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A Comprehensive Study on Immune System & the impact of various pathogens on it

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Abstract: The induction of immune responses requires critical interaction between innate parts of the immune system, which respond rapidly and in a relatively nonspecific manner, and other specific parts, which recognize particular epitopes on an antigen. A critical element in this interaction is the role played by dendritic cells (DCs), which represent "professional antigen-presenting cells." DCs also play a direct role with the stimulation of the B lymphocytes. It appears that DC can deliver antigen to the B lymphocytes in a more intact form than the processed form essential for stimulating T lymphocytes, and can release cytokines that assist the differentiation of the B lymphocytes into antibody-producing cells. This close relationship among the three cell types and the cytokines that are produced ensures the precise control and regulation necessary for immune response development. In this paper, the author has tried to conclude the various effects and demerits of pathogens on Immune System.

Keywords: dendritic cells; immune defenses; lymphocyte responses; diseases, system.

INTRODUCTION

The immune system is a collection of cells, tissues, and organs that are responsible for fighting off infection and disease. It helps us protect our body from viruses, bacteria, fungi, and parasitic worms, all trying to use our body's precious resources or destroy us outright. By that definition I think it's clear the connection between the immune system and your police force.

Immunity depends on an intricate homeostatic system aimed at maintaining a delicate balance between health and disease. Its function is maintained by a series of complex, highly regulated, multi-cellular, physiologic mechanisms designed to accomplish a singular goal: to differentiate self from non-self. The healthy immune system has the ability to distinguish between the body's own cells, recognized as "self" and foreign cells, or "non-self." When the immune system is challenged by a microbe, it has many defense barriers and types of responses to choose. The immune defenses normally coexist peacefully with cells that carry distinctive self marker molecules. Anything that can trigger this immune response is called an antigen. An antigen can be a microbe, or a part of a microbe such as a molecule. Tissues or cells from another person (except an identical twin) carry non-self markers and act as foreign antigens. In abnormal situations, the immune system can mistake self for non-self and launch an attack against the body's own cells or tissues. Immuno competence is maintained by the concert of lymphoid organs, specific and non-specific cellular and humoral factors. All immune cells begin as immature stem cells in the bone marrow. They respond to different cytokines and other chemical signals to grow into specific immune cell types, such as T cells, B cells, or phagocytes. Lymphocytes known as T lymphocytes or T cells ("T" stands for "thymus") mature in the thymus and then migrate to other tissues. B lymphocytes, also known as B cells, become activated and mature into plasma cells, which make and release antibodies or immuno globulins (G, M, A, E and D).

Almost all the human inventions have taken nature functions as the inspiration, especially human body and its functions lead to emergence of Artificial Intelligence Techniques. The Artificial Neural Networks are inspired by human neural network and its functions, Genetic Algorithms are inspired by biological genetic functions, and likewise the Artificial Immune System (AIS) is also inspired by Biological Immune System (BIS) and its functions. But not like artificial neural networks and genetic algorithms, the AIS has extracted almost all the functions of BIS, as BIS is a robust, error tolerance, decentralized and adaptive system[1]. The concept of AIS was proposed by Farmer, Packard and Perelson in late 1980s, but it has emerged in 1990s as a class of computational intelligence. In BIS, white blood cells protecting our body from unwanted attacks from fungus, bacteria and viruses, by having well established network system.

The job of the mammalian immune system is to defend the body against these pathogens, which include bacteria, viruses, fungi and parasitic worms. This task is so complex that mammals have evolved a very sophisticated network of defense

units that recognize and attack such a diverse array of potential enemies. The immune system is characterized by three universal features, which are namely specificity, diversity, and memory. We say the immune system is specific because it only reacts against certain specific molecular targets called antigens. It is very important that the immune system is able to select what it reacts to because this prevents it from attacking components of our own body: a phenomenon called autoimmunity. The immune system is described as diverse because it has the remarkable ability to react specifically to any molecule in the universe. At the end of a successful immune reaction, the immune system assigns a unique group of immune cells, called memory cells, the task of remembering the particular enemy encountered (virus, bacterium, tumor cell, etc) [2].

In this way, there will be immune combat units ready to attack and kill off the fresh invaders very swiftly if they are encountered in the future. The defense system of the human body consists of surface barriers such as skin, internal barriers such as mucus, and special groups of cells, chemicals, and hormones that act in concert to keep the body free of pathogenic invaders. In broad terms, the immune system is divided into two branches called the innate and adaptive defense systems. In evolutionary terms, the innate branch predates the adaptive branch by about 500 million years.

Innate Immune Defenses

The innate immune system evolved to protect host organisms about 900 million years ago. It consists of mechanical, chemical, microbiological, and cellular defense 9 networks. The function of the innate immune defense system is akin to "turning back the barbarians at the gates." We can view the skin as a huge missile defense shield that prevents the entry of pathogens and foreign substances into the body. In addition, the skin produces acidic substances that make it difficult for bacteria to grow on it. Nevertheless, there is a class of harmless bacteria and fungi that thrive on our skin [3].

Innate immune defenses are composed of numerous and variable components. The skin, mucosal secretions, and stomach and intestinal pH are physical/chemical barriers that form the first line of innate defense. When an infectious agent evades these barriers and invades the host, cellular innate immune defenses come into play. The agent first encounters histiocytes and monocytic cells. Other cells of the innate immune defenses include the NK cells, which attack infected host cells and mast cells involved in anaphylactic-type responses.

Further down the nasal cavity, en route to the respiratory tract are structures called cilia whose job it is to move trapped pathogens away from the respiratory tract. If the cilia fail to do their job properly, coughing and sneezing is induced to expel pathogens from the upper portion of the respiratory tract. Any pathogen that makes it passed all these road blocks into the stomach is assailed by a deadly potion called gastric juice: this is a mixture of concentrated acid and enzymes that chew up the invading pathogens into harmless bits of protein.

Apart from their normal function of lubrication and cleansing, our tears and saliva contain an enzyme called lysozyme that cuts and destroys the bacterial cell wall. Finally, the body produces mild acids into the vagina in order to prevent the growth of pathogens in the female reproductive tract. All these security barriers are part of the innate defense system because they are general protection mechanisms that are designed to keep pathogens out of the body [4].

As the first elements of the immune system to encounter an invading agent, innate defenses are activated more rapidly than the specific responses but are of shorter duration. Although cellular defenses of innate immune responses do not recognize specific epitopes on an antigen in the manner observed with the specific immune responses, they do rely heavily on the interaction of particular cell surface receptors with the pathogen in question. Such receptors are pattern recognition receptors, referred to as pathogen-associated molecular patterns. Examples are the TLR family, the complement receptors, the mannose receptor and CD14. C-type lectins, receptors for heat-shock proteins, and certain integrins are also important. Although integrins are involved in regulating cellular interactions during both innate and specific responses. Innate responses comprise a number of soluble factors. These factors include the serum proteins, which can bind to the surface of the invading agents and are called opsonins. Examples are complement, natural antibodies, lipopolysaccharide-binding protein, mannan-binding protein, and acute phase proteins. The latter, as well as certain by-products of the complement activation (complement cascade or factors), also plays a signaling role [5].

Overall, the immune system recognizes and rapidly responds to microbial pathogens via pattern recognition. A complex example of pattern recognition can be found in our extraordinary ability as human beings to recognize patterns in the environment using cognitive processes to distinguish visual images such as models of cars or species of birds. In the innate immune system, cell surface receptors (like PRRs) that recognize distinct biochemical patterns (like PAMPs) displayed by microbial invaders constitute a receptor-ligand interaction that forms the bedrock of the innate immune system.

Overview of BIS

The BIS is naturally well sophisticated, and decentralized, error tolerance, robust and adaptive system which plays two major roles; protecting the body against invading micro-organism such as fungi, bacteria and virus and keeping them out by failing them or destroying them and regulating bodily functions. The immunologists have found that, the BIS have two functional parts, namely innate immune system and adaptive immune system. The function of innate immune system is responding to known threats while the adaptive immune system is tackling the encountered threats. However within these two parts they have little cross over when they are functioning against pathogens [6] The key ability of BIS is, it can distinguish the body's own cells- called self-cells and foreign cells-called non-self-cells. Normally the immune system works with self-cells which are carrying molecules, but when noticed a cell or organism carrying foreign invaders (non-self), it will quickly launch the attack; this is so called immune response. Another major capability of BIS is, it can remember millions of distinguishing enemies.

Therefore they can produce secretions and can match up those cells and wipe nearly all of them out, by having a dynamic communication network. The organs of BIS that are spread throughout the body are called lymphoid organs, as they are generated by lymphocytes (white blood cells), and are the key players of BIS. Lymphocytes are produced by bone marrow (it's the source of all blood cells), which is in the hollow center of bones and by using blood vessels, lymphocytes are travelling throughout the body. The lymphocytes have three subclasses; namely B-cells, T-cells and NKT cells and AIS are mimicking the functions of these cells [7]. The B-cells works primarily by concealing solvable know as antibodies and they mill around a lymph node and wait for an antigen. Once the antigen arrives it will match up with a specific antibody and proceed the immune response. At that time the antigen binds the antibody, the Bcell overwhelm it and the B-cell becomes large plasma, which can produce number of antibody copies (up to 100 million copies an hour), after a special helper T-cell joins the action.

Then these antibodies will travel throughout the body by bloodstream to search more antigens. The antibodies of B-cells cannot kill an invading organism by themselves, but they make those antigens by their antibodies and let other immune cells to kill them. The T-cells contribute to immune action in two ways; some help to regulate the overall immune response while the others which are called cytotoxic directly contact the non-self –cells (the cell marked by the antibodies of B-cells) and abolish them. The helper T-cells play a major role here. They are responsible to activate many immune cells including B-cells and other T-cells. The Killer cells (NKT) can be divided into at least two parts; cytotoxic T-cells and natural killer cells and both contain granules filled with intoxicating chemicals to destroy on contact [8].

Immune Deficiency and Diseases

This is when your body, whether due to genetics or disease, doesn't have enough immune system cells to properly fight off disease or when it has dysfunctional tissues and organs that result in an inadequate production of immune cells.

Anyways, you can appreciate that if your police force is short on staff and has inadequate buildings, cars, and equipment, it cannot do a very good job of preventing crime or stopping criminals in their tracks. This causes an increase in thefts, fires, and an overall high crime rate around your neighborhood. Let's discuss how this scenario can arise in your body, resulting in a predisposition to disease, by discussing some immune deficiency problems.

One very famous example is AIDS, or acquired immunodeficiency syndrome. AIDS is caused by a virus known as HIV, or human immunodeficiency virus. Anyways, this virus is like a crook that enters your body and kills important immune system cells, called CD4+ T cells, the cells that are actually supposed to kill the virus!

This results in a depletion of police officers in the body and because there are fewer police officers at your disposal, they are unable to catch opportunistic pathogens, which are disease causing agents that attack the body when it is weak, meaning these guys are normally too afraid of the police, but when they see there are fewer of them, that's when they strike the body to cause disease [9].

But these immune deficiency disorders don't always have to strike at the already well-trained officers in your police force. Sometimes they strike at the police academy center, thereby ensuring your cadets never get the training they need, meaning these cadets never fully develop, and the few that do tend to be dysfunctional because of the poor training.

An example of this case is something abbreviated as SCID, or severe combined immunodeficiency. This disorder arises

due to a genetic mutation, meaning your genes, the architects and writers that design the training center and manual, are defective.

Another way by which your police force can be affected is due to a lack of equipment. I mean, if you had a lot of officers, but they didn't have any weapons to fight criminals, then obviously they'd be of little to use to you. Well, there is a disease abbreviated as CVID, or common variable immunodeficiency, that causes your police force to lose its weapons.

The Hypersensitivity, Autoimmune, and Immune-mediated [HAI] Diseases Study Section reviews applications from basic, pre-clinical, and clinical investigators, involving autoimmune and inflammatory diseases, hypersensitivity and allergic diseases, asthma, primary and secondary states of immunodeficiency syndrome (non-AIDS) and others diseases. Emphasis is on the etiology, initiation, immunopathophsiology, prevention and treatment of diseases in which the immune system (innate and adaptive) is the major contributor. Approaches include human studies, in vitro studies of patient material, animal models, and genomic and proteomic approaches to immune-mediated disease questions [10].

Immunosupression is a decrease in immune function measured as an effect on cellular, humoral, or non-specific immune parameters. Primary immune response is the more susceptible to suppression (e.g: macrophage phagocytic activity), although a wide range of subtle effects has been described. Heavy metals, polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), certain air pollutants, certain pesticides and drugs may cause significant and persistent immunosuppresive effects. The likely clinical sequels of immunosupression are increased rates of infectious diseases and neoplasia.

Hypersensitivity disorders are the most prominent forms of immunotoxicity recognized in humans. Hypersensitivity is an exaggerated response to an antigenic stimulus, commonly distinguished by a reduced threshold to antigen response. Regardless of their type, all hypersensitivity reactions are induced by recall antigens in or on a host that has previously caused an immune response to the antigen. This type of immunopathology can be antibodymediated, cell-mediated or a combination of both.

The developing immune system can be permanently altered or ‘programmed’ by the early exposure to environmental agents. A growing number of childhood diseases such as allergic disorders (e.g. allergic rhinitis, atopic dermatitis, asthma), cancer (e.g. acute leukemia and myeloid leukemia), and others (e.g. type 1 diabetes) have been linked to environmental exposures during prenatal and early postnatal development because the immune response plays a critical role in each of these diseases.

Health risks are significantly increased following early life versus adult immunotoxic exposures. The pre and postnatal periods are particularly sensitive to environmental agents. There are several examples suggesting that the developing immune system is altered by significantly lower doses of toxicants than those required to produce effects in the adult. Sensitivity to immunotoxicants may produce a wide spectrum and severity of effects. Different and unpredictable arrays of alterations may be expected when the exposure occurs in utero or in the early neonate versus the adult exposure. A number of chemicals produce different ranges or severities of outcomes depending upon age of exposure. The immunotoxic alterations after early exposure may be persistent and last long after exposure. Diethylstilbestrol (DES) is an example where early xenobiotic exposure results in a greater persistence of effects than would be predicted from adult exposure assessment [11].

Decreased immune responsiveness (immunosupression) may be caused by genetic / congenital disorders (primary immunodeficiency). The acquired immune deficiency syndrome (AIDS) represents the first recognised acquired epidemic chronic immunosuppressive defect caused by a viral infection. Functional activation of the immune system (hypersensitivity) may occur associated with chronic stress. Lymphocytes have membrane receptors to catecholamine, particularly NK cells. There is increasing evidence to support that infectious agents, radiation, therapeutic agents and chemicals of diverse origins may act as etiologic agents in the induction of both types of immune diseases.

Cellular Counterattack: The Second Line of Defense

The surface defenses of the vertebrate body are very effective but are occasionally breached, allowing invaders to enter the body. At this point, the body uses a host of nonspecific cellular and chemical devices to defend itself. We refer to this as the second line of defense. These devices all have one property in common: they respond to any microbial infection without pausing to determine the invader’s identity. Although these cells and chemicals of the nonspecific immune

response roam through the body, there is a central location for the collection and distribution of the cells of the immune system; it is called the lymphatic system. The lymphatic system consists of a network of lymphatic capillaries, ducts, nodes and lymphatic organs and although it has other functions involved with circulation, it also stores cells and other agents used in the immune response. These cells are distributed throughout the body to fight infections, and also stored in the lymph nodes where foreign invaders can be eliminated as body fluids pass through [12].

Cells That Kill Invading Microbes

Perhaps the most important of the vertebrate body's nonspecific defenses are white blood cells called leukocytes that circulate through the body and attack invading microbes within tissues. There are three basic kinds of these cells, and each kills invading microorganisms differently.

Macrophages are large, irregularly shaped cells that kill microbes by ingesting them through phagocytosis, much as an amoeba ingests a food particle. Within the macrophage, the membrane-bound vacuole containing the bacterium fuses with a lysosome. Fusion activates lysosomal enzymes that kill the microbe by liberating large quantities of oxygen free-radicals. Macrophages also engulf viruses, cellular debris, and dust particles in the lungs [13]. Macrophages circulate continuously in the extracellular fluid, and their phagocytic actions supplement those of the specialized phagocytic cells that are part of the structure of the liver, spleen, and bone marrow. In response to an infection, monocytes (an undifferentiated leukocyte) found in the blood squeeze through capillaries to enter the connective tissues. There, at the site of the infection, the monocytes are transformed into additional macrophages.

Neutrophils are leukocytes that, like macrophages, ingest and kill bacteria by phagocytosis. In addition, neutrophils release chemicals (some of which are identical to household bleach) that kill other bacteria in the neighborhood as well as neutrophils themselves [14].

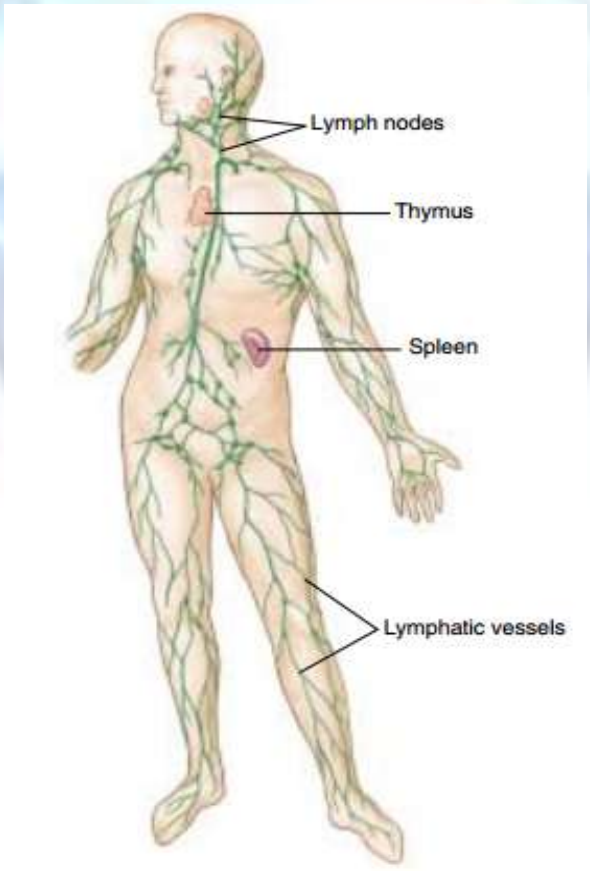

Fig 1: The lymphatic system consists of lymphatic vessels, lymph nodes, and lymphatic organs, including the spleen and thymus gland.

Fig 2: In this scanning electron micrograph, a macrophage is "fishing" with long, sticky cytoplasmic extensions. Bacterial cells that come in contact with the extensions are drawn toward the macrophage and engulfed.

Natural killer cells: Do not attack invading microbes directly. Instead, they kill cells of the body that have been infected with viruses. They kill not by phagocytosis, but rather by creating a hole in the plasma membrane of the target cell Proteins, called perforins, are released from the natural killer cells and insert into the membrane of the target cell, forming a pore. This pore allows water to rush into the target cell, which then swells and bursts. Natural killer cells also attack cancer cells, often before the cancer cells have had a chance to develop into a detectable tumor. The vigilant surveillance by natural killer cells is one of the body's most potent defenses against cancer [15].

The Inflammatory Response

The inflammatory response is a localized, nonspecific response to infection. Infected or injured cells release chemical alarm signals, most notably histamine and prostaglandins. These chemicals promote the dilation of local blood vessels, which increases the flow of blood to the site of infection or injury and causes the area to become red and warm. They also increase the permeability of capillaries in the area, producing the edema (tissue swelling) so often associated with infection [16]. The more permeable capillaries allow phagocytes (monocytes and neutrophils) to migrate from the blood to the extracellular fluid, where they can attack bacteria. Neutrophils arrive first, spilling out chemicals that kill the bacteria in the vicinity (as well as tissue cells and themselves); the pus associated with some infections is a mixture of dead or dying pathogens, tissue cells, and neutrophils. Monocytes follow, become macrophages and engulf pathogens and the remains of the dead cells (figure 3).

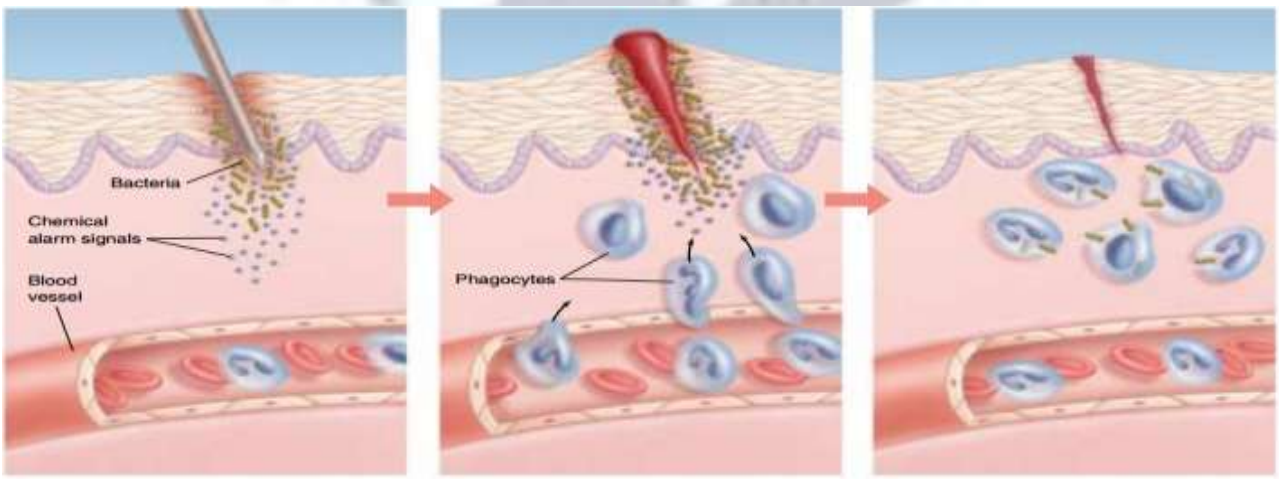

Fig 3: The events in a local inflammation. When an invading microbe has penetrated the skin, chemicals, such as histamine and prostaglandins, cause nearby blood vessels to dilate. Increased blood flow brings a wave of phagocytic cells, which attack and engulf invading bacteria.

The Temperature Response

Macrophages that encounter invading microbes release a regulatory molecule called interleukin-1, which is carried by the blood to the brain. Interleukin-1 and other pyrogens such as bacterial endotoxins cause neurons in the hypothalamus to raise the body's temperature several degrees above the normal value of 37°C (98.6°F). The elevated temperature that results is called a fever. Experiments with lizards, which regulate their body temperature by moving to warmer or colder locations, demonstrate that infected lizards choose a warmer environment - they give themselves a fever! [17]. Further, if lizards are prevented from elevating their body temperature, they have a slower recovery from their infection. Fever contributes to the body's defense by stimulating phagocytosis and causing the liver and spleen to store iron, reducing blood levels of iron, which bacteria need in large amounts to grow. However, very high fevers are hazardous because excessive heat may inactivate critical enzymes. In general, temperatures greater than 39.4°C (103°F) are considered dangerous for humans, and those greater than 40.6°C (105°F) are often fatal [18,19].

CONCLUSIONS

The immunologists try to expand the approaches of artificial immune systems by studying the BIS and its functionalities. By identifying more approaches the immunologists intend to address major unresolved problems like cancers, space optimization and network security issues. AIS would benefit more if there was more prominence in the use network security as it has been as a major issue now days. However, as research is still in early phases, it is apparent that there are much more research work to be done and has much promise in altering the world.

It is essential not only to recognize and understand the different, important roles of antibody-based and cytotoxic immune defenses but also to match the requirements for protection against the pathogen or toxin in question with the development of the protective immune responses. Despite the tremendous scientific progress that has been made over the years, a complete and precise understanding of the immune system's response to various diseases remains elusive.

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