Innate immune system components

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There are individual systems of the immune system, innate immunity which we are born with and it is non-specific. It is genetically based and passed on to our offspring and adaptive immunity in which we acquire through humoral and cell mediated immunity. Innate and adaptive immune systems are distinct systems but act together at numerous levels to develop a complete defense against invading pathogens. Both systems have mechanisms for distinguishing self from non-self, therefore, under normal situations they are not directed against the host’s tissues and cells.

Innate Immunity

Elements of the innate immune system (figure 1. 8) have been known for many years. However, in the past few years there has been a greater focus on innate immunity and its role in protection against infection and tissue injury and its role in tolerance to self-antigens.

Innate immunity defines a collection of protective mechanisms the host uses to prevent or minimize infection. The innate immune system operates in the absence of the specific adaptive immune system but is tied to adaptive immunity in many ways. The innate immune system is characterized by a rapid response to an invading pathogen or foreign or effete cells. In addition

to the rapid response, it is also non-specific and usually of a short duration. Innate immunity lacks immunological memory and there is no clonal expansion of lymphocytes as seen in the adaptive immune response. The innate immune response is also important in directing the specific, long-lived adaptive immune response.

The host defense mechanisms associated with innate immunity consist of a number of physical barriers (intact skin) and secretions accompanied by a number of serum factors such as complement, certain cytokines, and natural immunoglobulin’s. The cellular components of innate immunity include a number of cell types, many of which are found at potential points of entry of pathogens. Examples of these cells include natural killer (NK) cells, (figure 1. 2), polymorphonuclear neutrophils (PMNs), macrophages (figure 1. 3), and dendritic cells (DCs), (figure 1. 2).

The intact skin and mucosal tissues provide considerable protection against invading infectious agents. However, once the agents pass through the skin a number of important events take place. This includes activation of the complement cascade that triggers the development of a number of substances to attract phagocytes to the area.

A number of antimicrobial peptides are produced at epithelial cell surfaces. These antimicrobial peptides play an important role in local defense mechanisms, disrupt bacterial cell membranes, and probably play a role in preventing skin infections.

Antimicrobial Peptides (figure 1. 4)

Human Î²-defensins are produced by epithelial cells in the mucous membranes of the airways and intestinal tract. Defensins are small cationic peptides that have broad antimicrobial activities against a number of microbial agents including Gram-positive and Gram-negative bacteria, fungi, and enveloped viruses. Defensins are non-glycosylated peptides containing approximately 35 amino acid residues, and Î²-defensins have six cysteine residues that provide a distinct structure.

Stimulation of the epithelium by certain cytokines can induce defensin production.

The exact mode of action of defensins' antimicrobial activity is unknown.

There are three defensin subfamilies: Î±-defensins, Î²-defensins, and Î¸-defensins

- The Complement System

The complement system (figure 1. 5) is another important component of innate immunity. The system consists of 30 proteins found in serum or on the surface of certain cells.

Activation of the complement system results in a cascade of biochemical reactions that ultimately ends in lysis and disruption of foreign or effete cells. Without activation, the components of the complement system exist as pro-enzymes in body fluids.

As a by-product of the activation of the cascade, a number of biologically reactive complement fragments are generated. The complement fragments can modulate other parts of the immune system by binding directly to T

lymphocytes and bone marrow-derived lymphocytes (B lymphocytes) of the adaptive immune system and also stimulate the synthesis and release of cytokines.

- Natural Antibodies

Natural antibodies have been recognized for some time but recently they were described as a component of the innate immune system. Natural antibody is defined as an antibody that is found in normal, healthy individuals who have no evidence of exogenous antigenic stimulation. Natural antibodies are believed to develop in a highly regulated manner; they are usually found in low titer in serum and are low-affinity antibodies. A high percentage of the natural antibodies found in serum are of the IgM class. These antibodies are produced by a primitive B lymphocyte, called the B-1 lymphocytes. B-1 cells are usually CD5+ and considered to be long-lived and self-replicating.

Natural antibodies play an important role as a first line of defense against pathogens and other types of cells, including precancerous, cancerous, cell debris, and some self-antigens.

- Toll-Like Receptors (TLR)

TLRs (figure 1. 6) are found on phagocytic cells, including mononuclear phagocytes, circulating monocytes, tissue macrophages, and endothelial cells, and are important components of the innate immune system. TLRs make up a family of cell surface protein receptors present on several cell types that function to recognize certain conserved molecular components of microorganisms and signal that microbes have breached the body’s barrier

defences. TLRs serve as first responders in a mammalian host to recognize the presence of an invading pathogen. They also generate an inflammatory response to attempt to remove the invading agent.

Phagocytosis (figure 1. 7)

Polymorphonuclear neutrophilic leukocytes have been well-known components of the innate immune system for many years. Detailed studies of PMN phagocytosis and intracellular killing of microorganisms have led to a better understanding of important defense mechanisms against invasion by pathogenic bacteria, fungi, and enveloped viruses. PMNs are attracted to the site of microbial invasion, recognize the microbe, become activated, kill the microorganisms, resolve the infection, undergo apoptosis, and are then ingested and removed by either macrophages or neighbouring endothelial cells to resolve the inflammatory response.

PMNs arise as myeloid progenitors in the bone marrow. Specific growth factors and cytokines mediate the differentiation of myeloid precursors into mature PMNs. After entering the circulation, the PMNs have a half-life of about 8-12 h before undergoing a programmed cell death (apoptosis) and are reabsorbed through endothelial walls. The PMN turnover is about 1011 cells per day.

- Cytokines and Chemokines

Cytokines and chemokines are small, secreted polypeptides that regulate essentially all functions of the immune system. Cytokines participate in determining the nature of the immune response by regulating or controlling

cell growth, differentiation, activation, immune cell trafficking, and the location of immune cells within the lymphoid organs.

Cytokines are a group of “ intercellular messengers” that contribute to inflammatory responses through activation of the host’s immune cells. Cytokines are host-derived products that enhance the recruitment of circulating leukocytes as a response to the presence of pathogens. Cytokines also play important roles in leukocyte attraction by inducing the production of chemokines, which are known to be potent mediators of chemo-attractant activity for inflammatory cells. Chemokines and cytokines provide a complex network of signals that can either activate or suppress inflammatory responses

- Natural Killer Cells

Initially, NK cells were referred to as non-specific lymphocytes because NK cells could kill certain virally infected and malignant cells without known prior sensitization. NK cells were known to resemble large lymphocytes morphologically and were referred to as large granular lymphocytes.

Approximately, 10-15% of the lymphocytes circulating in peripheral blood are NK cells. NK cells are distinct from T- and B lymphocytes because they express neither immunoglobulin receptors nor T-cell antigen receptors. There are other distinctions including phenotype and function. NK cells have receptors that recognize major histocompatibility complex (MHC) class I antigens. Because NK cells have cytotoxic properties, their function is highly regulated in their interactions in both the innate and adaptive immune systems.

NK cells play important roles in innate immune responses and immune regulation.

They communicate with other cells through a complex of both activation and inhibitory signals through cell surface receptors.

- Dendritic Cells

The DCs develop in the bone marrow from hematopoietic pluripotential stem cells. Precursor DCs are constantly generated in the bone marrow and are released into the peripheral blood. After leaving the bone marrow, the precursor DCs “ home” to a number of different tissues where they reside as sentinels waiting to interact with antigen. The precursor DCs express low-density MHC class II antigens and after encountering a proper stimulus differentiate into highly endocytic and phagocytic iDCs. Precursor DCs circulate in the environment and on contacting a pathogen produce cytokines, that is, Î³-interferon, and undergo maturation to iDCs. The iDCs increased phagocytic and endocytic capabilities that lead to binding antigen by the iDCs and then maturation to mature DCs.

Adaptive Immunity

In contrast to innate immunity, adaptive immunity (figure 1. 8) is flexible, specific, and has immunological memory, that is, it can respond more rapidly and vigorously on a second exposure to an antigen. Immunologic memory provides a more powerful response to a repeated exposure to the same foreign substance or antigen. Adaptive immunity is more complex because it provides the ability to respond very specifically. Innate and adaptive immunity responses interact effectively to enhance the body’s defense

mechanisms against foreign or damaged host cells. Inherent in both innate and adaptive immune responses are the mechanisms to distinguish self from non-self.

The primary blood cell elements of the adaptive immune system are T lymphocytes and B lymphocytes. These T- and B-cells provide the unique specificity for their target antigens by virtue of the antigen-specific receptors expressed on their surfaces.

The B- and T-lymphocyte antigen-specific receptors develop by somatic rearrangement of germline gene elements to form the TCR genes and the immunoglobulin receptor genes. This recombination mechanism provides unique antigen receptors capable of recognizing almost any antigen encountered, and provides the specific immunological memory for a rapid, vigorous, and specific response to a later exposure to the same antigen. It is estimated that millions of different antigen receptors may be formed from a collection of a few hundred germline-encoded gene elements.

For many years, innate and adaptive immune responses were studied as separate systems because of their different mechanisms of action. However, it is now understood that synergy between the two systems is required to provide adequate immune reactivity against invading pathogens. Innate immune responses, through their barrier and relatively broad types of actions, represent the first line of defense against pathogens.

At the time the innate system is getting activated, the adaptive system becomes activated also. The adaptive response becomes evident a few days later because it requires time for sufficient antigen-specific receptors to be

generated through clonal expansion/proliferation. There are multiple interactions occurring between the two systems, which results in the co-amplification of each respective response and leads to the ultimate destruction and elimination of the invading pathogen.

- B lymphocytes

The primary function of B lymphocytes is the production of antibodies that are specific for a given antigenic component of an invading pathogen. Antibodies are encoded by the heavy (H)- and light (L)-chain immunoglobulin genes. Antibodies may be secreted or cell surface-bound on B lymphocytes. There are five classes of immunoglobulin's: IgM, IgG, IgA, IgD, and IgE; and the classification is based on the isotypes of the H chain. B lymphocytes represent roughly 10-15% of the peripheral blood lymphocyte population and free immunoglobulin's make up a considerable proportion of serum proteins. After an encounter with a specific pathogen and an antibody response is generated, the level of specific antibodies to that antigen decreases in serum over a relatively short period of time. However, immunological memory persists in the B-cell population, which is capable of rapid clonal expansion upon re-exposure to that same antigen.

- T lymphocytes

Whereas B lymphocyte products recognize extracellular pathogens, T lymphocytes are adept at identifying and destroying cells that have been infected by intracellular pathogens. For T cells to recognize antigenic peptides, the peptide must be presented in the context of cell surface MHC class I or class II proteins.

In other words, T cells can only recognize molecular complexes consisting of the antigenic peptide and a self-structure, that is, the MHC. Depending on whether the antigenic peptide has been synthesized within the host cell or ingested by the cell and modified by proteolytic digestion, either MHC class I or class II proteins are required. Proteins of the MHC are intimately tied to T-lymphocyte responses and recognition of antigenic peptides. The MHC class I proteins consist of three HLA classes: HLA-A, HLA-B, and HLA-C with hundreds of allelic variants of each. Structural studies have shown that class I molecules exist as cell surface heterodimers with a polytransmembrane Î±-chain associated (noncovalently) with a nonpolymorphic Î²2 microglobulin protein. The protein chains are folded in such a way as to form a physical groove capable of binding up to an 11 amino acid long peptide. Antigenic proteins are degraded by proteolytic enzymes to about this size for binding to the

MHC class I proteins for antigenic presentation. Antigenic peptides are bound in the groove of the HLA molecule and expressed to the cell surface for presentation to initiate a T-cell response.

Humoral Immunity (figure 1. 9)

The human immunoglobulins are a family of proteins that confer humoral immunity and perform vital roles in promoting cellular immunity. Five distinct classes or isotypes of immunoglobulin’s (IgG, IgA, IgM, IgD, and IgE) have been identified in human serum on the basis of their structural, biological, and antigenic differences. 1-4 IgG and IgA have been further subdivided into subclasses IgG1, IgG2, IgG3, and

IgG4 or subclasses IgA1 and IgA2 on the basis of unique antigenic determinants. Multiple allotypic determinants in the constant region domains of human IgG and

IgA molecules as well as kappa (Îº) light chains indicate inherited genetic markers.

Finally, there are several immunoglobulin-associated polypeptides such as secretory component (SC) and J chain that have no structural homology with the immunoglobulin’s, but serve important functions in immunoglobulin polymerization and transport across membranes into a variety of secretions (e. g., saliva, sweat, nasal secretions, breast milk, and colostrum). This diversity of the immunoglobulin components of the humoral immune system provides a complex network of protective and surveillance functions.

- Human IgA

Polymeric secretory IgA (figure 1. 10) is composed of two four-chain basic units and one molecule each of SC and J chain (approximately 400, 000 MW). It is the predominant immunoglobulin in colostrum, saliva, tears, bronchial secretions, nasal mucosa, prostatic fluid, vaginal secretions, and mucous secretions of the small intestine. In contrast, 10% of the circulating serum IgA is polymeric, whereas 90% is monomeric (160, 000MW). Together, they constitute approximately 15% of the total serum immunoglobulin’s. Trimers and higher polymeric forms can exist, but in small amounts. Two subclasses of IgA have been identified (IgA1 and IgA2), which differ by 22 of the 365 amino acids. In terms of complement activation, IgA poorly activates the classical pathway.

This process has been hypothesized as a host mechanism for attenuating inflammatory responses induced by IgG antibodies at the mucosal surface. In contrast, IgA reportedly activates the alternative pathway of complement to provide some direct protective functions. IgA, once bound to a bacterial or parasitic surface antigen, may bind CD89 (IgA receptor) on infl ammatory cells (monocytes, macrophages, neutrophils, and eosinophils), leading to their destruction by means of antibody dependent cell-mediated cytotoxicity (ADCC). Moreover, its binding to viral or microbial surface antigens may restrict the mobility of microorganisms and prevent their binding to mucosal epithelium. Finally, secretory IgA can play an important first line of defense in antigen clearance by binding to antigens that leak across an epithelium and transporting them back across to prevent their entry. To summarize, IgA’s unique structure resists proteolysis and it functions to block uptake of antigen, bacterial or viral attachment, limit inflammation induced by classical pathway complement activation, and promote microbial destruction through ADCC by binding to leukocyte receptors.

- Human IgD

IgD (figure 1. 11) is a four-chain monomer of approximately 180, 000 MW with a long hinge region that increases its susceptibility for proteolytic cleavage. Although IgD is normally present in serum in trace amounts (0. 2% of total serum immunoglobulin), it predominantly serves as a membrane-bound antigen receptor on the surface of human B lymphocytes. Despite suggestions that IgD may be involved in B-cell differentiation, its principal function is as yet unknown. As such, IgD is rarely quantified in a general workup of an individual suspected of a humoral immune deficiency or a B-

cell dyscrasia. Hyperimmunoglobulinemia D with serum IgD levels > 100 U/mL, however, has been noted in conjunction with periodic fever syndrome. This condition is a rare, autosomal recessive disorder that is characterized by recurrent episodes of fever accompanied by abdominal distress, lymphadenopathy, joint involvement, and skin lesions. It appears to be particularly responsive to anti-tumor necrosis factor (TNF) treatment. Mutations that lead to this disease occur in the mevalonate kinase gene, which encodes an enzyme involved in cholesterol and nonsterol-isoprenoid biosynthesis.

- Human IgE

IgE (190, 000 MW) was identified in 1967 as a unique immunoglobulin that circulates in serum as a four-chain monomer. Although IgE constitutes only 0. 004% of the total serum immunoglobulins, it possesses a clinically significant biological function by binding through its Fc region to the alpha chain on high-affinity receptors (FcÎµR1) on mast cells and basophils. On subsequent exposure to relevant protein allergens from trees, grasses, weeds, pet dander, molds, foods, or insect venoms, IgE antibodies on mast cells become cross-linked. This process triggers the production and release of vasoactive mediators (e. g., histamine, prostaglandins, and leukotrienes) that can induce mild to severe immediate type I hypersensitivity reactions in sensitized atopic individuals.

- Human IgG

In healthy adults, the four polypeptide chain IgG monomer (150, 000 MW) constitutes approximately 75% of the total serum immunoglobulin’s. IgG is

approximately equally distributed between intra- and extravascular serum pools. Moreover,

IgG possesses the unique ability to cross the placenta, which provides protection for the fetus and newborn. Human IgG has been subdivided into four subclasses on the basis of unique antigenic determinants. IgG1, IgG2, and IgG4 possess an MW of approximately 150, 000, whereas IgG3 is heavier (160, 000 MW) as a result of an extended 62-amino acid hinge region that contains 11 interchain disulfide bonds. IgG3's highly rigid hinge region promotes accessibility of proteolytic enzymes to sensitive Fc cleavage sites, which results in an increased fractional catabolic rate and a shorter biological half-life (7-8 days) than has been observed for IgG1, IgG2, and IgG4 (21-24 days). In terms of complement activation, IgG1 and IgG3 are the most effective, whereas IgG4 due to its compact structure does not readily activate the classical pathway of complement. IgG4 antibodies are also unique in that they appear to be functionally monovalent due to in vivo exchange of IgG4 half-molecules. As such, this is believed to lead to the formation of small IgG4 immune complexes that have a low potential for inducing immune inflammation. Moreover, IgG4 antibodies have the ability to interfere with immune inflammation caused by the interaction of complement-fixing IgG subclasses with antigen. Researchers in the field of allergy have speculated that IgG4 antibodies also scavenge antigen that prevents mast cell-bound IgE antibody from being cross-linked by antigen, and thus blocking IgE-mediated hypersensitivity reactions in atopic individuals who have undergone immunotherapy. Other important structural and biological differences among the human IgG subclasses relate to their Fc

receptor binding, and the different binding sites on the constant region domains for rheumatoid factors, complement components, and bacterial proteins (protein A and protein G).

- Human IgM

IgM (figure 1. 12) is a pentameric immunoglobulin of approximately 900, 000 MW that is composed of a J chain and five IgM monomers. Pentameric IgM constitutes approximately 10% of serum immunoglobulin's in healthy individuals. Along with IgD, monomeric IgM is also a major immunoglobulin that is expressed on the surface of B cells where it serves as an antigen receptor. The C-terminal portion of pentameric secreted IgM differs from that of its monomeric cell-bound form. Secreted IgM has a mu chain with a 20-amino acid hydrophilic tail and a penultimate cysteine that facilitates polymerization. Cell membrane-bound IgM has a 41-amino acid membrane tail that contains a hydrophobic 26-amino acid segment that anchors the IgM molecule in the B-cell membrane lipid bilayer. IgM antibodies are clinically important because they predominate as an antigen receptor in early immune responses to most antigens. With a functional valency of 10, IgM antibodies are highly efficient in activating the classical complement pathway. IgM's actual functional valency, however, is only 5 due to steric hindrance among its many antigen-binding sites.

Cell Mediated Immunity

Cell Mediated Immune response (CMIR) (figure 1. 9) is the functional " effectors" pf the immune response for phagocytosis, cell killing by cytotoxic T cells, NK and K cells

- Macrophage Activation

While the production of antibody through the humoral immune response can effectively lead to the elimination of a variety of pathogens, bacteria that have evolved to invade and multiply within phagocytic cells of the immune response pose a different threat.

- Cell Mediated Cytotoxicity

Cell Mediated Cytotoxic immune response is implicated in refusal of foreign grafts and the exclusion of tumors and virus-infected cells. The cells involved in these methods are cytotoxic T-lymphocytes, NK-cells and K-cells.

- NK cells

Also known as the “ large granular lymphocytes” are normally non-specific, MHC-unrestricted cells involved mainly in the elimination of neoplastic or tumor cells. Once the target cell is recognized, killing occurs.

- K cells

K-cells contain immunoglobulin Fc receptors. They are involved in Antibody-dependent Cell-mediated Cytotoxicity (ADCC). ADCC occurs as a result of an antibody being bound to a target cell surface via specific antigenic determinants expressed by the target cell. Once bound, the Fc portion of the immunoglobulin can be recognized by the K-cell. This type of CMIR can also result in Type II hypersensitivities.