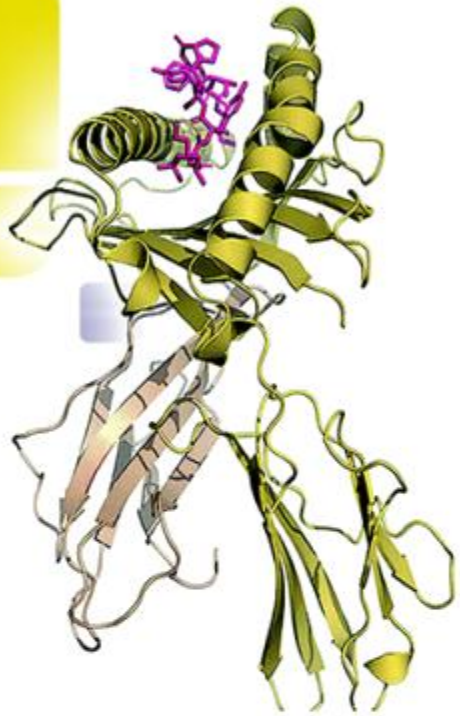
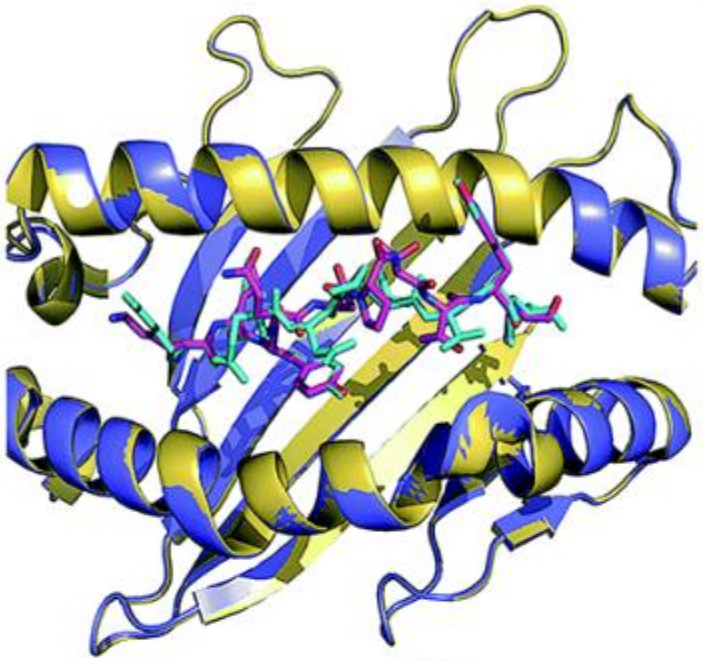
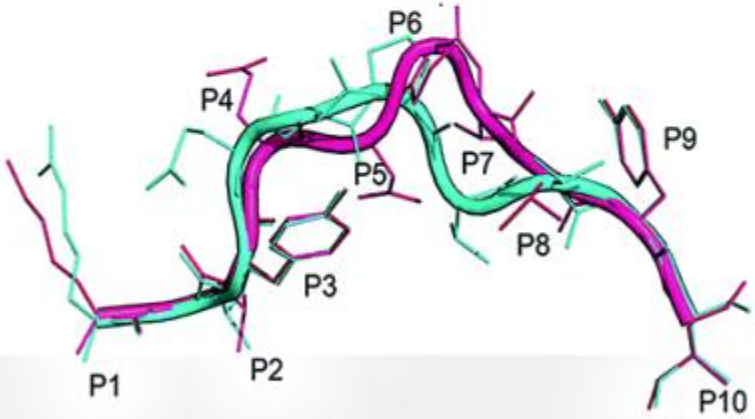






Guillermo Terán-Ángel
IDIC-ULA

HLA, procesamiento y presentación antigénica

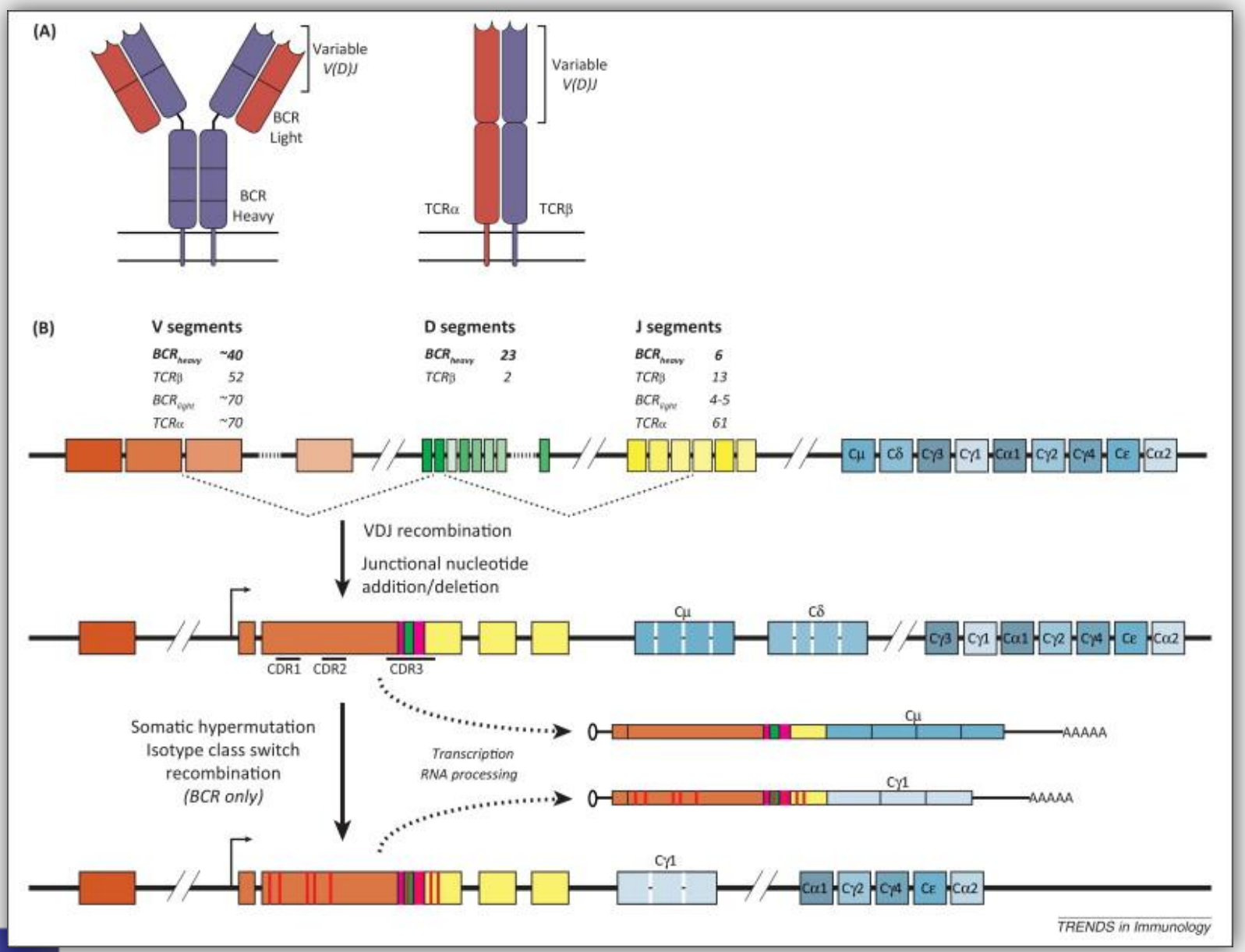
Interconsulta

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

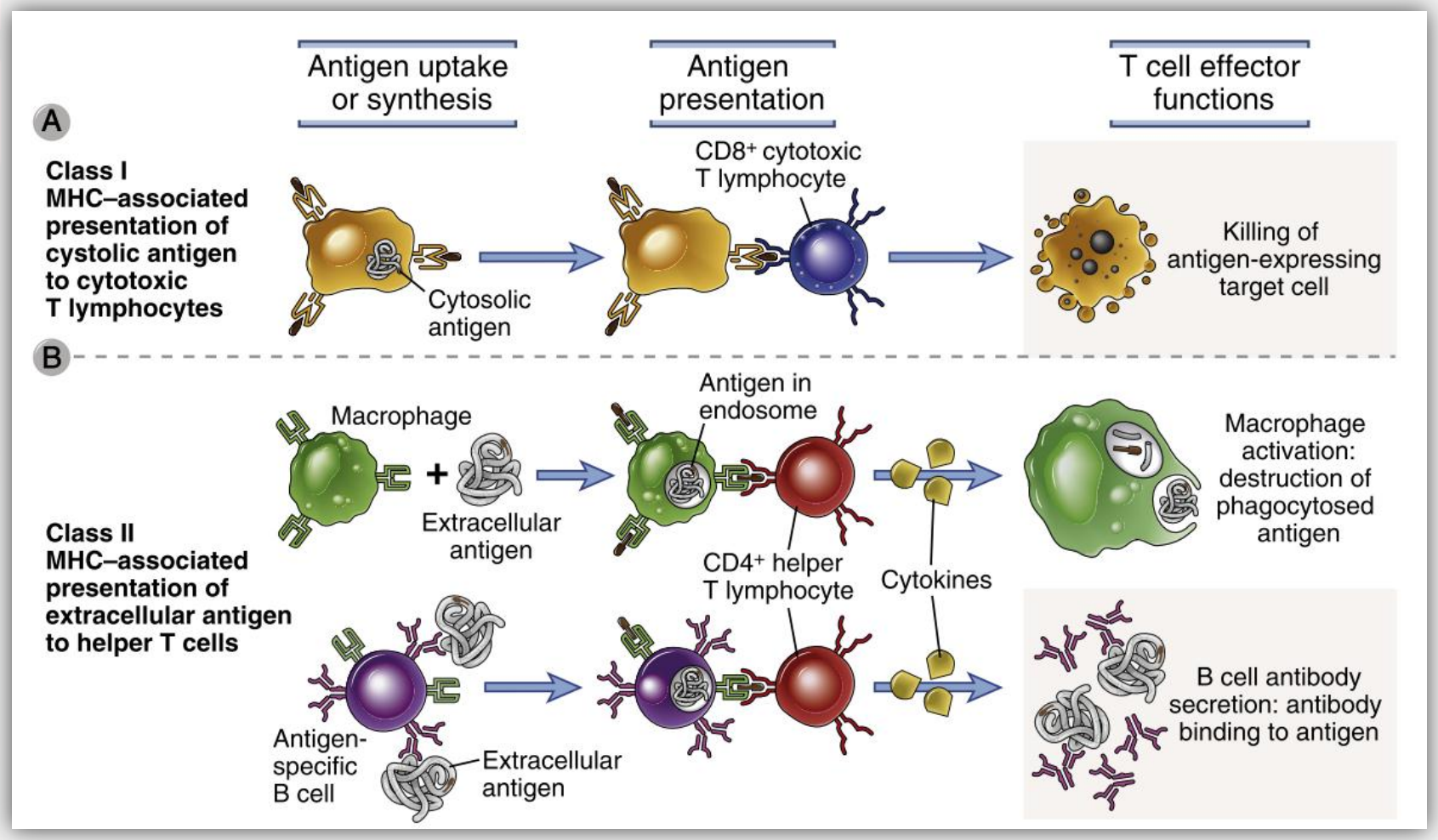
Donante 2:
HLA- A*0201
B*1602
Cw*0401
DRB1*0101
DQA1*0501

Ubicándonos

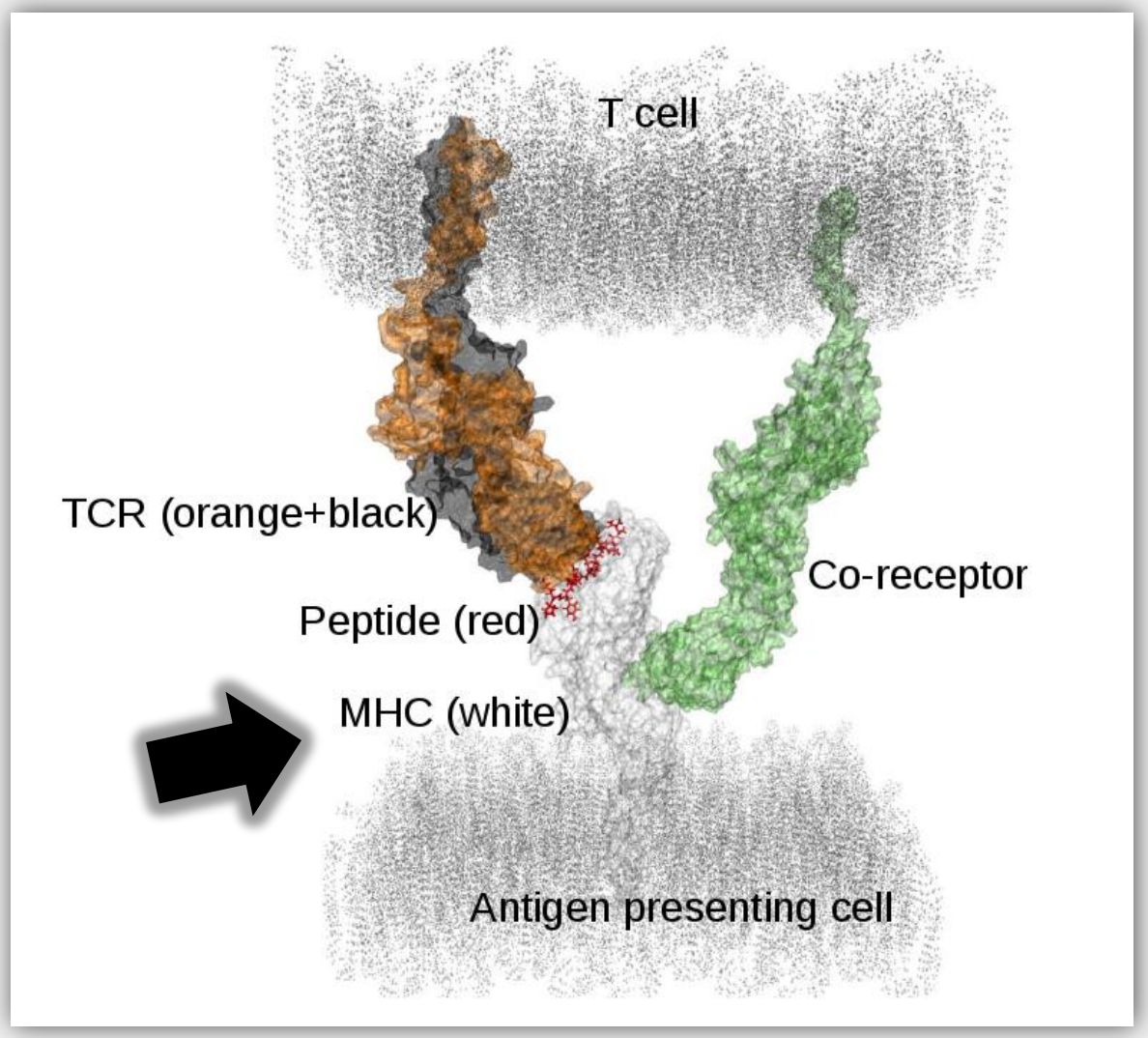


Trends in Immunology Volume 35, Issue 12, p581–590

Ubicándonos

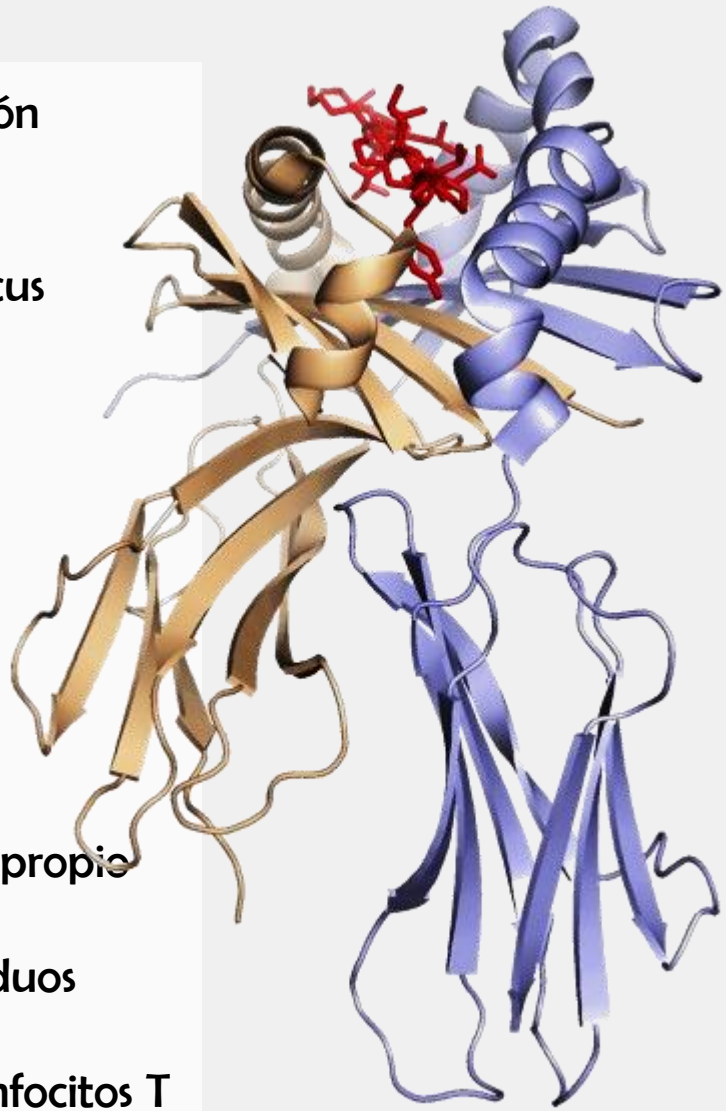


La piedra angular de la RI

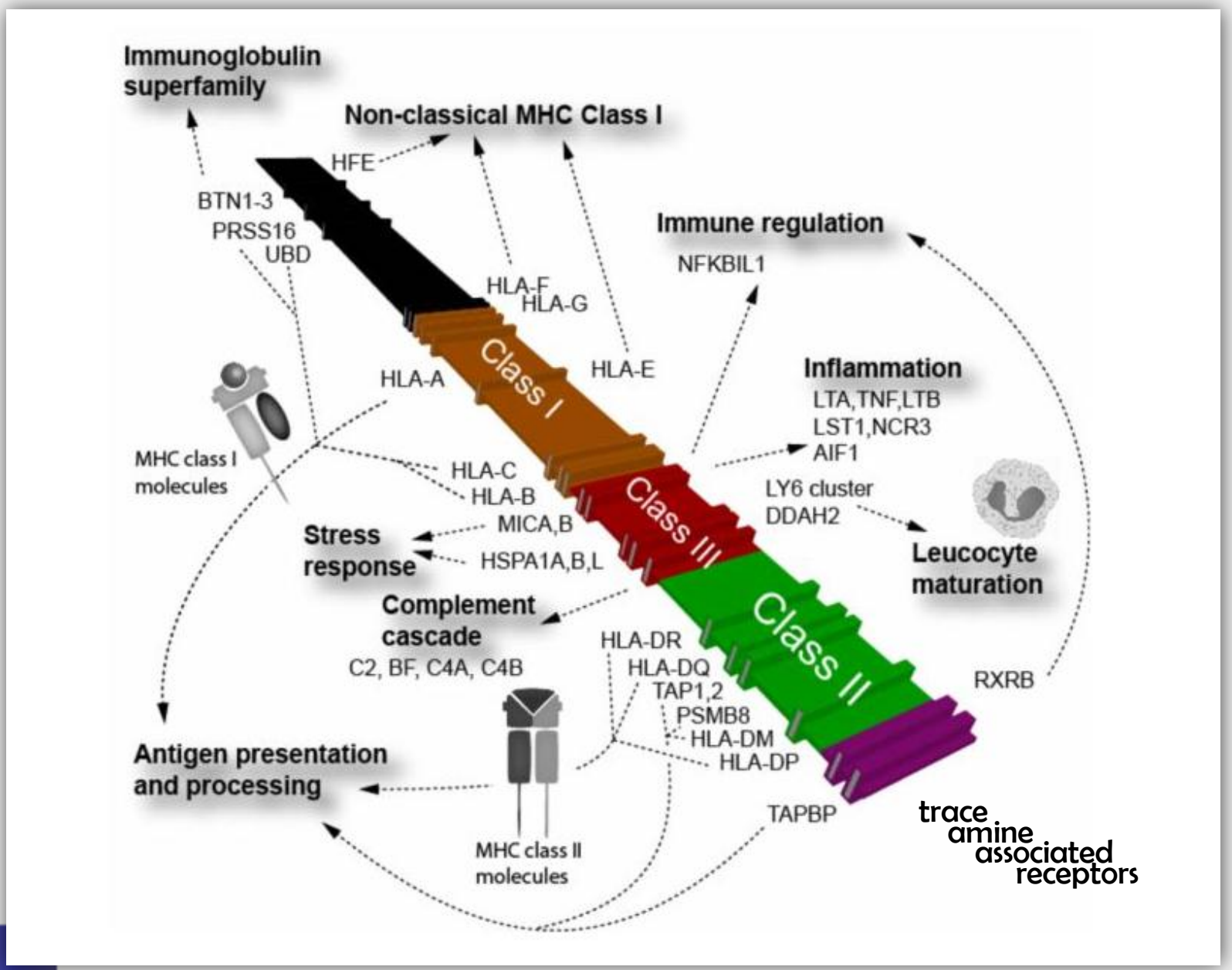


Comencemos por el HLA o MHC

- 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

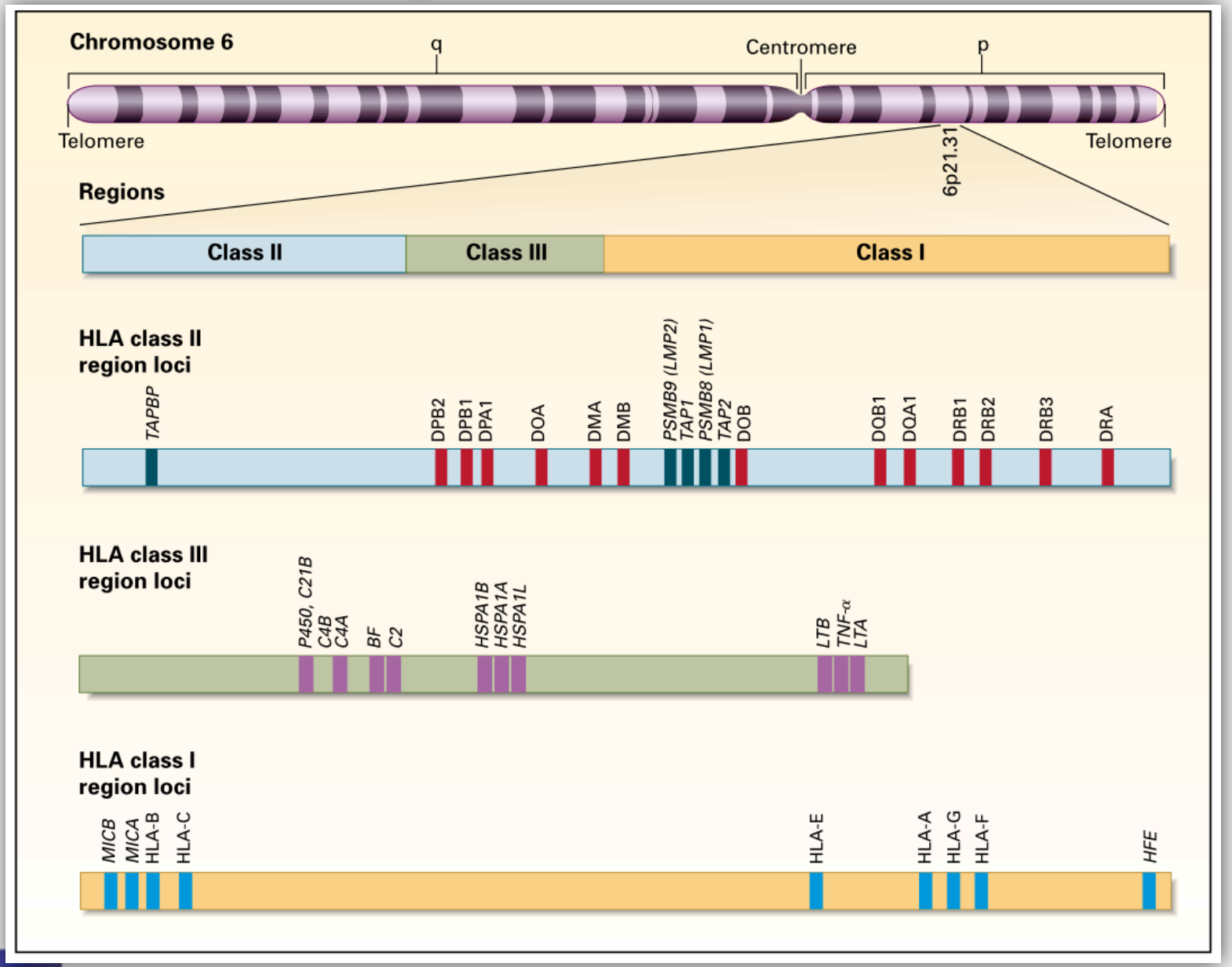


Genetic matchmaking

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

Sci Rep. 2016 Dec 12;6:38490. Mol Ecol. 2017 Jan;26(2):668-688.

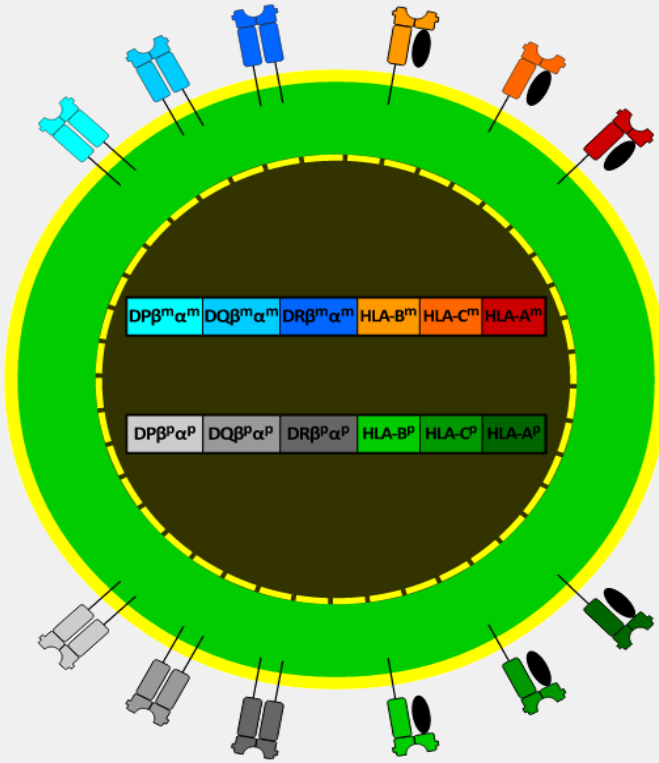
Estructura génica

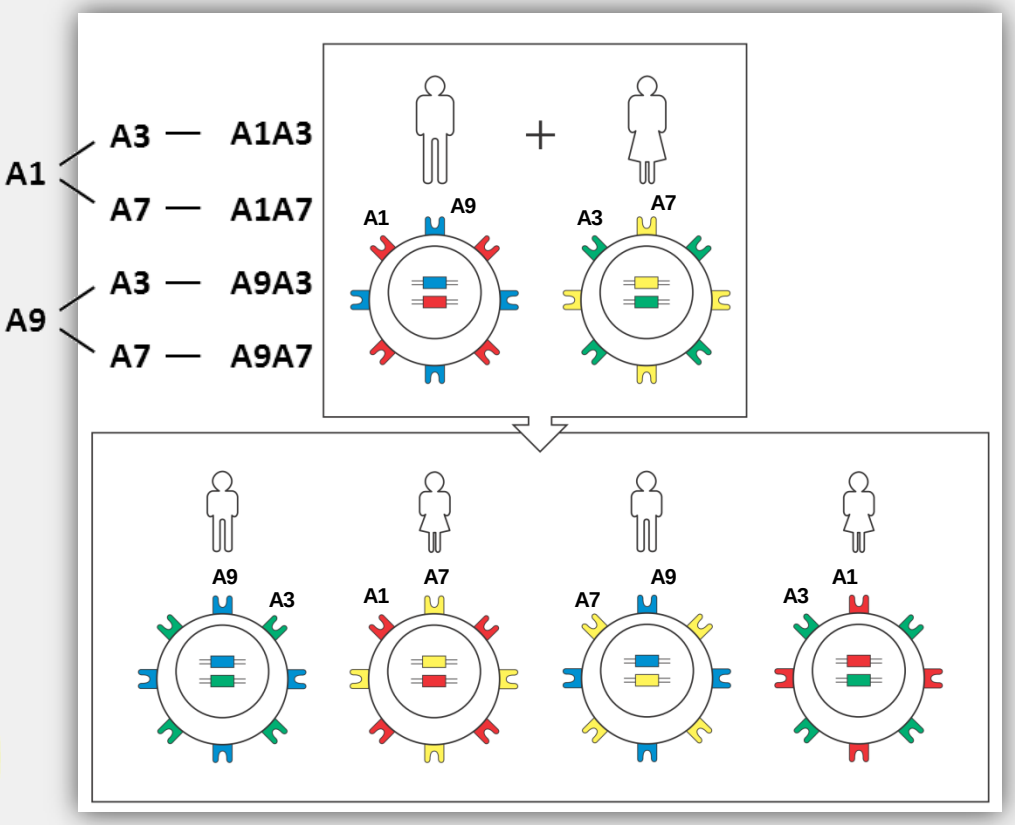


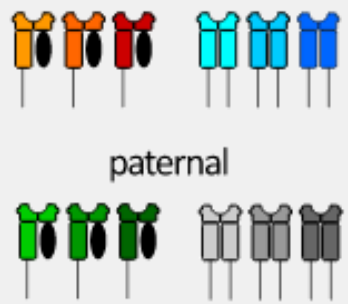
N Engl J Med 2000; 343:702-709

Herencia

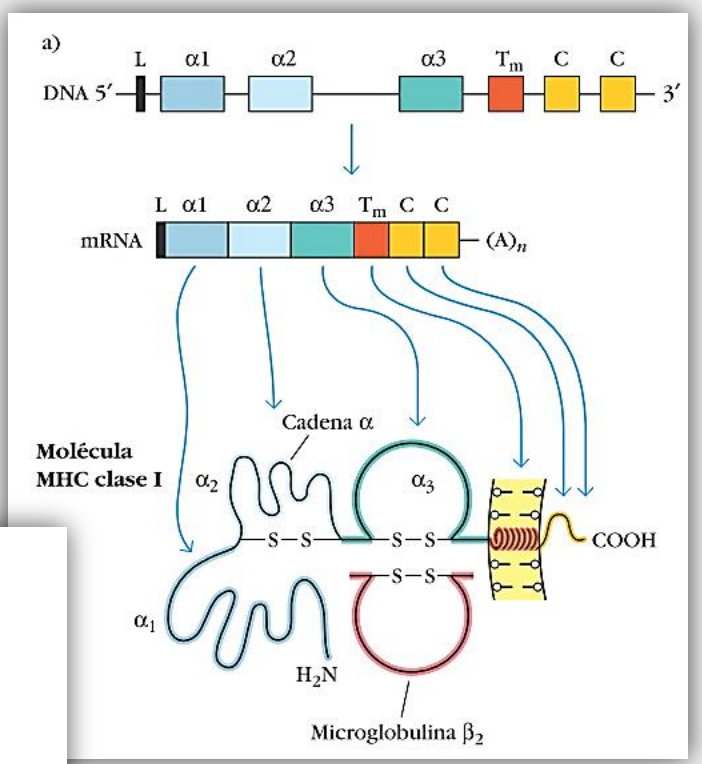
Codominancia

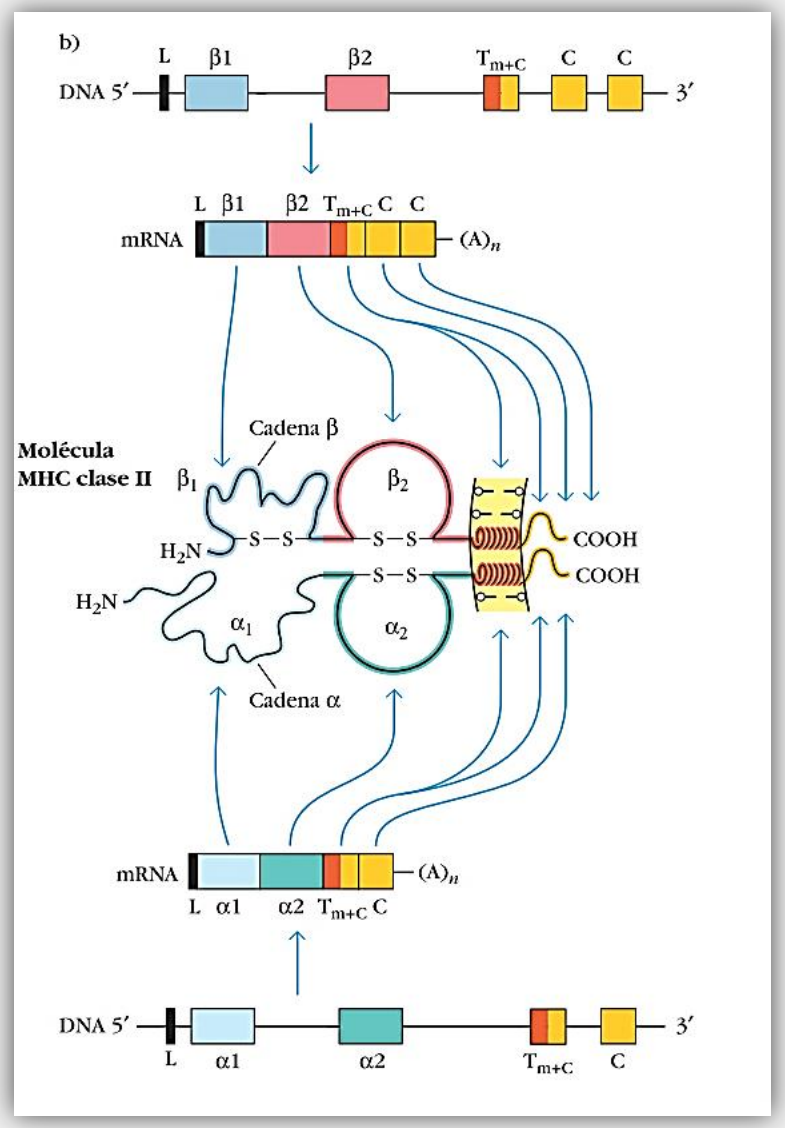


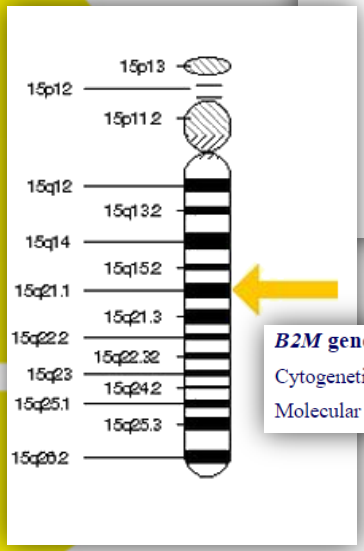




Expresión génica







***B2M* gene**

Cytogenetic Location: 15q21.1

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

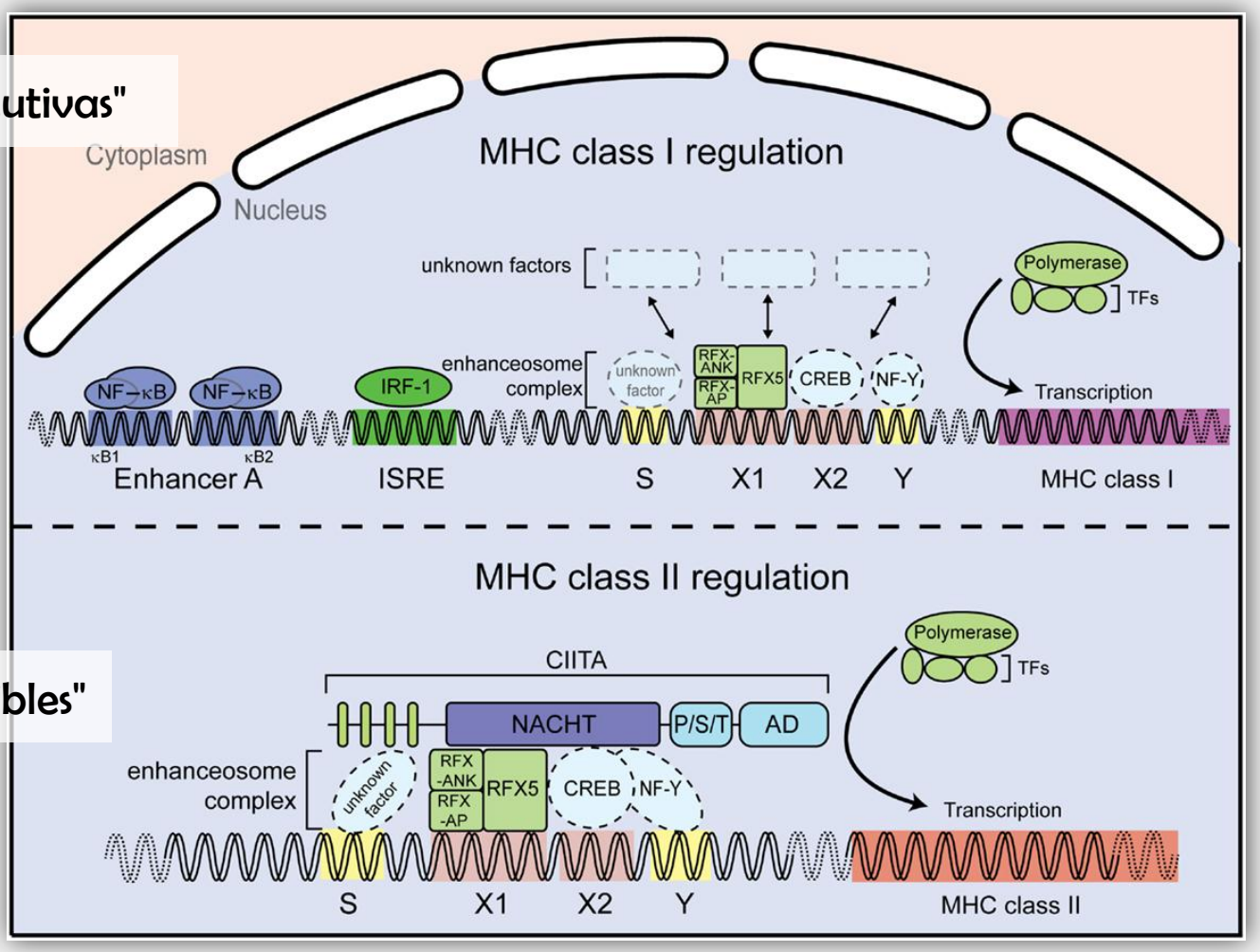
2007 @goldsby inmunologia de kuby

Regulación génica

- "pseudo Constitutivas"

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

- " pseudo Inducibles"



http://dx.doi.org/10.3389/fimmu.2013.00397

ICS

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

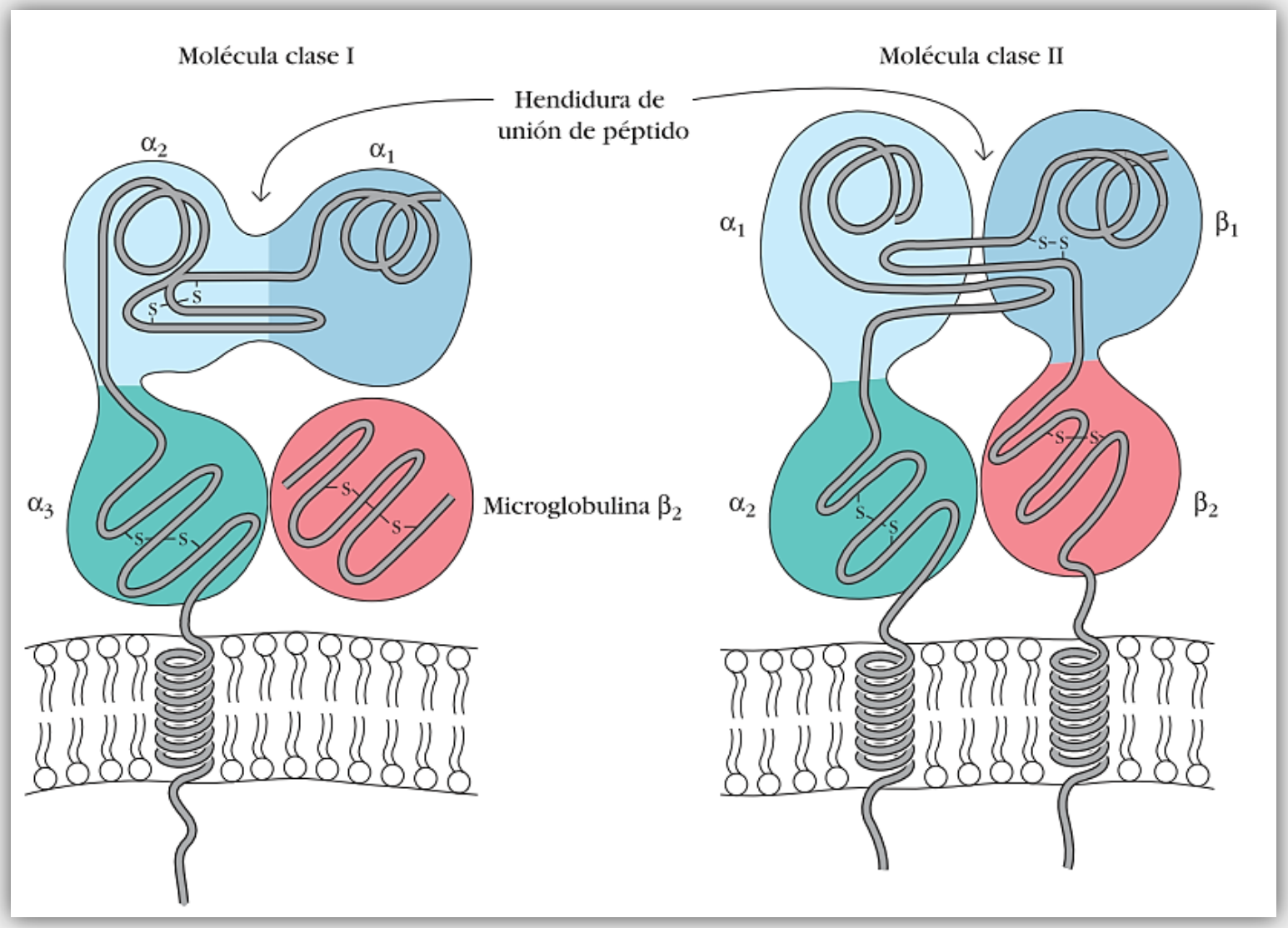
Tabla 2. Expresión fenotípica de las ICS según el defecto genético presente.

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)

Avan Biomed. 2013; Supl 1: 4-25.

Entendamos las moléculas



Características

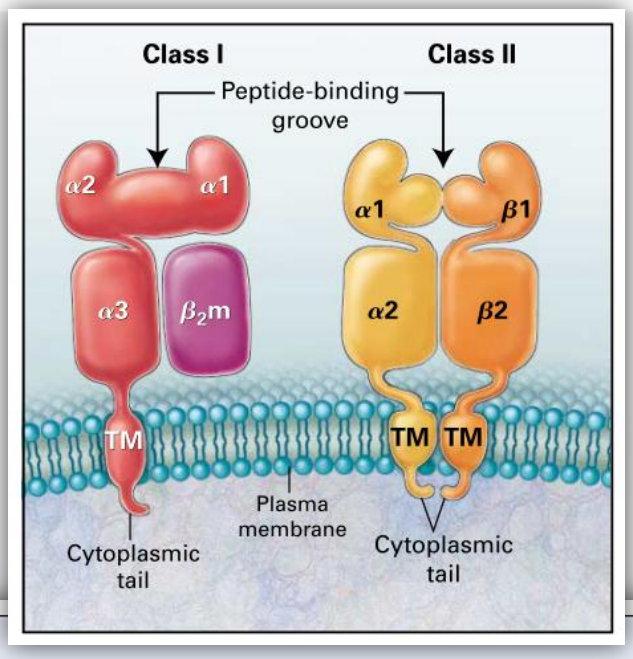
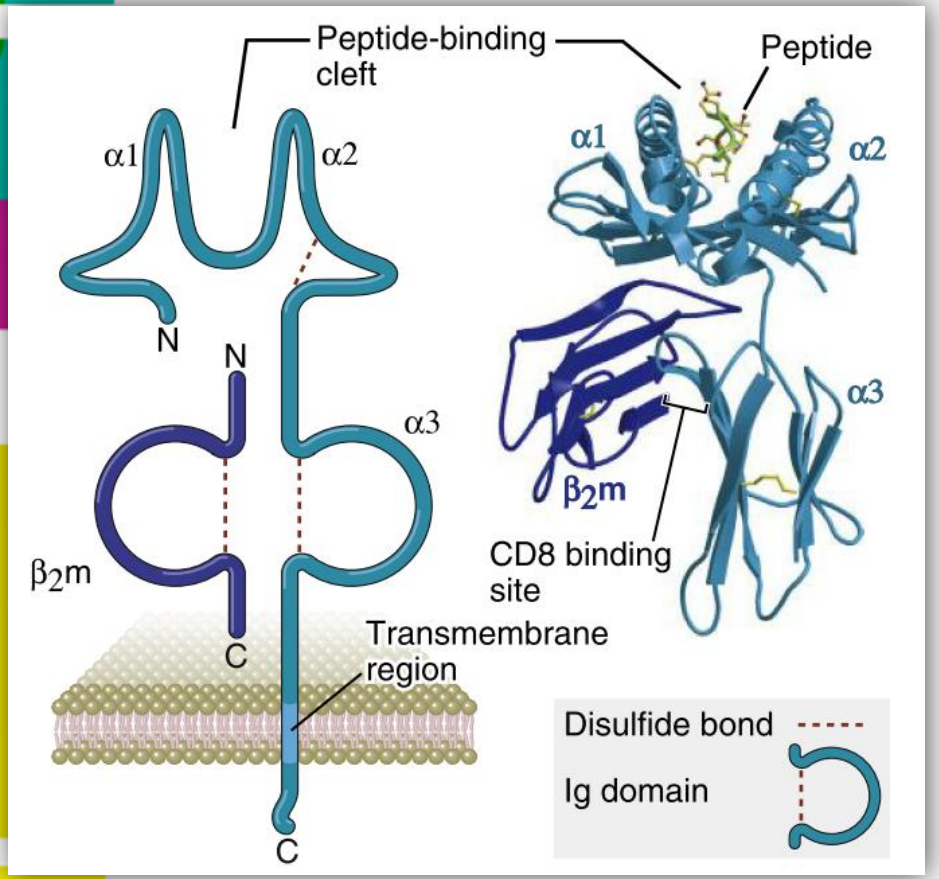


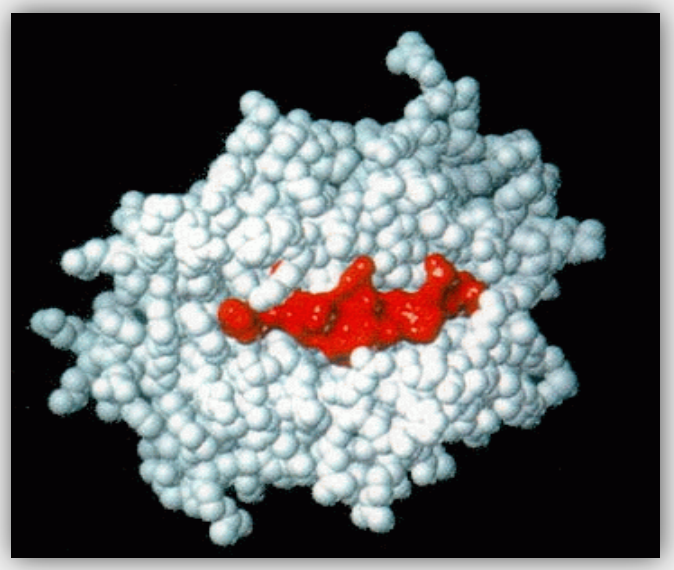
TABLE 6-4 Features of Class I and Class II MHC Molecules

Feature	Class I MHC	Class II MHC
Polypeptide chains	α β_2-microglobulin	α and β
Locations of polymorphic residues	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

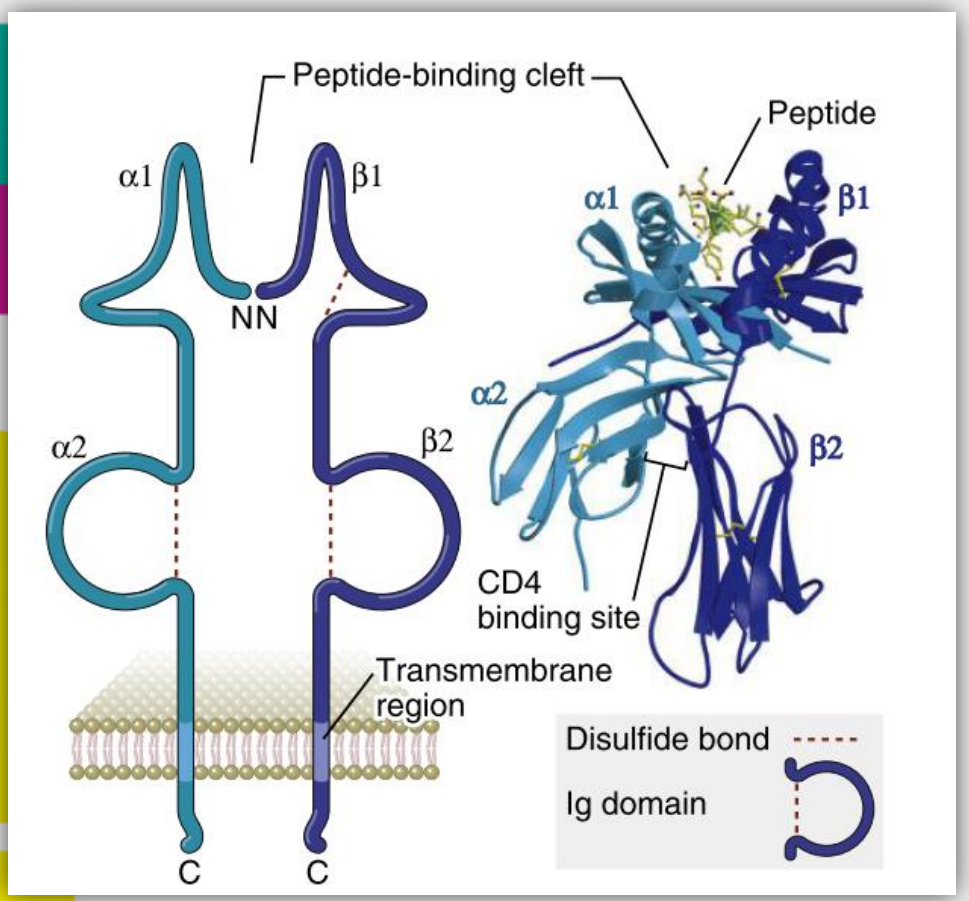
N Engl J Med 2000; 343:702-709

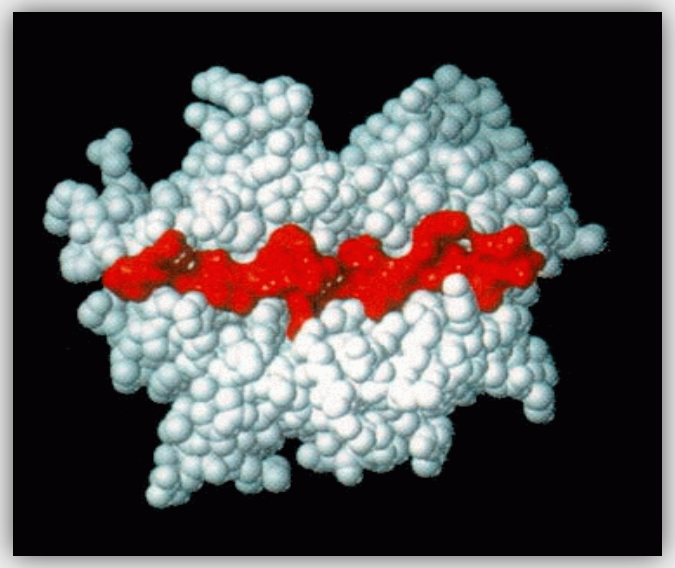
HLA clase I


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

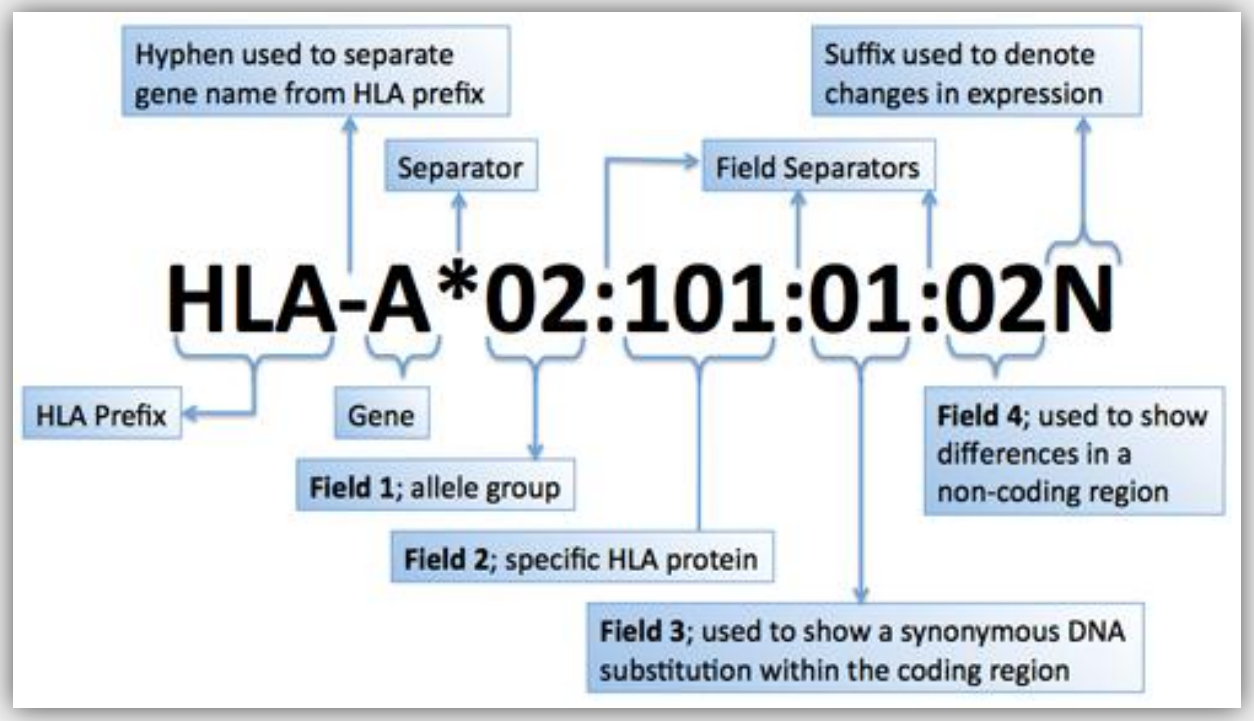


HLA clase II


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

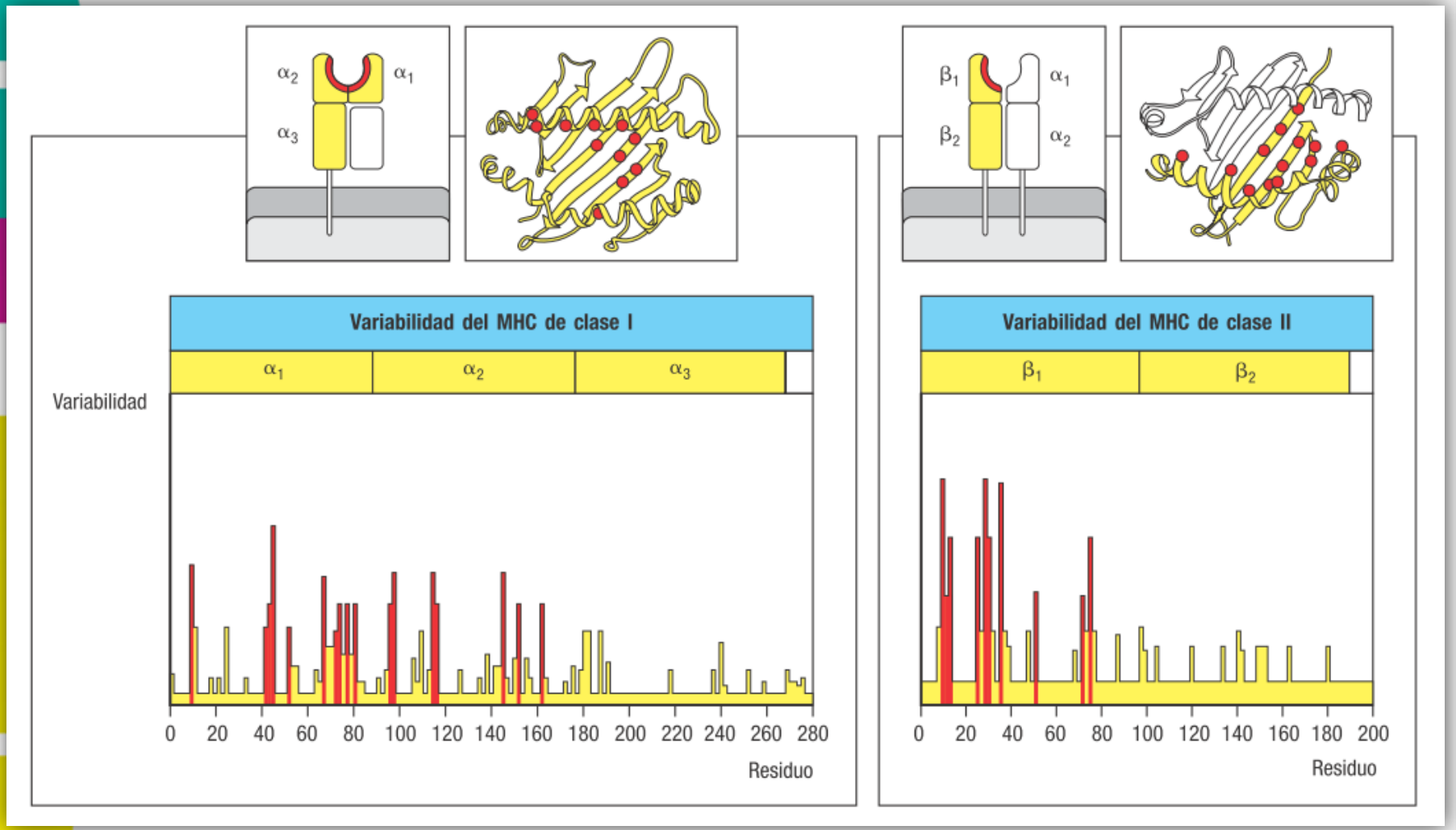


Nomenclatura



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

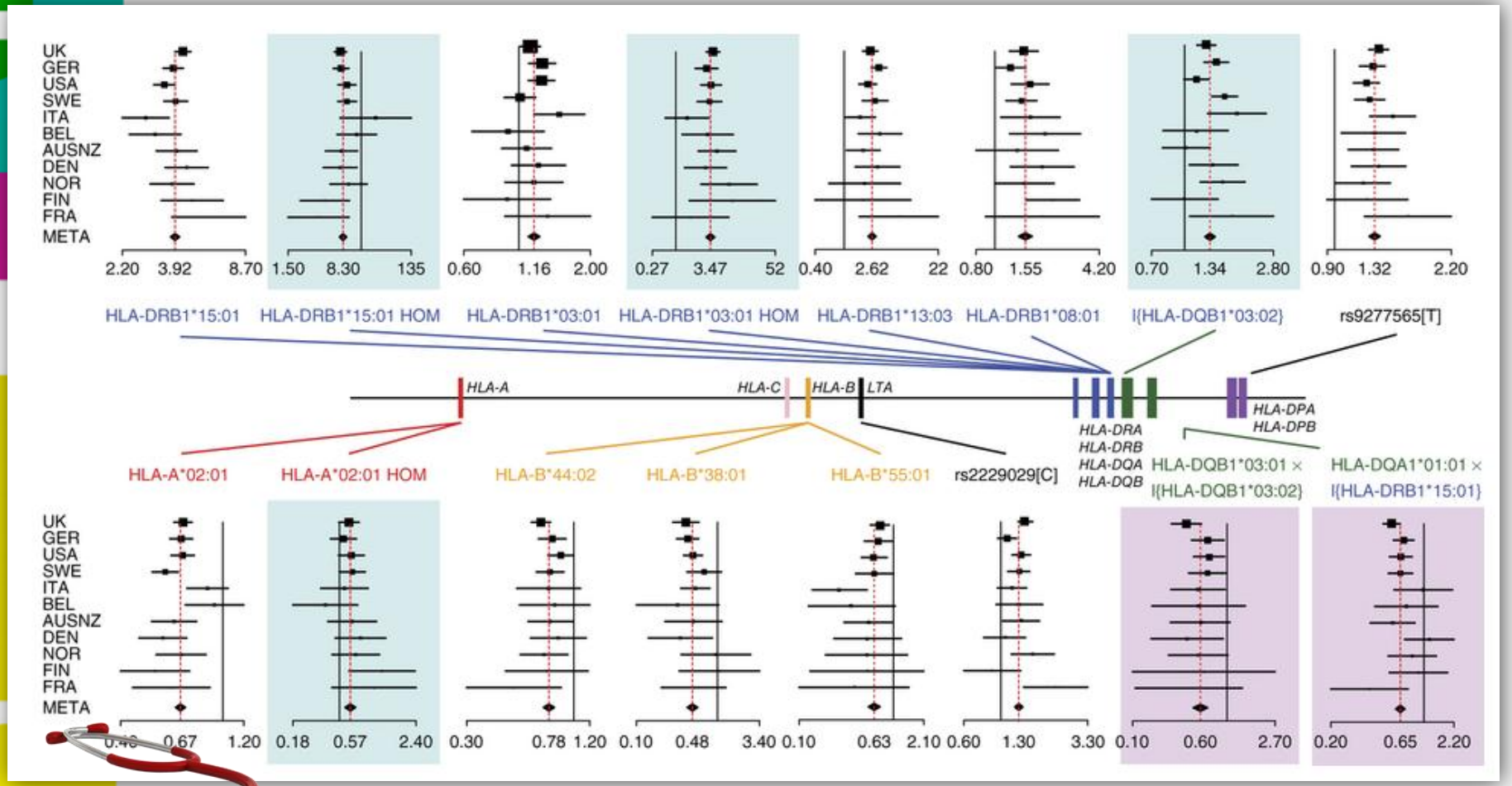
*Relative risk is calculated by dividing the frequency of the HLA allele in the patient population by the frequency in the general population:

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

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

Int J Immunogenet. 2014 Feb;41(1):1-12

Un ejemplo: EM



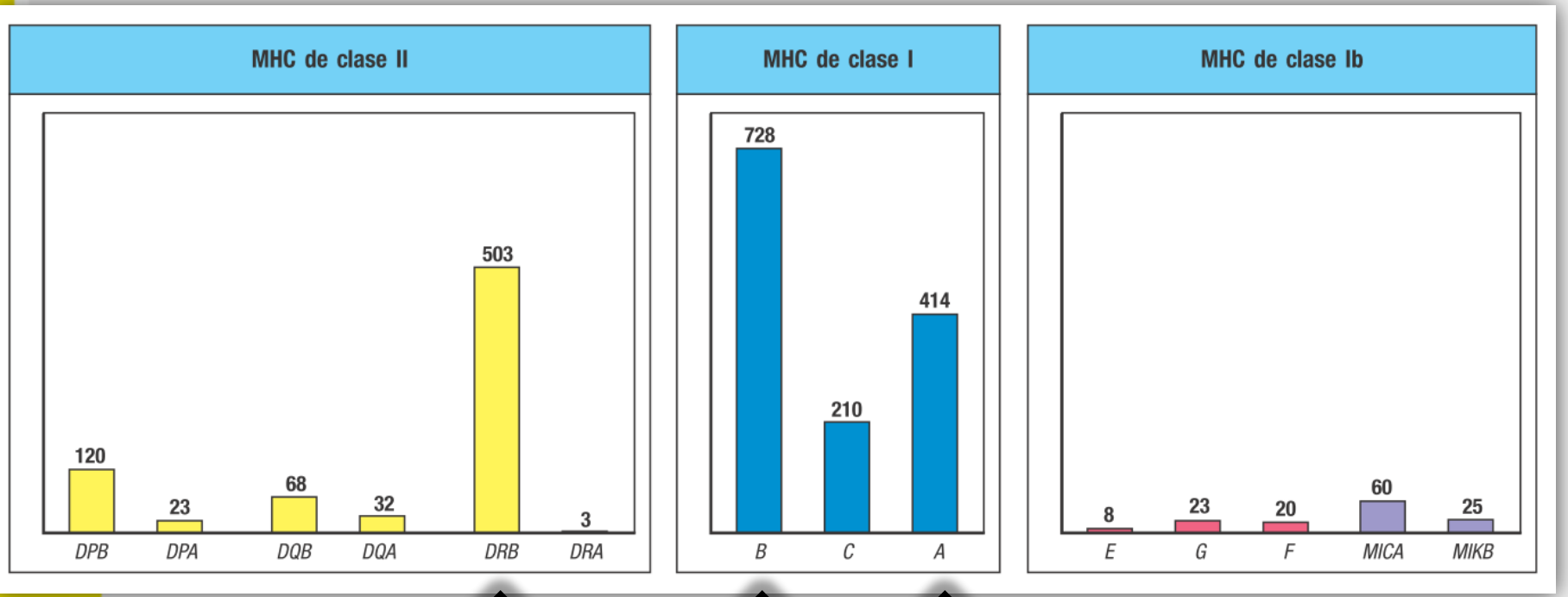
Nature Genetics 47, 1107–1113 (2015)

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

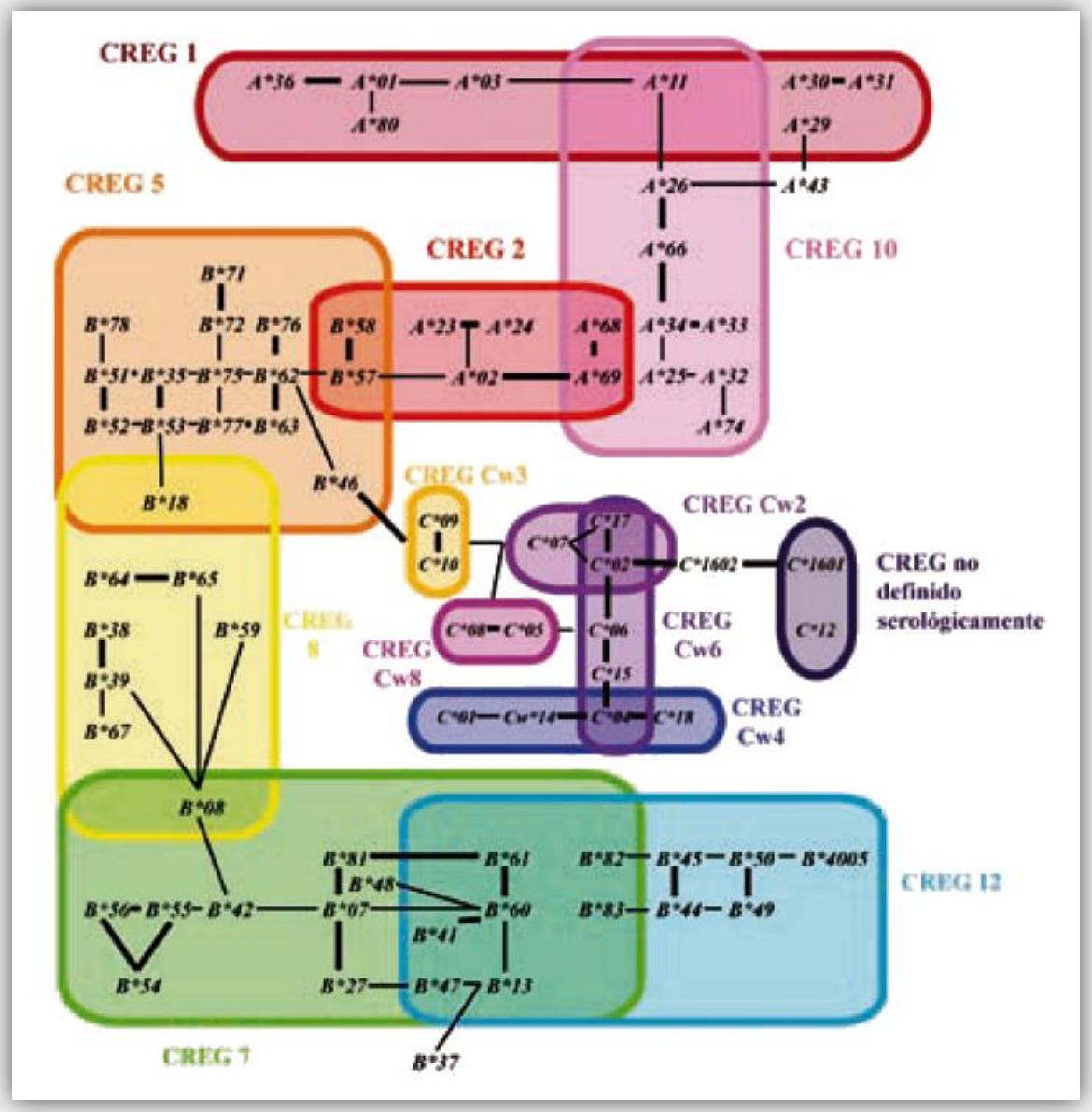
Variabilidad



- 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.

Blood. 2015 Feb 12;125(7):1058-9

CREGs



Blood. 2007 May 1;109(9):4064-70. & Gaceta Médica de México. 2012;148:52-67

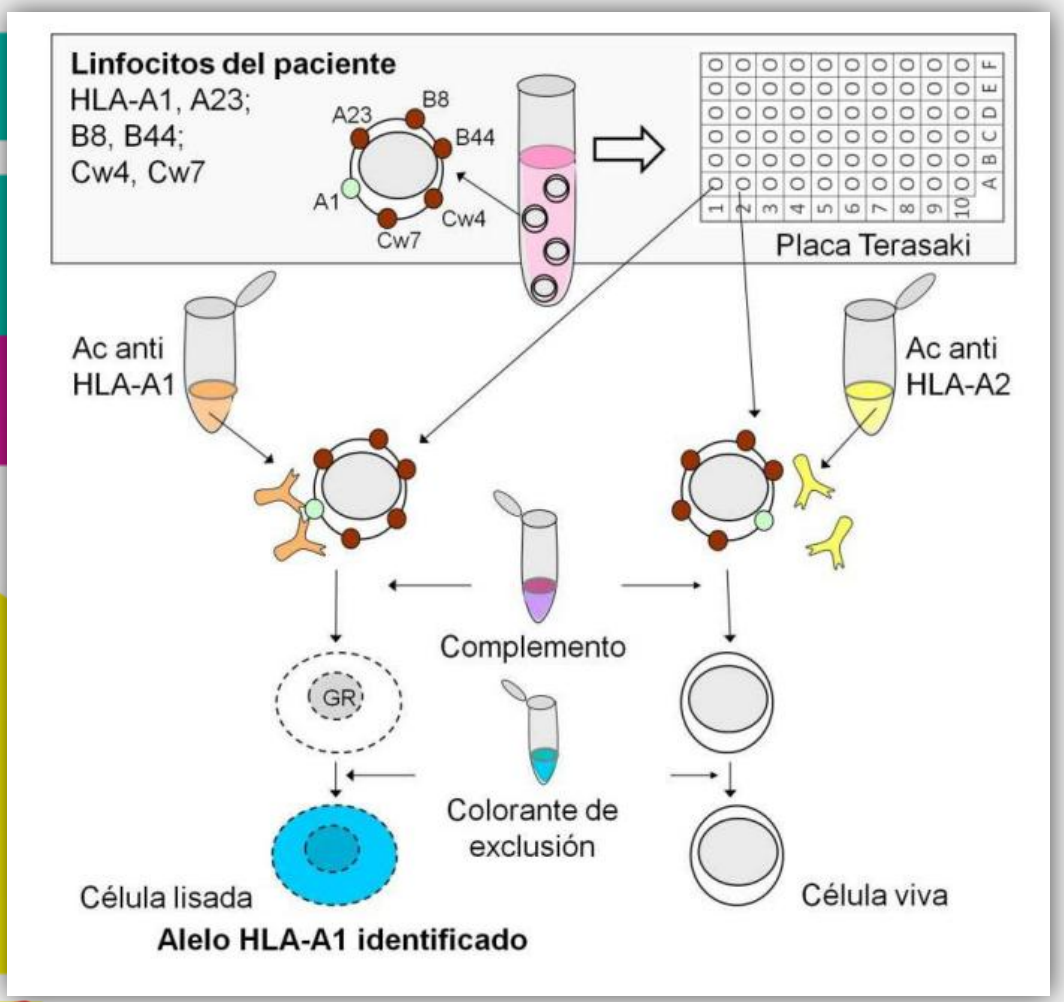
Tipificación

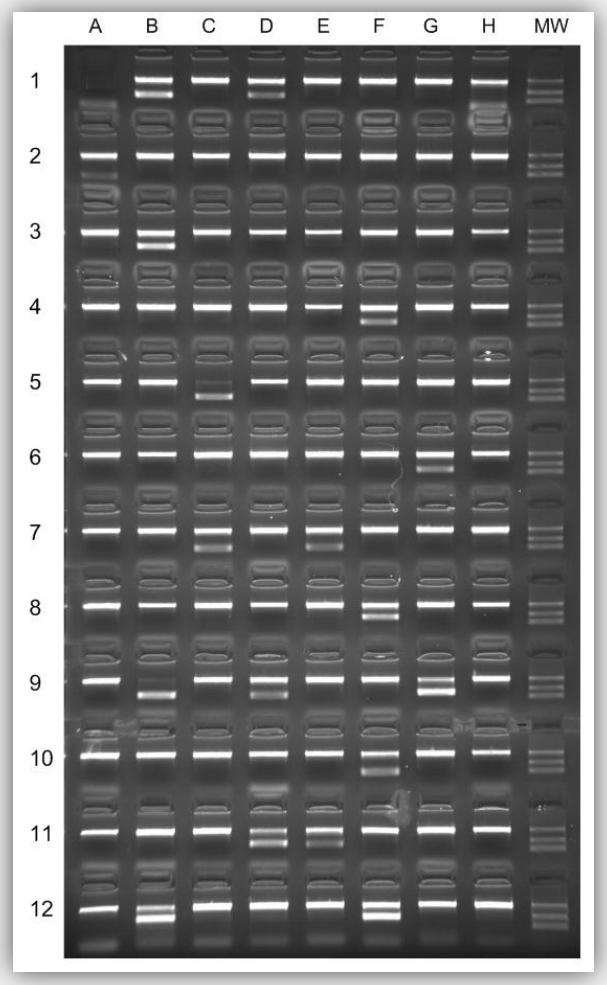
Typing Methods

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.	- Low Cost - Rapid - Traditional	- 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.	- Checking of specific target - Efficient	- 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.	- Used to sequence regions of interest - Fast - Base pair resolution - Coverage only 2x	- 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 preforming deep sequencing.	- Deep coverage (1000x) - Total MHC coverage - Rapid high throughput - Accurate and efficient - Phasing	- Data Analysis

illumina

Tipificación

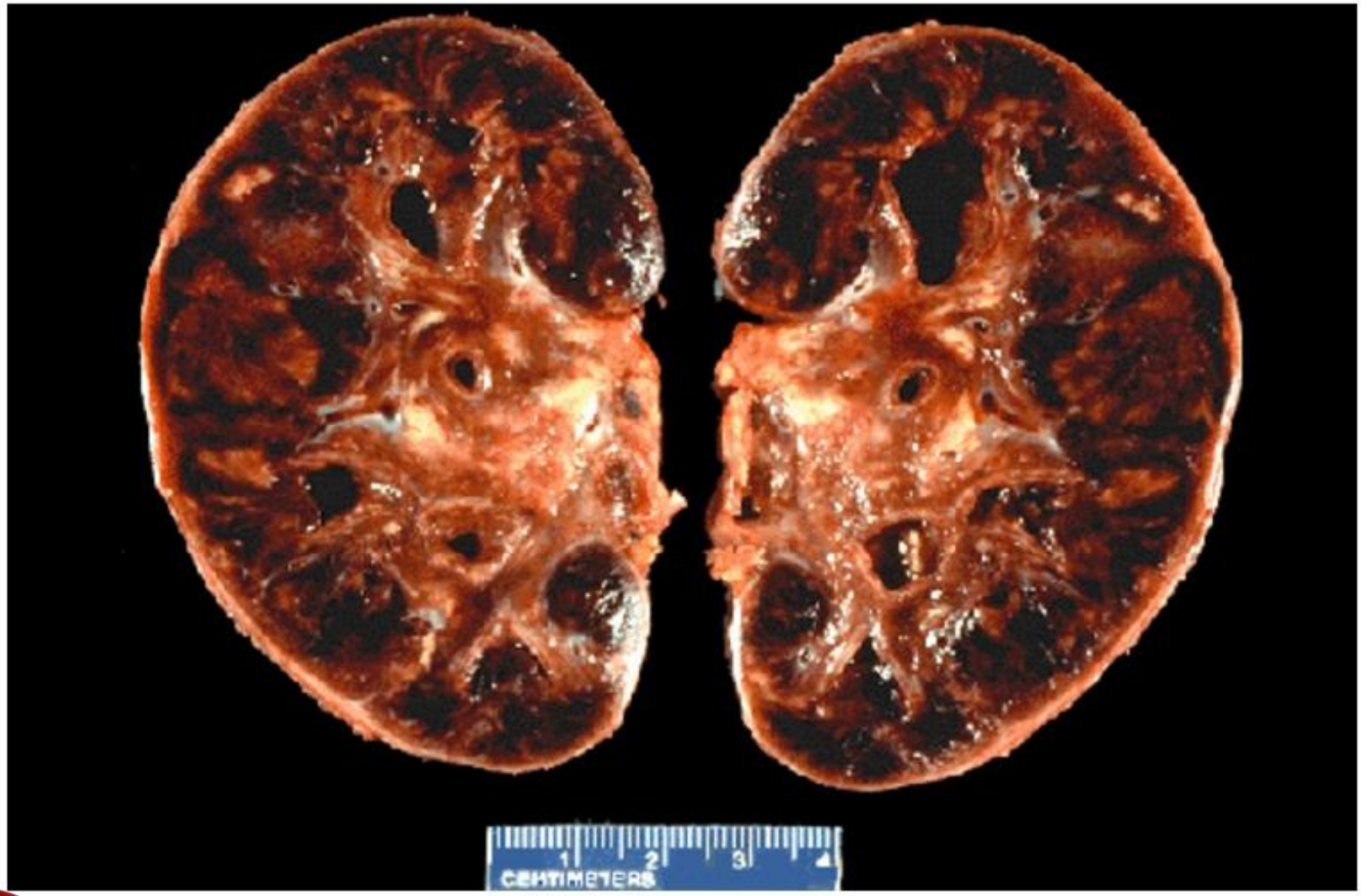




Prueba de microlinfocitotoxicidad
Prueba de Terasaki

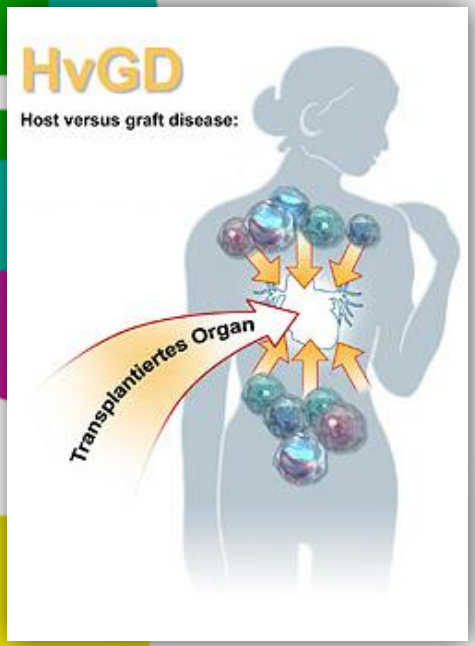
PCR-SSP

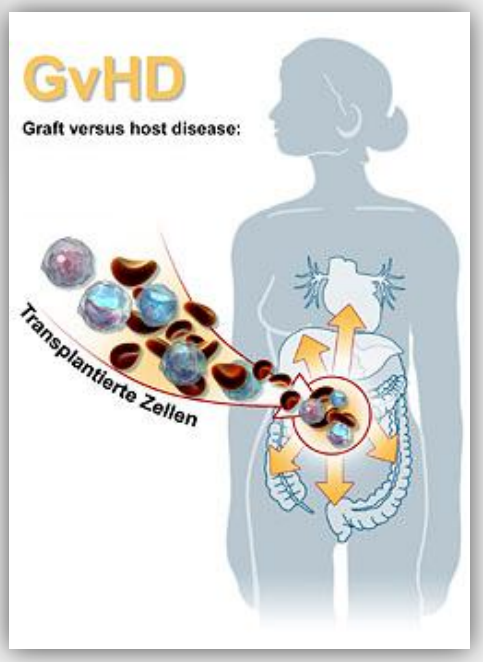
Implicaciones

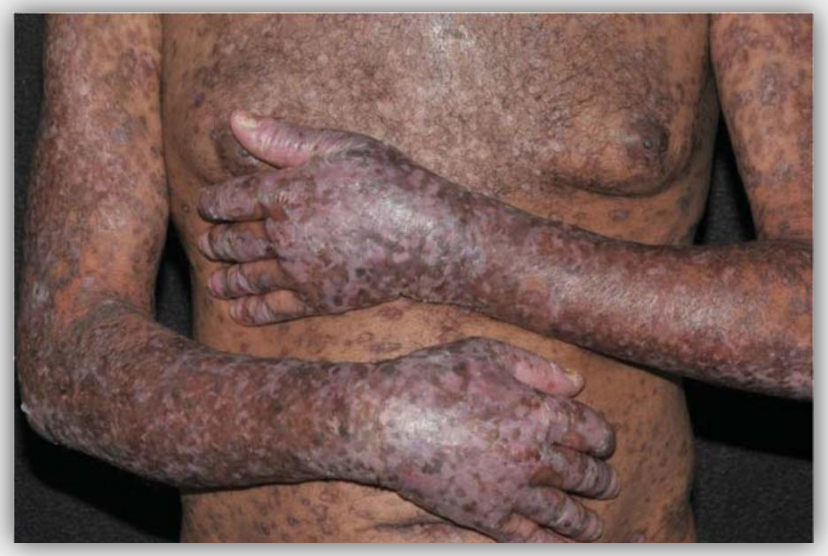


This kidney was removed because of acute transplant rejection. Note the swollen and hemorrhagic appearance of this entire kidney

GVHD

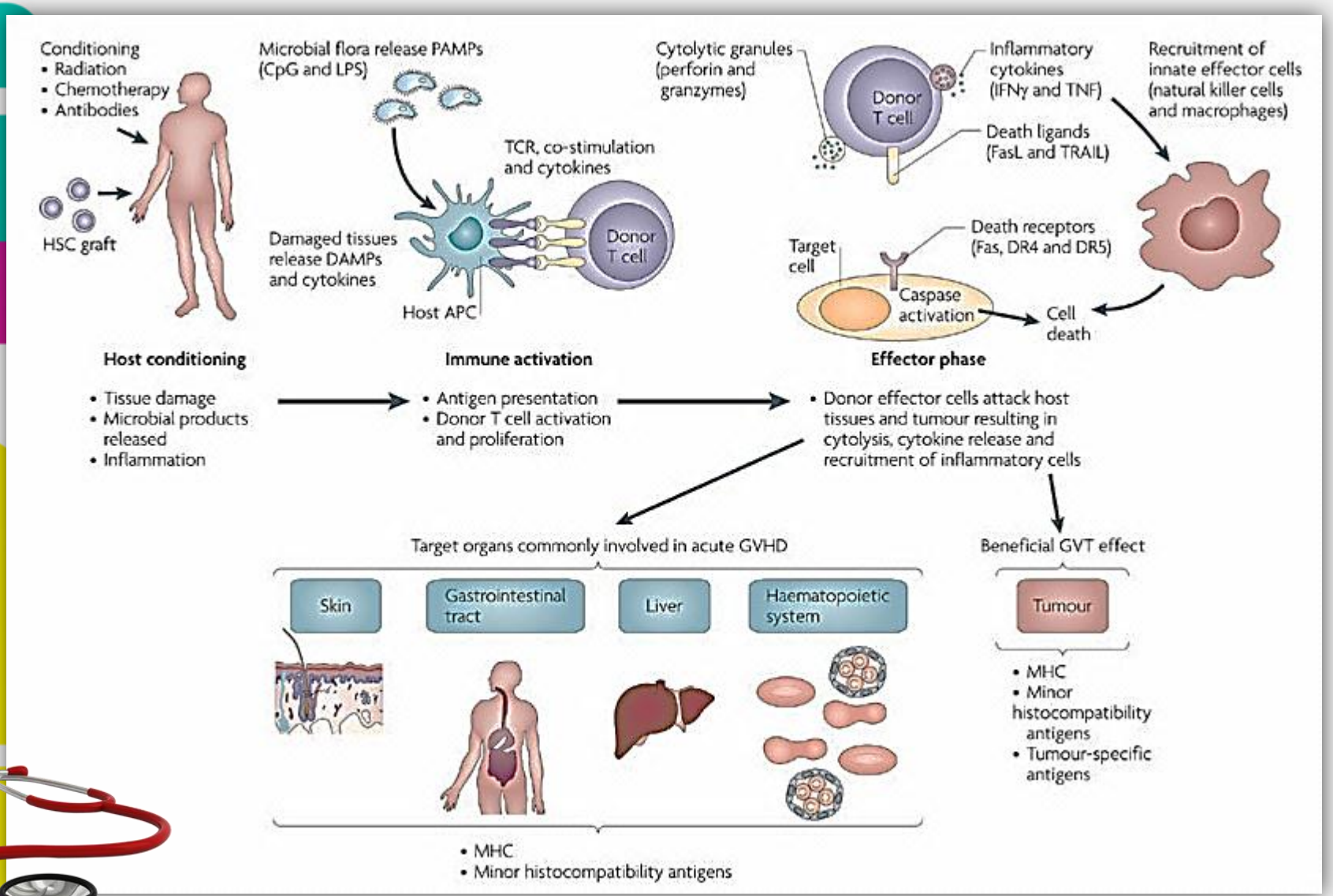






- La piel es el blanco mas frecuente, seguido por la mucosa oral, higado, ojo y tracto GI, no obstante, todos los organos puedes ser afectados

Graft-versus-host disease



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

Graft-versus-host disease

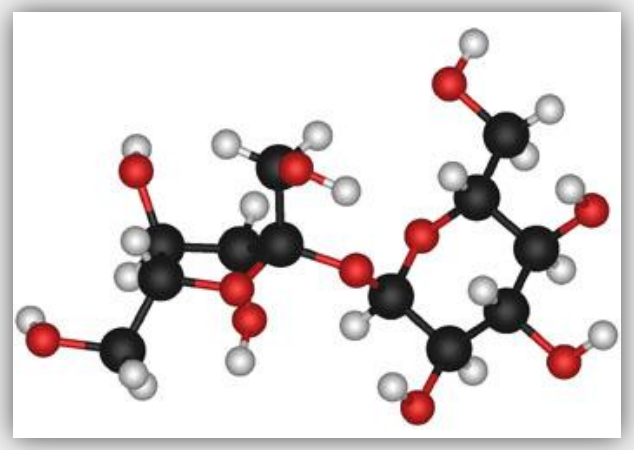
HLA	Match or mismatch*	N	Acute GVHD (Grade III-IV)† RR	95% CI	P	Acute GVHD (Grade II-IV)† RR	95% CI	P	N	Chronic GVHD‡ RR	95% CI	P
A	Match	7048	1.00		.001	1.00		.002	5892	1.00		.328
	Mismatch		1.29	1.10-1.51		1.18	1.06-1.32		636	1.06	0.94-1.21	
B	Match	7475	1.00		.001	1.00		.001	6217	1.00		.235
	Mismatch		1.42	1.16-1.73		1.28	1.11-1.48		311	1.10	0.94-1.30	
C	Match	5[illegible]5	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	5[illegible]8	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


Ahora si:
Presentación antigénica

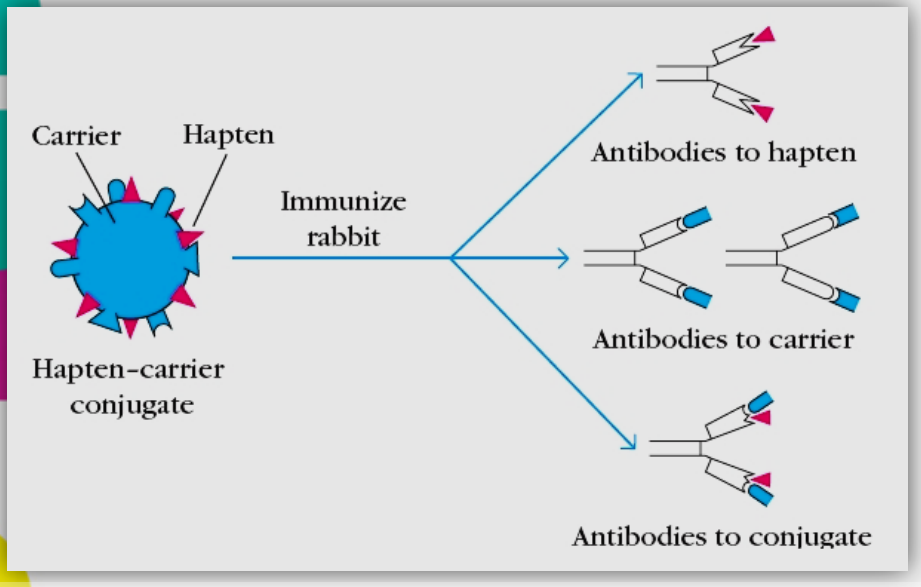
Pero ya va!!!! Antígenos???

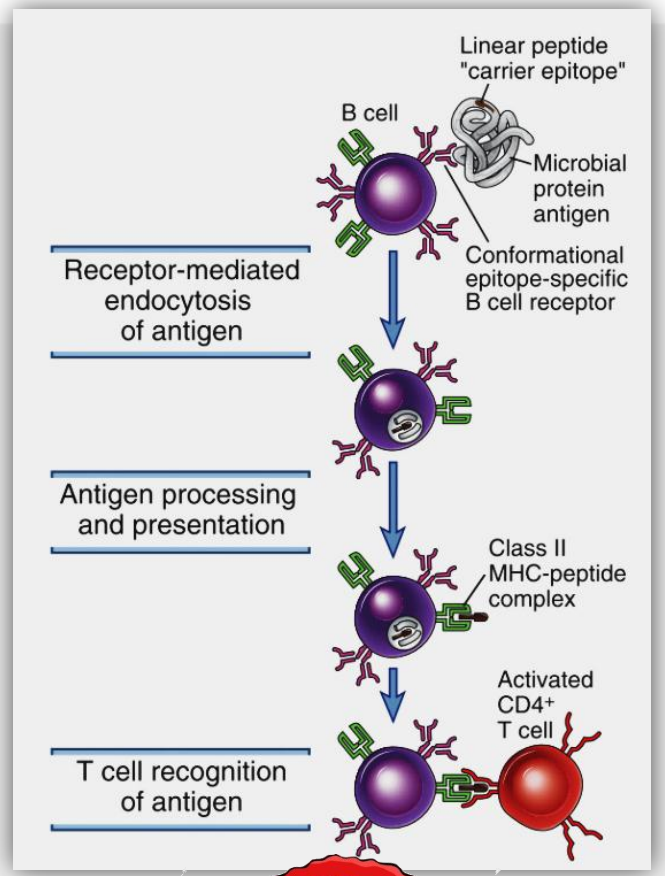
- Antígeno: Sustancia extraña capaz de ser reconocida por el sistema inmune, específicamente por el TCR o BCR
- Inmunógeno: es un antígeno que es capaz de provocar una respuesta inmune incluyendo la producción de anticuerpos
- Antigenicidad: es la capacidad de una sustancia para combinarse específicamente 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





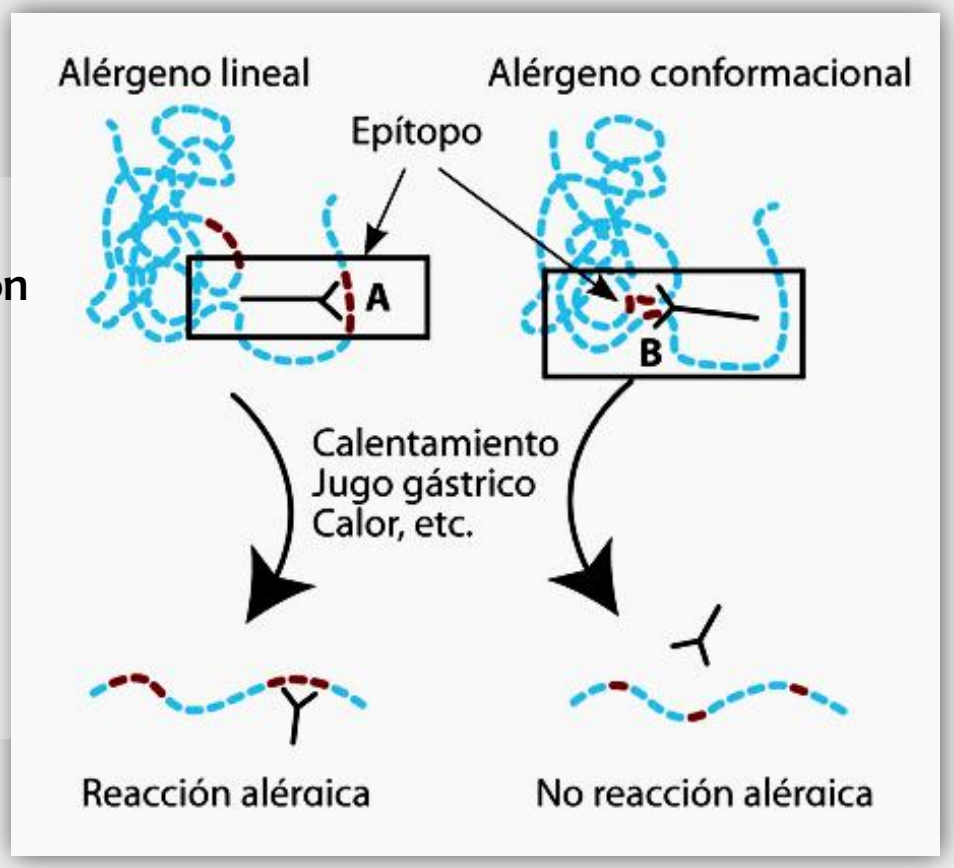
- Hapteno: Sustancia de bajo peso molecular que no es capaz de inducir una respuesta inmune por sí misma, pero que es capaz de reaccionar con los productos de una respuesta inmune específica (anticuerpos).

- Pueden comportarse como inmunógenos cuando se unen a una molécula portadora (Portador o Carrier)

Epítopes

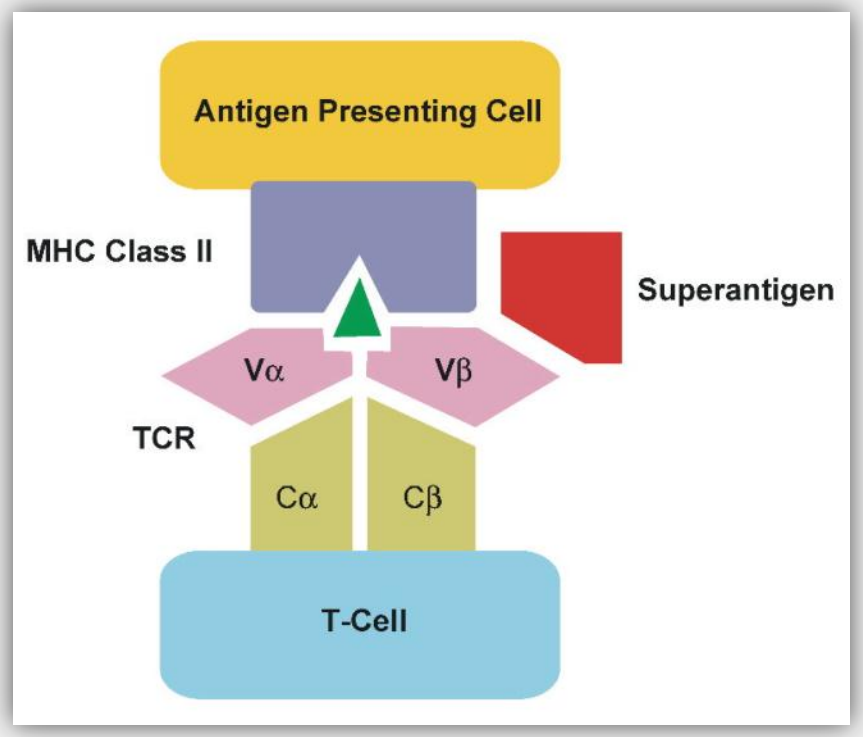
- Epítopo o determinante antigénico: Porción del antígeno que interactúa con el TCR, BCR o con los anticuerpos secretados

  - ✓ 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

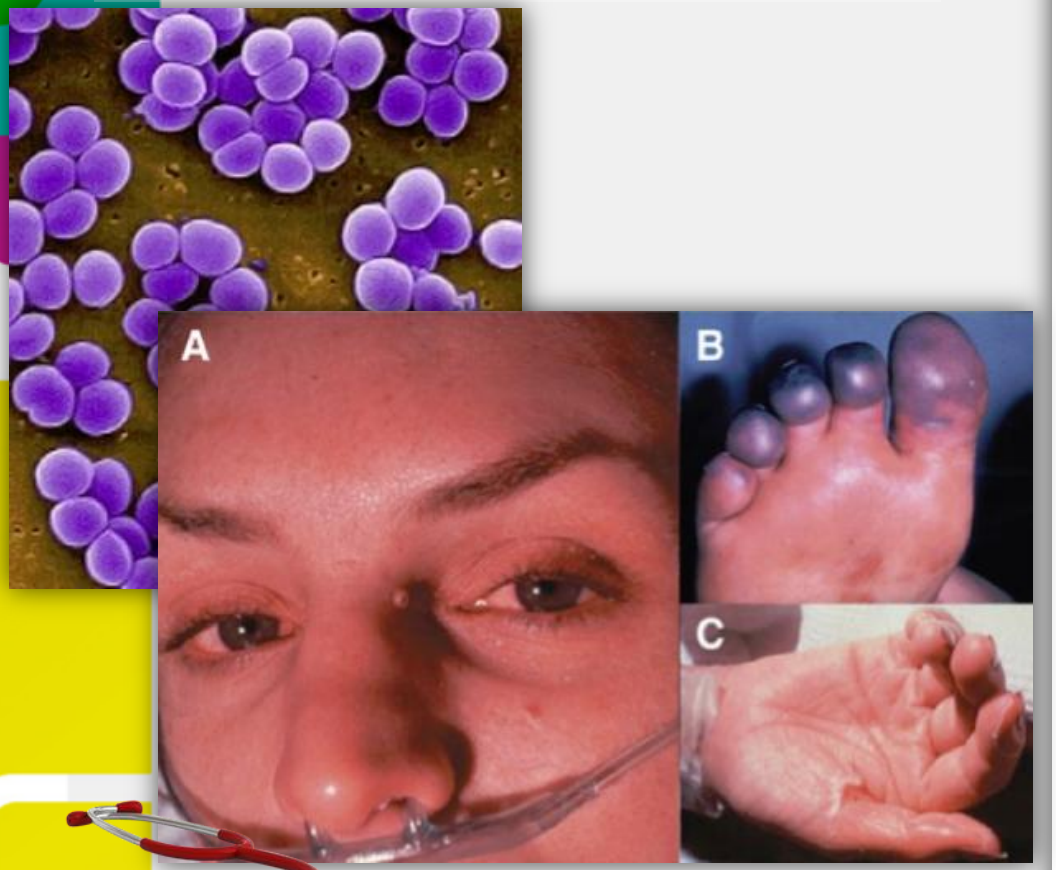
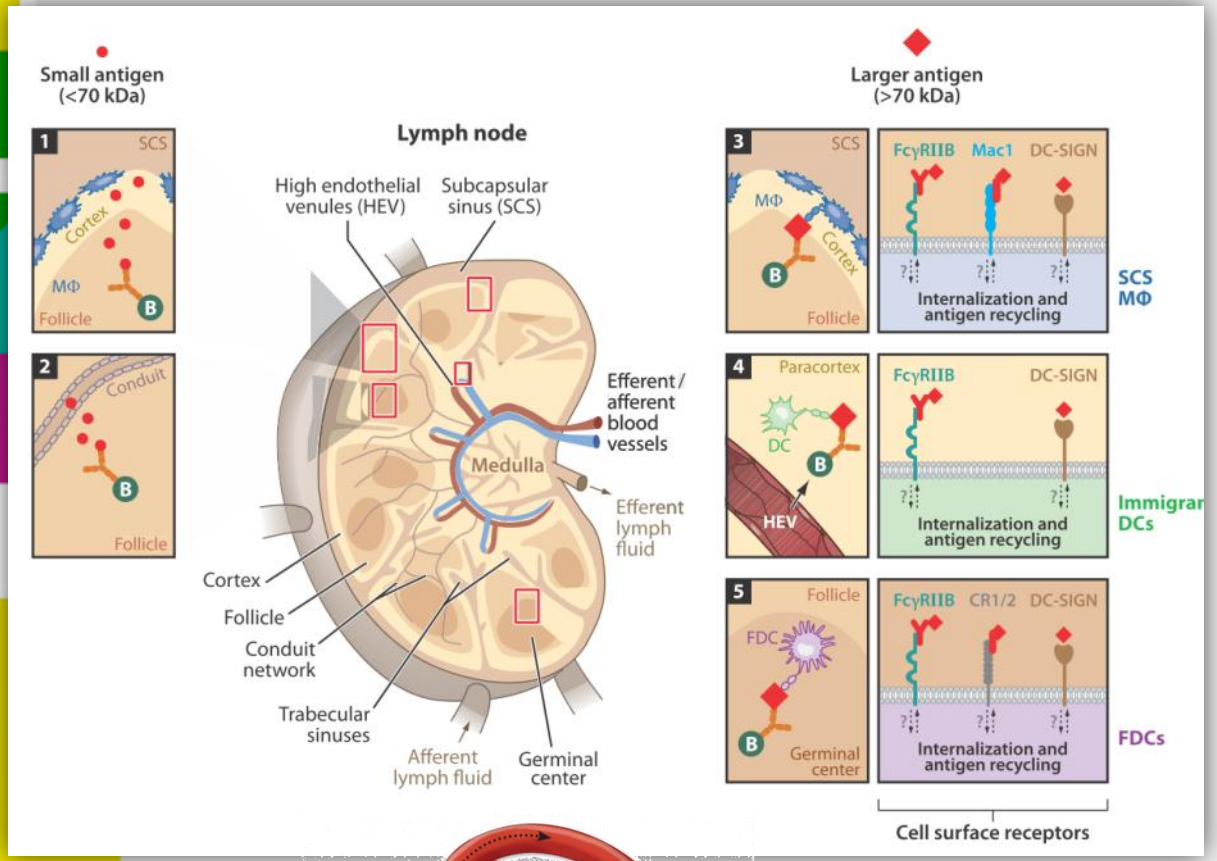


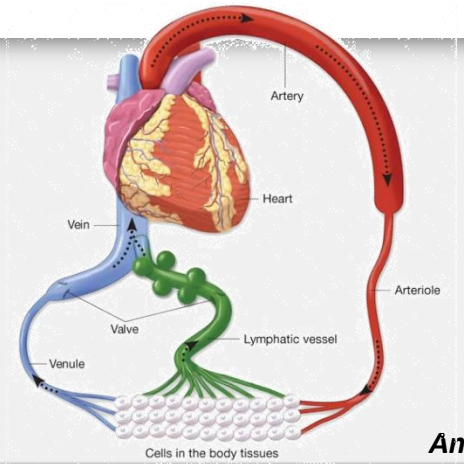
TABLE 2 | Common differentially expressed genes induced by superantigens *in vitro* and *in vivo*.

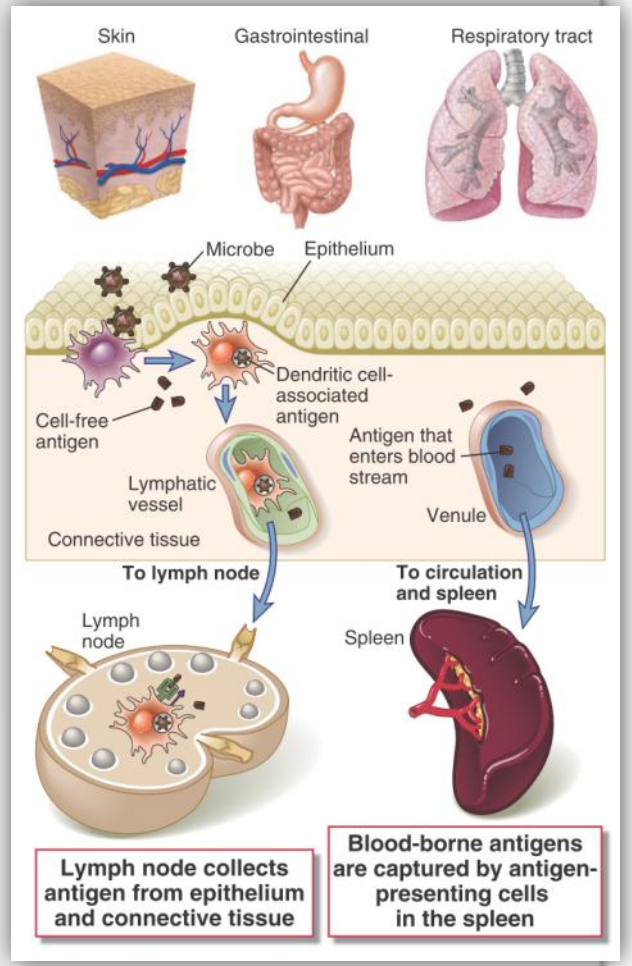
Pathway/network	Gene	Major function
Innate response	IL6, TNFα, LTA, IL17A, IL22	Host defense, inflammation
	IFNγ	Host defense, antimicrobial
	CXCL11, CXXC5, CCL7, XCL1	Host defense, cell migration
	CISH, CIITA, GBP2, TRAF1, RGS16	Signal transduction
	PDE4DIP, PDE4B, PTGER3, P2RY14	Signal transduction
	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, NFκBia	NFκB 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	

Front Immunol. 2016; 7: 23.

Fuente de Antígenos

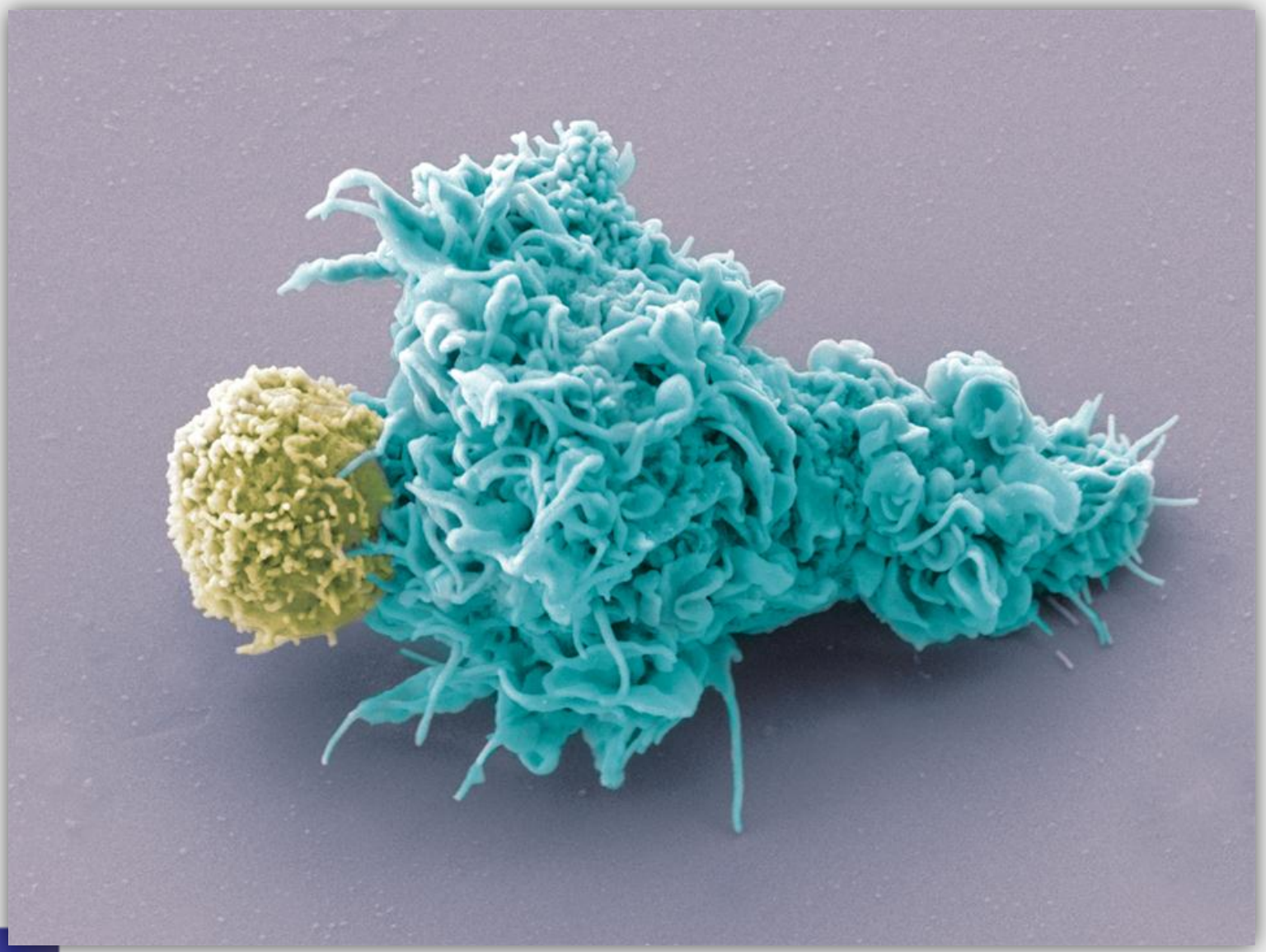






Annu. Rev. Immunol. 2010. 28:185–210

Y quien presenta???



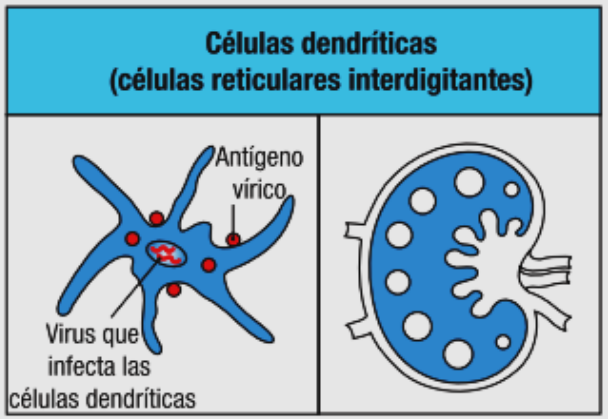
Tipos de APC

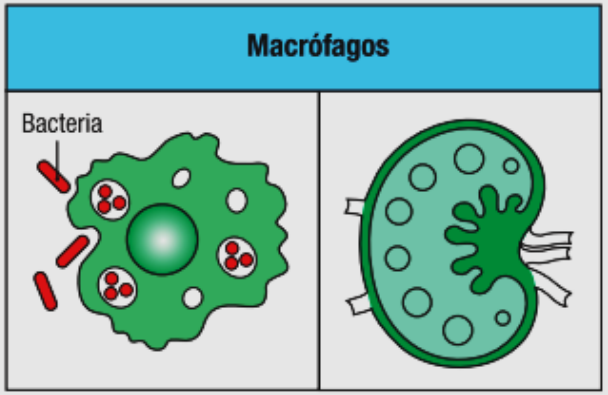
Profesionales vs no profesionales

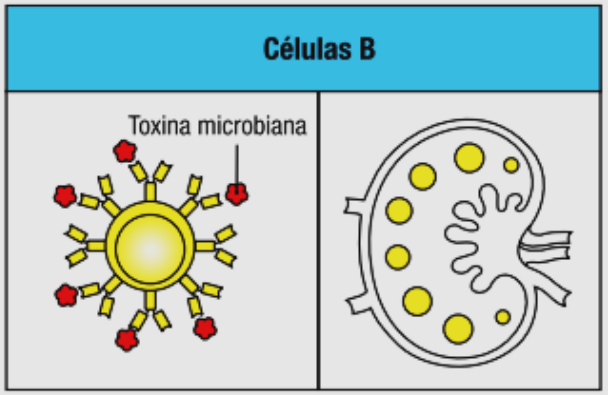
Profesionales
- Células dendríticas
- Macrófagos
- Células B

No profesionales
- Células endoteliales
- Fibroblastos
- Células epiteliales del timo

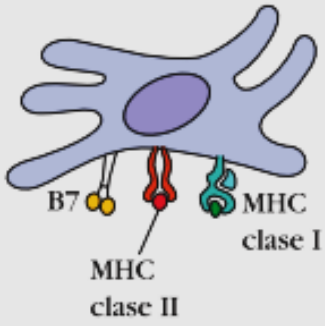
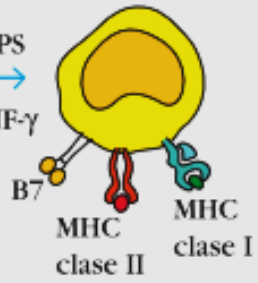
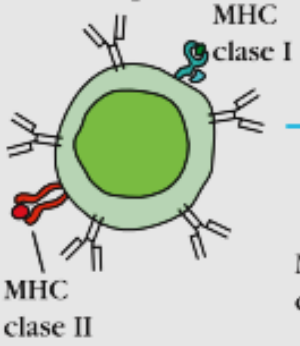
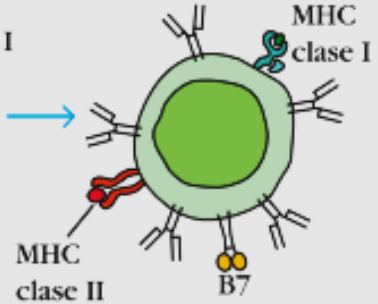
Y las otraaaas.....







Células presentadoras de Antígenos

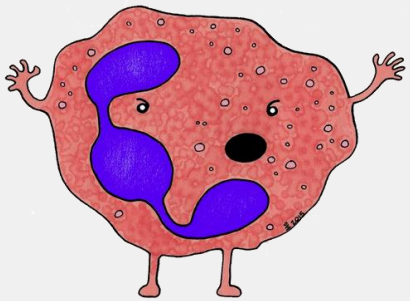
	Célula dendrítica	Macrófago		Linfocito B	
		En reposo 	Activado LPS → INF-γ 	En reposo 	Activado 
Captación de antígeno	Endocitosis, fagocitosis (por células de Langerhans)	Fagocitosis	Fagocitosis	Endocitosis mediada por receptor	Endocitosis mediada por receptor
Expresión de MHC clase II	Constitutiva (+++)	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

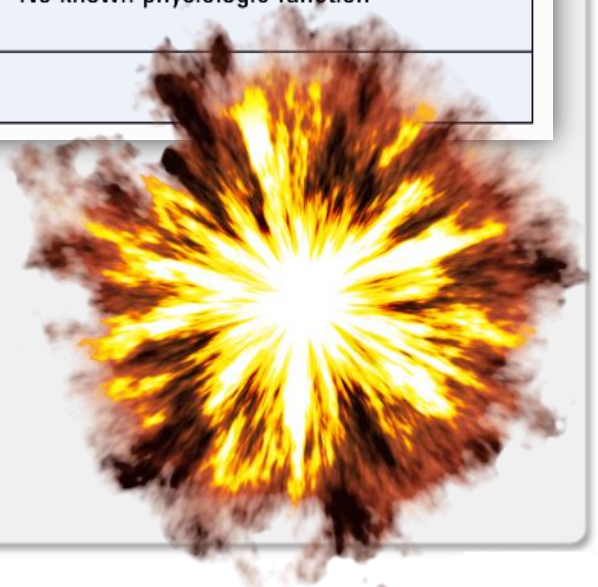
Propiedades y funciones de las APCs

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.





Y los granulocitos!!!

Neutrófilos???

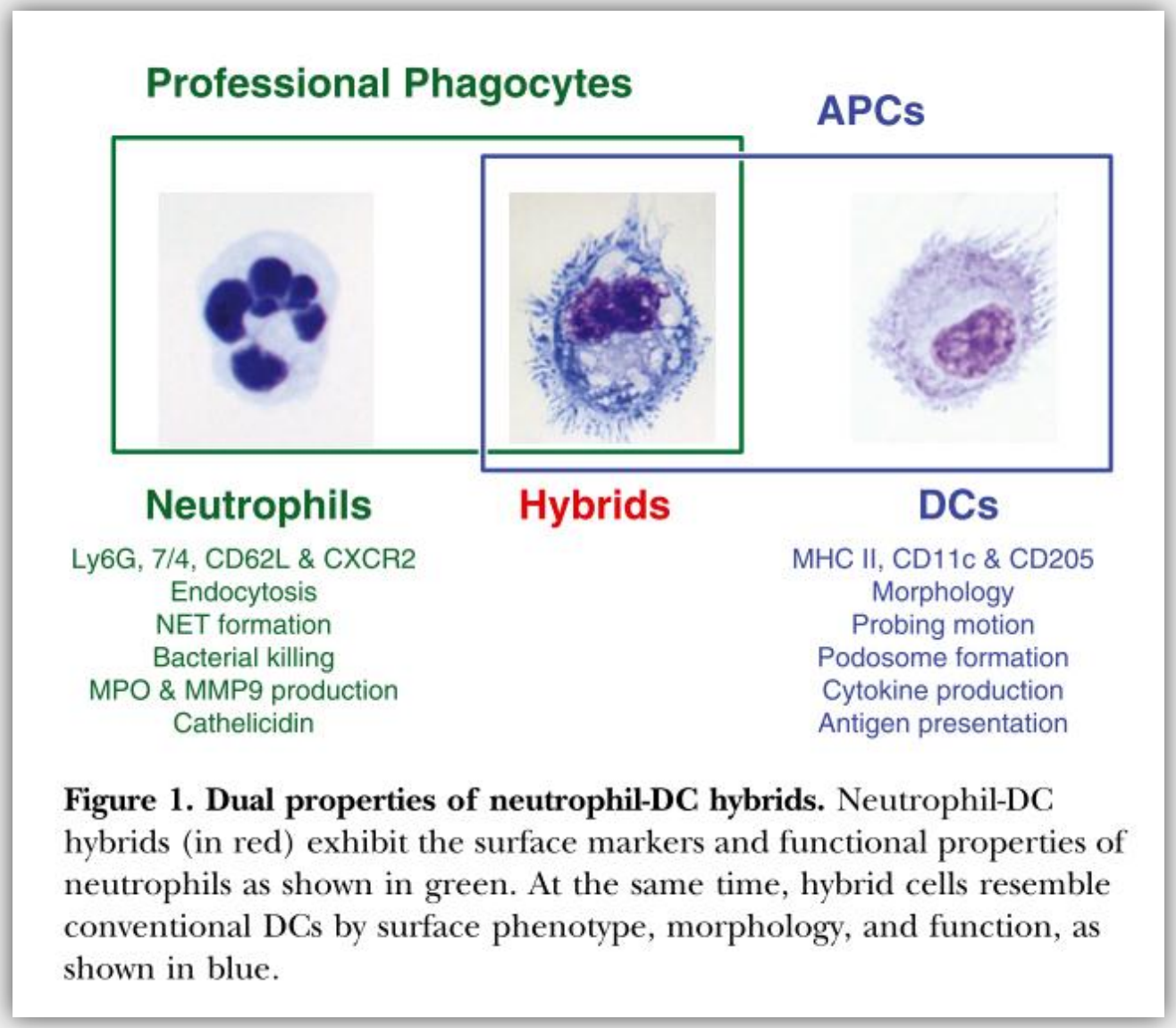
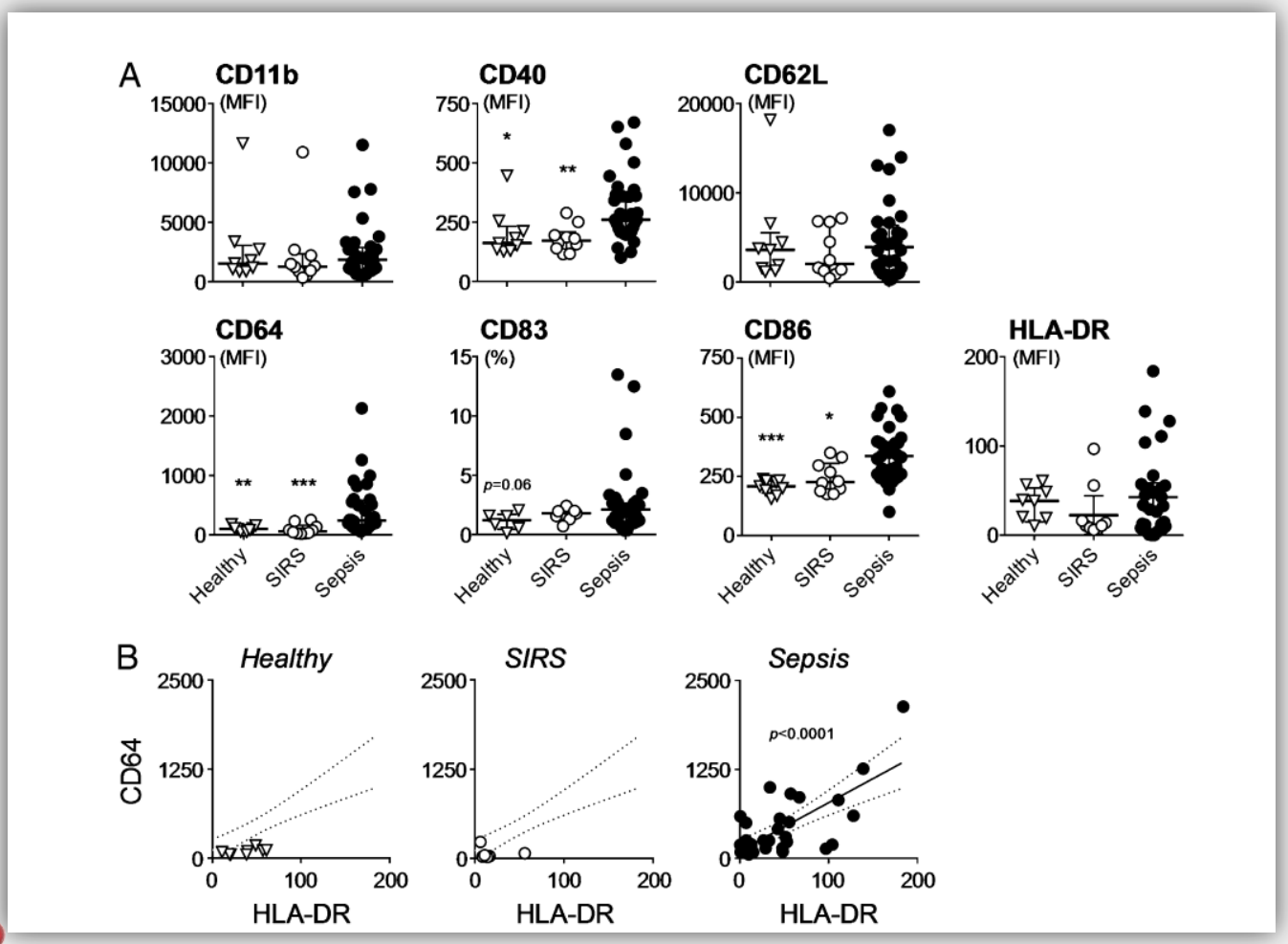


Figure 1. Dual properties of neutrophil-DC hybrids. Neutrophil-DC hybrids (in red) exhibit the surface markers and functional properties of neutrophils as shown in green. At the same time, hybrid cells resemble conventional DCs by surface phenotype, morphology, and function, as shown in blue.

J. Leukoc. Biol. 98: 000–000; 2015.

Solo en crisis???



J Immunol 2014; 193:3704-3716;

Eosinófilos????

International Archives of Allergy and Immunology

Original Paper

Int Arch Allergy Immunol 2008;146:227–234
DOI: 10.1159/000115891

Received: June 19, 2007
Accepted after revision: November 20, 2007
Published online: February 11, 2008

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

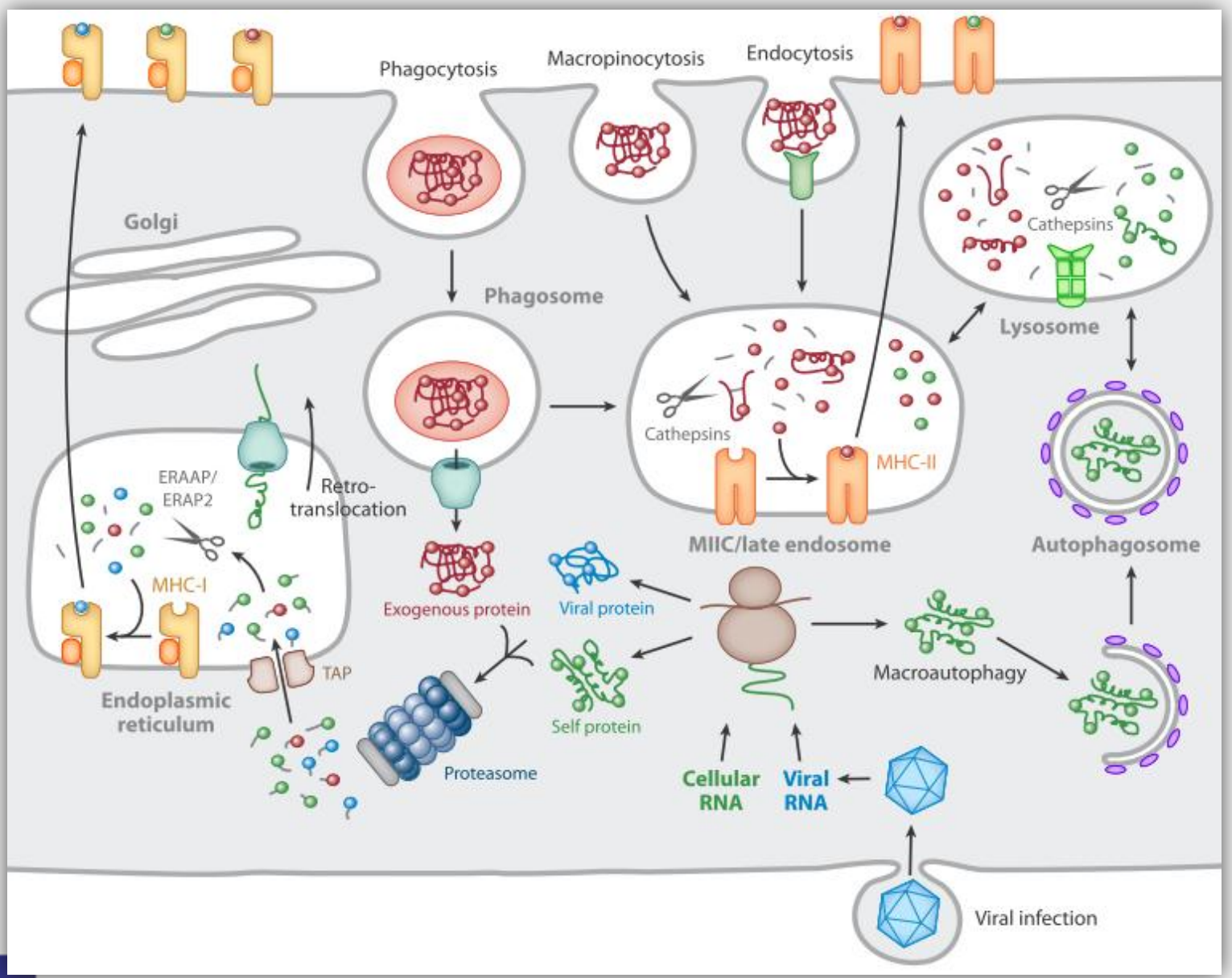
Yun-Jae Jung[a] So-Youn Woo[b] Myoung Ho Jang[c] Masayuki Miyasaka[d]
Kyung-Ha Ryu[e] Hae-Kyung Park[b] Ju-Young Seoh[b]

Eur. J. Immunol. 1992. *22:* 1919–1925

**Victoria Del Pozo◆,
Belen De Andrés◆,
Elena Martín▲,
Blanca Cárdaba▼,
Julio Cesar Fernández,
Soledad Gallardo,**

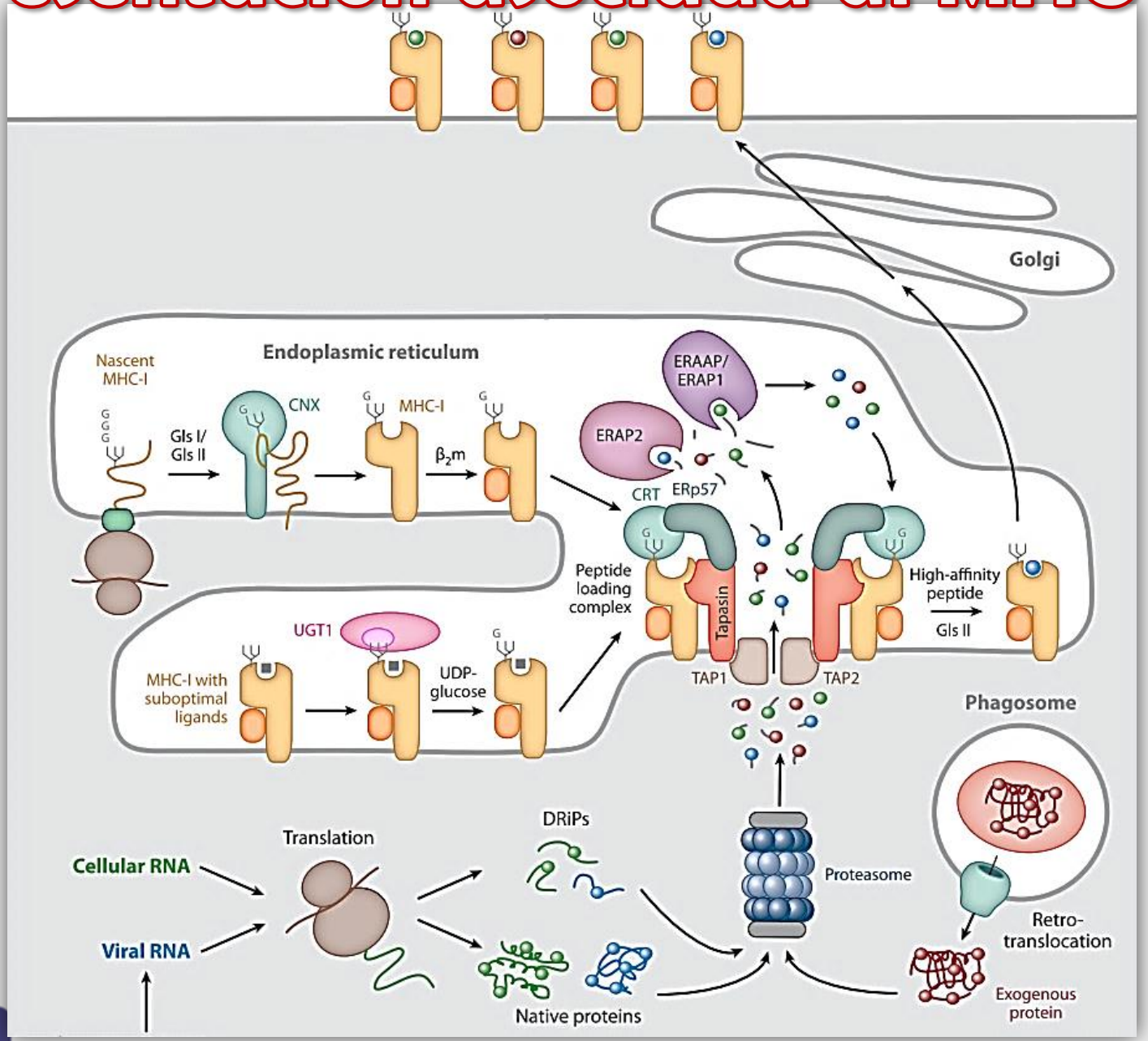
Eosinophil as antigen-presenting cell: activation of T cell clones and T cell hybridoma by eosinophils after antigen processing*

PRESENTACIÓN ANTIGÉNICA



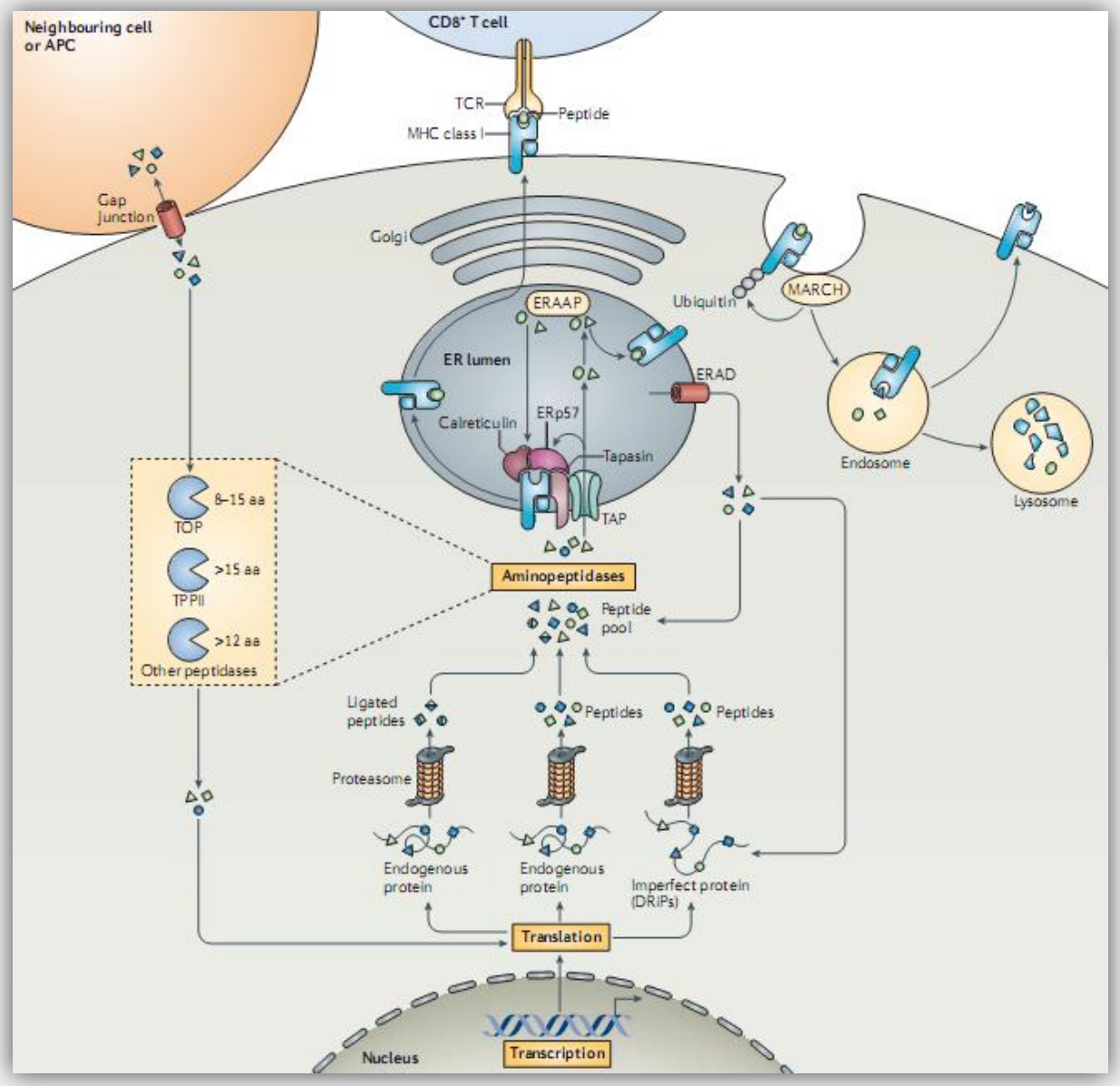
Annu. Rev. Immunol. 2013. 31:443

Presentación asociada al MHC I



Curr Opin Immunol. 2008 Feb;20(1):75-81.

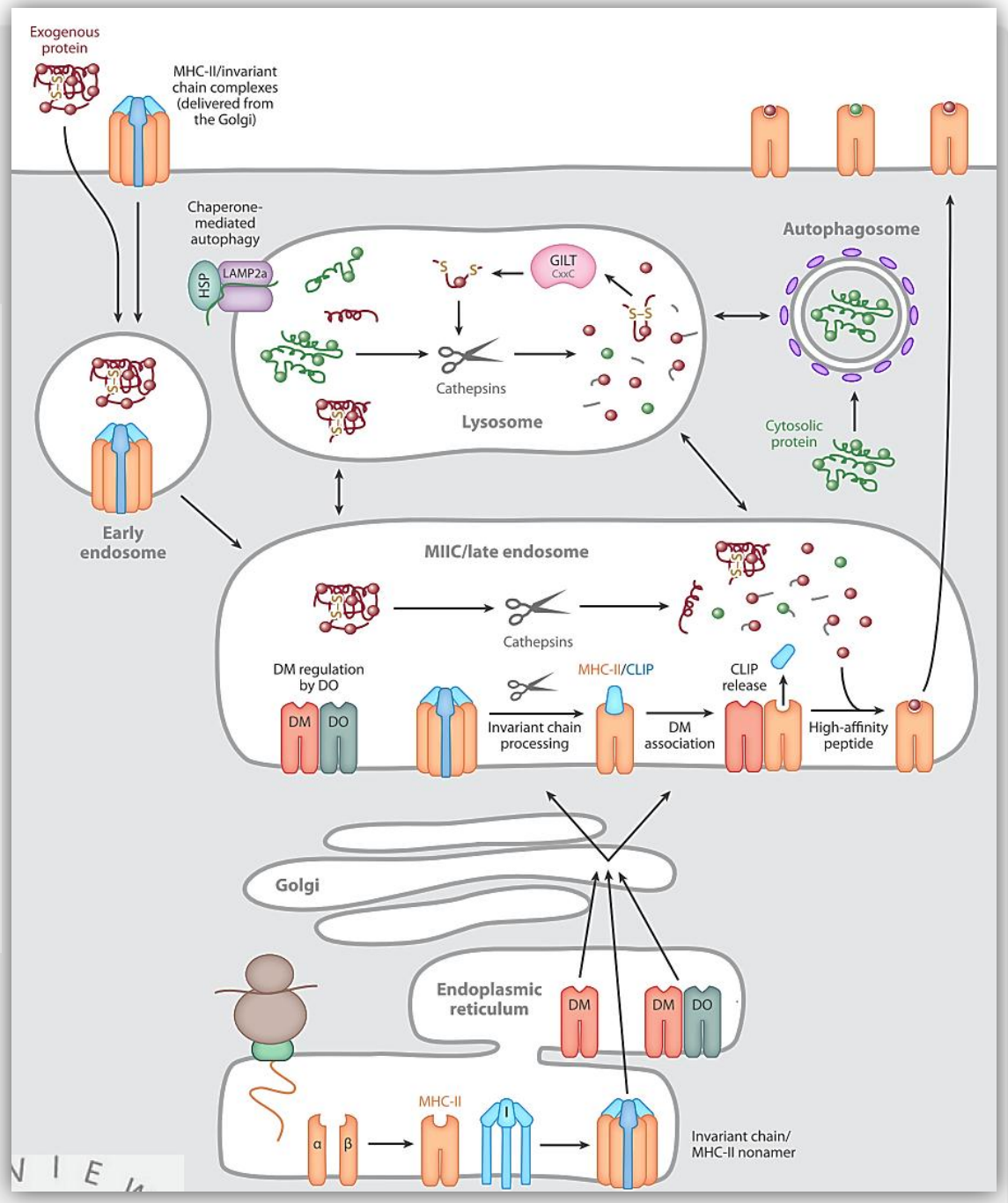
Ay hazlo tu!!!!



. J Immunol 2009;183;1083-1090.. J Immunol 2010;184:9-15. Nat Rev Immunol 2011; 11: 823

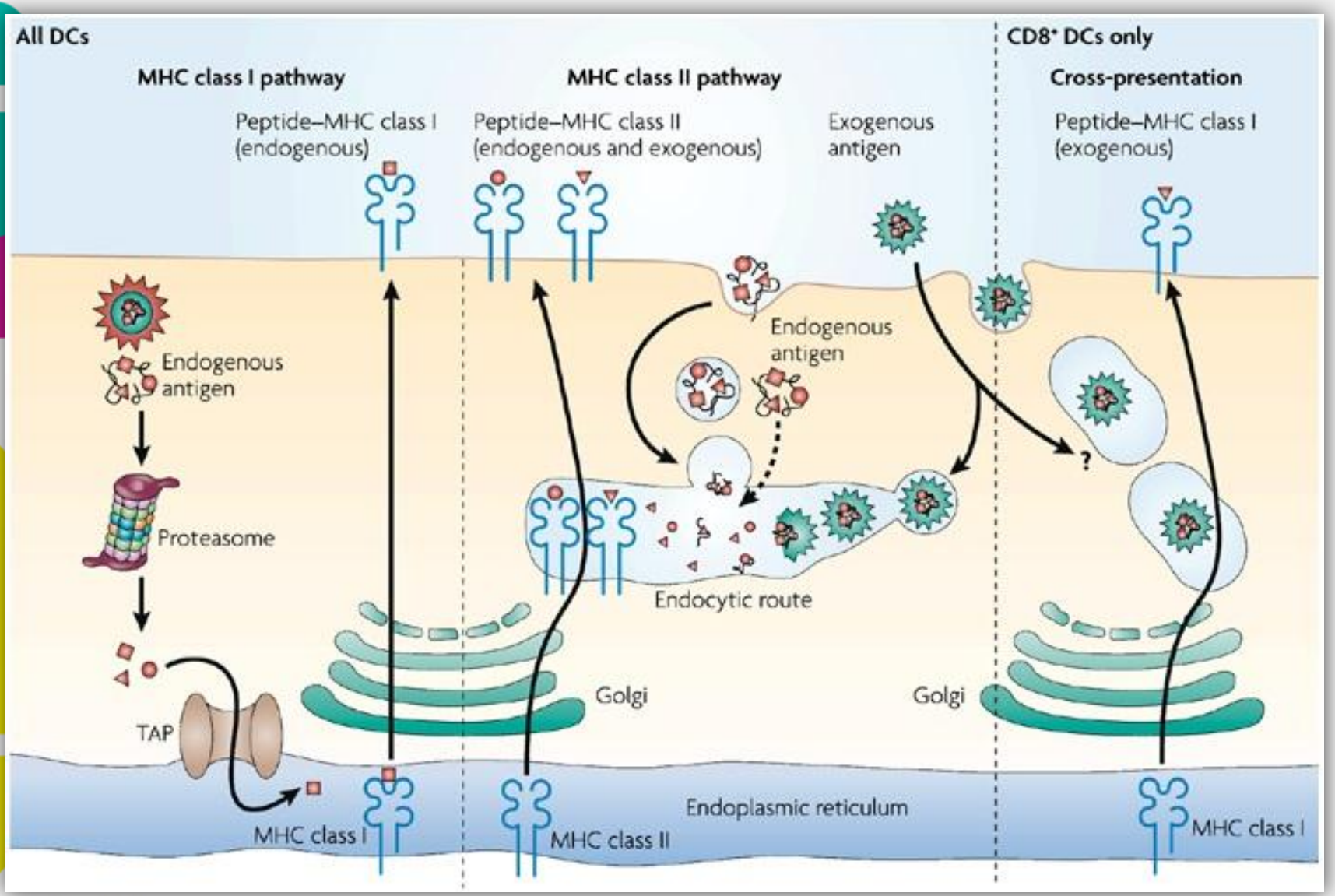
Presentación asociada al MHC II

- 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



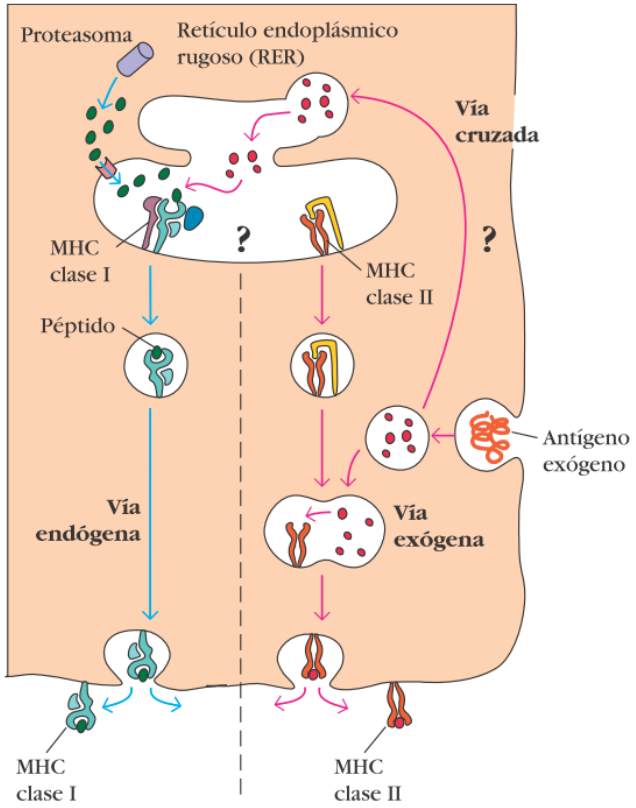
van Lith et al. 2010. J. Biol. Chem. 285:40800. Neefjes Nat Rev Immunol 2011; 11: 823. Blumm et al. Annu. Rev. Immunol. 2013

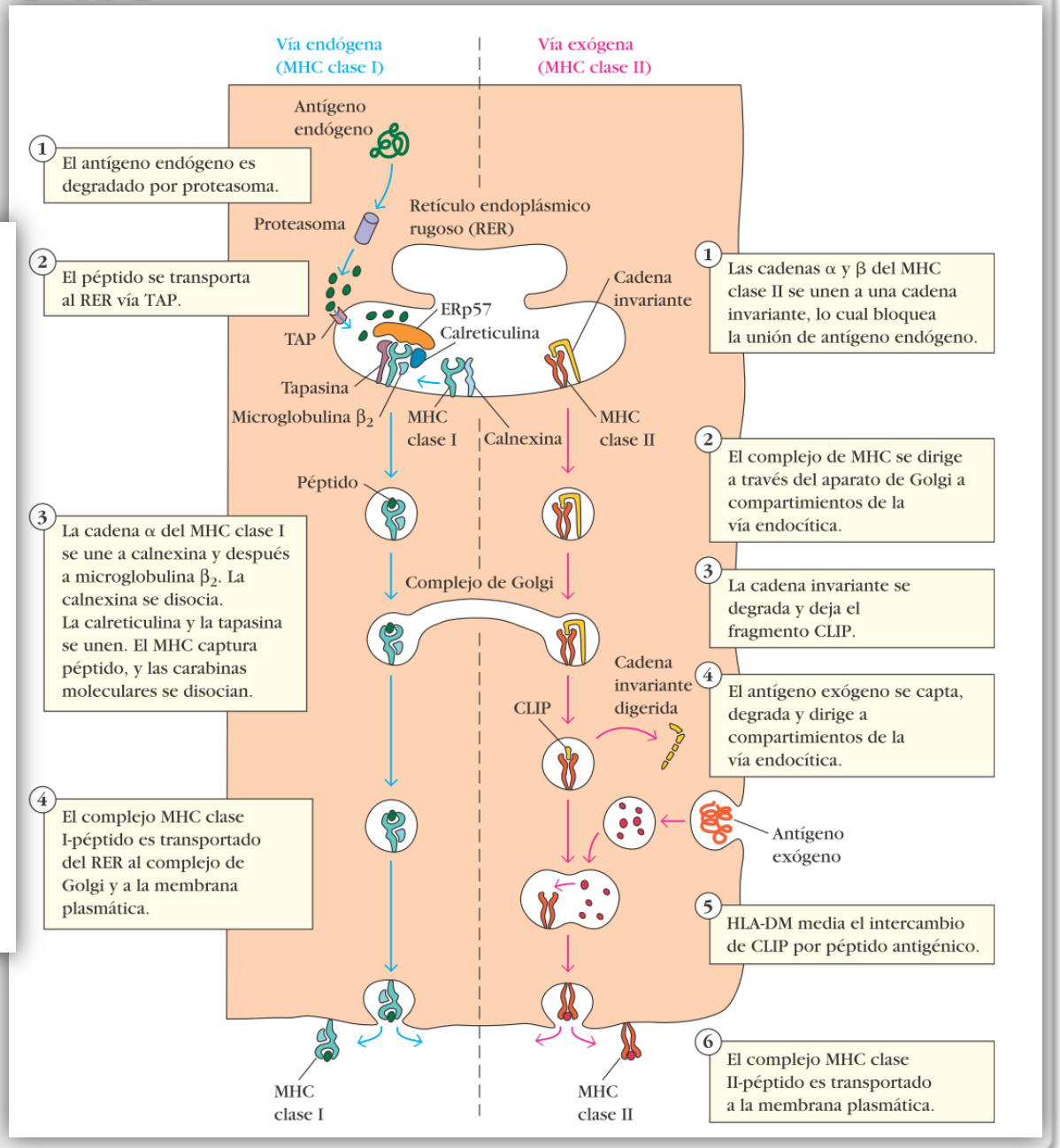
Presentación cruzada



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

Otra vez todo





Moléculas no clásicas

Clase I

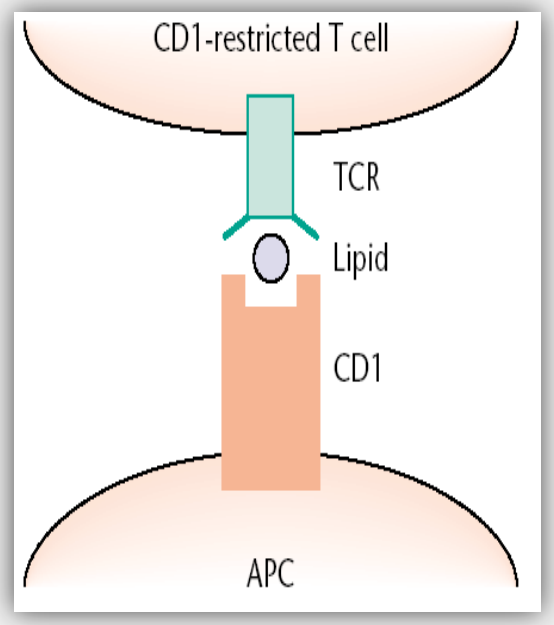
- En su mayoría son pseudogenes
- Polimorfismo escaso o nulo
- Pueden presentar péptidos a células T
- HLA-E-HLA-H, HLA-J, HLA-X
- Ligandos de NKG2D
- Familia MIC (MICA, MICE)
- CD1

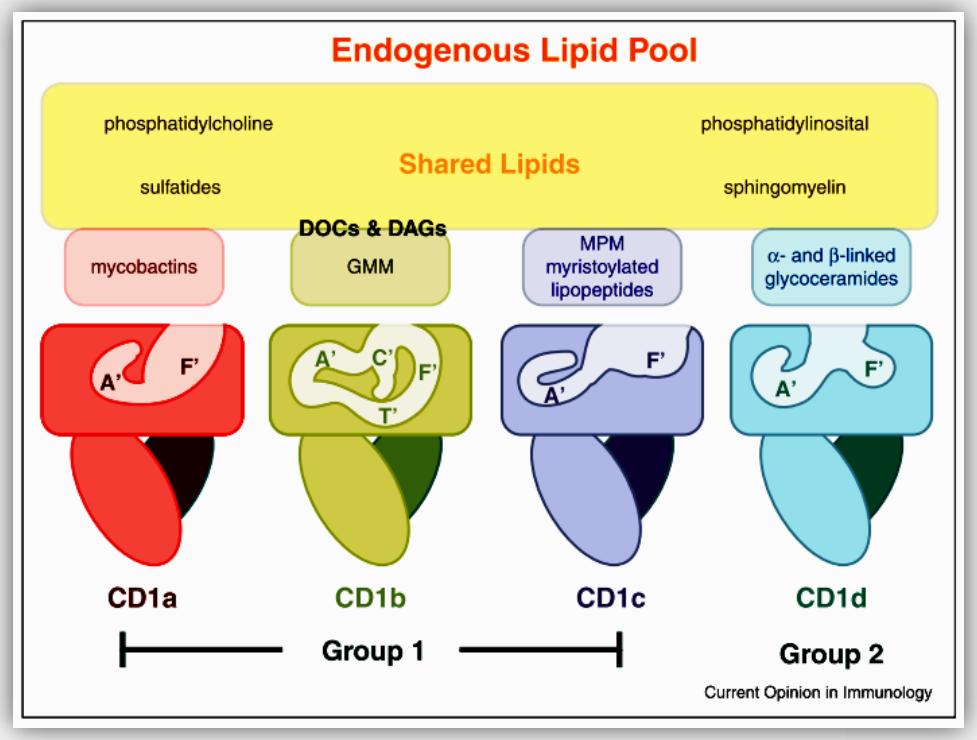
Clase II

- 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

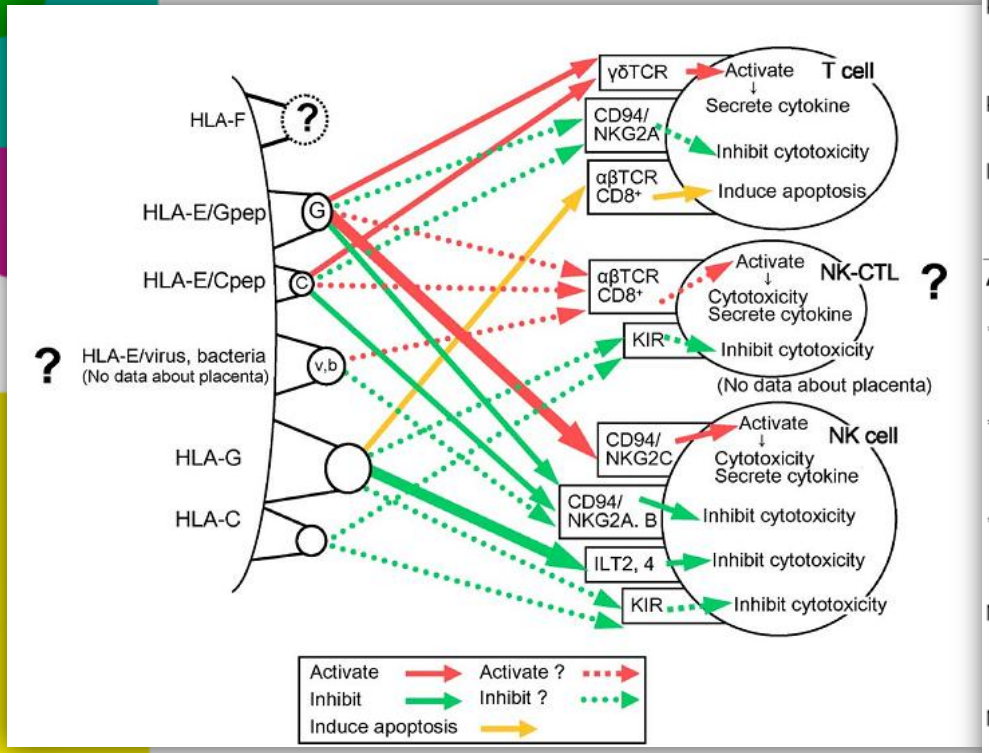
CD1

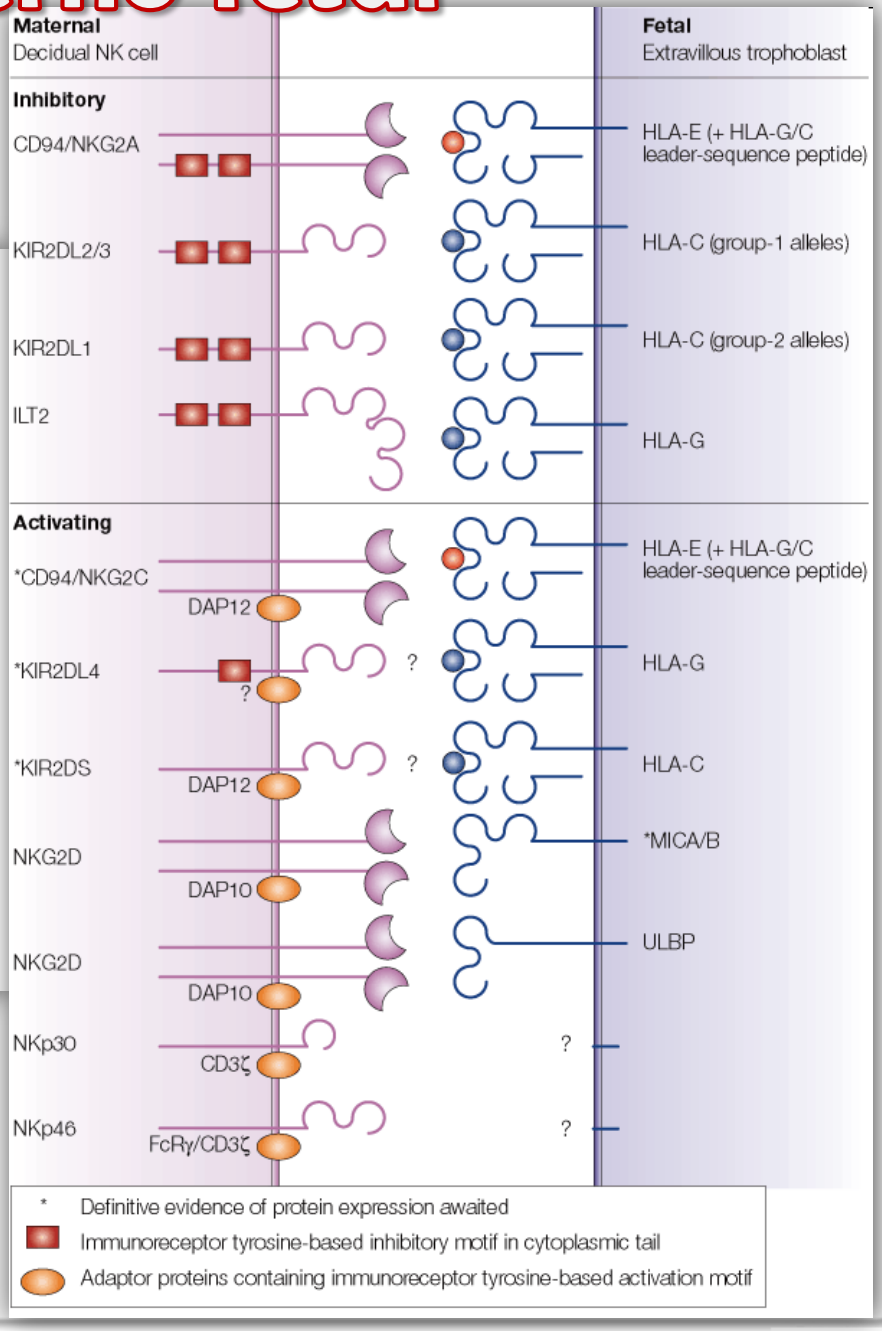




- Presente en compartimientos endosomales
- Glicolípidos microbiales
- Tolerancia central a lípidos propios
- CD1 a pesar de ser parecido a MHC-I, se comporta como MHC-II
- Los antígenos son lípidos y glucolípidos (micobacterias)
- Activa linfocitos T γδ y NKT

Tolerancia materno fetal





J Immunol Res. 2016;2016:4326495

Tolerancia materno fetal

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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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Journal of Reproductive Immunology 101–102 (2014) 111–119

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
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¡Gracias por la atención!