**Antigen presentation and cytotoxic T lymphocytes (CTLs): elucidating a common roadblock for students**

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In conjunction with HHMI Biointeractive

Class incorporation:

* Anatomy & Physiology II for pre-nursing majors at a 4-year comprehensive university.
* Conclusion of Immune System chapter
* 50 min of face-to-face lecture

Activity Overview:

* During class, students will participate in an active learning activity involving the functionality of cytotoxic T-cells (CTL) in recognizing self vs. nonself antigen and destroying viral-infected cells.
* The activity will be divided into sections using clips from an HHMI Biointeractive video (adapted for this activity), targeted student discussion (think/pair/share), and “clicker” questions designed to gauge understanding.
* A PPT is included. Any content figures included in the PPT have been obtained from OpenStax and are available for your use1. You can also incorporate your own textbook images where applicable. The video clips are adapted from HHMI Biointeractive2 and have been produced for your use.
* All other images were accessed from websites within the public domain3-5.

Learning objectives:

Students will:

1. Briefly describe how “nonself” viral proteins are incorporated into the MHC class I receptors of an infected “self” cell.
2. Outline the steps required for a CTL to recognize a nonself MHC class I.
3. Connect the roles of antigen presenting cells (APCs) and helper T cells in CTL activation.
4. Describe how a CTL destroys an identified nonself, virus-infected cell.

Assumed prior knowledge:

* The students have prior knowledge of the lymphatic system, general white blood cell actions, the basis of immune cell function (including APCs), humoral immunity, and MHC.

Teaching Notes:

**Case study:** A brief case study (Slides 3-4) is included introducing the idea of vaccinations which references a recent measles outbreak. This is included to relate the idea of CTLs to real life, as well as introduce the idea of vaccinations stimulating different portions of the immune response, which will be revisited later in the activity.

**Clip 1:** Prior to clip one, briefly explain how a virus causes new viral proteins to be made within an infected cell (Slide 5). Pieces of those viral proteins are the short protein fragments that we are referring to at the beginning of this clip. From there, the video (Slide 6) will explain how those peptides get incorporated into the MHC class I of the infected body cell (LO 1). Pose questions 1 and 2 below for students to think/pair/share. Question 3 should be posed through a real-time response system to gauge student comprehension (Slide 7).

1. Where are the short protein fragments coming from? ***The short protein fragments displayed in the video are coming from viral proteins. Once the virus has taken over the body cell, it begins using the cell’s machinery to produce its viral proteins. The body cell chops up those proteins and incorporates the pieces into the MHC class I.***
2. What is the MHC and where does it display antigens? ***The major histocompatibility complex (MHC) is a set of genes that code for a family of transmembrane proteins that are located on the surface of body cells.***
3. In general, what is the primary role of the MHC during an infection?
   1. Destroy invading pathogens directly.
   2. **Display antigens from pathogens for cell surface presentation to adaptive immune cells.**
   3. Signal infected body cells into apoptosis.
   4. Trigger the release of antibodies from B cells once an infection has been detected.

**Clip 2:** The video (Slide 8) goes on to explain how the CTL recognizes and binds to the nonself MHC on class I (LO 2-3). Pertinent topics to discuss at this time (Slides 9-11): antigen presentation variability between class I and class II MHC, helper T cell actions, and an introduction to cytotoxic T cells. A reminder about “self” vs “nonself” peptides would be appropriate. Pose questions 1 and 2 below for student think/pair/share. Question 3 should be posed through a real-time response system to gauge student comprehension (Slide 12).

1. Class I MHC protein display what type of antigen? ***Class I MHC proteins display foreign antigens that are discovered inside an infected body cell (endogenous).***
2. Vaccine application: The measles vaccine has been shown to primarily activate CD4 cells. Does this vaccine directly stimulate CTL? Why or why not? ***No, the measles vaccine would not directly stimulate CTLs because the virus would need to activate CD8 cells to stimulate CTLs. CD4 cells, when activated, become helper T cells rather than CTLs. In the case of measles, the viruses get taken into macrophages, which act as an APC to activate the CD4 cells into helper T cells.***
3. Explain the role of the helper T cell in terms of CTL activation?
   1. Helper T cells bind directly to CTL, which stimulate activation and proliferation.
   2. Helper T cells bind to MHC class I on an APC, which stimulates the CTL to bind to MHC class II, resulting in activation.
   3. **Helper T cells provide the signal for co-stimulation of CTL via the release of cytokines.**
   4. Helper T cells do not have a role in CTL activation.

**Clip 3:** The last video clip (Slide 13) discusses granzymes and perforins (LO 4). Elucidate the role of each of these enzymes in the destruction of a cell (Slide 14). Pose question 1 below for student think/pair/share. Question 2 should be posed through a real-time response system to gauge student comprehension (Slide 15).

1. Cancer application: With your group, brainstorm how researchers could use a person’s own CTLs as a personalized cancer therapy that wouldn’t also attack that person’s healthy cells. ***A few approaches are feasible. 1. Take the person’s dendritic cells and introduce cancer specific antigens to them ex vivo (some specific tissue cancer antigens have been identified). 2. Take the activated dendritic cells and present the specific cancer antigen to a CD8 cell (in vivo or ex vivo). Both of these approaches would ideally lead to the appropriate CD8 cell being activated to a CTL that can scour the body for that particular cancer-infected cell that is displaying that specific antigen on its MHC class I.***
2. How do granzymes destroy a body cell?
   1. **Trigger apoptosis.**
   2. Create small pores in the infected cell’s plasma membrane.
   3. Prevent the pathogen from continuing to replicate inside the cell.
   4. Create a hypotonic environment, forcing the cell to lyse.

Assessment of success:

* Student metacognition survey (to be included as bonus questions for this chapter’s post-lecture homework).
  1. On a scale of 1-5 (with 5 being the greatest), how confident do you feel that you understand how CTLs are activated?
  2. On a scale of 1-5 (with 5 being the greatest), how important were the 3 video clips in your understanding of CTL activation?
* Student success on exam question subset (see below).

Matching questions:

* 1. Directly kills infected cells via apoptosis **(cytotoxic T cell)**
  2. A lymphocyte that assists in B cell activation **(helper T cell)**
  3. Secreted by cytotoxic T cells to induce apoptosis of infected cells **(granzymes)**

Multiple Choice questions:

* 1. Cytotoxic T cells:
     1. function only to assist other parts of the adaptive immune system, such as B cell activation
     2. **are the other T cells that can directly attack and kill other cells**
     3. produce antibodies
     4. target antigens for destruction by other immune cells
  2. Class II MHC proteins:

1. activate cytotoxic T cells
2. **activate helper T cells**
3. activate naïve CD8 cells
4. are present on all body cells

References

1. OpenStax, Anatomy and Physiology. OpenStax CNX. May 2, 2019

Retrived from <http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@15.2>.

1. Adapted from HHMI Biointeractive. (2007). *Targeting infected cells for immune defense*. Retrieved from <https://www.hhmi.org/biointeractive/targeting-infected-cells-immune-defense>
   1. McNeil Jr., D.G. (2019, April 24). Measles outbreak infects 695, highest number since 2000. *The New York Times.* Retrieved from <https://www.nytimes.com/2019/04/24/health/measles-outbreaks-us.html>
   2. Lambert, J. (2019, April 30). Is Measles here to stay? *NPR*. Retrieved from <https://www.npr.org/sections/health-shots/2019/04/30/718220586/is-measles-here-to-stay>
   3. Kilgannon, C. (2019, May 2). What we know about the measles outbreak in N.Y. *The New York Times*. Retrieved from <https://www.nytimes.com/2019/05/02/nyregion/newyorktoday/nyc-news-measles-outbreak.html>