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Chapter 1

Introductory Chapter: Introduction on Physiology and Pathology of Immunology

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1. Introduction

Dynamic, variable, and diverse overtime and in action, the entire effort of the human body is to survive. Whether preplanned, i.e. innate immune reactions, or partly planned, i.e. adaptive immunity, immunity has evolved to counteract changes. Human immune response follows the inexorable schemes based on four main principals of action:

First – Early detection of unwelcome factor of change and activation of response systems.

Second – Setting the stage for an effective, least interfering, response with normal body function and activation of systemic responses.

Third – Activation of long-term survival and adaptation signals, and natural repair systems.

Fourth – Timely termination of the response and learning from the experience if need be!

The advent of molecular genetics, molecular pathophysiology, utilization of new imaging techniques, and advances in bioinformatics and health data, have shed light over novel etiologic factors of disorders and opened eyes to more pieces of the puzzle of diseases of the human body. Researchers in clinical medicine and basic science are deciphering the complex trails by which our immune response is both regulated by and controls many functions of a living creature, from fundamentals of a local response at the site of injury to the neurodevelopmental function of immune pathways in the developing brain, and to the inclusive mechanisms by which immunity regulates one's longevity and survival. It is not at all a daring claim that our immune system is the executive element in almost every defense mechanism of the human body to counteract threats. Whether it be invading microorganisms into the guts, an abnormally proliferating cell in the lining of our lungs, a blood clot in one of the cerebral

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arteries, aberrant aggregation of cholesterol in endothelium lining of the coronary artery, or an aging cell in the macula of the eye. Immune aspects of physiology and pathology of the human being are now the prevailing notion in research, therapeutic modalities, and day-to-day practice of clinicians.

This book is presented as the result of an effort to provide basics to this vast area of growing knowledge, on the basic actions of the immune system in health and disease. Uncertain nature of the "change", temporally and regionally, necessitates a 24-hour alert system to summon immune effectors and exert the proper scenario of action. The effector cells of the immune system are therefore distributed in a tightly regulated manner all throughout the body and over time. The mucosal-associated lymphoid tissue comprises the largest pool of immune effectors, followed by bone marrow and spleen, which are the primary training and regulation sites of immunity. Most interesting is that each and every organ system and each cell in the body is conferred with the intrinsic ability to respond to change, injury, or an adverse event, and set off a cascade of adaptation or maladaptation.

This makes us to the important crosstalk of immunity with three major regulatory bodies in human body. Immunity acts in consort with hemostatic response, neuroendocrine system, and circulatory/lymphatic system to exert potent internal regulatory signals. Later on, in this section, we look briefly at the fundamentals of the function of the human immune system to be able to move on to the exciting new dimensions of the role of immunity in cancer immunology, immunology of transplantation, autoimmunity, and immunodeficiencies.

Conventionally, there has been a trend to define the immune system, first by introducing the immune mediators, cells and organs involved in various responses, and then by dividing the responses into "innate" and "adaptive or acquired" response.

The innate immunity is as diverse and ancient as the structures of different parts of the human body. Each organ system has developed over time, barriers to minimize the scope of pathogen invasion, or better neutralize the attack at the site of entry. We believe that the evolution of human immune system is the product of and currently shaped by, an everlasting struggle with rapidly reproducing and frequently changing microbial pathogens. The various mechanisms of innate immunity are developed in order to quickly identify the stereotypes in pathogen structures [i.e., pathogen-associated molecular patterns (PAMPs)] and provide either mechanical barriers or respond by secretion or cell surface expression of antagonizing molecules, most importantly known as antimicrobial peptides. Pattern recognition in innate immunity is based on, but not confined to, identification of peptides, as well as carbohydrates and pathogen-associated nucleic acid segments [1]. Inflammation is a transitory and ongoing nonspecific mechanism of innate immunity. A full-armed activation of defense and repair mechanisms, and involvement of the pathogen-specific, acquired immune responses follow the initial inflammatory response. Inflammation could be defined as a harmonic array of activation of plasma proteins (complement system, antimicrobial peptides such as defensins and cathelicidins, cytokines, and vasoactive mediators), circulating and infiltrating leukocytes (polymorphonuclear leukocytes, lymphocytes, macrophages/monocytes etc.). Endothelial lining of the vessels and indolent cells of the parenchyma are known as non-specified, yet highly active players of inflammation.

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The primary goal of the inflammatory response is to recruit immune cells to the site of invasion. Yet, failure to remove the pathogen from the site of entry, as happens following the invasion of *Mycobacterium tuberculosis* to a hilar lymph node of the lung, failure to terminate the response, such as when antigen:antibody complex deposits in glomerular basement membrane a few weeks after streptococcal pharyngitis, excessive response to a benign pathogen, when resident alveolar macrophages, eosinophils, and neutrophils are drawn to the site where Aspergillus spores penetrate the respiratory system, each underlie formation of different types of immune diseases.

Before we move to describe the common scenarios by which the immune system operates its actions and the distinct disciplines in emerging fundamental of cancer immunology, immunology of transplants, systemic and organ-specific autoimmune disorders, and immunodeficiencies, let us move to the building blocks of immunity, tissue/cellular components of the immunity.

2. Cells of the immune system

2.1. Granulocytes

The polymorphonuclear granulocytes (PMNs) or neutrophils are the soldiers in the front of acute infection and inflammation. Other two types of granulocytes, the eosinophils and basophils deliver target specific phagocytosis and cytotoxicity. Ingestion and degradation of microbes and cellular debris, from the site of infection or tissue damage, is the primary role of PMNs. They do so with the help of surface display of pathogen-associated molecular pattern receptors, such as toll-like receptors, NOD-like receptors, and also receptors for the constant part of various antibodies (e.g., fc IgG) and complement system receptors (e.g., C3a). The macrophages, in turn, appear late in the inflammatory response, continue phagocytosis and elaborate long-term tissue remodeling mechanisms. IL-8 and specific chemotactic agents from injured cells, and complement mediators (C3 and C5) in the plasma, attract neutrophils, eosinophils, and basophils to the site of infection. Together they produce soluble products, IL-5, eotaxin, histamine, or reactive nitrogen and oxygen species, exerting potent cytotoxic or chemotactic on the bacterial, viral, protozoal, or allergic pathogen. Inborn errors in adhesion, migration, or degranulation of granulocytes are the basis of leukocyte adhesion deficiency (LAD) and chronic granulomatous disease (CGD), the two types of "primary immunodeficiencies."

2.2. Lymphocytes

Lymphocytes are categorized into four types, based on function, the B lymphocytes, T lymphocytes, natural killer cells (NKCs), and NK T cells. They all share the same common lymphoid progenitor in the bone marrow, yet, the first two cell lines develop their clonally unique surface receptor immunoglobulin (Ig) or T-cell receptors (TCR), in the bone marrow, ensuring strict selection criteria, before they release into the periphery for further maturation. As for the B cells, they later undergo involution into mature antibody producing plasma cells. The safe/nonsafe and self/nonself discrimination, the paradigm of action of the immune system, is

perceived to be a primary consequence of T-cell discrimination of self-/nonself-antigens. No T cell can recognize a self-protein unless it is endocytosed, digested, and presented in the form of a complex with either type of major histocompatibility (MHC) molecules, on the surface of an antigen presenting cell (APC). In contrast, the antibody on the surface of B cells can recognize and reproduce soluble immunoglobulins, as they travel from lymph nodes to the blood and the sites of invasion, against a wide array of antigens from polysaccharides, lipids, nucleic acids, and larger proteins.

By virtue of their membrane expression of killer cell inhibitory receptors (KIR) and CD16, NK cells and NK T cells, are omnipresent circulating security check systems. Via a direct cell-to-cell contact, mediated by KIR, the NK cells "scan and inspect" almost every cell type in the body, for uneventful intracellular events, a neo-epitope or a mutant protein from neoplastic alteration of the cell or a viral antigen, etc. Antigenic particles formed in this process are presented by class I of MHC molecules and consist of peptides of various sources, mostly from denatured and worn out proteins after they undergo normal senescence and degradation by proteasome complex. The NK cells own a unique receptor for the constant part of the IgG, that upon recognition of the Ag:Ab complex, mediates a burst out of cytotoxic granules from the lymphocyte. A targeted, direct cell-to-cell cytotoxicity is the result. NK cells provide the first line of antitumoral/antiviral defense of the immunity, while the machinery of antigen presentation to cytotoxic and helper variants of T cells is setting off in action.

2.3. Antigen presenting cells (APCs)

Antigen presentation is the groundwork for various types of cells that are active in displaying protein antigens to the naïve T-cell lymphocytes. The monocytes/macrophages, constituents of the reticuloendothelial system, the B cells, and foremost, the dendritic cells, are labeled as APCs, based on their mutual ability to express both class I and class II MHC molecules. Some APCs (monocytes/macrophages), particularly express surface receptors for Fc gamma of IgG and C3b and are very potent phagocytosis. Some, like dendritic cells, are less potent phagocytes but have evolved into very efficient antigen detectors. Conventional dendritic cells are strategically located at the body entrance sites, to capture microbes and to migrate to T-cell zones of sentinel lymph nodes to instruct further deployment of adaptive immune response. Cross-talks between TCR, costimulatory molecules on APCs, and the MHC class II molecules are the core of a series of tightly regulated mechanisms that orchestrate a robust and accurate plan to counteract offenses.

2.4. Lymphoid tissues

It is an incomplete introduction on immune cells if one does not mention the diffuse, yet amazingly systematized organs with a lead role in human immunity. While every cell and organ in the body is endowed with a primary and nonspecific defense system (e.g., mucosal membrane of mouth, lung, etc., special circulation conduits of the GI system, the urine flushing the urethra, or the mucociliary escalator of the bronchi), there are accumulations of lymphoid tissue in human body in charge of training lymphocytes, fostering immune interactions, and providing long-term reservoirs for memory cells residence. Based on the main lymphocyte population, they are divided into primary (Thymus and bone marrow)

and secondary (lymph nodes, spleen, and mucosal-associated lymphoid tissues). Primary lymphoid organs, harbor lymphocytes proliferation, selection, clonal expansion, and maturation. While the secondary organs, serve as homing and expansion sites for mature lymphocytes and facilitate acquired immune response via exclusive structural delicacies.

3. Stories about the immune system

3.1. Inflammation

Inflammation, as described, is the effort of injured cells, to communicate the danger signal, on the spot, to the first-line innate mechanisms to minimize the invasion hazards. These include, but are not confined to, vascular response, regarding vasodilation, increase in permeability, and activation of endothelial cells, leading to cellular response, with an increase in leukocyte chemotaxis, adhesion, and transmigration, into extracellular tissue. Infection is the most common trigger for inflammation, yet, tissue necrosis, aseptic trauma with or without necrosis, foreign bodies, and in the case of inflammatory disorders, hypersensitivity to a sustained assault or autoantigens, could all be the souls behind the face of inflammation. Resident phagocytes, dendritic cells, and epithelial cells, and depending on whether endothelial damage has occurred, platelets are the first to confront the products of tissue assault. These cells recognize the danger via the pathogen/danger-associated molecular pattern (PAMP) receptors. They produce a wide array of danger signals including proinflammatory cytokines, and in turn respond to histamine, thrombin, TNF-α, IL-1, and IL-6 by secretion of chemotactic agents, further facilitating leukocyte transmigration.

The endothelial expression of adhesion and selectin molecules (e.g., E-selectin surfaced in response to TNF-α and IL-1), and their interaction with a multitude of surface integrin and cell adhesion molecules on leukocytes, facilitates leukocytes allocation to the infection site. Activated indigenous or infiltrated phagocytes, in turn, ingest microorganisms and dead cells, produce reactive oxygen and nitrogen species, extracellular digestive enzymes, and products of lipoxygenase cascade such as leukotrienes and prostaglandins. These, together with the complement system and antibody response, form the main body of chemical moderators of inflammation.

The face of an inflammatory response changes when antigen presenting cells set the stage for specific recognition of the antigens and presentation to T cells. Antigen-specific T cells, macrophages, circulating plasma cells, and memory B cells are leading characters of immunity, in a durative inflammation.

3.2. B-cell and T-cell development and maturation

Genetic recombination is the most noteworthy feature acquired by the immune system, endowing an adaptive ability to generate a limitless array of receptors, while maintaining genetic stability and frugality of genetic material of a vertebrate cell.

The B-cell receptor (BCR) light and heavy chains (IgL and IgH), and the TCR α, β, γ, and δ chains, each form as result of a matchless system of genetic recombination/rearrangement of V(D)J regions, their assembly with different types of immunoglobulin constant regions to form an clonally unique and specific receptor for two main types of lymphocytes.

Either as a soluble immunoglobulin or as B-cell surface receptor, the BCR is a heterodimer of two heavy chains (with five types of constant regions, to which they are designated for IgG, IgA, IgM, IgD, and IgE) and two light chains, either kappa,or lambda, based on the sequence of their constant region. The TCR is either an $\alpha\beta$ chains or a $\gamma\delta$ chains heterodimer, with the $\alpha\beta$ being the most common type. Alike Ig heterodimers, each of the α, β, γ, or δ chains also has a constant and variable region.

Within the precursors of B cell and T cell in the bone marrow, the immunoglobulin gene segment undergoes a sequential allelic exclusion to recombine one of each type of V, D, or J genes at each locus, at a time. If the rearrangement is productive, and full-length light and heavy chains are produced, the resultant, pro–B cells and pro–T cells, undergo selection either through bone marrow stromal cells for B cells or the cortex epithelial and medullary cells of the thymus. Induction of "central tolerance" in lymphocytes, follows one principle, that is high avidity and low avidity self-antigen recognition are both discouraged, and only the nonantigen-responsive lymphocytes are selected and given a chance to survive. These later migrated from primary lymphoid organs to the periphery to be exposed to a set of secondary immune surveillance mechanisms or "peripheral tolerance."

Receptor selection of TCR is different from the BCR, as TCR must acquire the potential to react to self-antigen-MHC complexes, rather than soluble antigens, an eligibility acquired via positive and negative selection. Only thymocytes that can bind to bare MHC class I and II in the cortex of the thymus (positive selection), and later unable to bind or bind with low affinity to the medullary expressed self-antigen-MHC complexes (negative selection), will receive life signals to release to the periphery. Pre–B cells with "high avidity self-antigen recognition" are either given a second chance to rearrange their variable V(D)J region of the light chain (with the remaining options of the same gene or their pair on the homologous chromosome), before either receiving a go-ahead signal or undergoing apoptosis.

A final leap is required for a B cell to get matured, and that is, the naïve B cell undergoes switching of the receptor subtype (class switching), changing the antibody subtype of the BCR from IgM to IgG, and later into other immunoglobulin subtypes to be able to mediate various types of humoral responses to different antigens. The peripheral encounter of a B cell or T cell, bearing a self-reactive receptor, evokes peripheral tolerance mechanism, leading to activation-induced death or anergy of the autoreactive lymphocytes.

3.3. Humoral and cellular response to an infection

In this paragraph, we look briefly into a typical humoral and cellular response to an extracellular pathogen; e.g., *Streptococcus pyogenes* cultivating the throat. Acute innate immune response to an infection is neutrophils infiltration, chemo-attraction of distinct populations of leukocytes, and secretion of TNF-α, IL-1, IL-6, nitrous oxide, and proteases. Next, macrophages, dendritic cells, along with other tissue-specific and nonspecific APCs, present parts of the degraded pathogen on their surface MHC receptors, which are in this case the class II of MHC molecules.

Regulation of lymphocyte circulation is essential, for appropriate interaction of APCs and lymphocytes to happen. An elaborate system of chemokines and surface receptors, makes sure that the meticulously selected mature B and T lymphocytes, not only travel in a nonstop

trip, trafficking in and out of secondary lymphoid organs, but also, receive appropriate "homing signals," to the site or sites where the interaction of immune cells predominantly occur.

Recognition of antigens via Ig or TCR provides the primary signal for lymphocyte activation, named as signal 1. As a consequence of the negative selection of lymphocyte in bone marrow and thymus, T lymphocytes that bind with moderate to low affinity to MHC/antigen complex, do not receive a "go" signal for maturation, unless triggered with costimulatory molecules, usually from activated APCs, that provide the additional "signal 2."The innate immune response activates APCs for a more efficient phagocytosis and antigen presentation to T cells, upregulating costimulatory molecules and expressing IL-2 that is essential for T-cell proliferation and differentiation.

A good sample of APCs and lymphocytes reciprocal signals and cross-activation during formation of adaptive immune response is when activated B cells, act as antigen presenting cells, give and receive signal 2 for maturation, to and from naïve T lymphocytes. Cross-bridging of two Ig on the surface of B cell activates B cells and mediates a "receptor-mediated internalization of antigen," which is then presented on the surface as a complex with MHC class II molecule and upregulation of CD80 (B7). The antigen/MHC complex on the B-cell membrane provides signal 1 for the naïve T cell. Later, CD80 binding to CD28 (a constitutive B7 receptor on T cells) provides signal 2, and the activated T cell upregulates CD40L (CD154), a costimulator for B-cell maturation, class switching, and immunoglobulin expression.

4. What does the immunity has to say about?

4.1. Immunology of neoplasia

Footprints from the immune system could be found in many aspects of cancer pathogenesis. Cancer is not only defined now, by the genetic mechanisms that culminate in transformed cells with a senseless tendency to proliferate but also as an everyday challenge of the body with cells that undergo subtle yet malignant intracellular changes and mutations. Two theories of "cancer immune surveillance" and "cancer immune editing" focused on the crucial role of immunity in cancer [2]. The identification of tumor's ability to selectively and efficiently suppress components of the immune system in favor of its longevity and invasion put a further spin on this notion [3]. Immune elimination of cancer releases tumor-specific antigens and danger signals and creates a tumor-edited immunity. Everyone working in the field of cancer immunology is familiar with new entries added to the dictionary of cancer, tumor antigens, tumor infiltrating lymphocytes, and myeloid-derived suppressor cells [4]. Finally, the advent of drugs targeting the cutting-edge knowledge of immune culprits of cancer and "tumor-specific antigens" has brought hope for effective cancer immunotherapy for tumor suppression or even tumor ablation [5], and cancer vaccination has become a trending topic in cancer research [6].

4.2. Immunology of infection

It was the microbes that drew our attention to our immune system and led us to know more about it. Studying immunology has diverged into many branches and disciplines, yet studying the immunity of infection still has galaxies to explore. Microbes are the primary reason for

the evolution of immunity, the phylogenetic of this phenomenon tells us that if it were not for smart eukaryotes, learning how to fight back prokaryotic within a complex, multipotent herd, the human system would have never maturated into its current shape and complexity. The danger theory and the self-/nonself-paradigm that reigned the knowledge of immunology for years was a direct revelation from years of studying host defense to infectious agents [7].

The emergence of HIV/AIDS pandemic has made researchers to turn a clever eye on "immunity in infection" and "infections of immunity." Rays of hope have shed over this situation with endeavors to design and test an ultimate HIV vaccine [8].

4.3. Immunology of organ transplant

Transplant of solid organs was restricted, first due to technical problems of heavy surgeries, infections, and hardships of ligating blood flow to major organs for long. Next, the daring first transplant surgeons became aware of the fact that the first reason of the transplant failure was not complications of the surgery, but rather it was the failure of the transplanted organ that killed the patient. The development of efficient and target specific immunosuppressive therapy and biological agents has turned organ transplant, into a routine therapeutic option for various types of end-stage organ failures. Nowadays, it is a problem of organ supply, as up to one-third of the patients waiting on the list die before a donor can be found. Cadaveric organ transplant, marginal donor transplants are still facing a dilemma to achieve a long-term reduction in mortality [9]. The overall success rate, however, is approximated between 80 and 90%, and it is now the duty of immunological research to open a landscape for alternatives of organ donation, such as xenografts, to overcome the problem of organ shortage [10].

4.4. Autoimmunity

Autoimmunity is a term used to describe the chronic response of the immunity to self-antigens, resulting in tissue damage. Autoimmunity happens in a sequence of distinct phases, from genetic susceptibility, which involves at least one of the factors; impaired tolerance, reduced production, or activation of the regulatory subset of T cells, impaired clearance of antigen: antibody complexes, etc. Next, there is a trigger, an initiation phase that the self-antigens are exposed to the faulty system of antigen recognition, or a full-blown immune response that activates the dormant nonresponsive alive autoreactive lymphocytes. The initiation of the reaction further releases autoantigens and results in progression of disease and establishment of chronic tissue damage. Credentials for these phases have been investigated regarding specific auto-antibodies, markers of initiation, and progression and clinical stages of the disease. The next challenge would be the implementation of this knowledge into a precise diagnosis, appropriate monitoring, and care of patients with autoimmune diseases.

4.5. Immunodeficiencies

Immunodeficiencies could be divided into two groups of inherited (primary) or acquired (secondary) immunodeficiencies, the latter group being a cause of acquired factors such as HIV infection, protein-losing enteropathy, malnutrition, cancers, or immunosuppressive

drugs that impair immune-related functions in a previously healthy immune system. Primary immunodeficiencies are a heterogeneous group of disorders, caused by a gene defect, leading to defect(s) of the immune system. More than 300 different types of primary immunodeficiencies have already been described [11]. Haematopoietic stem cell therapy, immunoglobulin replacement, and the use of antibiotics have extended lives of patients with immunodeficiencies to an almost normal span [12].

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