



Immune System Design and the Primeval Garden

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Abstract: The mammalian immune system is required for life. It is a complex system that detects and destroys foreign bacterial, viral and fungal microbe invaders and involves many different types of immune cells and chemical messengers. Its interactions with microbes are highly focused on certain common molecules found on all microbes, primarily bacteria, viruses and fungi. Many harmless but essential microbes play important beneficial roles on and within the human body and in all ecosystems on earth, yet they appear to thrive in the midst of an active immune system that is poised to destroy them. Since there was no death in the Garden of Eden, and therefore no disease-causing microbes, our understanding of both the antimicrobial actions of the immune system and its ability to tolerate good microbes may give us clues to how the immune system operated in the primeval garden.

1

Introduction

Have you ever wondered if Adam and Eve had an immune system in the Garden of Eden before the fall? If so, what might its purpose have been? By studying how the immune system works today, we can identify certain phenomena that may help answer these questions.

The immune system is a wonder of design and complexity. It's a sensory device that protects us minute by minute against foreign invaders. Immune cells are central to the function of the immune system and act as sentinels, messengers, weapons, soldiers and clean-up crews and can even help repair wounds. And you might even wonder if our bodies had an immune system before the fall in Genesis 3. If so, what was its role if there were no diseases or decay?

Certain phenomena we observe today may contain answers to this question. For example, it is intriguing that the immune system can detect and potentially neutralize over 1400 different species of infectious microbes within a human body that also contains over 70 trillion benign, or helpful, bacteria and viruses, which make up the microbiome [nat11]. Bacteria, viruses and fungi are classified as **microbes**, and the **microbiome** is a name for all the beneficial or benign microbes that live on the human body. Microbiome microbes are thought to exist in a state of balance with the human body and promote health [Gom20]. You might think, then, that immune cells can distinguish disease-causing microbes from beneficial microbes. However, this is not necessarily the case, because immune cells use proteins on their surfaces called **receptors** that can detect both beneficial *and* harmful microbes. (More generally, all cells have proteins on their surface that act as receptors which bind to specific molecules and can inform the cell about its environment.)

Another curiosity is that the immune system has a very narrow focus — a phenomenon that will be discussed below. For instance, the number of immune cell receptors that are responsible for activating the immune system's response is small [LW21]. Once activated, however, a massive variety of new receptors are made to help neutralize invading infectious microbes.

Understanding these phenomena — how these receptors work, why the initial receptor interface is narrowly defined, and why immune cells can detect both harmful and beneficial microbes — may give us clues to the original role of the immune system and how it distinguishes friend from foe. For instance, could the function of the immune system in God's primeval good creation have been designed to preserve the beneficial microbiome and keep it free of unwanted microbes? Is this also the reason, then, that the immune system is very specifically tuned to only react with a few foreign proteins found on microbes, as we will see in the following sections? In this paper, we will explore these mysteries and see how they might shed light on the function of the immune system in the Garden of

Eden.

Clues to gaining understanding about this will come from a basic understanding of how the immune cells and their receptors work and function, which we will describe in the upcoming section on immune system basics. But first, let's start by considering the origin of the immune system and its primeval function.

2

Garden Variety Immunity: The First Immune System

To understand the role the immune system may have played before the fall, it is natural to wonder whether there were infectious, disease-causing microbes in the Garden of Eden. In this section, we will briefly contemplate this question.

What was the original immune system like? Did it exist? Before Adam and Eve sinned, in the Garden of Eden there was no death, pestilence or disease (Genesis 1). However, could Adam have scraped his knee? If so, the immune system could have been involved in repair but was probably not needed for defense against infectious microbes. Recently, we have discovered that some of the most abundant immune cells in our blood, called **phagocytes**¹, are involved in wound repair, helping to repair the tissue in a way that is similar to a cell-based suturing process [WJS⁺07]. But let's get back to the elephant-in-the-room question. *Were there infectious microbes in the garden?* Since microbes like bacteria and viruses have exquisitely designed complex structure, life cycles and biochemistry, we can predict that for most of them, they were part of God's good creation.²

Take a look at Figure 1, for instance, which illustrates bacterial complexity. In this bacterium we can see the **flagellum**, which is an acid-driven rotary motor which can turn at a rate of 1000 revolutions per minute and propel the bacteria in various directions toward food sources that it detects with receptors. The flagellum can be composed of over 30 parts. Also illustrated is DNA which holds the code to make proteins. This code is deciphered in several complex machine-like steps involving up to 80 different components. Also shown on the surface of the cell is a secretion device which is also intricately complex. Bacteria can possess up to seven different complex machine-like secretion apparatuses, where each secretion machine can contain dozens of parts. Bacteria use these machines to secrete factors to digest their food and absorb the nutrients. In addition, they can secrete antibiotics to curtail the advances of other competing microbes nearby. Two-way secretion devices further allow the bacteria to uptake messages from their surrounding environment and react to the message. For example, they can take up antibiotics for analysis and then release them before they can harm the bacteria. In short, such carefully designed complexities suggest that even infectious microbes may have been part of God's original design. But what were they doing?

We now know that most microbes on earth are part of a life-supporting net-

¹ Phagocytes derive their name from a term which means "to eat." The common function among phagocytes is to engulf foreign entities that enter the body, for instance foreign bacteria. However, they have other roles like warning other immune cells of the presence of foreign invaders.

² Some viruses are very small and look like pieces of larger viruses. It could be postulated, then, that some viruses were created for good functions in the garden and others were derived during the decay processes in the fallen world.

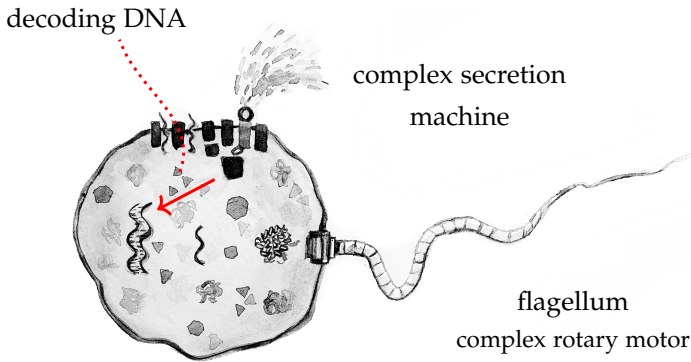


Figure 1: Bacteria and viruses can appear simple but, in reality, contain complex biochemistry and complex structures.

work or “biomatrix,” with many working together to recycle a great number of the atomic elements [Fra].³ In the case of bacteria, for instance, a very small fraction are involved in disease processes, and we could easily predict that less than 0.01% or fewer species of bacteria are involved in causing illness in living organisms today.⁴ We also know that for some bacteria that can promote world-wide scourges like cholera, many of their toxins can be involved in beneficial activities [FW]. The bottom line is that there were no infectious microbes actively causing disease in the perfect garden.

So, if the human body had an immune system in the garden, what was its function? As mentioned in the introduction, some clues to this question may lie in certain phenomena we observe today, such as the fact that the immune system is very narrowly defined and that it seems to interact with both “bad” and “good” microbes without discrimination. But to understand these phenomena, it’s important to first understand the basics behind how the immune system works today.

³ Microbes are involved in major recycling events like the carbon, oxygen and nitrogen cycles. Microbes can even recycle metals and eat oil and rusted metals. The Titanic may disappear from the bottom of the ocean in the near future, as it is being eaten by rust-eating microbes.

⁴ This is based on the estimate of 30 million for the number of species of bacteria on earth and 1000 for the number of bacterial species that are infectious microbes. Actually, 4–600 species of infectious bacteria have been described or postulated to exist and make up a large chunk of the 1400 infectious microbes which includes bacteria, fungi and viruses. The estimate of 30 million was derived from the DNA sampling of water and earth samples.

3

How the Immune System Works: The Basics

How does the immune system work? In this section, we will see that the immune response occurs in two phases. In the first phase, called the recognition phase, special cells known as “innate immune cells” detect infectious microbes and alert other cells called “effector cells” by sending chemical signals. Then the second phase begins, which is called the response phase. In this phase, the effector cells work to eliminate the infectious microbe.

A functioning immune system involves two important phases, namely recognition and response.

The Recognition Phase

Infectious microbes are identified by “sentinel” cells in the immune system that bear specific receptors for the outside and inside parts of the infectious microbes. These sentinel cells are also known as **innate immune cells** because they are the first line of defense and are ready to battle any foreign substance. There are also **effector cells**, which can adapt and change in response to the infectious microbe and produce an “effect” that is tailored specifically to the infectious microbe. The innate cells, on the other hand, are not as specifically fine-tuned to the infectious microbe and do not need to take time to adapt. They are ready to respond, and they work together with the receptor cells.⁵ It’s a great partnership.⁶

In more detail, innate cells are found throughout the body in immune system organs like the spleen and lymph nodes and also in the blood and tissues. The innate cells interface with certain infectious microbe parts using receptors, and then they report what they find by secreting factors called **cytokines** to alert the effector cells. A deeper look at this process will be given below, but for now, know that cytokines are extremely important factors similar to hormones, as they send chemical signals from cells to cells (Figure 2).

The Response Phase

After the recognition phase, the effector cells become activated to begin the response phase by alerting more effector cells. Together they can eliminate the infectious microbe threat by making products like antibodies or cytokines. Recall that

⁵ Adaptive effector cells are mostly in the category of cells we called **lymphocytes**. There are two categories of lymphocytes called the **T cells** and **B cells**. Together, they provide most of the “effector” response. The T cells are also the brains of the immune system and can direct many responses. This is also indicated by the HIV virus infection process which results in T cells being invaded and destroyed, thus suppressing the immune system and causing acquired immunodeficiency or AIDS.

⁶ Innate immune cells offer the first line of defense in the immune system, and they are ready to function immediately upon encountering the foreign infectious microbe. They are different from the more specific effector immune cells which often lay in wait for a signal. Once they receive a signal, they are activated to react to the intruder. They are considered to be more specific because they can induce a specific pathway of events to neutralize the invader, and they can develop memory about the specific invader.

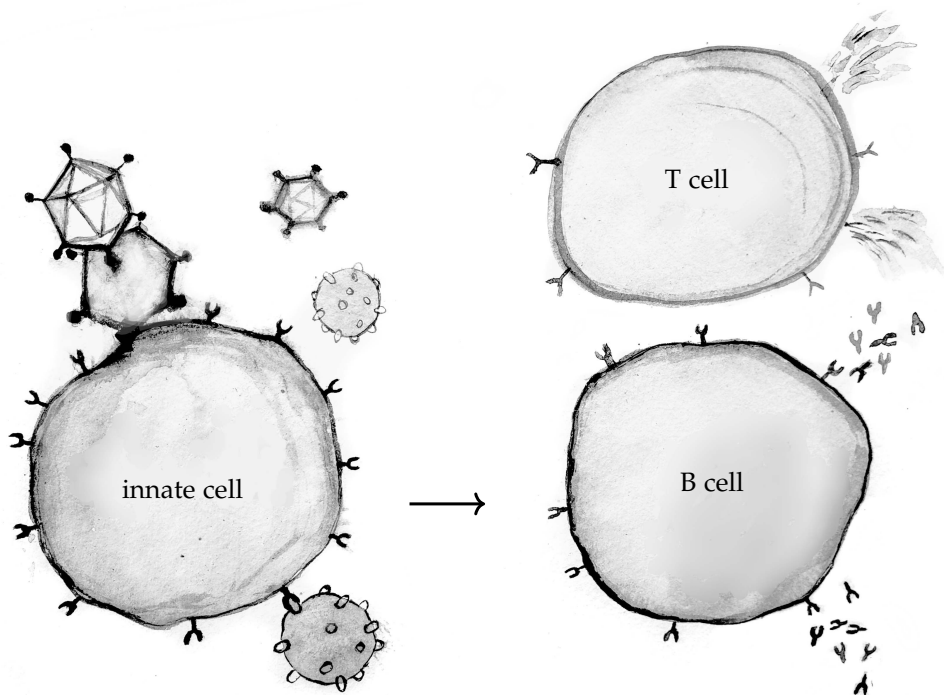


Figure 2: Innate cells, also called sentinel cells, are often the first line of defense against invading infectious microbes. Many of them are phagocytic-type cells which are found both in blood and tissue. Innate cells have very general receptors which interact with the surface of all viruses and bacteria. When they encounter and use their receptor to bind to a suspected infectious microbe or a piece of an infectious microbe, they can often engulf the foreign invader to destroy it. This triggers the innate cell to send "cytokine messages" to other cells, called effector cells, which include lymphocyte cells called T cells and B cells.

cytokines are chemical signals that allow cells to communicate with each other, and so they cause the response phase to amplify because many cells become alerted to the presence of the invader. **Antibodies**, on the other hand, are proteins which bind to infectious microbes and, along with other factors, specialize in destroying the invader. The antibody response is a significant part of the immune response, and the details will be discussed in depth in Section 5.

Now, in addition to sending signals and making antibodies, some effector cells also release toxic cell factors quickly and abundantly. Some phagocytes that were quiescent until this point are also activated and can spread pseudopods (arms) around the invader and internalize it. Once inside the phagocyte, a plethora of toxic enzymes and toxic oxygen species destroy the invader inside a compartment [PSJO19, chapter 1].

By now you can see that the response phase is intense and that distinguishing an infectious microbe from our own good bacteria or tissue cells is important to avoid “collateral” damage. To appreciate how intricate this is, let’s take a closer look at how the recognition process works at the receptor level.

4

Can You Hear Me Now?

Winning the Battle With Good Intel

In the previous section, we noted that innate immune cells can detect an infectious microbe and then alert nearby effector cells for help. But how are the innate cells able to detect the microbe in the first place? The answer lies in certain molecules found on the cells' surfaces, called receptors. In this section, we will discuss these surface structures and the recognition and response phases in more depth.

As we have discussed, most all immune cells are involved in some type of communication or interface with other immune cells or the infectious microbe. The interfaces involve exquisite molecular-level interactions between the immune cell's surface proteins (the receptors) and the surface structures of infectious microbes.

In fact, all living cells on earth contain cell surface structures made of proteins and carbohydrates, fats or lipids. Many cells have very similar or identical surface markers, but many cell *types* can have very *specific* surface markers that make each cell or cell group unique. For instance, red blood cells have surface markers that indicate blood type such as type A or B or O. As another example, there are some molecules that are only found on the surface of certain individual infectious microbes. But there are also other molecules that appear on the surface of all microbes, both benign and infectious.

In the case of an infectious microbe, the specific binding of receptors of the innate and effector immune cells to that microbe are essential to neutralizing the invader. However, timing is critical. If an infectious microbe escapes detection and reproduces, then there is a point in time in which the invader can overwhelm the "recognition and response" mechanism described above. In other words, slow immune cells can cause problems.

Since we know that this receptor recognition system was designed, we can ask the following question. To quickly recognize an infectious microbe, would it be better for an innate cell to search for the common surface features found on all microbes, or to only search for those that are unique to individual infectious microbes?

We now know from research that innate cells respond to the common surface features found on all microbes [PSJO19]. In this approach, we see the brilliance of the Designer. The innate cells need to make a fairly quick find of invading infectious microbes, so the immune response can take place in a timely fashion. So instead of using specific recognition receptors, which may take longer to find the specific surface of the invading microbe, the innate cells scan the infectious microbe landscape with a receptor that is directed toward the general surfaces found on most microbes. This helps ensure that the infectious microbe is "found out" quickly.

Calling a Friend For Help and Gaining a Trillion Helpers

What's incredible and very striking about the next step is the quick response from the effector cells as they are activated by the innate cells. If we could see it on a battlefield, it would be "shock and awe." It can involve secretion of antibodies,⁷ enzymes or toxic oxygen components — even hypochlorous acid (bleach) to digest the infectious microbe. Engulfment of the infectious microbe by an immune cell also can take place, as well as destruction of body cells which are infected. Infectious microbes can also be marked with sticky proteins and antibodies making a bigger target for phagocytes. It's quite thorough and effective. Sometimes it's too effective, as inflammation can occur.

In many cases, most all of these responses are required to clear the infection. Antibodies are particularly crucial to this part of the immune response, so let's take a closer look at them [Woo09].

⁷Notably, the production of antibodies typically occurs after innate immune cells recognize a foreign invader. However, as we will see, our innate system could identify our own good bacteria in the same way.

5

"Blue Light Special" Life Savers

During the immune system's response phase, effector cells are able to attack infectious microbes by producing antibodies. Antibodies play a vital role in this part of the immune response, so it's worth understanding them — what they are and how they help destroy bad microbes — in a little more detail.

Antibodies (Ab) are life-saving protein receptor molecules which are also crucial to long-term health in humans, mammals and other creatures. They can be found on the surface of immune cells but are mostly found as unattached proteins. Antibodies are produced by effector **lymphocyte cells** called **B cells** at a rate of over 100,000 Abs per minute per cell.⁸ Antibodies cannot destroy anything by themselves, but instead they are very efficient “taggers” of infectious microbes. They are like the blinking blue light you might find in a store to advertise a special sale, except in this case they inform nearby phagocytic cells and cells which secrete membrane-destroying proteins to encounter and destroy the invader.

How does an antibody protein inform an immune cell? They do this by changing their shape slightly when they bind to an infectious microbe. “Antibody-informed” phagocytic cells can then seek the infectious microbe and destroy it. Antibody tagging is very efficient, as high concentrations of antibodies can be readily infused into tissues from the protein rich blood serum.

How do antibodies “tag” or bind to their target? Antibodies are literally “Y”-shaped proteins that have two binding sites for certain molecules found on the surface of infectious microbes (See Figure 3 which illustrates antibody protein structure.) We call these surface markers **antigens**. Therefore, antibodies do their work by binding to antigens. However, antibodies can recognize many different parts of the antigen, where each small part is called an **epitope**. This allows antibodies to be very efficient at surrounding the entire antigen (Figure 4). In fact, thousands of antibodies with unique binding sites are made to each foreign antigen found on the surface of the invading infectious microbe.

⁸ The B cell is named after the Bursa, which is the anatomical location where B cells are found near the cloaca in the tail region of birds.

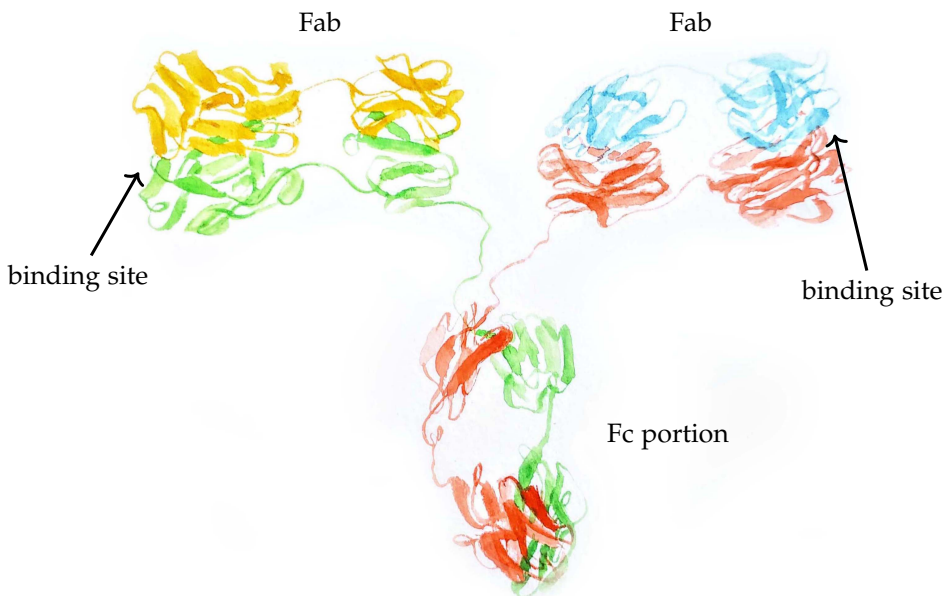


Figure 3: Proteins are made of long chains of amino acids. These chains fold in a predetermined manner contributing very specifically to protein function. An unfolded protein has no function. This ribbon diagram shows the antibody light chains in yellow and blue. The heavy or larger chains are in red and green. Both light and heavy chains contribute to the binding site of the antibody. The binding of antibodies to antigens, which are surfaces and internal structures found on foreign infectious microbes like bacteria and viruses, causes them to be neutralized and ineffective. This binding also results in the antigens being recognized by phagocytes and other immune cells. This sets off a cascade of events which cause removal or destruction of the infectious microbe.

A single B cell can make many different antibodies by using molecular methods to make slight changes in the antibody binding site. The binding sites found at the end of the Fabs are very narrow grooves and only bind to a very short peptide (short piece of protein) of the antigen. The Fc portion of the antibody is recognized by receptors found on phagocytic cells, which are cells that can engulf the foreign invader and destroy it.

The Fab or **Fragment antibody binding** portions of the antibody were named after the antibodies parts that were derived after digestion of antibodies with enzymes during the first experiments used to determine antibody structure. The Fabs were determined to be the binding sites for antigens, whereas the Fc or **fragment crystallized** was named for its ability to crystallize at low temperatures. The Fc portion is now known to interact with immune cell receptors.

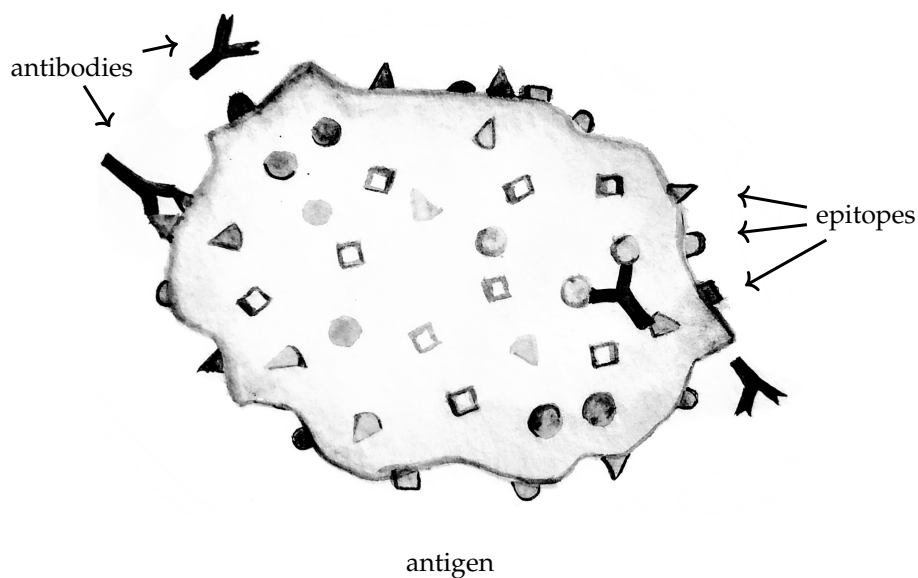


Figure 4: Antigens have antibody binding sites called epitopes. The large structure shown here is the antigen which contains smaller epitopes on its surface. Antigens are molecules typically found on the surface of a virus or bacterium. Antigens were first defined as substances that elicit antibodies when injected into a laboratory animal like a rabbit or mouse. Antibodies bind to the epitopes, and many different epitopes can be found on one antigen. This makes it possible for an immune system to make many different antibodies, each binding to a unique epitope. Also, during this antibody response time, a mixture of slightly different antibodies can be made that bind to the same epitope. This makes antibody binding more efficient.

Summary So Far

Let's now review where we are at. We noted that the immune system starts with a recognition process involving innate immune cells. They lie in wait for infectious microbes in our blood stream and all body tissues. Once a receptor is engaged, the innate immune cell can send a "cytokine message" to a nearby effector cell. That effector cell could be a phagocyte or a lymphocyte, such as a B cell. If a B cell binds to the cytokine message, then that engaged B cell can produce antibodies.⁹

There's a Lymphocyte School Nearby.

Perhaps at this point you have the following question: How do B cells, which make antibodies to foreign bacteria and viruses, know that the bacteria and viruses are foreigners? B cells could make antibodies to our own good bacteria and even to our own cell surfaces and proteins. A good part of this remains a mystery, but we can think about two possibilities.

One possibility is the standard evolutionary textbook answer that, over time, B cells made antibodies to different foreign microbes by random processes and that the B cells with reactive antibodies were "selected" by natural selection. The second possibility is that the antibodies were pre-designed and created to respond to potential infectious microbes. The evolutionary solution seems problematic here because the making of antibodies inside a B cell is not simple to begin with. So even though this remains a mystery in biology, it certainly supports the idea that a merciful Designer was involved in creating antibody diversity, so that each human has a full repertoire of antibodies ready to respond to infectious microbes the body has never seen before!

Also, some level of re-educating B cells needs to take place to avoid making antibodies that interact with the human body or "self." We now know that in the liver of the developing human fetus, individual B cells begin an education process

⁹ In many cases, this B cell activation is helped along by helper T cells, another kind of lymphocyte. The helper T cell can actually bind to a receptor on the B cell, helping to activate it to produce antibodies. Many new B cells and T cells are made and, in some cases, this cell reproduction can take five to seven days. This is why when we have a virus "cold" it can take a week for the cold symptoms to subside. However, if a B cell has already seen the antigen of a cold virus, then it can develop memory and be ready to make antibodies immediately. Thus even though there are many kinds of cold viruses, you probably have been protected from getting the same cold virus multiple times because of the memory B cells.

which will culminate in the secretion of finely tuned antibodies that are directed toward a specific antigen found on an infectious microbe that the body may someday encounter. During that education process, B cells that make self-reacting antibodies are eliminated. In the lymphocyte school of the pre-born human, the final grade given is truly final [FCLCo6]!

Some of the B cells are then kept for a lifetime as long-term B stem cells. Stem cells are pluripotent cells, meaning they can keep on dividing to produce more B cells. They are also immortal, in a way, with the ability to be transplanted to others. This ability to retain cells that are ready to fight against previously encountered infectious microbes is part of the phenomenon called **immunological memory**.

The Battle of the Clones!

The next step is where it gets even more interesting, fascinating and dicey, literally! Let's start at the beginning again. An innate cell recognizes an infectious microbe. It sends out cytokine signals activating other innate cells and a host of different effector cells, including B cells. Each B cell that recognizes antigens on the infectious microbe is selected to begin to clone, thus making more long-term memory B cells and can start the process of making antibodies. These particular B cells are educated as to what kind of antibody to make by also getting some instructions from T cells, which have responded to the alert and picked up some pieces of the foreign infectious microbe (Figure 2).

The T cells then help select certain B cells that have been pre-programmed to make a variety of antibodies that will bind to the selected infectious microbe. Why all the "extra" antibodies? The partial answer to that question is that antigens can be fairly large compared to the binding site of the antibody, so each antigen on the surface of the infectious microbe can have multiple binding sites, which, you may recall, are called epitopes. Each epitope can be shaped differently from the others. For instance, see the illustration of gene expression in Figure 5.

Producing antibodies that can bind to each epitope can cause the antibodies to surround the antigen, thus preventing the infectious microbe from binding to body cells where they can inflict damage or possibly even enter the cell, which is the specialty of viruses and some bacteria. If a virus gains entry, then it can hijack the cell and make many copies of itself, causing a ramp up of the infection which could be devastating and even deadly.

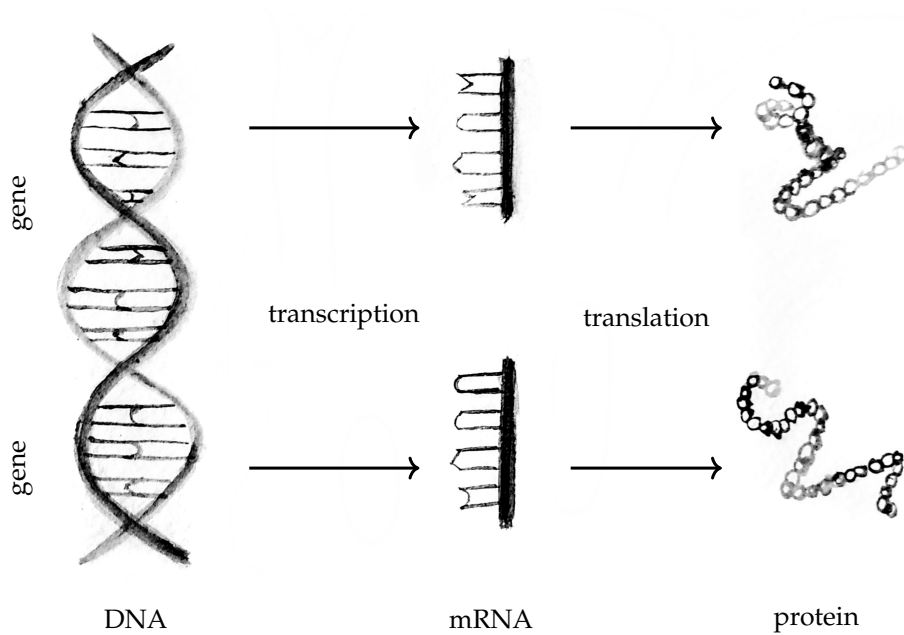


Figure 5: Proteins are made when the DNA code is first copied to RNA in a complex process called transcription. The RNA is then translated by complex protein machines to make the protein. In each case a strand of smaller pieces called nucleotides or amino acids form a nucleotide called a nucleic acid or an amino acid chain called a protein respectively during this process of making a protein from the nucleic acids. This process was elucidated in the 1950s and 60s and has been called the “central dogma” of biology. There are multiple genes that are dedicated to the construction of antibodies.

The intricacies of the antibody response continue even further at the DNA level. The next short section, labeled as optional reading, contains some of these highlights for the curious reader.

6

(Optional)

B Cell Factories

This optional section contains a closer look at how antibodies are made from DNA.

Antibodies, like all proteins, are constructed using a process that starts with a code on the DNA. This code region is called a **gene**. The first step in the decoding process involves copying or transcribing the gene into RNA, a process called **transcription**. The second step in the decoding process is the translation of the RNA to make the protein (Figure 5). However, there is an interesting problem here. The human body can make up to 10^{13} or 10^{14} different protein antibodies, but the human DNA contains only roughly 21,000 genes coding for about 100,000 proteins.

How, then, can the body make 10 trillion different antibody proteins with only 21,000 genes? The secret lies in the DNA itself. The DNA code used to make an antibody is divided into two main regions because each Y-shaped antibody molecule contains two groups of proteins, namely light chains and heavy chains. There are two light chains and two heavy chains in each antibody, and all four protein chains bind together to make a single Y-shaped antibody. See Figure 6, which shows DNA coding regions of the antibody heavy chains.

Also, each light chain and heavy chain coding region on the DNA has several copies of alternate genes for each light and heavy chains. An antibody, then, can be constructed from a choice of several different light chain genes and a choice of several different heavy chain genes. This process is called **gene shuffling** at the DNA level. Therefore, a single B cell can make several different varieties of antibodies for the same antigen using different combinations of heavy and light chains. To make different light and heavy chains, the DNA is cut and rejoined or spliced. In fact, this DNA shuffling only occurs in the DNA found in B cells in humans and mammals and nowhere else. If this splicing and shuffling of DNA happened in the entire DNA, it would be catastrophic.

So, to revisit the question introduced earlier, why are so many antibodies needed in the immune system response? For one, infectious microbes may have several antigens that are recognized by antibodies, but some antigens also lead a double life as potent and lethal toxins. To minimize the release of a toxin, a thorough antibody response is required.

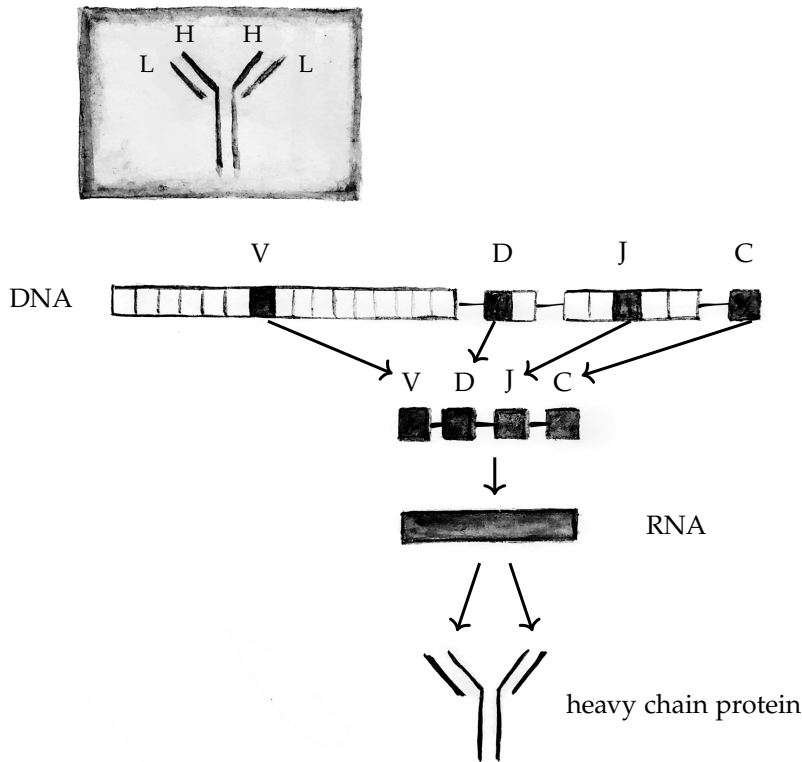


Figure 6: This illustration shows the making of the antibody heavy chain starting with antibody gene shuffling. The DNA code to make antibodies is a region of DNA that can be shuffled to make varieties of a single antibody type directed against a single antigen. For instance, antibodies are made of four protein pieces to make a "Y" shaped protein molecule. There are two light chains (L) and two heavy chains (H). The DNA gene region for light chains and heavy chains are separated on the DNA. Shown here is the DNA region for the heavy chains. Each heavy chain is made of a single protein which is coded by four DNA regions, V (variable), D (diversity), J (joining) and C (constant). The V and D regions form the binding site of the antibody sites which vary greatly among all antibodies. The J and C regions make up the constant regions of the antibody which have less variable sequences among antibodies. Each of these regions are eventually placed near one another to make a final transcript, which is transcribed into RNA. The RNA code is then translated into protein. Because different combinations of VDJC can be made by this shuffling process, thousands of different antibodies directed toward one antigen can be made. This can cause this group of antibodies to cover slightly different regions of the antigen (epitopes) providing a more effective response to the invading infectious microbe.

7

The Narrow Focus of the Immune System and a Proposal

We are now ready to revisit our opening question from Section . What might have been the role of the immune system in the Garden of Eden? In this section, we will see how some of the ideas discussed throughout the article may help shed light on this question. In particular, we propose a model for the immune system's original function, namely as carefully designed "filter."

Now that we have looked in-depth at how the immune system works and seen how intricate it is, let's take a step back and revisit our initial line of questioning. What role did this complex immune system play in the perfect garden, before the fall? Is it possible that some of the phenomena described in this article could help answer that question?

Overreaction and Cross-Reaction

Take the immune system's narrow focus, for instance. Even though the human body can make trillions of different antibodies, most of them typically bind to a small subset of molecules found on most microbes. However, in certain circumstances, the immune system seems to overreact. For instance, the immune system is very efficient at eliminating many infectious microbes, but some that persist can activate the immune system to a very high level causing life-threatening inflammation. This appeared to happen often with COVID-19 infection during the pandemic that began in 2020. Could it be that if our immune system was tamer, then we would have had better survival rates against SARS-CoV2? Perhaps.

Also, our immune system appears to overreact in other ways. For example, it interacts with entities like plant spores released from plants causing allergies. And there are immune related sensitivities to metals, asbestos, fabrics and insect bites. Since many of us have allergies, they seem to be a minor nuisance, they are not typically deadly, and they tend not to produce severe illness, although they can be seriously problematic for some individuals.

In addition, a good number of the immune cells and antibody types that appear to be specialized to bind to allergens also bind and neutralize parasites. Parasites—for instance, tapeworms—are larger than microbes but also cause disease in humans across the world. This is another good example of cross-reaction. In our fallen world, could our immune system be *overreacting* with some microbes and *cross-reacting* with pollen and other substances that it was never intended to interact with? This seems probable. It also shows why perhaps the immune system seems to be so narrowly defined to interact with antigens found on bacterial, viral and parasite surfaces of only a few microbes—that is, to avoid cross-reactions.

I think a clue to the design of God's original "very good" immune system is perhaps found in this phenomenon of how the immune system seems to be so narrowly focused on a few infectious microbes.

A Proposed Model

So let's now consider a model for how the immune system may have worked in the perfect garden by first looking at some summary statements derived from the analysis of the data and phenomena we have discussed so far:

- The immune system appears to be designed to primarily interact with only a few common molecules (antigens) found on a majority of microbes.
- The human microbiome only harbors a subset of microbial species compared to all the microbial species on earth.
- It's postulated that most microbes on earth are active in a life-sustaining network—the “biomatrix” on earth—as compared to a relatively few infectious microbes [Frao8].
- The immune system possesses the ability, via its receptors, to recognize many of the beneficial microbes on the human body as well as infectious microbes by interacting with antigens common among them.
- The immune system appears to be tuned to destroy invading infectious microbes using receptors, while it avoids or does not typically harm the beneficial microbes.
- Greater than 1000 species of bacteria and viruses exist on the human body in millions of copies and do not cause illness while, for instance, only a few of the 200 infectious viruses that are mostly neutralized by the immune system, persist long term on the human body [Fra22].

The general trend in these summaries is that infectious microbes are relatively rare in nature, in humans, and in ecosystems. Also, although the human microbiome is small in numbers and species count compared to global ecosystems, their members are prevalent in the human body at numbers greater than the number of human cells which make up the body. In addition, the immune system has common receptors which interact with all the infectious and benign microbes, yet it appears to only react with a small subset of microbes.

From these conclusions, we can postulate the following model. The first created immune system may have been a filtering system to help maintain the human body microbiome in the perfect garden, to keep it from being contaminated with extra-corporeal micro-organisms, and to help retrieve microbes from the garden that

could be used for replacement of underpopulated or lost microbiome microbes. This would help explain why the immune system has receptors to interact with microbes in general. And correspondingly it helps us understand how after the fall, as the system decayed somewhat, it began to cross react with other creatures and substances inappropriately. This immune-system-as-filter model is illustrated in Figure 7.

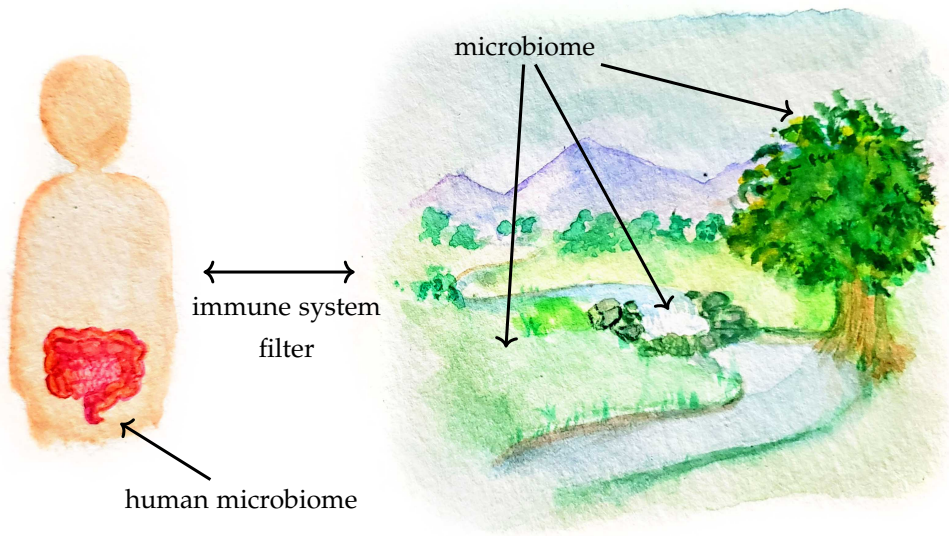


Figure 7: In the Garden of Eden we can predict that there was an absence of organisms which could cause illness in humans, as it was a death-free environment. However, we can also postulate that microbes were present in the garden because they are complex and show design features and are involved in many beneficial activities on earth including the recycling of nutrients which support life. In fact, microbes are the most numerous biological organisms forming a life-supporting matrix or microbiome on the earth. The human gut microbiome is the densest ecosystem on earth, containing thousands of different species of microbes. Since our immune system is designed to recognize and attach to general features of all microbes, we can predict that perhaps the original immune system could have acted as a filtering device that would help to maintain the human microbiome, allowing it to be populated by certain microbes from the surrounding environment while also preventing some from entering the human microbiome.

How did the immune system perform the filtering activity and make distinctions among the microbes as to what was beneficial or detrimental? And why would some microbes be beneficial and others be detrimental? We can get an idea about this discrimination activity for the following two reasons: first, so that the most beneficial microbes are secured in organisms or transferred to organisms, and second, to prevent the uptake of suboptimal or infectious microbes.

Although we do not know how this might have happened in this idyllic setting, we can formulate some hypotheses based on the fact that everything was “good” in the initial creation, and at the fall some organisms moved from the area they were created to be in to places where they acted differently, with some becoming infectious microbes. We can actually see this happening today. We call this phenomenon the **displacement hypothesis**, where good microbes in one location are infectious microbes in another location [Frao8, FW].

For instance, the common gut bacterium *Ecoli* has helpful strains (sub-types) that aid digestion as well as infectious strains that affect humans adversely. *Ecoli* O157 H7 is a strain of *Ecoli* that causes a deadly food poisoning of humans. It’s a proven killer. Interestingly, it is found in cattle, in what we believe is a natural reservoir. Spillage of cattle waste into crop fields is one way the bacterium is transferred to human food sources. Yet it appears benign in cattle and could be part of their beneficial microbes [HMH⁺19]. We could postulate, then, that if the immune system did encounter a microbe in the perfect garden which had the potential to be harmful, then it would have had abilities to avoid them or destroy them, thus performing the filter function.

We could also consider an example here to help us understand the displacement concept. We don’t think of the fuel we put in our cars or homes as evil. We know it is a good thing to have a running car and a heated or cooled home. However, we know that that same fuel could be deadly if it spilled on our car seat or dining room floor. We could use the same logic here as we consider the immune system and its design. We can make a case that microbes and immune cells in their proper place are helpful and even supportive of life on a global scale. In the wrong place, they both can be deadly.

In conclusion, in the Garden of Eden, the immune system would have acted as a perfect filter. But a glaring question still remains. *Why design an immune system to interact with both good and bad microbes without an apparent mechanism for distinction*

of the good versus the bad, which appears to be what occurs in our immune system? Furthermore, how do you avoid mistakes that result from trying to distinguish good microbes from bad microbes that look the same on their outer layers and surfaces? In other words, how do you stop the immune system from destroying the good bacteria, because they appear to the immune system as invaders? Also, it would seem that the immune system could also cause tissue-damaging inflammation during its interaction with bad bacteria.

It's All About Anatomy and Identifying Trojan Horses.

When we look at the human microbiome, the highest densities of members of the microbiome are in the gut and on the skin [SFM16]. These two places are actually sheltered from the immune system. Consider the gut for example, where billions of microbes representing thousands of species reside. It is the densest ecosystem on earth. No other place has thousands of species with such little real estate. Yet it is cut off from the immune system by several tissue layers and mucous. (Mucous is an amazing substance and barrier with complex protein and carbohydrates.) Furthermore, the bacteria of the gut microbiome may be covered in phages (viruses that specialize in associating with bacteria) which cloak their surfaces and cover their antigens, blinding the immune system in this area [Fra18].

The phages can also exist internally in bacteria and have the potential to eliminate the bacterium if its DNA is mutated. In addition, in humans, there is a specialized immune system that runs along the digestive track. It can use innate immune cells to actually reach into the gut cavities and sample bacteria looking for non-invited guests [MJF⁺21]. Also, skin is a tremendously good barrier to outside invaders as well as inside invaders. It contains multiple layers of strongly attached cells with an outer dead layer that is effective at shedding invaders also. The skin is so complex and important to life that it is considered to be an organ system.

And now we see why the immune system has the potential to interact with both good and bad microbes, for the very reason that any outsider may be a lurking, infectious microbe disguised as a good microbe. And because the immune system can recognize the surfaces of all microbes, it can shut down the ability of any “Trojan horse” microbe from entering the system if it breaches the barriers of skin and gut.

What a fantastic design. The immune system can interact with *all* microbes en-

sureing that it will also encounter illness-causing microbes. And the good and bad microbes are separated by anatomical barriers. This design feature is not really considered in immunology texts today, as the focus in those texts is on the complexity of the immune system and as something that evolved to promote survival. This leads to a challenge for evolution, because how does the human gut, for instance, evolve these important boundaries to keep out bad microbes, when it needs those boundaries a priori to keep out dangerous microbes and promote host survival? In addition, how do B cells evolve to make antibodies against many foreign substances before the human immune system has encountered those substances? There are so many aspects of the immune system that speak of design.

Summary

God is Relational and Wants Us to Experience Relationship via His Creation.

One final question to consider, then, is why not make a world where humans are made of completely different molecules than the rest of the living creation, so they avoid being invaded by sneaky foreigners?

One answer is obvious from Scripture. God made creatures to relate to one another. Relationship in God's created world provides a continual real-world prescient example of the relationship displayed in the Godhead. Thus, we have a world where we can relate to other humans and other creatures. The relational world also involves interaction, movement, touch and communication. We also know that God made an interactive world because "in Him we can move and live and have our being" (Acts 17:28). And that helps us make sense of our interactive physical and molecular world and helps us enjoy interacting with it, as we smell the flowers in our garden and partake of its bounty as food. Each food morsel, breath and activity involves churning and moving molecules around us and in us to support the mobile and interactive life that we cherish. The world God made allows us to move and thrive, but it also comes with boundaries that help preserve the uniqueness of each ecosystem and living creature. This also reflects the uniqueness and glory of the Creator.

In summary, the human and mammalian immune systems are exquisitely designed systems that protect us moment by moment. The marvel is that this system

shows a flexible design such that it could operate in two very different worlds. One in which the immune system could have acted as a filter to keep what is good in its proper place and another that allowed it to morph into a system that offers protection from many disease-causing entities. Furthermore, the multitude of pre-assigned antibodies not only speaks of a Designer but of a grand loving Creator who, with forethought and forbearance, cares for His human creation. This should draw us to worship and live lives of gratitude before our Creator King.

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