An Interpretative Introduction to the Immune System

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1 Introduction

This chapter is intended as a gentle introduction to the immune system for researchers who do not have much background in immunology. It is not a comprehensive overview, and certainly does not stand in for a good immunology textbook. The interested reader should consult [14, 4, 13]. The goal of this chapter is to sketch an outline of how the immune system fits together, so that readers may then go and consult detailed research papers, knowing where to look. For this reason, the emphasis here is on interpretation, not details, with an interpretative bias towards viewing the immune system from the perspective of information processing, that is, in terms of the architecture, algorithms and principles embodied by the immune system.

The basis of the interpretation is the teleological viewpoint that the immune system has evolved for a particular purpose. Fundamentally, such a viewpoint is wrong, but it is useful for expository purposes: it is easier to understand the immune system to a first approximation if the components and mechanisms are viewed with the assumption that they exist to solve a particular problem. It is thus assumed that the "purpose" of the immune system is to protect the body from threats posed by toxic substances and pathogens, and to do so in a way that minimizes harm to the body and ensures its continued functioning[1]. The term **pathogen** embraces a plethora of inimical micro-organisms, such as bacteria, parasites, viruses, and fungi, that constantly assault the body. These pathogens are the source of many diseases and ailments, for example, pneumonia is caused by bacteria, AIDS and influenza are caused by viruses, and malaria is caused by parasites. Replicating pathogens can lead to a rapid demise of the host if left unchecked.

There are two aspects to the problem that the immune system faces: the identification or *detection* of pathogens, and the efficient *elimination* of those pathogens while minimizing harm to the body, from both pathogens and the immune system itself. The detection problem is often described as that of distinguishing "self" from "nonself" (which are elements of the body, and pathogens/toxins, respectively). However, many foreign micro-organisms are not harmful, and an immune response to eliminate them may damage the body. In these cases it would be healthier not to respond, so it would be more accurate to say that the problem faced by the immune system is that of distinguishing between *harmful* nonself and everything else [7, 8][2]. Once pathogens have been detected, the immune system must eliminate them in some manner. Different pathogens have to be eliminated in different ways, and the components of the immune

[1] This is a limited view of "purpose"; in general, it may be better to adopt the viewpoint that the purpose of the immune system is to maintain homeostasis, which includes protecting the body from pathogens and toxins that could disrupt that homeostasis.

[2] However, the fact that the immune system does react to "harmless" micro-organisms is essential to immunization (see section 5).

system that accomplish this are called *effectors*. The elimination problem facing the immune system is that of choosing the right effectors for the particular kind of pathogen to be eliminated.

This chapter is structured as a narrative, introducing details as they become relevant to the story, to avoid overwhelming the reader with terms and technicalities. Whenever new terms are introduced, they appear in boldface, and explained soon afterwards. In addition a glossary of these terms appears in the appendix. The next section (2 gives a high-level description of the main components of the immune system architecture, and in the sections that follow these components are described in more detail. The problem of the detection of specific pathogens is discussed in section 3. Section 4 explains how the immune system produces sufficient cellular diversity to provide protection against a wide variety of pathogens. Section 5 describes how the immune system adapts to specific kinds of pathogens, and section 6 discusses how the immune system "remembers" pathogenic structures to facilitate rapid secondary responses. Section 7 describes how the immune system remains tolerant of the body, i.e. why the immune system does not attack the body. In section 8, the problem of detecting and eliminating pathogens hidden within cells is discussed. Some consequences of this are described in section 9, and in section 10, the problem of effector selection to eliminate pathogens is discussed.

2 The Architecture of the Immune System

The architecture of the immune system is multi-layered, with defenses on several levels (see figure 1). Most elementary is the skin, which is the first barrier to infection. Another barrier is physiological, where conditions such as pH and temperature provide inappropriate living conditions for foreign organisms. Once pathogens have entered the body, they are dealt with by the **innate** immune system and by the acquired or **adaptive** immune system. Both systems consist of a multitude of cells and molecules that interact in a complex manner to detect and eliminate pathogens. Both detection and elimination depend upon chemical bonding: surfaces of immune system cells are covered with various receptors, some of which chemically bind to pathogens, and some of which bind to other immune system cells or molecules to enable the complex system of signalling that mediates the immune response.

2.1 The Innate Immune System

The term "innate" refers to that part of the immune system with which we are born; that is, it does not change or adapt to specific pathogens (unlike the adaptive immune system). The innate immune system provides a rapid first line of defense, to keep early infection in check, giving the adaptive immune system time to build up a more specific response. Innate immunity consists primarily of a chemical response system called **complement**, and the **endocytic** and **phagocytic** systems, which involve roaming "scavenger" cells, such as **macrophages**, that detect and engulf extracellular molecules and materials, clearing the system of both debris and pathogens[3].

2.1.1 The Complement System

The complement system provides the earliest innate response. When complement molecules that exist in the plasma bind to certain kinds of bacteria, they help eliminate the bacteria through **lysis** or **opsonization**. Lysis is the process whereby complement ruptures the bacterial membrane, which results in destruction of the bacterium. Opsonization refers to the coating of bacteria with complement (or antibodies; see section 5), enabling the bacteria to be detected by macrophages. Self cells have regulatory proteins on their surfaces that prevent complement from binding to them,

[3] As an aid to remembering these terms, it is useful to recall their Greek origins: endo means "inside", phago means "eat", cyto means "cell". So, for example, endocytic means "inside-cells".

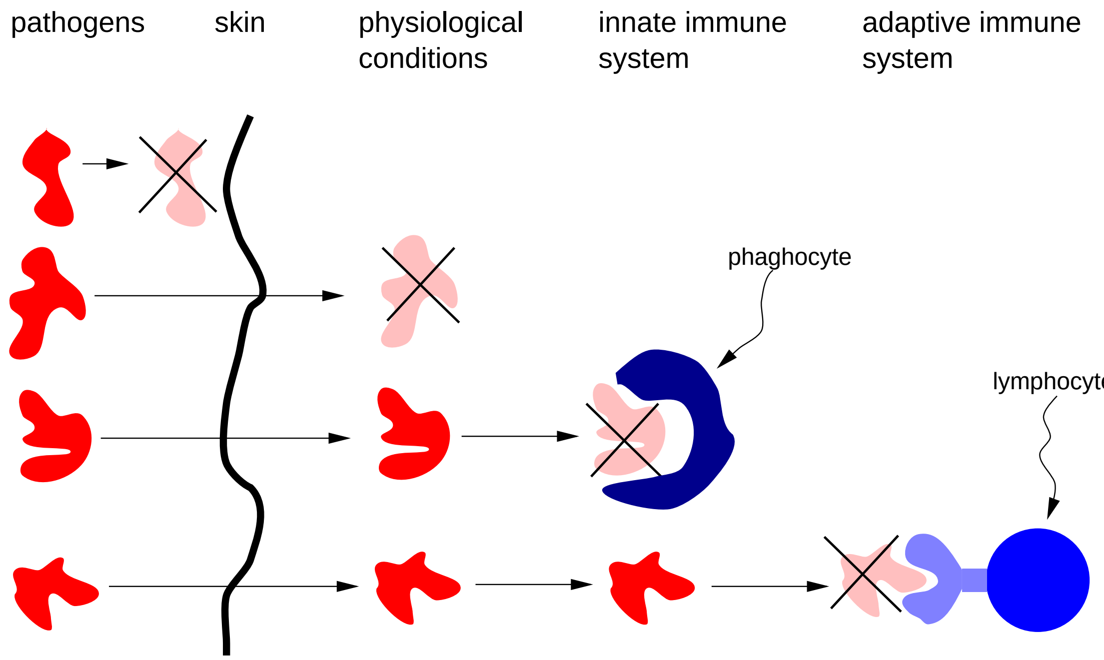

Figure 1: Immune system defenses are multilayered. The blobs on the left represent pathogens that could infect the body. The first layer of protection is the skin, which blocks most pathogens. Elimination is indicated by a cross through a faded representation of the pathogen. The second layer of defense is physiological, where conditions such as temperature make the bodily environment more hostile for pathogens. The third layer is the innate immune system, consisting of roaming scavenger cells such as phagocytes which engulf pathogens and debris. The final layer is the adaptive immune system, which consists of cells called lymphocytes that adapt to the structure of pathogens to eliminate them efficiently.

and so are protected against the effects of complement. The activation of complement and macrophages in the early stages of infection typically happens in the first few hours.

2.1.2 Macrophages

Macrophages are "scavenger" cells found in tissues throughout the body. They play a crucial role in all stages of immune response. In the early stages they have several different functions. For example, they have receptors for certain kinds of bacteria, and for complement, thus they engulf those bacteria and bacteria opsonized by complement. Additionally, macrophages that are activated by binding secrete molecules called **cytokines**. The release of cytokines activates the next phase of host defense, termed the early induced response.

2.1.3 Cytokines and Natural Killer Cells

Cytokines are molecules that function as a variety of important signals. Cytokines are not only produced by macrophages and other immune system cells, but also by cells which are not a part of the immune system, for example, cells that secrete cytokines when damaged. A major effect of the cytokines is to induce an **inflammatory response**, which is characterized by an increase in local blood flow and permeability between blood and tissues. These changes allow large numbers of circulating immune system cells to be recruited to the site of infection. Another effect of cytokines is inducing the increase in body temperature associated with fever. Fever is thought to be beneficial because the activity of pathogens is reduced with an increase in temperature, whereas elevated temperatures increase the intensity of the adaptive immune response. Yet another effect of cytokines is to reinforce the immune response by triggering the liver to produce substances known as **acute phase proteins** (ATP), which bind to bacteria, thus activating macrophages or complement.

Certain cells produce proteins, called **interferons**, when infected by viruses. Interferons are so-called because they inhibit viral replication, but they also have many other functions. For example, they also activate **natural killer** (NK) cells to kill virus-infected host cells. NK-cells bind to carbohydrates on normal host cells, but are normally not activated because healthy cells express molecules that act as inhibitory signals. Some virally-infected cells cannot express these inhibitory signals and are killed by activated NK-cells. Activated NK-cells release chemicals that trigger **apoptosis** in the infected cell. Apoptosis is programmed cell-death, a normal cellular response that is essential in many bodily functions other than immunity.

2.2 The Adaptive Immune System

The adaptive immune system is so-called because it adapts or "learns" to recognize *specific* kinds of pathogens, and retains a "memory" of them for speeding up future responses. The learning occurs during a **primary response** to a kind of pathogen not encountered before by the immune system. The primary response is slow, often first only becoming apparent several days after the initial infection, and taking up to three weeks to clear an infection. After the primary response clears an infection, the immune system retains a memory of the kind of pathogen that caused the infection. Should the body be infected again by the same kind of pathogen, the immune system does not have to re-learn to recognize the pathogens, because it "remembers" their specific appearance, and will mount a much more rapid and efficient **secondary response**. The secondary response is often quick enough so that there are no clinical indications of a re-infection. Immune memory can confer protection up to the life-time of the organism (measles is a good example).

The adaptive immune system primarily consists of certain types of white blood cells, called **lymphocytes**, which circulate around the body via the blood and lymph systems[4]. Lymphocytes co-operate in the detection of pathogens, and assist in pathogen elimination. However, we can abstractly view lymphocytes as mobile, independent *detectors*. There are trillions of these lymphocytes, forming a system of distributed detection, where there is no centralized control, and little, if any, hierarchical control. Detection and elimination of pathogens is a consequence of trillions of cells - detectors - interacting through simple, localized rules.

The remainder of this chapter concentrates on the adaptive immune system because it appears to have the most complex and interesting architecture. Where necessary, the interaction between the innate and the adaptive immune systems is mentioned, because they are closely linked in the detection and elimination of pathogens.

3 Specific Recognition in the Immune System

A detection or recognition event occurs in the immune system when chemical bonds are established between **receptors** on the surface of an immune cell and **epitopes**, which are locations on the surface of a pathogen or protein fragment (a **peptide**). Both receptors and epitopes have complicated three-dimensional structures that are electrically charged. The more complementary the structure and charge of the receptor and the epitope, the more likely it is that binding will occur. See figure 2.

The strength of the bond between a receptor and an epitope is termed the **affinity**. Receptors are deemed *specific* because they bind tightly only to a few similar epitope structures or patterns. This specificity extends to the lymphocytes themselves: receptor structures may differ between lymphocytes, but on a single lymphocyte, all receptors are identical, making a lymphocyte specific to a particular set of similar epitope structures (this feature is termed **monospecificity**). Pathogens have many different epitopes, reflecting their molecular structures, so many different lymphocytes may be specific to a single kind of pathogen.

A lymphocyte has on the order of 10^5 receptors on its surface, all of which can bind epitopes. Having multiple identical receptors has several beneficial effects. Firstly, it allows the lymphocyte to "estimate" the affinities of its receptors for a given kind of epitope, through frequency-based sampling: as the affinities increase, so the number of receptors binding will increase. The number of receptors that bind can be viewed as an estimate of the affinity between a single receptor and an epitope structure[5]. Secondly, having multiple receptors allows the lymphocyte to estimate the number of epitopes (and thus infer the number of pathogens) in its immediate neighbourhood: the more receptors bound, the more pathogens in the neighbourhood. Finally, mono-specificity is essential to the immune response, because if lymphocytes were not mono-specific, reaction to one kind of pathogen would induce response to other, unrelated epitopes.

The behaviour of lymphocytes is strongly influenced by affinities: a lymphocyte will only be *activated* (this can be termed a "detection event") when the number of receptors bound exceeds some threshold[6]. Thus, a lymphocyte will only be activated by pathogens if its receptors have sufficiently high affinities for particular epitope structures on the pathogens, and if the pathogens exist in sufficient numbers in the locality of the lymphocyte. Such activation thresholds allow lymphocytes to function as *generalized* detectors: a single lymphocyte detects (is activated by) structurally similar kinds of epitopes. If we consider the space of all epitope structures as a set of patterns, then a lymphocyte detects or "covers" a small subset of these patterns. Hence, there does not have to be a different lymphocyte for every epitope pattern to cover the space of all possible epitope patterns. There is evidence to suggest that certain kinds

[4]Lymphocytes are so-called because they exist in the lymph; an alternative term is **leukocyte**, where leuko means "white", a reference to the fact that leukocytes are "white blood-cells".

[5]Of course, this is an idealization, because the receptors may bind different epitope structures, so what is being "estimated" is a rather arbitrary mean of the affinities between the receptors and different epitope structures. However, as the affinities increase, the estimation becomes more accurate because the epitope structures must be increasingly similar.

[6]Lymphocytes require additional signals to be activated. This is termed costimulation, and is discussed in section 7.

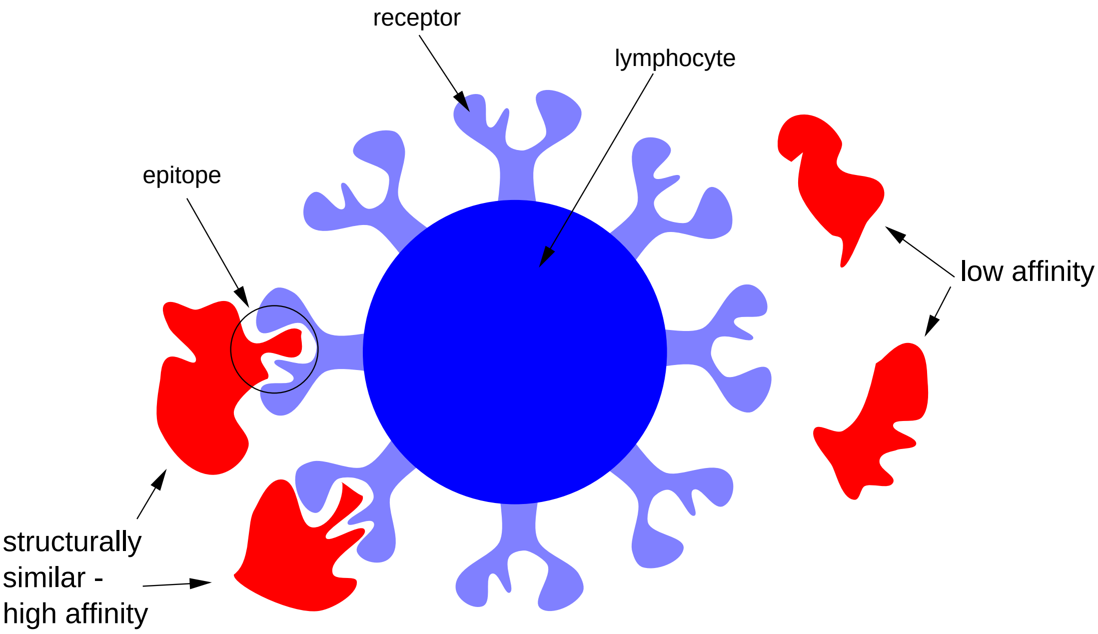

Figure 2: Detection is a consequence of binding between complementary chemical structures. The surface of a lymphocyte is covered with receptors. The pathogens on the left have epitope structures that are complementary to the receptor structures and so the receptors have higher affinities for those epitopes than for the epitopes of the pathogens on the right, which are not complementary.

of lymphocytes (memory cells) have lower activation thresholds than other lymphocytes, and so need to bind fewer receptors to become activated (more of this in section 6).

4 Generating Receptor Diversity

Because detection is carried out by binding with nonself[7], the immune system must have a sufficiently diverse **repertoire** of lymphocyte receptors to ensure that at least some lymphocytes bind to any given pathogen. Generating a sufficiently diverse repertoire is a problem, because the human body does not manufacture as many varieties of proteins as there are possible pathogen varieties of epitopes. [3] has estimated that the immune system has available about 10^6 different proteins, and that there are potentially 10^{16} different foreign proteins or patterns to be recognized. One of the main mechanisms for producing the required diversity is a pseudo-random process, in which recombination of DNA results in different lymphocyte genes, and hence different receptors[8].

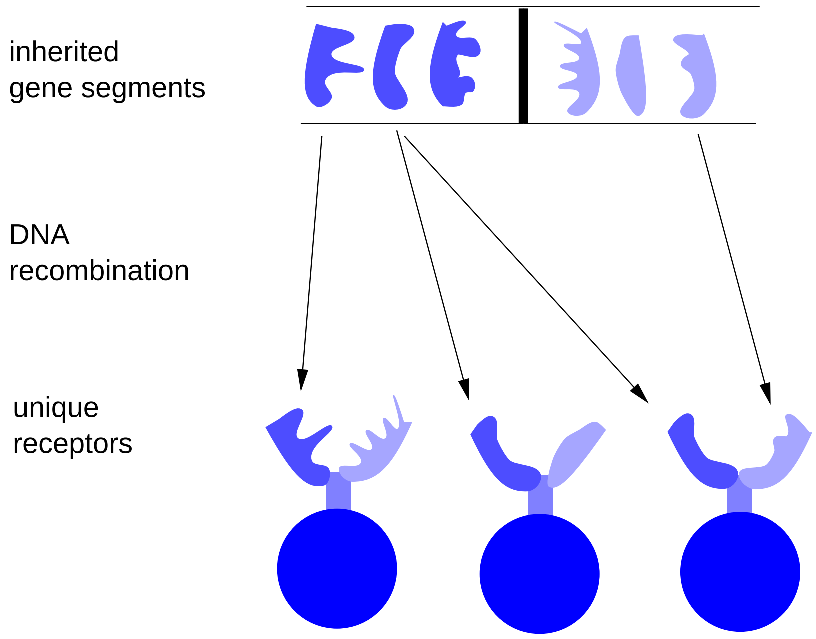

Figure 3: Generating receptor diversity. "Random" recombination of gene segments generates a combinatorial number of receptor varieties.

[19] has estimated that there are at most 10^8 different varieties of receptors. If we assume that there are 10^{16} different epitope varieties, then there will be insufficient repertoire diversity to bind every single possible pathogen. This problem is exacerbated because replicating pathogens are likely to evolve to evade detection from the existing repertoire. The immune system appears to address this problem by dynamic protection. There is a continual turnover of lymphocytes: each day approximately 10^7 new lymphocytes are generated [12]. Assuming that there are at any

[7] Recall from section 1 that the term nonself encompasses all pathogens, toxins, etc. which are foreign to the body.
[8] This is a simplification. For research concerning receptor diversity, see [11].

given time 10^8 different lymphocytes, and these are turned over at a rate of 10^7 per day, it will take ten days to generate a completely new lymphocyte repertoire. Over time, this turnover of lymphocytes (together with immune memory; see section 6) increases the protection offered by the immune system.

5 Adaptation

The immune system needs to be able to detect and eliminate pathogens as quickly as possible, because pathogens can replicate exponentially. The more specific a lymphocyte is to a particular variety of pathogen epitope, presumably the more efficient it will be at detecting at eliminating that kind of pathogen. Thus, the immune system incorporates mechanisms that enable lymphocytes to "learn" or adapt to specific kinds of epitopes, and to "remember" these adaptations for speeding up future responses. Both of these principles are implemented by a class of lymphocytes called **B-cells**[9].

When a B-cell is activated it migrates to a **lymph node**. The lymph nodes are glands in which the adaptive response develops. There are hundreds of lymph nodes distributed throughout the body. In the lymph node, the B-cell produces many short-lived (on the order of a few days) clones through cell division. B-cell cloning is subject to a form of mutation termed **somatic hypermutation** (because the mutation rates are nine orders of magnitude higher than ordinary cell mutation rates). These high mutation rates increase the chance that the clones will have different receptor structures from the parent, and hence different epitope affinities. The new B-cell clones have the opportunity to bind to pathogenic epitopes captured within the lymph nodes. If they do not bind they will die after a short time. If they succeed in binding, they will leave the lymph node and differentiate into **plasma** or **memory** B-cells (see figure 4). Plasma B-cells secrete a soluble form of their receptors, called **antibodies**, which play a key role in immunological defense[10]. Antibodies that bind to pathogen epitopes have two beneficial effects: firstly, they opsonize pathogens, and secondly, they **neutralize** pathogens, i.e. antibodies block binding between pathogens and self cells. The role of memory cells is described in section 6.

This cycle of activation-proliferation-differentiation is repeated, resulting in increasing selection of high-affinity B-cells, because the higher the affinity of the clones for the presented epitopes, the more likely it is that those clones will survive. This process, called **affinity maturation**, is essentially a Darwinian process of variation and selection: clones compete for available pathogens, with the highest affinity clones being the "fittest" and hence replicating the most (see figure 5). This primary response may take several weeks to eliminate the pathogens.

6 Immunological Memory

A successful immune response results in the proliferation of memory B-cells that have higher than average affinities for the pathogen epitopes that caused the response. Retention of the information encoded in these memory B-cells constitutes the "memory" of the immune system: if the same pathogens are encountered in future, the pre-adapted subpopulation of B-cells can provide a secondary response that is more rapid than the original primary response (see figure 6).

Our understanding of immune memory is problematic because B-cells typically live only a few days, and once an infection is eliminated, we do not know what stops the adapted subpopulation of B-cells from dying out. There are two theories that are currently dominant. According to one of the theories, the adapted memory cells are long-lived,

[9] The "B" in B-cell refers to the fact that B-cells mature only in the bone marrow.

[10] Immune responses are often measured in terms of antibody production. Anything that causes the production of antibodies is known as **antigen**, a term compounded from **anti**body-**gen**erating, but the term antigen has come to mean anything that evokes an immune response. The B-cell response is called the **humoral response** because the antibodies form a fluid or "humour". This is in contrast to the alternative **cellular response** mediated by T-cells; see section 8.

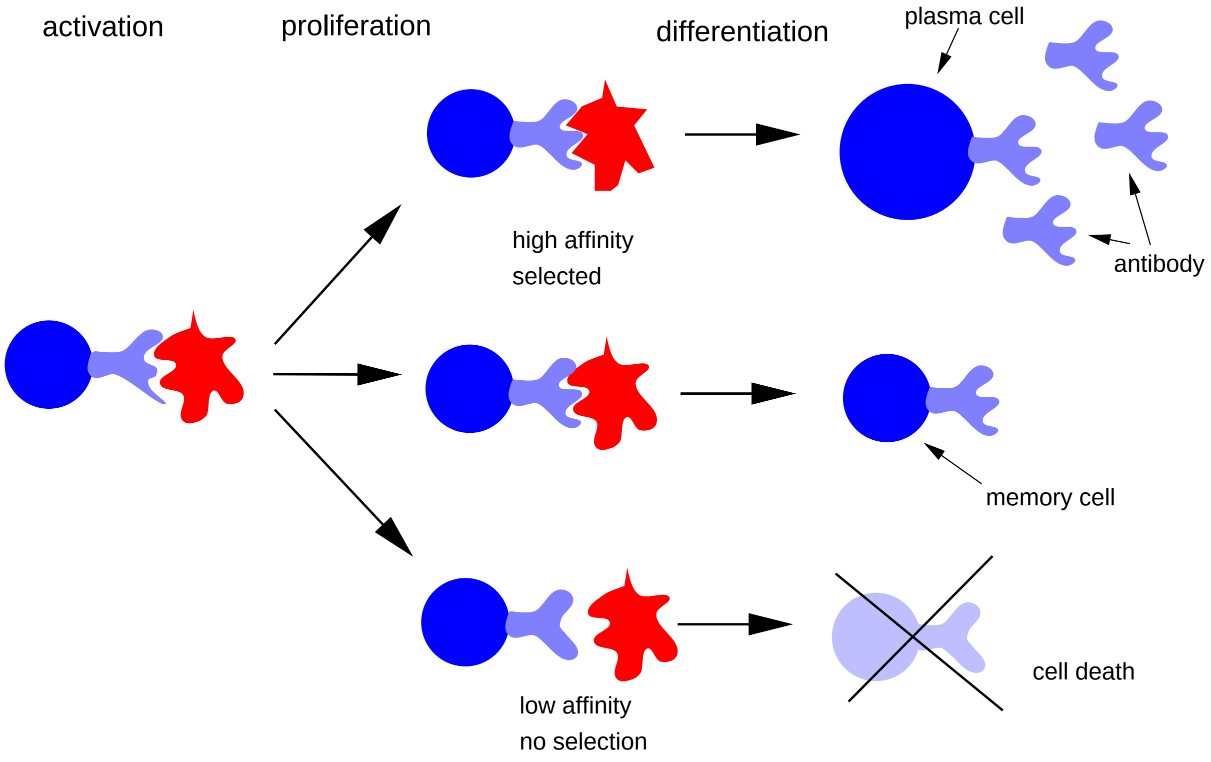

Figure 4: Affinity Maturation. Activated B-cells proliferate, producing mutated clones, which are subject to selection via epitope affinities. On the left is an activated B-cell. It proliferates, producing clones with mutated receptors. Clones with the highest affinity for the pathogenic epitopes survive and differentiate to become plasma or memory cells.

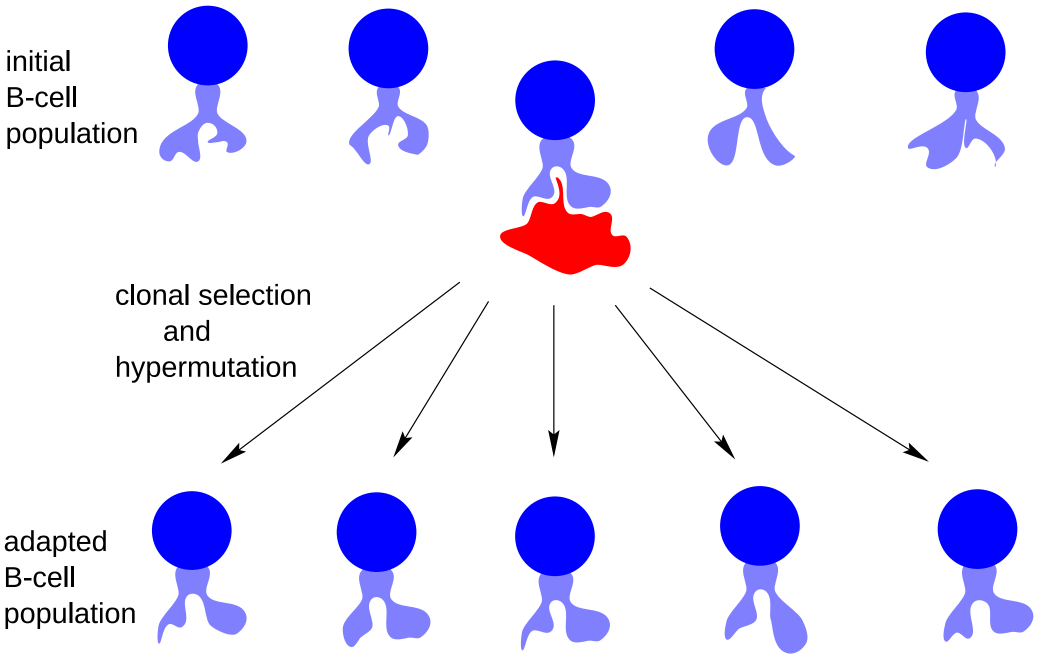

Figure 5: Affinity maturation is a Darwinian process of variation and selection. The variation is provided by somatic hypermutation, and the selection is provided by competition for pathogen epitopes.

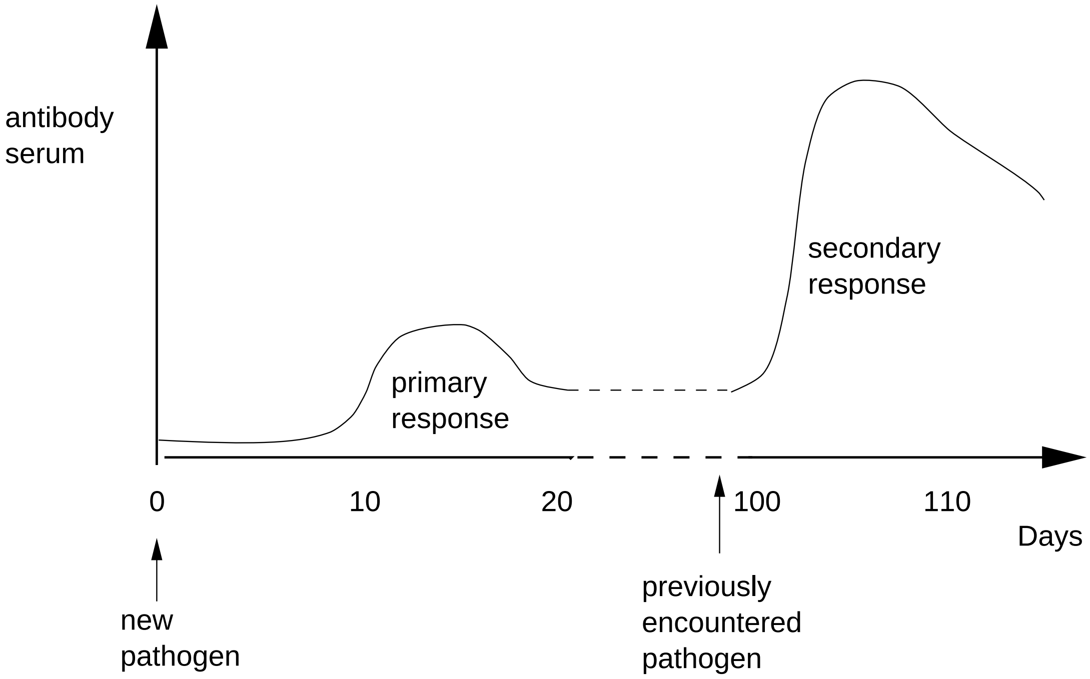

Figure 6: Responses in immune memory. Primary responses to new pathogen epitopes take on order of weeks; memory of previously seen pathogens epitopes allows the immune system to mount much faster secondary responses (on the order of days). The y-axis (**antibody**) is a measure of the strength of the immune system response.

surviving for up to the lifetime of the organism [5]. The other theory postulates that the adapted B-cells are constantly re-stimulated by traces of nonself proteins that are retained in the body for years [1].

A secondary response (via memory cells) is not only triggered by re-introduction of the same pathogens, but also by infection with new pathogens that are similar to previously seen pathogens; in computer science terms, immune memory is *associative* [17]. This feature underlies the concept of **immunisation**, where exposure to benign forms of a pathogen engenders a primary response and consequent memory of the pathogen enables the immune system to mount a more rapid secondary response to similar but virulent forms of the same pathogen (see figure 7).

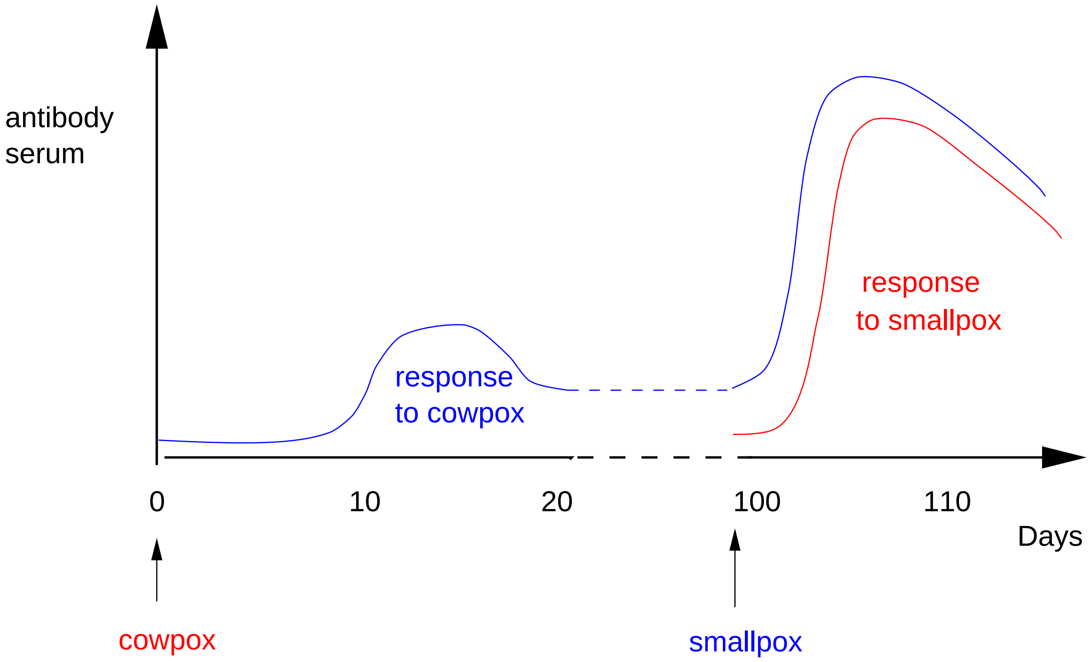

Figure 7: Associative memory underlies the concept of immunization. At time zero, the cowpox pathogen is introduced. Although harmless, it is recognized as foreign, so the immune system mounts a primary response to it, clears the infection, and retains a memory of the cowpox. Smallpox is so similar to cowpox, that the memory population generated by the cowpox reacts to the smallpox, eliminating the smallpox in a more efficient secondary response.

7 Tolerance of Self

The picture described thus far has a fatal flaw: receptors that are randomly generated and subject to random changes from somatic hypermutation could bind to self and initiate **autoimmunity**. Autoimmunity occurs when the immune system attacks the body. Autoimmunity is rare[11]; generally the immune system is **tolerant** of self, that is, it does not attack self.

[11] At the most, five percent of adults in Europe and North America suffer from autoimmune disease [18].

Tolerance is among the responsibilities of another class of lymphocytes, the **T helper** cells (Th-cells), so-called because they mature in the thymus, and "help" the B-cells. Most self epitopes are expressed in the **thymus** (an organ located behind the breast-bone) so during maturation Th-cells are exposed to most self epitopes. If an immature Th-cell is activated by binding self, it will be censored (i.e., it dies by programmed cell death) in a process called **clonal deletion** or **negative selection** (see figure 8). Th-cells that survive the maturation process and leave the thymus will be tolerant of most self epitopes. This is called **central tolerance**, because the immature Th-cells are tolerized in a single location (the thymus).

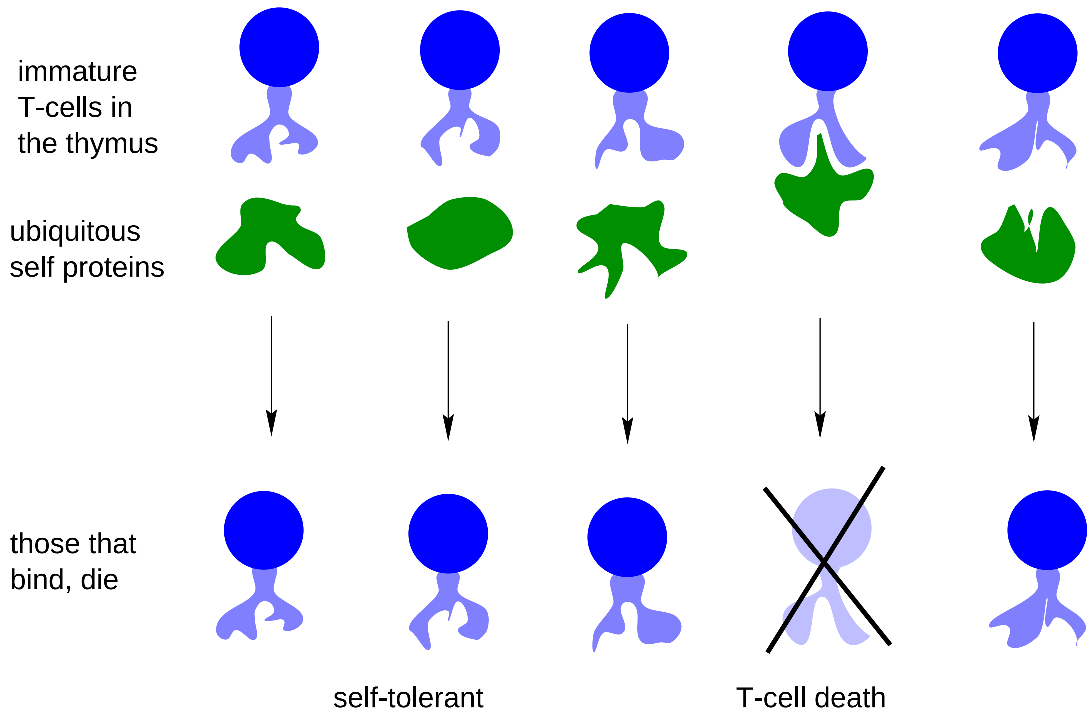

Figure 8: T-cells undergo central tolerization via clonal deletion in the thymus.

B-cells are tolerized in the bone-marrow, but this is not sufficient to prevent the development of **autoreactive** B-cells (those that bind to self epitopes). During affinity maturation B-cells hypermutate, which can result in previously tolerant B-cells producing autoreactive clones. Because affinity maturation occurs in many distributed locations (the lymph nodes), a form of peripheral (or distributed) tolerization is required. Th-cells provide this through a mechanism known as **costimulation**. To be activated, a B-cell must receive costimulation in the form of two disparate signals: **signal I** occurs when the number of pathogens binding to receptors exceeds the affinity threshold (as described in section 3), and **signal II** is provided by Th-cells. If a B-cell receives signal I in the absence of signal II it dies.

To provide signal II to a B-cell, a Th-cell must "verify" the epitopes detected by the B-cell. The way in which it performs this verification is complex. In a process known as **antigen processing** B-cells engulf pathogenic peptides and present these peptides on the surface of the B-cell, using molecules of the **Major Histocompatibility Complex** (MHC). These MHC molecules show the Th-cells what is inside the B-cell, that is, what the B-cell has detected. **T-cell receptors** differ from B-cell receptors in that they bind to MHC/peptide complexes. If a Th-cell binds to an

MHC/peptide complex presented on the surface of a B-cell, it will provide signal II to that B-cell, and the B-cell will be activated. Because Th-cells undergo central tolerization in the thymus, most mature Th-cells are self-tolerant, and so will not costimulate B-cells that recognize self. The Th-cell "verifies" that the detection carried out by the B-cell is correct, and not autoreactive (see figure 9).

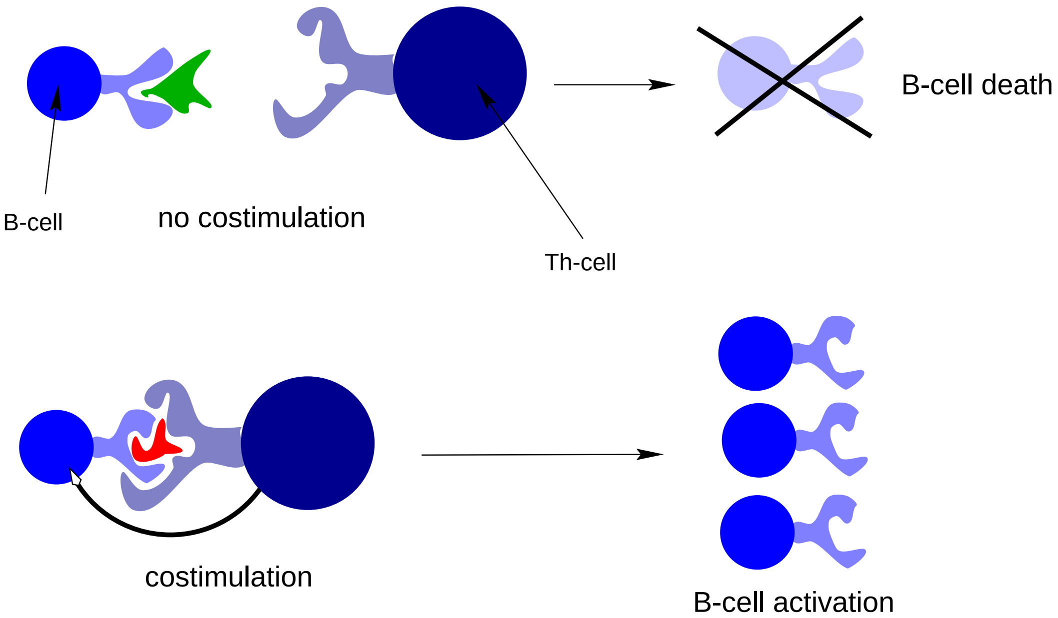

Figure 9: Costimulation from Th-cells implements distributed or peripheral tolerization for B-cells.

Unfortunately, the picture is not as simple as this. Some peripheral self proteins are never presented in the thymus (the exact fraction is unknown), and so Th-cells emerging from the thymus may still be autoreactive. Self-tolerance in Th-cells is also assured through costimulation: once again, signal I is provided by exceeding the affinity threshold, but signal II is provided by cells of the innate immune system. These innate system cells are thought to give out signal II in the presence of tissue damage[12].

An autoreactive T-cell could survive in regions of tissue damage, but as soon as it leaves the region of tissue damage, it will receive signal I in the absence of signal II and die. This can be termed *frequency-based* tolerization because an autoreactive Th-cell should encounter self in the absence of tissue damage with higher frequency than self in the presence of tissue damage, assuming healthy self is generally more frequent than nonself. If these frequencies change, then frequency tolerization will lead to a loss of immune function, which has been observed when overwhelming initial viral doses result in nonself becoming frequent [10]. The utility of frequency tolerization is emphasized by the fact that the loss of the thymus does not result in devastating autoimmunity, which is what we would expect if Th-cells were only tolerized centrally.

The specialization of the different lymphocytes gives the immune system the ability to provide a faster adaptive response that is not self-reactive. Th-cells have the "responsibility" for self-tolerance, thus freeing B-cells to hypermutate and adapt to a specific pathogen. Although Th-cells must be able to recognize the peptides presented by the

[12]This is a simplification. For a more detailed exposition of possible tolerization and costimulation mechanisms, see [6, 7, 8].

B-cells, both classes of lymphocytes are necessary. Th-cells are general, non-specific detectors, and so are not efficient at detecting specific pathogens. B-cells, by contrast, adapt to become more specific, and thus more effective at detecting particular pathogens. It has been estimated that B-cells detect specific pathogens 10 to 10000 times more efficiently than Th-cells [7].

8 Detection of Intra-cellular Pathogens

The immune system is vastly more complex than portrayed so far. Another important facet is the problem of *intra-cellular* pathogens. Intra-cellular pathogens are organisms such as viruses and certain bacteria which live inside host cells. Such pathogens are not "visible" to B-cells; all that the B-cell potentially binds to is the outside of the host cell, which has only self epitopes. What the immune system needs is some way to "look inside" host cells to see if they are infected.

The MHC molecules described in section 7 provide the solution. Almost all cells in the body have MHC molecules, which function as transporters, carrying fragments of proteins (peptides), from within the cell to the cell surface, where they are presented to the immune system, in the form of **MHC/peptide complexes**. If a cell is infected with a virus, MHC carries viral peptides to the surface, and present them to the immune system.

MHC molecules are divided into two **classes**: class I MHC and class II MHC. The immune system differs in its response to peptides presented with class I MHC and class II MHC. Class II MHC occurs only in cells of the immune system, such as macrophages and B-cells. As discussed before, Th-cells bind to class II MHC/peptide complexes, and when activated they stimulate an immune response in the presenting cell, for example, macrophages are stimulated to destroy whatever is in their vesicles, and B-cells are stimulated to proliferate and differentiate.

Class I MHC/peptide complexes are recognized by another class of lymphocytes, called **cytotoxic** or **killer**-T cells (Tk-cells). Both Tk-cells and Th-cells are types of T-cells. All T-cells mature in the thymus, are tolerized via clonal deletion, and do not hypermutate when cloning. Tk-cells, like all T-cells, are only activated by binding to MHC/peptide complexes with costimulation from the innate immune system. If a Tk-cell is activated, it will kill the infected host cell (hence the name). It does this through apoptosis, triggering the host cell into programmed death; or physically, by punching holes in the cell wall; or chemically, by the secretion of toxic chemicals (see figure 10).

9 MHC and Diversity

It is essential for host defense that MHC forms MHC/peptide complexes with as many foreign peptides as possible, so that those foreign peptides are recognized by Th-cells. Because of the nature of molecular bonding, a single type of MHC can form complexes with multiple, but not all pathogenic peptides. Hence, there is selective pressure on pathogens to evolve so that their characteristic peptides cannot be bound by MHC, because then they will be effectively hidden from the immune system. Therefore, it appears to be essential that the body have as many varieties of MHC as possible. However, as the diversity of MHC types increases, there is a resulting increase in the chance that immature Th-cells will bind to complexes of MHC and self, which means that more Th-cells will be eliminated during negative selection. Eliminated Th-cells are a waste of resources, so evolution should favour lower rates of Th-cell elimination during negative selection. Hence the number of MHC types is constrained from below by the requirement for diversity to detect pathogens, and from above by resource limitations imposed by negative selection. Mathematical models of this trade-off indicate that the number of MHC types present in the human body (about 4 to 8) is close to optimal [9].

MHC types do not change over the life of an organism and are determined by genes that are the most polymorphic in the body. Hence, MHC is representative of genetic immunological diversity within a population. This diversity is crucial in improving the robustness of a population to a particular type of pathogen. For example, there are some

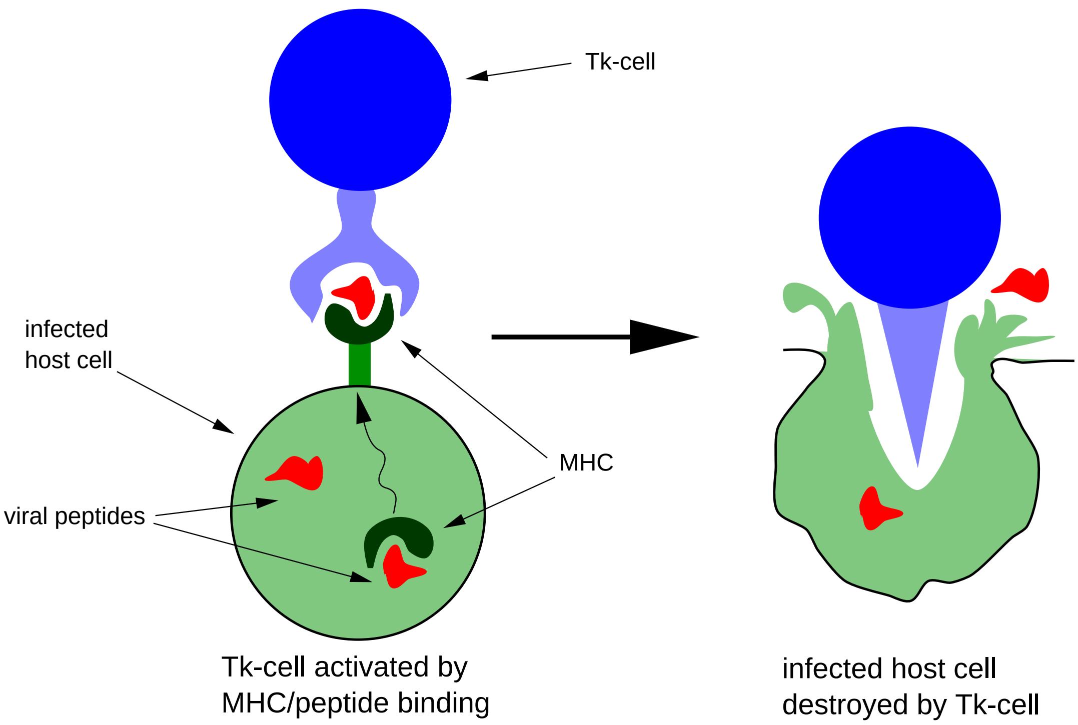

Figure 10: Tk-cells eliminate intra-cellular pathogens. Tk-cells activated by binding to a MHC/peptide complexes on a self cell and costimulated by the innate immune system will destroy the self cell that presented the MHC/peptide complex.

viruses, such as the Epstein-Barr virus, that have evolved dominant peptides that cannot be bound by particular MHC types, leaving individuals who have those MHC types vulnerable to the disease [4]. The genetic diversity conferred by MHC is so important that it has been proposed that the main reason for the continuance of sexual reproduction is to confer maximally-varied MHC types upon offspring [2]. There are some studies with mice that support this theory. These studies indicate that mice use smell to choose mates whose MHC differs the most from theirs [15].

10 Effector Selection and its Role in Pathogen Elimination

The immune system has a variety of *effector functions* because different pathogens must be eliminated in different ways. For example, intra-cellular pathogens such as viruses are eliminated via Tk-cells, whereas extracellular bacteria are eliminated by macrophages or complement, etc. After pathogens have been detected, the immune system must select the appropriate effectors so that the pathogens are efficiently eliminated. Selection of effectors is determined by chemical signals in the form of cytokines, but it is not clear how selection actually works. Mathematical models indicate ways in which selection could occur, if cytokines reflect the local state of the system (i.e. the damage suffered from pathogens, the damage suffered from the immune system, etc.) [16].

Both B and T-cells play a role in effector selection. After proliferation, Th-cells differentiate into two kinds: **Th1** and **Th2**-cells. Only Th1-cells can activate B-cells. Th2-cells (which are known as **inflammatory** T-cells, on the other hand, do not interact with B-cells, but instead are responsible for the activation of macrophages. When macrophages are infected with bacteria in their vesicles, they must be stimulated to destroy those bacteria; this is the role of the Th2-cells. To a first approximation, Th1-cells are implicated in the response against extracellular pathogens, whereas Th2-cells are implicated in the response against intra-cellular pathogens.

If Th-cells differentiate into the incorrect effectors for the pathogen threat, the consequences can be disastrous. This is clearly illustrated in the case of leprosy, a disease caused by the leprosy bacterium, which inhabits macrophage vesicles. In most cases of leprosy, Th-cells differentiate into Th2-cells, and stimulate the macrophages to destroy the bacteria, but in some cases, for reasons not understood, the Th-cells differentiate into Th1-cells, having little effect on bacteria which are isolated from the effects of B-cells. The consequence of this misguided response is that the bacteria proliferate in the macrophages, resulting in gross tissue damage which eventually leads to death.

B-cells play a role in effector selection via the antibodies they secrete. Antibodies have a y-shaped structure (see figure 11), with three different regions. The arms of the y are termed the **variable** regions, and the tail of the y is the **constant** region. The variable regions are randomly generated (as described in section 4) so that they bind to specific pathogen epitopes. The constant region, on the other hand, is not randomly generated (hence the name), but comes in a few structural varieties, called **isotypes**[13]. The constant region is the part of the antibody to which other immune system cells (such as macrophages) bind. Depending on the isotype of the constant region, different responses will be triggered upon binding, so it is this part of the antibody that determines effector function.

A single B-cell can clone multiple B-cells, each with a different isotype, even while the receptor variable regions remain the same. This is known as **isotype switching**, and enables the immune system to choose between various effector functions via chemical binding. For example, the isotype determines whether the primary immune response is neutralisation, opsonization, sensitization for killing by NK cells (see section 2.1), or activation of the complement system.

[13]There are many different isotypes, for example, IgA, IgG, IgM.

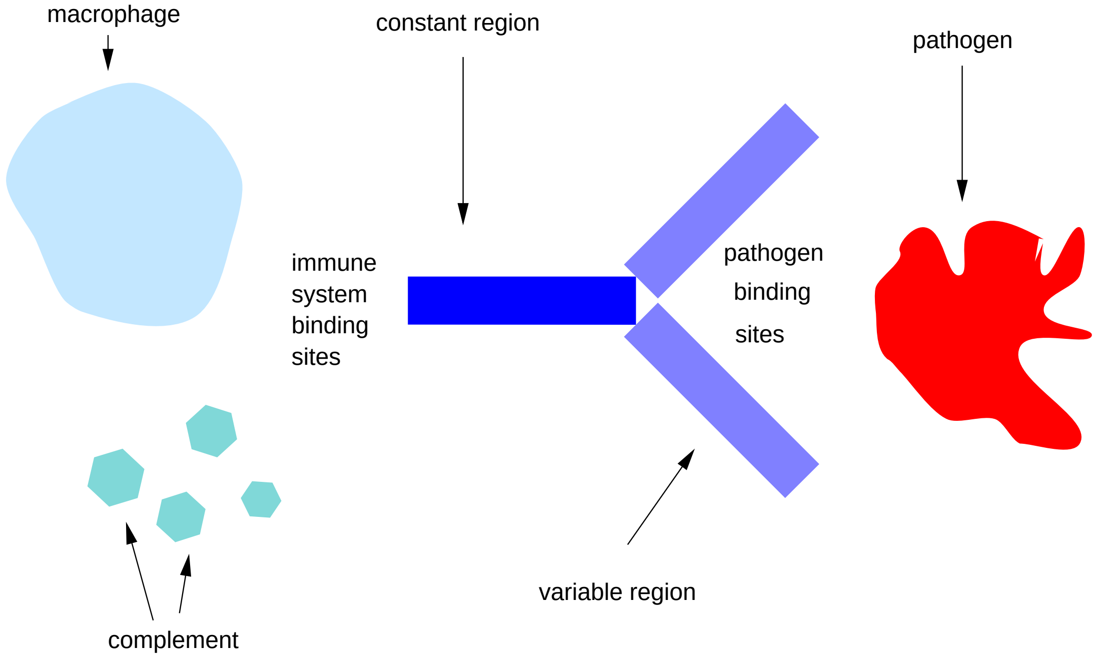

Figure 11: Variable and constant antibody regions. An antibody is y-shaped, with the arms of the y being the variable regions and the tail being the constant region. The variable regions provide specific binding of pathogen epitopes; the constant region defines the isotype that binds to other immune system components, such as macrophages and complement.

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