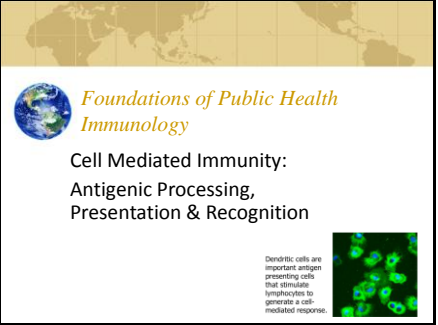
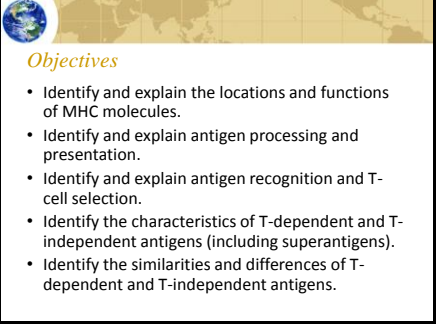
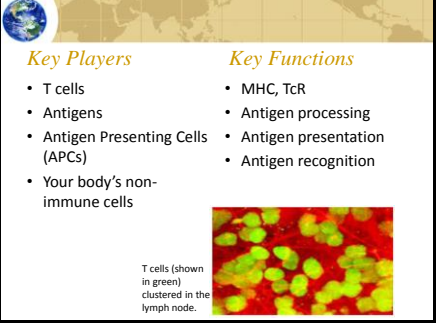
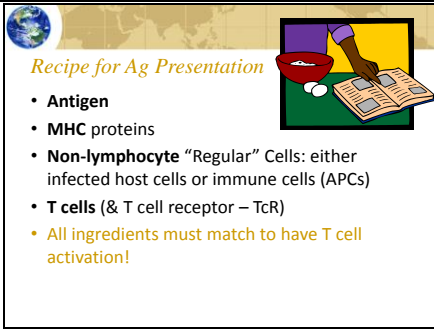


<p>Slide 1</p>	 <p><i>Foundations of Public Health Immunology</i></p> <p>Cell Mediated Immunity: Antigenic Processing, Presentation & Recognition</p> <p>Dendritic cells are important antigen presenting cells that stimulate lymphocytes to generate a cell-mediated response.</p>	<p>SLIDE 1 Antigen Processing, Presentation & Recognition. This week's lecture will describe how T cells recognize antigen in context of major histocompatibility molecules, with important accessory molecules that serve to control T cell activation and prevent autoimmune reactions. T cell activation must be tightly regulated, as it is difficult to slow down the cell- mediated immune response once it has started. Several cell types are involved, cytokine production increases, and activated T cells have the ability to target and kill other cells. The immune system has developed a system of checks that prevent T cells from deciding on their own what antigens to destroy. Consequently, it is necessary for other cells to process and then present foreign antigens to the T cells with additional signals required for recognition and full activation of the cell- mediated response.</p>				
<p>Slide 2</p>	 <p><i>Objectives</i></p> <ul style="list-style-type: none"> • Identify and explain the locations and functions of MHC molecules. • Identify and explain antigen processing and presentation. • Identify and explain antigen recognition and T-cell selection. • Identify the characteristics of T-dependent and T-independent antigens (including superantigens). • Identify the similarities and differences of T-dependent and T-independent antigens. 	<p>SLIDE 2 Learning objectives for Week Eleven: Antigen Processing, Presentation, and Recognition.</p>				
<p>Slide 3</p>	 <table border="0"> <tr> <td><i>Key Players</i></td> <td><i>Key Functions</i></td> </tr> <tr> <td> <ul style="list-style-type: none"> • T cells • Antigens • Antigen Presenting Cells (APCs) • Your body's non-immune cells </td> <td> <ul style="list-style-type: none"> • MHC, TcR • Antigen processing • Antigen presentation • Antigen recognition </td> </tr> </table> <p>T cells (shown in green) clustered in the lymph node.</p>	<i>Key Players</i>	<i>Key Functions</i>	<ul style="list-style-type: none"> • T cells • Antigens • Antigen Presenting Cells (APCs) • Your body's non-immune cells 	<ul style="list-style-type: none"> • MHC, TcR • Antigen processing • Antigen presentation • Antigen recognition 	<p>SLIDE 3 There are Several components that are necessary for a T cell mediated immune response. These include T cells, antigens, Major Histocompatibility Complex (MHC) proteins, and antigen presenting cells. All of these components have a role in processing, presentation, and recognition of antigens to T cells.</p>
<i>Key Players</i>	<i>Key Functions</i>					
<ul style="list-style-type: none"> • T cells • Antigens • Antigen Presenting Cells (APCs) • Your body's non-immune cells 	<ul style="list-style-type: none"> • MHC, TcR • Antigen processing • Antigen presentation • Antigen recognition 					

Slide 4

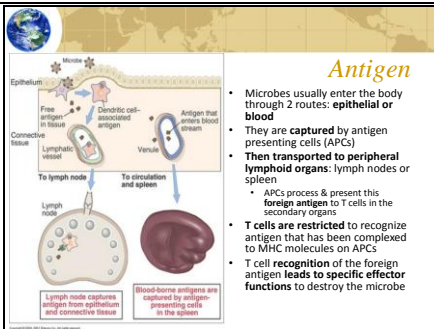


Recipe for Ag Presentation

- **Antigen**
- **MHC proteins**
- **Non-lymphocyte** "Regular" Cells: either infected host cells or immune cells (APCs)
- **T cells** (& T cell receptor – TcR)
- **All ingredients must match to have T cell activation!**

SLIDE 4 In order to present antigens to T cells, Several immune ingredients must come together: antigen, MHC molecules, either "regular" cells or APCs, and T cells.

Slide 5

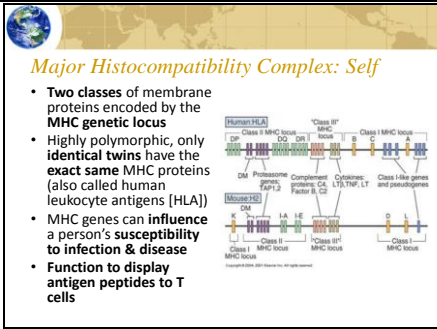


Antigen

- Microbes usually enter the body through 2 routes: **epithelial or blood**
- They are **captured** by antigen presenting cells (APCs)
- **Then transported to peripheral lymphoid organs:** lymph nodes or spleen
 - APCs process & present this foreign antigens to T cells in the secondary organs
- **T cells are restricted** to recognize antigen that has been complexed to MHC molecules on APCs
- T cell **recognition** of the foreign antigen **leads to specific effector functions** to destroy the microbe

SLIDE 5 This week we will discuss the T cell mediated immune response to antigens. Once an antigen enters the body, it will be captured and presented to T cells. T cells are extremely important to create an effective adaptive response to a pathogen, especially as CD4 T cells help B cells and the humoral immune response. We will discuss the importance of antigens that are processed and presented to T cells later in the presentation, as this mechanism is the basis for cell- mediated immunity. Remember that there is an epithelial cell lining that protects most of the body, including the skin, mucosal & gastrointestinal tracts. If a pathogen enters the body through this route, then antigen presenting cells that are present in the area will capture the microbe and process it to display pieces of the protein antigen on its surface. These antigenic peptides are displayed with MHC molecules. Next, these APCs migrate to the lymphoid organs draining the site of infection, where they come into contact with T cells that will recognize the antigen- MHC complex. The T cells will then initiate a cell- mediated immune response.

Slide 6

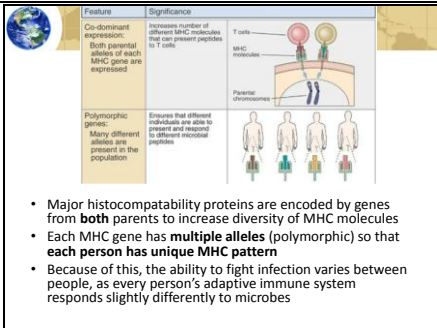


Major Histocompatibility Complex: Self

- Two classes of membrane proteins encoded by the MHC genetic locus
- Highly polymorphic, only identical twins have the exact same MHC proteins (also called human leukocyte antigens [HLA])
- MHC genes can influence a person's susceptibility to infection & disease
- Function to display antigen peptides to T cells

SLIDE 6 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. The human MHC molecule is located on chromosome 6. The Class I gene complex contains three major loci, B, C and A, and the Class II gene complex contains at least three loci, DP, DQ and DR, which are important for tissue typing and matching of proteins. 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 7



Feature	Significance
Co-dominant expression: Both parental alleles of each MHC gene are expressed	Increases number of different MHC molecules that can present peptides to T cells
Polymorphic genes: Many different alleles are present in the population	Ensures that different individuals are able to present and respond to different microbial peptides


- Major histocompatibility proteins are encoded by genes from **both** parents to increase diversity of MHC molecules
- Each MHC gene has **multiple alleles** (polymorphic) so that **each person has unique MHC pattern**
- Because of this, the ability to fight infection varies between people, as every person's adaptive immune system responds slightly differently to microbes

SLIDE 7 MHC genes are inherited as a group, one from each parent. The major locus of an MHC gene codes for a polypeptide, the alpha-chain which binds antigen peptides, and is polymorphic (many alleles). Alleles for MHC genes have co-dominant expression, meaning that products (polypeptide) of both parental genes are expressed on the cell surface. The high amount of polymorphism found in MHC genes is thought to confer evolutionary protection for the continuation of a species. Since not everyone in a species will be able to bind certain antigenic peptides or mount a good T cell response to fight an infection, it is likely that someone else in the species will be able to because of different MHC molecules. So, although an individual may not possess MHC molecules capable of binding certain antigenic peptides against a virulent organism, the likelihood is great that other MHC molecules in the species can do so & will prevent the extermination of a species.

Slide 8

MHC: Two Classes

- **MHC I**
 - Found on **every nucleated** cell in body
 - Except on mature RBC*
 - **All* cells are protected from infection**, as cytotoxic T cells will look for antigens complexed with MHC I
- **MHC II**
 - Found on **immune** cells
 - APCs, macs, B cells, dendritic cells
 - T cells will help the immune response if they see antigens here
 - T cells restricted to see either MHC I or MHC II



MHC-expressing cell types

Class II: Dendritic cells, Macrophages, B cells

Class I: All nucleated cells

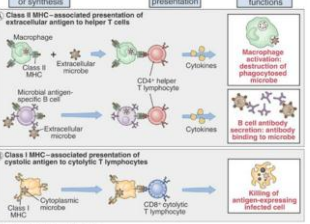
CD8+ T cells can only see Class I MHC

CD4+ T cells can see both Class I and Class II MHC

SLIDE 8 Not all cells express both MHC Class I and Class II antigens. MHC Class I molecules are expressed on all nucleated cells and platelets (mature human red blood cells are not protected). MHC Class II molecules are expressed on only a few cell types, such as dendritic cells, B cells, some macrophages and monocytes, skin associated (Langerhans) cells, and occasionally on other cells. MHC molecules are recognized by separate sets of T cells. Class I MHC molecules are recognized only by cytotoxic T cells (CD8+). Class II MHC molecules are recognized only by helper T cells (CD4+). Mature T cells respond to foreign antigens, but not self antigens. This is another level of control of immune responses. Cytokines can increase the level of expression of class I and class II MHC molecules on antigen presenting cells to capture more antigens (inducible expression).

Slide 9

Role of MHC in Antigen Presentation



Antigen uptake or synthesis | **Antigen presentation** | **T cell effector functions**

1. **Class II MHC - associated presentation of extracellular antigens to helper T cells**

Macrophage → Class II MHC → Extracellular microbe → CD4+ helper T lymphocyte → Cytokines → Macrophage activation: destruction of phagocytosed microbes

Microbial antigen-specific B cell → Class II MHC → Extracellular microbe → CD4+ helper T lymphocyte → Cytokines → B cell antibody secretion: antibody binding to microbes

2. **Class I MHC - associated presentation of cytosolic antigens to cytotoxic T lymphocytes**

Cytosolic microbe → Class I MHC → CD8+ cytotoxic T lymphocyte → Killing of antigen-presenting infected cell

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SLIDE 9 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. T cells are restricted so that they can only see antigens presented to them by a specific type of APC that displays either Class I or Class II MHC molecules.

<p>Slide 10</p>	 <p>MHC & Organ Transplantation</p> <ul style="list-style-type: none"> Extremely difficult to match donor & recipient because of unique MHC patterns Relatives usually have more similar MHC patterns, which improves chances that the organ will survive Once organ is transplanted, still need to take medications to suppress the immune system to allow for graft survival (life-long) Self vs. foreign is closely linked to MHC! Transplantation will be discussed further in Block Five <p>The immune system will recognize the organ as foreign because the MHC patterns are different from "self". Immune suppression is often necessary to prevent graft rejection. These processes will be covered in greater detail in two weeks.</p>	<p>SLIDE 10 Transplant rejection is primarily mediated by T cells. Cytotoxic T cells can directly kill the "nonself" cells that are in the graft or organ, and helper T cells contribute to rejection by secreting cytokines that activate B cells and neutrophils. Unless you have a donor organ from your identical twin, the following problems can occur with transplants: transplanted organs express donor MHC antigens that can be recognized by your immune system. Transplanted organs can then be attacked by your humoral immune response against ABO blood group antigens, vascular endothelial antigens, and histocompatibility (HLA) antigens by your T cells.</p>
<p>Slide 11</p>	 <p>Concept of Antigen Presentation</p> <ul style="list-style-type: none"> T cells are restricted in that the TcR can not bind free antigen in the body (unlike the B cell receptor & antibodies) Antigens must first be processed & presented to the T cells Antigen presenting cells often perform this function 	<p>SLIDE 11 Unlike B cells & antibodies, T cells cannot recognize antigen floating free in solution. Consequently, antigens have to first be presented to T cells (antigen presentation) before the T cell can notice the foreign antigen. It is this additional step that helps to regulate the T cell response and prevents T cells from deciding on their own to kill other cells. There are professional cells in the body that function in this capacity- appropriately named antigen presenting cells (such as dendritic cells, macrophages, etc). However, any infected cell in the body can also act like an APC to attract the notice of T cells that they have been hijacked by a virus or bacteria.</p>

Slide

12

Antigen Presenting Cells

- Several types of professional APCs:
 - Dendritic cells** often initiate T cell responses
 - Found in most organs & epithelia
 - Macrophages** are abundant in all tissues
 - B cells** also can serve in this capacity, with the B cell receptor

Cartoon of the process of antigen presentation by a dendritic cell.
 Photo Source: http://nobelprize.org/education/ai_games/medicine/immunity/immune-detail.html

SLIDE 12 Antigen presenting cells are extremely important to cell-mediated immunity, as they send the first signal to T cells that a foreign organism has been spotted. Dendritic cells are located throughout the body, and serve as professional antigen presenting cells They can be found in skin, the gastrointestinal tract, and in organs, where they patrol the body for foreign antigens. Once an APC captures an antigen, it migrates to the draining lymph nodes nearest to the site of capture (infection) where it “presents” its antigen to T cells.

Slide

13

Overview: Antigen-presenting cells

phago-cytosis	type	location	class II expression
phagocytes immature macrophage lineage	monocytes	blood	++
	macrophages	tissue	+++
	marginal zone spleen and macrophages lymph node		inducible
non-phagocytic constitutive antigen presenting cells	Kupffer cells	liver	+
	microglia	brain	+
immune cells	Langerhans' cells	skin	++
	migrating dendritic cells IDCs	lymphoid tissue	constitutive
	follicular dendritic cells	lymphoid tissue	-
lymphocytes	B cells and T cells	lymphoid tissues and all sites of immune reactions	++
	astrocytes	brain	inducible
facultative antigen presenting cells	follicular cells	thyroid	inducible
	endothelium	vascular and lymphoid tissue	+++
	fibroblasts	connective tissue	inducible
	other types appropriate tissue		inducible

Types of antigen presenting cells and their location in the body.

SLIDE 13 This table lists some types of antigen presenting cells and where they are located in the body. Note that monocytes function as APCs in the blood, whereas macrophages are located in tissues. In addition, Langerhans' cells are a type of dendritic cell located in the skin. Remember, dendritic cells are the best antigen presenting cell type that can also influence the T cell & the type of immune response that is produced to an antigen.

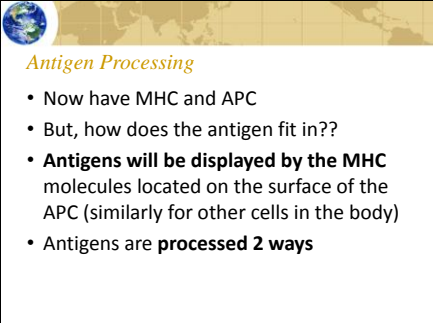
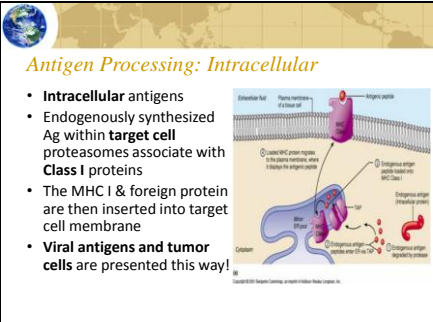
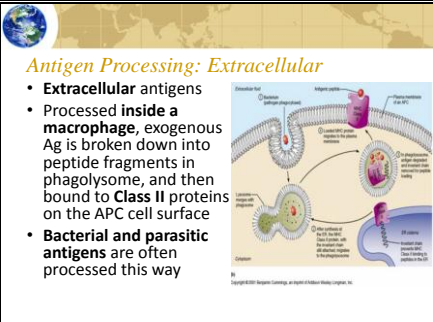
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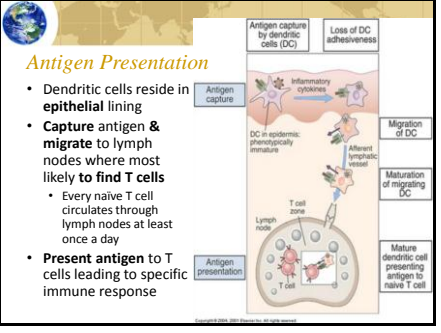
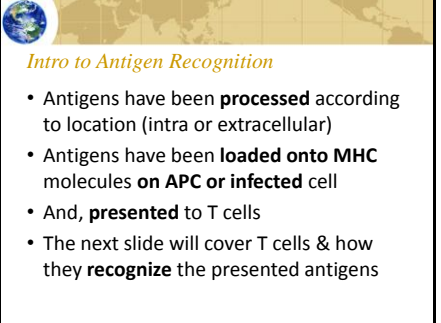
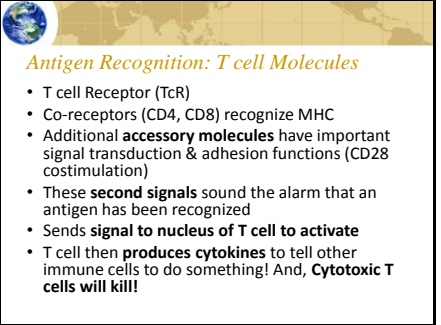
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	Dendritic cell	Macrophage	B Lymphocyte
	Resting	Resting	Resting
Antigen uptake	Endocytosis phagocytosis (by Langerhans cells)	Phagocytosis	Receptor-mediated endocytosis
Class II MHC expression	Constitutive (+++)	Inducible (-)	Constitutive (+++)
Co-stimulatory activity	Constitutive B7 (+++)	Inducible B7 (-)	Inducible B7 (-)
T cell activation	Naive T cells Effector T cells Memory T cells	Effector T cells Memory T cells	Naive T cells Effector T cells Memory T cells

Note how antigens are taken up by APCs and the types of T cells that can be activated by the APCs.

SLIDE 14 Table showing how antigens are taken up and processed by APCs and the types of T cells that are subsequently activated. Activated macrophages can induce higher expression of MHC II molecules on their surface to present more antigens on their surface to stimulate a stronger response.

<p>Slide 15</p>	 <p>Antigen Processing</p> <ul style="list-style-type: none"> • Now have MHC and APC • But, how does the antigen fit in?? • Antigens will be displayed by the MHC molecules located on the surface of the APC (similarly for other cells in the body) • Antigens are processed 2 ways 	<p>SLIDE 15 Antigens must first be processed before they can be presented on the surface of the cell to T cells. The entire antigen will not be presented to a T cell; instead a protein antigen will be “processed” so that small peptides are complexed with MHC molecules on the surface of the cell. Antigens are processed in two ways, through the endogenous or exogenous pathways. The pathway that is chosen depends on if the foreign microbe has infected a normal host cell (e.g. a virus that lives inside the cell) or if it has been phagocytosed by an antigen presenting cell (like a macrophage) from outside of the cell.</p>
<p>Slide 16</p>	 <p>Antigen Processing: Intracellular</p> <ul style="list-style-type: none"> • Intracellular antigens • Endogenously synthesized Ag within target cell proteasomes associate with Class I proteins • The MHC I & foreign protein are then inserted into target cell membrane • Viral antigens and tumor cells are presented this way! 	<p>SLIDE 16 Alter a cell has degraded endogenous antigen (intracellular) within its proteasome, it associates this antigen with a Class I protein then inserts it into its membrane. Afterwards, cytotoxic T cells normally respond to this antigen.</p>
<p>Slide 17</p>	 <p>Antigen Processing: Extracellular</p> <ul style="list-style-type: none"> • Extracellular antigens • Processed inside a macrophage, exogenous Ag is broken down into peptide fragments in phagolysome, and then bound to Class II proteins on the APC cell surface • Bacterial and parasitic antigens are often processed this way 	<p>SLIDE 17 Alter phagocytosis, exogenous antigen (extracellular) is broken down into peptide fragments in a phagolysome and then bound to MHC Class 2 proteins on the antigen- presenting cell surface. TH2 helper cells then respond to this antigen.</p>

<p>Slide 18</p>	 <p>Antigen Presentation</p> <ul style="list-style-type: none"> Dendritic cells reside in epithelial lining Capture antigen & migrate to lymph nodes where most likely to find T cells <ul style="list-style-type: none"> Every naive T cell circulates through lymph nodes at least once a day Present antigen to T cells leading to specific immune response <p>The diagram illustrates the process: Antigen capture by dendritic cells (DC) in the epithelial lining, followed by migration to lymph nodes. In the lymph node, DCs capture antigens from an inflammatory site, undergo maturation, and then present the antigen to a T cell in the T cell zone. Labels include: Antigen capture, Inflammatory site, DC in epidermal phenotypically immature, Antigen presentation, Lymph node, T cell zone, Mature dendritic cell presenting antigen to naive T cell, Migration of DC, Loss of DC adhesiveness, and Adherent synaptic vesicle.</p>	<p>SLIDE 18 Dendritic cells are extremely important antigen presenting cells because they are the most potent activators of native T cells. They can also influence the nature of the response once they activate the T cell by directing a CD4+ response against certain microbes. An amazing property of antigen presentation is that if an antigen is introduced anywhere in the body, a T cell response begins in the lymph nodes draining that site within 12 to 18 hours!</p>
<p>Slide 19</p>	 <p>Intro to Antigen Recognition</p> <ul style="list-style-type: none"> Antigens have been processed according to location (intra or extracellular) Antigens have been loaded onto MHC molecules on APC or infected cell And, presented to T cells The next slide will cover T cells & how they recognize the presented antigens <p>The diagram shows an antigen being processed and loaded onto an MHC molecule on an Antigen Presenting Cell (APC). The APC then presents the antigen to a T cell.</p>	<p>SLIDE 19 The next part of the presentation describes antigen recognition. Antigen recognition is how the T cell, the TCR, & associated co- receptors bind to the antigen presenting cell (via MHC molecules) to “see” the antigen. T cells must make cell to cell contact with antigen presenting cells because MHC molecules are membrane-associated & not soluble.</p>
<p>Slide 20</p>	 <p>Antigen Recognition: T cell Molecules</p> <ul style="list-style-type: none"> T cell Receptor (TcR) Co-receptors (CD4, CD8) recognize MHC Additional accessory molecules have important signal transduction & adhesion functions (CD28 costimulation) These second signals sound the alarm that an antigen has been recognized Sends signal to nucleus of T cell to activate T cell then produces cytokines to tell other immune cells to do something! And, Cytotoxic T cells will kill! <p>The diagram shows a T cell interacting with an Antigen Presenting Cell (APC). The T cell's T cell receptor (TcR) and co-receptors (CD4 or CD8) are shown binding to the MHC-antigen complex on the APC. Accessory molecules like CD28 are also shown interacting with the APC. Labels include: T cell, T cell receptor, CD4, CD8, CD28, Antigen Presenting Cell, and MHC-antigen complex.</p>	<p>SLIDE 20 This slide emphasizes the elements that must be present to have antigen recognition, as the T cell receptor and accessory molecules have important functions to activate the T cell. A brief review from last week: The T cell receptor (TcR) is critical for antigen recognition because it interacts with the MHC molecules complexed to peptide antigens. Coreceptors are important for recognition of MHC molecules (CD4-MHC II or CD8-MHC I), and are 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. Once the TcR binds to the MHC +Ag, these accessory molecules are involved in transmitting a signal to the nucleus of the T cell to activate it to either kill the cell or get help, depending on the type of T cell.</p>

Slide

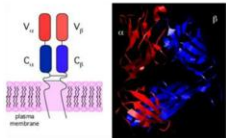
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T cell Receptor (TcR)

- **Antigen binding molecule** (receptor) on T cells
- Has a **low affinity** for antigen
- **Needs accessory molecules** to strengthen binding to antigen presenting cells
- **Can only bind antigen presented by other cells**

T cell receptor: Similar to antibody structure, with variable & constant regions, but with important differences to limit autoimmunity.

Photo source: http://www.biol.wisc.edu/ficorotet/book/index.php?module=Book&func=displayarticle&art_id=395



The diagram shows the T cell receptor (TcR) structure, consisting of two alpha (α) and two beta (β) chains, each with variable (V) and constant (C) regions. The chains are connected by disulfide bonds. The TcR is shown interacting with an antigen-presenting cell (APC) via its CD4 co-receptor. A fluorescence microscopy image shows the TcR (red) and CD4 (blue) on the surface of a T cell.

SLIDE 21 The TcR has many similarities to a B cell receptor or antibody. The TcR has tremendous diversity (similar to B cell Fab regions) as coded by variable gene segments V, D, J & C. Unlike antibodies, the TcR is found only as a cell surface molecule, and is not secreted which has made it more difficult to study. But, there are over 30,000 receptors per cell!! The TcR cannot recognize antigens in their native state- antigens must be processed first & presented. In addition, the T cell receptor does not undergo somatic hypermutation like the B cell receptor (antibodies) because it does not need a high level of variability (diversity) to bind to the MHC proteins on antigen presenting cells or infected host cells. This is an important concept because it does not allow the T cell to change (through hypermutation) its TCR after negative selection has occurred in the thymus. One of many checks & balances to prevent autoimmune reactions!

Slide

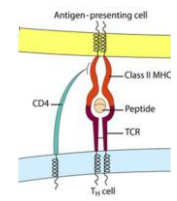
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Antigen Presentation (APC) & T cell Recognition

- **Antigen presenting cell**
- MHC + protein antigen (peptide)
- This is the **"key"**

↓

- **T cell**
- T cell receptor is the **"lock"** which recognizes the antigen-MHC complex ("key")
- T cell also recognizes a specific type of MHC (CD4)



The diagram illustrates the interaction between an Antigen Presenting Cell (APC) and a T_H cell. The APC is shown with a Class II MHC protein bound to a peptide antigen. The T_H cell is shown with its TCR (T cell receptor) and CD4 co-receptor. The CD4 co-receptor is bound to the invariant chain of the Class II MHC. The TCR is bound to the peptide-MHC complex. The diagram shows the T cell recognizing the antigen-MHC complex as a "key" that fits into the "lock" of the T cell receptor.

SLIDE 22 Antigen presentation is analogous to a key (MHC + Ag) on an antigen presenting cell turning the lock (T cell receptor) on a T cell to release it for action.

Slide

23

T cell Co-receptors & Accessories

- **Co-receptors** recognize the class of MHC molecule
 - CD4 recognizes MHC II
 - CD8 recognizes MHC I
- **Accessory molecules** function in signal transduction & adhesion
- **Adhesion molecules** stabilize the binding of the T cell to the APC

CD	Name	Expressed on
CD2	Adhesion molecule	T cell
CD3	Signal transduction	T cell
CD4	Co-receptor	T cell
CD8	Co-receptor	T cell
CD28	Adhesion molecule	T cell
CD137	Adhesion molecule	T cell
CD137L	Adhesion molecule	APC
CD138	Adhesion molecule	APC
CD152	Adhesion molecule	APC
CD152L	Adhesion molecule	APC
CD27	Adhesion molecule	T cell
CD27L	Adhesion molecule	APC
CD134	Adhesion molecule	T cell
CD134L	Adhesion molecule	APC
CD137A	Adhesion molecule	T cell
CD137B	Adhesion molecule	T cell
CD137C	Adhesion molecule	T cell
CD137D	Adhesion molecule	T cell
CD137E	Adhesion molecule	T cell
CD137F	Adhesion molecule	T cell
CD137G	Adhesion molecule	T cell
CD137H	Adhesion molecule	T cell
CD137I	Adhesion molecule	T cell
CD137J	Adhesion molecule	T cell
CD137K	Adhesion molecule	T cell
CD137L	Adhesion molecule	T cell
CD137M	Adhesion molecule	T cell
CD137N	Adhesion molecule	T cell
CD137O	Adhesion molecule	T cell
CD137P	Adhesion molecule	T cell
CD137Q	Adhesion molecule	T cell
CD137R	Adhesion molecule	T cell
CD137S	Adhesion molecule	T cell
CD137T	Adhesion molecule	T cell
CD137U	Adhesion molecule	T cell
CD137V	Adhesion molecule	T cell
CD137W	Adhesion molecule	T cell
CD137X	Adhesion molecule	T cell
CD137Y	Adhesion molecule	T cell
CD137Z	Adhesion molecule	T cell

SLIDE 23 In Figure A, the T cell is on the left side of the diagram. Note the accessory molecules such as the CD4 co-receptor that recognizes the MHC II molecule. Then on the right side of the diagram, the antigen presenting cell has processed the antigen that it has found in the body & is presenting it to the T cell to create a response to that specific antigen. Note the functions of the additional accessory molecules that improve adhesion or signal to other cells to regulate the immune response. Adhesion molecules stabilize the MHC - TcR complex and allow for antigen recognition. Figure B describes the various types of accessories on both the T cell and antigen presenting cell that are needed to activate a response. The binding of the TcR with the antigen peptide-MHC complex delivers the first signal to the T cell. However, this is not enough to activate the T cell. A second signal is necessary for activation & will be described further on the next slides.

Slide

24

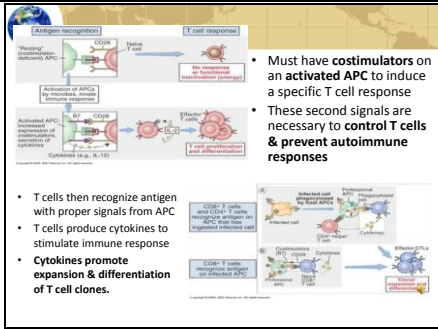
Signal Fire

- Once the **T cell** recognizes the antigen (via the TCR & MHC complex), **accessory molecules send signals to the nucleus**
 - TCR unable to send message to nucleus, need CD3 & ζ signaling proteins
 - Need at least 2 TCRs to be cross-linked to send this signal (only 1 shown in diagram)
- Results in **cytokine production, activation of the T cell, clonal expansion & differentiation**

SLIDE 24 CD3 complex is a group of proteins that are physically associated with the TcR. The CD3 complex functions to ensure the cell surface expression of the TcR, as well as to send activating signals to the interior of the T cell once antigen is bound. These signals include tyrosine kinases and transcription factors that function to increase expression of certain genes in the nucleus of the T cell. The transcription of these genes initiate growth and proliferation of the T cell, and cytokine production.

Slide

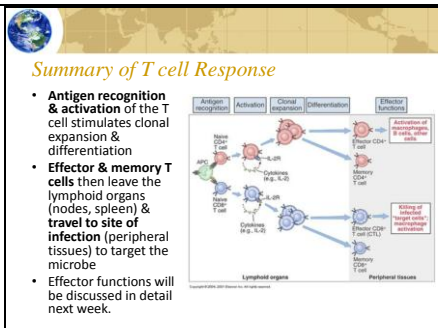
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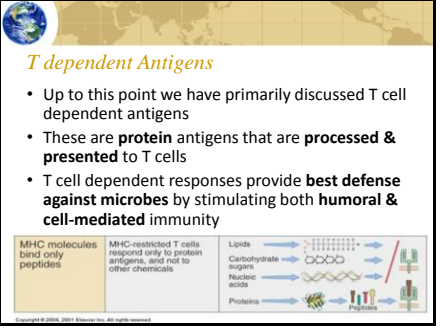
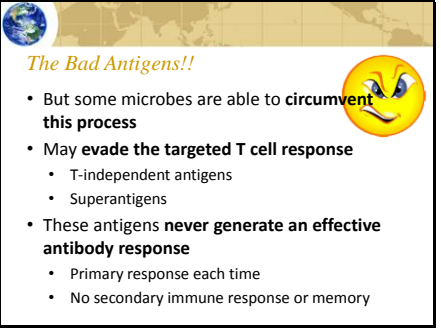
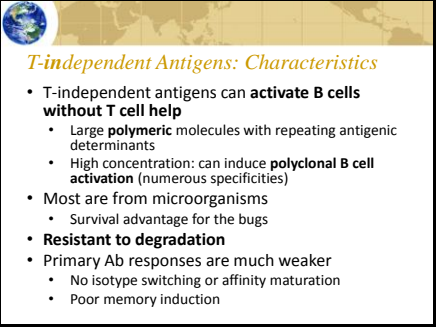
SLIDE 25 The binding of a T cell to an antigen presenting cell (APC) is by itself not enough for T cell activation that turns it into an effector cell. Costimulatory molecules must also bind to deliver a second signal required for T cell activation. The most important costimulatory molecule on the T cell is CD28, which binds to either B7-1 (CD80) or B7-2 (CD86). T cells are constantly on patrol throughout the body. They check the MHC molecules of all cells to see if it has bound antigen. In most cases, no antigen is bound, but the T cells “see” the self antigens, or MHC molecules on the surface of cells. So, although T cells may encounter these self antigens in the body, they will not respond unless they receive a second signal that causes them to recognize the antigen as foreign. In fact, binding of their TCR (signal one) without signal two causes them to self- destruct by apoptosis. After they receive both signals, they differentiate into effector cells that can either kill the APC (if it is a CD8+ cytotoxic T cell), carry out cell-mediated immune responses (if it is a CD4+ Th1 cell), or provide help to B cells (if it is a CD4+ Th2 cell).

Slide

26



SLIDE 26 Like B cells, T cells undergo clonal expansion and differentiation alter antigen recognition. Native T cells recognize antigen and costimulators from APCs in lymphoid organs (nodes, spleen, etc), which activate the T cell to expand (by cytokines) and differentiate into effector and memory cells. These differentiated T cells then leave the lymphoid organs and migrate to the peripheral tissues and the site of infection. Once there, they perform specific effector functions to target the microbe.

<p>Slide 27</p>	 <p><i>T dependent Antigens</i></p> <ul style="list-style-type: none"> Up to this point we have primarily discussed T cell dependent antigens These are protein antigens that are processed & presented to T cells T cell dependent responses provide best defense against microbes by stimulating both humoral & cell-mediated immunity <p>MHC molecules bind only peptides. MHC-restricted T cells respond only to protein antigens, and not to other chemicals.</p> <p>Lipids Carbohydrate antigens Nucleic acids Proteins</p>	<p>SLIDE 27 T dependent antigens are antigens that are first processed & then presented to T cells, as we have detailed in the lecture so far. Antigen presentation to T cells provides the best response to microbes, as it stimulates both humoral and cell-mediated immunity. But, this is not always the case!! Remember, antigens that produce a strong immune response typically are protein-based, and are more potent & generate the best immune response because they are presented to T cells.</p>
<p>Slide 28</p>	 <p><i>The Bad Antigens!!</i></p> <ul style="list-style-type: none"> But some microbes are able to circumvent this process May evade the targeted T cell response <ul style="list-style-type: none"> T-independent antigens Superantigens These antigens never generate an effective antibody response <ul style="list-style-type: none"> Primary response each time No secondary immune response or memory 	<p>SLIDE 28 T-independent antigens can activate B-cells without T-cell assistance. The primary antibody response to these antigens is normally rather weak and does not produce isotype switching or affinity maturation. In addition, there is minimal memory induction produced by these antigens. This means that there is no secondary antibody response produced with T-independent antigens.</p>
<p>Slide 29</p>	 <p><i>T-independent Antigens: Characteristics</i></p> <ul style="list-style-type: none"> T-independent antigens can activate B cells without T cell help <ul style="list-style-type: none"> Large polymeric molecules with repeating antigenic determinants High concentration: can induce polyclonal B cell activation (numerous specificities) Most are from microorganisms <ul style="list-style-type: none"> Survival advantage for the bugs Resistant to degradation Primary Ab responses are much weaker <ul style="list-style-type: none"> No isotype switching or affinity maturation Poor memory induction 	<p>SLIDE 29 T-independent antigens are normally large highly resistant polymeric molecules with repeating antigenic determinants. In sufficient concentrations, these antigens can induce polyclonal B-cell activation. These antigens are from microorganisms and may provide a survival advantage for the microbes. These characteristics may protect the microbe by causing the immune system to not generate secondary antibody responses & forget the organism over time.</p>

Slide
30

Comparison of T-dependent & T-independent Antigens

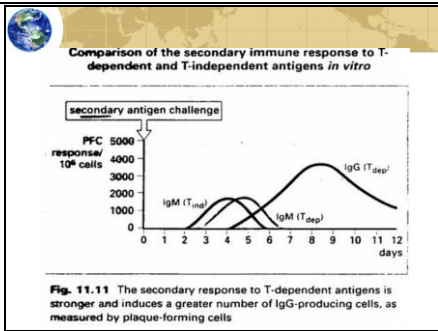
	T-dependent antigen	T-independent antigen
Chemical nature	Protein	Polysaccharides, lipopolysaccharides, flagellin, nucleic acids
Presence of adjuvants	Yes	Little or no need for using IgG
Antibody binding	Yes	Yes
Activity induction	Yes	Only with some antigens
Secondary response	Yes	Yes
Isotype switching	Yes	Yes

Antigen	Polymeric	Polyclonal Activation	Resistance to Degradation
Lipopolysaccharide (LPS)	+	+++	+
Ficoll	+++	-	+++
Dextran	++	+	++
Levan	++	+	++
Poly-D Amino Acids	+++	-	+++
Polymeric Bacterial Flagellin	++	++	+

Examples & properties of T-independent antigens

SLIDE 30 This slide provides examples of T-independent antigens (lipopolysaccharide [LPS], bacterial flagellin, etc.) and their characteristics. Note that isotype switching does occur with T dependent antigens, but not with T independent antigens.

Slide
31



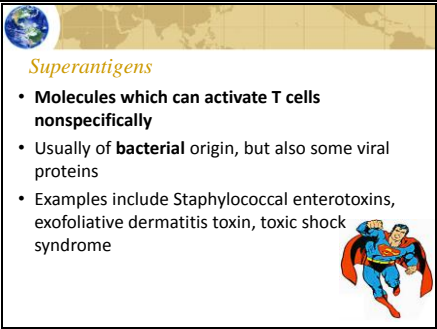
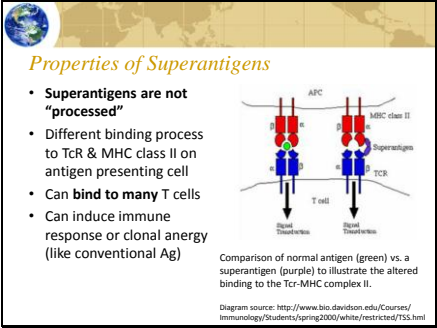
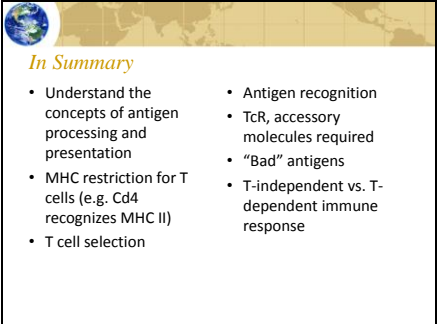
SLIDE 31 This slide compares the immune response of T-dependent and T-independent antigens. Notice that there is no secondary immune response with T-independent antigens therefore, there is no IgG production and no faster immune response.



Slide
32

T-cell Independent Host Defense Mechanisms

- How to defend against this if there are no Ag specific receptors?
- Answer: Phagocytosis
- Answer: Cytokine release
 - Triggered by microbial products (LPS)
 - Leukocyte recruitment
 - Activation of phagocytes
 - Signals for selection of T-cell response

SLIDE 32 Cell-mediated immunity involves T-cells which exhibit antigen specificity via the T-cell receptor or TcR. T-cells perform numerous functions including effector functions on macrophages and other T-cells, cell killing via Tc cells, Type 4 delayed hypersensitivity reactions, and interactions with natural killer cells and antigen-dependent cell-mediated cytotoxicity (ADCC). The subsets of T- cells help determine and regulate the cell-mediated response.

<p>Slide 33</p>	 <p>Superantigens</p> <ul style="list-style-type: none"> • Molecules which can activate T cells nonspecifically • Usually of bacterial origin, but also some viral proteins • Examples include Staphylococcal enterotoxins, exfoliative dermatitis toxin, toxic shock syndrome 	<p>SLIDE 33 Superantigens usually nonspecifically activate T-cells. They are normally bacterial components that can bind multiple T-cells and can either induce a stronger or weaker immune response.</p>
<p>Slide 34</p>	 <p>Properties of Superantigens</p> <ul style="list-style-type: none"> • Superantigens are not “processed” • Different binding process to TcR & MHC class II on antigen presenting cell • Can bind to many T cells • Can induce immune response or clonal anergy (like conventional Ag) <p>Comparison of normal antigen (green) vs. a superantigen (purple) to illustrate the altered binding to the Tcr-MHC complex II.</p> <p>Diagram source: http://www.bio.davidson.edu/Courses/Immunology/Students/spring2000/white/restricted/755.html</p>	<p>SLIDE 34 Superantigens are not “processed” by the immune system and have different binding properties from other antigens. These proteins bind to and activate all of the T cells in a person that express a certain set of VB T cell receptor. Superantigens bind to nonpolymorphic regions of the class II MHC molecules on antigen presenting cells & the VB regions of TcRs. They can activate many T cells at once, resulting in large cytokine production and toxic shock syndrome. Several staph organisms produce enterotoxins that act as superantigens.</p>
<p>Slide 35</p>	 <p>In Summary</p> <ul style="list-style-type: none"> • Understand the concepts of antigen processing and presentation • MHC restriction for T cells (e.g. Cd4 recognizes MHC II) • T cell selection • Antigen recognition • TcR, accessory molecules required • “Bad” antigens • T-independent vs. T-dependent immune response 	<p>SLIDE 35 What you need to know . . .</p>

<p>Slide 36</p>	 <p><i>Self-Test Questions</i></p> <ul style="list-style-type: none"> • What cell types have MHC I surface molecules? MHC II? • What T cells respond to MHC Class I? Class II? Why is this separation important? [Hint: you want certain T cells to respond to an intracellular organism vs. extracellular] • What are antigen presenting cells? How do they function? Where do they find T cells? What molecules on their cell surface enhance antigen recognition by T cells? Are all antigen presenting cells "immune" cells or can they be any cell? 	<p>SLIDE 36 Self test questions for antigen processing, presentation, & recognition.</p>
<p>Slide 37</p>	 <p><i>Self-Test Questions</i></p> <ul style="list-style-type: none"> • Describe antigen processing for extracellular vs. intracellular antigens. • Describe antigen presentation. • Describe antigen recognition. What molecules are on the surface of a T cell? What does TCR do? How do the accessory molecules function? What does signal transduction result in? • What are T-dependent antigens? T-independent antigens? Name 2 examples of T-independent antigens. How does the immune response differ between the 2 types? • What are superantigens? 	