Immunological Tolerance

Mirjam Schenk

Institut für Pathologie
Experimentelle Pathologie
Universität Bern

mirjam.schenk@pathology.unibe.ch

4540-FS2018-0: Selected topics in Clinical Immunology
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Tolerance to **self**

- Highly desired:
  - Central tolerance
  - Peripheral tolerance
  - Prevention of autoimmunity

Tolerance to **foreign** antigens

- Desired:
  - Inhaled antigens
  - Food antigens
  - Fetal antigens
  - Commensal flora
  - Organ transplants

- Undesired:
  - Transformed cells
  - Tumors
  - Pathogens
  - Vaccines

**Immunological Tolerance**

- Th1
- Th17
- CD4+CD25+
- Foxp3+
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 and hypersensitivity reactions
   - pathogenetic role of genetic and microbial factors
   - where does tolerance fail and how can it be assessed?
1. “Basic” mechanisms of self-tolerance

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Functional significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>Ensures that specific antigens elicit specific responses</td>
</tr>
<tr>
<td>Diversity</td>
<td>Enables immune system to respond to a large variety of antigens</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
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<td>Specification</td>
<td></td>
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<tr>
<td>Self-limination</td>
<td></td>
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<tr>
<td>Nonreactivity to self</td>
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</tbody>
</table>

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...

clonal deletion

abundance of self-antigens, numbers of TCR engaged, co-R’s, 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

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 |
|----------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                  |  cTECs         |  mTECs         |  DCs           |  Macrophages  |
| SAP                              | -/+            | +/+            | -/+            | -/+-          |
| CRP                              | +/+            | +/+            | +/+            | +/+-          |
| Complement C5                    | +/+            | +/+            | +/+            | +/+-          |
| α2-macroglobulin                 | -/+-           | +/+            | +/+            | +/+-          |
| Albumin                          | +/+            | +/+            | +/+            | +/+-          |
| Haptoglobin                      | +/+            | +/+            | +/+            | +/+-          |
| α-d-amylase                      | -/+-           | +/+            | +/+            | +/+-          |
| PLP                              | +/+            | +/+            | +/+            | +/+-          |
| MOG                              | -/+-           | +/+            | +/+            | +/+-          |
| S100β                            | +/+            | -/+            | +/+            | +/+-          |
| GAD65+                           | +/+            | +/+            | +/+            | +/+-          |
| GAD65-                           | +/+            | +/+            | +/+            | +/+-          |
| Somatostatin                     | +/+            | +/+            | +/+            | +/+-          |
| Trypsin2                         | -/+            | +/+            | +/+            | +/+-          |
| Elastase                         | +/+            | +/+            | +/+            | +/+-          |
| Insulin                          | +/+            | -/+            | +/+            | +/+-          |
| Tyrosinase                       | -/+            | +/+            | +/+            | +/+-          |
| Gp100                            | -/+            | +/+            | +/+            | +/+-          |
| PLA1                             | +/+            | +/+            | +/+            | +/+-          |
| Thyroglobulin                    | +/+            | +/+            | +/+            | +/+-          |
| Lactalbumin                      | +/+            | +/+            | +/+            | +/+-          |
| α1-crystallin                    | +/+            | +/+            | +/+            | +/+-          |
| Retinal S antigen                | -/+            | +/+            | +/+            | +/+-          |
| NACHRich                        | -/+            | +/+            | +/+            | +/+-          |
| IFABP                            | -/+            | +/+            | +/+            | +/+-          |
| Amylase1                         | -/+            | +/+            | +/+            | +/+-          |

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© 1997 Nature Publishing Group http://www.nature.com/naturegenetics

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)

Aire−/− 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 can be re-stimulated ex vivo!

Anergy

Co-expression of viral antigen with B7, CD40L, TNFα or: viral infection

Autoimmunity
Peripheral tolerance: Anergy

Immunizations:
- None
- "Immunogenic" dose
  - In particulate form
  - With adjuvants
  - S.c. or i.d.
- Large dose
  - In aqueous form
  - No adjuvants
  - I.v. or oral

Graphs and images showing proliferation levels in naive, tolerant, and primed states.
Peripheral tolerance: Anergy

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

The danger model:


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 actively 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:

- **competition for B7**
  (CTLA-4 has a higher affinity than CD28)

- **cell intrinsic inhibitory signaling**
  (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!

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

- CTLA-4-based therapeutics 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!)

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

self-antigens cannot be eliminated → chronic / repetitive stimulation

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

\[ \text{apoptosis} \]

**Diagram:**
- Immune response: expression of anti-apoptotic (survival) proteins
- Self antigen recognition: induction of pro-apoptotic proteins (e.g. Bim)
- Self antigen recognition: engagement of death receptors

**Pathways:**
- **Mitochondrial “intrinsic” pathway**
- **Death receptor “extrinsic” pathway**
Mice with mutations in either **Fas** (lpr/lpr), **FasL** (gld/gld) or **Bim** (Bcl2l11-/-): autoimmune lymphoproliferative disorders!

- Increased cellularity
- Auto-antibodies
- Immune complex deposition

**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. Middleton,‖ 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)
Peripheral tolerance: Suppression by regulatory T cells ($T_{\text{regs}}$)

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

**natural $T_{\text{regs}}$**

- CD4$^+$ CD25$^+$ Foxp3$^+$

**induced/adaptive $T_{\text{regs}}$**

Possible mechanisms:
- 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 ($T_{\text{regs}}$)

$\text{Foxp}3^+ \ T_{\text{regs}}$

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:

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

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\textsubscript{regs})

Further exemplary evidence for a role of T\textsubscript{reg} peripheral tolerance:

**mouse models of chronic inflammatory diseases, e.g.**

*Cutting Edge: Cure of Colitis by CD4\textsuperscript{+}CD25\textsuperscript{+} Regulatory T Cells\textsuperscript{1}*

Christian Mottet, Holm H. Uhlig, and Fiona Powrie

(vice versa: induction of disease by T\textsubscript{reg} depletion)

J Immunol 2003

**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

("natural" desensitization to bee venom in beekeepers related to the induction of IL-10\textsuperscript{+} T\textsubscript{regs})

Peripheral tolerance: Immune privileged sites

- physical barriers (e.g. BB-barrier)
- absence of lymphatic drainage (e.g. brain)
- low numbers of APC
- low MHC expression (e.g. fetal trophoblast)
- expression of FasL (e.g. testis)
- TGFβ-rich environment (e.g. eye)

sequestration of antigens (immunological ignorance)

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

- 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 fought 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

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

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

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

Muc2\(^{-/-}\) mice: penetrance of bacteria spontaneous colitis!

Johansson et al. PNAS 2008
Multi-layered adaptations of the GALT: Intestinal epithelial cells

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

- 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:

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

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!

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

(Nemo = IκB kinase γ)

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

e.g. production of:

- TGFβ
- IL-10
- TSLP
- retinoic acid
- April
- BAFF

modulation / conditioning of DC
bias of Th differentiation into Th2 / T\textsubscript{reg}
promotion of B cell IgA switching
Multi-layered adaptations of the GALT: Intestinal macrophages

Intestinal macrophages are continuously 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,1,2,3 Aiman Brawas,1,2,3 Jeremy A. Goettel,1,2,3 Katelyn McCann,1,2,3 Evan Conaway,3 Naresh S. Redhu,1,2,3 Ivan D. Mascarenhas,1 Ziad Al Adham,1 Sydney Lavoie,1 Moune Ibouk,1 Deanna D. Nguyen,4 Janneke N. Samsom,5 Johanna C. Escher,5,6,7 Raz Somch,5,8,9 Batia Weiss,5,8,9 Rita Beier,1,2,3,10 Laurie S. Conklin,5,10 Christen L. Ebens,5,10 Fernanda G.M.S. Santos,10,11 Alexandre R. Ferreira,12,13 Mary Sherlock,12,13 Atul K. Bhan,14,15 Werner Müller,16 J. Rodrigo Mora,16,7 Francisco J. Quintana,6 Christoph Klein,17,18 Alexio M. Muise,19,20 Bruce H. Horwitz,21,22 and Scott B. Snapper,17,21,22

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

Ehud Zigmond,1,2 Biana Bemshtein,1 Gilgi Friedlander,2 Catherine R. Walker,6 Simon Yona,1 Ki-Wook Kim,1 Ori Brenner,6 Rita Krauthgamer,1 Chen Varol,2 Werner Müller,16 and Steffen Jung1

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\(_{\text{regs}}\)

capacity lies within the CD103\(^+\) subset...

intestinal CD103\(^+\) DC have a propensity to induce Foxp3\(^+\) T\(_{\text{regs}}\) and are critically required for induction of oral tolerance

...is associated with production of TGF\(\beta\) and the vitamin A-derivative retinoic acid
Mucosal immunology: Oral tolerance

The phenomenon:
Oral administration of antigen can lead to suppressed immune responses to peripheral challenge with the same antigen.

tolerance can be transferred by T cells

TGFβ appears to be involved

Janeway / Travers
Mucosal immunology: Oral tolerance

The (likely) mechanism:

- (clonal deletion)
- induction of regulatory T cells

<table>
<thead>
<tr>
<th>Treg Type</th>
<th>Induction</th>
<th>Cytokine</th>
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</thead>
<tbody>
<tr>
<td>nT&lt;sub&gt;reg&lt;/sub&gt; (Foxp3&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>IL-2, TGFβ</td>
<td>TGFβ, IL-10, cytokine-independent suppression ?</td>
</tr>
<tr>
<td>Th3 (Foxp3&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>TGFβ</td>
<td>TGFβ, IL-10, IL-4</td>
</tr>
<tr>
<td>Tr1 (Foxp3&lt;sup&gt;-&lt;/sup&gt;)</td>
<td>IL-10</td>
<td>IL-10, TGFβ, IFNγ</td>
</tr>
<tr>
<td>iT&lt;sub&gt;reg&lt;/sub&gt; (Foxp3&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>TGFβ, IL-2, retinoic acid</td>
<td>TGFβ, IL-10, cytokine-independent suppression ?</td>
</tr>
</tbody>
</table>

feeding of ovalbumin (but not BSA) to Ovalbumin-TCR tg mice (lacking endogenous Tregs) _de novo_ induces Foxp3<sup>+</sup> CD4<sup>+</sup> T<sub>regs</sub> cells in the MLN  
Coombes et al., J Exp Med 2007
Evidence exists that oral tolerance mediated by T_{regS} is operative in humans.
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\(_{\text{regs}}\)
shift from IgE to IgG4
Mucosal immunology: Oral tolerance does not apply to commensal flora

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

mucosal IgA, but no systemic IgG against E. cloacae in (healthy) mice

induction of systemic IgG against E. cloacae!

MacPherson AJ et al., Science 2000

MacPherson et al. Nat Rev Immunol 2004
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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 generally 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target antigen</th>
<th>Mechanisms of disease</th>
<th>Clinicopathologic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Erythrocyte membrane proteins (Rh blood group antigens, I antigen)</td>
<td>Opsonization and phagocytosis of erythrocytes</td>
<td>Hemolysis, anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Platelet membrane proteins (gplb:lla integrin)</td>
<td>Opsonization and phagocytosis of platelets</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Proteins in intercellular junctions of epidermal cells (epidermal cadherin)</td>
<td>Antibody-mediated activation of proteases, disruption of intercellular adhesions</td>
<td>Skin vesicles (bullae)</td>
</tr>
<tr>
<td>Vasculitis caused by ANCA</td>
<td>Neutrophil granule proteins, presumably released from activated neutrophils</td>
<td>Neutrophil degranulation and inflammation</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli</td>
<td>Complement- and Fc receptor-mediated inflammation</td>
<td>Nephritis, lung hemorrhage</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen</td>
<td>Inflammation, macrophage activation</td>
<td>Myocarditis, arthritis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Antibody inhibits acetylcholine binding, down-modulates receptors</td>
<td>Muscle weakness, paralysis</td>
</tr>
<tr>
<td>Graves' disease (hyperthyroidism)</td>
<td>TSH receptor</td>
<td>Antibody-mediated stimulation of TSH receptors</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor</td>
<td>Antibody inhibits binding of insulin</td>
<td>Hyperglycemia, ketoacidosis</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Intrinsic factor of gastric parietal cells</td>
<td>Neutralization of intrinsic factor, decreased absorption of vitamin B₁₂</td>
<td>Abnormal erythropoiesis, anemia</td>
</tr>
</tbody>
</table>

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

The presence of auto-antibodies can also represent an epiphenomenon 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

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

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

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!

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

no evidence for classification as AID!
Autoimmune diseases: Role of genetic background: MHC alleles

Associations of AID with particular HLA-DR alleles:

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

*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**

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

**Abbreviations:** AIRE, autoimmune regulator gene; IL-2, interleukin-2; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; SHP-1, SH2-containing phosphatase-1.
Autoimmune diseases: Pathogenic role of microbial infections

Potential mechanisms for pathogen-triggered induction of autoimmunity:

- molecular mimicry

<table>
<thead>
<tr>
<th>AID</th>
<th>Cross-reacting sequences</th>
<th>Origin of Peptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAE</td>
<td>YGSLPQKSORQDDEN</td>
<td>Rat MBP</td>
</tr>
<tr>
<td></td>
<td>YGCLPRNPRTEDQ</td>
<td>Chlamydia pneumoniae protein</td>
</tr>
</tbody>
</table>

| Lyme arthritis | VVLEDGTA                      | Human LFA-1      |
|               | YVIEGSTQ                     | Borrelia burgdorferi OspA protein |

| MS | VVHFKNIV                      | Human MBP     |
|    | VYHFVKKHV                      | EBV protein |

| RF | QKMRRDLDEE                    | Human myosin     |
|    | KGLRRLDLDA                    | Streptococcus cell wall M protein |

- 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
### Pro:

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

Human disease:

• for most AID, no firm causal relationship with a specific pathogen exists
• “hygiene hypothesis”: increasing incidence of hypersensitivity diseases in developed countries

Can infections even protect from AID ?!
The hygiene hypothesis re-visited: The diet-microbiota hypothesis!

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 in 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?

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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 $T_{reg}$ in preventing onset of autoimmunity

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

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 generally innocuous (self- or foreign) antigen” (Tak W. Mak)

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

Examles for type IV
- chronic DTH
- chronic graft rejection
- autoimmunity

T cells directed against
- conventional foreign antigen
- allo-antigen in donor tissue
- self-antigen in target tissue

Tissue damage observed
- granuloma formation
- destruction of donor cells, fibrosis
- 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)
donset between 15-40 years; from first symptoms to diagnosis: > 2 years

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


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

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 $T_{\text{regs}}$?

- 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 $T_{\text{reg}}$ cells or TGFβ, IL-10 and CTLA-4 in preventing intestinal inflammation.

| CD25-depleted CD4 T cells | CD25-depleted CD4 T cells + CD25$^+$ CD4$^+$ $T_{\text{regs}}$ | CD25-depleted CD4 T cells + CD25$^+$ CD4$^+$ $T_{\text{regs}}$ | IL-10$^{-/-}$ TGFβ$^{-/-}$ CTLA4$^{-/-}$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>lymphopenic mouse</td>
<td>lymphopenic mouse</td>
<td>lymphopenic mouse</td>
<td>(spontaneous) colitis</td>
</tr>
<tr>
<td>colitis</td>
<td>no colitis</td>
<td>colitis</td>
<td></td>
</tr>
</tbody>
</table>
Inflammatory bowel diseases: Role for a defect in Tregs?

however:

in human IBD, CD4+ CD25+ Foxp3+ T cells are actually increased

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

where does tolerance fail then?
**Inflammatory bowel diseases: Role for genetic factors**

Experimental models of (spontaneous) IBD:

<table>
<thead>
<tr>
<th>Defective mucus layer</th>
<th>Muc2−/− mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired epithelial cell function</td>
<td>IEC-specific deletion of IKKγ</td>
</tr>
<tr>
<td>Aberant APC activation</td>
<td>STAT3−/− macrophages</td>
</tr>
<tr>
<td>Defect in regulatory T cells</td>
<td>IL-10−/−, TGFβ−/−, IL-2−/− mice</td>
</tr>
</tbody>
</table>

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 alleles Crohn’s disease

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

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?

**ATG16L1**
- Impaired anti-bacterial autophagy?
- Impaired Paneth cell exocytosis?

**IL-23R**
- Impaired IL-22 production in innate lymphoid cells?
- Decreased antimicrobial peptide expression by epithelial cells?

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!)

Impaired neutrophil accumulation in CD patients

i.v. injection of $^{111}$Indium-labeled neutrophils simultaneous s.c. injection of killed E. Coli
Crohn’s disease: an innate immune deficiency disease?

More circumstantial evidence:

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

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

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 😊
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