SLIDE 1 For the rest of the semester, we will discuss how it all goes wrong! Block Five will elaborate on how the immune system that is so important for our protection (as we saw with HIV/AIDS) can be a double-edged sword and cause serious, often fatal, diseases. Autoimmunity, Transplants, and Tumors. During this week’s presentation, we will discuss the immunologic basis of autoimmune diseases, organ transplantation & rejection, and the defense against cancerous tumors. At the center of the immune response is the concept of self. The immune response must be able to distinguish self antigens from foreign (non-self) antigens to destroy invading pathogens, and not attack healthy normal cells. Consequently, several mechanisms have evolved to prevent an autoimmune response, including keeping a constant watch on T & B cells & “policing” them to prevent their attack on self antigens. However, a combination of genetics & environmental factors can trick the immune system into attacking self & these reactions can lead to autoimmune diseases. In addition, we will discuss organ Transplants where the concept of self is critical to if the recipient’s immune system will reject the donors graft. Finally, we will discuss how the immune system recognizes our normal cells turned bad- cancer cells!

SLIDE 2 Learning objectives: Autoimmunity, Transplants, & Tumors

- 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

Autoimmunity is loosely defined as an immune response against self. Autoimmune diseases may affect different body systems (such as diabetes and insulin production vs. rheumatoid arthritis and joint destruction), and are a family of over 80 chronic illnesses. Defects in the immune system cause the body to attack its own cells, organs, and tissues, often leading to disabling diseases. Autoimmune diseases have been increasing over the last few decades. Estimates indicate that between 14.7 to 23.5 million people in the United States have an autoimmune disease, with 75% of the cases occurring in women. The exact cause of autoimmune disease is unknown, but two major factors contribute to impaired immune function: genetics and environment. A mix of these factors is believed to contribute to all autoimmune diseases. For example, the risk of developing an autoimmune disease can be attributed to heredity in 1 out of 3 cases, and it is believed that autoimmune diseases often run in the family.

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

Tolerance is the lack of an immune response after exposure to a particular antigen. Tolerance refers to the specific non-reactivity of the immune system to an antigen despite previous exposure to the same antigen. This can be both positive and negative!! On the positive side, there are innumerable harmless antigens in our environment that should not produce an immune response. And, the most important form of Tolerance is the non-reactivity to self antigens. However, for individuals with allergies, this Tolerance does not occur. On the negative side, certain microorganisms can induce immune Tolerance to their antigens. This means that those microorganisms can remain in the body without being eradicated. Tolerance is an active Ag-dependent process that needs continuous stimulation by that antigen (i.e. self antigens). It is specific and can exist in T & B cells like immunologic memory, although T cell Tolerance is longer lasting that B cell Tolerance. Tolerance can be broken naturally (in autoimmune diseases) or artificially (experimental drug treatments, irradiation, etc).
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 antigens in the thymus can develop into regulatory T cells
- Induced by repeated activation of immature T cells by self-antigens 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
SLIDE 8 With anergy, the T-cells recognize the antigen but do not produce an immune response to the antigen. This is an important mechanism to prevent recognition of self antigens, because T cells bump into self antigens constantly. That is why second signals are necessary to turn on a T cell because you want to avoid T cell activation against self antigens, which are in much higher concentrations than pathogen antigens at any time in the body. If adequate levels of costimulators on not present on APCs, then the T cell will become anergic and cannot be activated. The T cell will always behave this way, even if an APC later sends second signals to the T cell.

SLIDE 9 Or, some the T-cells that are reactive to self-antigens become regulatory T-cells and then “police” the other T-cells that may become self-reactive. Regulatory T cells major role is to shut down a T cell mediated immune response at the end of an immune reaction. Tight regulation of a T cell response is extremely important to prevent damage to healthy cells or tissues by the inflammatory response that accompanies T cell activation & cytokine release. The presence of an intracellular molecule called FOXP3 can distinguish T reg cells from other T cells. If this FOXP3 gene is mutated, regulatory T cells do not develop properly and can cause fatal autoimmune diseases (discussed more in Week Fifteen).
**Slide 10**

**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
  - Produce new antigen receptor that is not self-reactive

**Slide 10** B-cells also have both central and peripheral Tolerance. Central Tolerance in B-cells may develop through either negative selection or receptor editing. Receptor editing allows the B cell to change its B cell receptor (Y shaped antibody molecule, remember?) if it reacts against self antigens. The B cell will reactive its recombination genes to create a new BCR that is not self-reactive, thereby checking itself. This edited B cell can then move to peripheral lymphoid organs, whereas a self-reactive B cell will die by apoptosis. Recent research indicates that B cell Tolerance is also important to prevent autoimmunity, although T cell Tolerance dominates the immune response.

**Slide 11**

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

**Slide 11** Peripheral B-cell Tolerance may occur if plasma cells are continually exposed to high levels of self-antigens in secondary lymphoid organs.

**Slide 12**

**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 environmental factors

**Slide 12** Most types of autoimmunity in humans begin for no obvious reason, apparently by chance. Autoimmunity occurs when the immune system begins reacting to self-antigens. Normally, negative selection during the production of immune cells stops this process. But, both genetic and environmental factors can affect the development of autoimmunity. Certain genotypes have been linked to different autoimmune diseases and hereditary factors make some people have a higher risk than others, but even within families it is difficult to predict who will get the disease & who will not. Researchers suggest that human autoimmunity may begin with a chance event in the immune system (like an infection, or other environmental factor), and then develop into a continuous cycle. Autoimmunity can be both humoral and cell-mediated; and, disease may not always be detectable even though autoimmunity is
present. Autoimmunity is created by the breakdown of mechanisms responsible for self tolerance, which leads to an immune response against self. Because T cells direct “regular” immunity, it is thought that autoimmunity may start with T cells mistaking self for non-self. These self-reactive T cells would then direct the production of auto-antibodies by helping B cells to recognize self antigens. It has been shown that both antibodies and effector T cells are involved in the damage in autoimmune diseases.

SLIDE 13 Infections can induce autoimmunity. Some microorganisms can alter APCs by inducing costimulators on the APCs. These altered APCs then present self-antigens to T-cells thus inducing an immune reaction against self-antigens. Some microbes can also “mimic” self-antigens. The body develops a normal immune response against these microbes and eliminates them. However, the immune system has now been primed to attack self-antigens which resemble those microbial antigens. This process can occur with Streptococcus infections; and, the body can be primed to attack cardiac tissue (rheumatic heart disease)...

SLIDE 14 Insulin-dependent diabetes is an example of autoimmunity. The body develops an immune response against the beta cells in the Islets of Langerhans in the pancreas and destroys these extremely important beta cells. It’s the beta cells that produce insulin!! Insulin allows glucose to enter the body’s cells. Glucose is the primary energy source for the majority of the cells in the body. Just as a note, there is also non-insulin diabetes. Non-insulin diabetics do produce insulin; but, the amounts may be insufficient for their body’s needs or the body’s cells may have become unresponsive to the insulin even at increased insulin levels. Certain species of the malarial parasite can also induce autoimmunity. Plasmodium malariae can induce kidney damage.
**Slide 15**

**Periodontal diseases**

- Widely prevalent chronic inflammatory disorders induced by a bacterial biofilm found on teeth.
- Periodontosis
  - 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 response.

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**Slide 16**

**Multiple Sclerosis (MS)**

- MS is an autoimmune disease that primarily affects 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.

SLIDE 16 A T cell mediated attack of self often is deadly. This type of autoimmunity is seen in Multiple Sclerosis (MS). In MS, T cells are believed to attack nerve tissue, increase inflammation in the area, and demyelination of the axons results. The central nervous system (CNS) is heavily infiltrated by lymphocytes in this disease. Local immune reactions induce the production of inflammatory cytokines from T cells. It is not known exactly what leads to demyelination of the nerves, but potential theories include a direct T cell attack on myelin-producing oligodendrocytes or as a bystander effect from local inflammation.

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**Slide 17**

**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.

SLIDE 17 Transplantation of organs has been practiced for over a century. Of course, successful Transplants that resulted in at least 5 additional years of life has only been a common occurrence since the 1950s-1960s, when important classes of immunosuppressive drugs were found to prevent graft rejection. An organ transplant is the transplantation of a whole or partial organ from one person to another to replace the recipient's damaged or failing organ with a working one from the donor. This is called an allograft. A xenograft is an organ transplant between 2 different species, such as a pig heart valve into a human. An allograft is an organ transplant between 2 members of the same species, for example human to human. In
almost all cases, these two people are not identical twins & have a different genetic make-up. The high polymorphism present in the MHC gene complex makes it extremely difficult to find a “perfect” match between an organ donor & an organ recipient, but related donors generally share some MHC antigens which can improve graft acceptance. Recent advances in immunosuppressive therapy has made it possible to transplant organs between people that are not close relatives or have matching HLA antigens.

SLIDE 18 Donor antigens on transplanted tissues may be recognized either directly or indirectly by the new host’s immune system. With direct recognition, the donors APCs present donor MHC antigens to recipient T-cells thus resulting in acute rejection. With indirect recognition, the recipient's APCs present donor MHC antigens to recipient T-cells thus resulting in chronic rejection. Note the illustrations of antigen recognition in allore cognition as compared to normal.

SLIDE 19 There are both donor and recipient factors contribute to the immune response to the donor tissue. The major donor factor is the expression of MHC antigens on the donor tissue and the presence of APCs within the transplanted graft. In contrast, the major recipient factor is any previous sensitization against ABO and HLA antigens expressed on the graft or other foreign antigens.
There are several forms of organ rejection including hyperacute (and accelerated), acute, and chronic. The time duration and histopathology (cells involved in the rejection) determine the type of rejection. Note the illustration of the histopathologic characteristics and the type of damage caused in each type of rejection.

Hyperacute rejection can occur almost immediately and is a response against ABO blood group antigens, vascular endothelial antigens and/or histocompatibility (HLA) antigens.

Accelerated rejection is a variation of hyperacute rejection; however, this is a cellular immune response. Accelerated rejection can occur with days to a few weeks after a transplant.
**Acute Graft Rejection**

- Due to a cellular immune response involving mononuclear, cytotoxic and Th cells, monokines, and lymphokines.
- 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.

SLIDE 23 Acute rejection involves a cellular immune response that occurs when antigen is trapped in recipient macrophages and cannot be removed. Acute rejection may occur as early as a week after transplantation. However, the greatest risk of acute rejection is within the first 6 months after transplantation. Mononuclear cells, cytotoxic T-cells, and Th T-cells are important in acute rejection. Nonactivated Th cells encounter specific class II antigens on the donor organ and become activated, and then produce receptors for lymphokines that are concurrently released from monocytes. Activated monocytes release lymphokine IL-1 producing clonal expansion of the activated T-helper cells; and, lymphokine IL-2 which activates and produces the clonal expansion of cytotoxic T-cells.

SLIDE 24 Chronic rejection may take years to occur; but, it likely begins at the time of transplantation. Both T-cells and B-cells are involved in chronic rejection. Cytokine overproduction (including TGF-beta and platelet-derived growth factor) contributes to fibrosis and continuous production of antibody against the graft produces the arteriopathy.
**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

**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

**SLIDE 25** Organ transplantation is in high demand as the technology has far outstripped the supply of available organs. Modern immunosuppressive drugs, such as cyclosporine & its later derivatives, have revolutionized the field of transplantation. Now these classes of drugs are effective at dampening the T cell mediated immune response to non-self, donor organs. Remember, these organs have another person’s unique MHC molecules & will stimulate the recipient’s immune response to attack them. Consequently, these modern drugs often work on T cells and inhibit cytokine production & the inflammatory immune response that will reject the new organ. This has improved survival rates as the graft replaces a “broken” organ that would limit the recipient's life span.

**SLIDE 26** Human red blood cells can be grouped 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.
SLIDE 27 During blood transfusions, if the wrong type of blood is given, immune reactions can occur against the donated blood cells. For example, if AB-type blood is given to someone with Type A, Type B, or Type O blood, an immune response will occur due to the foreign antigens. This is why blood has to be typed before it is given. There are also other antigens found on red blood cells that can induce immune reactions; however, these reactions are usually not as severe as those that will develop with mismatching of the ABO system.

SLIDE 28 8.1 million new cancer cases are diagnosed each year, and cancer is perhaps one of the most dreaded diagnoses worldwide. Although some cancers are treatable, the procedures used to remove the tumor are painful, reduce a lifetime of immunity to zero, and may not “cure” the disease. The term cancer is used for a number of different diseases, but they all share 2 characteristics: The diseases develop from cells that divide and grow uncontrollably. Initially, the cancer is restricted to the site of origin, but early in the disease, malignant cells may break loose and travel to other regions of the body (metastasize) to create daughter tumors. In the normal situation, cells grow and divide to reproduce only when needed by the body. Sometimes abnormal cells keep dividing uncontrollably, often due to mutations of the genes within the cell. These cells form a mass called a tumor. Like autoimmune diseases, a combination of factors, including genetic susceptibility, environment and personal lifestyle, can work together to cause cancer. No single determining factor or cause for cancer is known.
SLIDE 29 Cancer cells are very effective at getting their way & dividing, dividing, dividing. The reason for this is that the normal immune response to a tumor is quite weak. The immune system has trouble recognizing the cancer cell as being bad, because at one time it was a normal cell & is still very similar to a healthy cell (except with lots of genetic abnormalities, and some altered surface proteins). As a result, the immune system fails to recognize the danger and does not initiate a strong immune response against tumor cells. Cytotoxic T cells provide the best defense against these cells because they recognize altered nucleated cells in the body.

SLIDE 30 Because the cancer cells can alter their appearance, it is difficult for the immune system to “see” them as no longer being self and now as a threat. It is the job of APC and helper T cells to activate the CD8+ T cells to kill the tumor cells. Cross-priming helps to activate the cytotoxic T cells, as an antigen presenting cell will actually come to the rescue & take up the tumor cell &/or tumor antigens. These professional APCs then will process the antigen as foreign & present it to both helper and cytotoxic T cells. These cells then can provide the necessary second signals to activate the CD8+ cells to differentiate & kill the tumor.
Tumor Evasion Strategies

- 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 Evasion

- There are many molecular differences between normal cells and tumor cells, but cancer antigens are not truly foreign to the body, as they are usually altered in subtle ways or more abundant normal proteins. As if this were not enough, cancer cells have also developed immune evasion strategies. Cancer cells can shed tumor antigens, reduce the number of molecules and receptors needed to activate T cells and other immune responses, and they can secrete cytokines that will inhibit a T cell 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

- Cancer vaccines may contain cancer cells, cancer antigens, or parts of cells. By adding parts of the cancer back into the body, these vaccines will enhance the immune response against cancer cells that are already present in the body & boost the weak immune response to cancerous cells. This type of vaccine is still mostly experimental. However, 2 vaccines have been approved that reduce cancers - both are to prevent viral infections. Hepatitis B virus has been shown to cause liver cancers and human papilloma virus (HPV) is an important cause of cervical cancers. Consequently, no “true” vaccine exists that will directly target a growing tumor, as these vaccines prevent the infections that may provide an environmental stimulus that triggers cancer development or loss of Tolerance. There are several types of cancer vaccines in development, including antigen/adjuvant vaccines, whole cell tumor vaccines, dendritic cell vaccines, idiotype vaccines, and viral vectors/DNA vaccines. Patient specific vaccines are a treatment option that seeks to use the patient’s own tumor cells to create a strong immune response to other cancerous cells in the body.
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 tolerance? 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 (bookend). 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.