CODICE OPIS
PATOLOGIA MOLECOLARE
E IMMUNOPATOLOGIA
(1041600)

JNJC76IT

PATOLOGIA MOLECOLARE
(1041600_2)

Meccanismi di induzione della tolleranza che operano sui linfociti T

Tolleranza centrale per selezione timica positiva e negativa

- Delezione clonale (apoptosi) di linfociti T immaturi che riconoscono antigeni self con elevata avidità

Tolleranza periferica

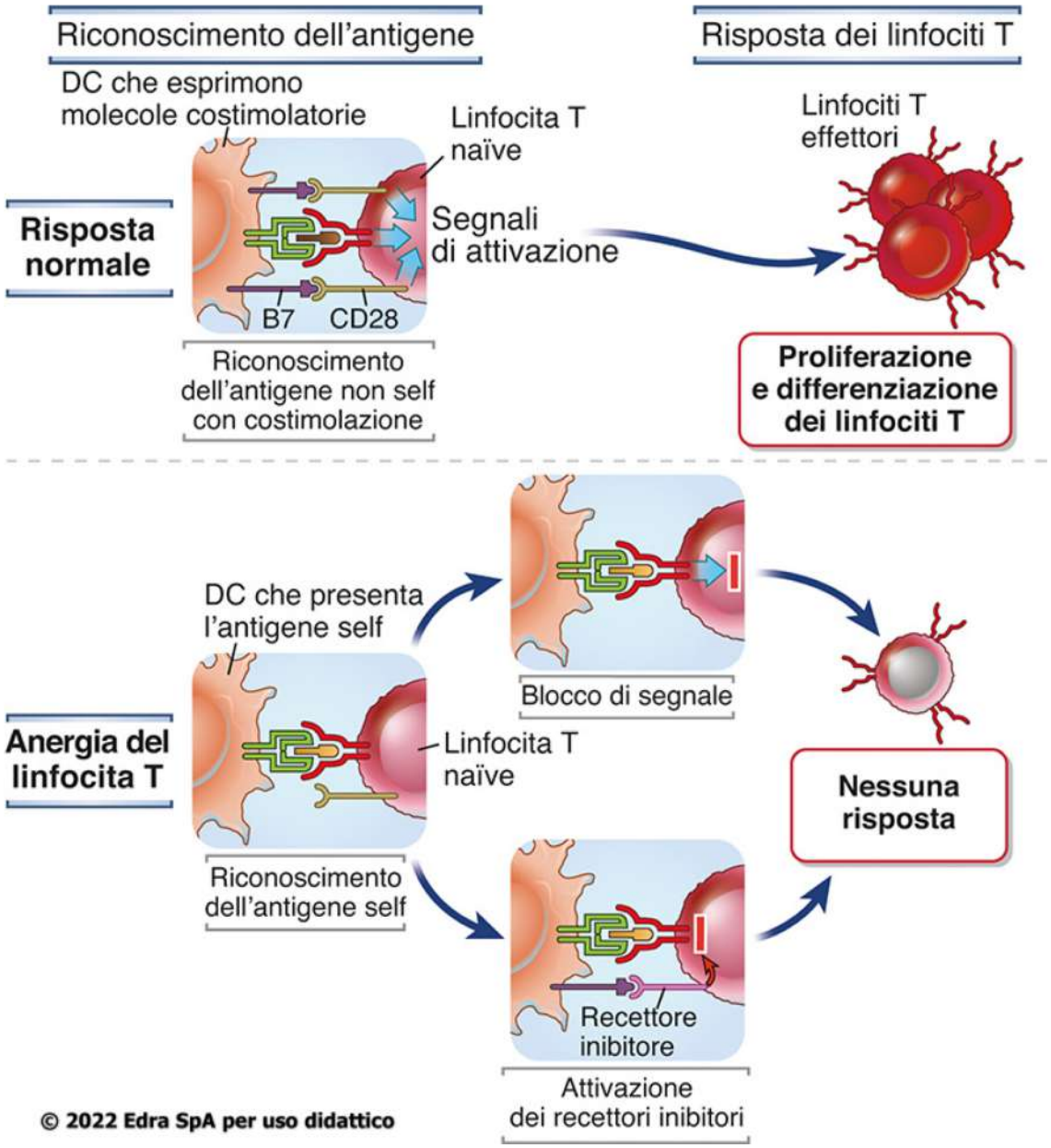
-inattivazione o anergia (parziale o totale) indotta dalla presentazione dell'antigene in assenza di segnali costimolatori e/o di attivazione dell'immunità innata

- delezione per apoptosi e AICD (activation-induced cell death)

-ignoranza immunologica (antigeni self a bassa concentrazione o anatomicamente sequestrati)

-blocco dell'attivazione (soppressione)

Meccanismi di anergia dei linfociti T



La risposta dei linfociti T è attivata quando le cellule riconoscono un antigene presentato da cellule accessorie (**APC**) e i recettori costimolatori sulle cellule T (come **CD28**) riconoscono molecole costimolatorie sulle APC (come **B7**). Se la cellula T riconosce un antigene self senza costimolazione, diventa **non responsiva all'antigene** a causa di un blocco nella segnalazione del complesso TCR o per l'ingaggio di recettori inibitori, "immune checkpoint inhibitors" (come **CTLA-4**; **PD-1**).

Il blocco della segnalazione può essere il risultato del **reclutamento di fosfatasi** nel complesso TCR o **dell'attivazione di ubiquitino-ligasi** che inducono degradazione delle proteine di segnalazione. Indipendentemente dal meccanismo, la cellula T rimane vitale ma non è in grado di rispondere all'antigene self.

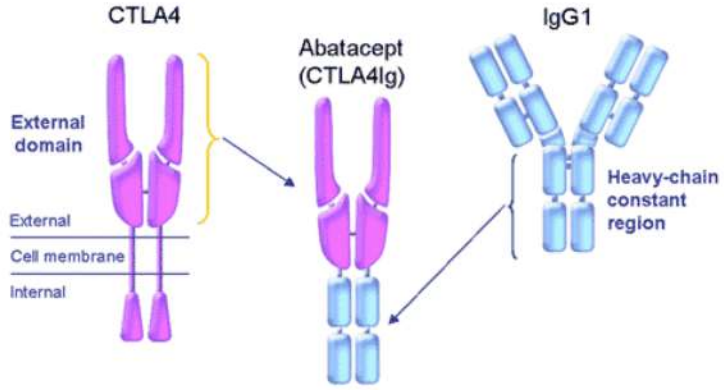
Modulazione vs potenziamento della risposta linfocitaria T

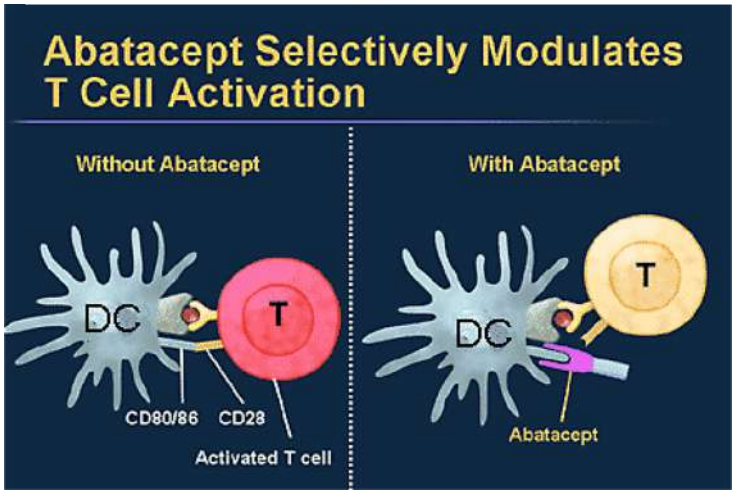
Uso di anticorpi monoclonali (mAb) con funzioni opposte nelle malattie autoimmuni rispetto ai tumori che agiscono sulla costimolazione e i recettori inibitori

AUTOIMMUNITA'

(obiettivo: inibire risposte T autoreattive)

ABATACEPT (farmaco biologico, mAb usato nella cura della RA; sCTLA4-Ig fusione del dominio extracellulare di CTLA4 con Fcγ1)



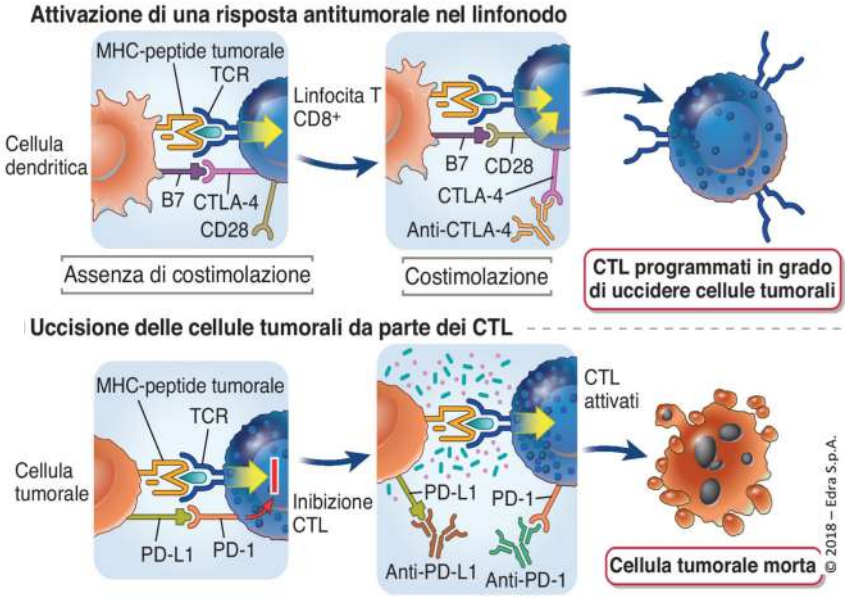


Tolleranza **Immunità**

TUMORE

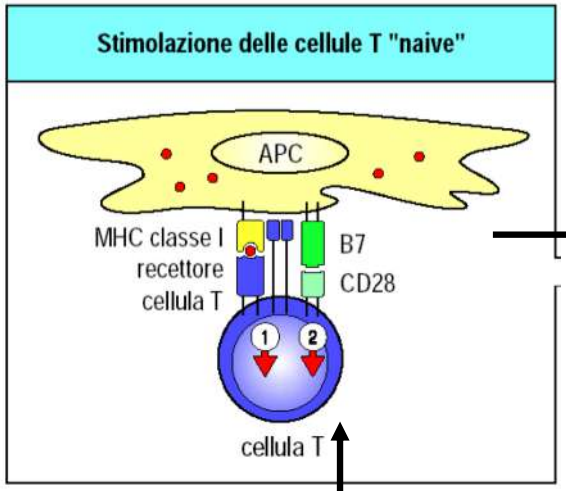
(obiettivo: potenziare risposte linfocitarie T specifiche per antigeni tumorali)

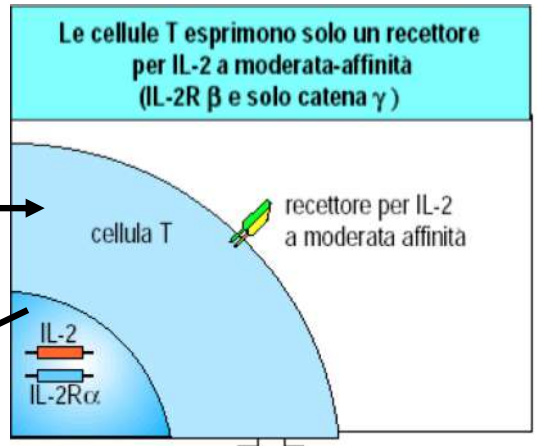
Blocco dei checkpoints immunologici nell'immunoterapia dei tumori usando anticorpi che bloccano CTLA4, PD1 o PDL1

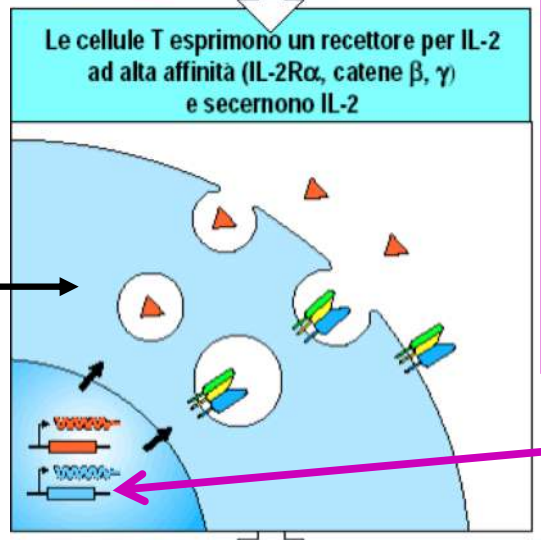


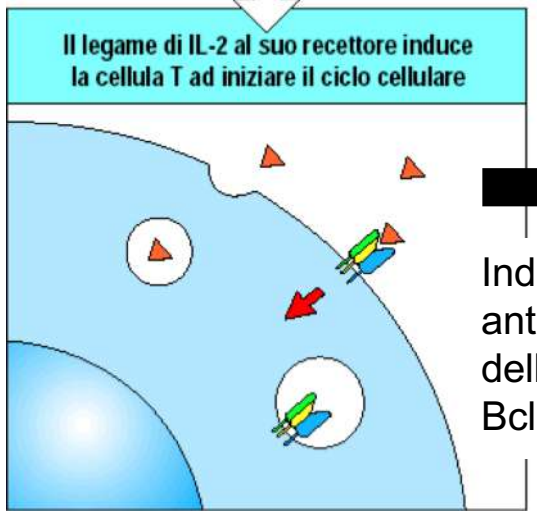
I pazienti neoplastici presentano spesso una risposta cellulare T inefficace verso i tumori a causa dell'aumentata espressione di CTLA4 e PD1, sulla superficie delle cellule T e l'espressione del PDL1 sulle cellule tumorali. Anticorpi anti-CTLA4 bloccanti (A), anti-PD1 o anti-PDL1 (B) sono altamente specifici per trattare diversi tipi di tumori in stadio avanzato, rimuovendo l'inibizione dei linfociti T tumore-specifici. Gli anticorpi anti-CTLA4 funzionano bloccando CTLA4 sui linfociti T effettori e suiilinfociti T regolatori (Treg).

Linfocita T CD4+ "Naive"









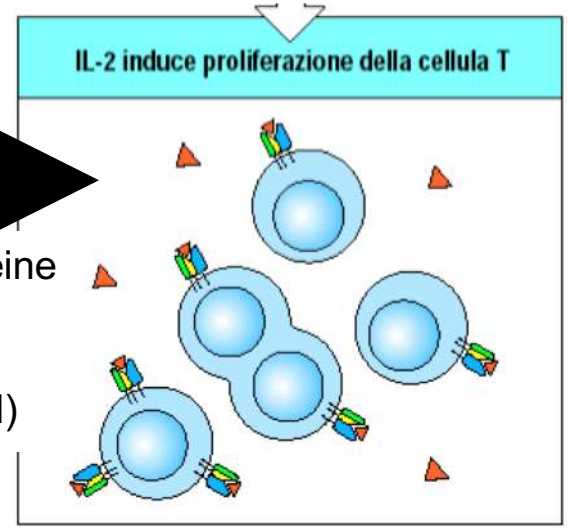
Importanza della costimolazione (2° segnale) nell'attivazione di un linfocita T "naive"

l'assenza di costimolazione ha molti effetti tra i quali la mancata espressione del recettore x IL2 ad alta affinita' ($IL2R\alpha\beta\gamma_c$) e la produzione di IL-2

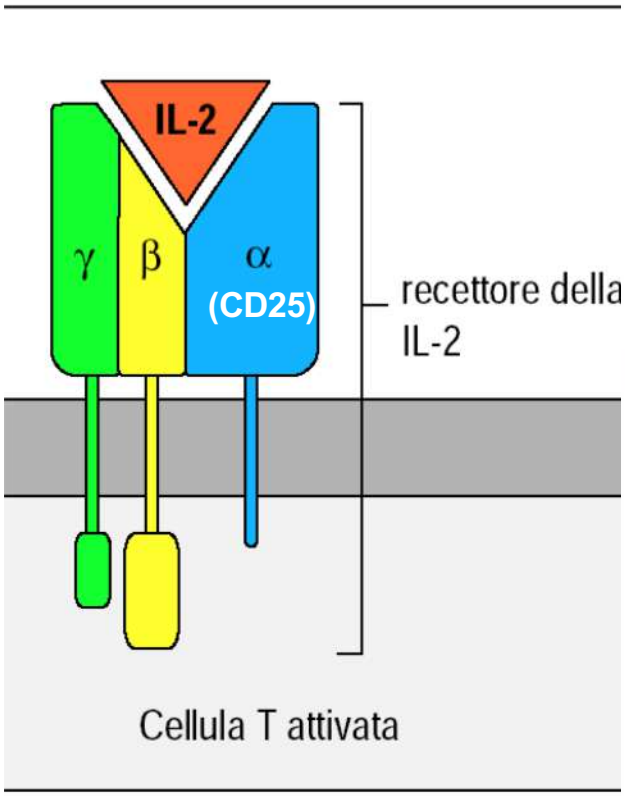
espressione di IL2Rα (CD25)

LINFOCITA T ATTIVATO
in presenza di costimolazione

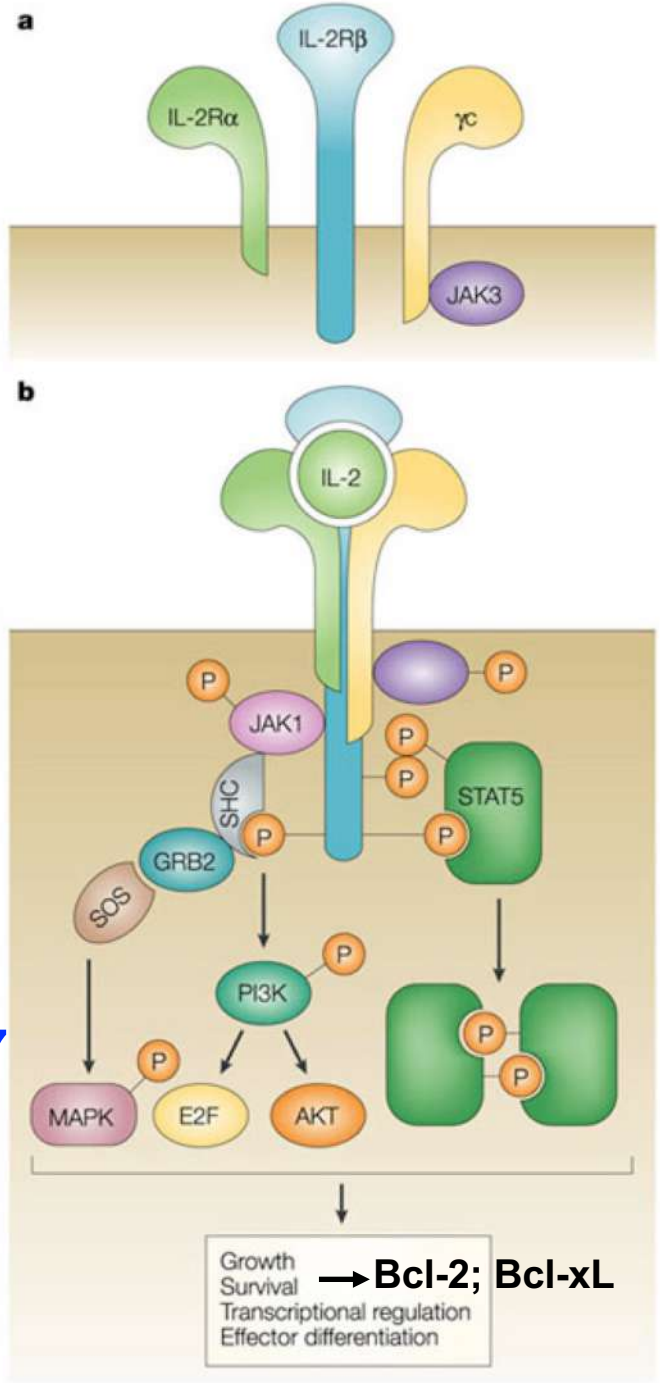
Induzione di proteine anti-apoptotiche della famiglia Bcl-2 (bcl-2; bcl-xl)



Recettore dell'IL-2 e trasduzione del segnale

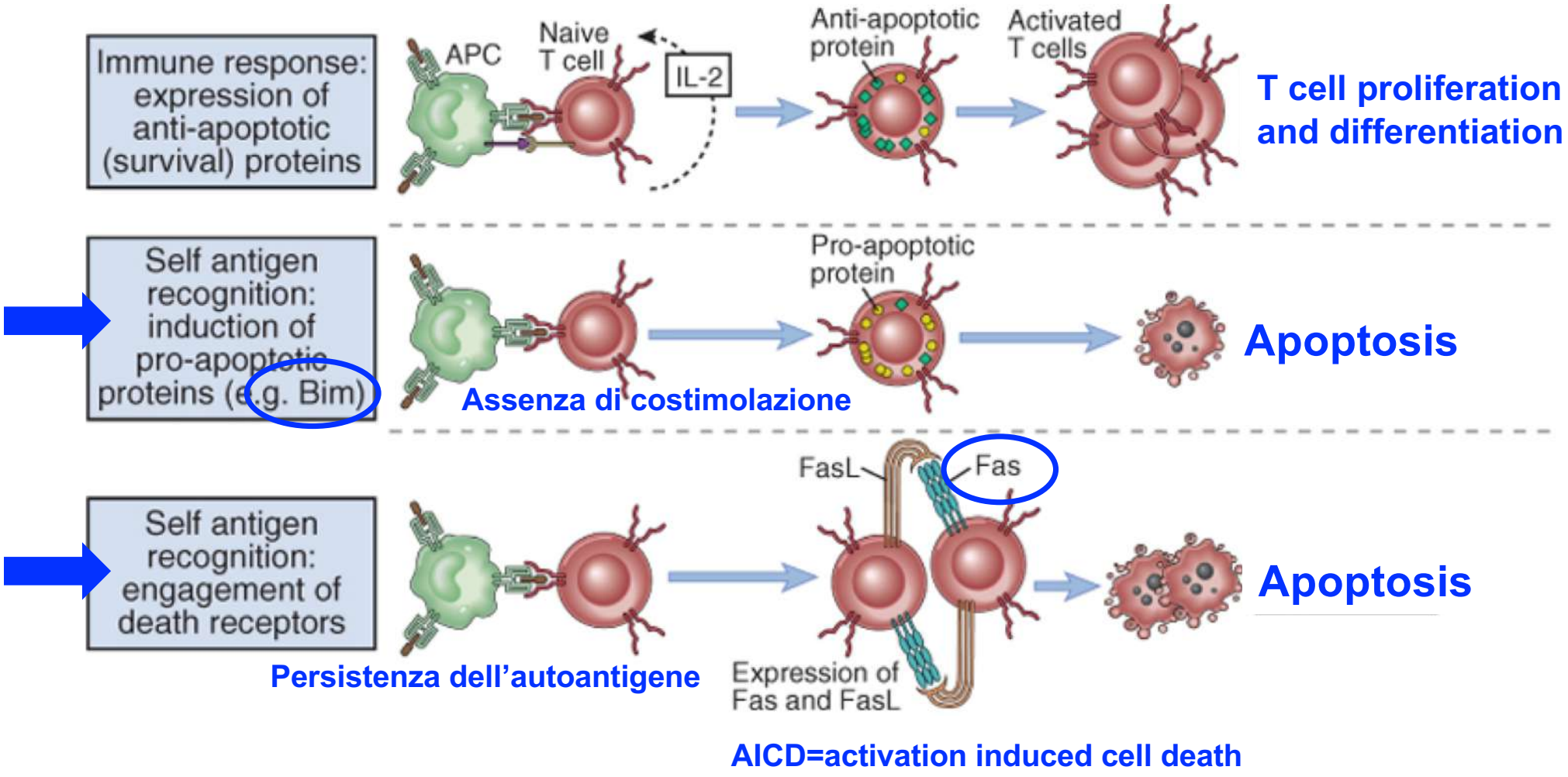


Catena γ in comune con i recettori di:
IL4, IL7, IL9, IL15, IL21, IL27



a | The high-affinity interleukin-2 receptor (IL-2R) consists of three subunits: the α-chain of the IL-2R (IL-2R; also known as CD25), the β-chain of the IL-2R (IL-2R; also known as CD122) and the common cytokine-receptor γ-chain (c; also known as CD132). It is thought that in the absence of IL-2, these subunits are not pre-assembled on the surface of an IL-2R-expressing T cell.
b | The binding of IL-2 to IL-2R α drives the association of this subunit with IL-2R β and the γc to form a stable heterotrimer, which then leads to the initiation of signal transduction. Janus activated kinase 3 (JAK3) molecules that are associated with the γc, and JAK1 molecules that are associated with IL-2Rβ, phosphorylate key tyrosine residues in the cytoplasmic tail of IL-2Rβ, the γc and the JAK molecules themselves. This amplifies the association of these tyrosine kinases and induces the association of the adaptor SHC (SRC-homology-2-domain-containing transforming protein C), and either signal transducer and activator of transcription 5 (STAT5) or STAT3, with the cytoplasmic tail of IL-2Rβ. The complexed SHC allows activation of the mitogen-activated protein kinase (MAPK)- and phosphatidylinositol 3-kinase (PI3K)–AKT-signalling pathways. Tyrosine residues in STAT5 are also phosphorylated, leading to the dimerization of STAT5 and its translocation to the nucleus where it regulates STAT5-responsive genes. GRB2, growth-factor-receptor-bound protein 2; SOS, son of sevenless homologue.

Morte cellulare indotta dall'attivazione dei linfociti T da parte di un antigene self (delezione)



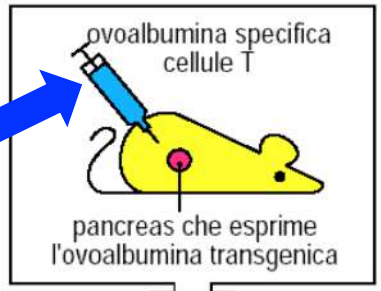
Self antigen-induced death of peripheral T lymphocytes. In response to immunogenic antigens and growth factors, lymphocytes express anti-apoptotic proteins that promote their survival and allow immune responses to develop (top panel). Self antigens may kill T cells by inducing an excess of pro-apoptotic proteins (middle panel), or by coexpression of Fas and FasL and engagement of Fas (lower panel).

Fattori che determinano immunogenicità o tollerogenicità di un antigene proteico

	Condizioni che STIMOLANO LE RISPOSTE IMMUNITARIE	Condizioni che favoriscono la TOLLERANZA
Quantità	Dosi ottimali, variano in base all'antigene	Dosi elevate
Persistenza	Breve (eliminati dalla risposta immunitaria)	Prolungata, associata ad un prolungato legame con i recettori per l'antigene
Via di ingresso; localizzazione	Assenza negli organi linfoidi primari Subcutanea, intradermica;	Presenza negli organi linfoidi primari Intravenosa, mucosale;
Presenza di adiuvanti	Antigeni con adiuvanti: inducono molecole costimolatorie e citochine	Antigeni senza adiuvanti: bassi livelli di molecole costimolatorie e citochine
Caratteristiche delle APC	Cellule dendritiche mature: livelli elevati di molecole costimolatorie	Cellule dendritiche immature (quiescenti): bassi livelli di molecole costimolatorie e citochine

Meccanismi di tolleranza periferica: la quantità di un autoantigene è cruciale nel determinare la delezione o l'ignoranza immunologica

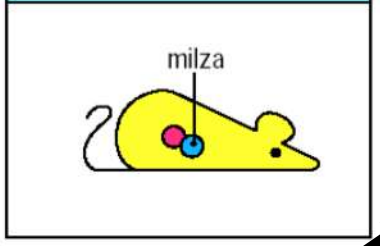
Iniezione di cellule T CD8+ specifiche per l'ovoalbumina



Due gruppi di topi che esprimono nel pancreas l'ovolbumina transgenica a livelli bassi o alti

3 giorni

4 settimane

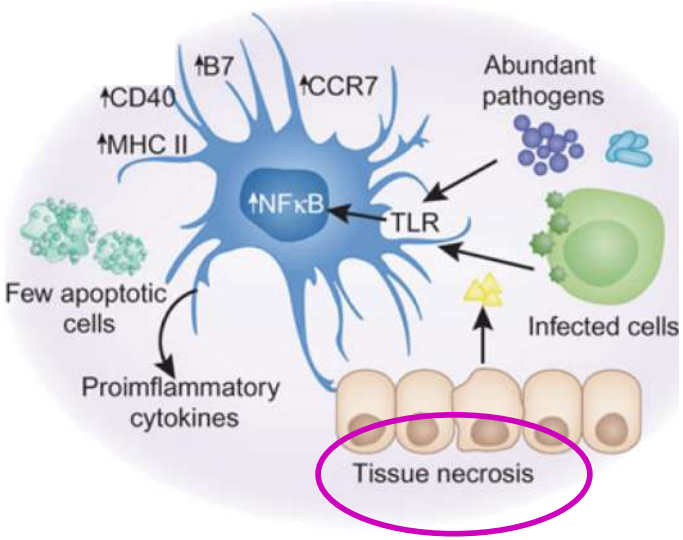


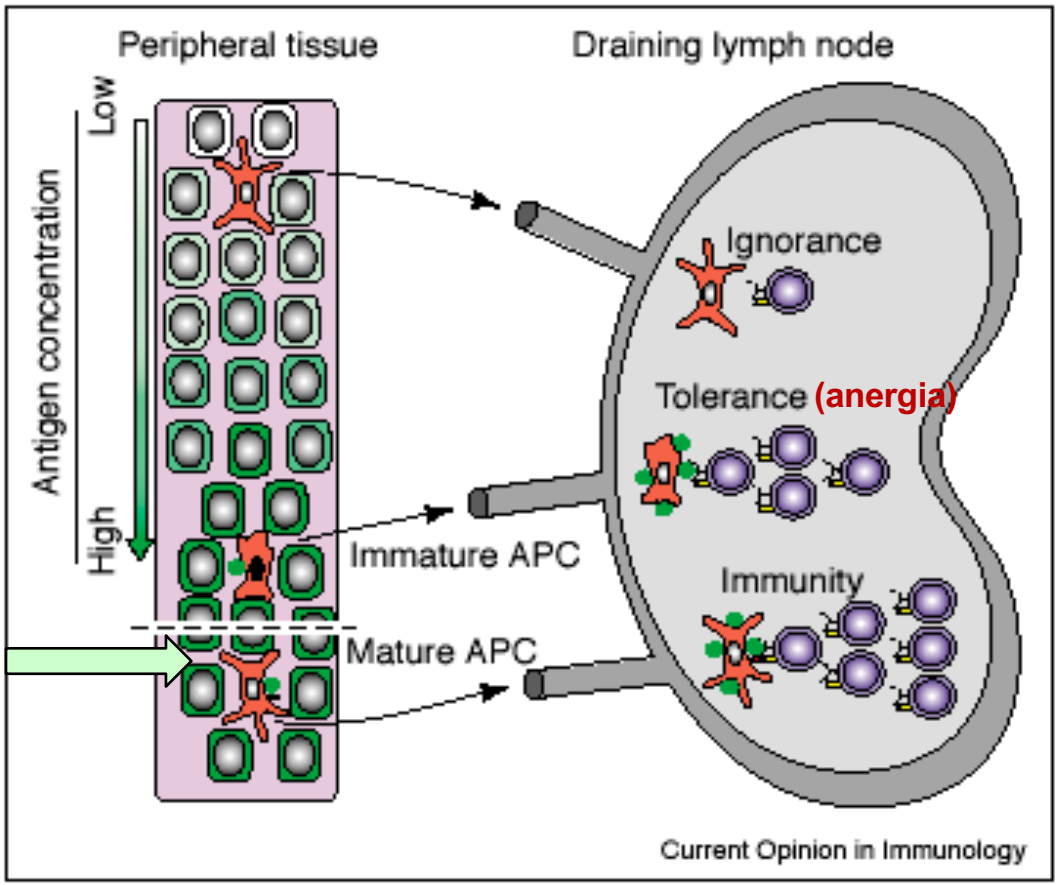
	Espressione pancreatica di ovoalbumina in un topo transgenico	
	Alta	**Bassa**
Cellule prese dalla regione dei linfonodi		
Proliferazione delle cellule T CD8 specifiche per l'ovoalbumina	+	–
Cellule prese dalla milza		
Ripresa delle cellule T specifiche per l'ovoalbumina dalla milza	–	++
Spontanea proliferazione delle cellule T specifiche per l'ovoalbumina	–	–
Risposta delle cellule T specifiche per l'ovoalbumina contro l'ovoabumina in vitro	–	++
Meccanismi di tolleranza periferica	**Delezione**	**Assente**

In vitro

I livelli di autoantigene e lo stato di maturazione delle APC influenzano la natura della risposta negli organi linfoidi secondari

maturazione delle APCs
indotta da PAMPs e DAMPs
(condizioni infiammatorie)





Quando i tessuti esprimono **bassi livelli di autoantigene** non sufficienti per la presentazione da parte delle APC, allora **le cellule T naive** nei linfonodi restano in uno stato di **ignoranza immunologica.**

Quando invece i tessuti esprimono livelli di **autoantigene sufficienti** per la presentazione allora le cellule T naive diventano tolleranti o si attivano a seconda dello stato di maturazione delle APC: **APC immature inducono uno stato di tolleranza,**

APC mature inducono immunità (ma anche autoimmunità)

Definizione degli stati immunologici

Si definisce **ignoranza immunologica** quella condizione in cui cellule T reattive non hanno incontrato l'antigene target. Non c'è alcuna risposta immunitaria

Si definisce **tolleranza** quella condizione in cui cellule T reattive hanno incontrato l'antigene target ma sono incapaci di una risposta immunologica efficace

Si definisce **immunità** quella condizione in cui cellule T reattive hanno incontrato l'antigene e sono capaci di montare una risposta immunitaria efficiente

Meccanismi di induzione della tolleranza che operano sui linfociti T

Tolleranza centrale per selezione timica negativa

-Delezione (apoptosi) di linfociti T immaturi che riconoscono antigeni self con affinità elevata

Tolleranza periferica

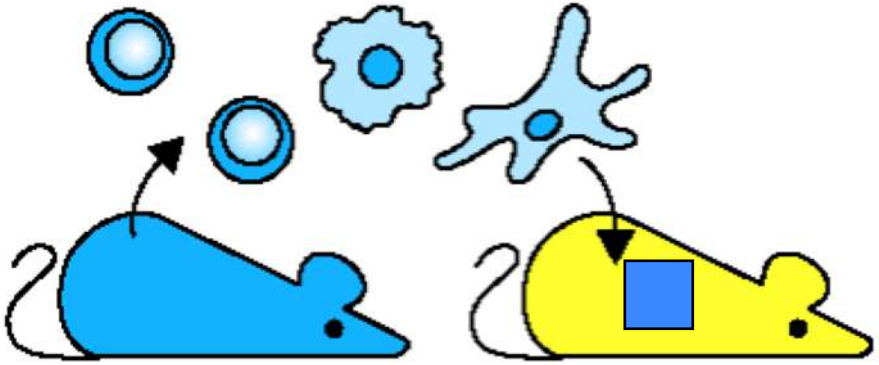
-inattivazione o anergia

-delezione per apoptosi

-ignoranza immunologica

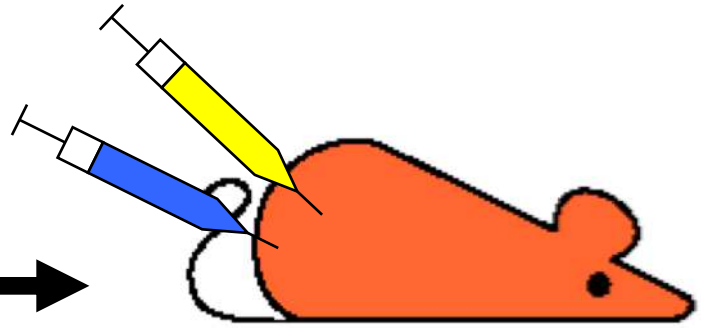
-blocco dell'attivazione (soppressione mediata dai linfociti Treg)

Tolleranza dominante e specifica indotta dalle cellule T regolatorie

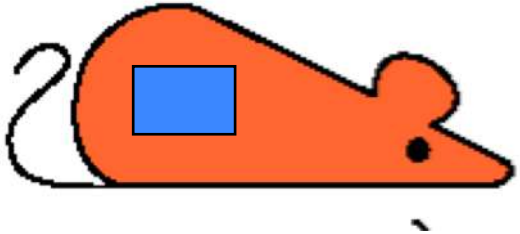


Topo neonato (chimerico in giallo) è reso tollerante al trapianto allogenico mediante trasferimento di cellule di midollo osseo

Ciò non si verifica in un topo ricevente adulto ma...

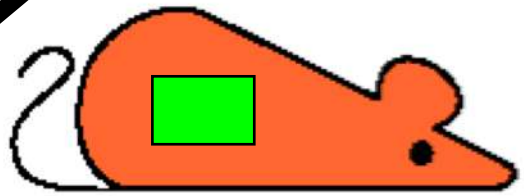


Un topo adulto inoculato con linfociti T del topo tollerizzato (giallo) e con cellule ematopoietiche allogeniche del donatore azzurro…



SONO OK!!

……..non rigetta il trapianto di cute del donatore azzurro

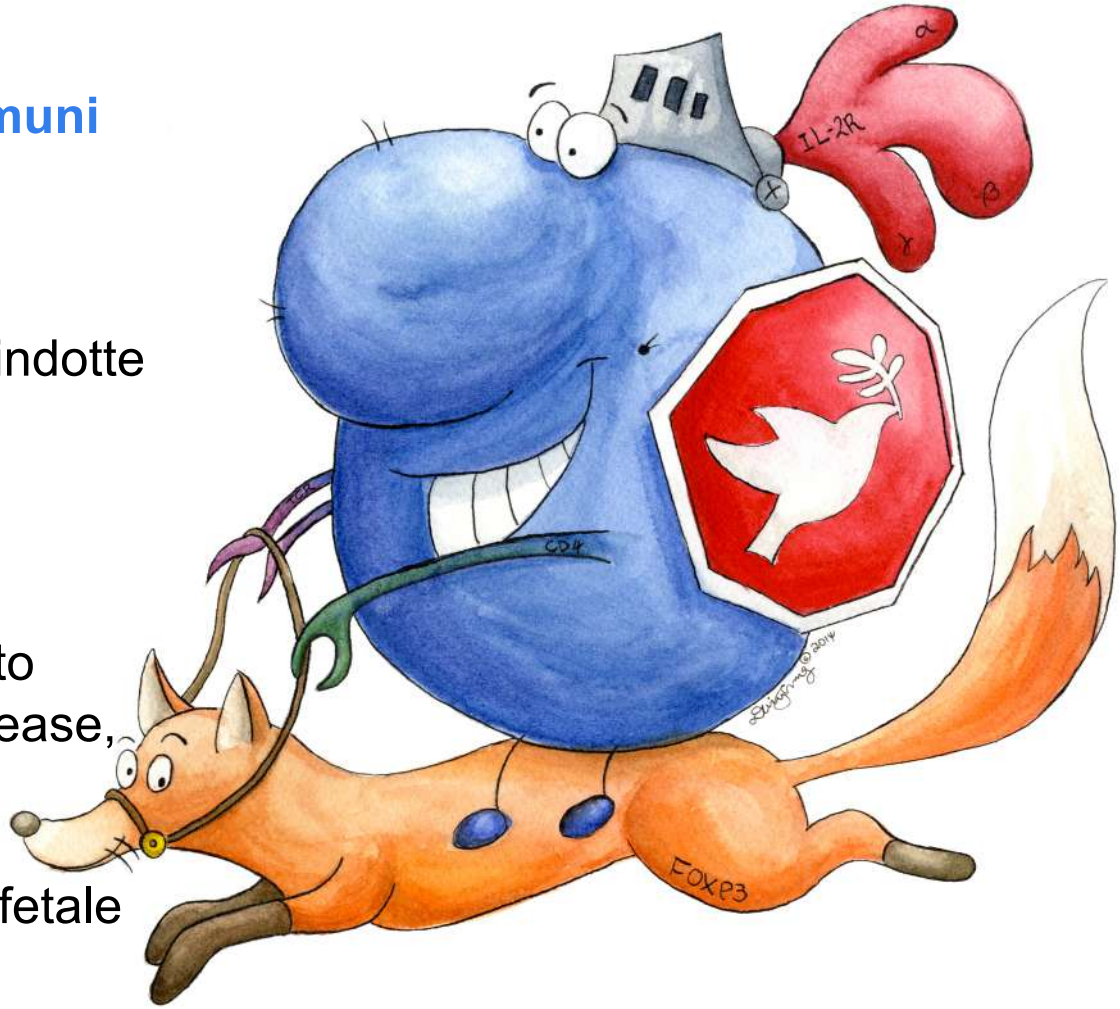


NON SONO OK!!

……..ma rigetta il trapianto di un altro donatore (soppressione specifica)

Le cellule T regolatorie

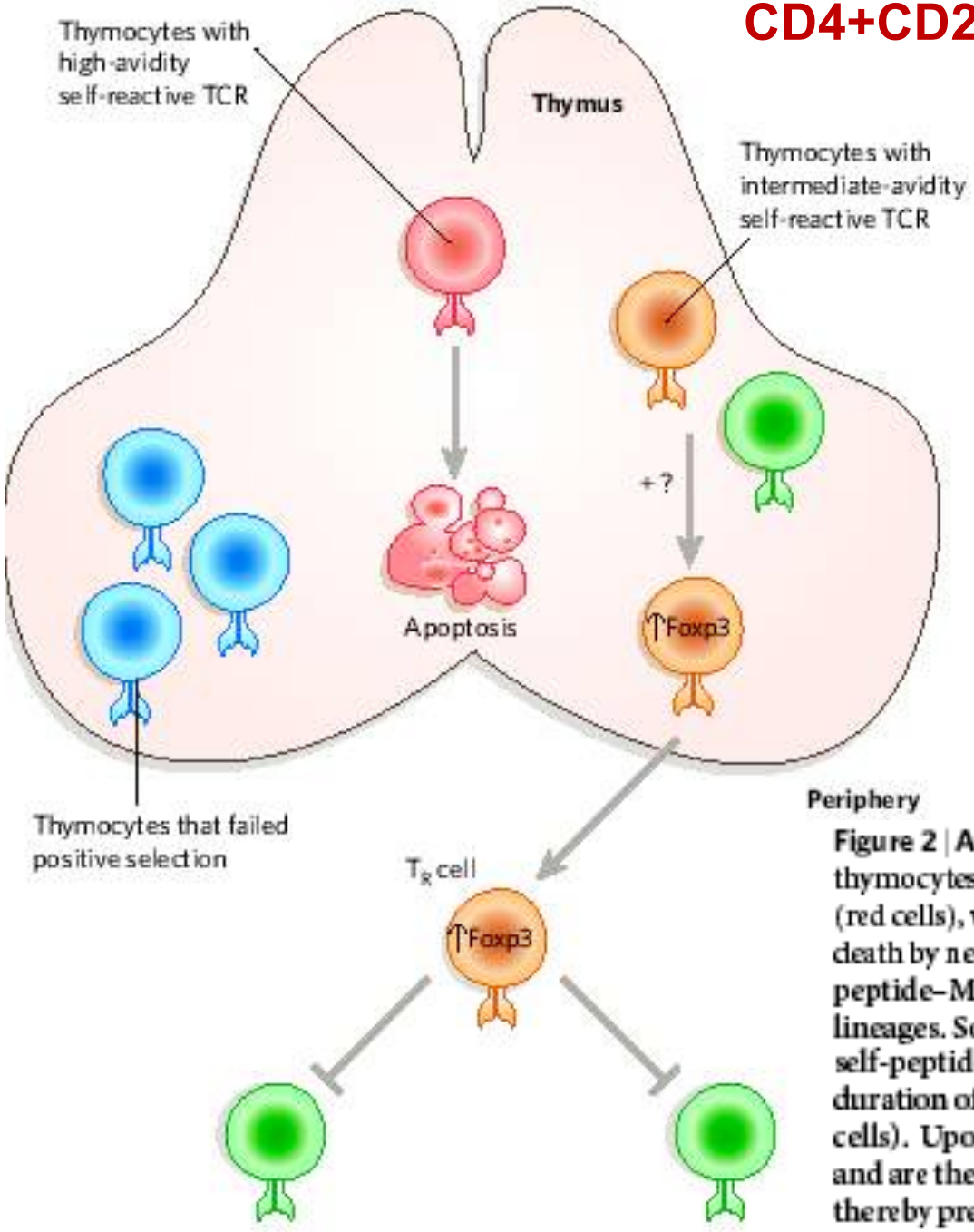
- **prevengono le patologie autoimmuni**
- prevengono le allergie
- prevengono le patologie di organo indotte dalle infezioni
- stabiliscono tolleranza al trapianto
- prevengono la reazione del trapianto verso l'ospite (graft versus host disease, GvHD)
- promuovono la tolleranza materno-fetale



Nei tumori, possono inibire l'attivazione di un'efficace risposta immunitaria antitumorale ma anche prevenire gli effetti di un'eccessiva infiammazione legata al tumore

Differenziamento dei timociti a cellule “Treg timiche o naturali”

CD4+CD25+FoxP3+CTLA4+ Treg



Modello dell’affinità per la selezione dei timociti

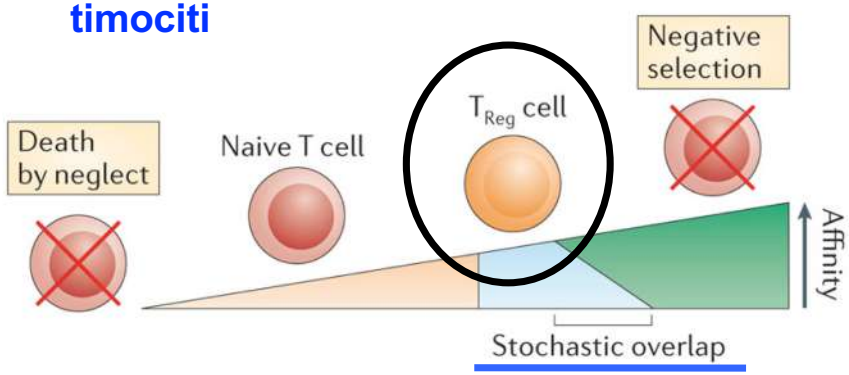


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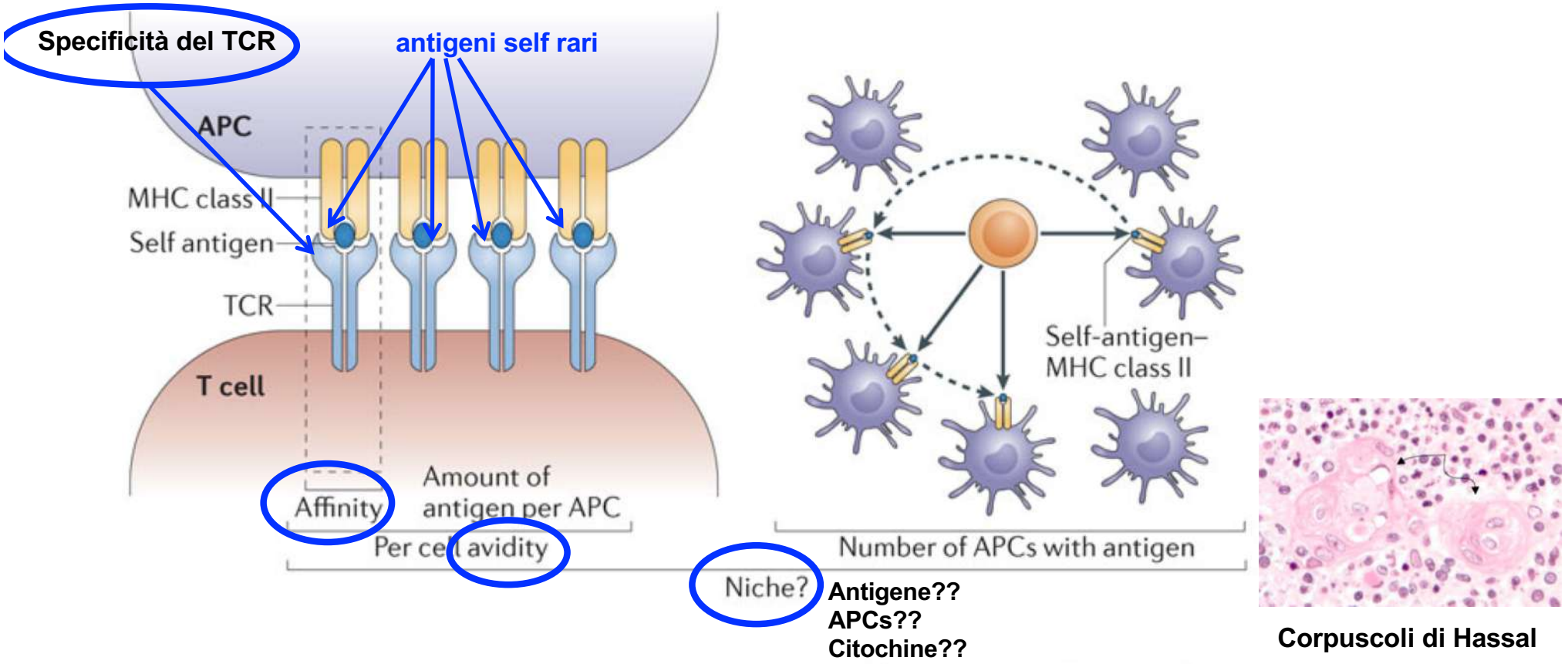
Figure 2 | Alternative fates for developing thymocytes. During development, thymocytes with a high affinity for self-peptide–MHC complexes are deleted (red cells), whereas thymocytes with TCRs that do not react to self undergo death by neglect (blue cells). Thymocytes with a low avidity for self-peptide–MHC are positively selected into the conventional $CD4^+$ and $CD8^+$ lineages. Some self-reactive thymocytes with an intermediate avidity for self-peptide ligands upregulate Foxp3 in response to increased strength or duration of a TCR signal in combination with an unknown signal (yellow cells). Upon Foxp3 induction, thymocytes commit to the T_R-cell lineage and are therefore capable of keeping other T-cell responses in check, thereby preventing autoimmunity.

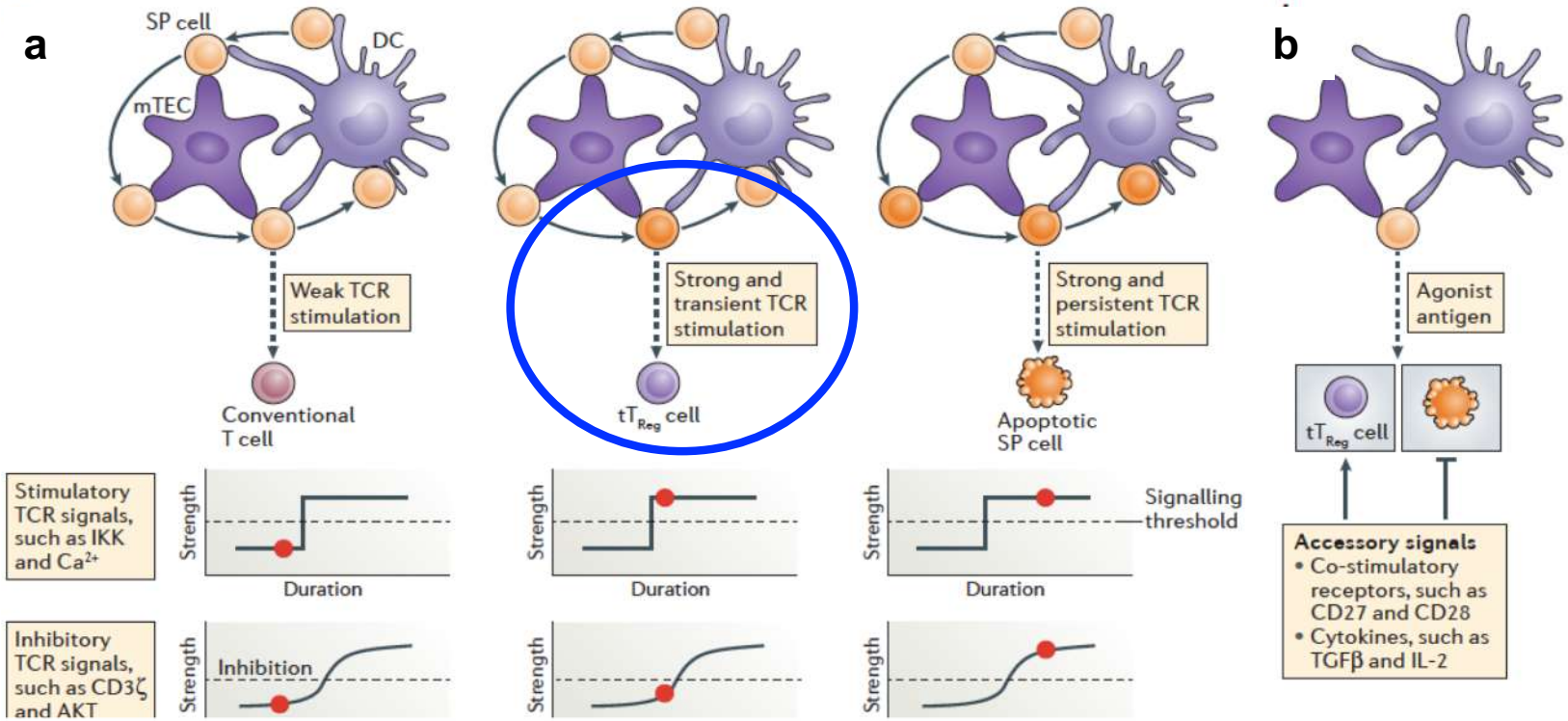
Fattori che determinano il differenziamento delle Treg nel timo



Corpuscoli di Hassal

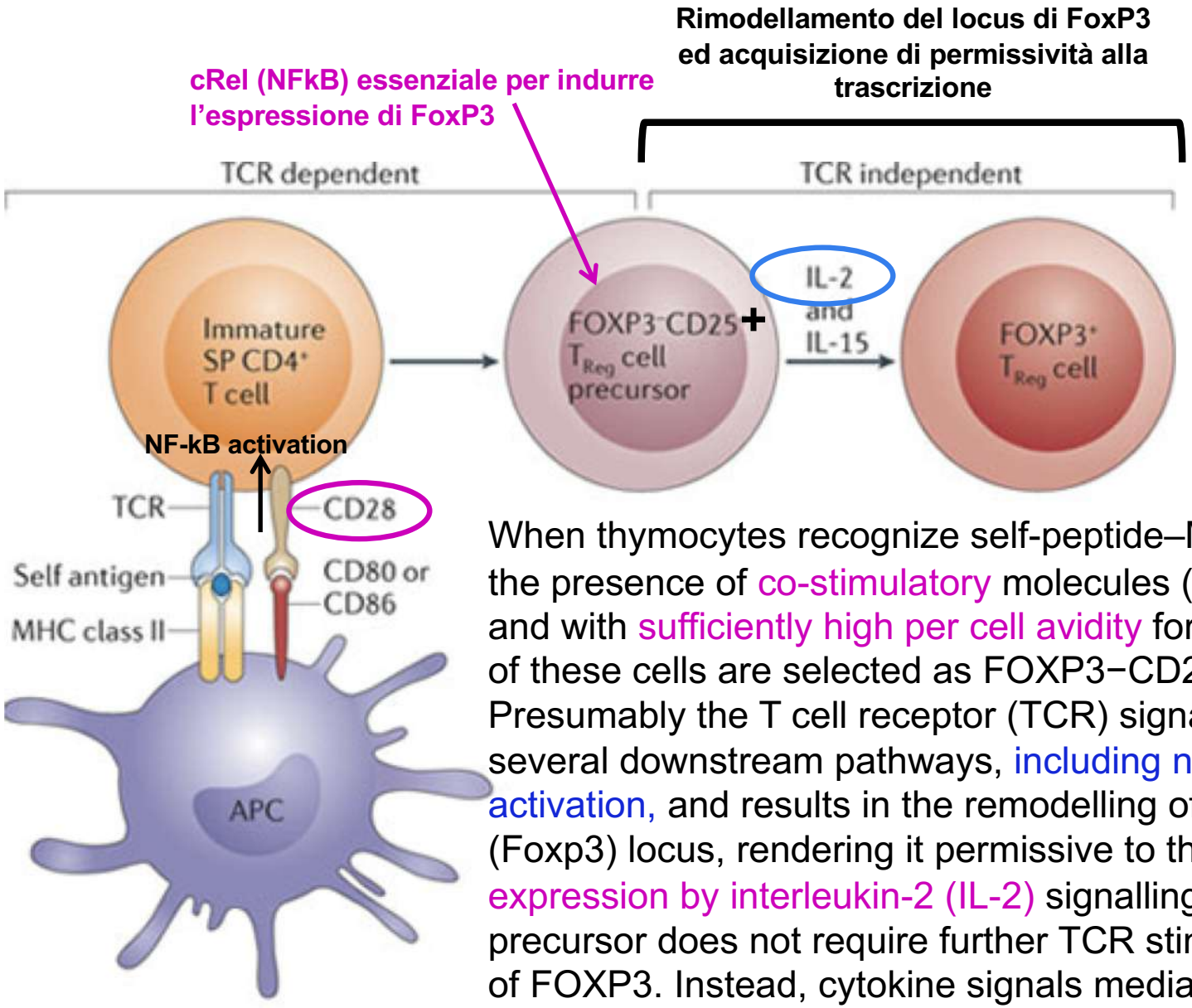
The T cell receptor (TCR) interactions that determine regulatory T (T_{Reg}) cell development may be affected by several factors. The first factor is the **affinity** of a single TCR molecule for a single self-peptide–MHC class II complex presented by a thymic antigen-presenting cell (APC). The second is the **avidity** of a single T cell–APC interaction, which is determined by the number of peptide–MHC ligands on the APC in conjunction with the TCR affinity. Third, **the size of the antigen-specific T_{Reg} cell 'niche'** — which is likely to be determined by the total number of APCs presenting a given self antigen, together with the affinity and avidity — affects the probability of T cell–APC encounter and thus determines the number of T_{Reg} cells that can differentiate at a given time. Finally, it is possible that T cell interactions with multiple APCs favour different cell fate decisions, such as negative selection rather than T_{Reg} cell differentiation.

A model of Treg cell fate specification by TCR and accessory signals



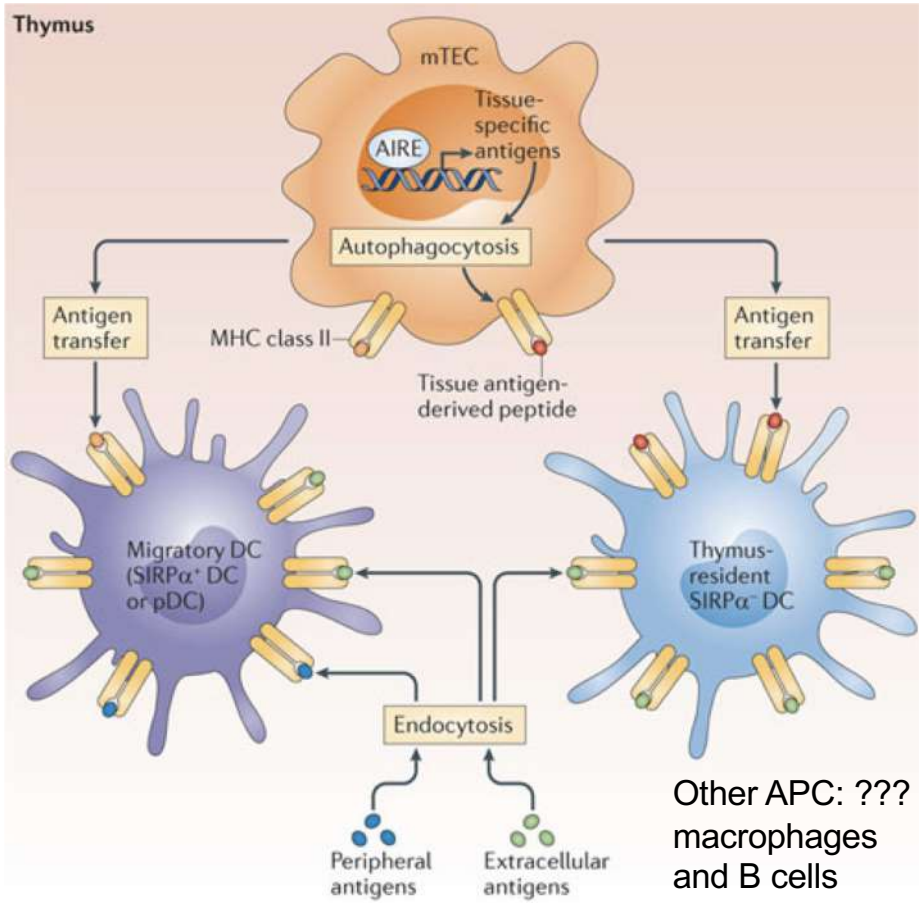
a | CD4 single-positive (SP) thymocytes are educated in the medulla by sampling antigens presented by medullary thymic epithelial cells (mTECs) and bone marrow-derived antigen-presenting cells such as dendritic cells (DCs). Antigen-triggered T cell receptor (TCR) signalling has a principal role in dictating the SP cell fates. Weak TCR stimulation promotes the continuous maturation of SP cells into conventional T cells. Transient stimulation of SP cells by high-affinity antigens is probably sufficient to activate the regulatory T (T_{Reg}) cell-stimulatory signalling pathways, including IκB kinase (IKK) and Ca^{2+}, whereas the activities of T_{Reg} cell-inhibitory signalling modules, including CD3ζ and AKT, may not reach an optimal level (signalling threshold demarcated by the dashed line). Persistent stimulation of SP cells by high-affinity antigens activates both T_{Reg} cell stimulatory and inhibitory signalling pathways, which is not permissive for thymus-derived T_{Reg} (tT_{Reg}) cell differentiation but may trigger T cell clonal deletion. The red dot depicts the level of antigen engagement (duration) and the signalling activity of the indicated modules (strength). **b** | Despite a relatively distinct mode of TCR signalling being involved in the control of tT_{Reg} cell differentiation and T cell deletion, the recognition of agonist antigen can induce overlapping T cell fates under certain conditions. Accessory signals that are provided by co-stimulatory receptors such as CD27 and CD28, as well as cytokines, including transforming growth factor-β (TGFβ) and interleukin-2 (IL-2), promote tT_{Reg} cell differentiation by suppressing T cell clonal deletion.

Modello a due step per lo sviluppo delle Treg nel timo



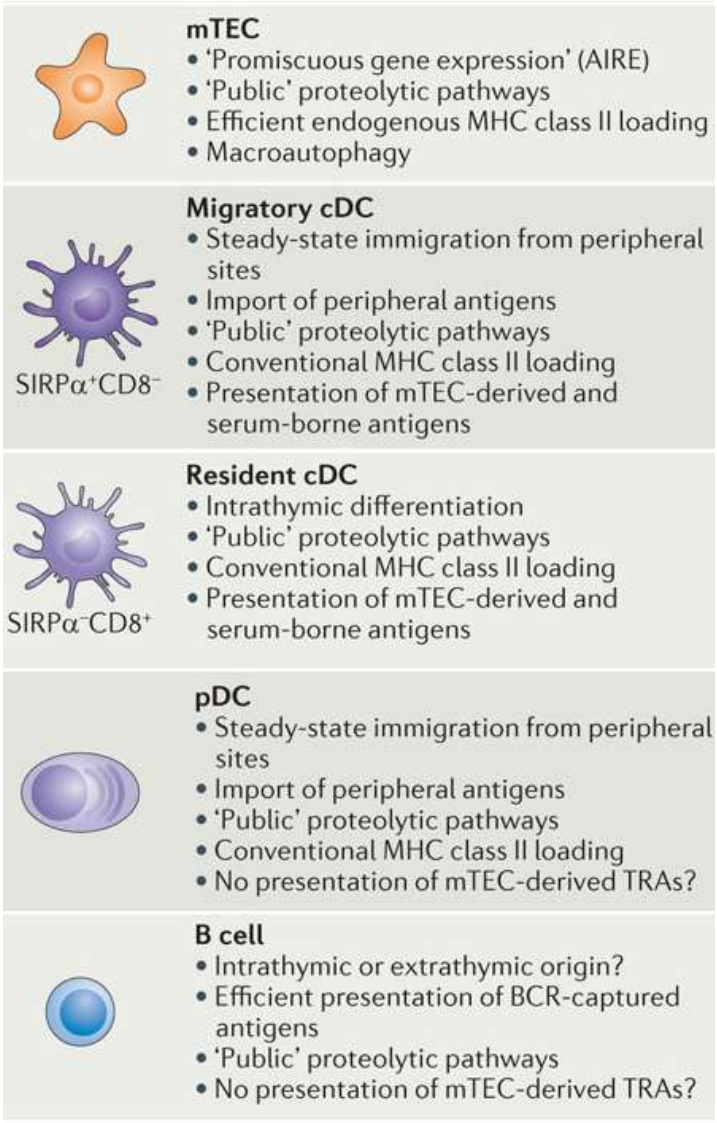
When thymocytes recognize self-peptide–MHC class II complexes in the presence of co-stimulatory molecules (such as CD80 or CD86) and with sufficiently high per cell avidity for Treg cell selection, some of these cells are selected as FOXP3−CD25+ Treg cell precursors. Presumably the T cell receptor (TCR) signal leads to the activation of several downstream pathways, including nuclear factor-κB (NF-κB) activation, and results in the remodelling of the forkhead box P3 (Foxp3) locus, rendering it permissive to the induction of FOXP3 expression by interleukin-2 (IL-2) signalling. At this point, the Treg cell precursor does not require further TCR stimulation for the expression of FOXP3. Instead, cytokine signals mediated by IL-2, or to a lesser extent IL-15, facilitate the induction of FOXP3 expression. APC, antigen-presenting cell; SP, single-positive.

APC timiche medullari coinvolte nel differenziamento delle Treg



Other APC: ???
macrophages
and B cells

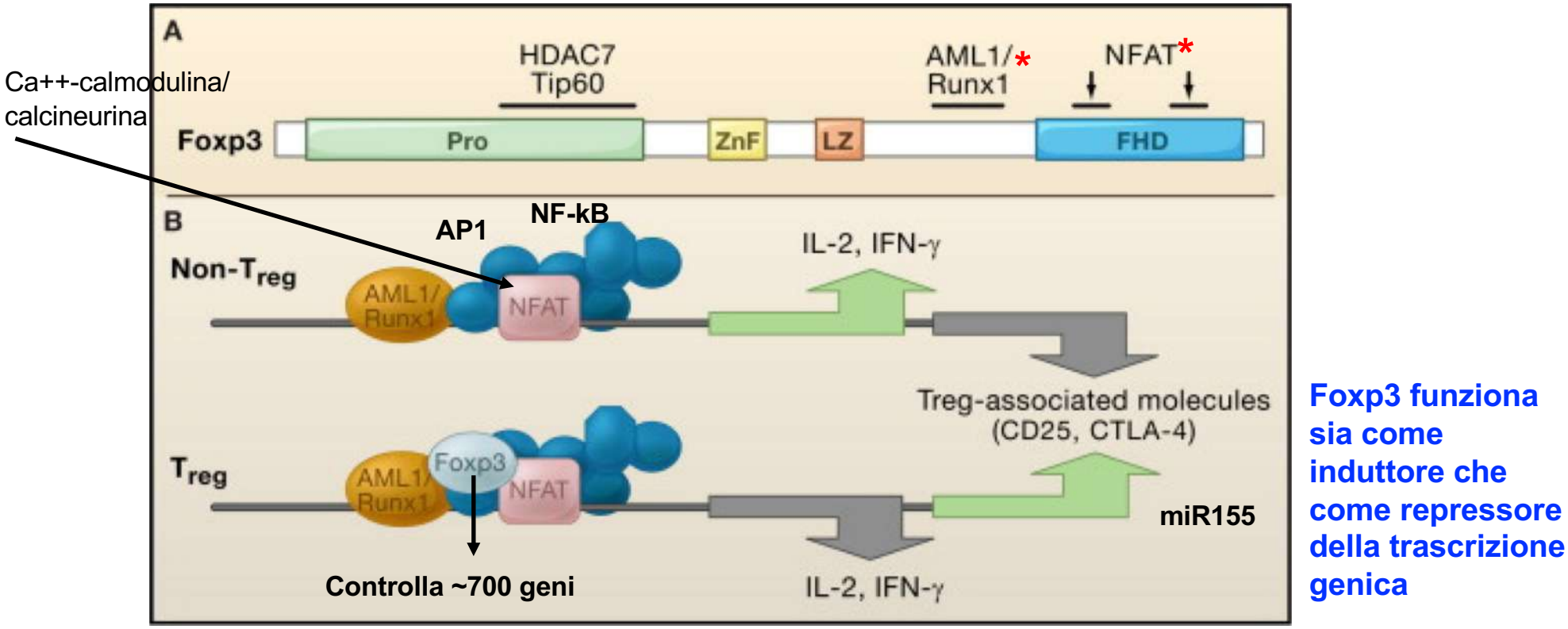
Non è ancora chiaro se le diverse APC timiche siano coinvolte nella selezione di popolazioni di Treg con differenti specificità del TCR. Tutte le APC timiche sono necessarie per generare un repertorio di Treg efficiente?



The antigenic repertoire presented by thymic medullary APCs

Multiple thymic antigen-presenting cell (APC) types are capable of facilitating thymic regulatory T (Treg) cell differentiation in the medulla. Stromal APCs, including medullary thymic epithelial cells (mTECs), can express and present tissue-specific antigens that are induced by autoimmune regulator (AIRE). Tissue-specific antigens are processed by autophagosomes and presented on the cell surface as peptide–MHC class II complexes. Haematopoietic APCs include dendritic cells (DCs), macrophages and B cells. However, the role of macrophages and B cells is unclear (not shown). The DC subsets include plasmacytoid DCs (pDCs) and SIRPα+ conventional DCs, which both migrate from the periphery and thus could potentially present extracellular antigens captured from the peripheral microenvironment. By contrast, resident SIRPα– conventional DCs originate in the thymus and thus probably present antigens from the thymus. In addition to presenting extracellular antigens, DCs can present mTEC-expressed antigens following antigenic transfer.

La funzione delle Treg è sotto il controllo di Foxp3



Foxp3 funziona sia come induttore che come repressore della trascrizione genica

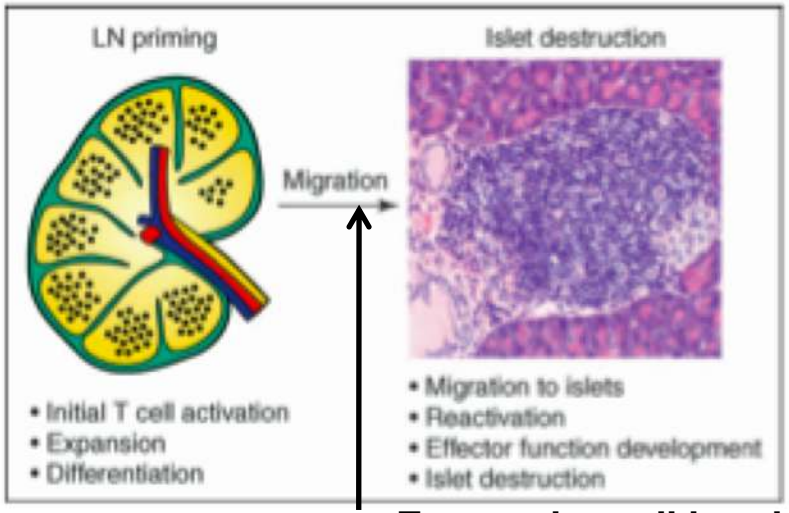
(A) The structure of the transcription factor Foxp3. Bars indicate the binding sites for other transcription factors or chromatin-remodeling enzymes. Pro: Proline-rich region, ZnF: zinc finger domain, LZ: leucine zipper domain, FHD: forkhead box. HAT(Tip60)/HDAC (histone acetyl transferase /histone deacetyl transferase)

(B) The transcriptional complexes involving NFAT (nuclear factor of activated T cells) and AML1 (acute myeloid leukemia-1)/Runx1(runt-related transcription factor-1) activate or repress the genes encoding cytokines and several cell-surface molecules in Treg and non-Tregs, depending on the presence of Foxp3.

T regolatorie naturali o timiche: T_{Reg} CD4+ CD25+ FoxP3+

- rappresentano circa il 10% dei linfociti T CD4+ periferici.
- altri markers: CTLA4; GITR (recettore del TNF indotto dai glucocorticoidi); $CD127^{low}$ (IL7αR).
- sono specifiche per antigeni self *e in vitro* si comportano come cellule anergiche.
- *in vivo* inibiscono la proliferazione delle cellule T naive ed il loro differenziamento a T effettori. Inoltre inibiscono le risposte mediate da cellule T effettrici (CD4+ e CD8+), linfociti B, macrofagi, cellule NK e APC (DC).
- *In vitro*, sopprimono la proliferazione e la produzione di citochine in cellule T responder (convenzionali)
- agiscono sia per contatto cellula-cellula (azione diretta) o mediante la secrezione di citochine IL-10, TGF-β, IL35 (azione indiretta).
- in modelli animali prevengono lo sviluppo di malattie autoimmuni o il rigetto dei trapianti; in topi normali la deplezione delle Treg dal periferico è causa di T1D, tiroiditi e gastrite.

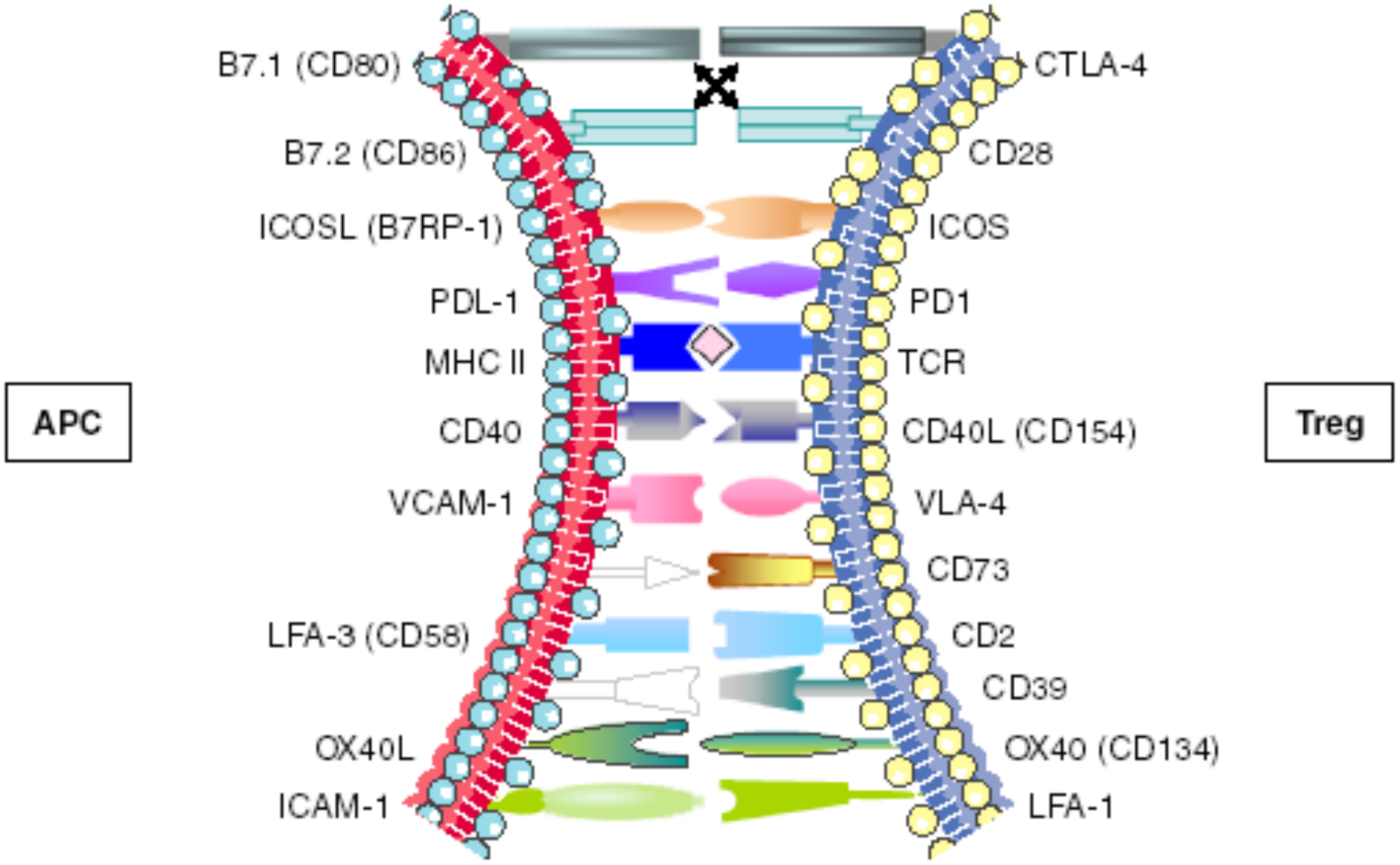
T reg FoxP3+
CCR7+
$CD62L^{high}$



Espressione di homing receptors

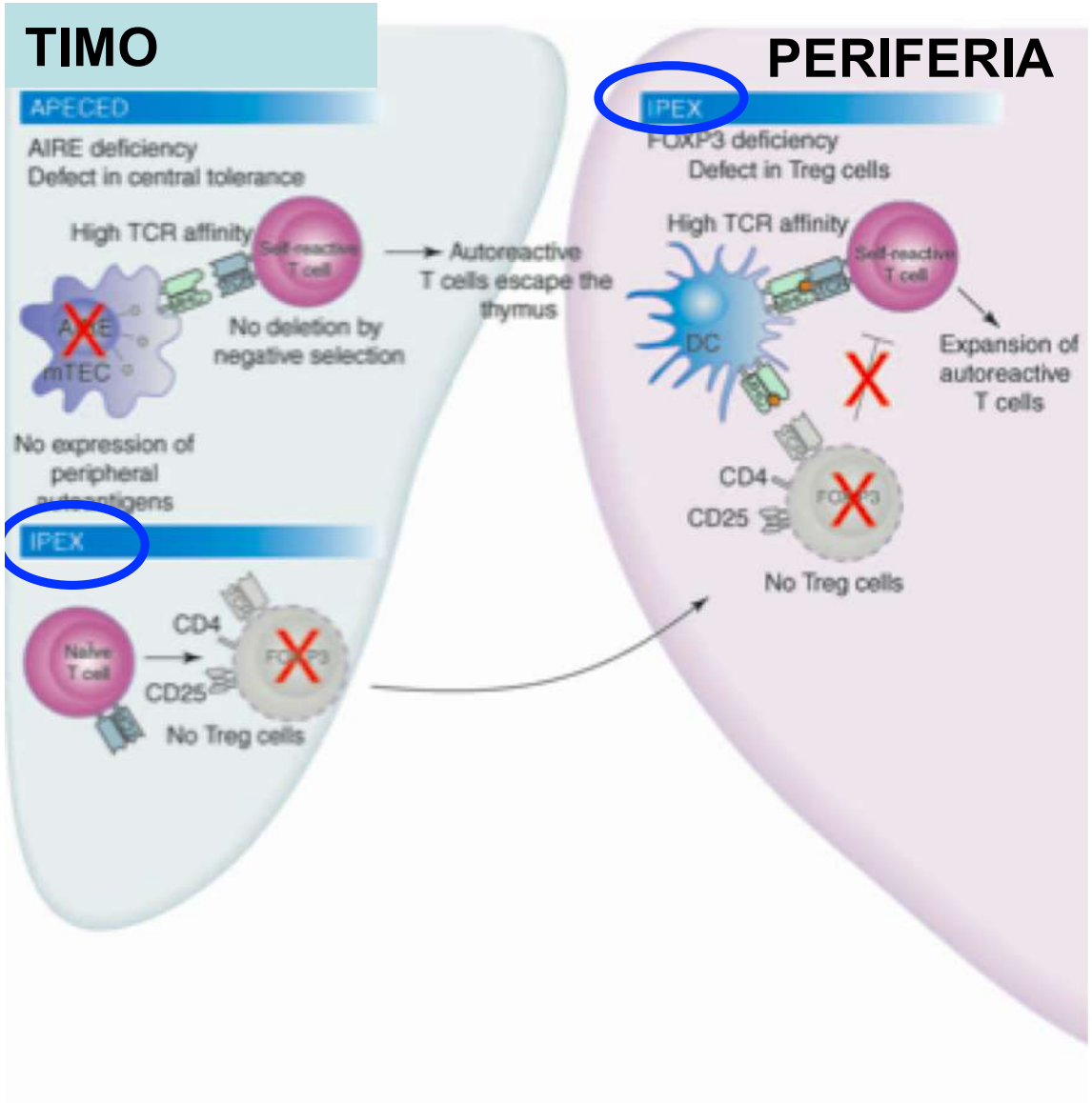
***In vivo, i* linfociti Treg agiscono sia nei linfonodi che nei tessuti**

Interazioni molecolari importanti che contribuiscono allo stato di attivazione delle Treg naturali



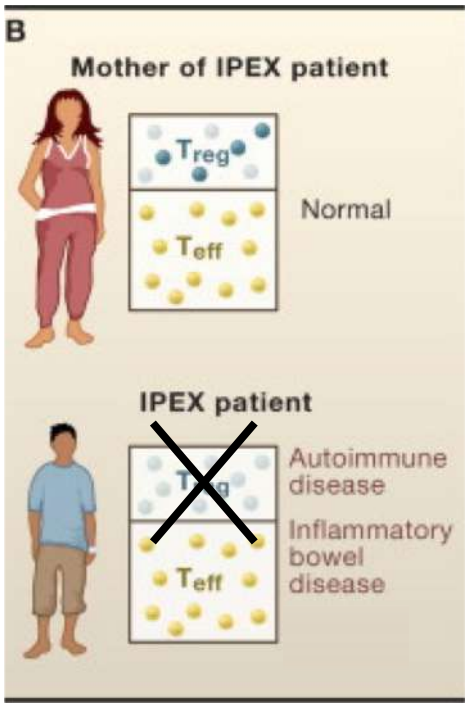
IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)

una patologia autoimmune, monogenica recessiva, legata al cromosoma X indotta da mutazioni del gene FoxP3

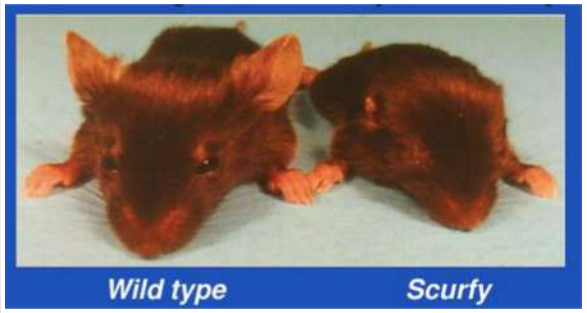


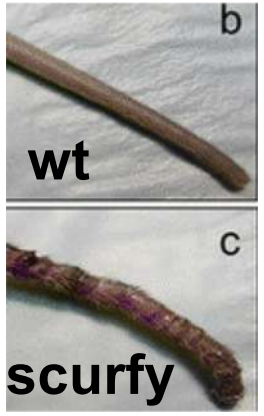
Pazienti con IPEX hanno uno sviluppo difettivo delle cellule T reg CD4+ CD25+

Manifestazioni: insufficienza delle ghiandole endocrine, anemia emolitica, diarrea, eczemi



Topi “scurfy” (squamosi): modello sperimentale FoxP3 $^{-/-}$





Nell'uomo deficienze del CD25 inducono manifestazioni cliniche e patologiche indistinguibili da quelle dell'IPEX

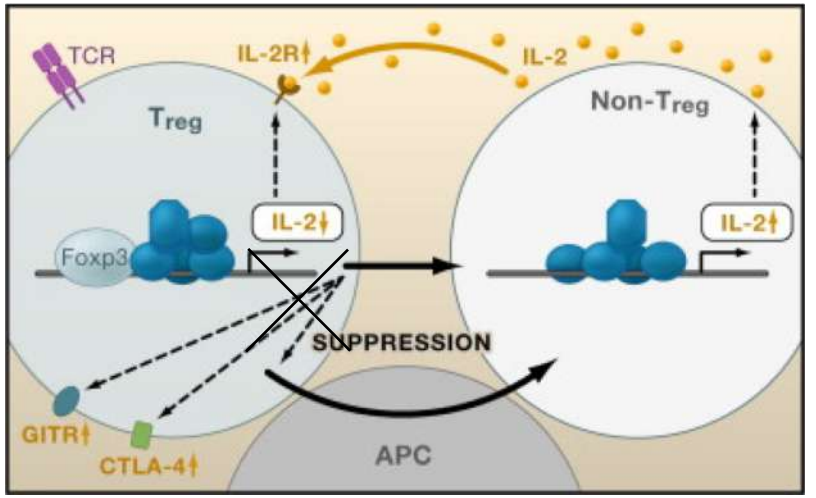
Importanza dell'IL-2 per la tolleranza periferica

Topi knockout per il gene dell'IL-2 o per IL-2Rα (CD25) o per IL-2Rβ sviluppano: **AUTOIMMUNITA' LETALE**

- splenomegalia e linfoadenopatia
- autoanticorpi anti-DNA
- anemia emolitica autoimmune
- infiammazioni intestinali croniche

perchè il signaling via IL2/IL2R

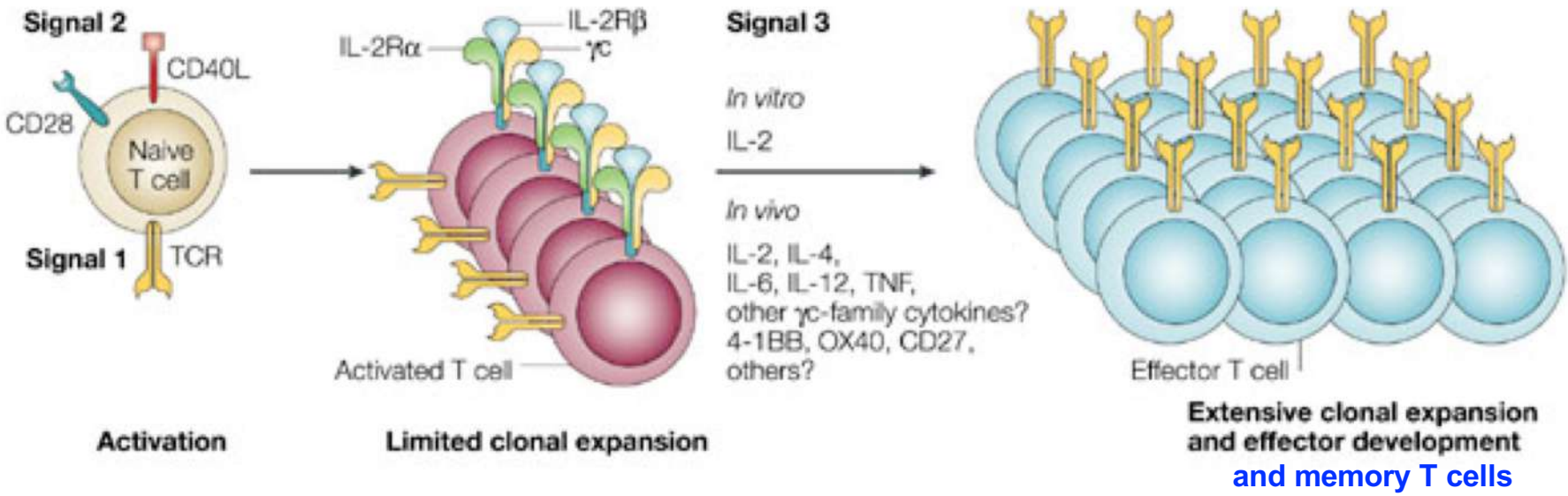
è essenziale per le cellule T regolatorie



Interazione tra cellule Treg , linfociti T non regolatori ed APC

Key roles of IL-2 in immune homeostasis. Feedback control of Treg function via IL-2. Foxp3, together with other transcription factors and coactivators/corepressors, represses the transcription of IL-2 in Tregs, rendering them highly dependent on exogenous IL-2 (mainly produced by activated non-Treg cells) for their maintenance and function. Foxp3 also activates the genes encoding Treg-associated molecules such as CD25, CTLA-4, and GITR and confers suppressive activity to Tregs, which directly suppress non-Treg cells or modulate the function of APC to activate non-Treg cells.

L'interleuchina 2 (IL2) non è strettamente necessaria per l'attivazione delle risposte immuni cellulo-mediate ma per la tolleranza



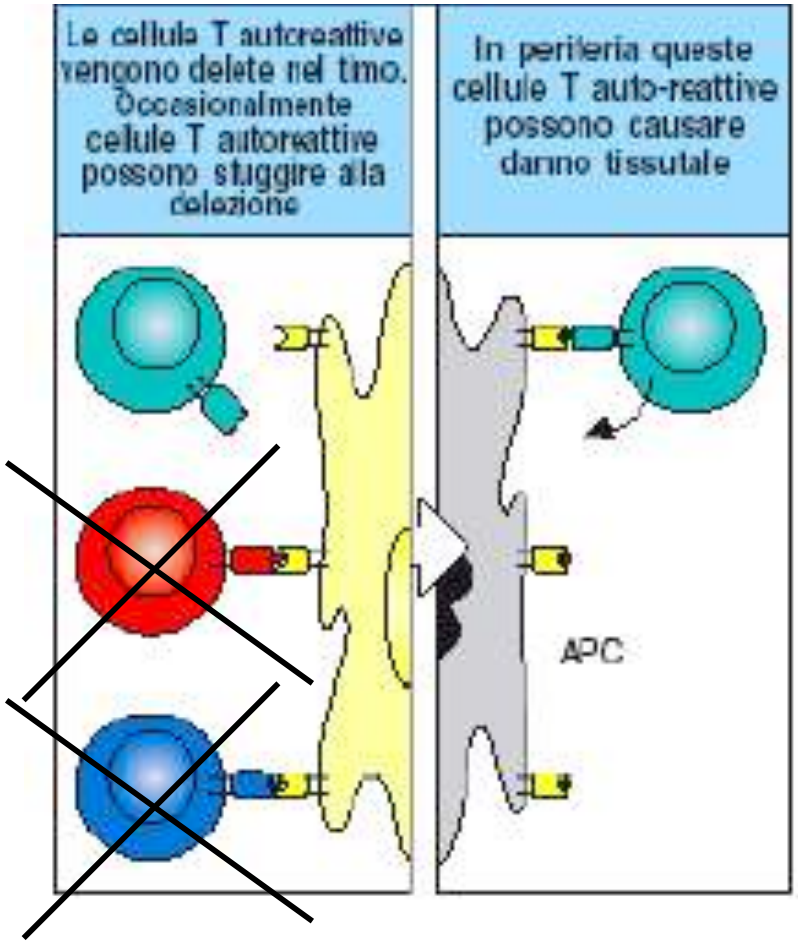
Il 3° segnale importante per produrre un'efficiente risposta linfocitaria T può essere fornito da fattori diversi dall'IL2

Modelli animali (topi IL-2 difettivi) dimostrano che l' IL-2 *in vivo* non è indispensabile per l'immunità mediata dalle cellule T convenzionali ma lo è per i linfociti Treg

A naive T cell is activated after ligation of its **T-cell receptor (TCR) (signal 1)** and engagement of the co-stimulatory molecules **CD28 and CD40 ligand (CD40L) (signal 2)** during antigen presentation by a dendritic cell (DC). This is sufficient to induce several rounds of T-cell proliferation; however, this interaction is not sufficient for an effective T-cell-dependent immune response. Signal 3 is a crucial checkpoint for substantial clonal expansion of antigen-specific T cells and development into effector cells. In tissue culture, engagement of the interleukin-2 receptor (IL-2R) is the main mechanism of passing the **signal 3 checkpoint**. **However, there are several sources of signal 3 *in vivo***. It is probable that redundancy in the molecules that provide signal 3 is not limited to other common cytokine-receptor γ-chain (γ c)-dependent cytokines. Candidates for signal 3 are shown. TNF, tumour-necrosis factor.

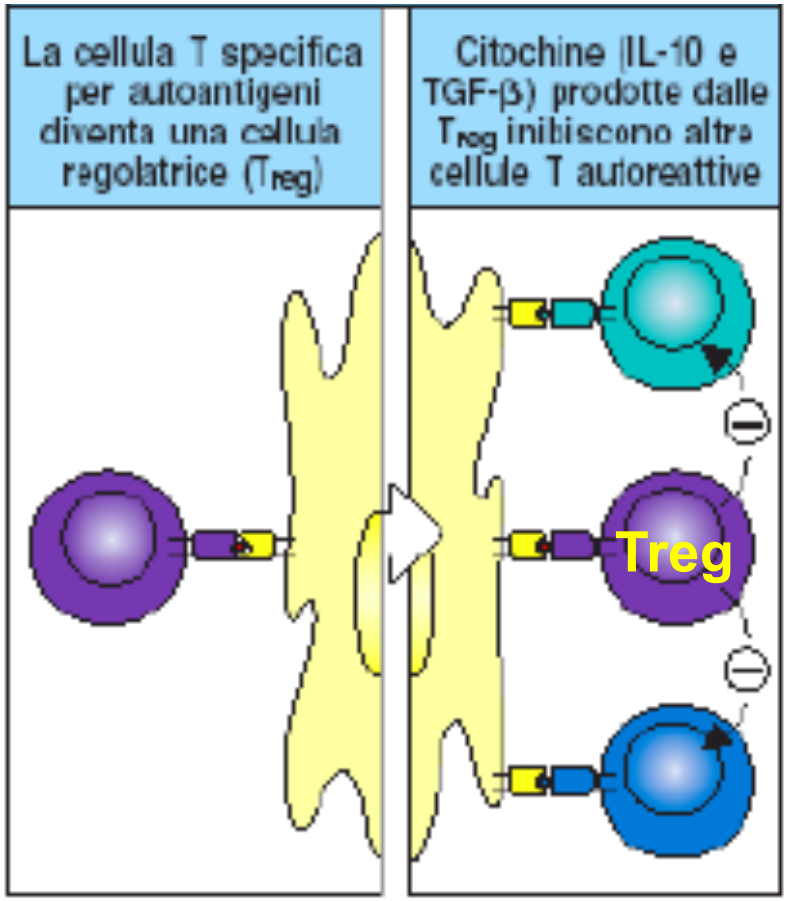
Tolleranza per delezione

recessiva



Tolleranza per regolazione (Treg)

dominante



Meccanismo: **intrinseco** **estrinseco**

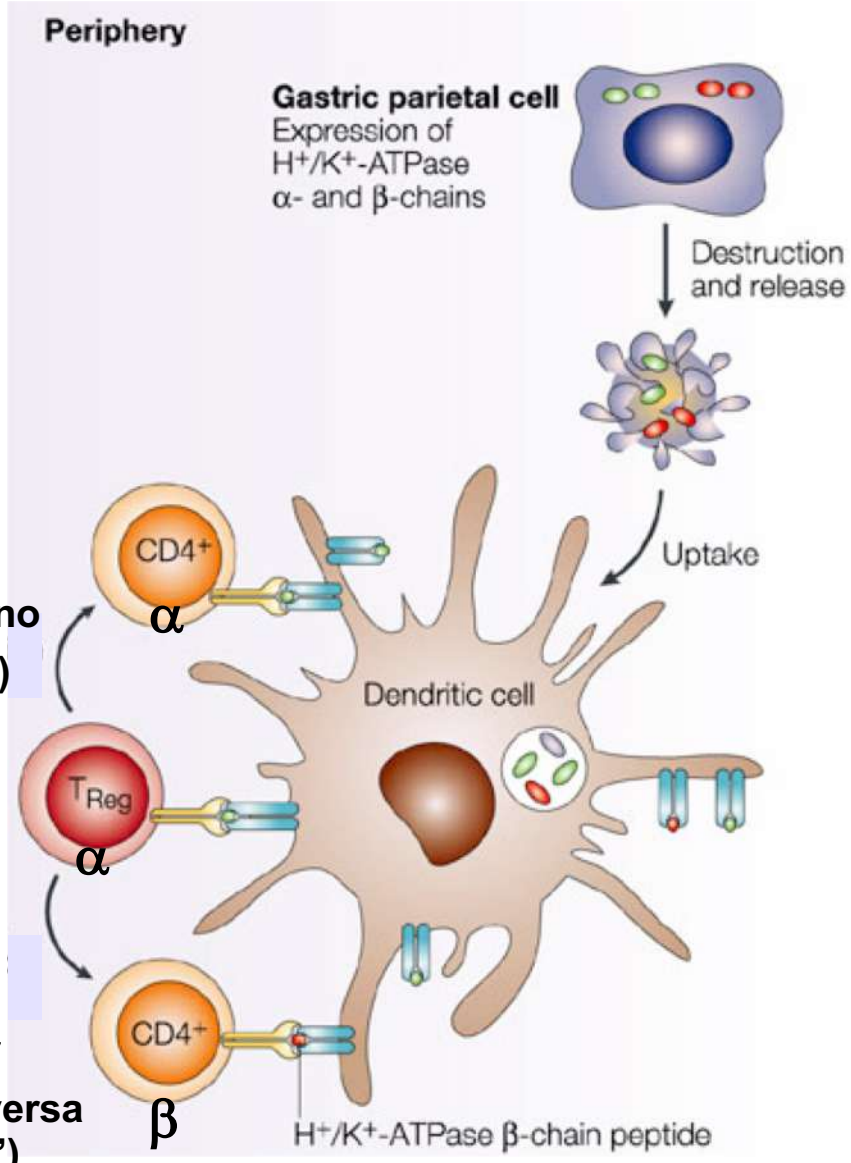
Meccanismi di soppressione linfocitaria

Soppressione

(Treg e T "soppresso" condividono la stessa specificità antigenica)

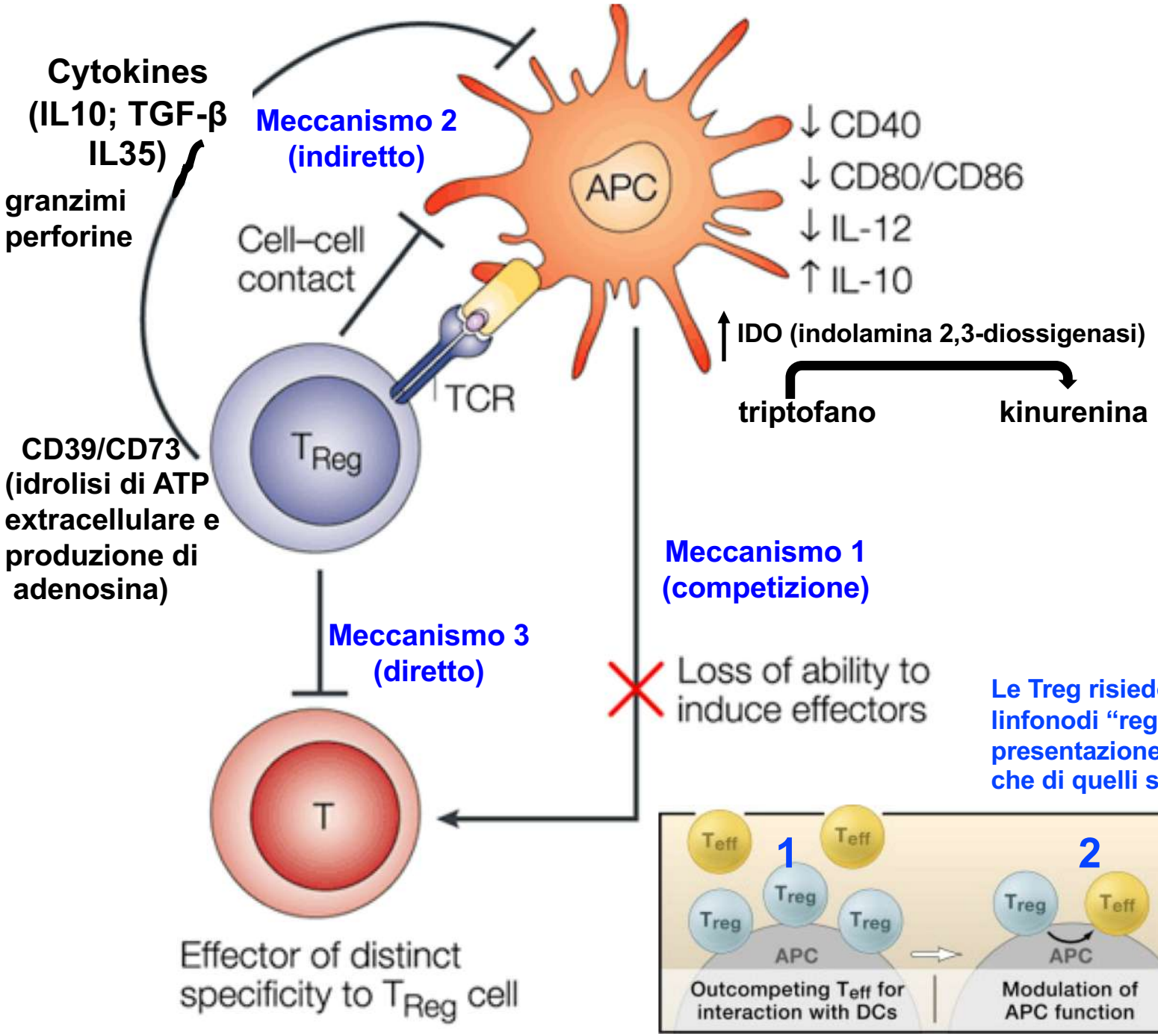
Soppressione bystander

(il Treg ha una specificità antigenica diversa da quella del linfocita T "soppresso")



Vantaggi terapeutici della soppressione bystander

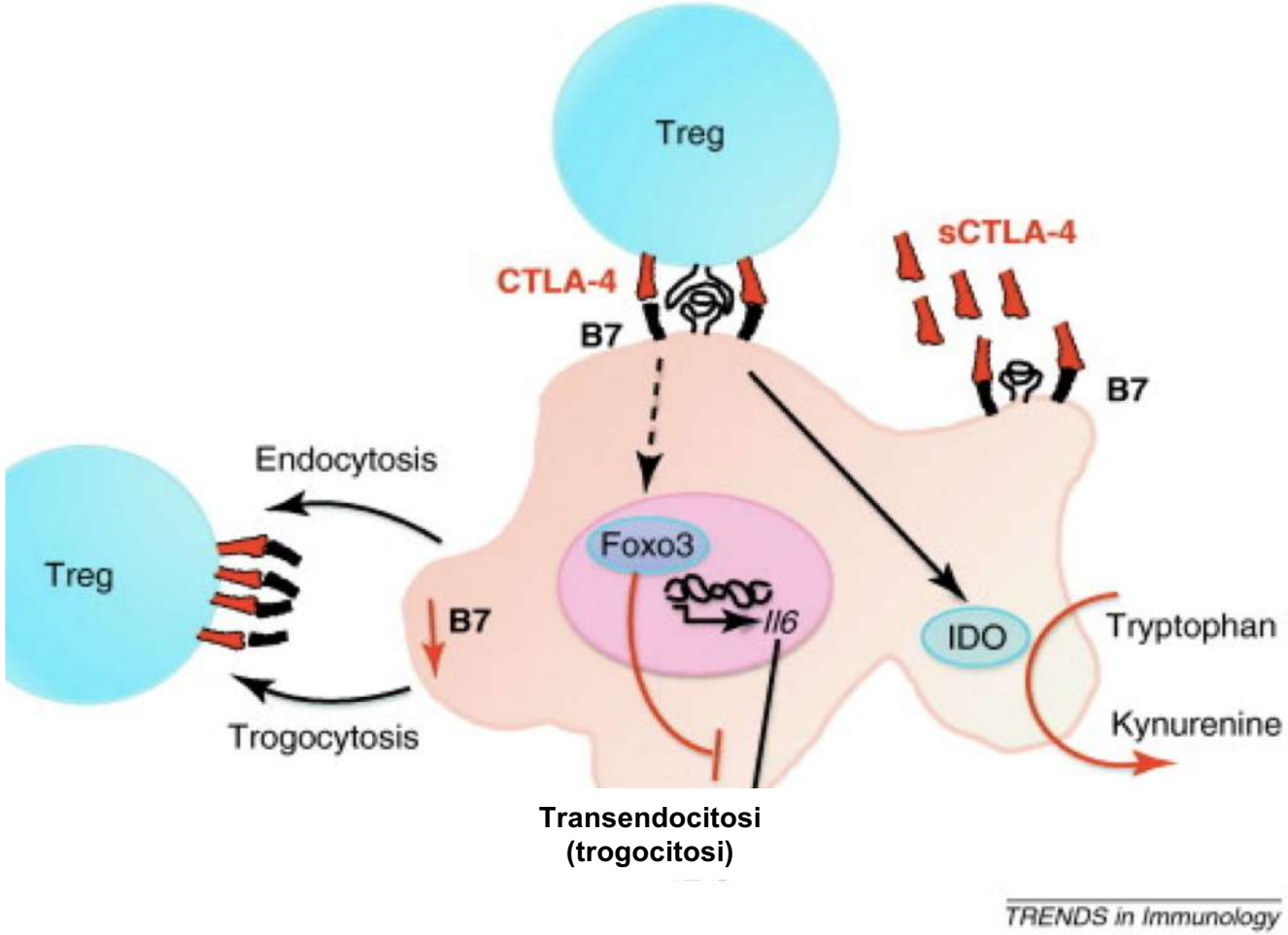
Azione delle T_{Reg} nel tessuto dove è espresso l'autoantigene riconosciuto



Local bystander suppression. Regulatory T (Treg) cells can act locally in tissues and draining lymph nodes. After trafficking through areas where cognate autoantigen is presented by local antigen-presenting cells (APCs), Treg cells become activated and suppress APCs directly through cell–cell interactions or indirectly through soluble mediators such as cytokines or chemokines. The result is a modulated APC that is rendered incapable of propagating autoaggressive effectors. Alternatively, Treg cells might act directly on autoaggressive effectors. IL, interleukin; TCR, T-cell receptor;TGF-β, transforming growth factor- β.

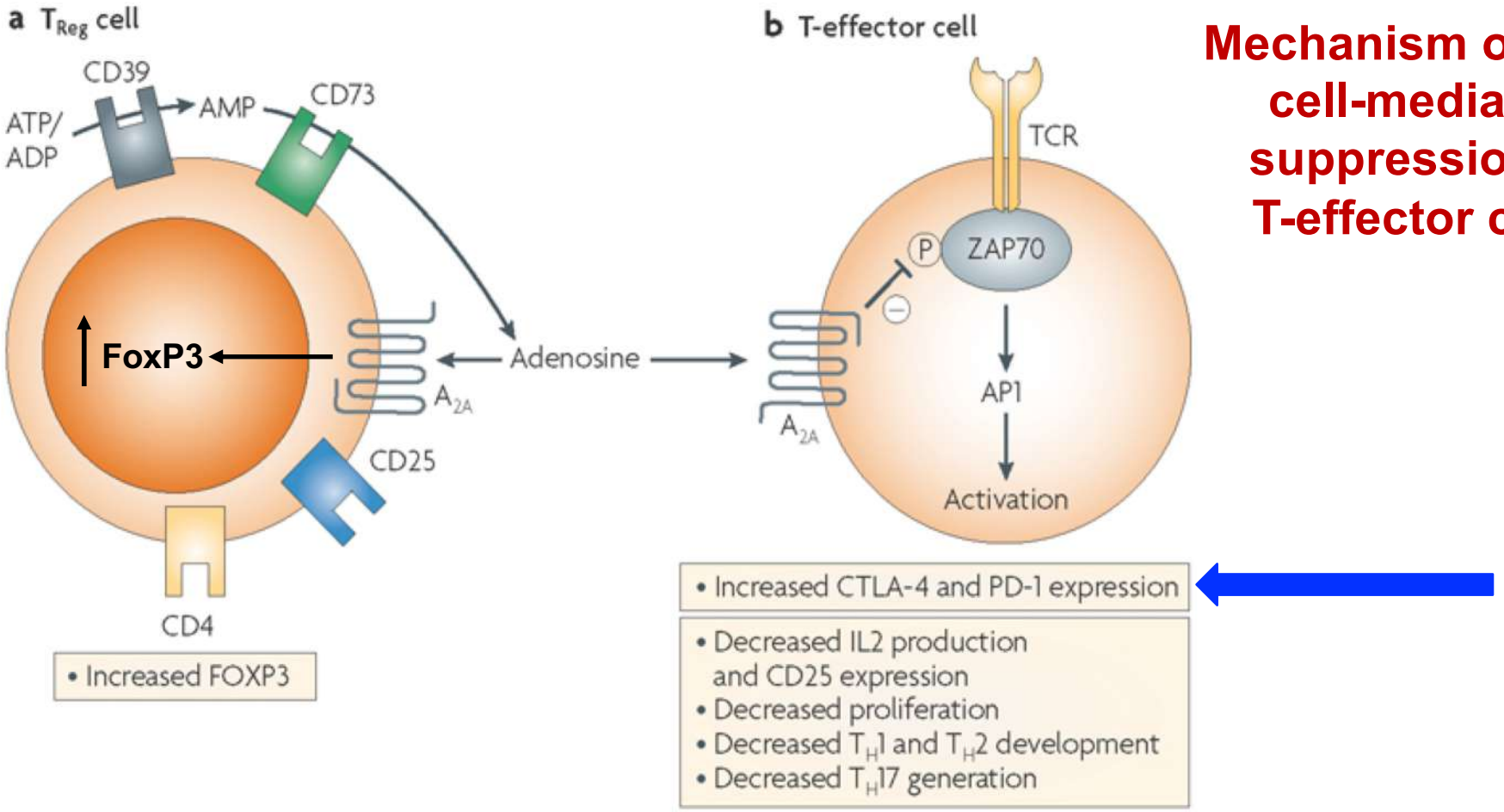
Le Treg risiedono maggiormente nei linfonodi "regionali" dove avviene la presentazione sia degli antigeni microbici che di quelli self tessuto-specifici

Azione delle Treg sulle APC



CTLA-4 can modulate APC function by several different mechanisms. CTLA-4-expressing T cells can decrease expression of the B7 (CD80 and CD86) molecules on APCs, and thereby modulate APC capacity to prime naïve T cells. For example, CTLA-4 can mediate **trogocytosis** of CTLA-4-bound CD80 and CD86 molecules from the APC to the Treg cell membrane or the Treg cells can endocytose them. CTLA-4 ligation can also affect the transcriptional machinery of APCs by inducing nuclear translocation of **Foxo3**, which downregulates IL-6 expression of DCs. Furthermore, it has been shown that CTLA-4 ligation induces **IDO-dependent catabolism of tryptophan** to the immunosuppressive kynurenine in DCs, which might lead to cell death. Furthermore, secreted soluble CTLA-4 might block CD80 and CD86, thereby preventing proper co-stimulation via CD28 on T cells.

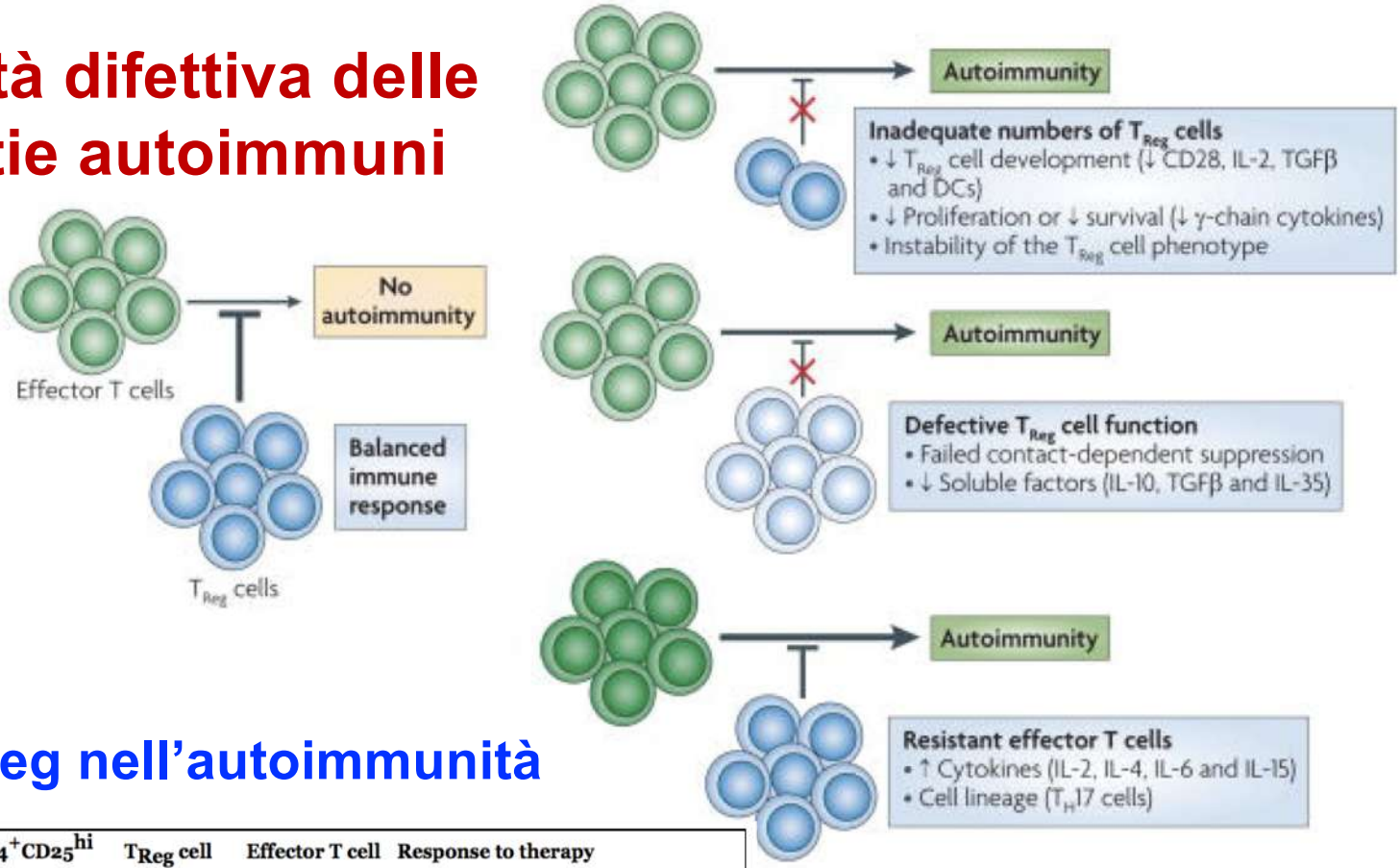
Mechanism of Treg cell-mediated suppression of T-effector cells



Regulatory T (Treg) cells produce **adenosine** following sequential degradation of **ATP/ADP** via **CD39** (ENTPD1; ectonucleoside triphosphate diphosphohydrolase 1) and **CD73** (ecto-5'-nucleotidase) (a). Adenosine activates A2A receptors on T-effector cells to inhibit T-cell receptor (TCR)-mediated signalling by preventing ZAP70 phosphorylation and activation of the transcription factor activator protein 1 (AP1) (b).

This decreased TCR signalling leads to **decreased interleukin 2 (IL2) production and CD25 expression** resulting in decreased T effector cell proliferation. In addition, the development of both T helper 1 (TH1) and TH2 cells, as well as the generation of TH17 lymphocytes is inhibited following A2A receptor stimulation. A2A receptor stimulation on T-effector cells increases expression of negative co-stimulatory molecules such as cytotoxic T-lymphocyte-associated antigen 4 (**CTLA4**) and programmed cell death 1 (**PD1**). A2A receptor stimulation on Treg cells augments FOXP3 expression in these cells.

Cause dell'attività difettiva delle Treg nelle malattie autoimmuni

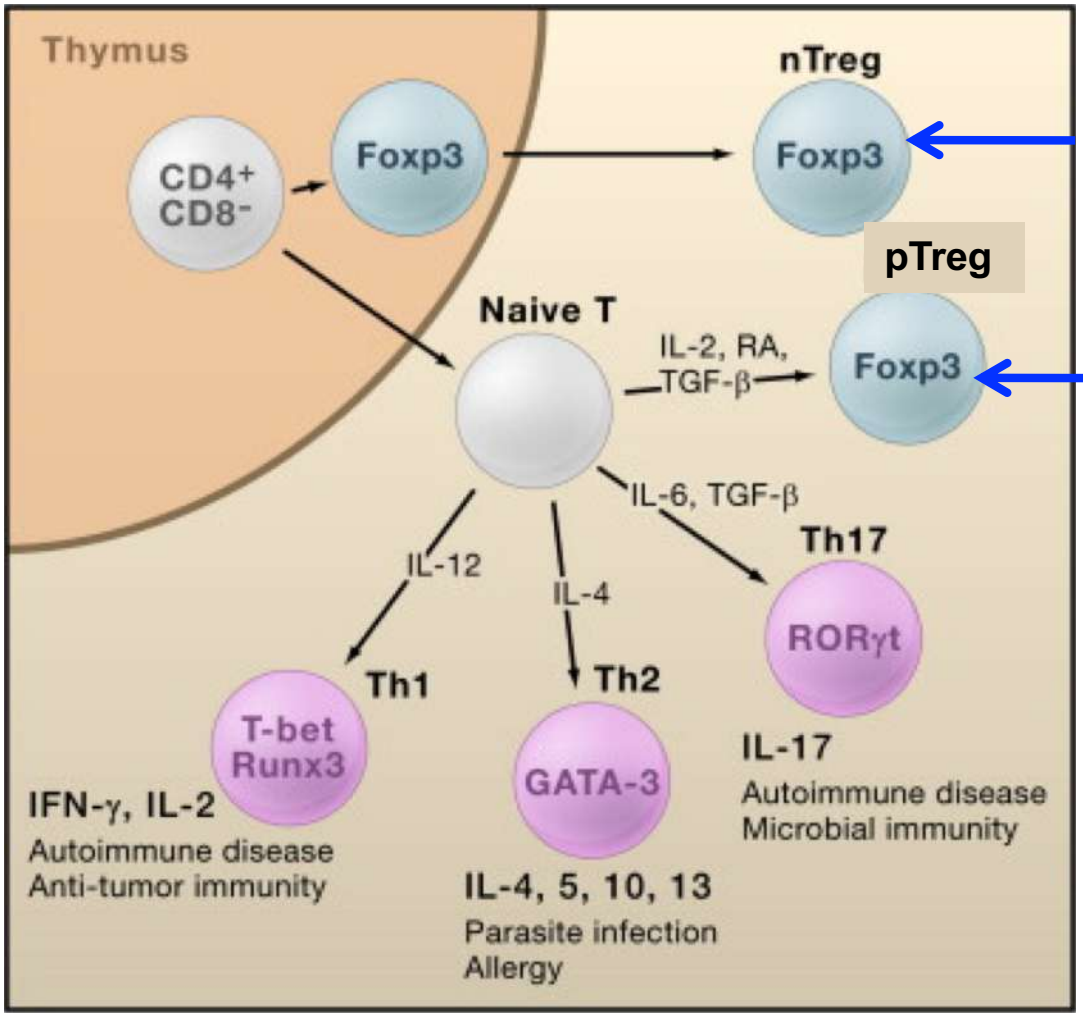


Overview delle Treg nell'autoimmunità

Disease	T_{Reg} cell number (percentage of $CD4^+CD25^{hi}$ or $CD4^+CD25^+FoXP3^+$ cells)		T_{Reg} cell function	Effector T cell resistance	Response to therapy
	Peripheral blood	Tissue			
Type 1 diabetes	Normal	ND	Decreased	Increased	ND
Multiple sclerosis	Normal; altered subsets of T_{Reg} cells	Increased in the CNS	Decreased	Normal	Increased T_{Reg} cell numbers with IFNβ therapy[53]
Systemic lupus erythematosus	Decreased	ND	Decreased	Increased	Increased T_{Reg} cell numbers with corticosteroids
Rheumatoid arthritis	Increased	Increased in the synovial fluid of active disease	Decreased	Normal	Increased T_{Reg} cell numbers with infliximab therapy correlating with change in C-reactive protein
Inflammatory bowel disease	Decreased in active ulcerative colitis; normal in Crohn's disease	Increased in the lamina propria and mesenteric lymph nodes	Normal	Normal	ND
Psoriasis	Increased	Increased in the skin	Decreased	Increased	ND

CNS, central nervous system; FOXP3, forkhead box P3; IFNβ, interferon-β; ND, not determined; T_{Reg}, regulatory T.

Particolari condizioni possono promuovere il differenziamento delle cellule T naive a Treg in periferia



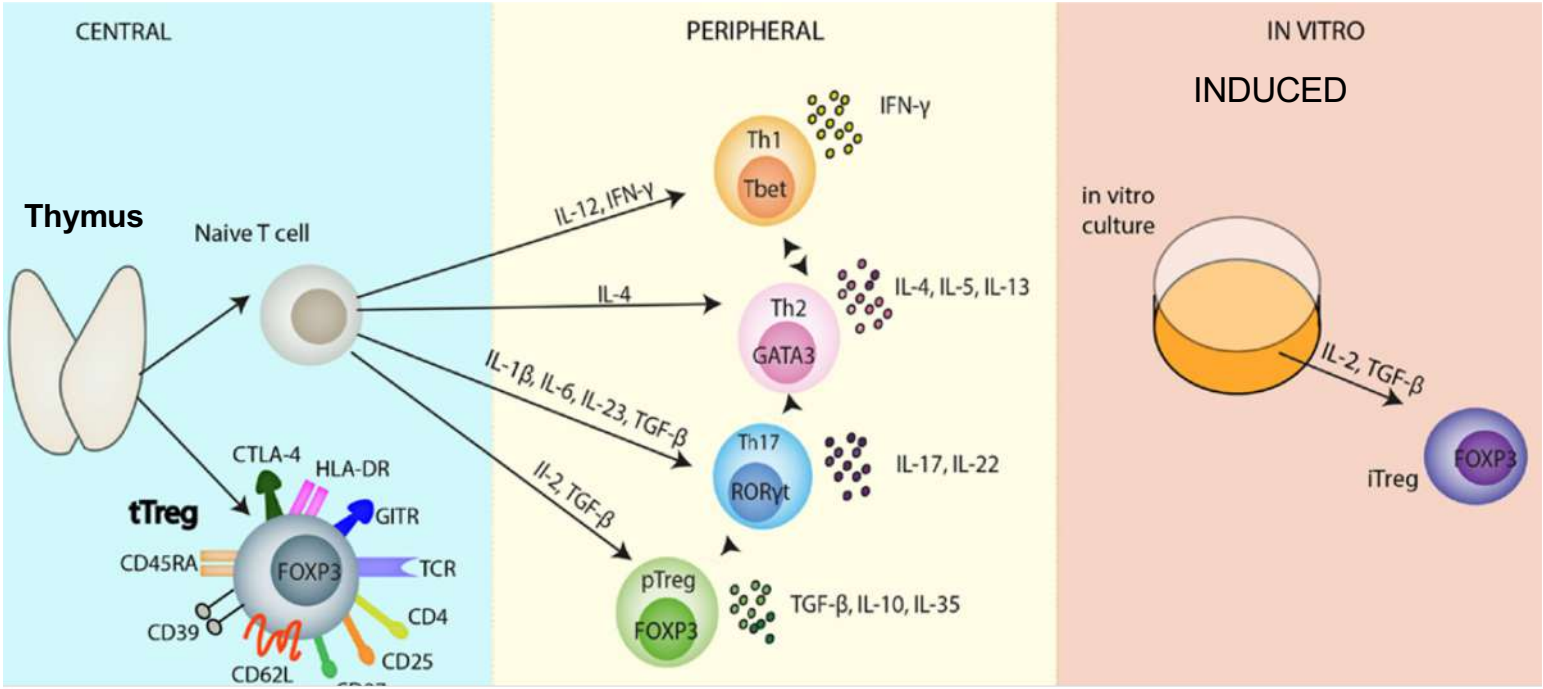
Naturali o timiche
(derivate dal timo)

Periferiche o indotte
(periphery-induced adaptive Treg)

Differentiation of Naive CD4+ T Cells into Tregs or Effector T Cells

Cytokines and transcription factors that promote the differentiation of naive T cells into Tregs or effector T cells are shown. The transcription factors T-bet and Runx3, GATA3, or RORγt are required for the differentiation of naive T cells into Th1, Th2, or Th17 cells, respectively. nTreg, natural Treg; iTreg, induced Treg; RA, retinoic acid.

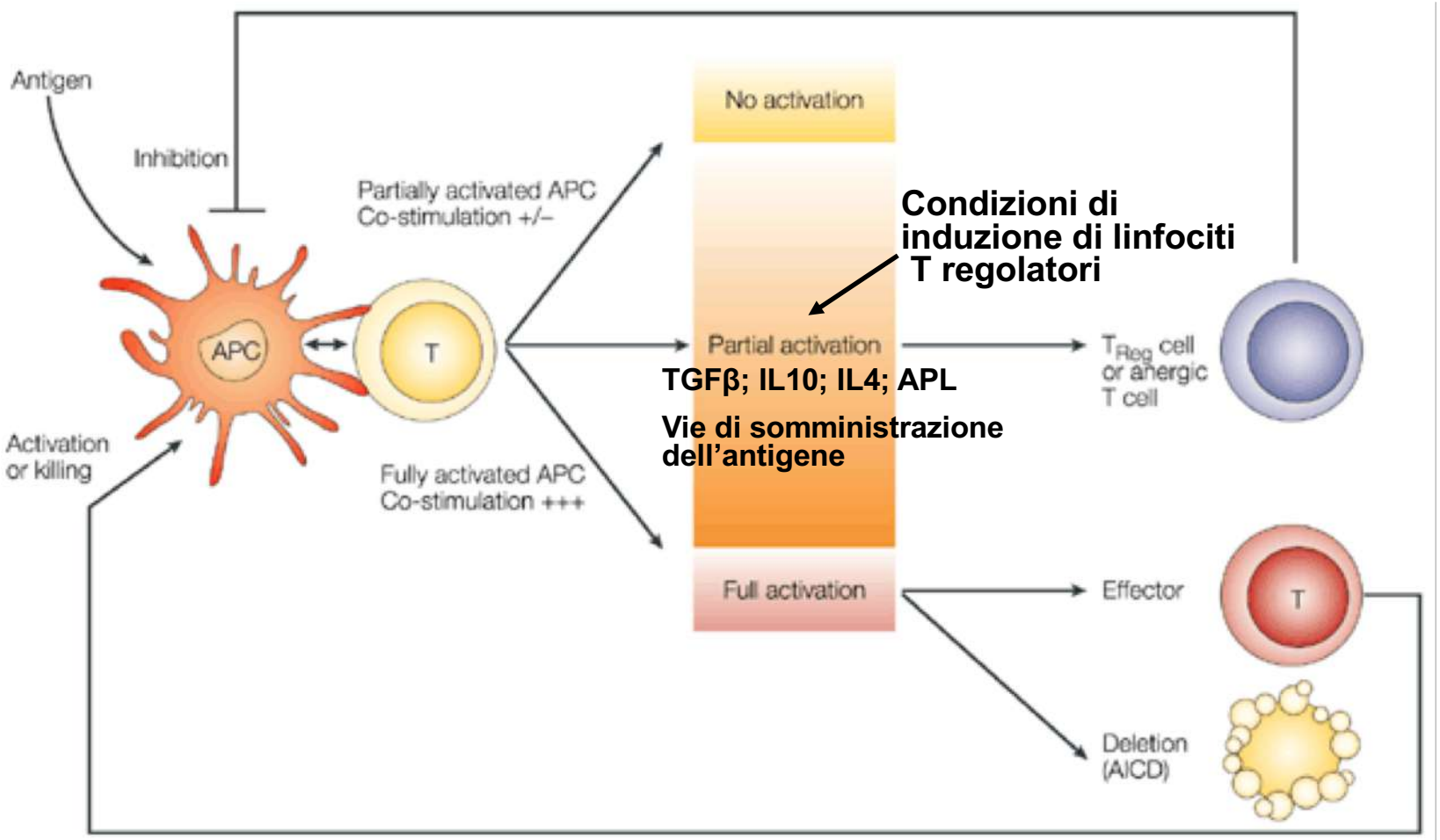
Regulatory T cell populations



Selection of naïve CD4⁺ T cells and natural Tregs occurs in the thymus. Naïve CD4⁺ T cells, subsequently, can differentiate into several different T cell subsets: Th1, Th2, Th17, induced Tregs, in the periphery, all heralding distinct immunological roles. Each subset has its own immunological role *in vivo*: Th1 cells secrete IFNγ, controlling immunity to foreign pathogens. Th2 cells produce various cytokines including: IL-4, IL-5, IL-13, IL-10, which are primarily involved in promoting humoral immunity, protecting against infection. Th17 cells produce predominantly the inflammatory cytokine, IL-17, and play an important role in controlling pathogens especially at environmental surfaces and the cytokine, IL-22. Despite the apparent terminal differentiation of all these cells, they cannot be considered to be committed to one cell fate. Lineage plasticity following differentiation is depicted by the dotted arrows between the cells. This diagram is far from comprehensive; it is most likely that the future will see various changes and additions to this diagram concerning the differentiation of CD4⁺ T cells. *In vitro* generation of Tregs in the presence of IL-2 and TGF-β polarizing conditions leads to the development of iTregs.

Abbreviations: APC, antigen presenting cells; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FOXP3, forkhead Box P3; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; iTreg, induced Treg; nTreg, natural Treg; pTreg, peripheral Treg; RORγt, retinoid related orphan receptor γ; T-bet, T box transcription factor; TCR, T cell receptor; TGF-β, transforming growth factor-β; Th, T helper cell;

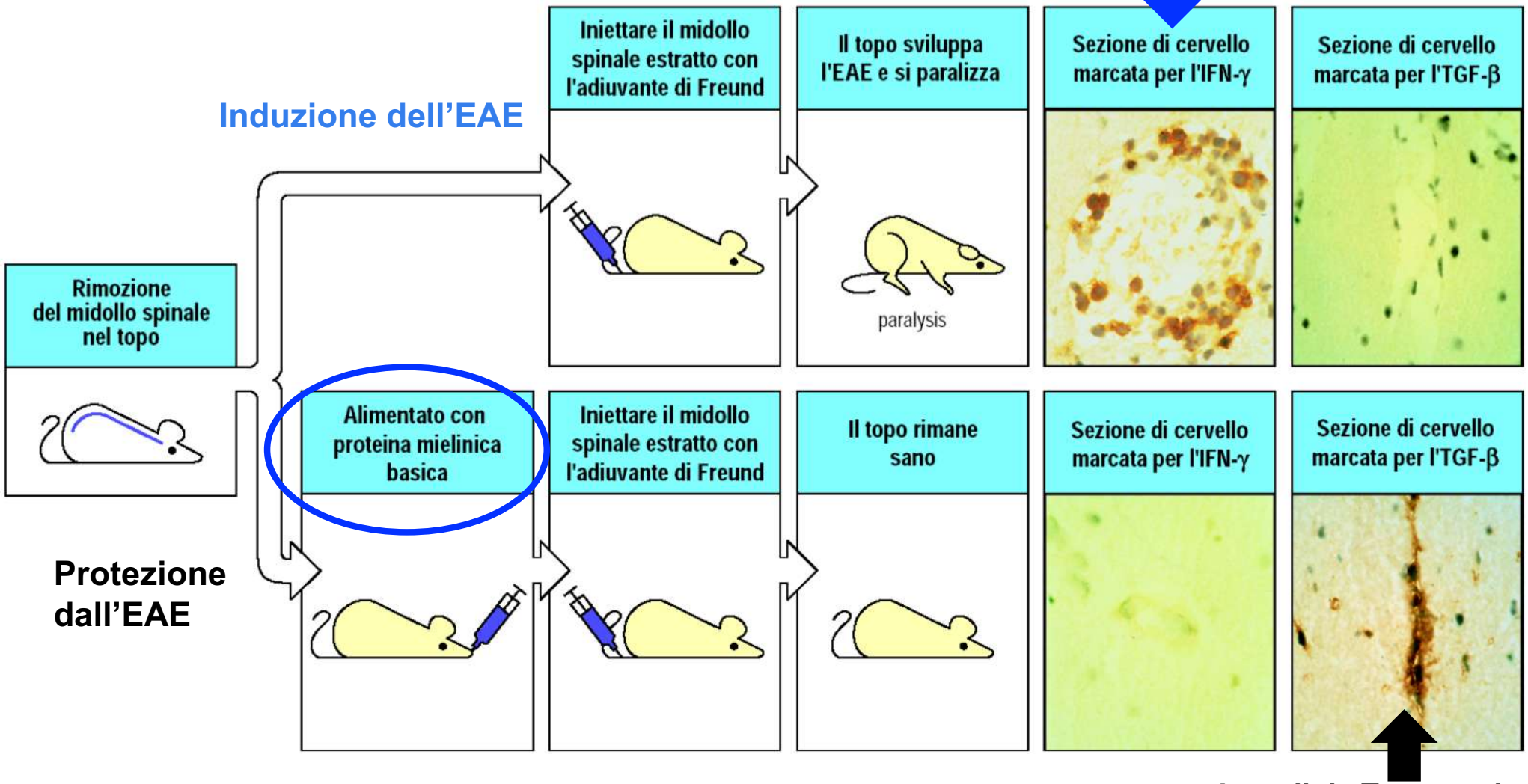
Immunità o tolleranza: dipendenza dallo stato di attivazione delle APC



Once antigen has been taken up by antigen-presenting cells (APCs) — prototypically dendritic cells — the activation state of the APC has a crucial role in determining the outcome of the ensuing APC–T-cell interaction. Unresponsiveness is tolerance in its purest sense — the absence of antigen-specific T cells. At the other end of the spectrum, a fully activated APC induces T-cell activation. Some activated lymphocytes might then undergo activation-induced cell death (AICD) and deletion by apoptosis. The intermediate zone between no activation and full cellular activation is of great interest with regard to regulatory T (TReg) cells. Partial activation can generate T cells that are anergic and that have properties of TReg cells, including the ability to render APCs 'tolerogenic'.

La somministrazione di un autoantigene per via orale può conferire protezione dalle malattie autoimmuni

Le cellule T presenti nel cervello sono di tipo Th1 e producono IFNγ



Le cellule T presenti nel cervello sono di tipo soppressorio e producono TGFβ

Nell'uomo gli autoantigeni somministrati per via orale potrebbero essere usati a scopo preventivo

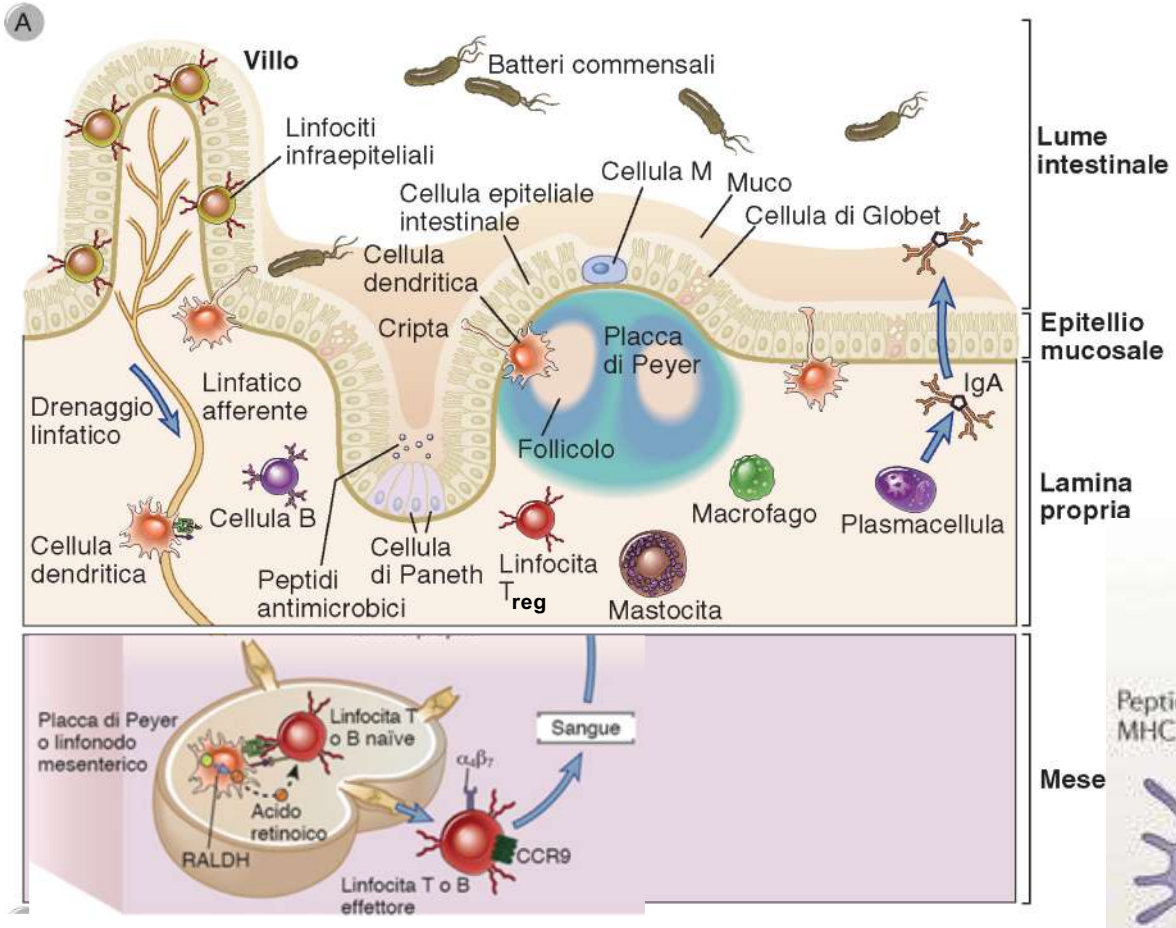
La tolleranza immunologica a livello mucosale è favorita da:

- **alte concentrazioni di citochine anti-infiammatorie (IL-10; TGF-beta) per cui le DC mucosali inducono preferenzialmente le T reg**

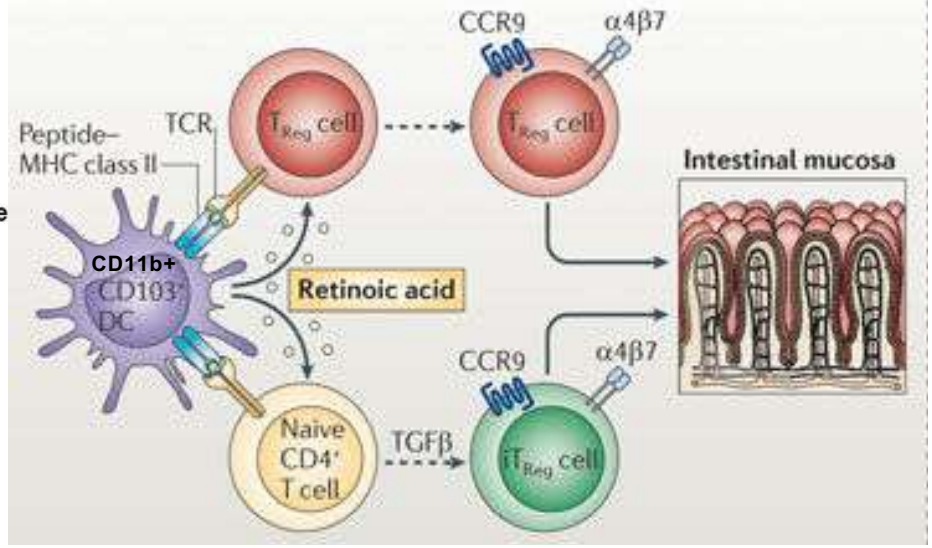
- **le cellule residenti possono esprimere le molecole MHC di classe II ma (es. le cellule epiteliali intestinali) non sono APC professioniste quindi non forniscono segnali costimolatori; queste condizioni favoriscono lo sviluppo delle Treg**

Le cellule T_{reg} del GALT sono essenziali per l'immunoregolazione delle risposte infiammatorie nell'intestino

Nel tratto gastrointestinale è necessario prevenire risposte infiammatorie indesiderate nei confronti degli antigeni introdotti con gli alimenti e di quelli derivati dal microbiota commensale. Ciò è favorito da un ambiente ricco di IL10, TGFβ e acido retinoico.



La generazione locale di Treg in risposta agli antigeni orali è favorita dalla presenza di una popolazione specializzata di DC CD11b+ CD103+.

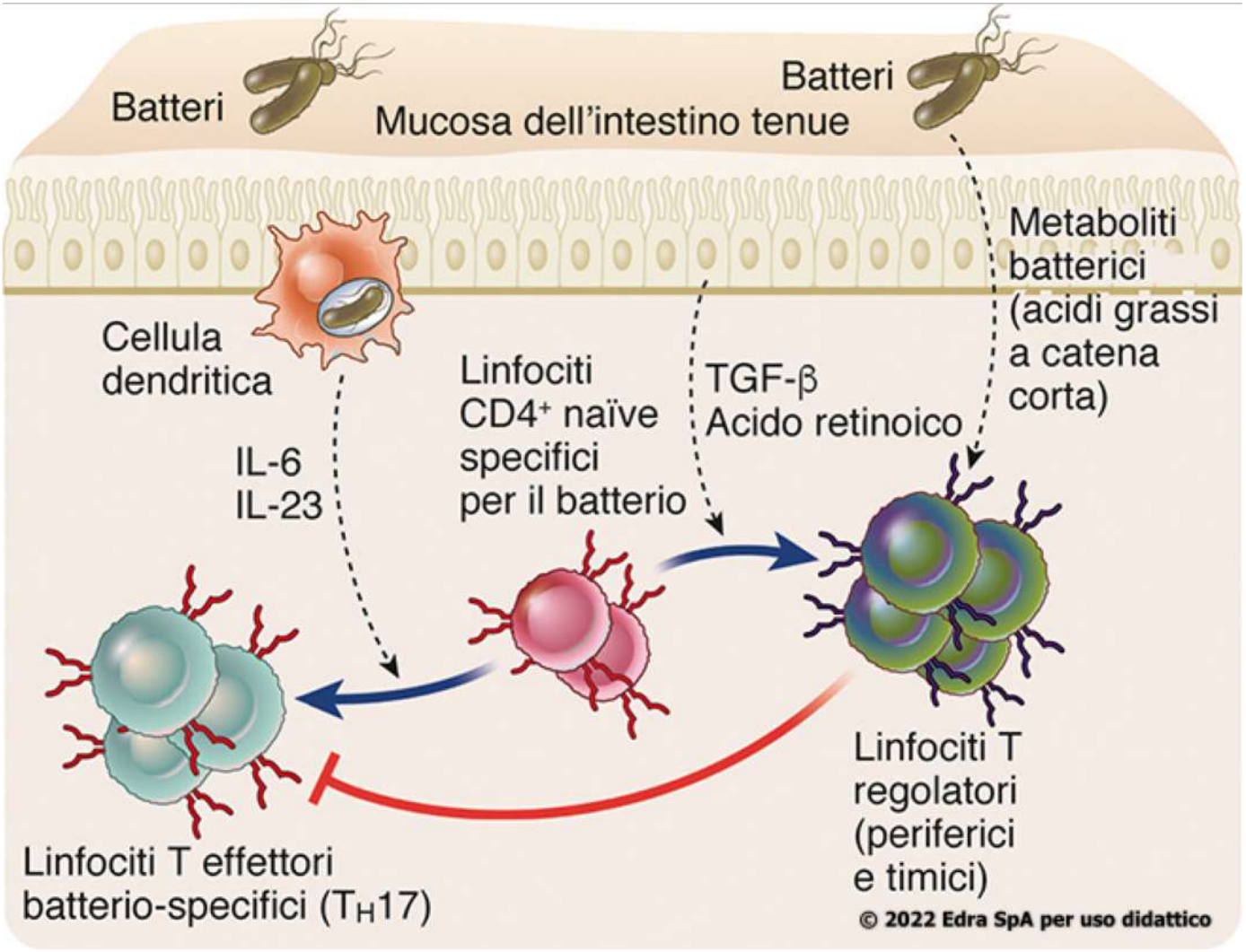


Anche il microbiota favorisce la generazione delle Treg attraverso produzione di specifiche proteine e metaboliti

GALT (gut associated lymphoid tissues)

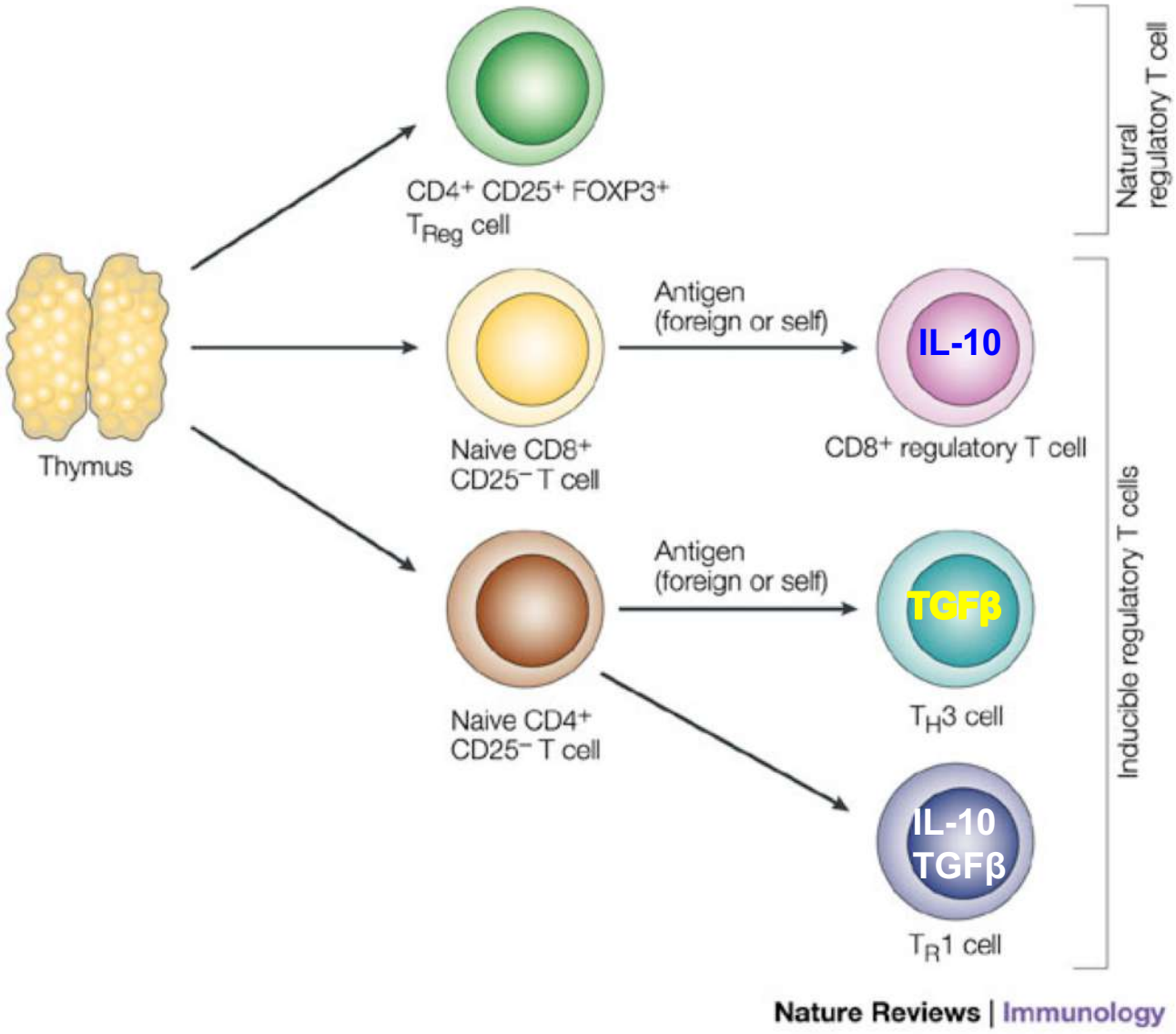
Modulation of Treg cell activity by different environmental factors. The vitamin A metabolite retinoic acid can boost regulatory T (T_{Reg}) cell activity within the intestine by inducing FOXP3 expression in naive T cells and upregulating the expression of the gut-homing receptors CC-chemokine receptor 9 (CCR9) and α4β7 integrin on both T_{Reg} and induced T_{Reg} (iT_{Reg}) cells.

I linfociti T_{reg} sono abbondanti nella mucosa intestinale



Il differenziamento dei linfociti T regolatori specifici verso antigeni batterici (Treg) è promosso dal fattore di crescita trasformante β (TGF-β) e dall'acido retinoico prodotto dalle cellule epiteliali intestinali. I linfociti T regolatori timici che migrano verso l'intestino si espandono sotto l'influenza dei metaboliti batterici. I linfociti T regolatori richiedono la presentazione di antigeni da parte delle DC (non mostrato); la natura di questi antigeni è sconosciuta.

Natural (thymus-derived) and inducible (periphery-induced) regulatory T cells



Natural regulatory T cells express the cell-surface marker CD25 and the transcription factor FOXP3 (forkhead box P3). These cells mature and migrate from the thymus and constitute 5–10% of peripheral T cells in normal mice. Other populations of antigen-specific regulatory T cells can be induced from naive $CD4^+CD25^-$ or $CD8^+CD25^-$ T cells in the periphery under the **influence of semi-mature dendritic cells, interleukin-10 (IL-10), transforming growth factor-(TGFβ) and possibly interferon-(IFNα).** The inducible populations of regulatory T cells include distinct subtypes of $CD4^+$ T cell: T regulatory 1 (T_R1) cells, which secrete high levels of IL-10, no IL-4 and no or low levels of IFNγ; and T helper 3 (T_H3) cells, which secrete high levels of TGFβ. Although $CD8^+$ T cells are normally associated with cytotoxic T-lymphocyte function and IFNγ production, these cells or a subtype of these cells can secrete IL-10 and have been called $CD8^+$ regulatory T cells.

Table 1 | **Antigen-induced T_{Reg} cells**

Cell phenotype	Examples of induction	Mechanism	References
$CD4^+ T_H1$	TCR-peptide specific	IFN-γ	121
$CD4^+ T_H2$	Autoantigen, such as insulin B-chain or GAD	IL-4	47
$CD4^+ T_H3$	Mucosal antigen, such as insulin B-chain	TGF-β	122
$CD4^+ T_R1$	Mucosal (nasal) peptides	IL-10	73,74
$CD8^+$	Priming by plasmacytoid dendritic cells (DC2)	IL-10 or IL-4	123,124
$CD8\alpha\alpha^+ \gamma\delta$ IEL	Mucosal insulin	IL-10	37
NKT (CD1D restricted)	α-galactosylceramide	IL-4	31

GAD, glutamic acid decarboxylase; IEL, intraepithelial lymphocyte; IFN-γ, interferon-γ; IL, interleukin; NKT, natural killer T; TCR, T-cell receptor; TGF-β, transforming growth factor-β; T_H, T helper; T_{Reg} cell, regulatory T cell.

Nei topi NOD allevati in condizioni "non germ-free" c'è espansione di cellule T intraepiteliali con un ruolo protettivo