IMMUNOLOGY: UNDERSTANDING THE BODY'S NATURAL DEFENSES

The ongoing pandemic has made the content of this newsletter—immunology and its effects on mental health—particularly relevant. Up until this very moment, countless families have suffered pain and the loss at the hands of the Sars-CoV-2 virus across the world, which has no doubt been exacerbated by complex issues such as vaccine hesitancy. Now, two years since the infamous pandemic began, we're still struggling along on what seems to be an ever-growing path to a mask-free normalcy. The reality, despite being jarring, is not entirely unexpected. As you'll learn in this newsletter, there are number of viruses that have wreaked havoc on humans—the swine flu, for example. In my opinion, what makes the current pandemic so startling is not the spread of a novel virus (viruses have and will continue to mutate), but more that, in spite of how technologically advanced we (the US) are, COVID-19 has really challenged our infrastructure, leadership, and even unity. Science is built upon empirical reasoning and so it *seems* like the pandemic and health guidelines would be taken seriously. Unfortunately, though, that's certainly not the case, and perhaps some of that has to do with factors like mistrust between the public and the health care system, a lack of transparency between scientists and the public, or the historical spread of misinformation accelerated by technological platforms. Clearly, the pandemic is complex, and I invite you all to think about some of these questions (and respond) as you work your way through this newsletter. Please know that, while we are not able to respond to each individual response, each entry is read and scanned to the PE digital archive.

INTRODUCTION TO THE IMMUNE SYSTEM

What are some things that come to mind when you think of your immune system? Perhaps it's a vivid recollection of being sick beyond belief, or maybe it's that time you got a shot at the doctor's office. I like to think of it as the body's army against threats constantly bombarded by the world around us. This analogy of the immune system as an army is key because an army is never made up of just a single defense! Rather, there are several moving pieces and considerable specialization of function tailored to each sort of threat. In this packet, there definitely won't be time to address everything extensively, but hopefully this will serve as an introduction to the subject. An enormous thank you to my immunology professor from Fall 2020 for the materials presented here.

The immune system responds to a number of threats including (but certainly not limited to!) viruses (this one should definitely be familiar…SARS-CoV-2), along with others such as fungi, bacteria, and cancerous cells. In all cases, immune system responses begin with recognition of the threat, followed by the appropriate response. Beyond immediate (innate immunity) and delayed responses (adaptive immunity), an important part of the immune system is cleaning up the aftermath of an immune response and forming memory cells. These memory cells help remember a particular pathogen and can speed up future responses (Lecture 1, Rhoades 2020).

Outside of general patterns of sensing and responding that we'll explore later on, one of the most important things to understand and keep track of in understanding the immune system is the various players involved, several of which are outlined in Figure 1 below.

This packet is intended to be read several times. There is a lot of information contained here that needs to be thought through. This is a lesson in reading comprehension. Let yourself slow down. Reread anything you don't understand on your first reading. Take your time. Understanding the marvel that is your own immune system lets you see the miracle and complexity of life. If anything is going to make an impression upon me about the marvel of life and creation it is studying the complexity of our existence. We are fortunate that Sara took the time to explain this to all of us. Let me know what you think of such a rigorous exercise in thinking. Should we have more science programs like this? When replying to this packet write ATTN SARA ON THE ENVELOPE. TRY RECOPYING THE ILLUSTRATIONS TO BETTER UNDERSTAND THEM
-Best always-Gary

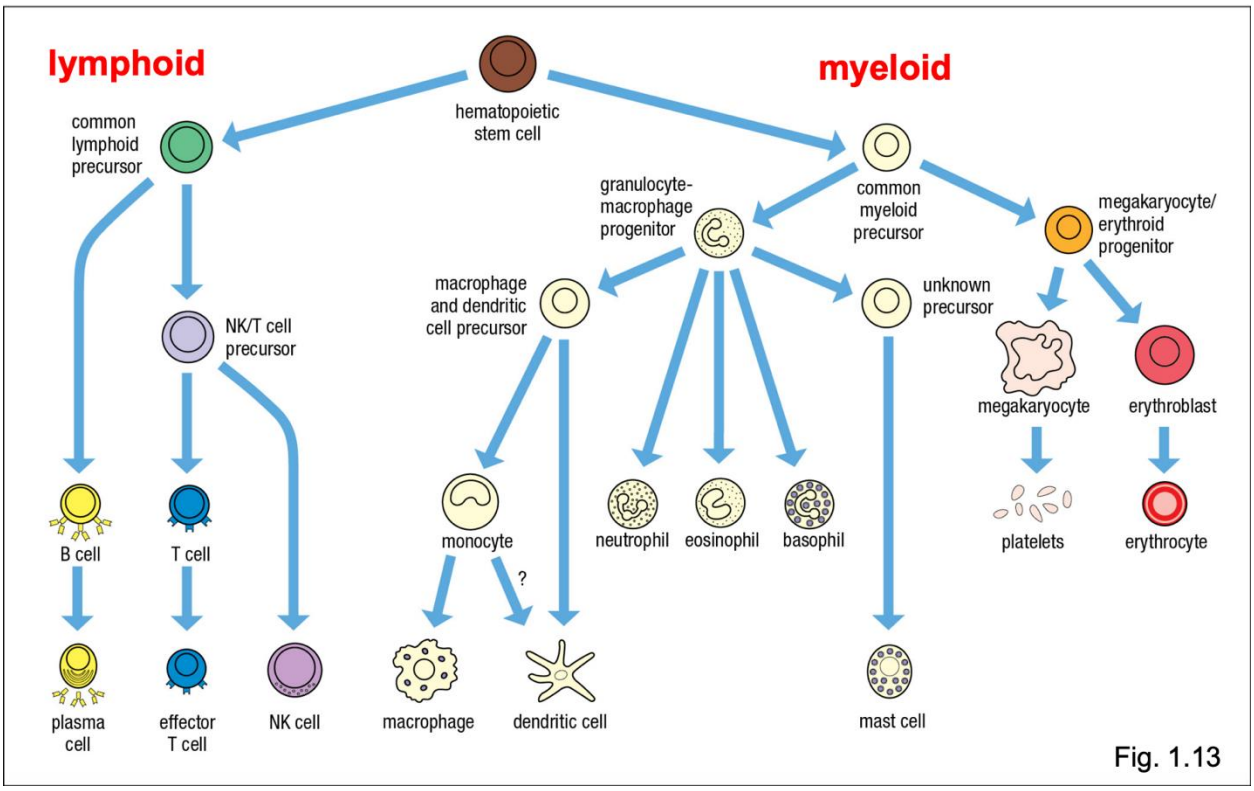


Figure 1. The development of various immune cells beginning with HSCs, or hematopoietic stem cells (Lecture 2, Rhoades 2020).

The left "arm," which begins with the cell titled "common lymphoid precursor," is responsible for the mediators of the adaptive, or specific, immune response. The right arm, on the other hand, which is titled "common myeloid precursor," gives rise to differentiated cells including erythrocytes. You might know erythrocytes as red blood cells (abbreviated RBCs), whose key function is circulating oxygen around the body using a key protein called hemoglobin. You may also recognize platelets, which are involved in blood clotting, keeping us from bleeding out following a paper cut, for example. The myeloid lineage is involved in the innate (initial) immune response and also includes the family of granulocytes, which can easily be recognized in Figure 1 by the dots inside the cell body. I'm referring to neutrophils, eosinophils, and basophils, which are named granulocytes because of the characteristic granules that they carry and unleash on invaders, represented in Figure 1 as dots.

WHAT COUNTS AS THE IMMUNE SYSTEM?

It would be easy to point to one contained organ and call it the immune system, but few things are this simple. Some of the important players of the immune system include the following:

- Bone marrow, which you may have guessed based on Figure 1 and the idea that hematopoietic stem cells (HSCs) in the marrow give rise to all of the moving parts of the immune system.
- Thymus. This is where T cells, involved in the body's adaptive response and infamously linked to HIV/AIDS, mature (T=thymus) (Lecture 2, Rhoades 2020). Following the pattern, B cells mature in the bone marrow (B = bone marrow) or in the spleen.
- The lymphatic system, which plays a role in gathering fluid from body tissues and serves as a highway for immune cells circulating around the body. Lymph nodes—you may have heard someone say that their lymph nodes are swollen, particularly when they're sick—are bean-shaped structures that represent toll booths. When an immune cell passes through a lymph node, it can be activated, which occurs upon exposure to what the body believes is a threat (Lecture 2, Rhoades 2020).

- The spleen. The spleen functions in blood filtration (Lecture 2, 2020), but also partakes in B cell activation. One way to visualize the spleen is as a toll booth—it is involved in activating circulating immune cells.
- Accessory structures such as the tonsils and appendix (think large toll booths in the lymphatic system), but we will not delve into these deeply here (Lecture 2, Rhoades 2020).

ADAPTIVE VS INNATE IMMUNITY (a brief introduction)

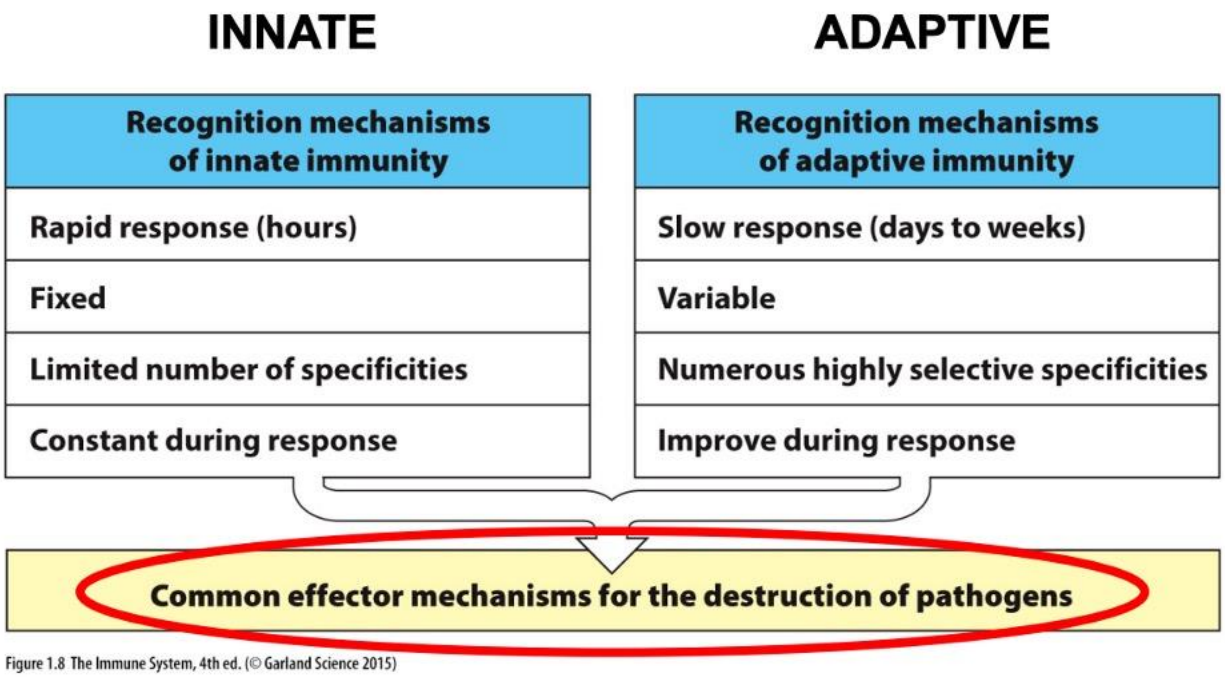


Figure 2. Comparing the innate and adaptive immune responses of the body (Lecture 2, Rhoades 2020).

You'll see that, while there are obvious differences between the two arms, they both recognize and respond to threats and converge on what are termed "effector mechanisms." Simply put, effector mechanisms are direct ways of destroying a threat sensed by the body (Lecture 2, Rhoades 2020). In the case of autoimmunity, what the body thinks is a threat is actually our own body's own tissue. While Figure 2 suggests that the two arms of the immune system are separate, they in fact work together very closely, as shown below in Figure 3.

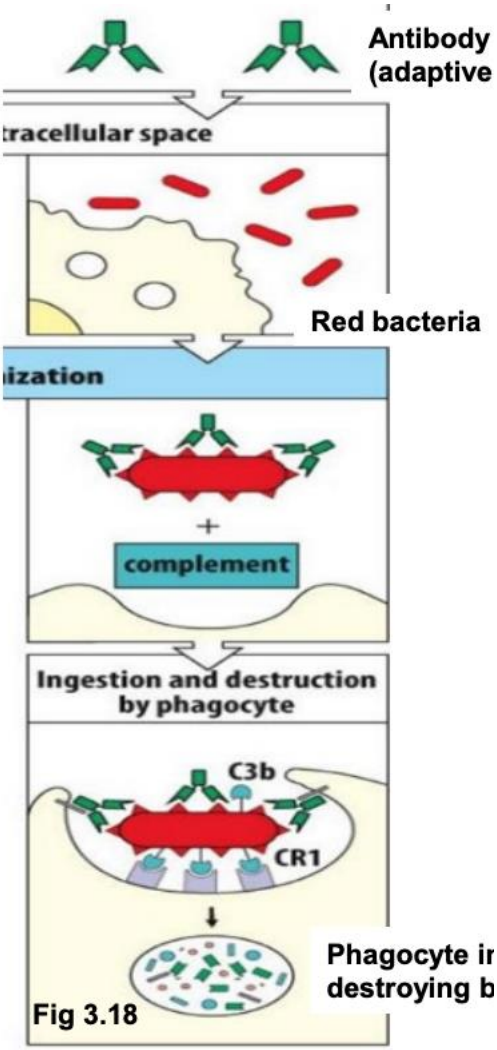


Figure 3. Adaptive and innate immunity working together (Lecture 2, Rhoades 2020) .

The first step shown in Figure 3 involves antibodies (Ab), soluble threat sensors, binding to the triangular regions around a red bacterium. We will discuss this more thoroughly later, but it is important to note that the Ab (presumably secreted from the SAME B cell) bind to one specific feature of the pathogen. In any case, the binding of many Ab to a pathogen is called "opsonization" and prompts the activation of complement, an integral part of the innate immune system. Complement induces the effector mechanism, which here is phagocytosis, or eating, by a cell called a macrophage. In summary, Ab, which are part of the adaptive immune system, trigger complement (innate immune system) to ultimately chop up the bacteria into little bits.

THE STAGES OF THE INNATE IMMUNE SYSTEM

The first stage of innate immunity responds without delay (within four hours after infection), while the secondary stage kicks in hours or even days after threat is sensed (Lecture 4, Rhoades 2020). The immediate response involves complement, which we touched on in Figure 3. Complement is a series of proteins that binds automatically to threats and induces phagocytosis (or eating) by macrophages, pokes holes in bacterial membranes by forming membrane attack complexes, and alerts other cells to respond (Lecture 3, Rhoades 2020). Another aspect of the immediate response are defensins (antimicrobial peptides, or proteins) that similarly disrupt microbial membranes (Lecture 2, Rhoades 2020).

LEVELING UP: INDUCED INNATE IMMUNITY

Not every infection or threat can be eliminated using just defensins and/or complement, which brings us to induced innate immunity. The defenses here include macrophages, which produce cytokines (SOS signals that effectively draw other immune components to the site of the invader) (Lecture 4, Rhoades 2020). The end result is inflammation, characterized by the following: swelling, redness, heat, and pain (Lecture 4, Rhoades 2020).

Let's take a closer look at the players involved in induced innate immunity. Both neutrophils (one of the granule-filled granulocytes I discussed earlier in reference to Figure 1) and macrophages have pattern recognition receptors (PRRs). Before we go into what this means, let's take a step back and look at what a receptor is. You can think of something simple like cell phone reception: if you have reception, then you have signal. The same principle applies to receptors, which are fundamental to how we function. Photoreceptors, for example, allow us to sense light and see things around us.

A receptor is only effective if it can communicate with both the outside and inside to pass a message along. If we go back to the immune system and pathogen recognition, one common example is the toll-like receptor (TLR) found on macrophages, which locks on to specific signatures found on pathogens externally (OUTSIDE of the cell). Binding triggers a signaling cascade and responses INSIDE the cell that ultimately result in a response like the transcription and translation of cytokines (Lecture 4, Rhoades 2020). So, going back to PRRs (an example of which is TLR), these are simply structures that can recognize parts of pathogens. An example of this would be carbohydrate structures on a bacterium (Lecture 4, Rhoades 2020).

Cytokines, like the various immune cells, carry incredible diversity. A couple examples of some cytokines are IL-1 beta, TNF-alpha, and IL-6, which all work to draw neutrophils from the bone marrow, where they are stored, into infected tissues (Lecture 4, Rhoades 2020).

VIRAL INFECTION AND DEFENSES

What are viruses? We've definitely heard of the SARS-CoV-2 virus, responsible for the pandemic, but what does the term mean? Unlike cells, viruses don't have any organelles or really anything outside of genetic material. Yet, because they cannot multiply on their own, they rely on cells (Lecture 5, 2020).

Key in viral control is being able to sense them outside and inside cells. Thus, the immune system senses patterns on viruses and signals from cells in distress because they have infected by viruses (called DAMPs). After infection, cells make DAMPS (damage associated molecular patterns) (Lecture 5, Rhoades 2020), which can be sensed by the immune system. Outside of DAMPs, PRRs also sense and respond to viral structures such as their tell-tale coats and nucleic acids (their genes) (Lecture 5, Rhoades 2020).

SO, WHAT DOES THE VIRAL IMMUNE RESPONSE LOOK LIKE?

As with all immune responses, we start with innate immunity, which here involves the manufacturing of interferon cytokines by virally infected cells. Basically, interferons instruct surrounding cells to "interfere" with the plans of viruses to infect, replicate, and spread to neighboring cells while simultaneously recruiting and activating NK cells, as seen in the "Immune Cell Dictionary". In addition, infected cells present viral bits to stimulate NK response (Lecture 5, Rhoades 2020). Almost all cells in the body are able to stave off viral infection via interferons.

In terms of adaptive immunity, the viral response involves both B and T cells. To understand the adaptive immune response to pathogens such as viruses, we have to first understand how adaptive immunity works:

SENSING: B AND T CELLS

A key difference between B and T cells is that they sense different kinds of molecules in different forms. B cells focus on extracellular molecules and sensing antigens that are unprocessed (Lecture 6, Rhoades 2020). T cells, on the other hand, focus on intracellular molecules (think protein fragments like snapshots of what is lurking inside and around a cell) (Lecture 6, Rhoades 2020). However, it is important to recognize that the T cell itself isn't the one to process the pathogen. Rather, T cells depend on other kinds of cells that specialize in breaking down pathogens and then redirecting them to the surface for presentation using an MHC molecule (Lecture 6, Rhoades 2020).

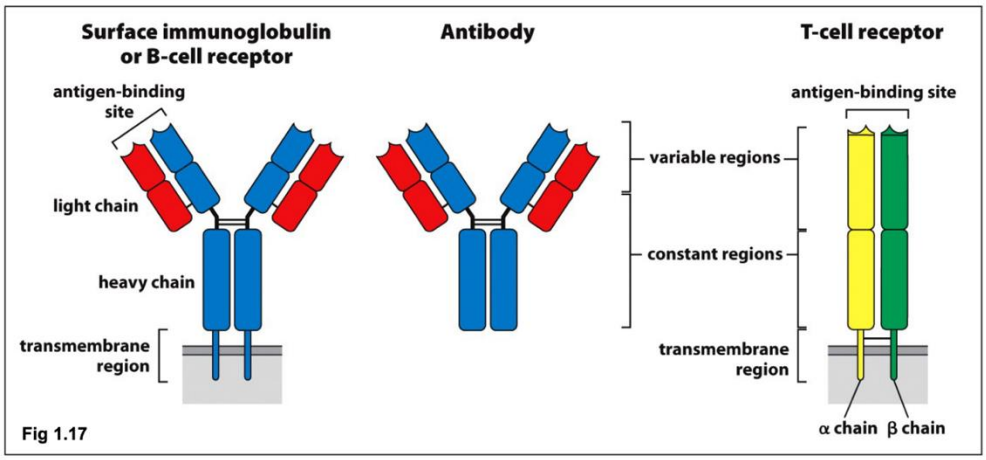
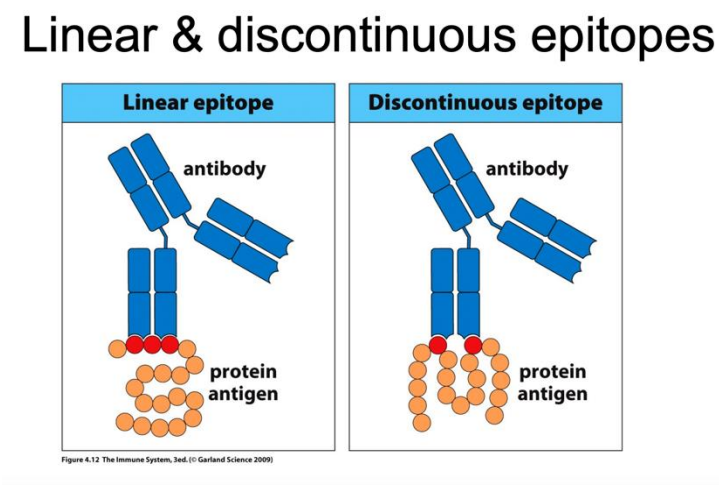


Figure 4a. Structures of (from left) B cell receptor, antibody (Ab), and T-cell receptor (Lecture 6, Rhoades 2020).

In Figure 4a, you'll see the structures of the B cell receptor (which is essentially an anchored antibody), an antibody, and a T-cell receptor. In both receptors, you should notice that there's what's termed the "antigen-binding site." This is the part of the receptor that recognizes and binds to a recognizable part of the antigen called the epitope (Lecture 6, Rhoades 2020).



Regions boxed off as variable are in fact variable; this means that there is recombination and rearrangement that occurs as each receptor tries its best to match a specific antigen. The constant regions of the receptor, however, cannot be rearranged—and

Figure 4b. Ab binding to a linear epitope in which parts of the protein interacting with the receptor are next to each other vs. a discontinuous epitope, where the protein bits are separated (Lecture 6, Rhoades 2020).

this is important, because this is the part of the receptor that must be sensed by effectors such as macrophages.

Within the antigen-binding site of the B cell receptor (and its soluble version, the antibody) is the complementarity determining region (CDR), which incorporates both heavy and light chain components (Lecture 6, Rhoades 2020).

T CELL IMMUNITY

As we discussed above, T cells have structures called T cell receptors that enable them to sense and respond to intracellular pathogens. Unlike B cell receptors, which can be secreted as antibody (Ab), T cell receptors are firmly anchored in the membrane (Lecture 6, Rhoades 2020). In looking at Figure 5 below, you'll see that a T cell receptor is composed of alpha and beta chains that interact with (i) antigen and (ii) MHC molecules presenting the antigen (Lecture 6, Rhoades 2020).

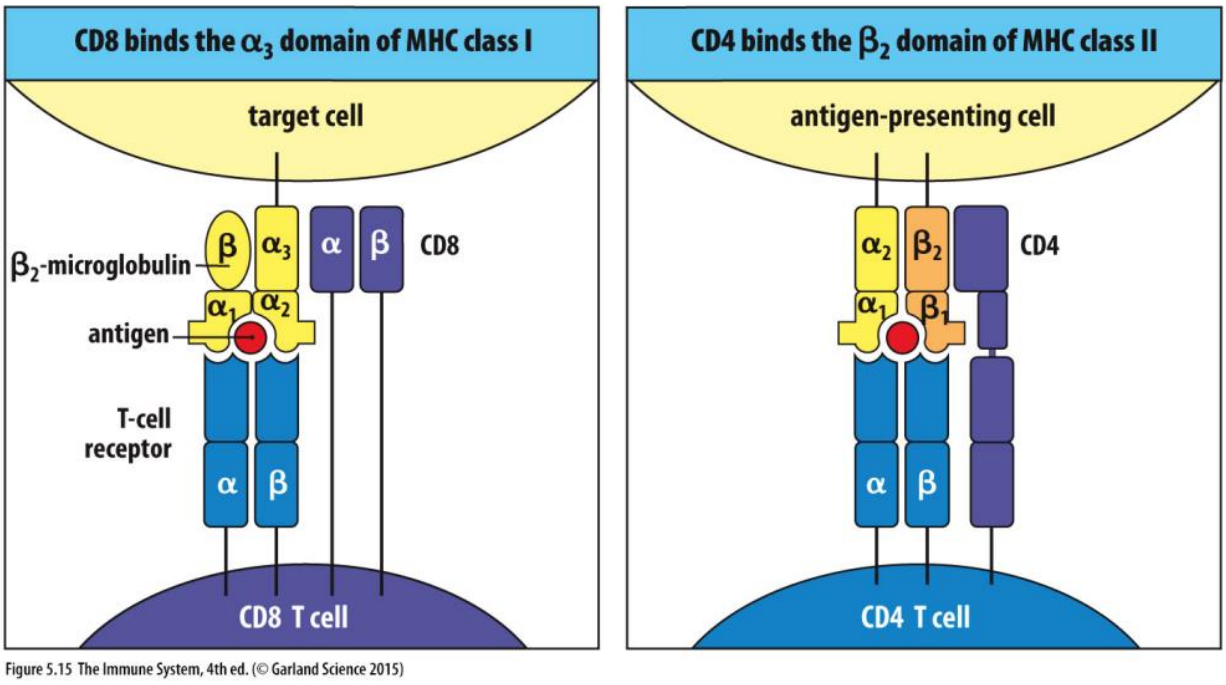


Figure 5. CD8 and CD4 T cell receptors interacting with MHC molecules and antigen (Lecture 6, Rhoades 2020).

The two types of T cells are CD8 and CD4 T cells named for the co-receptor they carry (either CD8 or CD4). This co-receptor, as you can see in Figure 5 above, also interacts with the MHC complex responsible for antigen presentation (Lecture 6, Rhoades 2020).

So, what are "MHC complexes?" I would think of them as billboards—they "advertise," in a sense, the presence of a pathogen. There are two different types of MHC molecules: MHC class I and MHC class II. MHC class I molecules are found in all cells with nuclei (this includes most cells with the notable exception of red blood cells, which have no nucleus). MHC class II molecules, on the other hand, are ONLY found on antigen-presenting cells (APCs). These cells are professionals in the sense that presenting antigen to jumpstart the

immune response is their main job. APCs include macrophages, dendritic cells, B cells, and some epithelial cells (Lecture 6, Rhoades 2020).

Going back to Figure 5, we can see that CD8 T cells, or T cells expressing the CD8 co-receptor, interact with MHC class I molecules advertising protein bits from cytoplasmic or nuclear pathogens (Lecture 7, Rhoades 2020). CD4 T cells, on the other hand, interact with MHC class II molecules advertising peptides from extracellular antigens that are shuttled into the cell via vesicles (Lecture 6, Rhoades 2020).

CD4 and CD8 T cells are characterized by diverse effector functions, with CD8 T cells participating in direct destruction ("cytotoxic T cells") and CD4 T cells participating in the activation of other immune cells such as macrophages and antibody-secreting B cells (see Figure 6 below).

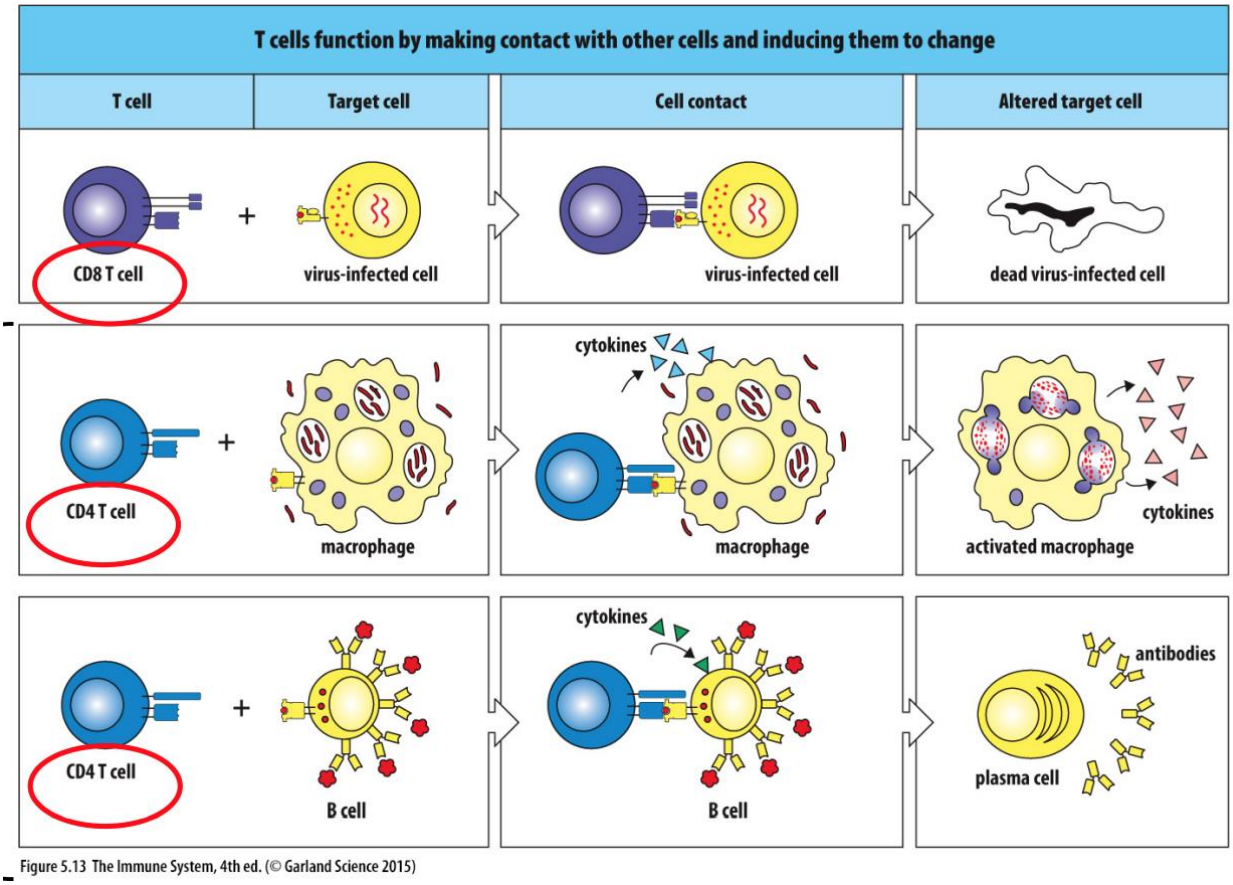


Figure 6. Functions of CD4 and CD8 T cells (Lecture 6, Rhoades 2020).

UNDERSTANDING MHC DIVERSITY AND RECOMBINATION

The versatility of the immune system arises from its ability to adapt to different kinds of threats; this confers specificity to the adaptive arm of the immune system. In order to understand where this specificity comes from, we have to take a closer look at MHC complexes, which you learned are responsible for presenting antigen and activating CD8 and CD4 T cells.

Humans have 46 chromosomes in total and 44 of these are autosomes. These 44 chromosomes are really 22 pairs of homologous chromosomes, which means that they have the same genes (so same information). The key point, however, is that one chromosome in each of these homologous pairs is inherited from our mother, while the other comes from our father. Now let's take a look at a portion of Chromosome 6, shown below in Figure 7.

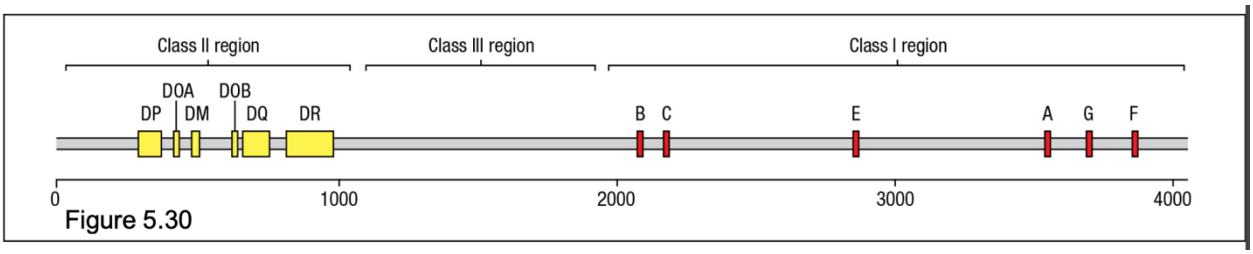


Figure 7. Map of chromosome 6, which includes genetic regions coding for MHC molecules (Lecture 8, Rhoades 2020).

The section labeled “Class II” region is the portion of the chromosome that contains loci (basically genetic “landmarks”) that specify different MHC class II complexes. The same applies for the class I molecules (these are instead specified by the area labeled “Class I region”).

Each of the rectangles shown above corresponds to a gene encoding a specific kind of MHC molecule. Diversity here comes from the different MHC genes; for example, you could have DOA or DM as an MHC class II molecule. Importantly, genes are NOT constant but instead appear in different forms (these are called alleles). The existence of multiple alleles of each gene (different sequences of the DOA gene, for example) is called polymorphism (Lecture 8, Rhoades 2020).

Why do we even need so many different kinds of MHC molecules? Remember that any given T cell interacts not only with the pathogen but also with the MHC molecule. Thus, genetic diversity in MHC molecules enables APCs (and other cells, if we’re talking about MHC class I molecules) to interact with and activate different T cells and intracellular/extracellular pathogens (Lecture 8, Rhoades 2020).

If you’ve heard of Mendel and his peas, you might be familiar with the term *dominance*. A dominant allele (version of a gene) is one that is expressed over another (recessive) allele. Human traits usually aren’t as simple as two alleles with one demonstrating complete dominance over the other, but it’s still useful in conceptualizing how and which traits are expressed. The reason I bring this up is because a similar idea applies to the expression of MHC molecules. As we learned previously, we have TWO chromosome 6s (one from each parent). The genetic sequence on each of these chromosomes can vary, however in what is known as allelic diversity. For example, there could be different alleles encoding the HLA-DR molecule on the two chromosomes. Rather than only one of these being expressed in the type of dominance I described above, BOTH versions will be expressed (Lecture 8, Rhoades 2020). This is similar to the expression of A, B, and O alleles that form our blood types. These alleles are called co-dominant—this is how we can end up with blood types like AB, in which blood cells express both A and B alleles.

GENERATING DIVERSITY IN ANTIBODIES

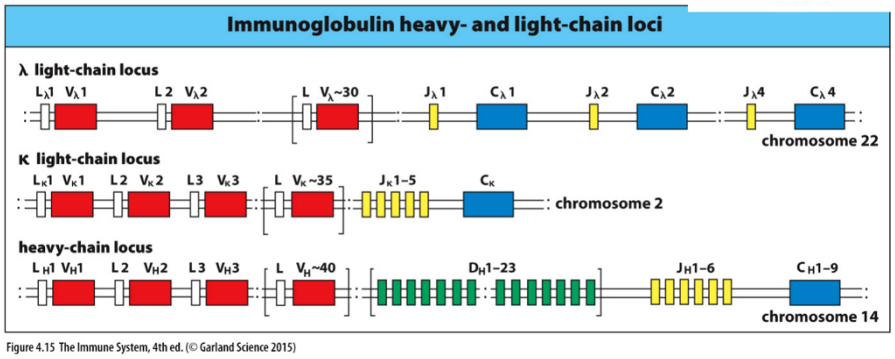


Figure 8. V D J recombination in Ab (Lecture 9, Rhoades 2020).

How does our body develop Ab that are specific to a given antigen? As shown in Figure 8 above, there are different types of V and J segments for both the light and heavy chains found in antibodies as well as various D segments for heavy chains. The various segments can be rearranged in different combinations to form B cell receptors (the tethered version of the soluble antibody) that carry specificity for different pathogens (Lecture 9, Rhoades 2020). Contrary to what you might expect, VDJ recombination occurs as B cells are maturing, so before the B cell has encountered the pathogen to which it will bind. This happens millions of times every day in the bone marrow, resulting in the production of millions of diverse B cells. The final receptor on a B cell is a combination of rearranged heavy and light chains that make up the antigen-binding site. Another thing to note is that the light chains can be formed from either lambda or kappa loci; this allows for additional diversity in receptor generation.

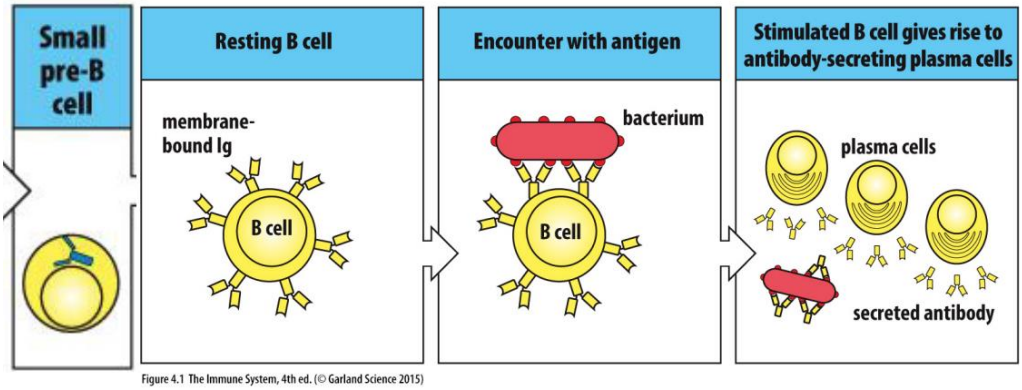


Figure 9. Development of B cell through Ab production (Lecture 9, Rhoades 2020).

The recombination we discussed above (refer to Figure 8) occurs in the "Small pre-B cell stage." By the time the B cell comes in contact with a pathogen (see "Encounter with antigen" in Figure 9), the B cell already has specific B cell receptors. Those B cells with receptors that can best bind to epitopes ("signatures") on the antigen will then multiple and differentiate into plasma cells. Plasma cells are able to secrete Ab that circulate in body fluids to attack pathogens (Lecture 9, Rhoades 2020).

THE B CELL RESPONSE

Imagine that some pathogen has breached the body's defenses and it has been collected in the toll booths that I mentioned, called lymph nodes or spleen. In the lymph node, there are B cells with receptors that bind to epitopes on the bacterium. After this initial recognition step occurs, what happens next?

The next step is clonal selection, which we discussed briefly above. Basically, a select few B cells that can bind to specific epitopes on the pathogen will multiply into an army of hundreds of activated soldier B cells that ultimately differentiate into antibody-secreting plasma cells. Some of the plasma cells will secrete IgM and IgD. These are two types of immunoglobulins (Ig), or antibodies, that are named by their constant region. Other B cells, however, will engage in affinity maturation to improve binding to the pathogen. Remember that B cells don't make their B cell receptors in response to a pathogen before they encounter it, so they take the opportunity when they encounter the pathogen to change and improve their receptors. They improve their B cell receptor via two paths: isotype switching, which involves changing the constant region of the Ig, or somatic hypermutation followed by affinity maturation, which we discuss below (Lecture 9, Rhoades 2020).

What is somatic hypermutation? As I mentioned above, the end goal of both (i) somatic hypermutation and (ii) isotype switching, is to generate B cells with receptors that are better able to bind to a pathogen. Somatic hypermutation involves the introduction of mutations that can improve Ab binding to its epitope. This can happen via an enzyme termed "Activation-induced cytidine deaminase." This enzyme works by taking C nucleotides (nucleotides are the building blocks of DNA and RNA) and converting them to U (Lecture 9, Rhoades 2020). The nucleotide U is normally found in RNA, not DNA, so DNA repair mechanisms can automatically replace the "U" nucleotide with a randomly chosen A, C, T, or G nucleotide. This rewrites the genetic DNA instructions for the B cell receptor to make one with a different antigen-binding site.

The random mutations can allow the B cell receptor to bind better or worse to the antigens on the pathogen. The mutated B cells then have to compete with each other to prove that they are the strongest in terms of their ability to bind and capture antigen. The ones that succeed in capturing antigen will multiply with the help of T cells (which we will discuss later) and leave the arena. These cells will become either (i) antibody-secreting plasma cells or (ii) memory B cells. Cells whose mutated receptors are too weak are unable to capture antigen and they die in the lymph node. This is called affinity maturation: cells that can best bind to epitopes on the antigen and eliminate threats receive signals to stay alive, while others that are less effective die (Lecture 9, Rhoades 2020). Even after specific B cells receive survival signals, they can continue to alter their variable and/or constant regions to improve their match with an antigen (Lecture 9, Rhoades 2020). Some B cells go through somatic hypermutation and affinity maturation competitions numerous times. B cells that emerge from this process are effective in fighting pathogens. This is why we get vaccine boosters, such as the COVID-19 booster.

WHAT'S THE POINT OF ANTIBODIES CHANGING THEIR CONSTANT REGIONS?

There are multiple classes of antibodies (and you'll see in Figure 10 that a class can be further divided into "subclasses"). Isotype switching, in which antibodies switch between the different classes of antibody by changing their constant regions, allows them to better adapt to specific pathogens. Antibodies with different

constant regions (different classes of antibodies) tell other immune components to do different things. Other times, a specific constant region allows an antibody to get to different sites in the body or last for a short or long time. If we look at IgG3 in particular in Figure 10 below, we can see that it is characterized by a long hinge region that is useful when flexibility is required to eliminate the pathogen (Lecture 9, Rhoades 2020). However, on the flipside, the hinge can easily be degraded in the blood; IgG3 lasts less than a week while other IgG classes shown in Figure 10 last for approximately three weeks.

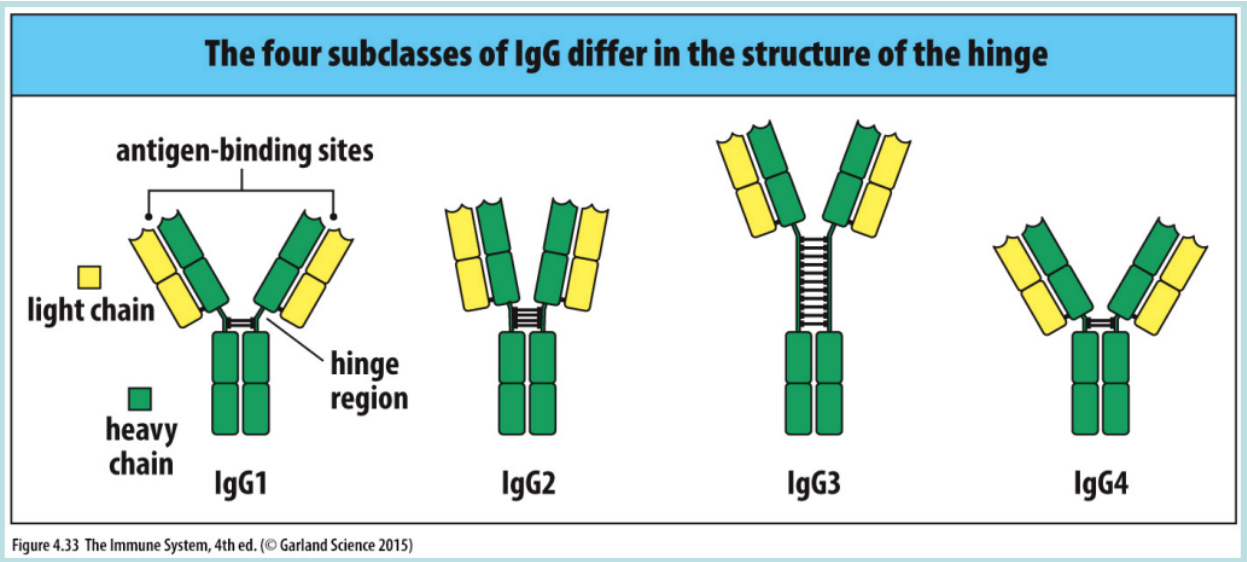
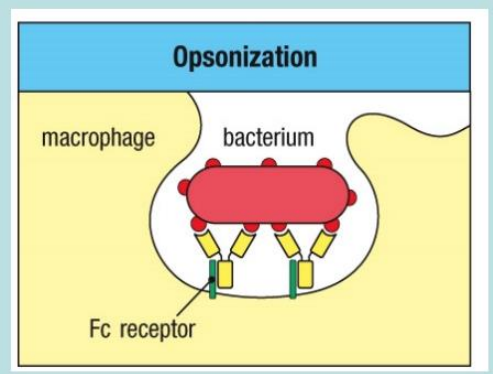


Figure 10. Different types of IgG antibodies (Lecture 9, Rhoades 2020).

WHAT ARE THE OUTCOMES TRIGGERED BY ANTIBODIES?

- Opsonization: Here, the Ab surrounds the threat, marking it by binding to specific epitopes that it can recognize. The Fc, or constant portion of the antibody, then interacts with receptors on cells such as macrophages. In the case of a macrophage, the pathogen is then internalized and destroyed via the formation of a phagolysosome.



F*igure 11. Bacterium being opsonized by Ab (Lecture 9, Rhoades 2020).*

- Neutralization: As we can see in Figure 12, the variable part of the Ab binds to the toxin, which effectively inactivates it (i.e., the toxin can no longer infect and destroy body cells). Neutralization is also important in blocking viruses that are moving between cells. This is one of the main protective effects of Ab that prevents infection by the SARS-CoV-2 virus within the few months after a person receives the COVID-19 vaccine.

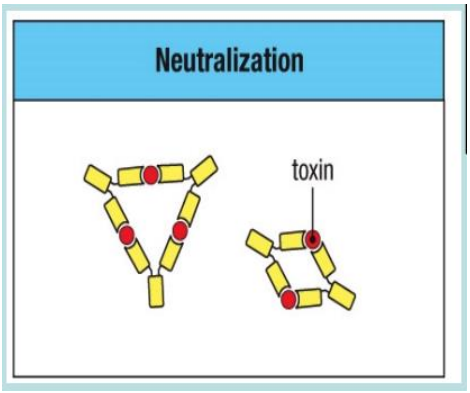


Figure 12. Neutralization of toxin by antibodies. (Lecture 9, Rhoades 2020).

- Agglutination: This term contains “glu,” which I think is helpful in understanding how agglutination works. The pathogen has multiple epitopes, which allows more than one Ab to bind to a single pathogen. In addition, it’s important to note that each Ab is

bivalent, meaning it has TWO arms that can each bind to pathogen. The ultimate effect (shown in Figure 13) is the formation of a network (sticky puddle of "glu") in which the antibodies and pathogen are clumped together. There are macrophages (especially in the spleen and liver) that capture and dispose of agglutinated antibodies and pathogens as they move through the blood or lymphatic system.

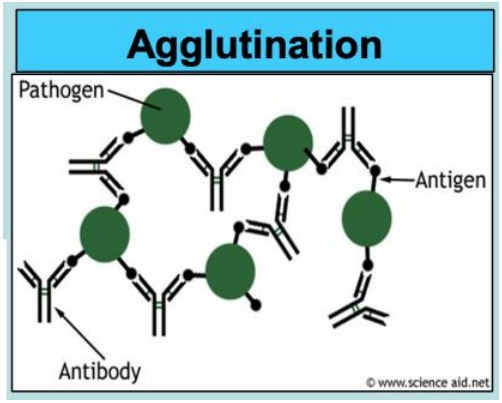


Figure 13. Agglutination of pathogen by Ab (Lecture 9, Rhoades 2020).

- Complement activation: The Fc (constant) portion of an antibody can also activate complement, which we discussed quite early on in our introduction to the immune system. Activation of complement results in (i) the formation of pores in the bacterium and (ii) lysis, as shown in *Figure 14*.

lysis

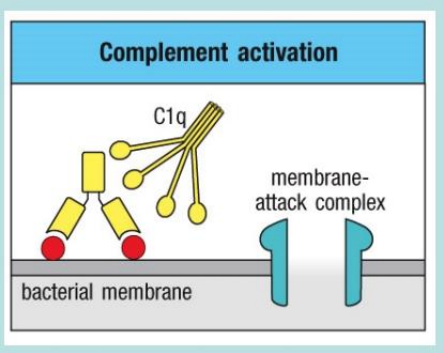


Figure 14. Complement activation by antibodies to induce bacterial (Lecture 9, Rhoades 2020).

- Activating other immune cells: Ab binding to a pathogen tags it for other immune cells to attack. Immune cells that have receptors that bind a specific Fc constant portion of the Ab are able to act on the pathogen. As we have learned, there are different types of immune cells with different effector functions. As a result, there are various Ab classes to induce activation of different cells. As shown below, once Ab bind to pathogen, the Fc (constant) region of the antibody can synapse with different kinds of cells such as NK (natural killer) cells—an important component of the body's innate defenses. Visit the dictionary for more information on NK cells are and how they work.

THE

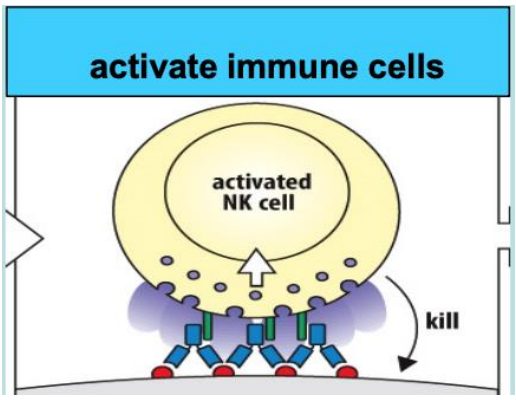


Figure 15. Activation of immune cells (like an NK cell) that carry receptors for Fc regions of different Ab classes. This NK cell is destroying the cell that is tagged by IgG3. (Lecture 9, Rhoades 2020).

DEVELOPMENT OF A FUNCTIONAL (MATURE) B CELL

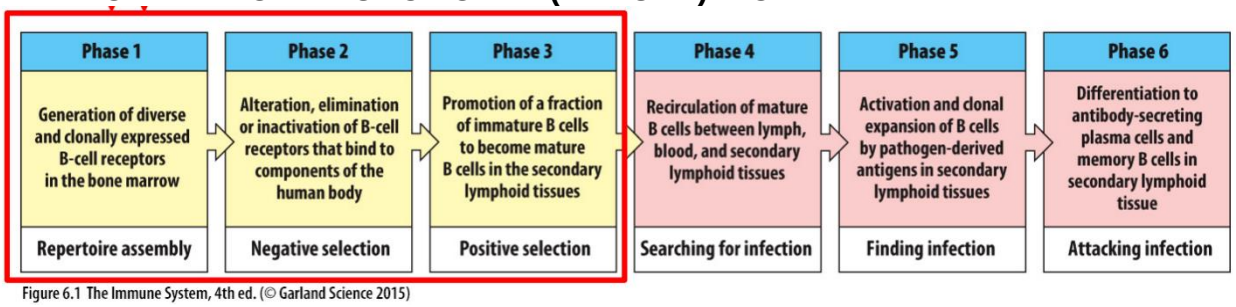


Figure 6.1 The Immune System, 4th ed. (© Garland Science 2015)

Figure 16. The life cycle of a B cell (Lecture 10, Rhoades 2020).

As discussed early on, ALL leukocytes (fancy term for white blood cells) begin as hematopoietic stem cells in the bone marrow. This includes the chief cells of the adaptive immune system: B and T cells (Lecture 10, Rhoades 2020). Interestingly, we can examine the transition from these stem cells to the B cell lineage using stage-specific proteins (Lecture 10, Rhoades 2020). In one experiment that eventually earned the Nobel Prize, researchers started with fully differentiated cells called fibroblasts and reprogrammed them by adding transcription factors (control gene expression) to a stem cell-like state. Stem cells are unique in that they can give rise to many different cell types. I mention this experiment because I want to highlight the idea that ALL CELLS (even fully differentiated cell types such as fibroblasts) carry the same genetic code. They only differ in the genes that they express, meaning that in different kinds of cells, different pieces of the overall genetic code are expressed.

In moving through different developmental phases, B cell phases have to receive survival factors (signaling is important!) Some of these factors include stem-cell factor (SCF) or IL-7 from bone marrow cells. It should be noted that bone marrow cells also physically connect with the B cells to deliver some survival factors, such as adhesion molecules and SCF (Lecture 10, Rhoades 2020).

While in the bone marrow, mature B cell precursors produce those diverse B cell receptors via somatic recombination (VDJ recombination), discussed earlier. Both heavy and light chains are generated in this way, and the B cell must receive survival signals in order to mature (Lecture 10, Rhoades 2020).

➔ TESTING HEAVY AND LIGHT CHAINS

B cell receptor formation begins with the rearrangement of the heavy chain, which then has to be tested. This occurs during the “pre-B” cell stage, and if testing goes well (the B cell gets a survival through the new heavy chain), the pre-B cell, which contains a functional heavy chain, multiplies into hundreds of daughter cells while rearranging the light chain that will be paired with the heavy chain (Lecture 10, Rhoades 2020). Each daughter cell randomly produces a different light chain that pairs with the original heavy chain. Thus, an army of B cells, each carrying a unique B cell receptor, is produced and tested. Again, if the light chain is functional, immature B cells with a functional B cell receptor proliferate (Lecture 10, Rhoades 2020). The working light chain and heavy chain send a survival cell that enables the B cell to move forward with additional testing described below.

➔ MORE TESTING: POSITIVE SELECTION

In positive selection, the immune system selects for B cells containing functional receptors that are able to move to lymph nodes and circulate in search of pathogens (Lecture 10, Rhoades 2020).

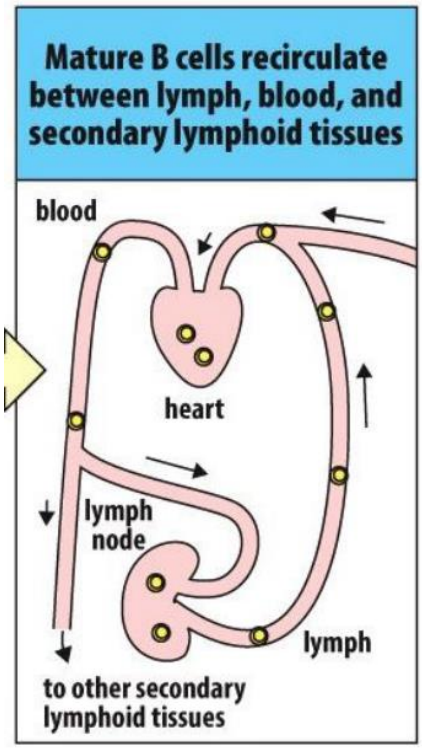
➔ MORE TESTING: NEGATIVE SELECTION

In negative selection, we eliminate B cells with receptor that respond to body tissues. If cells that sense and respond to self are not eliminated, we can end up with autoimmunity (Lecture 10, Rhoades 2020). Specifically, B cell receptors (containing both heavy and light chains) that bind to any “self” tissue in the antigen are trapped. The goal of negative selection is to make sure that newly produced B cells won’t attack the body’s antigens.

SO WHAT HAPPENS TO ANY IMMATURE B CELLS THAT FAIL NEGATIVE SELECTION?

As a recap, these failed cells are ones that bind and respond to proteins in our body, or self-antigens. These cells can: (i) continue to mutate their light chains, (ii) undergo apoptosis, or controlled cell death, or (iii) enter anergy, a state where cells don’t die, but also do not respond (Lecture 10, Rhoades 2020).

“Tolerance” describes selecting against immune cells that react to self. The two types of tolerance are (i) central and (ii) peripheral. Central tolerance involves negative selection (selection against self-reactive cells)



in primary lymphoid tissues (i.e., the bone barrow for B cells). The second type of tolerance is peripheral tolerance, which encompasses negative selection of self-reactive BCRs in blood (Lecture 10, Rhoades 2020).

HOW DOES POSITIVE SELECTION WORK?

From the bone marrow where they mature, B cells move to primary lymphoid follicles in the lymph nodes and spleen by sensing chemokines in these places. There are specific cells in the lymph node called follicular dendritic cells that produce a cytokine called BAFF. To successfully pass positive selection, B cells must show that they can respond to BAFF (i.e., they must have receptors for the molecule). Following progression through positive selection, the B cells are "mature" (Lecture 10, Rhoades 2020). As shown in the Figure 17 below, the mature B cells will the circulate throughout the body until they encounter an antigen that they can respond to.

Figure 17. Movement of B cells around body
Taken from Figure 6.21, Lecture 10 Rhoades 2020.

T CELL DEVELOPMENT

So far, we've talked about how B cells develop and the key checkpoints that they have to pass through. How does this process work for T cells, the second arm of adaptive immunity? The basic steps, as you'll see in Figure 18, are the same. Pay attention to the fact that
negative and positive selection, which we already discussed in the context of B cell development, reappear here (Lecture 11, Rhoades 2020).

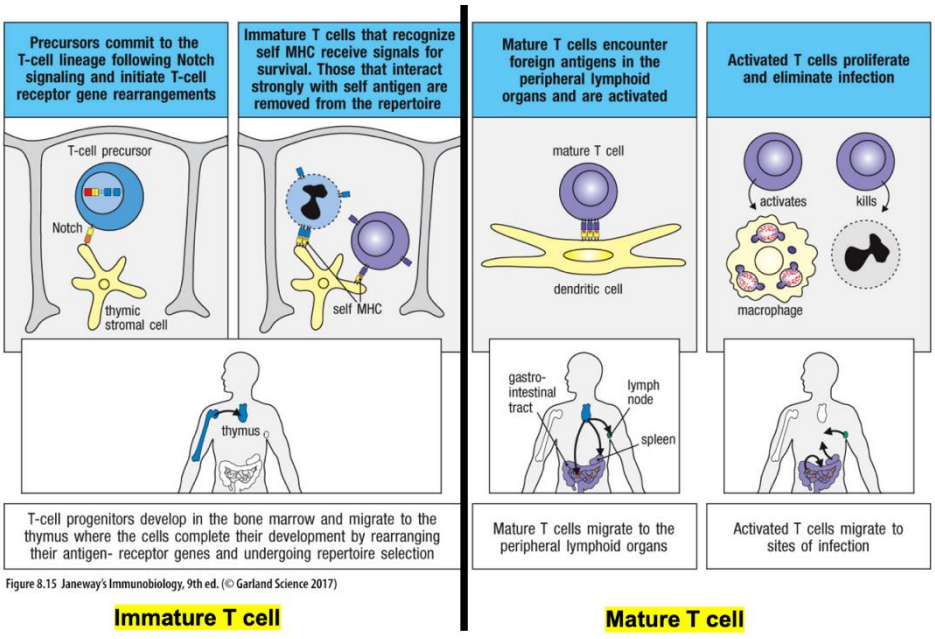


Figure 18. The development of T cells (Lecture 11, Rhoades 2020).

Useful T cell receptors have to be MHC-restricted. What does this mean? Remember how B cell receptors bind directly to antigen, while T cell receptors can only interact with processed antigen that is presented via MHC complexes. MHC-restriction describes T cell receptor interaction with an MHC molecule as well as the antigen that is being presented (Lecture 11, Rhoades 2020). The interaction is specific because the T cell receptor can only bind to a single antigen (Lecture 11, Rhoades 2020). An immune response is generated when T cell receptor binding to the MHC molecule and antigen results in intracellular

signaling. It is important to note that the co-receptor (either CD8 or CD4 depending on the T cell type) also interacts with the MHC molecule and contributes to intracellular signaling (Lecture 11, Rhoades 2020).

T cell development begins with the stromal cells shown in Figure 18. Epithelial cells in the thymus, the location in which T cells mature, express Notch ligand. This contact with Notch 1, a receptor, on the T cell progenitors (Lecture 11, Rhoades 2020). A signaling cascade occurs as Notch 1 moves into the nucleus, activating the expression of genes necessary and specific for T cell differentiation (Lecture 11, Rhoades 2020).

The next step involves recombination of the alpha and beta chains that constitute a single T cell receptor. The beta chain, similar to the heavy chain found in B cell receptors, involves recombination of V, D, and J genes. Once formed, the beta chain must be tested to ensure it can interact with the alpha chain to trigger intracellular signaling (Lecture 11, Rhoades 2020). Testing occurs as the beta chain binds to a substitute molecule called pT-alpha, which acts as a generic alpha chain. As long as the newly formed beta chain is able to bind to the alpha chain and associate with signaling chains (called the CD3 complex), the cell receives survival signals via the receptor. Beyond survival, the T cell proliferates via cell division. Cells with beta chains that are nonfunctional die in days.

Afterwards, the alpha chain is rearranged; this, like the light chain found in B cell receptors, is made up of V and J segments. Once both the alpha and beta chains of the T cell receptor have been formed, the TCR is tested again. Cells with working receptor complexes, which consist of the alpha beta and CD3 complexes receive survival signals and a signal that allows them to express the co-receptors CD4 and CD8. Interestingly, at this point in development, the T cells are called “double positive” because they express CD4 and CD8 co-receptors (Lecture 11, Rhoades 2020). Soon, though, each T cell loses one of the two co-receptors depending on the type of co-receptor required to bind the MHC complex. This occurs during positive selection.

POSITIVE SELECTION IN T CELLS

Positive selection in the context of T cells means selecting for those T cells that are able to bind and respond to MHC molecules and their associated antigens (Lecture 11, Rhoades 2020). As shown in Figure 19, T cells that are able to bind MHC and antigen with sufficient intensity receive survival signals. Cells that don’t receive these survival signals undergo apoptosis (Lecture 11, Rhoades 2020). Similar to what was mentioned earlier regarding recombination in B cell receptors that are unable to pass negative selection, there are second chances for T cell receptors. One of the T cell receptors shown in Figure 19 is unable to bind the antigen and its associated MHC complex. The T cell alpha receptor, which is functionally similar to the Ab light chain, is made up of V and J segments that can be mixed and matched. As a result, the alpha chain can alter V and J segments and try out different combinations to see if any of these will allow binding (Lecture 11, Rhoades 2020). Positive selection produces a T cell containing one specific T cell receptor and one of the two co-receptors (so EITHER CD4 or CD8). Essentially, the co-receptor that triggers signaling is kept, while the other one is lost.

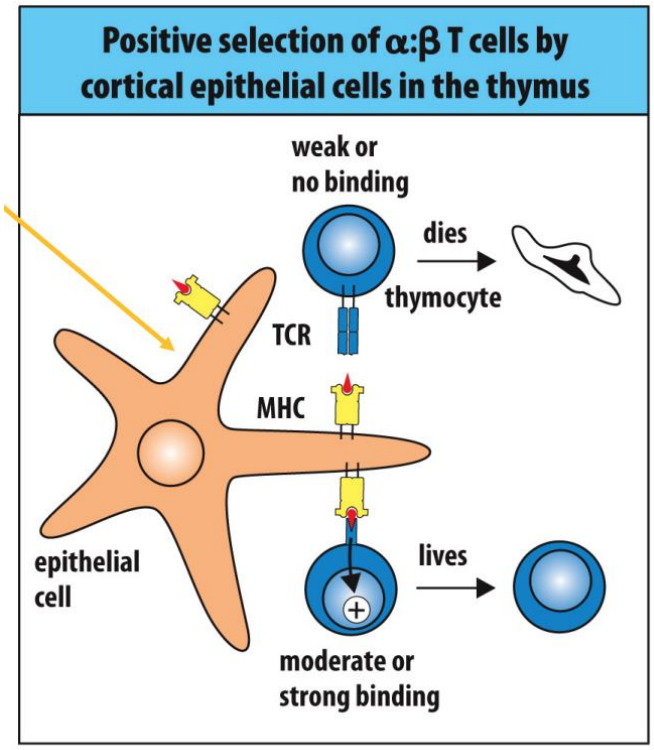


Figure 7.16 The Immune System, 4th ed. (© Garland Science 2015)

Figure 19. Positive selection in T cells (Lecture 11, Rhoades 2020)

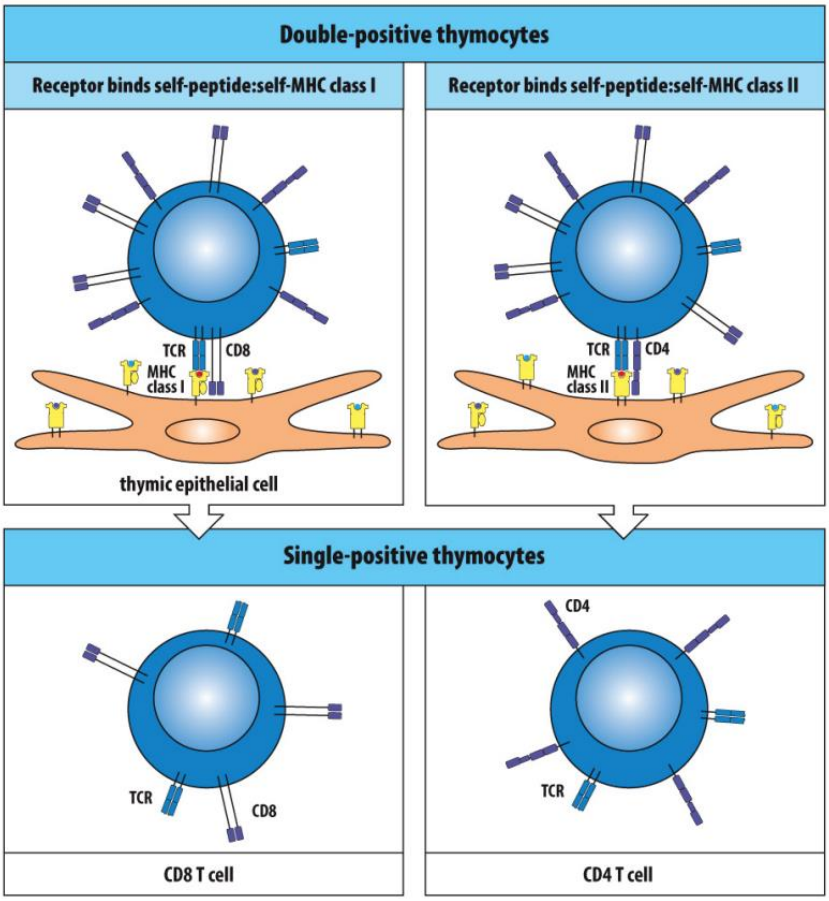


Figure 7.17 The Immune System, 4th ed. (© Garland Science 2015)

Figure 20. Generating T cells expressing one co-receptor from T cells that initially express both (Lecture 11, Rhoades 2020).

NEGATIVE SELECTION IN T CELLS

Negative selection, meant to prevent autoimmunity (the body attacking self), also plays an important role in the production of functional T cells. After all, we don't want T cells to respond to proteins and tissues in our body! There are cells in the thymus which present self-antigens meant to select against those T cells that will respond to self. Expression of such self-antigens is due to AIRE, a transcription factor (Lecture 11, Rhoades 2020). The two outcomes linked to negative selection (for those T cells that don't pass the test) are (i) apoptosis or (ii)reprogramming.

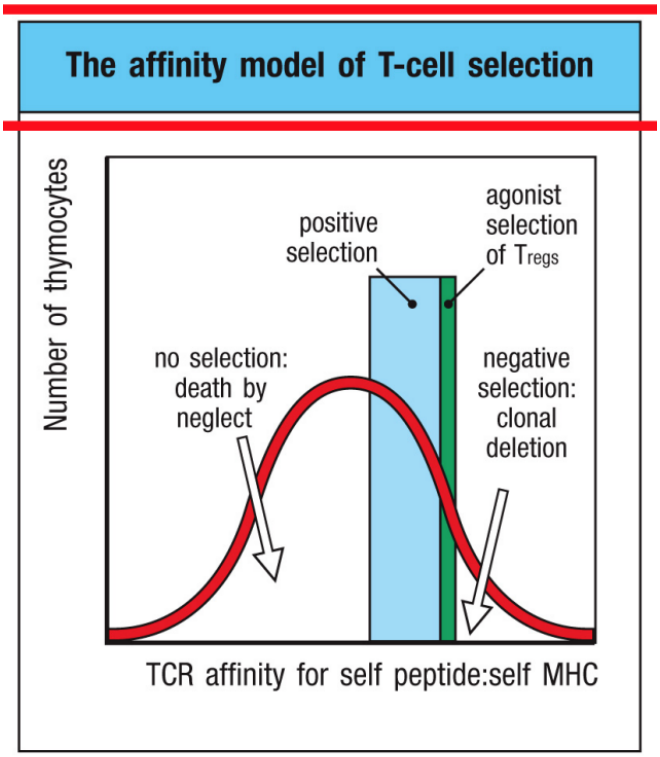


Figure 8.31 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

The green rectangle shown in Figure 21 describes T cells that bind strongly to self-proteins, but not strongly enough to be deleted via apoptosis. These cells are reprogrammed to become Treg: natural regulatory T cells. They express FOXP3, a master transcription factor which triggers anti-inflammatory responses. It is important to recognize that Treg cells are able to recognize antigen but PREVENT inflammation rather than activating it. Treg cells suppress antigen presentation and other T cells close by (Lecture 11, Rhoades 2020).

Figure 21. Diagram showing T cell selection. Most T cells fail to bind antigen and MHC and they die (death by neglect). Positive selection describes T cells selected following successful moderate-strength binding to self-MHC and associated antigen. T cells that bind too strongly are eliminated via negative selection (clonal deletion), and a small population that is on the edge of binding too strongly is turned into Tregs that will suppress instead of activate destructive defenses (described in the passage) (Lecture 11, Rhoades 2020).

HELPER T CELLS (TFH CELLS) AND HOW THEY HELP B CELLS

Tfh cells are a type of helper T cells that play an important role in B cell activation, which we will learn about in more detail in the following section. They play a role in processes such as: (i) co-stimulation (CD40 and CD40L), (ii) cytokines (which help B cells in forming plasma cells that secrete Ab, memory B cells, isotype switching, and proliferation), and (iii) somatic hypermutation (Lecture 13, Rhoades 2020). Additionally, Tfh cells are involved in making B cells via cytokines.

THE STEPS IN B CELL ACTIVATION

B cell activation cannot begin without the formation of a functional B cell! So, the first step is the development of a functional but naïve (meaning that it hasn't come into contact with antigen). This mature but naïve B cell can patrol the various lymphatic tissues and circulate in the blood (see Figure 17 for a refresher). When a B cell's receptor recognizes an epitope (a part of an antigen!), that particular B cell can then multiply. Processes such as somatic hypermutation and isotype switching offer opportunities for the B cell receptor to maximize binding to an epitope. The B cell then differentiates into an Ab-secreting plasma cell or lies in wait for future infection as a memory B cell.

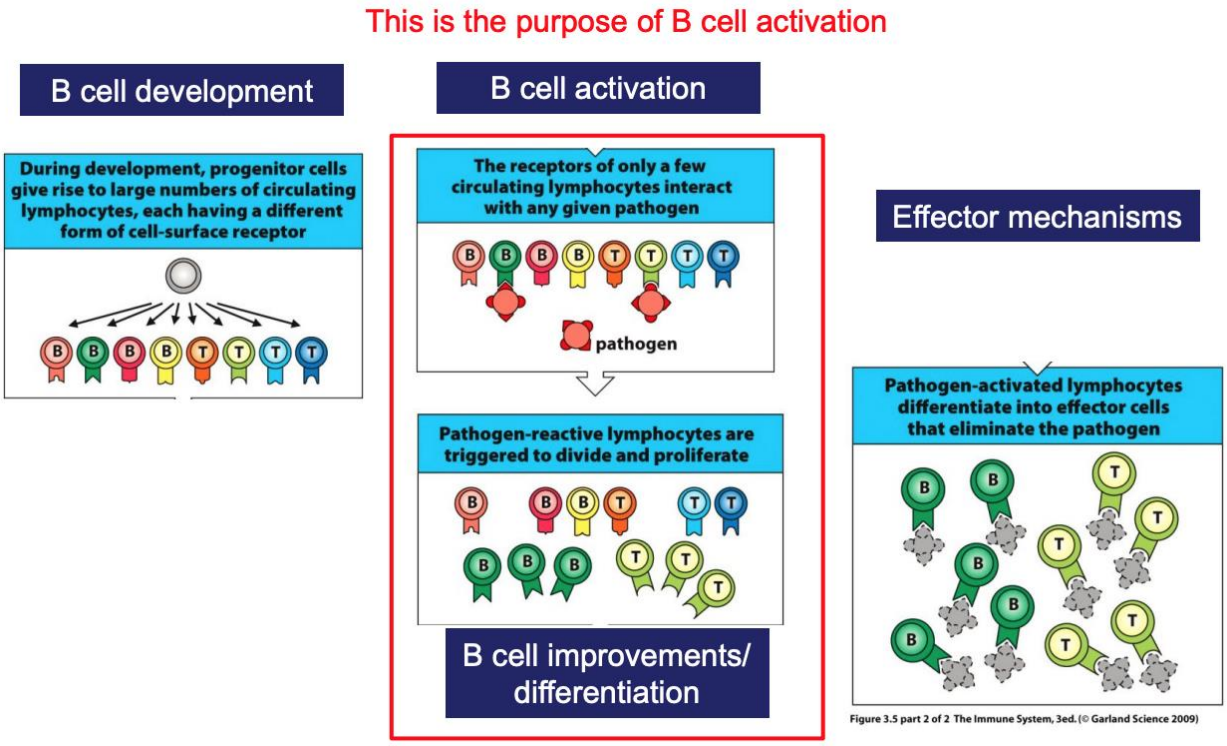


Figure 22. Progression from formation of naïve B cells to activation and ultimately response (see "effector mechanisms") (Lecture 14, Rhoades 2020)

B cells sense antigen with the help of antigen-presenting cells (APCs) such as follicular dendritic cells (FDCs). Complement proteins can attach to antigens, which induces APCs to "show" circulating B cells that there is a pathogen (Lecture 14, Rhoades 2020).

When we discussed T cell receptors, we mentioned that activation comes from the T cell receptor interacting with the MHC complex and its associated antigen as well as the co-receptor. The idea of there being multiple signals that converge to trigger a response also holds true for B cells. In this case, the first signal occurs after the variable portions of the B cell receptor interact with the antigen. Interaction with antigen results in phosphorylation, a common means of conveying signals within a cell (Lecture 14, Rhoades 2020).

B cells, like T cells, have co-receptors as well. The B cell co-receptor is made up of three parts—CD81, CD21, and CD19—that are shown in Figure 23 below. A piece of the co-receptor interacts with the antigen extracellularly, while another piece conveys signals intracellularly (Lecture 14, Rhoades 2020).

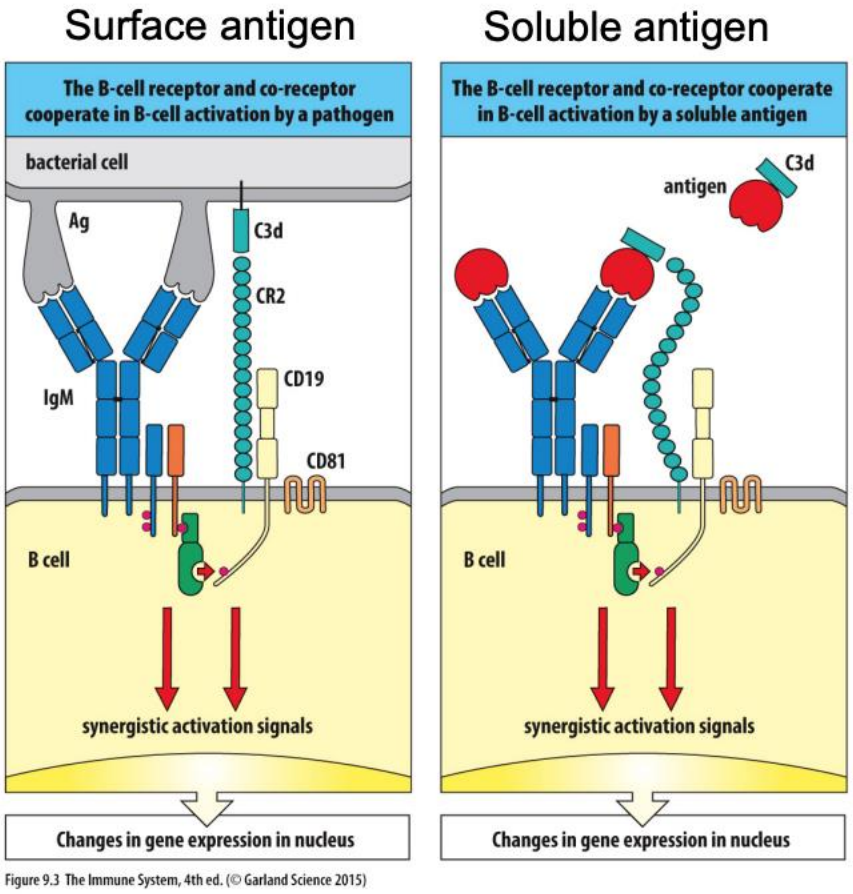


Figure 23. Signaling in B cells (Lecture 14, Rhoades 2020).

Sensing of antigens and activation, as shown above in Figure 23, occurs in lymph nodes around the body. After activation, B cells migrate towards helper T cells. One key concept you'll want to remember is that B cells are a type of professional antigen-presenting cell. So, after activation, the B cell will present a bit of the antigen using an MHC class II complex, which enables the T cell to recognize and respond; the connection between the B and T cells is called a cognate pair (Lecture 14, Rhoades 2020). In order for the B cell to multiply and differentiate (specialize, essentially), it requires two more signals. See, the idea that multiple signals come together to induce a response plays a role here as well! So, the first signal is the one we already discussed—it occurs due to interaction between the antigen/MHC molecule presented by the B cell and the T cell. The second signal happens because of interaction between CD40 ligand, which is expressed by the T cell, and a CD40 receptor found on the B cell. The third and last signal occurs via cytokines produced by the helper T cells (Lecture 14, Rhoades 2020).

The two places where B cells can multiply after all three signals are (i) the medullary cords, which are near the exit area of lymph nodes, or (ii) in the outer region—a cluster of B cells here is called a germinal center (Lecture 14, Rhoades 2020). What are germinal centers? Germinal centers are crucial for somatic hypermutation and isotype switching, the two means by which B cell receptors can change parts of their receptor to ensure a better fit with an antigen. The goal is to engineer an antibody with the absolute BEST match to an antigen's epitopes (Lecture 14, Rhoades 2020). After these mutation-generating processes comes affinity maturation, a competition in which B cells with the best receptors that form cognate pairs with T helper cells receive survival signals (Lecture 14, Rhoades 2020).

Additional isotype switching can occur in the germinal center following affinity maturation in response to cytokines produced by T helper cells. For other cells, however, affinity maturation precedes the formation of plasma cells that can produce Ab or memory cells. Memory cells, which linger even after an infection has passed, are formed via cytokines produced by helper T cells (Lecture 14, Rhoades 2020).

THE DIFFERENT TYPES OF ANTIBODIES

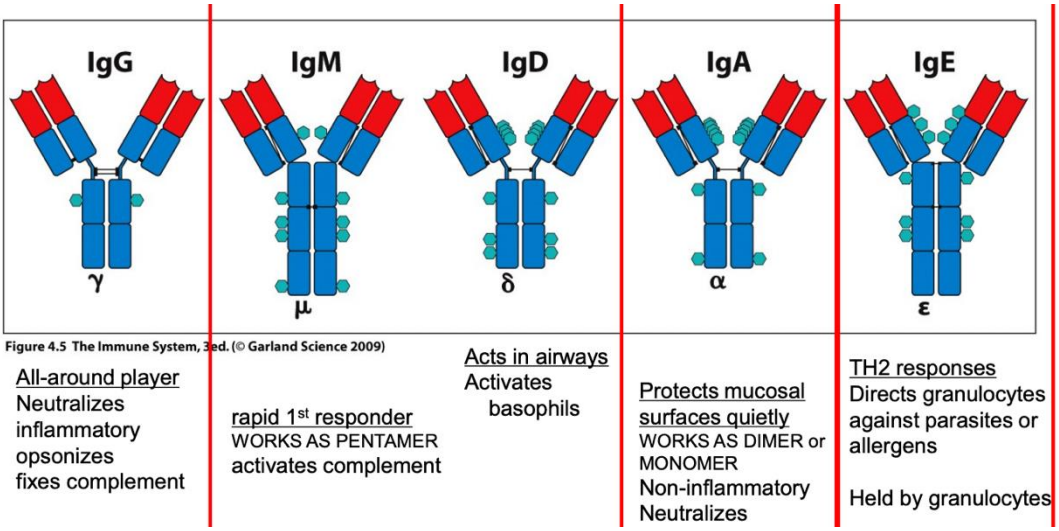


Figure 24. Different Ab isotypes and their unique functions (Lecture 15, Rhoades 2020)

The reason the various antibodies shown in Figure 24 are called "isotypes" in the figure caption is because, as we have discussed, they have different Fc, or constant regions. The constant region for each isotype is indicated by the Greek letter under the respective Ab. IgM, shown second from left, is the first Ab to be secreted; this is before the mutational processes of isotype switching and somatic hypermutation occur (Lecture 15, Rhoades 2020). In the description underneath IgM in Figure 24, you'll see it says that IgM is pentameric. The prefix "penta" (as in pentagon) means five. This means that five IgM antibodies will link together, creating TEN sites that can bind to epitopes, since each Ab has two arms that can bind (Lecture 15, Rhoades 2020). A pentamer is a type of multimer, since multiple Ab is linked together.

The Ab IgA is found in mucosal tissues, which we won't discuss in detail here. IgA, like IgM, can form a multimer (in this case, two Ab associate into what is called a dimer). Figure 25 to the left shows IgA functioning. In the lamina propria (the area just underneath a mucosal barrier that's the first place a microbe would invade/deliver toxins), which is the region labeled with "toxin," IgA arms can bind to antigen (in this case the red toxin dots). The IgA transporting toxin is then shuttled across the epithelium, which can bind to any dimeric IgA. Empty IgA can also be used to sense and bind to antigen on the other side of the epithelium (indicated by the villi, or fingers). This region is called the lumen and is a space outside of the body where many microbes can live and invade (Lecture 15, Rhoades 2020). IgA and IgG are both sources of passive immunity, which means that they can be transported from mother to child, for instance (Lecture 15, Rhoades 2020).

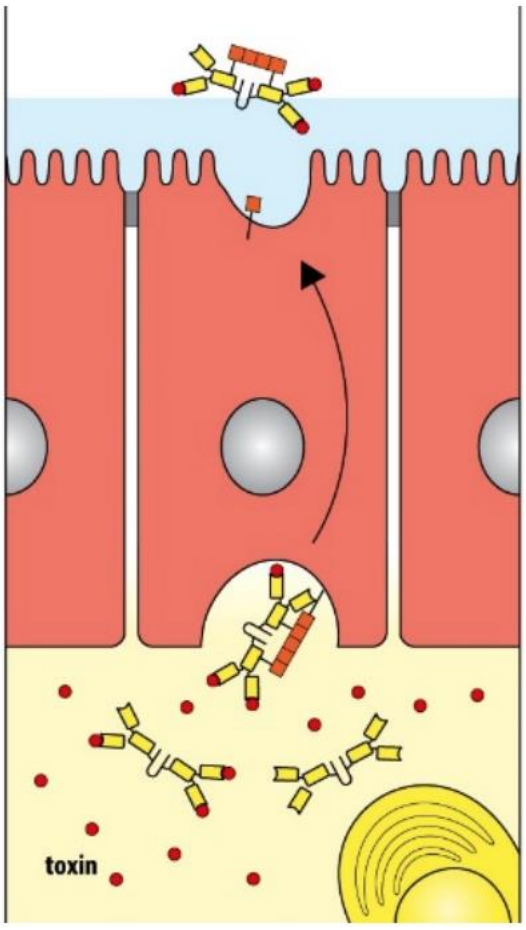


Figure 25. IgA moving toxins out of the host (lamina propria) across a single layer of epithelial cells to the outer surface of the host mucosal barrier (Lecture 15, Rhoades 2020).

What's the difference between passive and active immunity? Passive immunity is the transfer of preformed Ab, while active immunity involves our body sensing and responding to an antigen by producing its own B cells (and antibodies).

The Ab IgG is involved in complement activation; IgG arms will sense and bind antigen, while the Fc constant regions of several IgG antibodies provide a landing pad for a large molecule of C1q, activating complement (Lecture 15, Rhoades 2020).

FC RECEPTORS AND RESPONSES

Fc receptors, as indicated by their name, bind to the Fc (constant) regions of Ab. Most immune cells express several kinds of Fc receptors so that they can respond to antigens bound to various types of Ab. Depending on the type of the cell, Fc receptor interaction will result in different actions. Fc binding to Ab occurs extracellularly; intracellularly, the Fc receptors initiate signaling cascades. As a result, an Fc receptor has both extracellular and intracellular portions (Lecture 15, Rhoades 2020). Among the various types of Fc receptors is FcgammaRIII, which is the main Fc receptor of NK cells. Binding of several FcgammaRIII receptors to IgG Ab triggers degranulation in NK cells (Lecture 15, Rhoades 2020). It is important to note, however, that, not all Fc receptors induce destructive responses such as the one described above. For example, the Fc receptor FcgammaRIIB1 expressed on many types of cells such as naïve B cells binds to IgG and inhibits a response (Lecture 15, Rhoades 2020). Basically, this Fc receptor has an intracellular region that instructs cells to stop rather than activating.

T CELL ACTIVATION

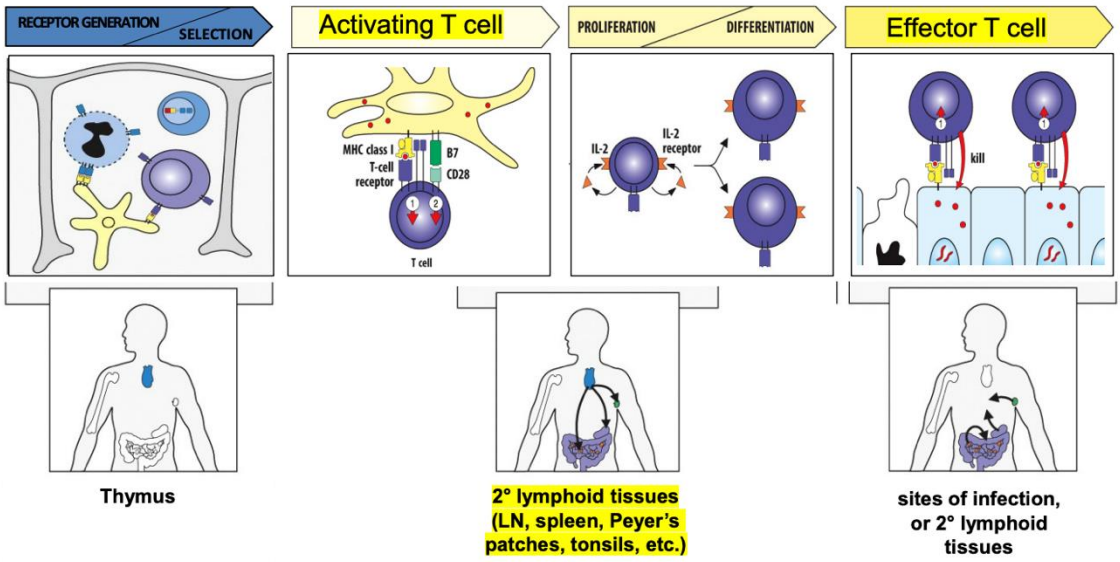


Figure 26. The figure above traces the pathway from T cell development, which we discussed at length earlier, through activation and effector mechanisms (Lecture 12, Rhoades 2020)

Similar to B cells, T cells are exposed to antigen in secondary lymphoid tissues (from Figure 26: lymph nodes, spleen, etc.) (Lecture 12, Rhoades 2020). One means of activation is antigen presentation by dendritic cells, a professional antigen-presenting cell.

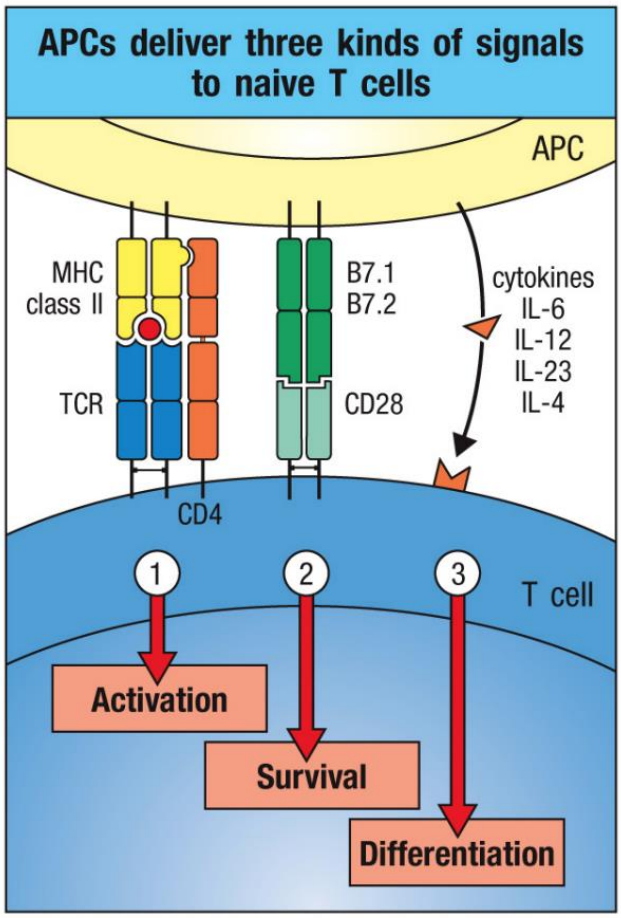


Figure 9.22 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

The first signal involved in T cell activation is triggered by binding/recognition between a T cell's unique, rearranged receptor and an antigen plus its MHC complex. This interaction, which occurs extracellularly, initiates a signaling cascade within the cell that aids in T cell activation (Lecture 12, Rhoades 2020). It should be noted that this first signal also includes interaction between the T cell's co-receptor (CD4 in the case of the example shown to the left) and the MHC II complex (Lecture 12, Rhoades 2020).

Figure 27. Signals involved in initiating T cell proliferation (Lecture 12, Rhoades 2020).

The second signal comes from costimulatory interaction between B7 (expressed by the antigen-presenting cell) and CD28, a costimulatory receptor expressed by the T cell (Lecture 12, Rhoades 2020). This interaction results, as shown in Figure 27 above, T cell proliferation. The last signal, shown in Figure 27, involves cytokines produced by the APC binding to receptors on the T cell and triggering differentiation into effector cells.

Key here is the idea that signals work together. One example of this is how TCR and costimulatory signaling initiate transcriptional changes—IL-2, which produces clonal expansion, is an example of this (Lecture 12, Rhoades 2020). When the signals shown in Figure 27 are absent, the T cell does not activate. Variations in specific cytokine-based signals in "3" can result in differentiation into different T cells involved in varying immune responses.

How do we STOP T cell activation?

B7, the costimulatory molecule, is NECESSARY for T cell activation. Without B7, the T cell will undergo anergy, which we can conceptualize as a loss of the T cell's "power" to respond (Lecture 12, Rhoades 2020).

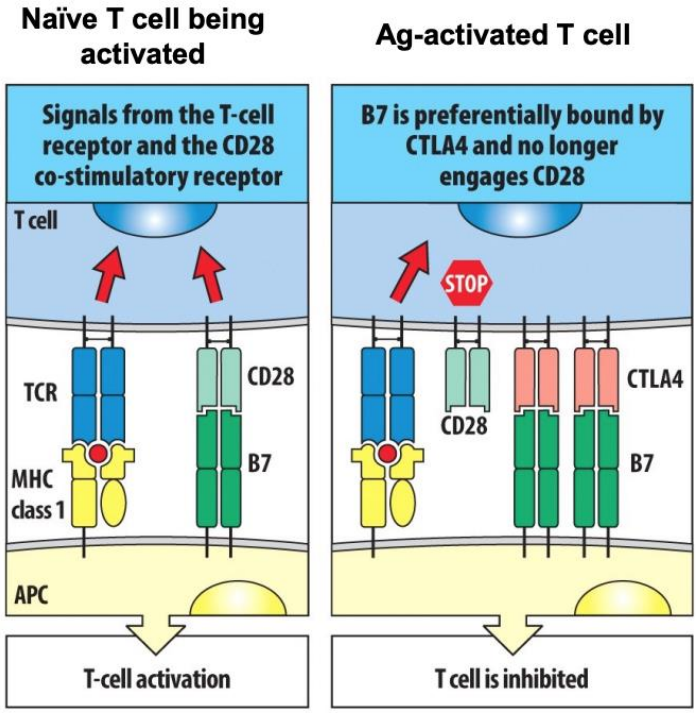


Figure 17.19 The Immune System, 4th ed. (© Garland Science 2015)

As shown in Figure 28 to the left, T cells start to express an inhibitory receptor called CTLA-4, which binds to the B7 ligand as well. When this occurs, the required proliferation signaling #2 can no longer be initiated and T cell activation is inhibited (Lecture 12, Rhoades 2020).

Figure 28. B7 and CTLA4 interaction stops T cell activation (Lecture 12, Rhoades 2020)

UNDERSTANDING THE DIFFERENCE BETWEEN CD4 AND CD8

How do CD8 T cells work?

Of course, the first step involves T cell activation, which occurs with T cell binding to an antigen and its associated MHC I molecule. The MHC I complex, as we have discussed, is one that is expressed by all nucleated cells. The co-receptor (CD8) must also associate with the MHC molecule (Lecture 12, Rhoades 2020). In terms of effector mechanisms, CD8 T cells are largely involved in killing, though they also make cytokines and molecules responsible for cell death called death ligands, an example of which is LTalpha.

One concept that is important to understand is apoptosis vs necrosis, which are two pathways through which cell death can occur. Apoptosis is contained, which is important because it prevents the spread of viral bits and kills cells quietly while preventing damaging inflammation. Necrosis, however, is not contained; rather, it describes a haphazard release of debris, which can trigger a damaging inflammatory response which some tissues in the body cannot abide (Lecture 12, Rhoades 2020).

What about helper T cells (CD4 T cells)?

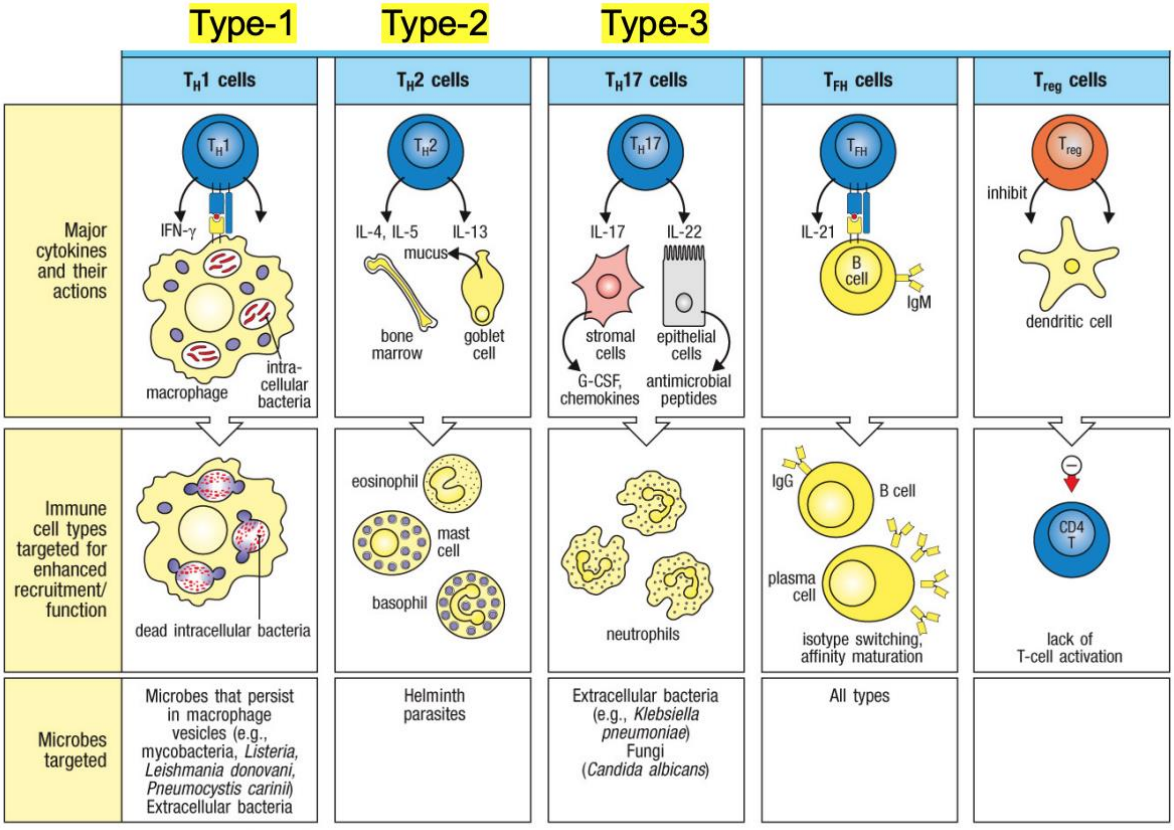


Figure 9.30 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Figure 29. The different types of T cells, how they initiate immune responses, and their pathogenic targets (Lecture 13, Rhoades 2020)

T cells, as indicated by the complexity of Figure 29 above, are considerably more complicated than CD8 T cells because there are several different types of helper T cells that serve different purposes in the body.

T cells, as we recently discussed, must receive three

signals in order to activate. The last of these signals is cytokine-mediated signaling. As indicated by the arrows coming off of each of the Th cells in Figure 29, each of the CD4 T cells secretes different cytokines, but it is also important to recognize that each type that is specified by different cytokines (Lecture 13, Rhoades 2020). As such, specific but different combinations of cytokines produce different types of CD4 T cells by altering transcription (Lecture 13, Rhoades 2020).

Cytokines that determine the type of CD4 T cell are termed fate-specifying cytokines and originate from cells such as dendritic and epithelial cells (Lecture 13, Rhoades 2020).

THE TYPE 1 RESPONSE

The Type 1 response is characterized by IFN-gamma secretion by the Th1 cell. This induces the macrophage to destroy intravesicular pathogens (Lecture 13, Rhoades 2020). The term intravesicular refers to existing within vesicles, formed when the cell internalizes something that was originally outside the cell; in this case, the cell membrane folds in on itself, forming a small bubble-like body. As is the case with much of immunology, macrophage activation is dependent upon additional signals as well (Lecture 13, Rhoades 2020).

THE TYPE 2 RESPONSE

The Type 2 response is more appropriate for large parasites and involves several responses such as (i) epithelial regeneration, intended to rid the body of infected cells, and (ii) activation of granulocytes (eosinophils, mast cells, basophils), shown in Figure 29 above. Activation of granulocytes is important in initiating parasite destruction (Lecture 13, Rhoades 2020). A form of type-2 macrophage activation (different from the Type 1 response) also helps by working with muscle cells to get rid of parasites and to fix tissues (Lecture 13, Rhoades 2020).

THE TYPE 3 RESPONSE

The Type 3 response is directed towards mucosal pathogens and harmless microbes living on mucosa like the gut and airways. Outcomes include targeting of pathogens on epithelial cells and inducing the replacement of epithelial cells (goal here is to make it more difficult for bacterial infections to take hold) (Lecture 13, Rhoades 2020). Two other effects are the induction of mucus production and antimicrobial compounds called defensins.

An important component of the Type 3 response is neutrophils—as such, responses in this category include (i) neutrophil proliferation and (ii) chemokine-mediated guiding of neutrophils (Lecture 13, Rhoades 2020).

TYPE 3 RESPONSE VS FORMATION OF TREG

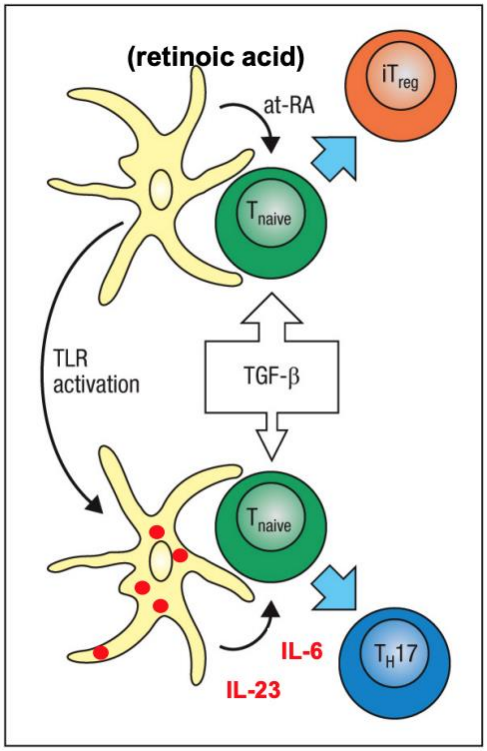


Figure 9.33 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Figure 30. Formation of Tregs vs Th involved in type 3 response (Lecture 13, Rhoades 2020).

Formation of both Th17 cells involved in the type 3 response and iTreg involve antigen. The differences arise in whether or not there's a threatening pathogen that is actively invading and triggering the production of inflammatory cytokines such as IL-23 and IL-6 (Lecture 13, Rhoades 2020). When there's a pathogen, the scale tips toward inflammation/Type 3 response in mucosal tissues, while NO pathogen results in the formation of iTreg and the mucosa remain intact (Lecture 13, Rhoades 2020).

So, what's the different between induced Treg (iTreg) and natural Treg (discussed earlier)?

iTreg are guided in tissues other than the thymus by cytokines (retinoic acid, indicated by RA in the figure above, and TGF-beta). Both types of Treg cells express FOXP3. Functionally, both natural Treg and iTreg exert anti-inflammatory effects (Lecture 13, Rhoades 2020).

The immune system is clearly dynamic. A good example of this is how one type of T cell discussed in Figure 29 can switch to another with the addition of different cytokines in a phenomenon termed "plasticity" (Lecture 13, Rhoades 2020). Then, it can guide a different type of immune response.

IMMUNE SYSTEM MEMORY

The immune system is effective because it can respond to specific antigens repeatedly via what we call memory.

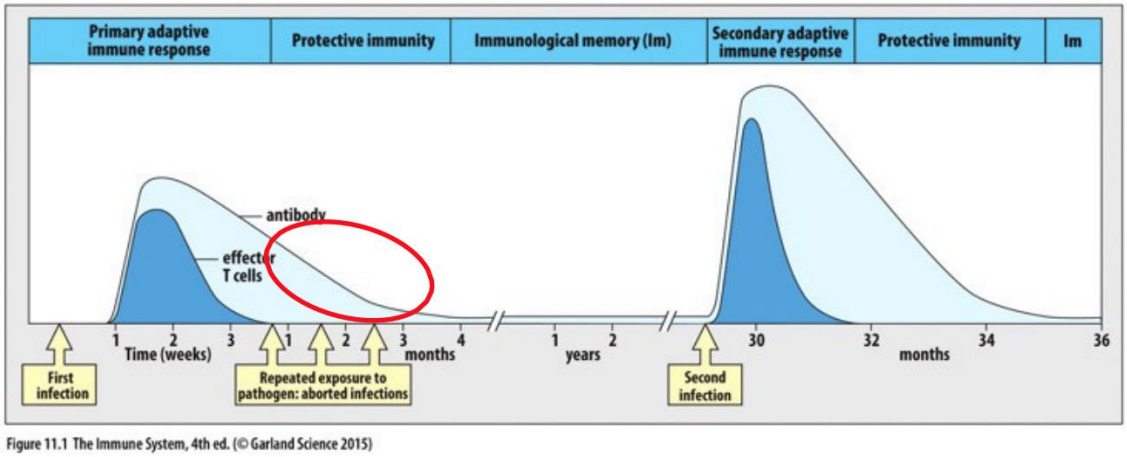


Figure 11.1 The Immune System, 4th ed. (© Garland Science 2015)

Figure 31. Timeline of the immune response (Lecture 16, Rhoades 2020).

The distinction between protective immunity and memory is clearly shown in Figure 29. Memory is long-lasting, spanning a period of YEARS, while protective immunity spans months. In protective immunity, as shown in Figure 31, there is still a considerable amount of Ab from the immune response. In memory, which we will discuss in more detail below, there are Ab-secreting plasma cells along with memory T and B cells (Lecture 16, Rhoades 2020). A key point regarding immune memory is that immune responses following reinfection occur more quickly, which can be visualized above: the time between initial infection and Ab/T cell response is greater than the time between second infection and the subsequent immune response). Additionally, we can clearly see that more Ab and effector T cells are produced with the 2nd response, since there's a taller peak (Lecture 16, Rhoades 2020).

THE PARTS OF OUR IMMUNE SYSTEM'S MEMORY

Immune memory includes (i) memory T and B cells and (ii) plasma cells, which are responsible for producing Ab (Lecture 16, Rhoades 2020).

There are several processes that contribute to the braking of the immune system until future infection: (i) anergy, which follows because there is no antigen to bind to and activate B/T cell, (ii) Ab production ceases because it is similarly reliant on signaling, and (iii) certain Fc receptors, as discussed earlier, repress the immune system response (Lecture 16, Rhoades 2020).

Yet, even when our bodies aren't fighting infection, there is circulating Ab produced by "long-lived plasma cells," shown in Figure 32 to the left. And, as expected, there are survival signals involved in the continued circulation of these long-lived plasma cells. APRIL and BAFF are two of the survival signals found in the bone marrow that will bind to receptors on long-lived plasma cells, ensuring their survival (Lecture 16, Rhoades 2020).

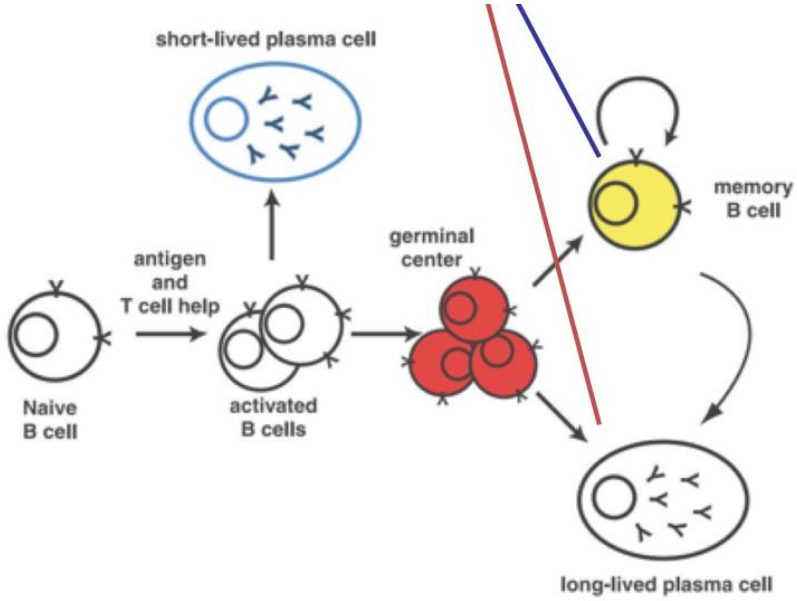


Figure 32. B cell memory (Lecture 16, Rhoades 2020)

And what about the memory B and T cells?

Memory B and T cells originate from the initial response or exposure to an antigen. It is thought that cytokines determine whether adaptive immune cells will differentiate into effectors designed to eliminate infection or become memory cells.

Like everything else, memory cells must respond to survival signals to survive. This response occurs in lymphoid follicles—inner portion for T cells (aptly named the T cell area) and outer edges of B cells (B cell area).

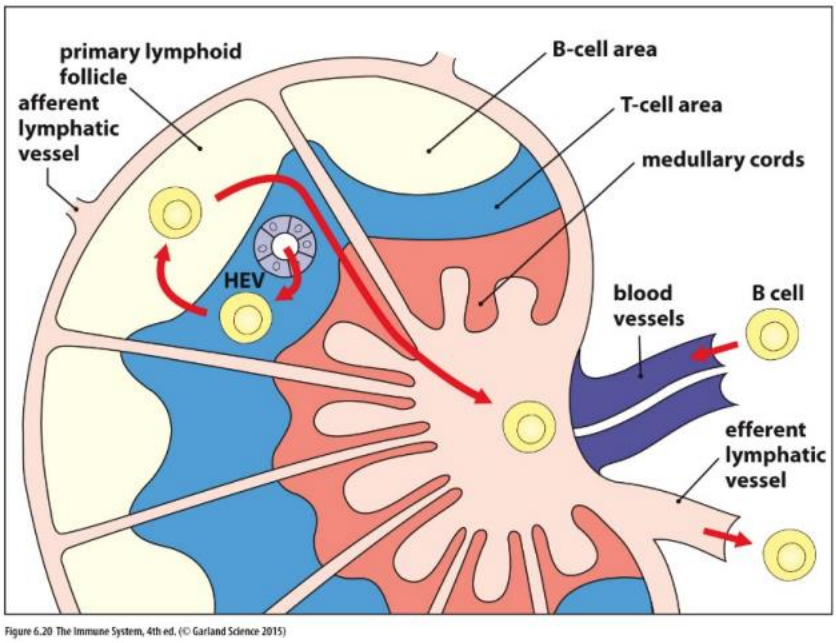


Figure 33. Visualizing the T cell and B cell areas in a lymphoid follicle (Lecture 16, Rhoades 2020).

What is it that makes second (and future) immune responses greater and better?

Well, following the first response, the generation of specific memory T and B cells that have already been exposed to pathogen certainly helps speed up the immune response. It therefore becomes easier to activate B and T cells. Also, instead of producing the generic IgM antibodies at first, the memory response jumps straight to the production of specific antibodies that can swiftly eliminate the pathogen. A key point to understand is that the memory response depends on memory B cells that have already formed specific Ab rather than the circulating naive B cells. Inhibition of circulating naïve B is mediated by IgG and the inhibitory response we discussed earlier (refer back to the discussion on FcgammaRIIB1). Thus, immune responses are effectively triggered in memory B cells but NOT in naïve cells (Lecture 16, Rhoades 2020).

VACCINES

Vaccines have been a topic of interest (and considerable controversy) in the last couple years with COVID-19. But how do they work?

There are two types of vaccines: pre-exposure and therapeutic. Pre-exposure, meaning before exposure to a pathogen, is usually what comes to mind when we think of a vaccine. Examples of this would be the various COVID-19 vaccines or the annual flu vaccine. The goal here to build immunity to a virus through prepared B cells, T cells, and antibodies that are able to recognize the specific virus. This jumpstarts an immune response that would take several weeks to reach full strength in someone who's unvaccinated. The reason we have to get the flu vaccine every year is because viruses constantly mutate to evade the defenses of the immune system. We've seen this with the Sars-CoV-2 virus as well and the various variants that appeared as the virus mutated. The goal of a pre-exposure vaccine is to ensure that we don't get sick if we do end up getting infected because our body's immune system has already been primed to fight off the invader. The vaccine is quite literally priming the immune system using bits of antigen; the goals here are therefore protective and memory-based immunity.

Therapeutic vaccines, on the other hand, are "post-exposure" vaccines. They still involve priming the immune system to respond, but occur after exposure. An example of this would be cancer vaccines or vaccines against AIDS for HIV-positive individuals (Lecture 16, Rhoades 2020).

BOOSTER VACCINES

The administration of booster vaccines offers the immune system an opportunity to generate Ab with the best affinity to an antigen via multiple immune responses. An important component of each adaptive immune response is the formation of memory cells, which prime the body for future infection (Lecture 16, Rhoades 2020). A booster reawakens memory B cells and gives them a chance to improve their antigen receptors each time they encounter the threat. This is why it's important to receive vaccine boosters.

THE BASICS OF VACCINES

There are different kinds of vaccines, as detailed below:

- Live whole antigen (attenuated): This is the complete antigen (so if we take the SARS-CoV-2 as an example, it would be the entire viral structure). Whole antigens best mimic what your body would be exposed to if infected. The term "attenuated" simple means that the antigen is administered in a

weakened form so that it can't cause serious disease. Even still, it goes through some steps that a living pathogen would go through to kickstart an immune response.

- Whole antigen (not live): This is again the complete antigen but is NOT alive, which reduces the immunogenicity of the antigen. Again, immunogenic refers to anything that can induce an immune response.
- Subunit vaccines: A subunit vaccine contains only a part of the complete antigen. For example, taking the example of the SARS-CoV-2, a subunit vaccine might include the spike proteins found on the virus.
- Nucleic acid-based vaccine: An example of this is the now-famous mRNA vaccines against COVID-19 Pfizer and Moderna. These are relatively adaptable and easily produced vaccines that can be designed once the sequence of a pathogen's antigen is known. For instance, the sequence of the SARS-CoV-2 virus was published and just 10 days later, mRNA vaccines against the virus were being tested in the first stages of clinical trials.

CANCER IMMUNITY AND HARNESSING THE ABILITY OF THE IMMUNE SYSTEM TO RESPOND TO CANCEROUS CELLS

Going back to the section on T cell activation, you'll see that T cells that express CTLA4 cannot be activated; this is because the CD28 receptor expressed by T cells cannot interact with the B7 ligand found on APCs. Based on this logic, inhibiting the repressive response should result in T cell activation. It's like taking your foot off the brakes—the car (or immune T cells) can then keep going and attack the tumor. T cells can clear cells in our own body that have become cancerous.

Interestingly, this is how checkpoint blockade therapy works; CTLA4 binding sites that would otherwise interact with B7 are bound by commercially made antibodies (Ab) that bind CTLA4. This results in T cell activation and ultimately tumor destruction (Lecture 12, Rhoades 2020).

IMMUNE SYSTEM AND MENTAL HEALTH

When I was starting out writing this newsletter, I thought that I would explore mental health and the immune system as they interact in great detail, but I realized that it was important (and hopefully interesting!) to first provide a comprehensive view of how one of our body's most important body systems works. Again, the immune system is far more complex than what I've presented in this newsletter here—we've barely just scratched the surface.

In research covered by verywellhealth.com, it has been reported that those who have had COVID-19 have a higher likelihood of experiencing mental health issues (1). I know that the pandemic overall was incredibly isolating and posed a mental health challenge, even for those who never had COVID-19. If anything, the pandemic stressed the importance of connections and feeling like a part of the larger world, something that was largely eliminated for several months. The research discussed by verywellhealth.com reported increased risk of developing conditions such as anxiety, substance abuse issues, and even sleep-related conditions. One study author believes that the effects of COVID-19 on mental health may be traced back to inflammation. As with health and disease, however, it is important to consider a comprehensive picture of the problem, which includes considering how demographics fit into the equation. A professional in the article specifically commented on the prevalence of COVID-19 among those already predisposed to mental illness. With the rise of mental illness linked to COVID-19, self-care and knowing when and how to reach out for help are key.

Another article by Discover magazine reflects on research related to stress and the immune system (2). Various research, as discussed in the article, has documented the relationship between stress and the immune system. For example, one study reported that immune cell motility is inhibited by stress, which can clearly be disastrous for the immune system. It was specifically observed that this was the case with noradrenaline, an important hormone that may have been discussed in the previous newsletter. Noradrenaline is a hormone that stimulates the fight or flight response.

This same article also discusses a study in which it was reported that masking psychological stress slowed down cancer growth.

The last article I wanted to mention was published in *The Virginian Pilot* and talks about the benefits of the outdoors at the level of the immune system, which I thought was interesting (3). Plant-derived phytoncides make their way into our respiratory system and increase NK cell counts. If you remember our previous discussions about NK cells (or look at the cell dictionary at the end of the newsletter), you'll see that NK cells are key in warding off viruses and cancerous cells, which is exactly what is reported in the article. Additionally, bacteria in the dirt called *Mycobacterium vaccae* carry anti-inflammatory properties and are able to boost serotonin (low serotonin is linked to depression).

QUESTIONS FOR YOU TO CONSIDER AND RESPOND TO:

1) Think of an immune disease you have heard of. Some examples to get you started are HIV/AIDS, multiple sclerosis (MS), or arthritis. See if you can read/research the mechanisms underlying the disease and explain what is happening at the cellular level based on what you know about the immune system.
2) Have you experienced stress during the pandemic? Write about how you are/were feeling. Did you notice any effects on your immune system (i.e., did you get sick at around the same time)?
3) What does help for mental health conditions look like in prisons? What kinds of resources do you turn/have you turned to if you have experienced mental health issues? What improvements/reforms do you feel are necessary?

<u>THE IMMUNE CELL DICTIONARY</u>

KEY TYPES OF CELLS IN THE IMMUNE SYSTEM:

- **Macrophages:** Macrophages are called monocytes while in circulation and engage in phagocytosis ("eating") (Lecture 2, Rhoades 2020), which allows them to ingest and break down foreign pathogens. You'll see in the schematic below that, even when the pathogen is taken up via phagocytosis, it is separated from the cell's contents in a vesicle termed the phagosome. The phagosome subsequently fuses with the lysosome, an organelle that has degradative acidic enzymes that successfully digest invaders (Lecture 2, Rhoades 2020). Macrophages also play an instrumental role in activating adaptive immunity (Lecture 2, Rhoades 2020).
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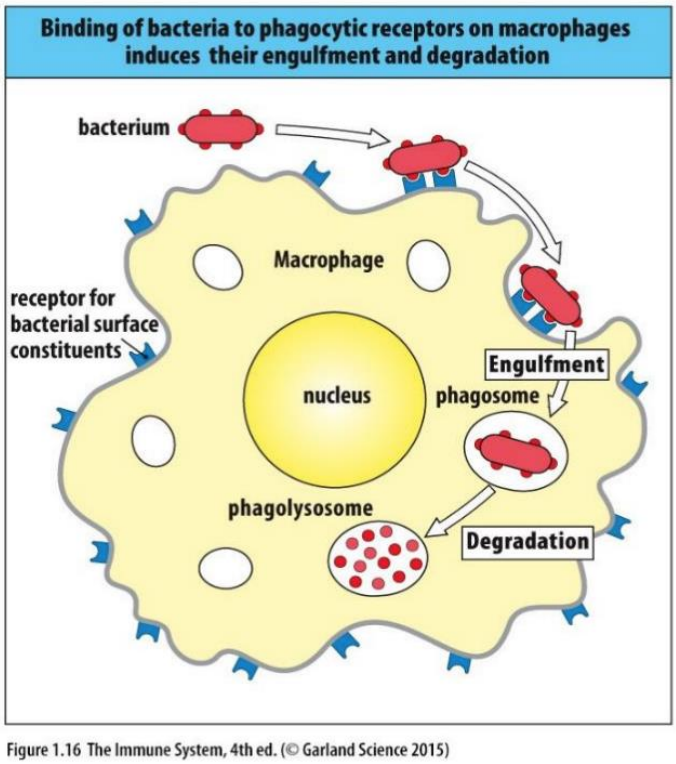

Figure 34. Macrophage effector mechanism (Lecture 2, Rhoades 2020).

- **Neutrophils:** Similar in function to macrophages owing to their phagocytic capabilities (Lecture 2, Rhoades 2020). A member of the granulocytic family that gets its name because its member cells contain antimicrobial granules that can be released (Lecture 2, Rhoades 2020), which makes them important in the containment of bacterial infection.
- **Natural killer (NK) cells:** These cells specifically target viruses. Interferon production by virus-infected cells drives NK recognition and response. One key idea that comes up over and over is the proliferation driven by the recognition of a pathogen and subsequent differentiation, which is shown in the third box.

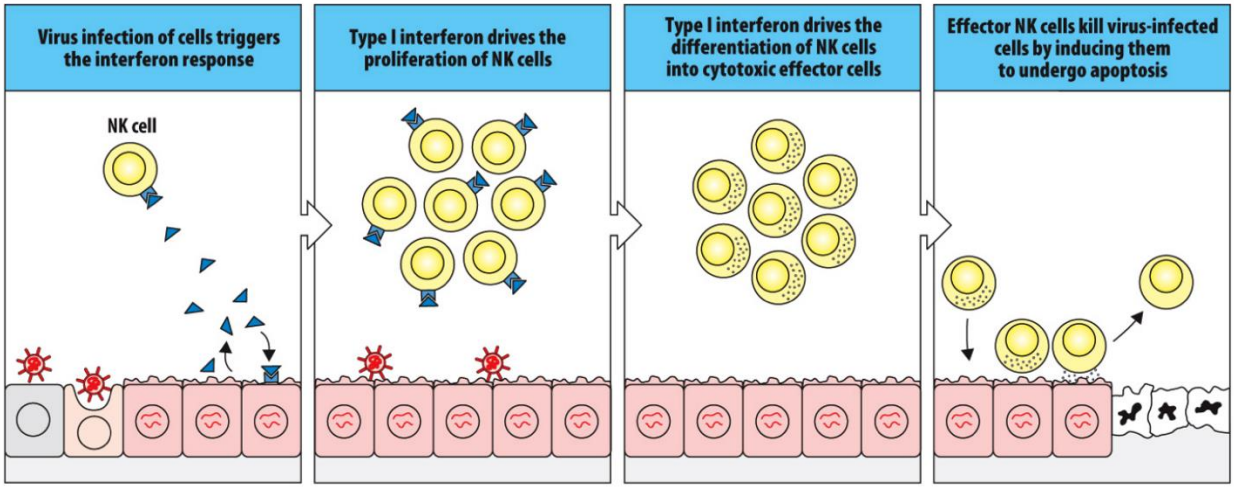

Figure 3.38 The Immune System, 4th ed. (© Garland Science 2015)

NK response to viral infection. Lecture 5, Rhoades 2020.

- **Dendritic cells:** Involved in antigen presentation, which is key for the activation of T cells (Lecture 7, Rhoades 2020). This is not a one-time event that occurs following subsequent infection. Rather, dendritic cells will constantly sense their surroundings; if and when they encounter danger, the pathogen is chopped to bits and presented in an MHC molecule (Lecture 7, Rhoades 2020).
- **B cells:** Adaptive immune cells that eliminate pathogens by producing specialized Ab formed to target a specific epitope.
- **T cells:** Adaptive immune cells that come in two varieties (depending on the co-receptor expressed): CD8 T cells or CD4 T cells. CD8 T cells sense intracellular pathogens and engage in destruction, while CD4 T cells sense extracellular pathogens such as parasites and largely focus on activation of other cells (i.e. macrophages or B cells, for example) to eliminate infection.

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1) https://www.verywellhealth.com/mental-health-covid-study-5220260
2) https://www.discovermagazine.com/health/what-stress-does-to-the-immune-system
3) https://www.pilotonline.com/life/wildlife-nature/vp-hl-in-full-bloom-allissa-bunner-finale-112721-20211126-6d56z27zpnggza53b5iruyqxaq-story.html
4)Various lectured from Dr. Rhoades. An enormous thank you to Dr. Rhoades for allowing me to use her class materials.

Gary here again. Wow1 what an introduction into the amazing body you inhabit. It is a miracle that all forms of life coexist. Everything is striving for balance and it seems also to reproduce. It is amazing how creation has evolved systems of checks and balances to keep the whole evolutionary shebang moving along to who knows where. As long as we inhabit these bodies, I guess the trick is to observe and enjoy the show while it lasts. Possibly be kind to others and hope they are kind to you as deep down it is all connected to one source.

Humans are incredibly smart to have figured all this out. I know everyone has taken a hit during the pandemic, and the only consolation is “this too shall pass”. Be well and happy spring! Tell us what you think