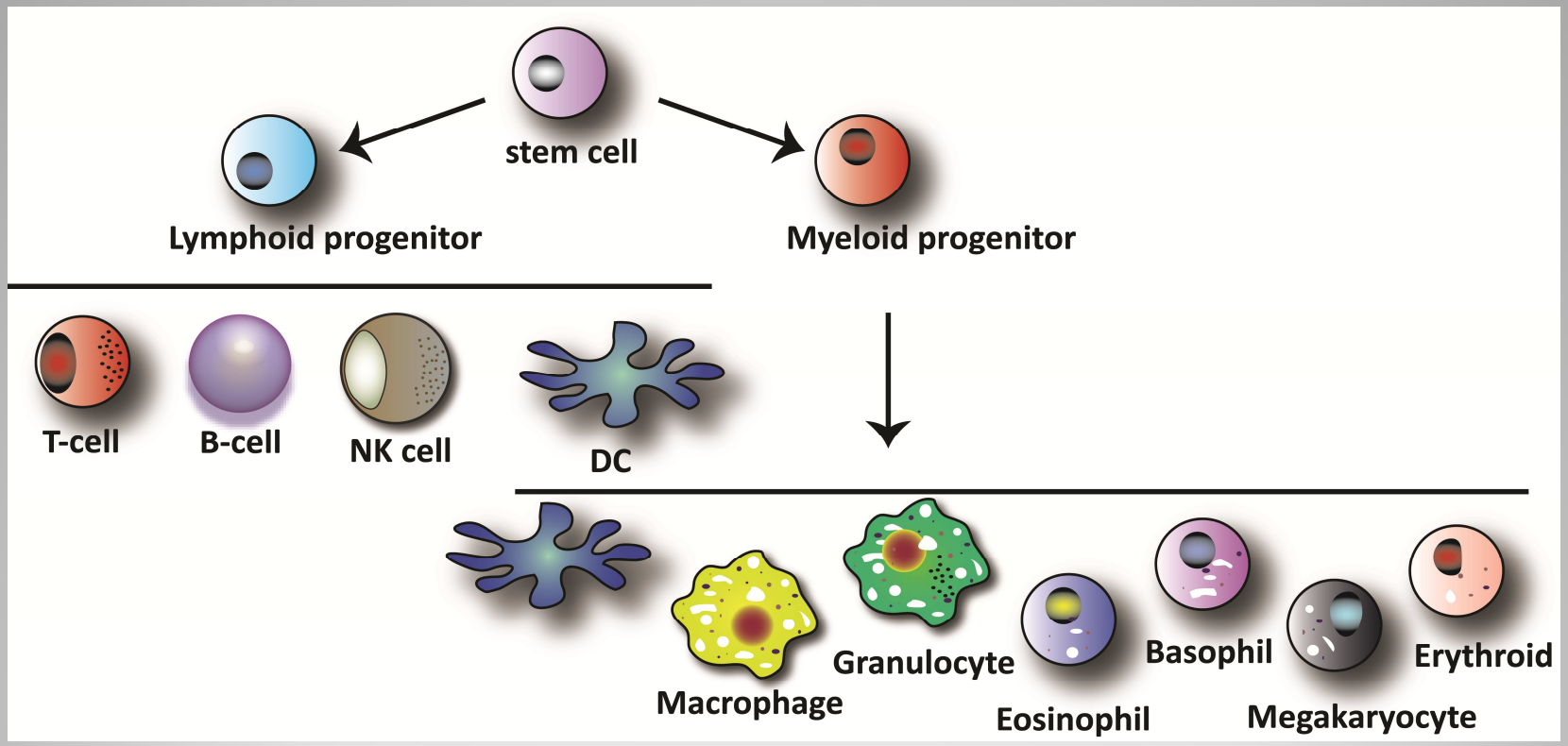
Advances in Cancer Immunotherapy

Immunology 101 for the Non-Immunologist
December 7, 2013



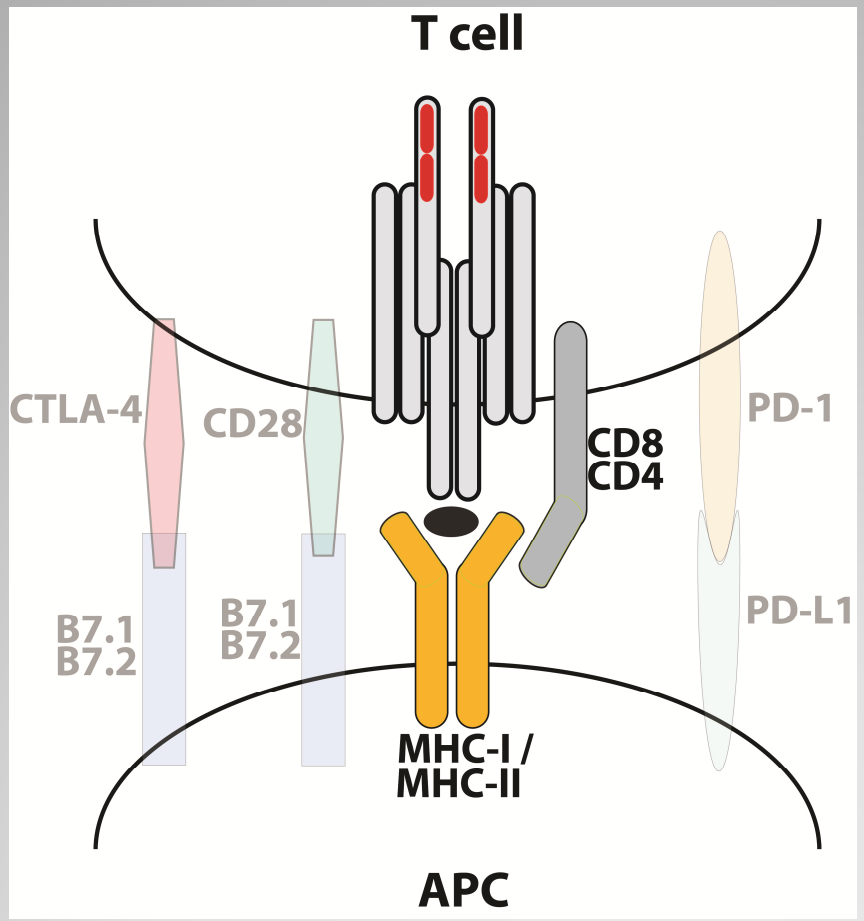
Cellular Origin

Innate vs Adaptive

- **Innate immunity:**
  - Resistance that exists before infection
  - First line of defense
  - Broad specificity
    - Macrophages
    - Neutrophils
    - Eosinophils
    - NK cells
- **Adaptive Immunity:**
  - Antigen specific receptors
  - Respond to antigen stimulation with proliferation and differentiation
  - Gives rise to immunologic memory
    - T lymphocyte
    - B lymphocyte – antibody producing cells
    - Professional Antigen Presenting Cells (APC)

Adaptive Immunity

- **Cellular immunity:**
  - Mediated by T lymphocytes.
  - Require antigen presentation by a professional antigen presenting cell (macrophage, dendritic cell, B cell)
  - CD4+ (helper) T cells: Produce cytokines for activation of other immune cells
  - CD8+ (cytotoxic) T cells: Recognizes and kills specific target cells
- **Humoral immunity:**
  - Antibody-mediated immunity
  - B cells with help from dendritic cells and T helper cells



Virally infected cell
Tumor cell

Dendritic cell
B cell

Antigen Presentation

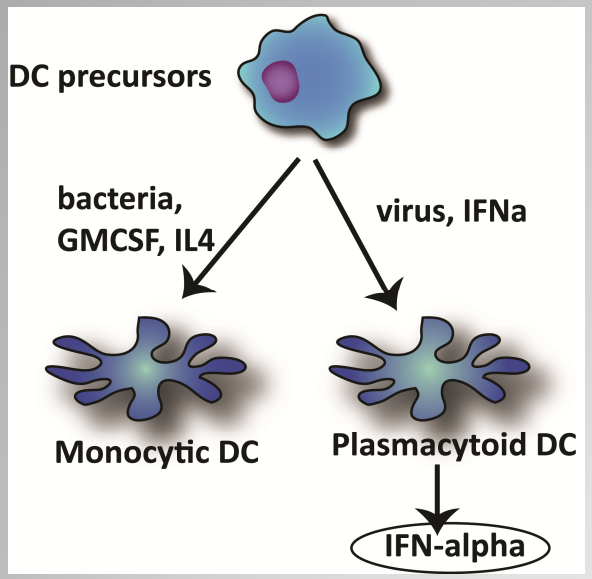
- **Major Histocompatibility Complex (MHC)**
- Present peptides for recognition on the cell surface
  - class I – CD8 T cells
    - Typically peptides derived from endogenous proteins
    - Restricted peptide size (8-11 aa), with anchor residues
  - class II – CD4 T cells
    - Typically peptides derived from exogenous proteins
    - Broader peptide size (1->30 aa), with anchor residues
- Cross presentation

MHC

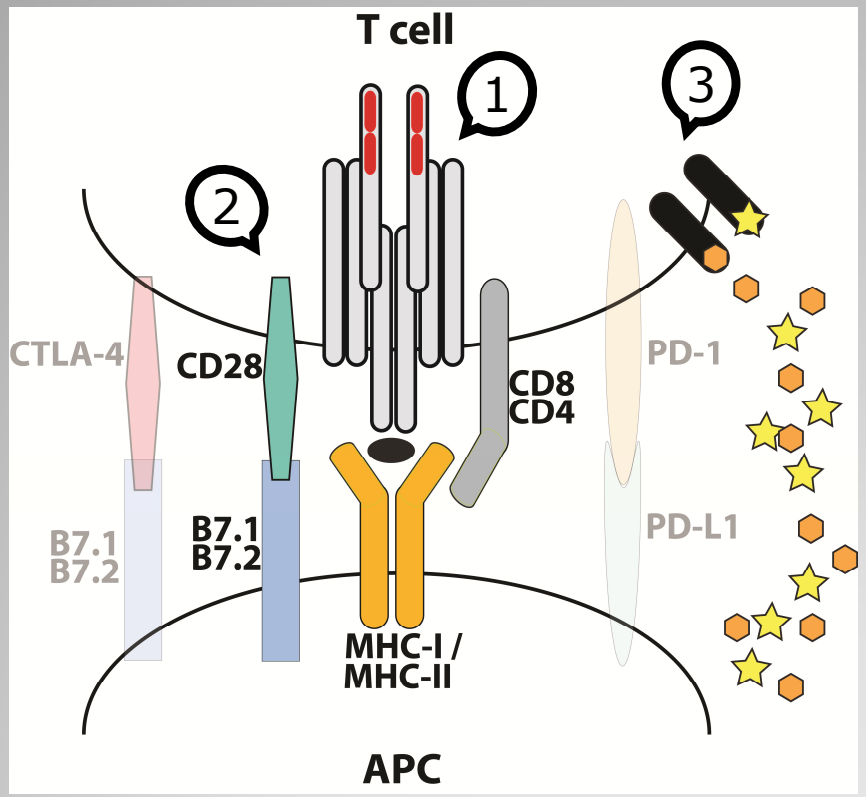
Antigen Presenting cells

- **Types of antigen presenting cells (APC)**
  - Conditional
    - Endothelial cells, Epithelial cells, T-cells
  - Semi-professional
    - B-cells, Macrophages
  - Professional
    - **Dendritic cells**
  - Provide co-stimulation signals (signal 2) and polarization signals (signal 3)

Dendritic cells



- Recognize and respond to many pathogens or non-self molecules
- Express multiple receptors
  - TLRs (TLR1 – TLR11)
    - Recognize common molecular patterns in pathogens
      - TLR3 – dsRNA
      - TLR4 – LPS
      - TLR7 - ssRNA
      - TLR9 – CpG DNA
  - Lectins
    - Facilitate antigen uptake, cell-cell signaling
      - CD206, DC-Sign, ect

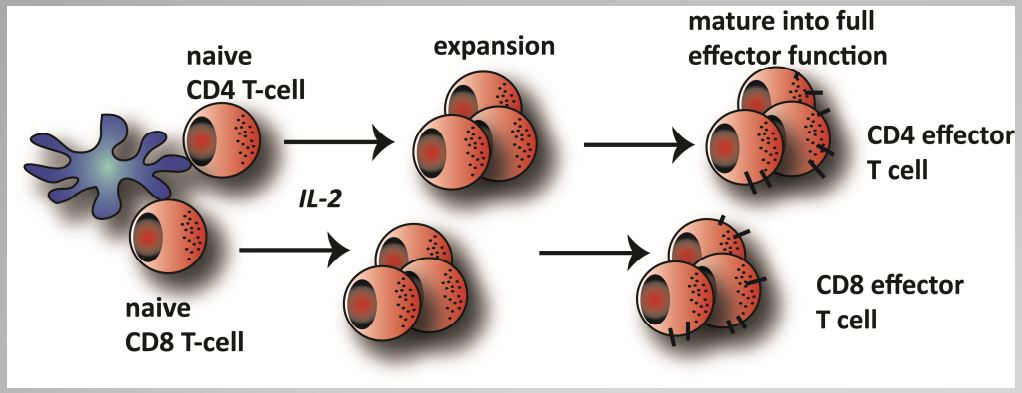


- Signal 1: Identity
- Signal 2: pathogenicity, magnitude
- Signal 3: character, polarization

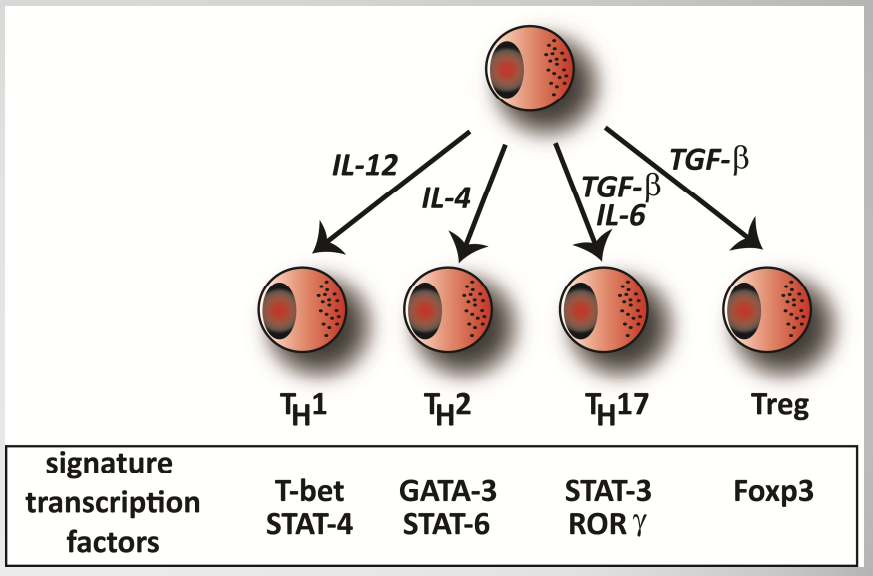
Input		
IFNg, polyI:C, Virus	DC1	Th1
TNFa, LPS	DC0	Th0
PGE2, IL-10, glucocorticoids	DC2	Th2

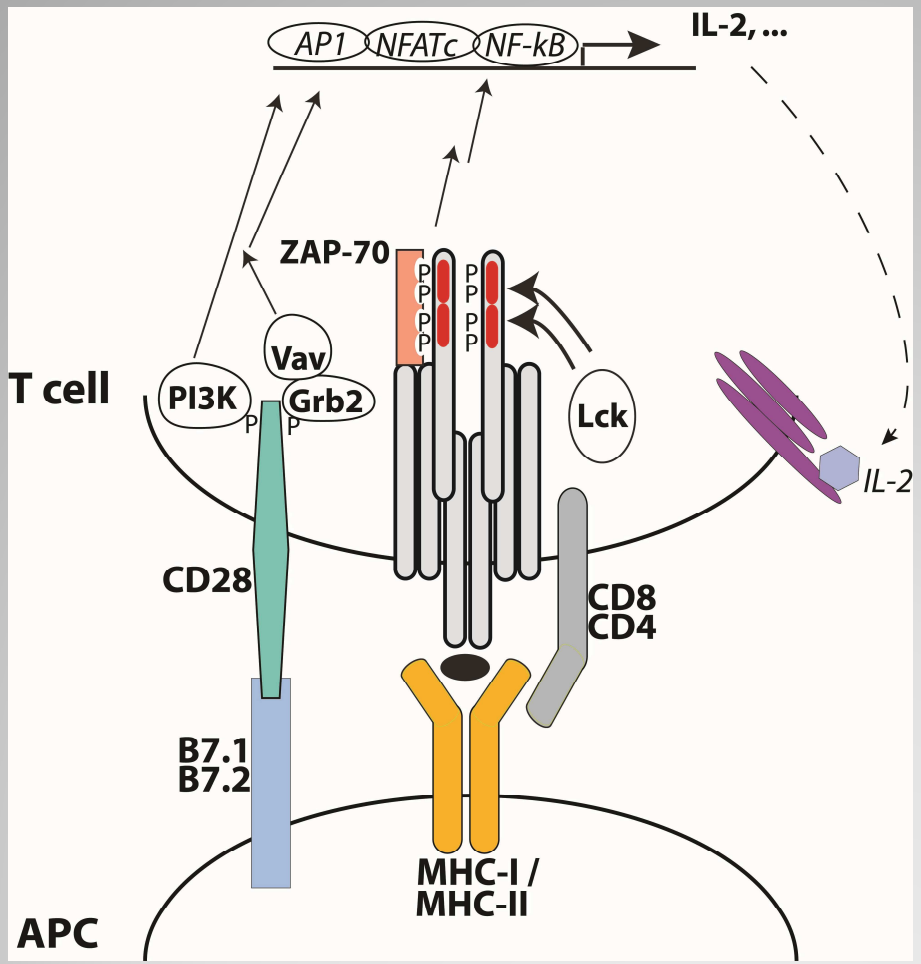
DC Signals

T cell subtypes



- CD4 T cells:
  - Activate B cells, macrophages, CD8 T cells, …
- CD8 T cells:
  - Kill target cells, activate macrophages

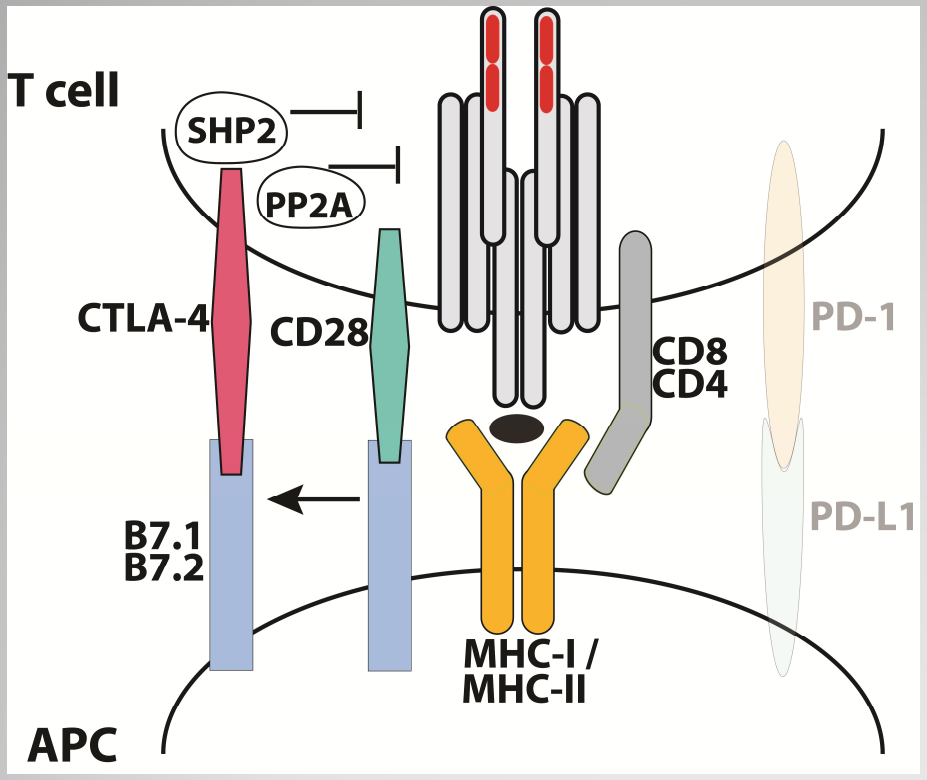




- CD28 - present on resting and naive T cells
  - Binds to CD80 and CD86 (B7.1 and B7.2)
  - Activates the T cells through multiple downstream signals including the PI3-kinase pathway

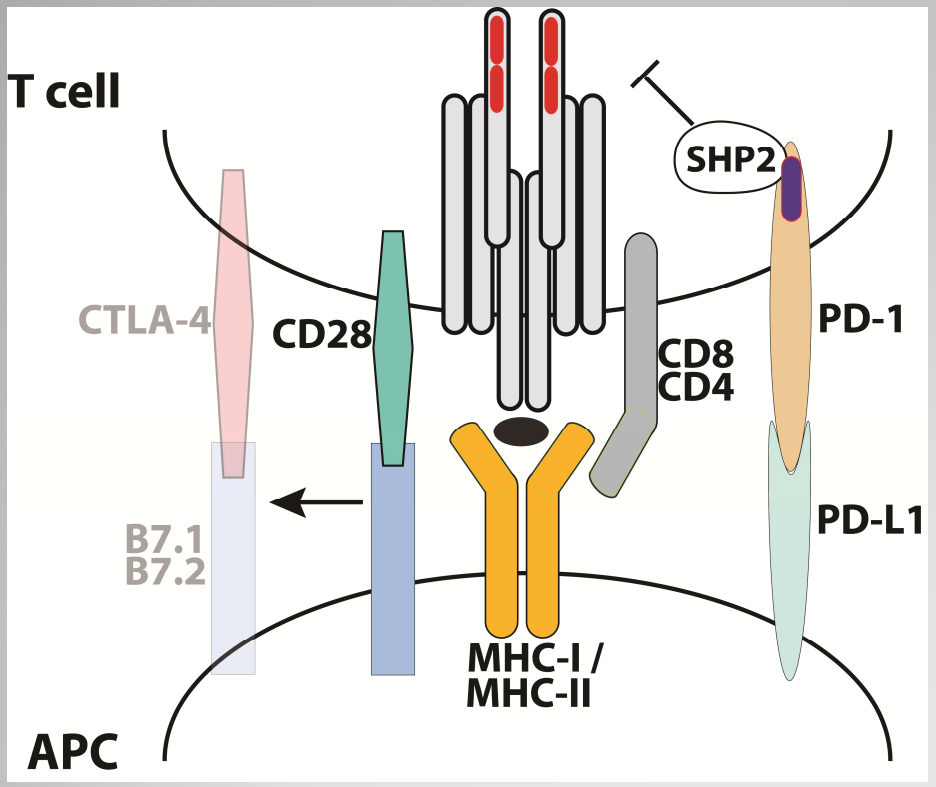
T cell activation

T cell suppression



- CTLA-4 – induced in activated T cells
  - Also binds to CD80 and CD86
  - Higher affinity than CD28
  - Squelches the CD28 signal
  - May also recruit negative regulators
  - High expression on Treg

T cell suppression



- PD-1
  - Transiently expressed in activated T cells, B cells, myeloid cells
  - Pro-inflammatory cytokines suppress expression
- PD-L1/PD-L2
  - Constitutively expressed on many cells and up-regulated in response to inflammatory signals
- Can reverse unresponsiveness in chronic viral infections by interrupting PD-1-PD-L1 interaction

Tolerance

- Protection from autoimmune attack
- Provides protection for tumors
- Mechanisms:
  - Clonal deletion of self reactive T cells
  - Clonal inactivation of T cells in periphery

- <u>Treg cells:</u>
  - CD4, CD25, Foxp3 positive T cells
  - Secrete TGF-beta, IL-10, IL-35 to inhibit T effector cells
  - High expression of CTLA-4 to inhibit DC function and maturation
  - Production of adenosine
  - Effector cell lysis

- MDSC – Myeloid derived suppressor cells:
  - Immature myeloid cells
    - Inhibits T cell function
      - Arginase 1 – depletes L-arginine
      - Cysteine sequestration
      - Peroxynitrite release – inhibits TCR
      - Decrease T cell homing
    - Promotes Tregs
    - Inhibits pro-inflammatory macrophages
  - Induced by chronic inflammation or tumor environment

Tolerance

Summary

- Normal immune state is in balance
  - Allows recognition of pathogens while avoiding reactivity to self
  - Has built in mechanisms to limit the immune response
  - Tumors tip the balance to a non-responsive state
  - Approaches to enhance activation while blocking the suppression mechanisms can allow immune recognition of the tumor