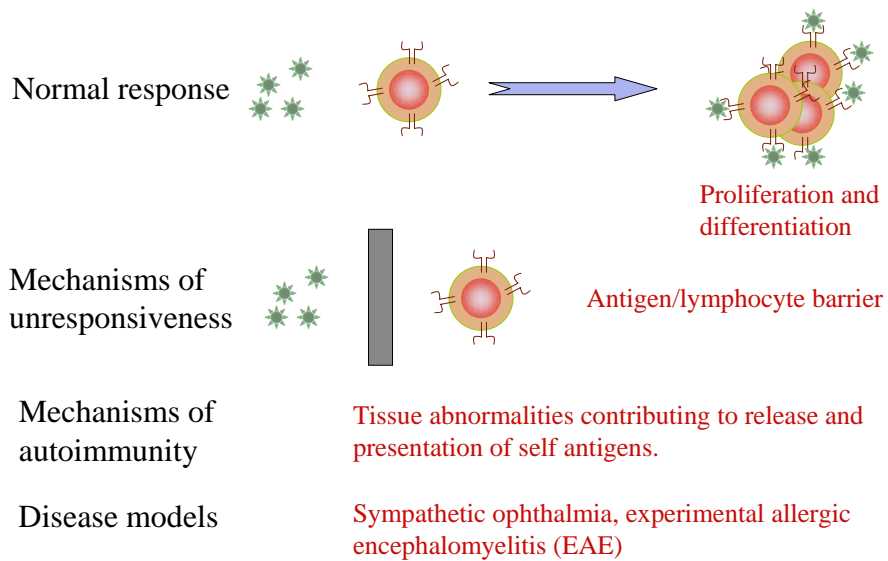




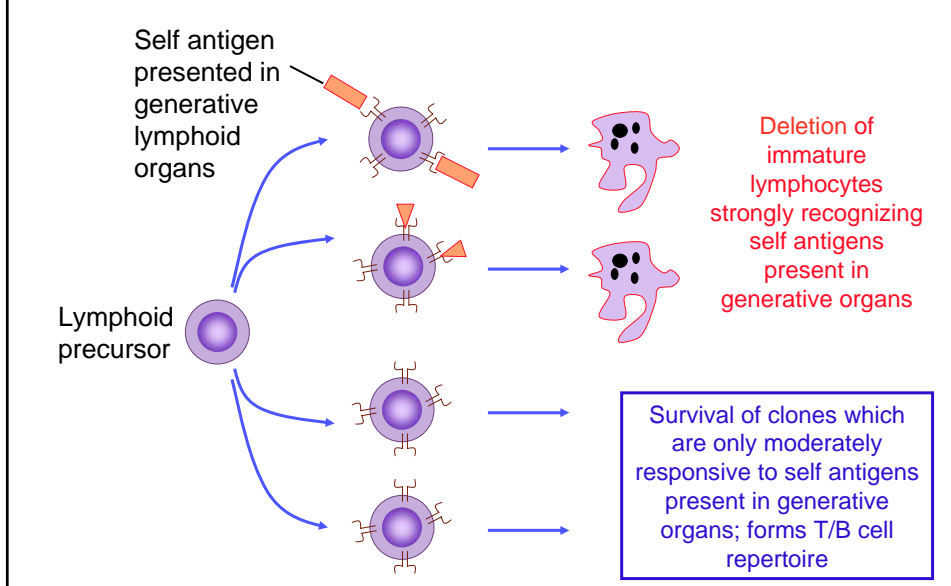
**Important features of immunoregulation:**

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

**Mechanisms of unresponsiveness:  
Immunological Ignorance**



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



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

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

Science 298:1395 (2002)

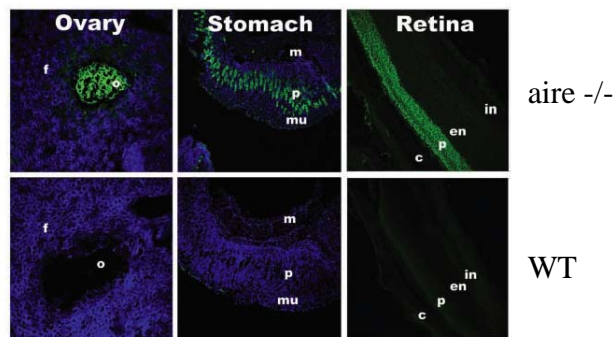
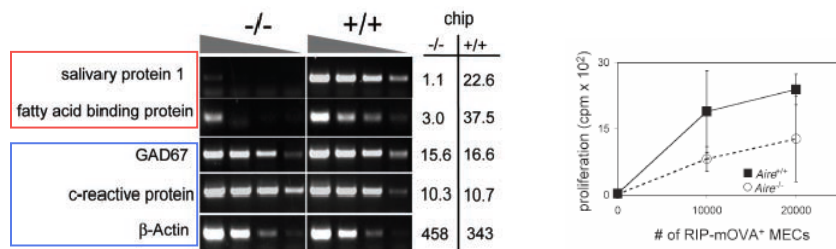
**The Cellular Mechanism of Aire Control of T Cell Tolerance**

Mark S. Anderson,<sup>1,2</sup> Emily S. Venanzi,<sup>1</sup>  
 Zhibin Chen,<sup>1</sup> Stuart P. Berzins,<sup>1,3</sup>  
 Christophe Benoist,<sup>1,\*</sup> and Diane Mathis<sup>1,\*</sup>

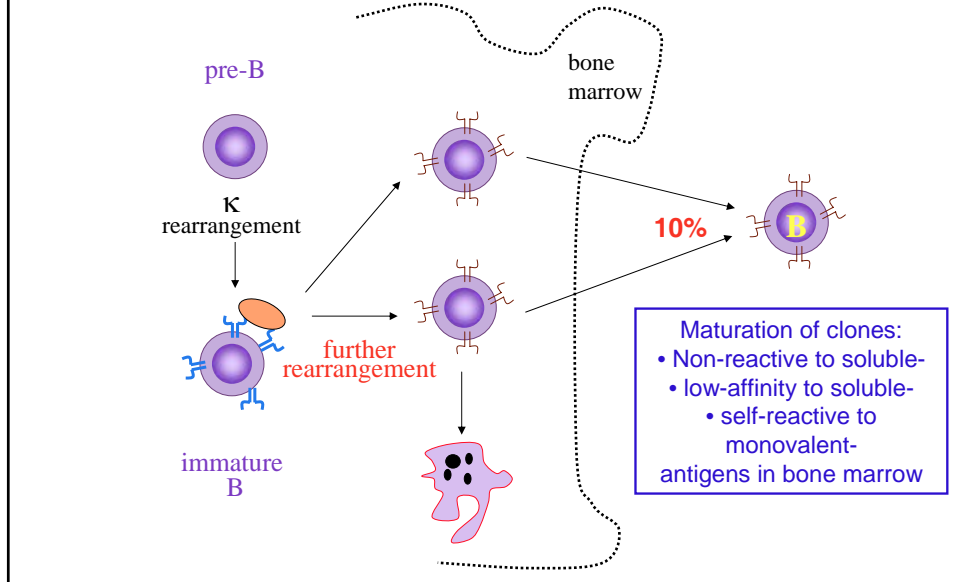
Immunity 23:227 (2005)

AIRE: Autoimmune regulator.

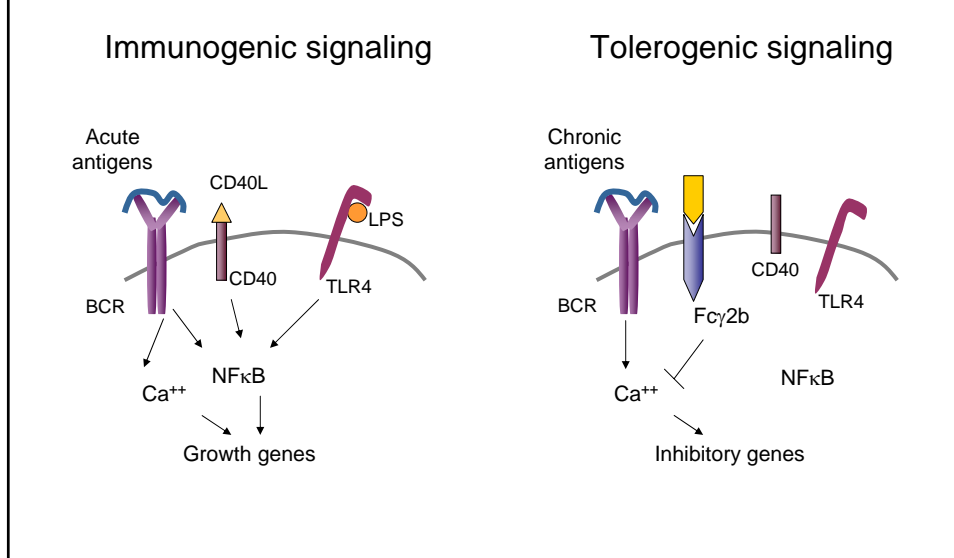
- Transcription factor.
- Expressed at a high level by thymic medullar epithelium cells.
- Autosomal recessive mutation leads to autoimmune polyendocrine syndrom - type 1 (APS-1).
- Inactivation of aire abolishes expression of some tissue specific genes in the thymic medulla.
- AIRE deficiency impairs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



Mechanisms of unresponsiveness:  
Central tolerance in B cells (II): Receptor editing

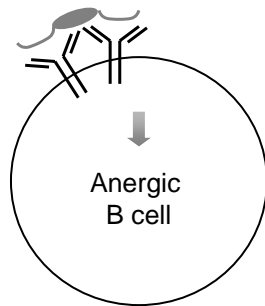


Mechanisms of unresponsiveness:  
Peripheral tolerance in B cells (I): Anergy



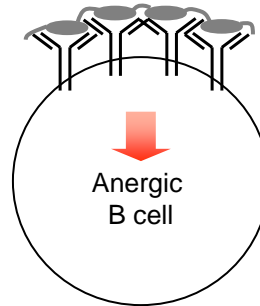
## Anergic B cells can respond to “Stronger” antigens

Oligovalent self antigens  
Constitutively exposed



Remains anergic

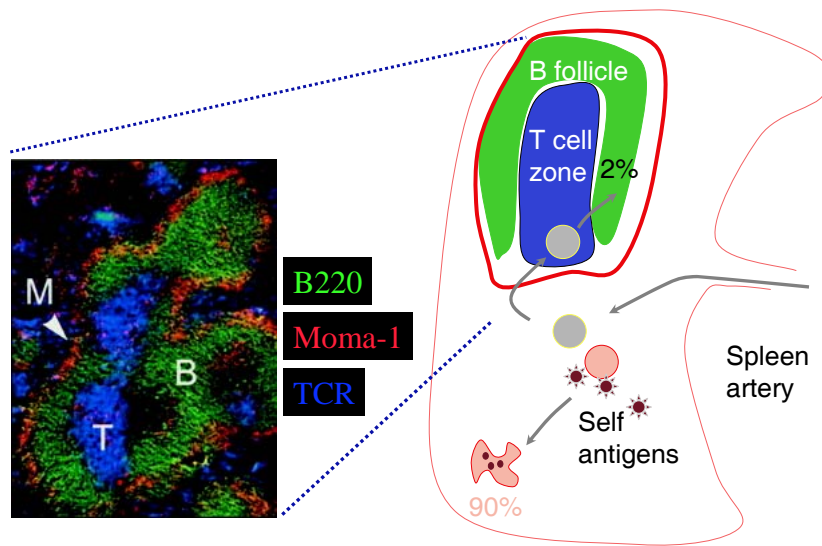
Multivalent foreign antigens  
Acutely exposed



Activated

## Mechanisms of immune tolerance

### Peripheral B cell Tolerance (II): Follicular exclusion

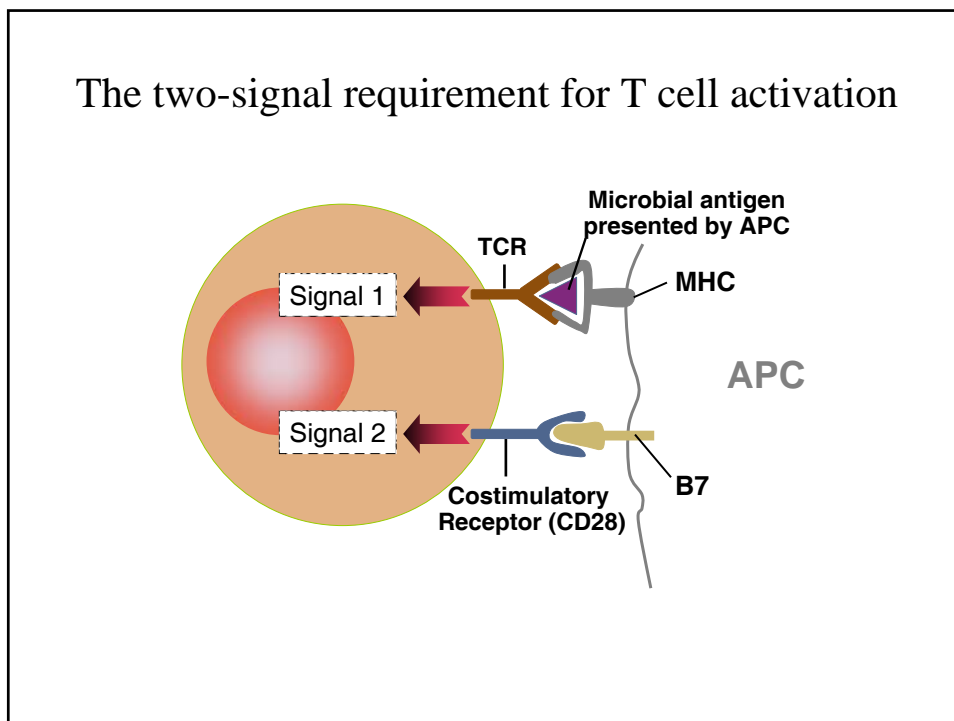
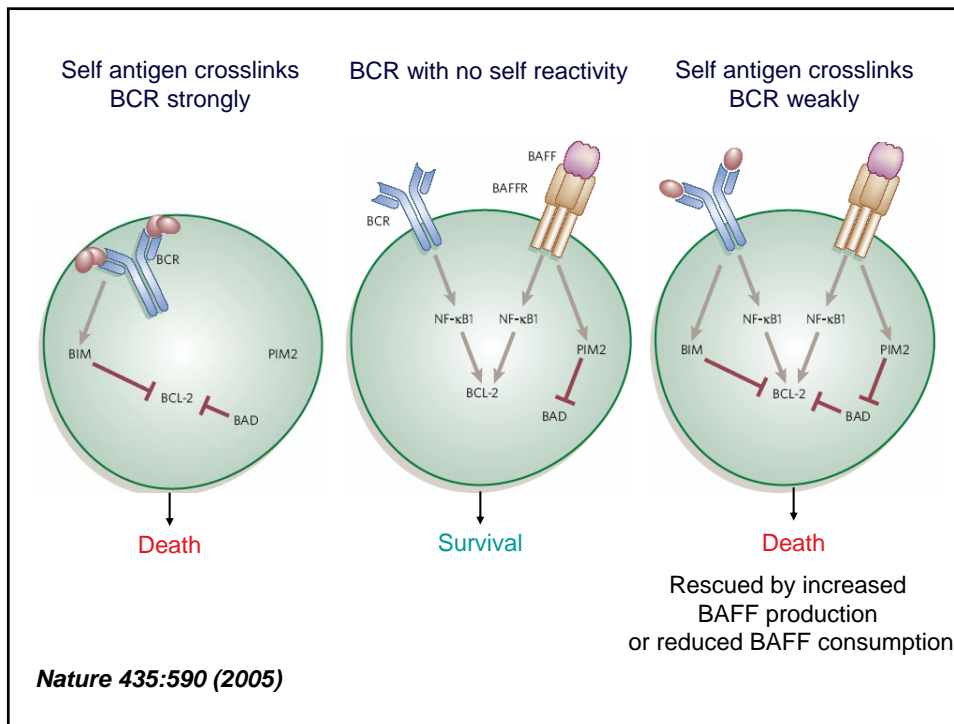


Mechanisms of unresponsiveness:  
Peripheral tolerance in B cells (II): Follicular  
exclusion

- 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*

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.

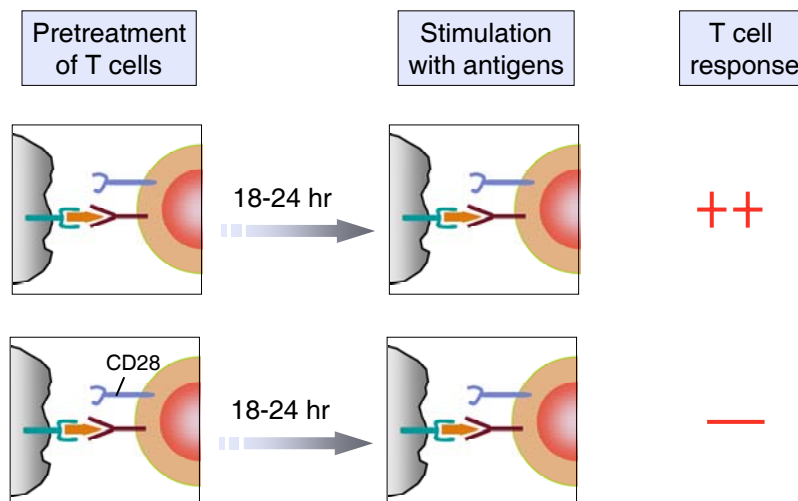




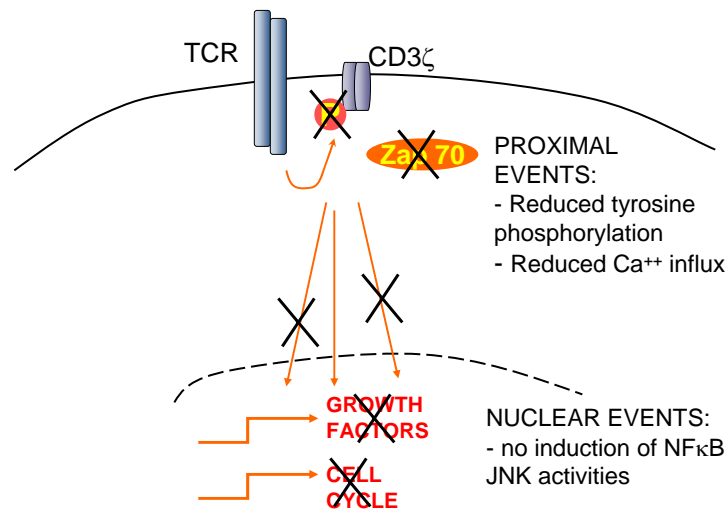
**Two- signal requirement for lymphocyte activation**

- 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 response 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.)

**Mechanisms of unresponsiveness:  
Peripheral tolerance in T cells (II): Anergy**



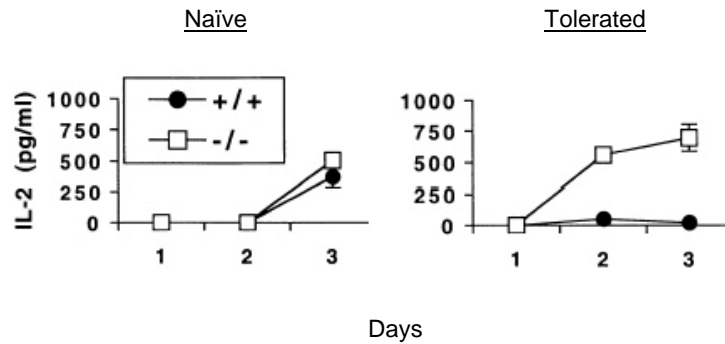
## Molecular basis of anergy in T lymphocytes



## Co-stimulatory pathways

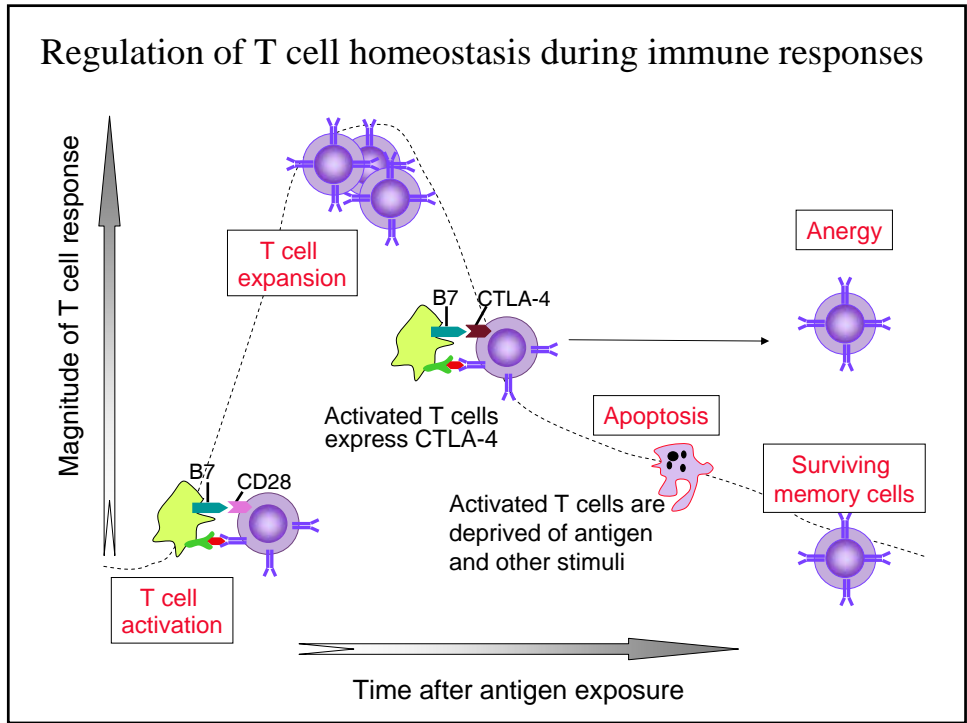
- CD28 interacts with CD80 (B7-1) CD86 (B7-2) to initiate T cell responses.  
Preferentially expressed in naive T cells
- ICOS (CD28 homolog) stimulate effector T cell responses.  
Preferentially expressed in activated T cells
- CTLA-4 and PD-1 inhibit T cell activation

## CTLA-4<sup>-/-</sup> T cells resist tolerance induction



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

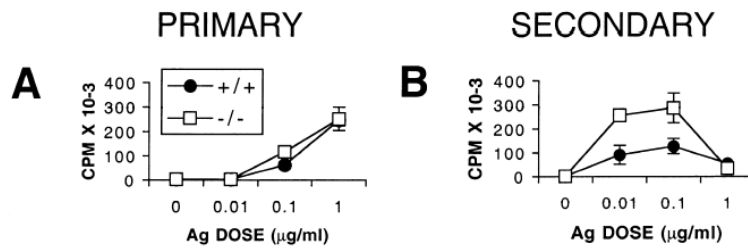
- Kinetics: B7 on APCs engages CD28 early, CTLA-4 late in T cell responses.
- Level of B7 expression on APCs: low levels favor CTLA-4 engagement (high affinity receptor).



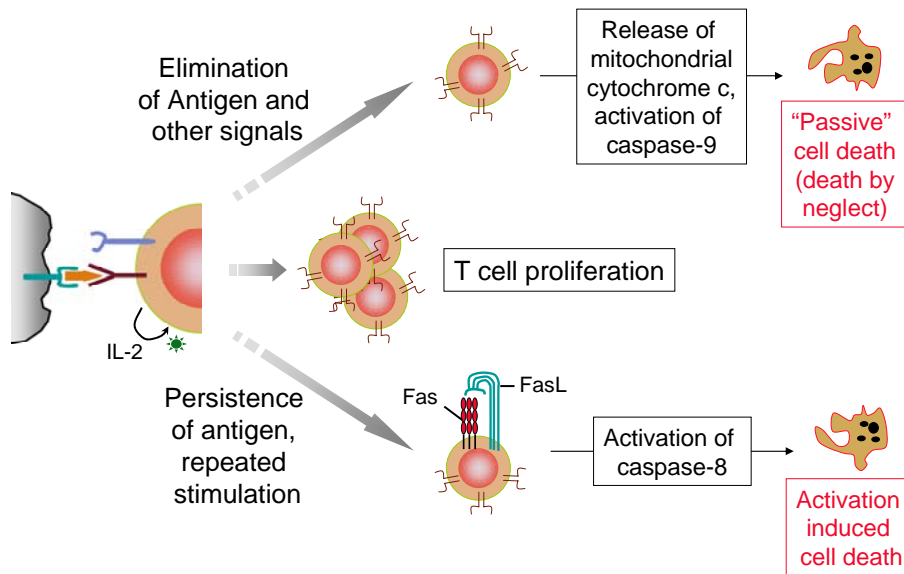
Mechanisms of immune tolerance:  
Peripheral T cell tolerance (III): [Activation-induced cell death \(AID\)](#)

To prevent over-expansion of the activated T cells  
 Control homeostasis of T cell responses

## Enhanced proliferation of activated CTLA4<sup>-/-</sup> T cells



## Pathways of apoptosis in T cells

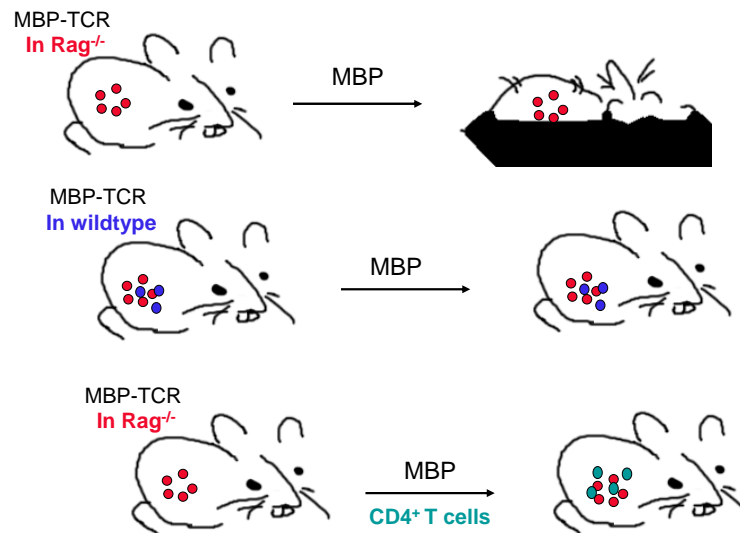


Mechanisms of immune tolerance:  
Peripheral T cell tolerance (IV): Suppression by T<sub>reg</sub>

**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<sup>+</sup> T cells.

T cell mediated suppression



## Regulatory T cells (T<sub>reg</sub>) in self tolerance

- **Phenotype and functions:**

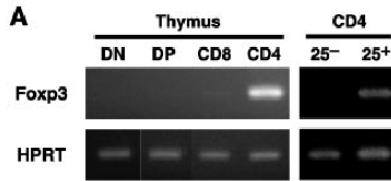
- CD4<sup>+</sup>CD25<sup>+</sup> cells, develop in the thymus.
- Recognize self-antigens.
- Express Foxp3. Foxp3 mutation causes the early onset of fatal autoimmune disorder observed in scurfy mutant mice and human IPEX patients (immune dysregulation, polyendocrinopath, enteropathy, X-linked syndrome).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

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

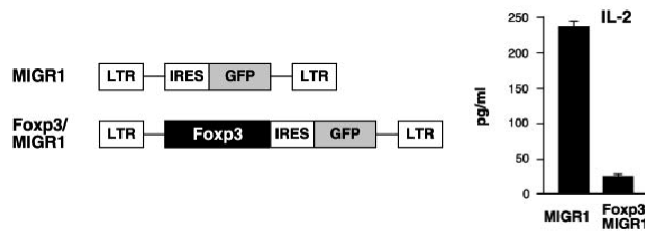
Shohei Hori,<sup>1</sup> Takashi Nomura,<sup>2</sup> Shimon Sakaguchi<sup>1,2\*</sup>

*Science* (2003) 299:1057

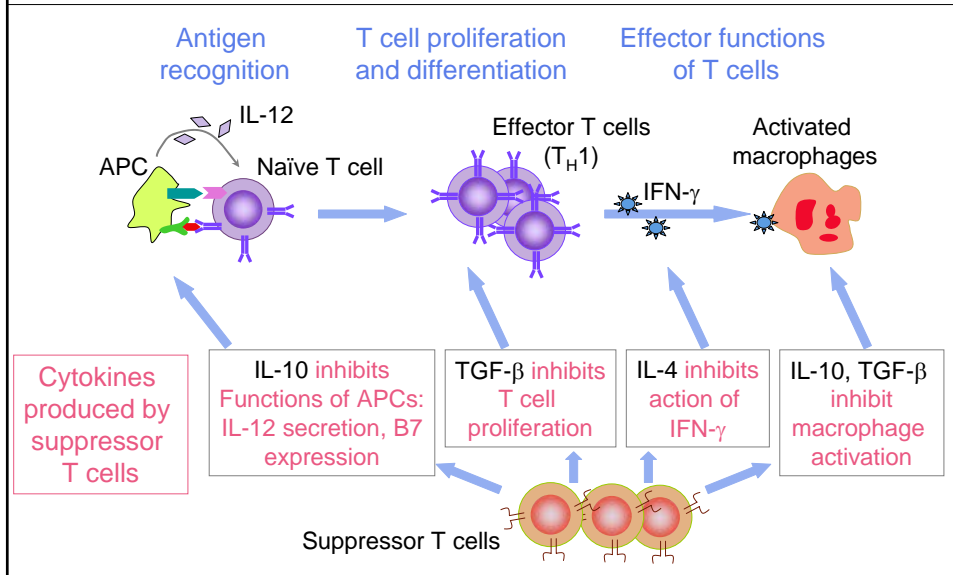
- Foxp3 is expressed specifically in  $T_R$



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

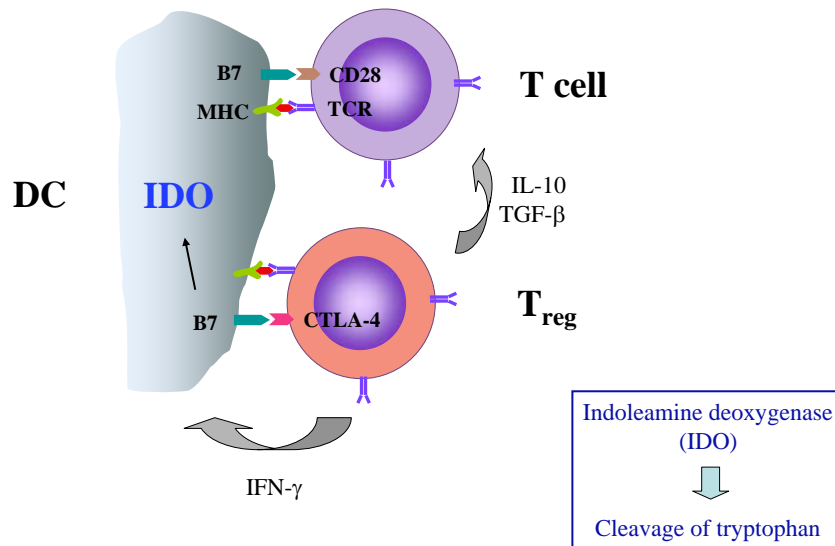


## Role of cytokines in suppression of cell-mediated immune responses





Mechanisms of immune tolerance:  
Peripheral T cell tolerance (IV): **Suppression by T<sub>reg</sub>**



## 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

Mechanisms of immune tolerance:

