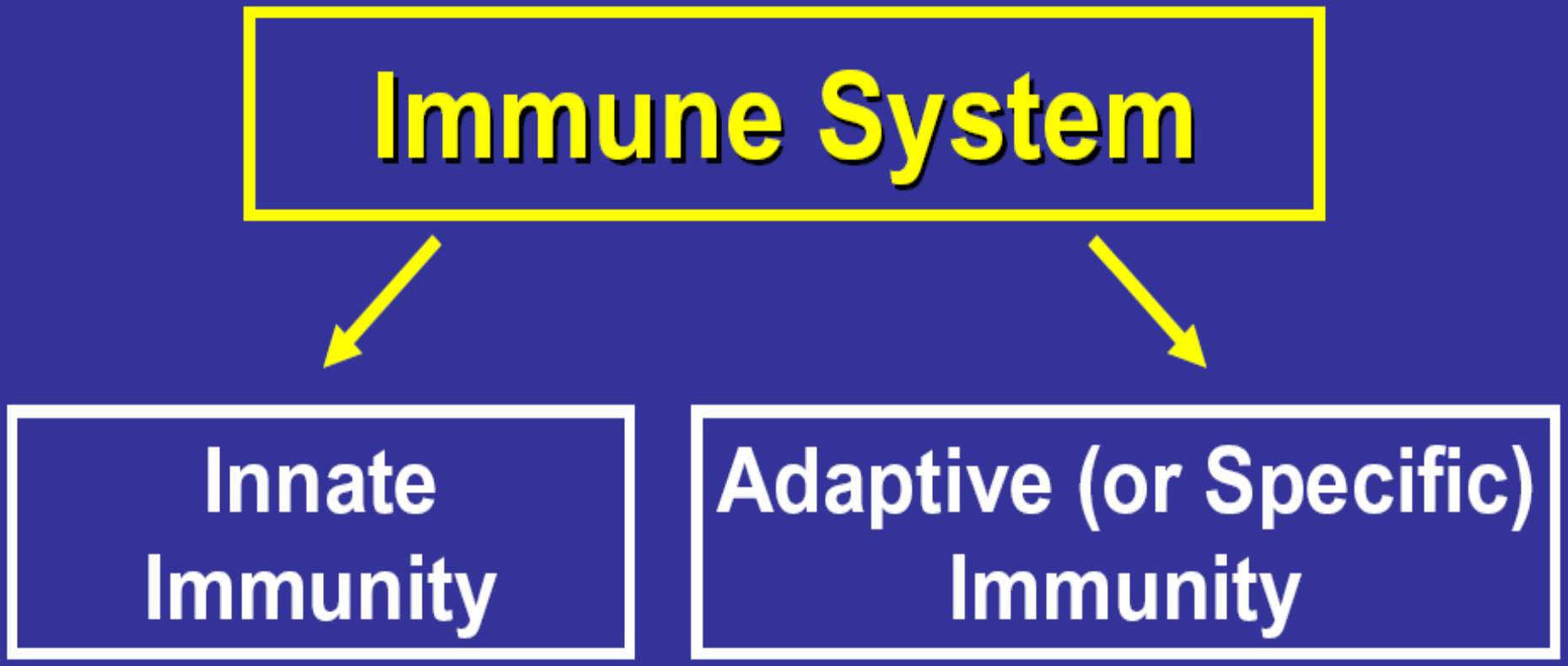
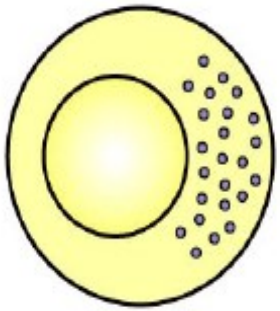

Immune System
Innate Immunity
Adaptive (or Specific) Immunity

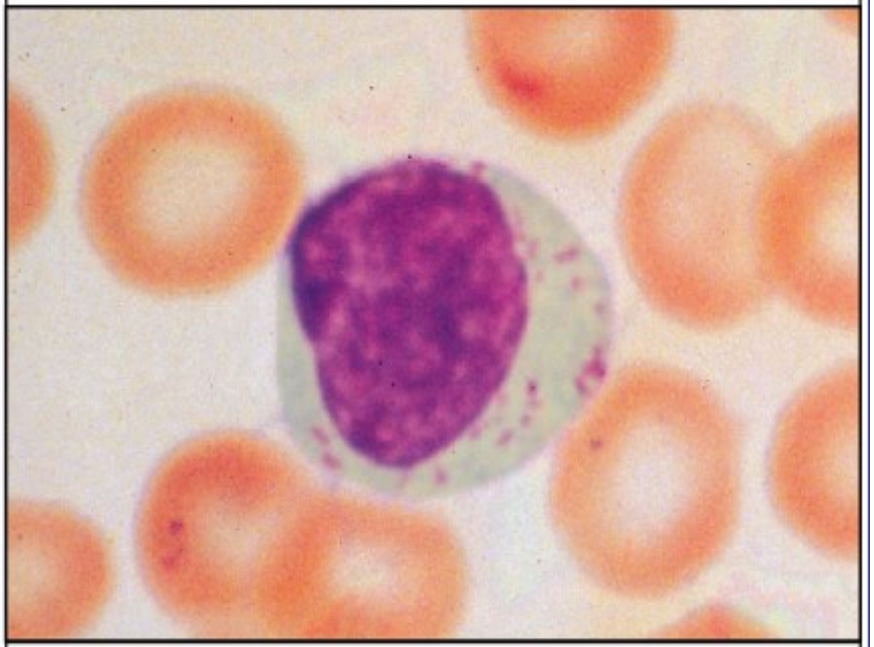
Compenente cellulare del sistema immunitario

CELLULE DENDRITICHE	GRANULOCITI	MONOCITI	LINFOCITI
Gruppo di cellule mobili diffuse in tutto l'organismo Attivano la risposta immunitaria producendo segnali (citochine) Immunità naturale-acquisita	1) Eosinofili 2) Basofili 3) Neutrofili Fagocitosi Immunità naturale	Si trasformano in macrofagi nei tessuti Fagocitosi Immunità naturale	1) Linfociti B Immunità umorale acquisita 2) Linfociti T Immunità cellulo-mediata • Helper – CD4 • Citotossici – CD8 • Soppressori 3) Natural Killer (NK) Non B e non T Immunità naturale antivirus e antitumorale

Natural killer cell: a major player of the innate immunity

Natural killer (NK) cell

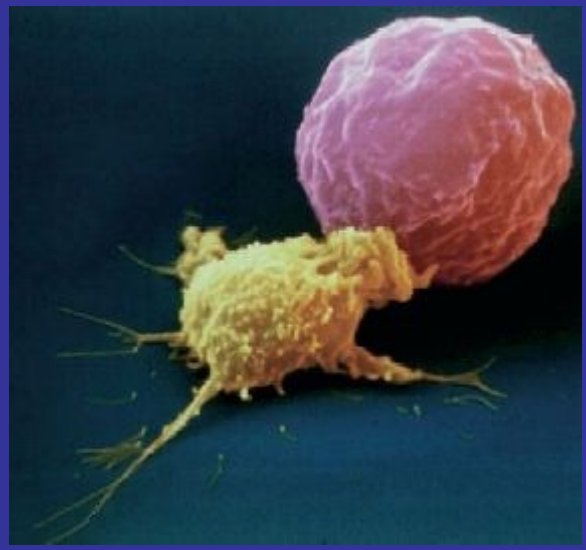




Releases lytic granules that kill some virus-infected cells

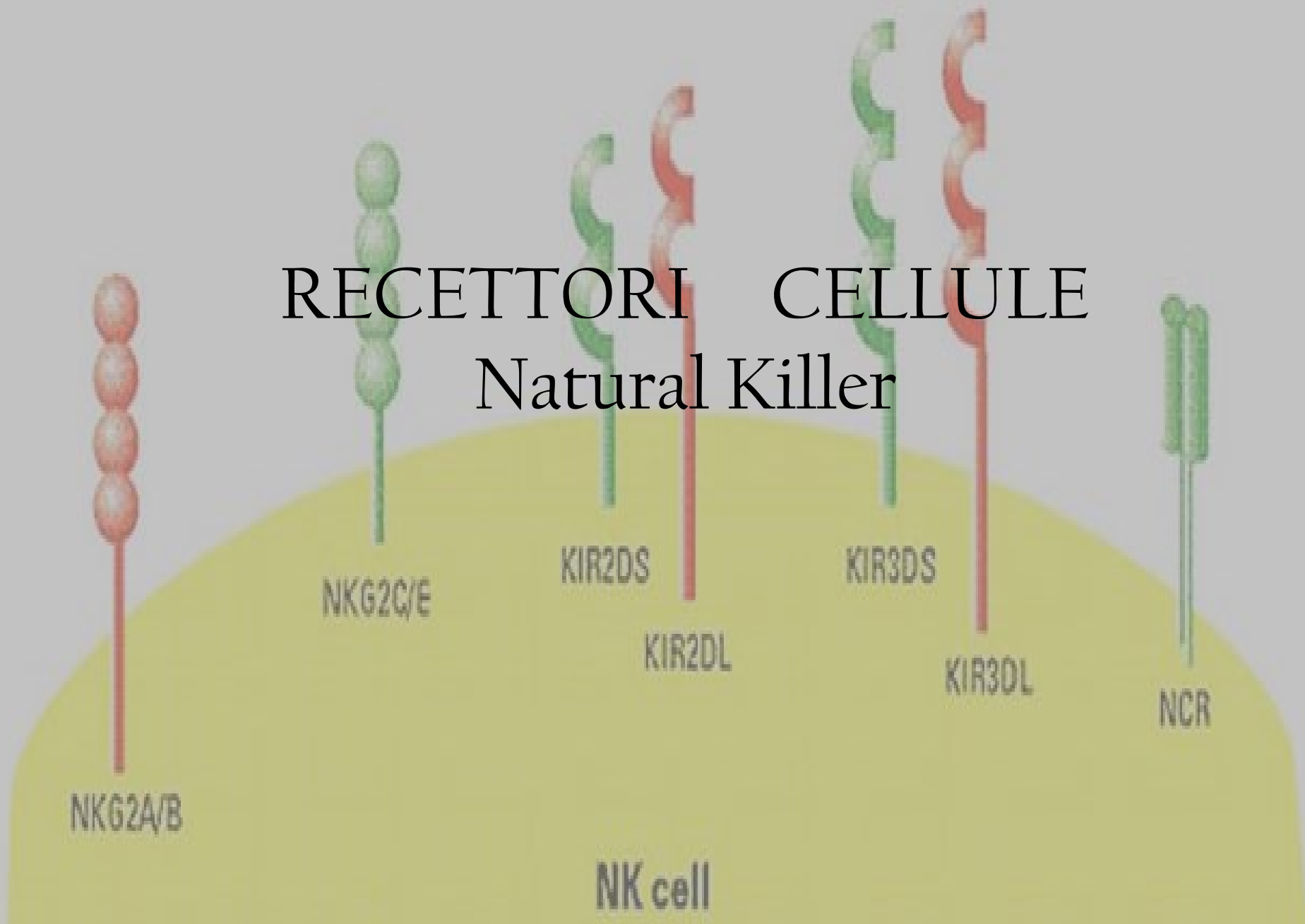
Figure 1-6 Immunobiology, 6/e. (© Garland Science 2005)

Linfociti Natural Killer (NK)



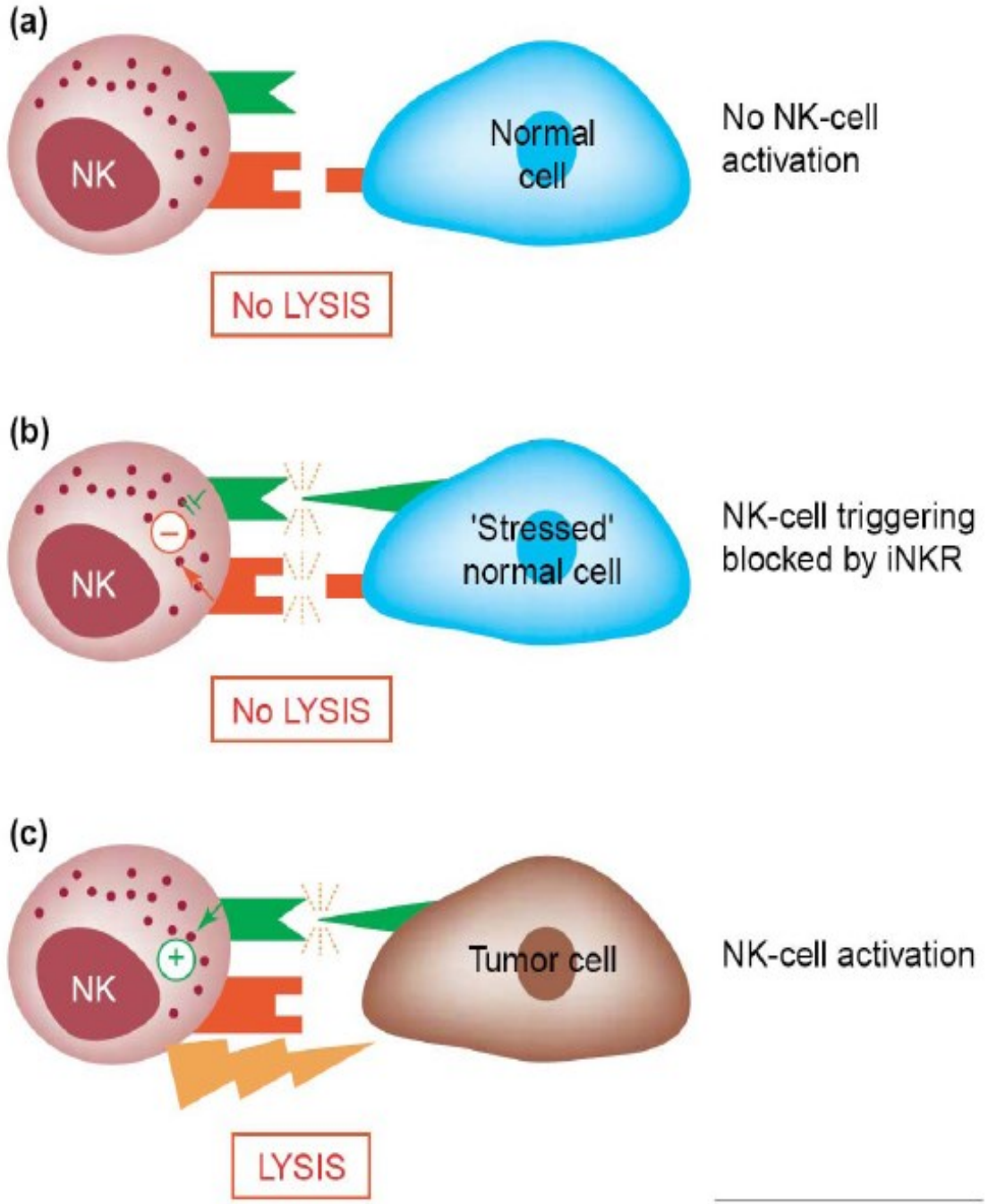
- 10% linfociti (CD56+CD3-)
- Lisi cellula bersaglio
- Regolati da recettori specifici
- Producono citochine immunoregolatorie (IFN-gamma)
- Regolano la risposta immune adattativa
- Induzione infiammazione

RECETTORI CELLULE
Natural Killer



NK cell activation is under the control of HLA-ClassI-specific inhibitory receptors, activating receptors and their cellular ligands

Schematic representation of the main interactions occurring between normal natural killer (NK) cells (expressing both HLA class I-specific inhibitory receptors and activating receptors) and potential target cells.



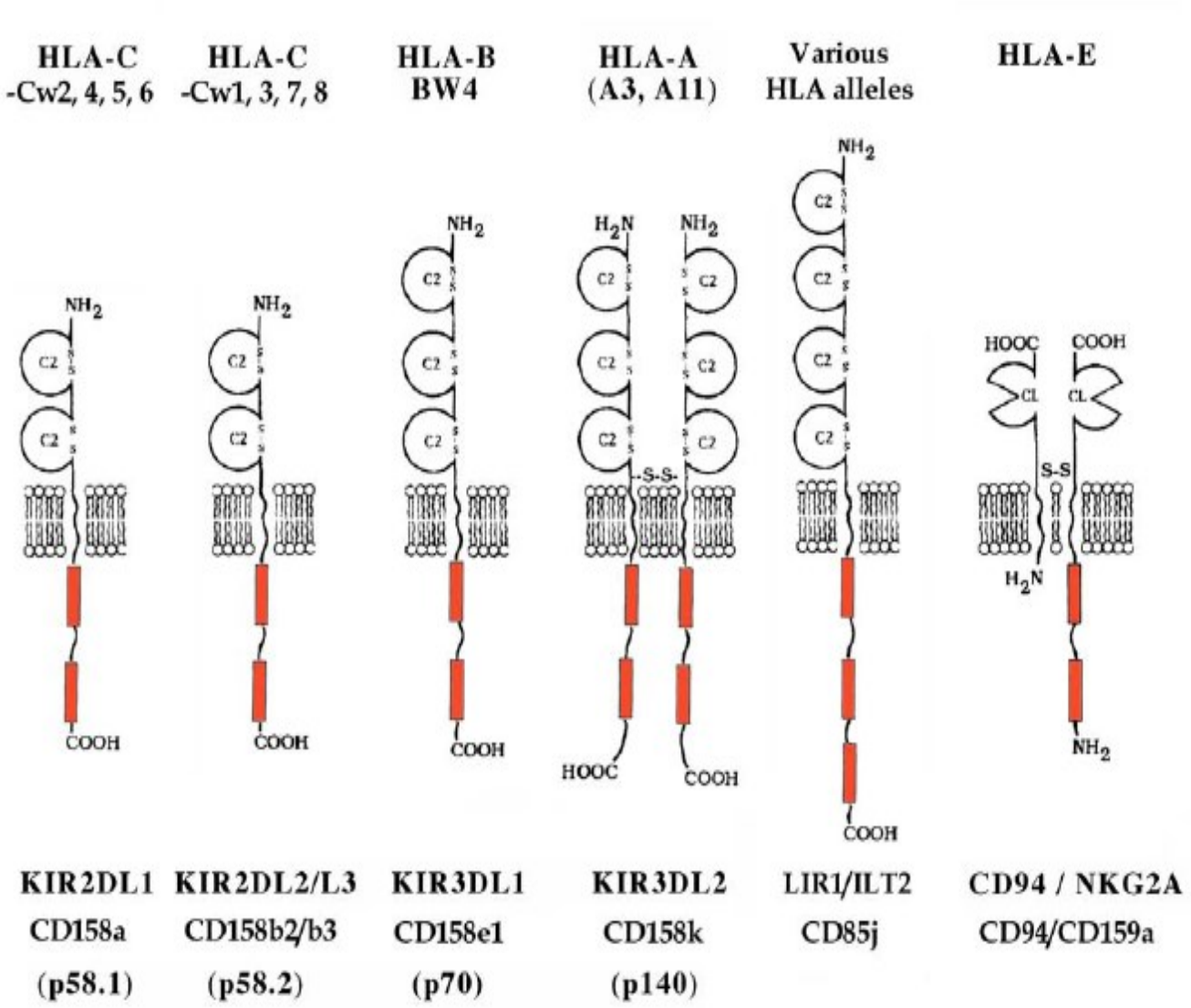
TRENDS in Immunology

Leukocyte receptor complex (LCR)

cr. 19

Multigene family: Leukocyte Ig-like Receptors (LILR)
Leukocyte-Associated Ig-like Receptors (LAIR)
Fca Receptor

HLA class I -specific inhibitory receptors



Killer cell
Immunoglobulin-like
Receptor

- Glicoproteine espresse sulla membrana di NK e alcune cellule T

DIVERSITA' KIR

Genica

Aplotipica

Allelica

Strutturale

Interazione

Funzionale

Clonale

DIVERSITA' GENICA

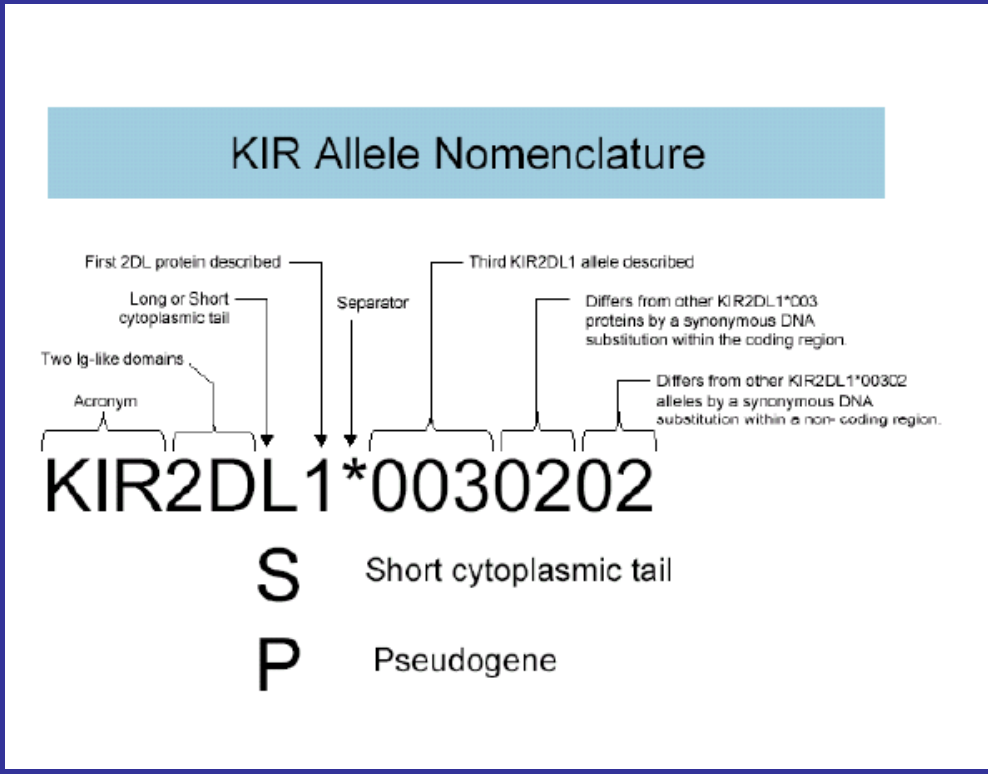
15 geni: KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1, KIR3DL2, KIR3DL3, KIR3DS1

2 pseudogeni: KIR2DP1 and KIR3DP1

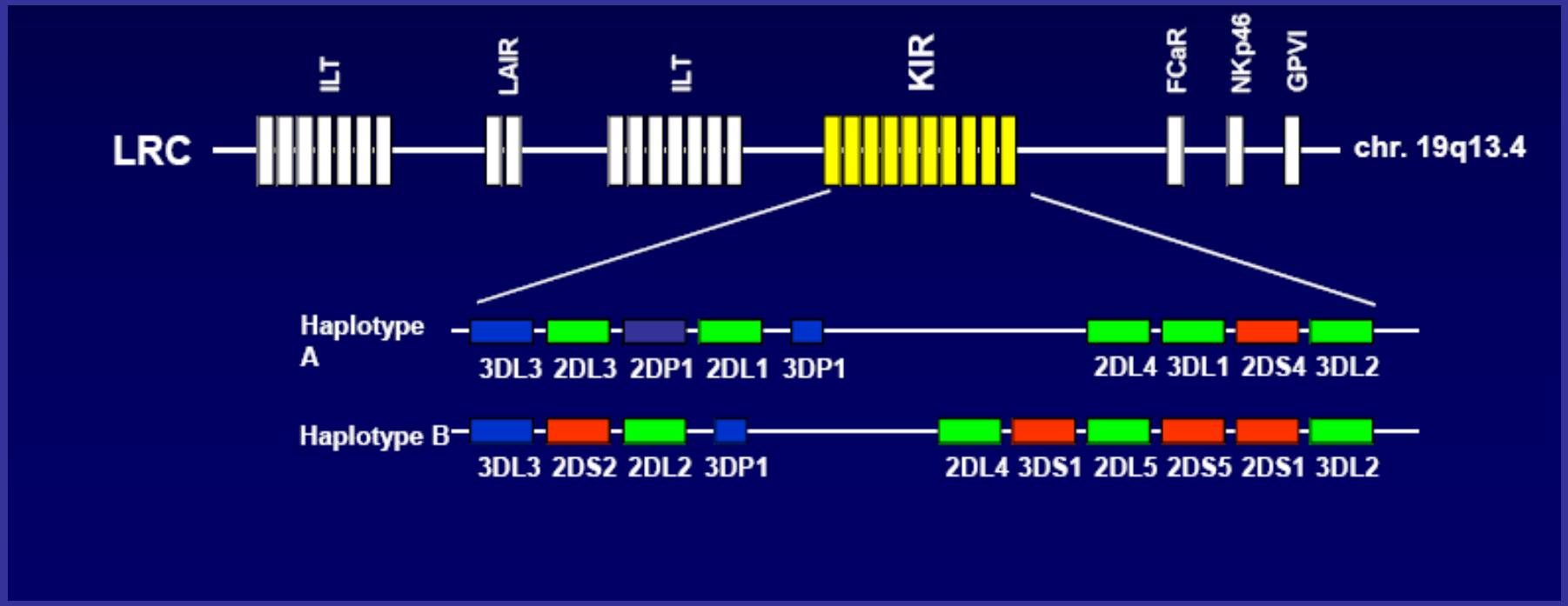
Nomenclatura: 2(2D) o 3 domini Ig-like (3D) (D0, D1, D2)

Coda citoplasmatica corta (S) o lunga (L)

P: pseudogene



DIVERSITA' APLOTIPICA



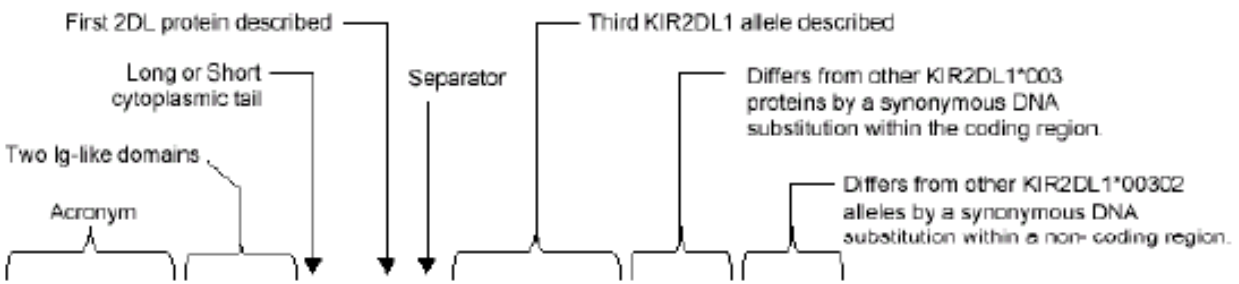
50% popolazione esprime aplotipi A

DIVERSITA' ALLELICA

Symbol	Aliases	No. of alleles
KIR2DL1	cl-42, nkat1, 47.11, p58.1, CD158a	10
KIR2DL2	cl-43, nkat6, CD158b1	5
KIR2DL3	cl-6, nkat2, nkat2a, nkat2b, p58, CD158b2	10
KIR2DL4	103AS, 15.212, CD158d	18
KIR2DL5A	KIR2DL5.1, CD158f	
KIR2DL5B	KIR2DL5.2, KIR2DL5.3, KIR2DL5.4	
KIR2DS1	EB6ActI, EB6ActII, CD158h	4
KIR2DS2	cl-49, nkat5, 183ActI, CD158j	8
KIR2DS3	nkat7	3
KIR2DS4	cl-39, KKA3, nkat8, CD158i	9
KIR2DS5	nkat9, CD158g	3
KIR2DP1	KIRZ, KIRY, KIR15, KIR2DL6	?
KIR3DL1	cl-2, NKB1, cl-11, nkat3, NKB1B, AMB11, KIR, CD158e1	22
KIR3DL2	cl-5, nkat4, nkat4a, nkat4b, CD158k	20
KIR3DL3	KIRC1, KIR3DL7, KIR44, CD158z	7
KIR3DS1	nkat10, CD158e2	6
KIR3DP1	KIRX, KIR48, KIR2DS6, KIR3DS2P, CD158c	4

DIVERSITA' ALLELICA

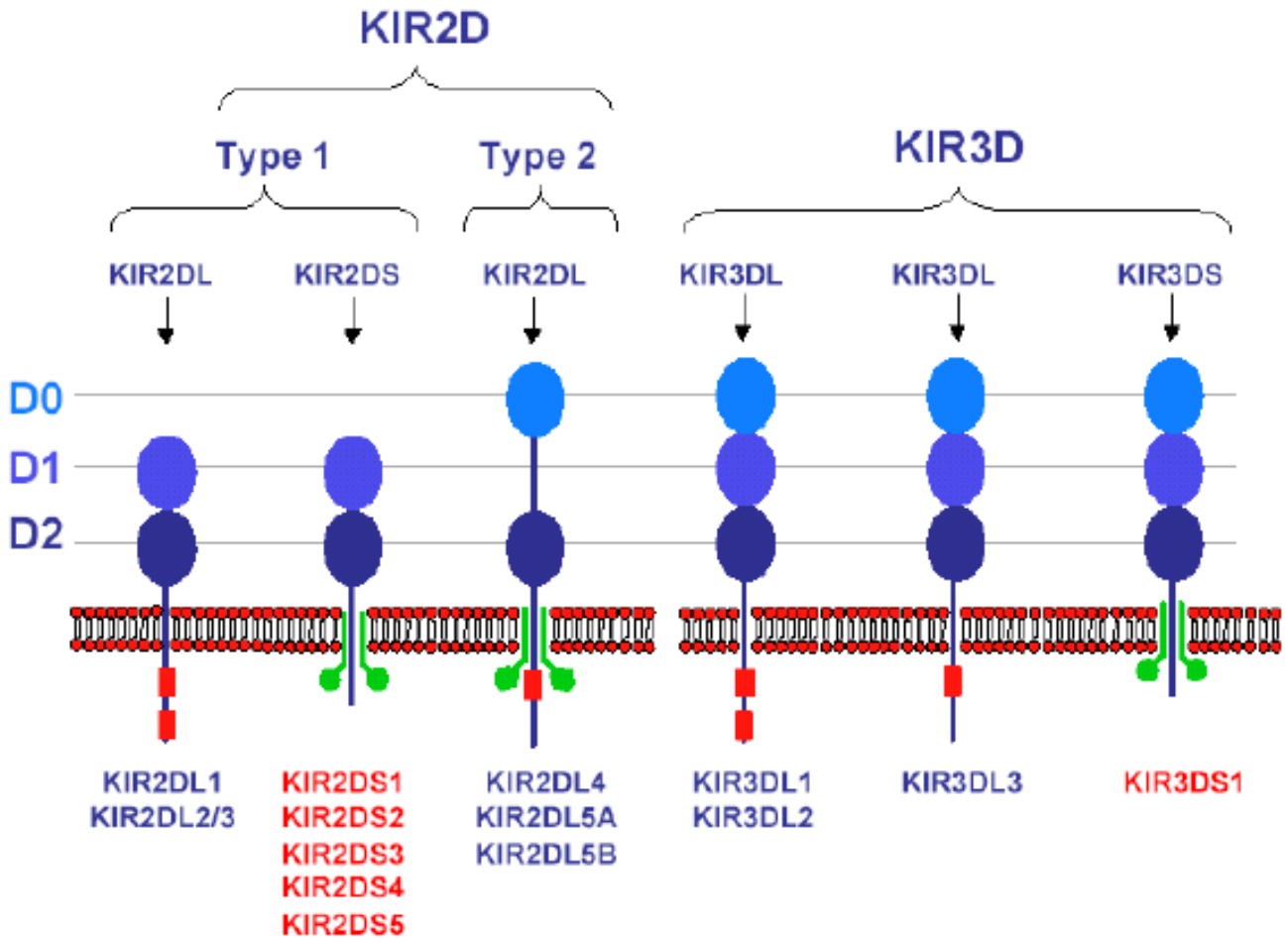
KIR Allele Nomenclature



S Short cytoplasmic tail

P Pseudogene

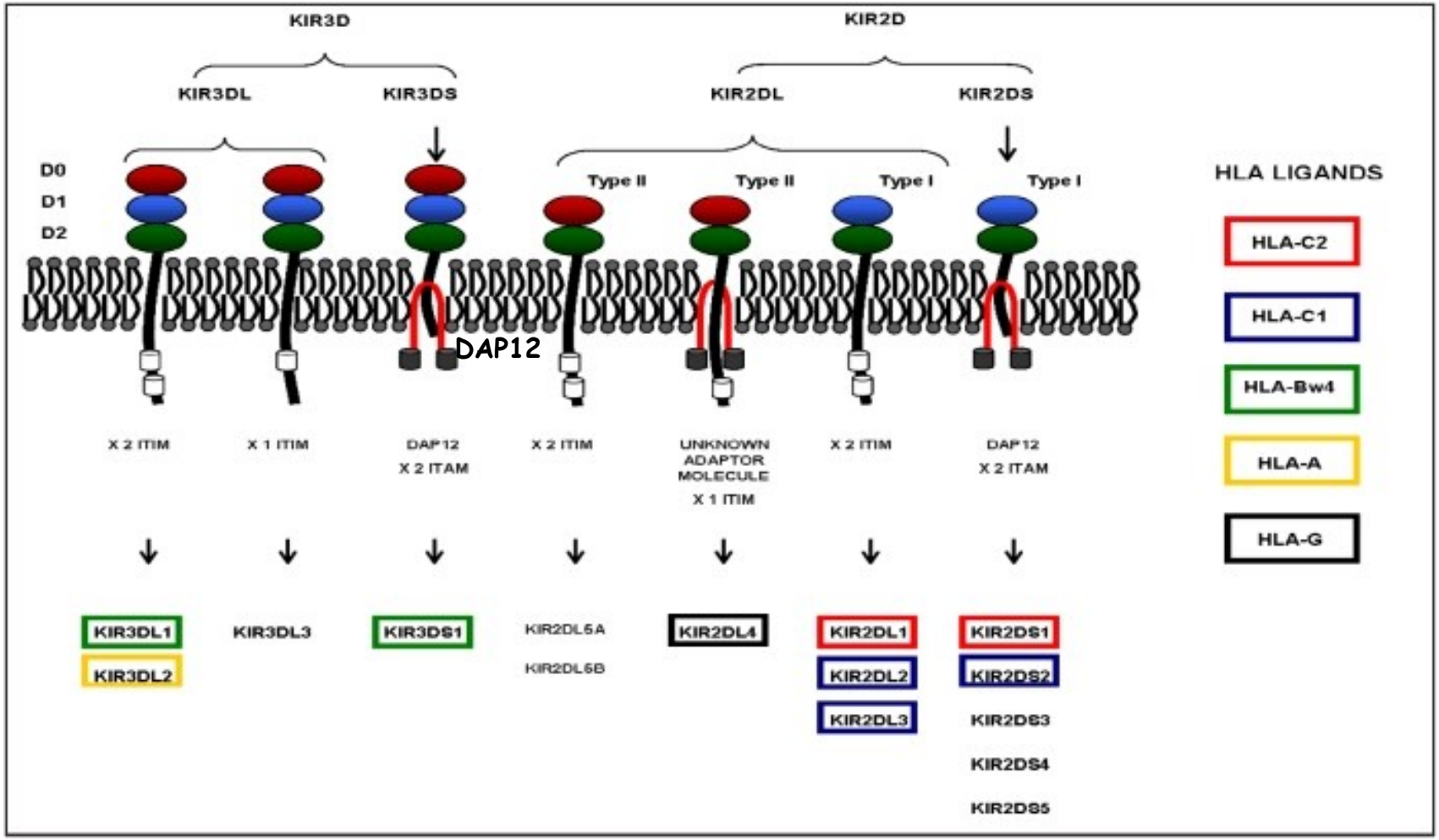
DIVERSITA' STRUTTURALE



KIR3D : D0-D1-D2

KIR2D : D1-D2 (tipo I) o D0-D2 (tipo II)

DIVERSITA' di INTERAZIONE

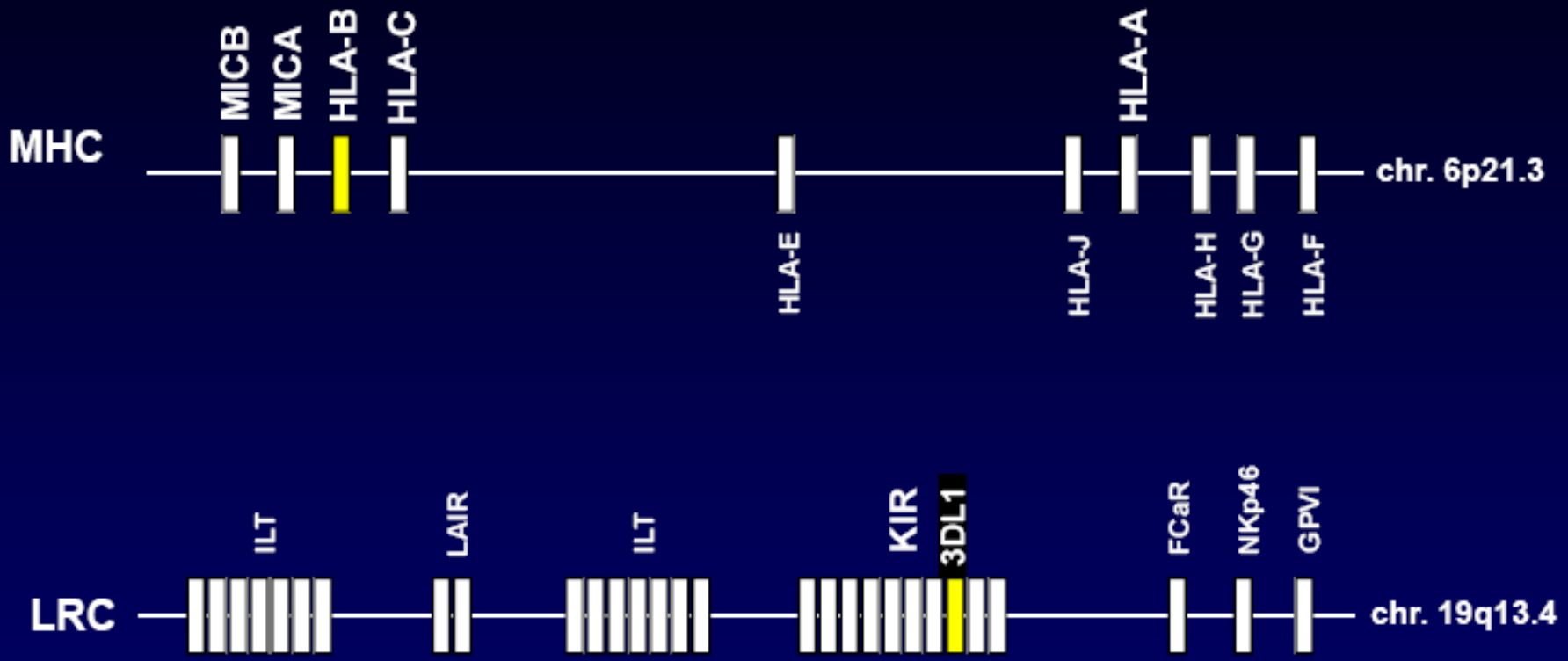


Adaptor molecules: DAP12

I ligandi per KIR3DL3, KIR2DL5, KIR2DS3 and KIR2DS5 non sono noti

HLA-B + *KIR3DL1*: Multiplicity of synergistic interactions

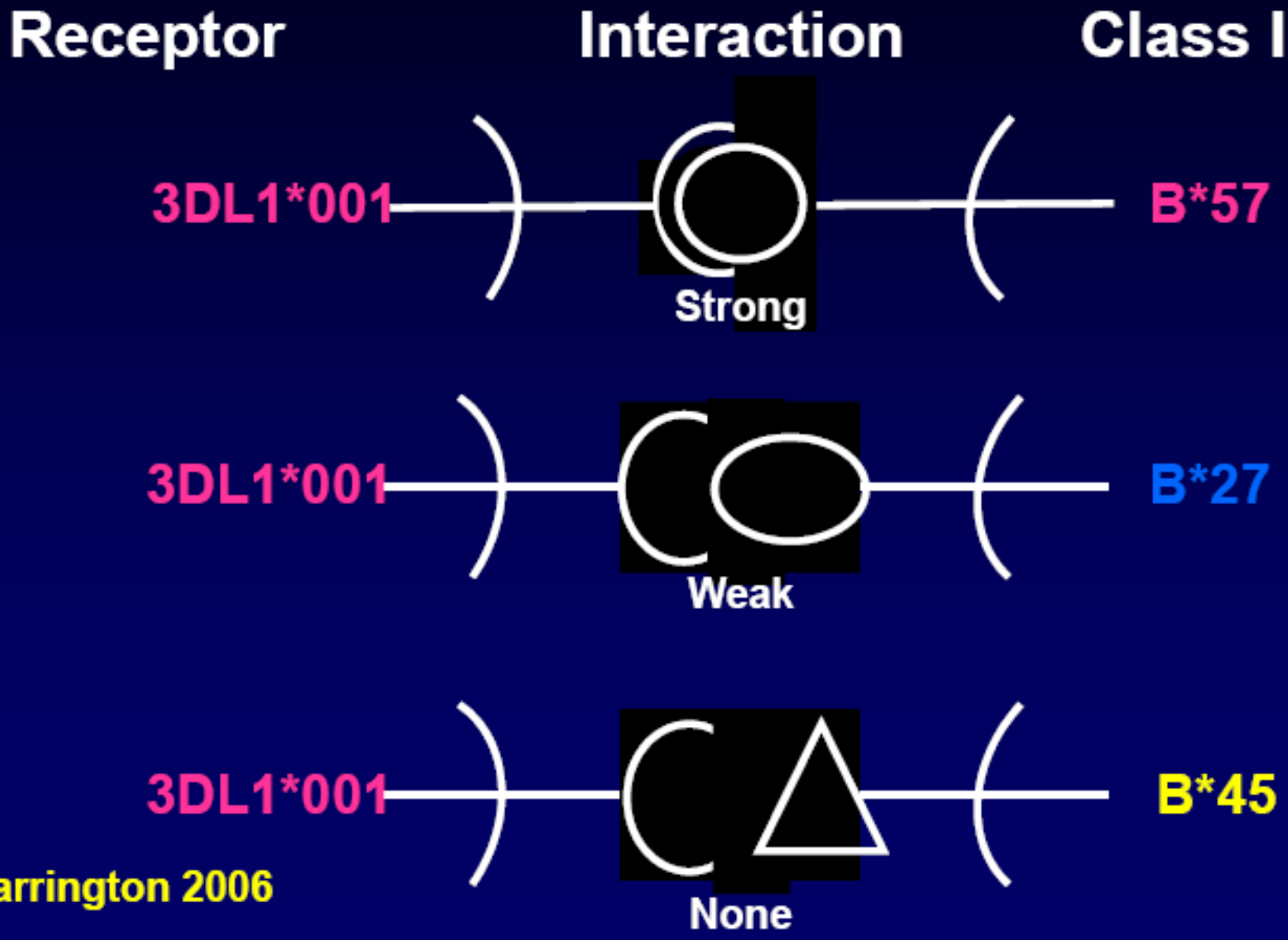
DIVERSITA' di INTERAZIONE



HLA-B: >500 alleles
KIR3DL1: >20 alleles

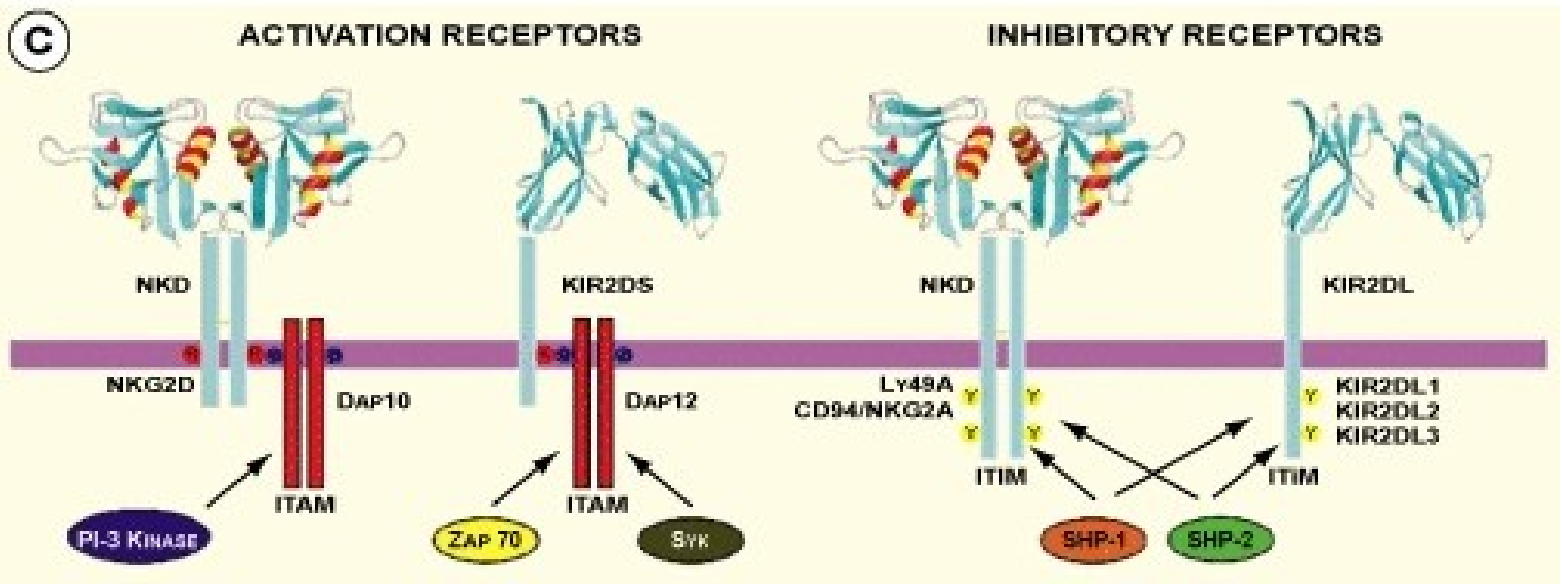
Carrington 2006

Differential binding between KIR3DL1 and HLA-B



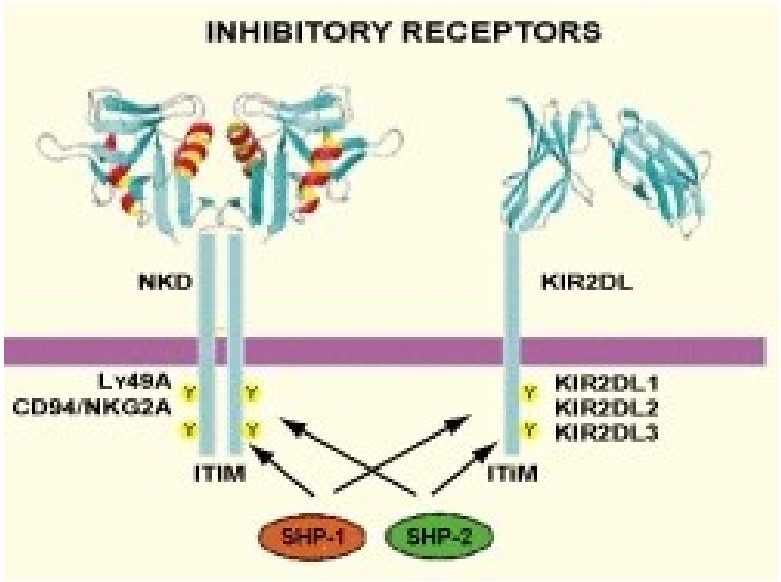
Carrington 2006

DIVERSITA' FUNZIONALE



Le code citoplasmatiche L portano due motivi inibitori (ITIM)

Le code citoplasmatiche S sono troncate prima del ITIM e contengono motivi ITAM

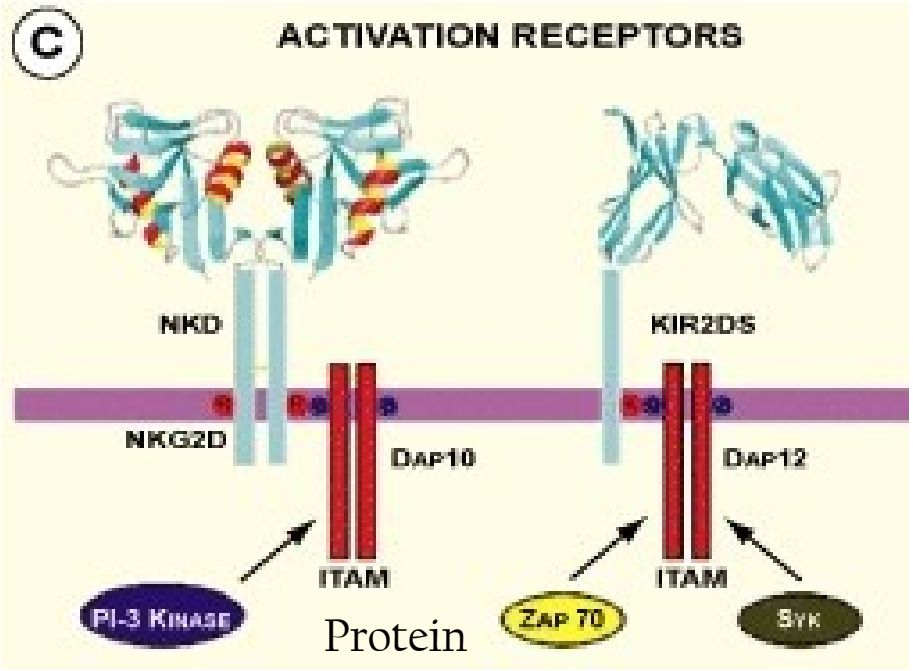


ITIM: immunoreceptor tyrosine-based inhibition motif

Leucina Tirosina Isoleucina

Aminoacidi conservati (S/I/V/LxYxxI/V/L) si fosforilano (Src kinases) e richiamano phosphotyrosine phosphatases SHP-1 e SHP-2, o inositol-phosphatase SHIP, le quali diminuiscono l'attivazione delle molecole coinvolte nel signaling

Immunotyrosine activation motifs (ITAM)



Protein chinasi

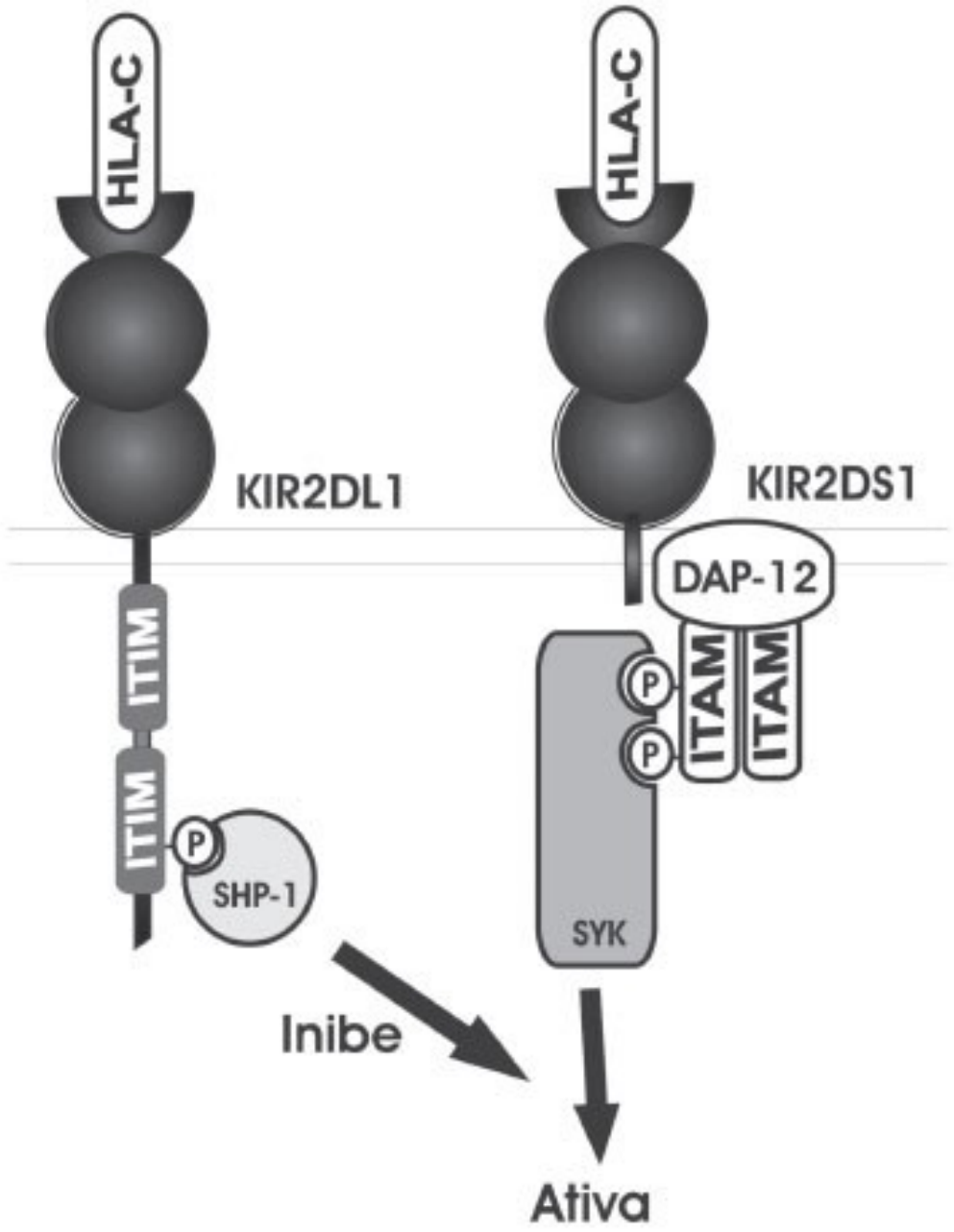
Ligand binding and receptor clustering result in recruitment of tyrosine kinases

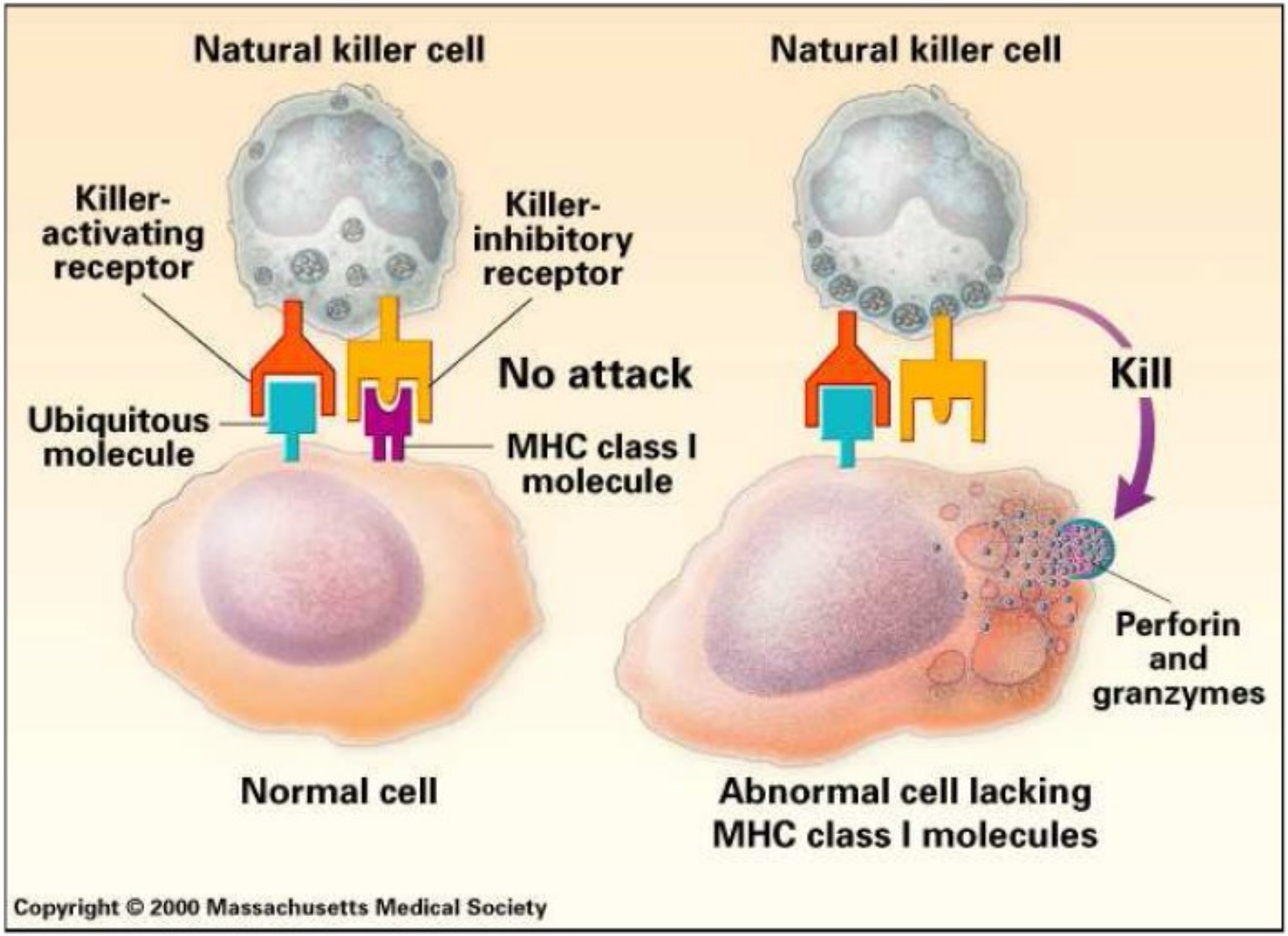
$YxxI/Lx_{(6\text{-}12)}YxxI/L$

2 tirosine separate da 9-12 aa:
...YXX[L/V]X6–9YXX[L/V]...,
Y: tirosina
L: leucina
V: valina

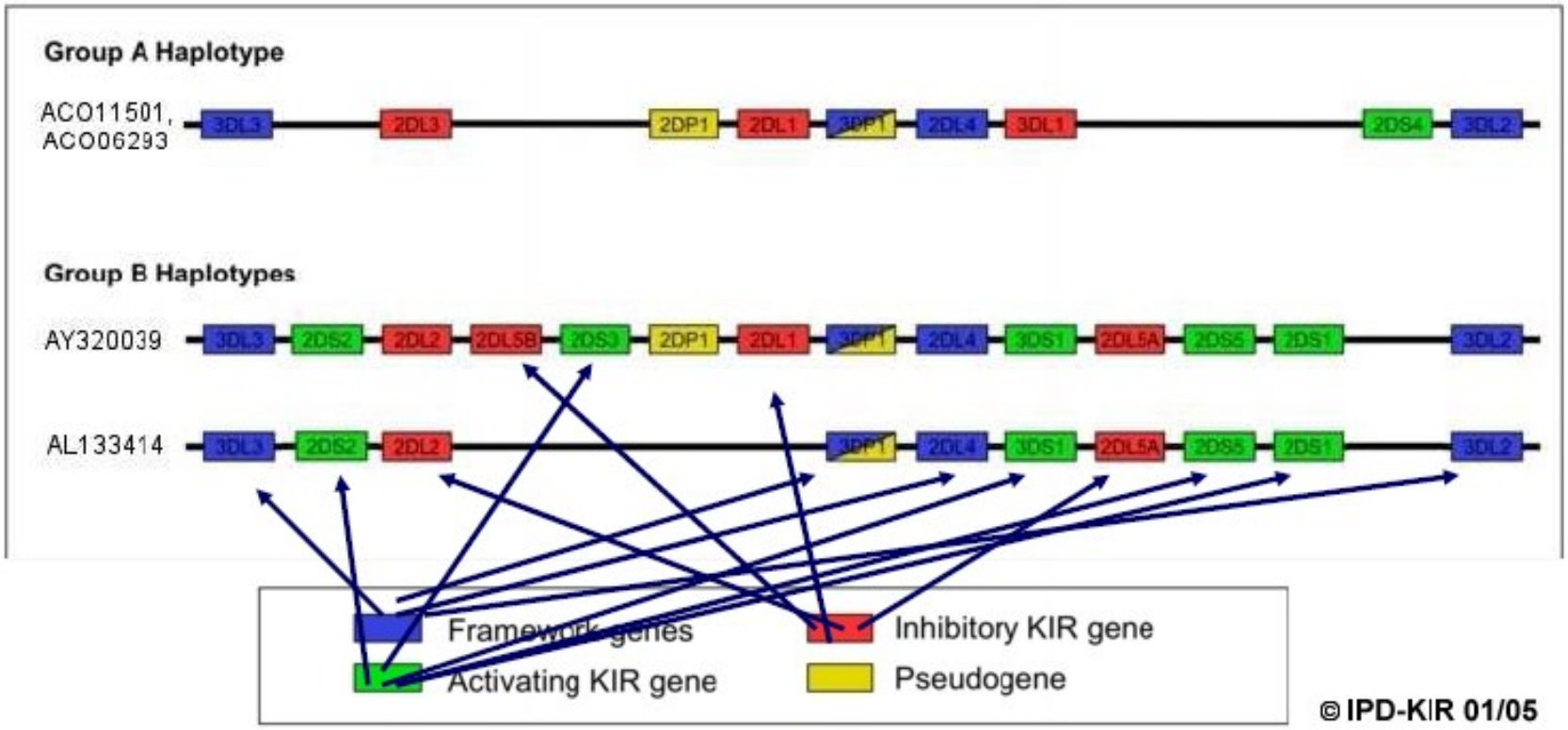
DAP12: adattatore con motivo ITAM

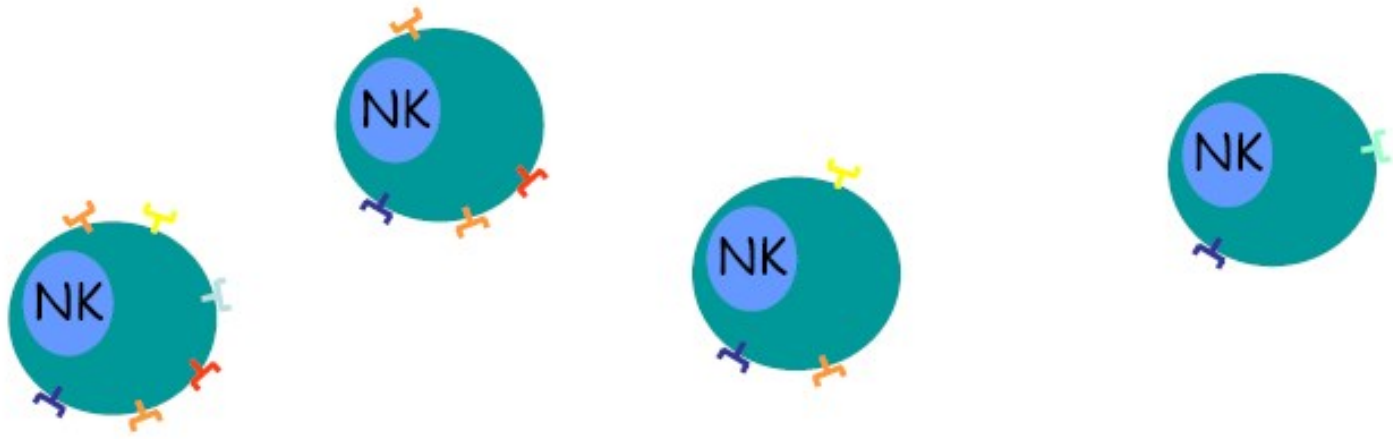
Activation leads to granule exocytosis and release of perforin and granzyme B, which mediate lysis of the target cell


HLA-C
HLA-C
KIR2DL1
KIR2DS1
DAP-12
ITIM
ITIM
ITAM
ITAM
P
P
P
SHP-1
SYK
Inibe
Ativa


Natural killer cell
Natural killer cell
Killer-activating receptor
Killer-inhibitory receptor
No attack
Kill
Ubiquitous molecule
MHC class I molecule
Perforin and granzymes
Normal cell
Abnormal cell lacking MHC class I molecules
Copyright © 2000 Massachusetts Medical Society

DIVERSITA' CLONALE





http://www. allelefrequencies.net

Line	Allele	Population	Phenotype frequency (%)	Allele frequency	Sample size	IPD-KIR database	Distribution
1	3DL1*01502	Venezuela Bari KIR		0-550	80	See	
2	3DL1*01502	South Korea KIR		0-507	154	See	
3	3DL1*01502	Thailand Bangkok KIR		0-480	119	See	
4	3DL1*01502	Japan KIR pop3		0-457	132	See	
5	3DL1*01502	USA California Asian American pop 2 KIR		0-437	37	See	
6	3DL1*00101	USA Caucasian NMDP KIR		0-338	75	See	

Figure 2. Killer cell immunoglobulin-like receptors (KIR) allele frequency search.

Table 2: Impact of KIR or KIR ligand matching on transplant outcome.

Reference	Overall survival	aGVHD	Graft failure	Relapse
Ruggeri et al. 2002 [3]	Better (missing KIR ligand)	Decrease (missing KIR ligand)	Decrease (missing KIR ligand)	Decrease (missing KIR ligand)
Bishara et al. 2004 [6]	Better (KIR match, GVH direction)	increase (donor aKIR)	No effect	No effect
Symons et al. 2010 [7]	Better (iKIR mm, D: haplotype B)	No effect	—	Decrease (iKIRmm; haplotype B: D/R: +/−) myeloid, lymphoid
Weisdorf et al. 2012 [8]	No effect	No effect	—	No effect (KIR increase ligand mm)
Cook et al. 2004 [9]	Unknown (haplotype A: CMV reactivation)	Unknown	—	Unknown
Hsu et al. 2005 [10]	Better (missing iKIR ligand)	No effect	—	Decrease (AML, MDS, and missing iKIR ligand)
Dalva et al. 2006 [11]	Better (aKIR m)	Decrease (iKIR m)	—	Decrease (aKIR m) Increase (D: haplotype B)
McQueen et al. 2007 [5]	Worse (donor but not recipient has haplotype B)	Increase (donor but not recipient has haplotype B, also Bw4)	—	Increase (haplotype B D/R: +/−) Decrease (D: 3DL1/3DL2; R: A3/11or Bw4+)
Kim et al. 2007 [12]	Better (D: aKIR)	Increase (D: aKIR: 2DS2-4)	—	Decrease (D: aKIR)
Giebel et al. 2009 [13]	Decrease (aKIR mm and group C2+)	Increase (aKIR mm)	—	Increase (aKIR mm)
Stringaris et al. 2010 [14]	Better (D: haplotype B)	Unknown	—	Decrease (D: aKIR or haplotype B) AML
Davies et al. 2002 [15]	Worse (missing KIR ligand) myeloid	No effect	No effect	No effect
Giebel et al. 2003 [16]	Better (KIR ligand mm)	No effect	Increase (KIR ligand match)	Decrease (KIR ligand mm) myeloid
Bornhäuser et al. 2004 [17]	No effect	No effect	—	Increase (KIR ligand mm)
Schaffer et al. 2004 [18]	Worse (increase infections)	No effect	—	No effect
Beelen et al. 2005 [19]	No effect	No effect	Increase (KIR ligand mm)	Decrease (KIR ligand mm)
De Santis et al. 2005 [20]	Worse (KIR epitope mm)	Increase (NK epitope mm)	Worse (NK epitope mm)	—
Kröger et al. 2005 [21]	No effect	Not significant	—	Decrease (KIR ligand mm)
Farag et al. 2006 [22]	No effect	No effect	No effect	No effect
Miller et al. 2007 [23]	—	Increase (KIR ligand mm)	—	Decrease (both KIR ligand and HLA mm)
Yabeet al. 2008 [24]	Worse (KIR ligand mm)	Increase (KIR ligand mm; D:2DS2)	—	No effect
Cooley et al. 2009 and 2010 [25, 26]	Better (D: haplotype B)	No effect	No effect	Decrease (D: haplotype B) AML but not ALL
Gagne 2009 [4]	No effect (D: haplotype B); Decrease (HLA identical, KIR3DL1: D+R− D: KIR3DL1+/3DS1+ R: Bw4+ R: C1 ligand−)	Increase (HLA I: 2DL5 mm HLA nonI: 2DS1mm) Decrease (HLA I: 2DS3 mm, D: haplotype B)	—	No effect (D: haplotype B) Increase (D: 3DL1+/3DS1+ R: Bw4−) Decrease (D: 3DL1+/3DS1+ R: Bw4+)
Venstrom et al. 2010 [27]	Better (D: KIR3DS1)	Decrease (D: KIR3DS1)	—	No effect (D: 3DS1)
Brunstein et al. 2009 [28]	Worse (only with RIC)	Increase (KIR ligand mm)(RIC)	—	Decrease (KIR ligand mm) (RIC)
Willemze et al. 2009 [29]	Better (KIR ligand mm)	Decrease	—	Decrease (KIR ligand mm)

M: match, mm: mismatch, RIC: reduced intensity conditioning, D/R: donor/recipient, HLA I: HLA identical, and HLA nonI: HLA nonidentical.

ALGORITMO DI SELEZIONE DEI DONATORI

(I) More Than One HLA-Matched Donor Available (Sibling, Unrelated, or Cord Blood)

Selection of donor with receptor-ligand mismatch in KIR.

Selection of donor with "B" haplotype in KIR.

No need to consider KIR-ligand mismatch (as KIR-ligands always match if HLA matches).

(II) HLA-Matched Donor Not Available; T Cells Not Depleted (Related and Unrelated)

Selection of donor with the least degree of HLA mismatch.

Selection of donor with receptor-ligand mismatch in KIR.

Selection of donor with "B" haplotype in KIR.

Avoid donor with KIR-ligand mismatch.

(III) HLA-Matched Donor Not Available; T Cells Depleted or Single-Unit Cord Blood Transplant

Selection of donor with receptor-ligand mismatch in KIR.

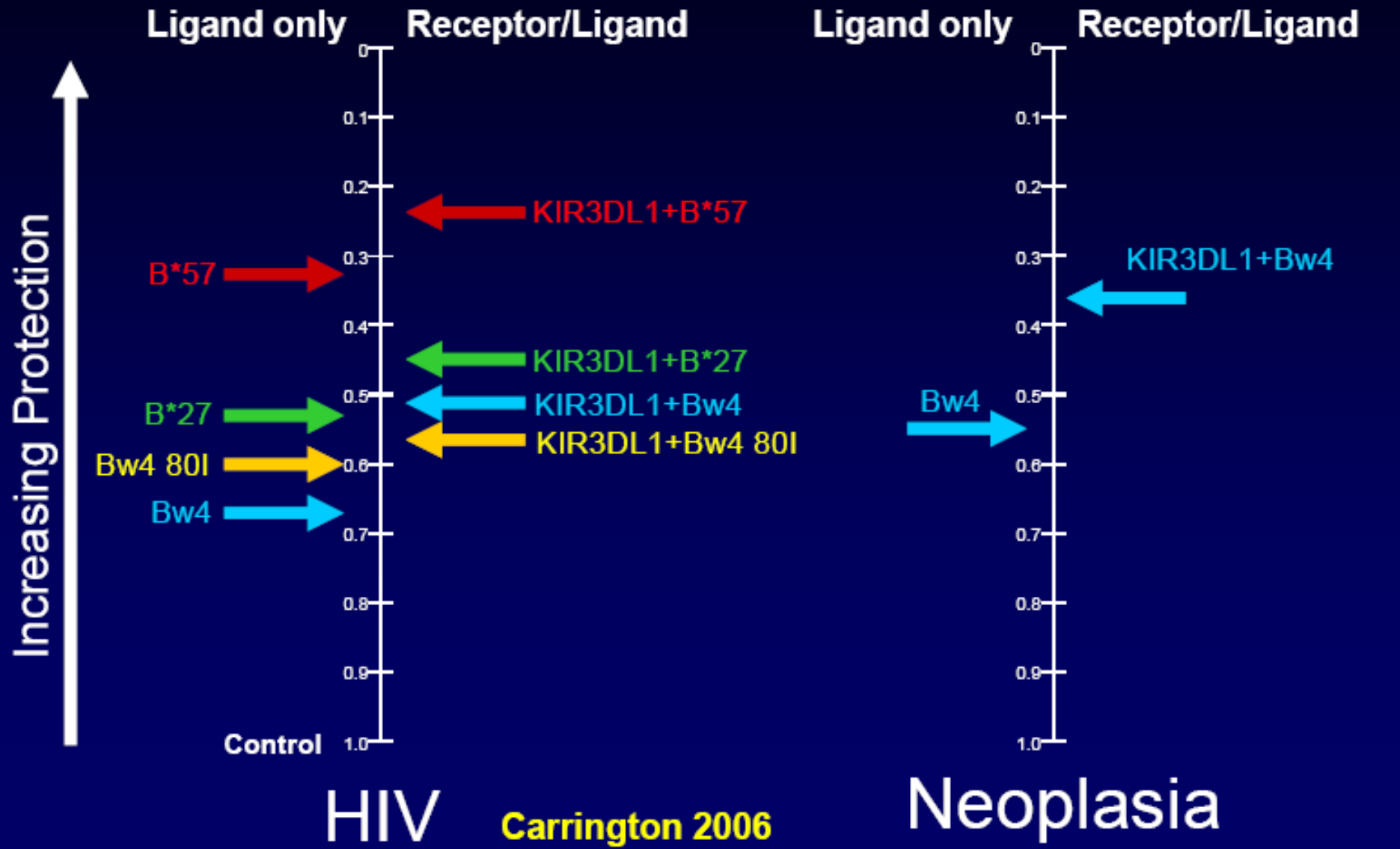
Selection of donor with "B" haplotype in KIR.

Selection of donor with KIR-ligand mismatch.

Perché è importante la diversità KIR?

- Vantaggio evolutivo
- Contribuisce alla variabilità della risposta immune sia innata che adattativa
- Tempi brevi e facile studio: significato epidemiologico
- Fattore di suscettabilità o protezione che influenza la risposta immune a :infezioni, malattie, autoimmunità, disordini infiammatori e trapianti di tessuti

Multiple, distinct *KIR3DL1* + *HLA-B* compound genotypes protect against HIV (and cervical neoplasia?)



Carrington 2006

Table 1. Human leucocyte antigen (HLA) and killer immunoglobulin-like receptor (KIR) disease associations.

Disease	KIR / HLA association	Observation	Referen
Infection			
CMV	> 1 activating KIR in donor	Reduced risk of CMV reactivation in recipient following bone marrow transplantation	[63]
HCV	2DL3/2DL3 - HLA-C1/C1	Resolution of infection	[51]
	3DS1 - HLA-Bw4	Resolution of infection	
	3DS1 - HLA-B-Bw4 80I	Protection against the development of hepatocellular carcinoma	[64]
HIV-1	3DS1 - HLA-Bw4 80I	Delays progression to AIDS	[43]
	3DL1 - HLA-B*57alleles that contain Bw4 80I	Delays progression to AIDS	[65]
Plasmodium falciparum	3DL2*002	High NK cell response to *P. falciparum*-infected RBC	[66]
Idiopathic bronchiectasis	HLA-Cw*03	Susceptibility	[53]
	HLA-Cw*06	Protection	
	2DS1 and/or 2DS2 - HLA-C1/C1	Susceptibility	
Autoimmunity			
Behcet's disease	Altered 3DL1 expression	Associated with severe eye disease	[67]
IDDM	2DS2 - HLA-C1	Susceptibility	[61]
	Decrease in inhibitory KIR-HLA genotype combinations	Susceptibility	[60]
Psoriatic arthritis	2DS1/2DS2; HLA-Cw group homozygosity	Susceptibility	[68,38
Rheumatoid vasculitis	2DS2; HLA-Cw*03	Susceptibility	[59]
Scleroderma	2DS2+ /2DL2–	Susceptibility	[58]
Spondylarthritides	3DL2 expression increased	May contribute to disease pathology	[62]
Acute coronary syndromes	*De novo* expression of 2DS2/DAP12 in CD4+ T cells	T cells acquire cytolytic capability that can bypass TCR triggering	[69]

Cancer			
Malignant melanoma	2DL2/2DL3; HLA-C1	Susceptibility	[70]
Cervical cancer	3DS1/absence of HLA-C2 and/or HLA-Bw4	Susceptibility	[71]
	Genotype 10 (2DL1/2/3/4, 3DL1/2/3, 2DS4	Susceptibility	[72]
	2DL5*002	Protection	
Nasopharyngeal carcinoma	EBV seropositive individuals with ≥ 5 activating KIR	Susceptibility	[73]
Leukaemia	2DL2	Susceptibility	[74]
	AB1 (AML) and AB9 (CML) KIR		
	3DL1/3DL1 +Bw4 (CLL)	Susceptibility	[75]
	3DL1/3DL1 Bw4 (CLL)	Protection	[75]
	2DL2/2DL3 +Cw1 (myeloid leukaemia)	Susceptibility	
	2DL3/2DL3 +Cw1 (myeloid leukaemia)	Protection	[76]
Cutaneous T cell lymphoma	Expression of 3DL2 on malignant cells	May contribute to disease pathology	[77]
Reproduction			
Pre-eclampsia	Maternal AA KIR genotype; fetus HLA-C2	Susceptibility	[78]
Recurrent spontaneous abortion	Mothers lacking inhibitory KIRs with specificity for fetal HLA-Cw alleles	Susceptibility	[79]