INSTITUT FÜR PATHOLOGIE
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Immunological Tolerance

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4540-FS2018-0: Selected topics in Clinical Immunology
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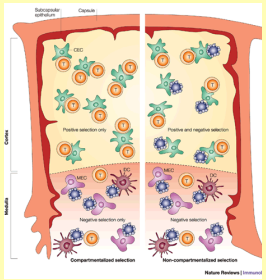
Immunological Tolerance

highly desired

Tolerance to **self**



CD4+CD25+
Foxp3+

Th1

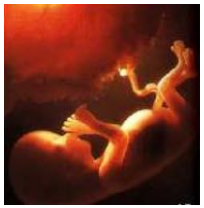
Th17

central tolerance
peripheral tolerance
prevention of autoimmunity

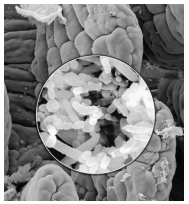
Tolerance to **foreign** antigens

inhaled antigens

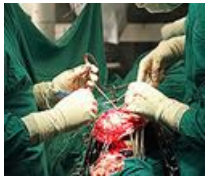
food antigens



fetal antigens



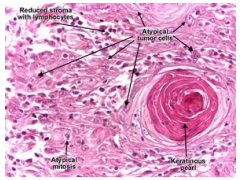
commensal flora



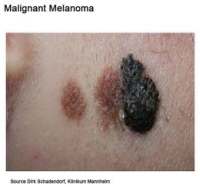
organ transplants

highly desired

undesired

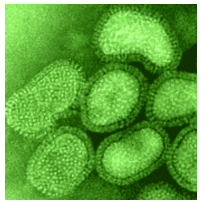


transformed cells

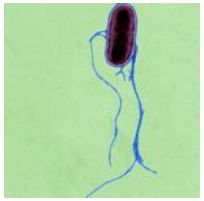


tumors

Tolerance to (altered) **self**



pathogens



vaccines

Tolerance to **foreign** antigens

undesired

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

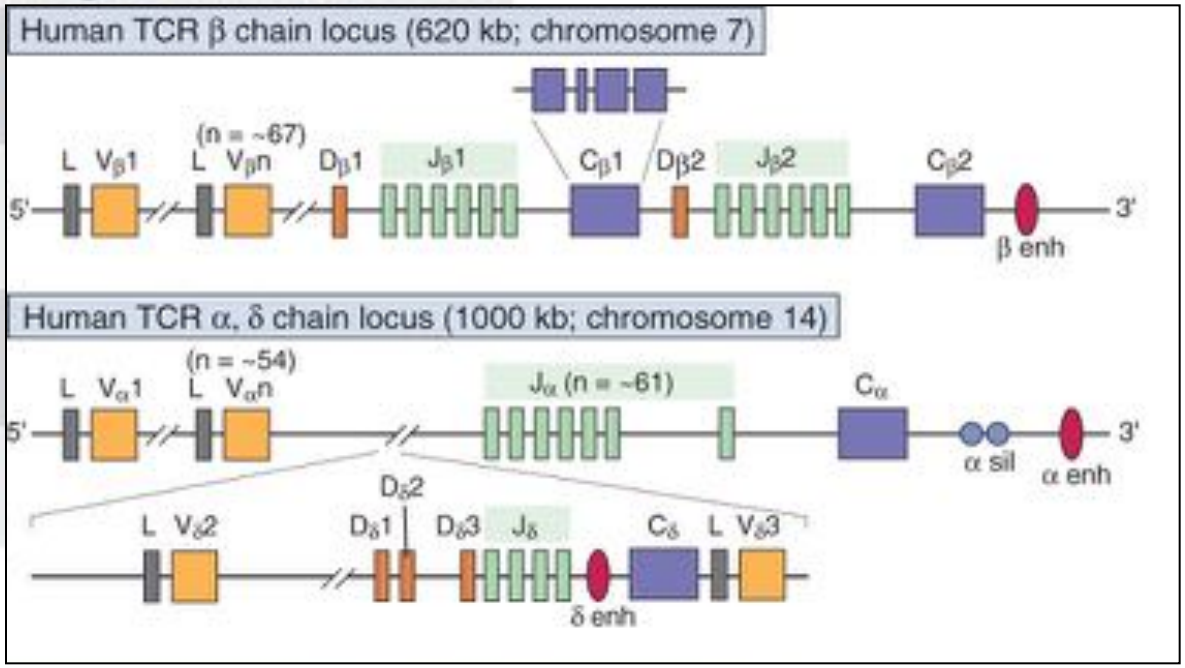
- autoimmune disease and hypersensitivity reactions
- pathogenetic role of genetic and microbial factors
- where does tolerance fail and how can it be assessed?

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:

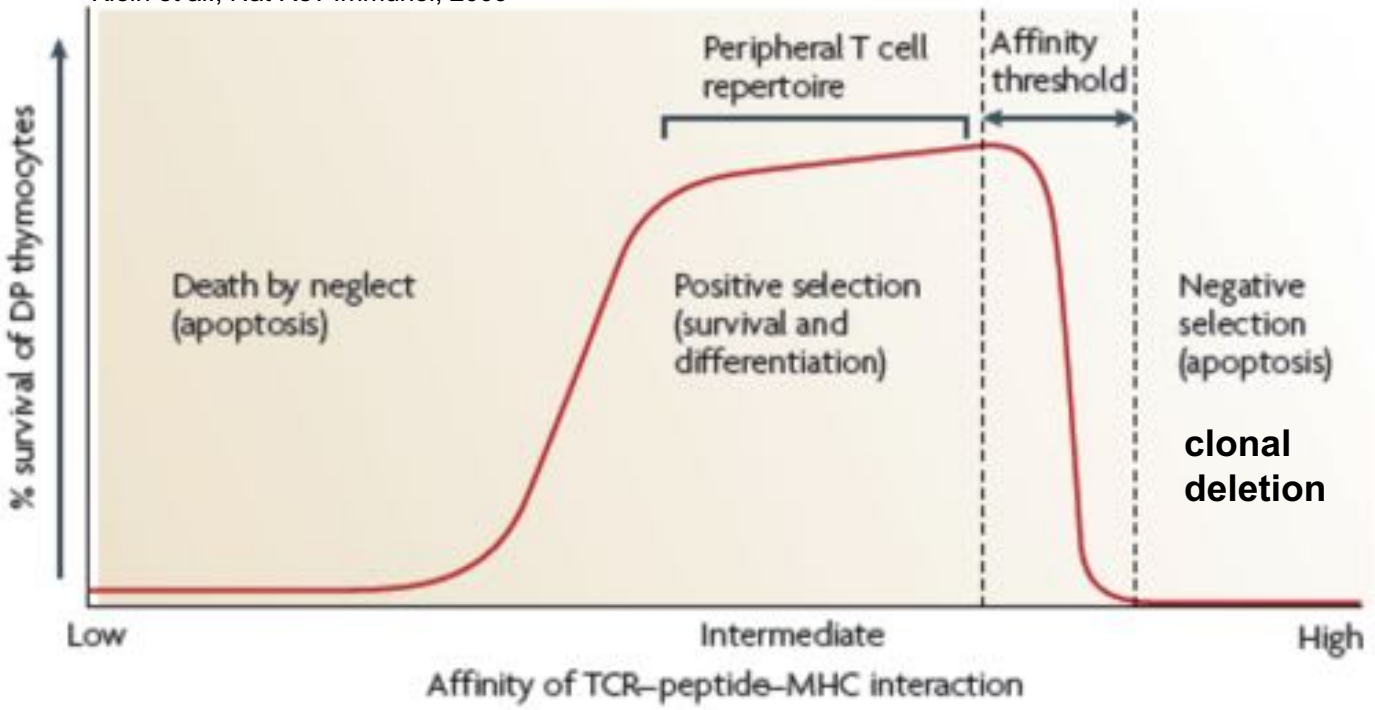
selective survival and expansion of thymocytes with TCR capable of recognizing self-MHC (with low avidity)

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, co-R's, overall avidity of bond…

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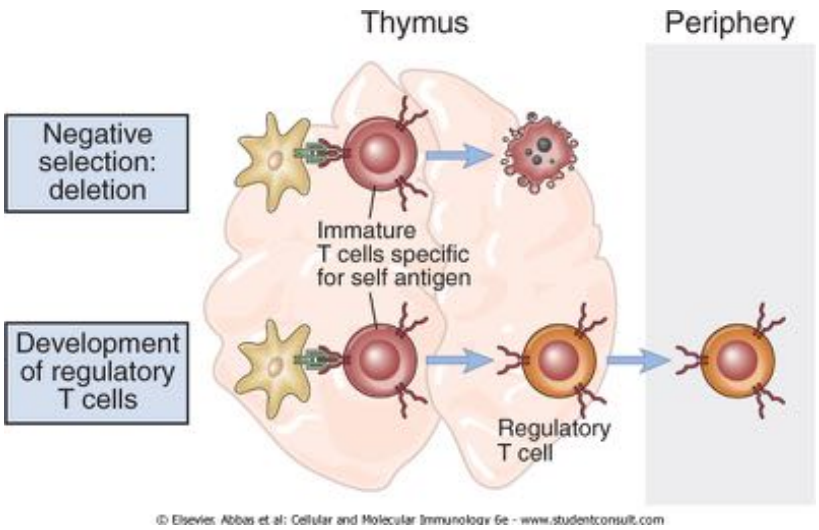
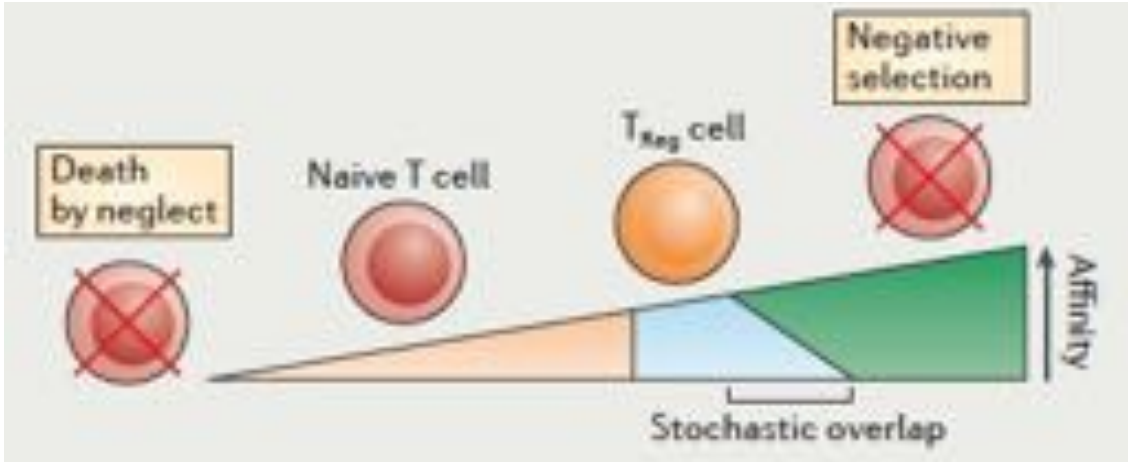
central tolerance in B cells (bone marrow): receptor editing or deletion by apoptosis

Central tolerance: Exceptions to the rules

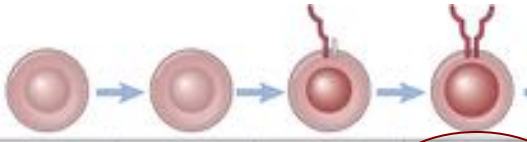


high avidity recognition of self-antigen by immature T cells in the thymus induces negative selection but can also promote the **development of CD4$^+$ CD25$^+$ regulatory T cells** (“agonist selection”)

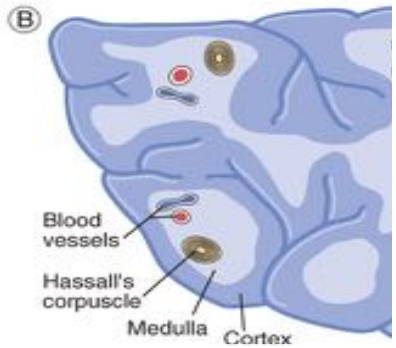
Klein et al., Nat Rev Immunol, 2014

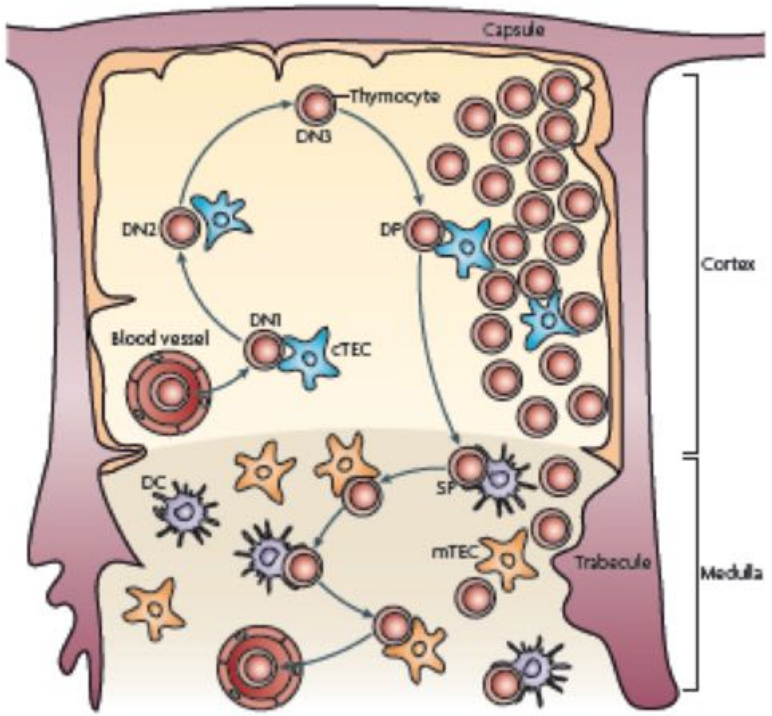


Central tolerance: Location and timing



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)

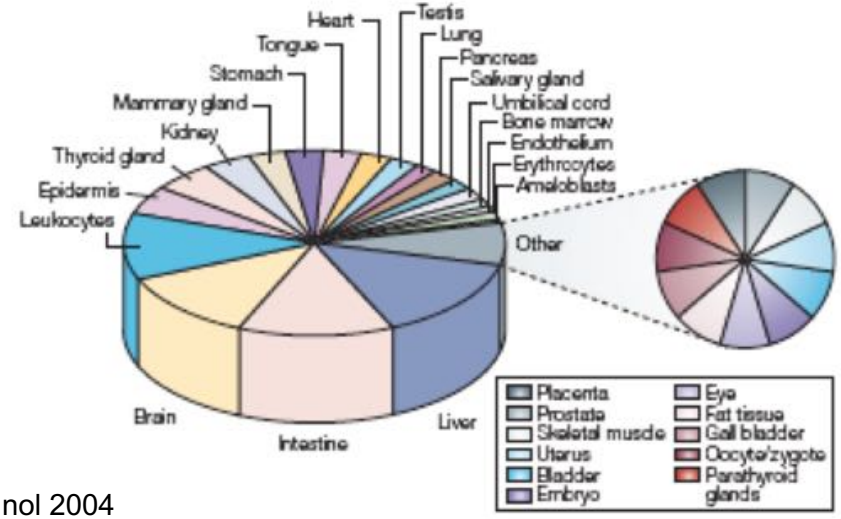
cTEC: cortical epithelial cell → positive selection
mTEC: medullary epithelial cell → negative selection

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

	SAP	CRP	Complement C5	α-fetoprotein	Albumin	Haptoglobin	α1-antitrypsin	PLP	MOG	S100β	GAD67[a]	GAD65[a]	Somatostatin	Trypsin2	Elastase	Insulin[a]	Tyrosinase	Gp100	PIA	Thyroglobulin	Lactalbumin	α1-crystallin	Retinal S antigen	NAChRα1	IFABP	Amylase1
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)

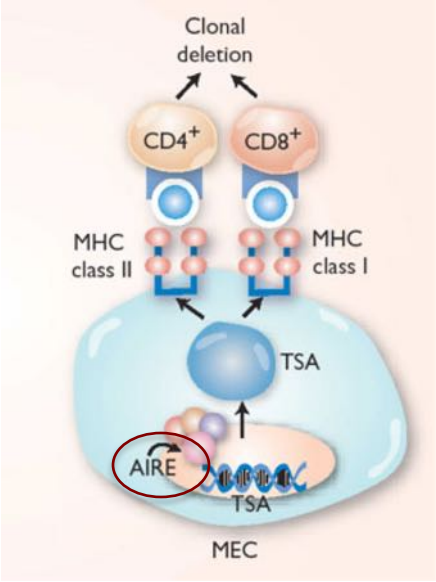
An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains

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…

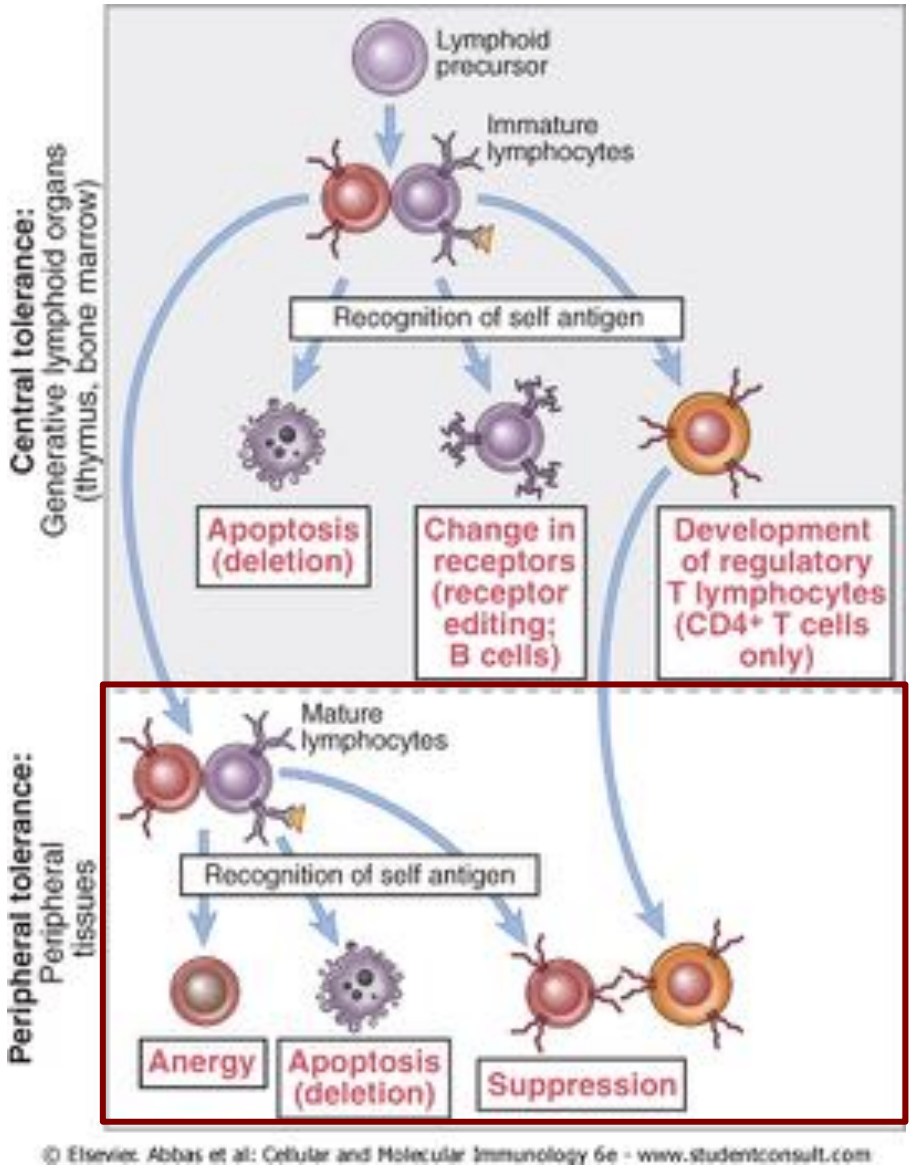
- not all tissue-restricted antigens are expressed in the thymus
- some tissue-restricted antigens are only expressed in adult life
- expression levels may be insufficient
- avidity-based selection is not “black and white”

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

⬇

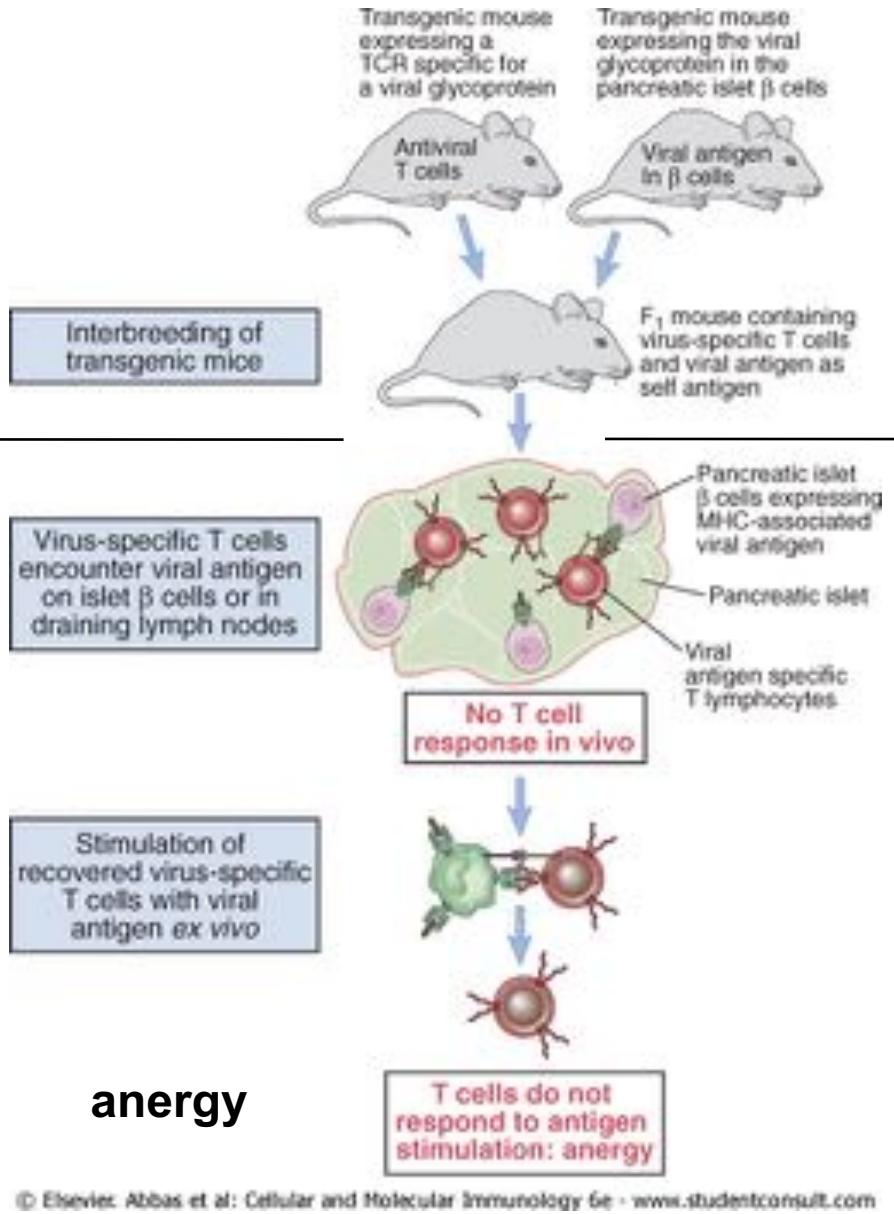
peripheral tolerance mechanism must be operative!

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

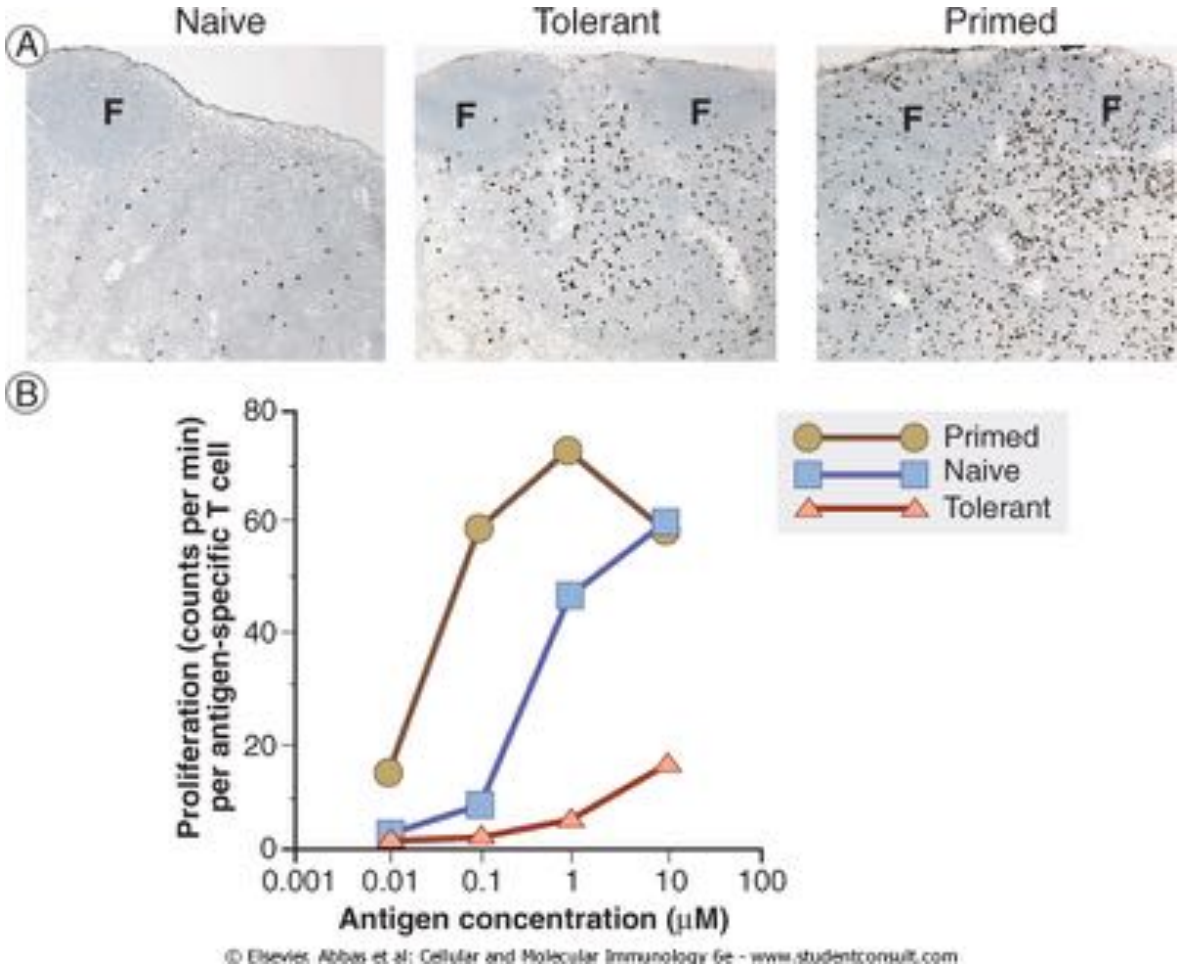
↓

autoimmunity

Peripheral tolerance: Anergy

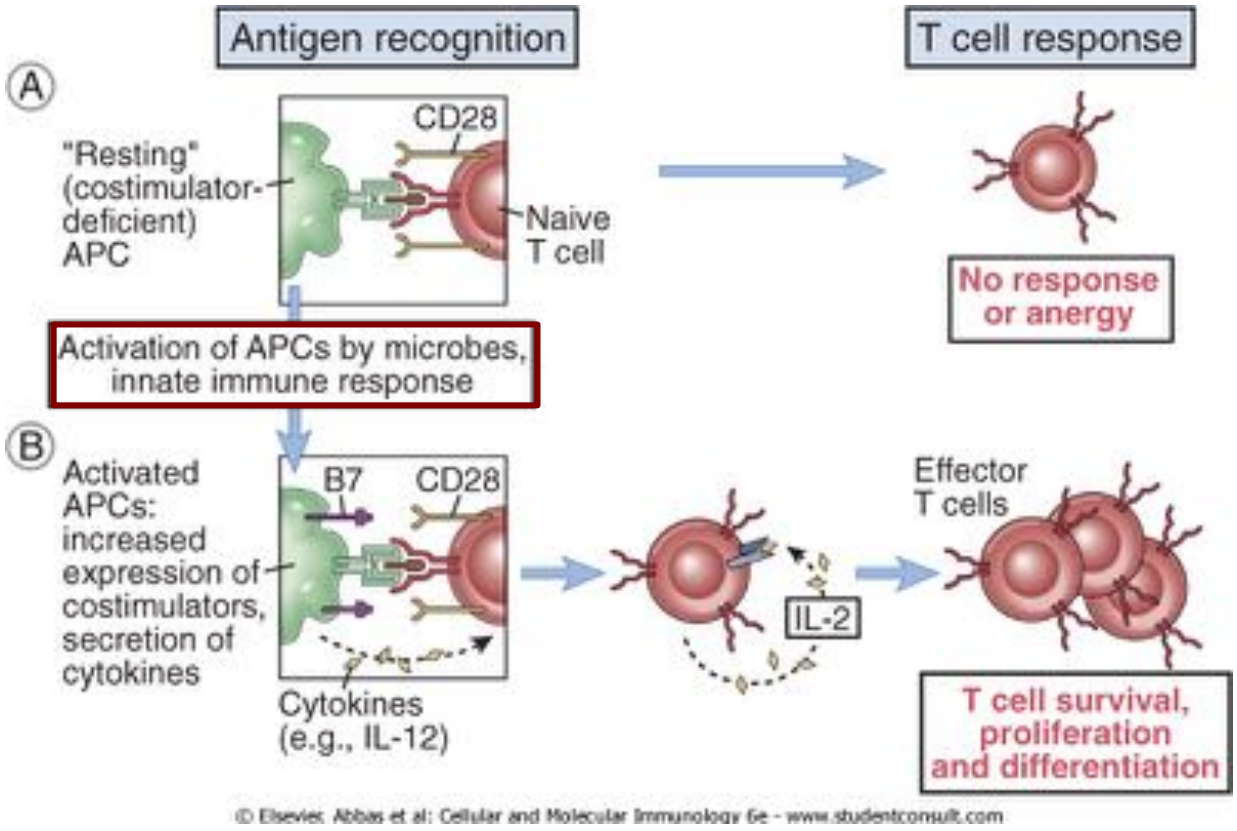
immunizations:

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

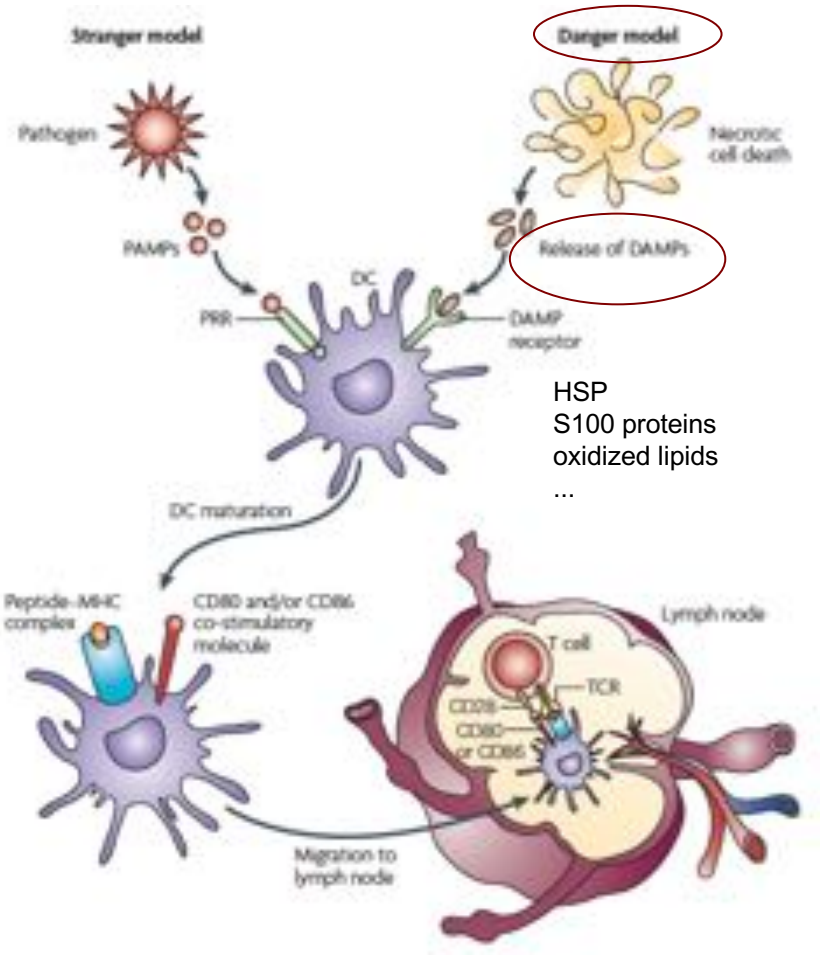


Peripheral tolerance: Anergy

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

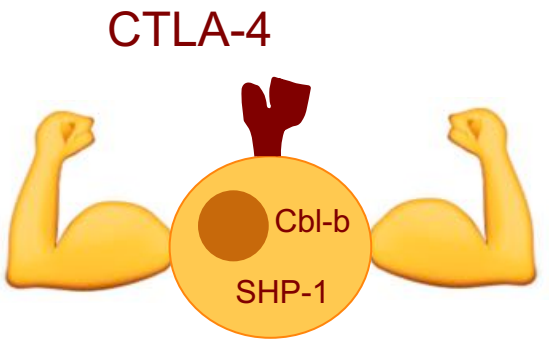
decision over immunity vs. tolerance is determined by recognition of "danger" (DAMPs) rather by self versus non-self (PAMPs) discrimination

endogeneous factors can trigger inflammation

tissues take a critical role in transmitting signals to immune cells

Peripheral tolerance: Anergy

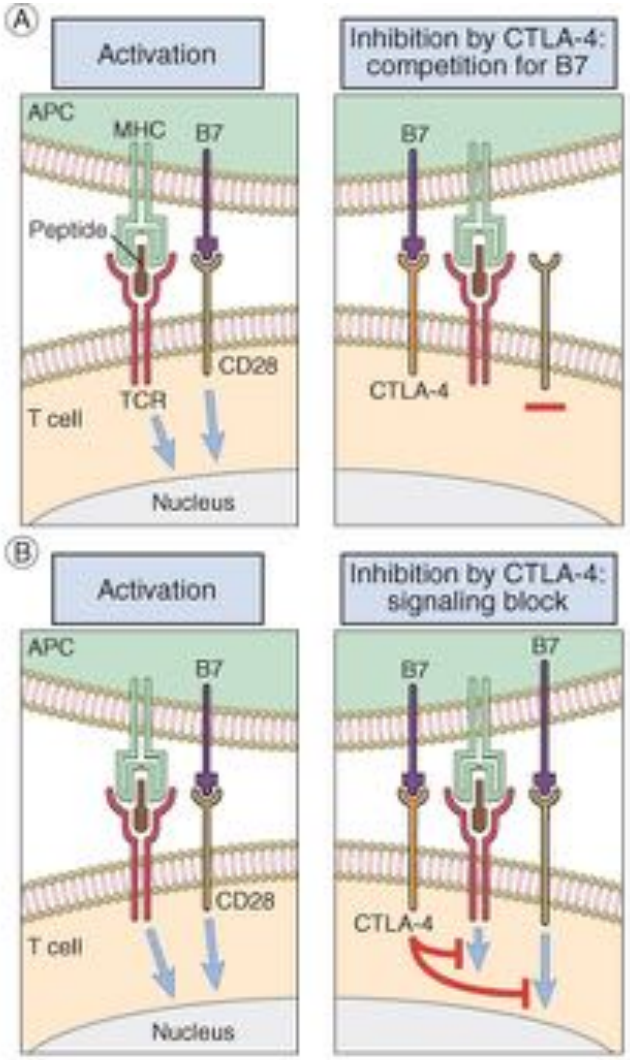
Anergy is induced and maintained <u>actively</u> by several mechanisms:



- 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"

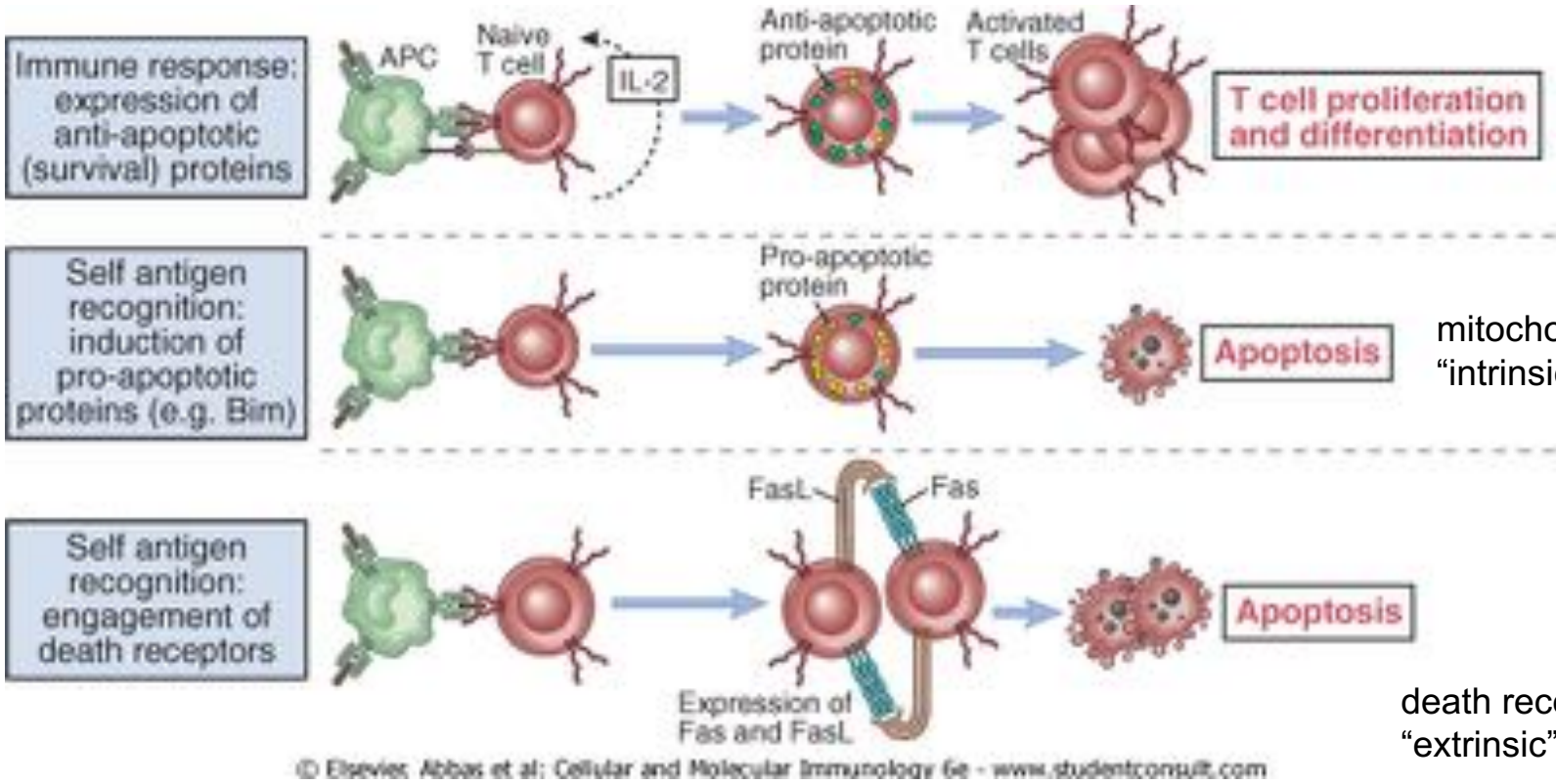
(autoimmune side effects!)

Peripheral tolerance: Deletion

self-antigens cannot be eliminated ⟶ chronic / repetitive stimulation

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

} apoptosis

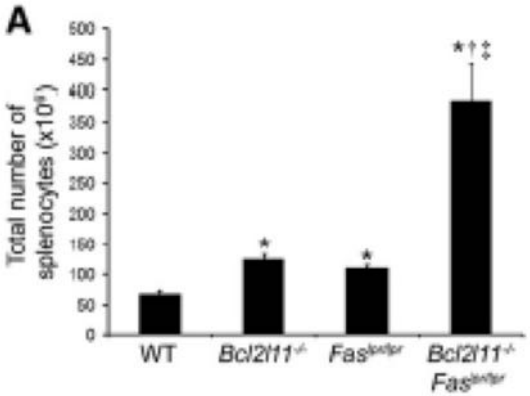


mitochondrial "intrinsic" pathway

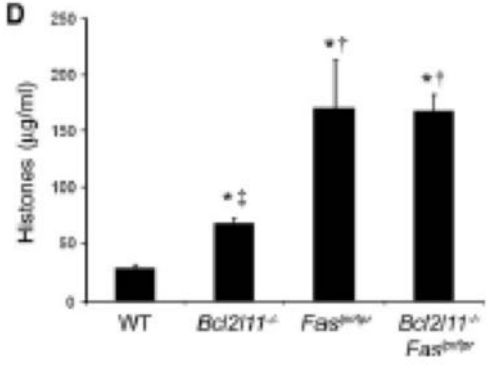
death receptor "extrinsic" pathway

Peripheral tolerance: Deletion

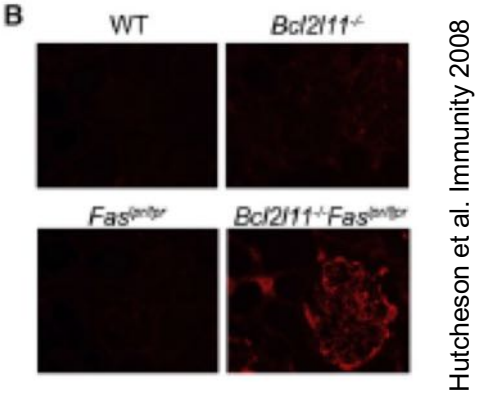
Mice with mutations in either **Fas** ($^{lpr/lpr}$), **FasL** ($^{gld/gld}$) or **Bim** ($^{Bcl2l11-/-}$): autoimmune lymphoproliferative disorders!



increased cellularity



auto-antibodies



Hutcheson et al. Immunity 2008

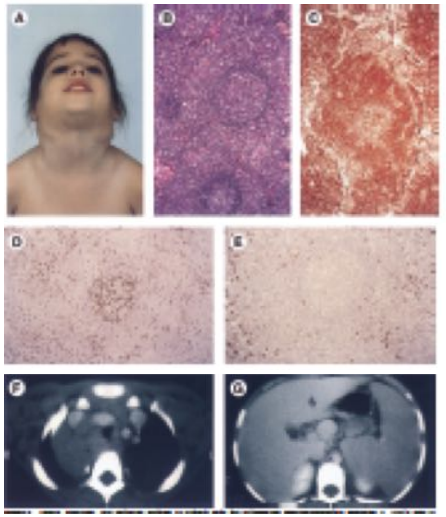
immune complex deposition

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)

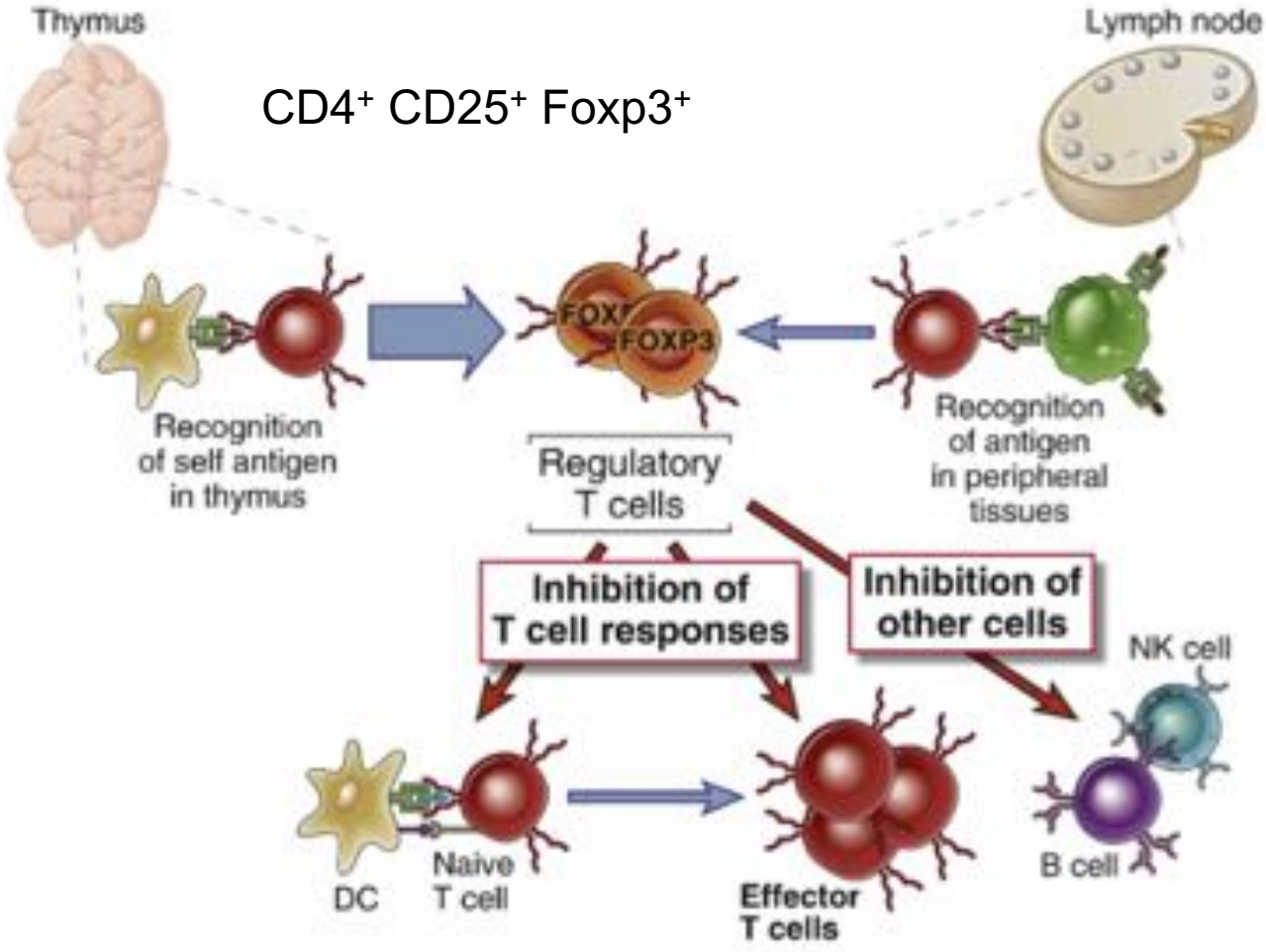


Straus et al. Ann Intern Med 1999

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}



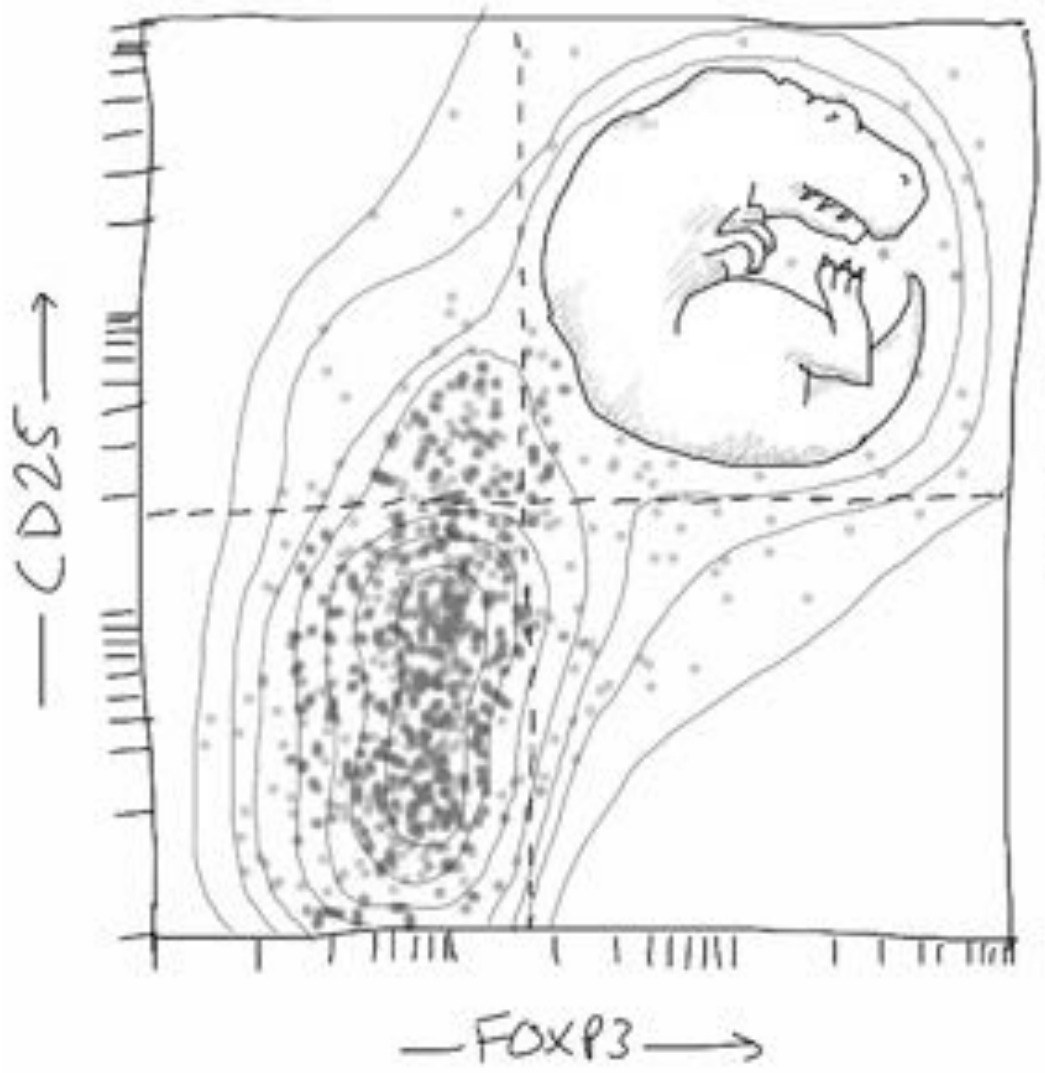
possible mechanims:

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.

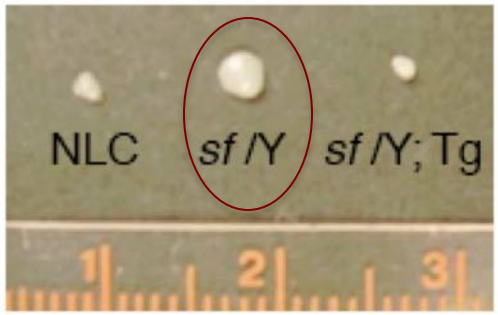
Peripheral tolerance: Suppression by regulatory T cells (T_{regs})

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]



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

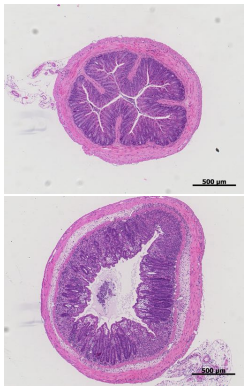
IPEX is a fatal disorder characterized by immune dysregulation, polyendocrinopathy, enteropathy and X-linked inheritance (MIM 304930). We present genetic evidence that different mutations of the human gene *FOXP3*, the ortholog of the gene mutated in scurfy mice (*Foxp3*), causes IPEX syndrome. Recent 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

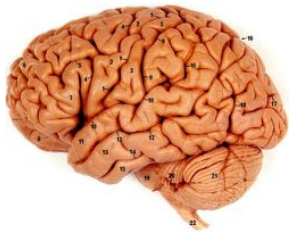
Swiss Institute of Allergy and Asthma Research, University of Zurich, 7270 Davos, Switzerland

J Exp Med 2008

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

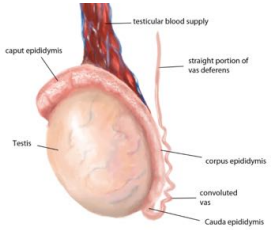
Peripheral tolerance: Immune privileged sites

brain

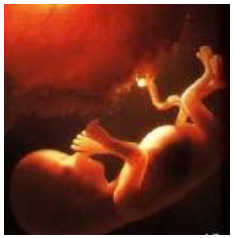


eye

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!

Overview

1. "Basic" mechanisms of self-tolerance

- central tolerance
- peripheral tolerance

2. Mucosal immunology

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

3. Analyzing tolerance in clinical disease settings

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

2. Mucosal immunology

MALT: mucosa-associated lymphoid tissues

BALT: bronchi-associated lymphoid tissues

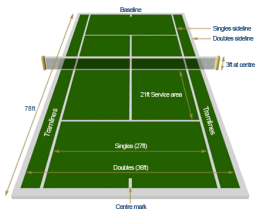
NALT: nasopharynx-associated lymphoid tissues

GALT: gut-associated-lymphoid tissues

MALT of the urogenital tract

- barriers between internal and external environments

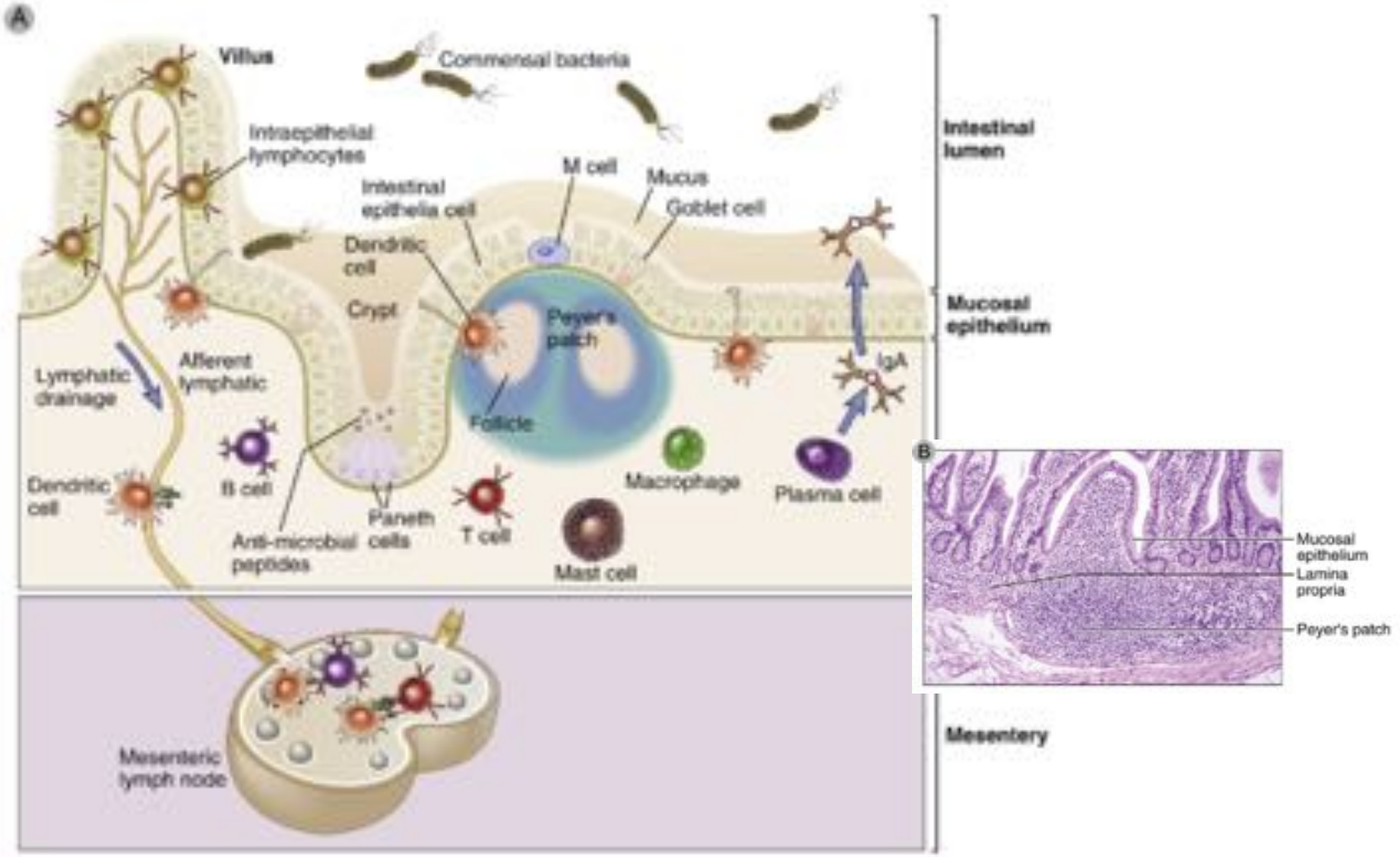
> 200 m^2



- confronted with a vast array of harmless and potentially harmful antigens

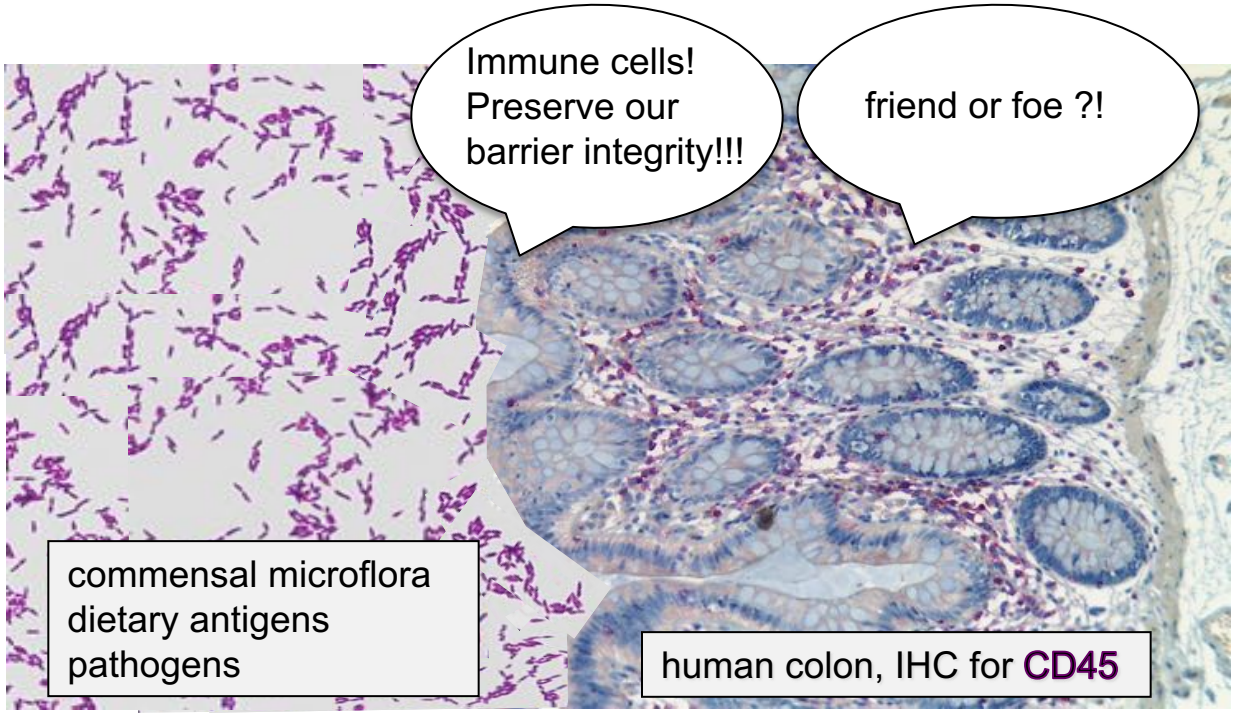
- contain lymphoid inductive and effector sites with specialized immune cells

Mucosal immunology: Organization of the GALT



Mucosal immunology: The difficult task of the GALT

…when two supersystems are confronted….



(abundant) commensal microbes and food antigens need to be tolerated while (rare) pathogens have to be recognised and fighted off

collateral tissue damage is a “no go” in order to prevent loss of sequestration and a potentially deleterious uncontrolled influx of antigens

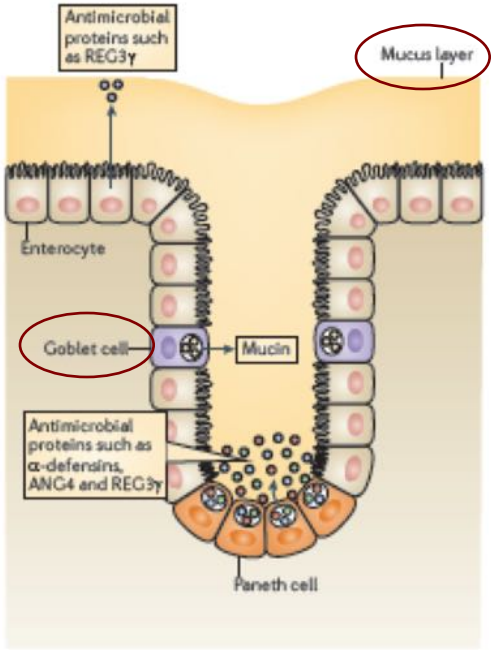
Mucosal immunology: Multi-layered adaptations of the GALT

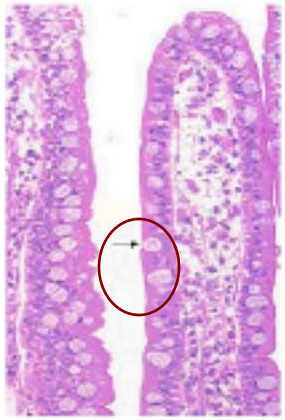
- ➢ intestinal epithelial cells
- • intestinal intraepithelial lymphocytes
- ➢ intestinal macrophages
- ➢ intestinal dendritic cells
- • intestinal innate lymphoid cells
- • intestinal B cells
- • intestinal CD4 T cells

tolerance mechanisms at the level of innate immunity also exist !

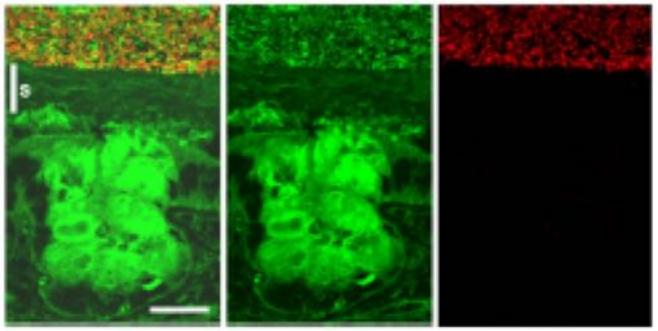
Multi-layered adaptations of the GALT: Intestinal epithelial cells

The first line of defense: the mucus layer





colon: two different mucus layers
the inner layer is devoid of bacteria !



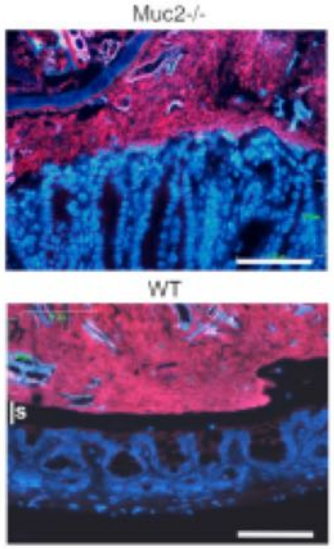
green: anti-MUC2
red: FISH using a bacterial probe

Johansson et al. PNAS 2008

functions of mucus layer:

- outer layer: providing optimal symbiotic habitat
- inner layer: segregation of bacteria,
  local concentration of antimicrobial peptides and IgA

- small intestine: delivery of tolerogenic functions to dendritic cells Cerutti et al. Science 2013



Johansson et al. PNAS 2008

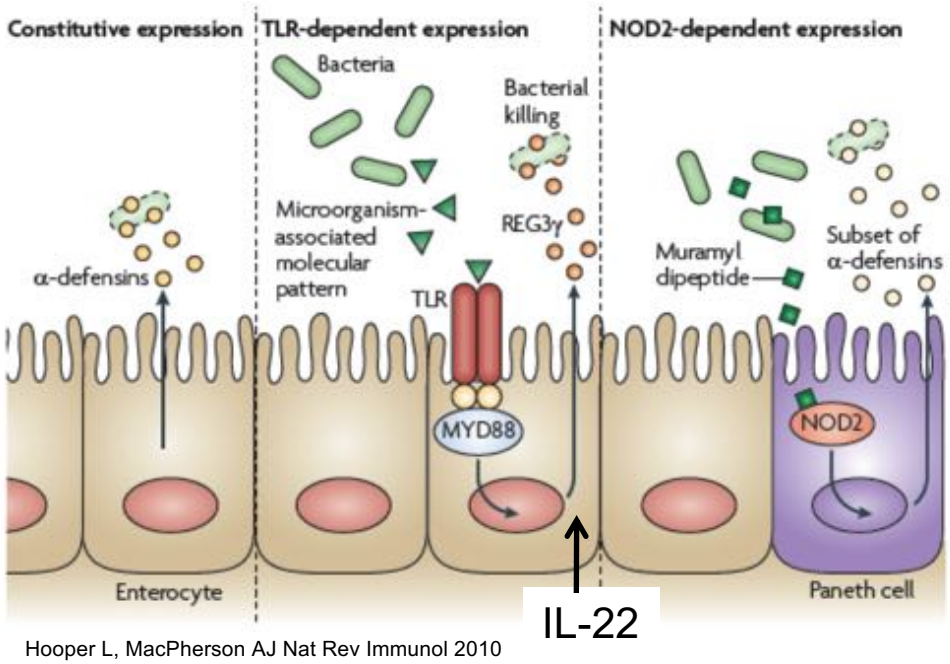
$Muc2^{-/-}$ mice:

penetrance of bacteria

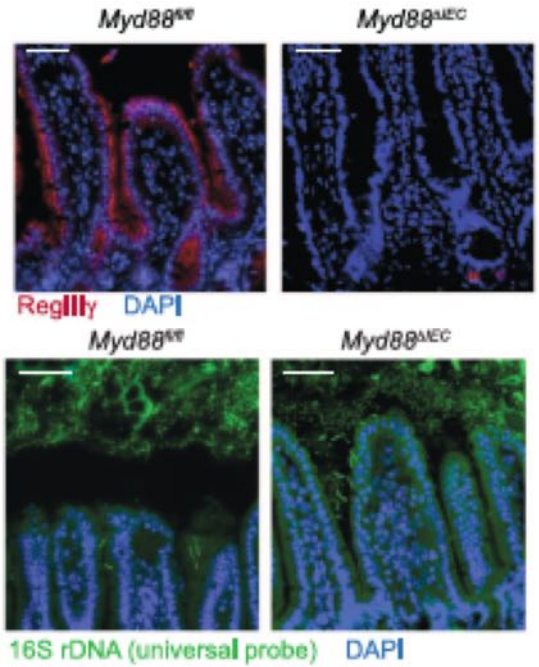
spontaneous colitis !

Multi-layered adaptations of the GALT: Intestinal epithelial cells

Production of anti-microbial proteins further limits bacterial-epithelial contact



Hooper L, MacPherson AJ Nat Rev Immunol 2010



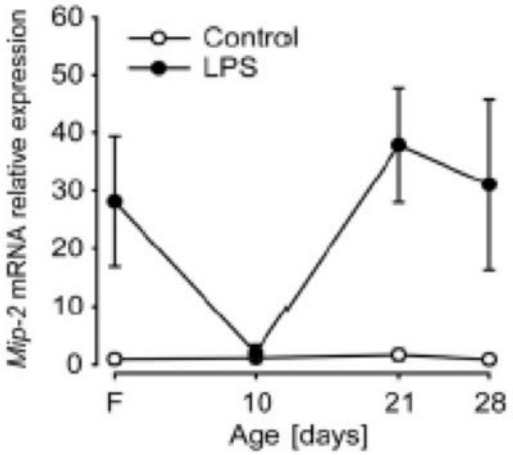
Vaishnava et al. Science 2011

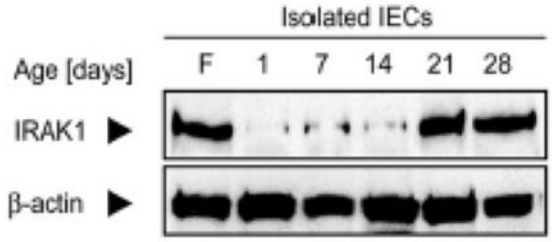
- defective anti-microbial peptide expression in experimental models (IL-22$^{-/-}$ or MyD88$^{-/-}$ mice): increased susceptibility to intestinal inflammation

- ATG16L1 is a disease susceptibility locus in Crohn's disease - disruption of ATG16L1 in mice results in a disturbed Paneth cell granule exocytosis

Multi-layered adaptations of the GALT: Intestinal epithelial cells

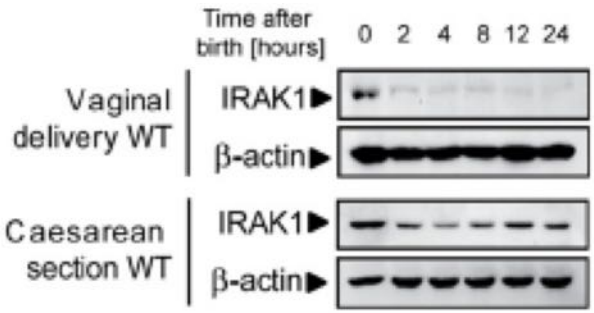
Highly regulated expression of TLRs during postnatal development:



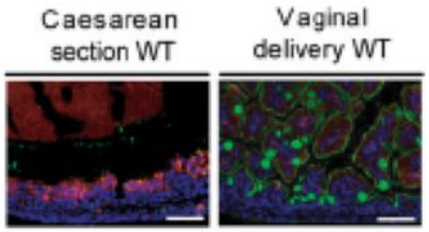


Chassin C et al. Cell 2010

immediately after birth,
IEC respond to LPS exposure
but then transiently acquire
endotoxin tolerance due to active
downregulation of IRAK1



active Caspase 3 (red)



lack of tolerisation of the
neonatal epithelium in
Caesarean section-born
mice results in massive
epithelial apoptosis after
oral exposure to E. Coli

first contact of neonatal IEC with colonizing bacteria is crucial to simultaneously allow for maturation of the intestinal immune system and to protect from inappropriate pro-inflammatory immune activation until vital structures have been established

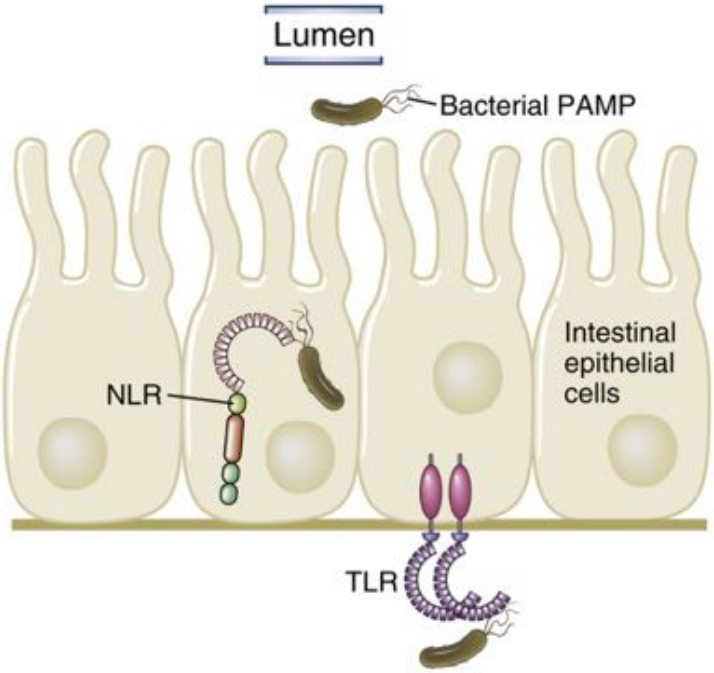
relevant in pathogenesis of necrotising enterocolitis in pre-term infants?

Multi-layered adaptations of the GALT: Intestinal epithelial cells

Highly regulated and compartmentalized expression of pattern recognition receptors also in mature enterocytes:

NLR family receptors for bacterial flagellin are located in the cytosol

TLR5 is only expressed on the basolateral, not the apical side



…allows for discrimination of commensal flora vs. invading pathogens!

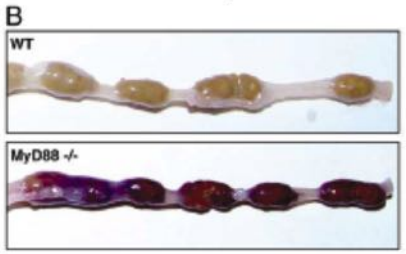
Multi-layered adaptations of the GALT: Intestinal epithelial cells

…however, “tonic” TLR signaling is vital for intestinal homeostasis!

Cell, Vol. 118, 229–241, July 23, 2004, Copyright ©2004 by Cell Press

Recognition of Commensal Microflora by Toll-Like Receptors Is Required for Intestinal Homeostasis

Seth Rakoff-Nahoum,[1] Justin Paglino,[2] Fatima Eslami-Varzaneh,[2] Stephen Edberg,[2] and Ruslan Medzhitov[1,*]



MyD88$^{-/-}$ mice suffer from an exaggerated DSS-induced colitis due to a lack of microbial TLR-induced tissue protective factors (and anti-microbial peptides) in the intestinal epithelium

NATURE|Vol 446|29 March 2007

Epithelial NEMO links innate immunity to chronic intestinal inflammation

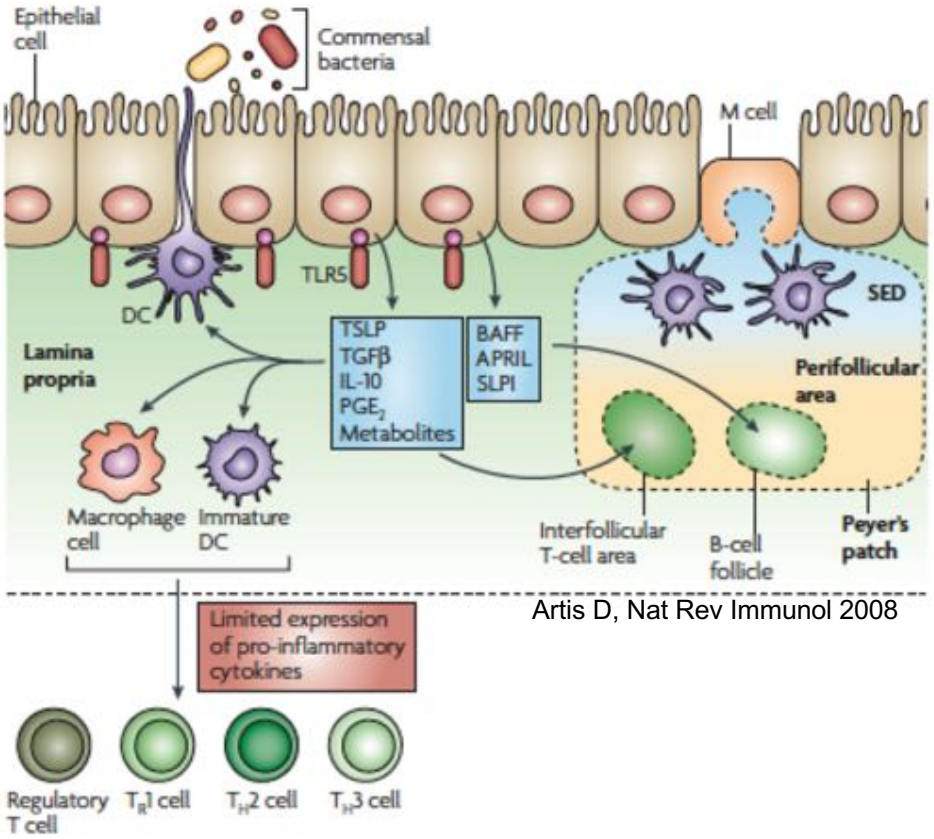
(Nemo = IκB kinase γ)

Arianna Nenci[1,2*], Christoph Becker[3*], Andy Wullaert[1], Ralph Gareus[1], Geert van Loo[2], Silvio Danese[4], Marion Huth[2], Alexei Nikolaev[3], Clemens Neufert[3], Blair Madison[5], Deborah Gumucio[5], Markus F. Neurath[3*] & Manolis Pasparakis[1,2]

Mice with an epithelial-specific inhibition of NFkB develop spontaneous intestinal inflammation due to impaired antimicrobial peptide expression, increased epithelial cell apoptosis and increased translocation of bacteria

Multi-layered adaptations of the GALT: Intestinal epithelial cells

by the production of a variety of cytokines and other factors, the intestinal epithelium can actively modulate immune responses and “educate” local immune cells towards tolerance



Artis D, Nat Rev Immunol 2008

e.g. production of:

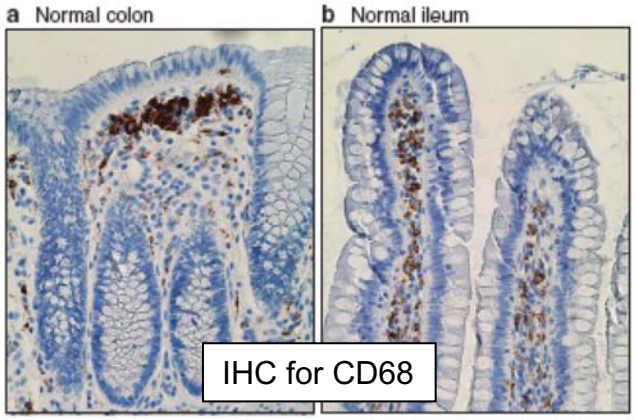
TGFβ
IL-10
TSLP
retinoic acid
April
BAFF

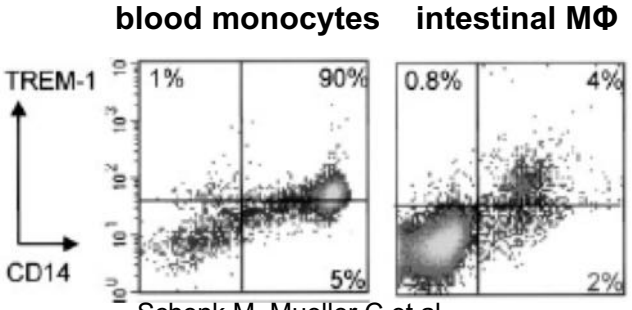
modulation / conditioning of DC

bias of Th differentiation into Th2 / T_{reg}

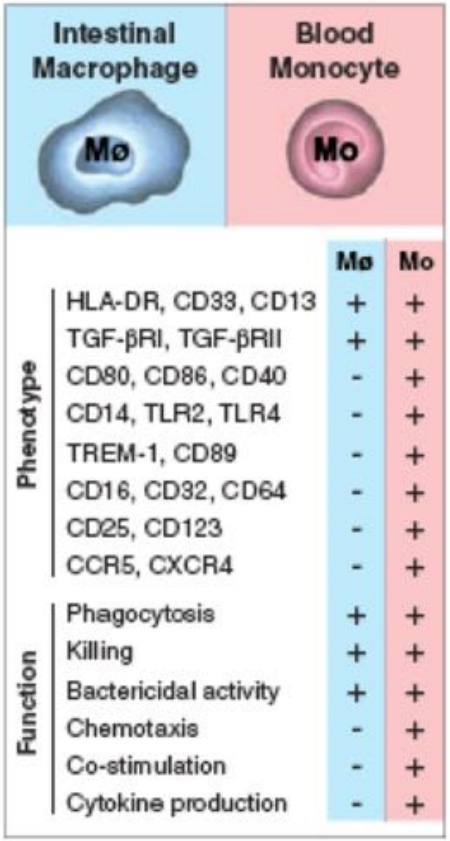
promotion of B cell IgA switching

Multi-layered adaptations of the GALT: Intestinal macrophages

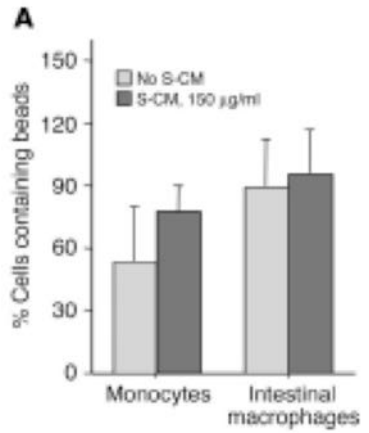




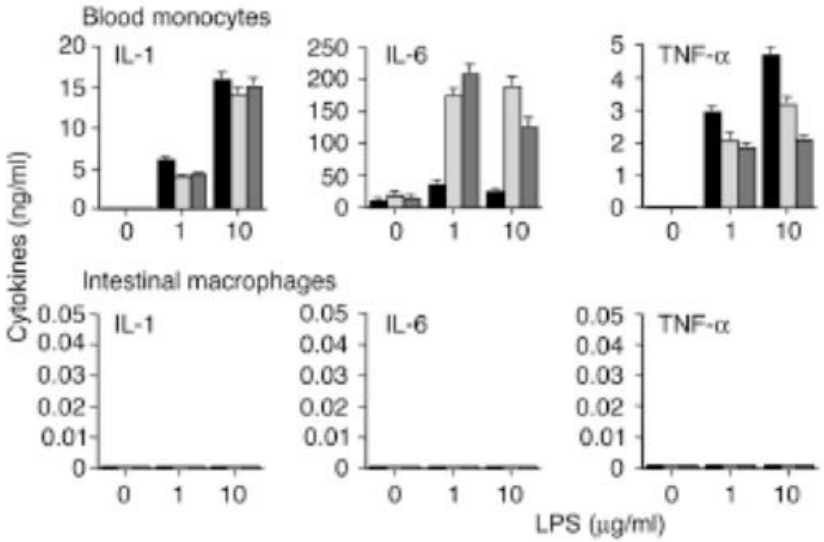
Schenk M, Mueller C et al.,
J Immunol 2005



Weber B, Mueller C et al.
Sem Immunopathol 2009



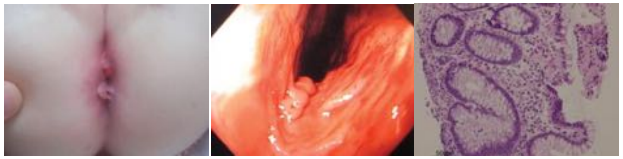
Smythies et al., JCI 2005



…are continuosly replenished from blood monocytes and educated by the local tissue environment (e.g. IL-10, TGFβ) to acquire the typical properties of resident intestinal Mϕ: IL-10 production, highly efficient phagocytosis and bacterial killing in the absence of pro-inflammatory cytokine secretion!

Multi-layered adaptations of the GALT: Intestinal macrophages

mutations in the human IL-10R gene: very-early-onset colitis



Moran CJ, Inflamm Bowel Dis 2013

IL-10-deficient (IL-10$^{-/-}$) mice: spontaneous intestinal inflammation

Interleukin-10 Receptor Signaling in Innate Immune Cells Regulates Mucosal Immune Tolerance and Anti-Inflammatory Macrophage Function

Dror S. Shouval,[1,2,25] Amlan Biswas,[1,2,25] Jeremy A. Goettel,[1,2,25] Katelyn McCann,[1,25] Evan Conaway,[3] Naresh S. Redhu,[1,2,25] Ivan D. Mascanfroni,[4] Ziad Al Adham,[5] Sydney Lavoie,[1] Mouna Ibourk,[1] Deanna D. Nguyen,[6,7] Janneke N. Samsom,[8,25] Johanna C. Escher,[9,25] Raz Somech,[10,11,25] Batia Weiss,[11,12,25] Rita Beier,[13,25] Laurie S. Conklin,[14,25] Christen L. Ebens,[15,25] Fernanda G.M.S. Santos,[16,25] Alexandre R. Ferreira,[16,25] Mary Sherlock,[17,25] Atul K. Bhan,[18,19] Werner Müller,[20] J. Rodrigo Mora,[6,7] Francisco J. Quintana,[4] Christoph Klein,[21,25] Aleixo M. Muise,[3,25] Bruce H. Horwitz,[2,3,25] and Scott B. Snapper[1,2,22,25,*]

Macrophage-Restricted Interleukin-10 Receptor Deficiency, but Not IL-10 Deficiency, Causes Severe Spontaneous Colitis

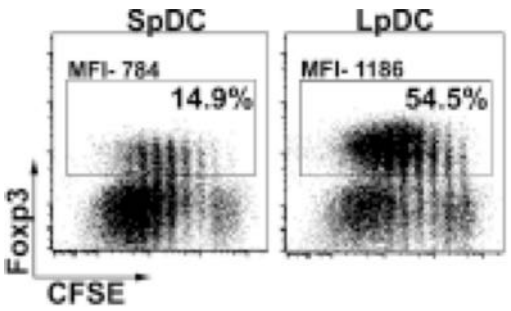
Ehud Zigmond,[1,2] Biana Bernshtein,[1] Gilgi Friedlander,[3] Catherine R. Walker,[4] Simon Yona,[1] Ki-Wook Kim,[1] Ori Brenner,[5] Rita Krauthgamer,[1] Chen Varol,[2] Werner Müller,[4] and Steffen Jung[1,*]

Immunity 2014

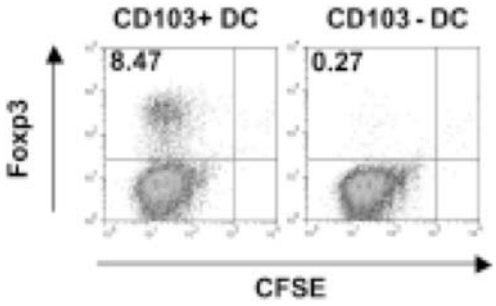
lack of IL-10 receptor signaling in intestinal macrophages prevents their anti-inflammatory conditioning & leads to intestinal inflammation

Multi-layered adaptations of the GALT: Intestinal dendritic cells

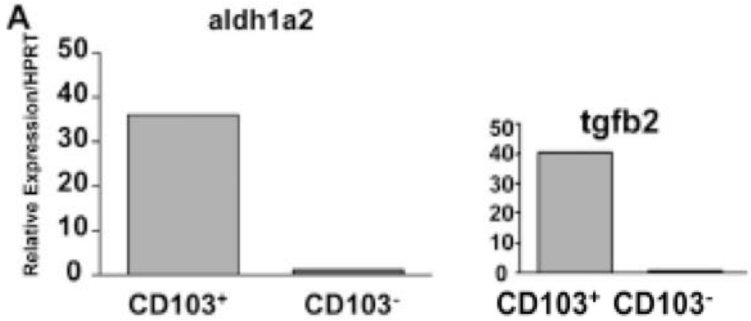
- DC in Lamina Propria (LP), Mesenteric Lymph nodes (MLN), Peyer's patches (PP)
- various subsets, two main subsets: $CD103^+$ vs. $CD103^-$ DC



LP-DC efficient inducers of $Foxp3^+$ T_{regs}



capacity lies within the $CD103^+$ subset...



…is associated with production of TGFβ and the vitamin A-derivative retinoic acid

intestinal $CD103^+$ DC have a propensity to induce $Foxp3^+$ T_{regs} and are critically required for induction of oral tolerance

Sun et al., JEM 2007
Coombes et al., JEM 2007

Mucosal immunology: Oral tolerance

The phenomen:

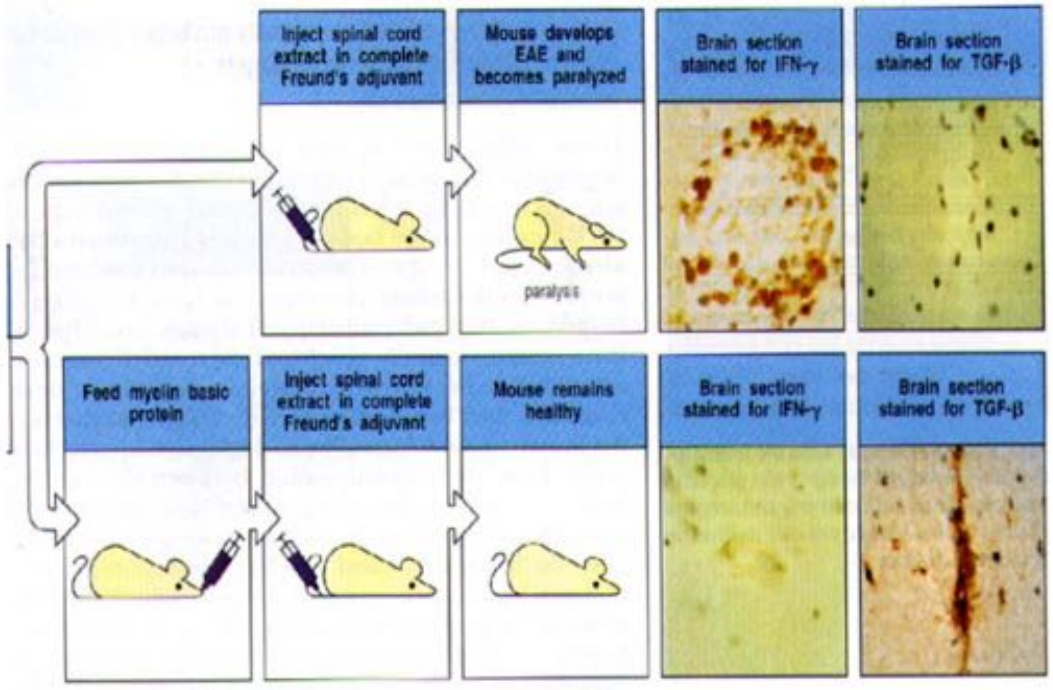
Oral administration of antigen can lead to suppressed immune responses to peripheral challenge with the same antigen

SUPPRESSION OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS BY ORAL ADMINISTRATION OF MYELIN BASIC PROTEIN AND ITS FRAGMENTS[1]

PAUL J. HIGGINS AND HOWARD L. WEINER[2]

THE JOURNAL OF IMMUNOLOGY

Vol. 140, 440–445, No. 2, January 15, 1988
Printed in U.S.A.



Janeway / Travers

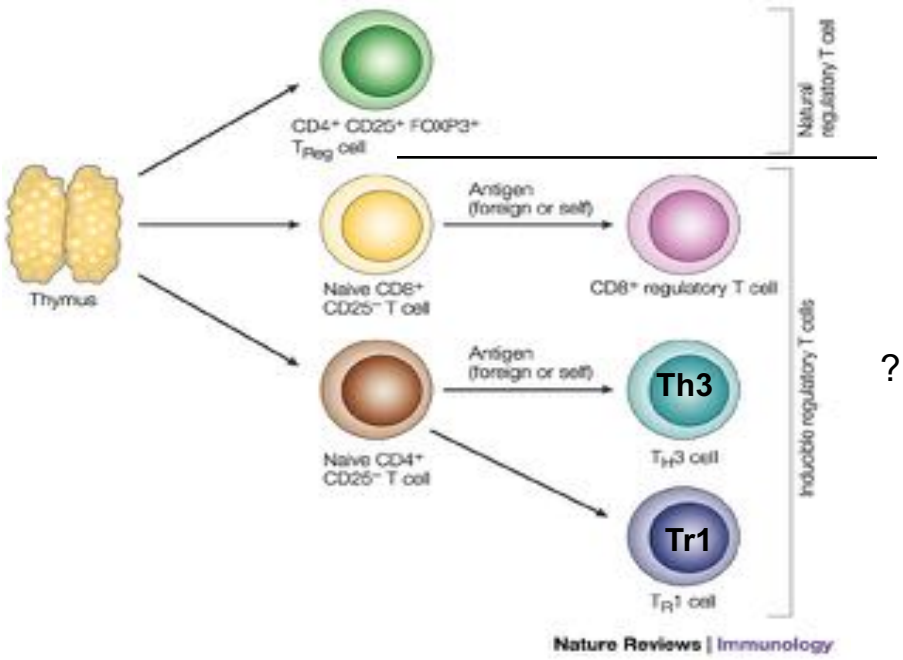
tolerance can be transferred by T cells

TGFβ appears to be involved

Mucosal immunology: Oral tolerance

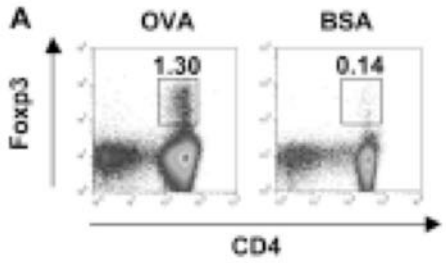
The (likely) mechanism:

- (clonal deletion)
- induction of regulatory T cells



?

	induction	cytokine
nT_{reg} (Foxp3+)	IL-2, TGFβ	TGFβ, IL-10, cytokine-independent suppression ?
Th3 (Foxp3+)	TGFβ	TGFβ, IL-10, IL-4
Tr1 (Foxp3-)	IL-10	IL-10, TGFβ, IFNγ
iT_{reg} (Foxp3+)	TGFβ, IL-2, retinoic acid	TGFβ, IL-10,… cytokine-independent suppression ?



feeding of ovalbumin (but not BSA) to Ovalbumin-TCR tg mice (lacking endogenous Tregs) *de novo* induces Foxp3+ CD4+ T_{regs} cells in the MLN Coombes et al., J Exp Med 2007

Mucosal immunology: Oral tolerance

Evidence exists that oral tolerance mediated by T_{regs} is operative in humans

Journal of Immunology, 1994, 152:

Oral Tolerance in Humans

T Cell but Not B Cell Tolerance After Antigen Feeding[1]

Steffen Husby,[2*] Jiri Mestecky,[†] Zina Moldoveanu,[†] Stephen Holland,[*] and Charles O. Elson[3*]

Table 1. *Delayed skin test response to KLH*[a]

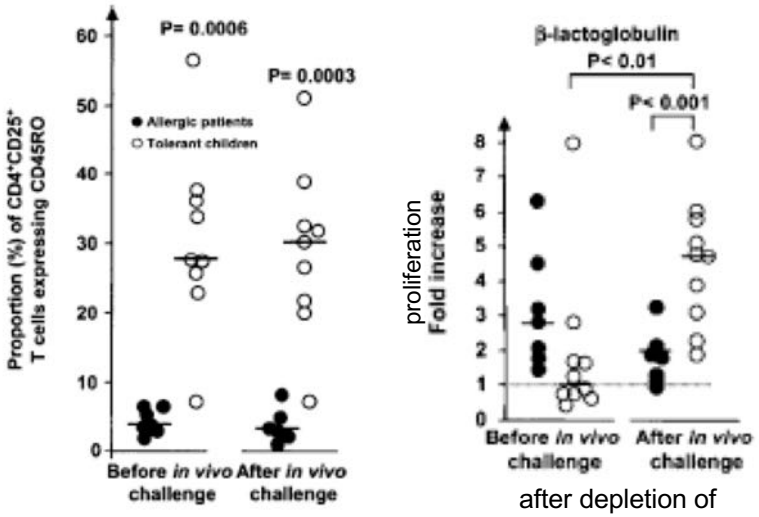
Group	24 h		48 h	
	Mean (range)	Number of positive/total	Mean (range)	Number of positive/total
KLH-fed	1.2 (0–10)	1/8	0 (0–0)	0/8
Controls	11.9 (0–23)	7/8	6.6 (0–20)	5/8
p-value	0.007		0.038	

[a] KLH (10 μg) was injected intracutaneously and the reaction measured as induration (mm) at 24 and 48 h after the injection.

J. Exp. Med. Volume 199, Number 12, June 21, 2004

Allergen-responsive $CD4^+CD25^+$ Regulatory T Cells in Children who Have Outgrown Cow's Milk Allergy

Malin R. Karlsson,[1] Jarle Rugtveit,[1,2] and Per Brandtzaeg[1]



after depletion of CD4+ CD25+

GASTROENTEROLOGY 2007;132:1705–1717

Severe Food Allergy as a Variant of IPEX Syndrome Caused by a Deletion in a Noncoding Region of the *FOXP3* Gene

TROY R. TORGERSON,[*] AVRIEL LINANE,[*] NICOLETTE MOES,[‡,§] STEPHANIE ANOVER,[*] VÉRONIQUE MATEO,[‖] FRÉDÉRIC RIEUX-LAUCAT,[‖] OLIVIER HERMINE,[¶] SHASHI VIJAY,[*] ELEONORA GAMBINERI,[#] NADINE CERF-BENSUSSAN,[§] ALAIN FISCHER,[‖,**] HANS D. OCHS,[*] OLIVIER GOULET,[‡,§] and FRANK M. RUEMMELE[‡,§]

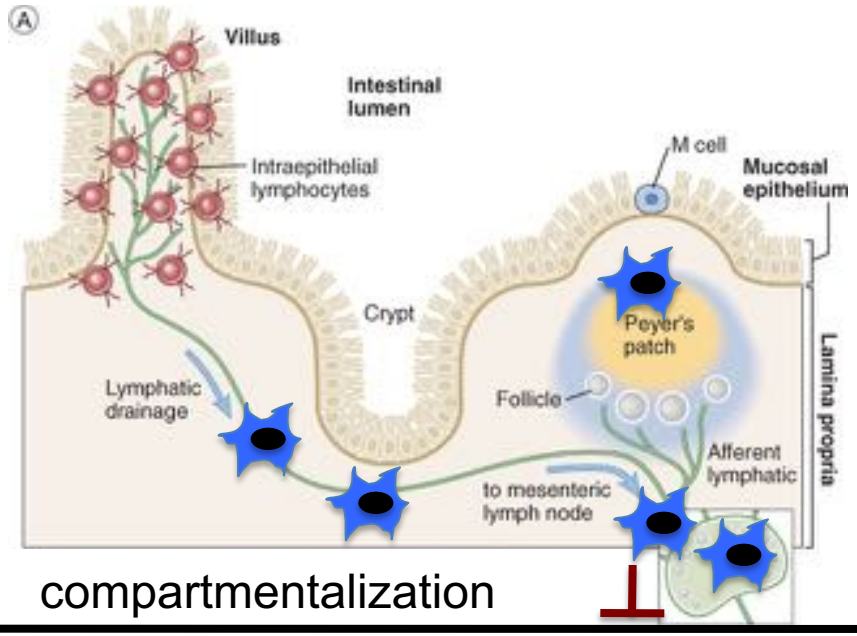
Mucosal immunology: Oral (mucosal) tolerance

Allergen-specific immunotherapy / desensitization

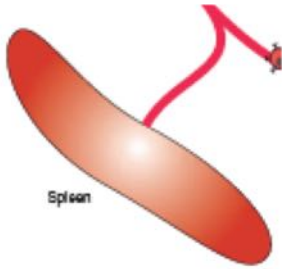
repetitive administration of antigens via the oral, sublingual (nasal) route or the skin

inhibition of basophil and mast cell activation
skewing of Th2 cells to allergen-specific T_{regs}
shift from IgE to IgG4

Mucosal immunology: Oral tolerance does not apply to commensal flora



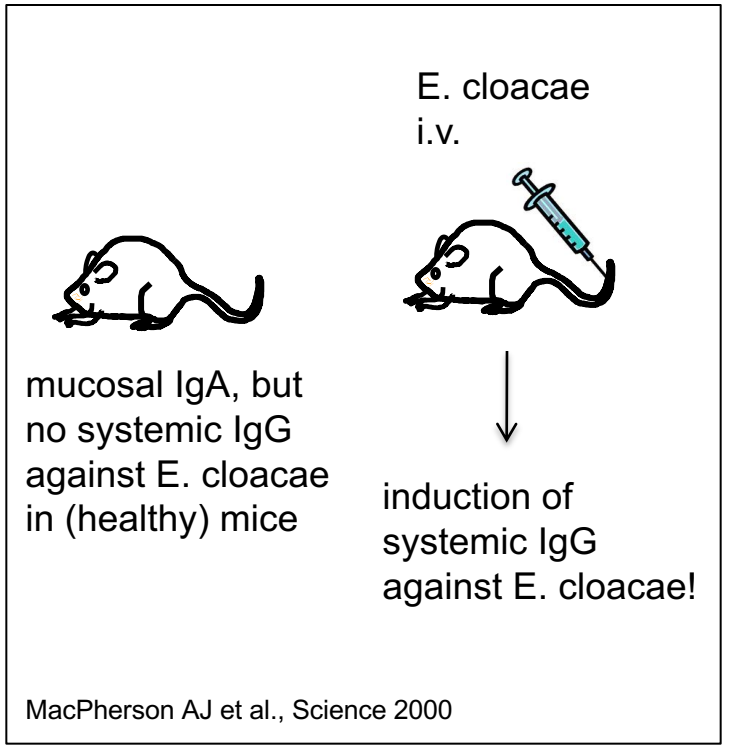
the mesenteric fire wall:



mucosal DC loaded with commensal bacteria do not traffic beyond the mesenteric lymph node!

MacPherson et al. Nat Rev Immunol 2004

the systemic immune system is ignorant, rather than tolerant of the intestinal commensal flora!



Overview

1. "Basic" mechanisms of self-tolerance

- central tolerance
- peripheral tolerance

2. Mucosal immunology

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

3. Analyzing tolerance in clinical disease settings

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

Tolerance in clinical disease settings

Autoimmune disease versus hypersensitivity reactions

Autoimmune disease:
"A disease caused by a break-down in self-tolerance such that the adaptive immune system responds to self-antigens and mediates tissue damage" (A.K. Abbas)

Hypersensitivity:
"Excessive immune reactivity to a generelly innocuous (self- or foreign) antigen" (Tak W. Mak)

Hypersensitivity reactions may well be operative during autoimmune disease but collateral damage to self mediated through excessive immune reactivity to foreign is not an autoimmune disease !

When considering immunological tolerance in its completeness (i.e. not just as tolerance to self but also to foreign - where required), hypersensitivity reactions may also be caused or driven by failure in tolerance mechanisms !

Autoimmune diseases: Examples of AID caused by auto-antibodies

Disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb:IIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture's syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

presence of auto-antibodies can also represent an epiphenomen and does not necessarily indicate a pathogenetic role for a particular auto-antibody

autoimmune diseases which are primarily mediated by auto-antibodies could still originate from a primary defect in T cell tolerance

Autoimmune diseases: Examples of AID caused by self-reactive T cells

Disease	Specificity of pathogenic T cells	Human disease	Animal models
Type I (insulin-dependent) diabetes mellitus	Islet cell antigens (insulin, glutamic acid decarboxylase, others)	Yes; specificity of T cells not established	NOD mouse, BB rat, transgenic mouse models
Rheumatoid arthritis	Unknown antigen in joint synovium	Yes; specificity of T cells and role of antibody not established	Collagen-induced arthritis, others
Multiple sclerosis, experimental autoimmune encephalomyelitis	Myelin basic protein, proteolipid protein	Yes; T cells recognize myelin antigens	EAE induced by immunization with CNS myelin antigens; TCR transgenic models
Inflammatory bowel disease (Crohn's, ulcerative colitis)	Unknown	Yes	Colitis induced by depletion of regulatory T cells, knockout of IL-10
Peripheral neuritis	P2 protein of peripheral nerve myelin	Guillain-Barre syndrome	Induced by immunization with peripheral nerve myelin antigens
Autoimmune myocarditis	Myocardial proteins	Yes (post-viral myocarditis); specificity of T cells not established	Induced by immunization with myosin or infection by Coxsackie virus

: CNS, central nervous system; NOD nonobese diabetic; TCR, T cell receptor

identification of potential target auto-antigens in human AID mostly relies on extrapolation of findings from experimental models

no evidence for classification as AID!

How identify a self-directed T cell response as a pathogenetic mechanism of an AID?

- experimental models: immunizations with the candidate auto-antigen, transfer of pathogenic T cells to lymphopenic recipients

- humans: T cell infiltrates in target tissues, enhanced T cell responses to target antigens *ex vivo*, altered Th profiles (compared to healthy controls) – only circumstantial evidence!

Autoimmune diseases: Role of genetic background: MHC alleles

Associations of AID with particular HLA-DR alleles:

Disease	HLA allele	Relative risk*
Rheumatoid arthritis	DR4	4
Insulin-dependent diabetes mellitus	DR3 DR4 DR3/DR4 heterozygote	5 5–6 25
Multiple sclerosis	DR2	4
Systemic lupus erythematosus	DR2/DR3	5
Pemphigus vulgaris	DR4	14
Ankylosing spondylitis	B27	90–100

*Relative risk is defined as the probability of development of a disease in individuals with a particular HLA allele versus individuals lacking that HLA allele. The numbers given are approximations.

in experimental animal models of AID, disease susceptibility strongly depends on the genetic background

prominent role of MHCII in selection and activation of CD4 T cells

prominent role of CD4 T cells in supporting and amplifying both innate & adaptive immune responses

Cave:

- most AID are polygenic / associated with several polymorphisms
- susceptibility alleles are also found in healthy individuals
- associations may differ between ethnic groups
- linkage disequilibrium may obscure the true causal association

Autoimmune diseases: Role of genetic background: non-MHC alleles

Gene	Phenotype of mutant or knockout mouse	Mechanism of failure of tolerance	Human disease?
AIRE	Destruction of endocrine organs by antibodies, lymphocytes	Failure of central tolerance	Autoimmune polyendocrine syndrome (APS)
C4	SLE	Defective clearance of immune complexes; failure of B cell tolerance?	SLE
CTLA-4	Lymphoproliferation; T cell infiltrates in multiple organs, especially heart; lethal by 3-4 weeks	Failure of anergy in $CD4^+$ T cells	CTLA-4 polymorphisms associated with several autoimmune diseases
Fas/FasL	Anti-DNA and other autoantibodies; immune complex nephritis; arthritis; lymphoproliferation	Defective deletion of anergic self-reactive B cells; reduced deletion of mature $CD4^+$ T cells	Autoimmune lymphoproliferative syndrome (ALPS)
FoxP3	Multi-organ lymphocytic infiltrates, wasting	Deficiency of regulatory T cells	IPEX
IL-2; IL-2Ra/b	Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies	Defective development, survival or function of regulatory T cells	None known
SHP-1	Multiple autoantibodies	Failure of negative regulation of B cells	None known
PTPN22	Increased lymphocyte proliferation, antibody production	Reduced inhibition by tyrosine phosphatase?	PTPN22 polymorphisms are associated with several autoimmune diseases

Abbreviations: AIRE, autoimmune regulator gene; IL-2, interleukin-2; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; SHP-1, SH2-containing phosphatase-1.

failure in central tolerance

failure in peripheral tolerance mechanisms

Autoimmune diseases: Pathogenic role of microbial infections

Potential mechanisms for pathogen-triggered induction of autoimmunity:

- molecular mimicry

AID	Cross-reacting sequences	Origin of Peptide
EAE	YGSLPQKSQRTQDEN	Rat MBP
	YGCLLPRNPRTEDQN	*Chlamydia pneumoniae* protein
Lyme arthritis	VVLEGTLTA	Human LFA-1
	YVIEGTSKQ	*Borrelia burgdorferi* OspA protein
MS	VVHFFKNIV	Human MBP
	VYHFVKKHV	EBV protein
RF	QKMRRDLEE	Human myosin
	KGLRRDLDA	*Streptococcus* cell wall M protein

TW Mak and ME Saunders

rheumatic fever: antistreptococcal antibodies crossreact with myocardial proteins

T1 diabetes — PC2 protein of Coxsackie — GAD of islet cells

- activation of APC and “bystander” activation of self-specific T cells

  (also: upregulation of MHCII on non-APC?)

- tissue damage mediated by hypersensitivity reactions to persistent microbes may lead to the release of normally sequestered self-antigens and induction of autoimmunity

Autoimmune diseases: Pathogenetic role of microbial infections

Pro:

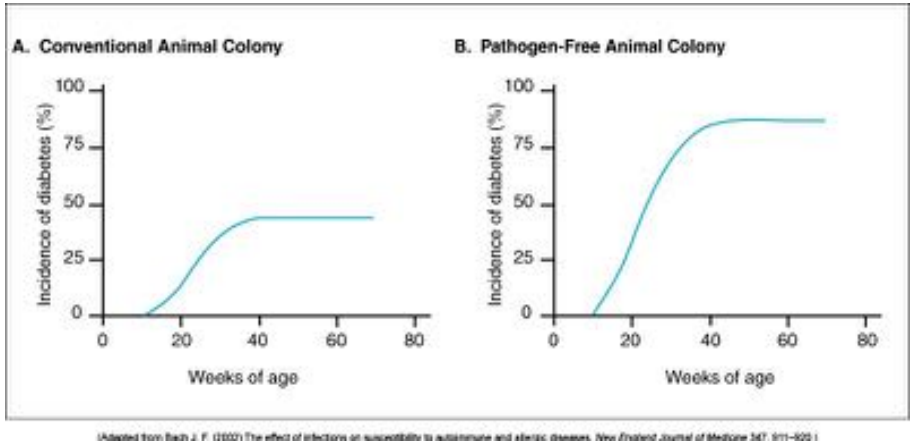
Experimental models:	Human disease:
(only some examples!) • in a spontaneous model of EAE, mice are less prone to disease when housed in a clean facility • in the NOD mouse model of diabetes disease onset (in adult mice) is accelerated after infection with rotaviruses	(only some examples!) • viral infections have been associated with flare-up of SLE and relapse of MS • viral antigens from EBV, HPV, influenza, measles virus a.o. can provoke the production of antibodies and T cells that crossreact with MBP *in vitro* • infection with enteroviruses often precedes or accompanies diabetes in children

Autoimmune diseases: Pathogenetic role of microbial infections

Contra: "Infections are common, autoimmunity is not" R. Inman, L. Albert; University of Toronto

Experimental models:

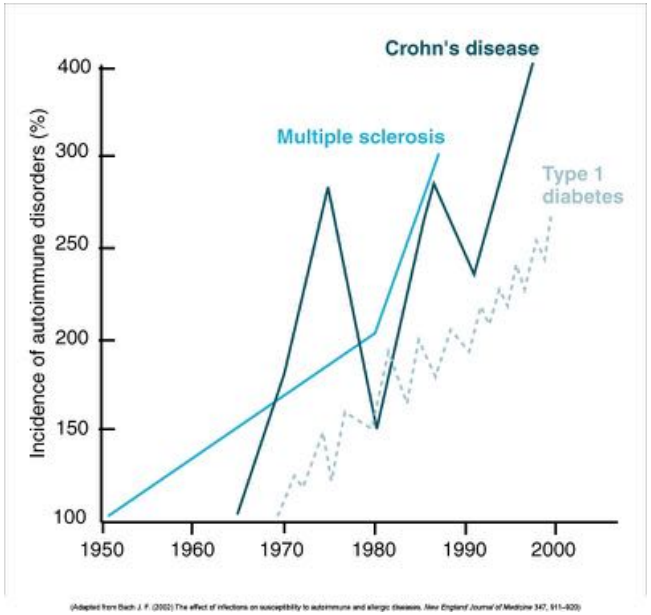
- a shift to a germ-free (GF) environment does not ameliorate disease in Aire$^{-/-}$ mice
- rheumatoid arthritis is equally inducible in germ-free rats
- SPF and GF NOD mice have a higher incidence of spontaneous diabetes



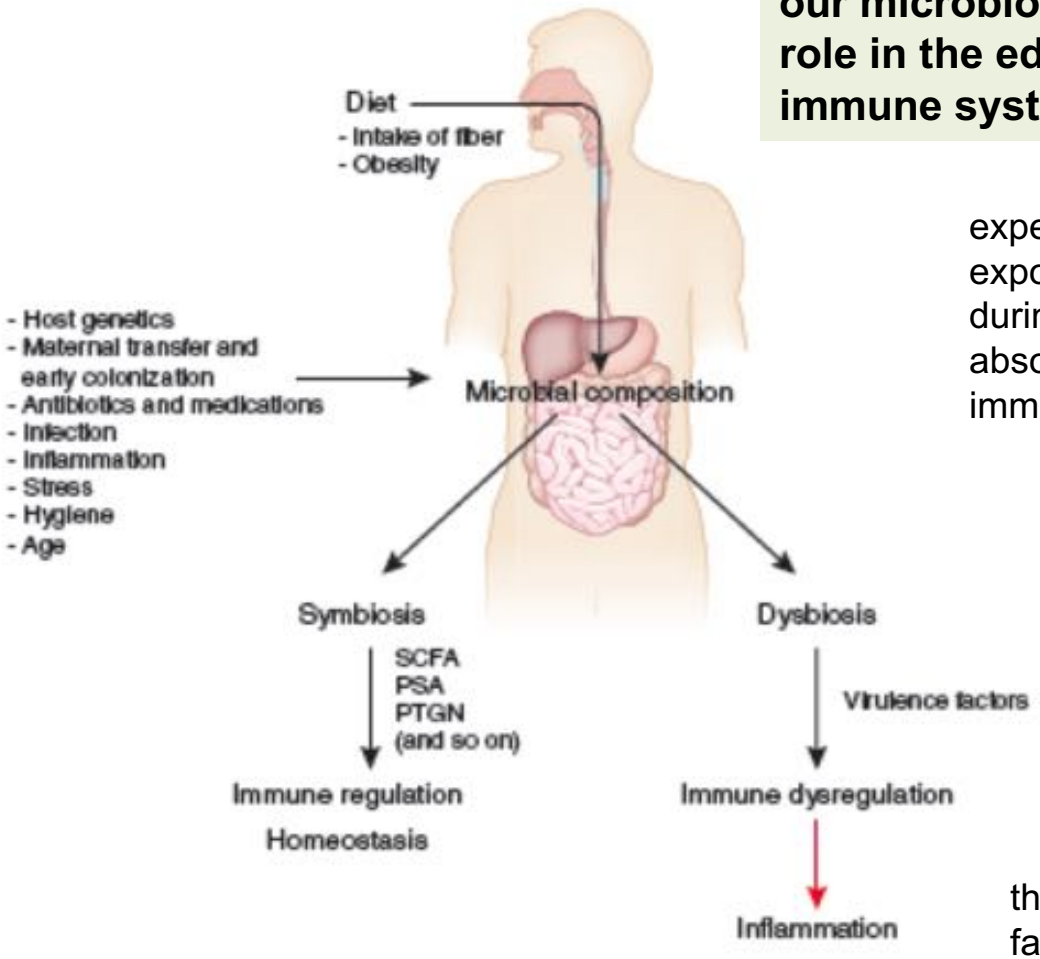
can infections even protect from AID ?!

Human disease:

- for most AID, no firm causal relation-ship with a specific pathogen exists
- "hygiene hypothesis": increasing incidence of hypersensitivity diseases in developed countries



The hygiene hypothesis re-visited: The diet-microbiota hypothesis!



Kendle M Maslowski & Charles R Mackay

NATURE IMMUNOLOGY VOLUME 12 NUMBER 1 JANUARY 2011

our microbiota and our diet play a considerable role in the education and regulation of our immune system:

experimental models indicate that exposure to a diverse microbial population during a critical time window early in life is absolutely required to set the baseline immune regulatory state for life

human populations that consume adequate or large amounts of dietary fibers and whose microbiota is enriched in Bacteriodetes show a lower incidence of inflammatory or atopic disease

the anti-inflammatory effects of short-chain fatty acids (SCFA) and polysaccharide A (PSA) on the intestinal immune system (e.g. by expansion of Tregs or modulation of colonic epithelial cells) are now acknowledged

Autoimmune disease: where does tolerance fail ?

	Gene	Phenotype of mutant or knockout mouse	Mechanism of failure of tolerance	Human disease?
central tolerance	MHCII		failure in binding of relevant peptides for negative selection	
central tolerance	AIRE	Destruction of endocrine organs by antibodies, lymphocytes	Failure of central tolerance	Autoimmune polyendocrine syndrome (APS)
central tolerance	FoxP3	Multi-organ lymphocytic infiltrates, wasting	Deficiency of regulatory T cells	IPEX
central tolerance	IL-2; IL-2Ra/b	Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies	Defective development, survival or function of regulatory T cells	None known
peripheral tolerance	C4	SLE	Defective clearance of immune complexes; failure of B cell tolerance?	SLE
peripheral tolerance	CTLA-4	Lymphoproliferation; T cell infiltrates in multiple organs, especially heart; lethal by 3-4 weeks	Failure of anergy in $CD4^+$ T cells	CTLA-4 polymorphisms associated with several autoimmune diseases
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peripheral tolerance	SHP-1	Multiple autoantibodies	Failure of negative regulation of B cells	None known
peripheral tolerance	PTPN22	Increased lymphocyte proliferation, antibody production	Reduced inhibition by tyrosine phosphatase?	PTPN22 polymorphisms are associated with several autoimmune diseases

most evidence today points to a role for defects in peripheral, rather than central tolerance mechanisms

evidence from experimental models suggests a pivotal role for T_{regs} in preventing onset of autoimmunity

in humans, most patients with AID exhibit normal numbers of functional T_{regs}

AID likely have a multifactorial aetiology with a complex interplay of genetic, microbial and even nutritional factors

Hypersensitivity diseases

Hypersensitivity:

"Excessive immune reactivity to a generelly innocuous (self- or foreign) antigen" (Tak W. Mak)

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity: Type I	IgE antibody	Mast cells and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling
Immune complex mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell mediated: Type IV	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell–mediated cytolysis)	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell killing, cytokine-mediated inflammation

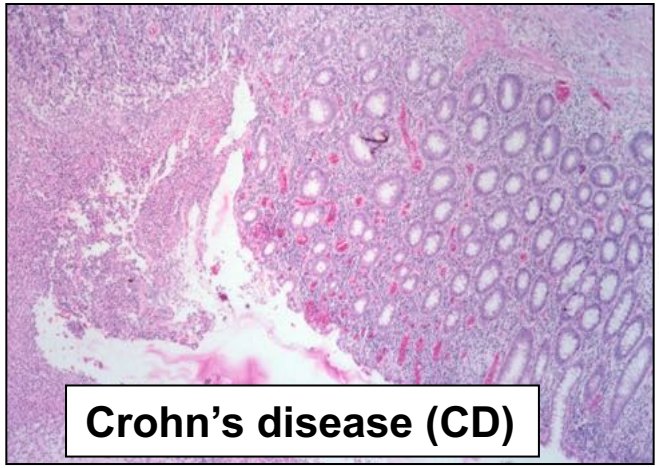
Examles for type IV	T cells directed against	tissue damage observed
• chronic DTH	conventional foreign antigen	granuloma formation
• chronic graft rejection	allo-antigen in donor tissue	destruction of donor cells, fibrosis
• autoimmunity	self-antigen in target tissue	destruction of self-cells, fibrosis

Inflammatory bowel diseases: Clinical / histological manifestation

Switzerland: ca. 1/500 inhabitants

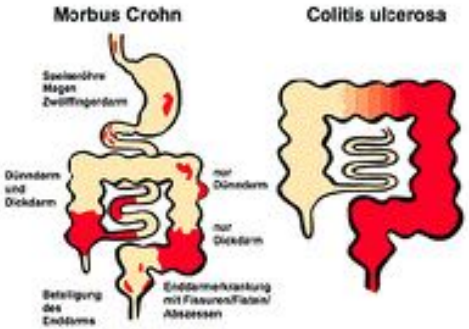
clinical symptoms: abdominal pain, diarrhea, fever, fatigue (chronic relapsing)

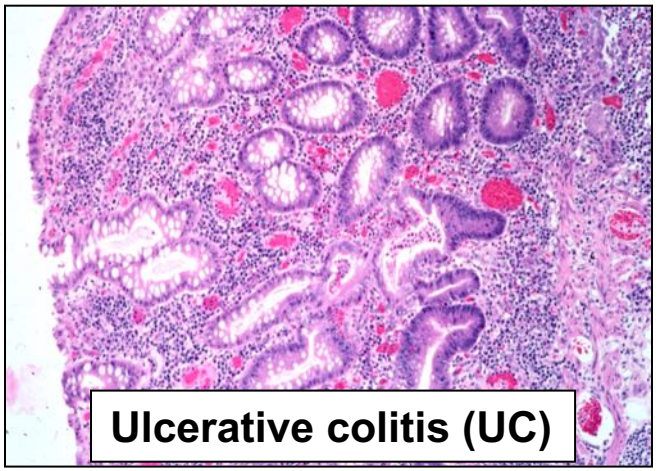
onset between 15-40 years; from first symptoms to diagnosis: > 2 years



Crohn's disease (CD)

- may affect entire gastrointestinal tract
- discontinuous, transmural, granulomatous inflammation





Ulcerative colitis (UC)

- continuous inflammation of entire colon
- crypt abscesses

treatment: anti-inflammatory / immunosuppressive drugs (5-ASA, methotrexate, steroids, anti-TNF)

Inflammatory bowel diseases (IBD): where do they belong…?

…the evolving paradigm…

IBD is a chronic immune-mediated but non-infectious disease

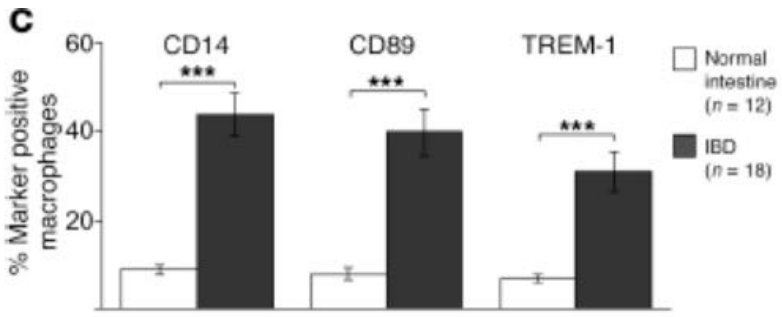
IBD is an autoimmune disease

IBD is a T cell-mediated hypersensitivity reaction against the commensal flora

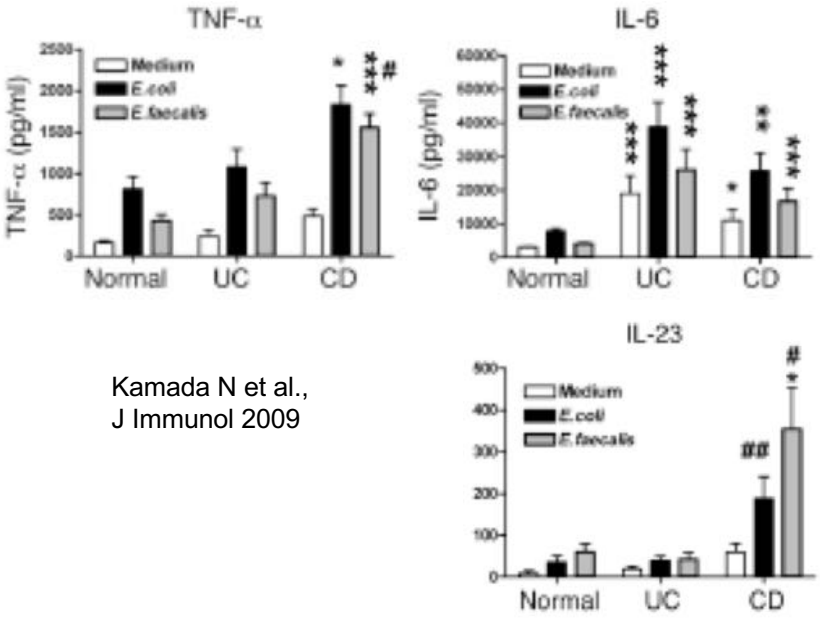
Is IBD an innate immunodeficiency disease ?

Inflammatory bowel diseases: atypical intestinal immune responses

aberrant phenotypes and functional responses of intestinal macrophages in IBD

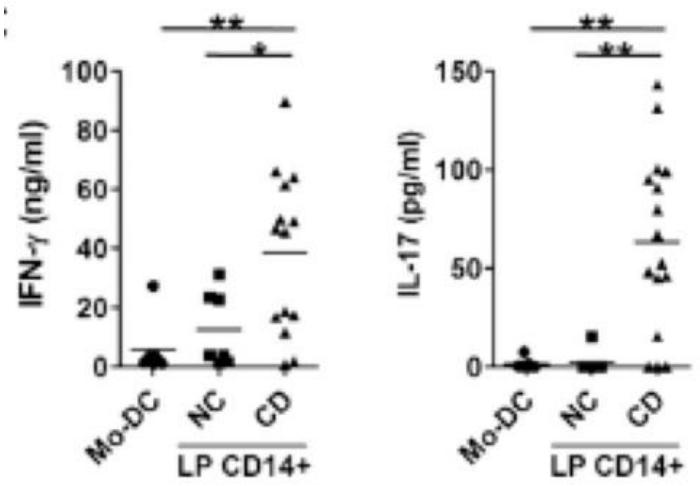


Schenk M, Mueller C et al., J Clin Invest 2007



Kamada N et al.,
J Immunol 2009

aberrant differentiation of intestinal CD4 T cells into Th1 and Th17 subsets in Crohn's disease (CD) patients



Kamada N et al., J Immunol 2009

Inflammatory bowel diseases: Role for microbial factors ?

- in human IBD patients, disease is ameliorated by antibiotic treatment or diversion of the fecal stream away from affected intestinal segments

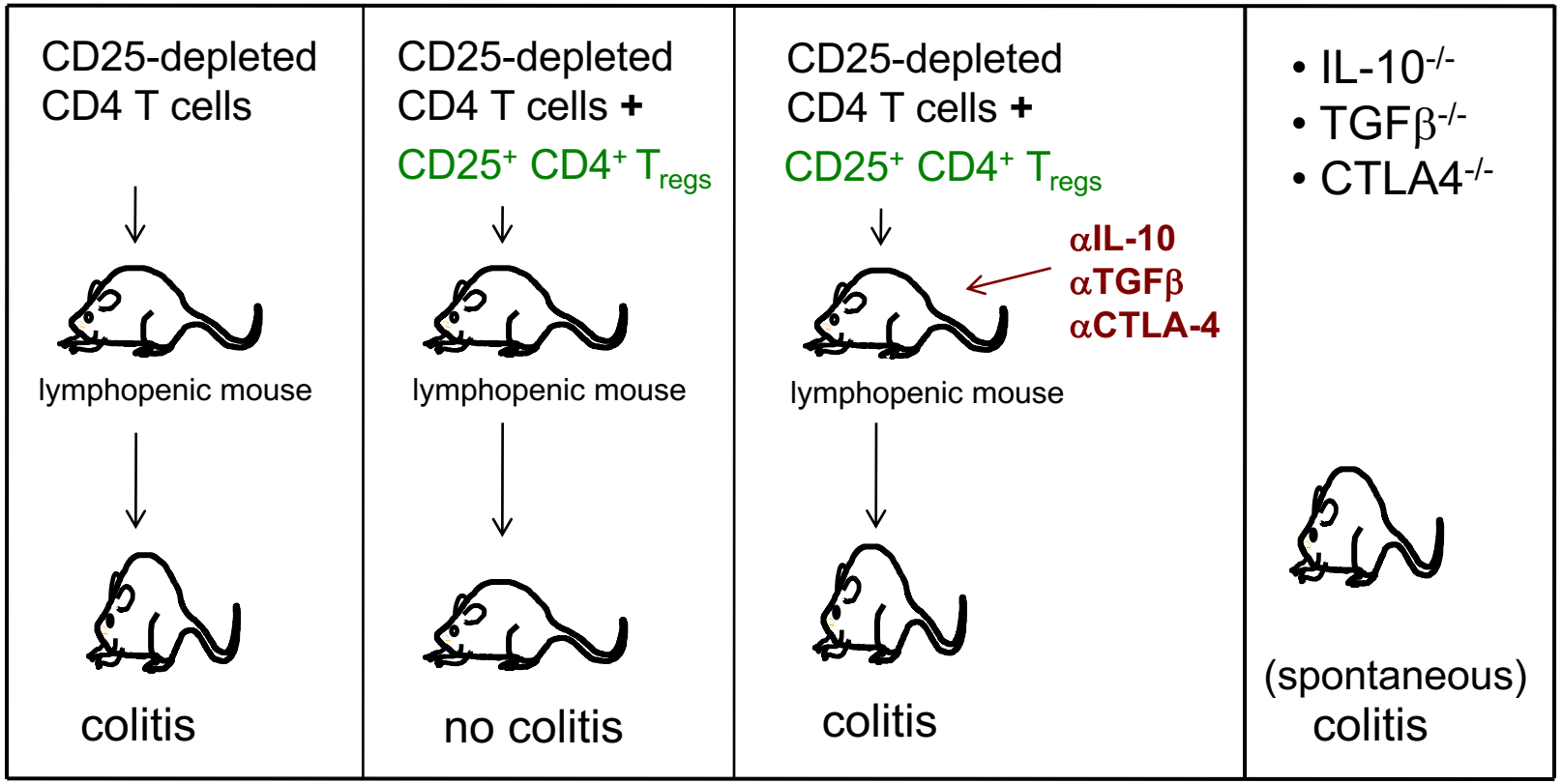
- in experimental disease models, disease cannot be induced in germ-free mice

Dysregulation of the normally tightly controlled immune response to commensal bacteria in susceptible individuals

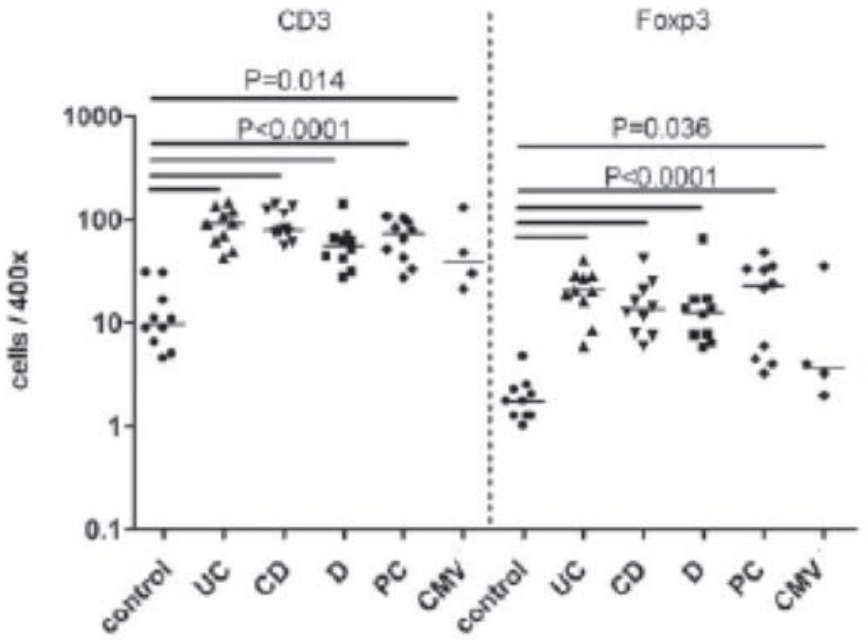
Failure in intestinal tolerance mechanisms to “foreign” ?

Inflammatory bowel diseases: Role for a defect in T_{regs} ?

- mutations in the human IL-10 receptor gene are associated with very severe early onset IBD in paediatric patients
- experimental models point to an important role for T_{reg} cells or TGFβ, IL-10 and CTLA-4 in preventing intestinal inflammation



Inflammatory bowel diseases: Role for a defect in Tregs ?

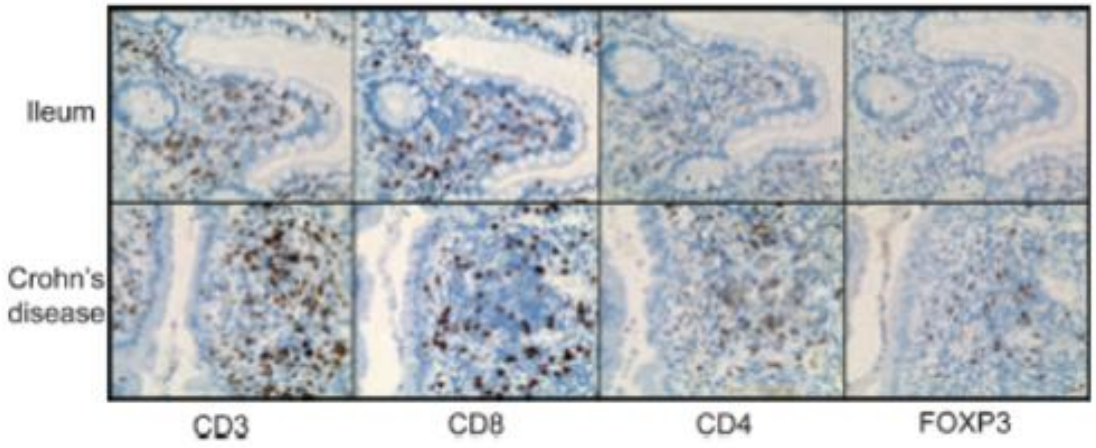


Uhlig et al., J Immunol 2006

however:

in human IBD, $CD4^+$ $CD25^+$ $Foxp3^+$ T cells are actually <u>increased</u>

no evidence for reduced production of IL-10 and TGFβ in inflamed tissues



Saurer L, Mueller C, Allergy, 2009

where does tolerance fail then ?

Inflammatory bowel diseases: Role for genetic factors

Experimental models of (spontaneous) IBD:

Defective mucus layer	$Muc2^{-/-}$ mice
Impaired epithelial cell function	IEC-specific deletion of IKKγ
Aberant APC activation	$STAT3^{-/-}$ macrophages
Defect in regulatory T cells	IL-$10^{-/-}$, TGF$\beta^{-/-}$, IL-$2^{-/-}$ mice

Different genetic defects, including innate immune defects, can lead to comparable clinical and histopathological signs of experimental colitis

Inflammatory bowel diseases: Role for genetic factors

susceptibility allelles Crohn's disease

gene	normal function
NOD2/ CARD15	intracellular PRR, recognition of bacterial peptidoglycan
IL-23R	subunit of IL-23 receptor, Th17 differentiation
IL-12B	p40 subunit of IL-23 and IL-12, Th1 differentiation
STAT3	various, involvement in Th17 differentiation
ATG16L1	autophagy

human susceptibility loci support the notion that IBD may initially originate from an aberrant innate immune response

Inflammatory bowel diseases: Role for genetic factors

A closer look at the functions of some of the disease-associated alleles reveals a potential innate immune defect rather than hyperresponsive state

NOD2

disease-associated polymorphism reduces function of NOD2:
- impaired handling of bacteria by macrophages?
- decreased antimicrobial peptide expression by epithelial cells?

IL-23R

- impaired IL-22 production in innate lymphoid cells?
- decreased antimicrobial peptide expression by epithelial cells?

ATG16L1

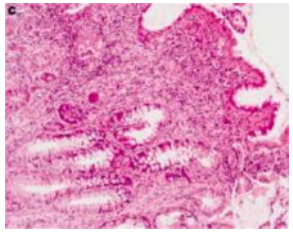
- impaired anti-bacterial autophagy?
- impaired Paneth cell exocytosis?

increased penetration of bacteria, uncontrolled activation of compensatory adaptive responses?

Crohn's disease: An innate immune deficiency disease ?

Circumstantial evidence:

IBD in ≈ 30% of patients with chronic granulomatous disease (NADPH defect!)

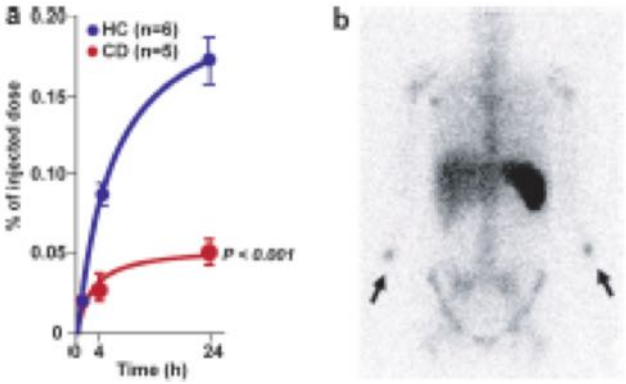


Inflammatory Bowel Disease in CGD Reproduces the Clinicopathological Features of Crohn's Disease

Daniel J.B. Marks, PhD[1,4], Kana Miyagi, MB BS, BSc[1,4], Farooq Z. Rahman, MRCP[1], Marco Novelli, PhD[2], Stuart L. Bloom, DM, FRCP[3] and Anthony W. Segal, PhD, FRS[1]

The American Journal of GASTROENTEROLOGY

Impaired neutrophil accumulation in CD patients



i.v. injection of ^{111}Indium-labeled neutrophils
simultaneous s.c. injection of killed E. Coli

JEM

Disordered macrophage cytokine secretion underlies impaired acute inflammation and bacterial clearance in Crohn's disease

Andrew M. Smith,[1] Farooq Z. Rahman,[1] Bu'Hussain Hayee,[1] Simon J. Graham,[4] Daniel J.B. Marks,[1] Gavin W. Sewell,[1] Christine D. Palmer,[1] Jonathan Wilde,[4] Brian M.J. Foxwell,[5] Israel S. Gloger,[4] Trevor Sweeting,[2] Mark Marsh[3], Ann P. Walker,[1] Stuart L. Bloom,[6] and Anthony W. Segal[1]

JEM VOL. 206, August 31, 2009

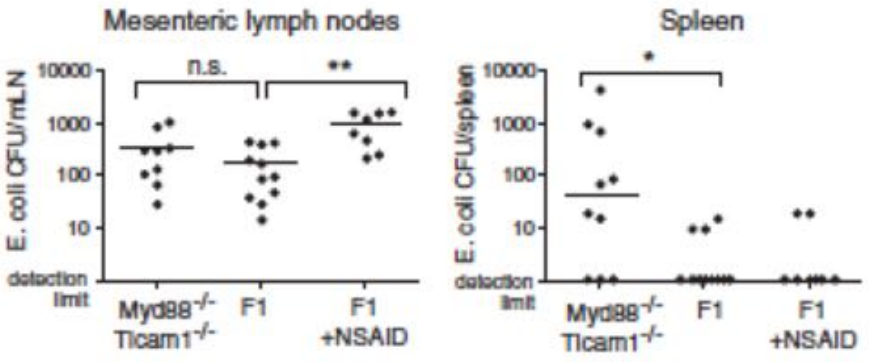
Crohn's disease: an innate immune deficiency disease ?

More circumstantial evidence:

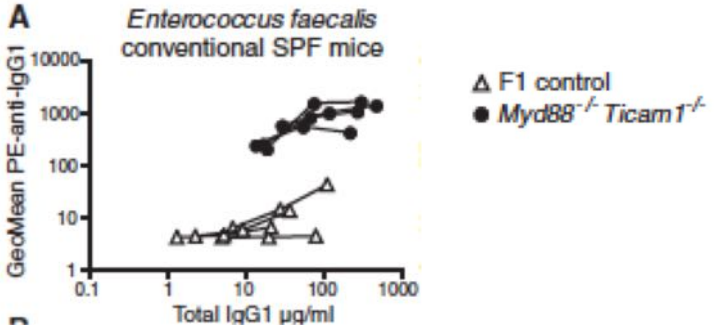
31 JULY 2009 VOL 325 SCIENCE

Innate and Adaptive Immunity Cooperate Flexibly to Maintain Host-Microbiota Mutualism

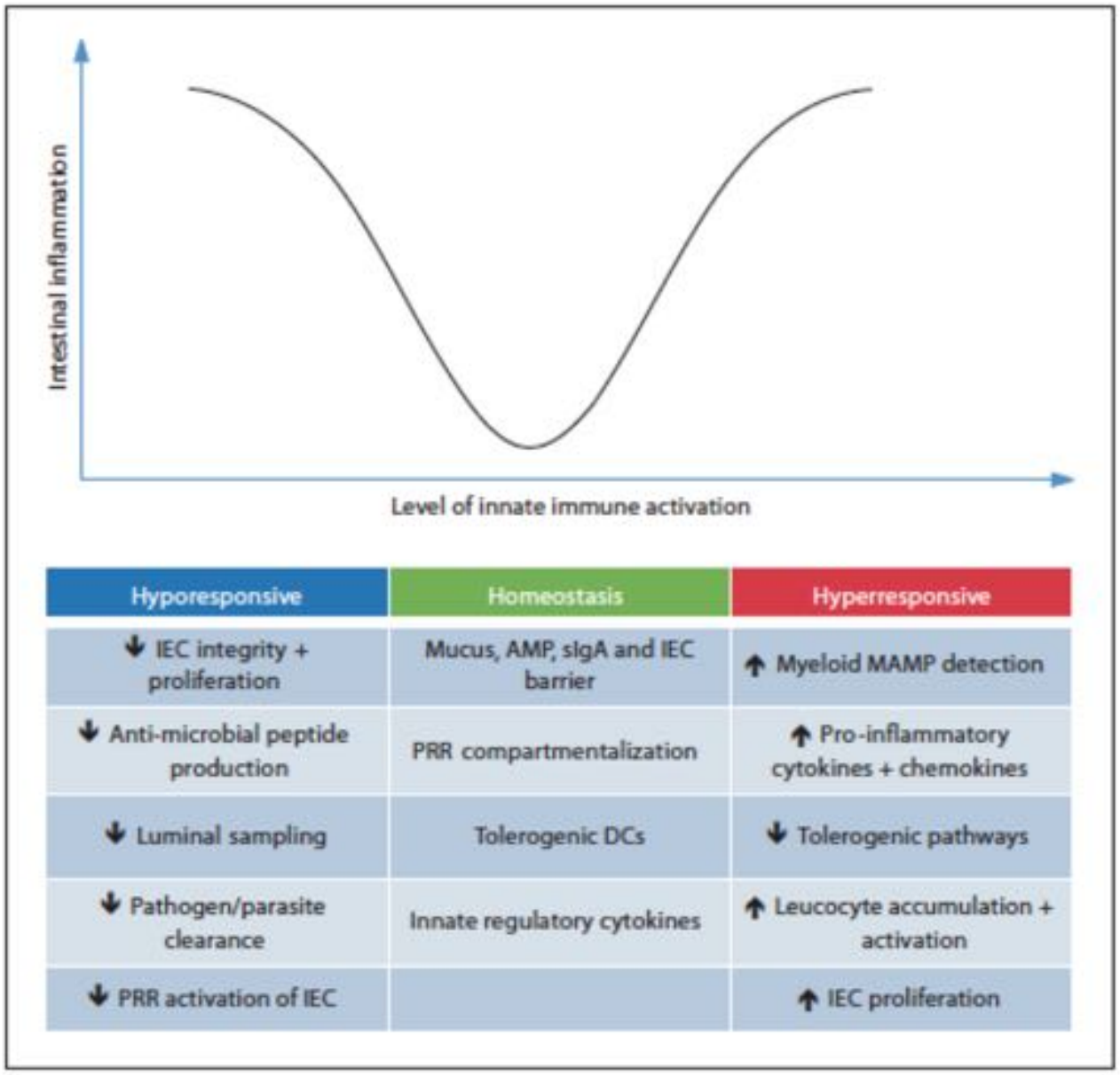
Emma Slack,[1,5]* Siegfried Hapfelmeier,[1,5] Bärbel Stecher,[2] Yuliya Velykoredko,[1] Maaike Stoel,[1] Melissa A. E. Lawson,[1] Markus B. Geuking,[1] Bruce Beutler,[3] Thomas F. Tedder,[4] Wolf-Dietrich Hardt,[2] Premysl Bercik,[1] Elena F. Verdu,[1] Kathy D. McCoy,[1] Andrew J. Macpherson[1,5]*



Mice deficient in Myd88 exhibit translocation of commensal bacteria to the spleen and loss of systemic ignorance to the commensal flora (priming of systemic adaptive immune responses)



Balanced innate immune activation maintains intestinal homeostasis



Hyporesponsive	Homeostasis	Hyperresponsive
↓ IEC integrity + proliferation	Mucus, AMP, sIgA and IEC barrier	↑ Myeloid MAMP detection
↓ Anti-microbial peptide production	PRR compartmentalization	↑ Pro-inflammatory cytokines + chemokines
↓ Luminal sampling	Tolerogenic DCs	↓ Tolerogenic pathways
↓ Pathogen/parasite clearance	Innate regulatory cytokines	↑ Leucocyte accumulation + activation
↓ PRR activation of IEC		↑ IEC proliferation

Harrison OJ, Maloy KJ
J Innate Immunity 2011

Sum-up: Immunological tolerance

- immunological tolerance (in its wider context – including tolerance to foreign) is involved in many areas of clinical immunology, including immunity to infectious agents, allergology, tumor immunology, vaccinology, autoimmunity, hypersensitivity diseases, transplantation immunology,…

- without the use of experimental models, our understanding of tolerance and breakdown of tolerance would still be in its infancy

- emerging data from clinical investigations is in line with many findings from experimental models (or vice versa) but discrepancies exist!

- future research directed at a better understanding of tolerance and breakdown of tolerance must continue to take into consideration aspects from both experimental and clinical immunology

- …replacing paradigms requires open minds ☺

"I expect you all to be independent, innovative, critical thinkers who will do exactly as I say!"

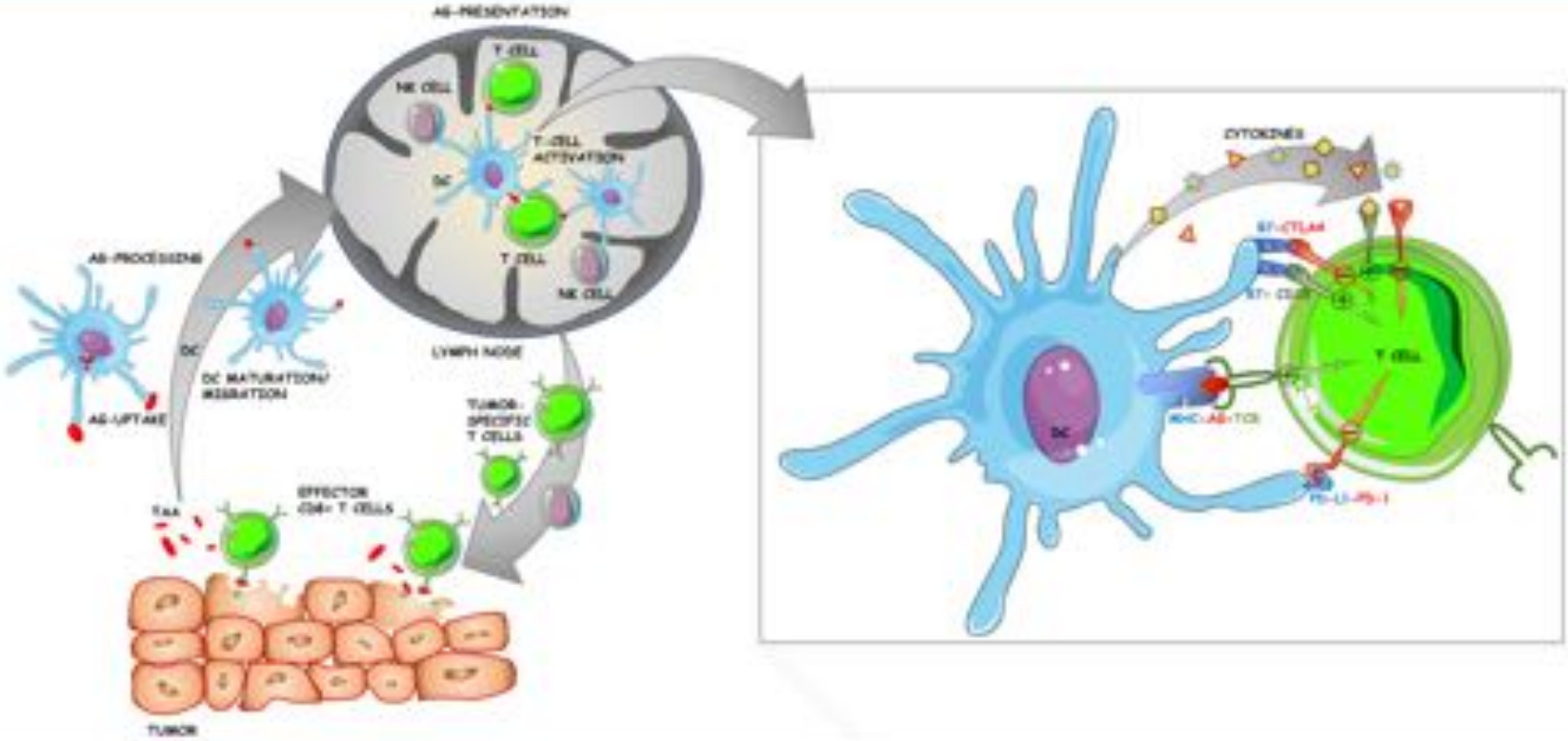
Mirjam Schenk Group

- Thomas Gruber, PhD student
- Hassan Sadozai, PhD student
- Mirela Kremenovic, PhD student
- Lukas Bäriswyl, research technician (50%)
- Fabienne Maibach, MD-PhD student

Research Goals:

- Generation of cross-presenting dendritic cells (DC) for immunotherapy in melanoma
- Targeting tumor infiltrating dendritic cells (TIDC) to enhance cytotoxic T cell responses
- Deciphering the role of DC subsets in regulating the immune response to cancer therapies

Mirjam Schenk Group: Tumor Immunology



Thank You!

Mirjam.schenk@pathology.unibe.ch