Immunological Tolerance

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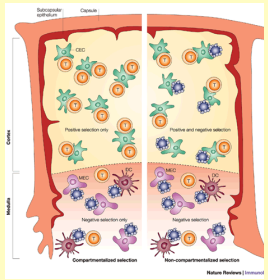
4540 FS2017-0: Selected topics in Clinical Immunology
May 4th 2017

Immunological Tolerance

highly desired

Tolerance to **self**



CD4+CD25+
Foxp3+

Th1

Th17

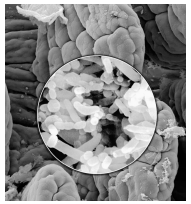
central tolerance
peripheral tolerance
prevention of autoimmunity

Tolerance to **foreign** antigens

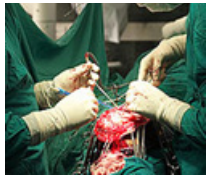
inhaled antigens

food antigens

fetal antigens



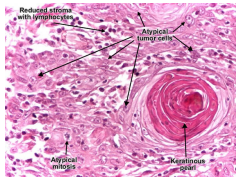
commensal flora



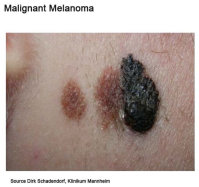
organ transplants

highly desired

undesired

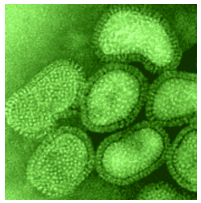


transformed cells

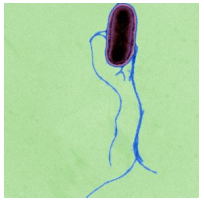


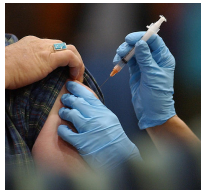
tumors

Tolerance to (altered) **self**



pathogens





vaccines

undesired

Tolerance to **foreign** antigens

Overview

1. "Basic" mechanisms of self-tolerance

Abbas 8th edition:

- central tolerance
- peripheral tolerance

Chapters 8, 15

2. Mucosal immunology

- role of innate immunity in tolerance to foreign
- oral tolerance

Chapter 14

3. Analyzing tolerance in clinical disease settings

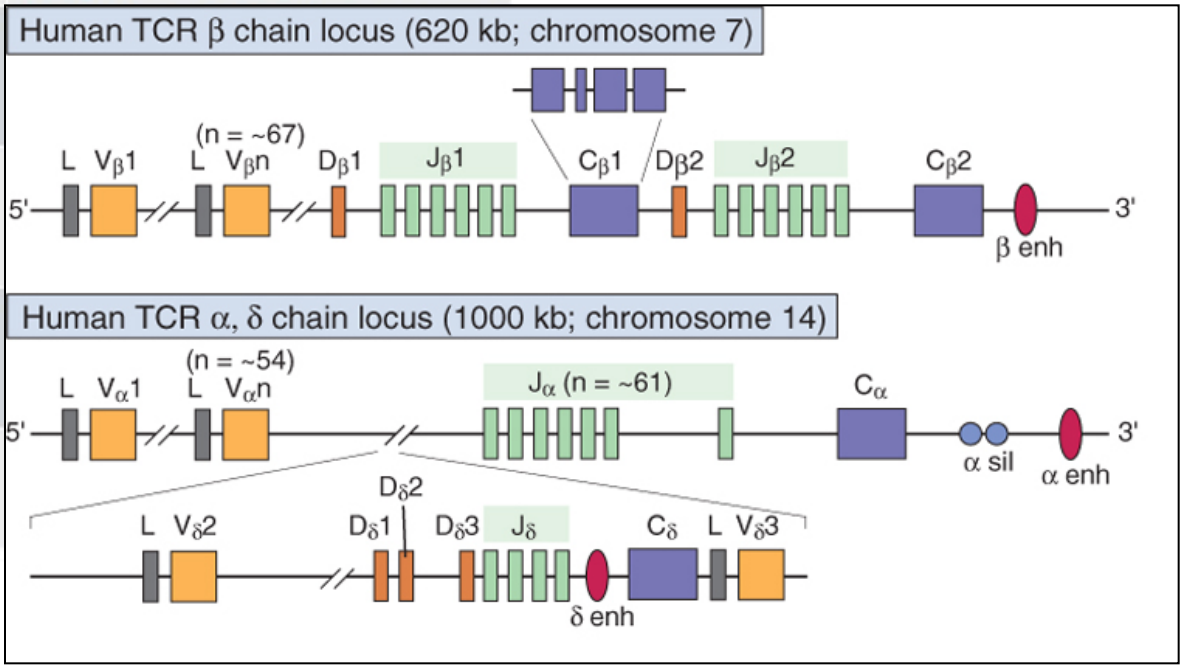
- autoimmune disease and hypersensitivity reactions
- pathogenetic role of genetic and microbial factors
- where does tolerance fail and how can it be assessed?

Chapters 15, 19

1. “Basic” mechanisms of self-tolerance

Feature	Functional significance
Specificity	Ensures that specific antigens elicit specific responses
Diversity	Enables immune system to respond to a large variety of antigens
Memory	
Specification	
Self-limitation	
Nonreactivity to self	

Diversity of Ig and TCR repertoires is generated by combinatorial associations of multiple germline genes



Ig: 10^{11} specificities
TCR$\alpha\beta$: 10^{16} specificities

also includes:

receptors not capable of recognizing self-MHC
receptors recognizing self-peptide-MHC complexes

Thymic selection processes

positive selection:

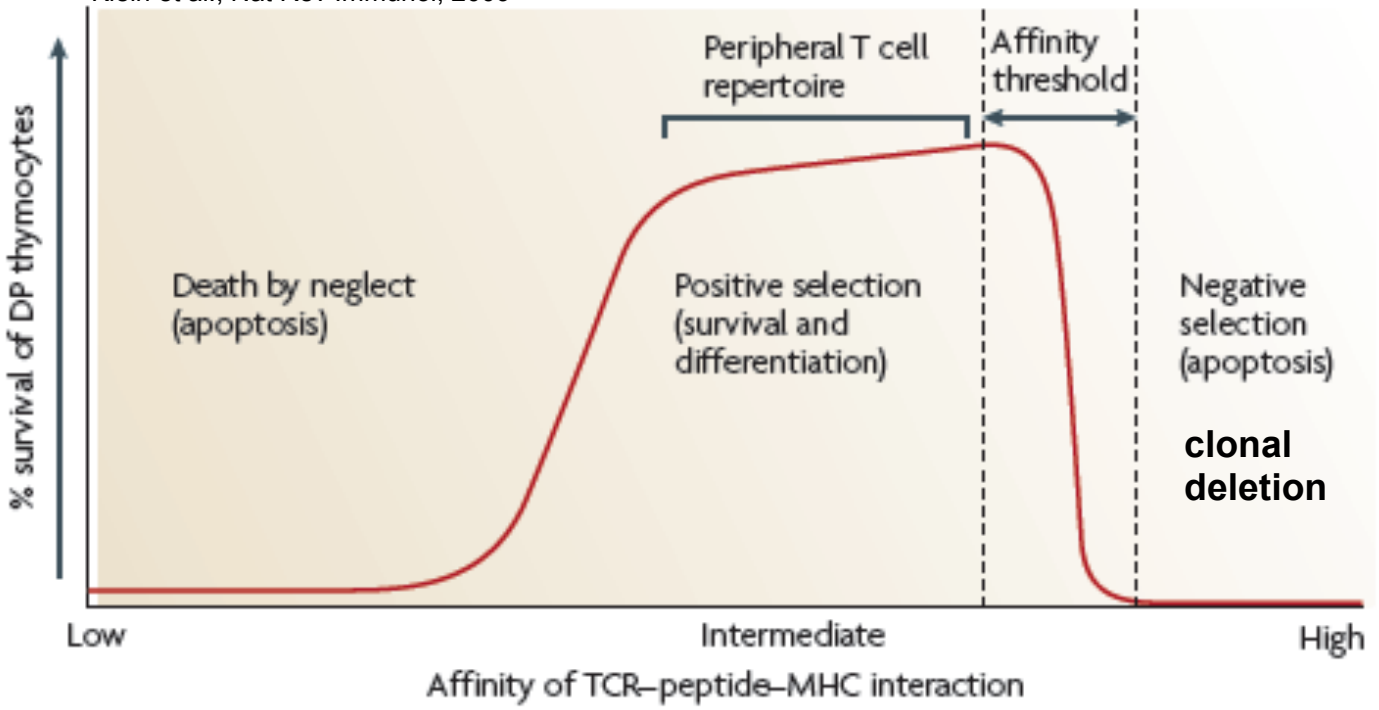
selective survival and expansion of thymocytes with TCR capable of recognizing self-MHC (with low avidity)

negative selection (central tolerance):

deletion of thymocytes with TCR capable of recognizing self-peptide-MHC complexes with high avidity

Thymic selection processes: Central tolerance

Klein et al., Nat Rev Immunol, 2009

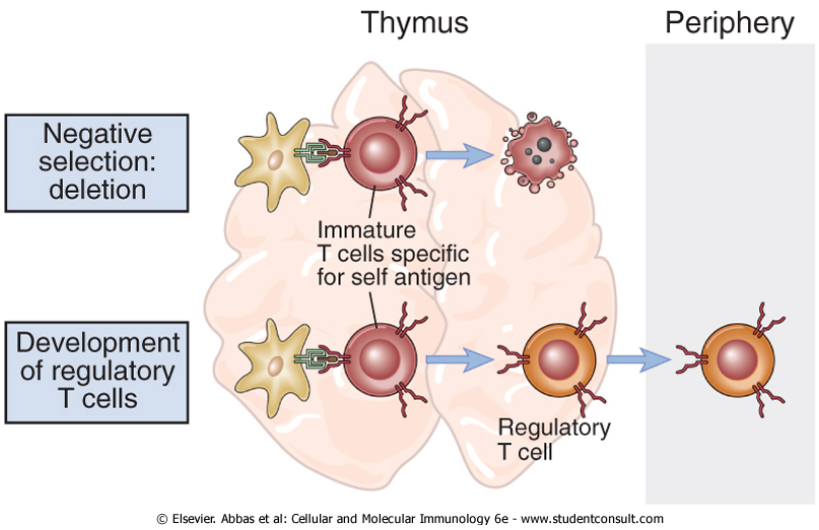


only 1-5% of thymocytes survive both selection processes…

abundance of self-antigens, numbers of TCR engaged, overall avidity of bond…

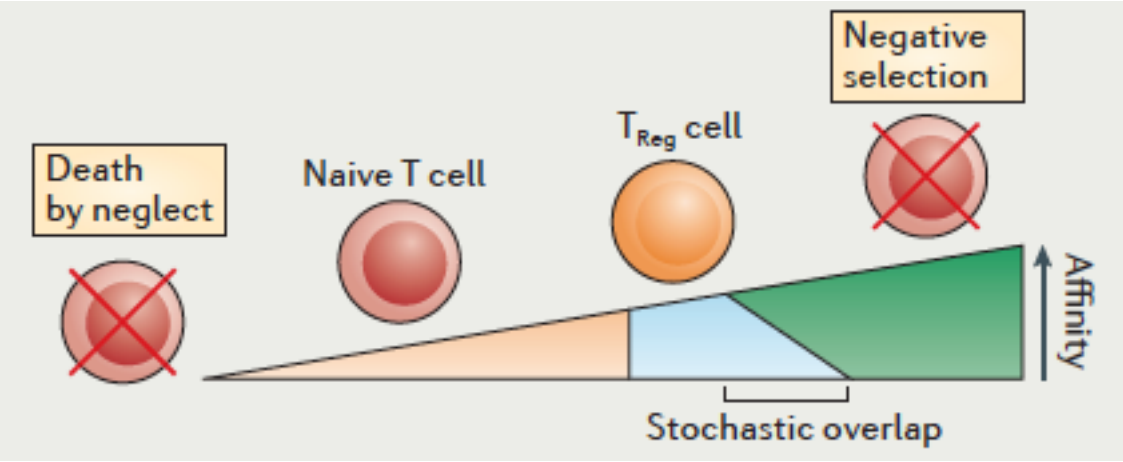
central tolerance in B cells (bone marrow): receptor editing or deletion by apoptosis

Central tolerance: Exceptions to the rules

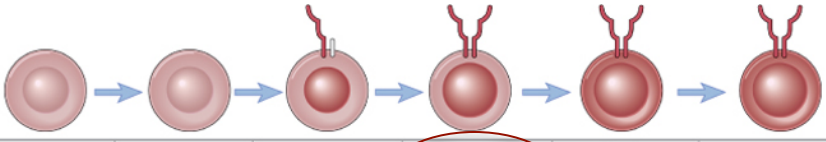


high avidity recognition of self-antigen by immature T cells in the thymus induces negative selection but can also promote the **development of $CD4^+$ $CD25^+$ regulatory T cells** ("agonist selection")

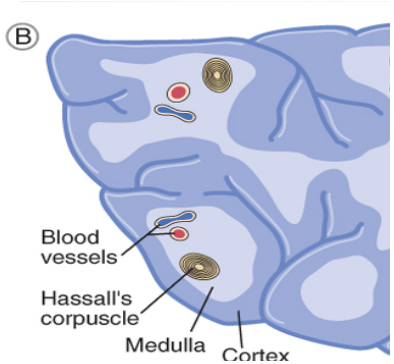
Klein et al., Nat Rev Immunol, 2014

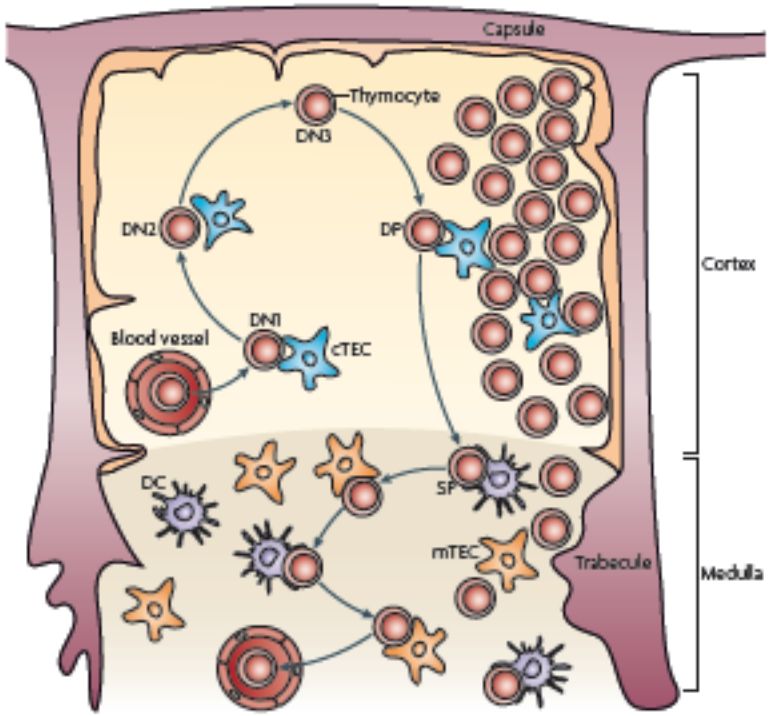


Central tolerance: Location and timing



Stage of maturation	Stem cell	Pro-T	Pre-T	Double positive	Single positive (immature T cell)	Naive mature T cell
Proliferation						
Rag expression						
TdT expression						
TCR DNA, RNA	Unrecombined (germline) DNA	Unrecombined (germline) DNA	Recombined β chain gene [V(D)J-C]; β chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA
TCR expression	None	None	Pre-T receptor (β chain/pre-T α)	Membrane αβ TCR	Membrane αβ TCR	Membrane αβ TCR
Surface markers	c-*kit*$^+$ CD44$^+$ CD25$^-$	c-*kit*$^+$ CD44$^+$ CD25$^+$	c-*kit*$^+$ CD44$^-$ CD25$^+$	CD4$^+$CD8$^+$ TCR/CD3^{lo}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}
Anatomic site	Bone marrow	Thymus				Periphery
Response to antigen	None	None	None	Positive and negative selection		Activation (proliferation and differentiation)





cTEC: cortical thymic epithelial cell
mTEC: medullary thymic epithelial cell

Klein et al., Nat Rev Immunol, 2009

Central tolerance: Role for thymic epithelial cells (TEC)

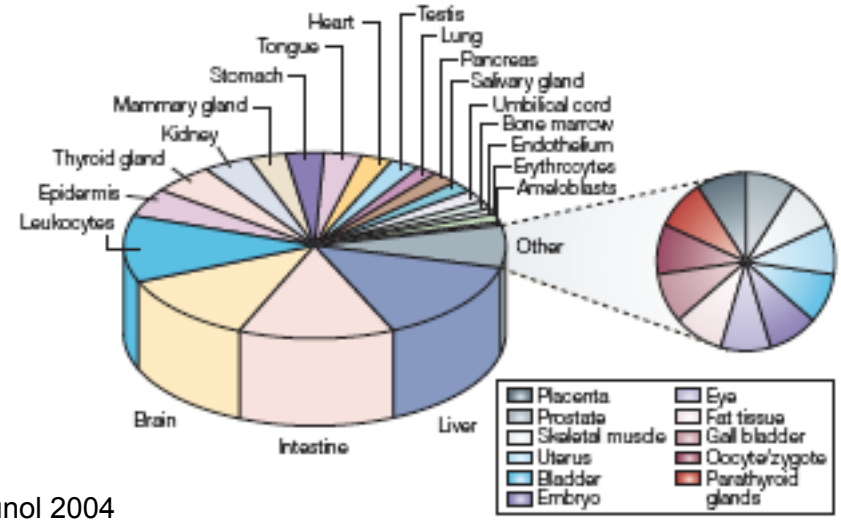
cTEC: cortical epithelial cell → positive selection
mTEC: medullary epithelial cell → negative selection

Table 1. Summary of the cell type–specific pattern of promiscuous gene expression

	SAP	CRP	Complement C5	α-fetoprotein	Albumin	Haptoglobin	αl-antitrypsin	PLP	MOG	S100β	GAD67[a]	GAD65[a]	Somatostatin	Trypsin2	Elastase	Insulin[a]	Tyrosinase	Gp100	PIA	Thyroglobulin	Lactalbumin	αl-crystallin	Retinal S antigen	NAChRαl	IFABP	Amylase l
cTECs	–	–/+	+	–	–	–	–	+	–	–	–	–	–/+	–/+	+	–	–	+	–/+	+	–/+	+	+	–	–/+	+
mTECs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DCs	–	–	+	–	–	–	–	–/+	–	+	–	–	–/+	–	–/+	–	–	+	–/+	–	–	+	–	–	–	–
Macrophages	–	–	–/+	–	–	–	–	–/+	–	+	–	–	–	–	+	–	–	+	–	–	–/+	–/+	+	–	–	–/+

Klein et al., Nat Immunol 2001

genes overexpressed in mTEC compared to cTEC



Kyewski et al., Nat Rev Immunol 2004

Central tolerance: Role for AIRE (autoimmune regulator)

An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains

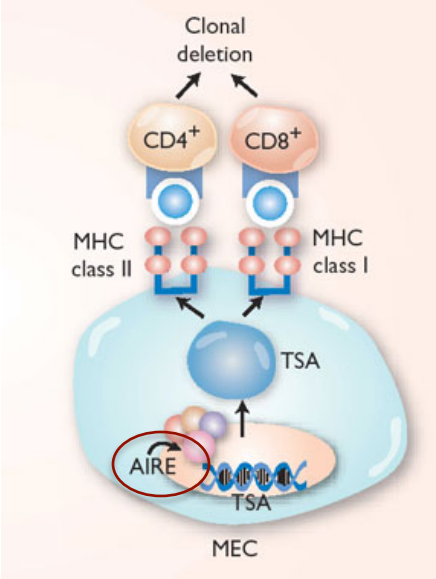
The Finnish-German APECED Consortium*

Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) is the only described systemic autoimmune disease with established monogenic background, and the first autoimmune disorder localized outside the major histocompatibility complex (MHC) region. The primary biochemical defect in APECED is unknown. We have isolated a novel gene, AIRE, encoding for a putative nuclear protein featuring two PHD-type zinc-finger motifs, suggesting its involvement in transcriptional regulation. Five mutations in AIRE are reported in individuals with this disorder. This is the first report of a single-gene defect causing a systemic human autoimmune disease, providing a tool for exploring the molecular basis of autoimmunity.

mTEC express high levels of the transcription factor AIRE...

and

....exhibit macroautophagic activity (delivery of endogenous proteins to MHCII)



reduced promiscuous gene expression in mTEC

multi-organ autoimmune disease!

Central tolerance: ...is not complete…

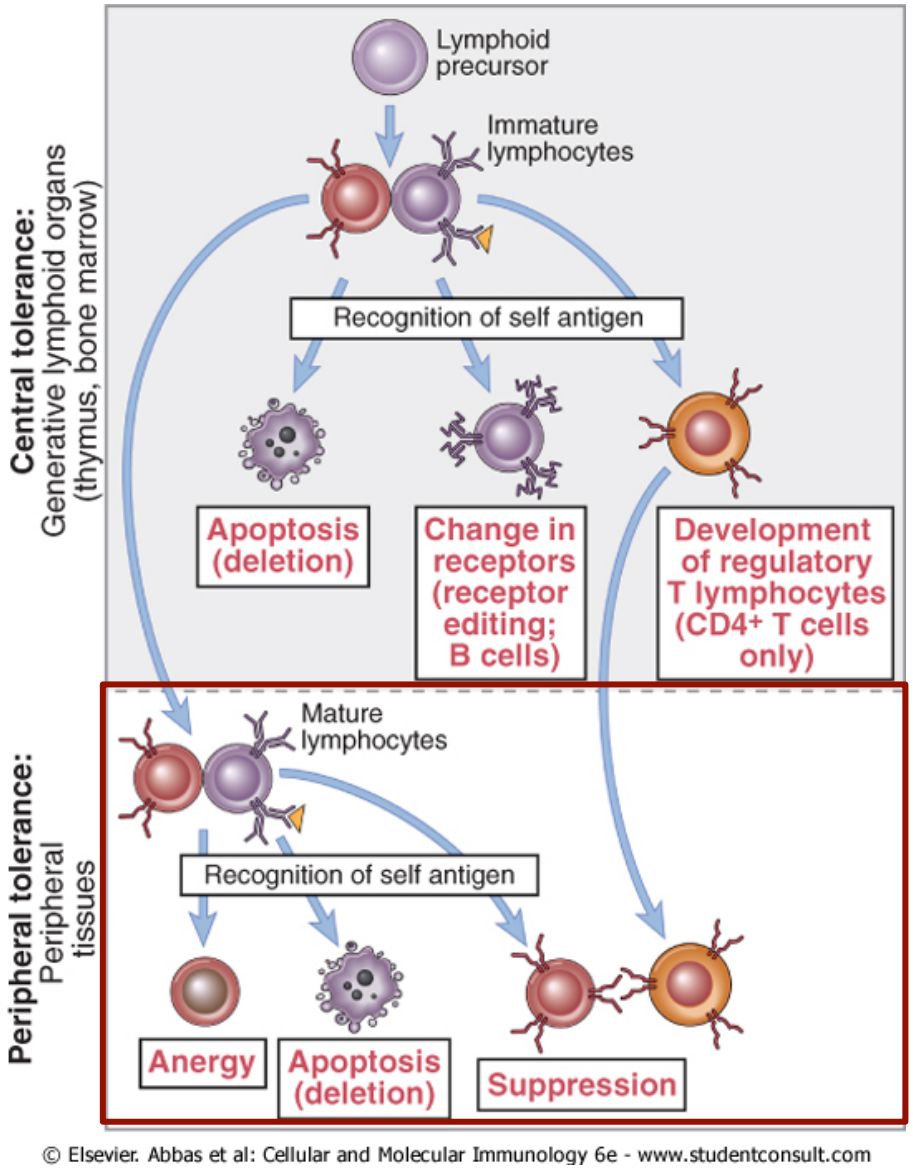
- not all tissue-restricted antigens are expressed in the thymus
- some tissue-restricted antigens are only expressed in adult life
- expression levels may be insufficient
- avidity-based selection is not “black and white”

- T cells with self-specific TCR can be isolated from most healthy individuals

⬇

peripheral tolerance mechanism must be operative!

Peripheral tolerance: Overview



- Anergy
  (functional unresponsiveness)
- Apoptosis / Deletion
- Suppression by T_{reg}
- (Immunological ignorance)
- (Immuneprivilege)

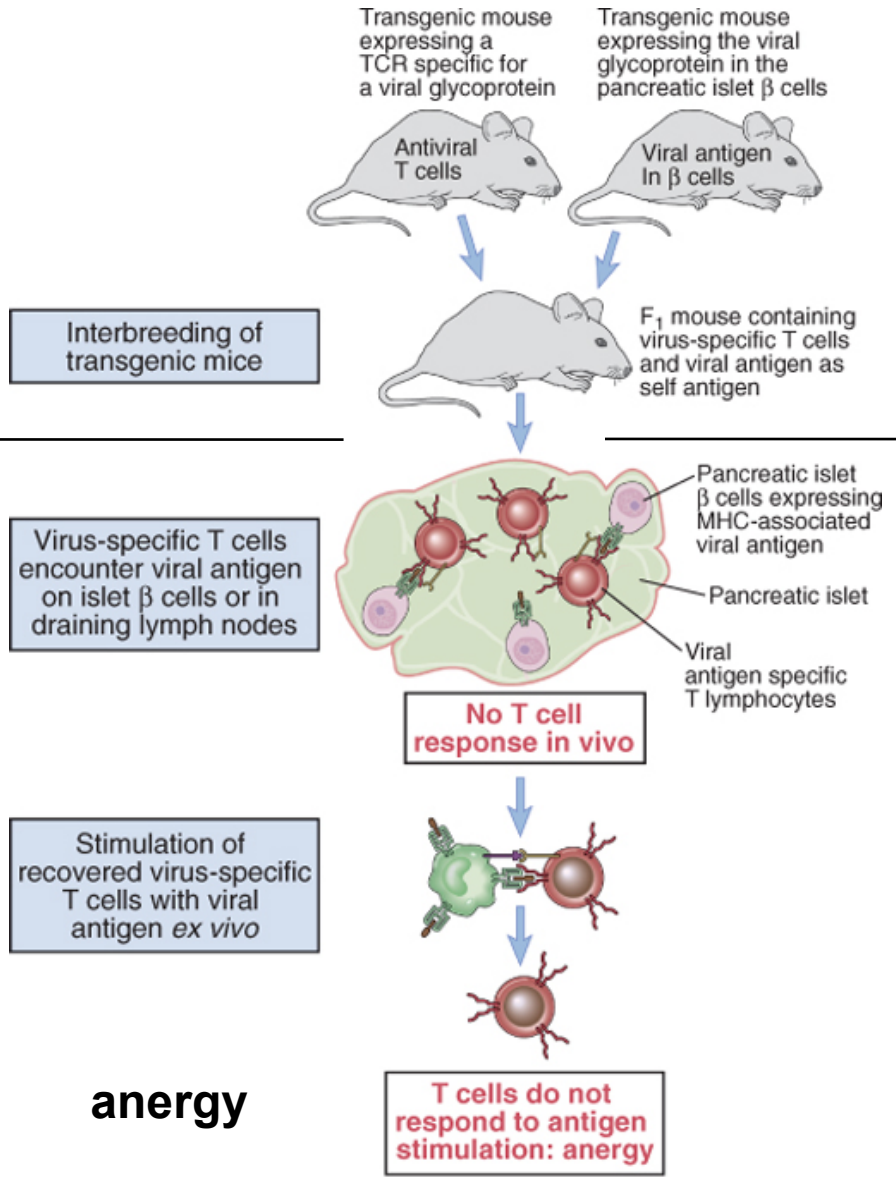
Peripheral tolerance: Anergy

alternative outcome:

immunological ignorance

↓

TCR tg cells <u>can</u> be re-stimulated *ex vivo*!



co-expression of viral antigen with B7, CD40L, TNFα

or: viral infection

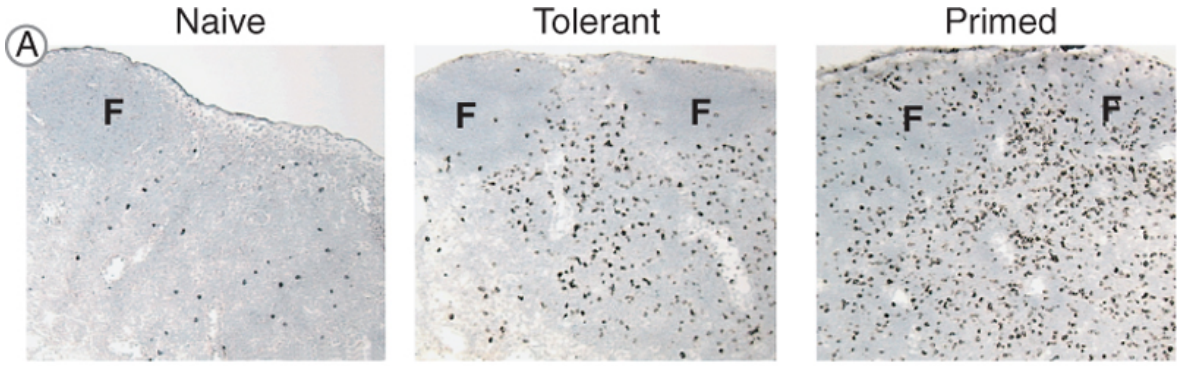
↓

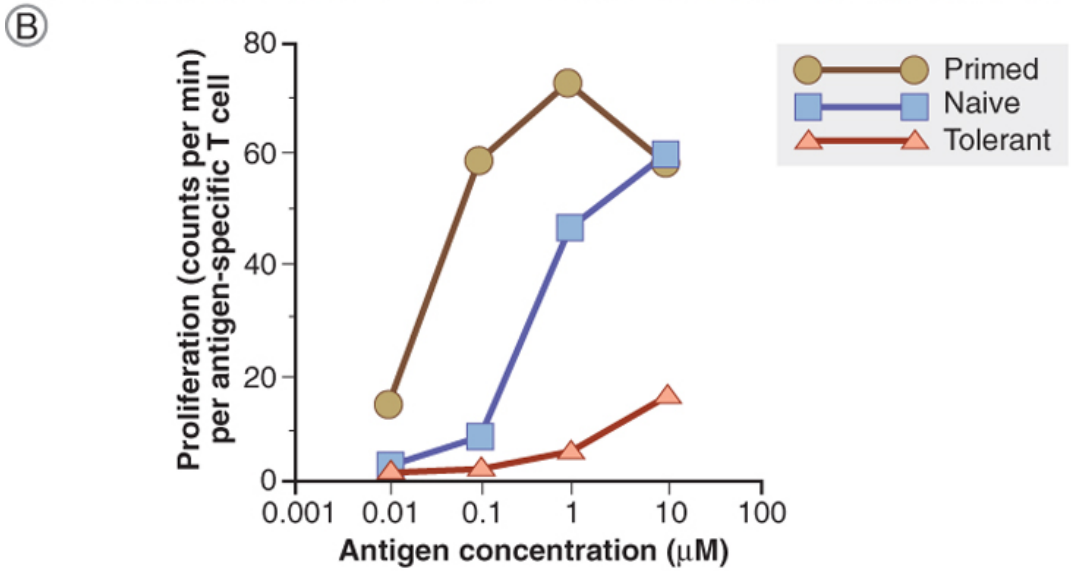
autoimmunity

Peripheral tolerance: Anergy

immunizations:

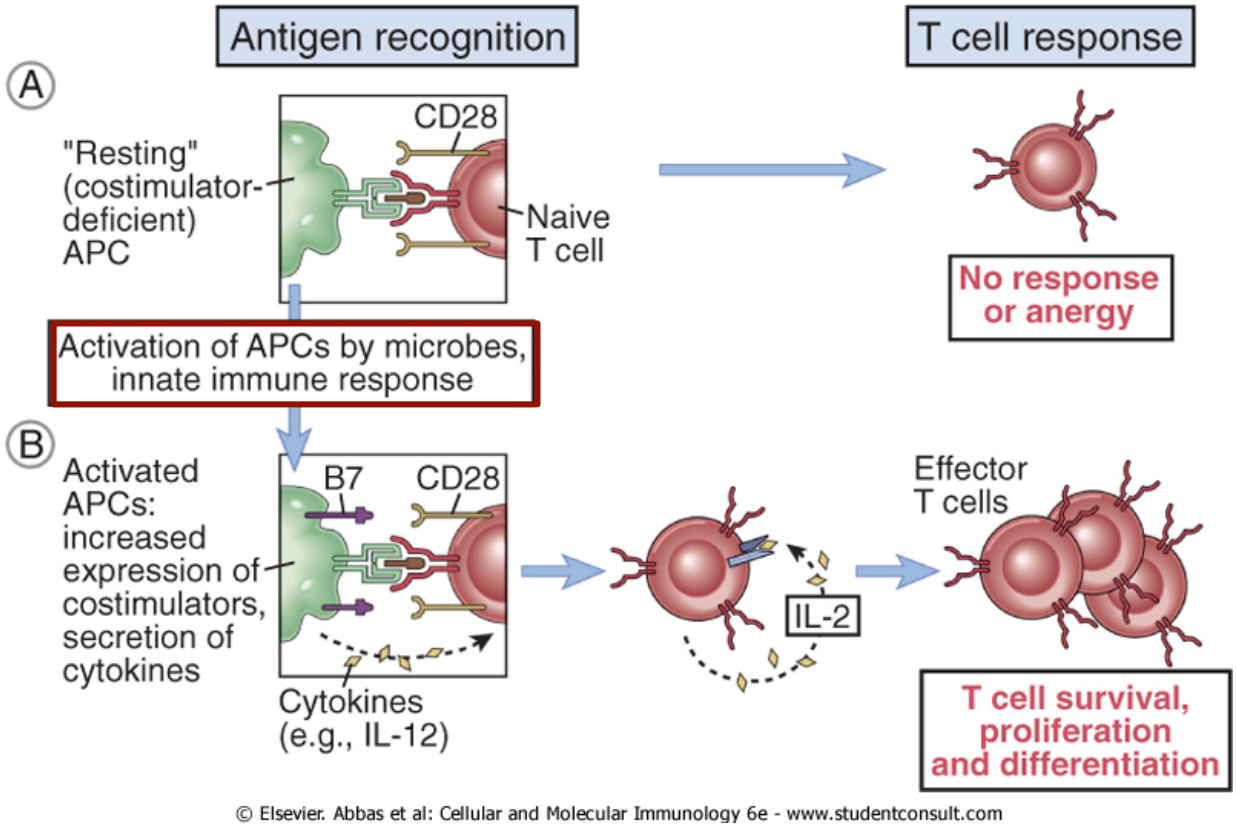
none	• large dose • in aqueous form • no adjuvants • i.v. or oral	• “immunogenic” dose • in particulate form • with adjuvants • s.c. or i.d.



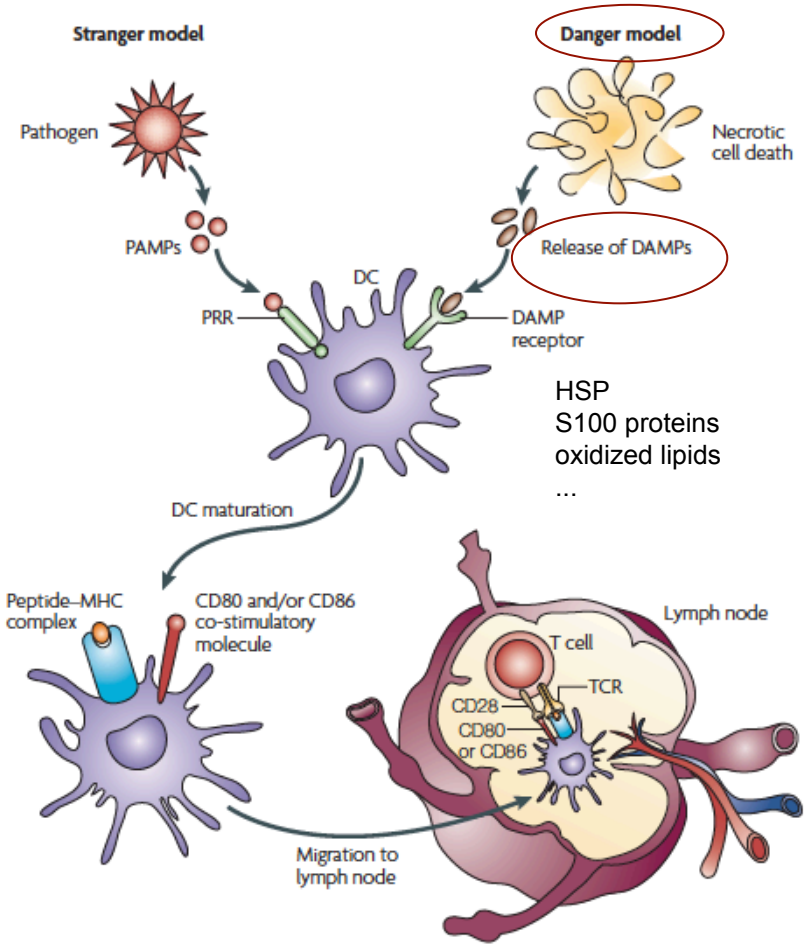


Peripheral tolerance: Anergy

Decision over immunity vs. tolerance lies with the antigen-presenting cells (importance of the "signal 2" concept!)



Peripheral tolerance: Anergy



Kono et al, Nat Rev Immunol 2008

The danger model:

Polly Matzinger, Science 2002: The danger model: a renewed sense of self

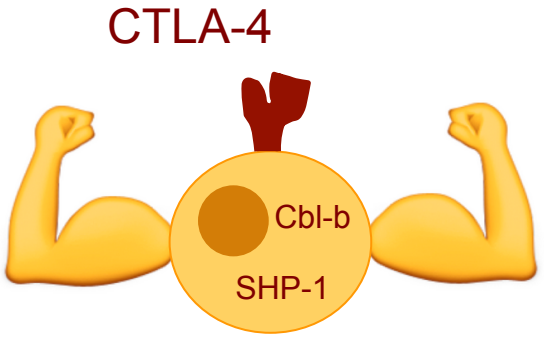
decision over immunity vs. tolerance is determined by recognition of "danger" (DAMPs) rather by self versus non-self (PAMPs) discrimination

endogeneous factors can trigger inflammation

tissues take a critical role in transmitting signals to immune cells

Peripheral tolerance: Anergy

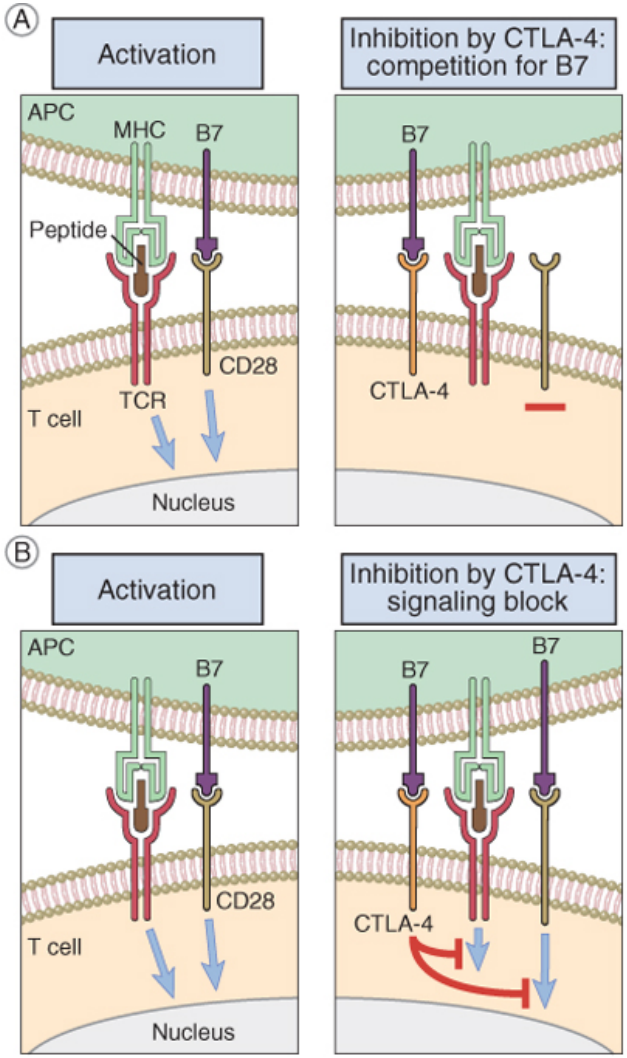
Anergy is induced and maintained <u>actively</u> by several mechanisms:



- Activation of protein tyrosin phosphatases (e.g. SHP-1 / SHP-2)
- Activation of cellular ubiquitin ligases (e.g. Cbl-b)
- Induction and engagement of inhibitory receptors (CTLA-4, PD-1)

Peripheral tolerance: Anergy

Two potential mechanisms behind CTLA-4 mediated immune attenuation:



<u>competition for B7</u>

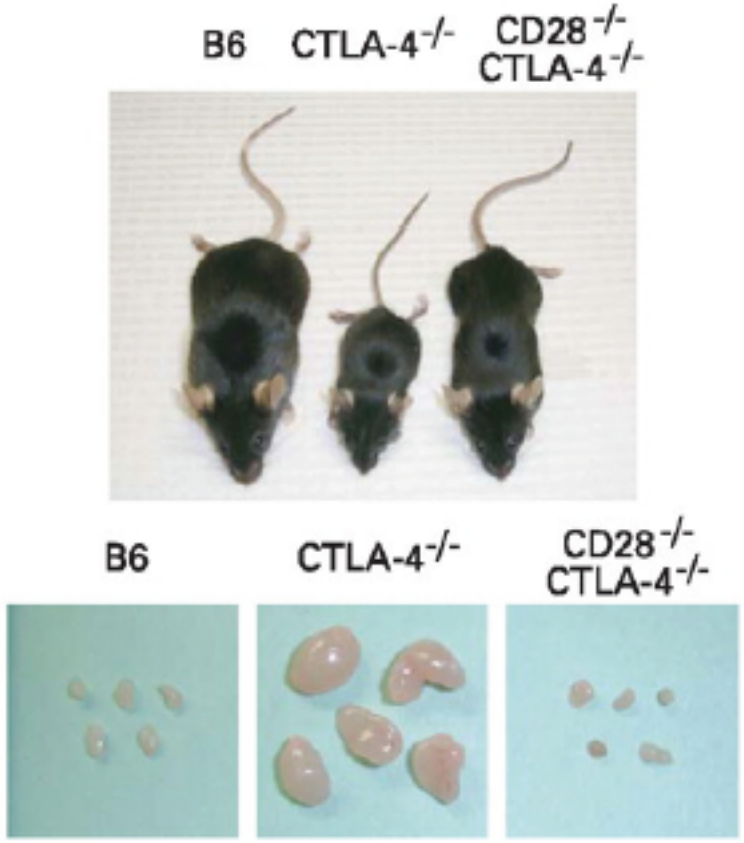
(CTLA-4 has a higher affinity than CD28)

<u>cell intrinsic inhibitory signaling</u>

(phosphorylated ITIM motifs on CTLA-4 recruit phosphatases that dephosphorylate signaling molecules in the vicinity)

Peripheral tolerance: Anergy

Significance of CTLA-4:



Loss of CTLA-4: Lymphoproliferation and fatal multiorgan tissue destruction. Critical regulatory role of CTLA-4 !

Tivol EA et al., Immunity. 1995 Nov;3(5): 541-7

polymorphisms in the human CTLA-4 gene are associated with several autoimmune diseases

CTLA-4-based therapeuticals exist!

CTLA-4 Ig fusion protein
for rheumatoid arthritis and kidney transplant patients

CTLA-4 neutralising antibody
for melanoma patients
"check-point inhibitor"

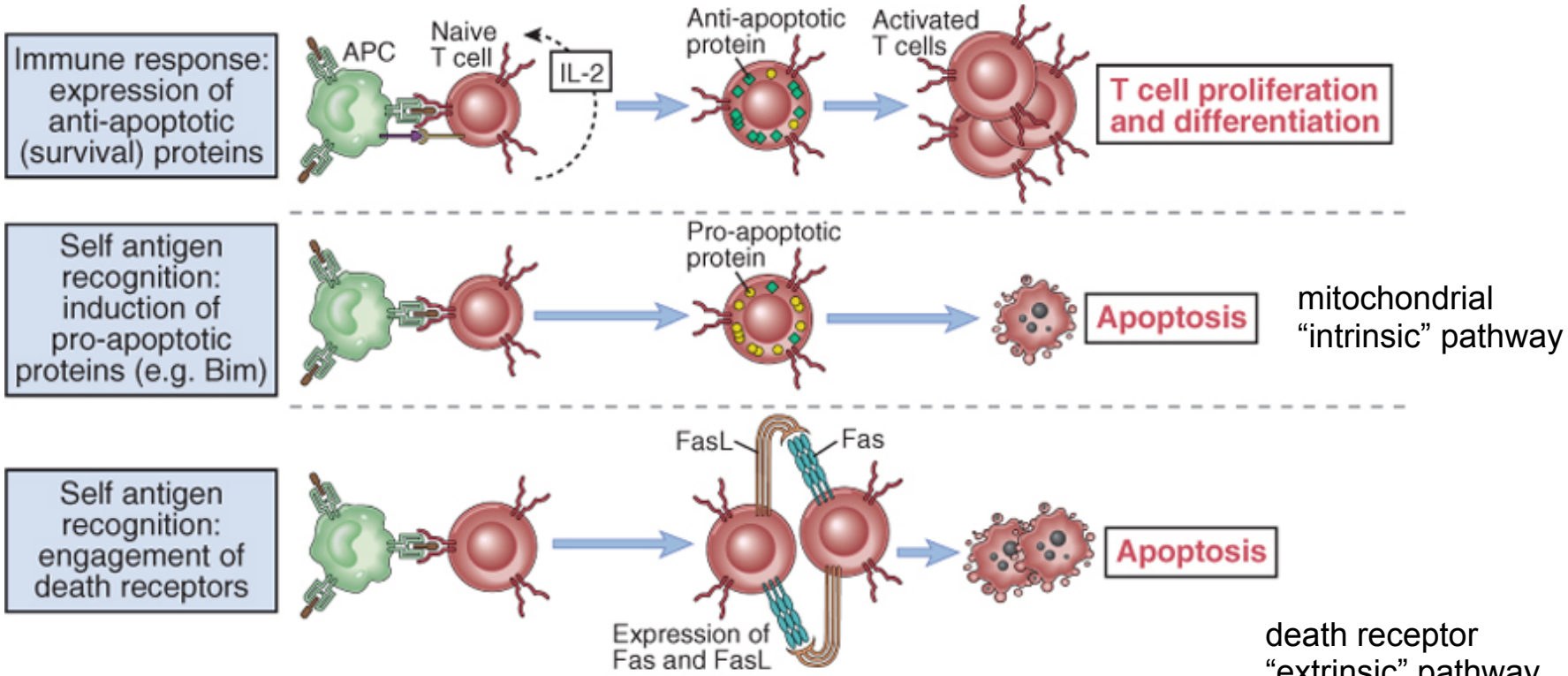
(autoimmune side effects!)

Peripheral tolerance: Deletion

self-antigens cannot be eliminated ⟶ chronic / repetitive stimulation

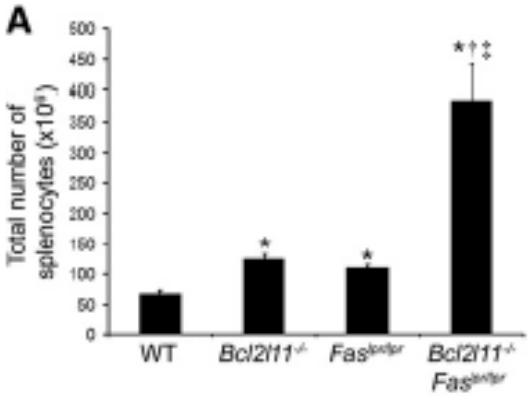
- deprival of survival factors, activation of Bim
- induction of Fas / FasL

} apoptosis

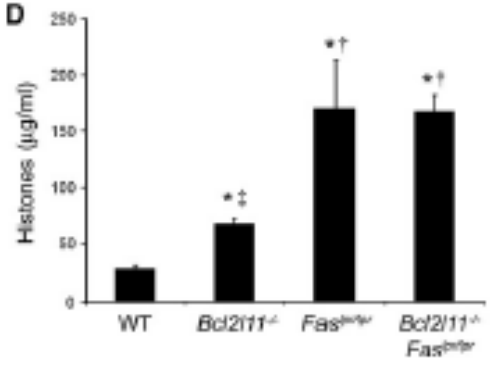


Peripheral tolerance: Deletion

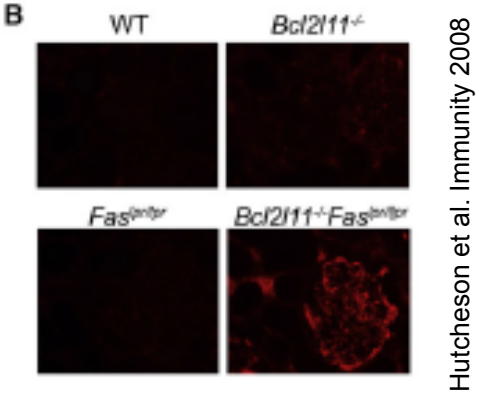
Mice with mutations in either **Fas** ($^{lpr/lpr}$), **FasL** ($^{gld/gld}$) or **Bim** ($^{Bcl2l11-/-}$): autoimmune lymphoproliferative disorders!



increased cellularity



auto-antibodies



Hutcheson et al. Immunity 2008

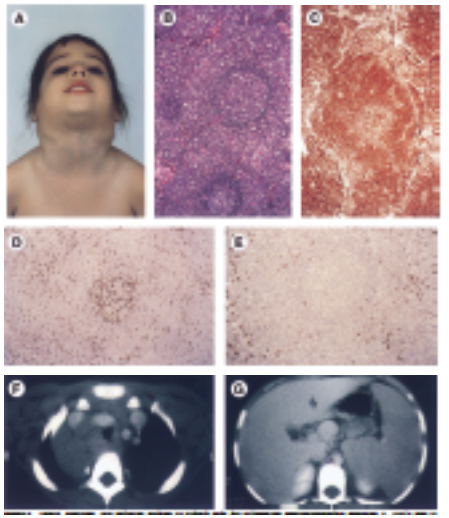
immune complex deposition

Cell, Vol. 81, 935–946, June 16, 1995, Copyright © 1995 by Cell Press

Dominant Interfering Fas Gene Mutations Impair Apoptosis in a Human Autoimmune Lymphoproliferative Syndrome

Galen H. Fisher,*† Fredric J. Rosenberg,*‡
Stephen E. Straus,§ Janet K. Dale,§
Lindsay A. Middelton,‖ Albert Y. Lin,#
Warren Strober,§ Michael J. Lenardo,†
and Jennifer M. Puck‡

(analysis of five children with enlarged spleens and lymph nodes, autoimmune hemolytic anemia, thromocytopenia and glomerulonephritis)

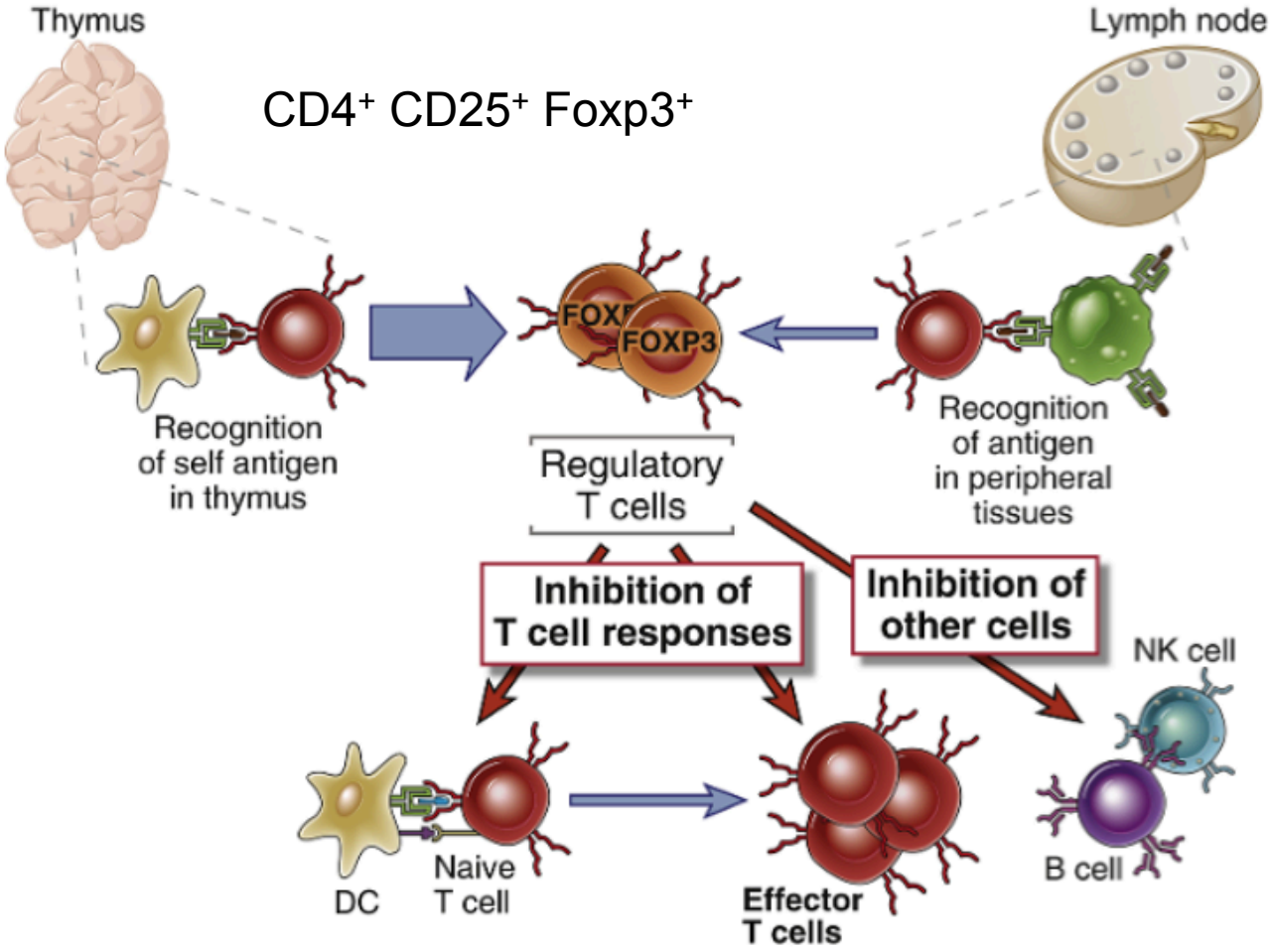


Straus et al. Ann Intern Med 1999

Peripheral tolerance: Suppression by regulatory T cells (T_{regs})

T_{regs} come in different shapes and flavours (nTreg, Tr1, Th3 cells,...)

natural T_{regs} **induced/adaptive** T_{regs}



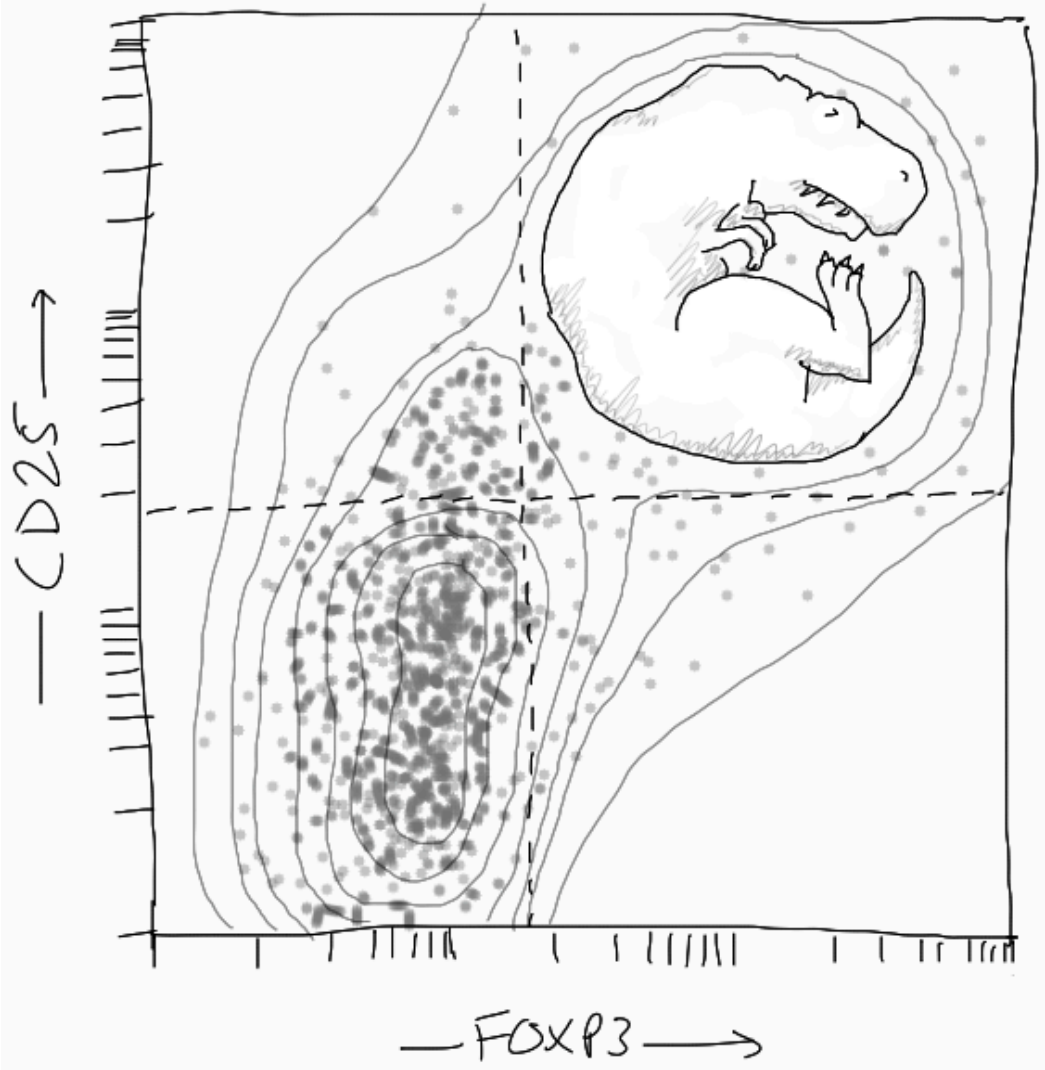
possible mechanims:

production of IL-10 and/or TGFβ

consumption of IL-2

competition for B7 molecules (high CTLA-4)

Peripheral tolerance: Suppression by regulatory T cells (T_{regs})



$Foxp3^+$ T_{regs}

THE master regulators of the immune system !

Sometimes I wish Trex, rather than Tregs, moderated the immune system.

Peripheral tolerance: Suppression by regulatory T cells (T_{regs})

Evidence for a role of Foxp3 and T_{regs} in the maintenance of peripheral tolerance:

letter

Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse

Mary E. Brunkow[1], Eric W. Jeffery[1], Kathryn A. Hjerrild[1], Bryan Paeper[1], Lisa B. Clark[1], Sue-Ann Yasayko[1], J. Erby Wilkinson[2], David Galas[3], Steven F. Ziegler[4] & Fred Ramsdell[1]

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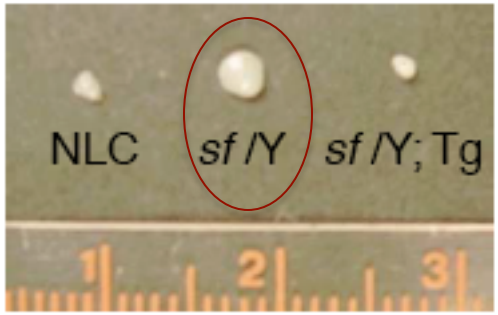


The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of *FOXP3*

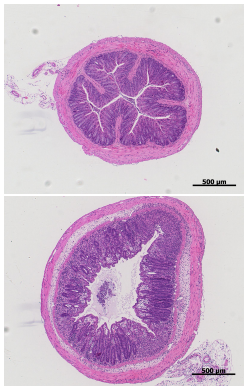
IPEX is a fatal disorder characterized by immune dysregulation, polyendocrinopathy, enteropathy and X-linked inheritance (MIM 304930). We present genetic evidence that different mutations of the human gene *FOXP3*, the ortholog of the gene mutated in scurfy mice (*Foxp3*), causes IPEX syndrome. Recent linkage analysis studies mapped the gene mutated in IPEX to an interval of 17–20-cM at Xp11.23–Xq13.3 (refs. 1,2).

Bennet et al. Nature Genetics 2001

Peripheral tolerance: Suppression by regulatory T cells (T_{regs})

Further exemplary evidence for a role of T_{reg} peripheral tolerance:

mouse models of chronic inflammatory diseases, e.g.



CUTTING EDGE

Cutting Edge: Cure of Colitis by $CD4^+CD25^+$ Regulatory T Cells[1]

Christian Mottet,[2] Holm H. Uhlig,[2] and Fiona Powrie[3]

J Immunol 2003

(vice versa: induction of disease by T_{reg} depletion)

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human individuals

In vivo switch to IL-10–secreting T regulatory cells in high dose allergen exposure

Flurina Meiler, Judith Zumkehr, Sven Klunker, Beate Rückert, Cezmi A. Akdis, and Mübeccel Akdis

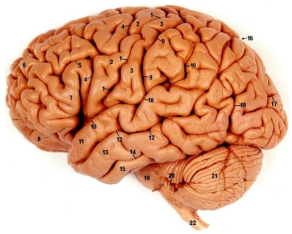
Swiss Institute of Allergy and Asthma Research, University of Zurich, 7270 Davos, Switzerland

J Exp Med 2008

("natural" desensitization to bee venom in beekeepers related to the induction of IL-10^+ T_{regs})

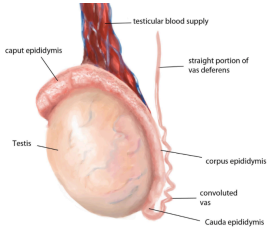
Peripheral tolerance: Immune privileged sites

brain



eye

testis



maternal / fetal interphase

- physical barriers (e.g. BB-barrier)
- absence of lymphatic drainage (e.g. brain)

} sequestration of antigens (immunological ignorance)

- low numbers of APC
- low MHC expression (e.g. fetal trophoblast)
- expression of FasL (e.g. testis)
- TGFβ-rich environment (e.g. eye)

} **induction of anergy or apoptosis**

↓

immune privilege must be considered as an active process rather than a merely passive state!