Day 2 (Adaptive Immunity)

Adaptive immunity comes into play when the innate immunity of our body fails. Adaptive immunity or specific immunity, is capable of recognizing and selectively removing specific foreign antigen or microorganism.
THe following are the features of adaptive immunity:

1. Specificity
2. Specialisation
3. Recognition of self from non-self
4. Slow and only develops after antigen exposure
5. Memory
6. Self-limitation

Adaptive immunity is of two types:

- humoral immunity
- cell-mediated Immunity

First we shall be looking at the main players of adaptive immunity.

1. **T cells** - responsible for cellular immunity
2. **B cells** - responsible for humoral Immunity

Antigenic Specificity

It was found that injecting an animal with almost any nonself organic chemical could induce production of antibodies that would bind specifically to that chemical. In fact, antibodies have an almost unlimited range of reactivity, uincluding responses to compounds that have only been recently synthesised in the laboratory and not found in nature. These antibodies can differentiate between molecules differing even in a single amino acid - and in order to explain this specificity, two theories were proposed :

1. selective theory
2. instructional theory

Selective theory

Ehrlich proposed that binding of the receptor to an infectious agent was like the fit between a lock and key. Ehrlich suggested that interaction between an infectious agent and a cell-bound receptor would induce the cell to produce and release more recep- tors with the same specificity (Figure 1-4). In Ehrlich's mind, the cells were pluripotent, expressing a number of different receptors, each of which could be individually "selected." According to Ehrlich's theory, the specificity of the receptor was determined in the host before its expo- sure to the foreign antigen, and therefore the antigen selected the appropriate receptor. Later it was found that each cell produces many copies of the receptors in soluble form, now called antibodies, once it has been selected by antigen binding.

This ultimately gave rise to the **clonal selection theory**, according to which, an individual B or T cell expresses many copes of a membrane receptor that is distinct for a single antigen. The unique recepetor specificity is determined in the lymphocyte before exposure to the antigen. Binding of the antigen to the specific receptor activates the cell, causing it to proliferate into a clone of daughter cells that have the same receptor specificity as the parent cell.

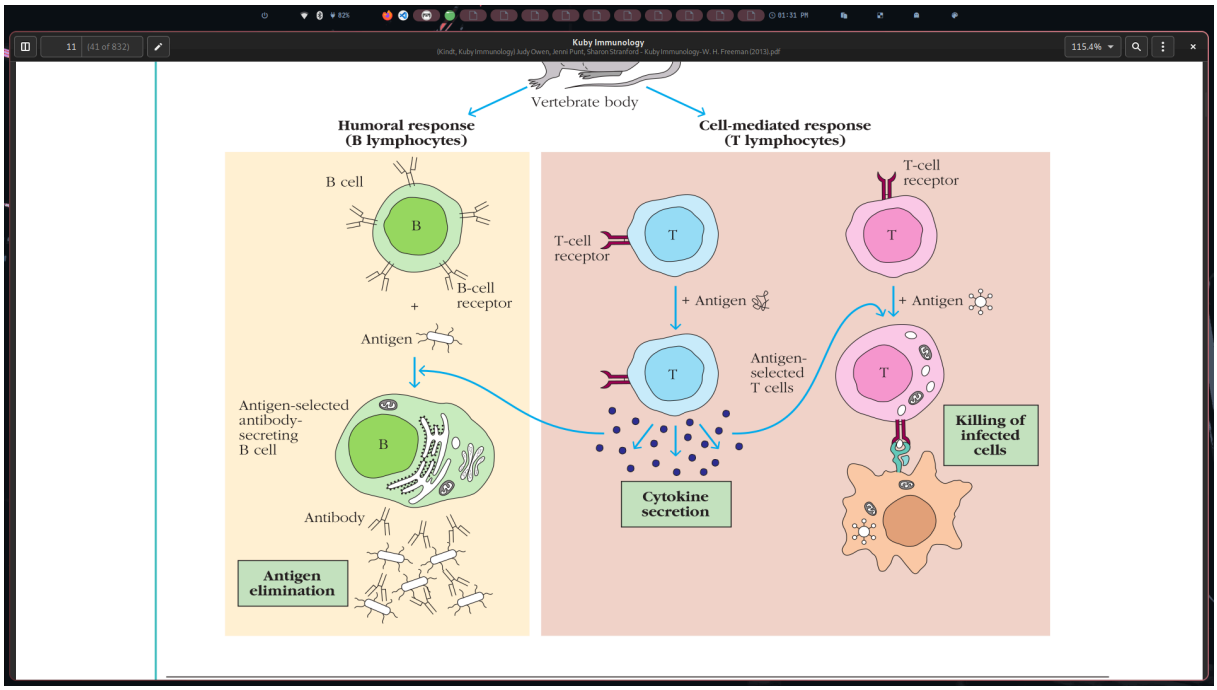

Figure 1: Clonal Selection Outline

The array of antigenic specificities of lymphocytes that exist at any given moment of time is tremendous (approximately one billion or more). This enormous diversity of specificities exists independently of exposure to antigens, and is being created by molecular mechanisms intrinsic to T and B lymphocytes. The total number of antigenic specificities of the lymphocytes in an indiviual called the lymphocyte repertoire.

Pathogen recognition molecules

Pathogen-associated molecular patterns (or PAMPs) are common foreign structures that characterize whole groups of pathogens. It is these unique antigenic structures that the immune system frequently recognizes first. White blood cells naturally express a variety of receptors, collectively referred to as pat- tern recognition receptors (PRRs), that specifically recognize these sugar residues, as well as other common foreign structures. When PRRs detect these chemical structures, a cascade of events labels the target pathogen for destruction. PPRs are proteins encoded in the genomic DNA and are always expressed by many different immune cells. These conserved, germline-encoded recognition molecules are thus a first line of defense for the quick detection of many of the typical chemi- cal identifiers carried by the most common invaders. A significant and powerful corollary to this is that it allows early categorizing or profiling of the sort of pathogen of con- cern. This is key to the subsequent immune response routes that will be followed, and therefore the fine tailoring of the immune response as it develops.

How can our DNA encode a recognition system for things that change in random ways over time? Better yet, how do we build a system to recognize new chemical structures that may arise in the future?

Thankfully, the vertebrate immune system has evolved a clever, albeit resource intensive, response to this dilemma: to favor randomness in the design of some recognition mole- cules. This strategy, called generation of diversity, is employed only by developing B and T lymphocytes. The result is a group of B and T cells where each expresses many copies of one unique recognition molecule, resulting in a population with the theoretical potential to respond to any antigen that may come along (Figure 1-7). This feat is accomplished by rearranging and editing the genomic DNA that encodes the antigen receptors expressed by each B or T lymphocyte. Not unlike the error-prone

DNA replication method employed by pathogens, this system allows chance to play a role in generat- ing a menu of responding recognition molecules. This process is not without risk - it takes place in the primary lymphoid organs, and cells have to survive the quality control processes that follow.
Surviving cells move into the circulation of the body, where they are available if their specific, or cognate, antigen is encountered. When antigens bind to the surface receptors on these cells, they trigger clonal selection.

Diversity
The diversity of antibodies is created by the combination of variable regions of H chains and L chains. It is reported that there are 10,530 types of H-chains and 200 types of L-chains, which make as many as 2,106,000 different types. Furthermore, because there are other mechanisms for producing diversity such as mutations, it is possible to produce antibodies that can bind to virtually any antigen. The diversity of antibodies is determined by a mechanism called gene restructuring.

The genes in the heavy chain variable region of an antibody are divided into VH gene regions, DH gene regions, and JH gene regions. Also, the gene in the light chain variable region of antibodies is divided into the VL gene region and JL gene region. These gene regions are assembled by selecting one type from multiple gene fragments.

In this way, a variety of antibodies are assembled by gene fragments from the heavy chain variable region and the light chain variable region.

Virtually all microbes can trigger an antibody response. Successful recognition and eradication of many different types of microbes requires diversity among antibodies, a result of variation in amino acid composition that allows them to interact with many different antigens. Antibodies obtain their diversity through 2 processes. The first is called V(D)J (variable, diverse, and joining regions) recombination. During cell maturation, the B cell splices out the DNA of all but one of the genes from each region and combine the three remaining genes to form one VDJ segment. The second stage of recombination occurs after the B cell is activated by an antigen.In these rapidly dividing cells, the genes encoding the variable domains of the heavy and light chains undergo a high rate of point mutation, by a process called somatic hypermutation. As a consequence of these processes any daughter B cells will acquire slight amino acid differences in the variable domains of their antibody chains.This serves to increase the diversity of the antibody pool and impacts the antibody's antigen-binding affinity. Point mutations can result in the production of antibodies that have a lower or higher affinity with their antigen than the original antibody.
B cells expressing antibodies with a higher affinity for the antigen will outcompete those with weaker affinities (called **affinity maturation**).

Tolerance of Self-Antigen
In order for the immune system to work effectively, it must avoid accidentally recognizing and destroying host tissues - a process called **tolerance**.

To establish tolerance, the antigen receptors present on developing B and T cells must first pass a test of nonrespon- siveness against host structures. This process, which begins shortly after these randomly generated receptors are pro- duced, is achieved by the destruction or inhibition of any cells that have inadvertently generated receptors with the ability to harm the host.

Memory
One particularly significant and unique attribute of the adaptive arm of the immune response is immunologic memory. This is the ability of the immune system to respond much more swiftly and

with greater efficiency during a sec- ond exposure to the same pathogen. During a first encounter with foreign antigen, adaptive immunity under- goes what is termed a primary response, during which the key lymphocytes that will be used to eradicate the pathogen are clonally selected, honed, and enlisted to resolve the infection. All subsequent encounters with the same antigen or patho- gen are referred to as the secondary response. During a secondary response, memory cells, kin of the final and most efficient B and T lymphocytes trained during the primary response, are re-enlisted to fight again. These cells begin almost immediately and pick up right where they left off, continuing to learn and improve their eradication strategy during each subsequent encounter with the same antigen.