The Immune System as an Illustrative Example

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Teacher Research Program

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Recommended Audience: AP Biology Teachers

Class Schedule: 3 quarters, 85 minutes/day

Curriculum Outline: This is not intended to be a stand-alone immunology unit, though it could be modified for that purpose. Instead, it is a method for incorporating immune system concepts within other units. Therefore, aspects of the immune system will be shared with students over multiple units. During the immune system unit, students put their prior learning together with additional learning culminating in a project that requires them to demonstrate their comprehensive understanding of immune topics.

To do this successfully, it will be helpful to set the stage for investigating the immune system early in the year. This can be done in a variety of ways, listed below:

- Brainstorming – Provide students with a list of questions, such as, "How does your body fight an infection? How do vaccines work? What are autoimmune disorders?" Give students a chance to discuss and then share ideas with the class. Record ideas and questions on posters placed around the classroom so they can be referred to later.
- Video and discussion – Show a video clip that highlights an interesting immune-based scenario. Provide students an opportunity to discuss what they watched and find out what questions the video prompted.
- Article and discussion – Same as above, but with reading an article.

In each unit, refer back to the conversation and questions that were discussed as a way to engage students with the current learning.

AP Biology Curriculum Framework Objectives: These are written in the style of the Curriculum Framework. Enduring Knowledge benchmarks are abbreviated to E.K. and L.O. stands for Learning Objectives. Science Practices are abbreviated S.P.

Biochemistry Unit

Background Knowledge:

This lesson is meant to be an illustrative example of the concepts students have learned during the biochemistry unit. They will demonstrate their understanding of those concepts in this applied example. Therefore, students should have ample background information. They should be familiar with basic chemistry including composition of atoms, types of bonds and how they form (covalent, hydrogen, disulfide bridges). They should have already learned about the major macromolecule groups, including proteins. Students should recognize that there are 20 amino acids found in living things, and that they are categorized by their R groups. Students should also be able to describe the 4 levels of protein structure (primary, secondary, tertiary and quaternary).

Lesson Duration: 1 block (85 minutes)

Objectives:

Identify and describe the levels of protein structure and the interactions/bonding that cause the levels of protein structure.

Visualize the structure of a given molecule using RCSB PDB resources.

Explore the structure to understand how its structure matches its function.

AP Biology Curriculum Framework Objectives:

L.O. ENE-1.A Describe the composition of macromolecules required by living organisms.

E.K. SYI-1.B.2 Structure and function of polymers are derived from the way their monomers are assembled—

b. In proteins, the specific order of amino acids in a polypeptide (primary structure) determines the overall shape of the protein. Amino acids have directionality, with an amino (NH_2) terminus and a carboxyl ($COOH$) terminus. The R group of an amino acid can be categorized by chemical properties (hydrophobic, hydrophilic, or ionic), and the interactions of these R groups determine structure and function of that region of the protein.

E.K. SYI-1.C.1 Directionality of the subcomponents influences structure and function of the polymer—

c. Proteins comprise linear chains of amino acids, connected by the formation of covalent bonds at the carboxyl terminus of the growing peptide chain.

d. Proteins have primary structure determined by the sequence order of their constituent amino acids, secondary structure that arises through local folding of the amino acid chain into elements such as alpha-helices and beta-sheets, tertiary structure that is the overall three-dimensional shape of the protein and often minimizes free energy, and quaternary structure that arises from interactions between multiple polypeptide units. The four elements of protein structure determine the function of a protein.

Lesson Details:

Students will need a device to access the video, or it can be shown to the class as a group.

Students will also need a device to access the 1hsa file at rcsb.org. The website works best on a computer. If using an iPad, students will be unable to mouse over the structure which prevents them from answering questions 13, 14, and 18.

It is important to provide students with a little background on how the structure of proteins has been investigated. Though x-ray crystallography is not a required component of the AP Biology curriculum, it helps to give students context for the models that are used in this activity. If you have students who express an interest in the area of x-ray crystallography, I recommend the book The Gene Machine by Venki Ramakrishnan which is about the discovery of the structure of the ribosome.

As with all student-led activities in this document, it is recommended that you bring students back as a group at the end of the class or at the start of the next class to discuss their answers, or collect their responses and provide personalized feedback in some other way.

Possible discussion questions:

How did this activity help deepen your understanding of protein structure?

What are you curious about now that you know how MHC holds peptides?

If students press to know the details of the immune system, at this point, it is best to keep them engaged with open-ended questions such as:

Based on your current understanding, what do you think?

What do you predict?

What would you need to know to answer that question?

What could you research to learn more?

Exploring MHC Protein Structure: Major Histocompatibility Complex
Teacher Notes with Key

Now that you've learned about protein structure, let's investigate a protein that is important in the immune system. But first, how do we know about the structure of proteins? And how is the MHC molecule important in our immune system?

Background on x-ray crystallography: https://www.youtube.com/watch?v=uqQlwYv8VQI
Discuss the video clip with students mentioning that not all molecules crystallize well, and since proteins are dynamic, sometimes it is a challenge to "trap" a protein structure in a particular structure. They'll read below that one part of MHC has not yet been elucidated.

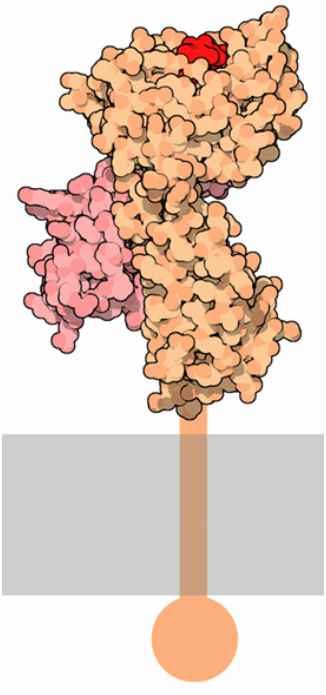
Background Reading:
This is an excerpt that has been slightly modified from the Molecule of the Month feature on MHC from the Educational Portal of the Protein Data Bank (PDB).

Major Histocompatibility Complex

MHC displays peptides on the surfaces of cells, allowing the immune system to sense the infection inside

Viruses are insidious enemies, so we must have numerous defenses against them. Antibodies are type of defense. Antibodies bind to viruses, mobilizing blood cells to destroy them. But what happens if viruses slip past this defense and get inside a cell? Then, antibodies have no way of finding them and the viruses are safe...but not quite.

Each cell has another type of defense that it uses to signal to the immune system when something goes wrong inside. Cells continually break apart a few of their old, obsolete proteins and display the pieces on their surfaces. The small peptides are held in MHC, the major histocompatibility complex, which grips the peptides and allows the immune system to examine them. In this way, the immune system can monitor what is going on inside the cell. If all the peptides displayed on the cell surface are normal, the immune system leaves the cell alone. But if there is a virus multiplying inside the cell, many of the MHC molecules carry unusual peptides from viral proteins, and the immune system kills the cell.



Major histocompatibility complex, with a displayed peptide in red. The portion crossing the membrane

Displaying Peptides

Like many proteins used in the immune system, MHC is composed of several functional parts connected by flexible joints. The structure shown here, PDB entry 1hsa , only shows the part found on the outside of the cell. The large chain colored orange has a groove at the top, which binds to the peptide, colored red. A smaller chain, colored pink, stabilizes the structure. In the whole protein, the orange chain extends down and crosses the cell membrane at the bottom, attaching the protein to the surface of the cell. This portion of the molecule, however, is too flexible for study by x-ray crystallography and was removed for the analysis.

is not included in the structure and is shown schematically.
Download high quality TIFF image

1. According to paragraph 2, what do MHC molecules do to alert the immune system to normal cells and cells infected with virus?
   They display viral peptides on the surface of the cell using MHC. This alerts the immune system to a foreign invader.

2. What portion of the MHC molecule is too flexible for study by x-ray crystallography?
   The transmembrane portion of the MHC molecule is too flexible for study.

Click here to open the summary page for the molecule described above, PDB entry 1hsa.
A computer is recommended. An iPad will work, but students will not be able to do #13, 14, 18.

Read the provided description here and answer the following questions:

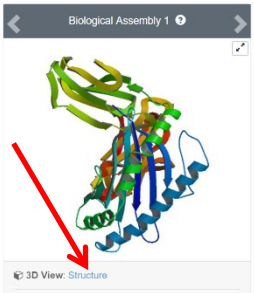
3. What is the source (organism) of the Class I Histocompatibility Antigen molecule in this structure?
   Homo sapiens

4. Name the authors who solved the structure of this protein.
   Madden, D. R.; Gorga, J.C.; Strominger, J. L.; Wiley, D. C.

5. Look on the left below the picture. Record the following:
   Total Structure Weight (measured in Daltons, or amu): 88840.30
   Atom Count: 6266
   Residue Count (this means how many amino acids are shown): 768
   Unique protein chains: 3 (note, only 2 protein chains make up the MHC; the other chain is the peptide being held in the groove of MHC)

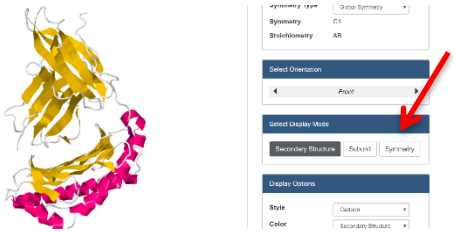
6. What level of protein structure is described as the sequence of amino acids?
   primary

   Explore the 3-D structure of this protein by clicking on Structure (hyperlink) next to 3D View as shown at right:
   The default view is rainbow colored.

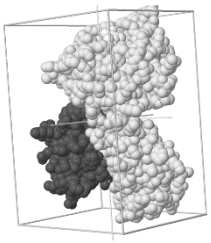


You should now see the image at right. Below the picture, it says Select a different viewer. Change it to JSmol (javascript).

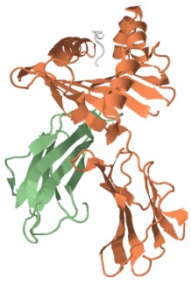
Now find the Select Display Mode menu at the right and change it to Symmetry.



You should now see the 3D Model shown at right.
In this space-filling model, each atom is represented by a sphere. Use the click and drag method to turn the molecule around. Do you notice that this view is the same as the orange and pink image shown at the start of this activity? Remember that the transmembrane portion of the MHC molecule is not depicted here.



Find Select Display Mode at the right and click on Subunit. You should see the model shown at right. When you compare this ribbon model to the space-filling model above, think about the ways in which they are similar, and how they are different.



7. What are the 3 colors of protein chains (polypeptides) that are shown in this model? (Be sure to click and drag the molecule to turn it around and look for 3 different colored strands.)
   orange, green, gray

8. What 2 secondary structures are evident in the model?
   alpha helices and beta sheets

9. What type of bond stabilizes these secondary structures?
   hydrogen bonds

10. Orient the view such that you can see the floating gray strand suspended in a pocket of the molecule. This is the peptide that was placed here to be

displayed by the MHC molecule on the surface of the cell. What secondary structure appears to be gripping the peptide from the sides?
alpha helices

11. Which secondary structure is holding the gray peptide from below?
beta sheets

12. These 2 secondary structures are what form the "grip" on the viral peptide that was described in the article above. Hypothesize how this pocket is able to "grip" the gray peptide.
Answers will vary; perhaps hydrogen bonds disulfide bridges, ionic bonding, or hydrophobic interactions between the MHC and peptide hold it in place.

13. Mouse over the strands and pause until a label pops up. The label shows the amino acid at that position and lists the type of amino acid in brackets, the number of the amino acid in sequence starting with the N-terminus, and then some other coding: [amino acid 3 letter code]#:(other coding)

    Mouse over the ends of each subunit until you find the N-terminus, which is #1 in sequence. Determine which amino acid is located at the N-terminus and C-terminus for each subunit, and record them below.

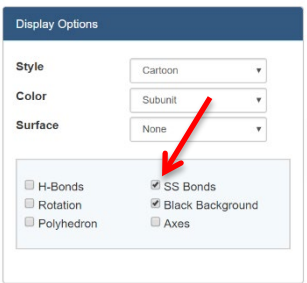
    smaller subunit
    N-terminus: Ile
    C-terminus: Met

    larger subunit
    N-terminus: Gly
    C-terminus: Pro

    (You may be surprised that the N-terminus does not contain methionine as the first amino acid. It is true that translation starts at the start codon AUG, which always results in methionine starting a polypeptide, but often, that first methionine is removed after translation. If you're curious, see this to read more.)

14. Starting at the N-terminus of the smaller subunit, count how many amino acids make up the coil BEFORE it becomes part of the beta sheet. How many amino acids are there?
5 (Students may say 6 because it is shown to begin before the flat portion of the beta sheet in the model. Accept this answer.)

15. Find the Display Options window as shown at right. Click on SS Bonds and if you don't see a black background, click on Black Background to toggle it on. Drag the molecule around until you can see the yellow lines, which represent disulfide bridges.

    How many disulfide bridges stabilize this structure?
    3

16. Disulfide bridges are involved in the tertiary level of protein folding. This means they form between which
    - the backbone structure of a polypeptide or
    - the R groups of a polypeptide?

17. Describe the location of those disulfide bridges. What role do they seem to be playing in the structure of the molecule?
    They join 2 beta sheets together or they join an alpha helix with a beta sheet. It appears the role of disulfide bridges in this protein are to stabilize its 3D structure.

18. In the Display Options window, click on H-Bonds. The dotted lines represent hydrogen bonds. In an alpha helix, every hydrogen bond occurs between amino acids that are separated by how many amino acids? (count by mousing over the structure)
    4

19. Is the same true for beta sheets? Are the amino acids joined by a hydrogen bond separated by the same number of amino acids?
    No, the number of amino acids between where 2 are joined by hydrogen bonds varies.

20. Does MHC exhibit quaternary structure? What evidence do you have to support your answer?
    Yes. There are 2 separate protein chains, one colored orange and one colored green that make up the structure. Since quaternary structure involves multiple polypeptides being held together to make up the protein, this MHC molecule exhibits quaternary structure.

21. As mentioned above, the transmembrane portion (the part that anchors MHC in the membrane) is too flexible for study by x-ray crystallography, so it has been removed. Given what you know about the structure of the cell membrane, predict the characteristics (acidic, basic, polar, or nonpolar) of the amino acids in the transmembrane portion of the protein and explain your prediction.
    The cell membrane has a hydrophobic interior where the lipid tails are. The transmembrane portion of the MHC molecule must contain some nonpolar (hydrophobic) amino acids. Those amino acids can exist alongside the nonpolar tails of phospholipids,
    which can help to anchor the protein in the membrane.

Exploring MHC Protein Structure: Major Histocompatibility Complex – Student Handout

Now that you've learned about protein structure, let's investigate a protein that is important in the immune system. But first, how do we know about the structure of proteins? And how is the MHC molecule important in our immune system?

Background on x-ray crystallography: https://www.youtube.com/watch?v=uqQlwYv8VQI

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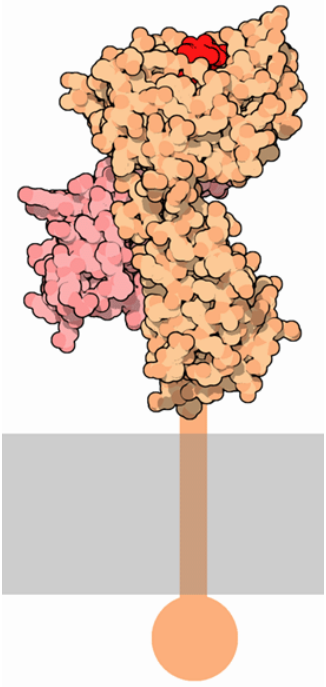

Major histocompatibility complex, with a displayed peptide in red. The portion crossing the membrane is not included in the structure and is shown schematically.
Download high quality TIFF image

1. According to paragraph 2, what do MHC molecules do to alert the immune system to normal cells and cells infected with virus?

2. What portion of the MHC molecule is too flexible for study by x-ray crystallography?

Click here to open the summary page for the molecule described above, PDB entry 1hsa.

Read the provided description here and answer the following questions:

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4. Name the authors who solved the structure of this protein.

5. Look on the left below the picture. Record the following:
   Total Structure Weight (measured in Daltons, or amu):
   Atom Count:
   Residue Count (this means how many amino acids are shown):
   Unique protein chains:

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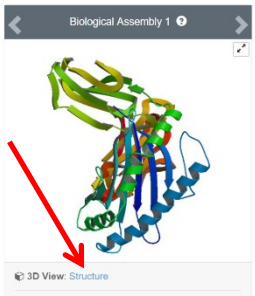

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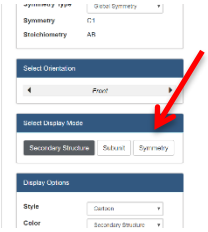

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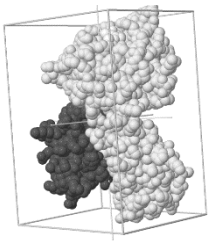

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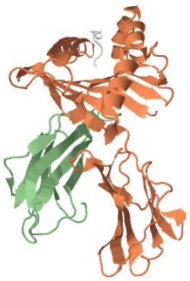


7. What are the 3 colors of protein chains (polypeptides) that are shown in this model? (Be sure to click and drag the molecule to turn it around and look for 3 different colored strands.)

8. What 2 secondary structures are evident in the model?

9. What type of bond stabilizes these secondary structures?

10. Orient the view such that you can see the floating gray strand suspended in a pocket of the molecule. This is the peptide that was placed here to be displayed by the MHC molecule on the surface of the cell. What secondary structure appears to be gripping the peptide from the sides?

11. Which secondary structure is holding the gray peptide from below?

12. These 2 secondary structures are what form the "grip" on the viral peptide that was described in the article above. Hypothesize how this pocket is able to "grip" the gray peptide.

13. Mouse over the strands and pause until a label pops up. The label shows the amino acid at that position and lists the type of amino acid in brackets, the number of the amino acid in sequence starting with the N-terminus, and then some other coding: [amino acid 3 letter code]#:(other coding)

    Mouse over the ends of each subunit until you find the N-terminus, which is #1 in sequence. Determine which amino acid is located at the N-terminus and C-terminus for each subunit, and record them below.

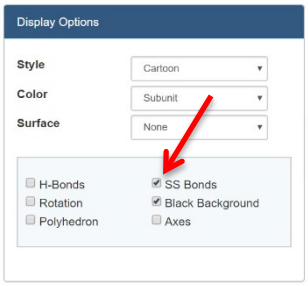
smaller subunit	larger subunit
N-terminus:	N-terminus:
C-terminus:	C-terminus:

    (You may be surprised that the N-terminus does not contain methionine as the first amino acid. It is true that translation starts at the start codon AUG, which always results in methionine starting a polypeptide, but often, that first methionine is removed after translation. If you're curious, see this to read more.)

14. Starting at the N-terminus of the smaller subunit, count how many amino acids make up the coil BEFORE it becomes part of the beta sheet. How many amino acids are there?

15. Find the Display Options window as shown at right. Click on SS Bonds and if you don't see a black background, click on Black Background to toggle it on. Drag the molecule around until you can see the yellow lines, which represent disulfide bridges.

    How many disulfide bridges stabilize this structure?



16. Disulfide bridges are involved in the tertiary level of protein folding. This means they form between which
    - the backbone structure of a polypeptide or
    - the R groups of a polypeptide?

17. Describe the location of those disulfide bridges. What role do they seem to be playing in the structure of the molecule?

18. In the Display Options window, click on H-Bonds. The dotted lines represent hydrogen bonds. In an alpha helix, every hydrogen bond occurs between amino acids that are separated by how many amino acids? (count by mousing over the structure)

19. Is the same true for beta sheets? Are the amino acids joined by a hydrogen bond separated by the same number of amino acids?

20. Does MHC exhibit quaternary structure? What evidence do you have to support your answer?

21. As mentioned above, the transmembrane portion (the part that anchors MHC in the membrane) is too flexible for study by x-ray crystallography, so it has been removed. Given what you know about the structure of the cell membrane, predict the characteristics (acidic, basic, polar, or nonpolar) of the amino acids in the transmembrane portion of the protein and explain your prediction.

Cell Unit

Background Knowledge: Students should be familiar with eukaryotic cells including major organelle structure and function including the nucleus, ER, Golgi, lysosome, mitochondria, ribosomes, etc. They should be able to describe endocytosis/phagocytosis and exocytosis.

Lesson Duration: 1 block (85 minutes)

Objectives:

Students will explain how viruses take advantage of a cell and its functioning parts in order to reproduce themselves.

Students will explain how the endomembrane system is used in the specific example of a cell manufacturing MHC, combining MHC with viral peptide, and displaying the viral peptide on the surface of the cell.

AP Biology Curriculum Framework Learning Objectives:

L.O. ENE-2.F Describe the mechanisms that organisms use to transport large molecules across the plasma membrane.

L.O. SYI-1.E Explain how subcellular components and organelles contribute to the function of the cell.

L.O. ENE-2.J Describe the processes that allow ions and other molecules to move across membranes.

Lesson Details:

This activity can be can be teacher-led with the teacher discussing with students after each section or completely student-led with the only teacher summarizing and reflecting with students at the end. If student-led, it requires that students have a device with access to the internet. It begins with students watching a video on how the influenza virus infects a cell and commandeers it to make more virus. Students should answer the 6 questions that go along with the video while they watch or shortly after.

Then the lesson transitions into learning how the immune system can prevent viruses from replicating inside of them. Students revisit the biochemistry lesson with MHC. Then they watch a Powerpoint presentation that helps animate the process of loading MHC with viral proteins and displaying on the surface of the cell.

Viruses and Immune Cell Response
Teacher Notes with KEY

This activity requires a device with access to the internet.

Now that we've learned about the inner workings of a cell, how can a cell be hijacked by a virus in order to make more virus particles? How does our body defend against these invaders?

Watch this video clip to see how a virus enters a cell, is replicated, and released.

You can show this video to the class or have students watch it on their own devices.

Consider these questions:

1. A virus is only able to enter a cell if the "keys" of the virus match the "locks" of the host. What are these locks on the host cell?

Answer: Receptors.

Mention that the keys on the virus are typically proteins, or at least have protein components. Discuss how keys on a virus are usually species specific, or specific to a few species. Prompt for examples of spill-over from one species to another due to mutations in the virus (Covid-19, swine flu, avian flu, HIV).

2. By what cellular process does the virus enter the cell?

Answer: Endocytosis.

Depending on your objectives, you could describe receptor-mediated endocytosis. If students ask what the "welcoming committee" is, you can mention clathrin, though it is beyond the scope of the AP exam.

3. After the viral genome is copied into mRNA, what organelles use it to make viral proteins?

Answer: Ribosomes.

Students may wonder how an RNA molecule is copied into more RNA. You could mention that some viruses include enzymes within their structure that enable this… You could expand into a conversation about negative sense and positive sense RNA.

4. Some of those proteins become embedded within the cell membrane. Others are used, along with a copy of the viral genome, to reassemble new viruses. By what process do viruses exit the cell?

Exocytosis.

Students may wonder how the viral genome is replicated since it isn't described in the animation. The virus either contains enzymes for synthesizing the negative sense DNA or has genetic information that results in synthesis of those enzymes.

5. How is the process of releasing viruses important to their structure?

Since viruses that leave by exocytosis end up coated in the cell's plasma membrane, any viral proteins that were incorporated into the plasma membrane will end up on the surface of the virus.

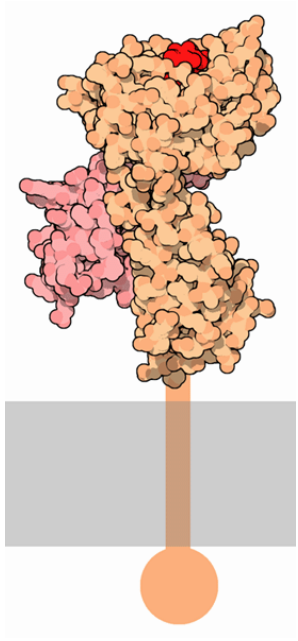
6. Hypothesize methods we could use to interfere with viruses. What could we target? What would we have to avoid targeting?

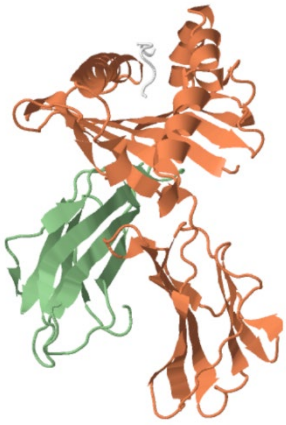
   Antigens (or viral proteins, if you don't want to introduce the vocabulary term here). Depending on your students' background knowledge you could ask what molecules are made by specialized immune cells that travel in the blood and attach to antigens, or explain antibodies. Guide students to understand that this targets the viruses that are traveling in our bodies OUTSIDE of cells, which isn't enough. Explain that we must also target virus reproductive cycle to stop the manufacture of new viruses. This sets the stage for understanding the 2 different branches of our adaptive immune system, humoral and cell-mediated, without necessarily getting into all the details yet.

   You don't usually target the cell's machinery itself. To do that, you'd need to give a person a drug that interfered with the basic cellular processes needed to keep cells alive and functioning. This would be toxic.

So how do we interfere with the virus reproduction cycle?

You might remember the images on the right. They are 2 different ways of representing the MHC molecule we studied in a previous unit. Answer the questions below to jog your memory about this molecule.





7. To which macromolecule category does it belong?
   protein

8. The MHC molecule plays an important role in which system?
   immune

9. The red molecule on the left image and the gray molecule in the right image represents what?
   viral protein (or cytosolic protein that's native to the cell itself)

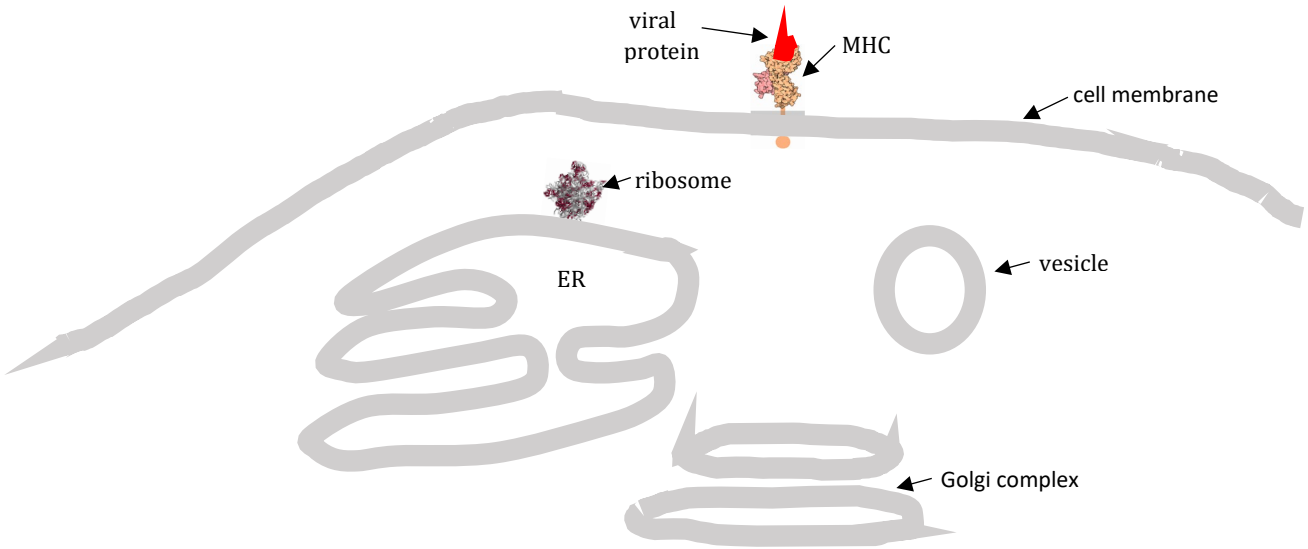
Read this excerpt from the Molecule of the Month on MHC to further refresh your memory:

> Each cell has another type of defense that it uses to signal to the immune system when something goes wrong inside. Cells continually break apart a few of their old, obsolete proteins and display the pieces on their surfaces. The small peptides are held in MHC, the major histocompatibility complex, which grips the peptides and allows the immune system to examine them. In this way, the immune system can monitor what is going on inside the cell. If all the peptides displayed on the cell surface are normal, the immune system leaves the cell alone. But if there is a virus multiplying inside the cell, many of the MHC molecules carry unusual peptides from viral proteins, and the immune system kills the cell.

So how are these MHC molecules made and then anchored in the cell membrane? How are cellular and viral proteins "loaded" into the MHC to be displayed on the cell's surface? See the presentation MHC displays antigen to find out how it works.

You can lead students through the presentation or have them click through it on their own.

10. Using the image below, label Golgi, ER, MHC, cell membrane, viral protein, ribosome, and vesicle. Draw arrows to indicate where the MHC starts and all the places it goes on its way to its current location embedded in the membrane.

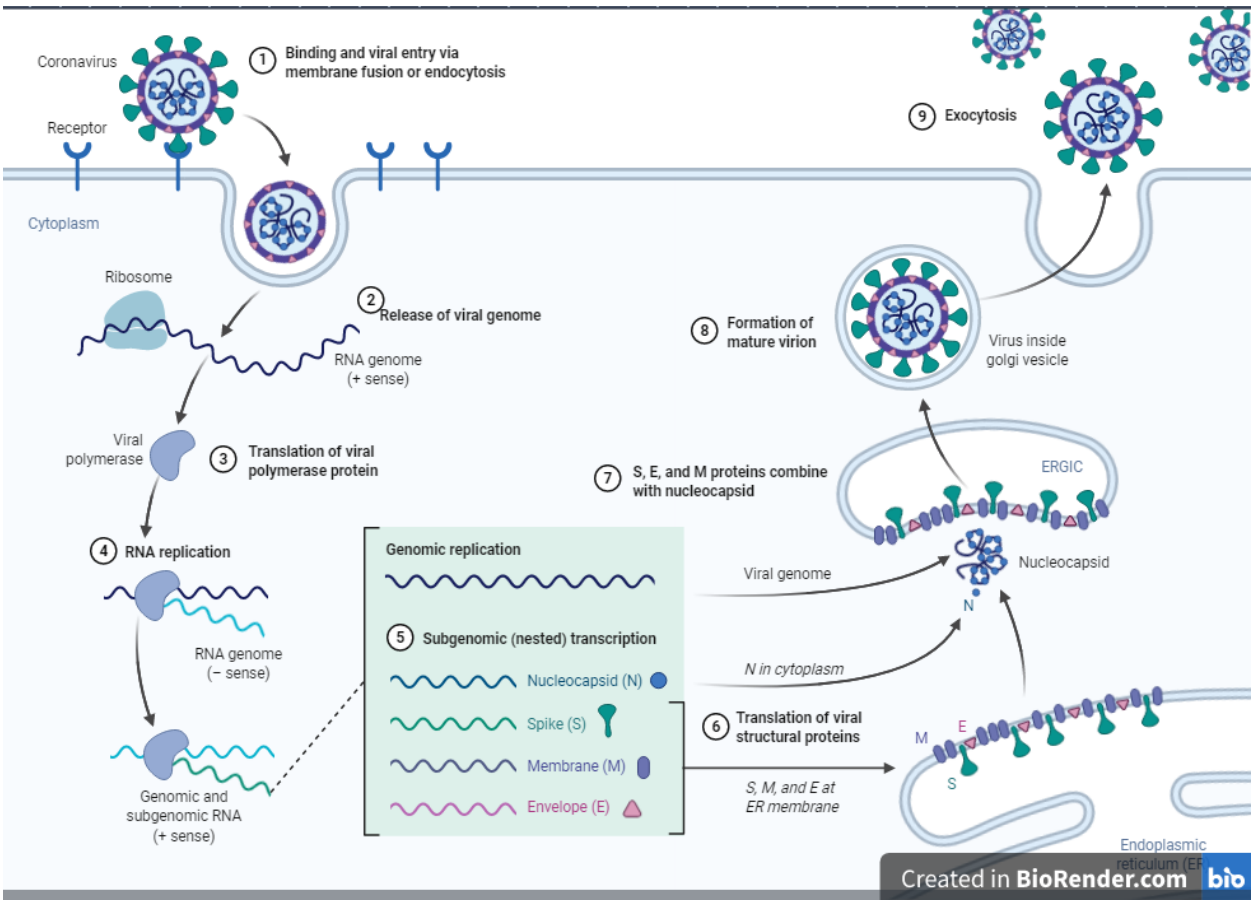


11. In your own words, describe how a cell can display viral protein on its surface starting with MHC in the ribosome all the way to MHC embedded in the plasma membrane.

Sample student response:

MHC molecules are made by ribosomes that are attached to the rough ER. The MHC ends up in the lumen of the ER with one part of it anchored to the ER membrane. A vesicle containing the MHC buds off of the ER and joins with the Golgi where it is further processed. A vesicle buds off the Golgi. Meanwhile, a virus has been degraded by the cell and is contained within a vesicle. The vesicle with viral proteins fuses with the vesicle containing the MHC molecule. A fragment of viral protein joins with the MHC in a groove. Then the vesicle fuses with the cell membrane resulting in the MHC displaying the viral protein to the extracellular environment.

If you're interested…
On the next page, a visual explains the reproductive cycle of SARS-CoV2.


Coronavirus
1 Binding and viral entry via membrane fusion or endocytosis
Receptor
Cytoplasm
Ribosome
2 Release of viral genome
RNA genome (+ sense)
Viral polymerase
3 Translation of viral polymerase protein
4 RNA replication
RNA genome (− sense)
Genomic and subgenomic RNA (+ sense)
Genomic replication
5 Subgenomic (nested) transcription
Nucleocapsid (N)
Spike (S)
Membrane (M)
Envelope (E)
6 Translation of viral structural proteins
S, M, and E at ER membrane
7 S, E, and M proteins combine with nucleocapsid
Viral genome
N in cytoplasm
N
Nucleocapsid
ERGIC
8 Formation of mature virion
Virus inside golgi vesicle
9 Exocytosis
M
E
S
Endoplasmic reticulum (ER)
Created in BioRender.com

Viruses and Immune Cell Response – Student Handout

Now that we've learned about the inner workings of a cell, how can a cell be hijacked by a virus in order to make more virus particles? How does our body defend against these invaders?

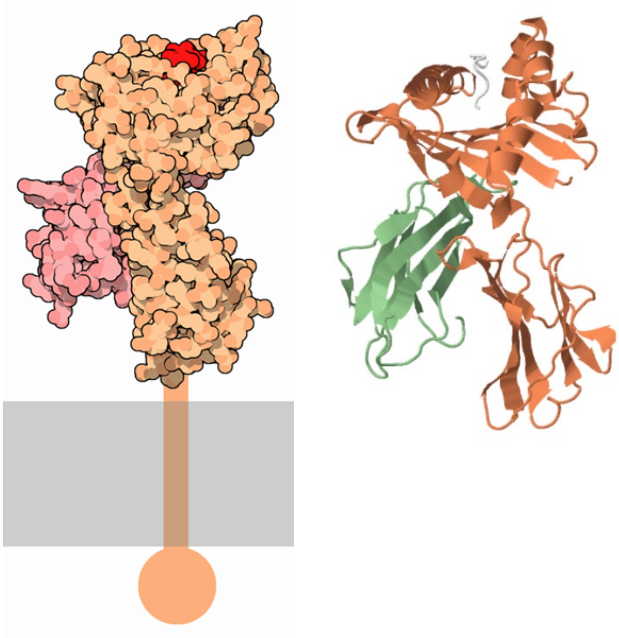
Watch this video clip to see how a virus enters a cell, is replicated, and released.

Consider these questions:

1. A virus is only able to enter a cell if the "keys" of the virus match the "locks" of the host. What are these locks on the host cell?
2. By what cellular process does the virus enter the cell?
3. After the viral genome is copied into mRNA, what organelles use it to make viral proteins?
4. Some of those proteins become embedded within the cell membrane. Others are used, along with a copy of the viral genome, to reassemble new viruses. By what process do viruses exit the cell?
5. How is the process of releasing viruses important to their structure?
6. Hypothesize methods we could use to interfere with viruses. What could we target? What would we have to avoid targeting?

So how do we interfere with the virus reproduction cycle?

You might remember the images on the right. They are 2 different ways of representing the MHC molecule we studied in a previous unit. Answer the questions below to jog your memory about this molecule.



7. To which macromolecule category does it belong?

8. The MHC molecule plays an important role in which system?

9. The red molecule on the left image and the gray molecule in the right image represents what?

Read this excerpt from the Molecule of the Month on MHC to further refresh your memory:

> Each cell has another type of defense that it uses to signal to the immune system when something goes wrong inside. Cells continually break apart a few of their old, obsolete proteins and display the pieces on their surfaces. The small peptides are held in MHC, the major histocompatibility complex, which grips the peptides and allows the immune system to examine them. In this way, the immune system can monitor what is going on inside the cell. If all the peptides displayed on the cell surface are normal, the immune system leaves the cell alone. But if there is a virus multiplying inside the cell, many of the MHC molecules carry unusual peptides from viral proteins, and the immune system kills the cell.

So how are these MHC molecules made and then anchored in the cell membrane? How are cellular and viral proteins "loaded" into the MHC to be displayed on the cell's surface? See the presentation MHC displays antigen to find out how it works.

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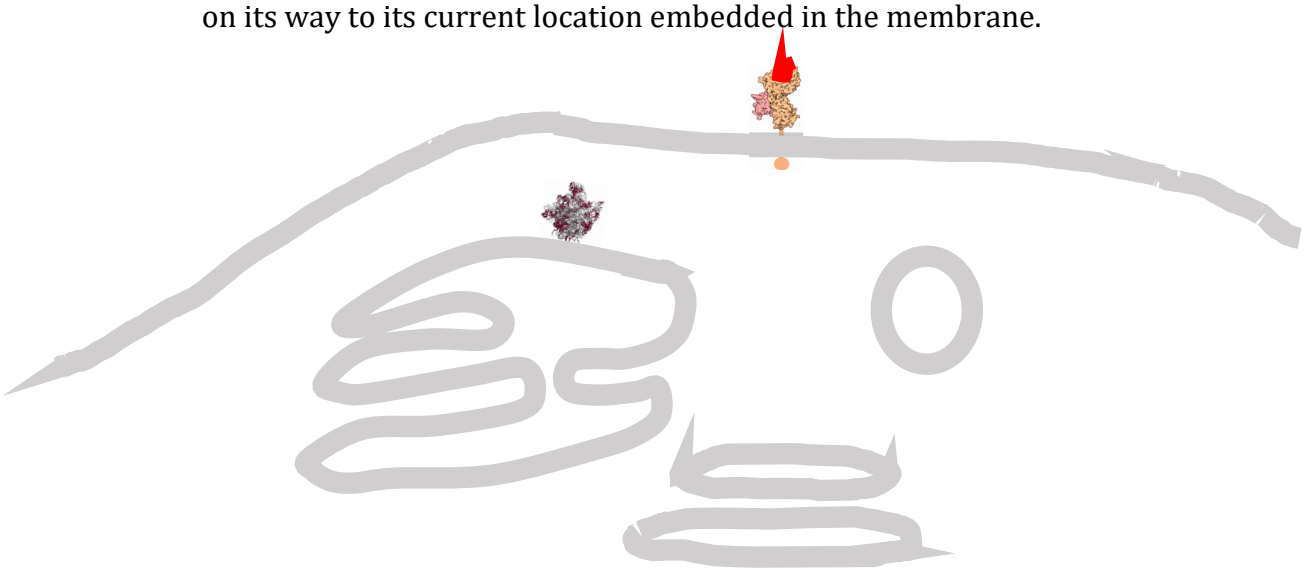

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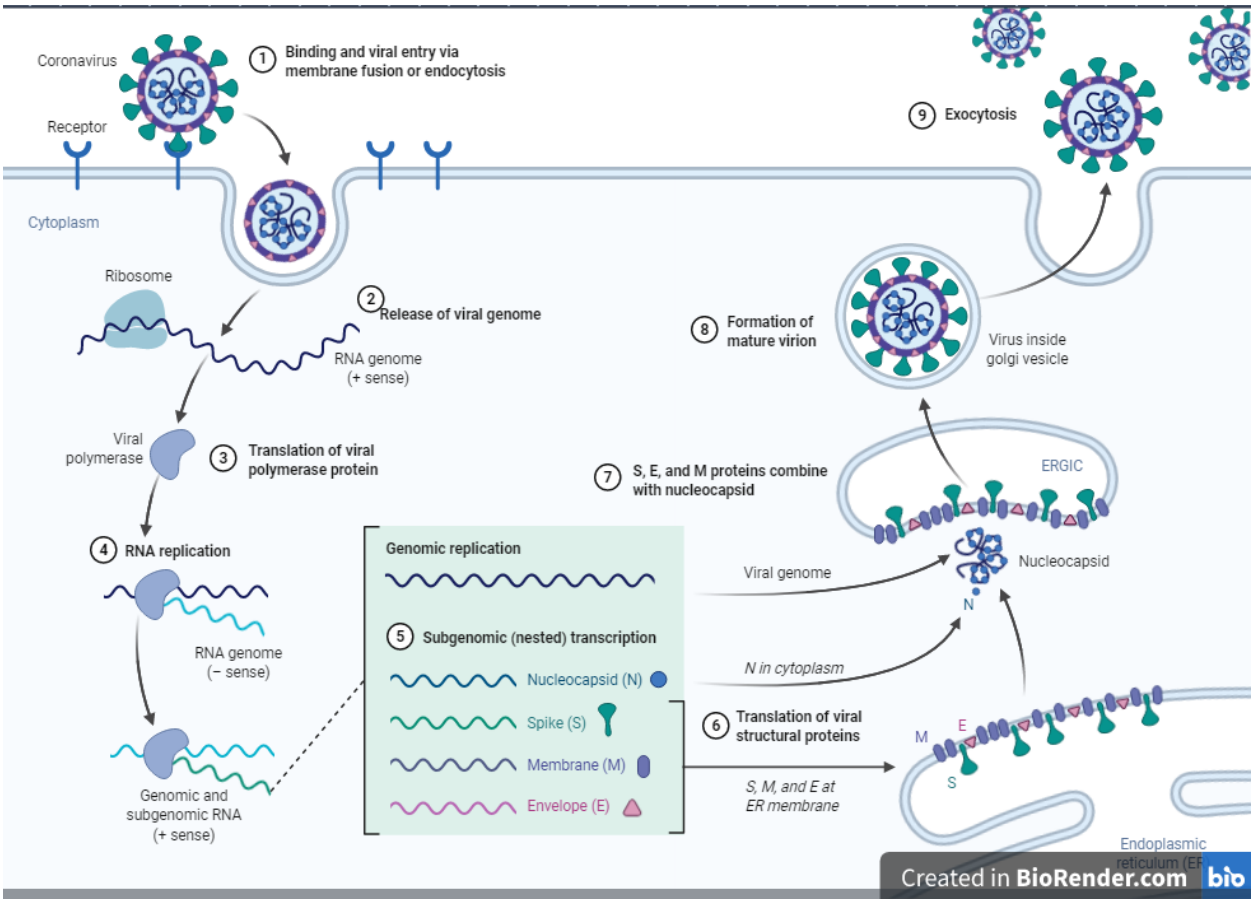


Cell Signaling Unit

Background information: Students should have learned about signal transduction pathways as an earlier part of this unit. They should be familiar with the types of receptors, roles of kinases, phosphatases, second messengers, and types of responses. They should also know the difference between autocrine, paracrine, and endocrine signaling.

Lesson Duration: 1/2 block (40 minutes)

Objectives:

Students will use a specific immune cell example to identify the components of a signal transduction pathway and explain their roles.

AP Biology Curriculum Framework Learning Objectives:

E.K. IST-3 Cells communicate by generating, transmitting, receiving, and responding to chemical signals.

L.O. IST-3.A Describe the ways that cells can communicate with one another.

E.K. IST-3.A.1 Cells communicate with one another through direct contact with other cells or from a distance via chemical signaling— a. Cells communicate by cell-to-cell contact.

L.O. IST-3.D Describe the role of components of a signal transduction pathway in producing a cellular response.

E.K. IST-3.D.1 Signaling begins with the recognition of a chemical messenger—a ligand—by a receptor protein in a target cell— a. The ligand-binding domain of a receptor recognizes a specific chemical messenger, which can be a peptide, a small chemical, or protein, in a specific one-to-one relationship.

E.K. IST 3.D.2 Signaling cascades relay signals from receptors to cell targets, often amplifying the incoming signals, resulting in the appropriate responses by the cell, which could include cell growth, secretion of molecules, or gene expression—a. After the ligand binds, the intracellular domain of a receptor protein changes shape initiating transduction of the signal. b. Second messengers (such as cyclic AMP) are molecules that relay and amplify the intracellular signal.

Lesson Details:

This activity enables students to apply their understanding of cell signaling to the immune system. Since it is only ½ block, it pairs well with other things, such as direct instruction. It is set up to be either teacher-led or student-led. If student-led, students need a device that is connected to the internet.

A possible extension to this activity is to have students simulate the process presented in this video with craft materials in small groups of students. They could investigate the key molecules a little more to better understand their role, and then choose materials such as beads, felt, construction paper, colored paper clips, etc to simulate the process.

Immune Cell Animation and Cell Signaling

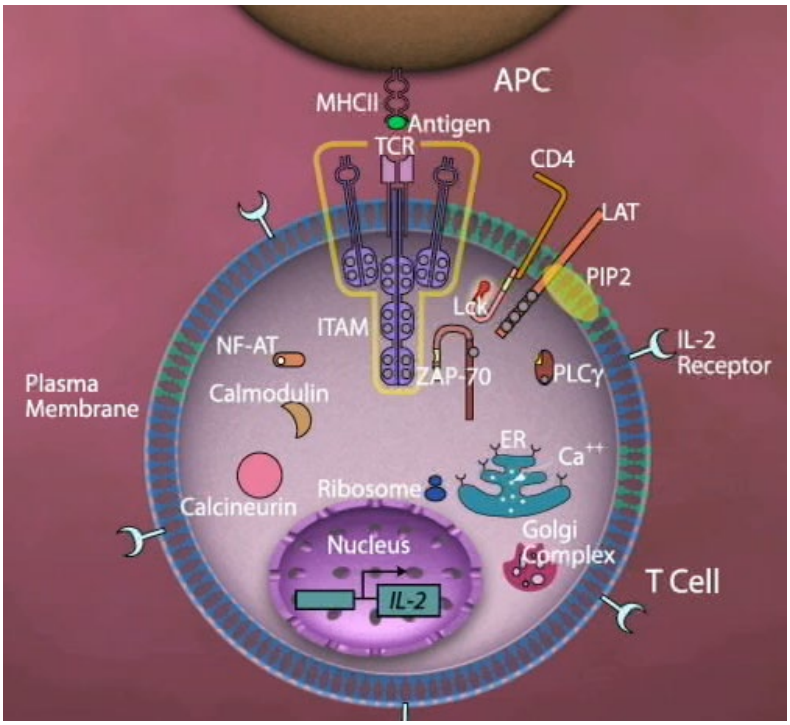
Teacher Notes and Key

Remember the immune system? We've learned about MHC molecules and how they can display viral proteins on cells. As it turns out, when an immune cell interacts with the displayed protein, it initiates a signal transduction pathway. We're going to learn more about how a particular interaction between 2 immune cells works. Though this example has been simplified, it is still very complex. Here are a few terms to get you on the right track.

Providing these definitions will help students make meaning of the animation. The animation is very detailed and beyond the scope of an AP class, yet there are parts that fit perfectly with our objectives. Alert students to the questions contained within the definitions below.

Vocabulary:

antigen – This is any substance that causes an immune response. In our previous lessons, we discussed viruses as the pathogen. We learned that viruses are broken down into viral proteins which can be displayed by MHC molecules. In the image, what color is the antigen?



APC – This is an antigen-presenting cell. In the image, what color is the APC?

MHCII – This is a specific type of MHC molecule. It isn't the one used by infected cells to alert immune cells to kill it. Instead, MHCII are used by special immune cells that can stimulate other immune cells, in this example, a T cell. In the image, how many units make up the MHCII molecule?

TCR – TCR stands for T cell receptor. The video is highlighting how a T cell responds to a cell that's displaying viral protein. What color is the TCR in the image?

Activity:

Open the T Cell activation video: http://www.hhmi.org/biointeractive/cloning-army-t-cells-immune-defense.

The whole animation is 4:23.

Starting at 1:21, watch through the end without stopping. Then start it again at 1:21, and answer the questions below while pausing when needed.

1. What does a kinase do (by definition)?

kinases add phosphates to other molecules

2. Which of the proteins in the animation would be classified as kinases?

LCK, Zap-70

3. What does a phosphatase do (by definition)?

phosphatases remove phosphates from other molecules

4. Which of the proteins in the animation would be classified as phosphatases?

the calmodulin/calcineurin complex (students may state only one or the other, which is fine, but it is actually the complex that acts as a phosphatase)

5. Which of the following components are present in this signal transduction pathway?

Reception – Tyrosine kinase receptor **OR** G-Protein coupled receptor

Transduction – Which second messenger is used? cAMP **OR** IP3 and Calcium

Response – changes in: cytoskeleton **OR** enzyme activity **OR** gene expression

6. What are the effects of this cell producing IL-2?

It causes the cell to divide. (The animation says it causes the cell to proliferate and differentiate.)

7. Is the release of the IL-2 chemicals an example of endocrine signaling or paracrine signaling? Explain why.

Autocrine because the cell releases IL-2, which binds with IL-2 receptors on its OWN membrane, further stimulating it.

8. Now that you've seen an example of a signal transduction pathway in an immune cell, what questions do you have about cell signaling or the immune response?

Answers will vary. This is an opportunity for students to share questions about cell signaling and questions about the immune system that can be used to stimulate more interest in it.

Immune Cell Animation and Cell Signaling – Student Handout

Remember the immune system? We've learned about MHC molecules and how they can display viral proteins on cells. As it turns out, when an immune cell interacts with the displayed protein, it initiates a signal transduction pathway. We're going to learn more about how a particular interaction between 2 immune cells works. Though this example has been simplified, it is still very complex. Here are a few terms to get you on the right track.

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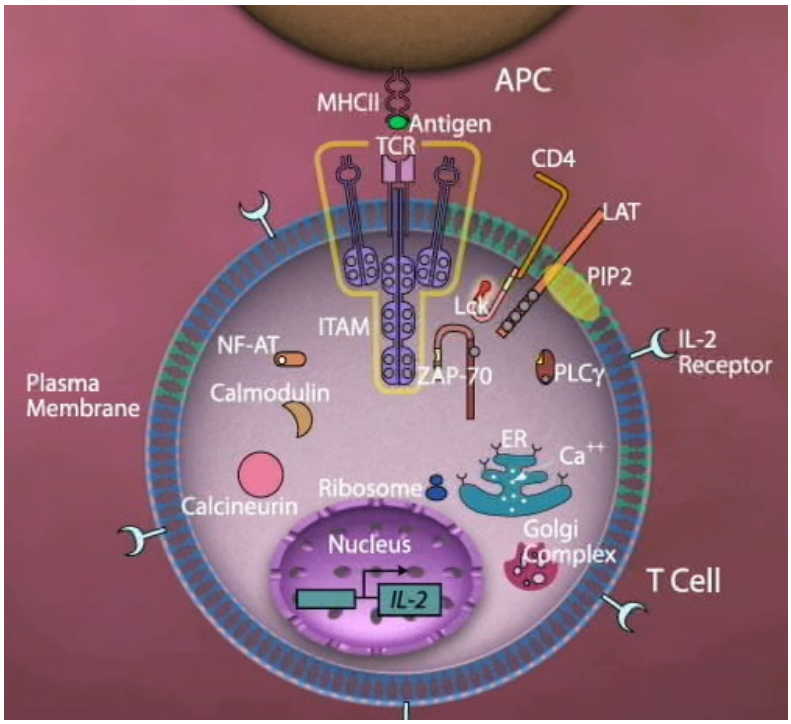

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8. Now that you've seen an example of a signal transduction pathway in an immune cell, what questions do you have about cell signaling or the immune response?

Immune System Unit

This lesson is split into 2 lessons.

Background Knowledge: Students should have learned about cells, their functions, and how their membranes are involved in transport and signaling. Students should understand signal transduction pathways including the types of receptors, roles of kinases, phosphatases, second messengers, and types of responses. A general understanding of mitosis is helpful as well.

Lesson 1 Duration: 1 block (85 minutes)

Lesson 2 Duration: 2 blocks (170 minutes)

Objectives:

Students will describe innate immunity including both barrier and internal defenses.

Students will explain how the adaptive immune response works including both humoral and cell-mediated defenses.

AP Biology Curriculum Framework Learning Objectives:

S.P. 1.A Describe biological concepts and/or processes.

S.P. 1.B Explain biological concepts and/or processes.

S.P. 1.C Explain biological concepts, processes, and/or models in applied contexts.

E.K. IST-3 Cells communicate by generating, transmitting, receiving, and responding to chemical signals.

L.O. IST-3.A Describe the ways that cells can communicate with one another.

E.K. IST-3.A.1 Cells communicate with one another through direct contact with other cells or from a distance via chemical signaling— a. Cells communicate by cell-to-cell contact.

Lesson Details:

In Lesson 1, the block will be divided up into 3 parts. In Part 1, students will use the textbook or a brief lecture to distinguish between the innate and adaptive immunity. Students will check their understanding with a short list of questions before moving on. In Part 2, a subset of students will act out a skit designed to simulate how the adaptive immune system works. The skit will involve gang members, a watch group, Batman,

Spiderman, and a variety of props. In Part 3, following the skit, students will use a concept map of adaptive immune terms to match them with the correct role and prop from the skit.

In Lesson 2, students will explain how the immune system works in one of several ways. 1) In groups of 2-3, students model how the immune system works by using pipe cleaners, beads, foam paper, or other craft materials. A list of required components for the model is included. Students record a video on a device to demonstrate their understanding. The video could be stop action photography, using the pieces to act it out, or simply calling the teacher over to simulate it live. 2) Students individually use the Explain Everything app on the iPad to draw the process of adaptive immunity while they explain verbally how the process works. 3) In groups of 2-3, students use expo markers on the surface of lab stations to draw out the adaptive immune response.

Immune System Unit: Lesson 1, Part 1 TEACHER NOTES

Students read Chapter 43.1 from Campbell Biology 9e, or a similar introduction to innate vs adaptive immunity. This should be an overview only.

Then use these Powerpoint slides and direct instruction to introduce innate and adaptive immunity.

Deepen the discussion by mentioning PAMPs, which are pathogen-associated molecular patterns that are commonly exhibited on pathogens. Our innate immune system can recognize these motifs as foreign and defend against them.

Vaccines use the adaptive immune response to protect us against future infections of the same pathogen.

A common misconception is that animals have immune defenses but other organisms don't. This is a great opportunity to mention that plants have defenses, too, including epithelial surfaces that are often reinforced with strong proteins, sugars.

To help students correctly categorize types of barrier and internal defenses, I use images. The fence is a great visual that represents barrier defenses. The person with a chest of gears is a visual for internal defenses.

Help students make connections with the terms. The term humoral is used because antibodies are found in the liquid in the body. In the past, the liquids were referred to as humors. Looking at the term cytotoxic, you can see it is made up of cyto- which means cell and -toxic which means deadly. This term fits its function.

Natural killer cells are able to target cancerous cells or virus-infected cells. Some cancer research is aimed at improving our NK cells to target cancer more effectively.

Antimicrobial proteins travel in the bloodstream and play a variety of roles in defending internally. Some are involved in the complement system, which works with antibodies to kill pathogens. Types are beyond the scope of the AP Biology.

The inflammatory response triggers a series of steps leading to the increase in diameter of blood vessels, release of cytokines and other stimulatory signaling molecules, and recruitment of additional immune cells to the site.

You may use the questions on the last PPT slides to check for student understanding, or you can use the Student Handout below, which has the same questions but in Word format.

Innate and Adaptive Defenses Questions – Student Handout

1. The esophagus produces a fluid that is rich in mucin and bicarbonate. This fluid provides protection. What type of defense is this?

2. A vaccine prompts your immune response to respond to future infections of that particular pathogen. If you encounter a pathogen for which you've been vaccinated, what response is activated?

3. What part of that response refers to the molecules that are released in mass quantity in the bloodstream?

4. While putting up a poster in your room, a push pin punctures your finger and you start to bleed. What defense have you compromised?

5. A bacterial cell is now roaming around in your blood stream. What type of immune cell may engulf it?

6. The area around the puncture site is red and feels warm to the touch. What response is activated now?

7. Which major categories of organisms do not have adaptive immunity?

Matching

<u>4 Major Categories</u>

Barrier defenses
- -
- -

Internal defenses
- -
- -
- -

Humoral response
- -

Cell-mediated response
- -

<u>Components within the 4 categories</u>

Antibodies

Skin

Secretions

Phagocytic cells

Antimicrobial proteins

Inflammatory response

Cytotoxic T cells

Natural killer cells

Mucous membranes

Innate and Adaptive Defenses Questions – KEY

1. The esophagus produces a fluid that is rich in mucin and bicarbonate. This fluid provides protection. What type of defense is this? Innate, Barrier: mucous membrane

2. A vaccine prompts your immune response to respond to future infections of that particular pathogen. If you encounter a pathogen for which you've been vaccinated, what response is activated? Adaptive: both humoral and cell-mediated

3. What part of that response refers to the molecules that are released in mass quantity in the bloodstream? Adaptive: humoral (the molecules are called antibodies)

4. While putting up a poster in your room, a push pin punctures your finger and you start to bleed. What defense have you compromised? Innate, Barrier: skin

5. The area around the puncture site is red and feels warm to the touch. What response is activated now? Innate, Barrier: inflammatory

6. A bacterial cell is now roaming around in your blood stream. What type of immune cell may engulf it? Phagocytic, which is part of Innate, Internal

7. Which major categories of organisms do not have adaptive immunity? invertebrates, plants, fungi

Matching

<u>4 Major Categories</u>

Barrier defenses
- skin
- mucuous membranes
- secretions

Internal defenses
- phagocytic cells
- natural killer cells
- antimicrobial proteins
- inflammatory response

Humoral response
- antibodies

Cell-mediated response
- cytotoxic T cells

<u>Components within the 4 categories</u>

Antibodies

Skin

Secretions

Phagocytic cells

Antimicrobial proteins

Inflammatory response

Cytotoxic T cells

Natural killer cells

Mucous membranes

Immune System Unit: Lesson 1, Part 2 TEACHER NOTES

As students begin working on the questions from Part 1, ask for 9 volunteers to participate in a skit. (They can finish the questions on their own time.)

Bring them into a separate area where you can assign roles, distribute props, and direct the skit while students read it.

Props (if the prop represents an immune component, it has been listed in caps):

Spiderman mask – Available online or in the party section of some stores

Batman mask - Available online or in the party section of some stores

Boomerang – (beyond the scope, but this represents perforin and granzyme which initiate apoptosis of the infected cell). This can be made of paper.

Bandanas (4) – ANTIGEN. Any bandana will do, though it is helpful if all 4 look identical.

Badge – MHC-II. A sleeve for a teacher badge on a lanyard works well, or it could be made with paper.

Brain – MEMORY B CELL. A printed picture of a brain will do, but I use a brain model I have in the classroom.

Bat symbol – INTERLEUKIN-2. Print a Batman outline from the internet and cut it so the paper is in the shape of the symbol.

Flood lamp or flashlight – any type of light will do; a student will hold the bat symbol in front of it to show the bat symbol as a shadow on the wall.

White flag – MHC-I. Attach a triangle of white paper to a dowel or popsicle stick.

CD – (not shown in the Cmap, but this represents MEMORY HELPER T CELL.) An old CD works well as a memory because CDs can be used to store things. Alternatively, you could use a memory stick, it's just harder to see. NOTE: this does not appear in the Cmap activity.

Silly string – ANTIBODIES. This part is optional, but it is intended to represent antibodies which neutralize, opsonize, and activate the complement system. It's a nice visual to imagine silly string as the webbing that Spiderman uses to neutralize the bad guy. Note: Avoid silly string with dyes as it may stain student clothing! Also, instruct to point at waist level to avoid getting it in the eyes. Goggles could be worn for that reason.

Glasses and clipboard – any old readers will do. The idea with these 2 props is to help the student who is playing Alfred the Butler to feel more involved!

Roles (with their immune system counterpart in caps):

Gang members (2) – PATHOGEN. If you dislike the idea of gang members, you could change this to villains instead.

Watch group – DENDRITIC CELL or MACROPHAGE. If you would prefer to use an individual called a "good guy" you could do that.

Innocent bystander – INFECTED CELL

Police dispatch – HELPER T CELL. Some students may be unfamiliar with the term dispatch. This could be changed to central command or headquarters.

Spiderman – B CELL. Choose someone for this role who you can trust with silly string!

Batman – CYTOTOXIC T CELL. Choose someone you trust who could gently toss a paper boomerang to another student!

Alfred the Butler – MEMORY CYTOTOXIC T CELL. This is a very small role.

Narrator

Choosing a good narrator is essential. Try to find a student who can watch the skit and match their reading of the skit to the acting. It works well to have students read through the script, act it out once, then act it out for the whole class. See other specific details in the Teacher Notes skit.

Immune Analogy Script – Teacher Notes

Actors are in green. Props are in blue.

Narrator reads italicized text

SCENE 1

Gang members (2)	wearing bandanas (gang symbols), carrying a couple more bandanas
Watch Group member	wearing a badge to identify him/herself
Innocent bystander	has a white flag that is hidden

It's a warm, muggy night.

Gang members prowl around, looking for trouble. They flash their gang symbols multiple times. Check out their goofy handshake. <wait for flashing of bandana and handshake; both gang members move through crowd>

One gang member recruits an innocent bystander to become part of the gang. He gives them a bandana to affirm membership to the gang. <Gang member solicits bystander and hands him the bandana. Bystander reluctantly takes it.>

The innocent bystander may be reluctant, but he takes the bandana.

A local member of a Watch Group enters the scene. Seeing one of the gang members, he stares at him until he crumples to the ground. The Watch Group snatches the bandana and displays it and his badge to the world. <The watch group takes 1 bandana and uses the badge to hold it up. This gang member will quietly exit the stage and will be used again as a different gang member shortly.>

SCENE 2

Watch group member	wearing a badge
Police dispatch	has the bat symbol and flood light; CD is hidden

The watch group member walks around displaying the bandana with the badge. He seeks a match. <Watch group member walks up to random students and says, "You're not a match… You're not a match.">

He approaches police dispatch and realizes he's found a match!

Watch group: "YOU'RE A MATCH! And look at my badge - I'm the good guy, not the bad guy!" <CLEARLY SHOW police dispatch the bandana, using the badge to hold it up.>

The police dispatch acknowledges it, but doesn't seem to be taking the threat seriously! The *watch group shows frustration and starts yelling!*

Watch group yells: "DO SOMETHING ABOUT THIS! WE HAVE A PROBLEM! COME ON!"

Finally, the police dispatch jumps into action by displaying the bat signal. <Bat signal should show up on the wall. Hold up bat symbol a few feet from the wall, then turn on the flood light to see the bat signal. LEAVE BAT SIGNAL ON!>

SCENE 3

Spiderman	wearing mask, holding silly string, keeping a brain hidden
Gang member	wearing bandana

Spiderman appears on the scene, not noticing the bat signal, YET. But he does see a gang member. Just like the Watch Group, Spiderman stares at him until he crumples to the ground, and takes his bandana away. <This gang member stays put and doesn't return to the skit.>

Wandering around, Spiderman comes across the police dispatch and shows him the bandana. Alerted by the bat signal, he realizes he's an expert at identifying gang members. He prowls around looking for more. Finding one, he sprays silly string at the gang member. This immobilizes the gang member! <DO NOT spray silly string in a person's face.>

Spiderman then uses his super spidey sense to store a memory of the gang member and symbol in his brain. <Spiderman holds up the brain and makes it clear that memories are stored there.>

SCENE 4

Batman	wearing mask, boomerang is hidden
Innocent bystander	holding white flag with a bandana
Watch group	holding the bandana along with his badge
Alfred the butler	wearing glasses and holding clipboard

Police dispatch	holding the CD

<The innocent bystander is holding a white flag with a bandana attached at the tip. Batman appears on the scene not noticing the bat signal.>

Now Batman comes around. The Watch Group is so happy to see more superheroes on the scene. He waves the bandana in Batman's face. Batman looks around and is suddenly alerted by the bat signal. He realizes that he, too, is an expert at identifying individuals who will start recruiting more gang members. He seeks out any innocent bystanders who have been converted to the dark side.

<Batman notices the innocent bystander.>

AH! He's found one!

The innocent bystander is waving his white flag… He knows he's been targeted. He shows the bandana in an act of surrender.

Innocent bystander: "I'M SORRY I'VE BEEN CONVERTED TO THE DARK SIDE!"

Batman knows there's only one thing he can do now. He throws the boomerang at the bystander which causes the bystander to slowly, and carefully destroy himself. <Batman throws boomerang at bystander. Bystander slowly shrivels up and ends up as a heap on the floor.>

<Alfred the butler walks in holding his clipboard.>

Luckily, Alfred the butler takes notes about the gang symbol which serves as a memory for Batman to recognize it again in the future. Back at police dispatch, a permanent record is being stored there as well.

<Police dispatch holds up the CD to show the permanent record.>

THAT'S IT!

Immune Analogy Script

Actors are in green. Props are in blue.

Narrator reads italicized text

SCENE 1

Gang members (2)	wearing bandanas (gang symbols), carrying a couple more bandanas
Watch Group member	wearing a badge to identify him/herself
Innocent bystander	has a white flag that is hidden

It's a warm, muggy night.

Gang members prowl around, looking for trouble. They flash their gang symbols multiple times. Check out their goofy handshake. <wait for flashing of bandana and handshake; both gang members move through crowd>

One gang member recruits an innocent bystander to become part of the gang. He gives them a bandana to affirm membership to the gang. <Gang member solicits bystander and hands him the bandana. Bystander reluctantly takes it.>

The innocent bystander may be reluctant, but he takes the bandana.

A local member of a Watch Group enters the scene. Seeing one of the gang members, he stares at him until he crumples to the ground. The Watch Group snatches the bandana and displays it and his badge to the world. <The watch group takes 1 bandana and uses the badge to hold it up. This gang member will quietly exit the stage and will be used again as a different gang member shortly.>

SCENE 2

Watch group member	wearing a badge
Police dispatch	has the bat symbol and flood light; CD is hidden

The watch group member walks around displaying the bandana with the badge. He seeks a match. <Watch group member walks up to random students and says, "You're not a match… You're not a match.">

He approaches police dispatch and realizes he's found a match!

Watch group: "YOU'RE A MATCH! And look at my badge - I'm the good guy, not the bad guy!" <CLEARLY SHOW police dispatch the bandana, using the badge to hold it up.>

The police dispatch acknowledges it, but doesn't seem to be taking the threat seriously! The *watch group shows frustration and starts yelling!*

Watch group yells: "DO SOMETHING ABOUT THIS! WE HAVE A PROBLEM! COME ON!"

Finally, the police dispatch jumps into action by displaying the bat signal. <Bat signal should show up on the wall. Hold up bat symbol a few feet from the wall, then turn on the flood light to see the bat signal. LEAVE BAT SIGNAL ON!>

SCENE 3

Spiderman	wearing mask, holding silly string, keeping a brain hidden
Gang member	wearing bandana

Spiderman appears on the scene, not noticing the bat signal, YET. But he does see a gang member. Just like the Watch Group, Spiderman stares at him until he crumples to the ground, and takes his bandana away. <This gang member stays put and doesn't return to the skit.>

Wandering around, Spiderman comes across the police dispatch and shows him the bandana. Alerted by the bat signal, he realizes he's an expert at identifying gang members. He prowls around looking for more. Finding one, he sprays silly string at the gang member. This immobilizes the gang member! <DO NOT spray silly string in a person's face.>

Spiderman then uses his super spidey sense to store a memory of the gang member and symbol in his brain. <Spiderman holds up the brain and makes it clear that memories are stored there.>

SCENE 4

Batman	wearing mask, boomerang is hidden
Innocent bystander	holding white flag with a bandana
Watch group	holding the bandana along with his badge
Alfred the butler	wearing glasses and holding clipboard

Police dispatch	holding the CD

<The innocent bystander is holding a white flag with a bandana attached at the tip. Batman appears on the scene not noticing the bat signal.>

Now Batman comes around. The Watch Group is so happy to see more superheroes on the scene. He waves the bandana in Batman's face. Batman looks around and is suddenly alerted by the bat signal. He realizes that he, too, is an expert at identifying individuals who will start recruiting more gang members. He seeks out any innocent bystanders who have been converted to the dark side.

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Immune System Unit: Lesson 1, Part 3 TEACHER NOTES

The concept map included here was created using CMap which is a free concept-mapping program that works on PCs and iPads.

CMap file of student handout – this will only open in the CMap software

CMap file of KEY – this will only open in the CMap software

PDF of CMap of Student Handout

PDF of CMap KEY

As soon as students return to their seats from the skit, have students access the concept map. Students should match the roles and props from the skit (in the Word Bank) with the cells and chemicals that are described on the concept map. They may struggle a little, but that's where the learning takes place. Allow them to pair and share in order to fill in all the blanks.

Use the Key to go over the answers with students.

Below is a picture of the CMap Student Handout.