What is Immunology?

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Introduction

Immunology has its origins in the study of how the body protects itself against infectious diseases caused by microorganisms, such as bacteria, viruses, protozoa, and fungi, and also parasitic organisms, such as helminth worms.

Important initial barriers to infection are physical (e.g. the **skin**), enhanced by substances secreted by the body, such as saliva and tears, that contain molecules that can neutralise bacteria. The internal **mucosal tissues** (e.g. **lungs & airways**, and the **gut**) are coated with mucus that is able to trap potential infectants. In the airways, mobile ciliate hairs work together to transport contaminants away from vulnerable areas. Tissues such as the skin, mucosal surfaces and airways also contain populations of immune cells that can respond to infectants that breach these physical defences.

In its most complex forms, the immune system consists of two branches: the **innate immune system** that utilises certain 'hard-wired' strategies to provide a rapid, general, response when alerted by certain typical signals of infection (essentially forming a first-line of defence); and the **adaptive immune system** that is able to develop highly specific responses (and a persistent 'immune memory') to target infection with extraordinary accuracy. Both systems work in close cooperation and, to an important extent, the adaptive immune system relies upon the innate immune system to alert it to potential targets, and shape its response to them.

Immune tissues

All immune cells originate in the **bone marrow**, deriving from **haematopoietic stem cells**, but an important set of immune cells (T lymphocytes) undergo maturation in an organ known as the **thymus**. The thymus and bone marrow are known as **primary lymphoid tissues**. **Secondary lymphoid tissues**, namely the **lymph nodes**, **spleen** and **mucosa-associated lymphoid tissues** (**MALT**) are important sites for generating **adaptive immune** responses and contain the **lymphocytes** (key adaptive cells). The **lymphatic system** is a system of vessels draining fluid (derived from blood plasma) from body tissues. Lymph nodes, that house lymphocytes, are positioned along draining lymph vessels, and monitor the lymph for signs of infection. MALT tissues are important in mucosal immune responses, and reflect the particular importance of the gut and airways in immune defence. The spleen essentially serves as a 'lymph node' for the blood.

Innate immunity

Mast cells and **basophils** are innate cell types that, when activated, secrete histamine, which can be an important inflammatory mediator produced in response to initial tissue damage as a result of infection. Mast cells are tissue resident (e.g. in mucosal tissues) whilst basophils are found in the blood. In particular, they play a key role in the so-called **allergic response**.

Innate immunity comprises both cellular and humoral ('in solution') elements. The cellular elements are represented notably by **phagocytes** (specifically **neutrophils** and **macrophages**) that can respond to signs of infection (i.e. inflammation) in the tissues and home-in on infective bacteria before neutralising and engulfing them ('**phagocytosis**'). Recognition of microorganisms by the innate system occurs via characteristic **pathogen-associated molecular patterns** (**PAMPs**) on microbial surfaces, and an important family of innate receptors called **pattern-recognition receptors** (**PRRs**) are responsible for this (notably including **Toll-like receptors** [**TLRs**]). The **natural killer** (**NK**) **cell** is another important innate cell that is able to detect and target intracellular infection of body cells by viruses. A further specialised innate cell is the **eosinophil** that plays a particular role in targeting larger infective organisms, such as parasitic worms.

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The **complement system** represents the humoral arm of innate immunity, and consists of a number of proteins (found in solution in the blood) that can interact directly, or indirectly, with infective bacteria (through different activation pathways). Inflammation, as a result of infection, allows plasma, containing complement proteins, to enter infected tissues. Once activated, the member proteins assemble to form complexes on the surface of microbes that punch holes in the membrane. The complement activation pathways are termed: the **classical pathway**, the **alternative pathway**, and the **mannose-binding lectin pathway**.

Adaptive immunity

Key to the adaptive immune response is the **lymphocyte**. There are several subtypes, however these fall under two broad designations: **T lymphocytes** and **B lymphocytes** (commonly known as **T cells** and **B cells**). Although both originate in the bone marrow, T cells mature in the **t**hymus, whilst B cells mature in the **b**one marrow. During an organism's early development a large number of B- and T cells are produced, each of which has the ability to recognise a specific, and essentially unique, molecular target. An important aspect of this maturation process is that, for both of these cell types, cells that recognise targets within the body ('self' tissue) are identified and weeded-out. An additional aspect of the maturation process for T cells is that further distinct subsets are produced – **helper T cells** (also called **CD4+ T cells**) and **cytotoxic T cells** (also called **CD8+ T cells**). The individual specificity of lymphocytes is key to the generation of adaptive responses.

Adaptive immunity utilises many kinds of receptor to coordinate its activities. T cells carry **T-cell receptors** (**TCR**), whilst B cells carry **B-cell receptors** (**BCR**), and variations in the fine structure of these receptors account for the individual specificity described above. In addition, another set of receptors, encoded by the **major histocompatibility complex** (**MHC**), play an important role in adaptive immunity. **MHC class I receptors** are displayed on a majority of body cells, whilst **MHC class II receptors** are restricted to **antigen-presenting cells** (**APCs**). Both of these receptor types interact with TCRs.

The adaptive immune response consists of two branches, a **cellular adaptive response** (effected by cytotoxic T cells) and a **humoral adaptive response** (effected by B cells). The former is directed especially towards pathogens that have colonised body cells or body cells that have become malignant (as in cancer). The latter generally targets pathogens or molecules (antigens) that are free in the bloodstream or present at mucosal surfaces. As suggested by its name, the **helper T cell** plays a central role in both of these responses since, once activated, it can shape the subsequent immune response through the particular molecules that it secretes – in particular, controlling the activation of other cell types – as such it is an important 'gatekeeper'. Two subtypes of helper T cells (Th1 and Th2) have been identified as being responsible for guiding adaptive responses towards either a cellular profile (**Th1**) or a humoral profile (**Th2**). **Th17** cells have recently been identified and are thought to play a further specialised role. Effective regulation of immune responses is also vital to ensure that they don't themselves cause unnecessary tissue damage, and **regulatory T cells** (**Tregs**) are a subset of T cell that play an important role in this process.

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Initiation of adaptive immunity

Antigen-presenting cells are functionally-defined cells that are able too initiate adaptive immune responses by presenting antigen to T cells. Major APCs are **dendritic cells** (**DCs**), which are found throughout the body – however macrophages and B cells may also serve as APCs, with the former providing an important link from innate immunity. Dendritic cells continuously monitor the bodily environment by absorbing protein fragments that they acquire from their surroundings, and presenting them on the their cell surface in association with MHC receptors. DCs may be activated by local innate immune signals (induced by infection) causing them to migrate through the lymph (or blood) to lymph nodes where they present antigen to T cells. If a protein fragment is recognised by a particular cytotoxic T cell this will suggest that it is of foreign origin (due to elimination of cells recognising ‘‘self’’) leading to a cellular adaptive response. Similarly, B cells in the lymph node may encounter free antigen carried in the lymph, leading to a humoral adaptive response. In both cases, concurrent activation of helper T cells is usually necessary to ensure an effective overall response.

The cellular adaptive response

Body cells are continuously processing protein derived from the internal cellular environment and presenting it in association with MHC class I receptors. This will typically be ‘self’ antigen (that is ignored by the immune system), but can also be peptides derived from infecting viruses or bacteria, or aberrant cancer peptides. Activated cytotoxic T cells of a given specificity proliferate in the lymph and then migrate to sites of infection where they monitor body cells for signs of intracellular infection or aberrant self proteins associated with cancer – presented on MHC class I molecules – using their TCRs. If they encounter antigen that they recognise, this indicates infection or malignancy, and they are then able to induce **apoptosis** (autodestruction) of targeted body cells. This constitutes the cellular adaptive response.

The humoral adaptive response

As already stated, B cells can recognise antigen through direct recognition of antigen via their BCRs, without the need for prior processing or presentation via a receptor – so they are key to identifying extracellular pathogens (e.g. bacteria in the lymph). Once activated, B cells differentiate into **plasma cells** that are capable of secreting **antibody** molecules into the circulation (small molecules that match the individual specificity of the parent cell) that are then able to find their targets elsewhere in the body. Once bound to a target, antibody molecules can activate the **classical pathway** of the **complement system**, thereby directing it to neutralise its targets with great specificity. Binding of antibody also enhances phagocytosis.

Immune memory

It is important to note that an effective **primary adaptive response** (e.g. relating to a pathogen that hasn’t previously been encountered) takes some time to develop, since only small numbers of target-specific B- and T cells are present initially and, once activated, they must first proliferate through a process known as **clonal selection**, to form **effector cells**. A proportion of these effector cells go on to form a stock of long-lived **memory cells** ensuring that if a particular pathogen is encountered again, any subsequent **secondary adaptive response** (or ‘memory response’) develops more quickly and is thus more effective.

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Cytokines and chemokines

Cytokines form an important family of proteins that function as immune mediators and have important roles during immune responses – they can serve to both stimulate or inhibit the differentiation, proliferation or activity of immune cells. A subset of cytokines, **chemokines**, play an important role in guiding immune cells to sites of infection by forming a chemical 'trail'.

Immune dysfunction

Important pathologies may result from immune dysfunction. Inborn ('congenital') immunodeficiencies, with a genetic basis, can disable all, or part, of the immune response (both innate and adaptive) – resulting in vulnerabilities to infection or cancers. Examples include **severe combined immunodeficiency** (**SCID**) and **common variable immunodeficiency** (**CVID**). In addition, **autoimmunity** occurs when the immune system mistakenly targets self tissues, resulting in chronic inflammatory conditions and tissue destruction. Examples include: **type 1 diabetes**, **rheumatoid arthritis**, and **multiple sclerosis**.

Transplantation science

Identification of the important role of the MHC in allowing the body to discriminate between **self/non-self tissues** has greatly enhanced the success of **tissue and organ transplantation**, by allowing **tissue matching**. This has been aided by the development of **immunosuppressive drugs** that are becoming increasingly sophisticated as we identify more specific elements within the immune system to target.

Vaccines

Vaccines can utilise harmless elements from particular pathogens to prime the immune system, so that if the pathogen is actually encountered, it is met with a stronger secondary ('memory') response and dealt with more quickly. Alternatively, vaccines may also utilise live, but attenuated, variants of the pathogen to induce a protective immune response. The role of vaccines remains central to the importance of immunology as a healthcare science – with keystone contributions in the disease areas of **smallpox**, **polio**, **tuberculosis**, **measles**, **mumps**, **rubella** and **papillomavirus**, amongst many others. However, success can depend on the target pathogen, and effective vaccines for **HIV**, **hepatitis C** and **malaria** remain elusive, in large part due to the mutability of these organisms as targets for the immune system.