

AN OVERVIEW OF THE IMMUNE SYSTEM

Recommended reading

Abbas et al. 4th ed. Chapter 1; Janeway et al., 5th ed. Chapter 1.

The survival of members of most vertebrate species to an age at which they can reproduce depends critically on their ability to resist infection. The specialized cells and organs that protect these animals from infection and death make up the immune system. This system continuously monitors every tissue and organ in the body for invaders. When the presence of cells or molecules that "do not belong" is confirmed, the immune system activates a battery of weapons designed to eliminate or contain the source of the infection. Growing awareness about inherited and acquired immunodeficiency diseases has helped underscore how absolutely crucial this protective system is for our survival.

The study of immunology, as distinguished from other areas of biology, revolves around two central questions. How does the immune system recognize the enormous variety of foreign shapes that must be targeted in order to ensure survival? How do we manage to discriminate between self structures and shapes that are foreign? The explosion in our knowledge of immunology at the molecular and cellular level has considerably simplified our understanding of the immune system. As a result, it is now possible to describe immunological phenomena such as the "generation of diversity" and "self-nonsel self recognition" in fairly simple cellular and molecular terms.

The primary goal of the immune system is to protect us from disease. One cannot seriously discuss this subject without reference to disorders that result either from the absence of an immune response or from an immune response gone awry. In this course we will briefly look at a number of diseases largely from a mechanistic point of view. Indeed there is little doubt that we are likely to witness a new era in which an increased understanding of immune function will contribute to novel therapeutic approaches to immunodeficiency diseases, organ transplantation and cancer. Understanding the immune system may open the door to a very exciting and intriguing world.

Innate Immunity

The immune system as we know it in its highly evolved form is extraordinarily versatile. A considerably simpler version existed before the evolution of vertebrates. This more ancient immune system represents the principal defense machinery in invertebrates (animals such as insects and worms, which lack a backbone). The basic elements of this early protective system have been preserved in all animals including man. This primitive system, now frequently described as the "*innate*" *immune system*, is made up primarily of proteins called agglutinins and cells called phagocytes.

One of the underlying principles in nature's grand design for host defense is the requirement that the immune system should discriminate between *self* and "*non-self*". *Agglutinins* are multivalent proteins which recognize structures that are not found on host cells but which are commonly found on the surface of microorganisms. The term multivalent here refers to the presence of more than one recognition site in a single protein. Having more than one recognition site allows agglutinins to "agglutinate" or clump target cells such as bacteria with the appropriate coat sugar for instance. An agglutinin which recognizes carbohydrates is called a *lectin*. Lectins that are capable of specifically agglutinating certain microbes are secreted by cells of the host. These lectins do not recognize sugars on the surface of host cells and thereby discriminate between self and non-self. *Phagocytes* (*phagos*=to eat) are specialized cells which engulf invading microorganisms. They either use specific receptors which discriminate between self and foreign shapes or they recognize microbes that have been coated by host agglutinins.

Another important component of the innate immune system is a set of circulating *complement* proteins. These proteins obtain their name from their ability to complement the function of antibody molecules in the immune system. They help destroy target cells coated by antibody proteins by punching holes in the cell membrane. The concentration of sodium chloride outside cells is relatively high - the holes in the membrane permit salt and water to rush into target cells which swell up and burst, a process known as *lysis*. Complement proteins however existed in invertebrates before the evolution of antibodies. A subset of complement proteins can directly coat certain bacteria, thus either lysing them or targeting them for ingestion by phagocytes. The complement system will be discussed in a subsequent lecture.

Vertebrate immune systems recognize a tremendous diversity of shapes

The innate immune system has remained valuable over millions of years of evolution. We, as a species, retain this machinery as a first line of defense even though we possess a superimposed and more refined system for host protection. This more sophisticated and specific immune system evolved in vertebrates probably because the innate immune system could not effectively guarantee the survival of creatures with a longer potential life span.

The earliest vertebrates were very primitive fish and it is in these animals that the evolution of the immune system made a quantum leap. The immune system in its highly evolved form permits the specific recognition of an incredible variety of shapes that are identified as being foreign. **Acquired or specific immunity** as seen in vertebrates, is designed to be able to deal with any conceivable foreign shape that nature can present or that any synthetic chemist may choose to create at any time in the future. A particularly interesting characteristic of vertebrate immune systems is their ability to respond more readily to foreign shapes that they have seen before, a phenomenon known as **immunological memory**.

Lymphocytes and the clonal selection hypothesis

A major strategy in the evolution of vertebrate immune systems was the development of a means to synthesize a tremendous repertoire of distinct molecules that can recognize and thus help dispose of an almost infinite variety of pathogens. The cells responsible for the vast repertoire of the immune system, so far referred to as immune cells, are known as **lymphocytes**. One lineage of lymphocytes develops in the bone marrow of most vertebrates and in a specialized organ in birds known as the bursa of Fabricius. These lymphocytes are known as **B lymphocytes** (for bursal or bone-marrow derived).

Each individual B lymphocyte makes a distinct protein known as an **antibody** molecule which can recognize a different shape from those recognized by other antibodies made by other B cells. An **antigen** is most simply defined as any structure that can be recognized by the immune system. A given antigen may trigger the expansion of a specific B cell expressing the appropriate antibody molecule on the cell surface. This type of distinct antibody molecule expressed on the cell surface is known as an **antigen receptor or a membrane immunoglobulin**. Each antigen receptor bearing cell may expand on exposure to a cognate antigen to form a **clone** of B lymphocytes that secrete a specific antibody molecule. The concept of distinct antibodies being synthesized by individual lymphocytes which can be clonally expanded by a specific cognate antigen was proposed by Burnet and Talmage in 1955. The **clonal selection theory** is a central paradigm of vertebrate immunology.

While it is useful to think of the immune system as an army of lymphocytes primed to recognize and destroy invaders, we now appreciate that this is not a faceless army, but a force made up of highly specialized individual soldiers. When an invader enters the body, the majority of lymphocytes it encounters may be totally impervious to its existence. The few specialized lymphocytes with the "right" receptors that specifically recognize antigenic shapes on the invader are stimulated. They respond by proliferating (**clonal expansion**) and also activate an impressive battery of weapons designed to wipe out this pathogen.

Humoral and cellular immunity

Immunity mediated by circulating antibodies or agglutinins is called *humoral immunity* - the term "humor" refers to body fluids. Antibodies are secreted by activated clones of B lymphocytes. Serum that contains antibodies against an extracellular pathogen may be transferred to another recipient, conferring passive resistance or *passive immunity*. This is in contrast to the immunity conferred by an actual infection or immunization event which is referred to as *active immunity*.

A second arm of the immune system is referred to as *cellular* or *cell mediated immunity*. Cellular immunity is mediated by thymus derived *T lymphocytes*. Just as distinct membrane antibody molecules constitute distinct receptors for antigen on individual B lymphocytes, individual T cell clones possess distinct T cell antigen receptor molecules each of which recognizes a different antigenic shape.

T cells see only see antigens bound to cell surfaces

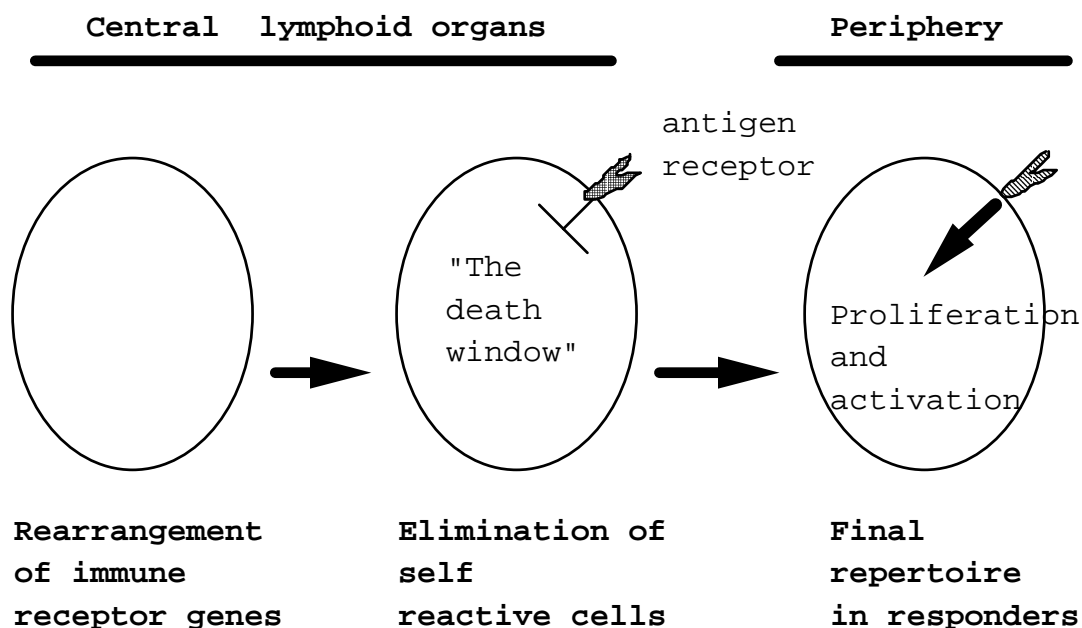
Why do we need T cells? What do T cell receptors see that cannot be seen by antibodies? Humoral immunity is directed against extracellular microbes and antibodies can also block viruses and other pathogens from entering host cells. However antibodies cannot enter or "look into" cells. Viruses and other intracellular pathogens which are established within host cells therefore cannot be seen by antibodies. T cell receptors however are designed to, in a sense, look inside target cells. These receptors monitor whether certain specialized cell surface molecules are bound to fragments of proteins known as peptides that are generated within cells. Peptide fragments are bound to a specialized cleft in molecules known as MHC proteins (the reason why these proteins are called MHC molecules will be discussed later). These MHC proteins carry peptides to the cell surface. If the peptides "presented" on the cell surface are derived from foreign or non-self proteins then they will be recognized by specific T cell receptor bearing T cells. T cell receptors are essentially designed to ignore free antigens and to only recognize peptide complexed to MHC molecules; they thus specifically recognize cells that have been apparently taken over by intracellular pathogens. As a result T cells can recognize and target infected cells that would be left untouched by antibodies.

B and T cell development both involve repertoire generation and the deletion or silencing of self reactive cells

Two unique goals need to be achieved during lymphocyte development. The first is the generation of a diverse immune repertoire - it is necessary to have lymphocytes with receptors that can recognize a very wide variety of shapes. The second requirement is that lymphocyte receptors should be directed against foreign shapes and not against structures prevalent in the host. These requirements are generally referred to as the "generation of diversity" and "self-nonsel discrimination".

The *generation of diversity* will be discussed in some detail in subsequent lectures. Immunoglobulin and T cell receptor genes come in pieces. The V domain of each antibody light chain for instance is encoded by one of a large number of V gene segments. In individual B cells one particular V gene may be selected and physically joined to DNA that encodes the constant regions of the light chain. This recombinational process by which different variable gene segments are joined to DNA encoding constant regions is termed *DNA rearrangement*. The use of this rearrangement process permits, as we shall see, a relatively small amount of the genome to be shuffled around to generate a large number of immune receptors

Once lymphocytes with a wide repertoire have been generated, the need exists to ensure that this repertoire is directed only against foreign antigens. The primary means by which self-nonself discrimination is achieved is by eliminating cells that make receptors directed against self antigens. When lymphocytes are generated in **central** lymphoid organs (the bone marrow for B cells and the thymus for T cells) they pass through a 'developmental window' during which time they respond to antigen not by proliferating but by being inactivated. Very tight binding to antigen during this time period leads to cell death. As lymphocytes pass through this developmental window the antigens that they usually encounter are self antigens. Those lymphocytes with receptors that bind very well to self antigens are thus eliminated. The process by which cells expressing self reactive receptors are eliminated is known as **negative selection** or **clonal deletion** or **central tolerance**. Following development in central lymphoid organs lymphocytes acquire the ability to leave these organs and to seed lymph nodes in the **periphery**.



A simple overview of lymphocyte ontogeny.

In summary, the immune system in vertebrates has two arms. Humoral immunity is the province of B cells and cell mediated immunity is generated by T lymphocytes. Individual lymphocytes have distinct antigen receptors that each recognize a specific shape. The tremendous diversity of antigen receptors is primarily achieved by gene rearrangement. During lymphocyte development most self reactive lymphocytes are tolerized by being triggered by self antigens during a narrow developmental window when cells are wired to be turned off. Beyond this window, cells respond to foreign antigens and divide and differentiate into effector cells of the immune system. Once activated by antigens the immune system exhibits a form of memory and subsequent antigenic challenges meet more aggressive responses.

Additional reading:

Panum, P.L. (1847) Beobachtungen uber das Masercontagium. Virchows Arch. 1, 497-502
The epidemiological argument for immunological memory was made before anyone had actually described the immune system.

GETTING YOUR BEARINGS

This first lecture is meant to be an introduction. Many of the concepts will be reinforced in Lecture II. The terms listed in the glossary above should begin to make sense. In particular you should begin to get a feel for the differences between innate/natural immunity and adaptive/specific immunity

Glossary for Lecture 1:

Active immunity: Immunity conferred by immunization (as opposed to Passive Immunity)

Adaptive Immunity: aka Specific Immunity. Lymphocyte dependent immune system which has very diverse antigen receptors and exhibits memory.

Agglutinins: Multivalent proteins that recognize structures on cell surfaces or on other proteins. They can precipitate pathogens or coat them for removal by phagocytes. They may “fix” complement proteins on the surfaces of pathogens.

Antibodies: Y shaped proteins of adaptive immunity, which are the bullets of the humoral immune system (B lymphocytes are the warriors).

Antigens: Structures recognized by the immune system. May or may not be an immunogen.

B lymphocytes: “Bursal” or “Bone-marrow” derived lymphocytes. Responsible for antibody mediated humoral immunity.

Cell Mediated Immunity: Immune responses mediated by cells.

Complement: Serum protein cascade which is generally activated either by certain pathogens or by agglutinin or antibody coated microbes.

Humoral immunity: Immune responses mediated by circulating secreted molecules

Immunogens: Antigens that can *induce* specific immune responses. Some antigens can be recognized by the immune system but do not induce responses – they are NOT immunogens.

Innate Immunity: aka Natural Immunity. Immune system which responds in minutes and hours to noxious stimuli. Less specific than Adaptive immune system and does not exhibit memory.

Natural Immunity: aka Innate Immunity

Passive Immunity: Immunity that is passively obtained without immunization by the transfer of cells or serum

Phagocytes: Cells which gobble up microbes and other particles

Specific Immunity: aka Adaptive Immunity

T lymphocytes: Thymus derived lymphocytes. Mediate cellular immunity during adaptive immune responses.