T Cell Immunity

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B Cells vs. T Cells: Which arm of the immune system is likely to be more relevant for anti-viral or anti-tumor responses?

- recognition of *extracellular* versus *intracellular* pathogens
  - B cells produce antibodies which bind to circulating pathogens or toxins, leading to 'neutralization' of pathogenic activity
  - T cells, in contrast, directly bind to abnormal cells (i.e., infected or neoplastic), leading to target cell destruction

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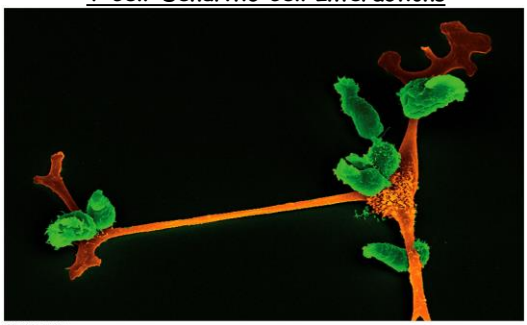
T Cell-Dendritic Cell Interactions



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The Central Players of the T Cell Response

- $CD8^+$ cytotoxic T lymphocytes (CTLs)
- $CD4^+$ T_h1 (induces the generation of CTLs)
- $CD4^+$ T_h2 (promotes antibody production)

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Role of the Antigen Presenting Cell in the Activation of Naïve T Cells

Dendritic cells are essential for the induction of the naïve T cell response, and do so through regulation of three major events known as the 3-signal model:

1. Recognition of MHC-peptide complex (& conjugate formation)
   i. antigen processing
   ii. antigen presentation
   iii. co-receptors (CD4 or CD8)
   iv. adhesion (LFA-1/ICAM-1; CD2/LFA-3)
2. positive co-stimulation (CD28/CD80 or CD28/CD86)
3. cytokine production (e.g., Interleukin-2; IL-2)

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Surface Interactions Important for T Cell Activation

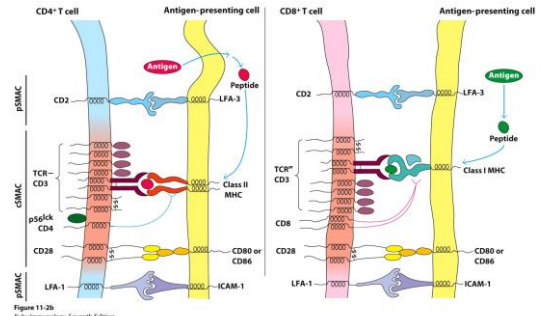

Figure 11-2b
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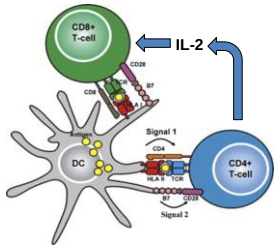
Generation of T Cell Immunity: an Indispensable Role of the Antigen-Presenting Cell



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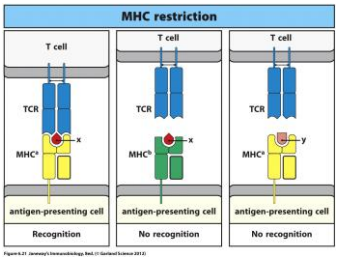
Signal 1: T Cell Recognition of MHC-Peptide Complexes



Antigen specificity is governed by the TCR, which recognizes an antigenic peptide in the context of self-MHC, a concept known as MHC restriction. MHC restriction is absolutely essential to ensure and instruct immune reactivity against 'alterations of self'.

MHC class I=heavy/light pair
MHC class II=similar size pair

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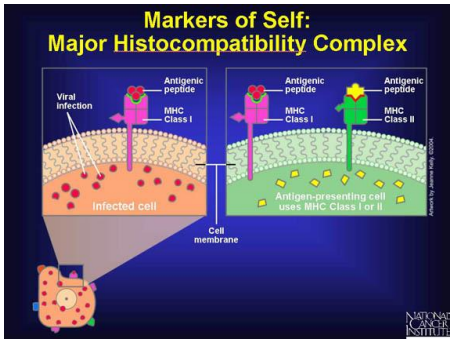

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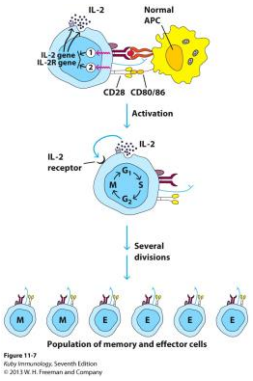
Signals 2 & 3: Costimulation, Cytokine Production and Clonal Expansion



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Summary: The Generation of MHC-Peptide Complexes for T Cell Receptor Recognition

1. MHC class I and class II molecules deliver peptides to the cell surface from two distinct intracellular compartments.
2. Peptides presented by MHC class I molecules are generated within the cytosolic compartment (aka, endogenous pathway)
3. Peptides presented by MHC class II molecules are generated in acidified endocytic vesicles (aka, exogenous pathway).
4. Cross-presentation allows exogenous proteins to be presented on both MHC class I and II molecules (i.e., via dendritic cells, which are highly effective).
5. $CD8^+$ T cells recognize MHC class I-peptide complexes
6. $CD4^+$ T cells recognize MHC class II-peptide complexes

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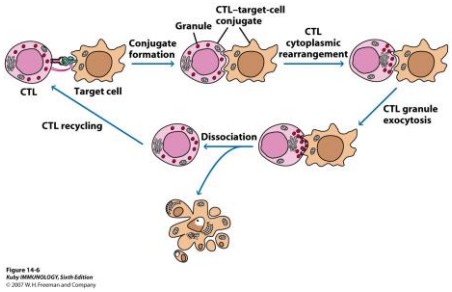
Steps of CTL-Mediated Target Cytolysis



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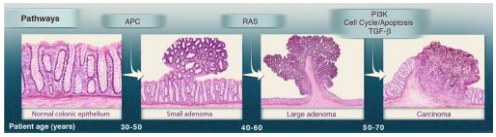
Tumor Development and Progression

- Intrinsic mechanisms
  - genetic and epigenetic alterations within normal organs or tissues



Vogelstein et al. Science 2013;339:1546-1558

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Table 1. Noncancerous Cells of the Tumor Organ

Cell Type	Effect on Tumors	References
Normal epithelial cells	inhibit	Dong-Le Bourhis et al., 1997
Myoepithelial cells	inhibit (invasion, growth)	Gudjonsson et al., 2002; Hu et al., 2008
Fibroblasts	promote (proliferation, angiogenesis, invasion)	Bhowmick et al., 2004; Olumi et al., 1999; Orimo et al., 2005
Mesenchymal stem cells	promote (metastasis)	Karnoub et al., 2007
Adipocytes	promote (tumor growth, survival, angiogenesis)	Iyengar et al., 2005; Landskroner-Eiger et al., 2009
Endothelial cells	promote (angiogenesis, niche?)	Ausprunk and Folkman, 1977; Calabrese et al., 2007
Perivascular cells	promote (vascularization)	Song et al., 2005
	inhibit (metastasis)	Xian et al., 2006
Bone marrow-derived cells	promote (proliferation, invasion, angiogenesis)	Coussens et al., 2000; Du et al., 2008; Lyden et al., 2001
Dendritic cells	inhibit (stimulate antitumor immunity)	Knight et al., 1985; Mayordomo et al., 1995
Myeloid-derived suppressor cells and immature myeloid cells	promote (angiogenesis, metastasis, reduce antitumor immunity)	De Palma et al., 2005; Sinha et al., 2007; Yang et al., 2004, 2008b
Macrophages, M1-like	inhibit	Sinha et al., 2005
Macrophages, M2-like	promote (invasion, angiogenesis)	DeNardo et al., 2009; Lin et al., 2001, 2006
Mast cells	promote (angiogenesis)	Coussens et al., 1999; Soucek et al., 2007; Yang et al., 2008a
Neutrophils, N1	inhibit (stimulate antitumor immunity)	Fridlender et al., 2009
Neutrophils, N2	promote (angiogenesis, reduce antitumor immunity)	Nozawa et al., 2006; Schmielau and Finn, 2001; Shojaei et al., 2008
T cells, CD4+, T helper 2	promote (metastasis)	DeNardo et al., 2009
T cells, CD8+, cytotoxic	inhibit (tumoricidal)	Romero et al., 1998
T cells, CD4+CD25+ regulatory	promote (reduce antitumor immunity)	Casares et al., 2003; Curiel et al., 2004
T cells, gamma/delta	inhibit (stimulate antitumor immunity)	Girardi et al., 2001
T cells, Th17	promote (proliferation, angiogenesis)	Numasaki et al., 2005
	inhibit (stimulate T-cell antitumor immunity)	Hirahara et al., 2001
B cells	promote (reduce antitumor immunity)	Inoue et al., 2006
B cells, immunoglobulins	promote (stimulate inflammation-associated progression)	Andreu et al., 2010
Platelets	promote (metastasis)	Camerer et al., 2004; Nieswandt et al., 1999

23 cell types
Egeblad et al. *Dev Cell* 18:884, 2010

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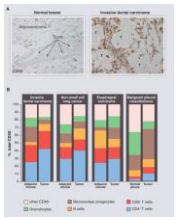
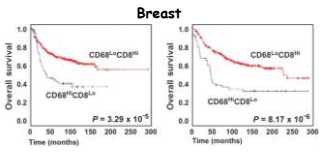
Tumor Development and Progression



Coussens et al. *Science* 339:286; 2013



DeNardo et al. *Cancer Disc* 1:54, 2011

Extrinsic mechanisms: 'host-tumor interaction'
positive and negative consequences on tumor outcome

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Approaches for the Treatment of Human Cancer

- Surgery - to debulk; effective if cancer has not spread
- Radiation – local/regional tumor spread
- Chemotherapy - systemic spread, but approaches are generally toxic to normal cells/tissues (limits its therapeutic potential)

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Immunotherapy: A Fourth Modality?

- Immunotherapy principles:
  - improve patient's immune response against their own cancer
    - 'vaccines'
    - 'adoptive cell transfer'
  - rationale and goals:
    - a highly potent immune reaction
    - target cancer cells with high specificity
    - diminish toxicity toward normal cells

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Metastatic Disease is a Major Challenge in Cancer Treatment

- Most cancer patient deaths are due to metastatic disease or disease resistant to conventional treatments
- Metastasis typically is not accessible to surgery because it can give rise to many lesions at multiple locations, some of which can be small and undetectable

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Manipulation of T Cell Responses for Therapeutic Purposes in Cancer

Based on basic biology to clinical practice…

1. Signal 1: dendritic cell vaccines expressing relevant MHC/peptide complex (e.g. 'Provenge' in prostate cancer)
2. Signal 2: 'immune checkpoint inhibitors' to prevent negative costimulation (anti-CTLA-4 or anti-PD-1 mAbs)
3. Signal 3: IL-2 administration
4. Adoptive T cell transfer of *ex vivo*-expanded tumor-infiltrating lymphocytes

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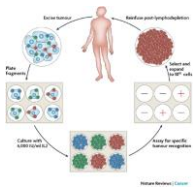
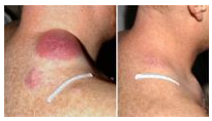
Benefits of Clinically Engaging the Antitumor T Cell Response Against Cancer

Melanoma





Before and after pictures of a patient with advanced melanoma who underwent treatment with tumor-infiltrating lymphocytes. Within 2 weeks of treatment, the large tumor had disappeared. Source: Cancer.gov

Rosenberg et al. *Nature Rev Can* 8:299, 2008

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Immunotherapy Interventions

- **Cancer vaccines** (most appealing)
  - similar in concept to classical vaccination
  - immunize against tumor ('foreign') proteins that are selectively or uniquely expressed
  - two recent examples of vaccines:
    - HPV vaccine (Gardasil)
    - Prostate cancer vaccine (Provenge)
    - http://www.bing.com/videos/search?q=provenge+video&view=detail&mid=7E023EB99306DAFA4B087E023EB99306DAFA4B08&FORM=VIRE&adlt=strict

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