Session 3: Bridging Innate & Adaptive Immunity

Overview:
It's crucial that the immune system is activated only when needed. Therefore, the body has evolved a series of steps that prevent unwanted activation. This session provides an overview of regulation of the acquired immune system and the crosstalk that happens between innate and adaptive immunity. It explains how, upon infection, a subset of innate immune cells known as antigen-presenting cells (APCs) are primed to present antigen via their MHC-II molecules to helper-T cells. Activated helper T cells then modulate the acquired and humoral immune responses. On the other hand, virally infected cells present antigens via their MHC-I molecules to activate cytotoxic-T cells, which release cytokines to kill infected cells. In addition to the binding of peptide-MHC complexes, T cells require additional signals for full activation. These signals arise from the activation of antigen presenting cells via Pattern-Recognition Receptor (e.g. Toll-Like Receptor) binding. These systems ensure proper activation of the immune system.

First video:
Title: Antigen Presentation and Dendritic Cells
Speaker: Ira Mellman
Time: 25:31

Concepts: Link between innate immunity and adaptive immunity, difference between MHC-I and MHC-II mediated activation, and general function and maturation of dendritic cells

Questions for First Video:

1. Which of the following are antigen-presenting cells that interact with helper T cells?
    a. NK cells and monocytes.
    b. Macrophages and plasma cells.
    c. Dendritic cells and macrophages.
    d. Mast cells and B cells.
    e. Memory T cells and memory B cells.

2. Indicate whether the following statements are true or false. If false, explain why.
    a. During the maturation process, the pH in dendritic cells lysosomes decreases.
    b. Dendritic cells internalize antigens upon endocytosis, which activates the maturation pathway.
    c. All nucleated cells in the human body can present antigens to cytotoxic T-cells via MHC-I.

3. Compare and contrast the following sets of terms:
    a. MHC class I and MHC class II molecules.

    b. Antigen processing and antigen presentation.

    c. Immature and mature dendritic cells (DCs).

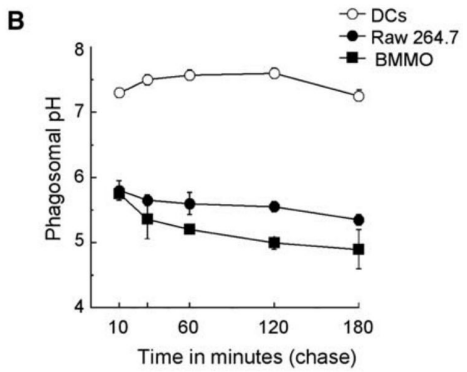
    d. The use of reactive oxygen species (ROS) in dendritic cells (DCs) vs. in macrophages.

4. Studies have shown that there is a connection between the innate immune system and the acquired immune system. How is the innate immune system able to activate the acquired immune system? Briefly explain and mention the cells and proteins involved in this process.

5. Predict the outcome of a mutant MHC class II molecule that is unable to associate with the invariant chain. Explain your prediction at the cellular and organismal level.

6. What would be the effect of a virus that is able to bind to and enter cells that express MHC II proteins? Briefly explain.

7. The pH of phagosomes in immature dendritic cells (DCs), a macrophage cell line (RAW 264.7), and bone-marrow derived macrophages (BMMO) was measured following activation of phagocytosis. Data are shown below. (Reference: Amigorena et al. Cell, 2006)



   a. Compare and contrast the response of phagosomal pH to activation of phagocytosis in each cell type.

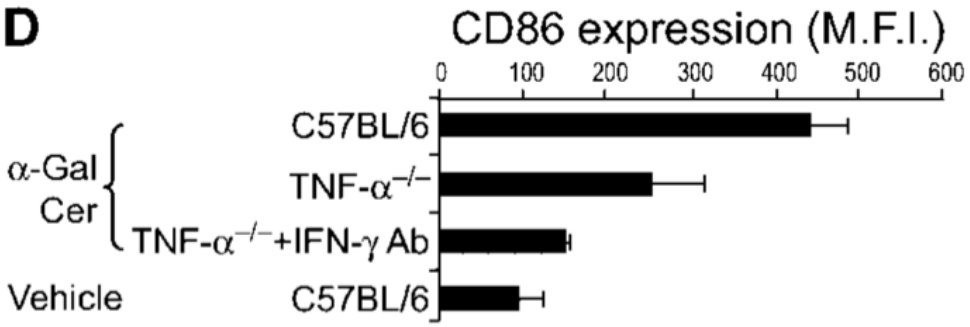
   b. Describe the major functions of macrophages and dendritic cells. Use only one sentence for each cell type.

   c. Predict how the differences you observed in phagosomal pH assist each cell type (macrophages vs. dendritic cells) in their major function.

8. You discover a bacterial protein that binds to a proton pump that controls lysosomal pH in dendritic cells.
    a. What do you predict is the function of this protein?

    b. Why would bacteria evolve to have a protein that functions this way?

9. CD86 is a known marker of dendritic cell (DC) maturation. In the experiment below, researchers sought to determine which cytokines are necessary for DCs to mature. They used an experimental system in which treatment with an antibody called α-GalCer activates DCs. C57BL/6 is a strain of mice commonly used in biomedical research. “TNF-α-/-” and “IFN-γ Ab” represent inhibition of TNF-α and IFN-γ signaling, respectively.



a. Based on the results above, are TNF-α and IFN-γ necessary for DC maturation? How do you know?

b. [Open-ended optional] Based on the results above, which cytokine (TNF-α or IFN-γ) do you predict is more important for DC maturation? Why?

c. [Open-ended optional] Design an experiment to test your hypothesis using an alternative method than the one shown in this figure.

Second video:
Title: Antigen Presentation and Dendritic Cells
Speaker: Ira Mellman
Time: 14:35

Concepts: Antigen cross-presentation, activation of T cells by dendritic cells, T cell tolerance, and regulatory T cells (Tregs)

Questions for Second Video:

1. If an individual carries a mutation that results in a complete lack of MHC class I proteins, how would the individual's immune response be affected? (Select all that apply.)
    a. Memory B cell antibodies would not be able to attach to antigen epitopes.
    b. Cytotoxic T cells would not be able to target (and destroy) infected cells.
    c. Helper T cells would not be able to interact with antigen-presenting cells.
    d. Plasma cell antibodies would not be able to attach to antigen epitopes.

2. Upon viral integration, Virus A starts producing a protease, which is crucial for proper viral function.
    a. Briefly explain how the immune system can detect and react to this protease.

    b. How might a virus "react" to this immune response through evolution? Briefly explain.

3. Lung epithelial cells are preferentially infected by influenza virus during the flu. Like dendritic cells, lung epithelial cells express toll-like receptors (TLRs). Yet, they are not "professional" antigen-presenting cells.
    a. Predict how lung epithelial cells respond to TLR activation. How is this response similar to and different from TLR activation in dendritic cells (DCs)?

b. In addition to lung epithelial cells, TLRs are expressed on other non-immune cells including endothelial cells and fibroblasts. Defend the necessity of TLR expression on both immune and non-immune cells.

4. Predict the result of a mutation that renders the TAP1/TAP2 transporter nonfunctional in cells. Explain your prediction at the cellular and organismal level.

5. Major histocompatibility complex (MHC) proteins are important to the acquired immune system.
    a. Briefly explain how MHC I proteins promote the activation of the immune system specifying the cells involved in the process.

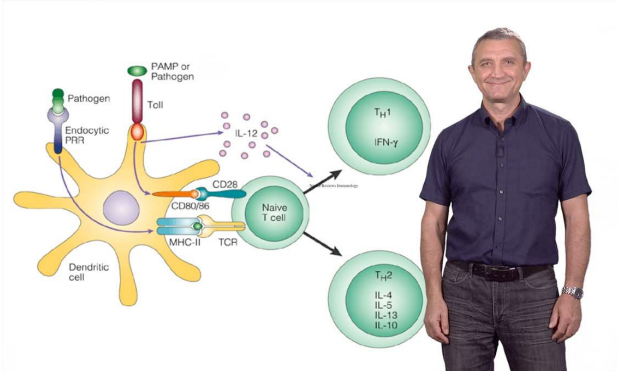
    b. Briefly explain the outcome of MHC I directed activation of the immune system.

    c. Dendritic cells can convert an MHC-I type signal into an MHC-II type signal. Why? Briefly explain.

Optional Review:
Medzhitov R. (2001) Toll-like receptors and innate immunity. Nat Rev Immunol. 1(2):135-45

Third video:
Title: The Role of Toll-Like Receptors in the Control of Adaptive Immunity
Speaker: Ruslan Medzhitov
Time: 20:58

Concepts: Immune recognition of self versus non-self, identification and characterization of Toll-Like Receptors, activation of adaptive immunity



Questions for Third Video:

1. A molecule recognized as foreign by cells of the immune system is a(n)
    a. Antibody.
    b. Antigen.
    c. Immunoglobulin.
    d. Interferon.
    e. Cytokine.

2. Indicate whether the following statement is true or false. Briefly explain your answer. Pathogen-associated molecular patterns (PAMPs) are unique to pathogens.

3. Microorganisms can express both Pathogen-associated molecular patterns (PAMPs) and virulence factors.
    a. Compare and contrast Pathogen-associated molecular patterns (PAMPs) and virulence factors.

    b. Why is it evolutionarily advantageous for the innate immune system to recognize PAMPs and not virulence factors? Briefly explain.

4. There are three levels of communication that occur between dendritic cells and T cells.
    a. List each and describe its main function.

    b. Now, imagine each level is defective. What would be the effect of the loss of each type of DC-T cell interaction on T cell activation?

5. It is critical that the immune system does not attack the body. Dendritic cells present one line of defense against autoimmunity.
    a. What signals does an antigen presenting cell use to differentiate “self” antigen from “non-self” antigen?

    b. How does it translate that knowledge to a T cell?

6. Toll-like receptors (TLRs) are pattern-recognition receptors (PRRs) that detect conserved molecular patterns from pathogens.
    a. Predict why pathogens haven’t evolved to stop making molecules with such recognizable patterns.

    b. A bacterial gene X produces a protein that is recognized by a Toll-like receptor. Provide a few common characteristics of pathogen-associated molecular patterns (PAMPs) recognized by PRRs that would help you narrow down the function of gene X. Briefly explain.

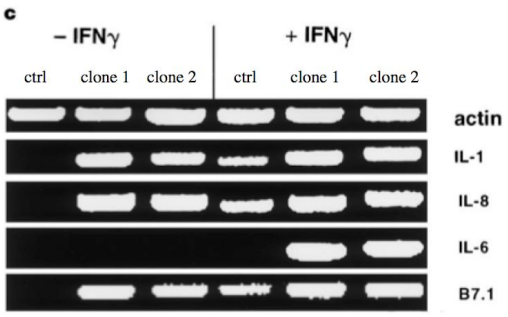
7. The immune system is “trained” to not react to self-antigens.
    a. Briefly explain how pathways like Toll-Like Receptor signaling prevents the immune system from reacting to self-antigens.

    b. (Optional) Which other mechanism does the human body have to prevent self-recognition? Briefly compare both mechanisms.

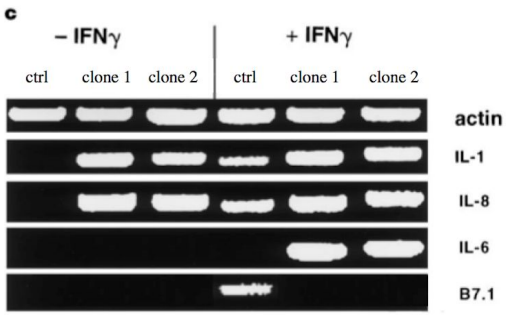
8. Bobby is homozygous recessive for a toll-like receptor 4 (TLR4) gene mutation that causes his TLR4 protein to get trapped in the endomembrane system. Therefore, his immune cells do not express TLR4 at their surface. What do you predict is the phenotypic outcome of Bobby’s mutation?

9. In the seminal paper that describes the discovery of toll-like receptor 4, the researchers generated a chimeric TLR protein that was constitutively active. This chimeric protein was transfected into a monocytic cell line (represented by clones 1 and 2 in the data below) and the cellular response to interferon-gamma (a pro-inflammatory cytokine) was measured via gene expression analysis (Northern Blot). The left panel represents the original data from the paper, while the panel on the right represents hypothetical data.

Original



Hypothetical



    a. What is the difference between the data in the “original” panel and the data in the “hypothetical” panel?

b. If you observed only the data on the right, what would you predict is the role of this receptor in T cell activation?

c. If you observed only the data on the right, would you come to the same conclusion as the research group (i.e., that this receptor directly links pathogen detection to T cell activation)? Why or why not?

10. B cells have antibodies that directly recognize pathogens, while T cells recognize antigen presented at the surface of cells. Briefly explain why, evolutionarily, you need both T and B cells.

Answers for Session 3:

Questions for First Video:

1. Which of the following are antigen-presenting cells that interact with helper T cells?
    a. NK cells and monocytes.
    b. Macrophages and plasma cells.
    c. Dendritic cells and macrophages.
    d. Mast cells and B cells.
    e. Memory T cells and memory B cells.

2. Indicate whether the following statements are true or false. If false, explain why.
    a. During the maturation process, the pH in dendritic cells lysosomes decreases. **(True)**
    b. Dendritic cells internalize antigens upon endocytosis, which activates the maturation pathway. **(False – Maturation only occurs if TLR are activated as well)**
    c. All nucleated cells in the human body can present antigens to cytotoxic T-cells via MHC-I. **(True)**

3. Compare and contrast the following sets of terms:
    a. MHC class I and MHC class II molecules.
    Both present antigen to T cells. MHC I is expressed by all nucleated cells and presents endogenous antigen (ie, viral peptides). MHC II is expressed by antigen presenting cells, and presents exogenous antigen that has been phagocytosed.

    b. Antigen processing and antigen presentation.
    Both are necessary for T cell activation and are processes performed by antigen presenting cells. Antigen processing is an intracellular process that chops up microbial proteins into short (9-10 AA) peptides. Antigen presentation is the process of loading the peptide antigen on MHC proteins for presentation to T cells.

    c. Immature and mature dendritic cells (DCs).
    Immature DCs are in the periphery while mature DCs travel to secondary lymphoid tissues. Major function of immature DCs is immune surveillance. Major function of mature DCs is antigen presentation to T cells. Immature DCs are highly endocytic, while mature DCs shut down endocytosis. In immature DCs, MHC is restricted to the lysosomes. In mature DCs, MHC-antigen complexes are presented at the plasma membrane.

    d. The use of reactive oxygen species (ROS) in dendritic cells (DCs) vs. in macrophages.
    ROS in macrophages is used to kill phagocytosed microbes. ROS in DCs is used to regulate the acidity of lysosomes. (Reference: Amigorena et al. Cell, 2006)

4. Studies have shown that there is a connection between the innate immune system and the acquired immune system. How is the innate immune system able to activate the acquired immune system? Briefly explain and mention the cells and proteins involved in this process.
   Phagocytic cells (e.g. macrophages) ingest and lyse pathogens. Peptide fragments from the pathogen are then loaded onto MHC II complexes and presented on the surface of the phagocytic cell. Helper-T cells interact with these antigen-MHC II complexes.

   (Alternative answer) Stimulation of Pattern Recognition Receptors (i.e., Toll-Like Receptors) on dendritic cells leads to their activation. They then activate T cells, in part through release of cytokines.

   (Alternative answer) After a pathogen (virus) infects a cell, pathogen-derived antigens inside the cell will be loaded onto MHC I and presented at the plasma membrane. This will activate cytotoxic-T cells to proliferate and kill the pathogen-infected cell. Cytotoxic T cells release perforin, which induces infected cells to lyse.

5. Predict the outcome of a mutant MHC class II molecule that is unable to associate with the invariant chain. Explain your prediction at the cellular and organismal level.
   If MHC II is unable to associate with the invariant chain, then regulation of MHC II localization and peptide loading would be impaired. Specifically, MHC II translocation to the phagolysosome would be impaired, which means that it ultimately wouldn't get loaded with antigen or be presented at the plasma membrane. This means that activation of the adaptive immune response by antigen presenting cells would be hindered, leading to more severe microbial infections.

6. What would be the effect of a virus that is able to bind to and enter cells that express MHC II proteins? Briefly explain.
   MHC II is found on the surface of antigen-presenting cells (APCs): B cells, macrophages, and dendritic cells. These cells are going to be affected by this virus. This will have a generalized effect on the immune system. If this virus kills the cell, macrophages/dendritic cells would not able to activate helper-T cells and therefore activation of the innate immune system will not lead to activation of the acquired immune system. Also, given that B cells will be affected, there would not be the proper release of antibodies, which will deteriorate the acquired immune system as the memory cells would not be produced.

7. The pH of phagosomes in immature dendritic cells (DCs), a macrophage cell line (RAW 264.7), and bone-marrow derived macrophages (BMMO) was measured following activation of phagocytosis. Data are shown below. (Reference: Amigorena et al. Cell, 2006)
   a. Compare and contrast the response of phagosomal pH to activation of phagocytosis in each cell type.
      In the macrophages, phagosomal pH decreases after initiation of phagocytosis, whereas the pH of DC phagosomes stays steady. In addition, the pH of dendritic cell phagosomes is overall higher than that of macrophage phagosomes.

b. Describe the major functions of macrophages and dendritic cells. Use only one sentence for each cell type.
Macrophages are the immune system's "professional' phagocytic cell, helping to clear microbes and cells dying from infection. Dendritic cells are the immune system's "professional" antigen-presenting cell, translating information on infection in the periphery to activate lymphocytes in lymph nodes.

c. Predict how the differences you observed in phagosomal pH assist each cell type (macrophages vs. dendritic cells) in their major function.
A lower pH overall (and a decrease in pH upon phagocytosis activation) allows macrophages to efficiently digest the microbes and debris that they phagocytose from the periphery. A higher pH overall (and a pH that stays stable upon activation of phagocytosis) allows dendritic cells to preserve microbial antigen for efficient presentation to lymphocytes.

8. You discover a bacterial protein that binds to a proton pump that controls lysosomal pH in dendritic cells.
    a. What do you predict is the function of this protein?
    Presumably, it keeps the pH in dendritic lysosomes higher than 5 by inhibiting the proton pump.

    b. Why would bacteria evolve to have a protein that functions this way?
    During maturation, dendritic lysosomes lower their pH below 5. By keeping the pH in dendritic lysosomes higher than 5, this prevents the host from efficiently degrading pathogen.

9. CD86 is a known marker of dendritic cell (DC) maturation. In the experiment below, researchers sought to determine which cytokines are necessary for DCs to mature. They used an experimental system in which treatment with an antibody called α-GalCer activates DCs. C57BL/6 is a strain of mice commonly used in biomedical research. "TNF-α-/-" and "IFN-γ Ab" represent inhibition of TNF-α and IFN-γ signaling, respectively.
    a. Based on the results above, are TNF-α and IFN-γ necessary for DC maturation? How do you know?
    Both are necessary. Ablation of TNF-α alone reduces DC maturation. Ablation of TNF-α combined with inhibition of IFN-g signaling inhibits DC maturation further.

    b. [Open-ended optional] Based on the results above, which cytokine (TNF-α or IFN-γ) do you predict is more important for DC maturation? Why?
    Based on these results, we cannot conclude whether one or the other is more important. However, some students might predict that TNF-α is more important.

    c. [Open-ended optional] Design an experiment to test your hypothesis using an alternative method than the one shown in this figure.
    Could design an experiment where TNF-α and IFN-γ signaling are completely inhibited (for example, KO mice are made for each), and the results of each compared. Alternatively, researchers could try the opposite approach to that shown here: combine α-GalCer treatment with exogenous TNF-α and/or IFN-γ. Readout would be the same: amount of CD86 expression.

Questions for Second Video:

1. If an individual carries a mutation that results in a complete lack of MHC class I proteins, how would the individual's immune response be affected? (Select all that apply.)
    a. Memory B cell antibodies would not be able to attach to antigen epitopes.
    b. Cytotoxic T cells would not be able to target (and destroy) infected cells.
    c. Helper T cells would not be able to interact with antigen-presenting cells.
    d. Plasma cell antibodies would not be able to attach to antigen epitopes.

2. Upon viral integration, Virus A starts producing a protease, which is crucial for proper viral function.
    a. Briefly explain how the immune system can detect and react to this protease.
    Antigens produced intracellularly can be presented to cytotoxic T cells via MHC class I proteins.

    b. How might a virus "react" to this immune response through evolution? Briefly explain.
    A virus could produce a mechanism by which it prevents activation of the MHC I pathway. For example, by inhibiting the TAP1/2 transporters.

3. Lung epithelial cells are preferentially infected by influenza virus during the flu. Like dendritic cells, lung epithelial cells express toll-like receptors (TLRs). Yet, they are not "professional" antigen-presenting cells.
    a. Predict how lung epithelial cells respond to TLR activation. How is this response similar to and different from TLR activation in dendritic cells (DCs)?
    Lung epithelial cells likely respond by producing pro-inflammatory cytokines, leading to a localized innate immune response. This response likely involves initiation of gene expression, as it does in DCs, but the output is an innate rather than an adaptive response.

    b. In addition to lung epithelial cells, TLRs are expressed on other non-immune cells including endothelial cells and fibroblasts. Defend the necessity of TLR expression on both immune and non-immune cells.
    It makes sense to have TLRs present on cells that line lumen (such as epithelial and endothelial cells), because they often serve as mechanical barriers to infection. Fibroblasts are motile cells within tissues, similar to DCs. Each of these cell types can induce a localized inflammatory response, which can help clear an infection more quickly than waiting to mount an adaptive response.

4. Predict the result of a mutation that renders the TAP1/TAP2 transporter nonfunctional in cells. Explain your prediction at the cellular and organismal level.
    If TAP function is compromised, then microbial peptides would not be able to enter the endoplasmic reticulum from the cytosol. This means that loading of peptides onto MHC class I would be greatly impaired. This would affect the ability of the immune system to detect, for example, virally infected cells and clear them. It is likely that microbial infections would be more widespread and persistent in individuals with impaired TAP function.

5. Major histocompatibility complex (MHC) proteins are important to the acquired immune system.
    a. Briefly explain how MHC I proteins promote the activation of the immune system specifying the cells involved in the process.
    MHC I proteins activate T cell receptors on cytotoxic-T cells. Infected cells load pathogen-derived antigen on MHC I, which will be presented at the plasma membrane for T cell receptors to bind to.

    b. Briefly explain the outcome of MHC I directed activation of the immune system.
    This activation will make cytotoxic-T cells proliferate and induce a cellular immune response. These cytotoxic-T cells will go to other pathogen-infected cells and release proteins (e.g. perforin), which would cause infected cells to die.

    c. Dendritic cells can convert an MHC-I type signal into an MHC-II type signal. Why? Briefly explain.
    Cross presentation of exogenous antigens on MHC class I. Cross presentation can inform cytotoxic T cells of a specific infection, so that they are primed to kill cells that present the same MHC I-antigen presented by the dendritic cells. This links the MHC I and MHC II pathways, which is evolutionarily advantageous.

Questions for Third Video:

1. A molecule recognized as foreign by cells of the immune system is a(n)
    a. Antibody.
    b. **Antigen**.
    c. Immunoglobulin.
    d. Interferon.
    e. Cytokine.

2. Indicate whether the following statement is true or false. Briefly explain your answer.
Pathogen-associated molecular patterns (PAMPs) are unique to pathogens.

    False – PAMPs can be produced by non-pathogenic microorganisms.

3. Microorganisms can express both Pathogen-associated molecular patterns (PAMPs) and virulence factors.
    a. Compare and contrast Pathogen-associated molecular patterns (PAMPs) and virulence factors.
    PAMPs are common factors in microorganisms. PAMPs are typically metabolic or essential factors needed for the survival of the microorganism (essential genes). Virulence factors evolved to interact with the host, and these genes do not need to be active at all times (just during infection). They can be pathogen-specific.

    b. Why is it evolutionarily advantageous for the innate immune system to recognize PAMPs and not virulence factors? Briefly explain.
    Virulence factors could vary between pathogens and may not be essential for the pathogen (mutations would help pathogen evade the immune system). Virulence factors aren't active at all times (immune system would only be able to detect pathogen when the virulence factor is present).

4. There are three levels of communication that occur between dendritic cells and T cells.
    a. List each and describe its main function.
    1. MHC II-antigen:TCR binding helps to prime T cells that are specific to a particular antigen.
    2. CD80/86:CD26 coreceptor binding confirms that the DC has detected a true pathogen.
    3. Cytokine release by DCs tells the naive T cell what type of cell it should mature into.

    b. Now, imagine each level is defective. What would be the effect of the loss of each type of DC-T cell interaction on T cell activation?
    1. If the first one is defective then T cells that are highly specific to a particular pathogen won't be primed.
    2. If the second one is defective then naive T cells won't be activated to mature into effector T cells.
    3. If the third one is defective then naive T cells will be activated but won't mature into the right effector cells.
    All of this will mean that adaptive immunity is impaired.

5. It is critical that the immune system does not attack the body. Dendritic cells present one line of defense against autoimmunity.
    a. What signals does an antigen presenting cell use to differentiate "self" antigen from "non-self" antigen?
    Activation of Toll-Like Receptors indicates to antigen presenting cells that they have taken up pathogenic antigen.

    b. How does it translate that knowledge to a T cell?
    By simultaneously presenting MHC II+antigen with a co-receptor such as CD80/CD86. The co-receptors give the T cells the confirmation that the APC has detected pathogen in the periphery.

6. Toll-like receptors (TLRs) are pattern-recognition receptors (PRRs) that detect conserved molecular patterns from pathogens.
    a. Predict why pathogens haven't evolved to stop making molecules with such recognizable patterns.
    PAMPs are associated with structures that serve critical functions for microbes. Thus, it is evolutionarily very difficult for pathogens to change these structures and still survive. This is an example of how "smart" the immune system has evolved to be.

    b. A bacterial gene X produces a protein that is recognized by a Toll-like receptor. Provide a few common characteristics of pathogen-associated molecular patterns (PAMPs) recognized by PRRs that would help you narrow down the function of gene X. Briefly explain.
    PAMPs are only microbial, they're not produced by the host cell. PAMPs are often essential genes, typically genes in metabolic pathways. Some of these pathways are involved in housekeeping functions and their products are conserved among microorganisms of a given class and are essential for their survival.

7. The immune system is “trained” to not react to self-antigens.
    a. Briefly explain how pathways like Toll-Like Receptor signaling prevents the immune system from reacting to self-antigens.
    MHC class I and class II can present both self and non-self-antigens. TLR ensures that T cell activation only occurs upon pathogenic interactions.

    b. (Optional) Which other mechanism does the human body have to prevent self-recognition? Briefly compare both mechanisms.
    T-cells and B-cells get “trained” to not recognize self-antigens during their development. This “training” eliminates cells capable of reacting to self-antigens. However, some self-reactive cells can escape. The TLR-like pathways ensure that even when self-reactive cells escape, the immune system cannot mount an immune response upon self-antigen recognition.

8. Bobby is homozygous recessive for a toll-like receptor 4 (TLR4) gene mutation that causes his TLR4 protein to get trapped in the endomembrane system. Therefore, his immune cells do not express TLR4 at their surface. What do you predict is the phenotypic outcome of Bobby’s mutation?
    Bobby is unable to mount an adaptive immune response to pathogens that are recognized only by TLR4. For pathogens that are recognized by a combination of TLR4 with other TLRs, Bobby’s immune response is impaired but not completely ablated.

9. In the seminal paper that describes the discovery of toll-like receptor 4, the researchers generated a chimeric TLR protein that was constitutively active. This chimeric protein was transfected into a monocytic cell line (represented by clones 1 and 2 in the data below) and the cellular response to interferon-gamma (a pro-inflammatory cytokine) was measured via gene expression analysis (Northern Blot). The left panel represents the original data from the paper, while the panel on the right represents hypothetical data.
    a. What is the difference between the data in the “original” panel and the data in the “hypothetical” panel?
    In the hypothetical results, B7.1 is not activated in either the presence or absence of IFNγ in the transfected cells.

    b. If you observed only the data on the right, what would you predict is the role of this receptor in T cell activation?
    I would predict that this receptor responds to microbial binding by releasing cytokines that aid in the mounting of an immune response. There are no data to indicate that the receptor specifically induces an adaptive response. However, these cytokines may help naive T cells mature.

    c. If you observed only the data on the right, would you come to the same conclusion as the research group (i.e., that this receptor directly links pathogen detection to T cell activation)? Why or why not?
    No. Because the transfected cells do not express B7 (the coreceptor that is necessary for naive T cell activation), they alone cannot activate T cells. If the group had found the hypothetical results instead, they would have continued their search for a receptor that links antigen presentation with T cell activation via coreceptor binding.

10. B cells have antibodies that directly recognize pathogens, while T cells recognize antigen presented at the surface of cells. Briefly explain why, evolutionarily, you need both T and B cells. **B cells recognize extracellular pathogens (e.g. microbes), but can't detect intracellular pathogens (e.g. viruses or intracellular parasites). Therefore, two separate mechanisms are needed. One that can detect pathogens outside the cell, and one that can detect pathogens inside the cell. Infected cells present pathogen-derived antigens on the MHC I complexes. These are detected by T cells to activate an immune response.**