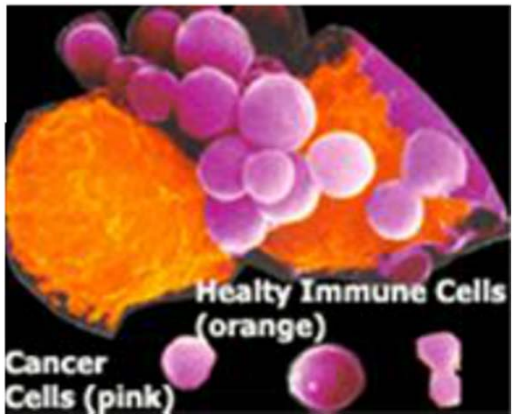
Transplant surgeons bring donor organ to operating room.

Foundations of Public Health Immunology

Autoimmunity, Transplants & Tumors

T cells (orange) have an important role in the fight against cancer cells (pink).

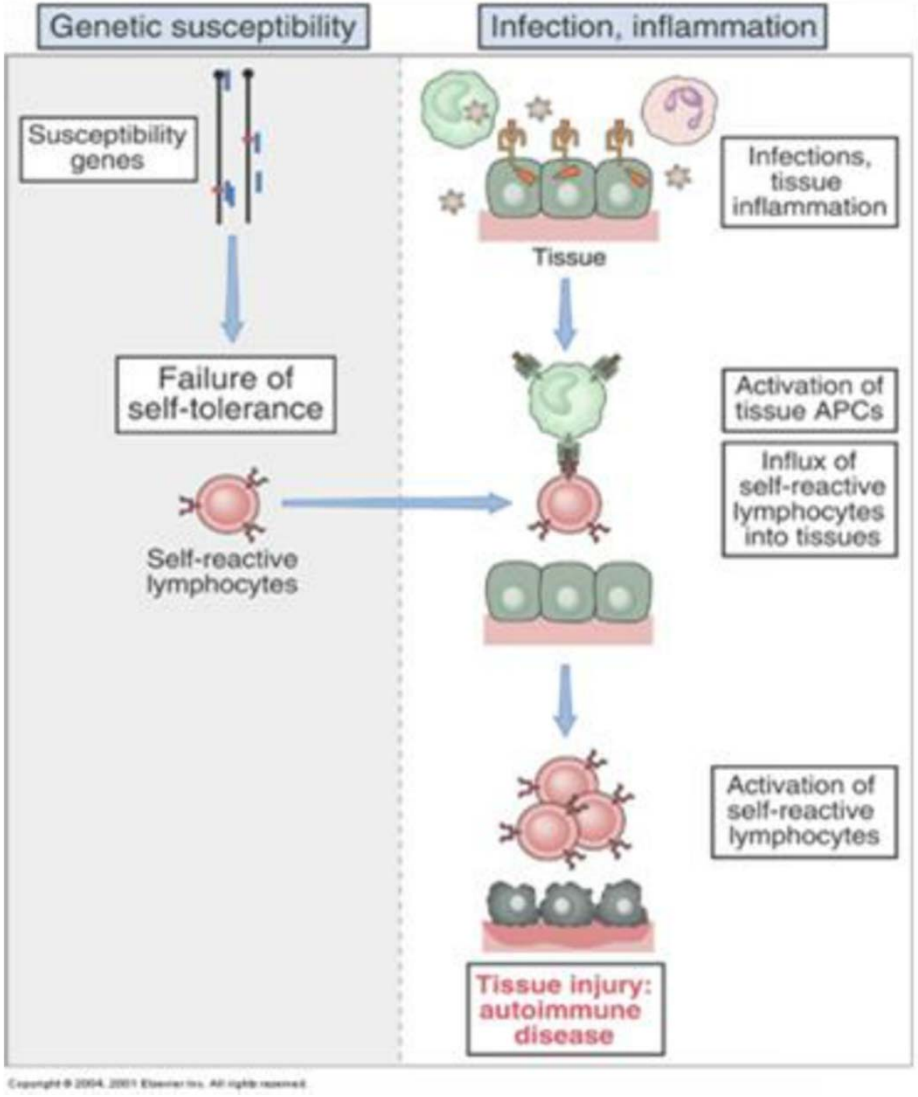


Objectives

- Define autoimmunity, tolerance, & ignorance
- Identify the mechanism involved in development of autoimmunity
- Identify the mechanism involved in the control of autoimmunity (central vs. peripheral)
- Identify selected disorder of autoimmunity
- Identify and explain the types, mechanisms of donor organ rejection
- Identify drug therapies to prevent graft rejection
- Describe how the immune system can recognize * kill tumor cells
- Identify the mechanisms tumor cells use to evade the immune response
- Identify novel approaches for cancer vaccines

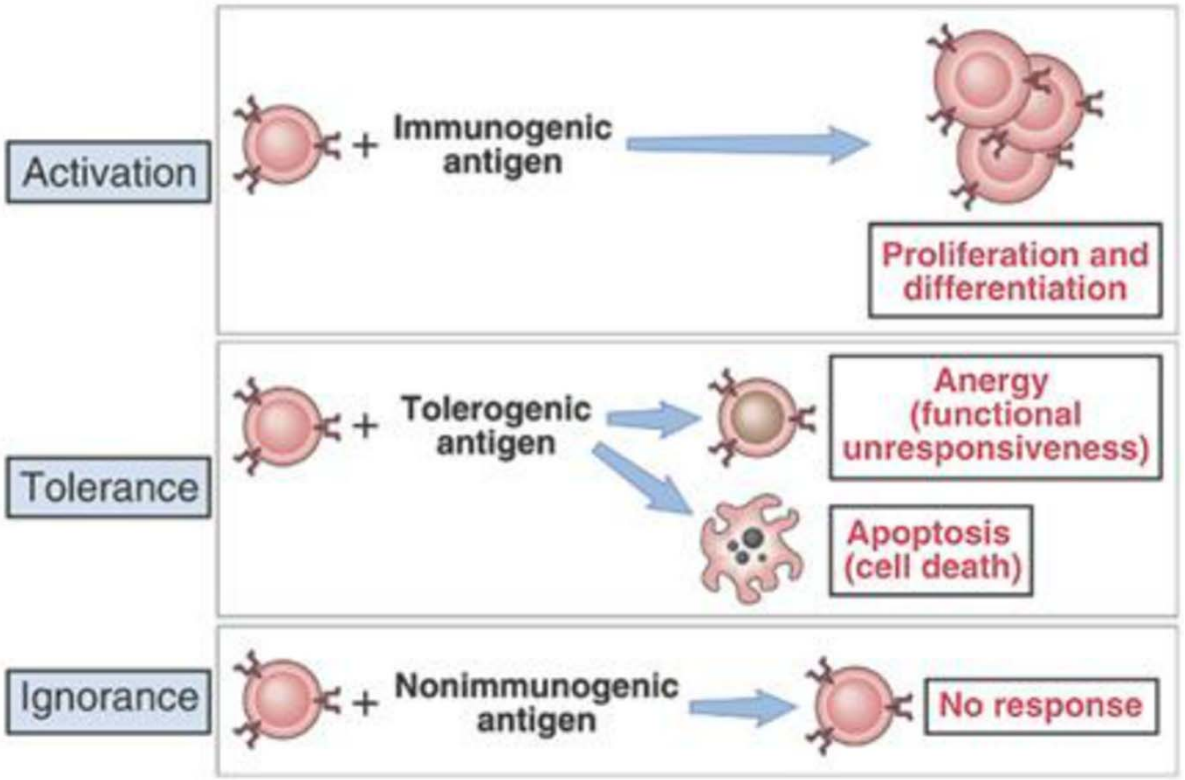
Autoimmunity

- **Definition: an immune response against self antigens**
- Between 1-2% of people suffer from autoimmune diseases worldwide (up to 8% in US)
- 2 major factors contribute to autoimmunity developing in a person:
  - Inheritance of **susceptibility genes**
  - **Environmental triggers** (i.e. infections)
  - These factors can lead to reactivation of lymphocytes that recognize self



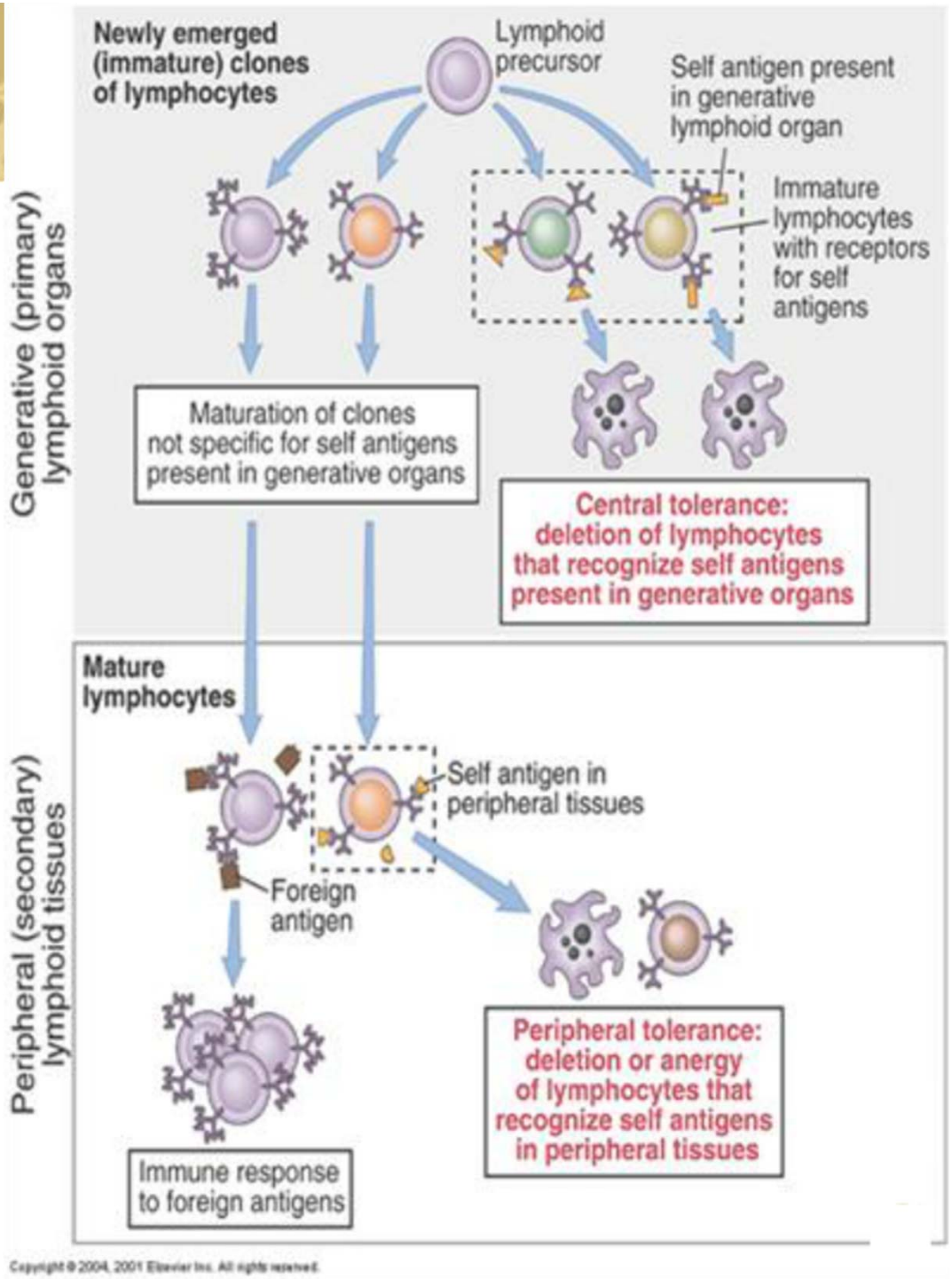
Tolerance

- Lack of immune cell response to an antigen that is induced after exposure to that particular antigen



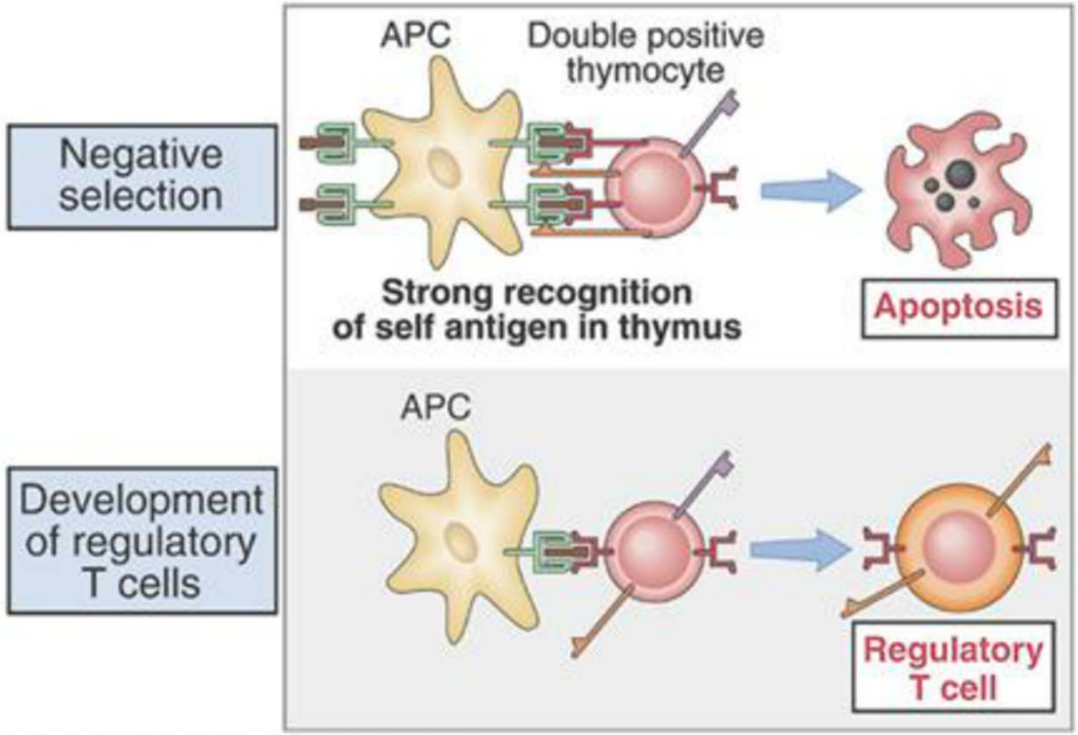
Central T-cell Tolerance

- **Thymus is the site of central T-cell tolerance**
- Involves **negative selection** of immature T-cells that react strongly to self-antigens
- Defective central tolerance may predispose to autoimmunity



Central Tolerance: Apoptosis & Treg cells

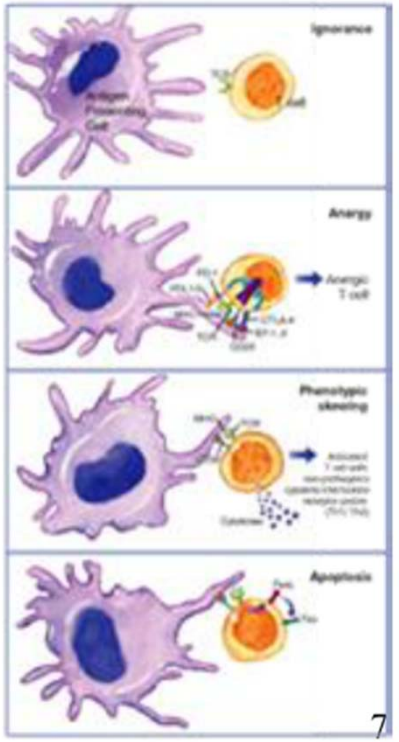
- Occurs in thymus
- Apoptosis (Deletion) happens if T cells strongly recognize self antigens [negative selection]
- T cells that recognize ag in the thymus can develop into **regulatory T cells**
  - Induced by **repeated activation** of immature T-cells by self-antigen and/or repeated recognition of self-antigens **without second signals**
  - Play a critical role in **preventing** autoimmune reactions



Peripheral T-cell Tolerance

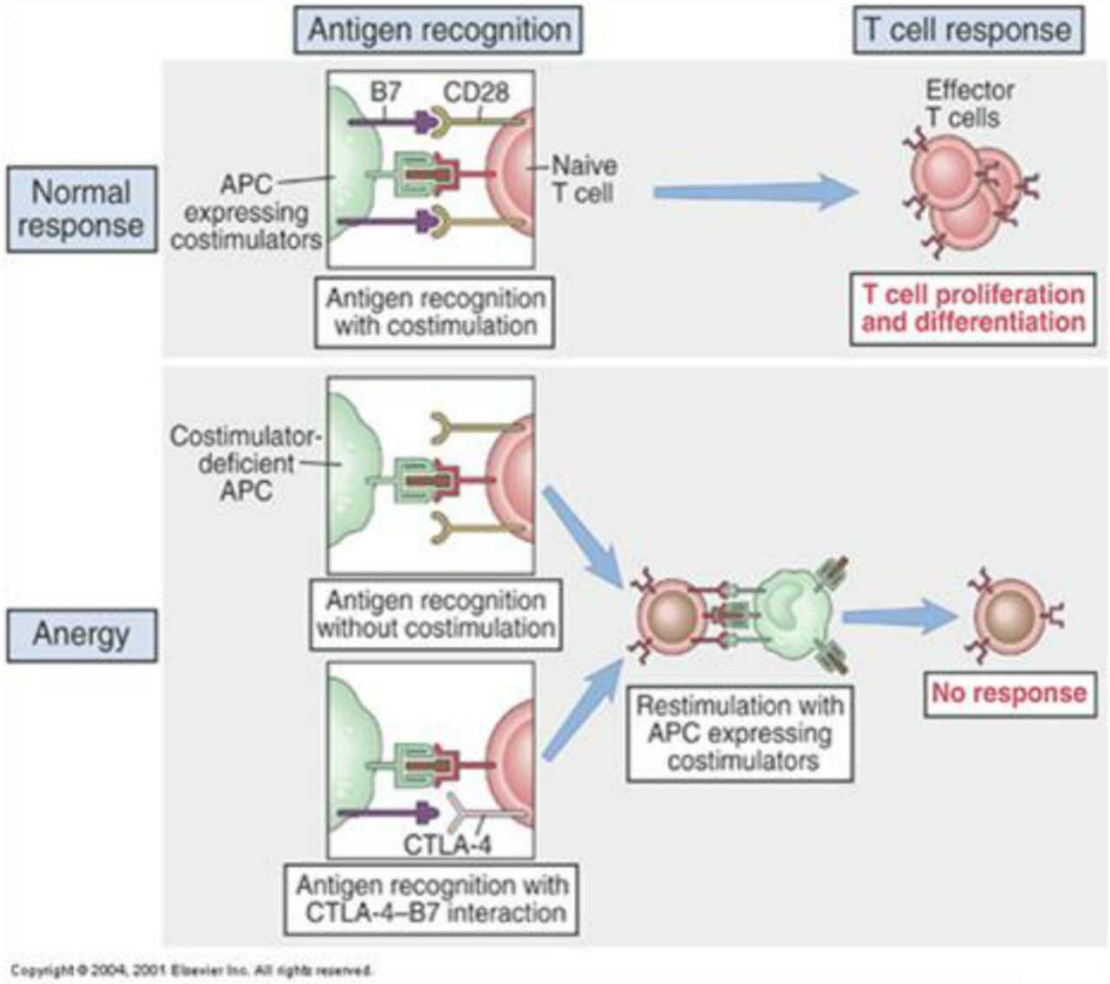
- Occurs when mature T-cells recognize self-antigens in **peripheral** tissues or in **secondary lymphoid organs**

- Two possible outcomes:
  - Anergy or death
  - Regulatory T cell suppression



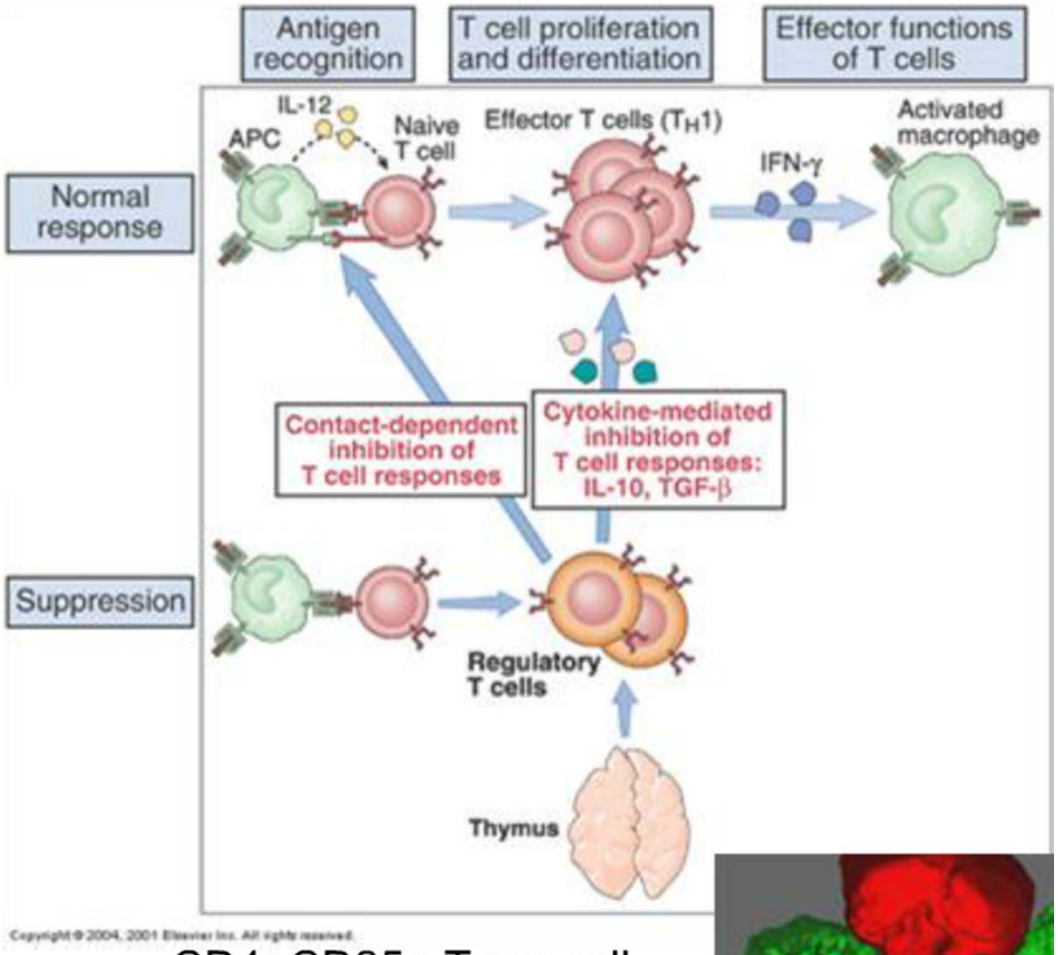
Anergy

- **Functional inactivation** of T-cells due to recognition of antigens without adequate levels of costimulators
  - Despite ag recognition, need these second signals for full T-cell activation
- **T cells become anergic without ag+ costimulators**



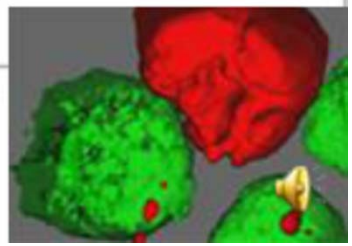
Suppression

- Suppression by Treg cells
- Exposure to self-antigens induces some **self-reactive T-cells to become regulatory cells**
- Most regulatory cells are CD4+ & express high levels of CD 25
- **Inhibit T cells & effector functions in tissues**
- Critical to downplay inflammatory response, prevent autoimmunity & immunopathology



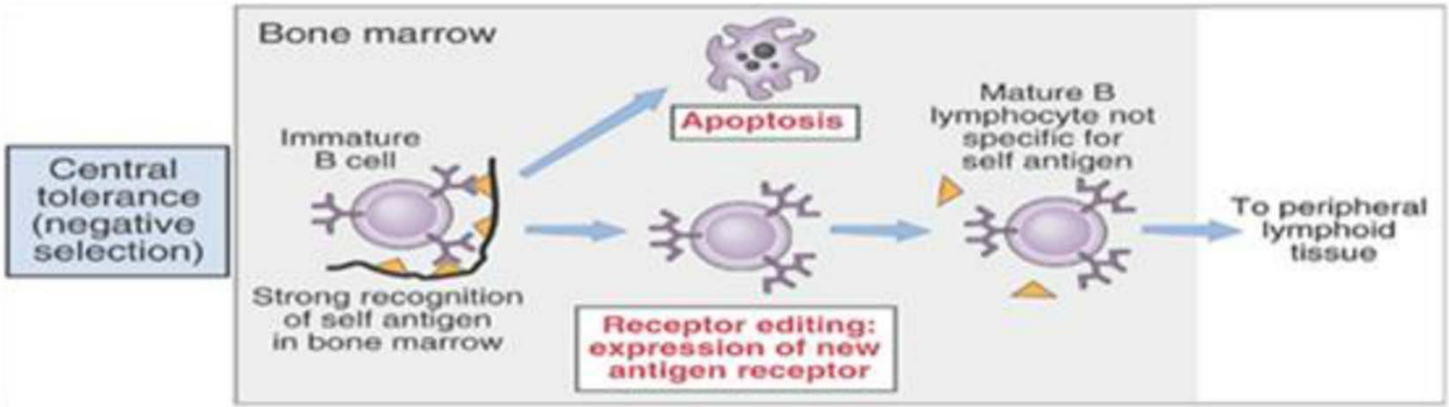
CD4+CD25+ T reg cell

Source:http://www.mcgill.ca/microimm/department/professors/piccirillo/



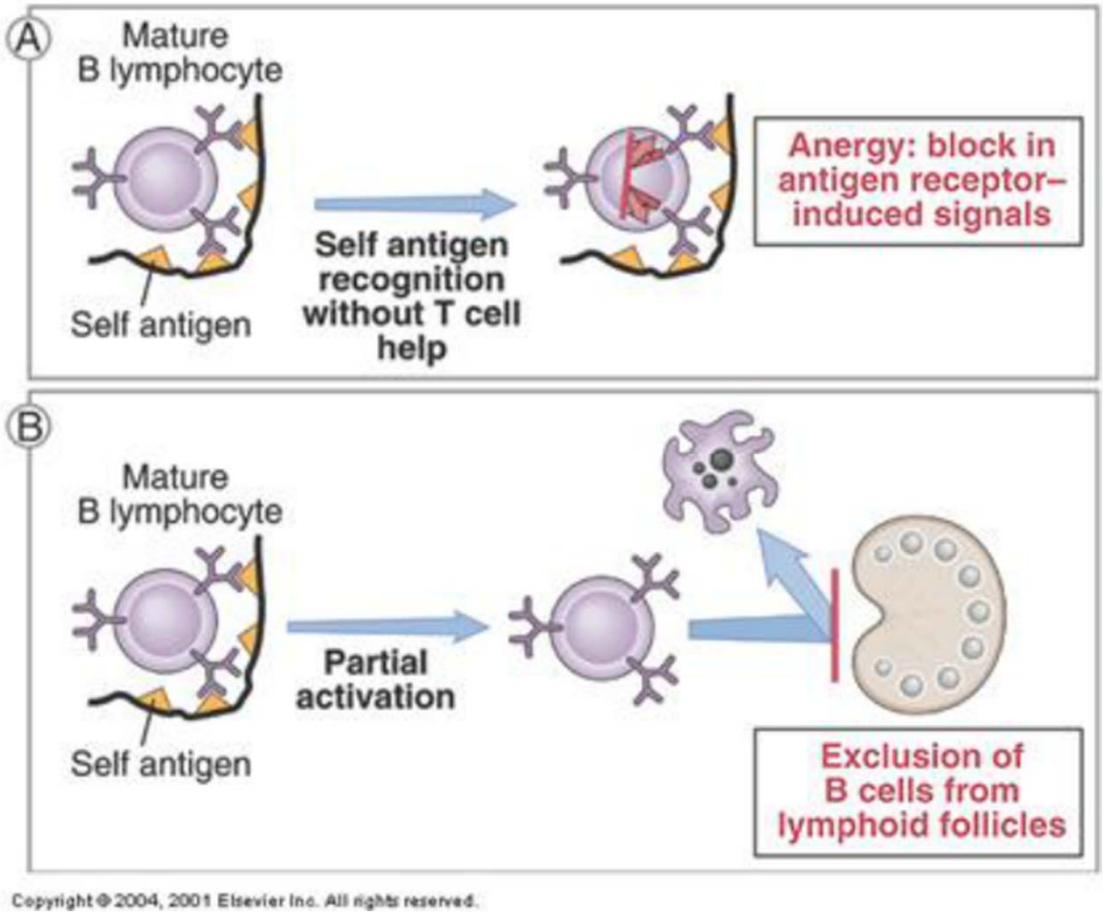
Central B-cell Tolerance

- B-cell central tolerance may occur by:
  - Negative selection
  - Receptor editing
    - Self-reactive B cells may **reactivate** their immunoglobulin **recombination genes**
    - Express **new Ig light chain** which binds the previous Ig heavy chain
    - Produces **new antigen receptor** that is not self-reactive



Peripheral B-cell Tolerance

- Mature B-cells exposed to **high levels of self-antigen in secondary** lymphoid organs become anergic to self-antigens

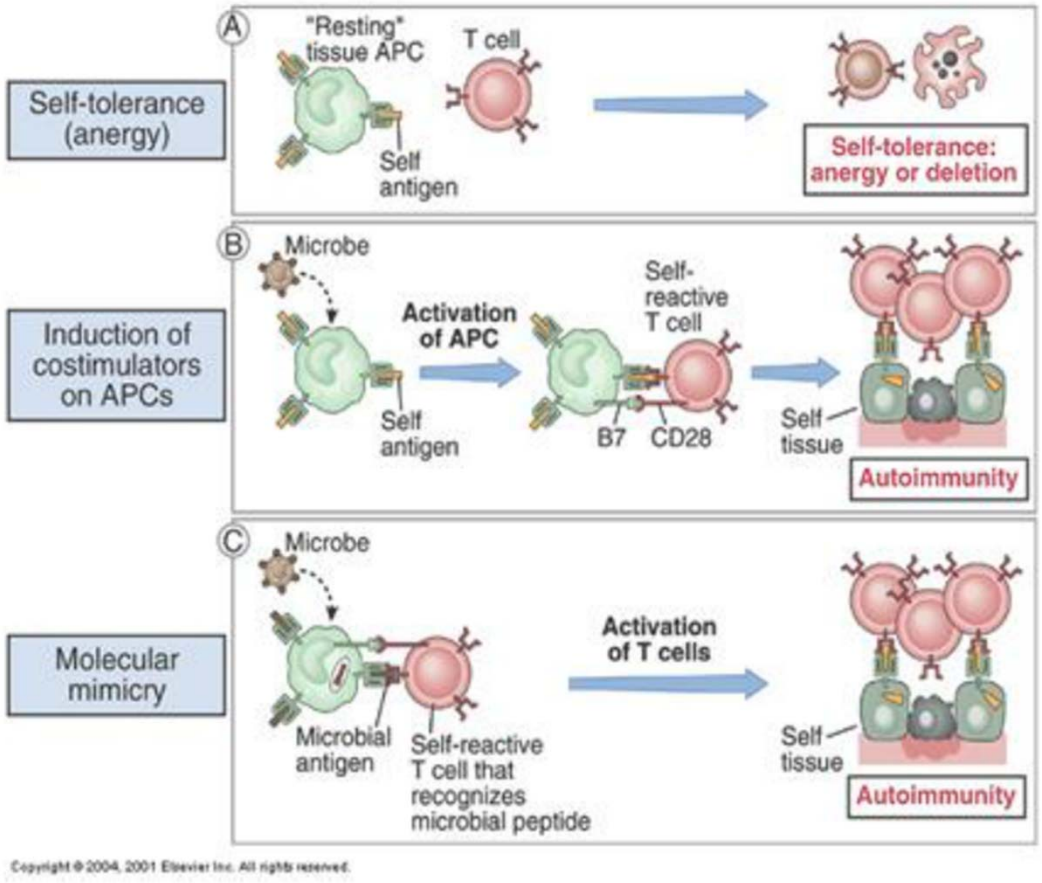


Autoimmunity

- Situation in which the immune system exhibits reactivity to self-antigens
- May or may not always be accompanied by detectable disease
- May be antibody or cell-mediated
- Development of autoimmunity is affected by genetic and environment factors

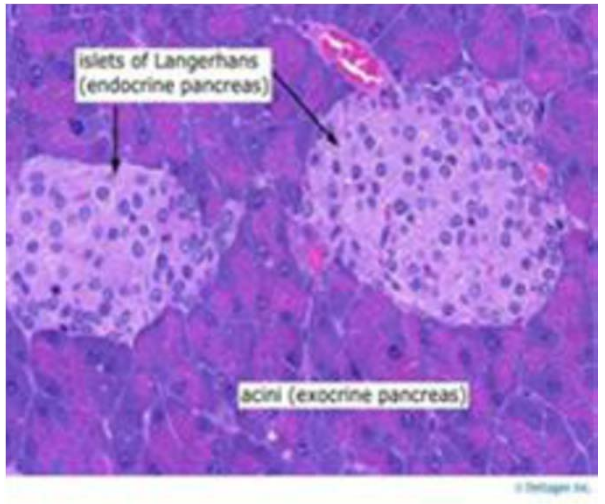
Autoimmunity

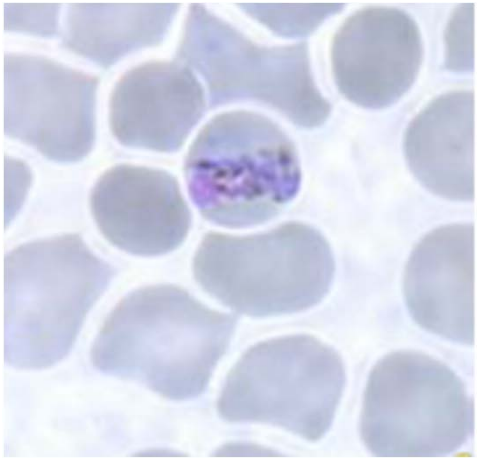
- **Infections** may induce the development of autoimmunity
- **Induction of costimulators** on APCs by microbes
  - Presentation of self-antigens by these altered APCs to T-cells results in T-cell activation against self-antigens
- **Molecular mimicry**
  - Some microbial antigens may cross-react with self-antigens
  - Immune reactions to the microbial antigens result in attacks against the self-antigens



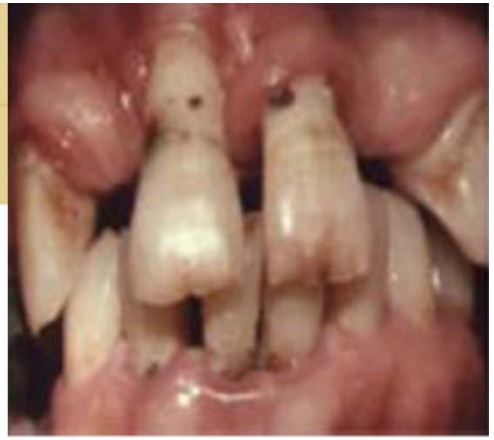
Autoimmunity continued

- Insulin-dependent diabetes mellitus
  - **Autoimmune destruction of the beta cells** in the Islets of Langerhans in the pancreas
  - Results in little to no insulin being produced by the body
- Malaria
  - Four species of malarial protozoa exist worldwide
  - The species, Plasmodium malarie, can induce **glomerulonephritis** in the kidneys



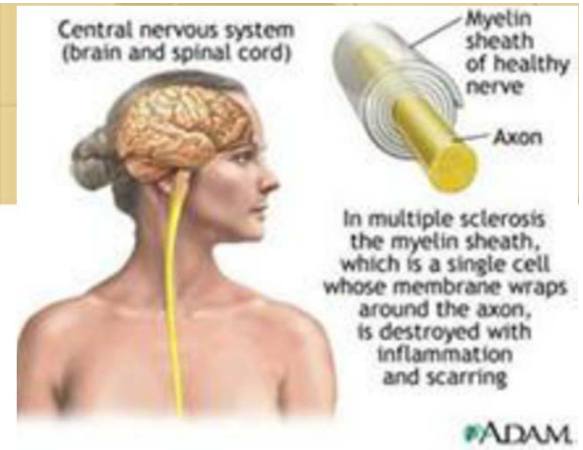


Periodontal diseases



- Widely prevalent **chronic inflammatory** disorders induced by a bacterial biofilm found on teeth
- Periodontitis
  - Most destructive form of periodontal disease
  - Affects approximately 30% of the U.S. population, one of the most significant causes of tooth loss in adults
  - Characterized by irreversible destruction of soft tissue and bone
    - Results from a complex interplay between the host response and specific plaque microorganisms, such as Porphyromonas gingivalis
    - Both innate and acquired immunity are involved in the host resposne

Multiple Sclerosis (MS)



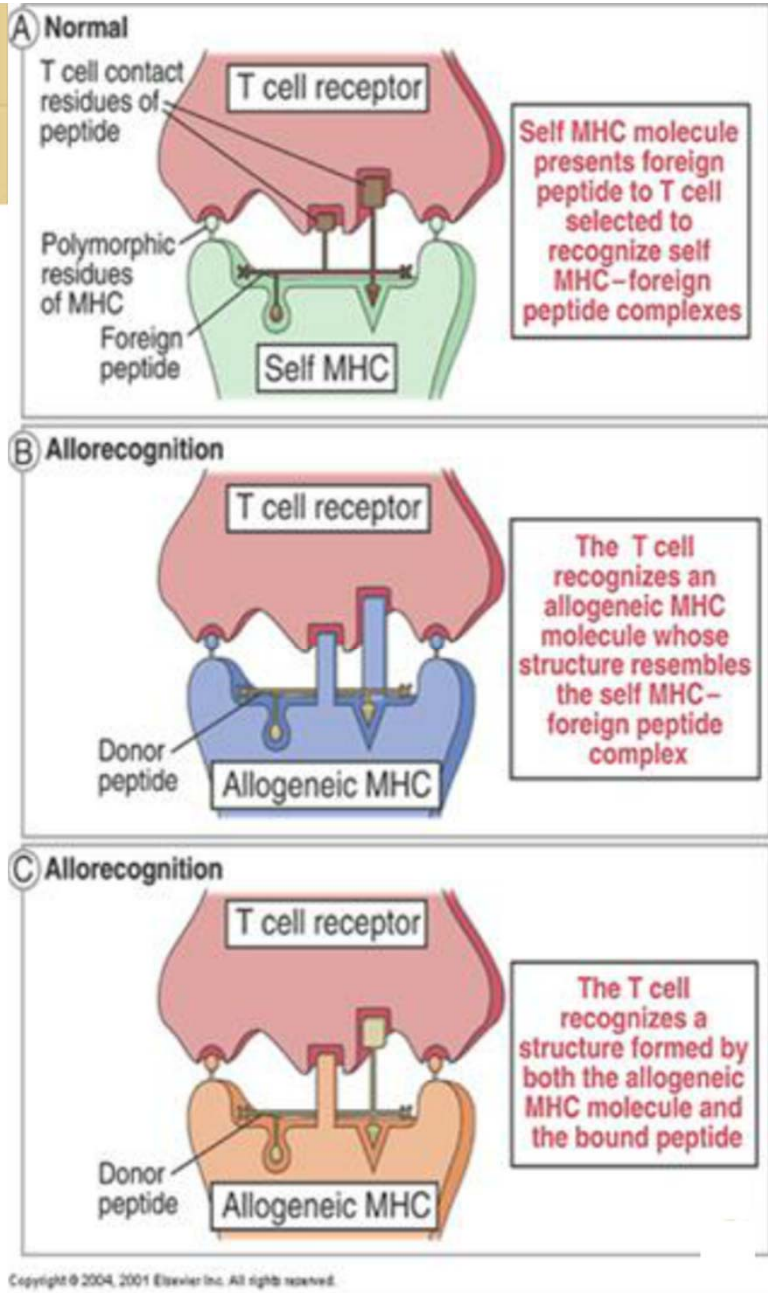
- MS is an **autoimmune disease** that primarily effects whites in North America & Europe
- MS affects proper functioning of the central nervous system, leading to systemic loss of motor, sensory, and bladder control
- Primarily causes by **T cell mediated attacks on nerve tissue** and subsequent demyelination of axons

Organ Transplants & Immune Rejection

- Transplant nearly any solid organ (heart, lung, liver, skin, etc)
  - Allograft: transplanted organ or tissue with a **different** genetic makeup (non-identical twins) from same species
  - Xenograft: transplanted organ or tissue between 2 **different species**
- Donor to recipient matching not as critical due to immunosuppressive drugs

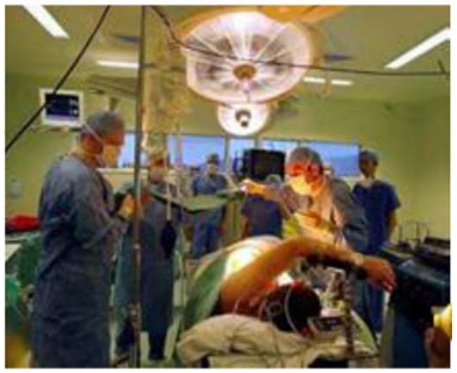
Ag Recognition of Organ Transplants

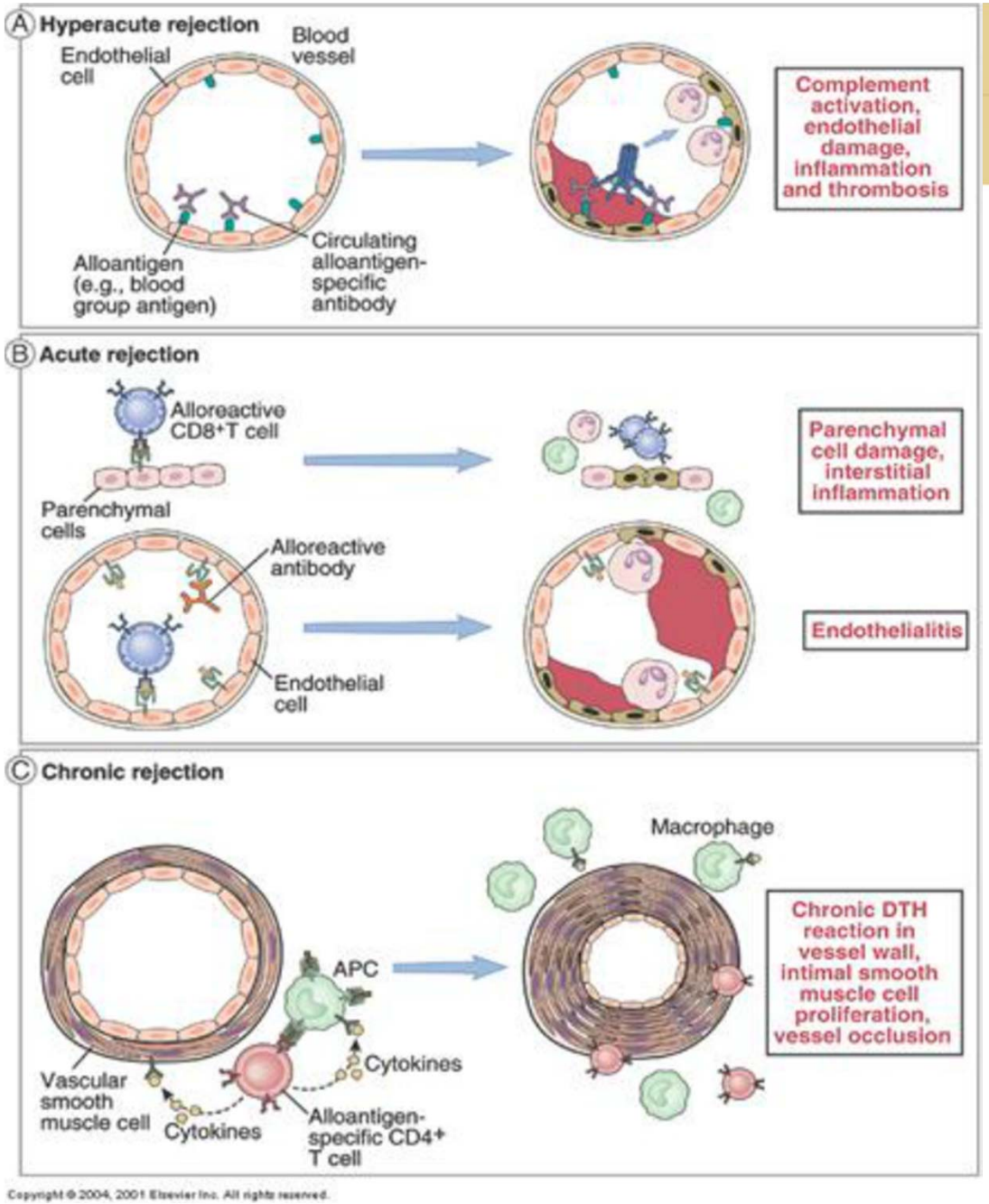
- Transplanted organs express **donor MHC molecules** that can be **recognized by the recipient** immune system
- Two pathways of antigen recognition (allorecognition) by the recipient's T cells:
  - **Direct** – recipient T cells recognize intact donor MHC molecules combined with peptide and expressed on donor cells
    - Responsible for acute rejection
  - **Indirect** – recipient APCs process the donor-MHC antigen then present it to recipient T cells
    - Responsible for **chronic** rejection



Antigen Recognition of Organ Transplants

- Both donor and recipient factors contribute to the immune response to transplanted tissue
  - Major **donor** factor – expression of MHC antigens on the donor tissue and the presence of APCs within the transplanted graft
  - Major **recipient** factor – previous sensitization against ABO and HLA antigens expressed on the graft or other foreign antigens



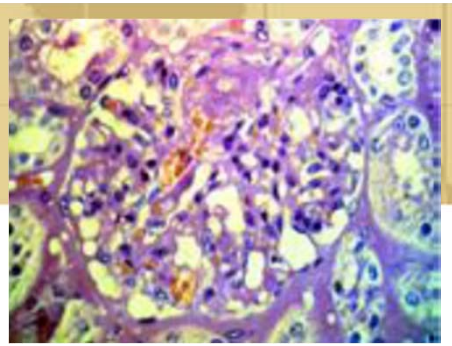


Types of Rejection

- Hyperacute
  - Accelerated
- Acute
- Chronic

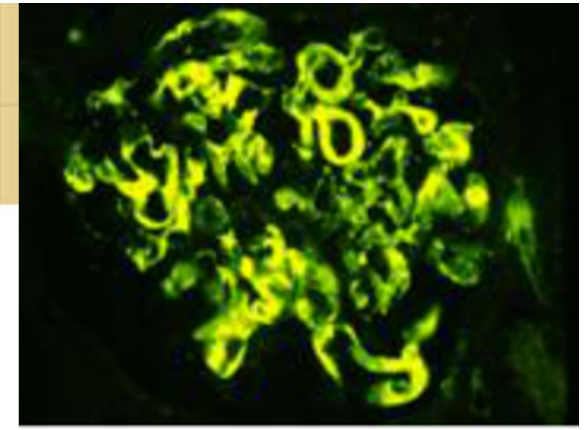
- **Type of rejection** is determined by the **time frame & histopathologic characteristics** of the transplanted organ

Hyperacute Rejection



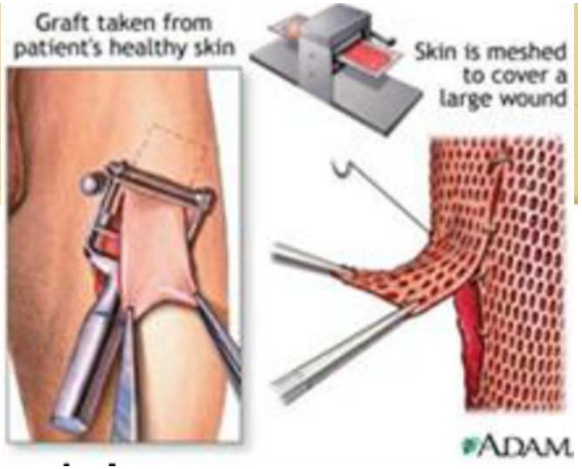
- Occurs **immediately** (within minutes to hours of the vascularization of the transplanted graft)
- Caused by **humoral immune response** against ABO blood group antigens, vascular endothelial antigens, and histocompatibility (HLA) antigens
- Hyperacute rejection results in:
  - Complement activation
  - Massive intravascular coagulation
  - Decreased tissue perfusion
  - Eventual graft necrosis and death

Accelerated Acute Rejection



- Variation of hyperacute rejection
  - However, it is a cellular immune response (not humoral)
- Can occur if the recipient has been previously exposed to low levels of donor tissue antigens
  - Creates a rapid memory response after the transplantation
- Accelerated acute rejection occurs within a few days to few weeks following transplantation
- Leads to graft death

Acute Graft Rejection



- Due to a **cellular** immune response involving mononuclear, cytotoxic and Th cells, monokines, and lymphonkines
- May occur within a week to approximately 4 months after transplantation
  - Greatest risk during the first 6 months after transplantation
  - Aggressive treatment prevents graft loss
  - Acute graft rejection is the greatest predictor of chronic rejection
- Produces nonspecific signs that need definitive diagnosis through biopsy

Chronic Rejection

- Cause of chronic rejection is unclear
  - **Both T cells and B cells** contribute to the damage
- Hallmarks of chronic rejection:
  - Slowly developing graft fibrosis
  - Widespread arterial disease (arteriopathy)
  - Eventual graft malfunction and loss
- Probably **begins at the time of transplantation**, but may take **months or years to be clinically detectable**
- Prevention is the best method to limit chronic rejection although retransplantation is possible

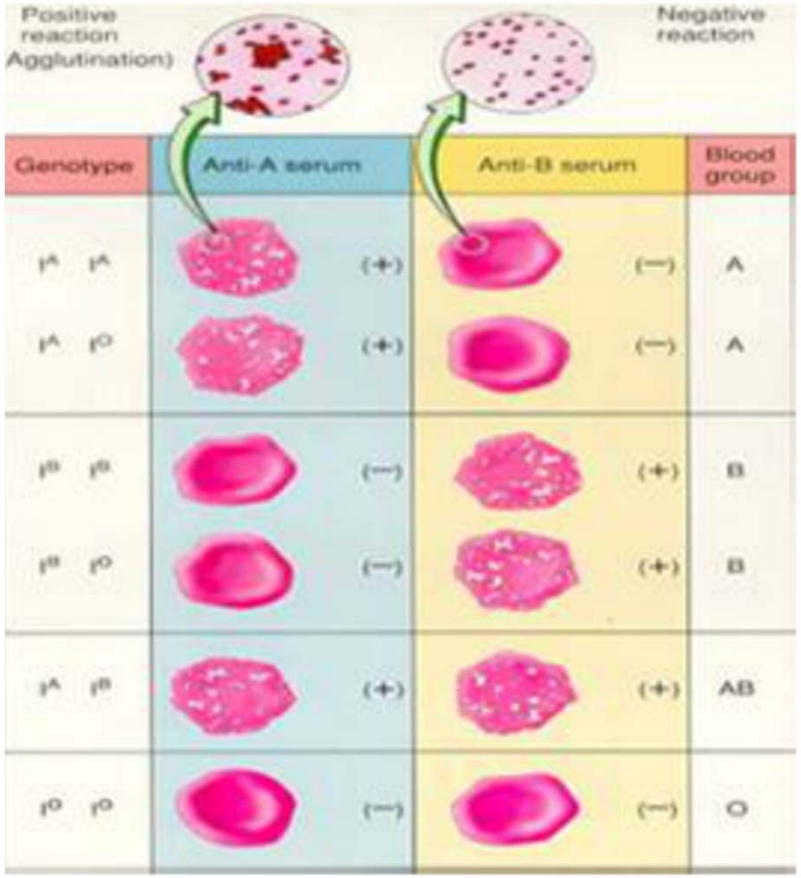
Drug Therapy

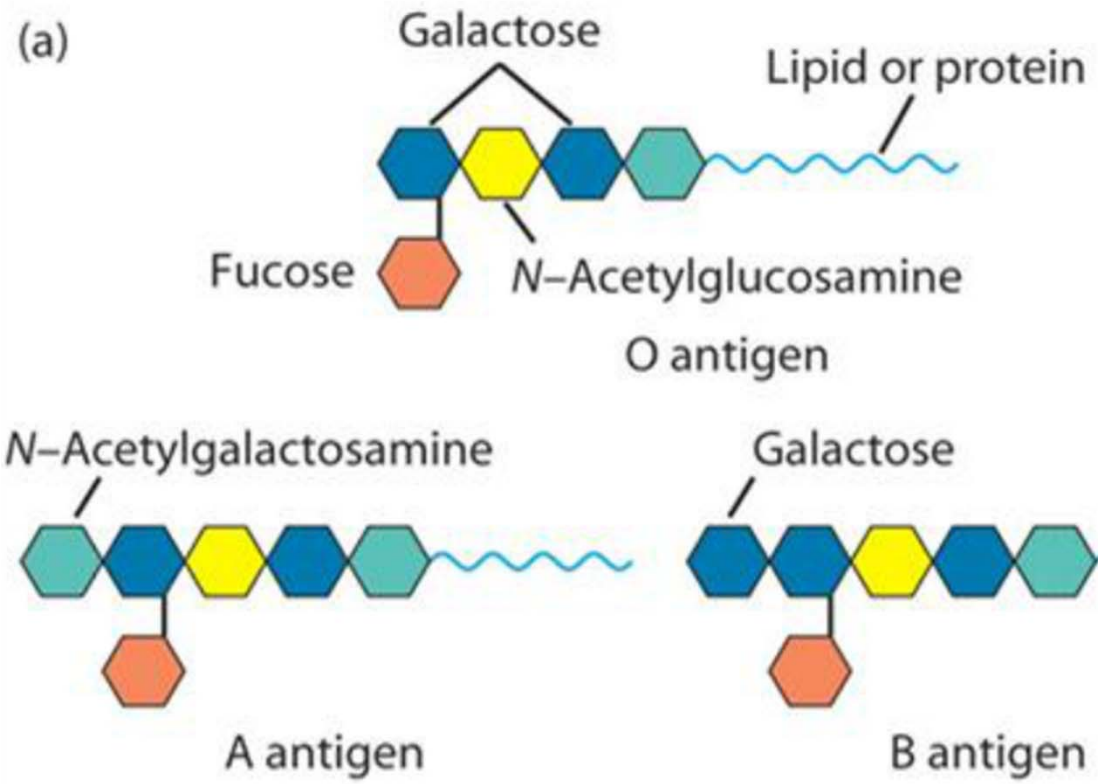
- Need **lifetime of immunosuppressive drugs** to prevent graft rejection
  - Most organ transplants are successful now because of drugs
- New experimental therapies are being developed to decrease side effects & toxicity of steroidal drugs

Drug	Mechanism of action
Cyclosporine and FK506	Blocks T cell cytokine production by inhibiting activation of the NFAT transcription factor
Mycophenolate mofetil	Blocks lymphocyte proliferation by inhibiting guanine nucleotide synthesis in lymphocytes
Rapamycin	Blocks lymphocyte proliferation by inhibiting IL-2 signaling
Corticosteroids	Reduce inflammation by inhibiting macrophage cytokine secretion
Anti-CD3 monoclonal antibody	Depletes T cells by binding to CD3 and promoting phagocytosis or complement-mediated lysis (Used to treat acute rejection)
Anti-IL-2 receptor antibody	Inhibits T cell proliferation by blocking IL-2 binding. May also opsonize and help eliminate activated IL-2R–expressing T cells
CTLA4-Ig	Inhibits T cell activation by blocking B7 costimulator binding to T cell CD28; used to induce tolerance (experimental)
Anti-CD40 ligand	Inhibits macrophage and endothelial activation by blocking T cell CD40 ligand binding to macrophage CD40 (experimental)

Blood Types & Immunopathology

- Antigens on blood cells also can lead to recipient rejection (& death) from incorrect transfusions
  - Sugar ags (no T cell response)
- Blood transfusion reactions
  - ABO systems (See next slide)
  - Reaction involves IgM & complement





ABO System

Human blood cells can be groups according to the presence or absence of surface antigens.

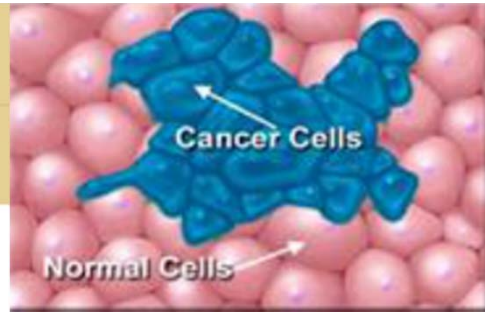
For example, an individual with A-type blood has A antigens on their erythrocytes and anti-B antibodies in their serum.

However, individuals with O-type blood have no A or B antigens on their erythrocyte surfaces and have both anti-A and anti-B antibodies in their serum.

This lack of surface antigens allows Type O blood to be transfused into individuals with other blood types.

(b)

Genotype	Blood–group phenotype	Antigens on erythrocytes (*agglutinins*)		Serum antibodies (*isohemagglutinins*)
AA or AO	A	A		Anti–B
BB or BO	B	B		Anti–A
AB	AB	A and B	Universal Acceptor	None
OO	O	None	Universal Donor	Anti–A and anti–B

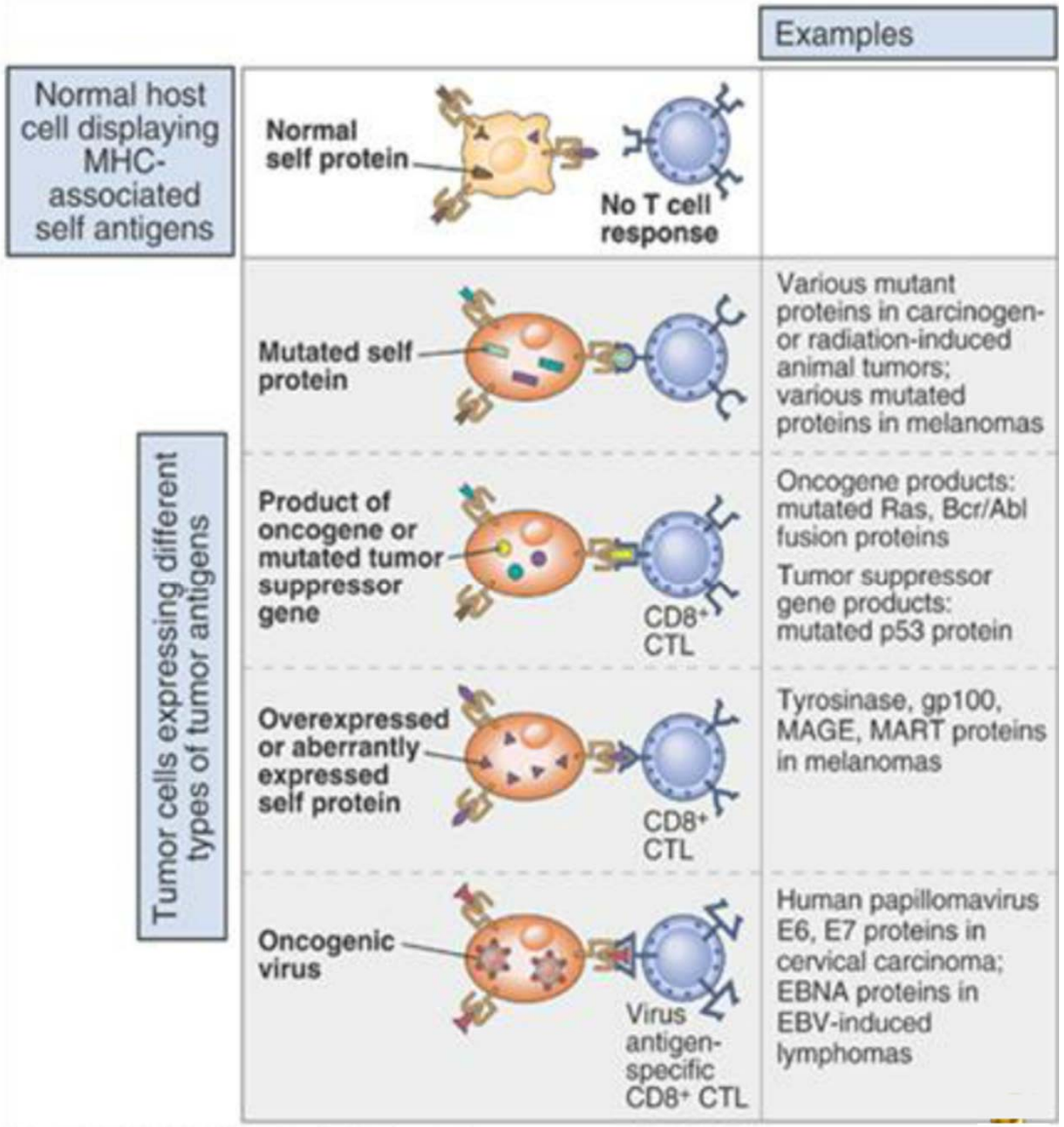


Cancer

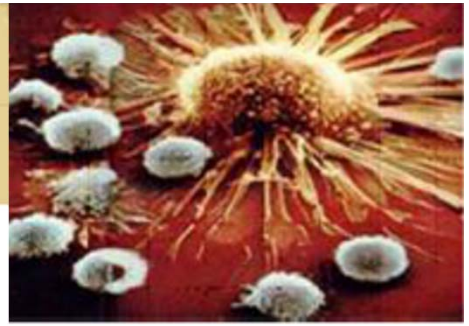
- Definition: group of more than 100 disease **characterized by uncontrolled growth**, spread of abnormal cells
  - Cancer cells ignore signals to specialize, stop dividing, or to die
- Cells divide in a haphazard manner & usually form a non-structured mass or tumor
  - Benign tumors generally stay in one place
  - Malignant tumors can **metastasize** & spread to other parts of the body
- Cancers have been **associated with genetic, dietary, & environmental factors**, as well as **smoking & infectious agents**

Tumor Rules

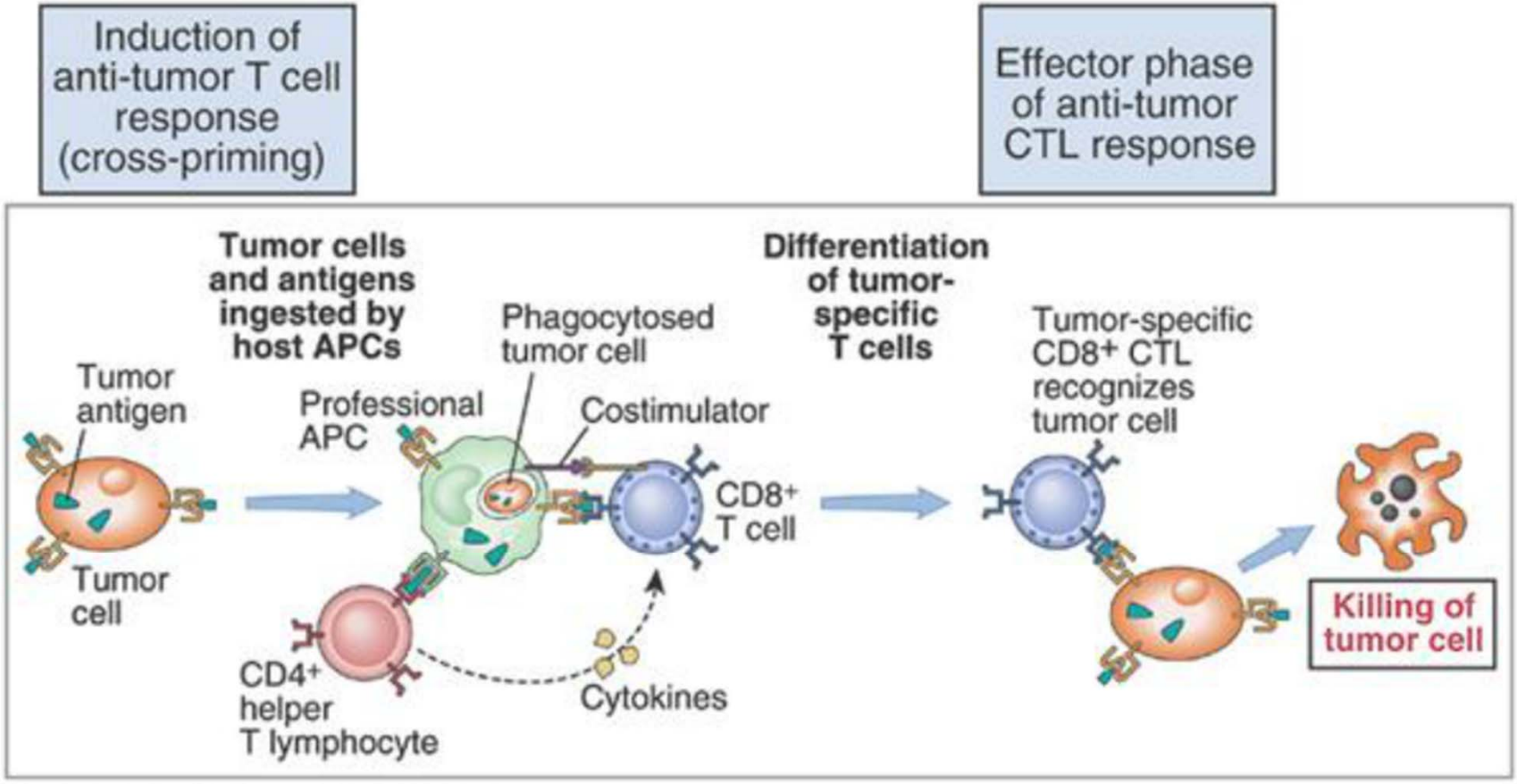
- **Tumor cells are normal host cells that have mutated or changed**
- They can be characterized by their **location** in the body, or by **what triggered** the changes
  - **Altered surface proteins** (ags) may appear from radiation
  - **Oncogenes** can be triggered to make **mutated products inside the cell**
  - **Too many self proteins** can be expressed on some melanoma cells
  - **Oncogenic viruses** can also generate **mutated proteins** in certain cancers
- These tumor cells can be recognized by CD8+ T cells



CD8+ T cell Response to Tumors

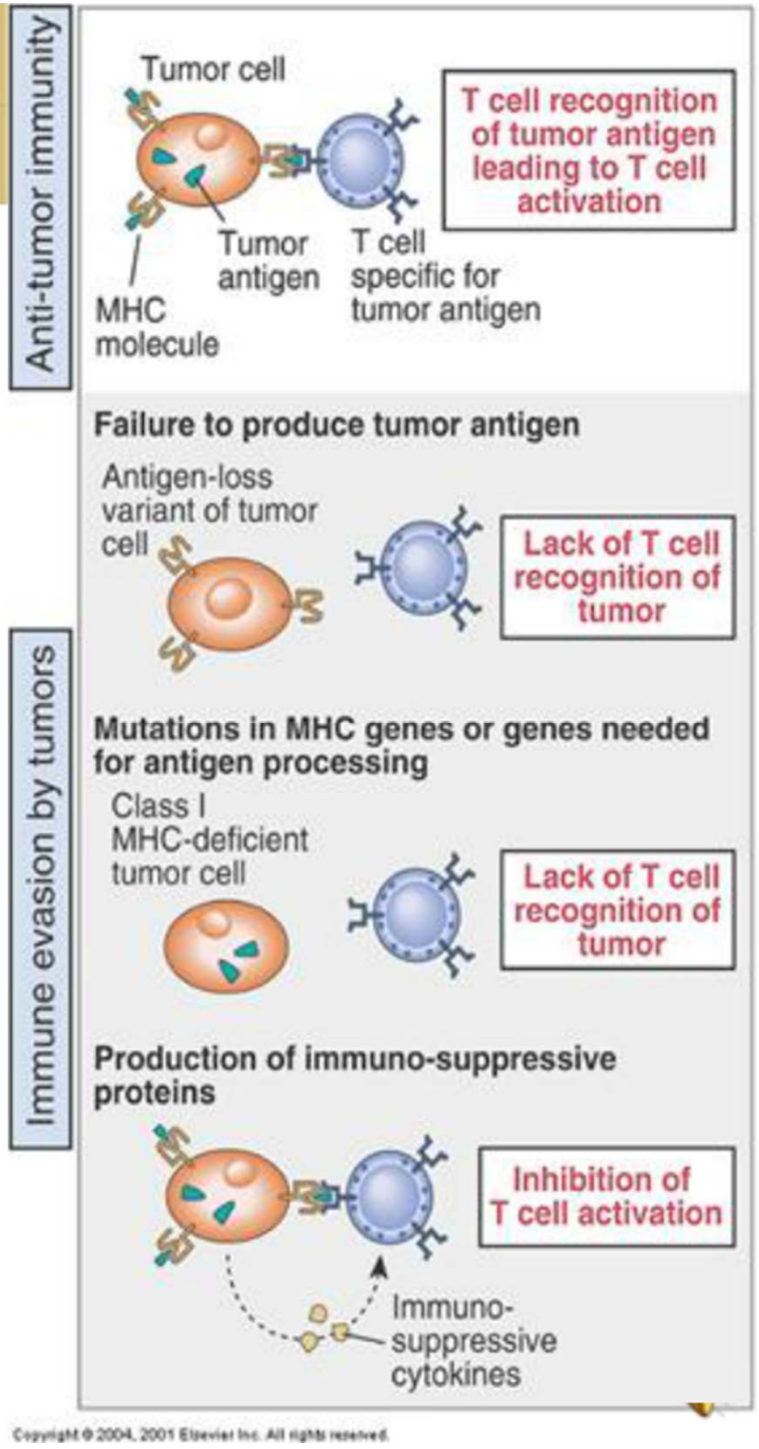


Cytolytic T cells (grey) show attacking a tumor.



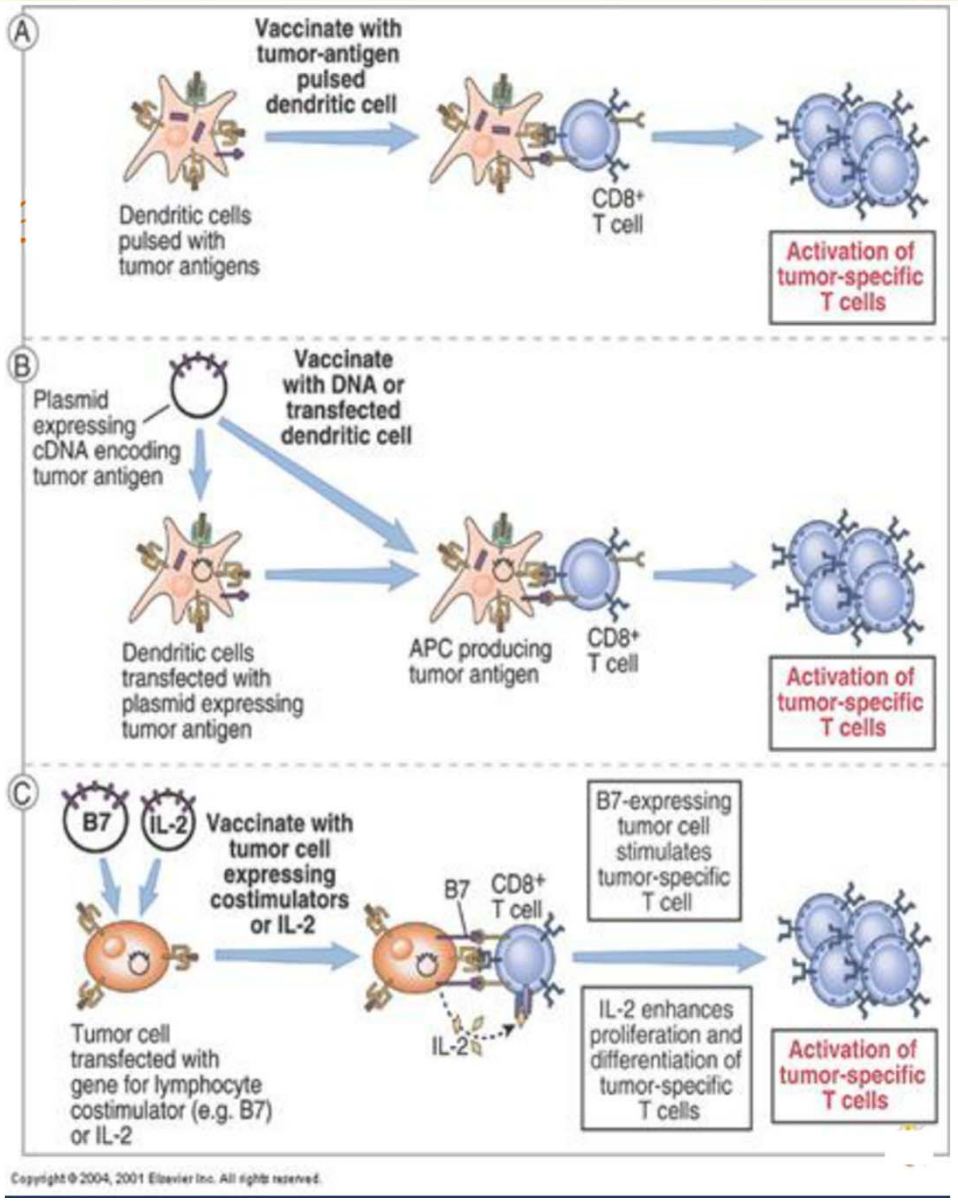
Tumor Evasion Stratagies

- Tumors are difficult to contain – **grow extremely rapidly**
- Tumor antigens also **closely resemble "self"** as they were at one time normal host cells
- Also have evolved several **evasion strategies** to beat the immune response
  - Lose expression of tumor antigens
  - Down-regulate production of MHC I molecules (prevent CD8+ cells from knowing that the normal cell is now cancerous, no ag presentation)
    - **NK cells** provide redundancy in immune response to prevent this strategy
  - Secrete cytokines that inhibit the cellular immune response



Cancer Vaccines

- **Only 2 vaccines currently available** that prevent cancers (both due to infectious causes)
- Need for vaccines that can treat (& prevent) oncogenic cancers
- **Personalized tumor vaccines** – inject own tumor cells with modifications to **induce stronger immune response**



Good News: Cancer Therapies

- Until the last several years, successful cancer therapies included radiation, chemotherapy, and surgery (or a combo of all 3) to remove or diminish the cancerous cells
  - However, these therapies have significant side effects, including immunosuppression of the good guys while killing off the cancer (bad cells)
- Watch the brief videos listed this module in Canvas that describe significant breakthroughs in cancer treatment & vaccines that attempt to minimize damage to the normal cells

In Summary

- Understand the principles of T & B cell tolerance (central & peripheral) to control autoimmunity
- Identify mechanisms that lead to autoimmunity
- Define & identify examples of autoimmune diseases
- Describe each of the 3 types of organ rejection
- Identify the mechanisms of organ rejection
- Identify how tumor cells are not “normal”
- Identify immune evasion strategies employed by cancer cells
- Identify types of cancer vaccines

Self-Test Questions

- Define autoimmunity. What 2 factors influence the development of autoimmune diseases?
- What is central T cell tolearnce? How does it differ from peripheral tolerance?
- What do regulatory T cells do? What is receptor editing in B cells? How do these functions prevent autoimmunity?
- What is molecular mimicry?
- Describe allorecognition (textbook). How does this influence organ rejection?
- What are the 3 types of rejection? How is the type of rejection characterized?
- Name 2 classes of drugs that limit immune rejection of transplants. How do they work?
- What is the ABO system?
- How are tumor cells different from normal cells?
- How do CD8+ T cells kill tumor cells? What provides the second signals, if they are targeting self (cancerous) cells?
- How do tumor cells evade the immune response?
- Describe 2 types of cancer vaccines.