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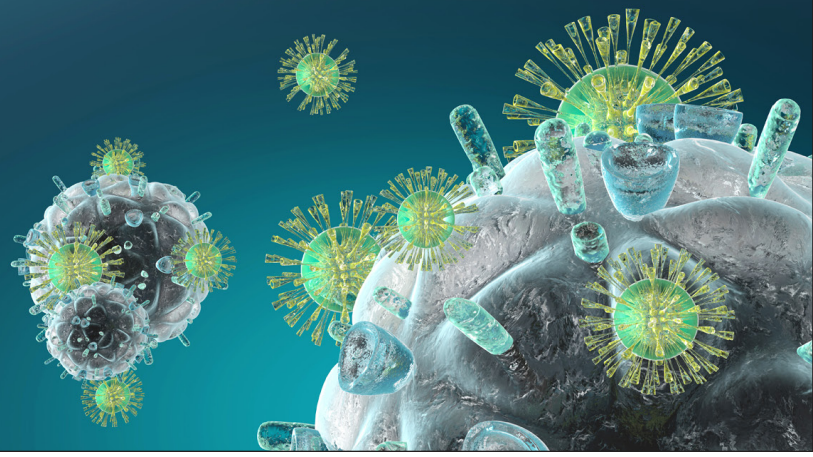
Host-Pathogen Interactions: A Magnificent Battle in an Evolutionary Arms Race



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Part I – The Complexity of the Immune System

Charlie was a freshman getting ready to take his first set of college exams. He was hunkered down in the library, trying to avoid his roommates who were all sick with a viscious cold. Between all of the coughing and sneezing he hadn't been able to concentrate so he had left the dorm to try and find some quiet to help him study. His biology test was focused on the human body. He was reviewing his text about the various tissues that make up organ systems including the circulatory and endocrine systems. His thoughts began to drift as he started thinking about the immune system, which his professor had not gotten to yet. He skimmed through the upcoming chapter to see if he could figure out how this system would work to help him fight the cold that his roommates and all of his friends seemed to have. He started to read and found some interesting information.

He found that the host immune system is a vast and versatile collection of cells and molecules that have evolved to protect the host from invading pathogenic organisms and from tumor development. Pathogenic organisms include viruses, bacteria, fungi and parasites. Each of these has its own strategies and mechanisms that it employs to infect and cause illness in a host. Upon encounter with a pathogen, the body becomes a battleground in which the host immune system must fight off the establishment of the pathogen (1–3). If the immune system wins, the host remains healthy with few repercussions. But if the immune system is evaded, the host succumbs to the effects of the pathogen and ultimately gets sick. Charlie thought to himself, "Gee, I hope that doesn't happen to me."

Charlie continued to read and learned that the human immune system is highly adaptable as it must defend against a large number of different invaders. Generally, the response can be divided into two subcategories involving recognition of the pathogen and then the overall response by means of effector functions.

Questions

1. Charlie created a chart in order to keep track of the arms of the immune system so that he could figure out how his body would keep him healthy. Complete the chart with respect to the key hallmarks of the innate and adaptive responses. It is okay to look this information up in a text or on the internet.

Hallmark	*Innate*	*Adaptive*
Level of specificity		
Involvement of memory		
Time for first response to an antigen		
Time for secondary/repeated response to an antigen		
Level of self discrimination		
Duration of the response		
Key cells involved		

2. Anatomical barriers play a large role in preventing the entrance of a pathogen into the body. They provide a critical first line of defense. Think about what a potential pathogen like a bacteria or a virus would have to overcome in order to get into your body, or Charlie's body, and then into the target tissue to untimely make you sick. List several (at least three) of these critical barriers and how they help to eliminate pathogens. Describe how these mechanisms are or could be related to the symptoms you often get when someone falls ill (for example with the cold or a stomach flu).

Part II – The Battle Is Set

Charlie began to yawn as the hours passed by. He decided to put his head down for a quick nap. It seemed like only a few minutes had passed before he found himself in the middle of what looked like a battle, and an epic one at that. On one side of the field were what appeared to be spiky aliens, and on the other were a variety of different shaped figures that looked like cells. He asked one of them, "What are you guys fighting?" "Today what we've got on our turf is a rhinovirus," growled the cell. "We're trying to block these viral particles from replicating in the respiratory tract in order to prevent the development of a cold." It then marched, or rather floated, off to engage with the enemy.

Charlie watched as the cells began to interact with the virus. He was reminded of battles he had seen in movies, but this time the troops fighting against the virus were immune cells. Charlie remembered that these cells, also called white blood cells or leukocytes, arise from a stem cell precursor in the bone marrow. Through a process called hematopoiesis, the stem cells in the bone marrow receive signals from the body to differentiate or become specialized and multiply. This process is continuous as the body always needs to make blood cells, however in times of an infection the process is amplified, producing millions of white blood cells that are armed and ready to enter into battle (Figure 1). "Wow," thought Charlie as he watched the cells continue to stream in one after another to engage with the viral enemy. He wondered how the cells knew where to go and what to do. Charlie asked another cell that was passing by, "Hey, excuse me, but how do you guys talk to each other or know what to do once you leave the bone marrow?" "That's easy," the little cell said. "We have a communication system! We can't speak to one another but we have ways to signal each other and other parts of the body."

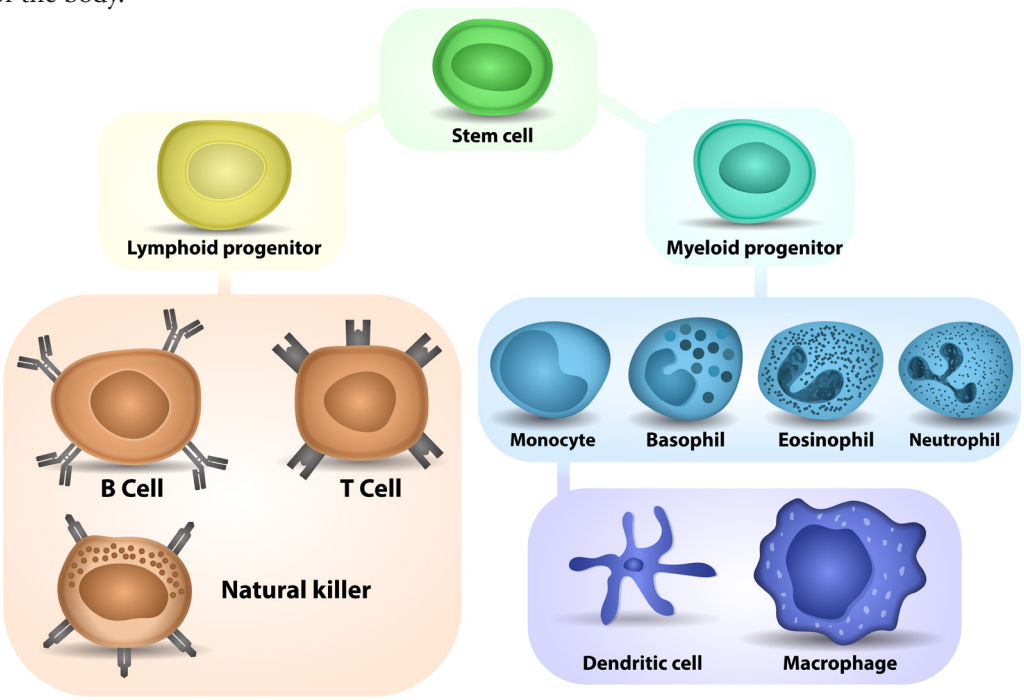

Figure 1. Immune cell generation. Stem cells from the bone marrow are stimulated by external stimuli, typically initiated by pathogenic attack, to differentiate and multiply into the desired cell type.

After his conversation Charlie remembered from his reading that there are numerous mechanisms for cell-to-cell communication, however cytokines play a predominant role in the immune response. Cytokines are small, secreted proteins that allow for direct communication and can in some instances directly target a pathogen (4). Another integral part of the ongoing communication between cells and organs of the immune system is the capability to identify the target. Antibodies and antigens are a prime example of the incredible recognition system that exists in the human body. Antigens are small molecules that are used to distinguish between self and non-self. Antigens can be small pieces of the pathogen that provide information to the immune cells regarding the pathogen's identity, or they can be a part of the host tissue, signaling to the immune system not to attack. The antigens that are a part of the host body are called

"self" antigens. All other antigens that enter the body are considered to be foreign. Epitopes are the immunogenic portion, or the part that initiates an immune response, and provide a unique fingerprint for pathogen identification. Antibodies, on the other hand, are proteins that directly identify and bind to antigens and elicit a cellular response to foreign antigen in order to eliminate the invader (5) (Figure 2).

The specificity of the adaptive immune response and the reason why hosts can develop memory to pathogens is based on these specific antigen-antibody interactions. As Charlie had just read, the cells that are important for interacting with antigen from antigen presenting cells such as dendritic cells, are T and B cells. T cells and B cells have membrane receptors known as the TCR (T cell receptor) and BCR (B cell receptor). The receptors are encoded by genes assembled by the recombination of segments of DNA during the maturation process of the cell. The genes that code for these receptors are numerous and shuffle like a deck of cards so that the cells that are produced can increase their ability to bind to a diverse array of antigens. While it is important to generate receptors that have the capability to bind to a large number of antigens, it is important to note that each BCR and TCR binds specifically to only one antigen. This drives the specificity of each immune response to a given pathogen (6).

Charlie now understood that once the troops of the innate system have effectively communicated throughout the body that a pathogenic organism is present, and the pathogen has been identified via its antigens, the innate cells that participate in antigen presentation will then present that information to the adaptive T and B cells so that they can initiate the second phase of the response. There are a number of effector mechanisms that range from direct killing by the release of toxic granules, to poking holes in the cell wall causing cell lysis, to engulfing organisms (phagocytosis). Each cell employs its own mechanism of cellular destruction in an effort to eliminate the enemy and restore the body back to normal. "Wow, this is even cooler than I thought, but it's getting harder to keep track of all of these moving parts!" thought Charlie.

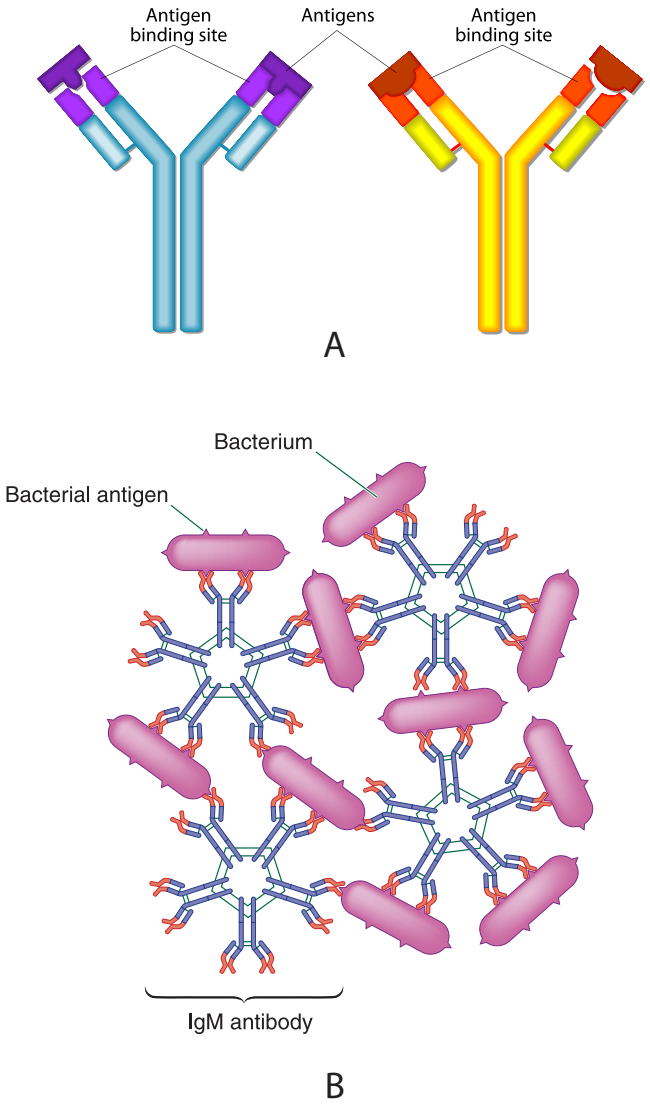

Figure 2: Antigen and antibody recognition. (A) Antigens are recognized by non-conserved portions of the antibodies. (B) Antibodies can target and destroy pathogens such as bacteria by recognizing the highly conserved antigens on the cell surface.

Questions

1. It is clear that the innate and adaptive arms of the immune response work interdependently to clear pathogens, however key cells also play vital roles in each arm of the response. Help Charlie keep the working parts straight by filling in the chart below. Indicate a role for the following cells and whether they are key players in the innate or adaptive arm of the immune response.

Cell Type	*Role During an Infection (Identify the effector mechanism employed by the cells to stop infection)*	*Arm of the Response (Innate or Adaptive)*
Macrophage		
NK cell		
B cell		
T cell		
Mast cell		
Dendritic cell		
Neutrophil		
Eosinophils		

2. What is antigen presentation and why is it critical during an immune response?

3. What happens when self-determination mechanisms break down? This would be when your body mistakes your self-tissues for foreign agents. Can you give specific examples of when this occurs and what the end result is?

4. Find a primary literature article that discusses in more detail one of the autoimmune responses you have identified in Question 3. This can be an article that describes a new finding in the disease, something to do with treatment of the disease or anything you might find intriguing to read about in more depth. Briefly describe the contents of the paper in a paragraph summary including what results the authors found and what impact it has on the field of immunology.

5. Cytokines are of critical importance for communication. Indicate a role for the following cytokines during an infection and which cells can produce that cytokine: IFN α/β, IFN-γ, TNF-α, IL-12, IL-6 and IL-10. Based on what you find, can you briefly comment on how cells interact together to produce this cytokine network?

Part III – And the Victor Is . . .

Charlie watched the battle before him as closely as he had when John Snow battled the night walkers or Luke Skywalker dueled with Darth Vader. The struggle was just as brutal, but it seemed the tide was turning. The viruses were dwindling in number as the carnage grew. Charlie now had a new question: if the immune system always battled so well, then why is it that we get sick? Why doesn't the immune system always win and clear the pathogen at hand?

Each individual battle between host and pathogen is different and can play a vital role in the evolutionary development of such interactions. Just as vertebrates have developed many different immune defenses against pathogens, pathogens too have evolved elaborate strategies to evade these defenses. Therefore, the host-pathogen battle is continuous and evolving. Immune defenses have changed through time to deal with the multitude of pathogenic attacks. In order to persist, pathogens must overcome host immunity and find new opportunities to break down barriers to infection. The most successful microbial pathogens have therefore evolved complex and efficient methods to overcome innate and adaptive immune mechanisms, which can result in disease or chronic infections. Examples of some of these immunomodulatory effects are given below.

Antigenic Variation

Antigenic variation is widely used by extracellular pathogens, or those that replicate outside of the host cell such as bacteria or parasites. These organisms are best targeted via antigen-antibody interactions. Therefore, it makes sense that the best way to avoid recognition and killing is to vary the antigen. This would be like changing the locks on your doors. The key recognizes the lock specifically, and when it does it opens the door. The antibody recognizes the antigen specifically and when it does, the pathogen is destroyed. If the lock is changed, the key does not fit and the door remains locked. If the antigen is changed, the antibody does not recognize it and the pathogen is allowed to persist. Antigenic variation has been successful in bacteria, viruses and parasites.

Inhibition of Cytokines and Chemokines

Cytokines are necessary to allow for communication. Chemokines are a subset of cytokines that specifically modulate cellular recruitment to a site of injury or pathogenic attack. They are necessary for getting the immune cells, which are circulating in the blood stream, to the tissues where the battle or infection is taking place. A great way to avoid enemy attack would be to dysregulate communication. There are many examples of viruses and bacteria that have evolved anti-cytokine mechanisms to inhibit or confuse host cell communication. These pathogens have been described as expressing secreted chemokine mimics that trigger host chemokine receptors inappropriately or chemokine binding proteins that interact with host chemokines and inhibit the ability of host chemokines to attract and activate white blood cells to the sites of virus infection. Viral and bacterial homologs of cytokines have also been described in the literature that again work to confuse the host immune system by blocking activation or targeting cellular responses inappropriately. Binding agents have been discovered and secreted by pathogens that effectively render a cytokine useless. This is particularly alarming for cytokines such as IFN, which have been shown to directly kill viruses.

Blocking Cellular Effector Mechanisms

Each immune cell has its own effector mechanism that is used to control and eliminate a pathogen. In turn, successful pathogens can specifically block a key cell function allowing it to establish an infection and increase the chances of spread to another host. For example, T cells must proliferate or grow rapidly upon encounter with an antigen. This mounting response is required to generate enough cells to effectively fight the infection. Some bacteria for example, have been shown to alter IL-2 signaling, which is a required signal to trigger cellular division. By blocking this pivotal pathway, the production of T cells is limited and this interruption allows the pathogen a head start in establishing itself and the subsequent infection.

Interfering with Cell Death Pathways

Viruses and bacteria are often kept at bay by the host cell when the host cell is targeted for cell death. Blocking cell death initiation in the host cell allows viruses, for example, more time to complete their life cycle and go on to infect additional host cells and spread throughout the host and possibly to other hosts. The longer the host cell is alive, the more time the virus has to flourish. Additionally, many pathogens falsely trigger apoptotic cell death pathways instead of necrotic cell death pathways as apoptosis is far less immunostimulatory in nature. Therefore, the host would have more difficulty in identifying the presence of a pathogenic organism.

So the question still remained for Charlie; who ultimately wins? The evolutionary arms race between human populations and pathogens continues. The vertebrate immune system is a well-oiled machine that battles the continual barrage of organismal attack on a daily basis. The aggressive nature of the immune system to fight these battles is always kept in check so as not to cause harm to the host itself by destroying self-tissue. On the other hand, pathogens like the flu virus, malarial parasite and bacterial plague have persisted for as long as medical records have been kept due in large part to the capability to quickly evolve. Additionally, newly emerging diseases have continued to keep our immune system in check by introducing completely new material into the game. Therefore, there is no real clear winner. Host-pathogen interactions continue to occur and can be addressed on an individual and population-wide basis. The balance between health and illness relies on the ability of our immune system to continually fight both new and old pathogenic organisms and the success of the immune system heavily relies on evolution. Coevolution, in which organisms influence each other in their evolution, occurs with pathogens and the immune system. The constant pressure put on the immune system by pathogens drives the evolution of immune components. In turn, in an effort to maintain their existence, pathogens continually evolve to change surface components or mask antigenic components to hide from immunity. This evolutionary arms race will continue for as long as immune systems and pathogens exist, driven by the basic mechanisms of natural selection (7–8).

Questions

1. You are a microbe trying to establish an infection in a host. You are trying to evade the immune system as best you can. Explain how you would avoid the immune response in the following scenarios.

   A. You are a virus trying to avoid being killed by NK cells.

   B. You are a bacteria trying to avoid macrophage killing.

   C. You are a parasite trying to block cells from reaching you.

   D. You are a bacteria trying to avoid dendritic cell functions.

   E. You are trying to block B cell activation and antibody production.

Epilogue

Charlie woke up to find himself drooling on his notes. He wiped his mouth and then, "Ah..., ah..., AHCHOO!" Charlie sneezed. And sneezed again. "Uh oh," he thought. "I think I know who might be winning this battle in my body." He closed his notes, packed up his belongings, and hiked back to his room. Thankfully he had a few days before his exams so he could recover from the cold he got from his roommates. At least now he knew what was going on inside his body to help him fight off that cold. "What a cool dream!" he thought as his own cellular army began to mount its defense. "The cold virus may be winning this battle, but next time, it won't be so lucky."

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