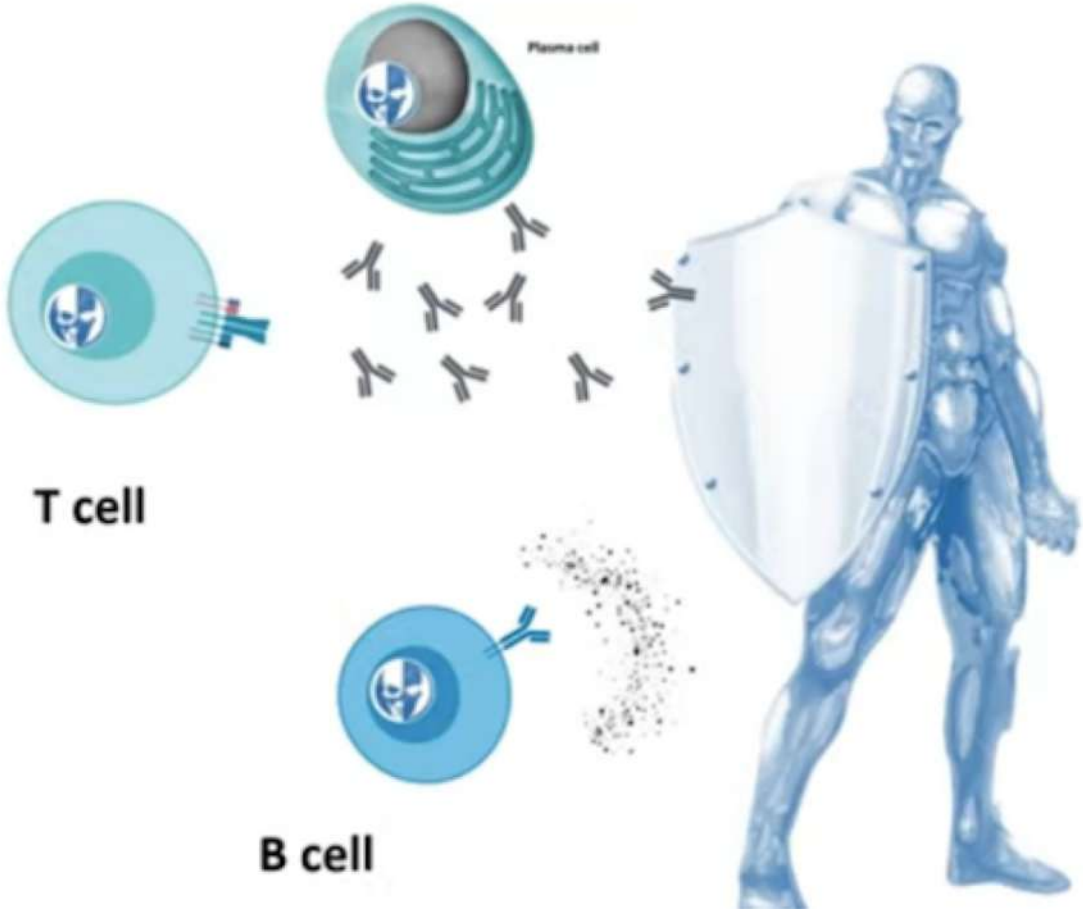
CODICE OPIS
PATOLOGIA MOLECOLARE
E IMMUNOPATOLOGIA
(1041600)

JNJC76IT

PATOLOGIA MOLECOLARE
(1041600_2)

Meccanismi di tolleranza dei linfociti T



Meccanismi di induzione della tolleranza che operano sui linfociti T

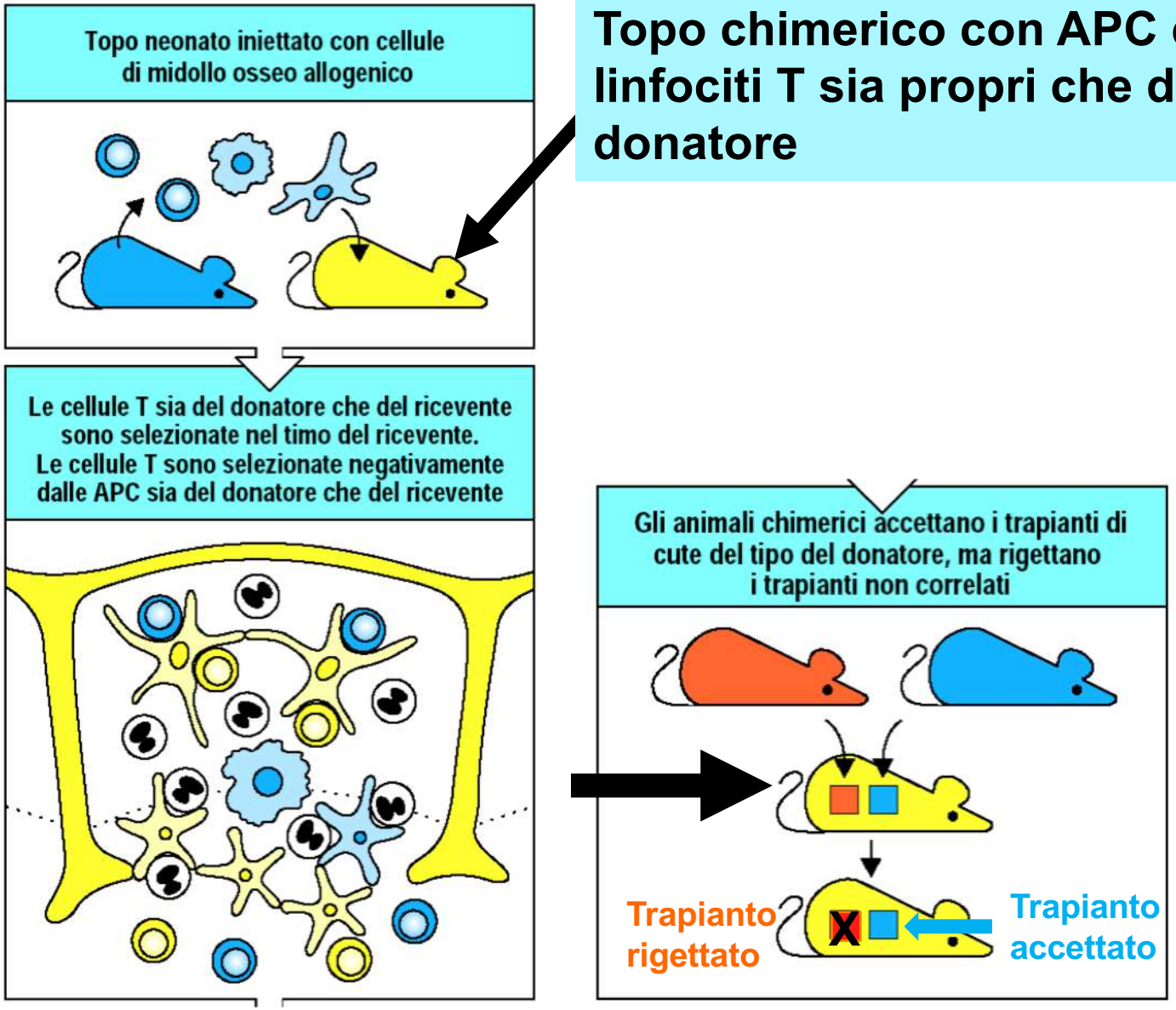
Tolleranza centrale per selezione timica positiva e negativa

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

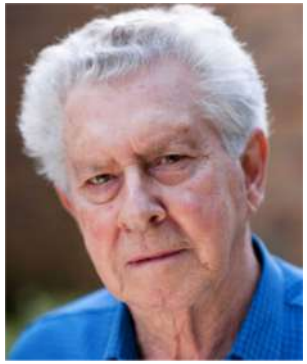
Tolleranza periferica

- **delezione (apoptosi)**
- **inattivazione o anergia (parziale o totale) indotta dalla presentazione dell'antigene in assenza di costimolazione o in un contesto non infiammatorio (assenza di attivazione delle cellule dell'immunità innata)**
- **blocco dell'attivazione (soppressione)**
- **ignoranza immunologica**

Il trasferimento di midollo allogenico in un topo neonato (non nell'adulto) stabilisce una tolleranza permanente e specifica verso i tessuti del donatore di midollo



Peter Medawar insignito del premio Nobel nel 1960 per studi condotti da negli anni 50 del 1900 sui trapianti e rigetto da parte del sistema immunitario



Jacques Miller negli anni 60 nel 1900 identificò le due popolazioni di linfociti T e B ed il ruolo del timo

Organizzazione cellulare del timo umano

Cellule presenti nel timo

cTEC
- Unique 'private' proteolytic pathways
- Efficient endogenous MHC class II loading
- Constitutive macroautophagy
- Thymic nurse cell formation

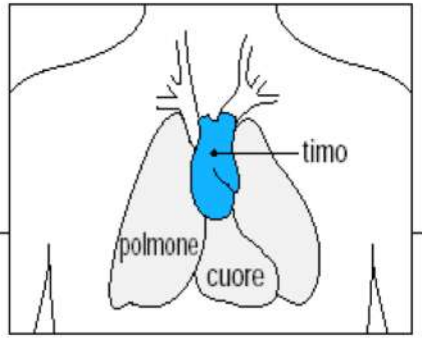
mTEC
- 'Promiscuous gene expression' (AIRE)
- 'Public' proteolytic pathways
- Efficient endogenous MHC class II loading
- Macroautophagy

Migratory cDC
SIRPα⁺CD8⁻
- Steady-state immigration from peripheral sites
- Import of peripheral antigens
- 'Public' proteolytic pathways
- Conventional MHC class II loading
- Presentation of mTEC-derived and serum-borne antigens

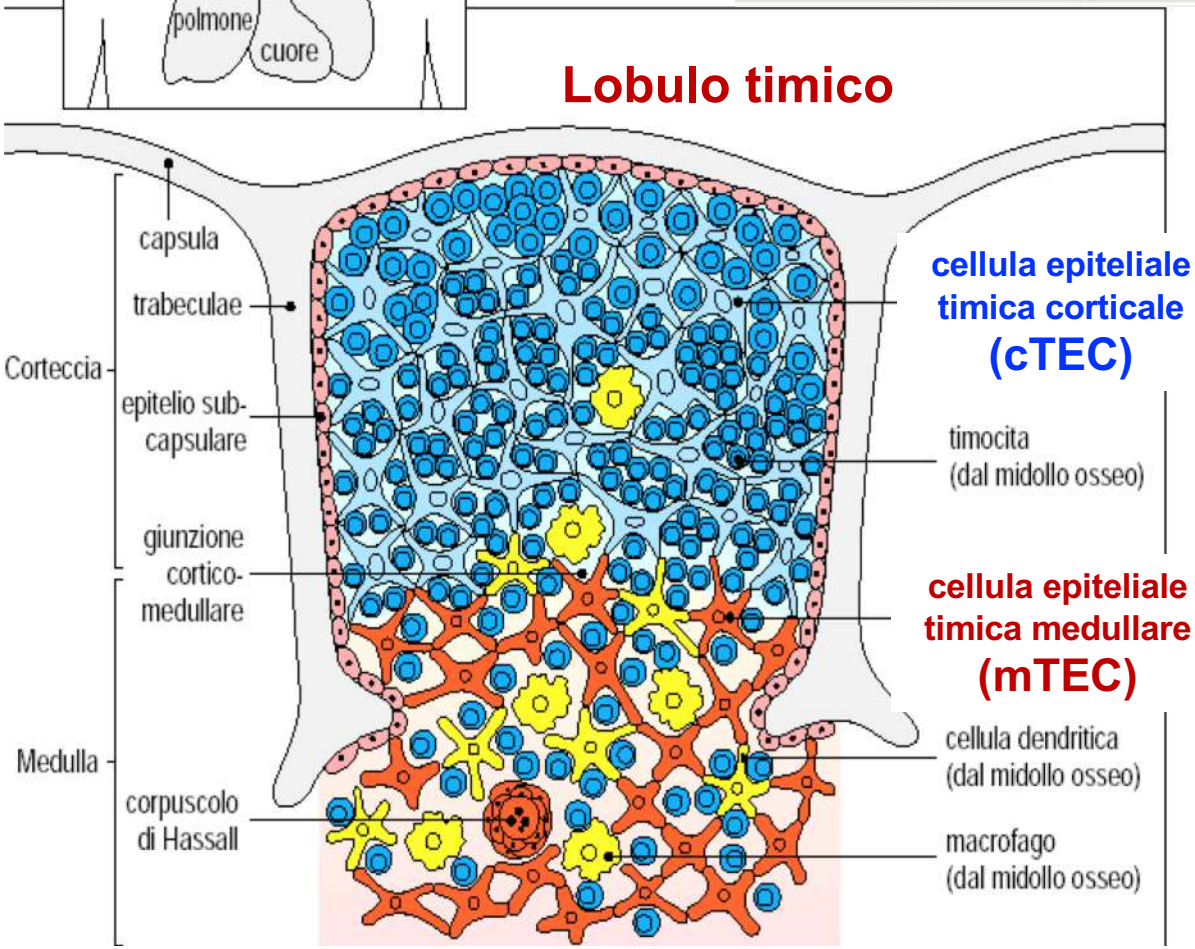
Resident cDC
SIRPα⁻CD8⁺
- Intrathymic differentiation
- 'Public' proteolytic pathways
- Conventional MHC class II loading
- Presentation of mTEC-derived and serum-borne antigens

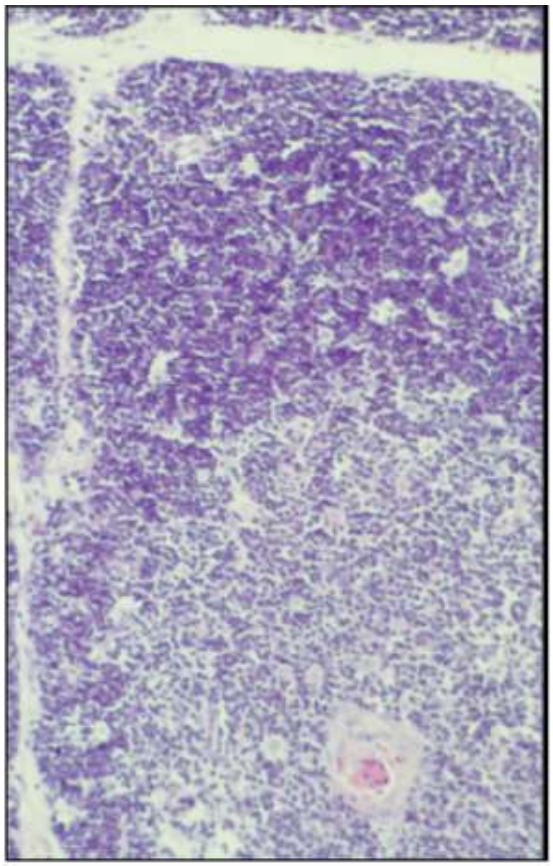
pDC
- Steady-state immigration from peripheral sites
- Import of peripheral antigens
- 'Public' proteolytic pathways
- Conventional MHC class II loading
- No presentation of mTEC-derived TRAs?

B cell
- Intrathymic or extrathymic origin?
- Efficient presentation of BCR-captured antigens
- 'Public' proteolytic pathways
- No presentation of mTEC-derived TRAs?

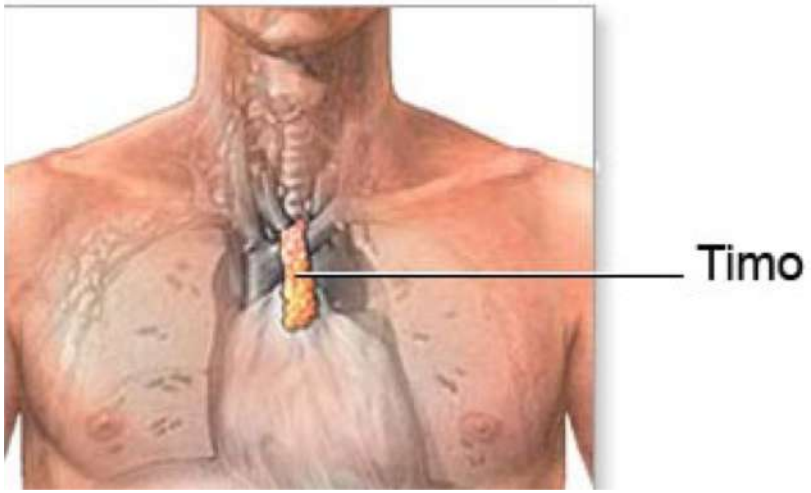


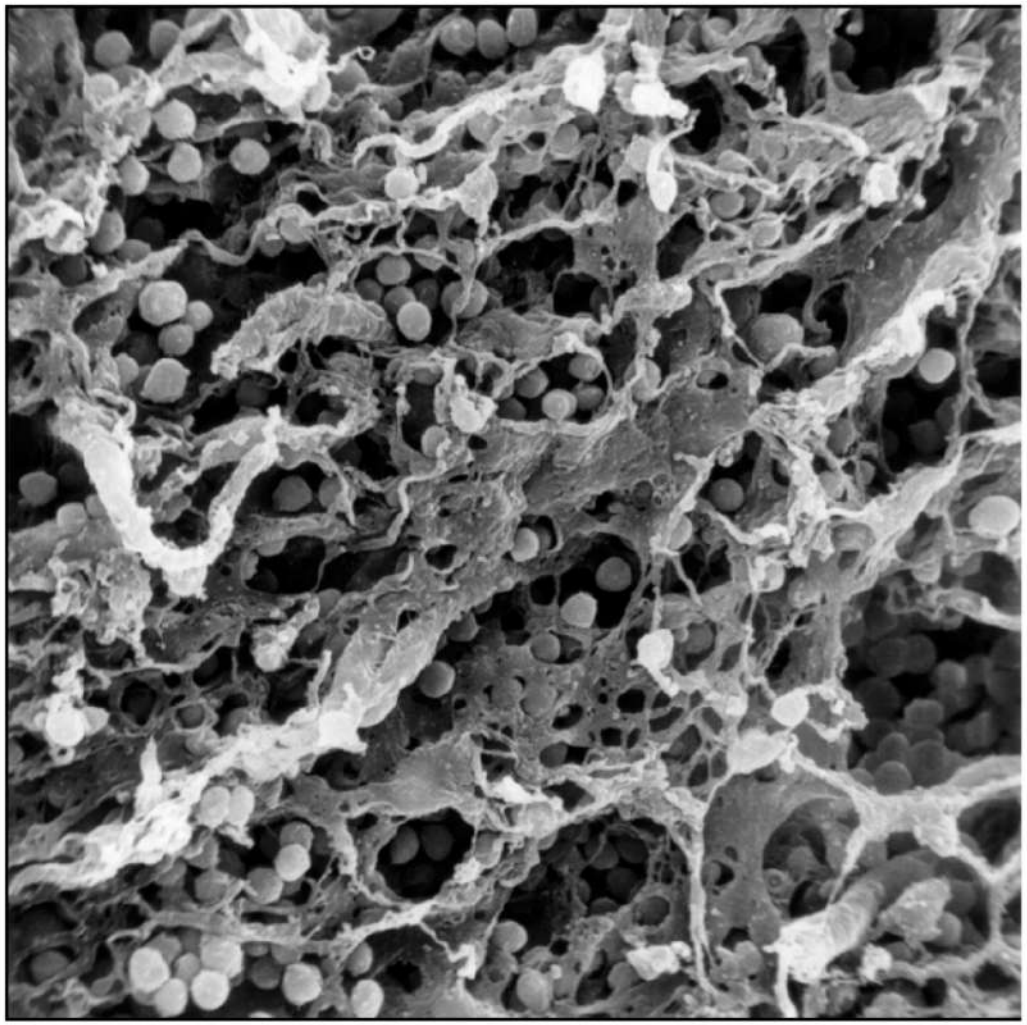
Lobulo timico





Il timo al microscopio elettronico a scansione

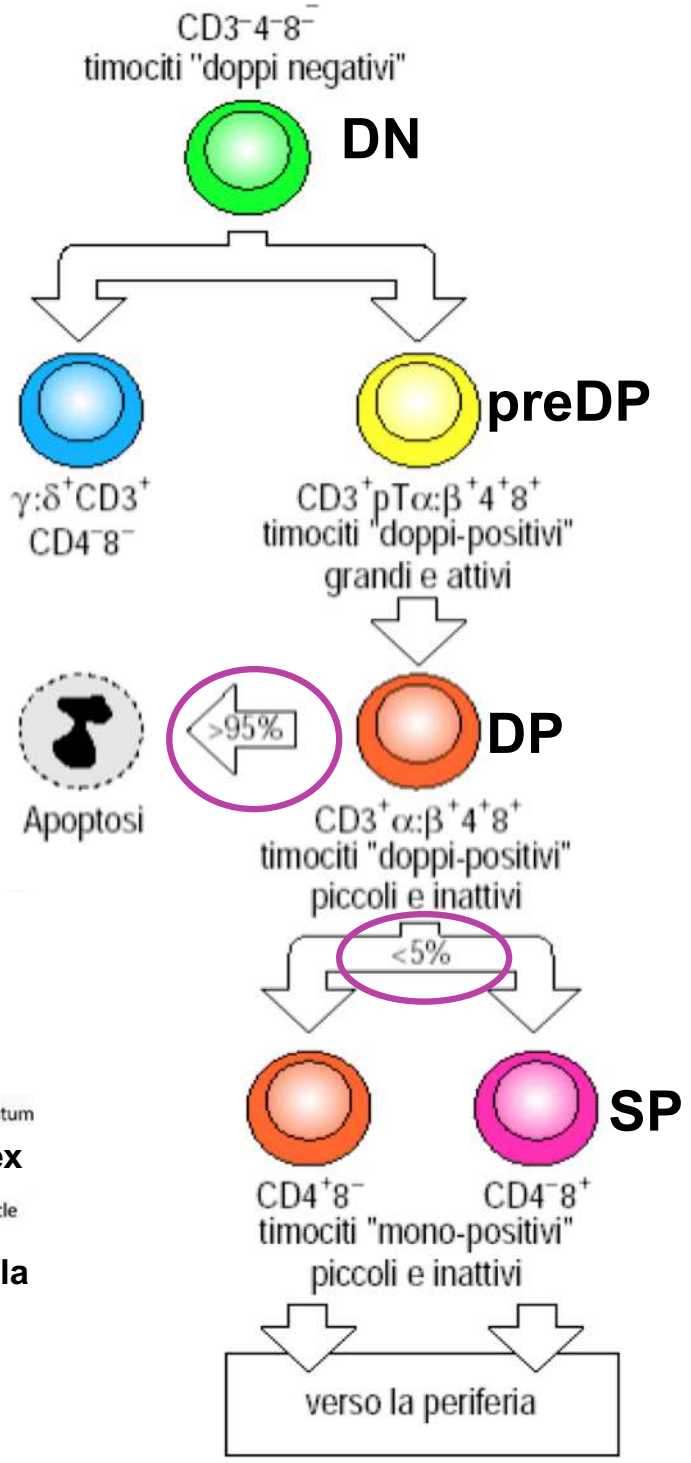


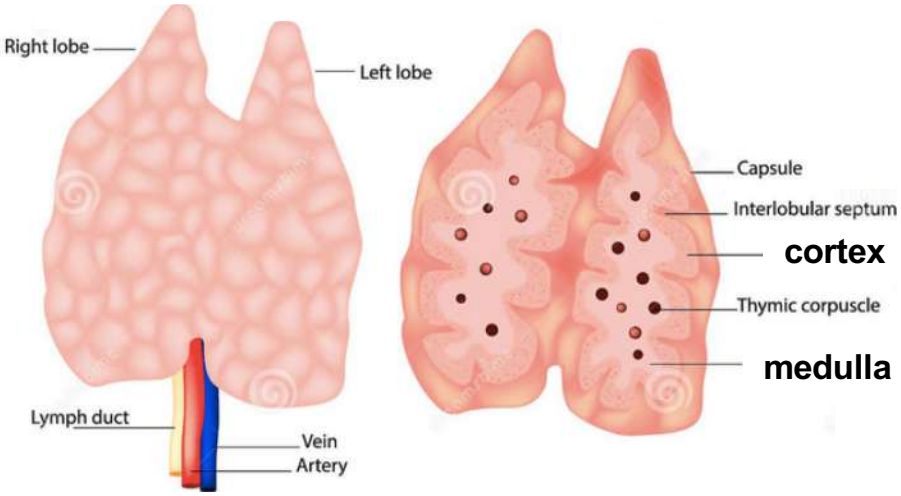


Topo ”nude” atimico

TIMO

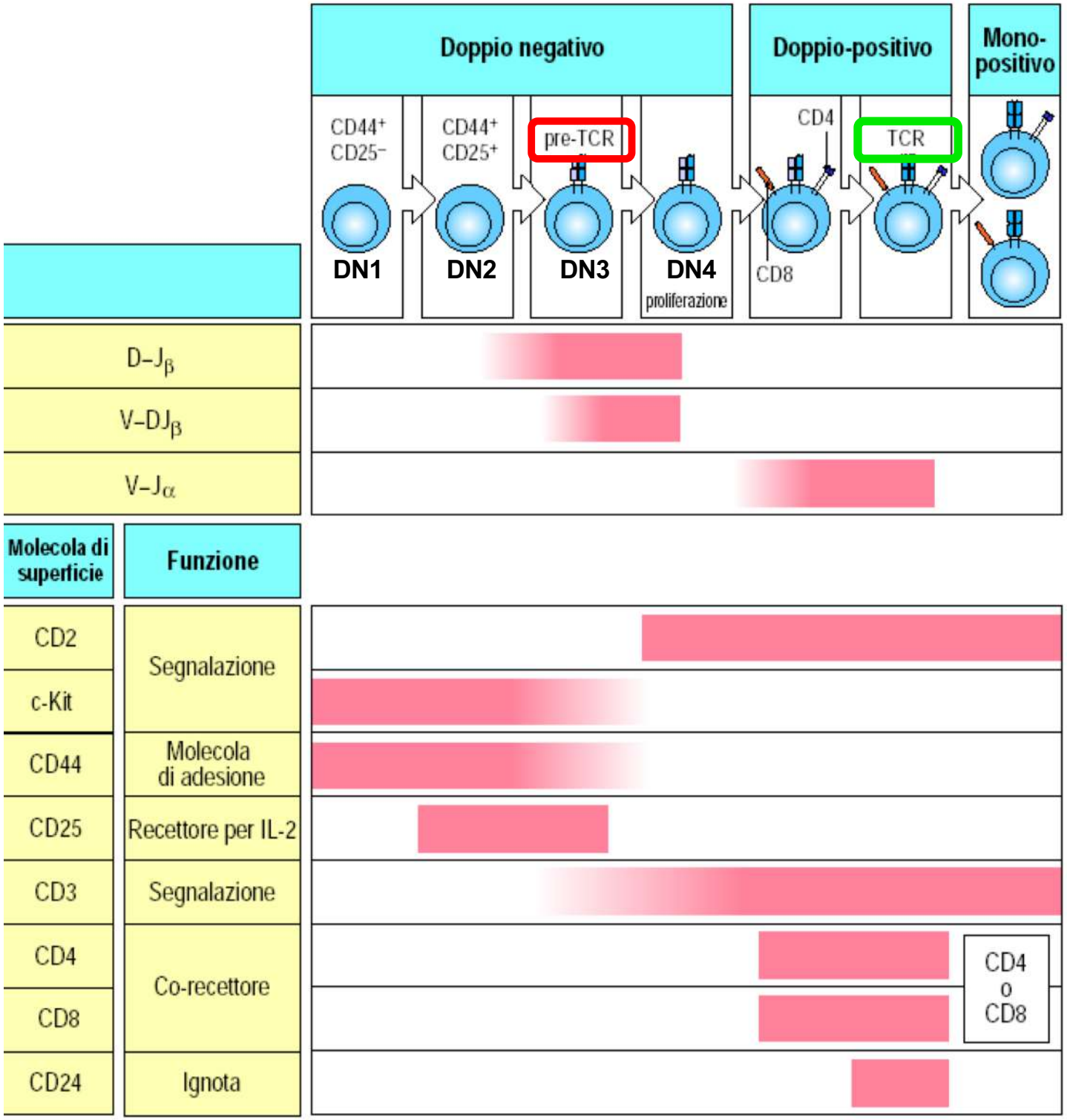
Gli stadi di sviluppo dei timociti sono identificabili attraverso l'espressione di molecole specifiche sulla superficie cellulare





REGIONE CORTICALE TIMICA (Selezione positiva)

REGIONE MIDOLLARE TIMICA (Selezione negativa)

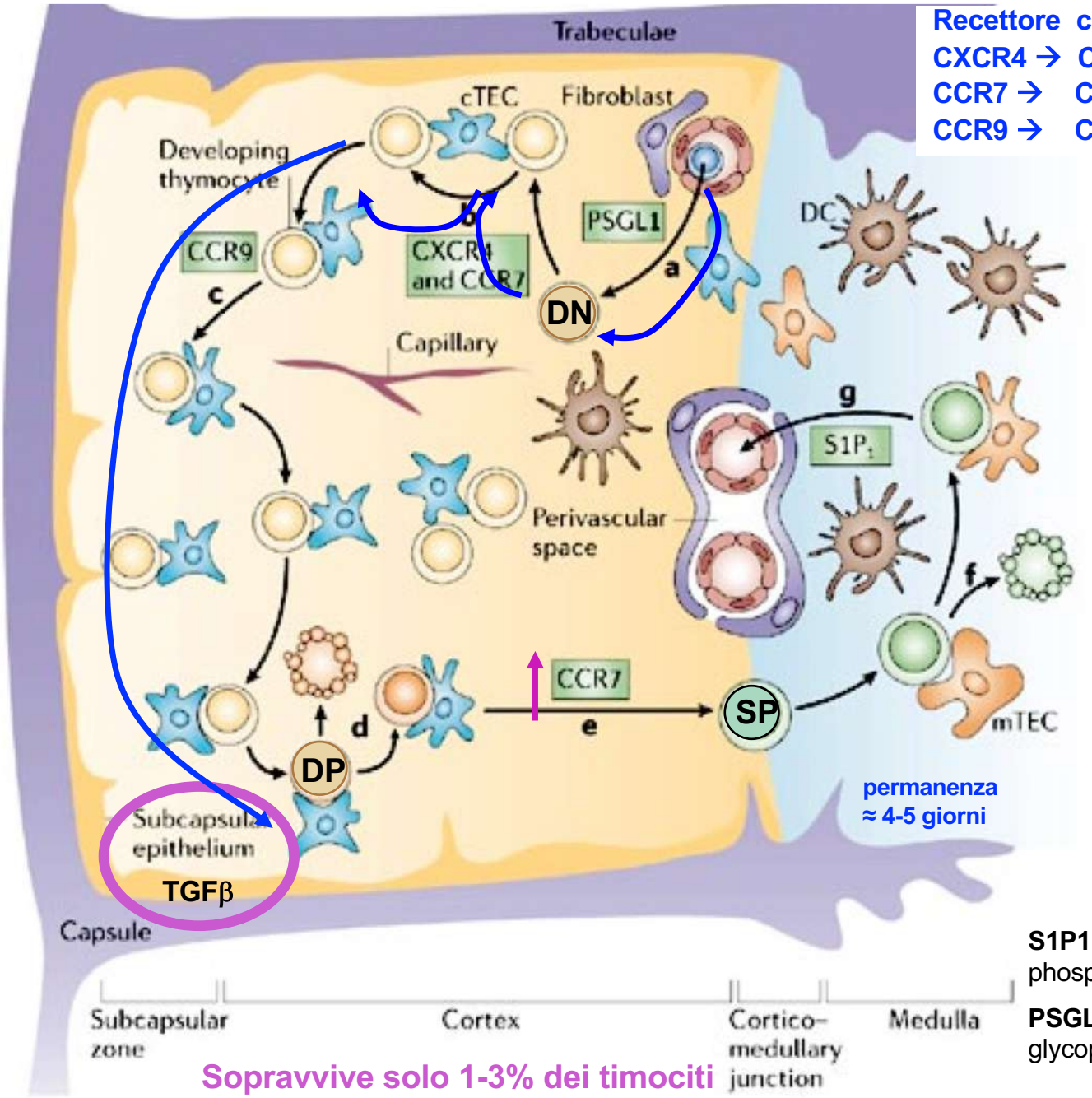


Correlazione tra gli stadi di sviluppo dei linfociti T αβ, il riarrangiamento dei geni per il TCR ed espressione di proteine di membrana

Il percorso dei linfociti T immaturi nello stroma del timo è essenziale per il loro sviluppo e selezione

Eventi chiave degli stadi di sviluppo dei timociti DN:

- signaling via Notch per interazione con il ligando Delta-like 4 (DLL4)
- Riarrangiamento produttivo del TCRβ
- espressione del preTα
- proliferazione sostenuta da IL7 e SCF (stem cell factor)
- Riarrangiamento produttivo del TCRα



Recettore	chemochina
CXCR4 →	CXCL12 (SDF)
CCR7 →	CCL19 e CCL21
CCR9 →	CCL25

permanenza ≈ 4-5 giorni

S1P1: Sphingosine-1-phosphate receptor 1

PSGL1: P-selectin glycoprotein ligand 1

Sopravvive solo 1-3% dei timociti

a | In the postnatal thymus, circulating T-lymphoid progenitor cells migrate into the thymic parenchyma through the vasculatures that are enriched around the cortico–medullary junction.

b | The outward migration of CD4-CD8- double-negative (DN) thymocytes to the capsule is regulated by chemokine signals through CXC-chemokine receptor 4 (CXCR4) and CC-chemokine receptor 7 (CCR7).

c | Further outward migration of the DN thymocytes to the subcapsular region is mediated by CCR9 signals.

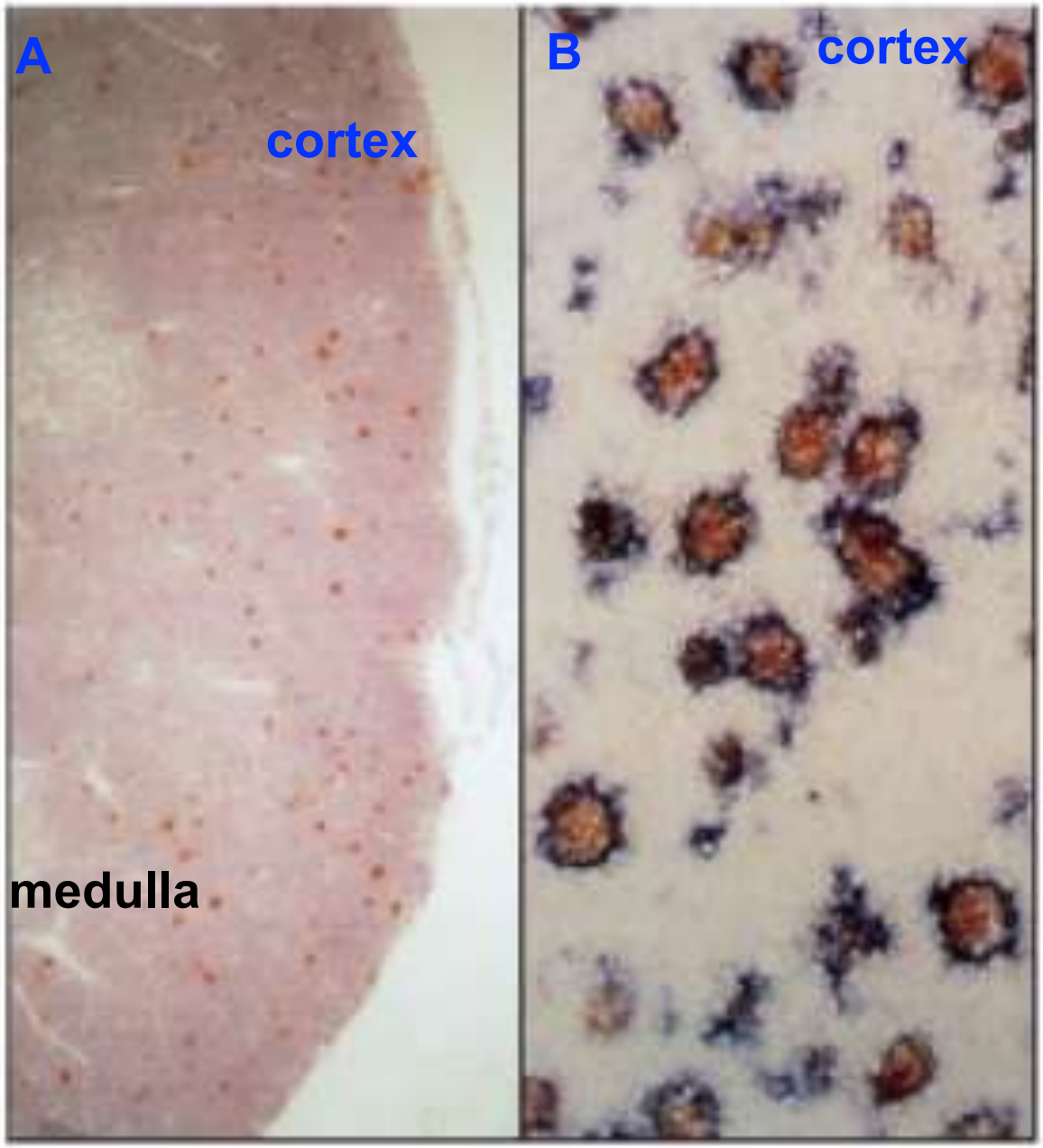
d | CD4+CD8+ double-positive (DP) thymocytes generated in the outer cortex are motile, interacting with stromal cells that are localized in the cortex for positive and negative selection.

E | Positively selected DP thymocytes that gain the capability to survive and differentiate into CD4 or CD8 single-positive (SP) thymocytes show an increase in the surface expression of CCR7, through which the cells are attracted to the medulla, which expresses CCR7 ligands.

f | In the medulla, further selection of SP thymocytes includes the deletion of tissue-specific-antigen-reactive T cells and the generation of regulatory T cells.

g | Mature SP thymocytes express **sphingosine-1-phosphate receptor 1 (S1P1),** through which the cells are attracted back to the circulation that contains a high concentration of sphingosine-1-phosphate. cTEC, cortical thymic epithelial cell; DC, dendritic cell; mTEC, medullary thymic epithelial cell; **PSGL1, P-selectin glycoprotein ligand 1.**

Nella corticale del timo, i timociti in apoptosi sono eliminati dai macrofagi

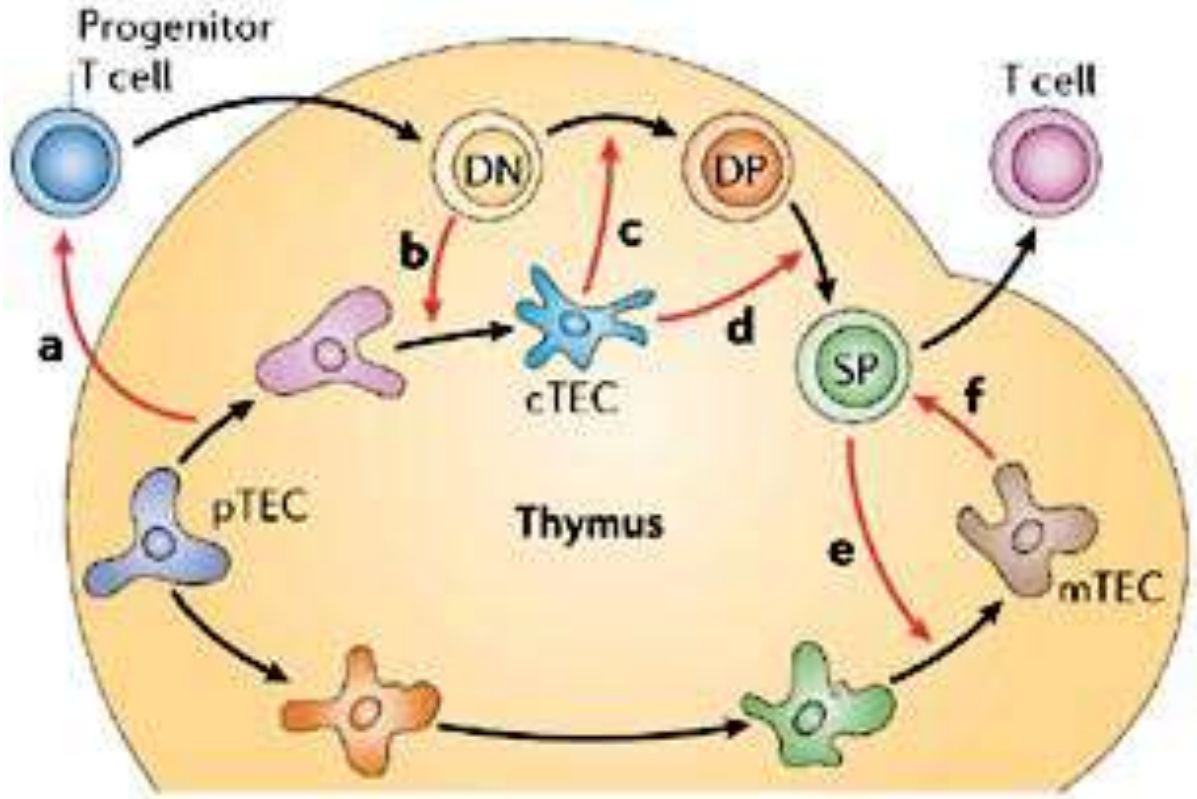


A Corticale del timo (a destra) e parte della midollare (sinistra) dove le cellule apoptotiche sono colorate in rosso.

B Sezione della corticale del timo a maggiore ingrandimento dove le cellule apoptotiche sono colorate in rosso ed i macrofagi in blu. Si possono apprezzare i corpi apoptotici all'interno dei macrofagi.

pTEC

Il crosstalk tra timociti e cellule stromali timiche è essenziale per la maturazione di entrambi i tipi cellulari



a) Le pTEC attraggono i progenitori linfoidi T nel timo

b) i timociti DN in sviluppo sono necessari per la generazione delle cTEC a partire dalle pTEC

c) cTEC forniscono l'ambiente appropriato al passaggio da DN a DP

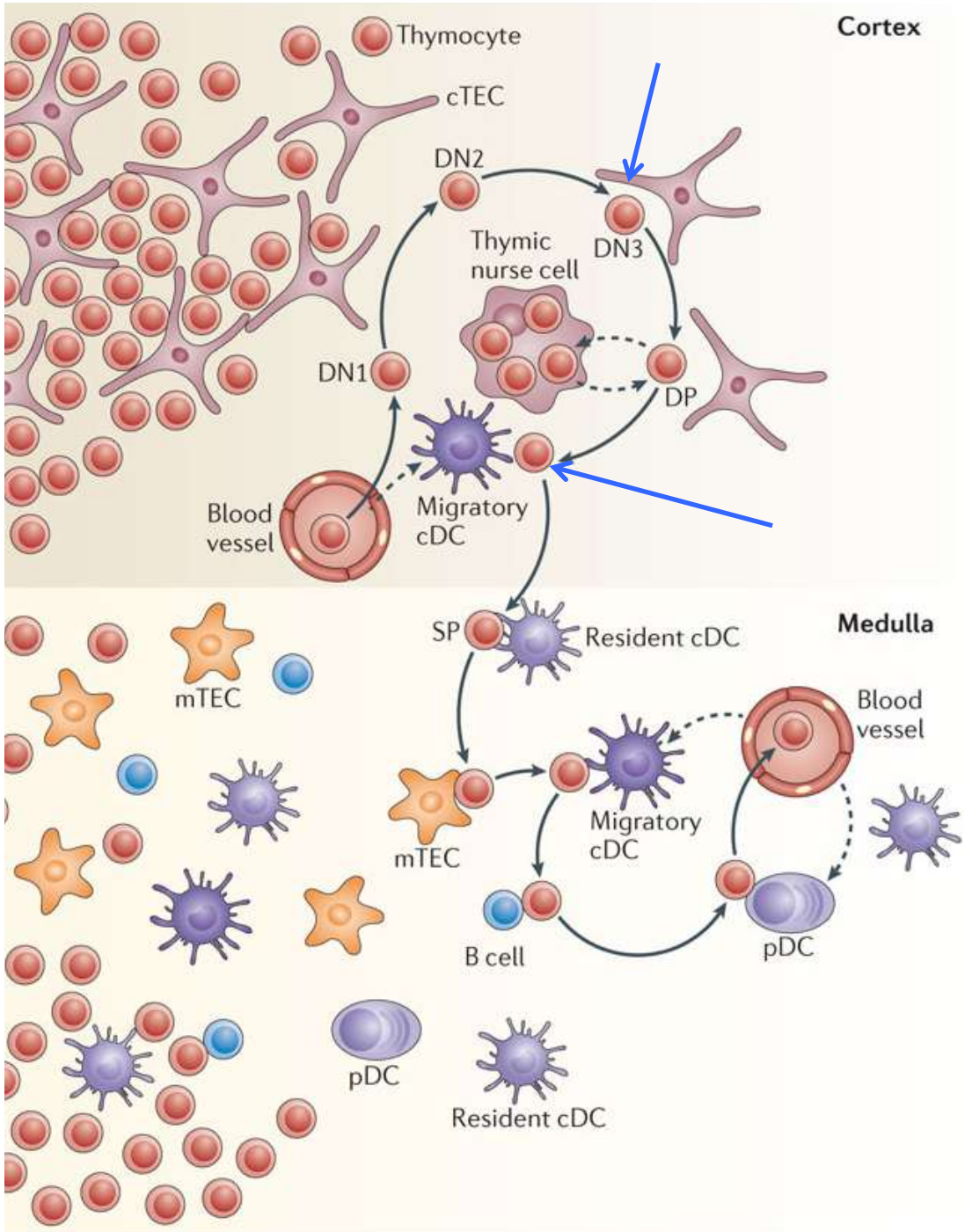
d) cTEC promuovono anche la selezione positiva delle DP a SP

e) i SP sono essenziali per la maturazione delle mTEC

f) mTEC forniscono le condizioni per l'ulteriore selezione (negativa) e maturazione dei SP che sono pronti ad uscire dal timo

pTEC = progenitor Thymic Epitelial Cell

Stromal cell interactions during T cell development



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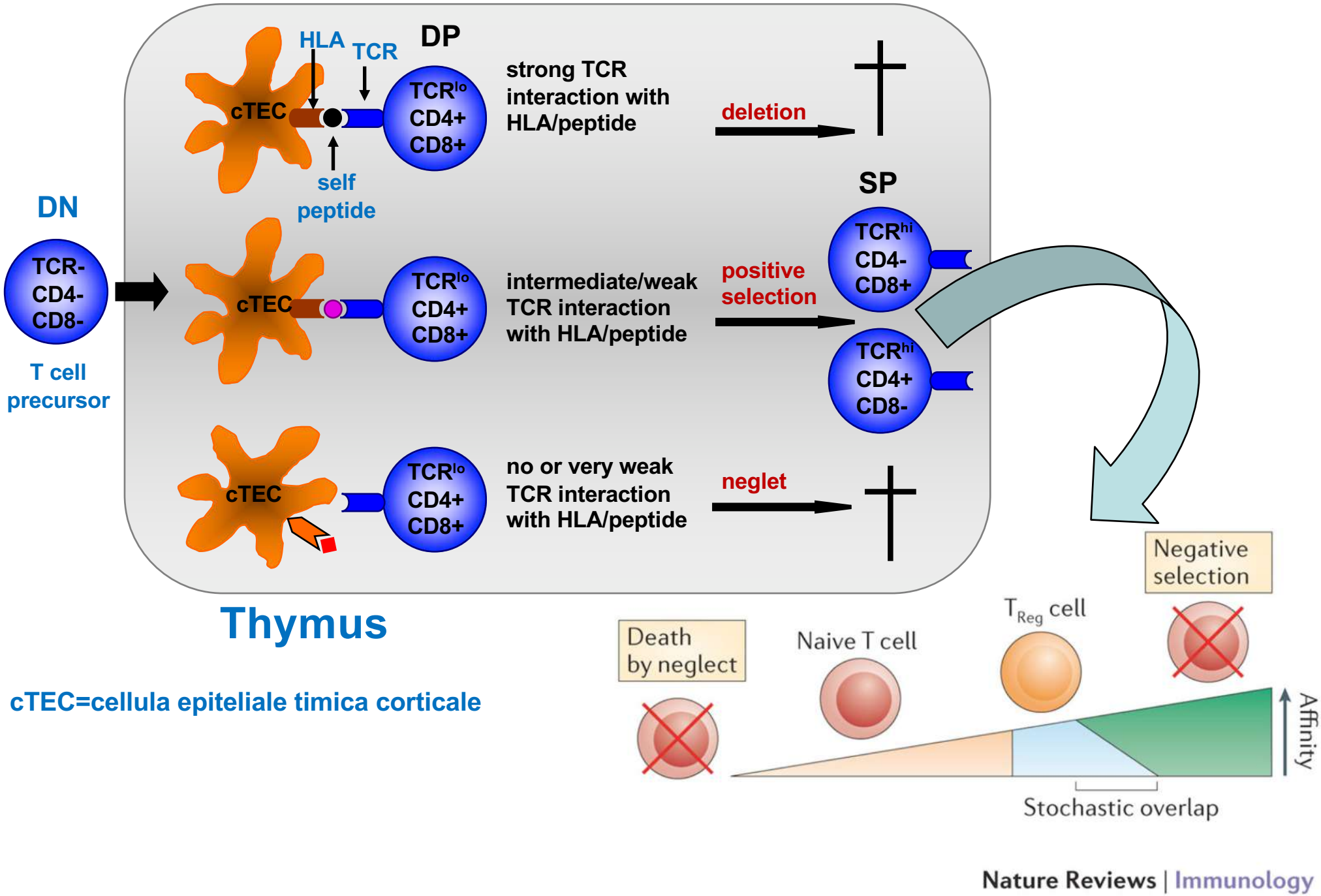
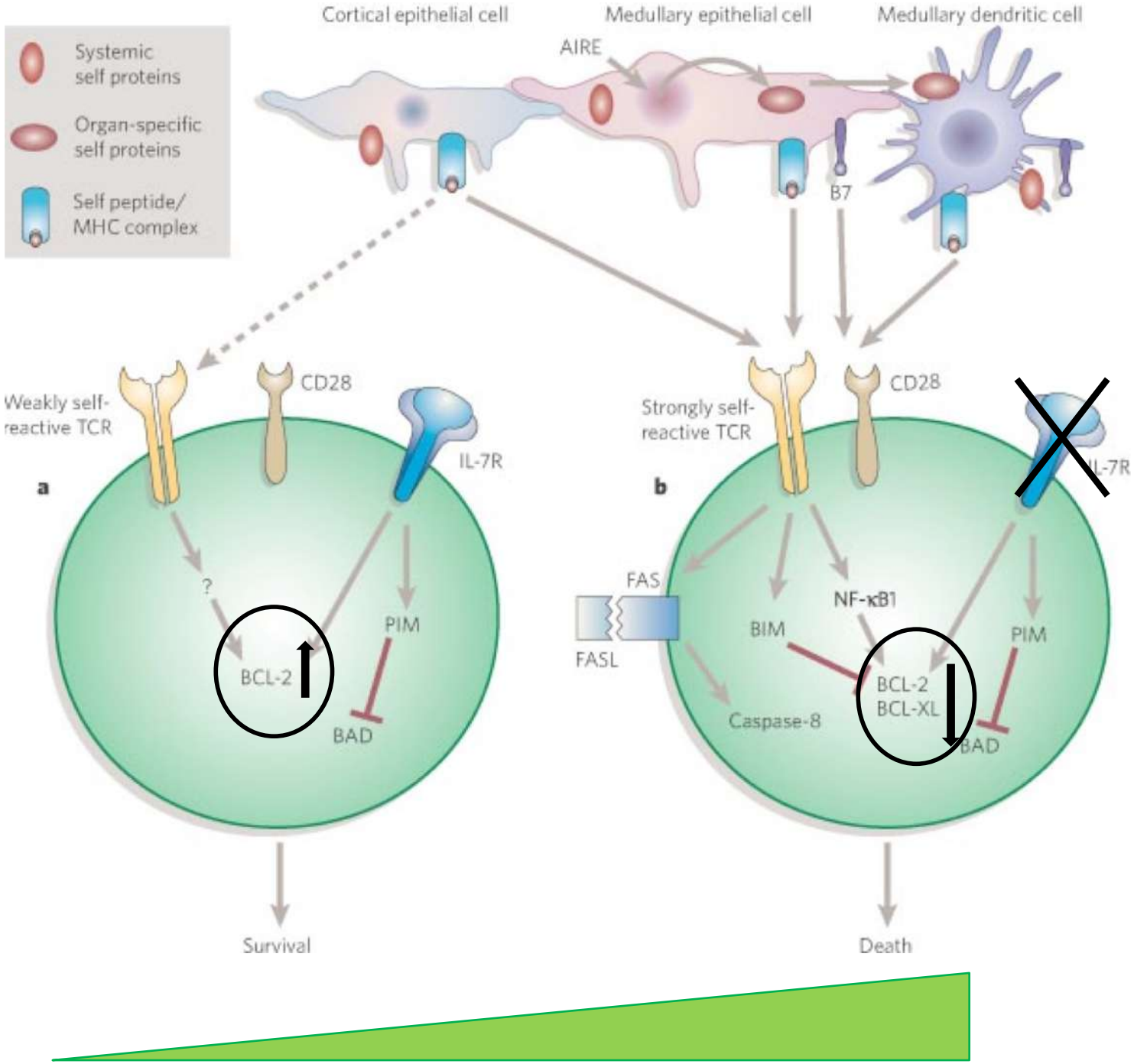
Successive stages of **double-negative (DN) T cell development** are accompanied by an outward movement of thymocytes towards the subcapsular zone. Subsequent to β-selection at the DN3 stage, double-positive (DP) cells 'randomly walk' through the outer cortex, which possibly facilitates the 'scanning' of cortical thymic epithelial cells (cTECs) for positively selecting ligands. At this stage**, DP thymocytes** may be engulfed by cTECs and form so-called **thymic nurse cells**; however, the molecular control and physiological relevance of this process remains to be established. Interactions between DP cells and cortical conventional dendritic cells (cDCs) may lead to negative selection. It remains unknown whether these cortical cDCs exclusively belong to the migratory signal-regulatory protein-α (SIRPα)-expressing subset.
Positively selected CD4 or CD8 lineage-committed thymocytes relocate into the medulla by directed migration. Upon reaching the medulla, single-positive (SP) cells again assume a 'random walk' motion pattern. Through this random migration, SP cells may now 'scan' resident and migratory cDCs, plasmacytoid dendritic cells (pDCs), medullary thymic epithelial cells (mTECs) and B cells. It is estimated that SP cells engage in around five contacts with antigen-presenting cells (APCs) per hour, so that during their **4- to 5-day** residency in the medulla, T cells may serially interact with several hundred APCs. Solid arrows indicate main migratory pathways that are involved in thymocyte selection. Dashed arrows indicate other relevant migratory pathways. b | Key functional properties of thymic APCs that are discussed in this Review. AIRE, autoimmune regulator; BCR, B cell receptor; TRA, tissue-restricted antigen.

Affinity model of thymocyte selection



cTEC=cellula epiteliale timica corticale

Nel timo, l'avidità del TCR è determinante per la selezione del linfocita T immaturo



Map of pathways for deleting T cells with strongly and weakly self-reactive TCRs in the thymus. Two examples are shown of what is likely to be a continuum:

a, a TCR with weak self reactivity, where TCR and IL-7R pro-survival pathways dominate;

b, a TCR with strong self reactivity where TCR-induced BIM and FAS death pathways predominate. Similar pathways also act in mature peripheral T cells, where competition for limiting IL-7 and self-peptide/MHC, and induction of B7 ligands for CD28, add extra levels of extrinsic control.

Peculiarità delle cTEC nella generazione di un set “speciale” di peptidi che si associa alle molecole MHC di classe I e II favorendo la selezione timica positiva

Per generare un repertorio ottimale di timociti SP CD4+, le cTEC esprimono:

- **La catepsina L (proteasi lisosomiale)**
- **Una serin-proteasi timo-specifica (TSSP) presente nei compartimenti endosomiali-lisosomiali**

Per generare un repertorio ottimale di timociti SP CD8+, le cTEC esprimono:

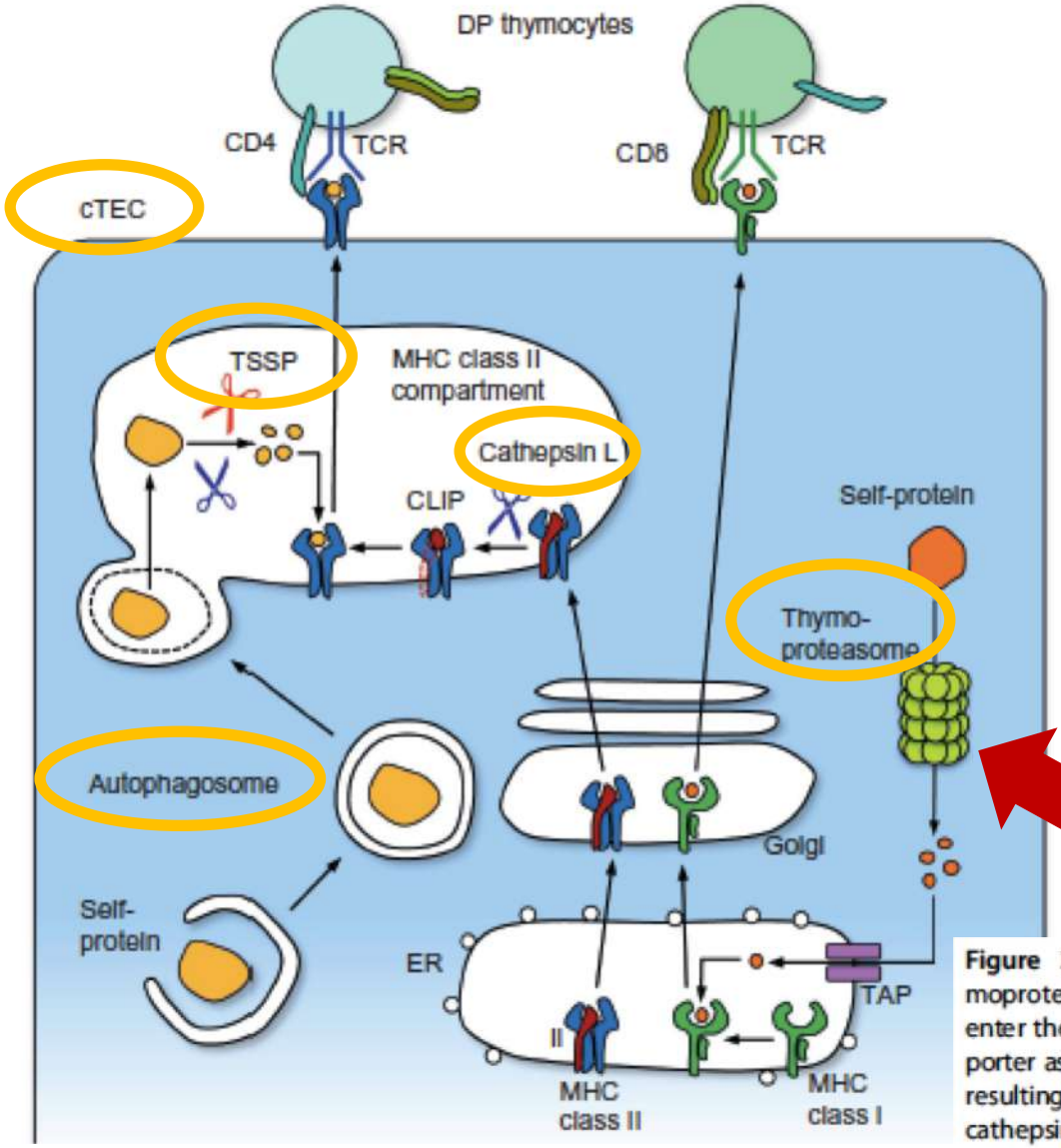
- **Il timoproteasoma**

Inoltre, le cTEC mostrano livelli elevati di macroautofagia

SP= singolo-positivo

Le cTEC sono dotate di pathways “unici” di presentazione dell’antigene da parte di MHC classe I e II (formazione di un pool di peptidi “peculiari”)

Pathways classici di presentazione dell’antigene



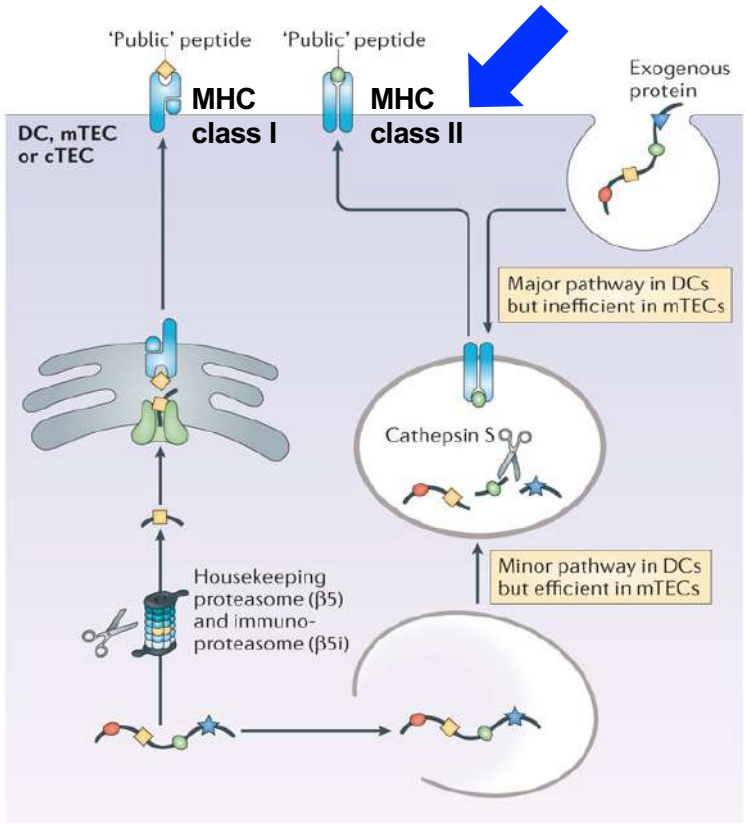
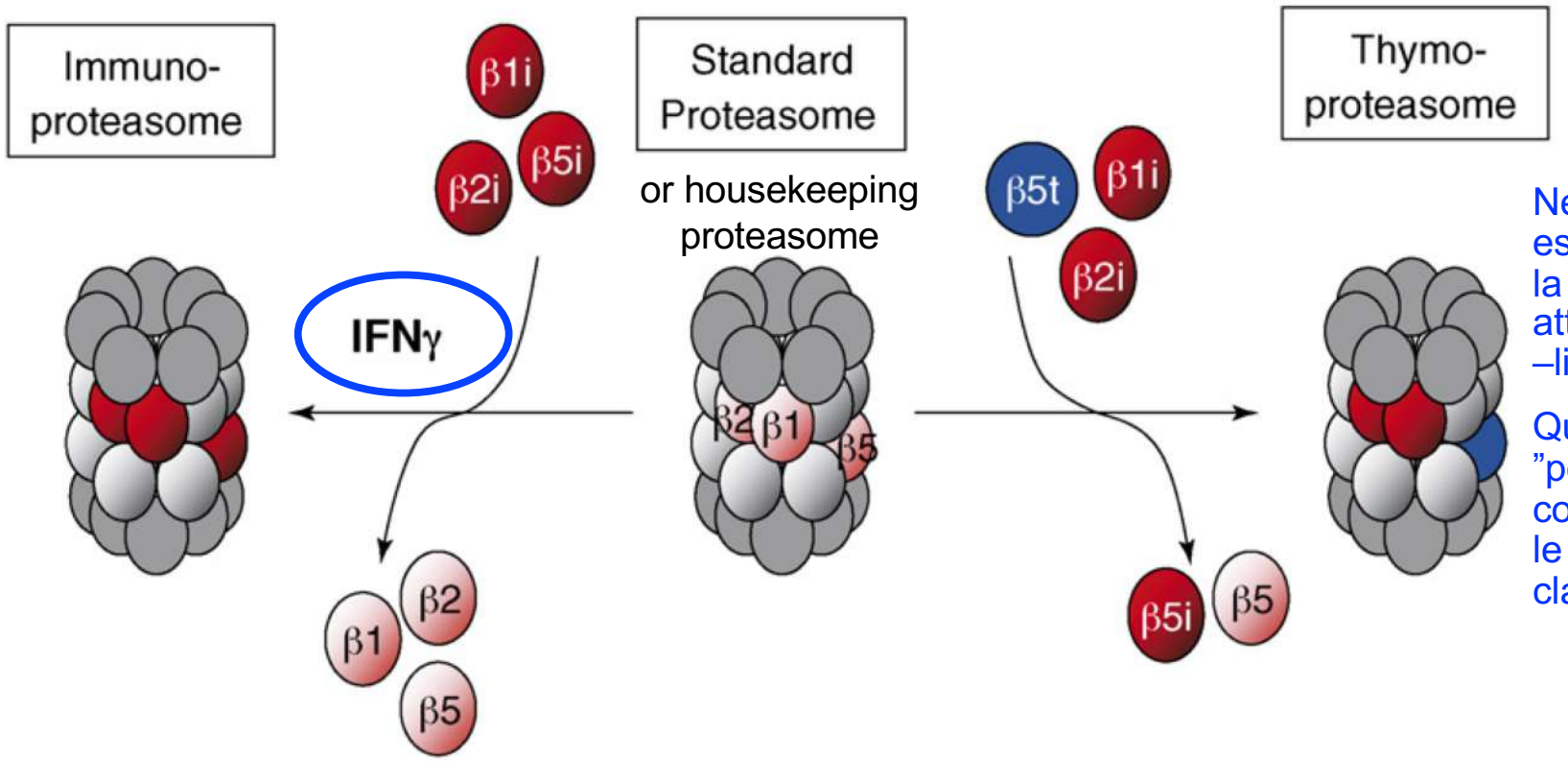


Figure 3 Unique antigen presentation pathways in cTECs. β5t-containing thymoproteasomes generate a set of self-peptides presented by MHC class I. The peptides enter the lumen of the endoplasmic reticulum (ER) through an ATP-dependent transporter associated with antigen processing (TAP) and are loaded onto MHC class I. The resulting complexes are transported to the cell surface. Endosomal proteases, including cathepsin L and TSSP, generate a set of self-peptides presented by MHC class II. Cathepsin L is also involved in the maturation of MHC class II by degrading the Ii chain. Constitutive autophagy is also involved in the production of MHC-associated self-peptides in the majority of cTECs. Such proteolytic processes unique to cTECs are important for the production of self-pMHC complexes that induce the positive selection of DP thymocytes.

Il timoproteasoma genera un set di peptidi ottimale per la selezione positiva di timociti CD8+ SP

Il proteasoma 20S contiene 3 subunità β (β1, β2 e β5) che tagliano le proteine preferenzialmente dopo residui aminoacidici con carica negativa, positiva o aminoacidi idrofobici (attività caspasica, “tripsina-like” e “chimotripsina-like”), rispettivamente.



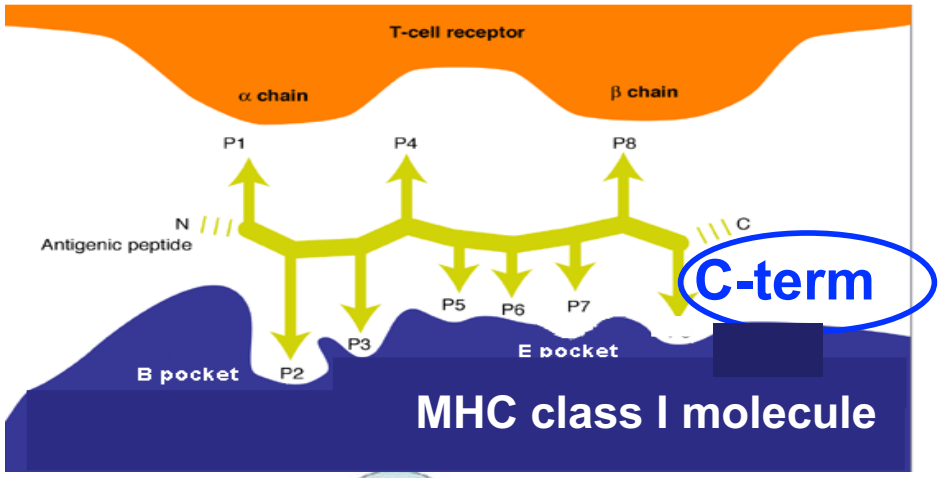
Nel timoproteasoma espresso dalla cTEC, la subunità β5t ha un’ attività chimotripsina –like ridotta.

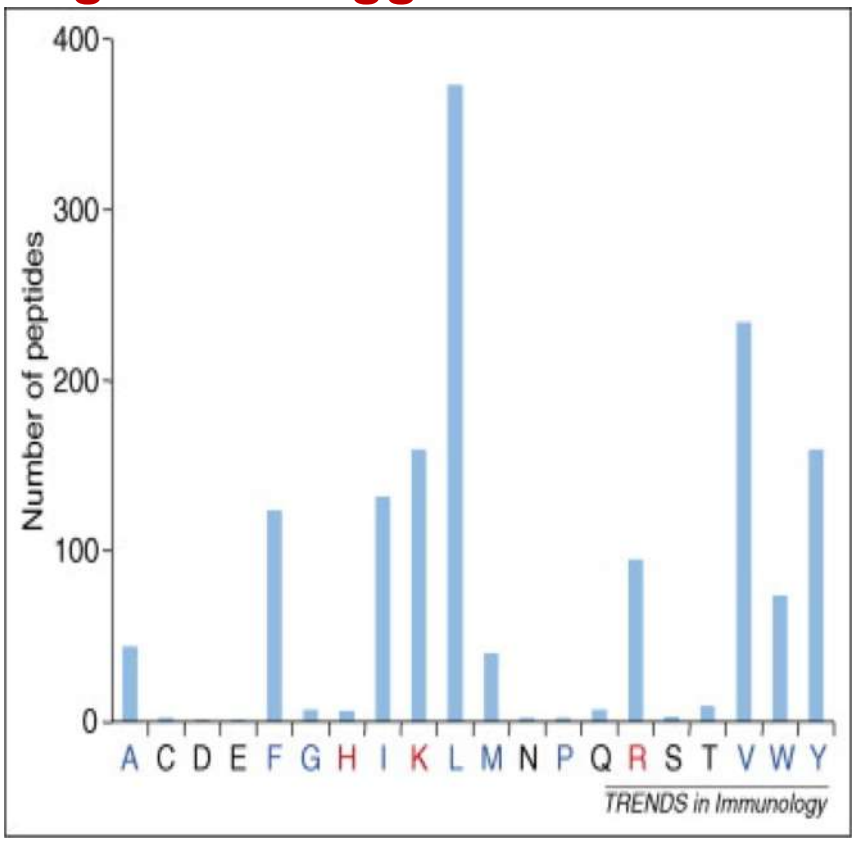
Questo genera un set ”peculiare” di peptidi con bassa affinità per le molecole MHC di classe I.

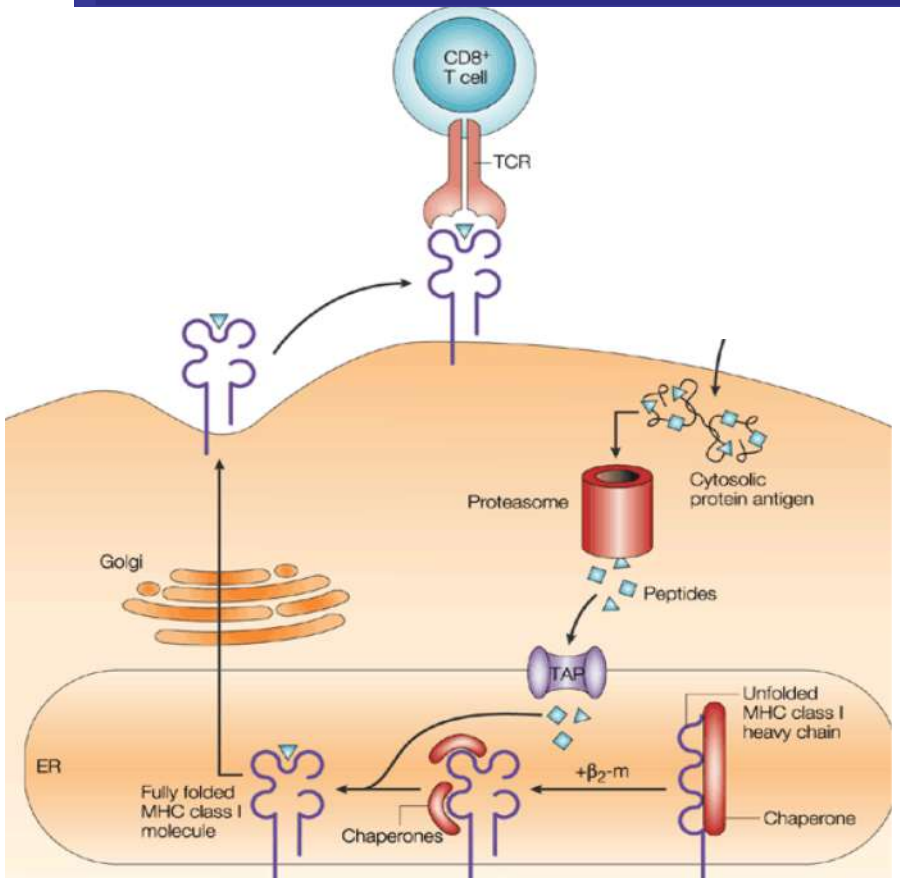
Topi knockout per la subunità β5t hanno un numero ridotto di timociti CD8+ SP

Proteasomes, immunoproteasomes, and thymoproteasomes. 20S proteasomes are responsible for proteolytic activity of the proteasomes and are composed of 28 subunits arranged as a cylinder in four heteroheptameric rings with a α1–7 β1–7β1–7 α1–7 configuration. Constitutive or standard proteasome configuration is shown in the middle and is expressed by the majority of cells in the body. In vertebrates, three additional subunits, β1i, β2i, and β5i, are induced by interferon-γ and preferentially incorporated into proteasomes, producing so-called immunoproteasomes (left). A newly identified catalytic subunit of 20S proteasomes, β5t, is incorporated in place of β5 or β5i, and together with β1i and β2i forms the so-called thymoproteasome, which is specifically expressed in cortical epithelial cells (right).

Gran parte delle molecole MHC di classe I lega con maggiore affinità i peptidi con C-terminale idrofobico



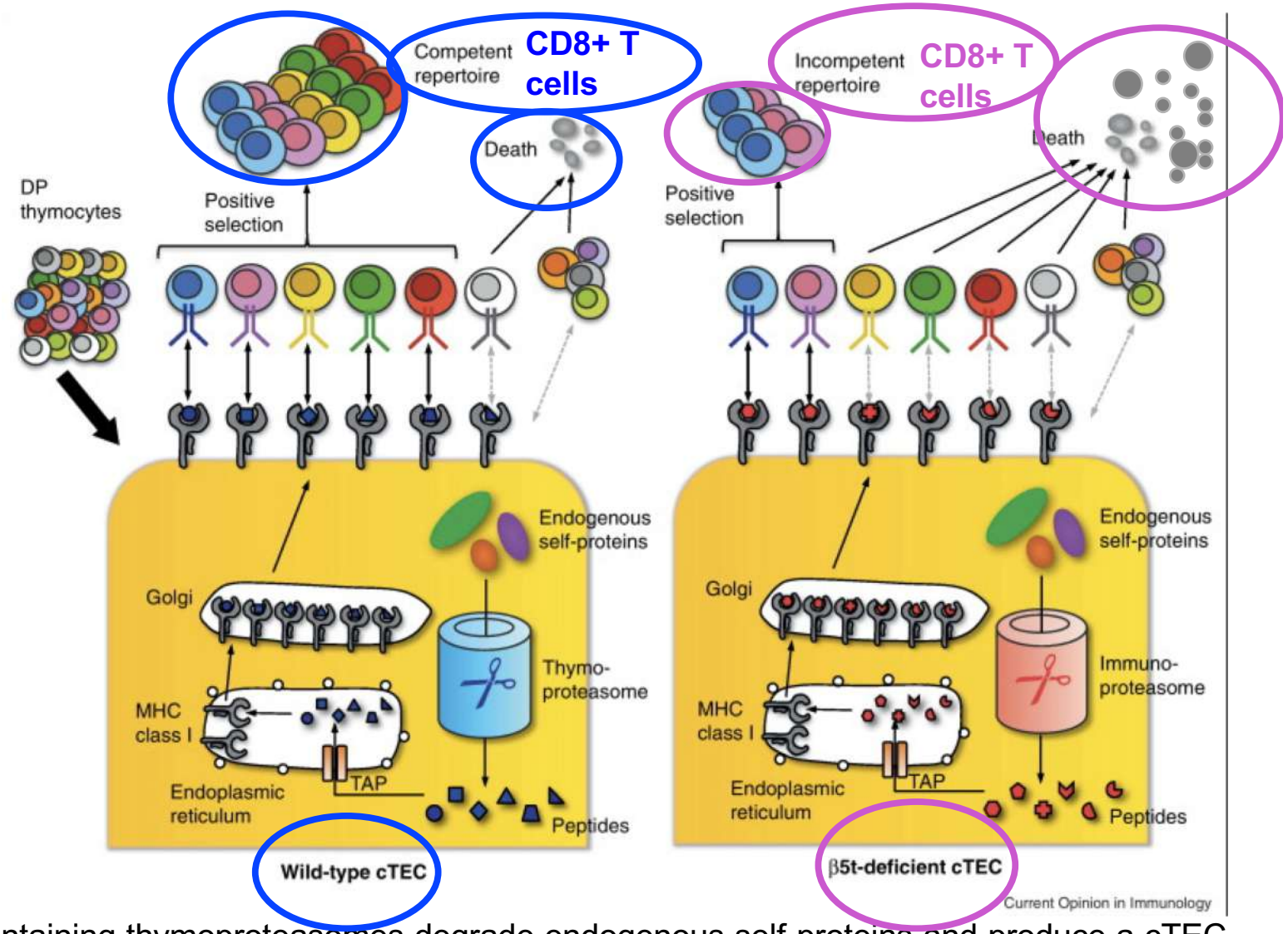




Most peptides presented by major histocompatibility complex (MHC) class I have hydrophobic C termini. A total of 1474 peptides of eight to ten residues in length presented by human leukocyte antigen (HLA)-A and HLA-B with high affinity binding were collected from the EPIMHC database (http://bio.dfci.harvard.edu/epimhc/index.html), and the frequency of the C-terminal amino acids were determined. **Approximately 80% of the high-affinity binding peptides have hydrophobic C termini (i.e. A, F, G, I, L, M, P, V, W, Y in blue letters).** More rarely, some alleles of MHC class I prefer peptides with basic C termini (H, K, R in red letters; 17% of the presented peptides).

Il timoproteasoma genera un pool di peptidi che, complessivamente, ha una più bassa affinità per le molecole di classe I

Rilevanza del timoproteasoma nella selezione positiva dei linfociti T CD8+



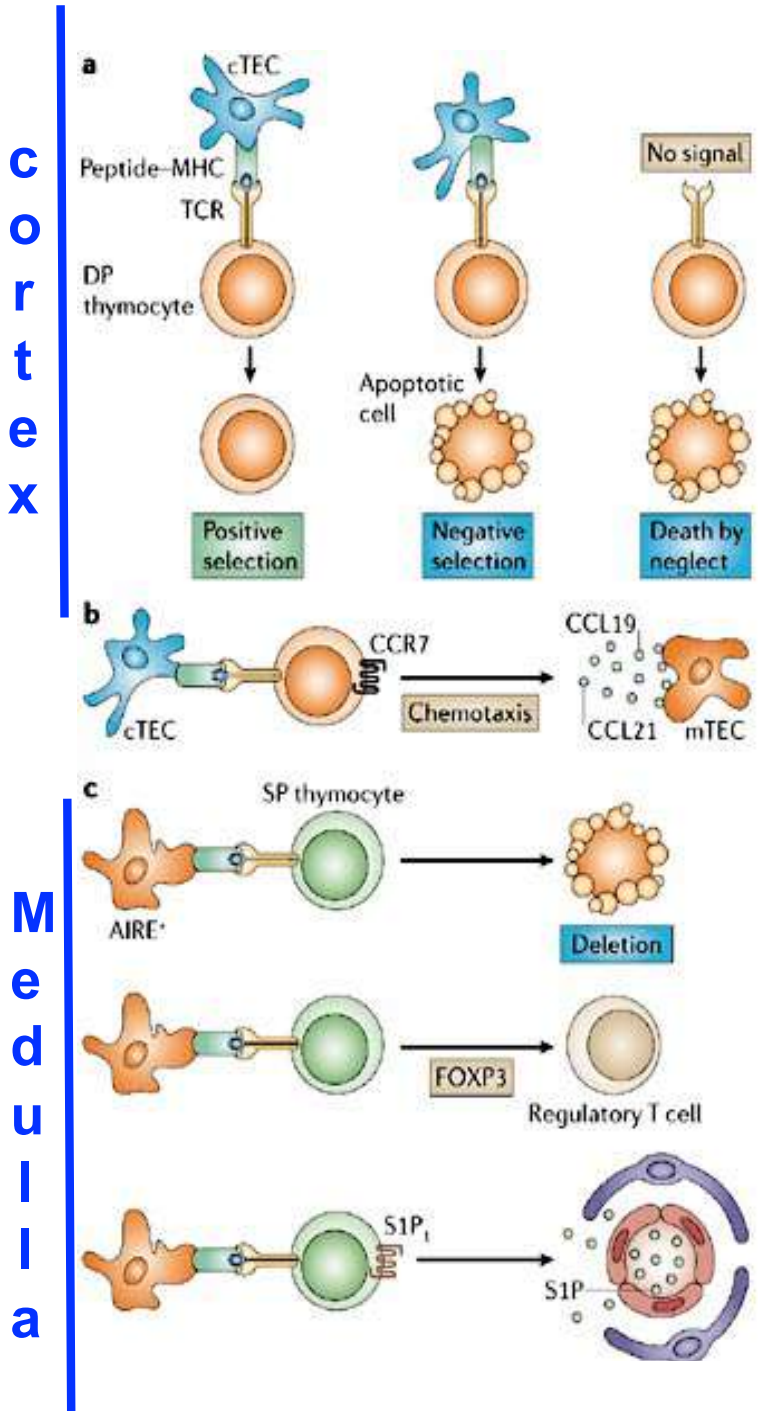
In wild type cTECs, β5t-containing thymoproteasomes degrade endogenous self-proteins and produce a cTEC-specific set of self-peptides that are transported into the lumen of endoplasmic reticulum and are associated with class I MHC molecules. Consequently, cTECs display a unique repertoire of class I MHC-associated peptides and positively select a functionally competent repertoire of CD8+ T cells. By contrast, cTECs in β5t-deficient mice probably express β5i-containing immunoproteasomes instead of β5t-containing thymoproteasomes, thereby producing a different set of self-peptides that are associated with class I MHC molecules. **In β5t-deficient mice, the thymus positively selects a reduced number and functionally incompetent repertoire of CD8+ T cells**

Selezione dei timociti e passaggio dal cortex alla medulla e dalla medulla alla circolazione periferica

NEL TIMO

a | Double-positive (DP) thymocytes that are generated in the thymic cortex are selected for their T-cell receptor (TCR) recognition specificity by interacting with peptide–MHC complexes that are presented in the cortex by cortical thymic epithelial cells (cTECs) and dendritic cells.

b | Positively selected thymocytes are induced to express CC-chemokine receptor 7 (CCR7) as well as to undergo the programme of differentiation into single-positive (SP) thymocytes, and CCR7-expressing thymocytes are attracted to the CCR7 ligands, CC-chemokine ligand 19 (CCL19) and CCL21, which are produced by medullary TECs (mTECs) and mainly localized in the medulla. **c** | In the medulla, newly generated SP thymocytes are further selected by the medullary stromal cells, including autoimmune regulator (AIRE)-expressing mTECs, so that the cells that are reactive to tissue-specific antigens can be deleted. The maturation of SP thymocytes in the medulla includes the production of regulatory T cells and the expression of sphingosine-1-phosphate receptor 1 (S1P1). S1P1-expressing mature T cells seem to be attracted to the circulation, where the concentration of S1P is high. FOXP3, forkhead box P3.



$S1P_1$= recettore per la sfingosina 1 fosfato

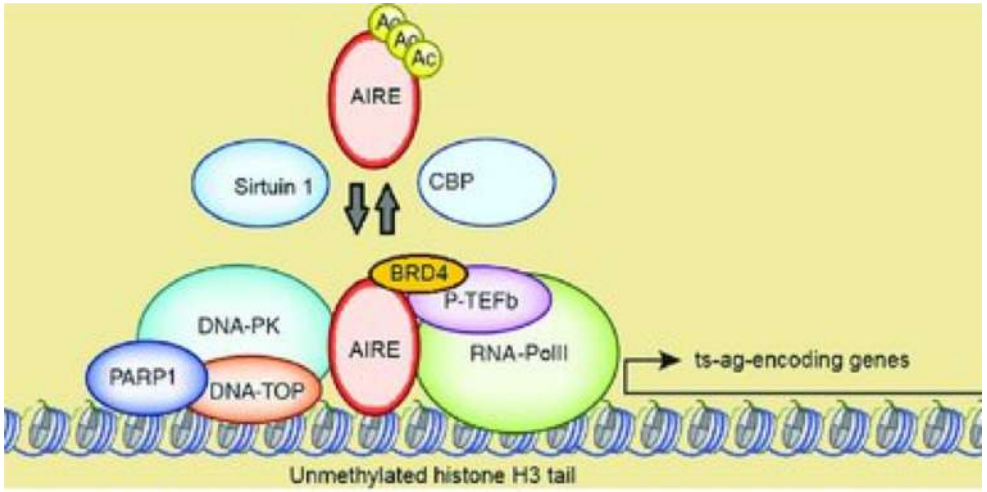
AIRE= autoimmune regulator

FoxP3= forkhead box P3

Identificazione di **AIRE (AutoImmune REgulator)** come mediatore fondamentale dei meccanismi di tolleranza centrale

che determina

la selezione negativa dei timociti nella midollare del timo
e l'eliminazione dei timociti autoreattivi che riconoscono
antigeni self, organo e tessuto-specifici (TRA)
ma anche la generazione delle Treg



APS-1 (autoimmune polyendocrine syndrome type 1) definita anche APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy)

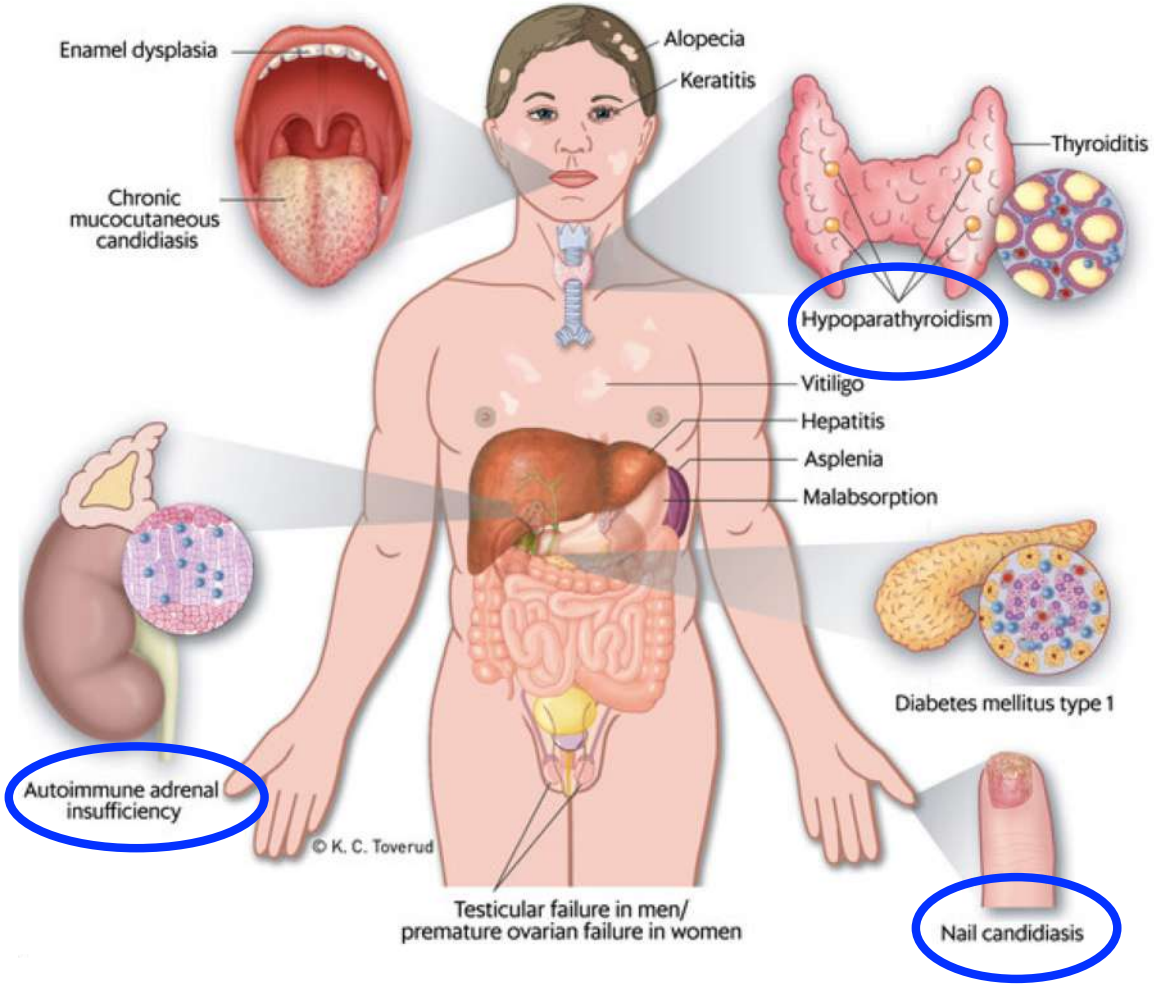
- Malattia monogenica autosomica **recessiva** prevalente in certe popolazioni. Non c'è evidente associazione con un genotipo HLA

- Nei pazienti si riscontrano combinazioni variabili di malattia di Addison, T1D, vitiligine, alopecia ed assorbimento intestinale difettivo.

- La patologia è associata a mutazioni del gene **AIRE** che mappa sul cromosoma 21q22.3 e codifica per una proteina di 545 aa

- **AIRE** è espresso principalmente dalle **cellule epiteliali timiche medullari (mTEC)** dove **agisce da induttore di geni organo** e **tessuto-specifici** ma è espresso anche nella milza, fegato fetale e linfonodi

- I topi deficienti per l'espressione di AIRE presentano infiltrati di linfociti autoreattivi in diversi organi periferici e producono autoanticorpi tessuto-specifici

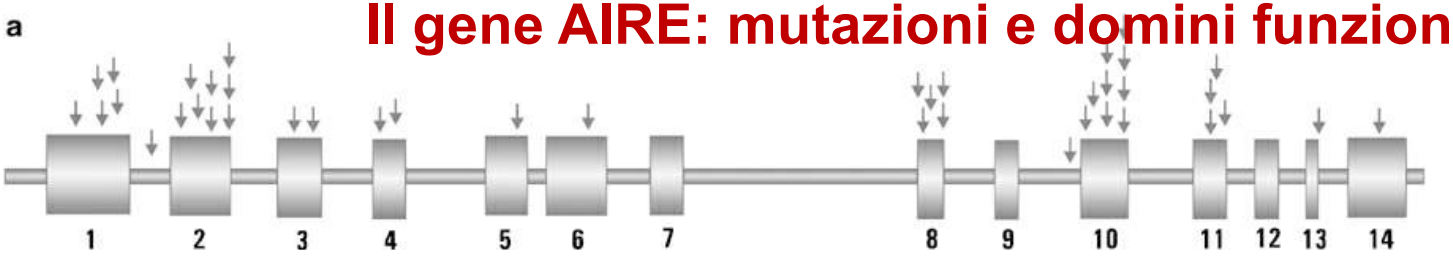


- **Quadro clinico:** candidosi mucocutanea, ipoparatiroidismo, insufficienza surrenalica, infertilità, cheratinopatia e distrofia dello smalto dentale e delle unghie.

Autoantigeni più frequenti nell'APS-1:

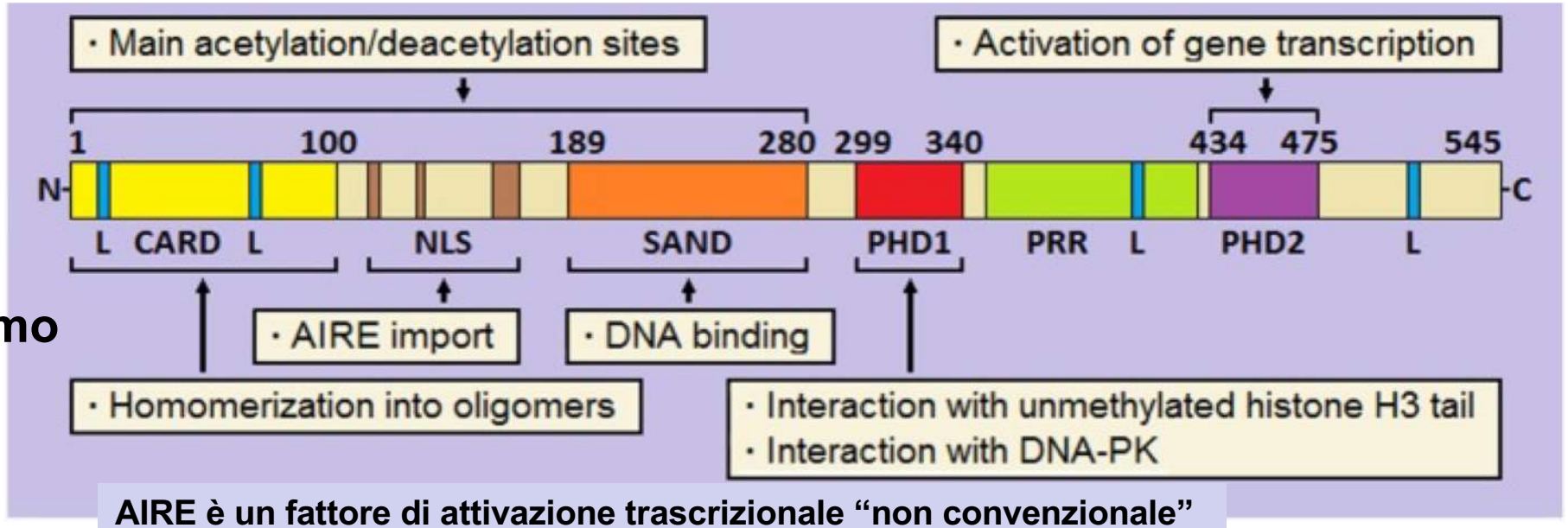
- **enzimi steroidogenici (P450c17; P450c21)**
- **proteine pancreatiche (insulina, GAD65 e 67)**
- **proteine epatiche**
- **proteine tiroidee (perossidasi tiroidea, tireoglobulina)**
- **proteine espresse dai melanociti**

Il gene AIRE: mutazioni e domini funzionali



Le frecce indicano le mutazioni associate all'APS-1

Aire nell'uomo



AIRE è un fattore di attivazione trascrizionale "non convenzionale"

Structural elements of the AIRE protein. (A) The domains and functional elements of the AIRE protein. The caspase-recruitment domain **(CARD) is critical for AIRE homo-oligomerization, nuclear-dot formation,** and its association with nuclear matrix. Three conserved putative nuclear-localization signals (NLS) (110–114; 131–133; and 159–167) have been implicated in AIRE's nuclear transport.

The **SAND** (SP100, AIRE1, NucP41/P75, and DEAF1) **domain is a putative DNA-binding domain.**

Two sequential plant homeodomain (PHD) zinc fingers are both essential for AIRE's transcription-transactivation capacity – the former interacts with **unmethylated histone H3 lysine 4 (H3K4me0) and with the DNA-dependent protein kinase (DNA-PK) complex,** the interacting partners of the latter one are still unknown. Four LXXLL motifs, scattered throughout the AIRE protein (7-11, 63–67, 414–418, 516–520), have been implicated in the formation of AIRE homo-oligomers and/or in protein–protein interaction with other LXXLL-containing proteins.

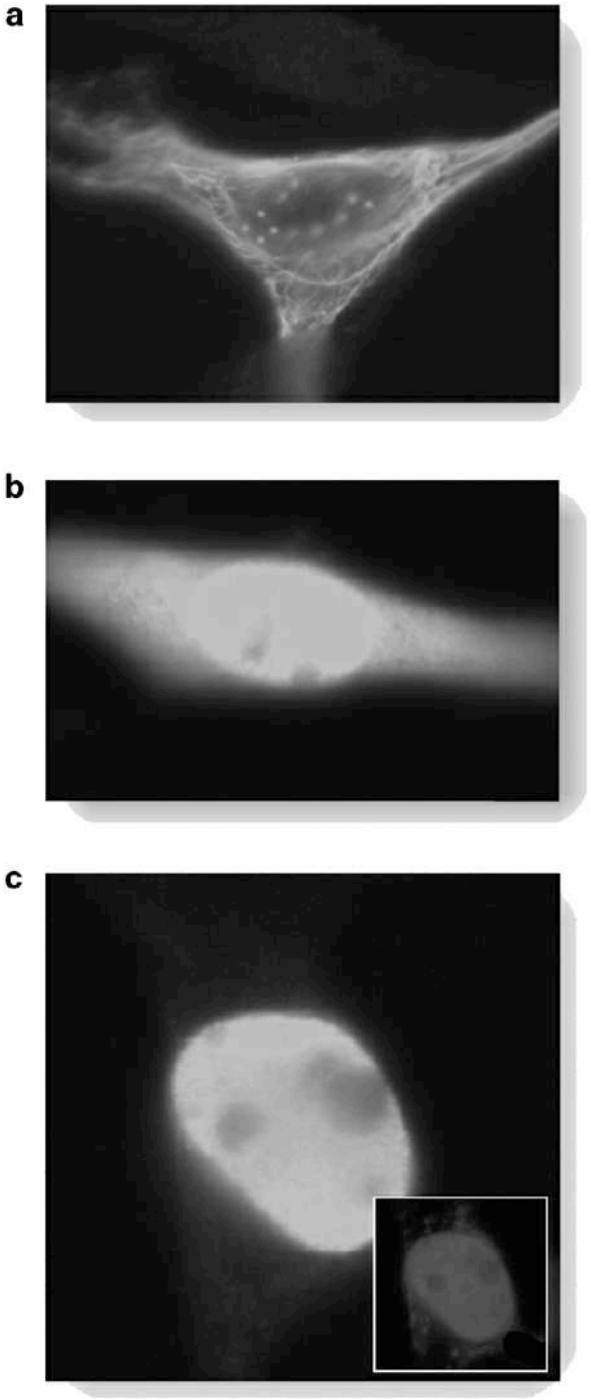
A **Proline-rich region (PRR) is a putative binding platform for multiple proteins containing proline-binding** domains such as SH3 or WW.

Localizzazione subcellulare di AIRE (regolatore trascrizionale)

a) La proteina wt è presente nel nucleo con una distribuzione punteggiata (AIRE nuclear bodies) e nel citoplasma con una distribuzione fibrillare.

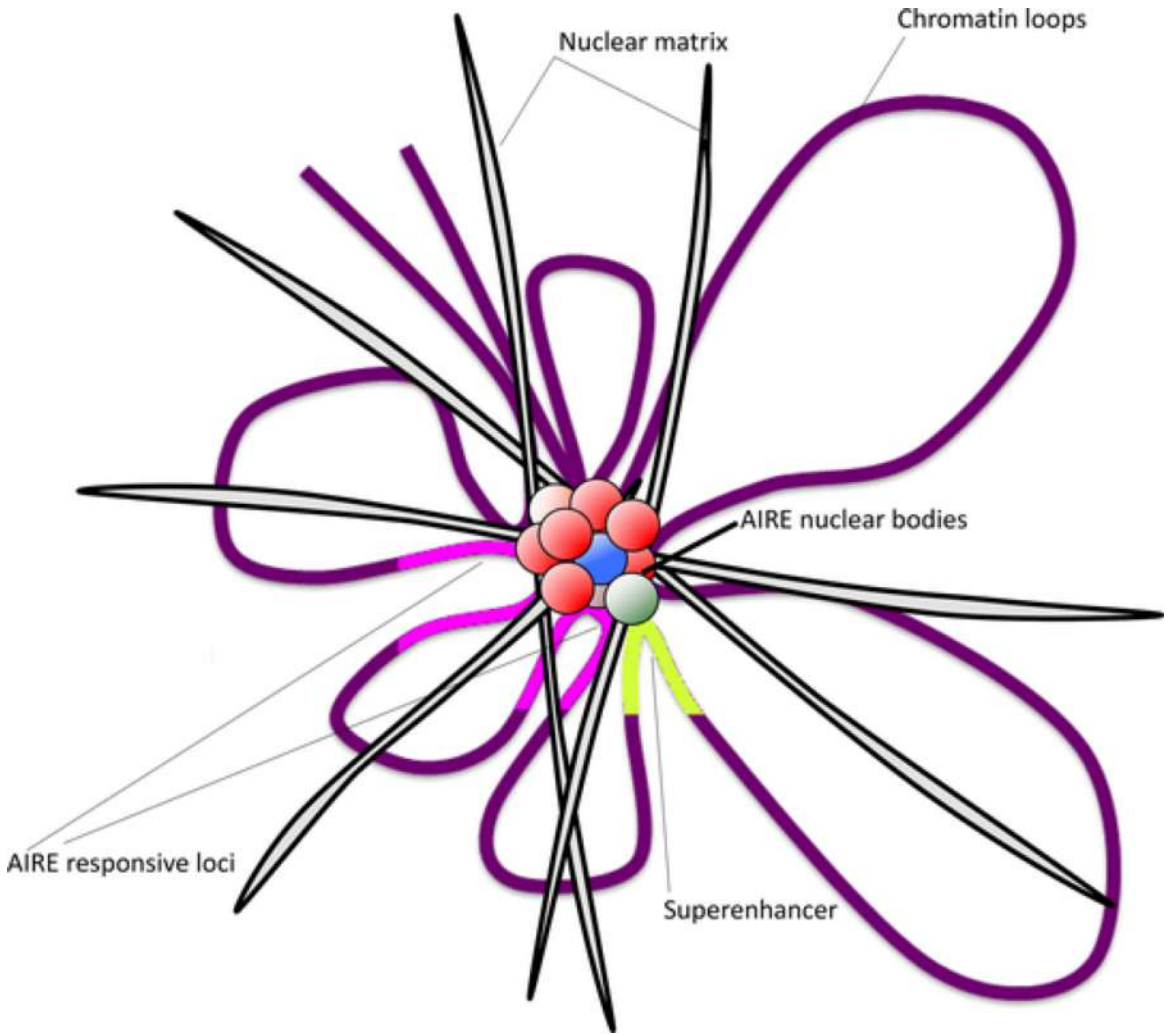
b) La mutazione L28P induce una diffusa distribuzione di AIRE sia nel nucleo che nel citoplasma.

c) AIRE (84-545) privo del putativo NES (nuclear export sequence) localizza esclusivamente nel nucleo (inserto) colorazione del nucleo con DAPI



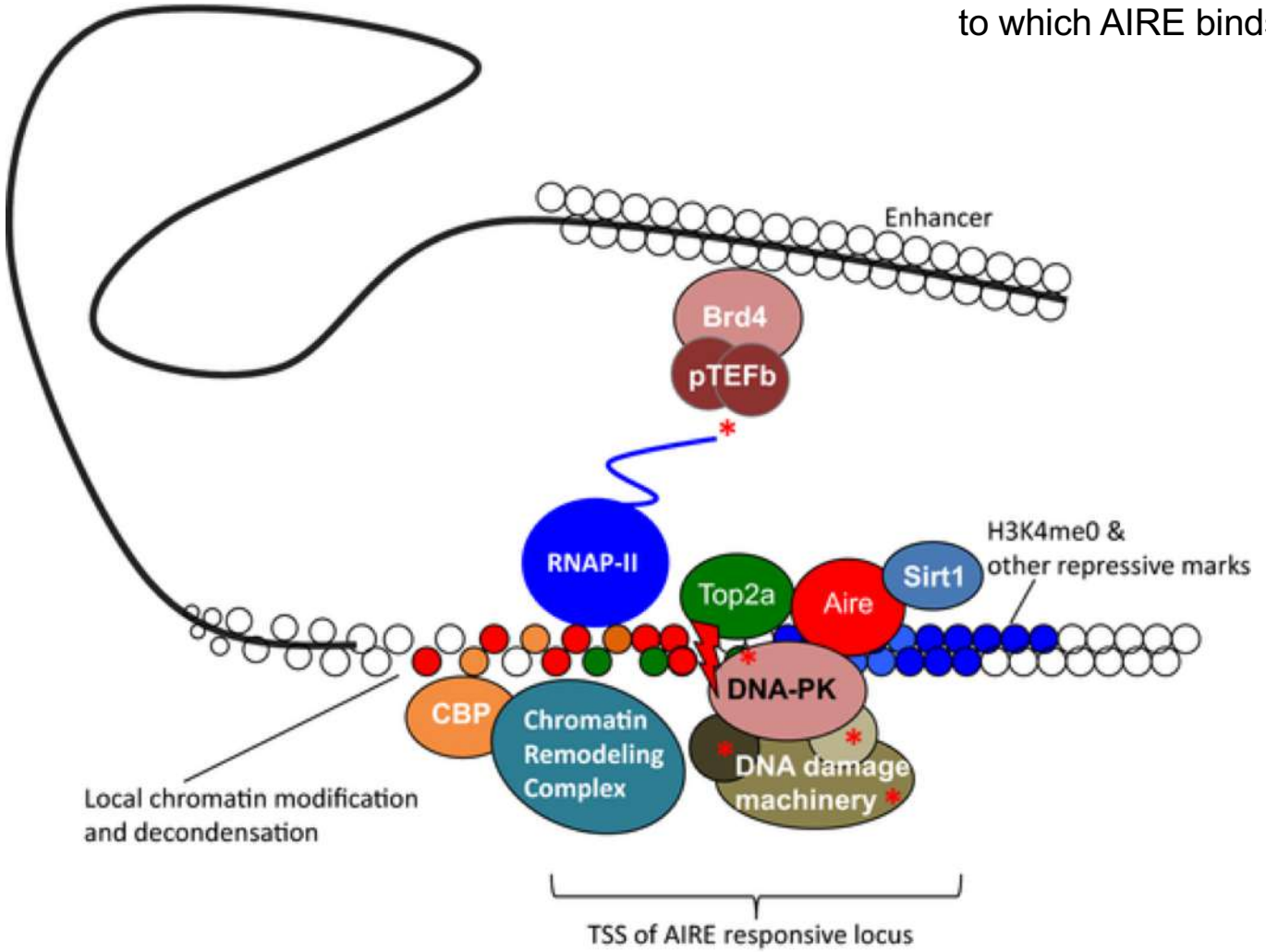
HeLa cells trasfettate con il gene AIRE

Proposed model for association of AIRE with nuclear matrix and chromatin



In the nucleus, **AIRE localizes into unique nuclear bodies, which are strongly associated with nuclear matrix**. These matrix-anchored AIRE nuclear bodies might serve as **nuclear hubs** where regulatory machinery for gene expression is organized through chromatin looping, thereby bridging AIRE-responsive loci with the transcriptional machinery and/or super-enhancers.

Proposed model for AIRE-mediated gene activation (or repression)

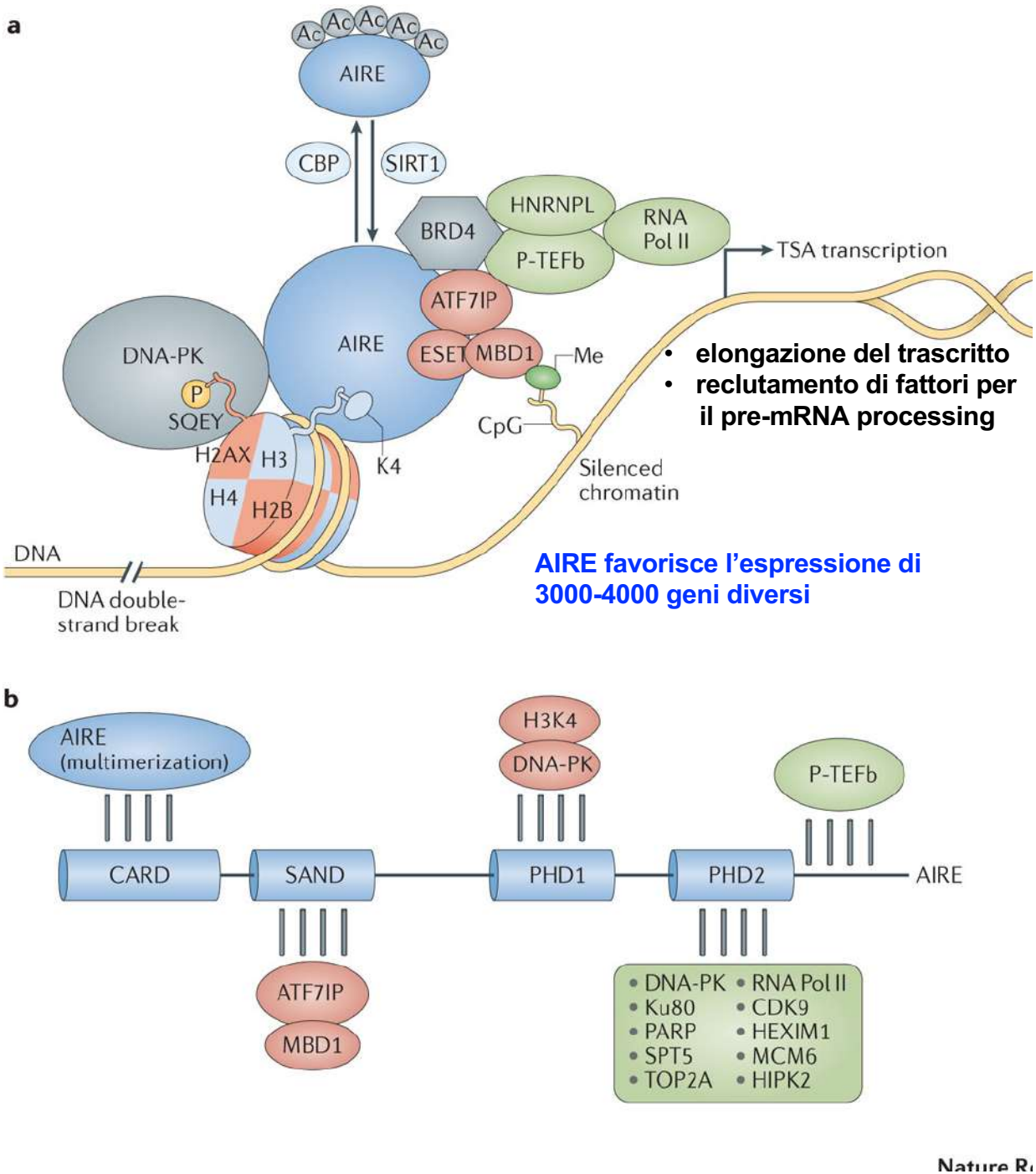


AIRE binds to the chromatin at the TSS of most genes, whether active or inactive, and its transcription-transactivation capacity is positively regulated by **protein deacetylase Sirt1**. The **repressive epigenetic signature** of AIRE-responsive genes includes H3K4me0 (blue circles), to which AIRE binds directly via its PHD1 finger.

This binding stabilizes AIRE and allows the formation of **TOP2**-initiated breaks at the TSS of AIRE's responsive genes. These breaks in turn recruit and activate **DNA-PK** and other AIRE partners, whose actions result in local chromatin relaxation, characterized by epigenetic changes (red circles) in the surrounding chromatin (e.g. histone acetylation through CBP). These events are then accompanied by the recruitment of several downstream mediators of gene expression, such as the pTEFb/BRD4 complex which releases stalled RNAP-II, enabling the complete transcription of AIRE-dependent genes.

AIRE non funziona come un fattore di trascrizione convenzionale

AIRE and its binding partners



- **elongazione del trascritto**
- **reclutamento di fattori per il pre-mRNA processing**

AIRE favorisce l'espressione di 3000-4000 geni diversi

a) Schematic illustration of a partial set of autoimmune regulator (AIRE)-interacting partners. Dozens of AIRE-interacting partners with diverse functions have been identified. AIRE interacts with histone core proteins, either directly or through its interactions with DNA-dependent protein kinase (DNA-PK), the activating transcription factor 7-interacting protein (ATF7IP)–methyl-CpG-binding domain protein 1 (MBD1)–ESET complex that interacts with methylated DNA, and with positive transcription elongation factor b (P-TEFb), heterogeneous nuclear ribonucleoprotein L (HNRNPL) and RNA polymerase II (RNA Pol II) to release stalled polymerases. AIRE also interacts with sirtuin 1 (SIRT1) and CREB-binding protein (CBP), which control AIRE acetylation.

b) A map of the regions of AIRE that are known to interact with binding partners. Ac, acetyl; BRD4, bromodomain-containing 4; CARD, caspase recruitment domain; CDK9, cyclin-dependent kinase 9; HIPK2, homeodomain-interacting protein kinase 2; Me, methyl; P, phosphoryl; PARP, poly(ADP-ribose) polymerase; PHD, plant homeodomain; SAND, SP100, AIRE1, NucP41/P75 and DEAF1; TOP2A, topoisomerase 2A.

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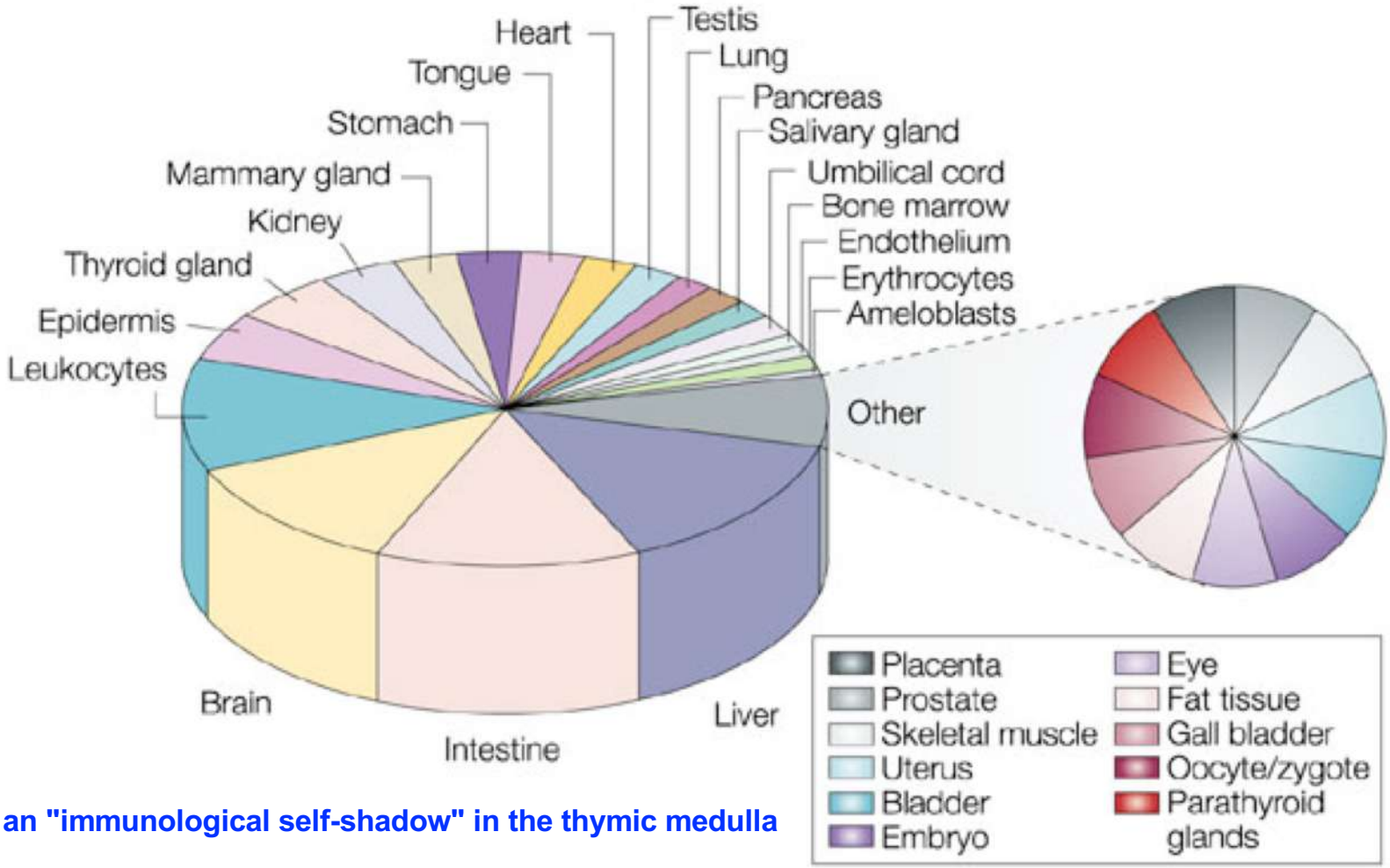
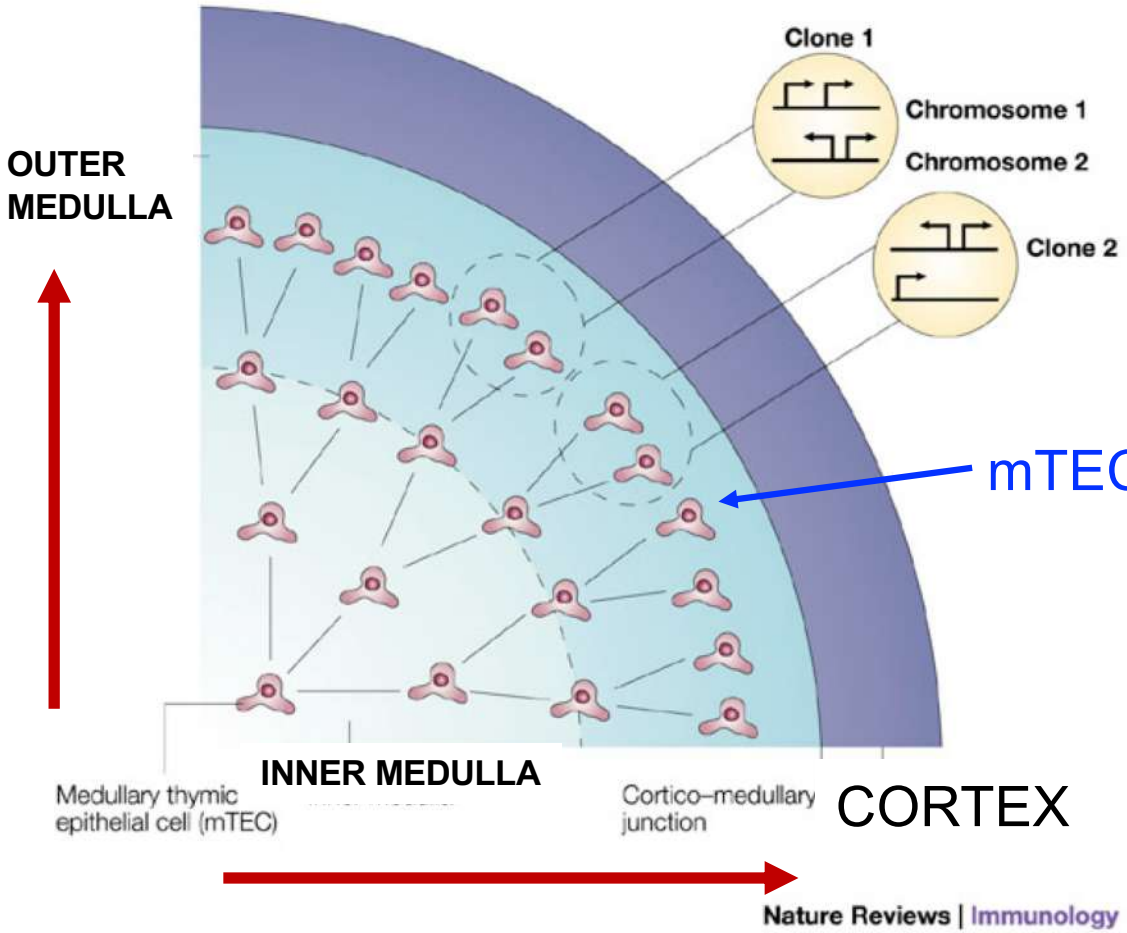
AIRE induce l'espressione genica promiscua nelle cellule epiteliali timiche della medulla (mTEC) ovvero l'espressione di un ampio repertorio di antigeni tessuto- e organo-specifici



AIRE creates an "immunological self-shadow" in the thymic medulla

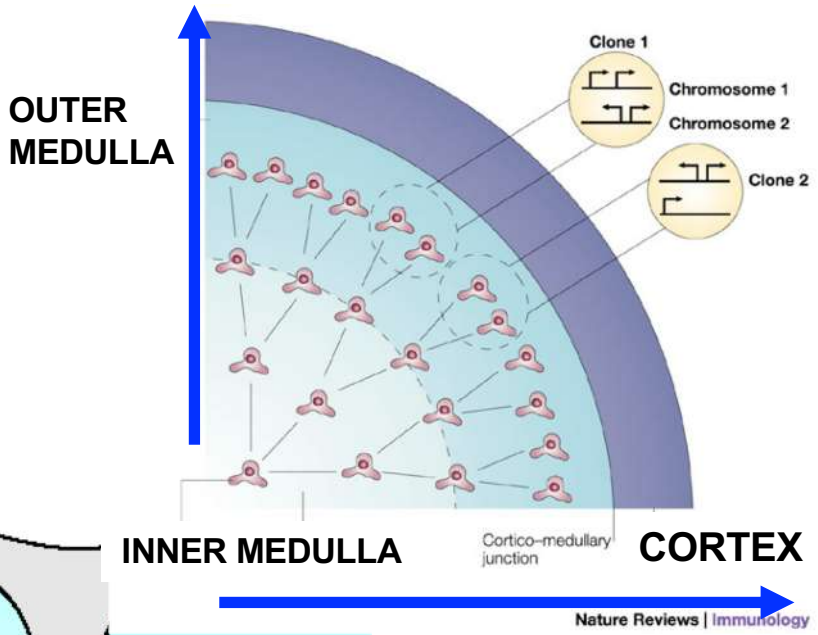
Genes identified as overexpressed in mouse **mTECs** compared with cortical TECs using **gene chip analysis** were assigned to tissues according to their predominant expression (where applicable) using combined information from the public databases GNF Gene Expression Atlas and Swissprot (see online links box) and the literature. About one quarter of all mTEC-overexpressed genes could be categorized as tissue-restricted according to this approach and are shown. Note the diversity of tissues that meet these criteria. The fraction of tissue-restricted genes is probably underestimated given their low expression levels in mTECs and the limited sensitivity of the gene array method.

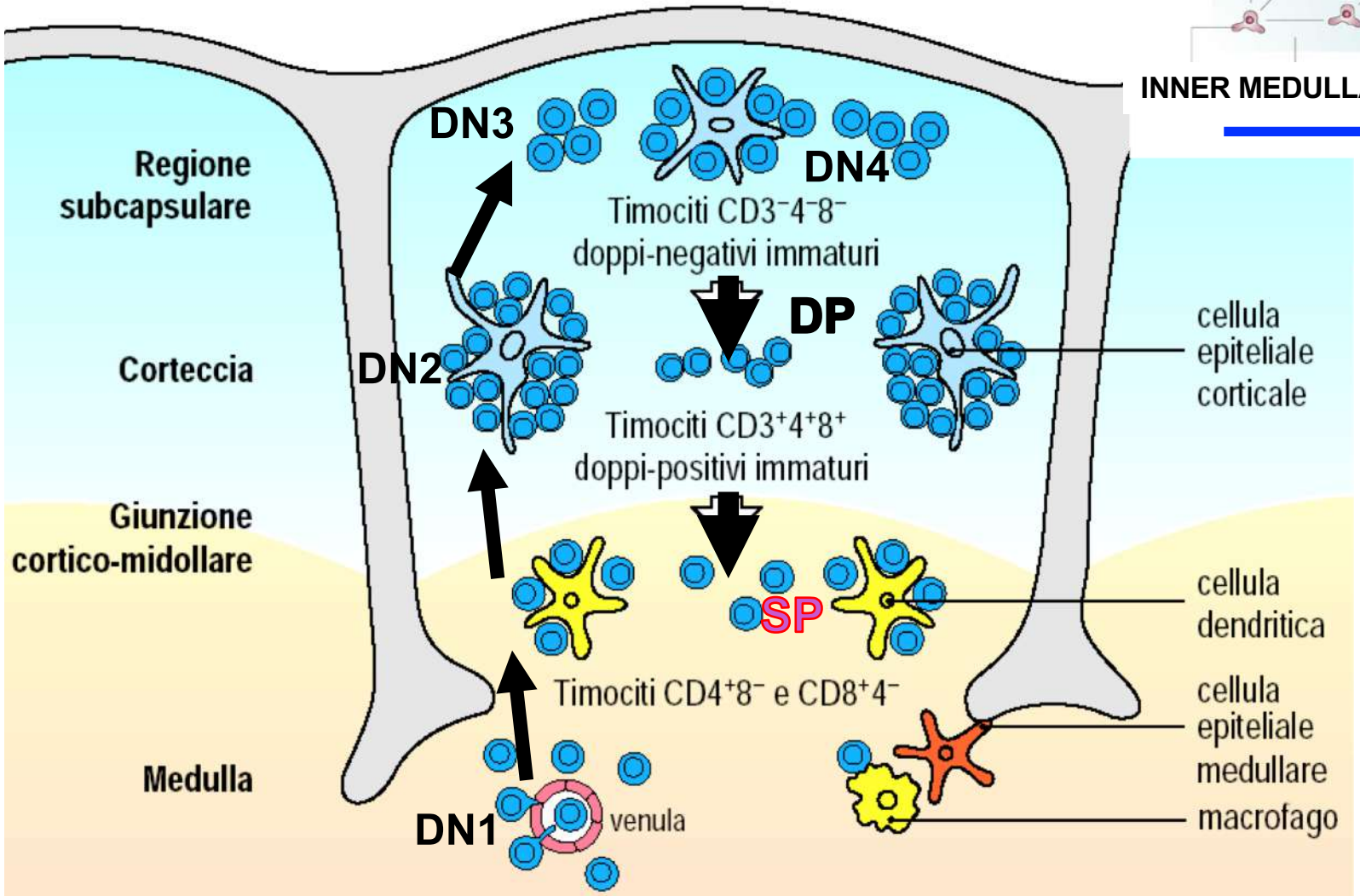
Piccoli cloni di mTEC esprimono un set limitato di antigeni tessuto-specifici



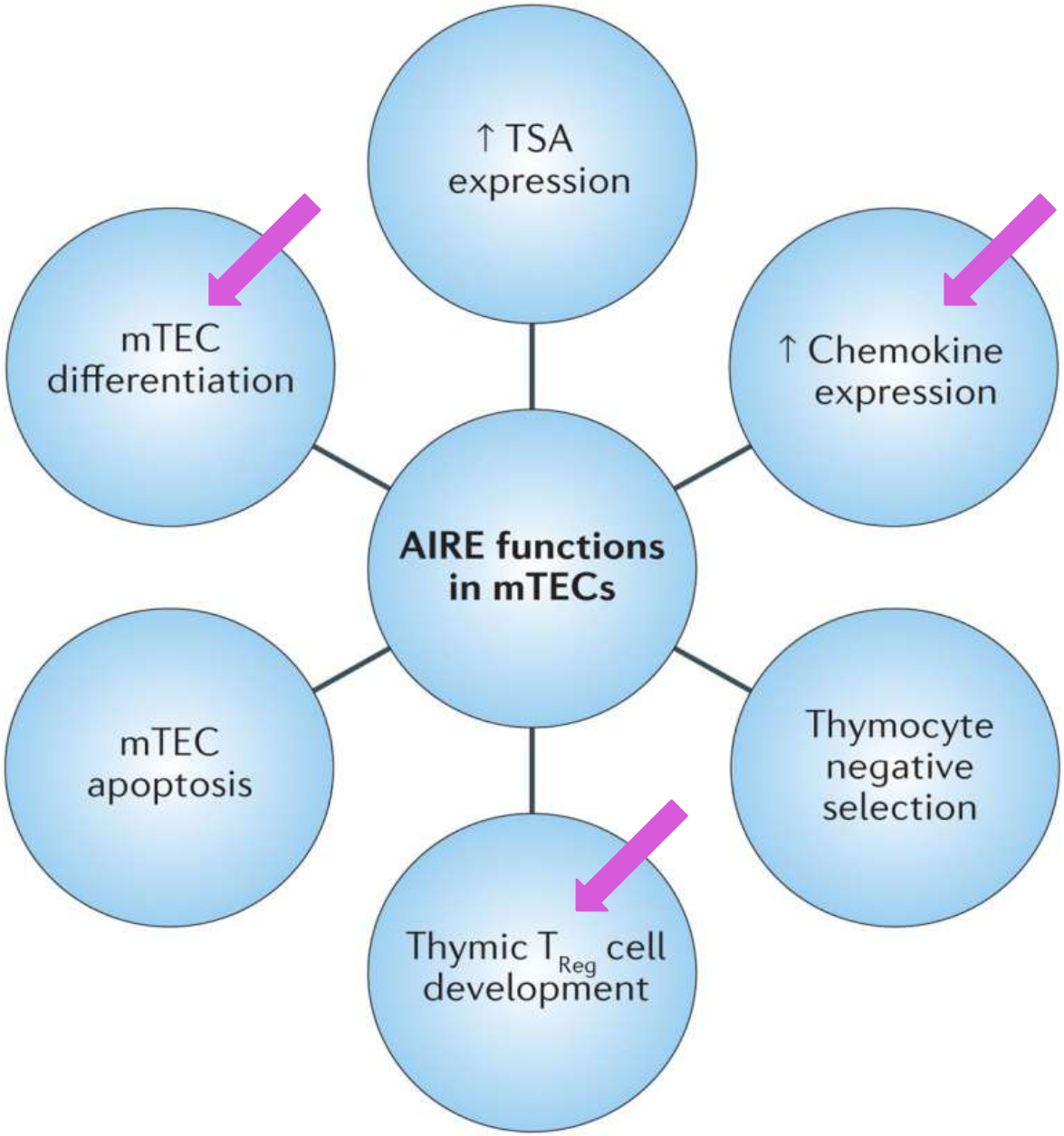
We propose the continuous *de novo* generation of small clones of terminally differentiated medullary thymic epithelial cells (mTECs), each of which, according to a **stochastic event**, expresses a limited number of different tissue-restricted antigens. For example, in this figure, distinct patterns of expression of genes encoded on chromosomes 1 and 2 in distinct mTEC clones are depicted. This model is based on the observation that tissue-restricted self-antigens frequently localize to small clusters of 2–4 cells in the outer medulla. The small clone size might be dictated by the limited life span of these cells once certain genes are turned on. Their location in the outer medulla might be the result of an outward differentiation of mTECs in analogy to directional differentiation of stratified epithelium. In this way, the **outer medulla**, through which all thymocytes have to traverse, **would represent a zone of high self-antigen density**. This proposition extends the model of stratified microenvironments that was originally described for the cortex to the medulla.

I timociti in sviluppo passano dalla corteccia (selezione positiva) alla medulla (selezione negativa) del timo





The various functions of AIRE in mTECs



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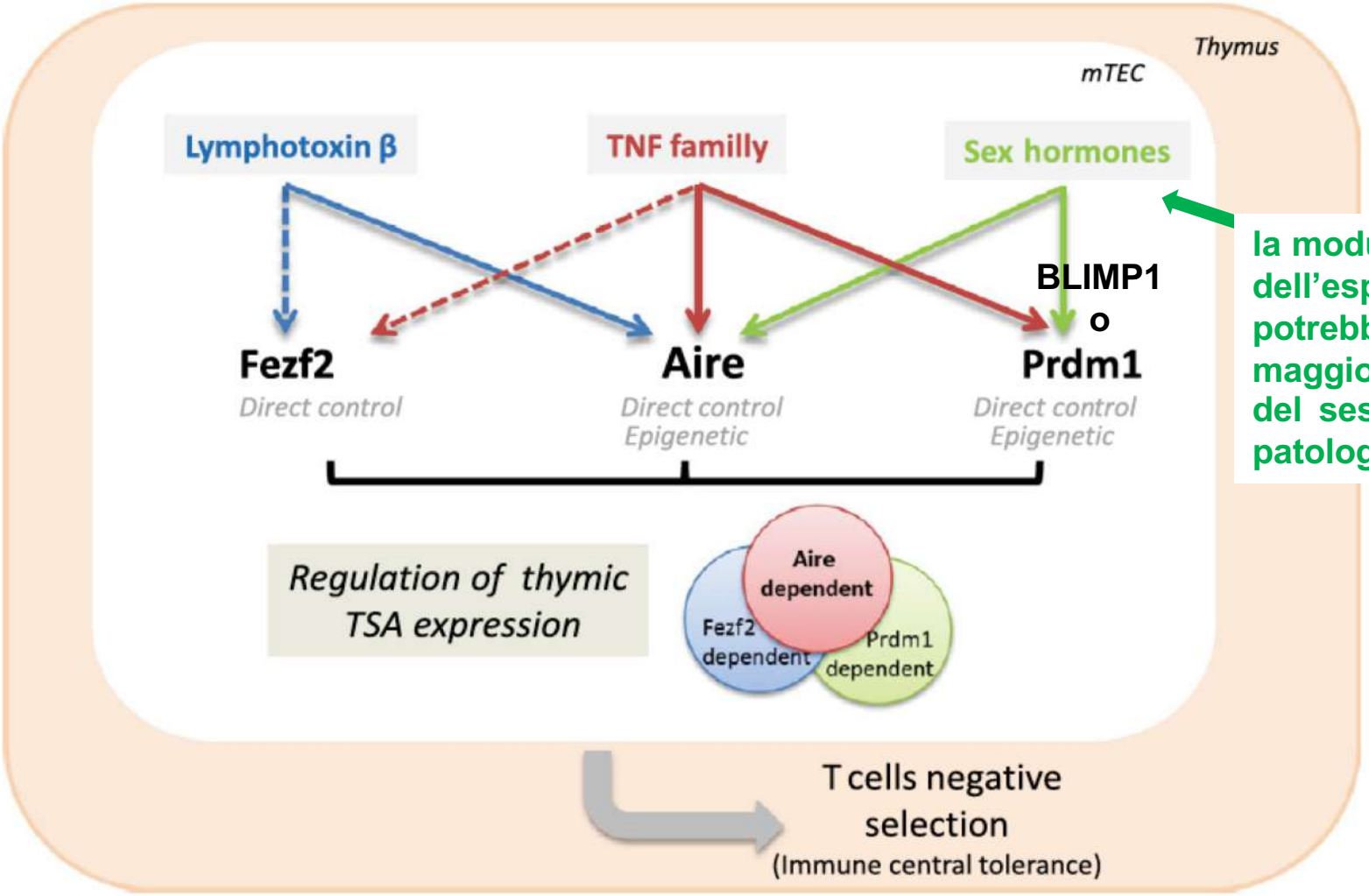
In addition to the role of autoimmune regulator (AIRE) in increasing tissue-specific antigen (TSA) expression, several other roles have been identified, some of which are shown here. mTEC, medullary thymic epithelial cell; T_{Reg} cell, regulatory T cell.

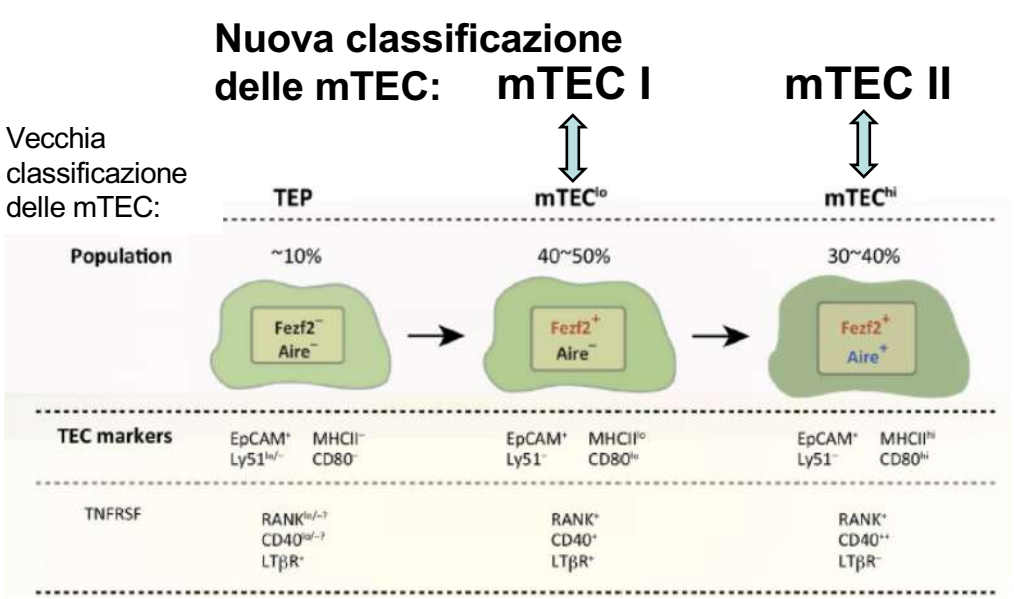
Oltre ad Aire anche Fezf2 e Prdm1 inducono l'espressione genica promiscua nella midollare del timo

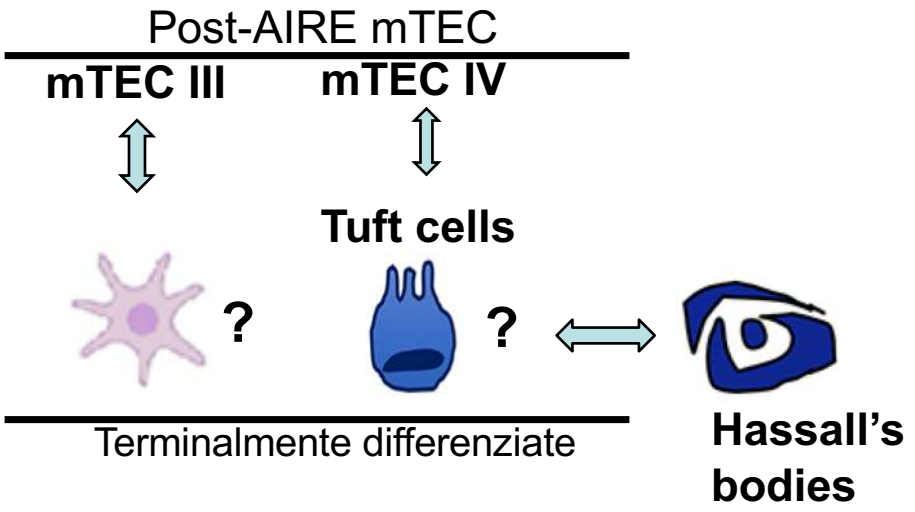


la modulazione ormonale dell'espressione di AIRE potrebbe spiegare la maggiore suscettibilità del sesso femminile alle patologie autoimmuni

Figure 3. Immune central tolerance is promoted in mTECs by the ability of at least three key transcription modulators to control tissue-specific antigen expression. Expression of each transcription factor (TF) is regulated by various transduction pathways: lymphotoxin β, sex hormones (estrogen and androgen), and TNF family members (RANKL and CD40). In addition, epigenetic changes (methylation status) and SNPs can play roles in the expression levels of each TF, resulting in variable TSA thymic expression.

The Role of Fezf2 and Aire in mTEC Differentiation



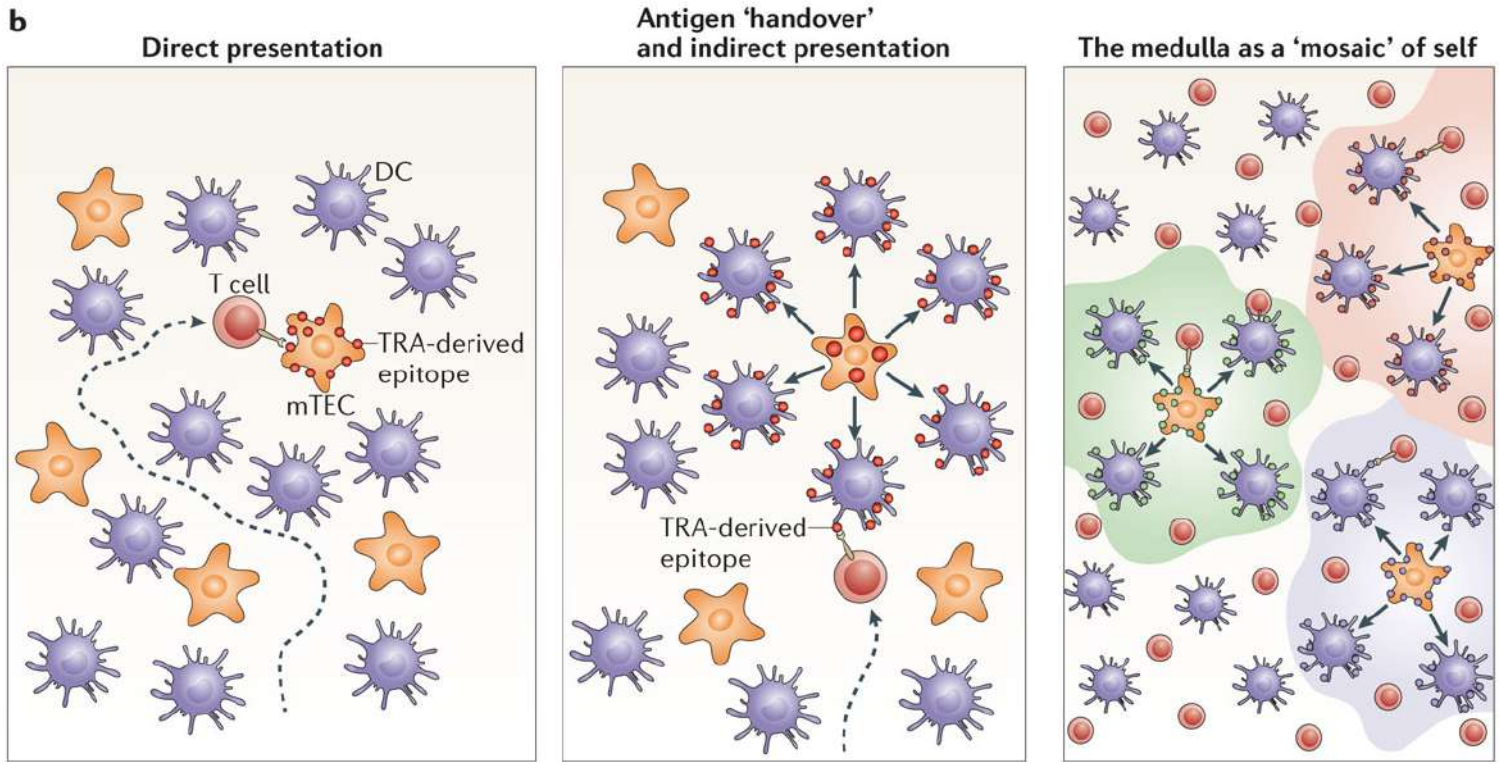


The Role of Fezf2 and Aire in mTEC differentiation. (A) TEPs, the common progenitors of mTECs and cTECs, differentiate into mTECs, which are divided into mTEClo and mTEChi according to the expression level of MHC class II and CD80. Each population is characterized by distinct TEC marker genes. Fezf2 is expressed in mTEClo and mTEChi, but Aire is expressed only in mTEChi. The signaling through TNF receptor superfamily members is essential for mTEC development. (B) The various functions of Fezf2 and Aire in mTECs. In addition to the role of TRA expression, Aire has several other roles involving the mTEC development and T cell selection. However, there remain many unanswered questions regarding the roles of Fezf2 in the mTEC. Abbreviations: cTEC, cortical thymic epithelial cell; mTEC, medullary thymic epithelial cell; TEP, thymic epithelial progenitor cell; TNF, tumor necrosis factor; TRA, tissue-restricted antigen.

Functions \ Transcriptional regulator	Fezf2	Aire
DNA binding	Yes	No
TRA expression	Yes	Yes
Thymic microenvironment (mTEC development)	Yes	Yes
TRA processing	?	No
Chemokine induction	?	Yes
TRA transfer (cross presentation by DC)	?	Yes
Negative selection	Yes?	Yes
Treg cell development	?	Yes
γδ T cell development	?	Yes

Oltre ad AIRE anche Fezf2 (fattore di trascrizione classico) induce l'espressione degli antigeni tessuto-specifici nelle mTEC

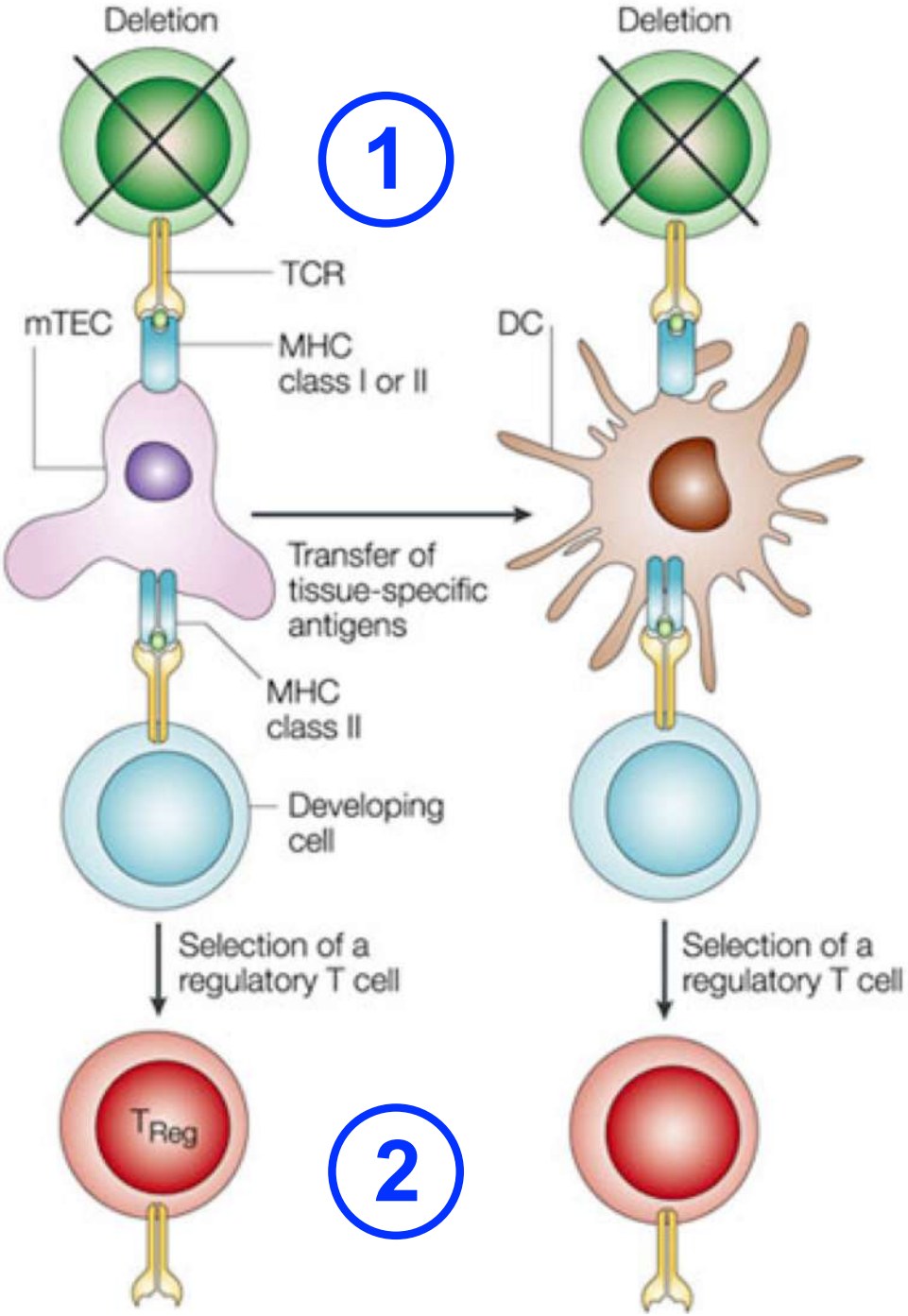
Direct versus indirect presentation of tissue-restricted antigens



Tolerogenic presentation of Tissue restricted antigens (TRAs) that are expressed by few mTECs may occur in two ways that are not mutually exclusive. The first is through direct presentation by TRA-expressing mTECs themselves, whereby efficient endogenous MHC class II loading by mTECs in conjunction with serial 'scanning' of multiple medullary antigen-presenting cells (APCs) by thymocytes increases the likelihood of cognate self antigen interactions (left panel).

The second is by 'antigen handover' to neighbouring conventional dendritic cells (cDCs; middle panel), which may extend the area of tolerogenic presentation in a mosaic fashion beyond the topologically restricted expression pattern (right panel). The mechanistic details of this **'directional antigen transfer'** remain to be established. It is conceivable that **TRAs are released or shed in a soluble form** to be subsequently captured and processed by cDCs for presentation on MHC class I or class II. Apoptosis of terminally differentiated mTECs may lead to the release of apoptotic fragments that can also transfer mTEC-derived self antigens to cDCs. In addition, functional peptide–MHC ligands are unidirectionally translocated from mTECs to DCs.

Ruolo delle mTEC: selezione negativa dei linfociti T autoreattivi e selezione di linfociti T regolatori



Central tolerance to tissue-restricted self-antigens by recessive and dominant mechanisms.
Induction of self-tolerance in the thymic medulla includes at least two cell populations, medullary thymic epithelial cells (mTECs) and haematopoietic antigen-presenting cells (APCs), such as dendritic cells (DCs), and two modes, deletion and induction of CD4+CD25+ regulatory T (TReg) cells.
mTECs are autonomously competent to delete self-reactive T cells that are specific for promiscuously expressed (neo)-self antigens. TECs have also been shown to efficiently select Treg cells specific for antigens that have restricted expression by TECs. In addition, cross-presentation of mTEC-derived self-antigens by DCs has been shown to occur *in situ* and, in one transgenic model, to be mandatory for deletion of self-reactive T cells. Similarly, haematopoietic APCs can induce Treg-cell selection. At present, it is unclear to what extent the different stromal-cell types contribute to the presentation of the array of promiscuously expressed antigens under steady-state conditions. The apparent redundancy of antigen presentation is, however, limited by the unidirectional flow of antigen from mTECs to DCs.
TCR, T-cell receptor.

Fattori che influenzano la tolleranza verso autoantigeni tessuto-specifici