Slide 1

SLIDE 1 Cell Mediated Immunity. This presentation introduces the cell-mediated immune response, which is the second arm of the adaptive immune response. Important topics will include antigens, T cells, and characteristics of cytokines. Like the humoral immune response, the cell mediated immune response is extremely effective and specific for a pathogen. The importance of T cells to the immune system and health will be emphasized through our discussion of HIV and Acquired Immunodeficiency Syndrome (AIDS).

Slide 2

SLIDE 2 Learning objectives for Week Ten: Cell Mediated Immunity.

- Describe the cell mediated immune response and characteristics of T cells
- Identify the characteristics of antigens, haptens, & mitogens
- Describe the process of positive & negative selection of T cells in the thymus
- Identify the similarities & differences of CD4 vs. CD8 cells
- Identify the similarities & differences of Th1 and Th2 cells
- Identify the characteristics and functions of cytokines

Slide 3

SLIDE 3 In this Block, we will cover the second arm of the acquired, or adaptive, immune response. Cell mediated immunity (CMI) is largely a response of T lymphocytes that serve to defend the body against intracellular microbes. T cells can also influence other cell types through the production of cytokines to recruit macrophages to injury sites, or stimulate B cells to produce antibodies to the foreign organism. Overall, this response must be tightly regulated because cytotoxic T cells have the ability to directly kill other cells. In addition, it takes time to slow an active T cell response, especially as T cells produce many cytokines to stimulate other cells. It is critical to ensure that it is for the right reasons!!
SLIDE 4 Cell mediated immunity is extremely important in the defense against certain organisms. A T cell response is necessary to protect the body from these intracellular organisms as antibodies cannot reach inside cells. T cells have the ability to specifically target infected cells, and may either kill the infected cell or help B cells make antibodies to the organism. Consequently, if T cells are not present in the body to bridge the “intracellular” gap, these organisms (such as viruses or mycobacteria) may multiply unchecked in the body because the humoral immune cannot defend against intracellular pathogens. Keep in mind that most AIDS patients die as a result of innocuous infections that a healthy immune system can control, except for the destruction of T cells and the cell mediated response! Without cell mediated immunity, we would all share a similar fate.

SLIDE 5 First, a fundamental concept of this lecture is to appreciate the ability of the immune system to correctly identify a foreign microbe or antigen (often a fraction of the size of a red blood cell) within the midst of the billions of cells that are normally present in the body. T cells constitute a large part of the CMI defense, as they continually “patrol” the body on the lookout for foreign invaders or abnormal cells (such as cancer cells). Consequently, T cells must be able to see both the good (normal host cells) & the bad stuff (foreign antigens) in the body. This lecture will describe some of the mechanisms that T cells use to distinguish between self and non-self.
### Slide 6

**What is self?**  **Answer: MHC**
- How does a B or T cell know that it is bumping into one of our cells or into a bacteria or virus (foreign antigen)?
- The immune system first needs to know what is foreign vs. what is self
- Major Histocompatibility Complex (MHC) molecules are the “self” identifiers.

SLIDE 6 Major histocompatibility complex molecules are present on all cells in the body. These proteins are like name tags, in that they identify each cell as “self” to a T cell. That way there is little chance of T cells accidentally mistaking a host cell as foreign & killing it! We will discuss MHC molecules in much greater detail next week as we further describe their role in antigen presentation.

### Slide 7

**Major Histocompatibility Complex**
- Two classes of membrane proteins encoded by the MHC genetic locus
- (MHC I & MHC II)
- These genes are found in all mammals, not microorganisms (i.e. self!)
- Function to display antigen peptides to T cells

SLIDE 7 Major Histocompatibility Complex (MHC) is a membrane bound protein that functions to display antigen peptides to T cells. The genes that encode these proteins are highly polymorphic, meaning that no person has the exact same MHC as another person (except identical twins). In people, these molecules are more accurately called human leukocyte antigens (HLA), which is important in tissue typing to match transplant organs, etc. These genes are found in all mammals, but not in microorganisms. Consequently, the immune system uses these MHC proteins to recognize cells in the body as “self”.

### Slide 8

**What is foreign?**  **Answer: Antigens**
- Substances foreign to the host which are capable of inducing an immune response and of reacting specifically with the products (cells / antibodies) of that response
- These substances are more accurately called immunogens

SLIDE 8 Antigens are substances that are foreign to a host. They are capable of inducing an immune response and reacting specifically with the immune system.
### Slide 9

**Potent Antigen Characteristics**
- Proteins > Polysaccharide > Lipid
- **Chemical complexity**: bacterium > homopolymer
- Molecular size – macromolecules (MW > 10 Kb)
- **Immunodominant** epitopes: exposed & flexible
- **Rigidity** – particular Ags taken up by cells of RES (phagocytes)
- **Foreign** – degree of difference from host
- **Host factors** also play a role, including physiological conditions, genetic make-up (MHC)

### Slide 10

**Definitions:**
- **Antigenic determinants** (Epitope): actual portion of Ag molecule that determines specificity and binds to product of immune response
- **Lock & key theory** – binding of the epitope (via MHC & the TcR) is the key that opens the locked T cell, priming it for action

### Slide 11

**Antigen does not necessarily = Immunogen**
- An antigen simply can be a molecule that binds to an antibody or to the TcR
- However, not all antigens are capable of eliciting an immune response (immunogen)
- Haptens & mitogens are 2 examples

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SLIDE 9 Antigens that produce a strong immune response typically have the characteristics that are listed on this slide. Antigens that are protein-based are the most potent and generate the best immune response, because they are presented to T cells.

SLIDE 10 An epitope is the portion of an antigen that determines the antigenic specificity; and, it is the epitope that actually binds with antibodies and immune cells. The epitope can be considered the key that opens the lock to trigger an immune response.

SLIDE 11 However, not all antigens are immunogens that react specifically with the immune system. The following slide will describe 2 examples of these antigens: haptens & mitogens.
**Slide 12**

In contrast, a hapten is an incomplete antigen because it cannot elicit an immune response but can react with antibodies and immune cells. In order for a hapten to elicit an immune response, it must be bound to a larger carrier.

Mitogens are substances that can nonspecifically activate T-cells and B-cells. Mitogens can be used as an indicator of cell type and function. For example, certain mitogens may only trigger T-cell activation or only B-cell activation. With the correct mitogen, the activated immune cells will rapidly multiply.

**Slide 13**

The thymus is the site of T cell maturation. Pre-cursor T cells are produced in the bone marrow & then migrate to the thymus to complete their development. These T cells begin as pro-T cells or double-negative T cells and then undergo a maturation process to differentiate into two different classes of T cells. This maturation process is designed to select T cells with T cell receptors (TcR) that can recognize MHC molecules (remember the process of antigen presentation!).

**Slide 14**

Refer to pages 73-74 & 80-81 in the textbook for information on negative & positive selection of T cells, with a nice illustration of the process (p. 81). T cells undergo this strict selection process because the immune system must ensure that T cells that strongly recognize “self” antigens (MHC) are destroyed to prevent T cell attacks on self, autoimmunity. This is negative selection- most T cells never make it out of the thymus due to this strong recognition and they die by apoptosis. In positive selection, the T cell receptor (TcR) weakly recognizes self antigens (MHC) and is allowed to mature. Again, the TcR must be able to “see” self antigens, so that it can participate in antigen presentation from the body’s own cells.
In the thymus, T cells will mature into two T cell subsets: CD8+ class and the CD4+ class. Initially, double-positive T cells contain both the CD4 & CD8 coreceptors. After positive selection, these T cells weakly recognize MHC with their TcR. If the T cell recognizes Class I MHC molecules, then it will lose the CD4 coreceptor & become a CD8+ cell. If the T cell recognizes Class II MHC molecules instead, then it will lose the CD8 coreceptor & become a CD4+ cell. These single-positive T cells are then allowed to leave the thymus, as either cytotoxic (CDB) cells or helper (CD4) cells.

T cells can be divided into 2 major classes: cytotoxic and helper. The CD8+ class display a CD8 co-receptor on their surface and only recognize major histocompatibility complex I proteins. These cells have the ability to kill other cells and are essential to the control of intracellular pathogens. Cytotoxic (or cytolytic) t cells must be closely regulated because of this special ability that may cause autoimmune destruction of normal cells. The CD4+ class display a CD4 co-receptor on their surface and recognize major histocompatibility complex II proteins. These cells are more commonly known as helper t cells because they are essential for antibody mediated immunity. They can present antigens to B cells and stimulate antibody production. The CD4+ class can then be broken down into 2 subsets: Th1 and Th2. Th1 cells increase a cell mediated response (usually by macrophages) to ingest and destroy a pathogen, whereas Th2 cells are the ones that stimulate B cells.
SLIDE 17 This slide shows the differences in antigen recognition between Tc cells, Th cells, and B cells. Notice also how helper effector T cells can stimulate other cells to kill ingested microbes and have an important role in inflammation, whereas CD8 T cells can directly kill an infected cell.

SLIDE 18 The T cell receptor (TcR) is critical for antigen recognition because it interacts with the MHC molecules complexed to peptide antigens. The TcR has tremendous diversity (similar to B cell Fab regions) as coded by variable gene segments V, D, J & C. Unlike B cells that use somatic mutation to increase antibody affinity for an antigen, the TcR does not undergo additional mutations. Coreceptors are important for recognition of MHC molecules (CD4-MHC II or CD8-MHC I), and rare functionally segregated into helper and cytotoxic cells. In addition, several accessory molecules are present on the surface of a T cell & antigen presenting cell with important signal transduction and adhesion functions.

SLIDE 19 T-cells recognize antigen in association with the major histocompatibility (MHC) molecules. MHC II is a recognition signal between antigen-presenting cells and T-helper cells. In contrast, MHC I is used by T cytotoxic cells for recognition.
SLIDE 20 This slide compares Tc (cytotoxic) and Th (helper) cells. Notice the different receptors on each cell type. Depending on the type of cell infected, either the CD4 or the CD8 T cell subset will respond (also known as antigen presentation & recognition). These concepts be described further next week.

SLIDE 21 This slide shows diagrams of B-cells, T-helper (Th) cells, and T- cytotoxic (Tc) cells. Notice the different receptors on each cell type.

SLIDE 22 Human immunodeficiency virus (HIV) is an RNA virus that can transcribe its RNA into DNA to make copies of itself inside the host. The virus then exits the host cell and takes part of the host cell membrane to envelope itself. Something that also helps it evade the immune response and infect more cells! Vaccines have been developed to target several of these embedded viral proteins, but so far none has proven successful. This retrovirus causes AIDS, acquired immunodeficiency syndrome, a condition where the immune system fails from depletion of T cells leading to life- threatening opportunistic infections. It was first recognized in 1981 and has killed more than 25 million people.
SLIDE 23 The importance of CD4+ cells in protecting the body has been dramatically proven by the human immunodeficiency virus (HIV). This virus needs the CD4 co-receptor to enter a cell and continue to replicate. Once the virus enters the body, it is taken up by dendritic cells (APCs with MHC II on the surface, which then presents the antigen to CD4 cells) & then CD4 cells come to the rescue and become infected. These cells are then depleted over time, as the body does not produce enough new CD4 cells to replace the ones that are killed by HIV.

SLIDE 24 Decreased numbers of CD4 cells also influence CD8 (cytotoxic) T cell activation. Consequently, the virus is allowed to replicate unchecked, as CD8 cells are not activated to kill the viral-infected cells. In addition, HIV also depletes memory T cells (as they have the most CD4 co-receptors) and this leads to an inability of the immune system to fight other infections. Immunodeficiency and eventual death will result, primarily from opportunistic infections that the body cannot control.

SLIDE 25 This graph shows both the HIV viral load and the level of CD4+ T cells in the body during the course of an untreated infection. Currently, HIV treatment options have improved health and extended life expectancy for persons with the disease as they attempt to control the level of HIV in the body & maintain CD4+ counts.
SLIDE 26 HIV was first discovered in gay men 25 years ago. Despite intensive prevention & educational campaigns in the last decade to slow the spread of HIV, millions of new infections occur each year. In 2005, global estimates indicate that more than 38 million people were living with HIV, with as many as 46 million people actually infected because of the probability that millions of people that have the virus do not know their status. Currently, Sub-Saharan Africa is most impacted by this virus, where many are too poor to afford the medications to control the infection. It is believed that India and China may also have millions of undiagnosed cases because of cultural beliefs and poor access to health care.

SLIDE 27 This table provides a look at HIV infections & the number of AIDS death by region around the world. Note that Sub-Saharan Africa leads the world with the number of cases, new infections, and deaths due to HIV. In addition, over 6% of adults are infected with the virus. Compare that to 0.5% in North America and some parts of Europe. The numbers of deaths from AIDS in 2005 also indicate that access to health care & HAART drugs is not uniformly distributed around the world. The following information was taken from the 2005 UNAIDS global fact sheet: ‘There are more new HIV infections every year than AIDS-related deaths.’ Worldwide, less than one in five people at risk of becoming infected with HIV has access to basic prevention services.. Across the world, only one in eight people who wish to be tested currently has the ability to do so.’ Each day, 1800 children worldwide become infected with HIV, the vast majority of them newborns. In 2005, only 9% of pregnant women in low- and middle-income countries were offered services to prevent transmission to their newborns. HIV can be transmitted by breast milk, and many HIV + women cannot afford to purchase formula for their infants.
SLIDE 28 Cytokines are known by a variety of terms. There are several functionally related groups of cytokines and, cytokines may be produced by different cell types.

SLIDE 29 Cytokines influence the development of all immune cells. The type of cytokine produced decides if a stem cell will differentiate into the myeloid lineage or the lymphoid lineage. Then additional cytokines influence the differentiation of these lymphoid cells into T cells, B cells, NK cells, etc.

SLIDE 30 Cytokines are low molecular weight glycoproteins that act as signals between cells and are involved in the regulation of all biological processes. They are actively synthesized and secreted then produce a local effect. Cytokines have high affinity thus they are very potent at low concentrations.
**Slide 31**

Cytokines: Characteristics

- **Actively** synthesized & secreted (not stored)
- **High affinity** – great potency at low concentrations
- May act locally by binding to cell receptors
- May be **multifunctional**
- Rarely exert effect alone (words in a sentence)
- Involved in the **regulation of all biological processes** (not just immune response)

**SLIDE 31** Cytokines can be multifunctional and rarely exert their effect alone. They are also involved in all biological processes, and not just in immune regulation. They provide cellular communications throughout the body.

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**Slide 32**

Cytokines & Regulation

- Cytokine production is transient and tightly regulated
- Act **synergistically** or **antagonistically**
- Regulate expression of receptors, self & other cells
  - Cytokine receptors shed and bind soluble cytokine molecules
  - Receptor antagonists bind to specific receptor, don’t transmit signal
  - Cytokine inhibitory Proteins may bind to receptor or cytokine

**SLIDE 32** Cytokine production is transient and tightly regulated. Cytokines act in either a synergistic or antagonistic manner to regulate the expression of receptors. Receptor antagonists bind specific receptors and prevent signal transmission. Cytokine receptors are also shed and can bind soluble cytokine molecules.

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**Slide 33**

Cytokine World

**SLIDE 33** Diagram of the immune cytokine world. Note again how the type of cytokine influences different immune cells. Cytokines act as the communication link between the different cell types.
Cytokines are extremely important to maintain the immune system and other physiological functions. This slide shows the numerous and vital interactions of cytokines in the immune response. Cytokines are extremely important to the immune response as they effect many different cells.

In Summary
- Cell mediated immune response & intracellular organisms
- Self vs. foreign
- MHC restriction for T cells (e.g., CD4 recognizes MHC II)
- Different types of antigens – immunogen, hapten, mitogen
- T cell selection is thymus
- Types of T cells
- Cytokines

Self-Test Questions
- How is cell mediated immunity different from humoral immunity?
- How can the immune system recognize self? What is foreign?
- What happens if the T cell receptor (TcR) strongly recognizes self MHC?
- What are the 2 types of T cells?
- What MHC does each type recognize?
- What type influences CMI? AMI?
- How does HIV deplete the immune system & memory?
- Name 3 characteristics of cytokines.