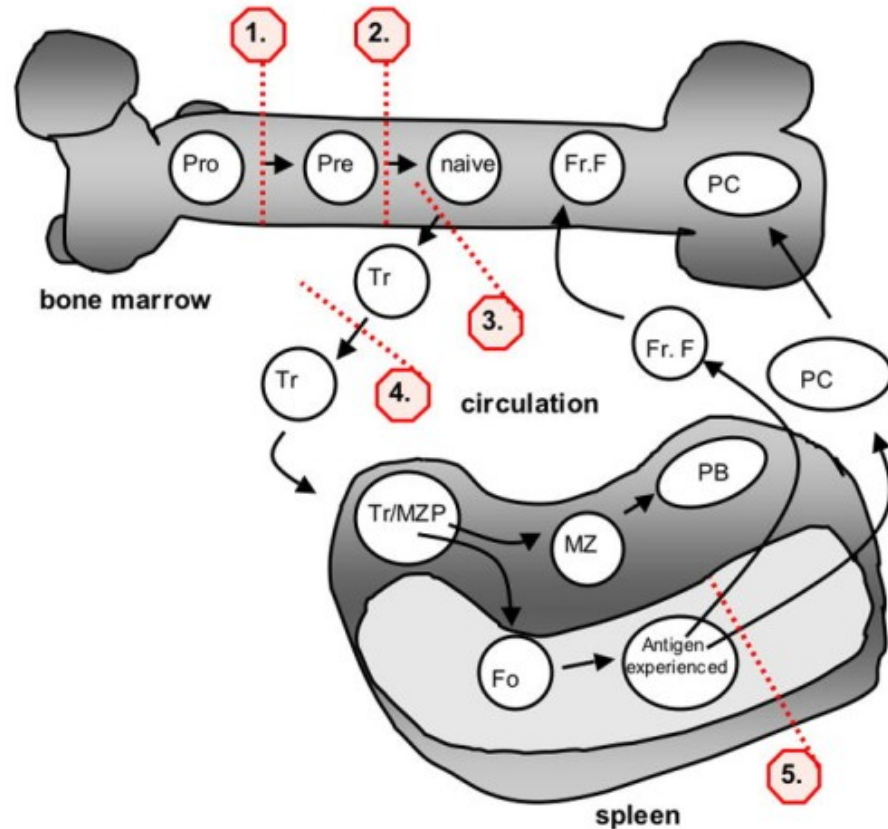


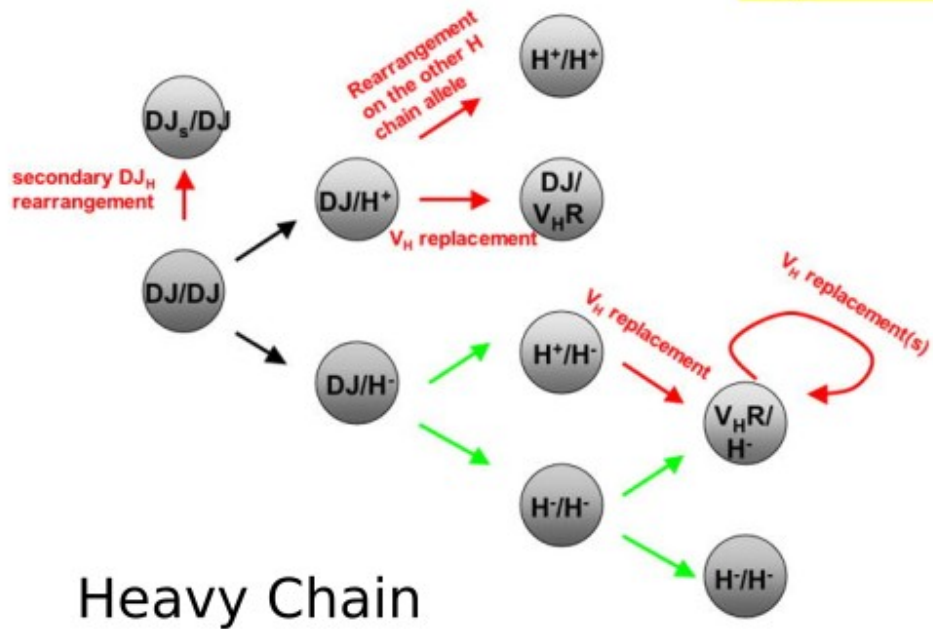
Tolerans ve otoimmünite

Luning Prak ET, Monestier M, Eisenberg RA. B cell receptor editing in tolerance and autoimmunity. *Ann N Y Acad Sci.* 2011 Jan;1217:96-121. doi: 10.1111/j.1749-6632.2010.05877.x. Epub 2011 Jan 5. PMID: 21251012; PMCID: PMC3077556.



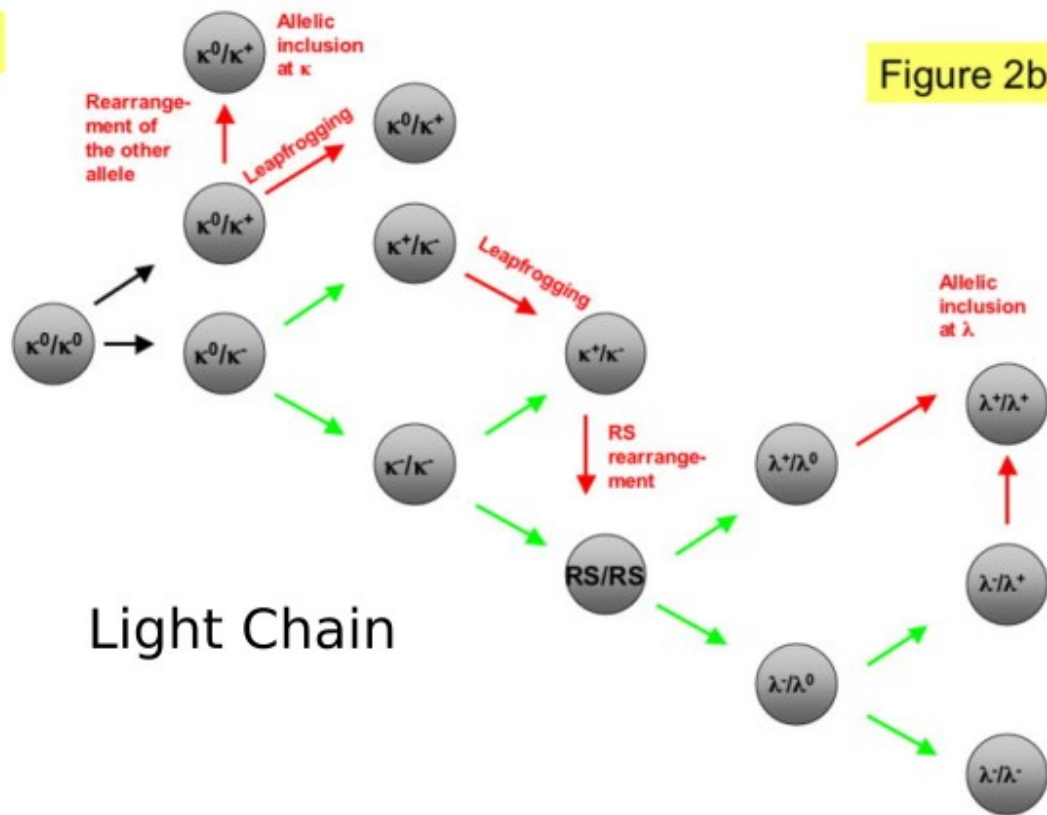
1. proB -> preB cell stage: H chain selection
2. preB -> naiveB cell stage: autoreactive BCR may revert to sIg(-) state
- 3-4. IgM expressing cells:
editing: additional rearrangement in BM
revision: additional rearrangement after BM
5. receptor revision in more mature B cell

Figure 2a



Heavy Chain

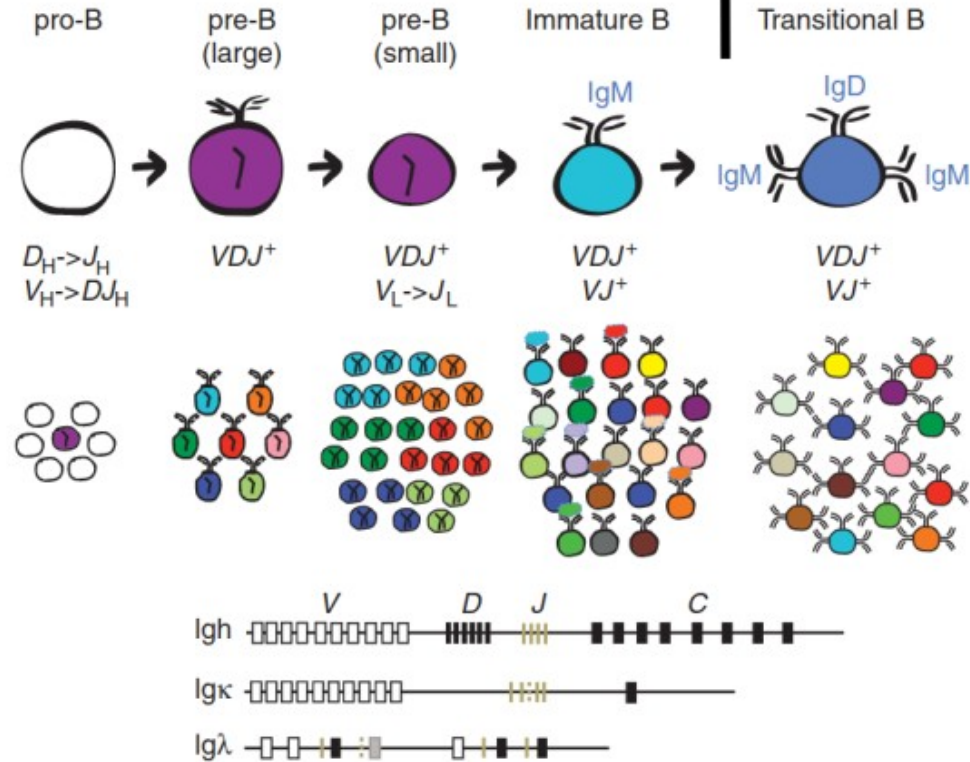
Figure 2b

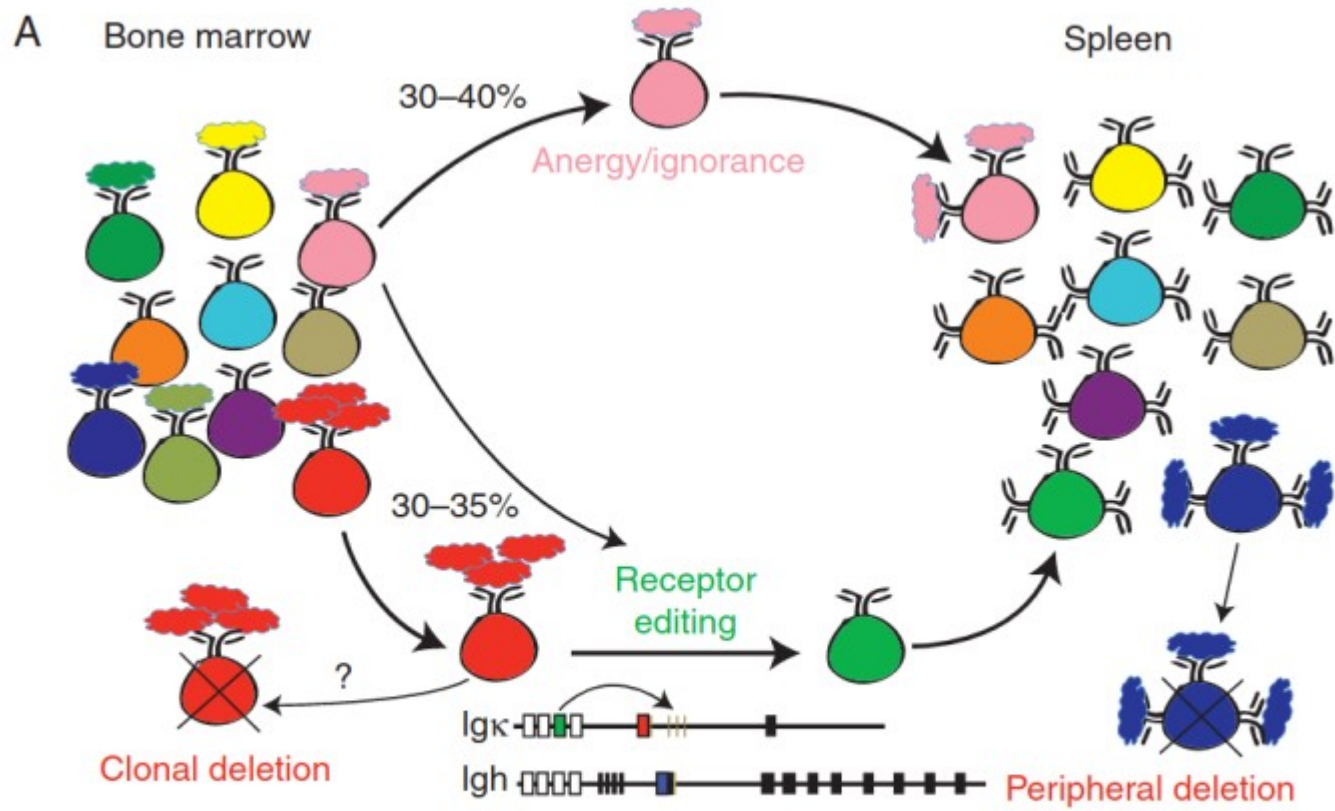


Light Chain

2° lymphoid organs 20-40% self reactive BCR

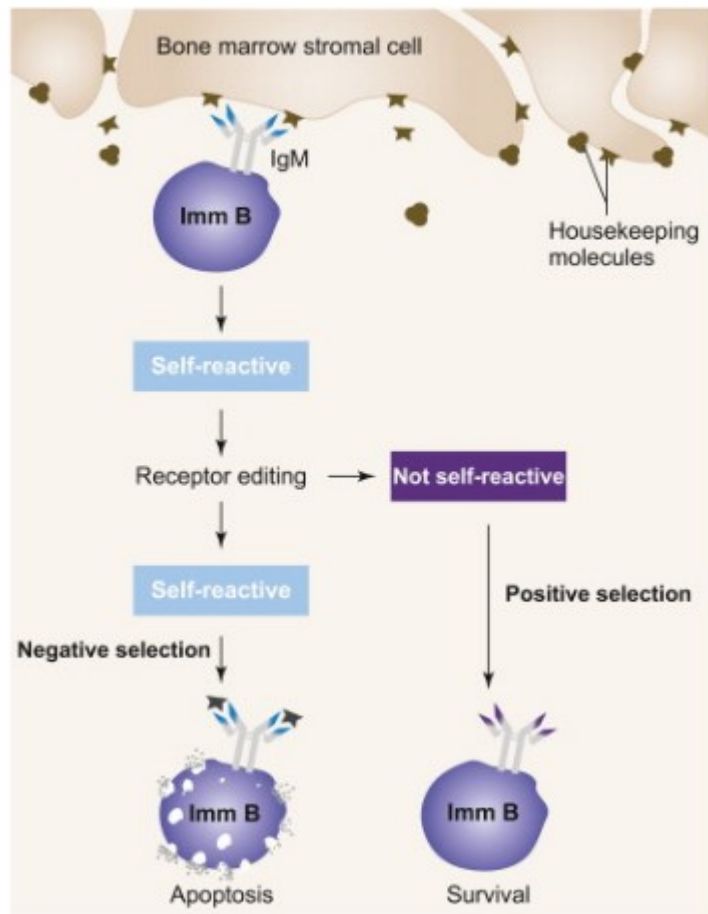
Bone marrow 50-75% self reactive BCR

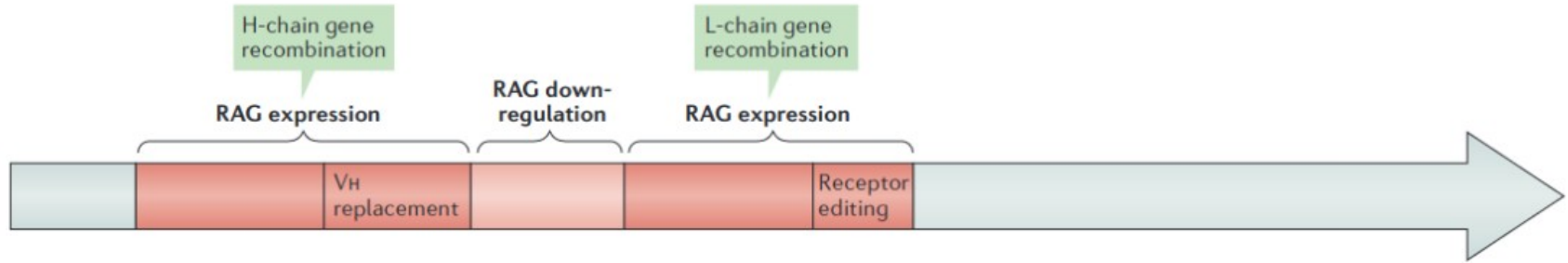




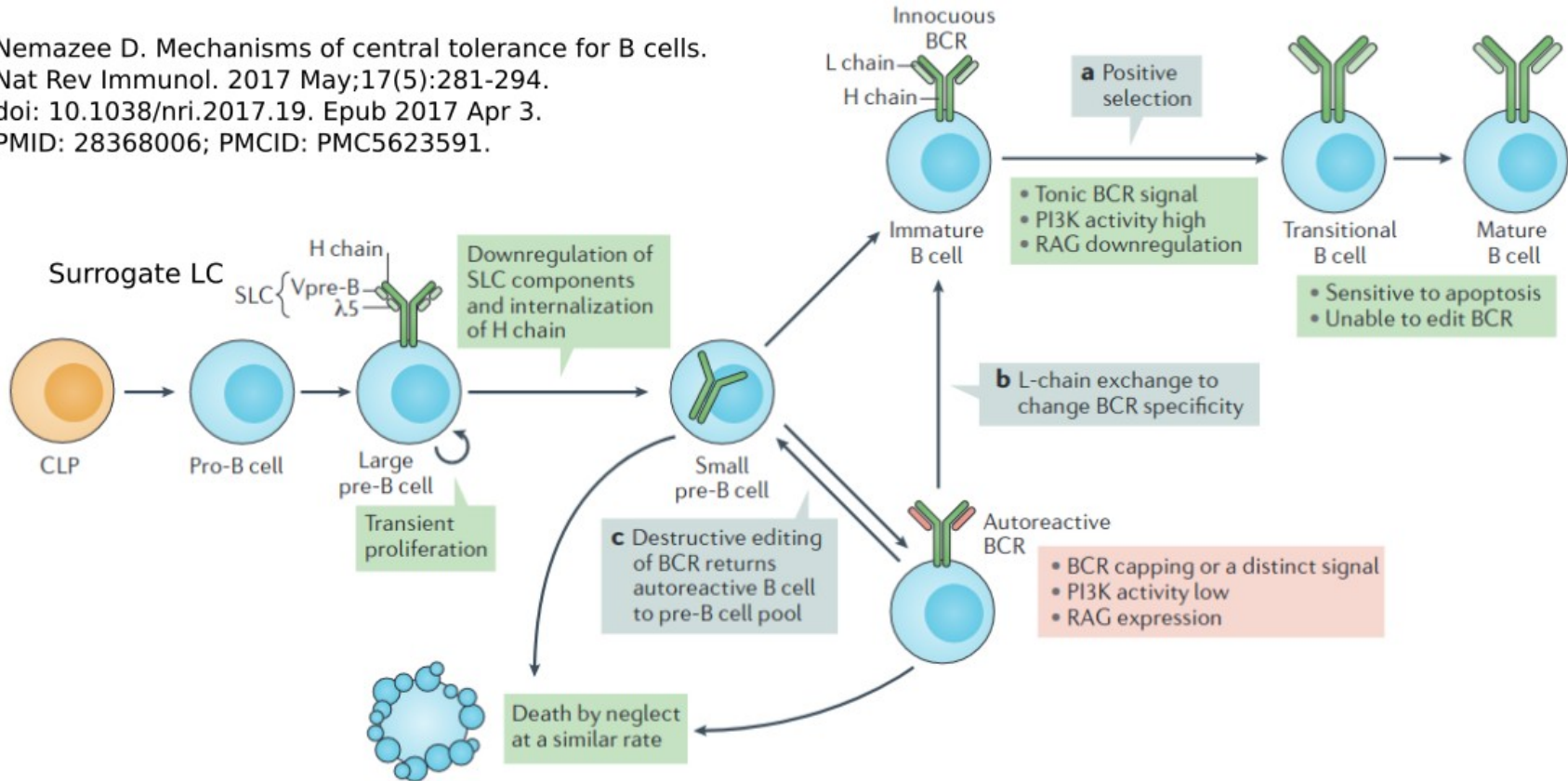
High avidity binding
 -> arrest & apoptosis

<https://doi.org/10.1016/C2009-0-62217-0>

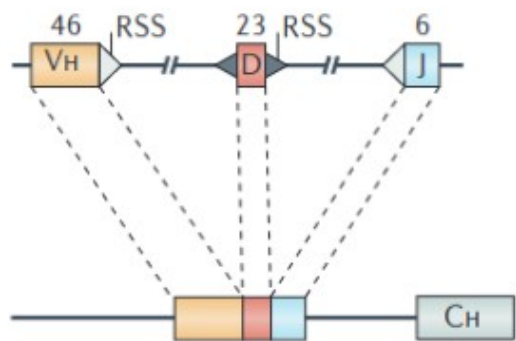




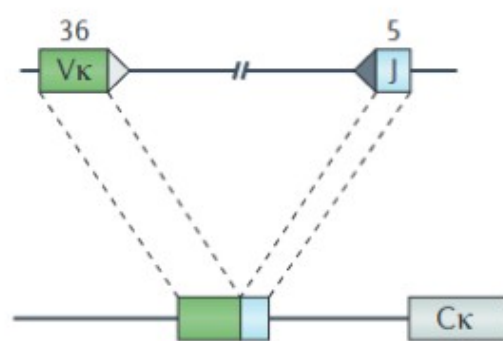
Nemazee D. Mechanisms of central tolerance for B cells. *Nat Rev Immunol.* 2017 May;17(5):281-294. doi: 10.1038/nri.2017.19. Epub 2017 Apr 3. PMID: 28368006; PMCID: PMC5623591.



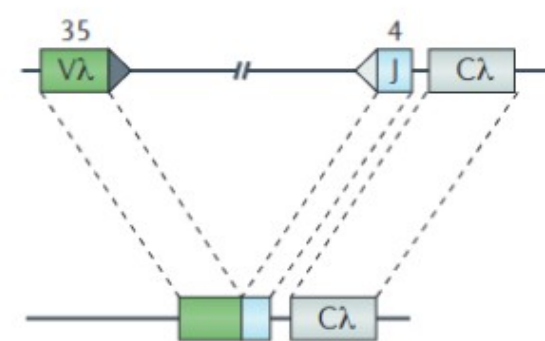
a Immunoglobulin H-chain locus



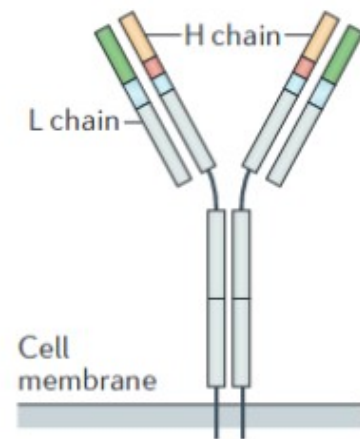
b Immunoglobulin κ L-chain locus

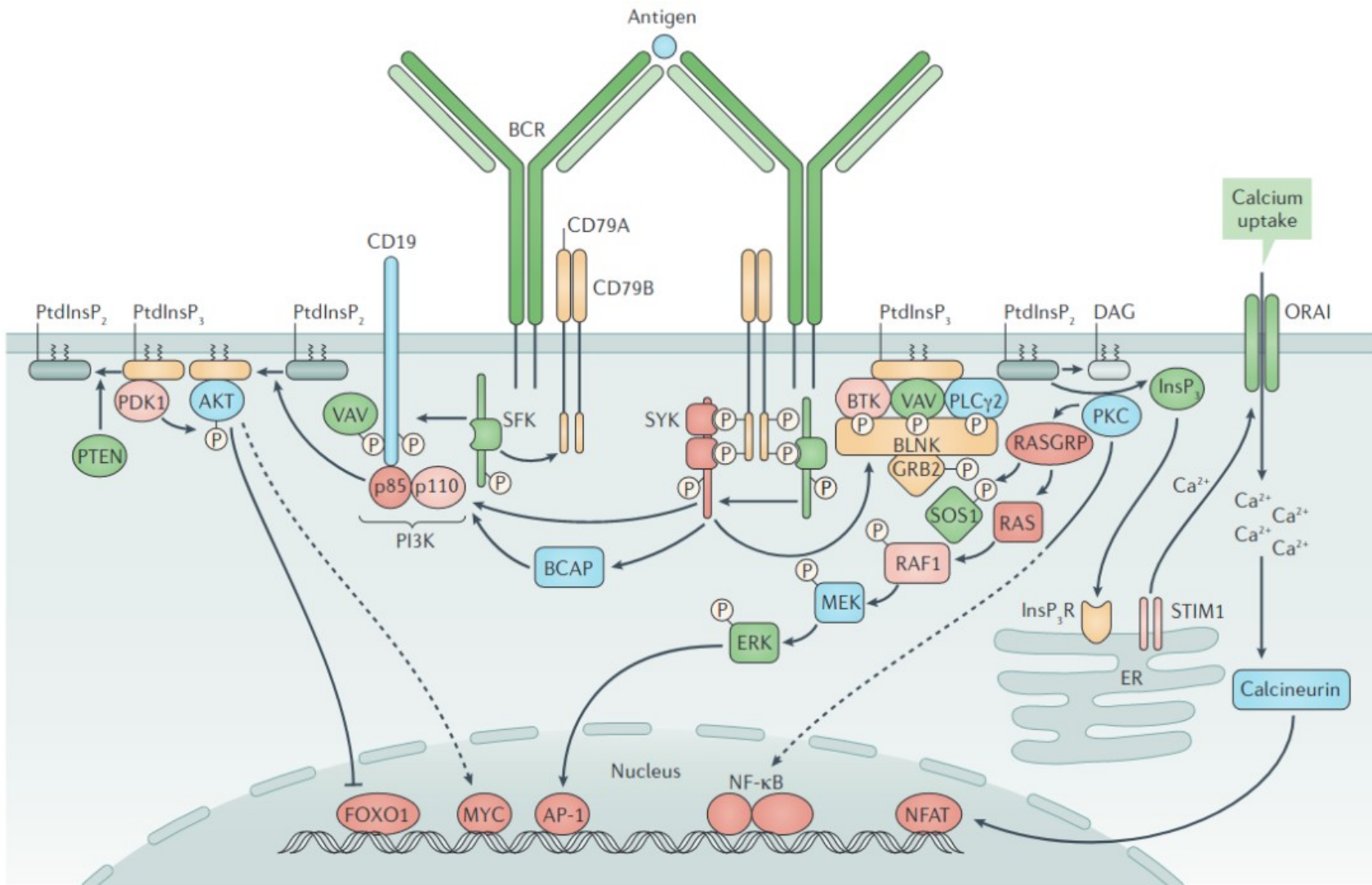


Immunoglobulin λ L-chain locus

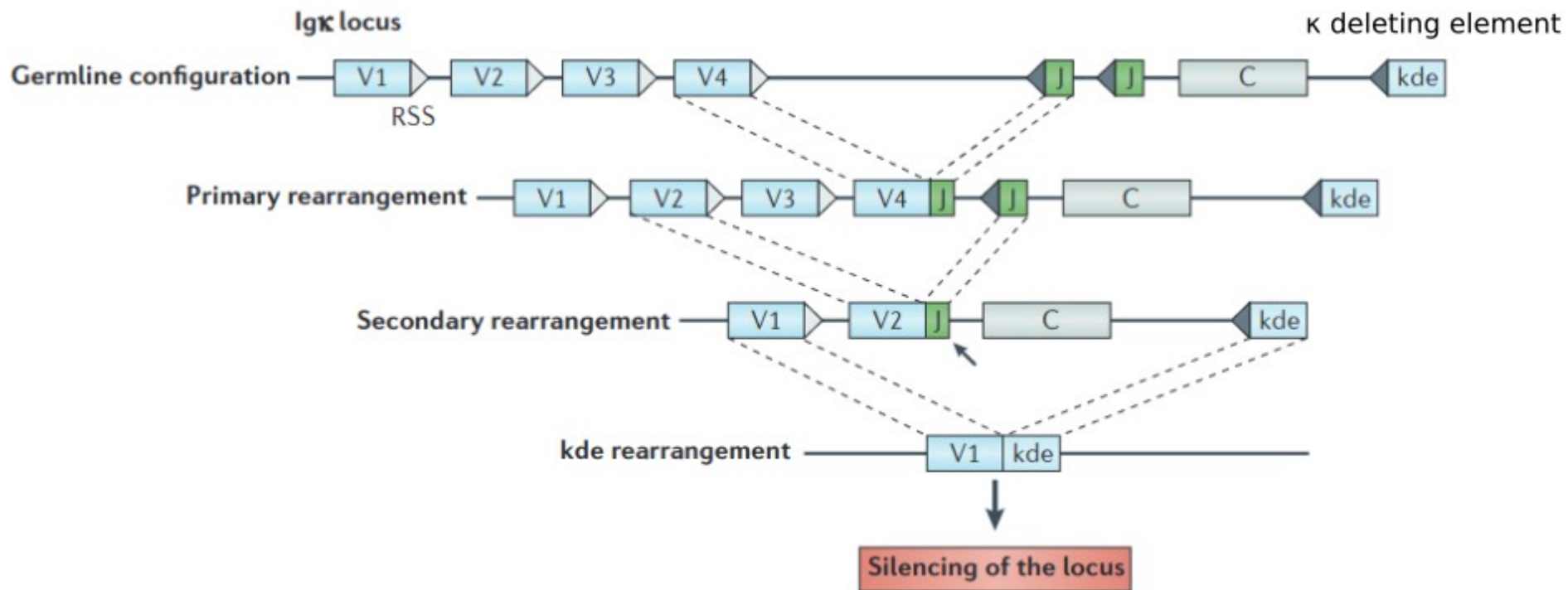


c Membrane IgM



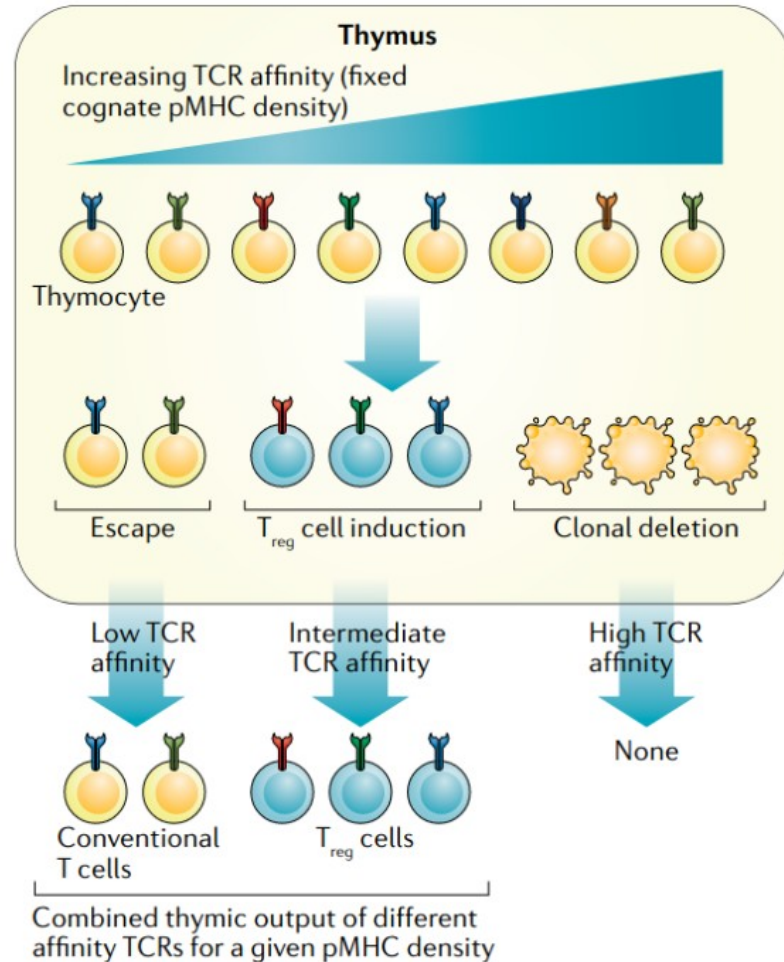


miRNAs ---> regulation of tolerance...

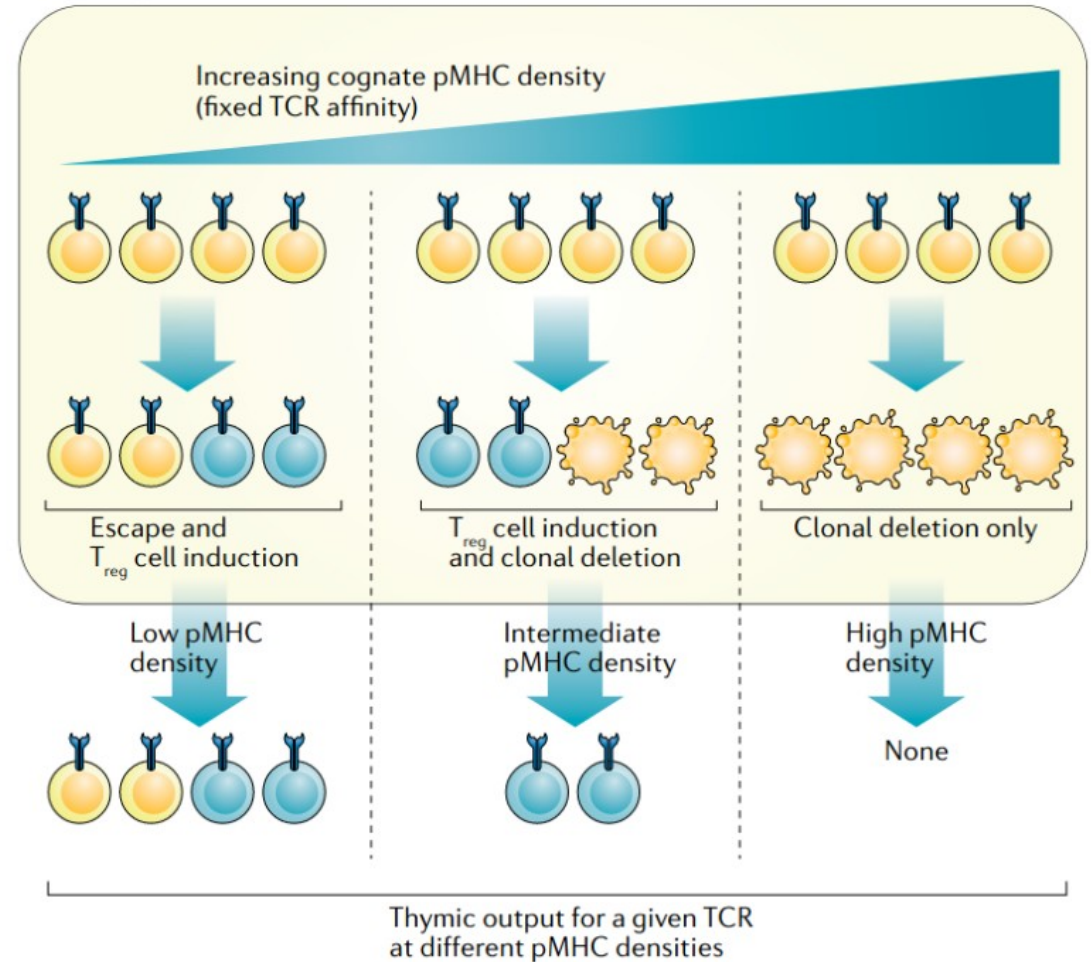


Klein L, Robey EA, Hsieh CS. Central CD4+ T cell tolerance: deletion versus regulatory T cell differentiation. *Nat Rev Immunol.* 2019 Jan;19(1):7-18. doi: 10.1038/s41577-018-0083-6. PMID: 30420705.

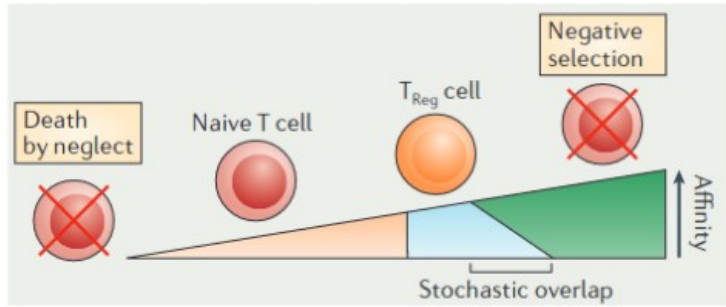
a Affinity-based model



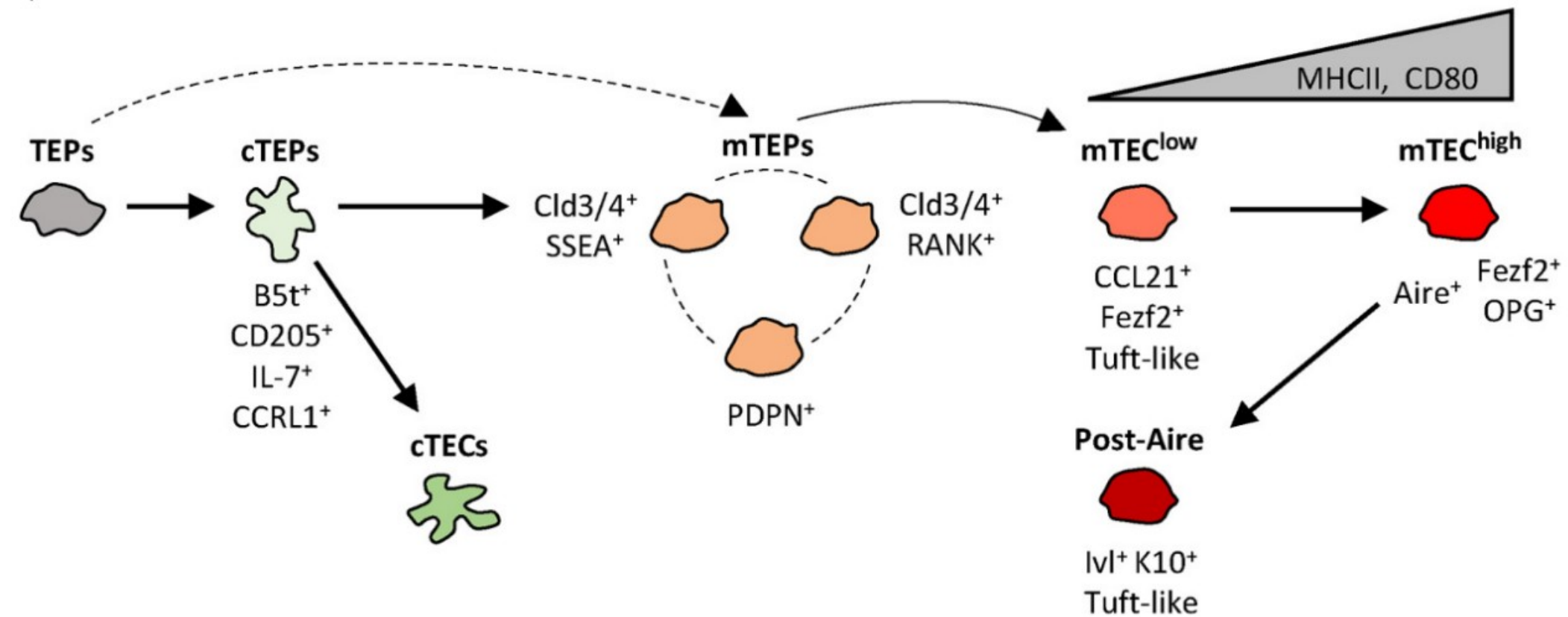
b Avidity-based model



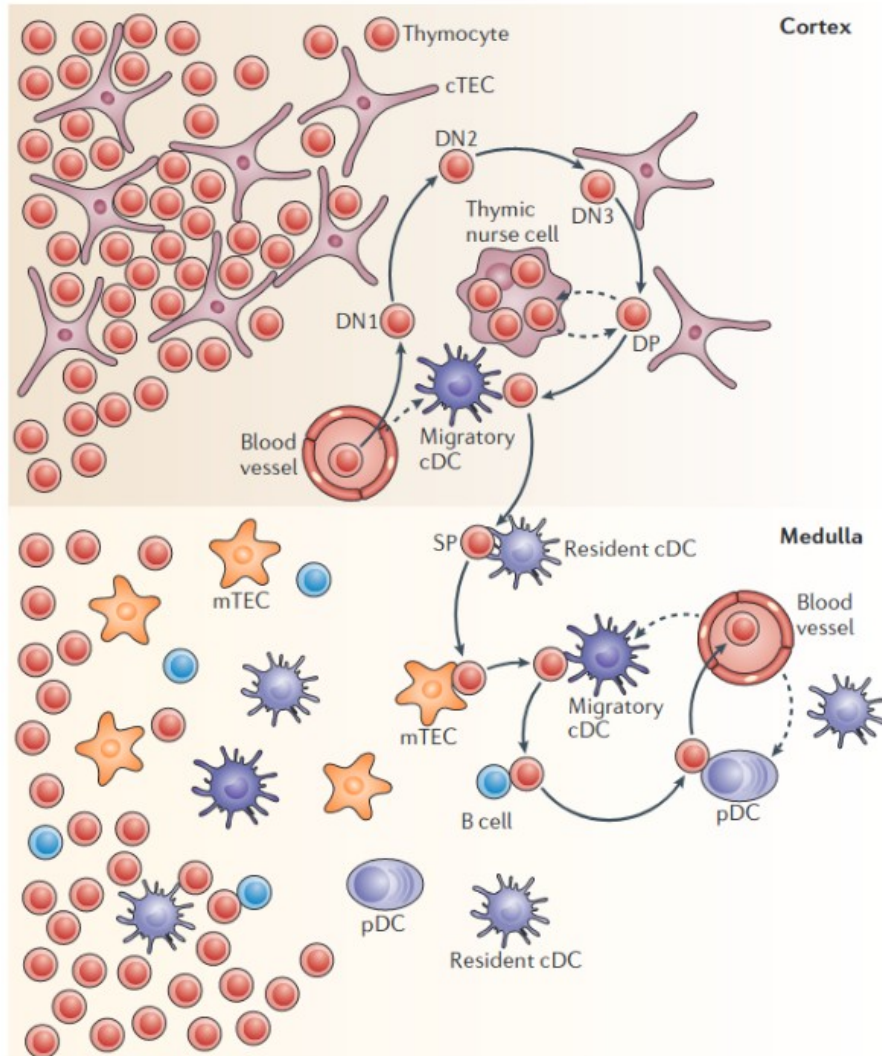
**mouse thymus generates ~50 million
CD4+CD8+ double-positive (DP) thymocytes / day**









Klein L, Kyewski B, Allen PM, Hogquist KA. Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). *Nat Rev Immunol.* 2014 Jun;14(6):377-91. doi: 10.1038/nri3667. Epub 2014 May 16. PMID: 24830344; PMCID: PMC4757912.

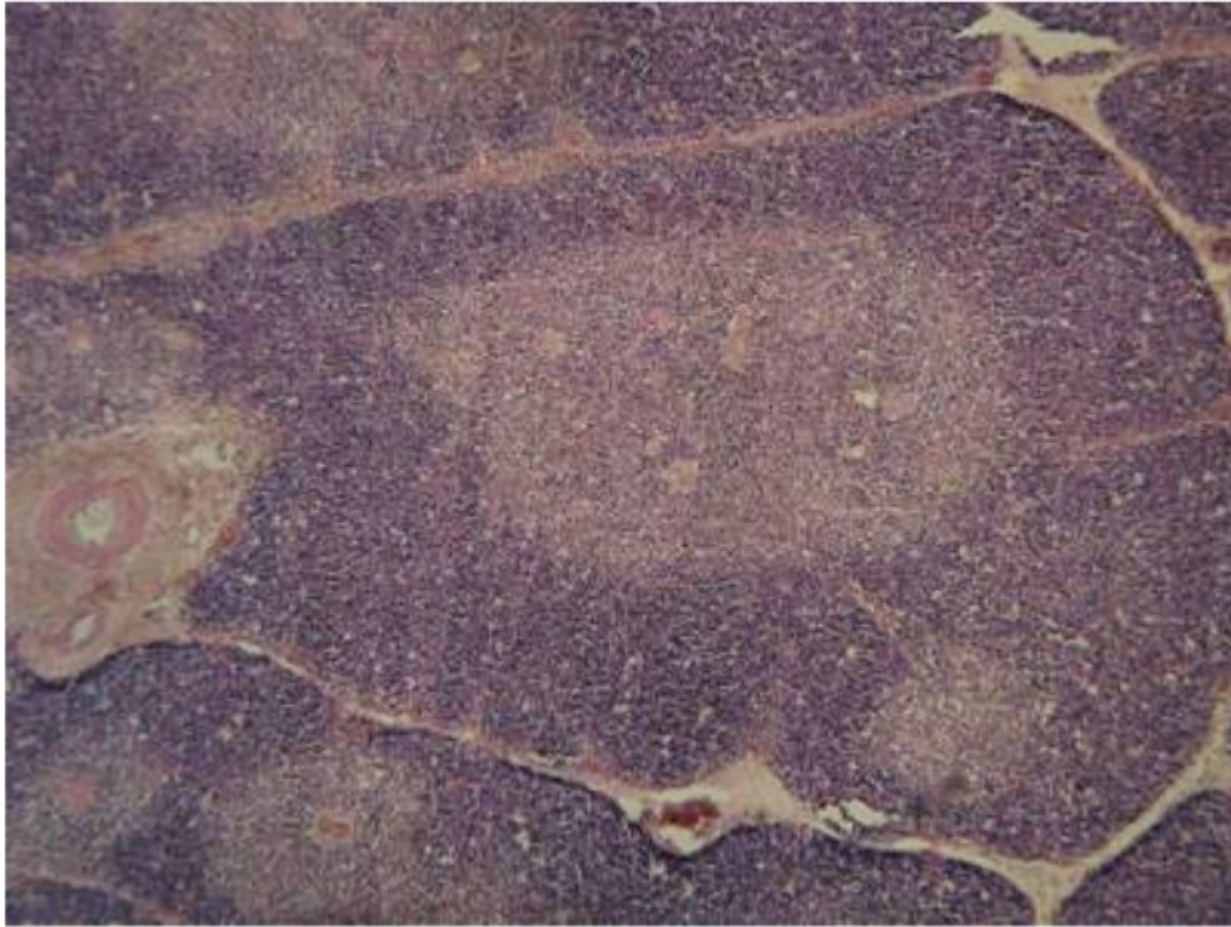


Medullary Thymic Epithelial Cells (mTEC)

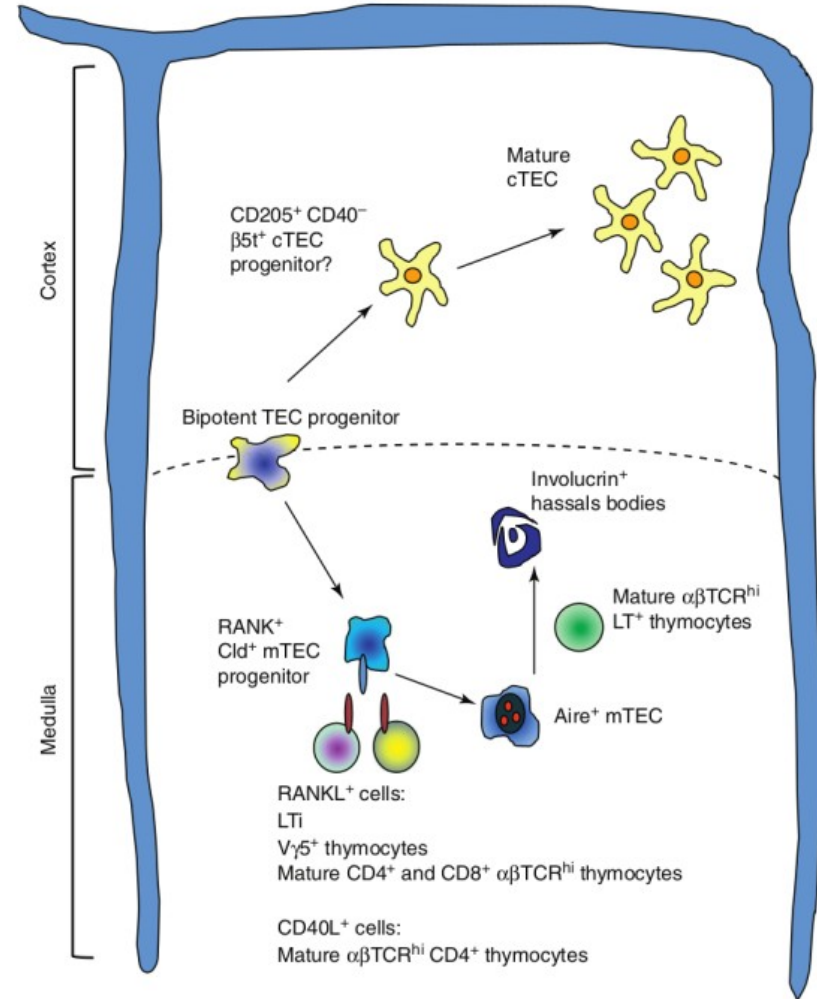
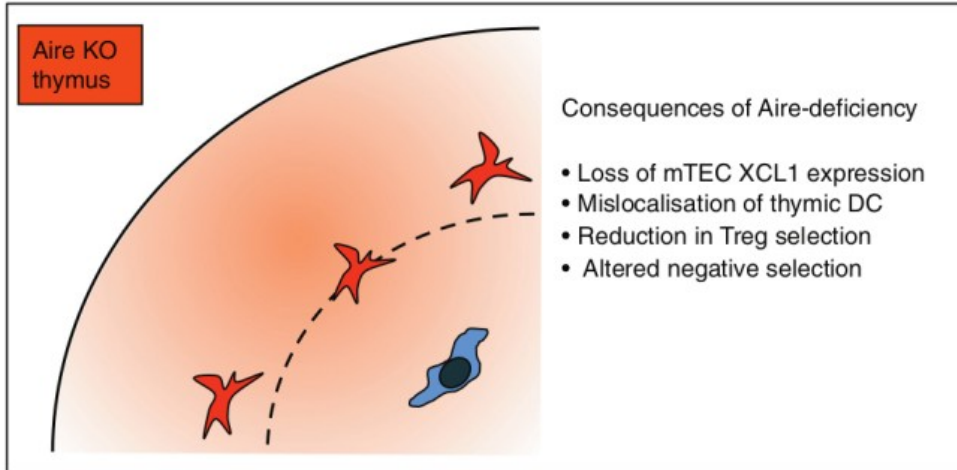
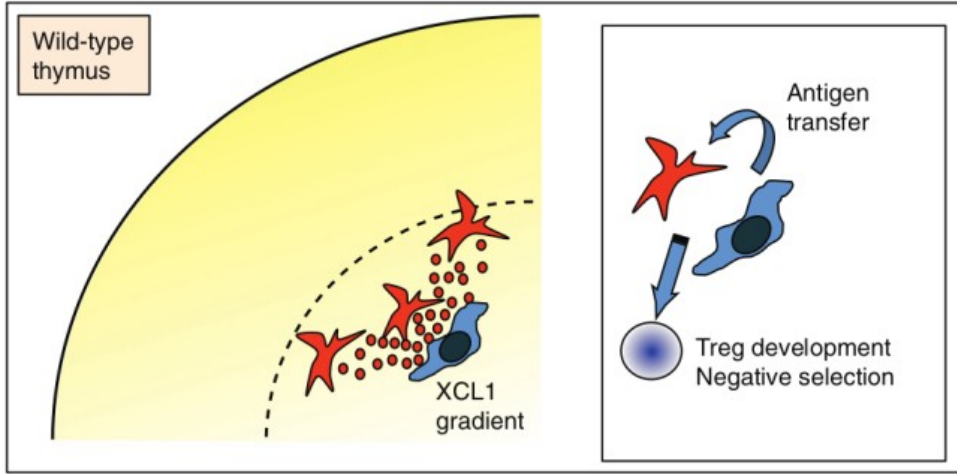


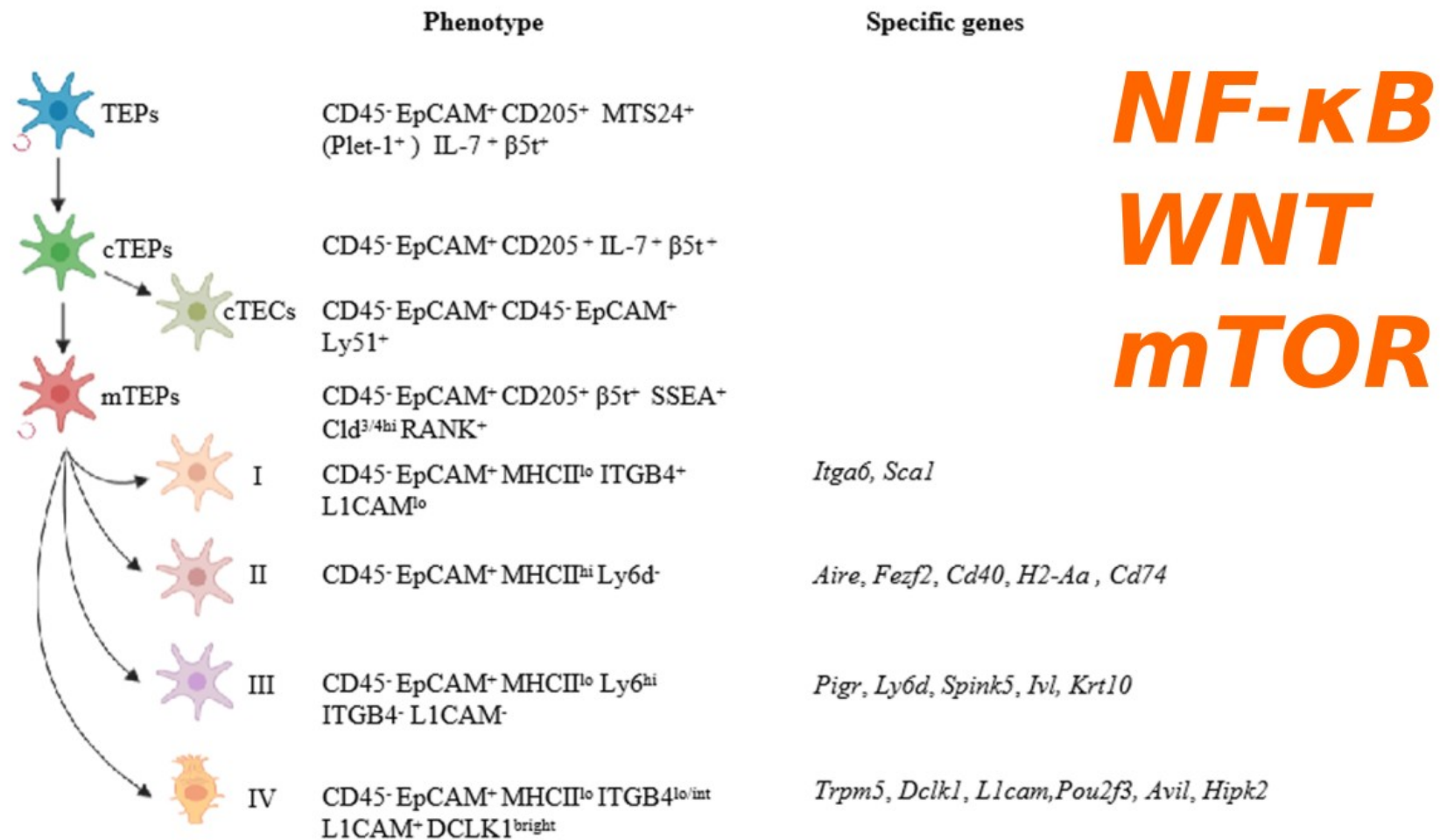
	<p>cTEC</p> <ul style="list-style-type: none"> • Unique 'private' proteolytic pathways • Efficient endogenous MHC class II loading • Constitutive macroautophagy • Thymic nurse cell formation
	<p>mTEC</p> <ul style="list-style-type: none"> • 'Promiscuous gene expression' (AIRE) • 'Public' proteolytic pathways • Efficient endogenous MHC class II loading • Macroautophagy
	<p>Migratory cDC</p> <ul style="list-style-type: none"> • 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 <p>SIRPα⁺CD8⁻</p>
	<p>Resident cDC</p> <ul style="list-style-type: none"> • Intrathymic differentiation • 'Public' proteolytic pathways • Conventional MHC class II loading • Presentation of mTEC-derived and serum-borne antigens <p>SIRPα⁻CD8⁺</p>
	<p>pDC</p> <ul style="list-style-type: none"> • Steady-state immigration from peripheral sites • Import of peripheral antigens • 'Public' proteolytic pathways • Conventional MHC class II loading • No presentation of mTEC-derived TRAs?
	<p>B cell</p> <ul style="list-style-type: none"> • Intrathymic or extrathymic origin? • Efficient presentation of BCR-captured antigens • 'Public' proteolytic pathways • No presentation of mTEC-derived TRAs?

<https://en.wikipedia.org/wiki/Thymus>



Anderson G, Takahama Y. Thymic epithelial cells: working class heroes for T cell development and repertoire selection. Trends Immunol. 2012 Jun;33(6):256-63. doi: 10.1016/j.it.2012.03.005. Epub 2012 May 14. PMID: 22591984.





Wang HX, Pan W, Zheng L, Zhong XP, Tan L, Liang Z, He J, Feng P, Zhao Y, Qiu YR.
Thymic Epithelial Cells Contribute to Thymopoiesis and T Cell Development.
Front Immunol. 2020 Jan 31;10:3099. doi: 10.3389/fimmu.2019.03099.
Erratum in: Front Immunol. 2020 Nov 30;11:628464. PMID: 32082299;
PMCID: PMC7005006.



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



SIRPα⁺CD8⁻

Migratory cDC

- 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



SIRPα⁺CD8⁺

Resident cDC

- 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?

cTEC

MHCI

β5t (PSMB11) proteasomes 'thymoproteasomes'.
substrate preference that is distinct from regular proteasomes
housekeeping proteasomes
immunoproteasomes

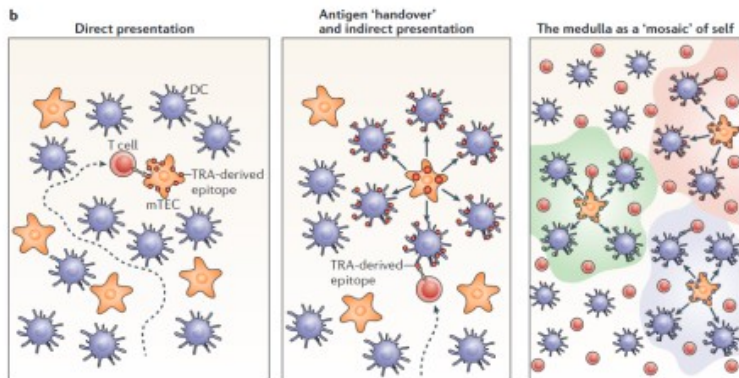
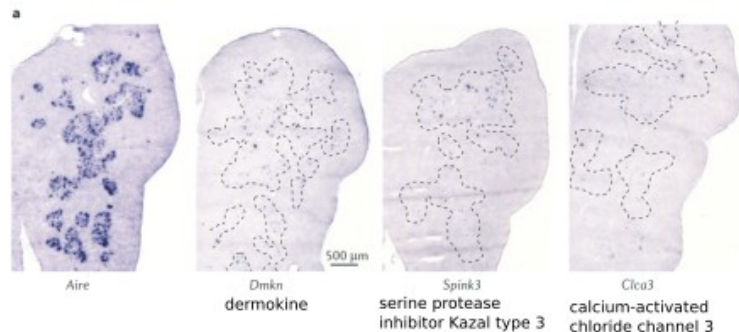
MHCII

unique lysosomal proteases cathepsin L (cathepsin L1)
thymus-specific serine protease (TSSP)

mTEC

Tissue Restricted Antigens

AIRE: Autoimmune Regulatory Proteins



private vs public peptides...

