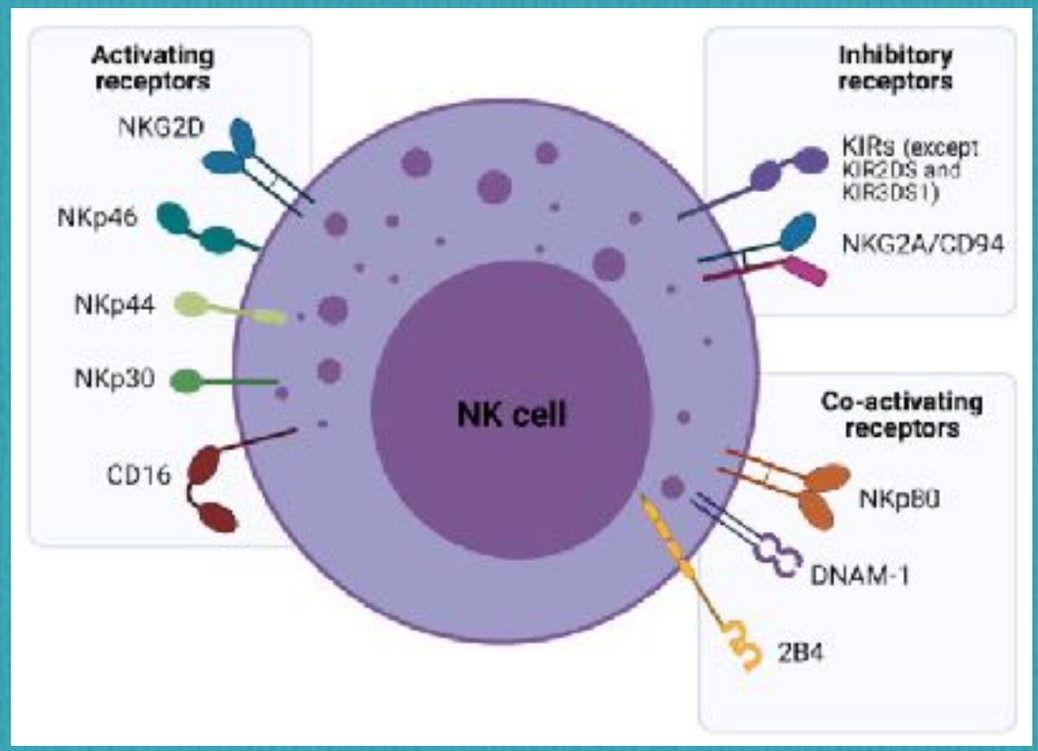
Programa de Pôs-graduação em Imunologia ICB/USP

Disciplina BMI 5904
Reconhecimento no Sistema Imune

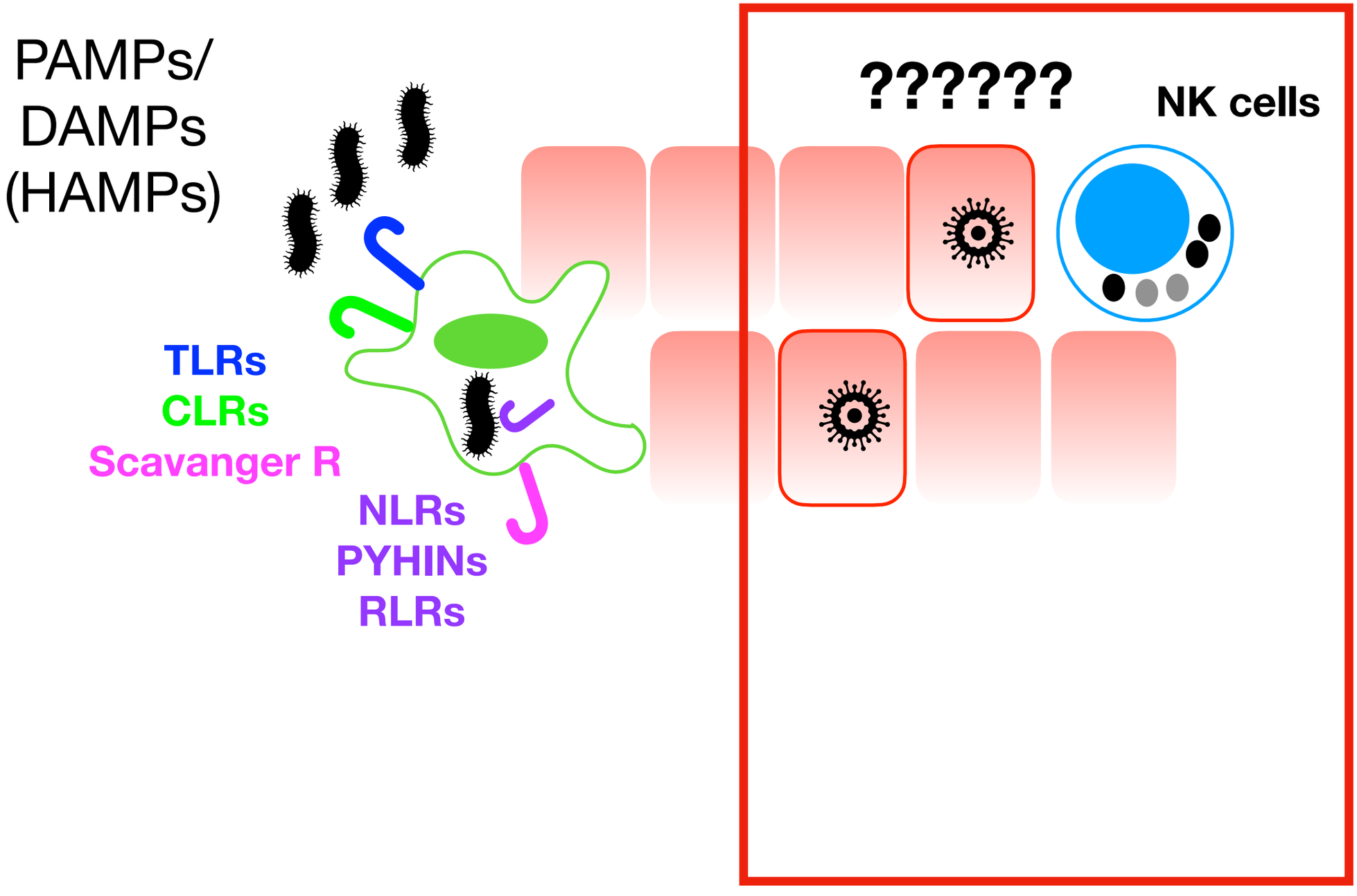


Aula 6

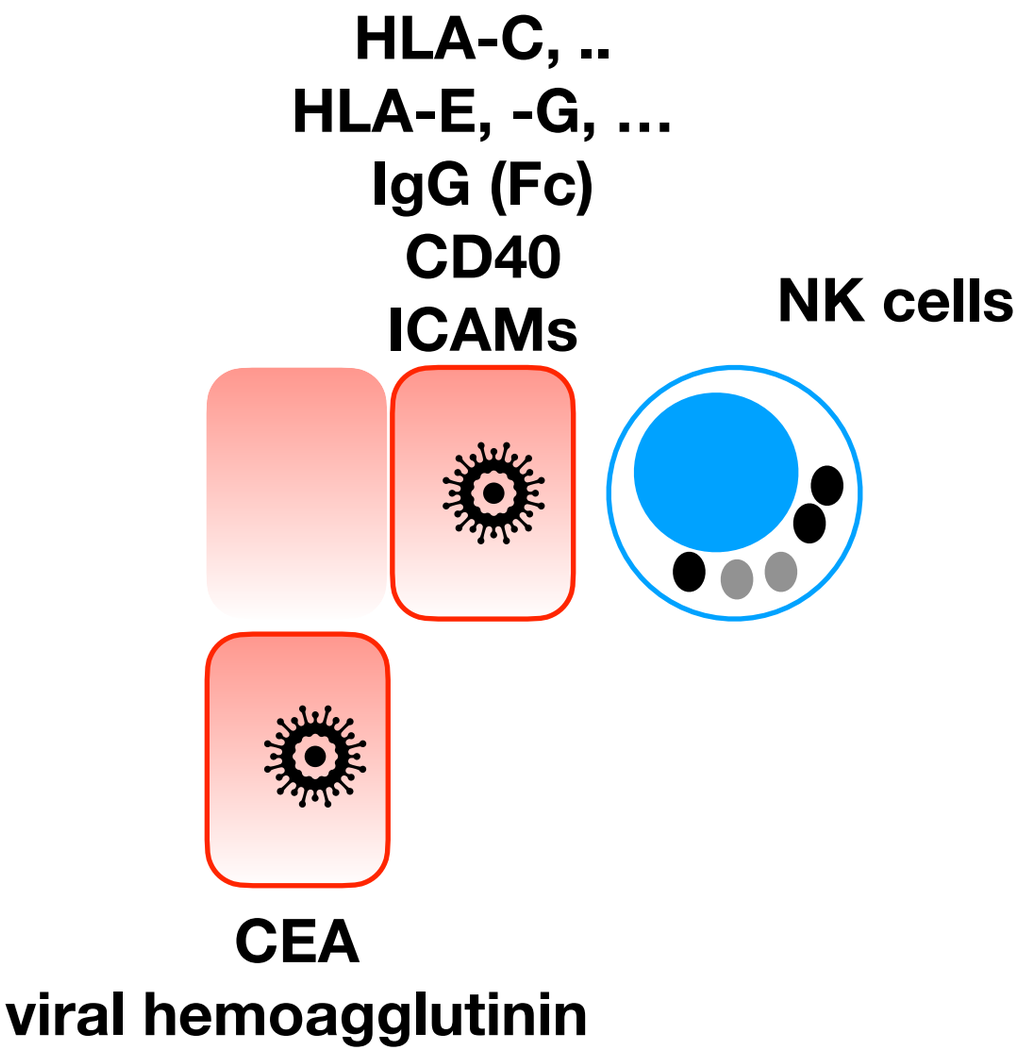
Alessandra Pontillo

Lab. Imunogenetica/Dep.Imunologia/ICB/USP

Reconhecimento de células “self” danificadas

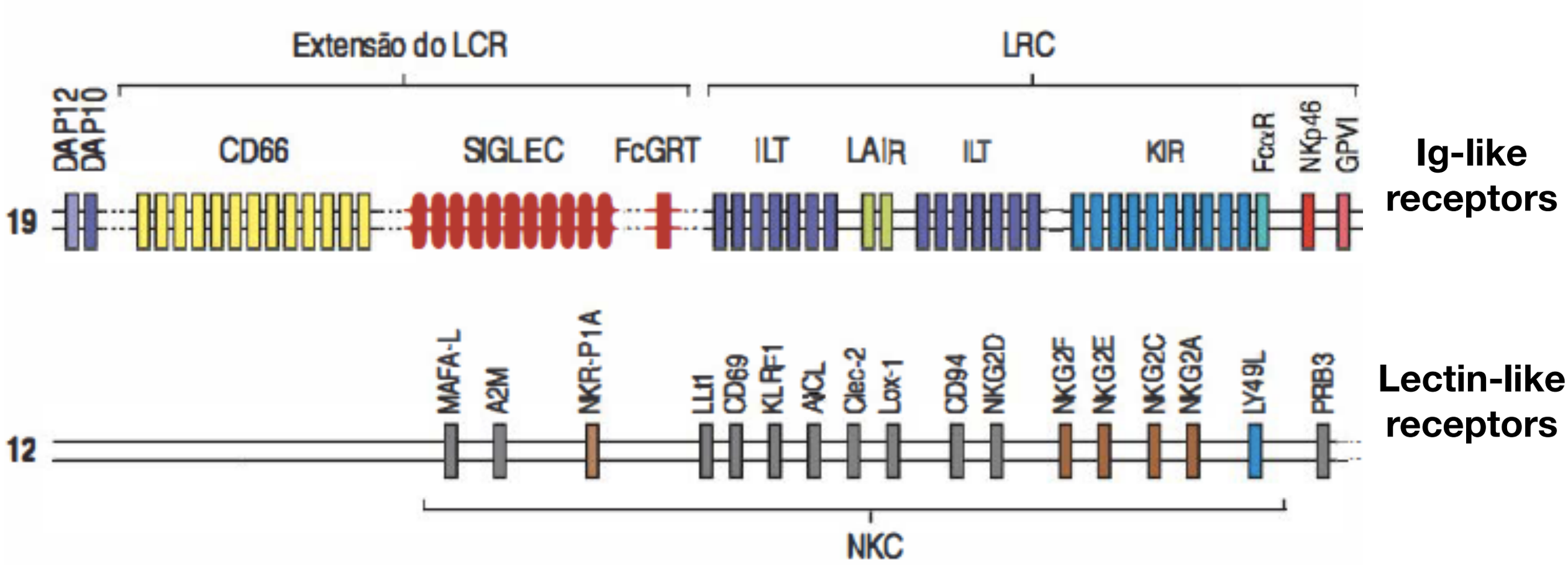


Reconhecimento de células “self” danificadas



Receptores das células NK

sinalização **complexo receptor de leucocitos (LRC)**

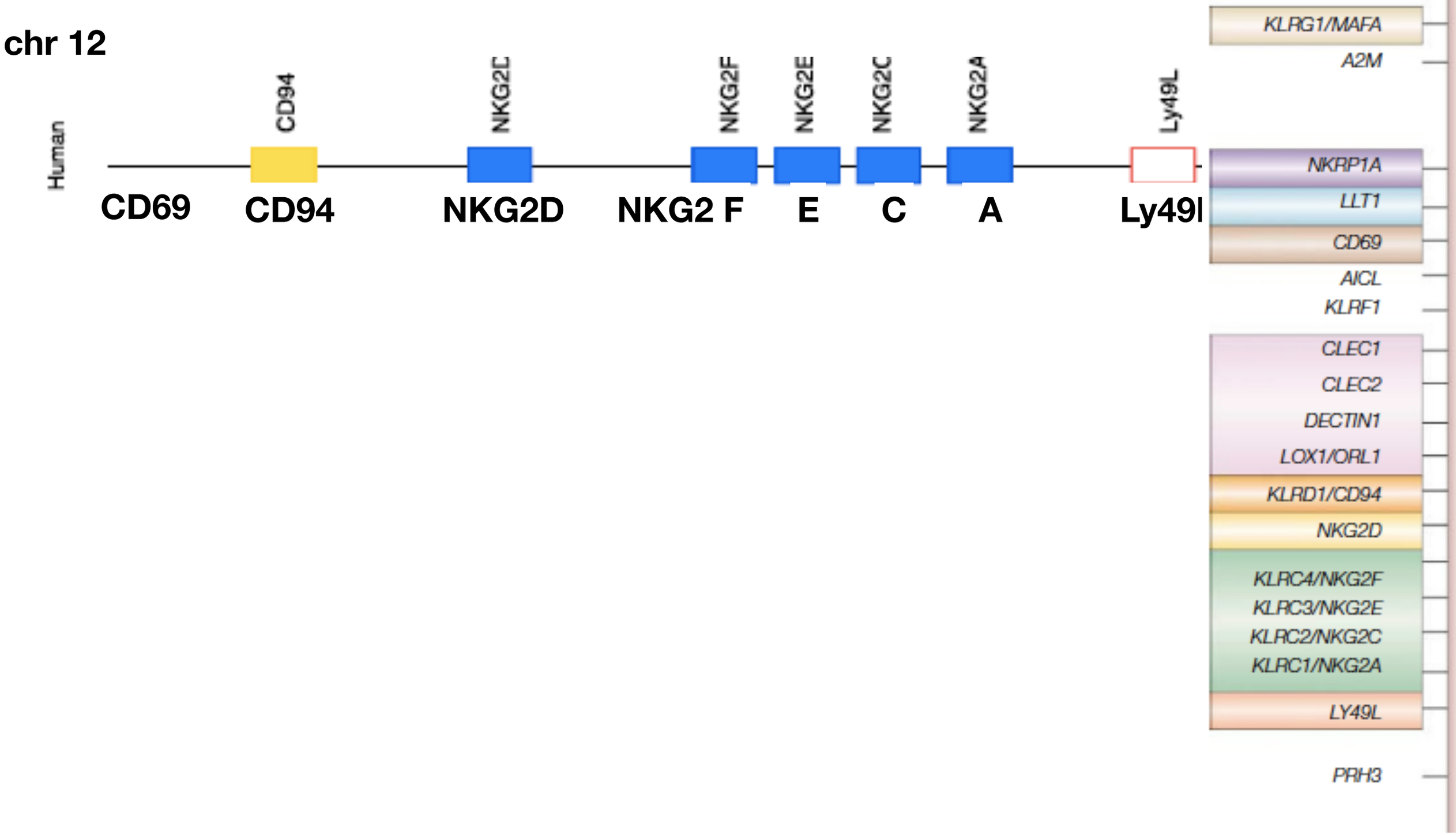


complexo do receptores NK (NKC)

- em ambas as famílias de receptores tem ativadores e inibidores
- a ação depende do domínio citosólico (ITAM ou ITIM)

Receptores das células NK

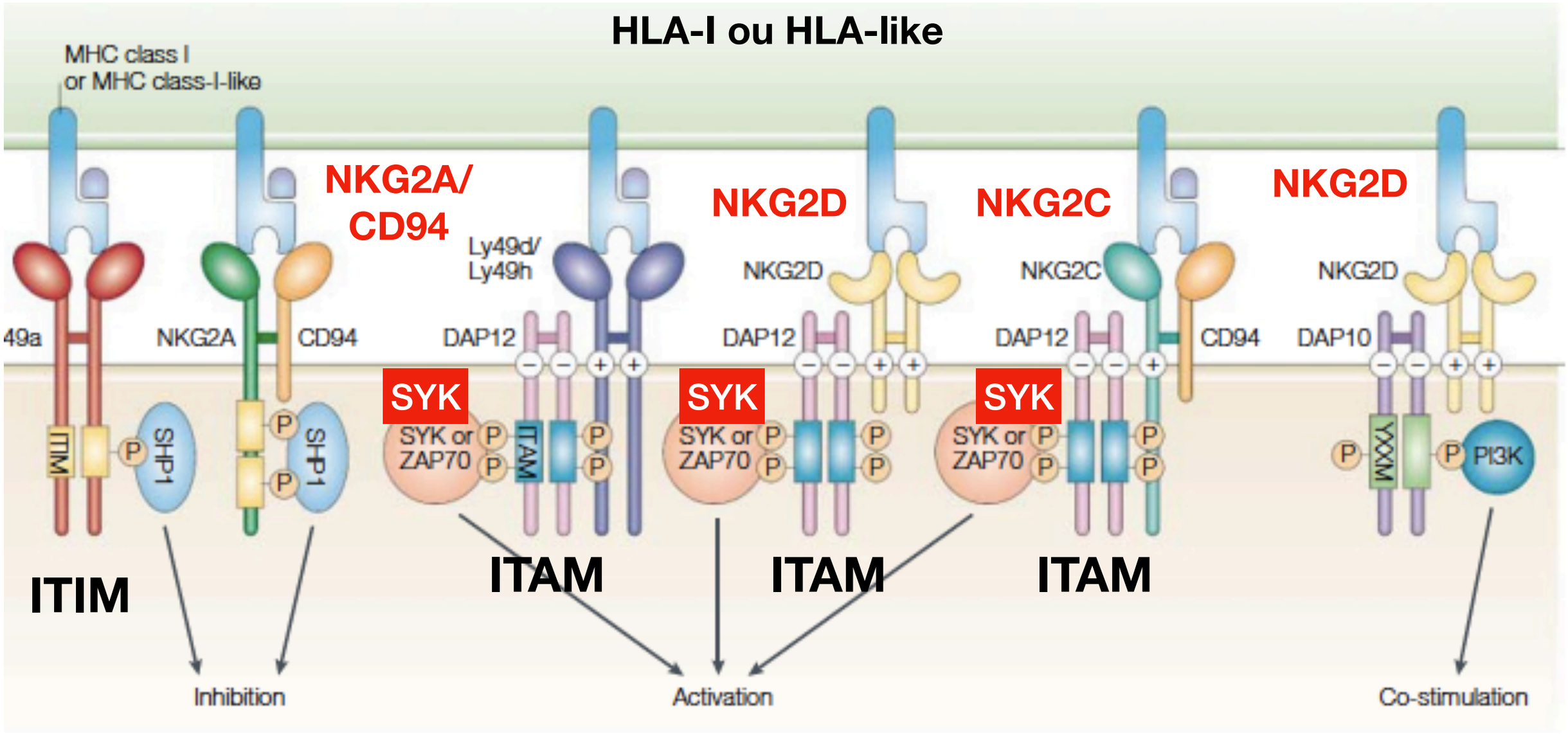
complexo do receptores NK (NKC)



Carillo-Bustamante et al Immunogenetics (2016)

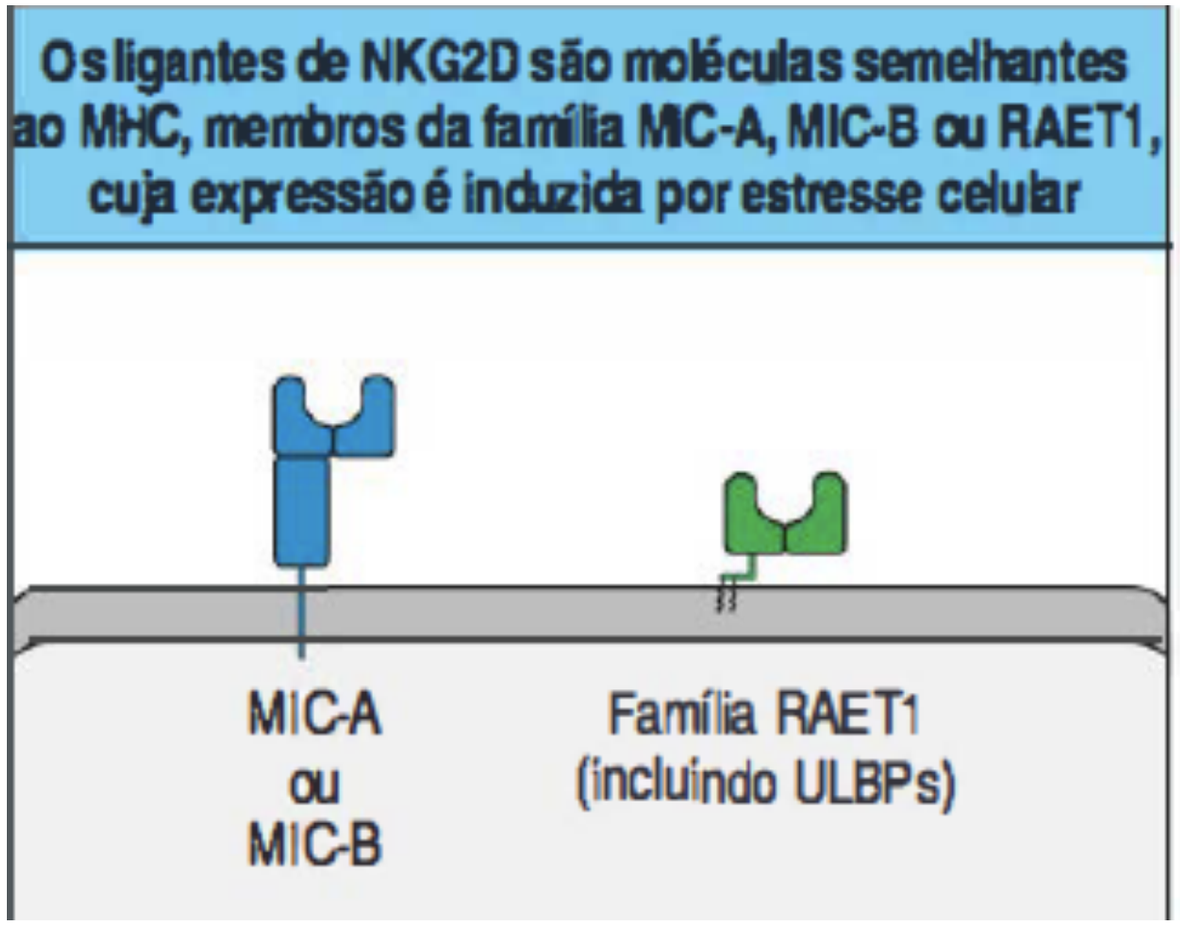
Receptores das células NK

complexo do receptores NK (NKC) = CLRs



Receptores das células NK

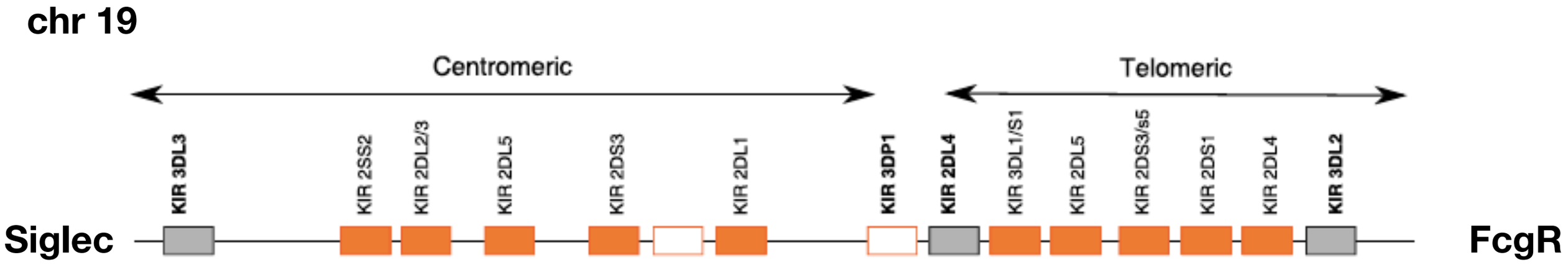
NKC	Ligand
NKG2A/CD94	HLA-E
NKG2C (CD159a)	
NKG2D (CD314)	MIC-A, MIC-B, ULPBs

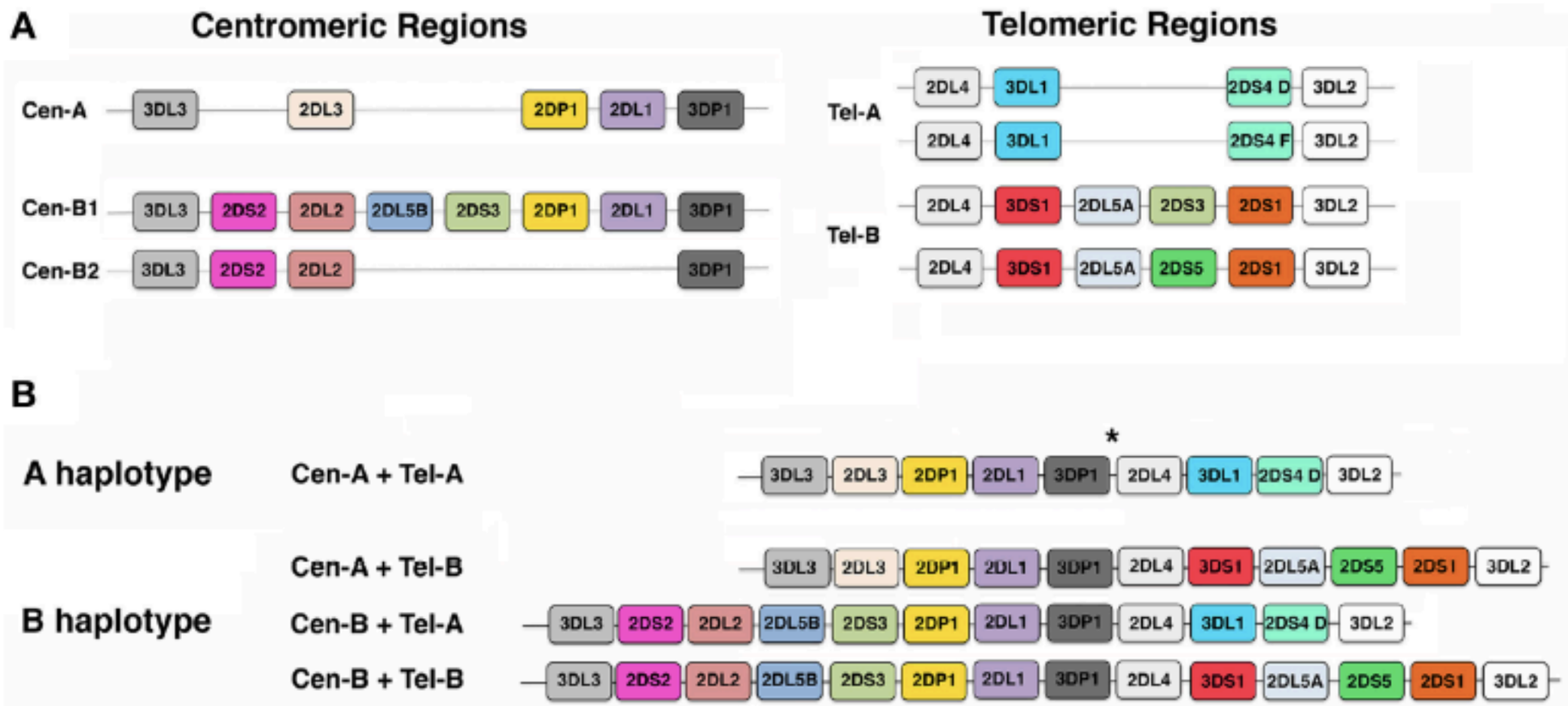


Hiper expressos em resposta a stress celular ou metabólico, infecção ou neoplasia

Receptores das células NK

complexo receptor de leucocitos (LRC)

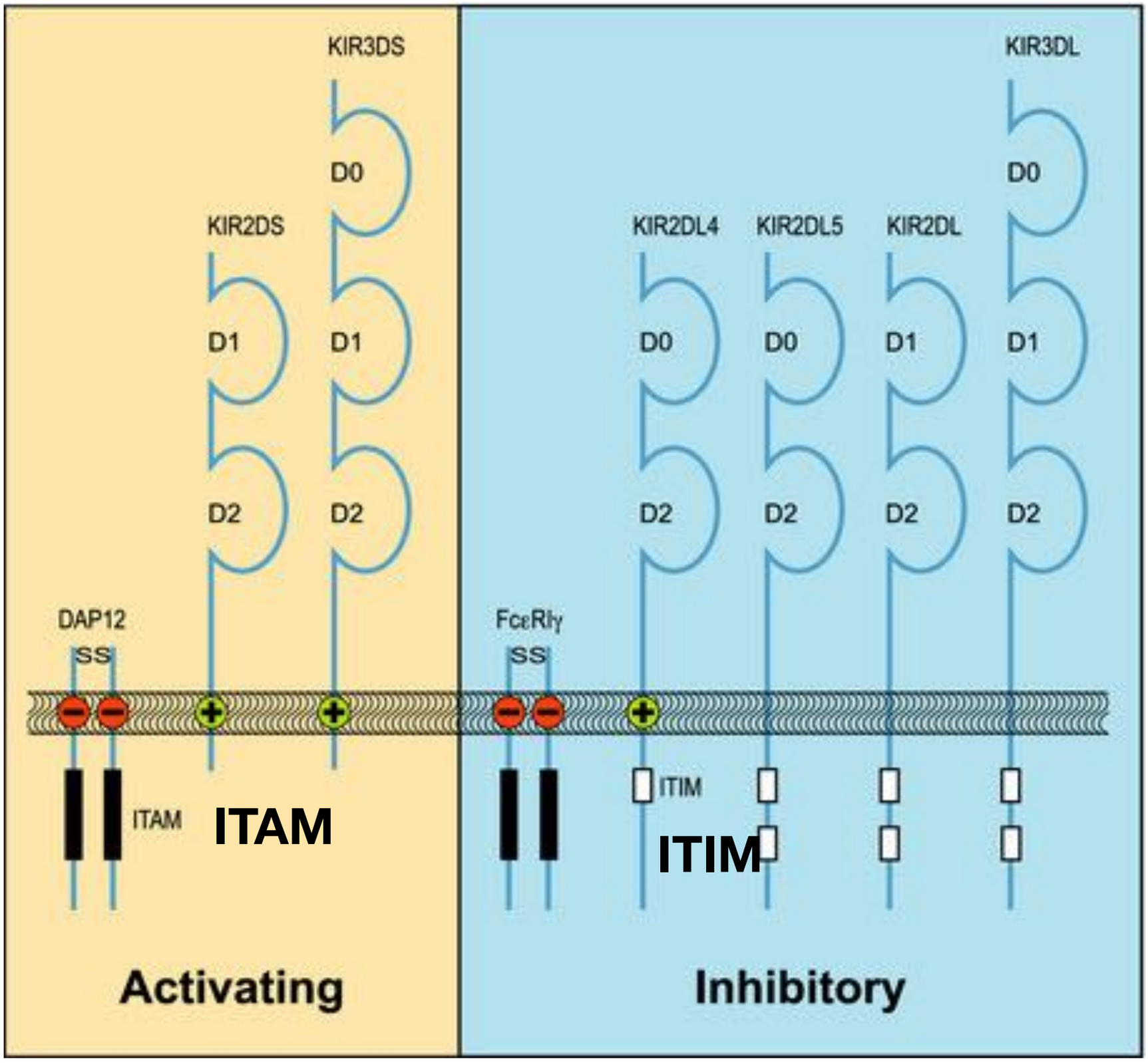




Pende et al. Front. Immunol. 2019

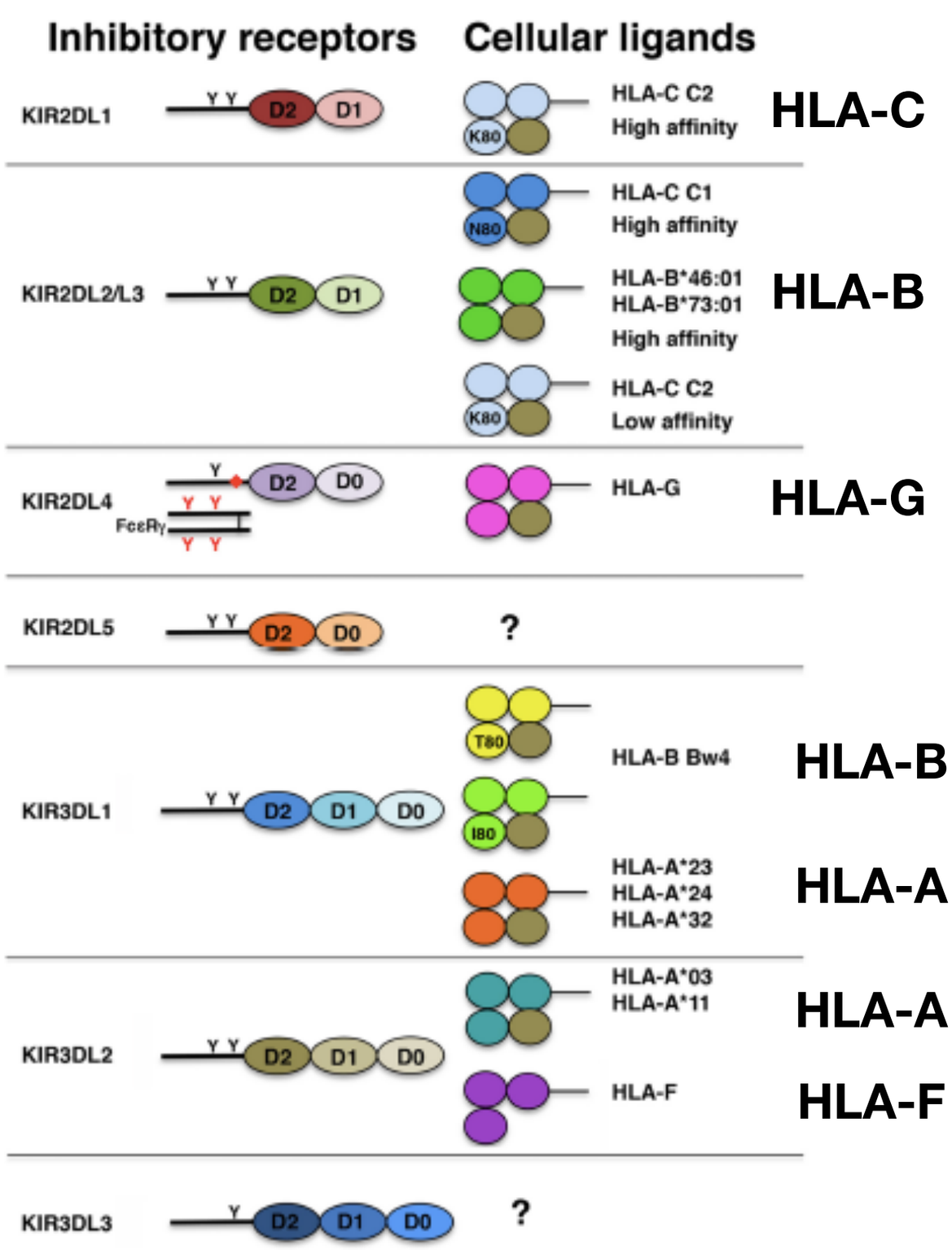
KIRs

Ig Superfamily



De Groot et al, Immunological Reviews 2015

KIRs

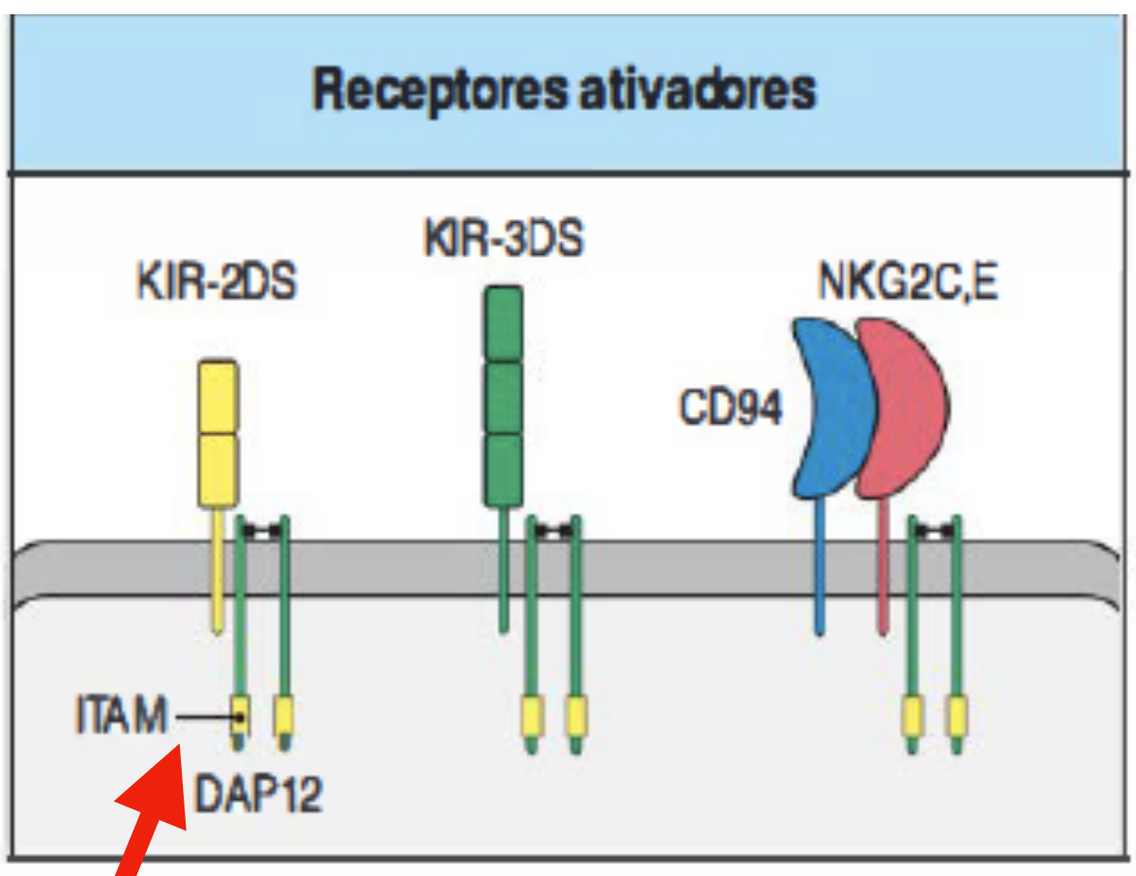


Pende et al. Front. Immunol. 2019

Virus & HLA

Virus protein	Downregulated HLA allotypes	Expressed HLA allotypes
HCMV US2/US11	HLA-A, HLA-B	HLA-C, HLA-E, HLA-G
HCMV UL40	not applicable	HLA-E
HIV Nef	HLA-A, HLA-B	HLA-C
KSHV K5	HLA-A, HLA-B, HLA-C (weakly)	HLA-E
EBV BILBF 1	HLA-A, HLA-B, HLA-E	HLA-C

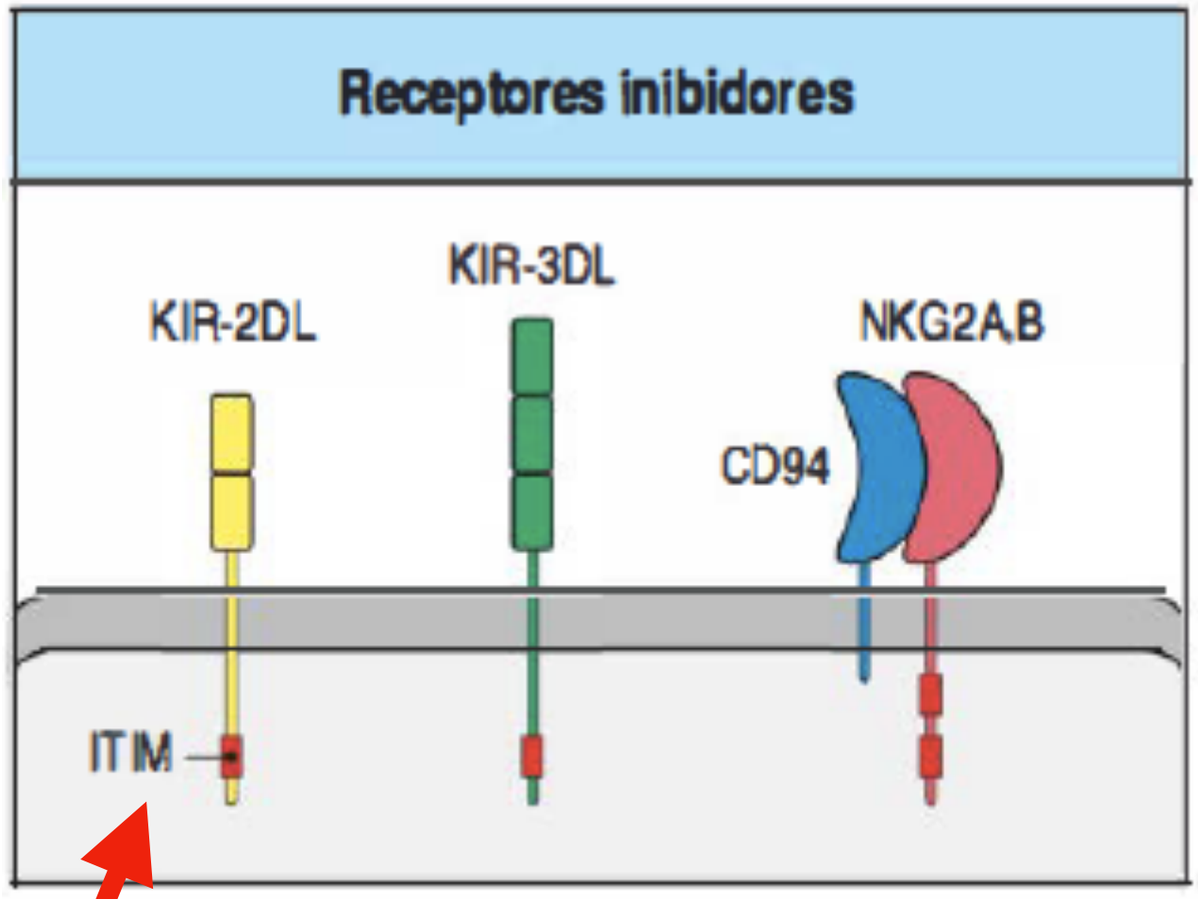
Receptores das células NK



Ig-like receptors

Lectin-like receptors

fosforilaçao
Syk, ZAP70



Ig-like receptors

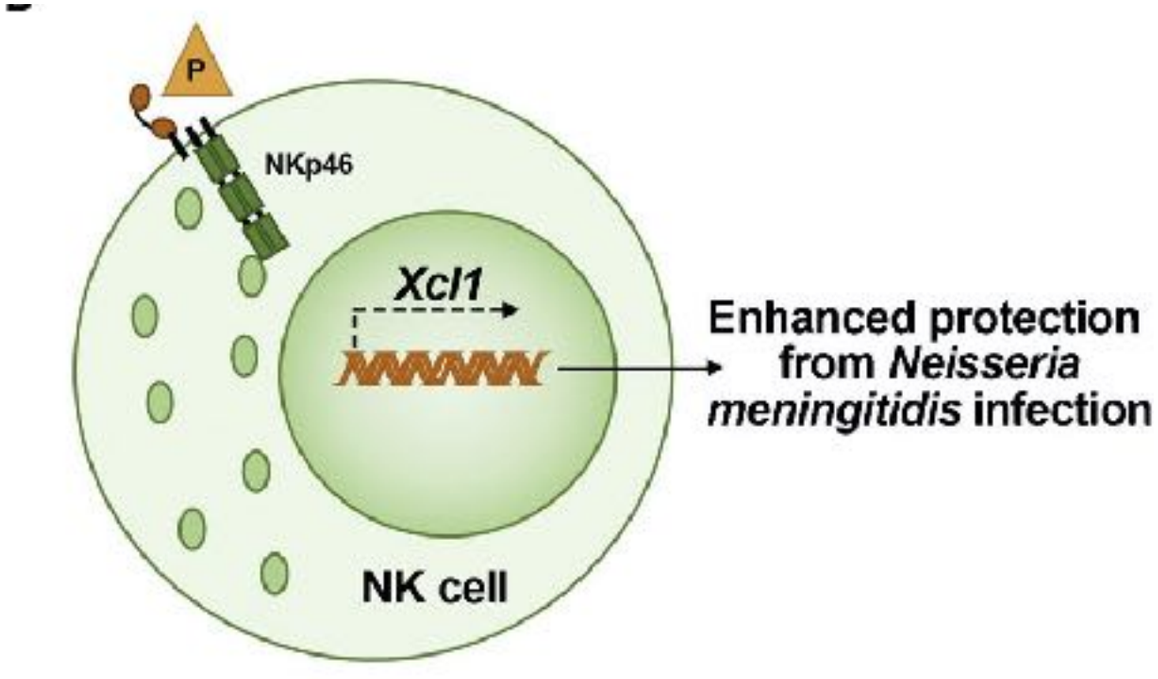
Lectin-like receptors

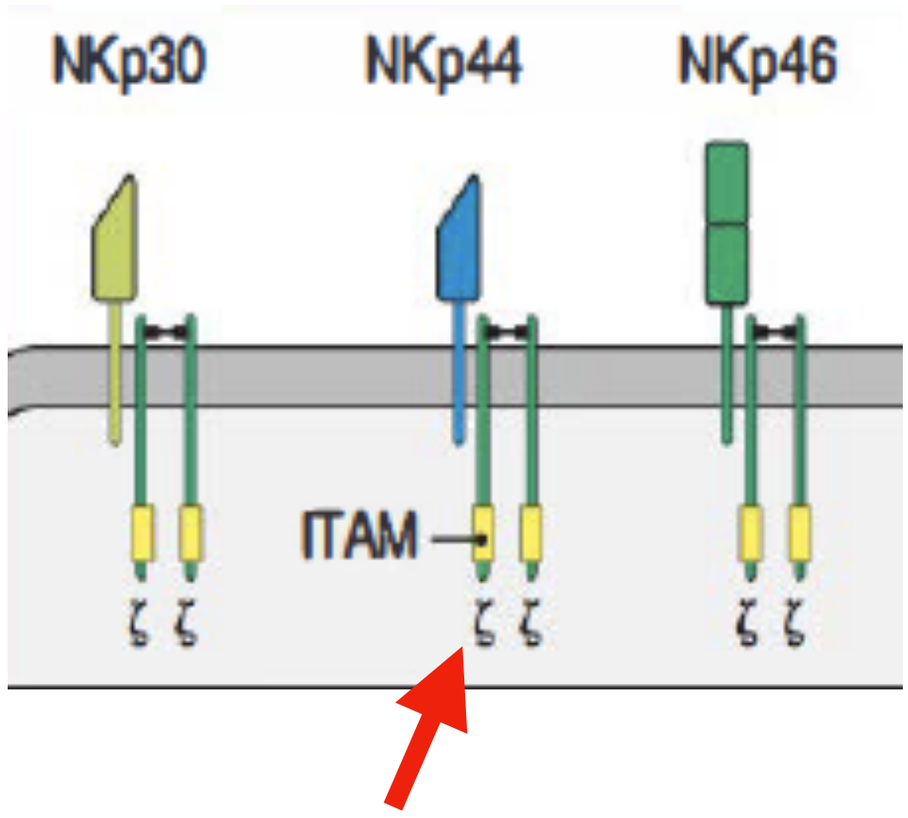
Ligandos nas celulas alvo: HLA-C (KIR-2DS), HLA (KIR-3DS)

Receptores das células NK

Receptores de citotoxicidade natural (NCRs) Ig-like receptors

NCRs	Ligand
NKp30 (CD337)	BAG6/BAT3, B7-H6) *
NKp44 (CD336)	Nidogen-1 (NID1) *
NKp46 (CD335)	Properdin (CFP), viral HA and HN

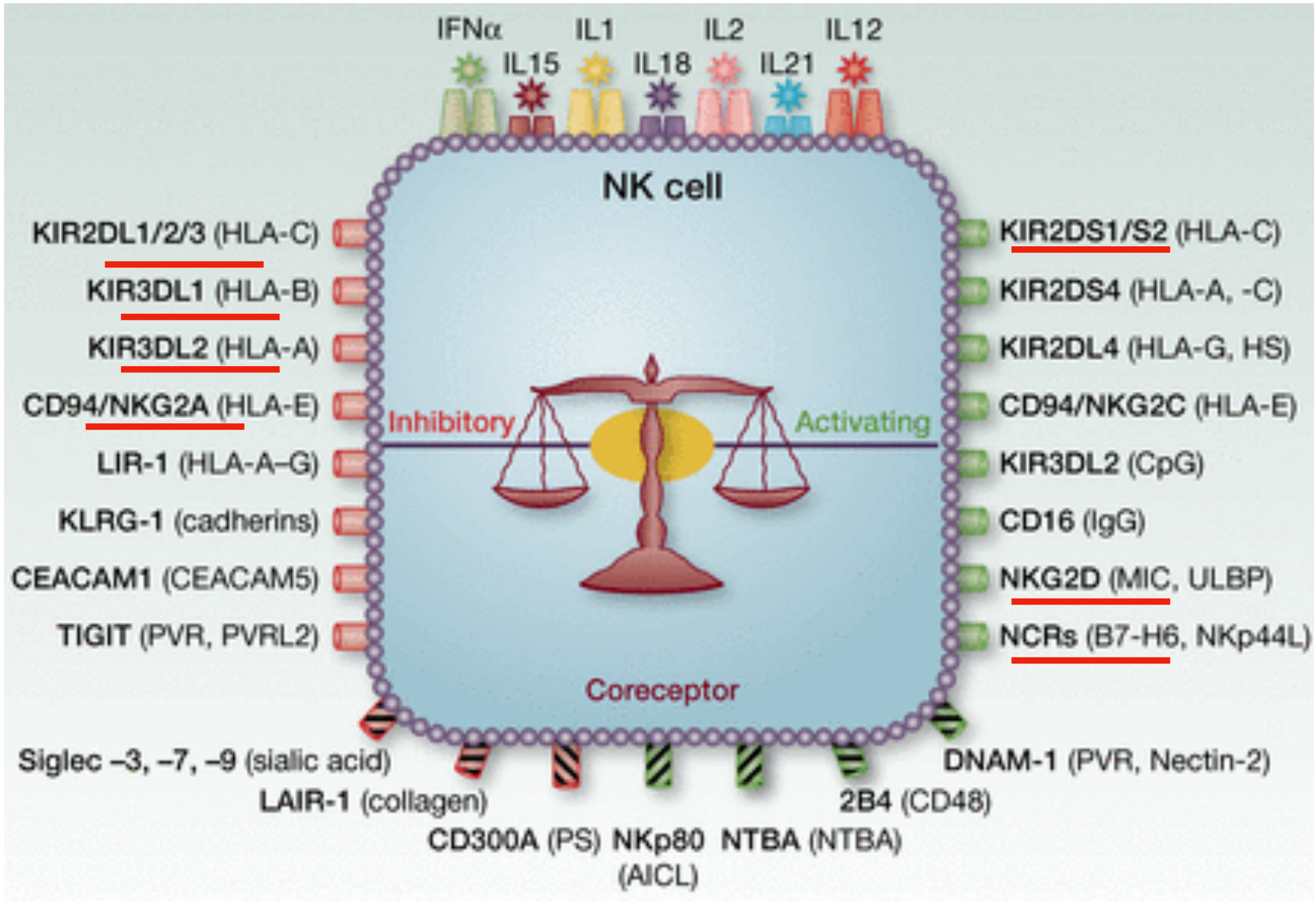




fosforilação
Syk, ZAP70

** Quando o ligando è na forma soluble pode atuar como "decoy" e inibir a ativação da NK*

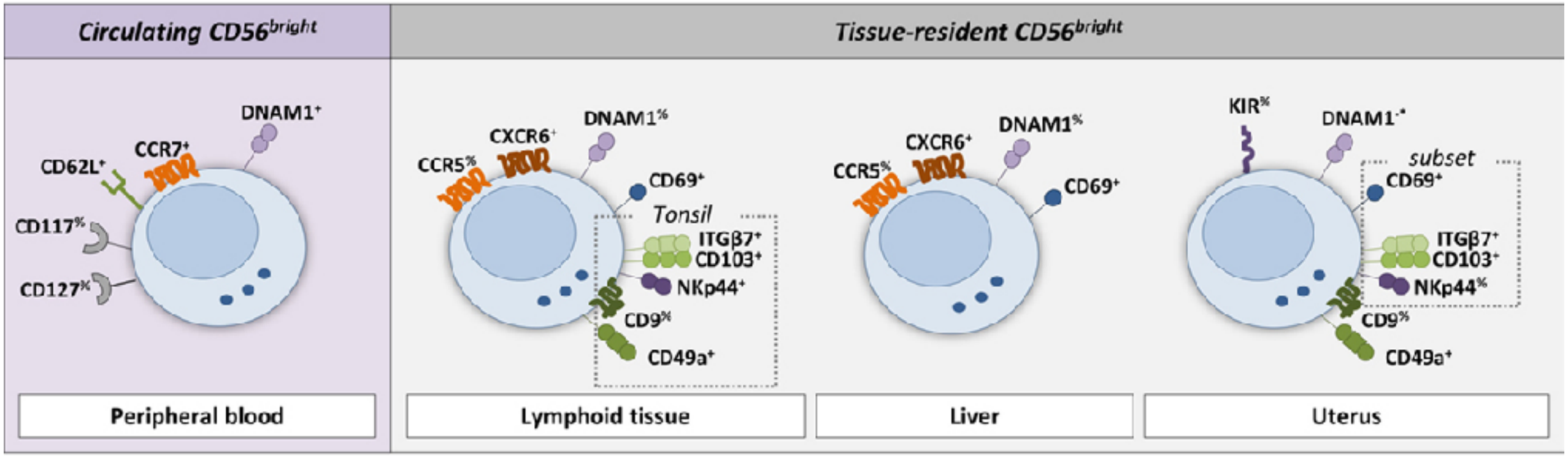
Receptores das células NK



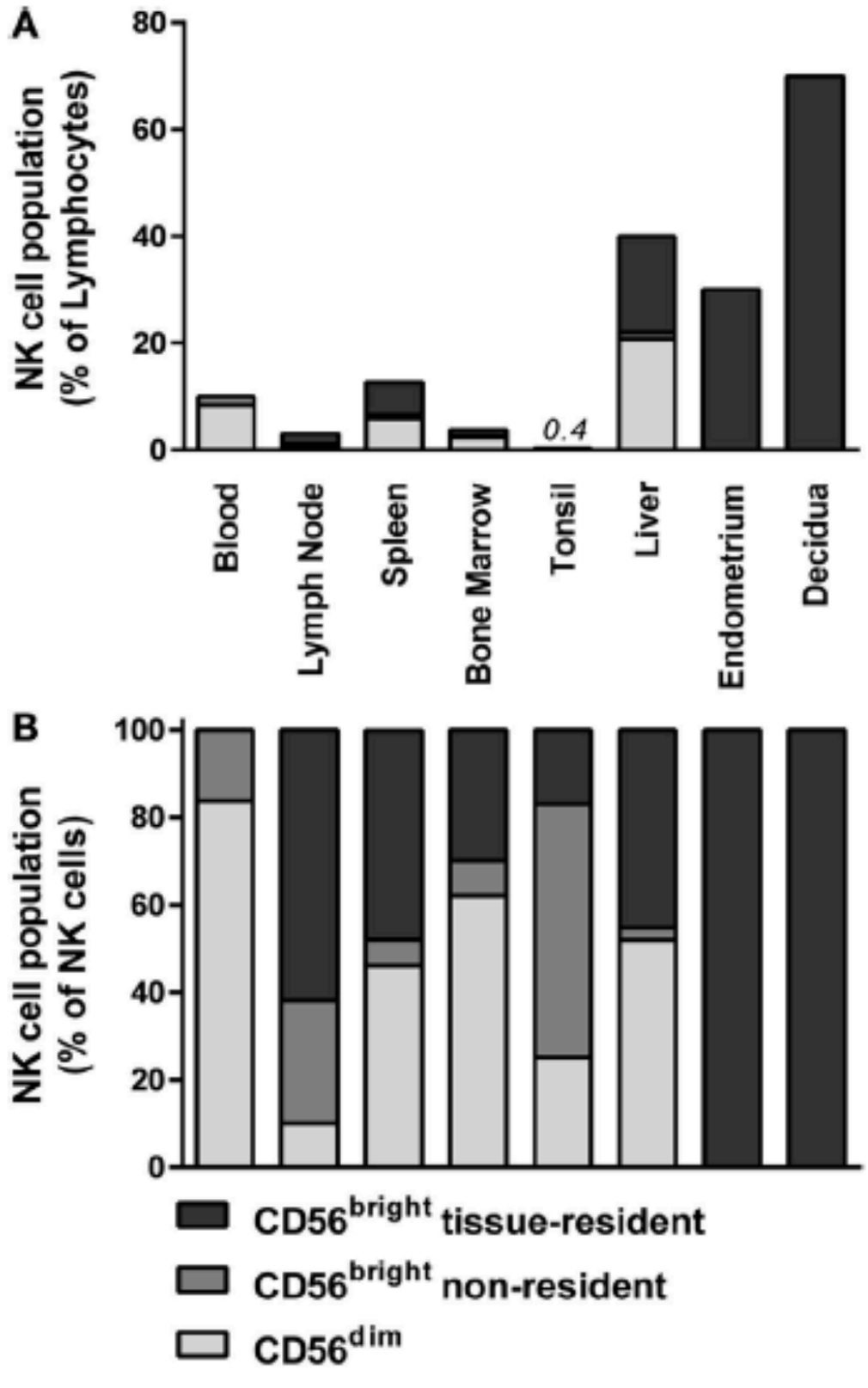
Wing Leung 2014

Receptores das células NK

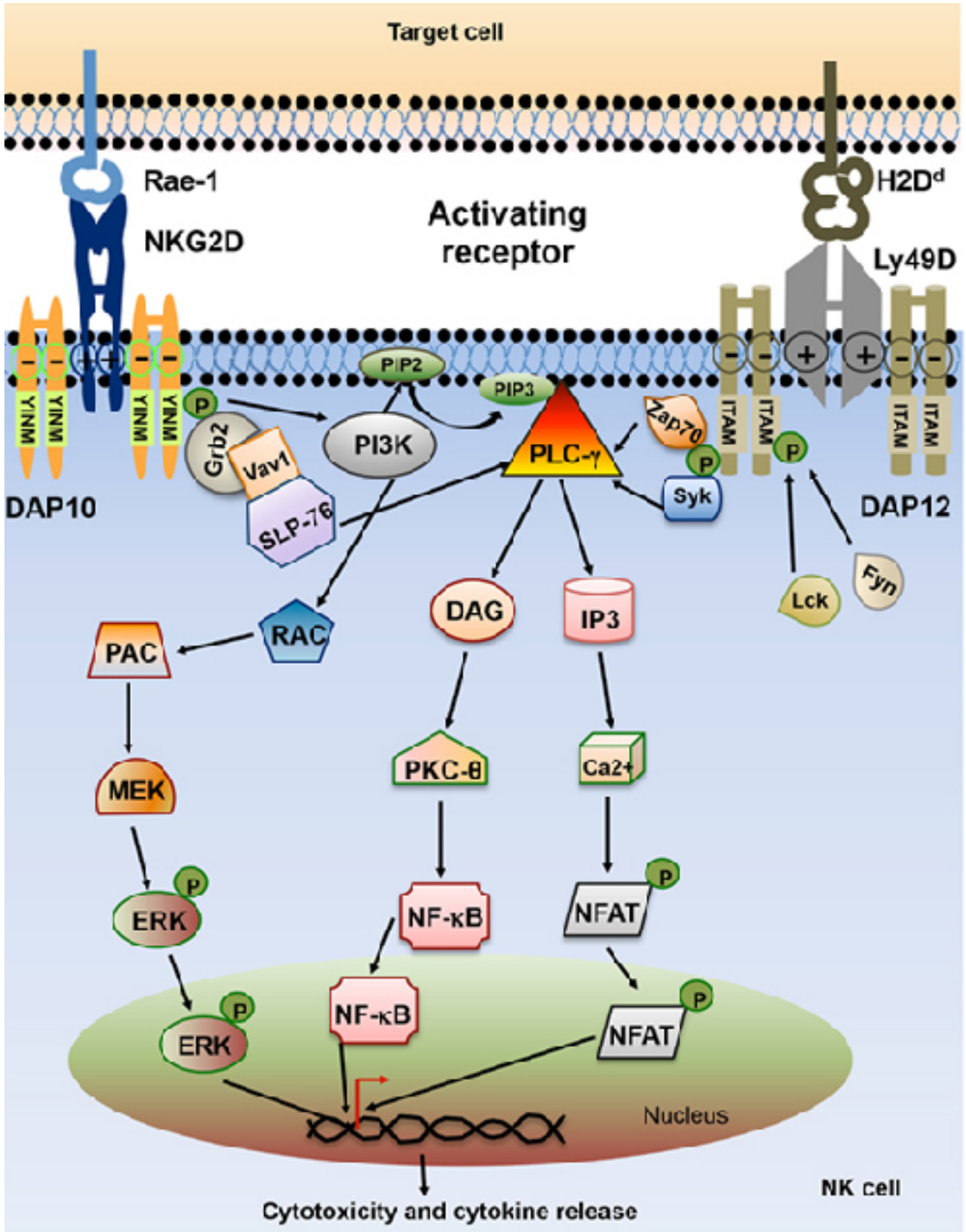
- cada cella NK possui um repertório típico de receptores
- duas maiores distinções: **CD56^{bright}** /CD16$^{+/-}$ (tecido linfoide e non) e **CD56^{dim}** /CD16^{+} (sangue, tecido inflamados)
- **CD56^{bright}** preferencialmente produtora de citocinas
- **CD56^{dim}** preferencialmente citotoxicas
- CD56^{bright} precisam ser ativadas por citocinas (IL-2/-12/-15/-18)
- CD56^{dim} facildiade de ativaçao
-



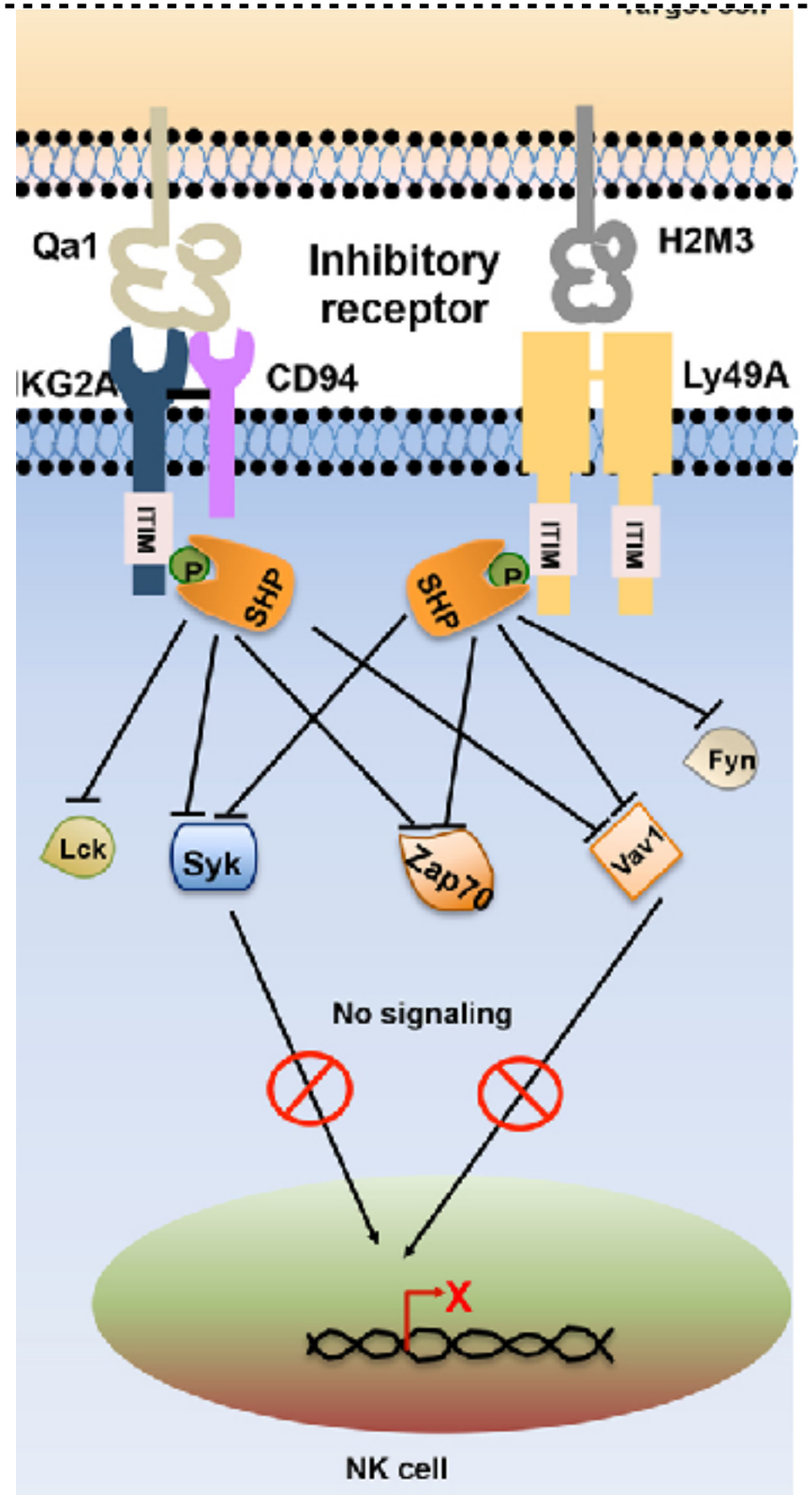
Receptores das células NK



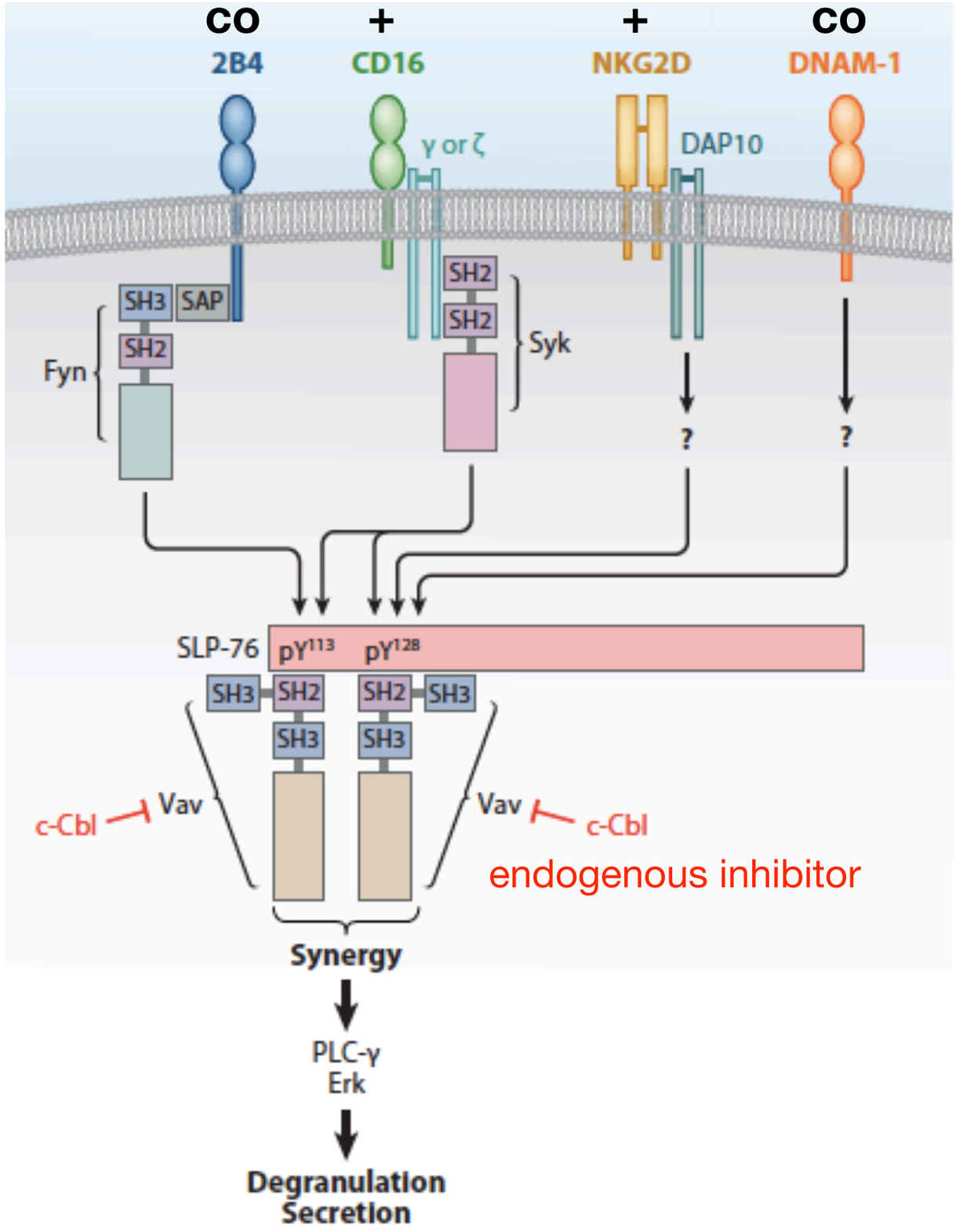
Receptores ativatórios



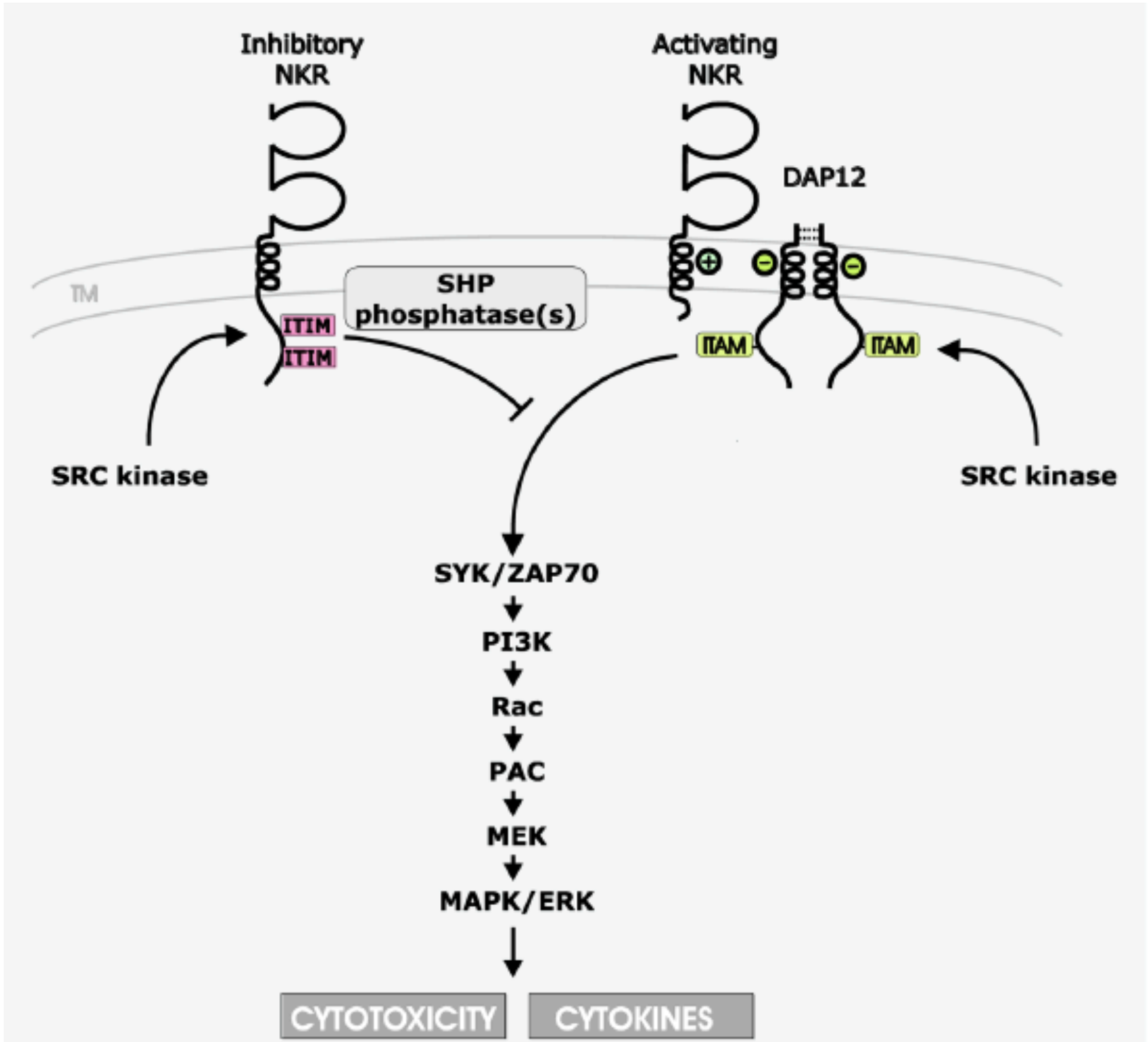
Receptores inibitórios



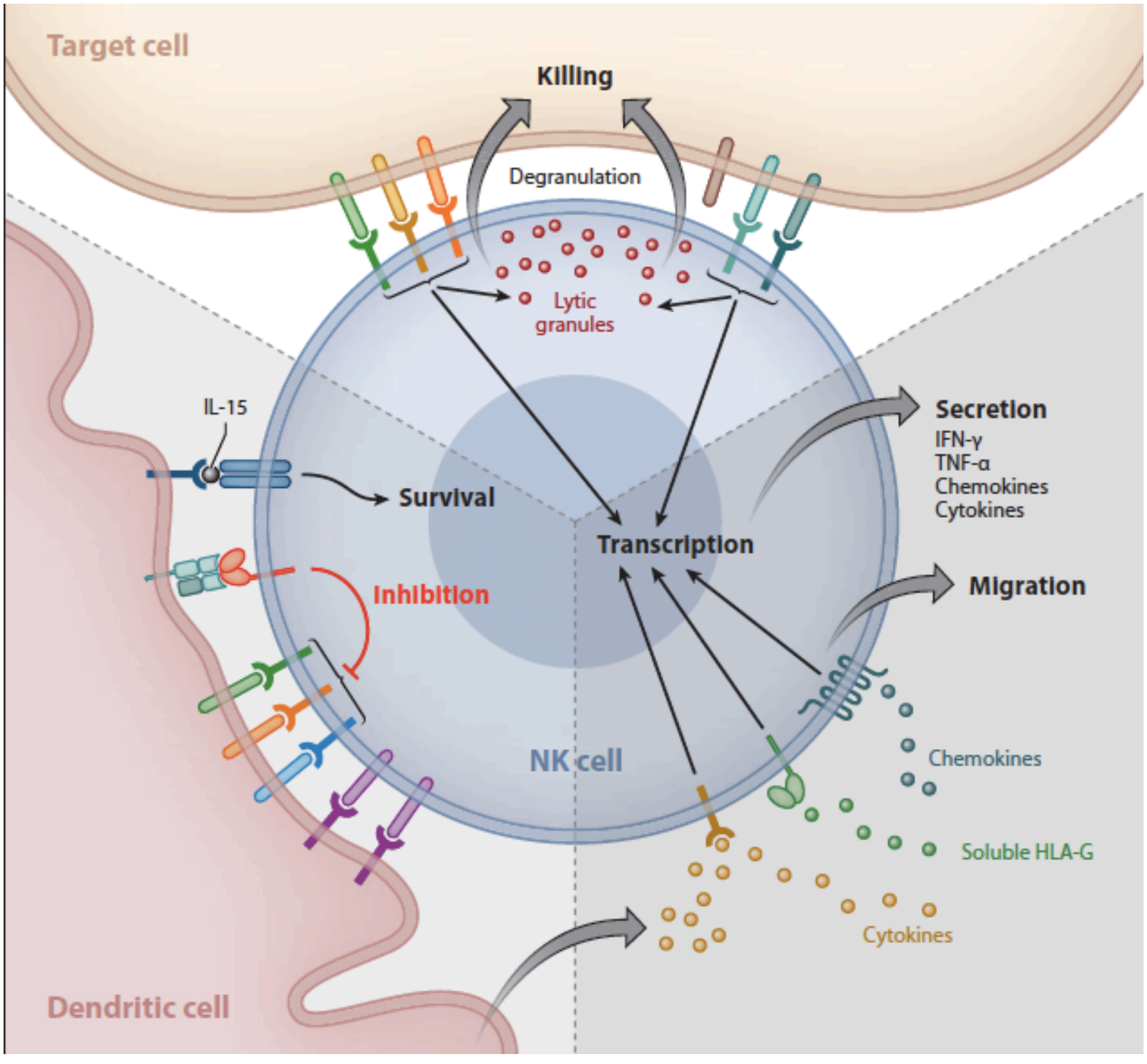
Sinergia de receptores



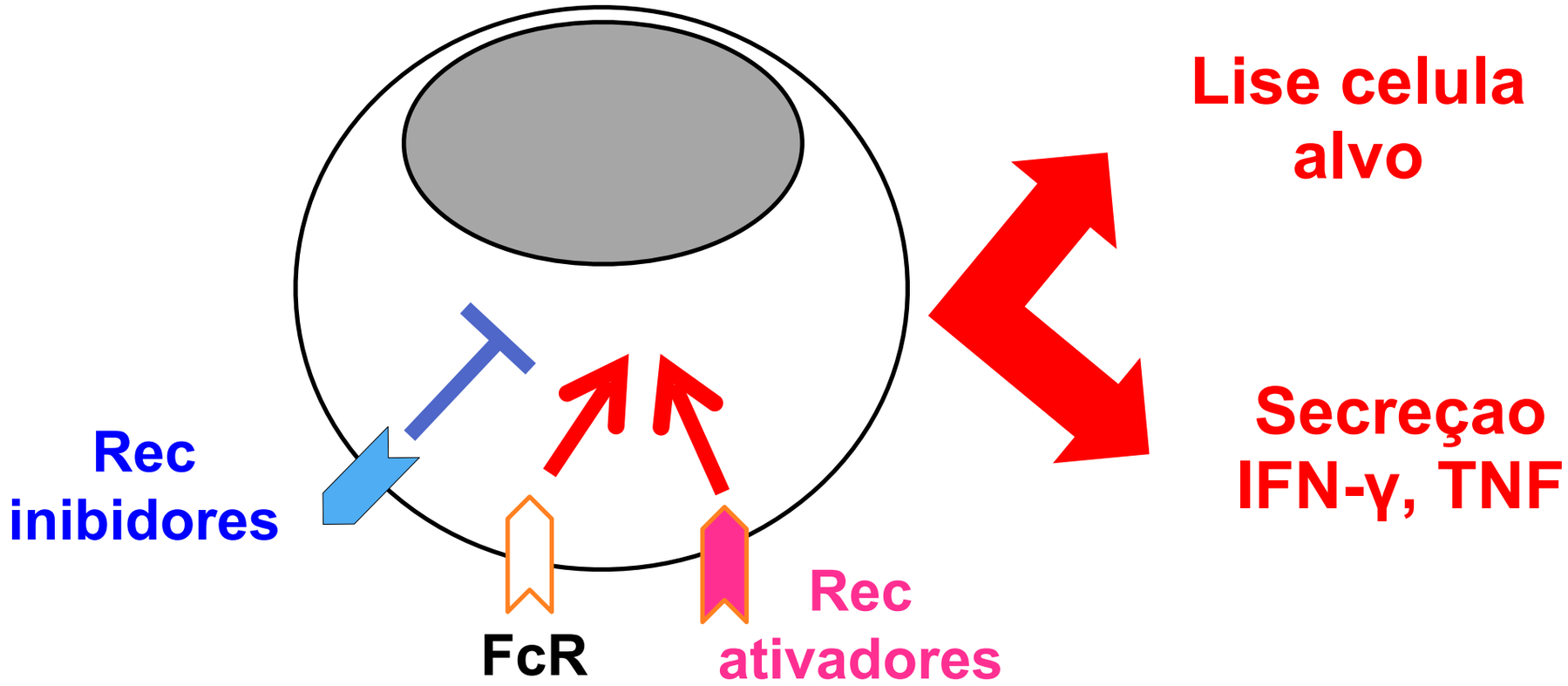
Balanço de receptores



Receptores das células NK



Reconhecimento por celulas NK



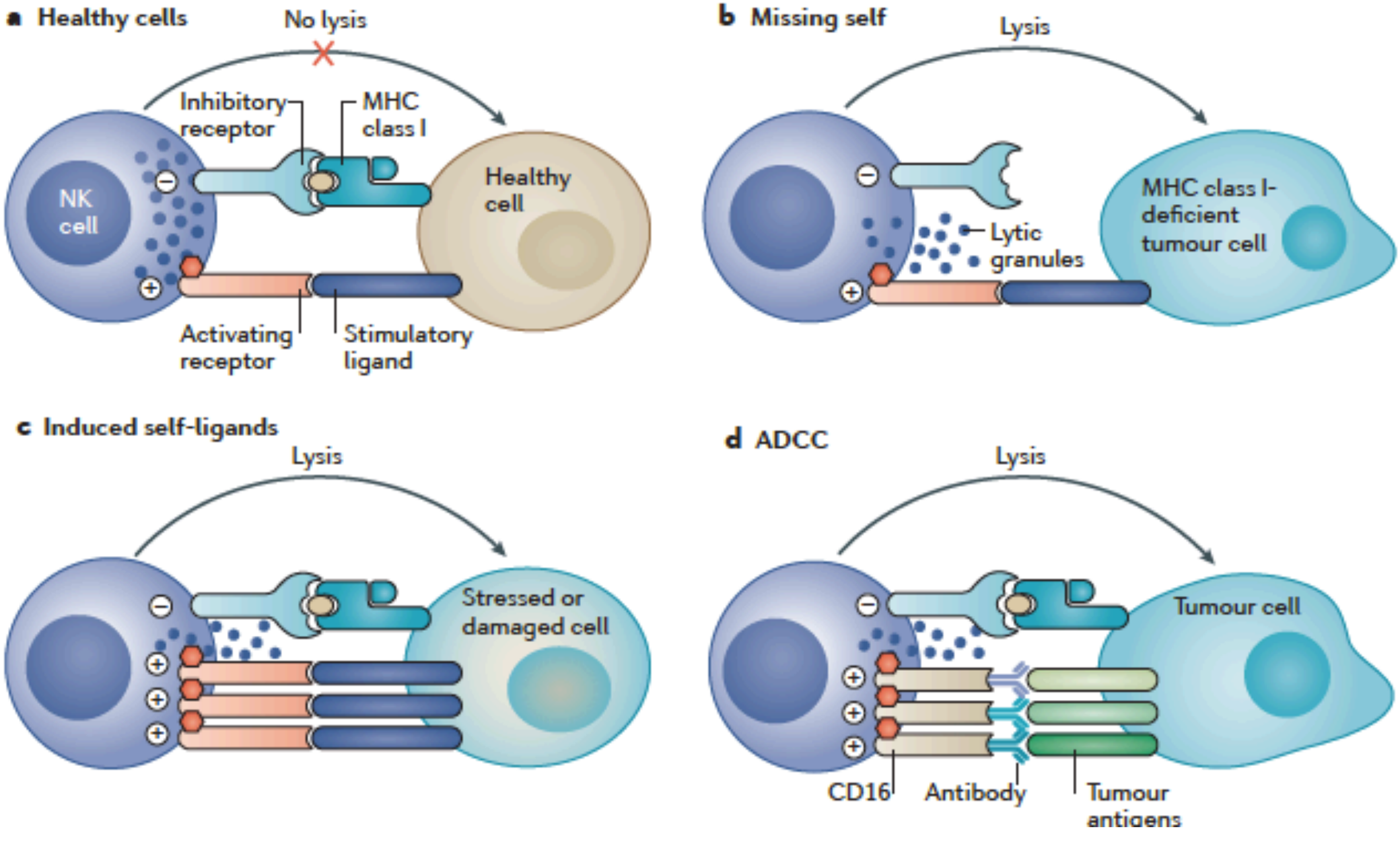
Receptores de celulas danificadas/infectadas

- **<u>Inibidores</u>** reconhecem ligandos nas celulas saudaveis
- *Rec Inib para MHC-I*
- **<u>Ativadores</u>** reconhecem ligandos nas celulas danificadas/infectadas
- **FcγR** ligam AC (ADCC)

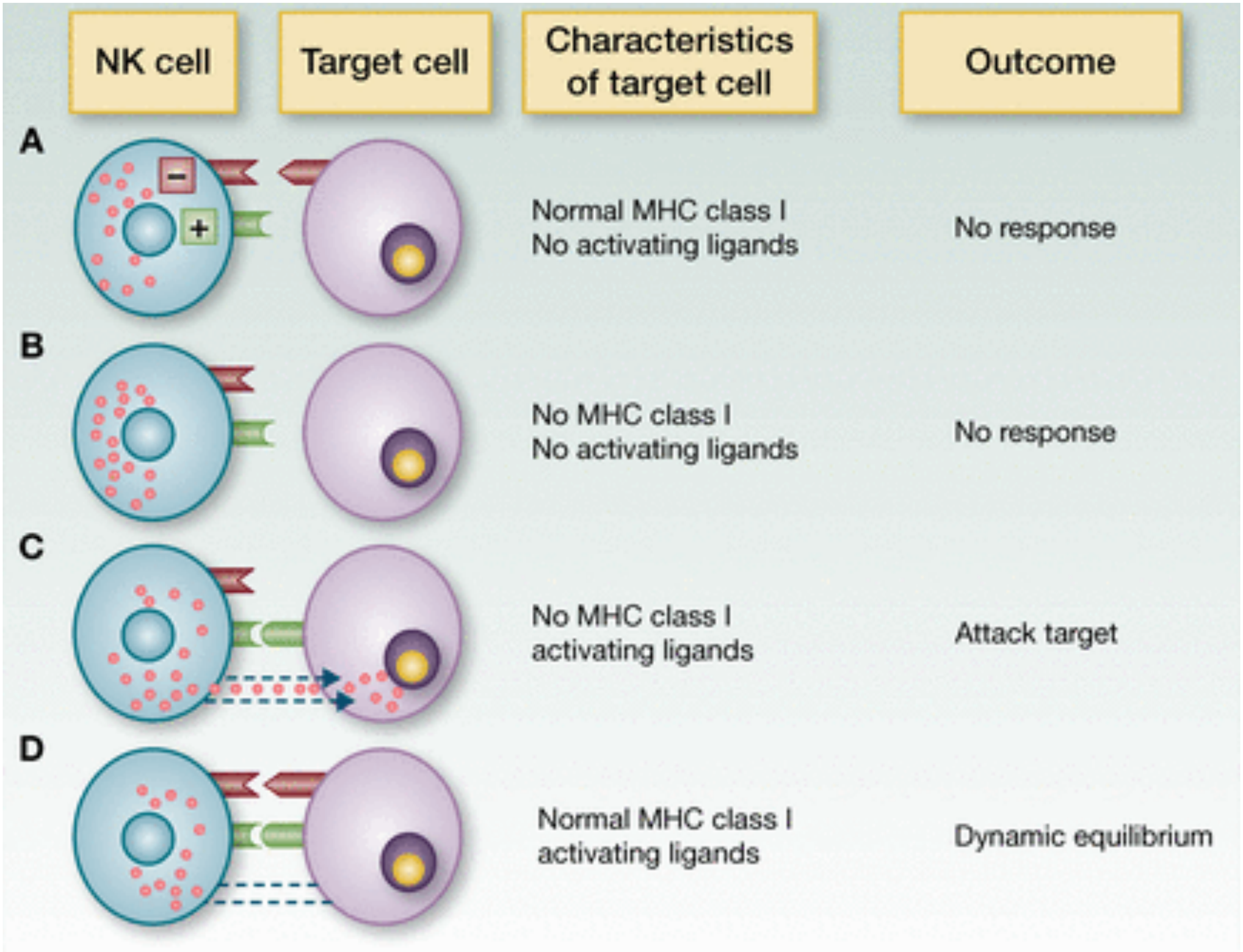
Receptores das células NK

Receptor (*Ligand*)	Degranulation	Polarization	Killing
NKG2D (*ULBP1*)	No	No	No
2B4 (*CD48*)	No	No	No
NKG2D + 2B4	Yes[a]	No	No
LFA-1 (*ICAM-1*)	No	Yes[b]	No
NKG2D + 2B4 + LFA-1	Yes	Yes	Yes
CD16 (*anti-S2 IgG*)	Yes	No	No
CD16 + LFA-1	Yes	Yes	Yes
NKG2D + 2B4 + IR[c] (*HLA-E*)	No[a]	No	No
LFA-1 + IR (*HLA-C, HLA-E*)	No	No	No
CD16 + IR (*HLA-E*)	Less	No	No
CD16 + LFA-1 + IR (*HLA-C, HLA-E*)	Yes / Less[d]	No	No

Reconhecimento pelas células NK



Reconhecimento pelas células NK



Wing Leung 2014

Moleculas induzidas pelos NK R

citocinas	***Produtor***	***Alvo***	***Acao***
TNF	Monocytes, macrophages, dendritic cells, mast cells, NK cells, epithelial cells	Macrophages	Activates
		Vascular endothelium	Activates, increases vascular permeability, fluid loss, local blood clotting
		Liver	Induces acute-phase response
		Hypothalamus	Fever
		Tumors	Cytotoxic for many tumor cells
IFN-γ	NK cells, T lymphocytes	Mø, NK cells, B lymphocytes	Activate Mø and increase killing activity Increase NK activity, modulate AC production by B lymphocytes

Moleculas liticas

perforina	NK cells, T CD8+ lymphocytes	Celulas danificadas, Infectadas, tumorais	Pore formation in plasma membranes
granzima	NK cells, T CD8+ lymphocytes	Celulas danificadas, Infectadas, tumorais	Induçao de apoptose