas (células reticulares interdigitantes)



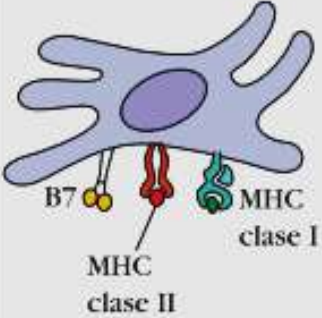

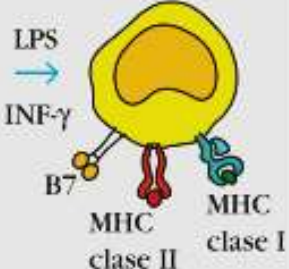
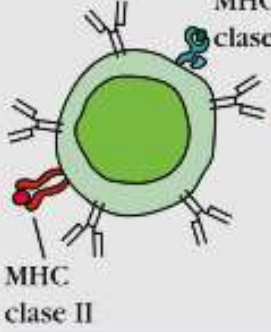
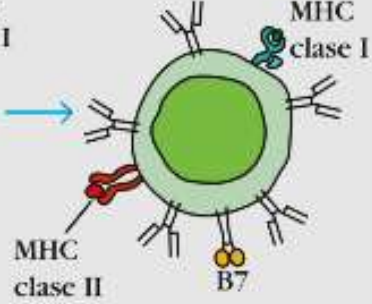
Macrófagos



Células B



Células presentadoras de Antígenos

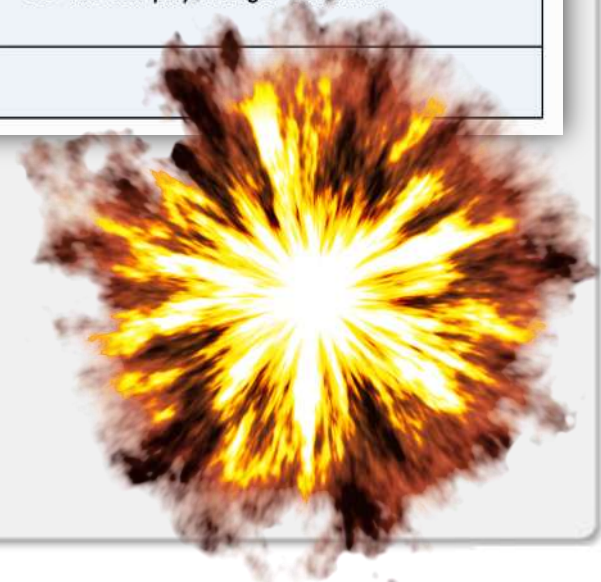
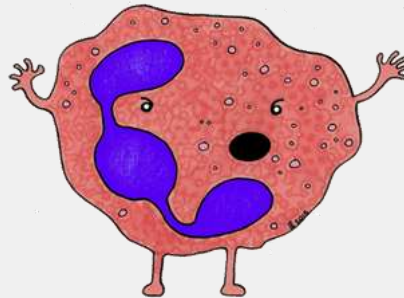
	Célula dendrítica	Macrófago		Linfocito B	
		<p>En reposo</p> 	<p>Activado</p> <p>LPS → INF-γ</p> 	<p>En reposo</p> 	<p>Activado</p> 
Captación de antígeno	Endocitosis, fagocitosis (por células de Langerhans)	Fagocitosis	Fagocitosis	Endocitosis mediada por receptor	Endocitosis mediada por receptor
Expresión 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

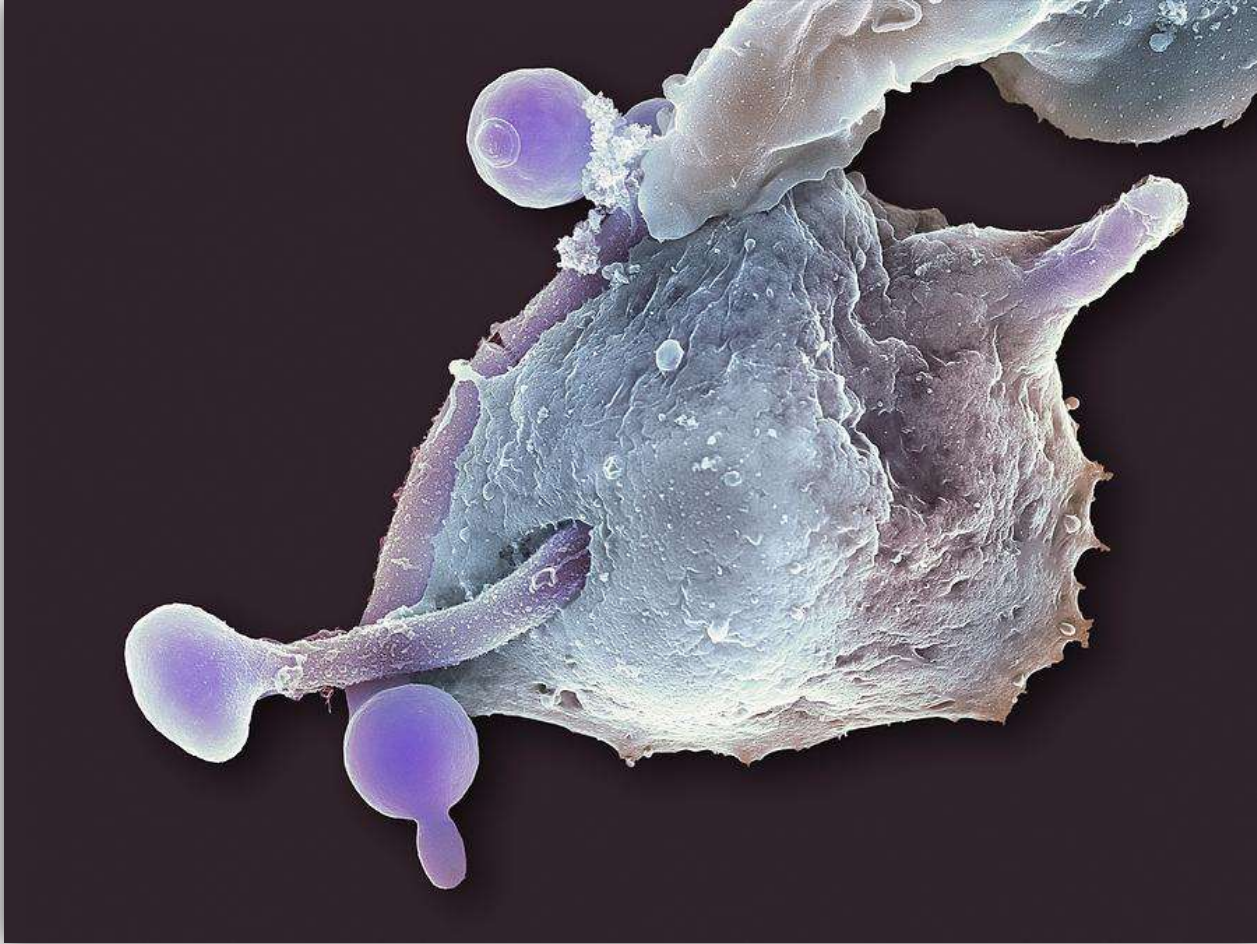
TABLE 6-2 Properties and Functions of Antigen-Presenting Cells

Cell Type	Expression of		Principal Function
	Class II MHC	Costimulators	
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.



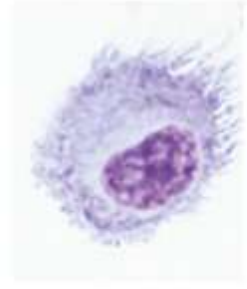
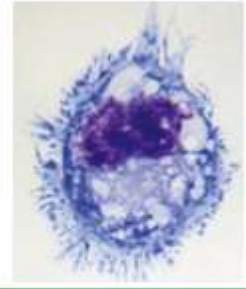
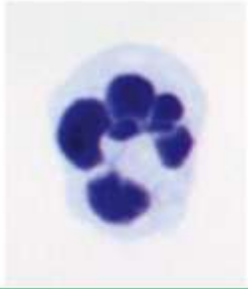
Y los granulocitos!!!



Neutrófilos???

Professional Phagocytes

APCs



Neutrophils

Hybrids

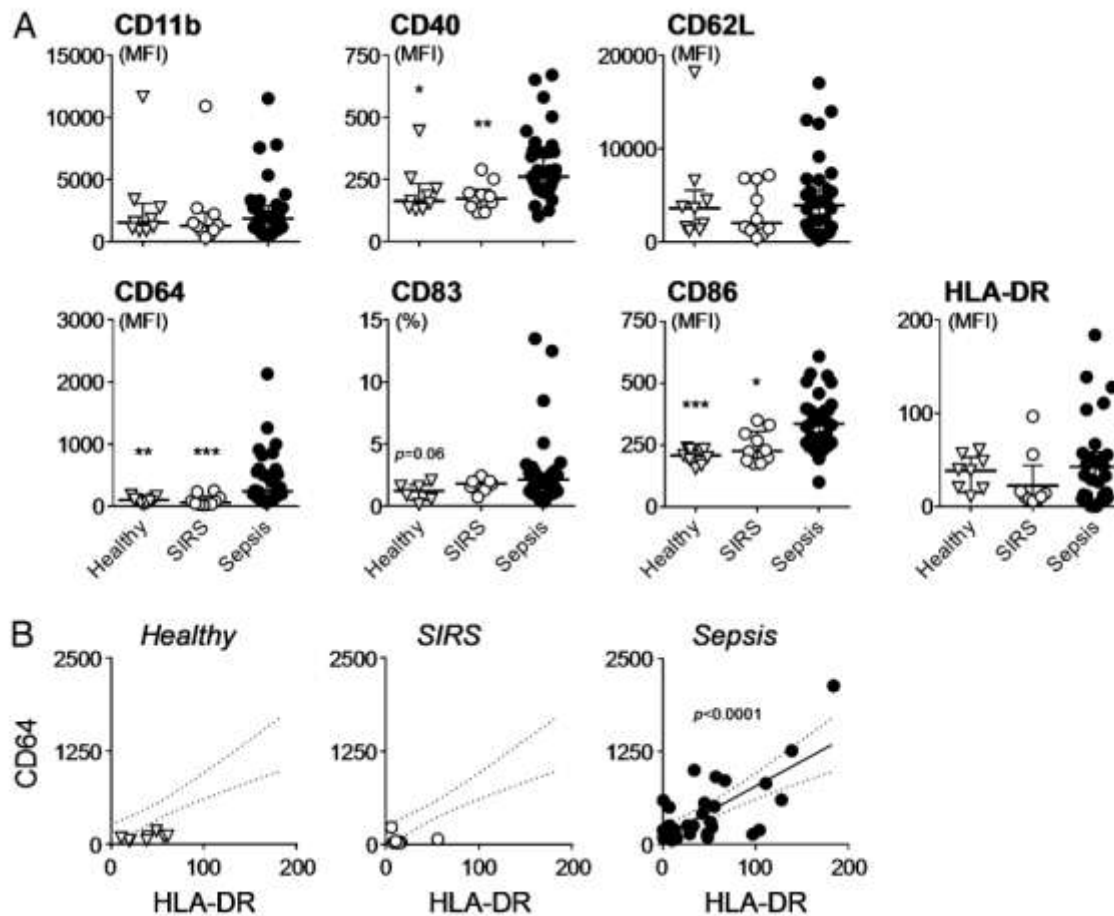
DCs

Ly6G, 7/4, CD62L & CXCR2
Endocytosis
NET formation
Bacterial killing
MPO & MMP9 production
Cathelicidin

MHC II, CD11c & CD205
Morphology
Probing motion
Podosome formation
Cytokine production
Antigen presentation

Figure 1. Dual properties of neutrophil-DC hybrids. Neutrophil-DC hybrids (in red) exhibit the surface markers and functional properties of neutrophils as shown in green. At the same time, hybrid cells resemble conventional DCs by surface phenotype, morphology, and function, as shown in blue.

Solo en crisis???



Eosinófilos?????

International Archives of
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Original Paper

Int Arch Allergy Immunol 2008;146:227–234
DOI: [10.1159/000115891](https://doi.org/10.1159/000115891)

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Human Eosinophils Show Chemotaxis to Lymphoid Chemokines and Exhibit Antigen-Presenting-Cell-Like Properties upon Stimulation with IFN- γ , IL-3 and GM-CSF

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Kyung-Ha Ryu^e Hae-Kyung Park^b Ju-Young Seoh^b

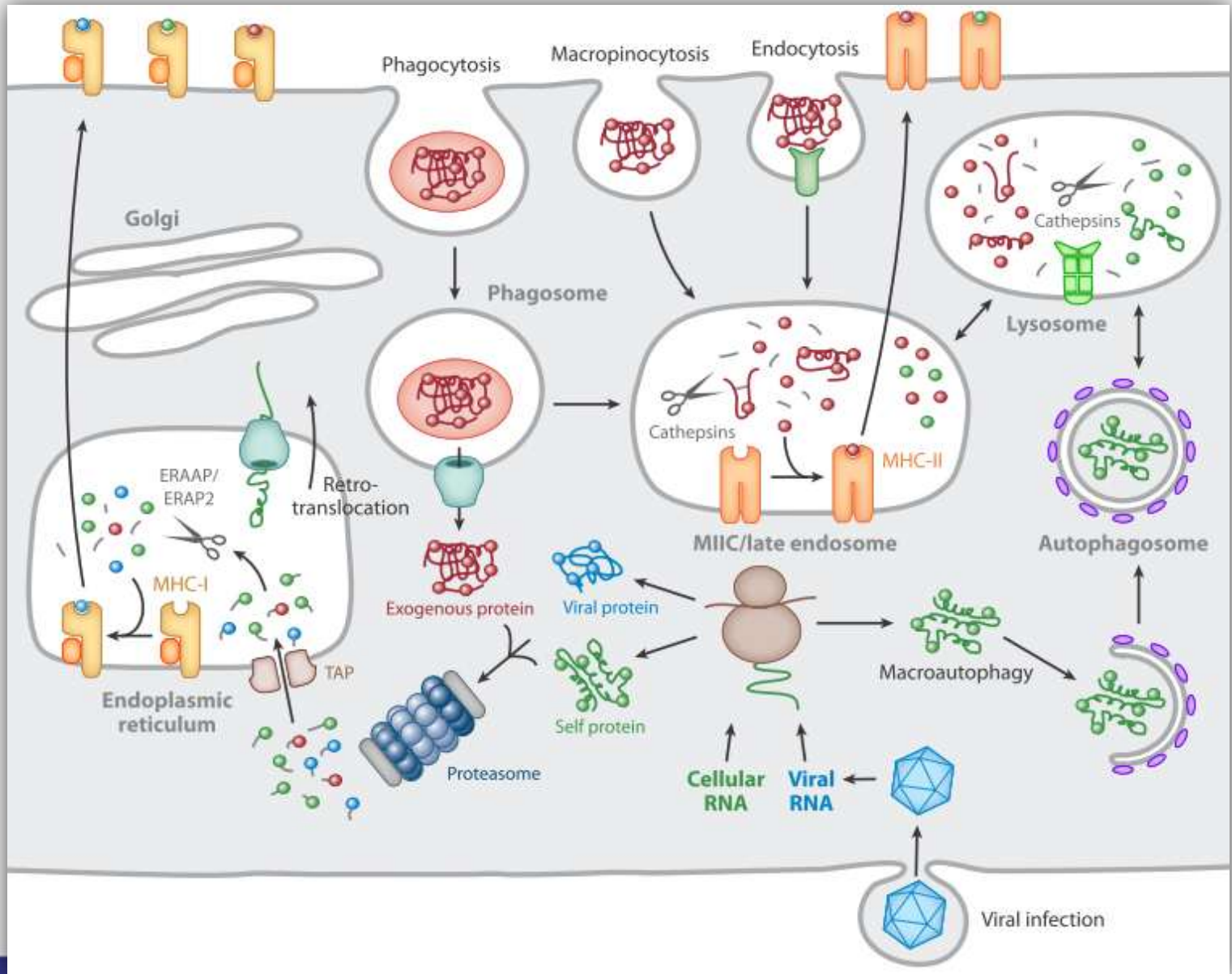
Eur. J. Immunol. 1992. 22: 1919–1925

Eosinophil as antigen-presenting cell 1919

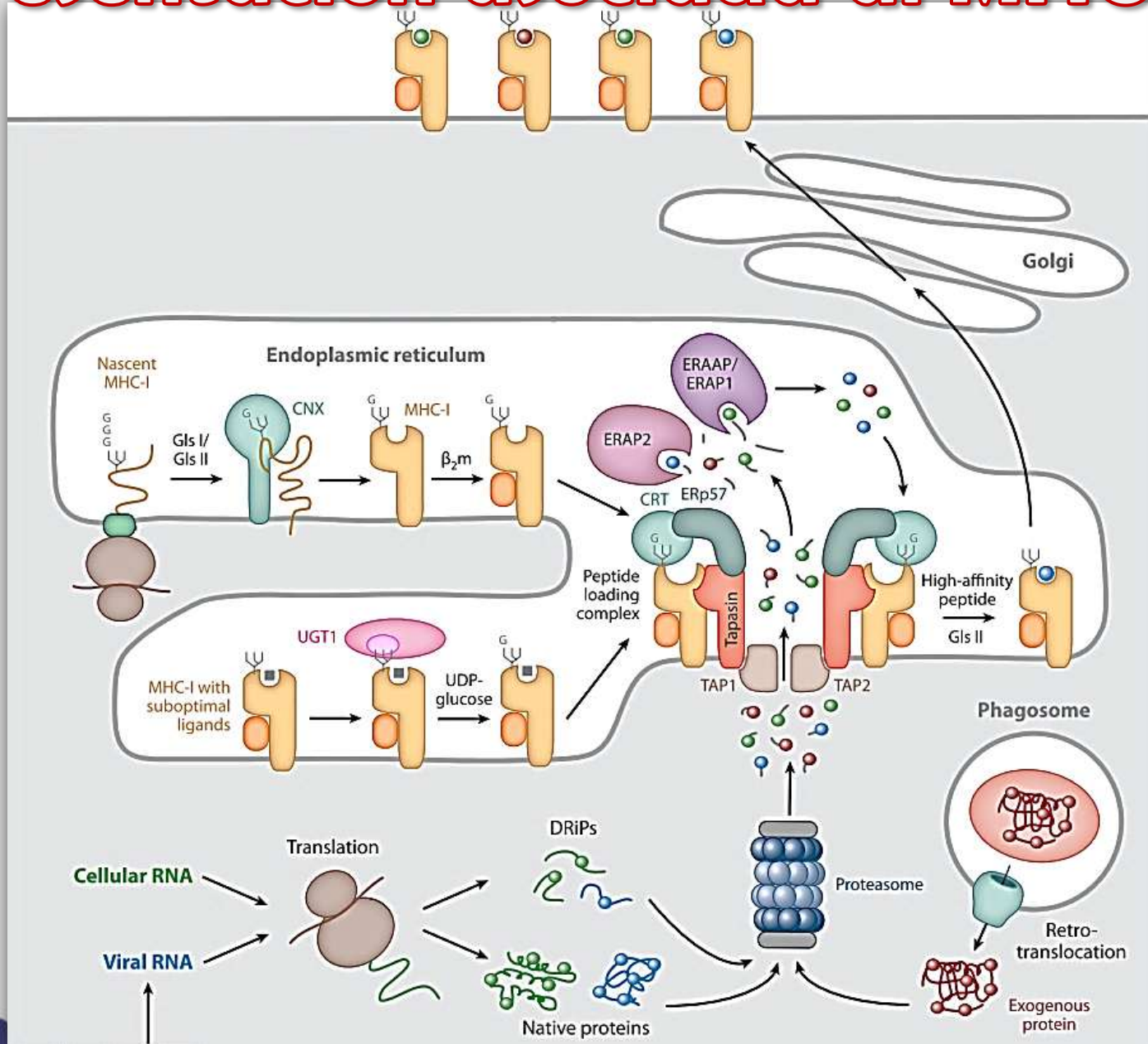
Victoria Del Pozo[◆],
Belen De Andrés[◆],
Elena Martín[▲],
Blanca Cárdbaba[▼],
Julio Cesar Fernández,
Soledad Gallardo,

Eosinophil as antigen-presenting cell: activation of T cell clones and T cell hybridoma by eosinophils after antigen processing*

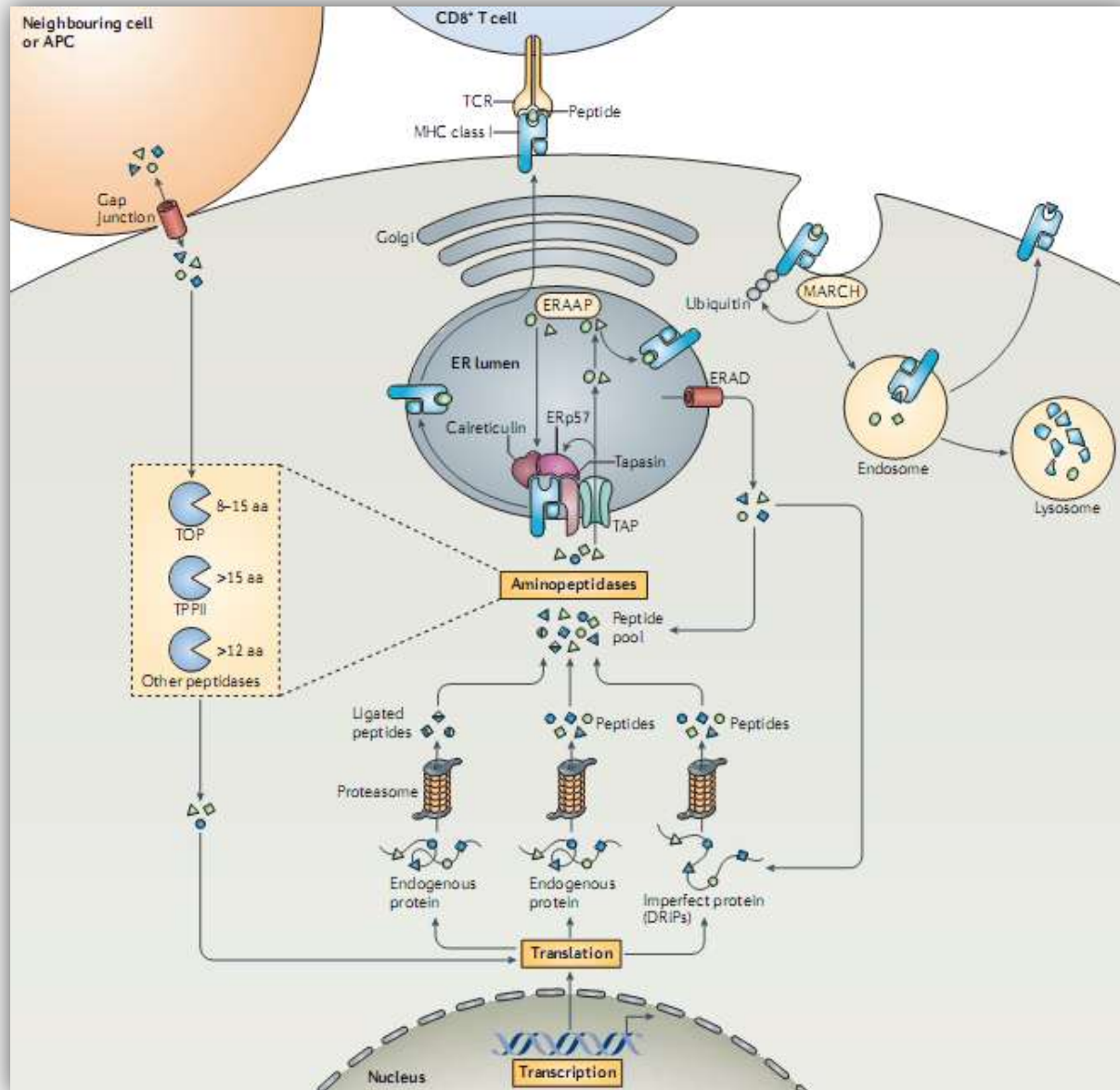
PRESENTACIÓN ANTIGÉNICA



Presentación asociada al MHC I

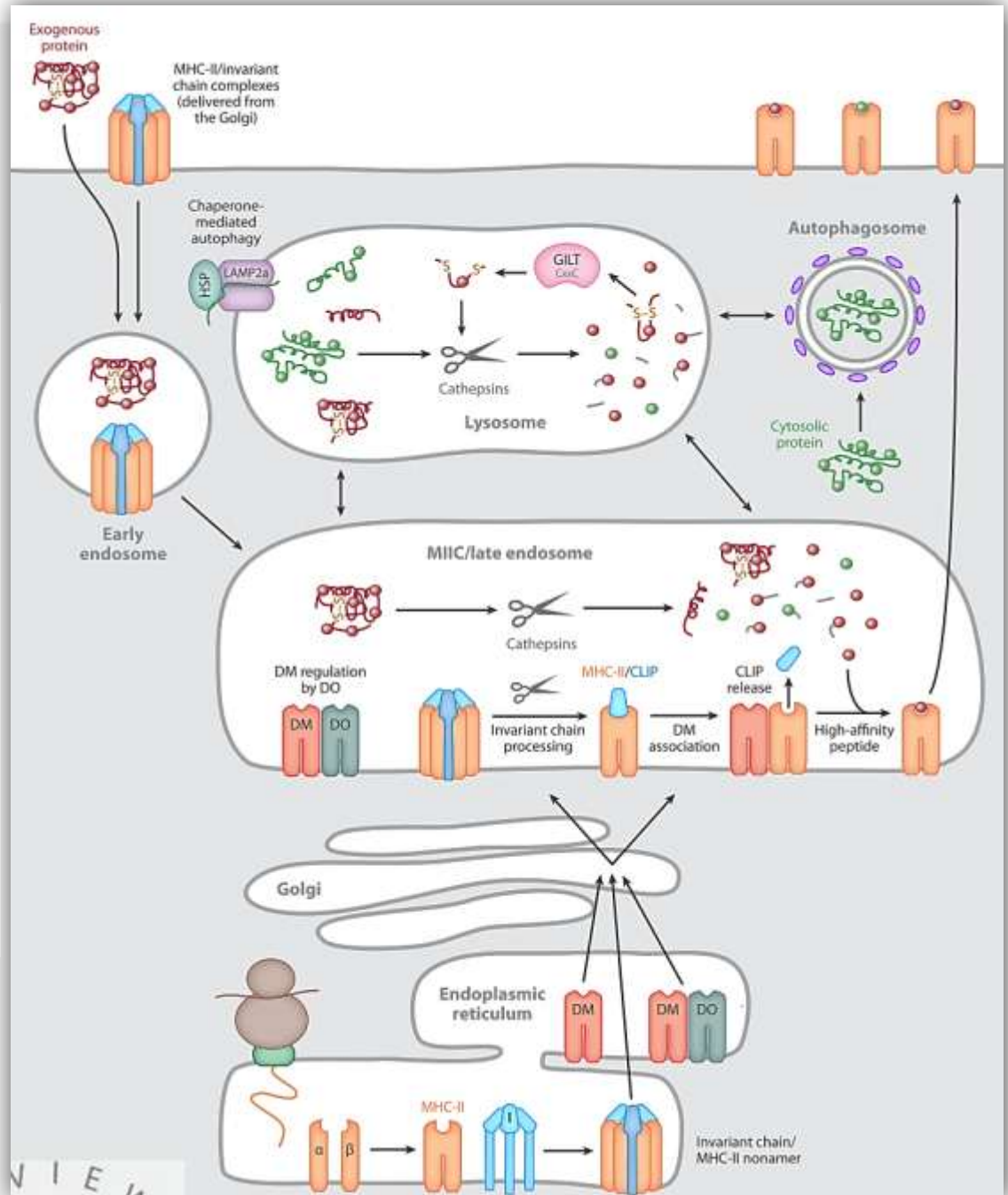


Ay hazlo tu!!!!

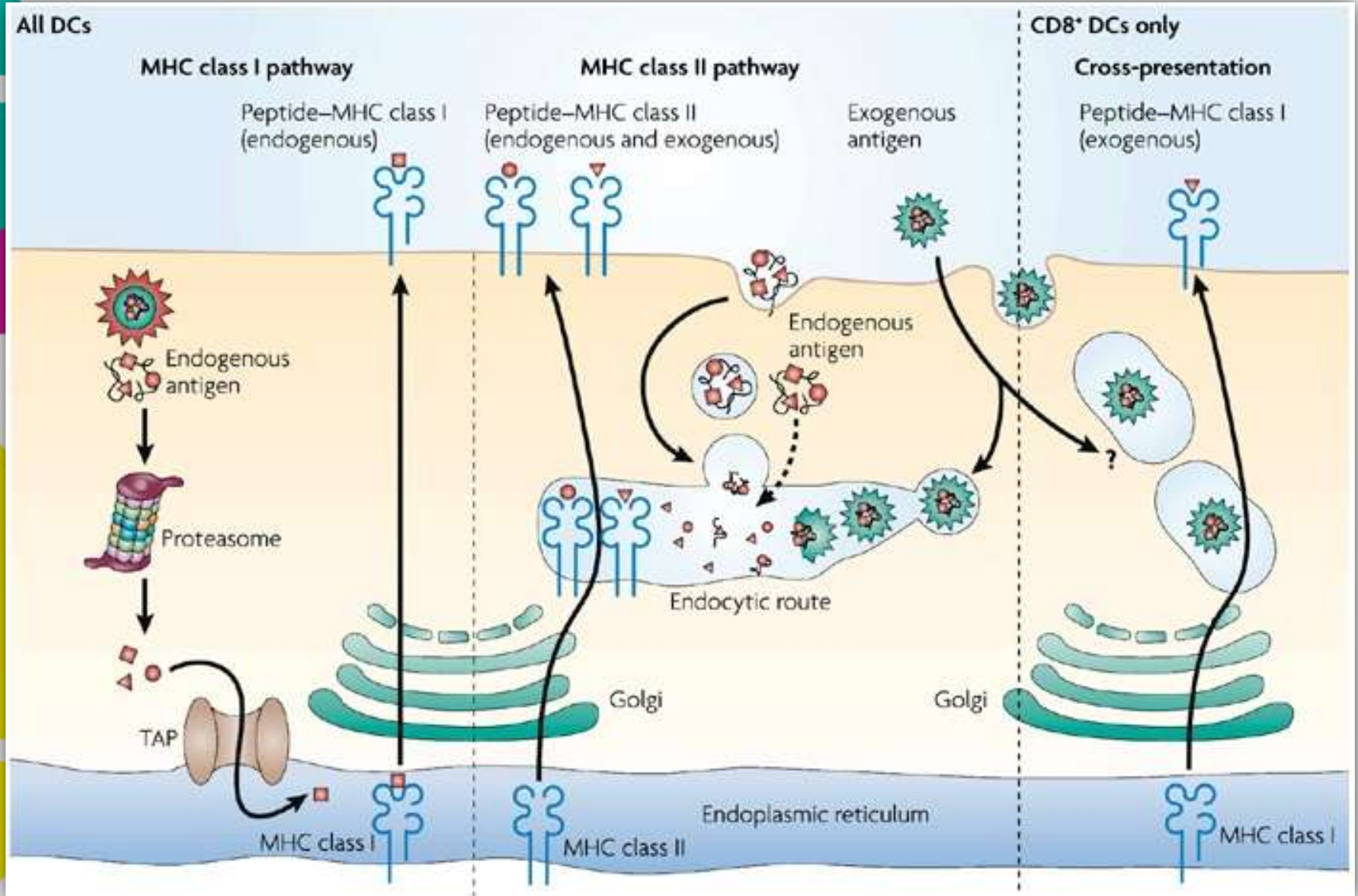


Presentación asociada al MHC II

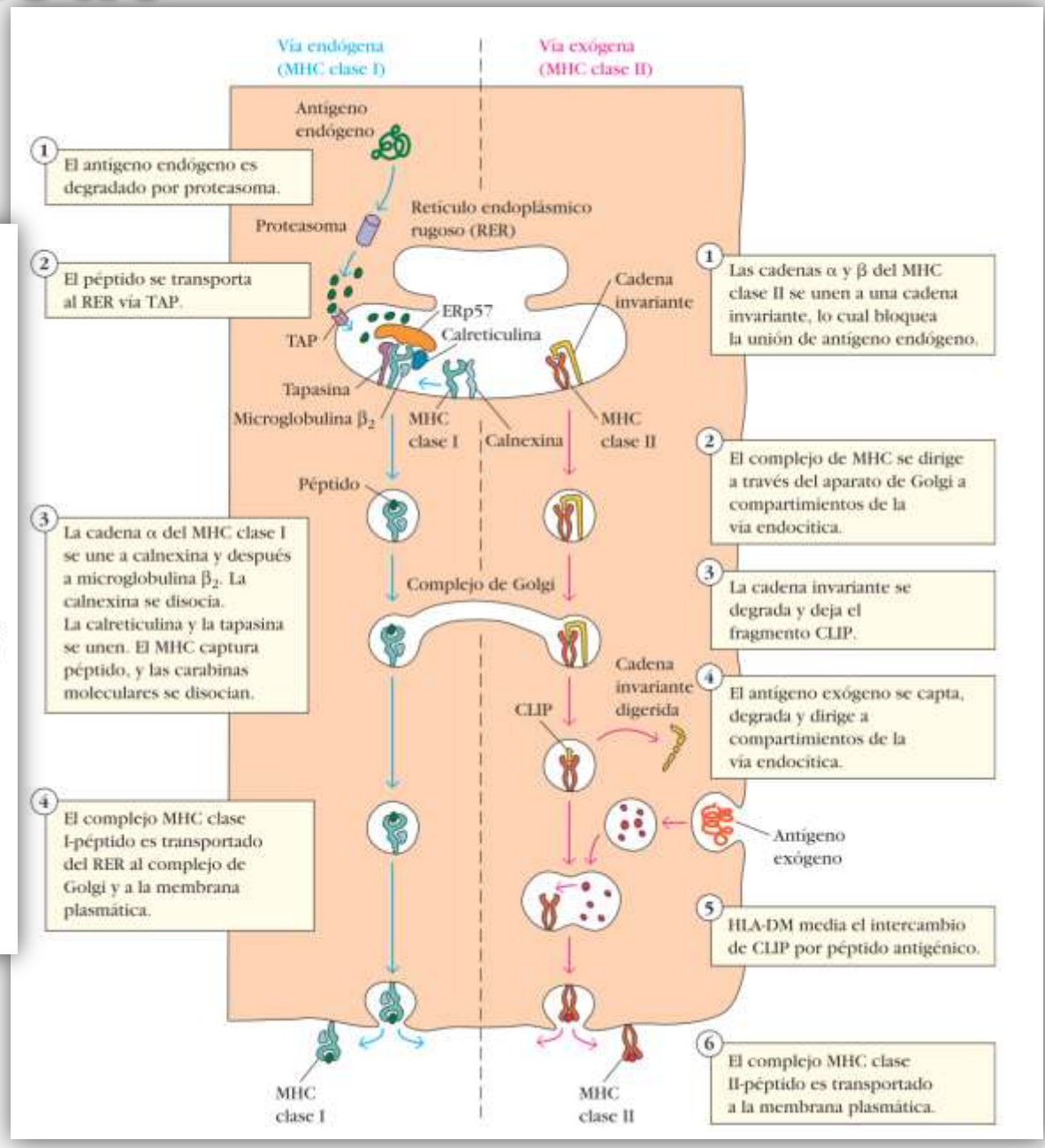
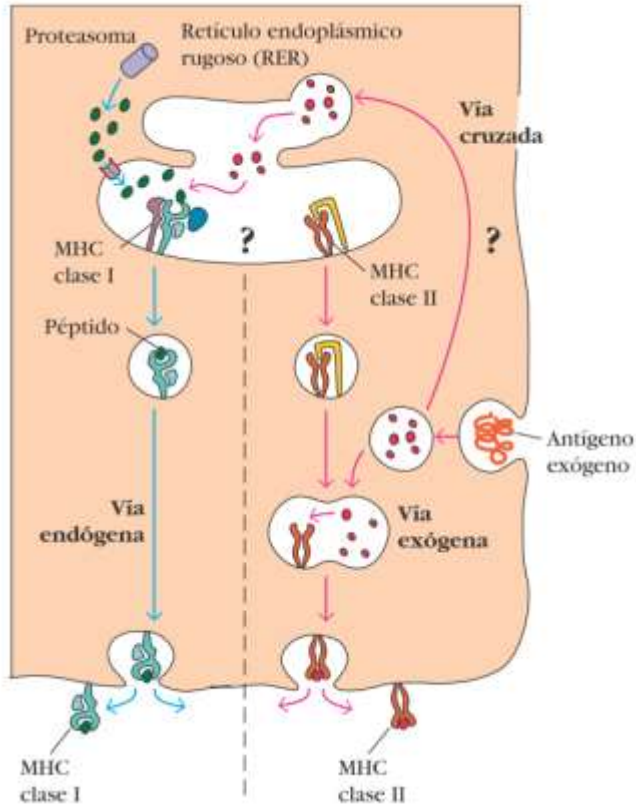
- Cadena invariante (Ii)
- Glicoproteína transmembrana
- Distintas isoformas
- Chaperona de MHC-II
 - ✓ CD1, MHC-I, receptor Fcγ neonatal
- Direcciona el tráfico del MHC-II a endosomas



Presentación cruzada



Otra vez todo



Moléculas no clásicas

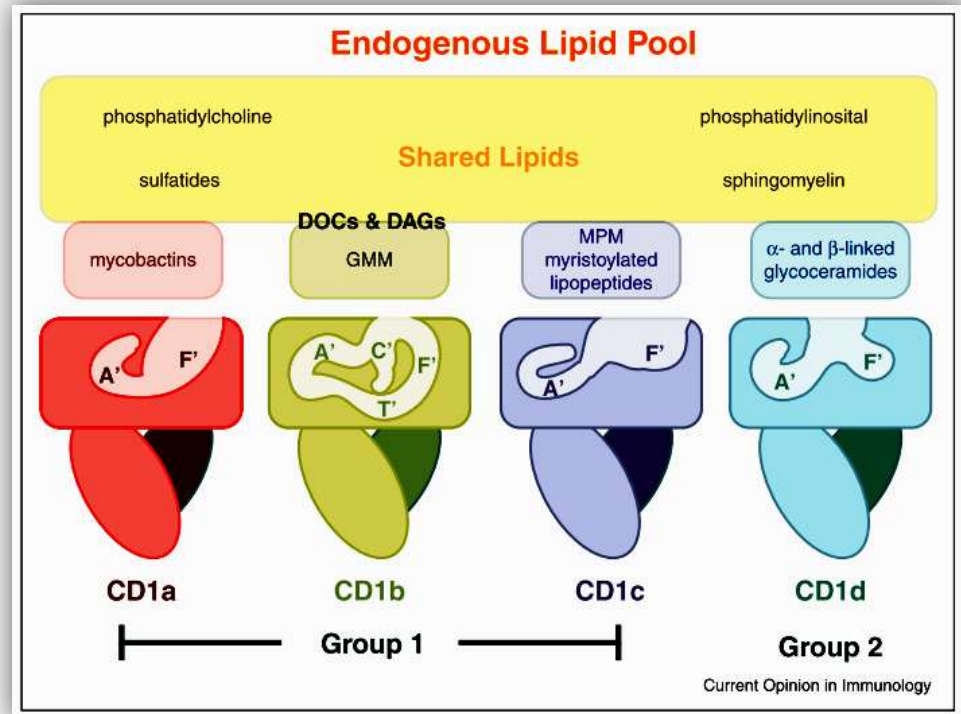
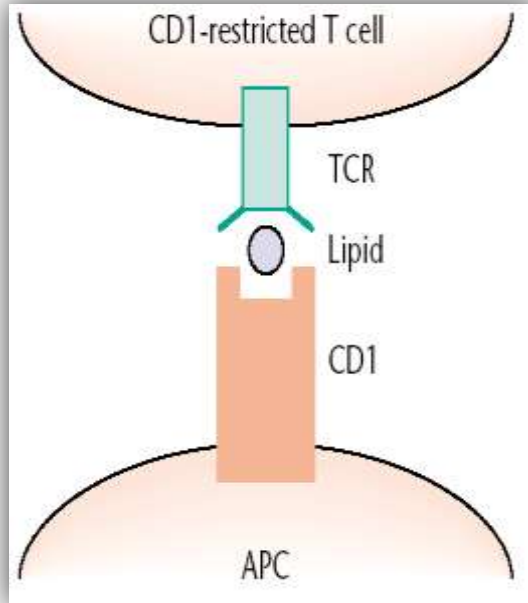
Clase I

- 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

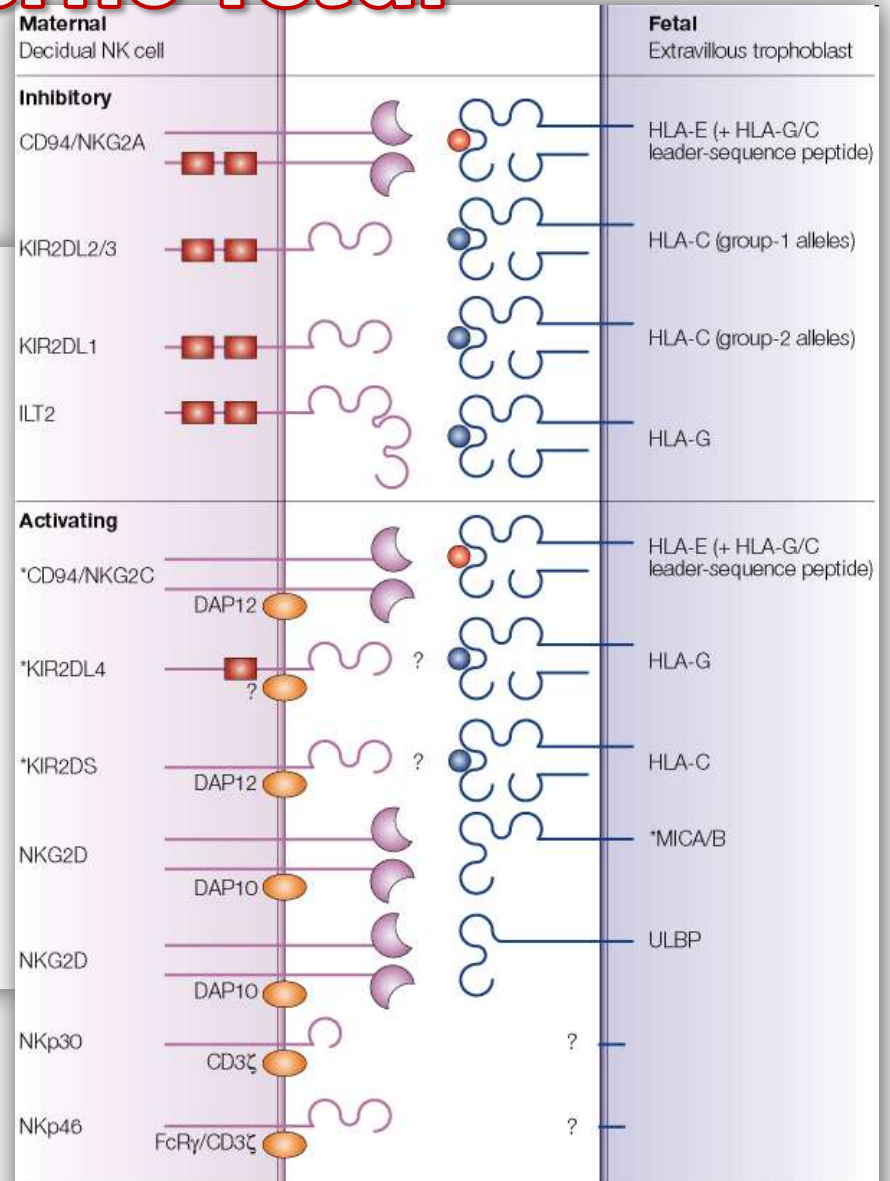
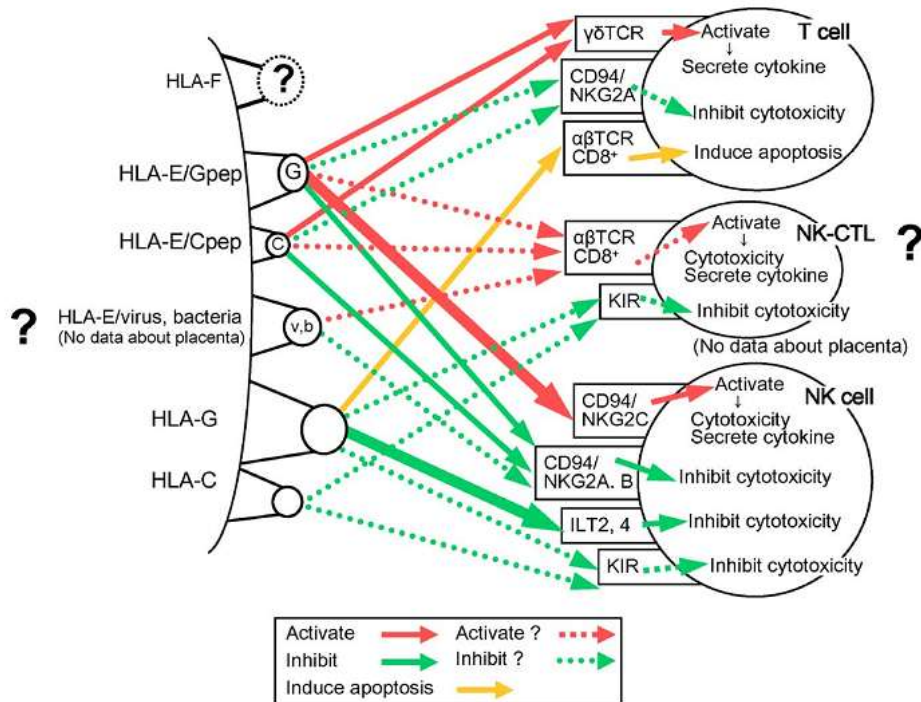
- Limitado polimorfismo
- Unión del péptido a moléculas clase II
- Regulación de la presentación de antígenos mediada por el MHC II
 - ✓ HLA-DM
 - ✓ HLA-DO

CD1



- Presente en compartimentos 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 $\gamma\delta$ y NKT

Tolerancia materno fetal



* Definitive evidence of protein expression awaited

Immunoreceptor tyrosine-based inhibitory motif in cytoplasmic tail

Adaptor proteins containing immunoreceptor tyrosine-based activation motif



Tolerancia materno fetal



Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jreprimm



Maternal–fetal HLA sharing and preeclampsia: variation in effects by seminal fluid exposure in a case–control study of nulliparous women in Iowa

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Interconsulta



Paciente:

HLA- A*0201
B*0702
Cw*0401
DRB1*0101
DQA1*0501

Donante 1:

HLA- A*0202
B*0702
Cw*0401
DRB1*0104
DQA1*1206

Donante 2:

HLA- A*0201
B*1602
Cw*0401
DRB1*0101
DQA1*0501

¡Pregunten Ahora o Callen Para Siempre!



Guillermo Teran-Angel
guillermondi@gmail.com
<http://guillermo.vv.si>

A tropical beach scene at sunset. The sky is filled with dramatic, dark clouds illuminated from below by the setting sun, creating a warm orange and yellow glow. The sun is partially obscured by the clouds, casting a shimmering reflection on the water. The beach is sandy and curves along the shore. In the background, a dense line of palm trees stands against a backdrop of rolling mountains. The water is calm, with gentle waves lapping at the shore. In the foreground, a large, dark rock is partially submerged, with waves crashing against it, creating white foam. The overall atmosphere is serene and beautiful.

**¡Gracias por la
atención!**