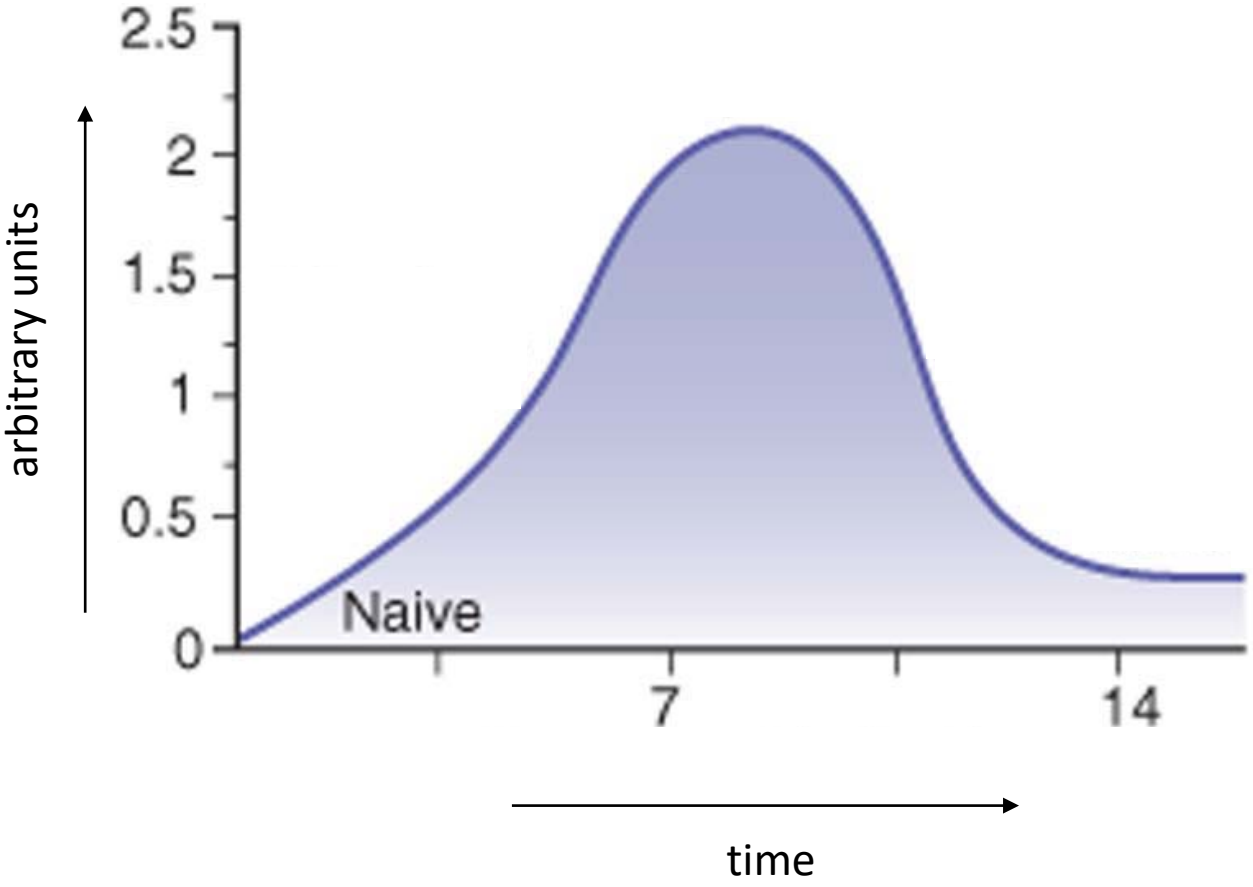
Immune responses control and negative feedback mechanisms

Inflammation/innate immunity control

Lymphocytes activation control

Effects of chronic antigen exposition

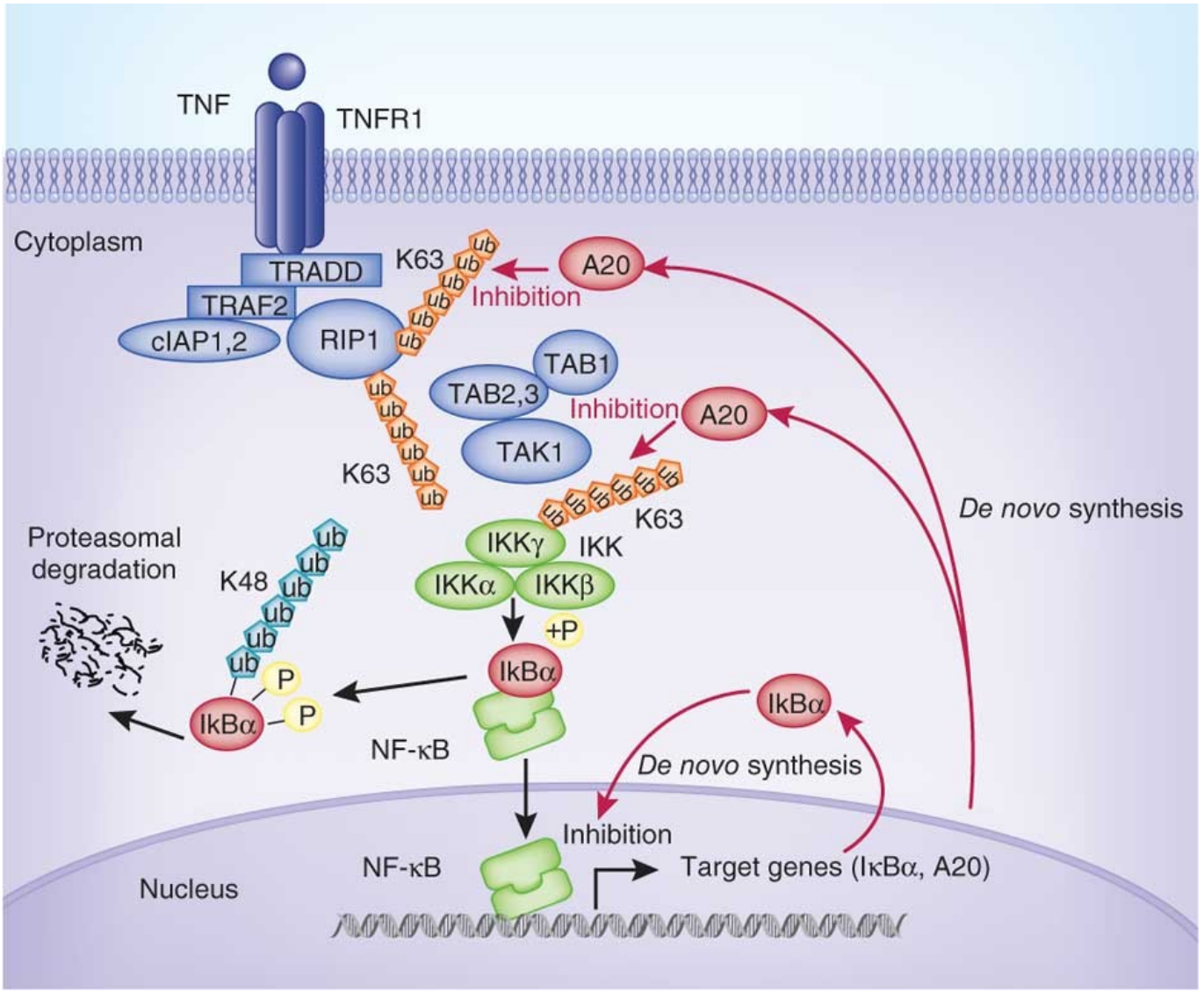
Response dynamic



In the absence of signals – responses are downregulated

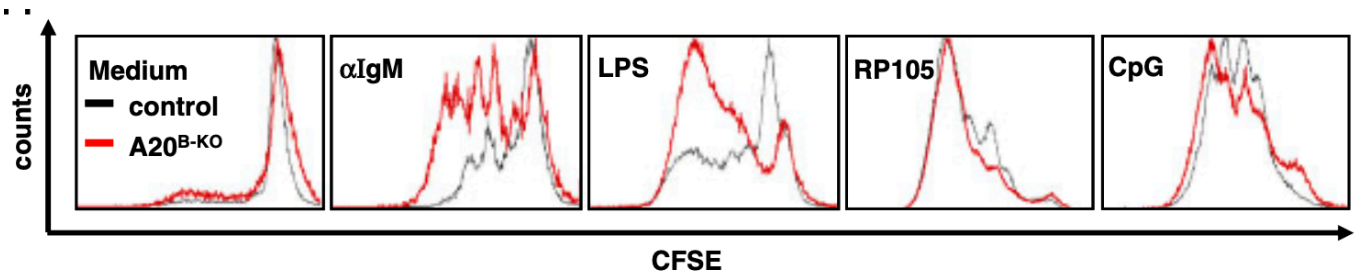
Responses are downregulated by negative feedback mechanisms

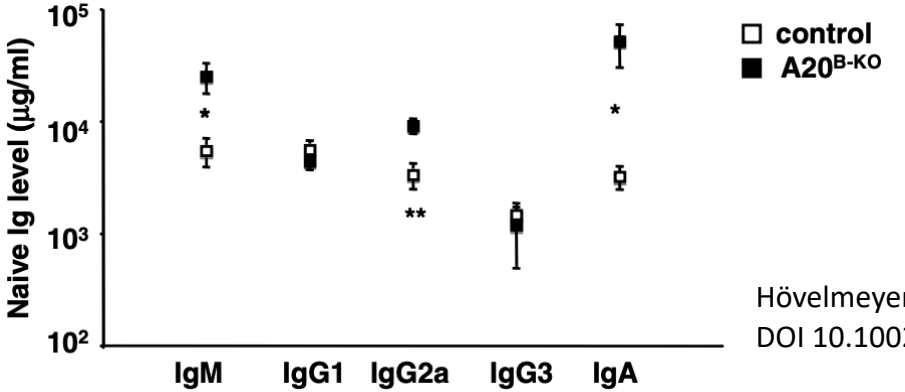
NFkB downregulation - target genes' products inhibit the pathway and its activation



- controls inflammation mediated by innate cells

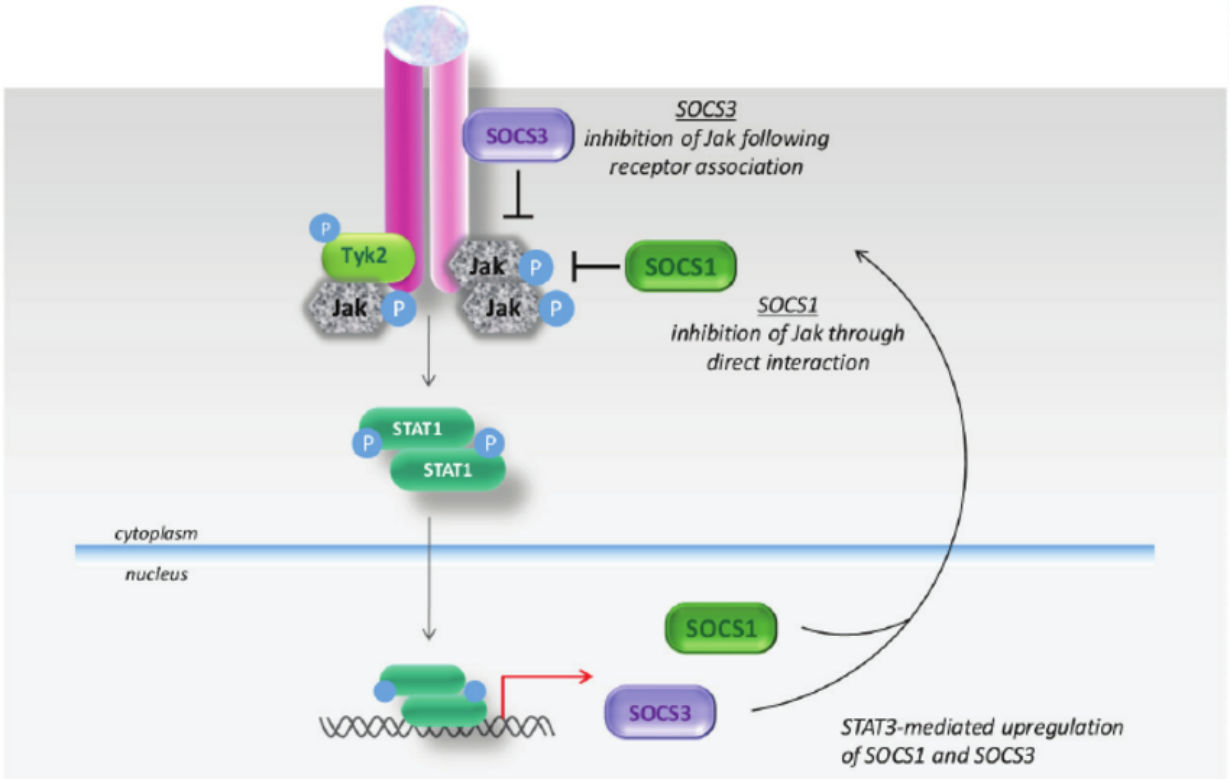
- controls B lymphocyte responses to CD40L signal (A20 mutations in autoimmune diseases and lymphomas)



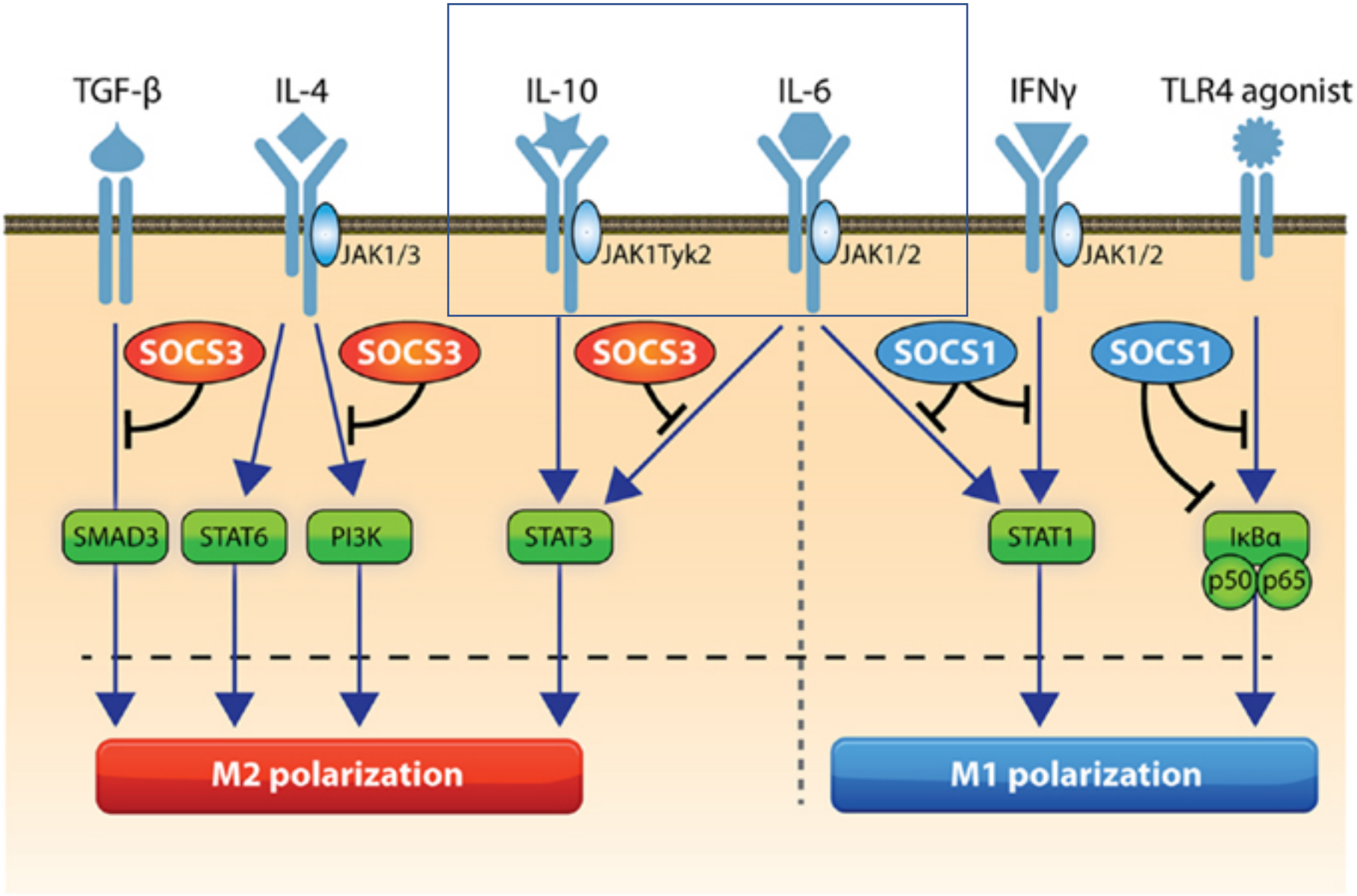


Hövelmeyer et al,
DOI 10.1002/eji.201041313

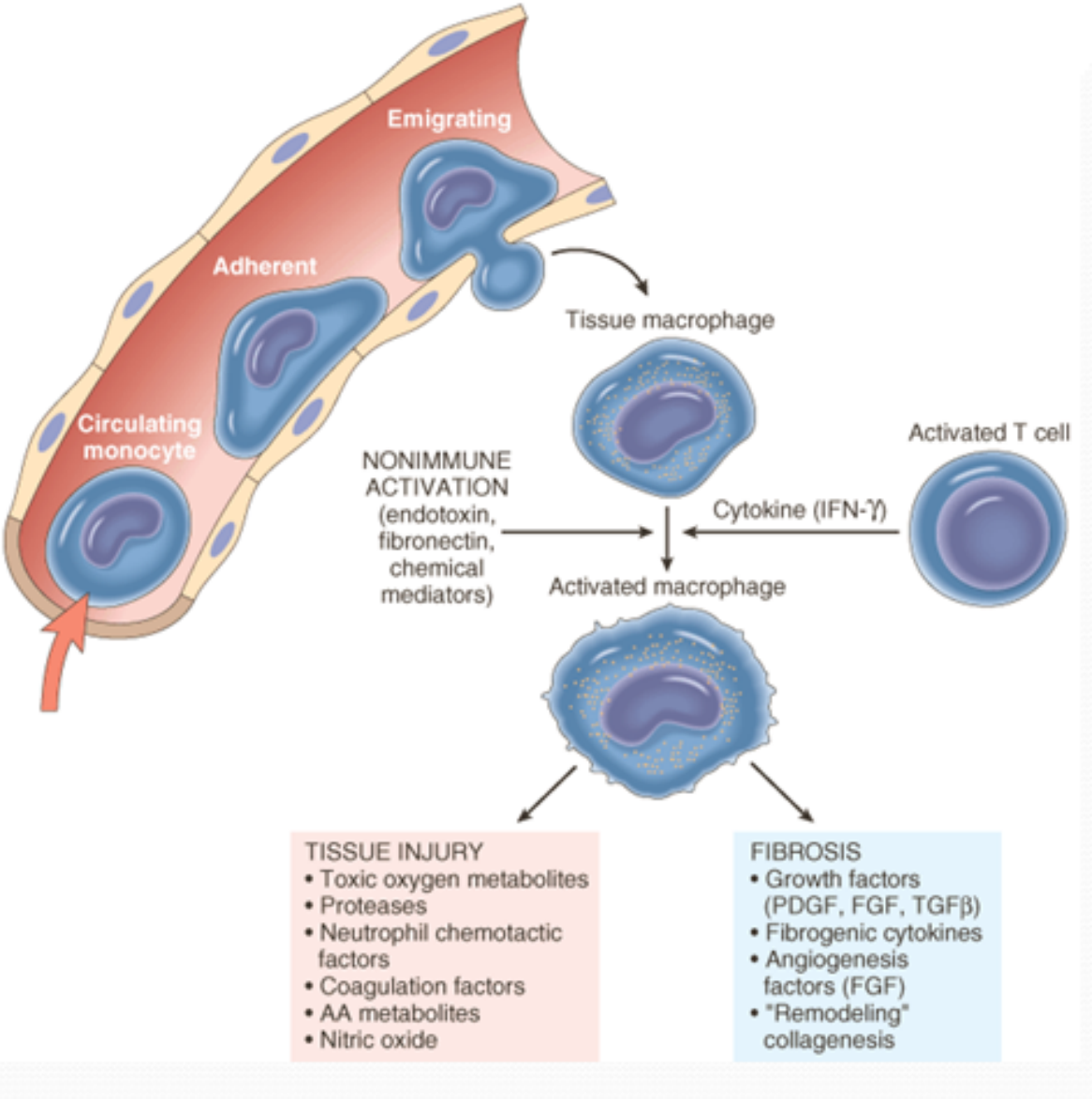
STAT3 negative feedback – SOCS are inhibitors of STAT activation



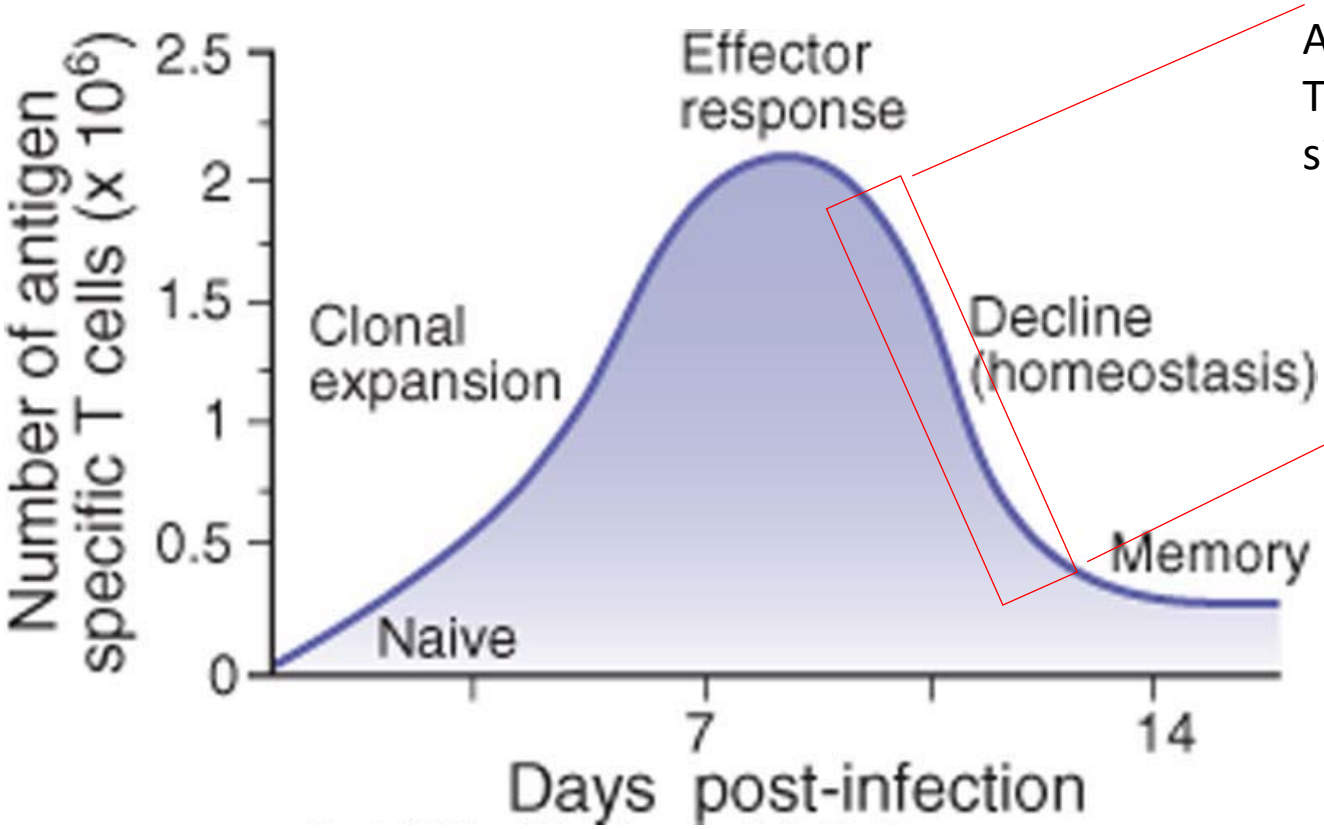
SOCS display different inhibitory potential on different pathways



Macrophage plasticity



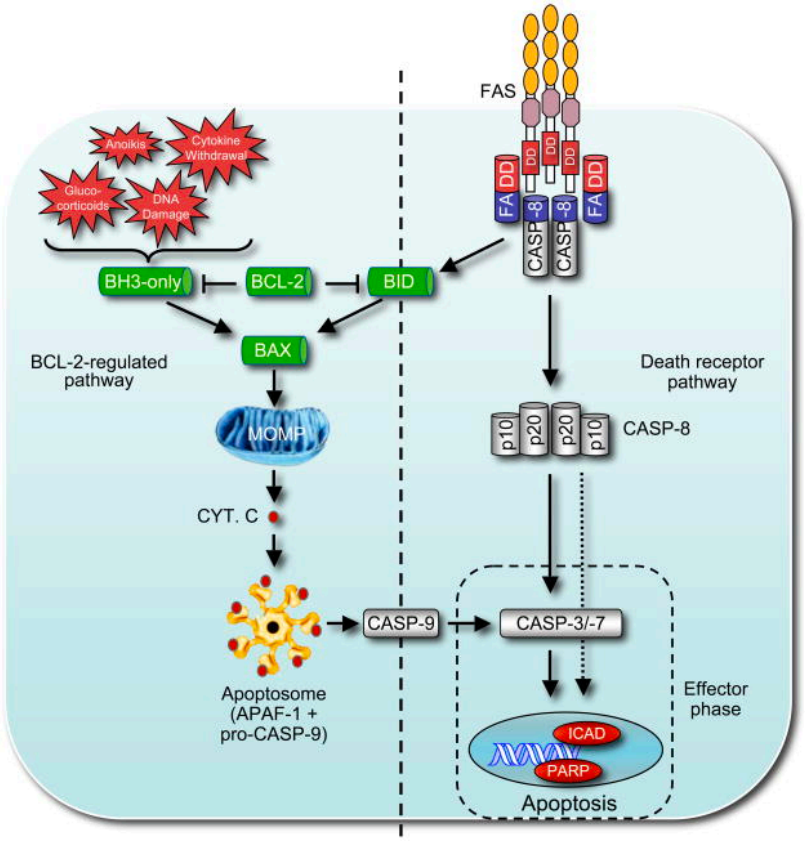
Lymphocyte activation control

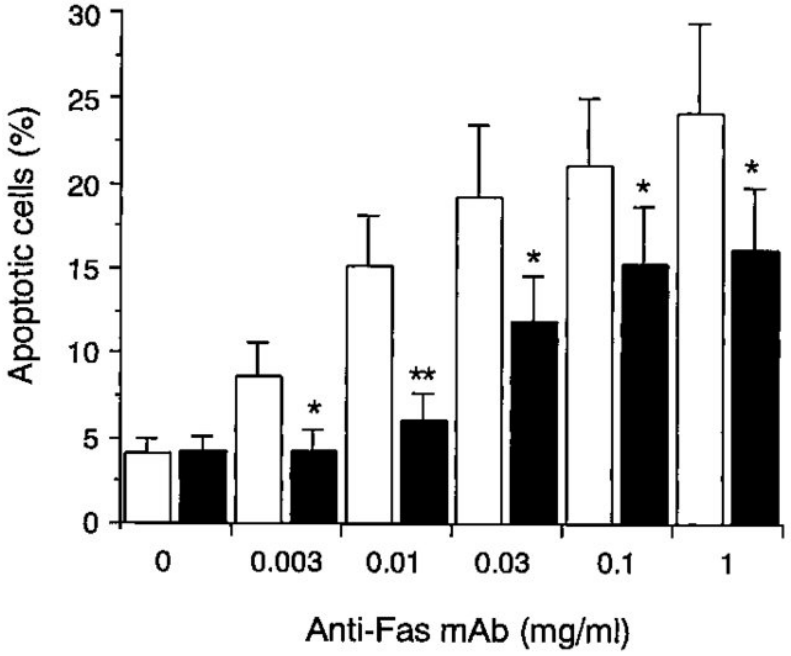


Ag concentration reduction
TCR (the same for BCR) signaling downregulation

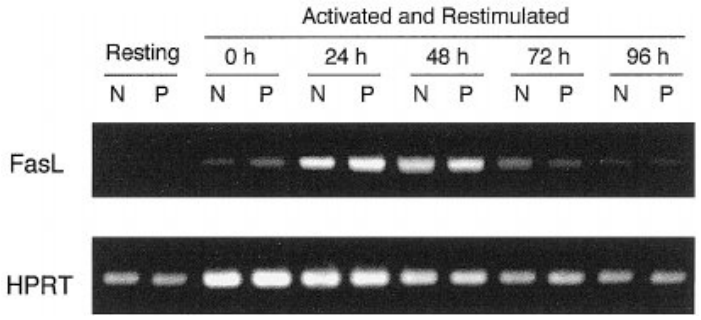
T lymphocytes

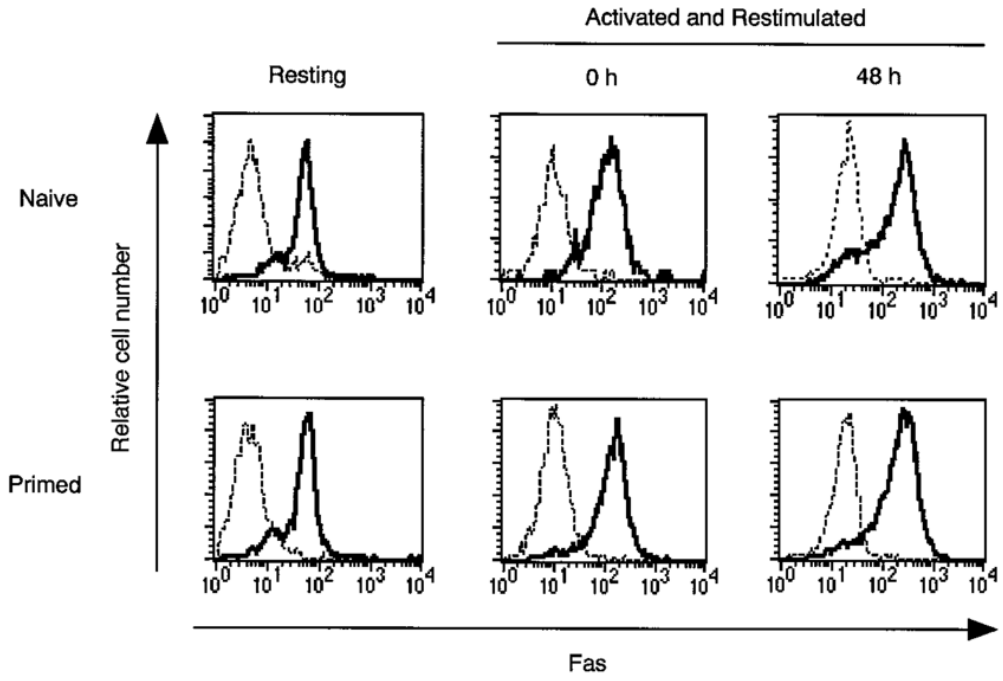
Cell death induced by FAS/FASL





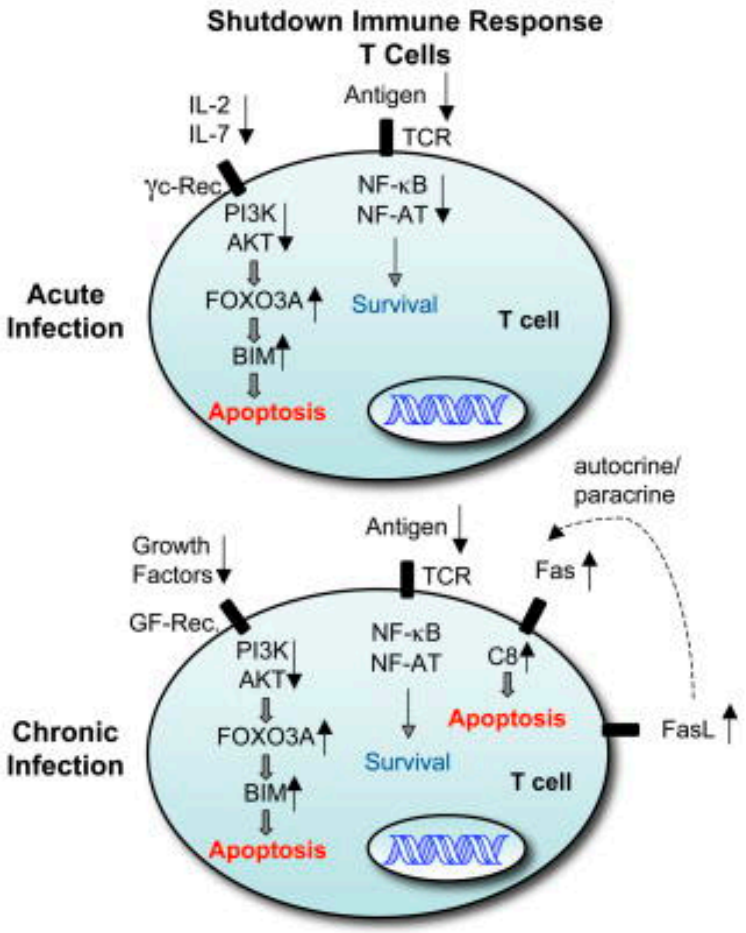
FAS and FASL expression are regulated by activation

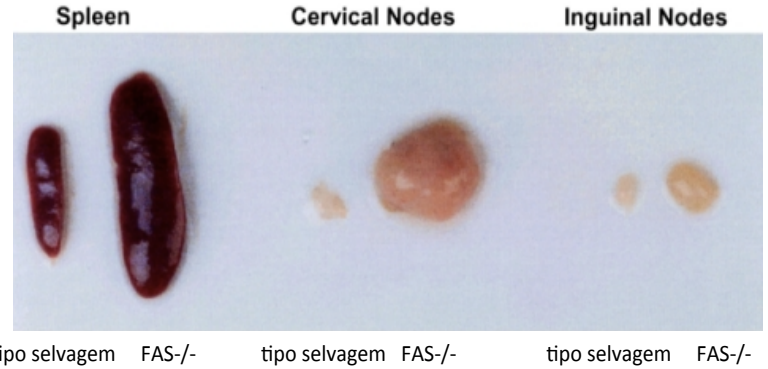


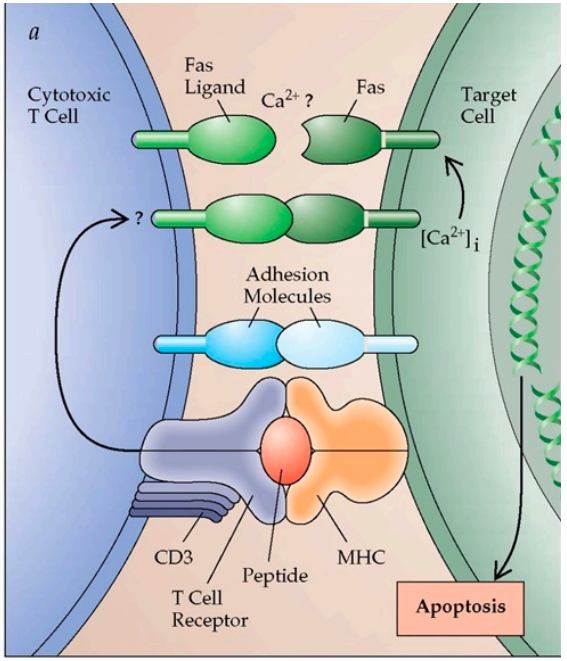


Ova stimulated DO10 splenocytes
(MHC-II ova restricted)

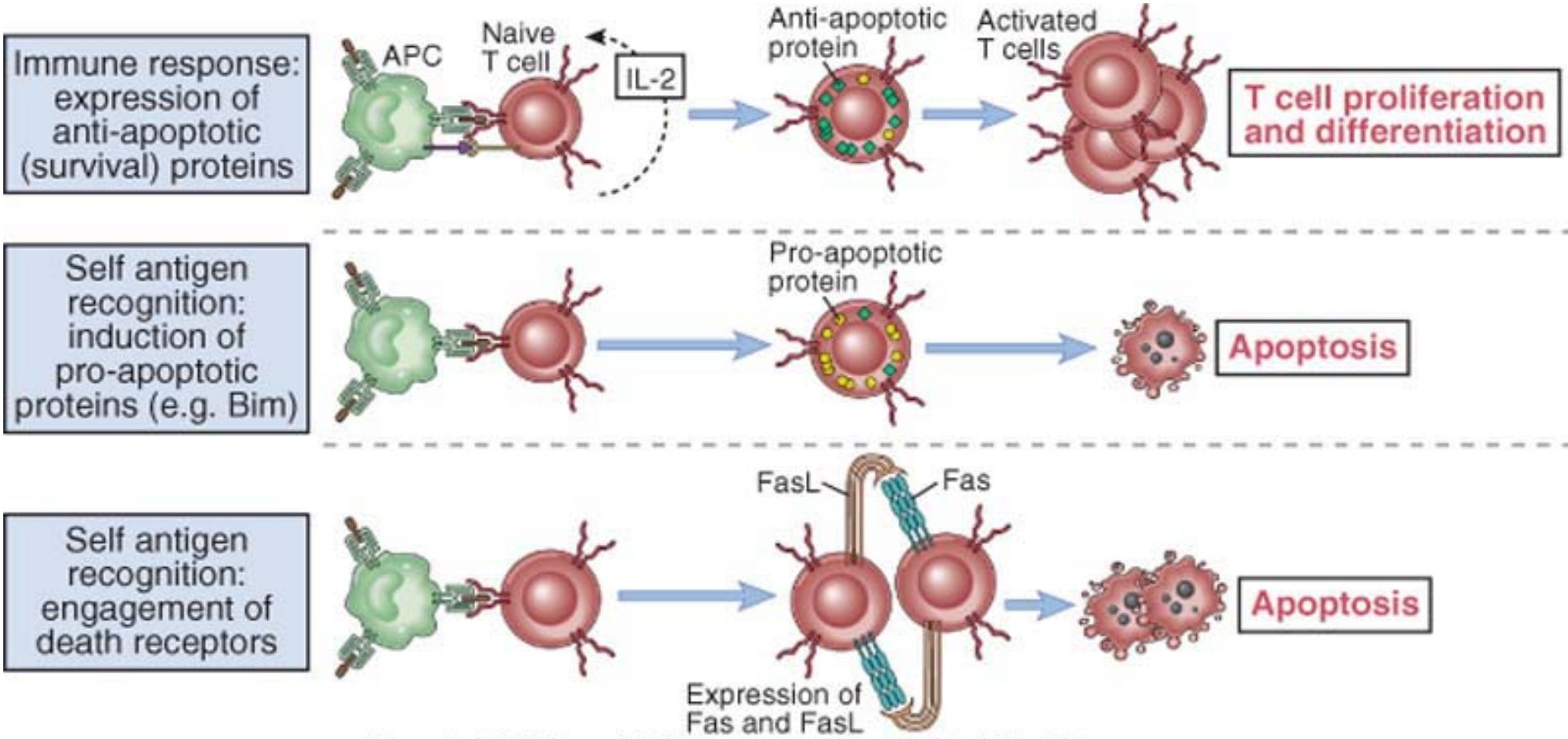
Cell death induced by FAS/FASL







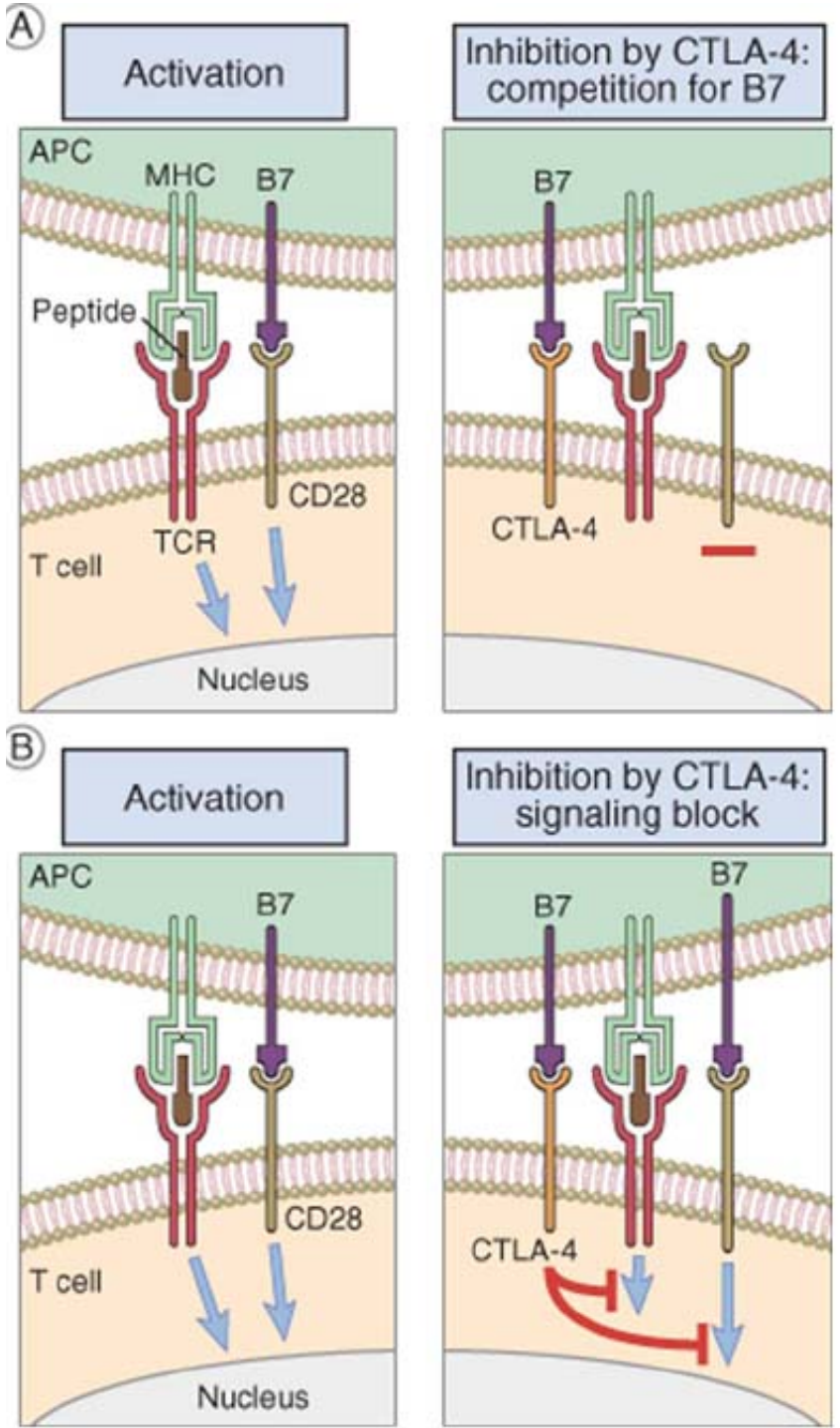
Cell death induced by activation with co-stimulation (anergy)



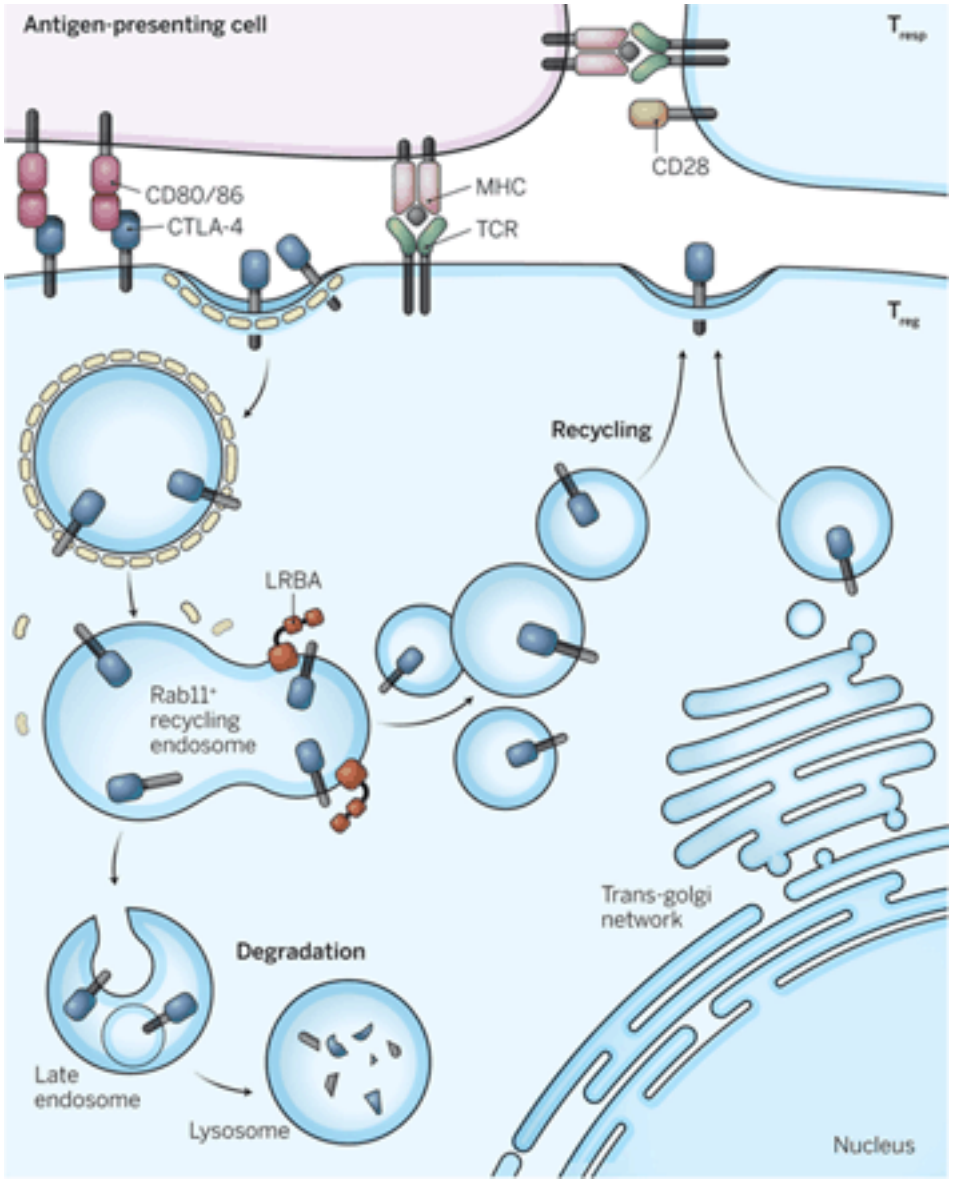
CTLA-4
Cytotoxic T Lymphocyte Associated Protein 4

Intrinsic and extrinsic regulation mechanisms;

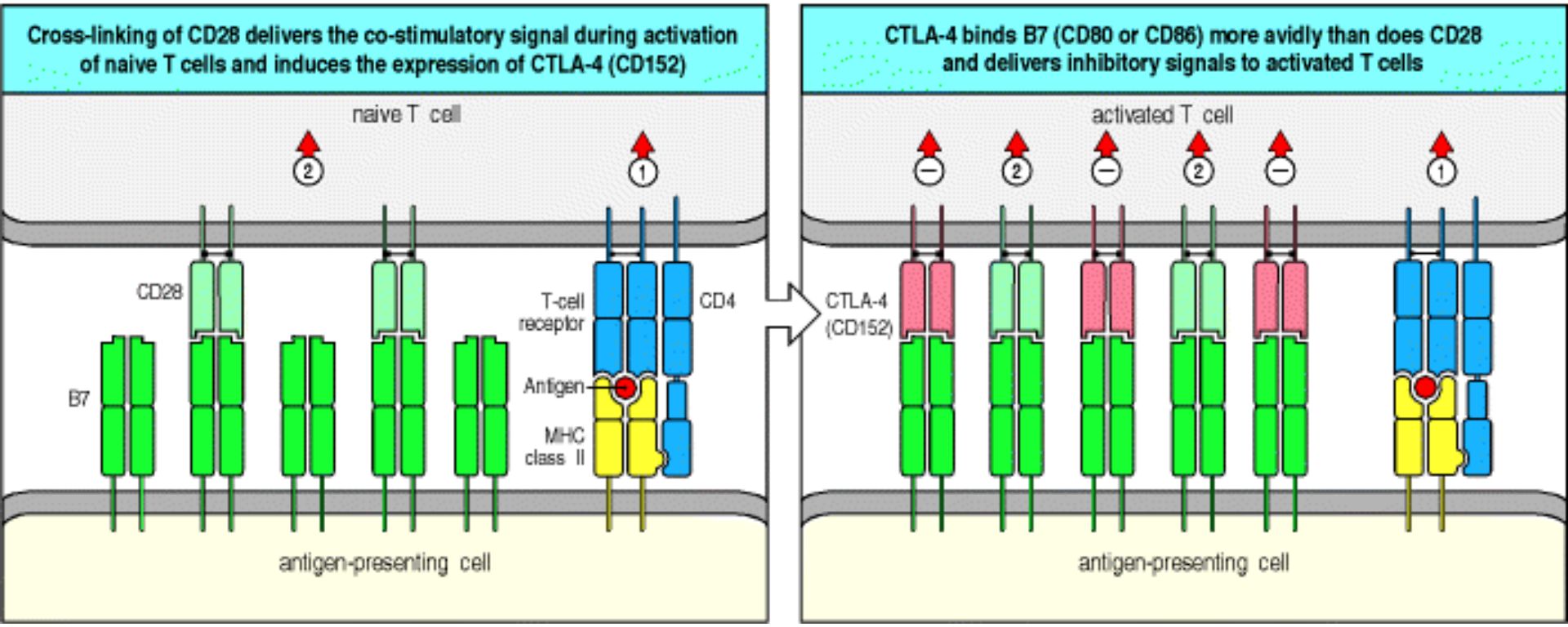
stored in intracellular vesicles, move to the membrane upon T cell activation;



In regulatory T cells, CTLA4 is constantly recycled to the cell membrane

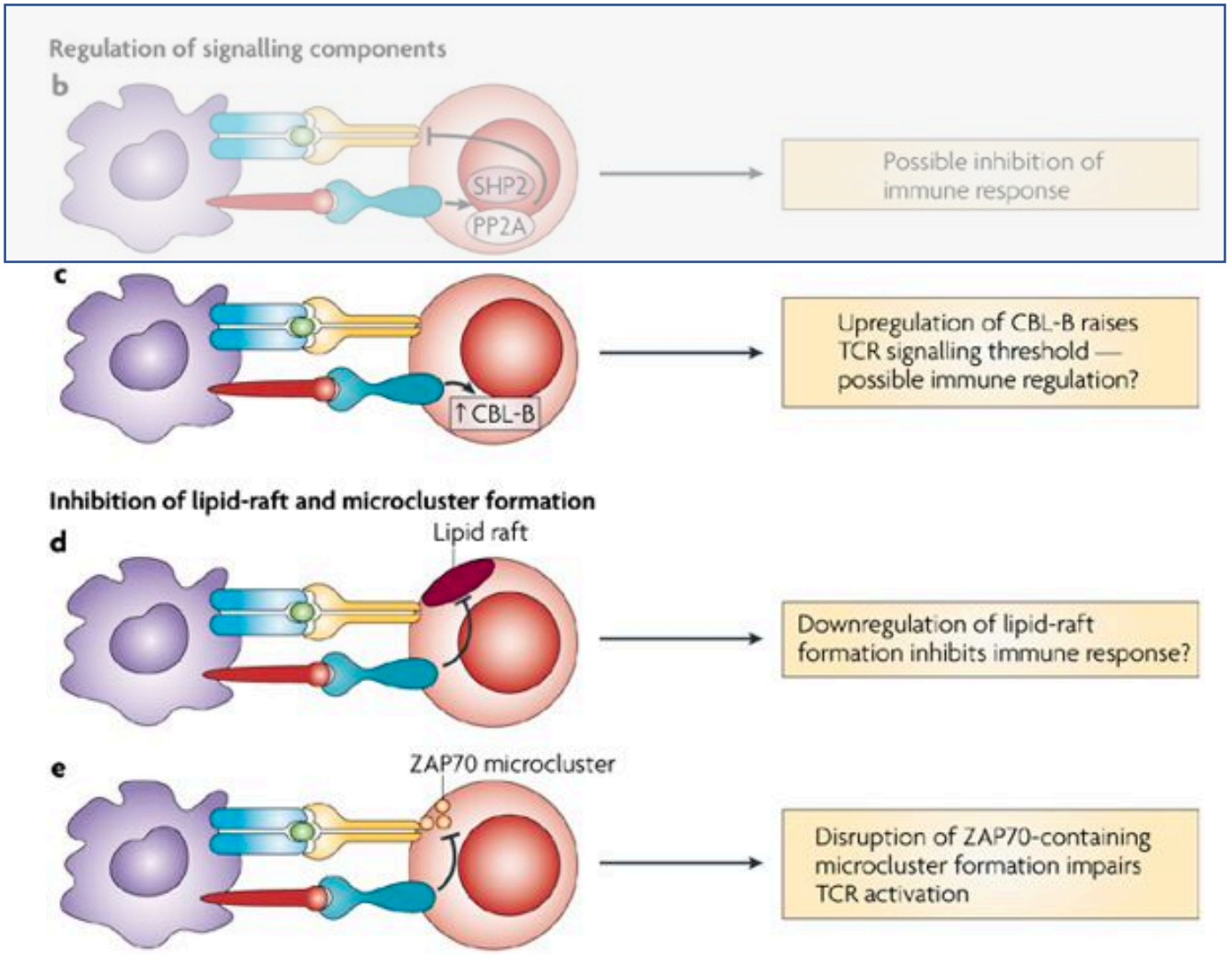


Intrinsic – binding to B7 and imparing CD28 signaling



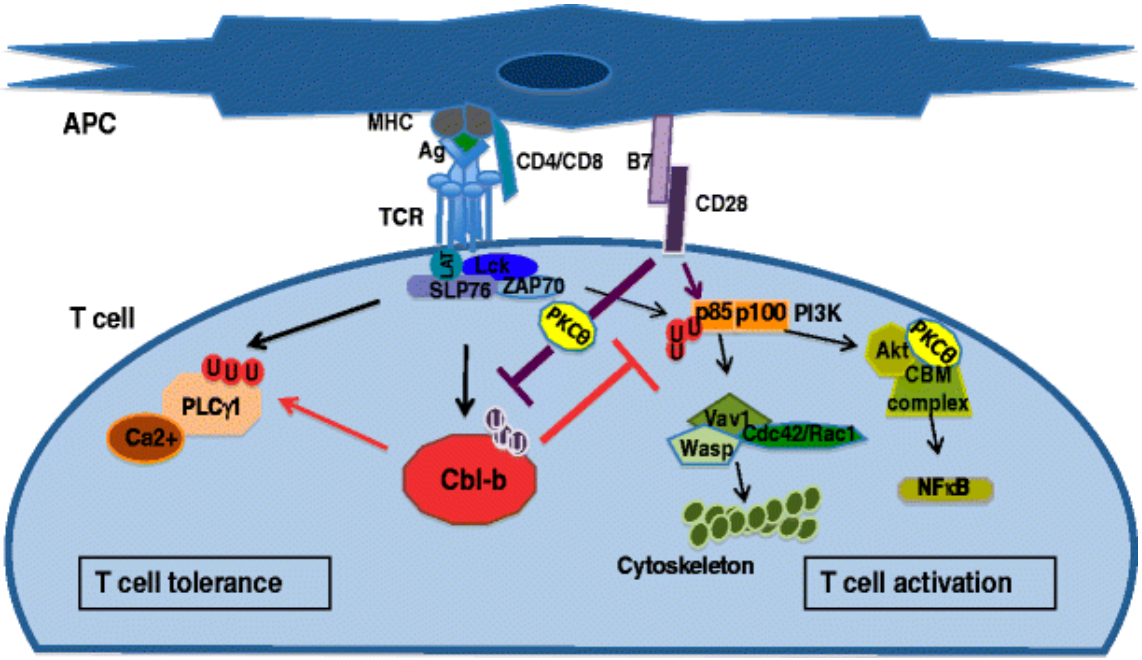
CTLA has higher binding affinity to B7 molecules

Other intrinsic mechanisms



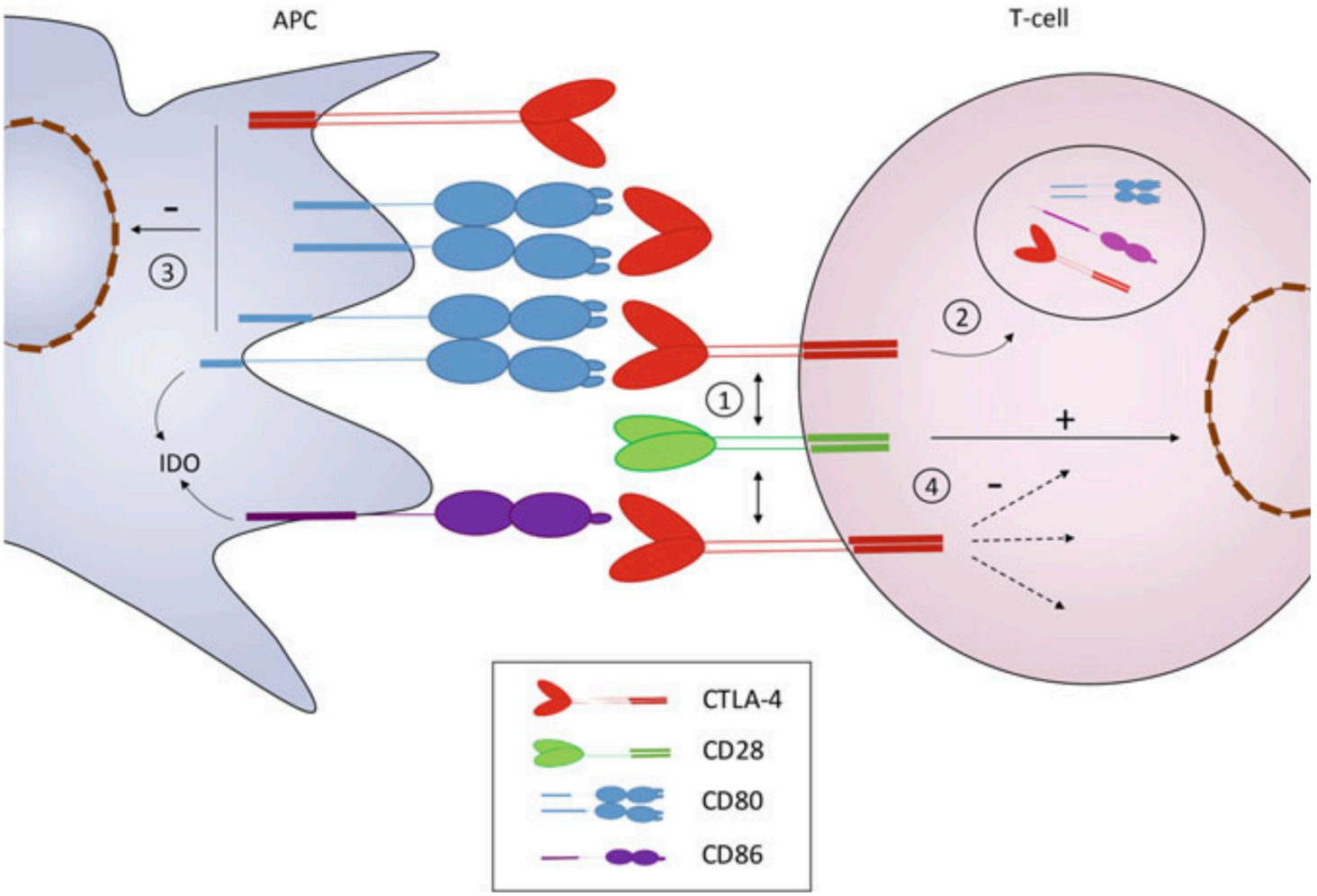
The reverse stop-signal model for CTLA4 function
Christopher E. Rudd
Nature Reviews Immunology volume 8, pages 153–160 (2008)

CBL-B – subunidade E3 de ubiquitina ligase

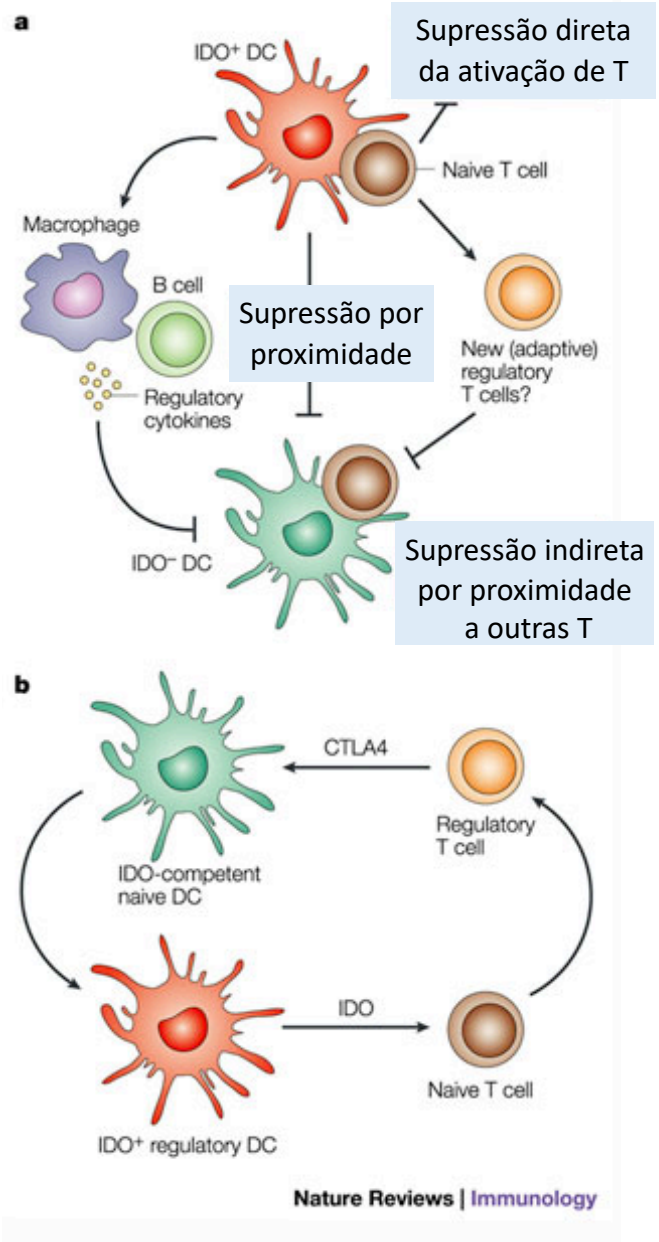


Extrinsic – APC antigen presentation modulation

B7 quenching, internalization and degradation



Extrinsic – induction of APC tolerogenic phenotype

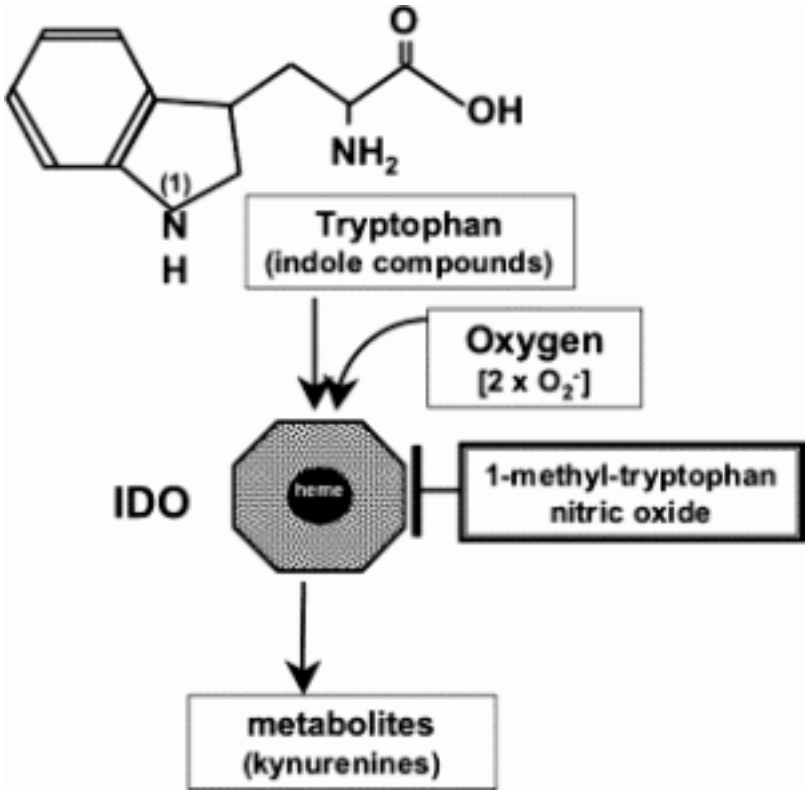


Supressão direta da ativação de T

Supressão por proximidade

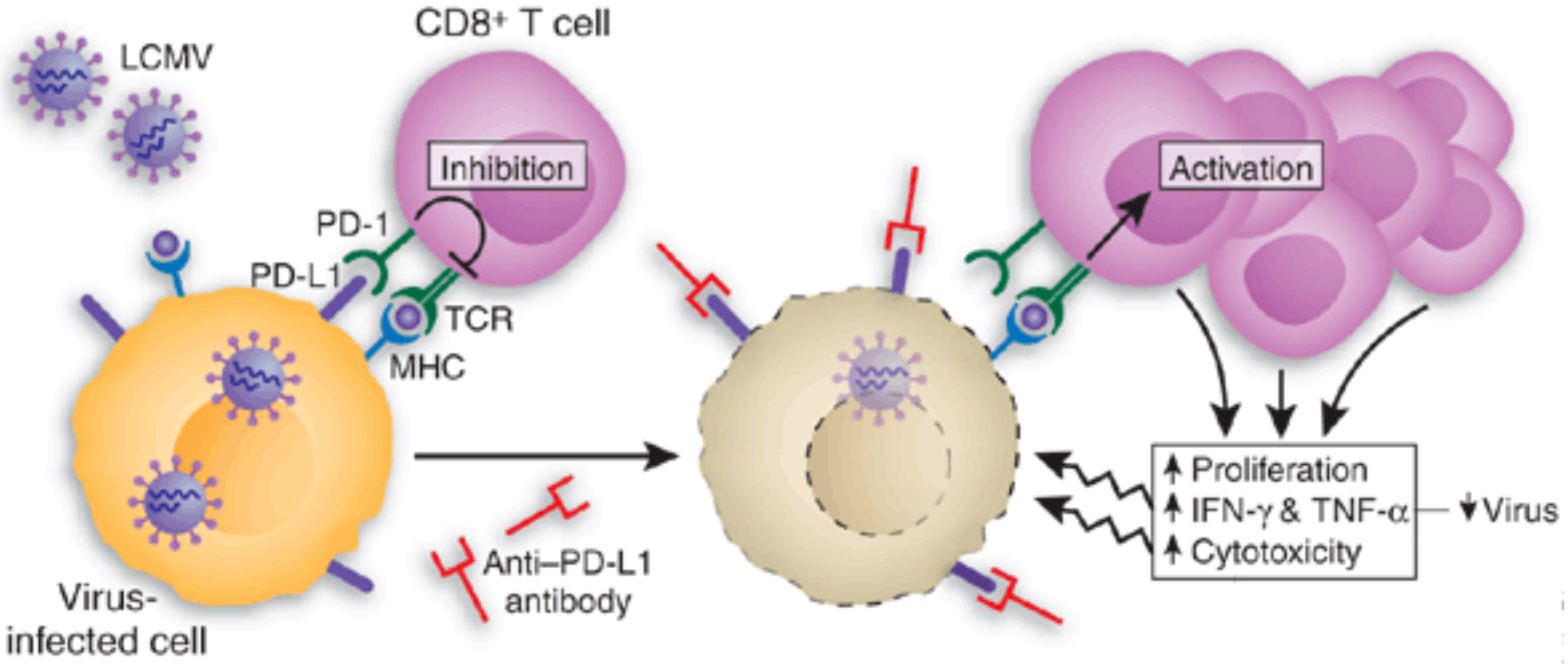
Supressão indireta por proximidade a outras T

Amplificação de sinal regulador entre T reguladoras e DCs



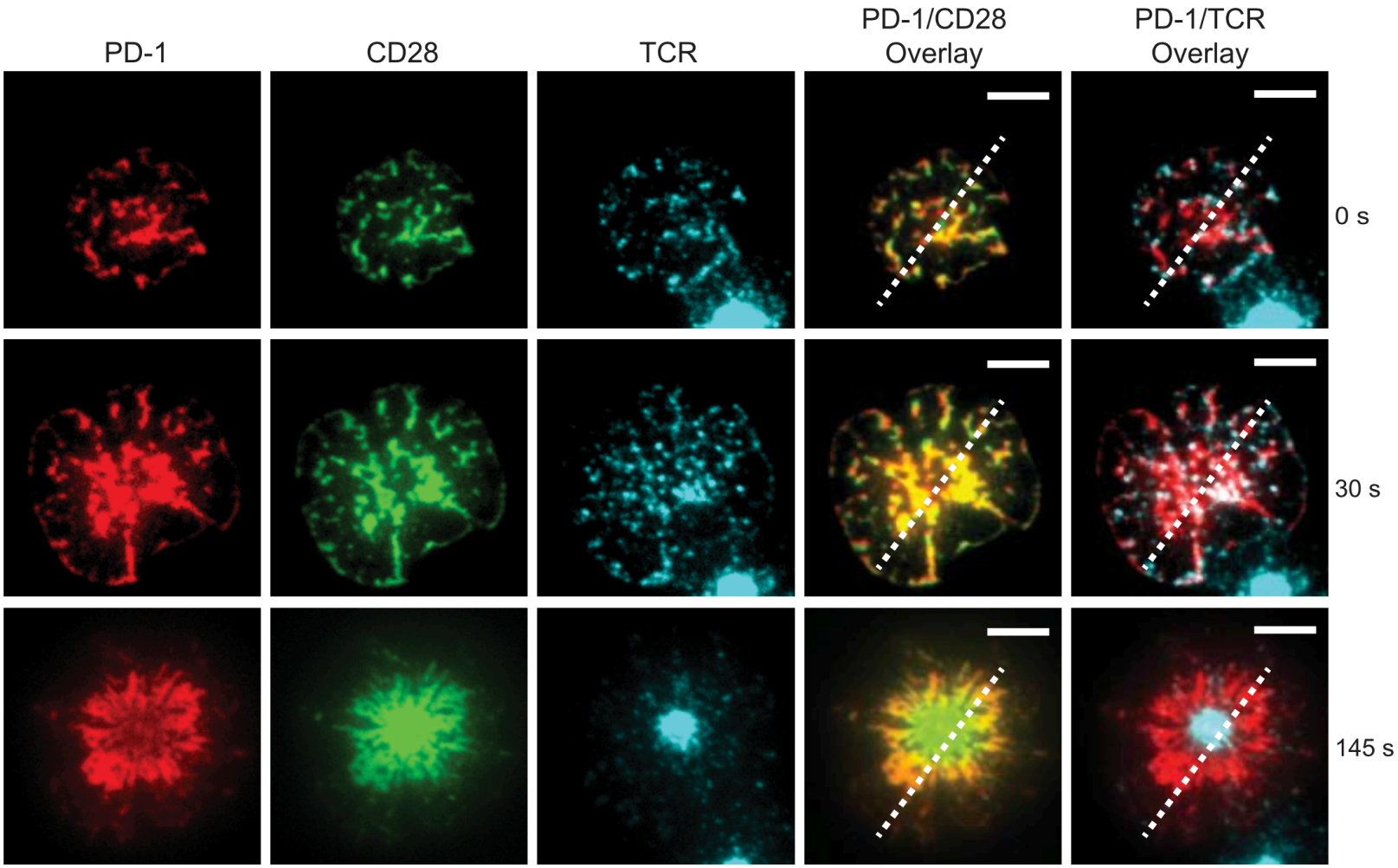
http://www.jri.ir/article/382

PD-1/PD-1L – control of chronic responses

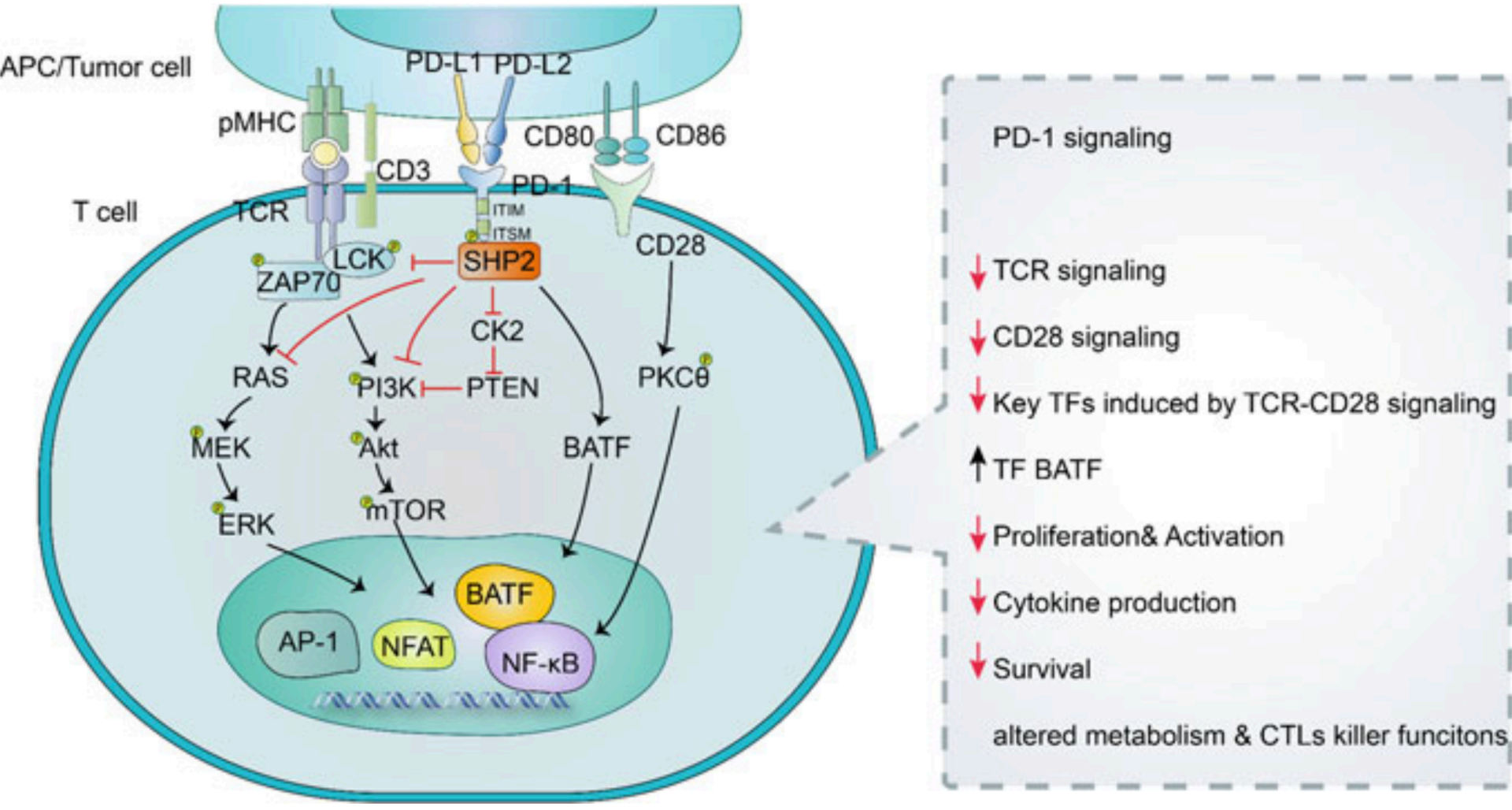


Associated with exhaustion phenotype

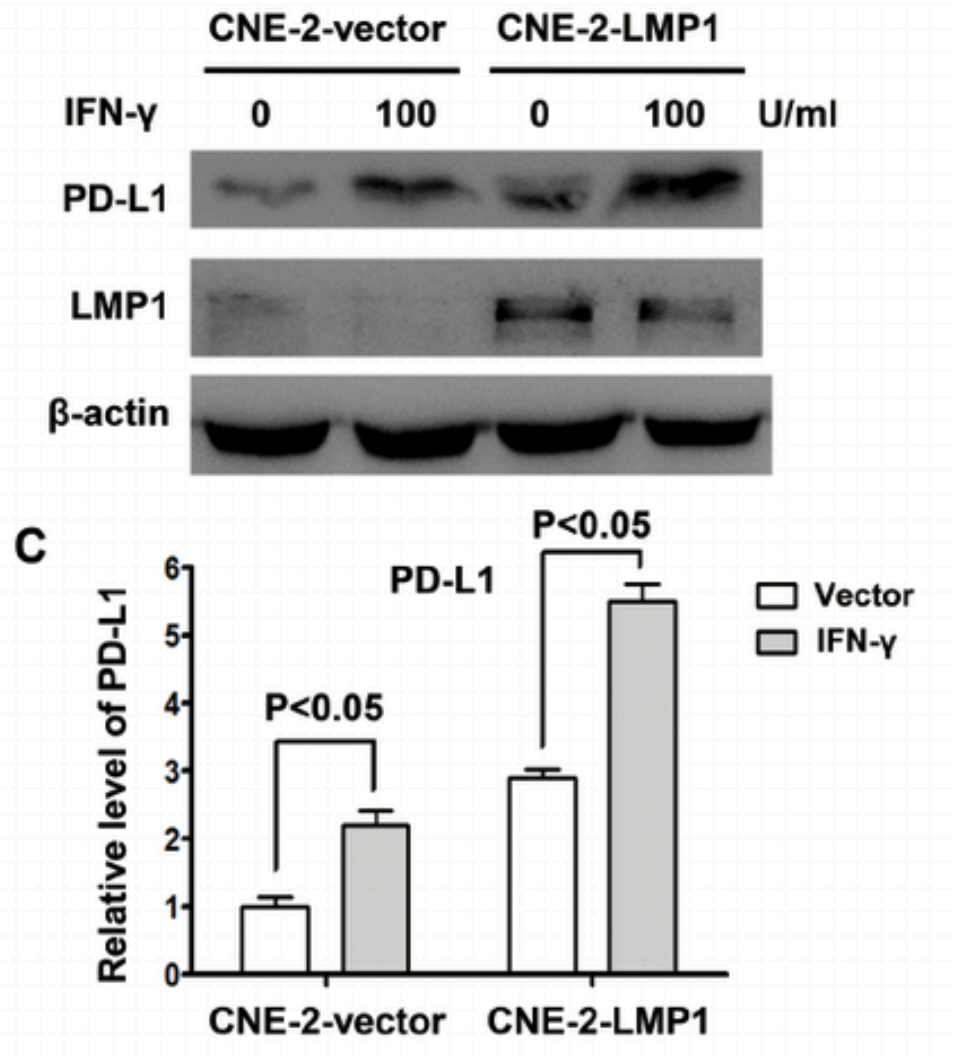
PD-1 co-localizes with CD28 in activated T cells



PD-1 blocks T cell signaling, mainly antigen activation signals



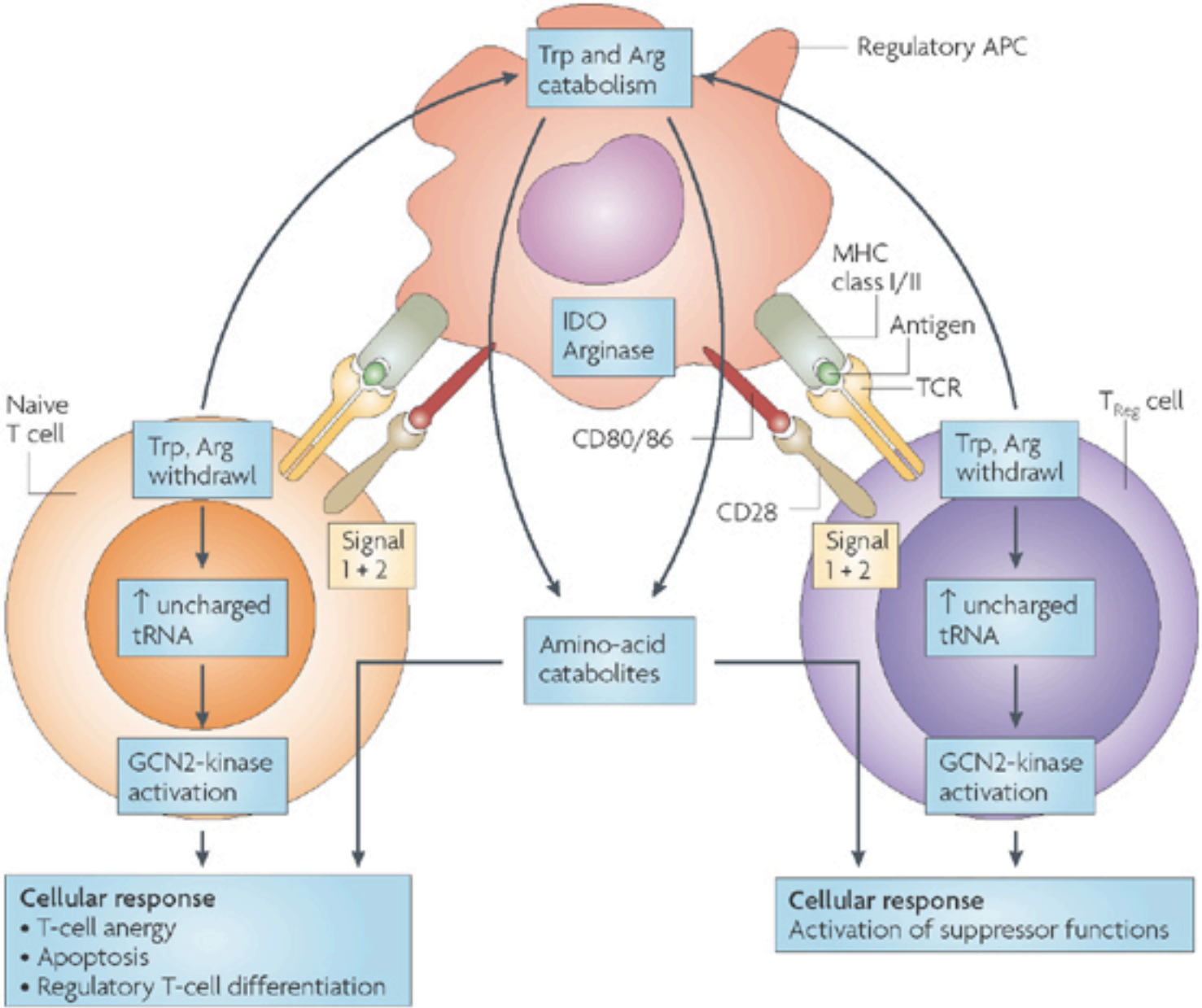
IFNγ induces PD-L1 expression



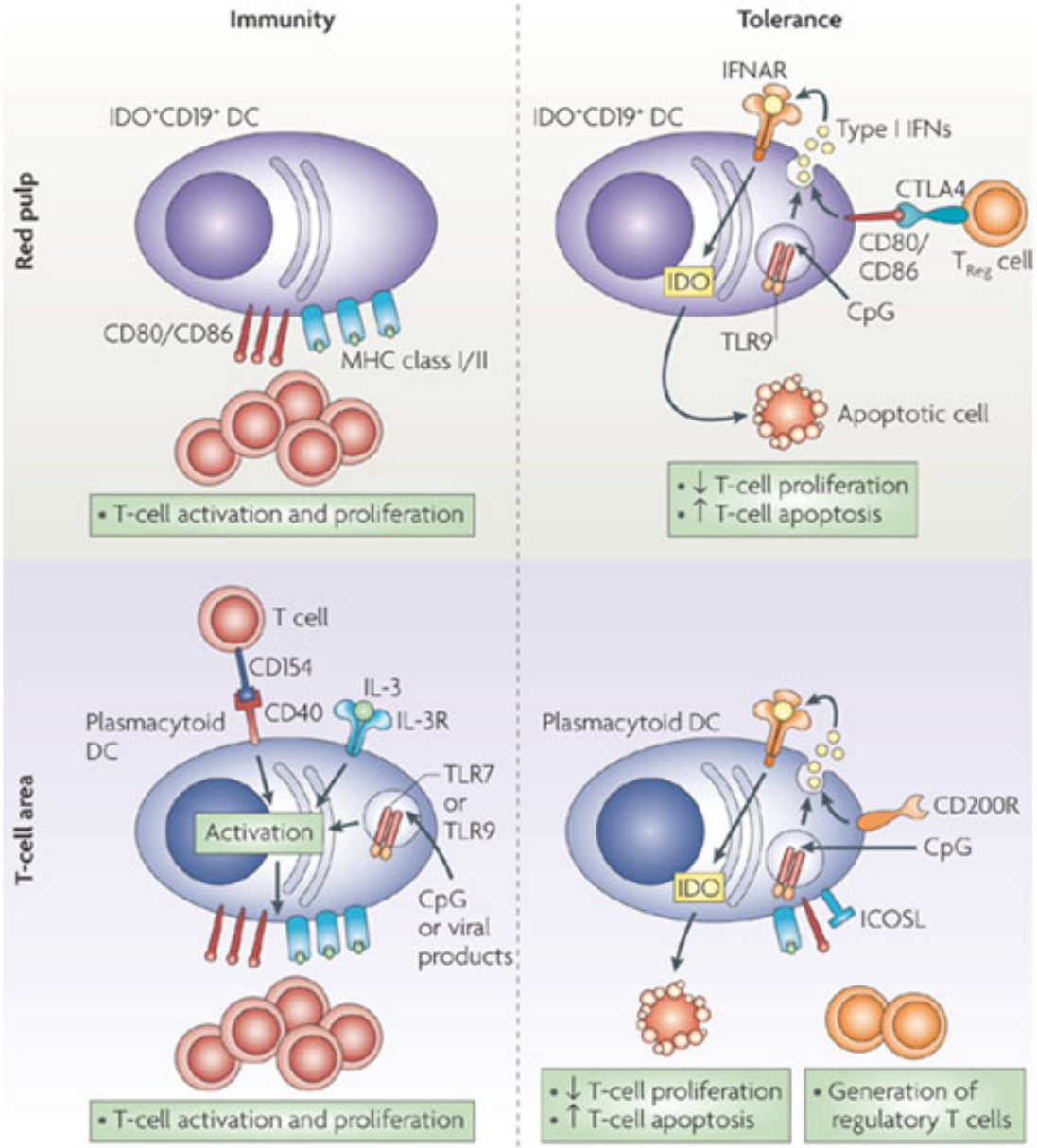
What about tolerogenic APCS?

Exs:
IFNγ –PD-L1
IFNγ – IDO
IL-6 + PGE2
Hypoxia

MECANISMOS REGULADORES



B lymphocytes can also suppress T cells



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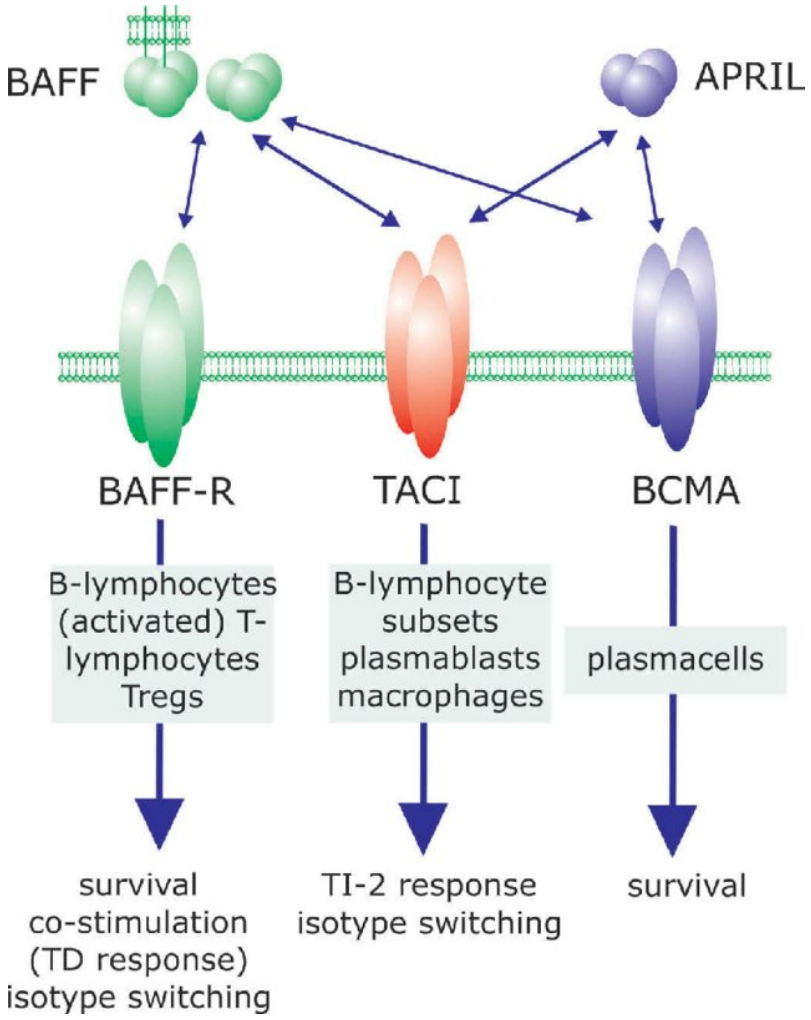
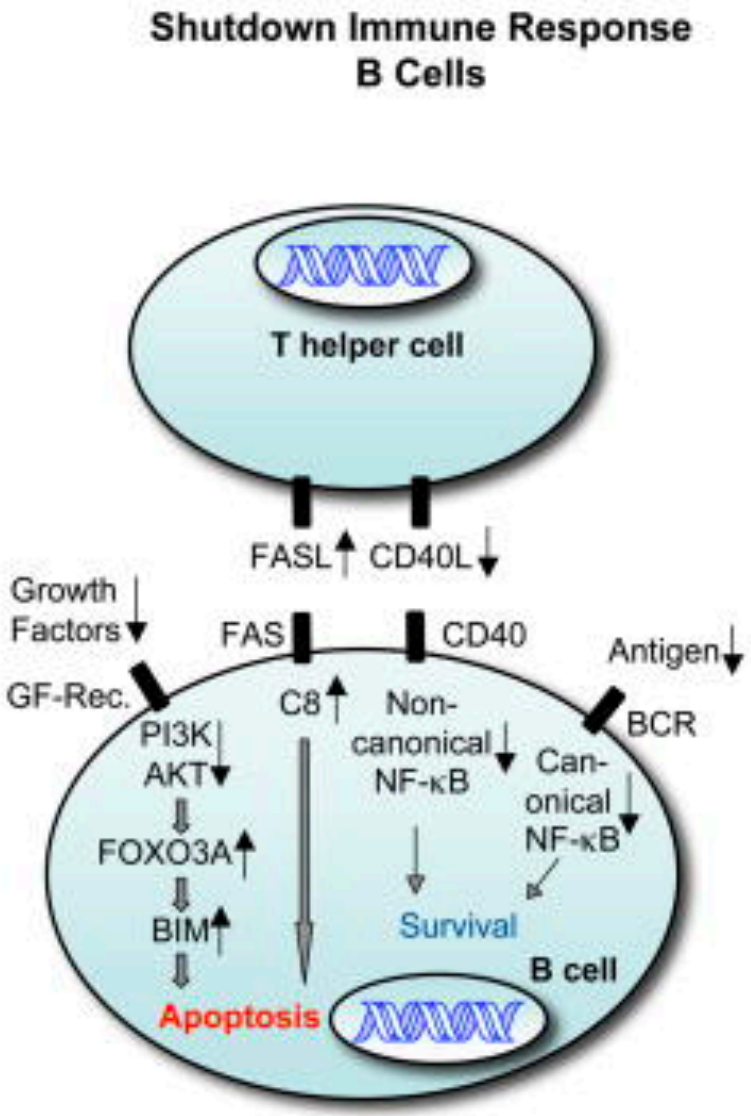
B lymphocytes

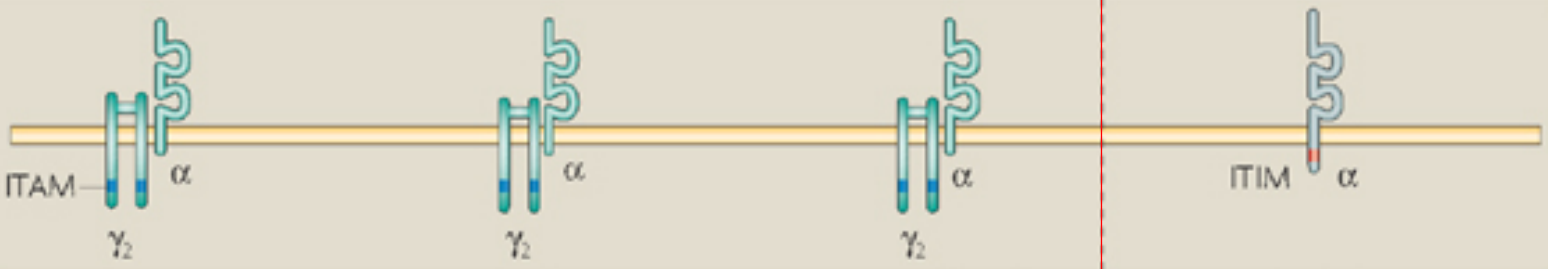
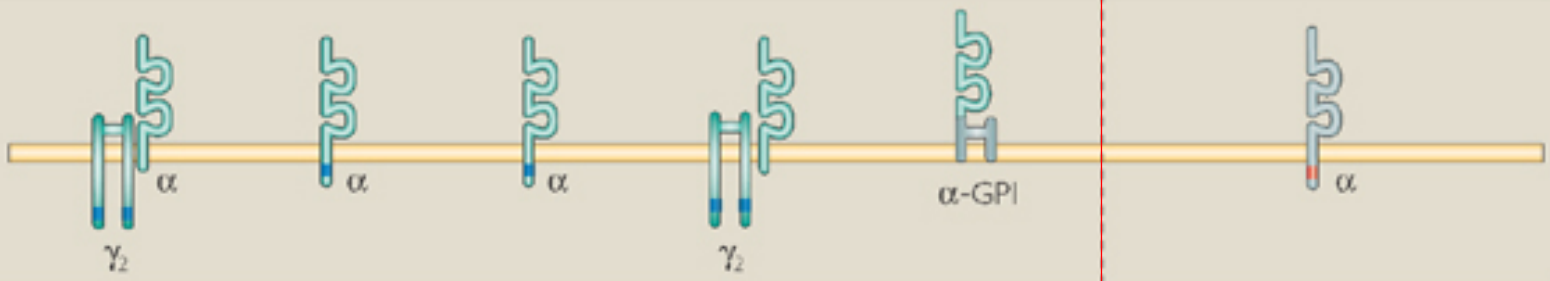
As infection is controlled – expression of cytokines that increase B lymphocyte survival decreases



INDUÇÃO DE MORTE POR FAS/FASL

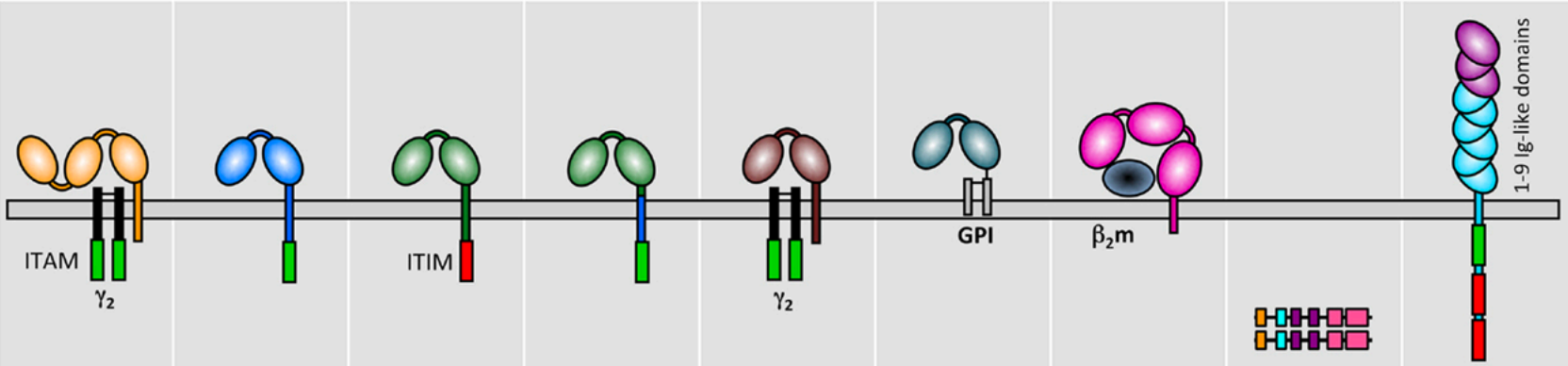


Fcγ RECEPTORS

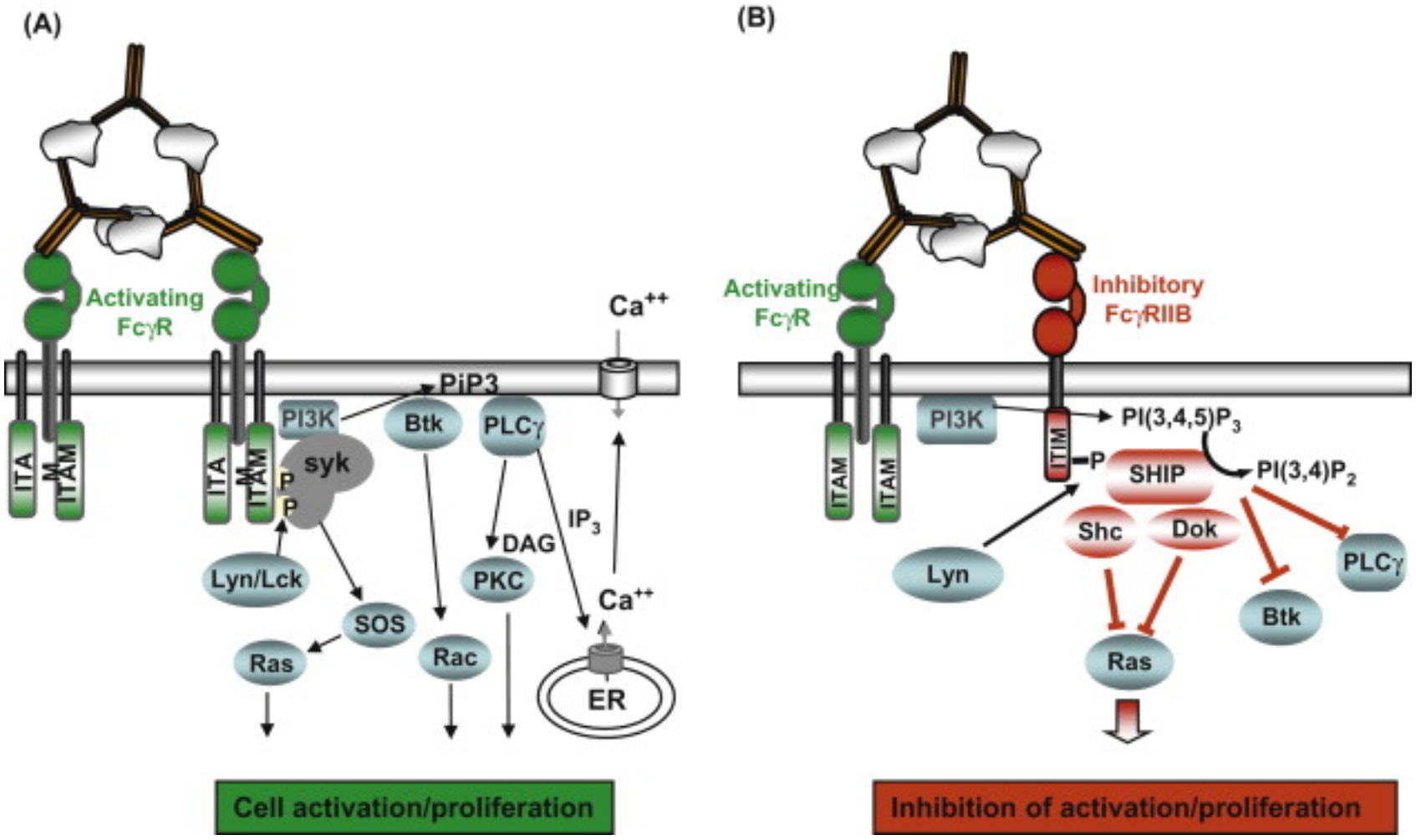
	Activating Fc receptors					Inhibitory Fc receptor
Mouse						
Structure						
Name	FcγRI		FcγRIII		FcγRIV	FcγRIIB
Affinity	High		Low to medium		Low to medium	Low to medium
Human						
Structure						
Name	FcγRI	FcγRIIA	FcγRIIC	FcγRIIIA	FcγRIIIB	FcγRIIB
Affinity	High	Low to medium	Low to medium	Low to medium	Low to medium	Low to medium
Alleles		FcγRIIA^{131H} FcγRIIA^{131R}		FcγRIIIA^{158V} FcγRIIIA^{158F}	NA1 NA2	FcγRIIB^{232I} FcγRIIB^{232T}

FcγRIIB in autoimmunity and infection: evolutionary and therapeutic implications
Kenneth G. C. Smith & Menna R. Clatworthy
Nature Reviews Immunology volume 10, pages 328–343 (2010

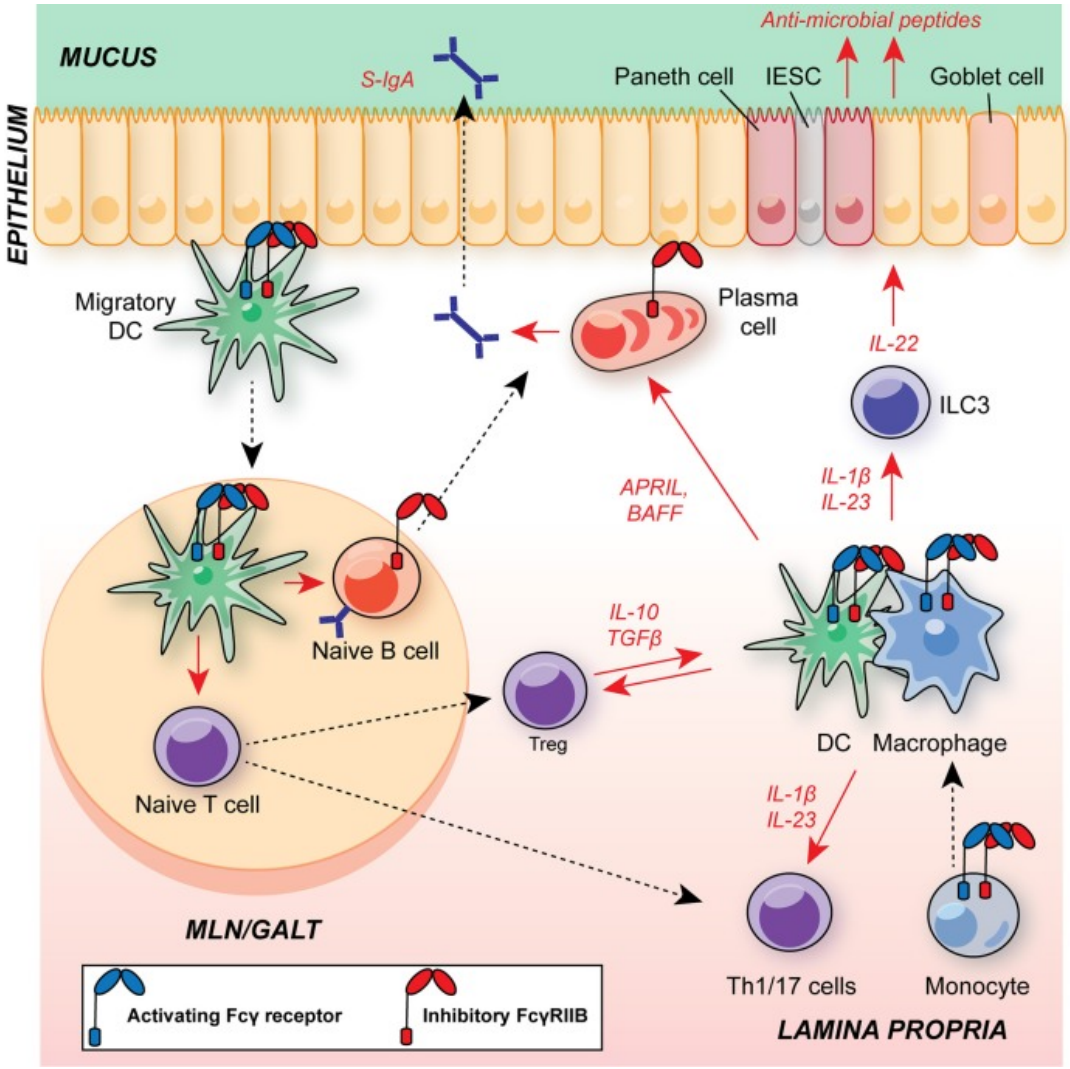
A little more detail on FcγR

Human IgG receptors									
Name	**FcγRI**	**FcγRIIA**	**FcγRIIB**	**FcγRIIC**[¤]	**FcγRIIIA**	**FcγRIIIB**	**FcRn**	**TRIM21**	**FcRL5**
CD	CD64	CD32A	CD32B	CD32C	CD16A	CD16B	-	-	CD307
									
B cell	-	-	+	-	-	-	-	+	+
T cell	-	-	-	-	-	-	-	+	-
NK cell	-	-	-[♯]	+[¤]	+	-	-	+	-
Mono/Macro	+	+	+/-	+[¤]	+	-	+	+	-
Neutrophil	(+)	+	+/-	+[¤]	-	+	+	+	-
Dendritic Cell[§]	+	+	+	-	-	-	+	+	-
Basophil	-	+	+	-	-	+/-	-	+	-
Mast cell	(+)	+	-	-	-	-	NA	+	-
Eosinophil	-	+	-	-	-	-	-	+	-
Platelet	-	+	-	-	-	-	NA	NA	-
Endothelium	-	-	-	-	-	-	+	+	-

FcR role is important in autoimmune diseases
cells express activating and inhibitory molecules – balance is key



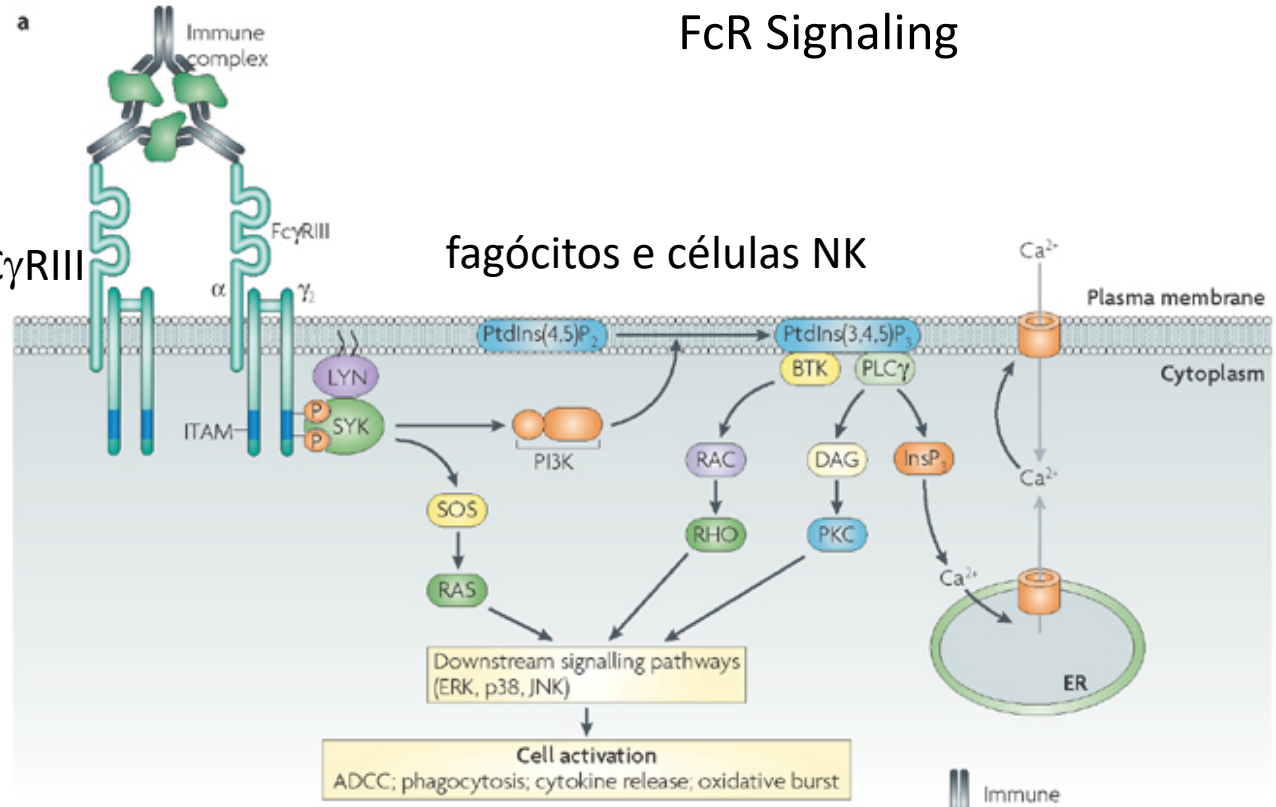
IgR balance in myeloid cells help control B lymphocytes

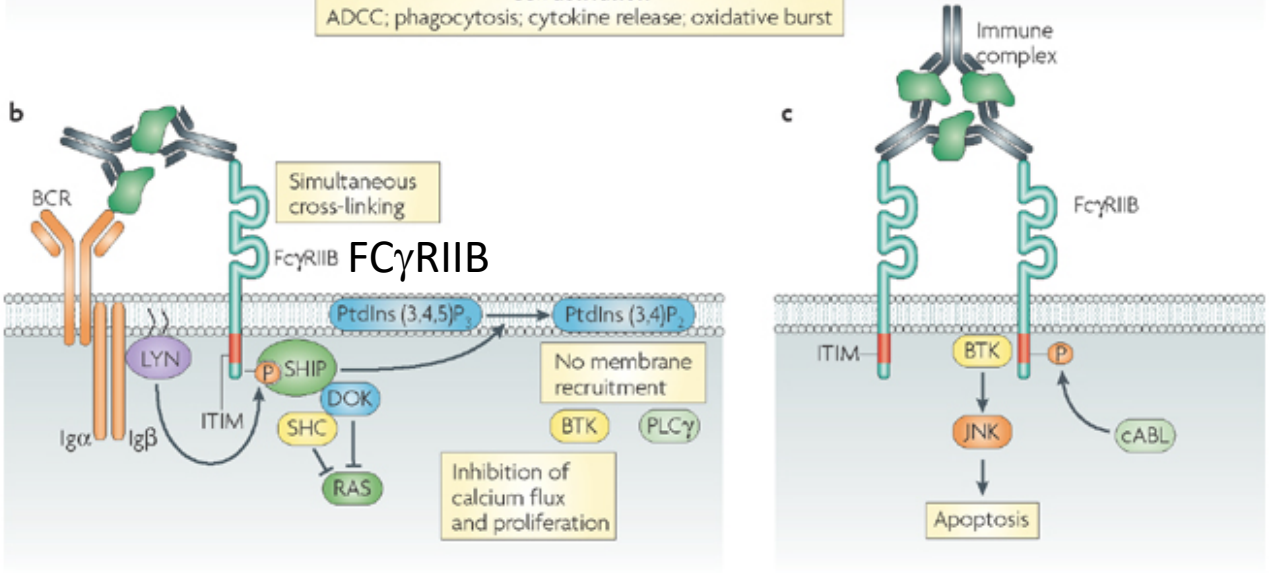


FcR Signaling

FCγRIII

fagócitos e células NK





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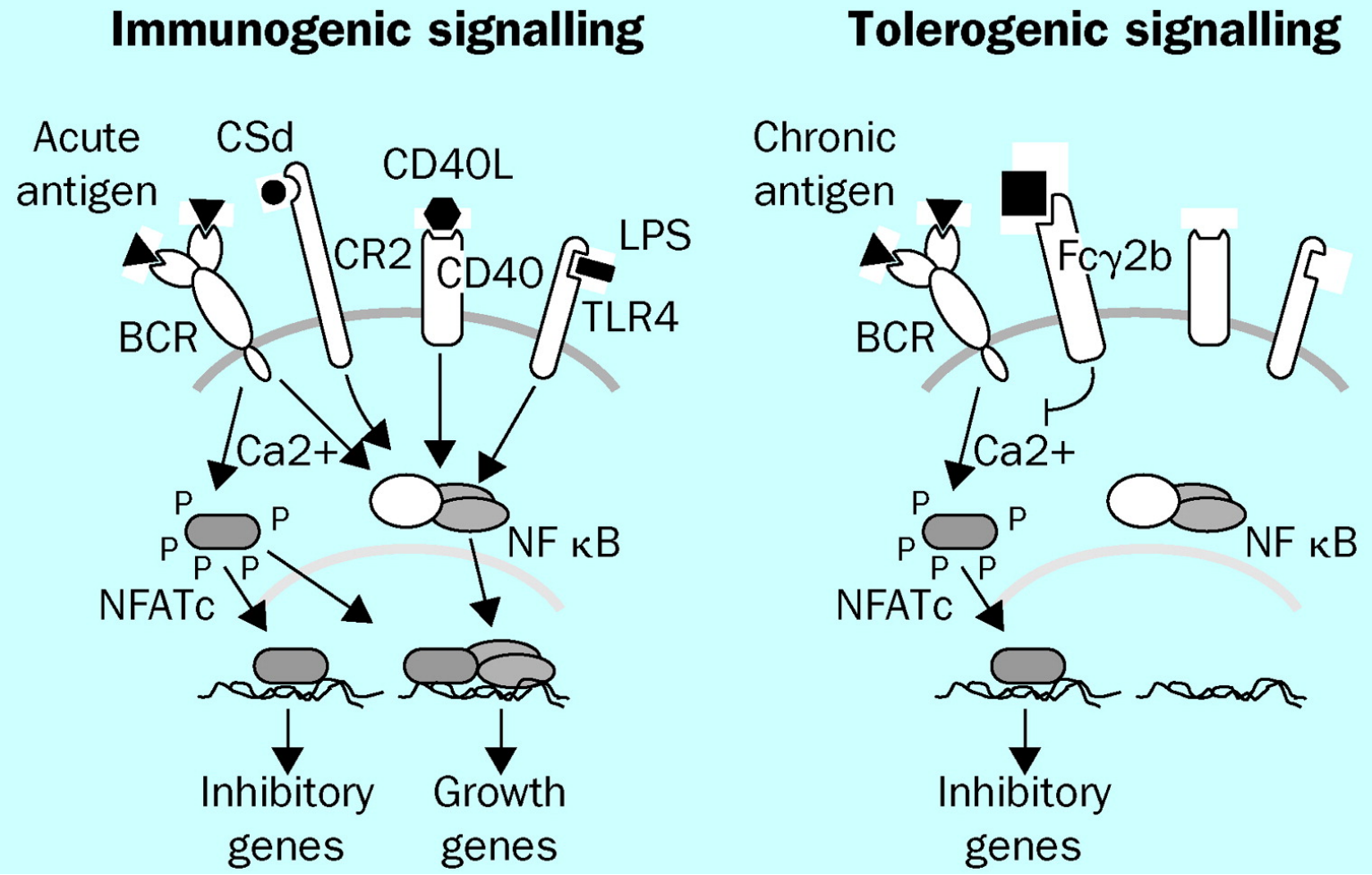
imunocomplex =
Ag + Ab

Response control



The Lancet 2001 357, 2115-2121DOI: (10.1016/S0140-6736(00)05185-0)