Immune Regulation and Tolerance

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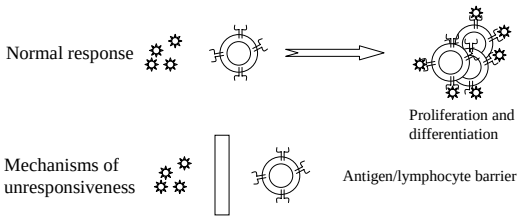
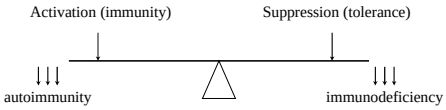
Mechanisms of unresponsiveness:
Immunological Ignorance



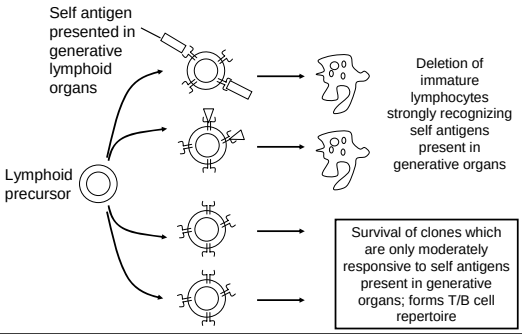
Mechanisms of autoimmunity	Tissue abnormalities contributing to release and presentation of self antigens.
Disease models	Sympathetic ophthalmia, experimental allergic encephalomyelitis (EAE)

Immunoregulation: A balance between activation and suppression of effector cells to achieve an efficient immune response without damaging the host.



Significance: The induction of tolerance may be exploited to prevent graft rejection, to treat autoimmune and allergic diseases, and to prevent immune responses in gene therapy.

Mechanisms of unresponsiveness:
Central tolerance in B and T cells (I): Clonal Deletion



Important features of immunoregulation:

1. Antigen specific; affects T or B lymphocytes
2. Tolerance vs. activation? Determined by the nature of antigen and associated stimuli, and when and where the antigen is encountered

Projection of an Immunological Self Shadow Within the Thymus by the Aire Protein

Mark S. Anderson,[1] Emily S. Venanzi,[1] Ludger Klein,[2] Zhibin Chen,[1] Stuart P. Berzins,[1] Shannon J. Turley,[1] Harald von Boehmer,[2] Roderick Bronson,[3] Andrée Dierich,[4] Christophe Benoist,[1]* Diane Mathis[1]*

Science 298:1395 (2002)

The Cellular Mechanism of Aire Control of T Cell Tolerance

Mark S. Anderson,[1,2] Emily S. Venanzi,[1] Zhibin Chen,[1] Stuart P. Berzins,[1,3] Christophe Benoist,[1,*] and Diane Mathis[1,*]

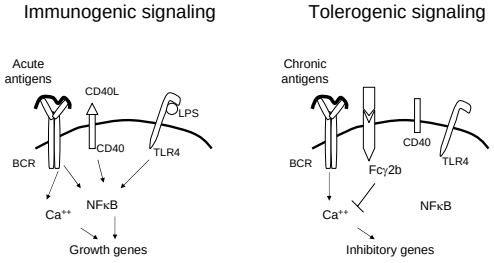
Immunity 23:227 (2005)

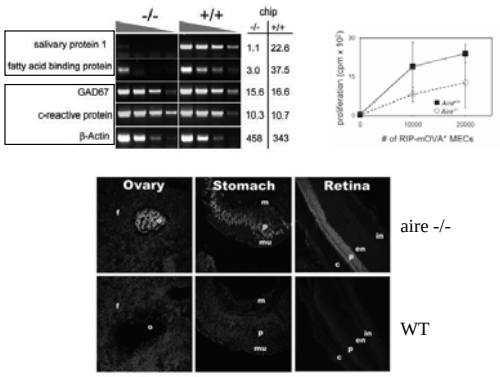
AIRE: Autoimmune regulator.

- Transcription factor.
- Expressed at a high level by thymic medullar epithelium cells.
- Autosomal recessive mutation leads to autoimmune polyendocrine syndrom - type 1 (APS-1).
- Inactivation of aire abolishes expression of some tissue specific genes in the thymic medulla.
- AIRE deficiency impairs antigen-presentation ability of medullary epithelial cells.

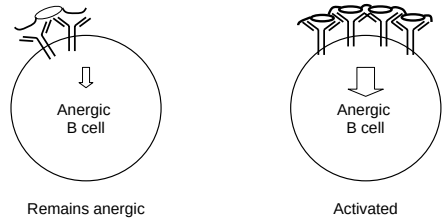
Mechanisms of unresponsiveness:

Peripheral tolerance in B cells (I): Anergy



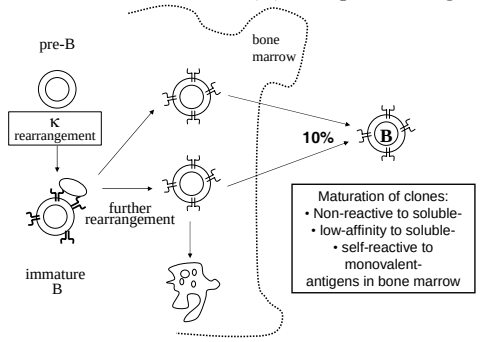


Anergic B cells can respond to "Stronger" antigens



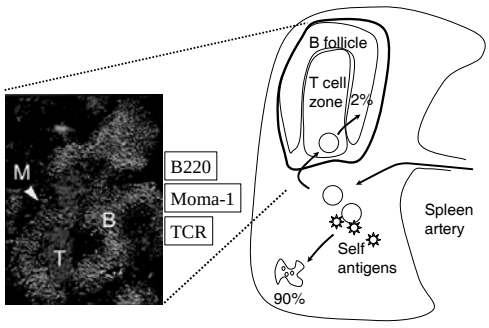
Mechanisms of unresponsiveness:

Central tolerance in B cells (II):Receptor editing



Mechanisms of immune tolerance

Peripheral B cell Tolerance (II): Follicular exclusion



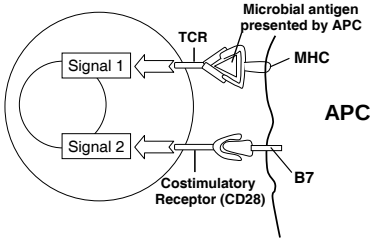
Mechanisms of unresponsiveness:

Peripheral tolerance in B cells (II): Follicular exclusion

- B cells binding to autoantigens in the periphery may be excluded from follicles.
- Excluded B cells undergo apoptosis independent of Fas and T cells.
- Rapid elimination depends on the presence of a normal repertoire of B cells.

competition between B cells for BAFF

The two-signal requirement for T cell activation

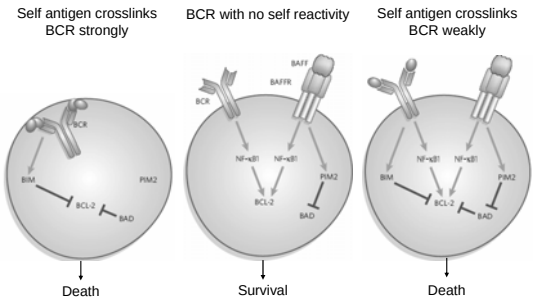


BAFF: B-cell activating factor belonging to TNF family.

- TNF family proteins, expressed by stromal cells in the spleen.
- Plays a critical role as a survival factor for mature B cells.
- BAFF transgenic mice develop autoimmune disorder.

Two-signal requirement for lymphocyte activation

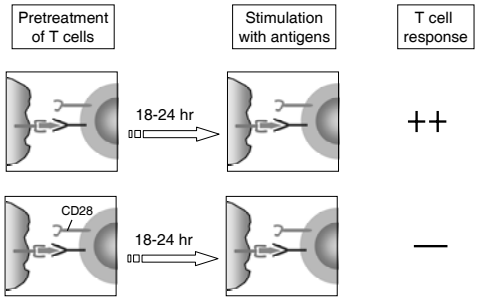
- Naïve lymphocytes need two signals to initiate responses
- Signal 1: antigen recognition
  → Ensure that the immune response is antigen-specific
- Signal 2: microbes or substances produced during innate immune responses to microbes
  → Ensure that the immune system responds to microbes and not to harmless antigenic substance
  (Second signals for T cells are costimulators on APCs and cytokines produced by APCs.)



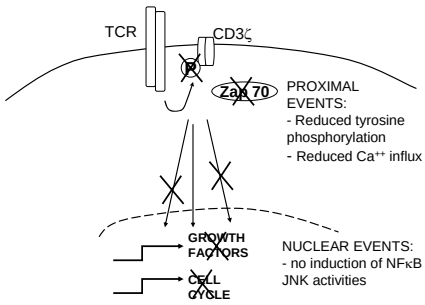
Nature 435:590 (2005)

Mechanisms of unresponsiveness:

Peripheral tolerance in T cells (II): Anergy



Molecular basis of anergy in T lymphocytes



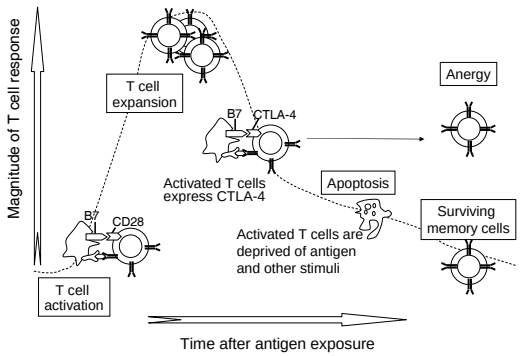
How do T cells choose between CD28 and CTLA-4?

- Kinetics: B7 on APCs engages CD28 early, CTLA-4 late in T cell responses.
- Level of B7 expression on APCs: low levels favor CTLA-4 engagement (high affinity receptor).

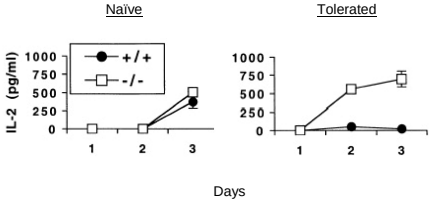
Co-stimulatory pathways

- CD28 interacts with CD80 (B7-1) CD86 (B7-2) to initiate T cell responses.
  Preferentially expressed in naive T cells
- ICOS (CD28 homolog) stimulate effector T cell responses.
  Preferentially expressed in activated T cells
- CTLA-4 and PD-1 inhibit T cell activation

Regulation of T cell homeostasis during immune responses



CTLA-4$^{-/-}$ T cells resist tolerance induction

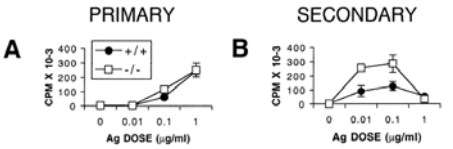


Mechanisms of immune tolerance:
Peripheral T cell tolerance (III): Activation-induced cell death (AID)

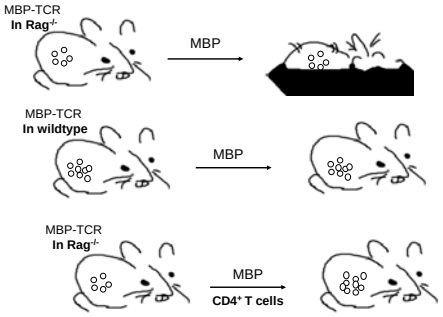
To prevent over-expansion of the activated T cells

Control homeostasis of T cell responses

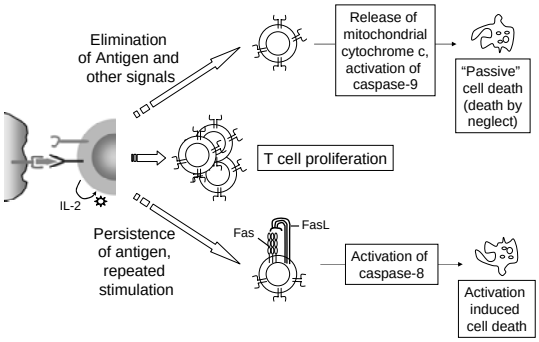
Enhanced proliferation of activated CTLA4$^{-/-}$ T cells



T cell mediated suppression



Pathways of apoptosis in T cells



Regulatory T cells (T_{reg}) in self tolerance

- **Phenotype and functions:**
  - CD4$^+$CD25$^+$ cells, develop in the thymus.
  - Recognize self-antigens.
  - Express Foxp3. Foxp3 mutation causes the early onset of fatal autoimmune disorder observed in scurfy mutant mice and human IPEX patients (immune dysregulation, polyendocrinopath, enteropathy, X-linked syndrome).
  - Prevent T-cell activation; supress cell proliferation and IL-2 production.

Mechanisms of immune tolerance:
Peripheral T cell tolerance (IV): Suppression by T_{reg}

Neonate thymectomy --> Autoimmune diseases

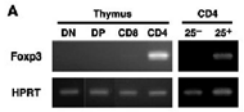
1. The disease is transferable by T cells.
2. The disease can be prevented by delayed thymectomy or by transplantation of normal CD4$^+$ T cells.

Control of Regulatory T Cell Development by the Transcription Factor *Foxp3*

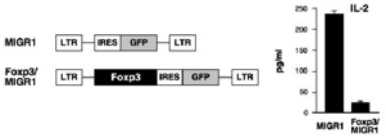
Shohei Hori,[1] Takashi Nomura,[2] Shimon Sakaguchi[1,2]*

Science (2003) 299:1057

• Foxp3 is expressed specifically in T_R



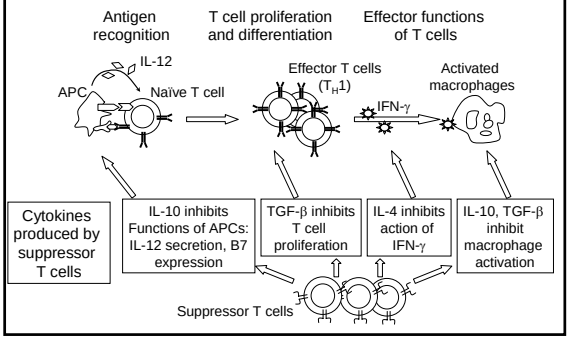
• Expression of Foxp3 converts naïve $CD4^+$ T cells to T_R



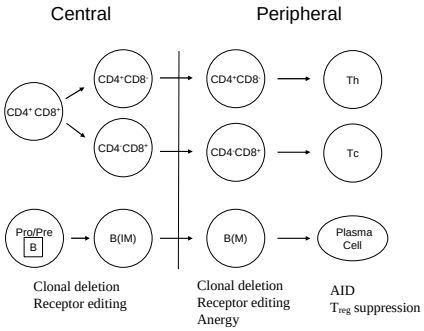
Conclusions: Tolerance *vs.* Immunity

- Immune responses are the outcome of a balance between the need to make a protective response and the need to maintain self-tolerance
- Mechanisms of unresponsiveness:
  - Central tolerance: Deletion; Receptor editing
  - Peripheral tolerance: Clonal ignorance; Clonal deletion; Anergy; Suppression

Role of cytokines in suppression of cell-mediated immune responses



Mechanisms of immune tolerance:



Mechanisms of immune tolerance:

Peripheral T cell tolerance (IV): Suppression by T_{reg}