IMMU2101 – INTRODUCTORY IMMUNOLOGY

LECTURE 1 – WHAT IS THE IMMUNE SYSTEM

The immune system is defined as the collection of molecules, cells, and tissues that work together to mediate resistance to infections (prevent and eradicate), as well as remove tumours. Immunology therefore, must be studied to protect one from infectious disease and tumours. The immune response refers to the method by which the immune system seeks to react to infectious microbes. Rather than functioning as a standalone system, immunity (resistance to disease) is integrated with the other systems (GI, cardiovascular, etc.) as well as in the epithelial cells (mucus, glands, skin, etc.). This integration occurs as the immune system seeks to prevent infection across the entire body and since infections can enter from anywhere, immune cells must be found everywhere. Some immune cells migrate and search for pathogens, dealing with them as they find them and hence act like police. Others are strategically positioned to act when required, but remain in the same location for long periods of time (resident cells). The key methods of communication in the immune system are autocrine (act on the cells that produce them and hence, like-cells), paracrine (act locally), or endocrine (distant cells). Immunity itself can be caused by infections (bacterial, viral, fungal, or parasitic), or tumours.

Vaccines are integral in preventing against disease, with the number of deaths due to infectious diseases having decreased greatly as a direct result of this. Vaccines are an example of active immunity where the immune system directly responds to the molecules, with it contrasting passive immunity where antibodies are transferred (like babies fed with breastmilk). However, much of the knowledge of the importance of immunity arises from a study of those with defective immune systems. These can be congenital (primary) immune deficiencies which some are born with, or acquired (secondary) immune deficiencies. An example of a primary immunodeficiency is when the patient does not have the required cells and molecules to undertake the immune response. This can arise from not having a nucleotide, resulting in the wrong protein formed; this effect is even more pronounced when the protein is integral in the immune response. Children with congenital immunodeficiencies are susceptible to myriads of infections.

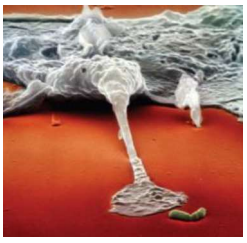
However, secondary immunodeficiencies include HIV, with this killing the required molecules and cells. Another example is drugs during transplantation, with drugs used to suppress the immune system to prevent graft vs host disease. Furthermore, the suppressed immune system can also render the body prone to opportunistic infections. During autoimmune diseases, asthma, and allergic (atopic) reactions, the power of the immune system can be noted as the reaction is excessive, resulting in many unwanted issues. The issue is that the immune system cannot recognise self from non-self → allergies and so one must try to understand the mechanism used to recognise self from non-self; allergies are usually caused by the binding of IgE with the antigen/allergen. Tumour immunity is important with tumours formed due to mutations and hence the immune systems play the role. The effect is most overt in the fact that suppressed immune systems are more likely to develop tumours. It must be understood that immune manipulation is necessary to prevent,

treat, and cure these infections, with manipulations only possible through an extensive understanding of the key components.

As the immune system seeks to prevent infection, there are many physical and chemical barriers employed. These include physical and chemical barriers such as:

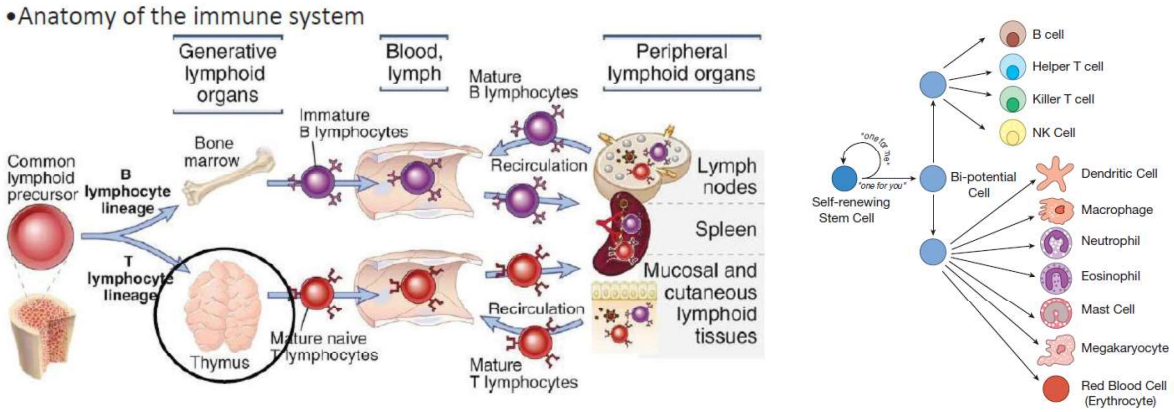
- Epithelial cells of the skin, gut, and respiratory tracts
- Secretions including sweat, wax, and tears
- Mucus in the nose, trachea, and GI tract
- Proteolytic enzymes (break down protein) and lysosomes (break peptidoglycan bacterial cell wall)
- Low Stomach pH
- Normal gut flora
- Inteferon proteins (cytokines that bind to cells and induce anti-viral state)
- Collectins (proteins that kill bacteria by destroying lipid membrane or allowing them to be taken into the cell via phagocytosis)

Despite this, the skin is arguably the most important barrier is the skin as this is the outside protection and first layer in the case of most pathogens. This can be noted through observing burns victims as they have lost this essential barrier and hence, require many drugs to prevent infections. For immune cells to access the required organs, they travel via lymphatic vessels (which use the continual cycle of blood to escape tissues and travel to organs) or blood vessels. The role of the lymph system is to drain extracellular fluid from tissues and deposit it back into the blood. It must be noted that these are all part of the innate immune system, which also includes phagocytic cells (neutrophils and macrophages), DCs, and NK cells. Once the barrier of the skin is penetrated, pathogens can enter the bloodstream which is warm and nutrient-rich, providing the ideal foundation for reproduction and hence multiplication. It is in the lymphoid organs that the antigens and lymphocytes interact, with the antigens carried from infection sites by DCs to these tissues. This allows the lymphocytes to proliferate and differentiate, forming effector cells which then leave through the efferent lymphatic vessel. Through a chemokine gradient, the DCs travel into lymph nodes, as do the free antigens (these diffuse normally). However, this chemokine gradient allows lymphocytes to enter from the blood with the DCs (professional antigen presenting cells) aiding in their maturation and subsequent activation.



The immune defence begins with anatomic barriers, followed by complement/antimicrobial proteins, innate immune cells, and finally adaptive immunity. It is referred to as the innate immune system as it is present in all animals. The image on the left is a macrophage that is reaching for a bacterium to engulf it. It uses the pattern recognition receptors on its surface to detect the common molecules associated with microbial invaders, providing the signal to engulf it. Once engulfed, the membrane folds inside of itself, forming a phagosome which can then combine with a lysosome to form a phagolysosome. Given the chemicals and enzymes within the lysosome, this destroys the bacterium; without being enclosed in vesicles, the lysosomal chemicals would kill the macorophage.

Immune cells originate from bone marrow stem cells, with immune cells either maturing there, or travelling to central or peripheral sites where they mature. Central sites refer to lymphoid tissues and organs, with the primary lymphoid organs being the bone marrow and thymus as these refer to the locations where the cells originate and are activated (like T cells). The secondary lymphoid organs include the spleen, lymph nodes, mucosal, and cutaneous associated lymphoid tissues. All other parts of the body are peripheral sites (all non-lymphoid tissues/organs), with immune cells scattered across the body. Immune cells are produced in the bone marrow and then can for lymphocytes, they begin in the primary lymphoid organs after which they reside in the secondary lymphoid organs.



Bone marrow stem cells are used to produce leukocytes, whilst self-renewing hematopoietic progenitor cells (also in bone marrow) are multipotent, including myeloid progenitor cells (which then go to the innate immune system of neutrophils, basophils, macrophages, and monocytes), and lymphoid progenitor cells that produce B and T lymphocytes (adaptive immunity). The cells that mature into macrophages enter the bloodstream first and are referred to as macrophages. They enter tissues through gaps between endothelial cells, maturing into macrophages. During the immune response, macrophages produce and secrete cytokines that signal to monocytes and other immune cells, attracting them to this area with the response inflammatory in nature.

The different immune responses (adaptive and innate) are both necessary as they deal with the pathogen in different ways; the innate system is the initial, quick response but is generalised whilst the adaptive immune response is carefully managed, precise, and sophisticated. One of the issues associated with the innate immune system is its inability to easily distinguish between closely related microbes. The innate immune system is less specific when compared to the adaptive immune system, but it is still able to recognise the most common molecules and their associated molecules. Also, the adaptive immune response increases in strength with each subsequent exposure, with it recognising and reacting to a foreign substance. However, it also uses immunological memory (refers to the ability to recognise previous molecule) to improve the response in terms of speed and magnitude with each exposure. The table below summarises the key differences:

Table 1: Innate vs Adaptive Immune System

	Innate	Adaptive
Response Time	Hours	Days
Specificity	Limited and fixed	Highly diverse; improves during the course of an immune response
Response to repeat infection	Identical to primary response	Much more rapid than the primary response
Major components	Barriers (skin etc.), phagocytes; Pattern recognition molecules	Lymphocytes; antigen-specific receptors; antibodies.

Naïve lymphocytes are those that are yet to encounter an antigen whilst activated lymphocytes have. Immature lymphocytes cannot respond to foreign antigens because they do not have the antigen-specific receptors. Maturation of these immature lymphocytes occurs in the primary lymphoid organs (thymus and bone marrow) where they develop the appropriate antigen-specific receptors so that they can respond to antigens. From here, they travel to peripheral sites and secondary lymphoid tissues (i.e. across the body). For example, a cut in the skin requires cells to take the infectious agent to the lymph nodes from where mature lymphocytes can detect it as foreign, activating an effector population that rush to the site and act upon the signal. Essentially, primary lymphoid organs are where lymphocytes are generated whilst secondary lymphoid organs are where the mature, naïve lymphocytes are maintained and adaptive immune responses initiated. Lymph nodes are much like bars, as the lymphocytes and APCs interact to activate the lymphocytes.

There are many types of lymphocytes:

- B Lymphocytes: These mature in bone marrow (lymphoid progenitor cells from bone marrow) and are part of the humoral immune response. Without this maturation, they are unable to deal with self and non-self, meaning they cannot be used in the adaptive immune response. B lymphocytes secrete antibodies which are proteins that bind to these antigens, and block infections as well as eliminate extracellular antigens (bacteria not viral as viral proteins are inside). They are called B lymphocytes as they were discovered in the bursar of Fabricus. B cells can be effector B cells (plasma cells that produce soluble antibodies that travel through the bloodstream) or memory B cells (contain cell-surface receptor that use immunological memory to ensure that it can easily respond to the antigen in the future).
- T Lymphocytes: These are produced by the other primary lymphoid organ – the thymus – which is matured in the thymus using positive selection in the cortex and negative in the medulla. It is in these regions of the thymus that the T cells learn to recognise self-nonself and hence, it must be understood for autoimmune disorders. This is not used in the humoral response, but in the cell-mediated immune response, allowing for the elimination of phagocytosed microbes. The elimination is done by killing the infected cells. There are distinct types of T lymphocytes which include:

- Helper T-Cells (CD4+ T cells): These are characterised by the surface expression of the CD4 (Cluster of Differentiation 4) molecule, with their role being to help other cells in the immune response by releasing cytokines and other soluble mediators through membrane bound molecules. Instead of activating the immune response, some of the helper T cells (or CD4+ T cells) are used to regulate/suppress the immune response. They can also use receptor-ligand interactions to engage other cells.
- Cytotoxic T cells (CD8+ cells): These are identified by the surface expression of the CD8+ cells and use the helper T cells (CD4+) to kill target cells. This is a highly specific process, with it necessary to deal with viral infections and provide effective anti-tumour immunity.

It must be noted that normally, the B and T cells are at rest but they are activated by the presentation of an antigen. Despite its specificity, the responses are slow (initially 7-10 days). However, clonal selection ensures that the response is specific with this referring to the process by which B cells express Immunoglobulin (or antibodies) that are specific to an epitope. Once the infection is detected, only the B cell with the antibody specific to the epitope will be able to respond and proliferate, with this called clonal selection as the soluble receptor (Ig) is secreted into the bloodstream from where they bind onto the antigen.

Antigens are defined as foreign substances that induce an immune response and include proteins (such as those produced by viruses), carbohydrates (bacteria produce these), lipids, and haptens. Haptens on their own, are incapable of eliciting an immune response (cannot function as an immunogenic epitope or antigenic determinant [part of the antigen that antibodies, B cells, or T cells recognize using antigen-specific receptors; this can be a sugar or a few amino acids]) but when combined with a carrier molecule, it can function as an immunogen (antigen)]. Note that the term antigen is a portmanteau of the words antibody generator. After recognising this, the adaptive immune response is able to understand what protein it is and since lymphocytes are involved in the adaptive immune response, they respond in a specific manner; each cell can only respond to a specific type of receptor and not the other.

Cytokines are proteins that are secreted by different immune cells, initiating the immune response and inflammation. They can also activate, potentiate, suppress, or inhibit these reactions and are the main mediator of communication between immune cells. It has target cells that act in autocrine, paracrine, and endocrine manners but cells can only respond to cytokines if they express the specific receptor. Inhibition is necessary as too much inflammation can cause many issues. Also, the interactions are fine-tuned based on the presence of the cytokine specific receptor.