

HOW DO WE FIGHT FOR OUR LIVES?

THE POWER OF INNATE AND ADAPTIVE IMMUNITY

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ABSTRACT

The current understanding of the evolutionary emergence of the immune system in organisms is still unclear to this day. It is acknowledged that some aspects of the immune system definitely improved the survival of living organisms, whether it be plant, or bacteria, vertebrates or invertebrates. The different immune proteins and complexes are constantly being studied to understand exactly how the immune system play a role in the human development. In this review, we propose a developmental and evolutionary explanation to how we present an immune system, understand the selective pressure in immune cells, explain the relationship of bacteria or viruses to their host, and analyze the augmentation of human vulnerability to diseases.

KEYWORDS: IMMUNE SYTEM, EVOLUTION, INNATE IMMUNITY, ADAPTIVE IMMUNITY

INTRODUCTION

The idea that the **immune system** is able to expand its abilities over time in a way that it can automatically perform its defense mechanisms is difficult to grasp as it involves a very complex process with thousands of microorganisms working together. Some of the more important players of the immune system cells include **macrophages (M ϕ)**, **neutrophils**, **dendritic cells(DC)**, **natural killer cells (NK cells)**, **T-lymphocytes (T-Cells)**, **B-lymphocytes (B-Cells)**, and **Eosinophils**. These cells have an **intraspecific** relationship among each other and are able to project and enhance the production of immunity to pathogens and diseases. The main function of the immune system, as a whole, is to protect the host from any threats that could terrorize the host's body, developed in order to better cope with survival against disease (Marin,

J.M. 2017). For instance, the immune system is solely responsible for an individual to sneeze during times of high pollen concentration in air quality. These inflammatory responses are triggered by the innate and adaptive immune system collectively.

THE EVOLUTIONARY HISTORY OF THE IMMUNE SYSTEM

There are two main aspects of the immune system: the **innate immune system** and the **adaptive immune system**, both of which have then worked together to increase the efficiency of the other. The emergence of the innate immune system has been demonstrated to be similar to the evolution of unicellular organism, **protozoans**. Innate immune system possesses a mechanism that is closely related to the **endosymbiotic** genesis of the mitochondria and chloroplasts. The origin of mitochondria and chloroplasts were from the engulfment of a bacteria into a cell which ultimately created an inner membrane and over time, adapted as the host cell's own organelle; this evolutionary event was found in fossils aging about 1.5-1.8 billion years old (Garg, et al 2017). Much like endosymbionts, a process called **phagocytosis** is used in the innate immune system's ability to fight infections. Phagocytes like macrophages, dendritic cells, and neutrophils are molecules of the innate immunity that engulf the infection or virus into the cell and destroy it (Aderem, 2003).

Neutrophils and M ϕ both act as the main phagocytes that mediate the killing of fungal pathogens as they are the first leukocytes to migrate to the infection site. Neutrophils are the most abundant leukocyte and function by secreting extracellular traps that capture microbes, allowing them to be phagocytosed. M ϕ are then recruited to the infection site and replace the neutrophils by killing and removing neutrophils. Once enlisted to the infection site and replaced the neutrophils, M ϕ can then envelop the pathogen into a phagosome where it releases granules

or chemicals that are toxic to the pathogen, transforming it to an antigen. (Segal, 2005).

Phagocytes have the efficiency to attack fungal cells due to the abundance of the neutrophils and constant regulation of the epithelia by the macrophages.

The significance of these leukocytes has then been continually tested on mice by observing the changes in the mice health after knocking out specific cells or proteins in their immune system. An instance is by observing the susceptibility of an individual to acquire the fungal infection, *Candida albicans*. Those who have neutrophils and macrophages knocked out from their systems, or those who have neutropenia, a state where an individual has abnormal neutrophils, are more likely to be infected by *Candida albicans* (Erwig, et Al 2017). Studies also show that depletion of M ϕ causes an imbalance in their homeostasis causing reverse obesity and decreased immunity. Mice were used to model the human immune system to see the effects of M ϕ knockout and results show that depletion of M ϕ causes extreme loss of body weight in fat and lean mass. To recuperate with the lack of M ϕ , neutrophils began to infiltrate, and appearance of pro-inflammatory **cytokines** were observed (Feng, et. Al, 2014).

The cells of innate immunity act as the first system to resolve any complications or changes in the body, acting in seconds after a problem has occurred. It is often referred to as the first line of defense against foreign particles such as allergen, parasites, or bacteria. When an intruder poses a threat in the body, the innate immune system is automatically triggered by different signals. (Nicholson 2016). An antigen or a pathogen enters the body which triggers phagocytes to be recruited to the site of infection where they use a structure that recognizes specific patterns on the pathogen ultimately allowing the phagocyte to determine that the antigen is harmful.

Using the tool of a **pattern recognition receptors (PRR)** in the germ-line cells induce different immune responses that ultimately allows the body to attack harmful antigens.

Pathogen-Associated Molecular Patterns (PAMPs) and **Damage-Associated Molecular Patterns (DAMPs)** are two types of patterns the host's cells recognize via PRR in order to differentiate from 'self' and 'non-self' cells, meaning that PAMPs and DAMPs are able to distinguish whether a molecule is harmful, damaged, or directly a host's own healthy cells. (Lee, et. al 2015). Pathogens, mutated cells, and viruses conclusively present a pattern that allows phagocytes simulated by the PAMPs and DAMPs to recognize that these particles are foreign. Once the PRRs on phagocytes have recognized a PAMP or DAMP on a toxic particle, the neutrophil or macrophage can then engulf the pathogen and release **perforins or granzymes** that induce the cytotoxic responses that kills the pathogen. These also often induce production of certain cytokines that can then activate the adaptive immune system to begin its responsorial actions.

HOW ADAPTIVE IMMUNE SYSTEM DERIVED FROM THE INNATE IMMUNE SYSTEM

The emergence of **gnathostomes**, or jawed vertebrates, trace back to over 400 million years ago. (Brazeau et al. 2015). Consecutively, the adaptive immune system also emerged which led researchers to believe that the adaptive immune system is an instrument that was adapted by jawed vertebrates, allowing better survival because of the specificity and the memory it can hold. Researchers led to conclude that the adaptive immune system's evolution occurred from two paths: the emergence of the **RAG transposon** and the duplication of whole genomes. Japanese-American evolutionary biologist, Susuno Ohno, suggested that the two whole genome duplication that gnathostomes underwent is one of the key components of the evolution of the

adaptive immune system. Though this proposal is still poorly understood and contain very few evidences, it has been a widely accepted hypothesis and has then been classified as the adaptation that led to the evolution from the innate immune system to adaptive immune system. (Flajnik, et al. 2010) Unlike innate immunity, adaptive immunity holds the capability to create a “memory” in which it studies and learns the antigen presented and remember it for future references. As a result, when a host is presented with the same type of antigen for a second time, it allows the immune system to respond to the antigen and destroy the pathogen much faster. (Joosten, et. al 2018).

The adaptive immune system also utilizes PRRs to recognize pathogens, but as innate immune system is very broad and general, the adaptive immune system is the complete opposite (Figure 2A). It requires specificity in which there are different antibodies activated by different distinct antigens. The structure of antibodies has a **constant region (FcRegion)** that is membrane bound and interacts with immune cells which are displayed similarly among all isotypes. It also has a **variable region** that interacts with antigen and are the cause of the specificity of the antibodies. The variable regions of antibodies are made up of about 1 to 35 amino acids that are folded uniquely, conformed variously, and hold different affinity according to the antigen hence it is only able to bind to very specific antigens (Stanfield, et. Al 2014). The adaptive immune system also requires the activation of the innate immune system before it is induced. This is solely because the adaptive immune system must wait for phagocytes to process pathogens to release the antigens which are then recognized by the antibodies present on B- lymphocytes.

INNATE	ADAPTIVE
<ul style="list-style-type: none"> • First responders that resolve complications or changes in the body. • Pattern Recognition Receptors- <ul style="list-style-type: none"> • Receptors that can recognize different patterns or codes • i.e. TLR5- flagellum • NK CELLS 	<ul style="list-style-type: none"> • Also uses PRR's but has specificity • Only in jawed-vertebrates • Has a “memory” <ul style="list-style-type: none"> • Remember the strains of infections

FIGURE 1: DIFFERENCE BETWEEN INNATE AND ADAPTIVE IMMUNITY

THE ACTIVATION OF LYMPHOCYTES

In order for T-cells to be activated, an antigen must be presented by an **antigen presenting cell (APC)**, such as DCs, M ϕ , and B-cells. The antigen is then recognized by the **T Cell Receptor (TCR)**, a receptor on the T-lymphocyte that bind with the antigen from the APC presented by either MHC class I or MHC class II. MHC I and MHC II are present in almost all healthy cells and classify the T-cell to activate either as a **CD8+** cytotoxic cell or a **CD4+** helper cell. (Jordan, et al, 2009). Once the MHC:Antigen bind to the TCR, **signal 1** is induced but it is not able to surpass the LAT cascade unless the B7:CD28 complex is co-stimulated with the **CD40:CD40L** to promote **signal 2**. Activation of signal 1 and 2 automatically upregulates the secretion of IL-2 cytokines by APCs which triggers **signal 3**. Once all three signals have been activated, transcription and replication of immune cells -- specifically the transcription of **NFAT**, **NFK β** -- are then initiated.

The two methods in which B-cell activation is induced depend heavily on whether or not T-lymphocytes are needed; they are referred to as **T-cell independent antigen** and **T-cell dependent antigen**. As the name states, T-cell independent activation does not require the help of the T-lymphocytes to drive its immune activities. It naturally gets activated by the presence of the antigen, causing the **B1 B-cell subset** to secrete the **IgM antibody** isotype. However, this approach is not exactly the most efficient way to target antigens and pathogens because certain isotypes of antibodies can only acknowledge the company of very specific antigens. Since B-cells automatically produce IgM antibody and display it on its membrane, there will be a lack of differentiation or variation of antibodies without T-independent activation. This implies that certain diseases and pathogens will not be able to be detected causing a perilous environment for the host. (Abbas, et Al.)

SELECTIVE PRESSURE AMONG B-LYMPHOCYTES

The importance of the presence of T-lymphocytes, specifically CD4+ T helper cells is extremely crucial in the immune system of jawed vertebrates as T-lymphocytes are what mediates the B-cell to be able to class switch from one isotype to another. This is done by allowing B-lymphocytes to go through the same exact process of activation, but rather than attaching itself to an APC, a T-cell binds with the B-cell via the CD40:CD40L complex which allows the T-lymphocyte to educate the B-cell to **class (isotype) switch**. Since B-cell antibodies have variable regions specific to antigens, class switching will enable the cell to switch the isotype of the antibody that the B-cell can produce. Once activated, the B-cell enters the germinal-center where it can proliferate and replicate. It then goes through **somatic hypermutation**.

In the germinal center, lies a **follicular dendritic cell (FDC)** that demonstrates the selective pressure among B-cell (Linterman, et. Al 2017). Somatic hypermutations are random mutations that can either increase its affinity or decrease its affinity; mutation that can either be beneficial, deleterious, or neutral hence the B-cell has no control on the affinity it will be able to display. This results in select B-lymphocytes to reach **affinity maturation**, a state where it has gone through mutations enough to reach its highest level of affinity. FDCs favor those who have reached affinity maturation so in the environment that has an abundance of B-cells (Figure 1.A). Only the ones who are fittest are able to exit the germinal center and be able to perform its immune responsive duties (Abbas, et. Al). The altruism of T-lymphocytes is necessary in order to allow random mutations on B-cells, the main mediators of the adaptive immune system.

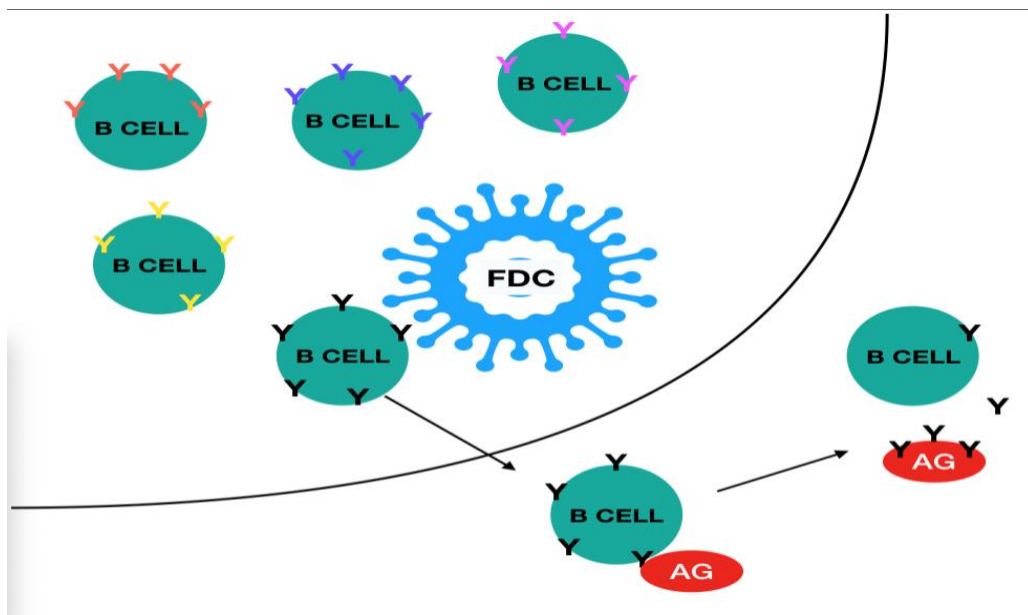


FIGURE 2: FDCs SELECTIVE PRESSURE ON AB AFFINITY

THE RELATIONSHIP BETWEEN MICROBIOTA AND THE IMMUNE SYSTEM

Current research shows that the human body is composed of about 100 trillion **microbiota cell**; bacteria naturally living inside the human body. The population of the microbiomes inhabiting the human body is almost, if not, more than the number of somatic cells. Microbiomes can either serve a purpose in the body in which it can be essential for that maintenance of homeostasis or metabolism, but it can also be the source of progression of diseases. Over time, bacteria and viruses have slowly learned how to co-evolve with the immune system, allowing them to survive more effectively in their host. As the immune system increases its ability to fight pathogens and as modern technology begin to promote new ways to rid of infections, microbiomes are also evolving to prevent interactions with immune cells.

The evolution of microbiota is evident in the certain virus development of **cap-snatching**. Cap-snatching is a mechanism that viral RNA uses in order to avoid being recognized by immune cells. Self mRNA contains a **7-methylguanosine** cap on the end of the RNA strand and that tells immune cells that the RNA is not of any harm. Viral RNA, on the other hand, do not present this cap which act as a PAMPs for the PRR, **Rig-like-receptors (RLR)**. RLR recognize the **5'triphosphate RNA** generated by virus and trigger the transcription of Type I IFN (interferon), upregulating MHC class II expression on cells, thus inducing CD8+ cytotoxic T cell functions (Bahl, et. Al, 2012). Cap-snatching allows viral RNA to act as a pseudo-self mRNA where the normal mRNA whose cap has been snatched is now opened to be detected by immune cells, causing a negative tolerance to self RNA, decreasing self-tolerance and inducing the wrong immune response. Furthermore, the capped viral mRNA promotes the synthesis and

reproduction of the virus which allows it to proliferate causing an infection, decreasing immune cells abilities to destroy the virus (Krug, et. Al, 2003).

VULNERABILITIES OF THE IMMUNE SYSTEM

The immune system is the basis of the development of modern medicine as researchers progressively search for new ways to defeat newly synthesized microbiomes that are slowly emerging. However, a vulnerability that is very common is the rate of which **vaccinations** are being produced. Bacteria and other microorganisms are able reproduce at a much faster rate causing their population to expand exponentially. They are also able to asexually reproduce which implies that they do not need to mate in order to replicate. (Bergstrom & Dugatkin, 2016) Natural selection act upon microorganisms much quicker in comparison to their hosts and the host is incapable of keeping up with the microbiomes' pace.

One issue concerning immunity that often arise is the negative effects of medicine. Medicine works in the subset of immune system **passive immunity** which refer to the transfer of antibodies from one source to another. This is very helpful to organisms that lack a specific antibody needed to fight an antigen specific pathogen or infection. This is the type of immunity that vaccinations have in which it contains the antibody that will enable to attack the pathogen. This mechanism has been widely used to prevent diseases and promote the “memory” in adaptive immune system where when an antigen is presented for the first time, the body will not present any symptoms as the antibodies in the medicine has already allowed the immune system to recognize it(Keller et al 2000). However, many people are led to believe that taking medication or getting vaccinations during adolescence will decrease an individual's immune system tolerance or sometimes even lead to mutations in the child's genes causing autism or

some sort of disorder. There is no evidence directed to the correlation of abnormal development of individuals to vaccinations. Needless to say, there is an acute lack of education in the significance of the evolution of the immune system which prevents many from understanding why some conditions are necessary in medicine and in an individual's life span as a whole.

CONCLUDING REMARKS

Evolution is constantly acting on the immune system whether it's through the advancement of the adaptive immune system or constant adaptations microbiomes are composing. The development of the immune system is a widely complex process that opens up new research in order to further understand the possibility of resistance to certain diseases. Further research is being done of the development of passive immunity through medicine which will allow prevention of extreme widespread infections such as measles and cancer. However, vulnerabilities of the immune system in accordance to its co-evolving relation to bacteria and viruses must be taken into account.

GLOSSARY

- 5'triphosphate RNA – a molecular structure generated by a virus that is responsible for the transcription of type 1 interferon.
- 7-methylguanosine – a cap on the end of self mRNA that allows cells to know that it is not harmful.
- Adaptive Immunity – a type of immunity that requires the activation of innate immune system to function.
- Affinity Maturation – a process in which a B-cell reaches its highest level of affinity.
- Antigen Presenting Cell – cells that are able to hold an antigen through a form of peptides allowing antigens to be recognized by T-lymphocytes.
- B1 B-cell subset – innate-like B-cells that develops most Ig M antibodies and are responsible for most T-independent responses.
- B-Lymphocytes – lymphocytes that are able to secrete antibodies.
- Cap-Snatch – a process in which viral RNA snatches the 7-methylguanosine cap on normal
- CD4+ Helper Cells – a type of T-lymphocytes that induces helper immune responses.
- CD8+ Killer Cells – a type of T-lymphocytes that induces cytotoxic immune responses.
- CD40: CD40L – a complex that stimulated the expression of B7 molecules, secretion of cytokines, and dendritic cells.
- Class Switching – process in which antibodies switch Fc domains but keep their variable region to be able to respond to more cytokines.
- Constant Region – a region on an antibody that allows interaction with immune cells.
- Cytokines – hormones of the immune system

- Damage-Associated Molecular Patterns – a pattern consisting of damages among the cell that can be recognized by pattern recognition receptors.
- Dendritic Cells – immune cells whose main function is to present antigen to T-cell receptors.
- Endosymbiosis – a process in which an organism has been engulfed inside another and remains alive in the cell.
- Eosinophils – white-blood cells that causes inflammatory responses.
- Follicular Dendritic Cells – dendritic cells found in lymphoid follicles allowing the activated B cells in the extrafollicular focus into the follicle.
- IgM Antibody – the first antibody to be developed and the only isotype that can be activated without T-cell.
- Immune System – a system that is responsible for defending and protecting against pathogens and diseases.
- Innate Immunity – a type of immunity that act as the first responders in attacking foreign substances.
- Intraspecific – a relationship in which two similar subjects exist in the same area.
- Interspecific – a relationship in which two different subjects exist in the same area.
- Gnathostomes – jawed vertebrates.
- Granzymes (see perforin) – particles that are released by PAMPS or DAMPS that induce cytotoxic response.
- Macrophages – phagocyte that envelops a pathogen and transforms it into an antigen.
- Microbiota cells – bacteria that naturally lives inside the body.

- Natural Killer Cells – immune cells that are responsible for targeting virally infected cells.
- NFAT – proteins that are responsible for the development of T-lymphocytes.
- NFκβ -- A protein complex that allows DNA to be transcribed and regulates the genes that are responsible for innate and adaptive immunity.
- Neutrophils – a phagocyte that captures pathogens and allow it to be phagocytosed.
- Passive Immunity – a type of immunity regulated by the transfer of antibodies from one source to another.
- Pattern Recognition Receptors – Receptors that are able to detect specific patterns in the cell
- Pathogen-Associated Molecular Patterns -- a pattern consisting of damages among the cell that can be recognized by pattern recognition receptors.
- Perforins (see granzymes) - particles that are released by PAMPS or DAMPS that induce cytotoxic response.
- Phagocytosis – a process in which a foreign substance is engulfed into the cell and destroyed.
- Protozoans – unicellular organisms.
- RAG Transposon – enzymes responsible for mediating the rearrangement during VDJ recombination.
- Rig-like-receptors -- viral RNA that are also cytosolic PRRs responsible for inducing the production of antiviral interferons.
- Signal 1/2/3 – The three cascading signals that regulates the

- Somatic Hypermutation -- mutations induced by the isotype switching of ig V genes and allows B cells to migrate to the light zone
- T-Lymphocytes – Lymphocytes that are activate and kills harmful cells in the body.
- T-cell Dependent Antigen – antigens and responses that are stimulated by antibodies with the presence of T-cells.
- T-cell Independent Antigen -- antigens and responses that are stimulated by antibodies with the absence of T-cells.
- T-Cell Receptor – a receptor on T-cells that recognize antigen on antigen presenting cells.
- Variable Region – a region on an antibody that interacts with antigens and cause antigen specificity.

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