Immune Regulation

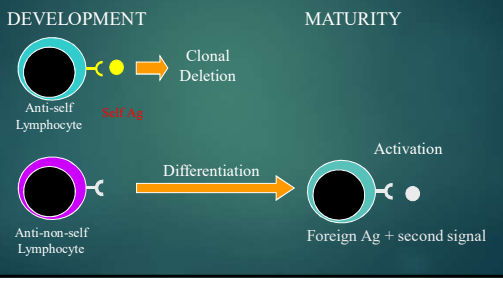
Immune regulation

- How the Immune System Maintains the Delicate Balance Between Effective Defense and Auto-immunity.
  - To accelerate or to brake?
  - Where to kill?
  - Which cell to kill?
  - How to maintain the diversity in the arsenal while avoiding self-destruction?

Concept of Immune Regulation

- Immune responses are tightly regulated complex interaction of cells & mediators through mechanisms that prevent anti-self reactivity
- Failure of regulatory control can occur leading to:
  - Enhancement of immune responses or infection generating autoimmune reactions (loss of self–tolerance)
  - Decrease of immune responses leading to immunodeficiency state
  - Shift in immune responses leading to allergy

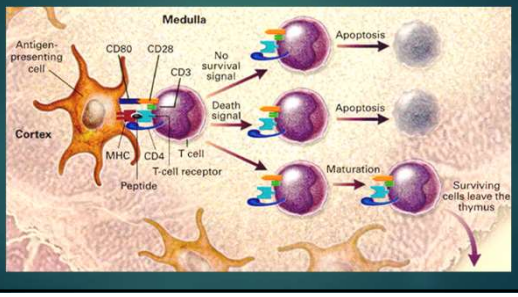
Burnet's Clonal Selection Model: Central Tolerance



Immunological Tolerance

- Definition and Properties
  - Specific unresponsive state induced by exposure to antigenic epitopes
    - Tolerance to self is initially induced during embryonic life, and is maintained by antigen
    - Tolerance occurs in both T and B cells
    - Multiple mechanisms of tolerance exist

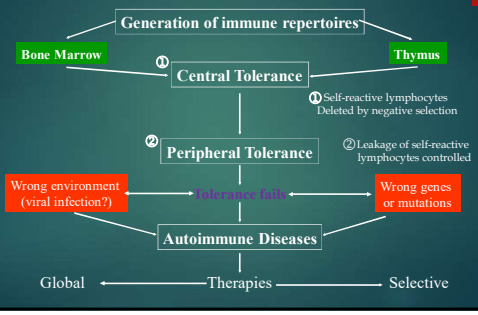
Central Tolerance



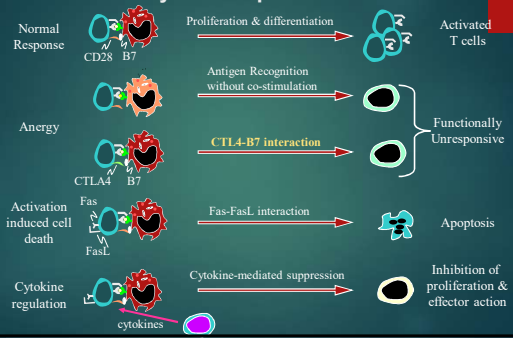
Mechanisms of Immunological Tolerance - Overview

- Central Tolerance through Clonal Deletion
  - Clones of cells that have receptors for self-antigens are deleted during development
- Peripheral Tolerance
  - Clonal Anergy-failure of APC to deliver a second signal during antigen presentation (example: B7-CD28 interaction)
  - Suppression of responses may occur by production of regulatory T cells that inhibit immune response to self-antigen (example: TGF-, IL10 and Th1 vs. Th2 cytokines)
  - Ignorance to some self antigens may also exist

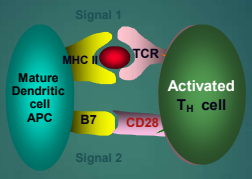
Tolerance: Establishment and Failure



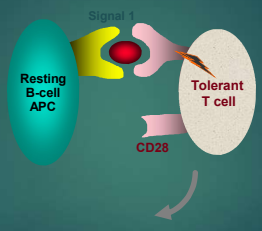
Pathways to Peripheral Tolerance



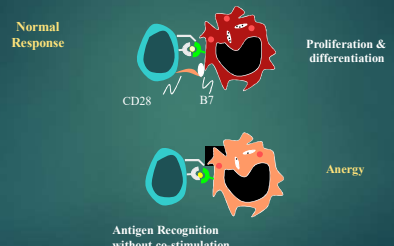
The Two Signal Hypothesis for T-cell Activation



Hypothetical mechanism of tolerance in mature T cells

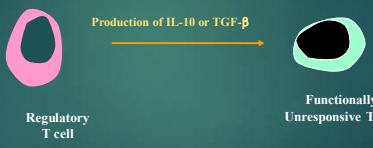


Summary: Lack of co-stimulation can lead to tolerance (anergy)

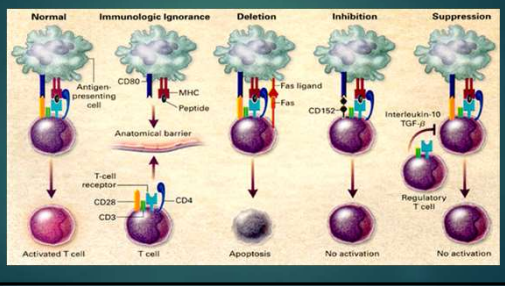


Regulation by CTLA-4

Regulatory T cells



Pathways to Peripheral Tolerance



Inhibition by Antibody Feedback

- Passively administered antibody can prevent an antibody response
- Antibody produced during an immune responses leads to elimination of antigen (stimulus)
  - Less antigen available to stimulate specific cells
  - Immune complexes can bind to inhibitory receptors
  - Application: RhoGam for Erythroblastosis Fetalis

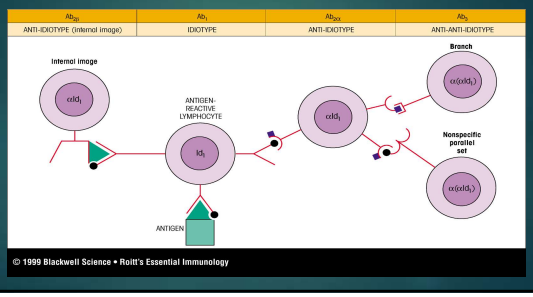
Major Immune Inhibitory Receptors

- B cells
  - FcgRII
- T cells
  - CTLA4
- NK cells
  - KIR (killer cell Ig-like receptors),

Anti-Idiotypes and Immune Regulation

- Definition
  - anti-idiotype response-antibody produced against immunoglobulin or TCR idiotypes that serve to down-regulate immune response
  - The epitope for an responsive anti-idiotype molecule (antibody, BCR, or TCR) is the internal image formed by the CDR region of the respective epitopes antigen receptor

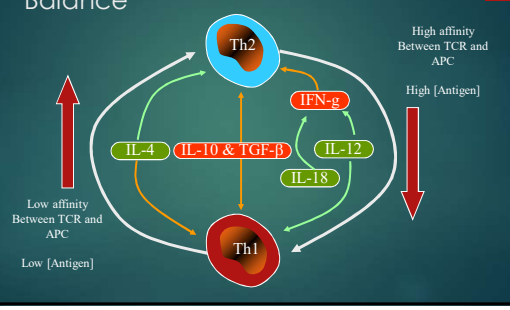
Idiotype/Anti-idiotype network



Cytokines and Immune Regulation

- Definition
  - Soluble mediators
  - Made by a variety of cells
  - Multifunctional proteins and peptides
    - Involved in initiating immune response
    - Involved in turning off immune response
    - Some serve as direct effector molecules (e.g., TNFα)

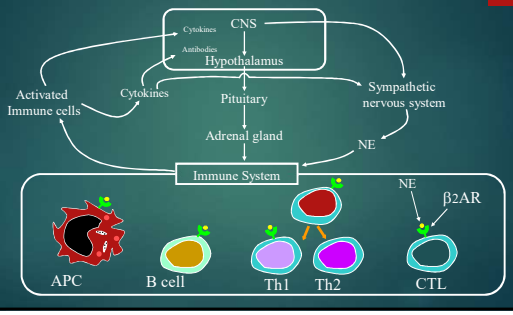
Cytokine Regulation via T_H1 – T_H2 Balance



Th1 versus Th2 Balance

Disease	Th1	Th2
Experimental Leishmaniasis	**Cure**	Progression
Experimental autoimmune encephalomyelitis	Progression	**Prevention**
Tuberculosis	**Cure/Prevention**	Progression
Atopy	**Prevention?**	Progression
Type 1 Diabetes (NOD)	Progression	**Prevention**

CNS–Immune System Interactions



Immunosuppression (adapted from Roitt)