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In Shortly about Immunity

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Abstract

Immunology is a branch of biomedical science that studies the body's overall resistance to the action of foreign substances, ie antigens. In practical terms, immunology studies all forms of defense against infection and harmful consequences of the immune response. Immunology stemmed from the cognition that, after healing of certain infectious diseases peoples are, as a rule, resistant to the disease.

Keywords: *Immunity; Immunology; Agents; Vaccines*

Introduction

Those who received their biomedical education around 1960 could not even have suspected that one of the most significant revolutions in life-sciences was taking place at that time: the transformation of serology-centered immunology into immunobiology [1]. Students could not have possibly been informed about this, as the university textbooks at that time were only allowed to contain solid, well-established facts of science, notably those that had survived at least a decade without being refuted. Thus little wonder that the students missed out the birth of immunobiology. As a matter of fact, immunology at that time was not considered as a science in its own right, it usually occupied a single chapter in the students' microbiology textbook, describing at most vaccination, antibodies, serological reactions, and the use of antibodies for typing of bacteria. The most sophisticated piece of science included was the description of how to render antisera 'monospecific' by sequential absorption. Concerning the possible nature and origin of antibodies, a single laconic statement was made, namely that they were localized in the gamma-globulin fraction of serum, implying cautiously that not all gamma-globulins were necessarily antibodies. Indeed, the bulk of gamma-globulins was thought to represent 'normal' serum proteins that were probably produced in the liver (by the motto that substances of unknown nature and origin are best to be blamed on the liver; nota bene, even old, conservative textbooks could contain not all that solid facts!). Naturally, nothing about the cellular basis of immunity passed the inclusion criteria, since the first discoveries in this direction were at most a couple of years old.

The last third of the twentieth century was the period when the 100-year-old pursuit for the meaning and molecular basis of immunological specificity was finally crowned with success, and it was therefore a time of crucial importance in the history of immunology [1]. The highlights of the first decade were the clarification of immunoglobulin structure, the interaction of antibody with antigen, and the mechanisms for generation of antibody diversity, and in the following 20 years, the T-cell antigen receptor and the nature of its ligand were discovered. Beyond doubt, these three decades represented the unsurpassable peak of research into the adaptive (i.e., somatically generated) immune system. By the mid-1990s, practically everything had become known about antigen recognition, and although there

is disagreement on some details, it is no longer expected that new facts could fundamentally change our view, in other words, the study of adaptive immune system can be regarded as (more or less) complete.

The knowledge gained about antigen recognition then gave impetus to other research areas. For example, the information on immunoglobulin gene structure triggered a technological course of development that culminated in the production of synthetic human antibodies without immunization. Furthermore, the characterization of T-cell recognition enabled from the 1980s on a renaissance of tolerance and autoimmunity studies that had to do largely with the clarification of the role T cells play in these two processes. But mechanistic studies into tolerance and autoimmunity are still relatively recent, and thus much remains to be done before our understanding of these fields reaches the level of knowledge on antigen recognition.

Immune system

The immune system evolved so as to defend our bodies against infectious microorganisms such as viruses, bacteria, fungi and parasites [2]. Throughout history it has been observed that people who survive an infectious disease acquire protection against that disease, which is otherwise known as immunity. As far back as the fifteenth century attempts have been made to induce immunity against infectious diseases, a process referred to as vaccination. The realisation that immunity can be transferred from one person to another demonstrated that soluble factors exist in the blood and body fluids that protect against pathogens. It is now known that cellular components of the immune system are also present throughout the entire body and that these immune cells engage with any harmful substance or microorganism in order to preserve the integrity of host tissues. The defence against microorganisms is fought on many fronts and there are immune cells and innate components of the immune system within every tissue and organ. There are a multitude of cells and soluble factors that can be considered part of the immune system. For example, the barrier function of the outer layers of the skin, the mucus produced in the airways, the antibodies secreted into the gut lumen or the circulating lymphocytes that destroy virus-infected cells. The immune system comprises a number of different cell types and a multitude of secreted factors and surface bound molecules.

The immune system has a multi-layered organisation that provides immunity to infectious organisms. Each layer of the immune system can also be considered to have an increasing complexity. The first layer is provided by physical barriers such as the skin and the mucosal epithelium of the respiratory and gastrointestinal tracts. These barriers aim to prevent pathogens gaining access to underlying tissue. The next layer is the non-specific chemical barrier that consists of antimicrobial compounds and factors of the humoral immune system (soluble factors found in body fluids). Other chemical immune defence mechanisms include the acidic environment of the stomach and the proteolytic enzymes produced in the intestines. The third layer is composed of all the cells of the immune system. Therefore, if a pathogen breaches the physical barriers and chemical barriers then the immune system utilizes its immune cells.

Most interactions between the human host and the microbial world occur either at the skin or at mucosal surfaces, such as the gastrointestinal tract and the respiratory tract [3]. Immunity at these sites is referred to as mucosal immunity. Despite its importance, our understanding of mucosal immunity is quite limited, due to the difficulty of obtaining tissue or secretions from mucosal surfaces (in contrast to the ease of obtaining blood for study of systemic immune responses).

The gastrointestinal tract provides an ideal environment for bacterial growth and contains trillions of bacteria. The host must be protected from invasion by these bacteria, but this must be accomplished without the vigorous inflammatory response that maintains the sterility of the host's internal environment, because such a strong response would destroy the mucosal protective barrier. Thus, mucosal immunity differs in fundamental ways from systemic immunity, and mechanisms that operate in systemic immunity cannot be assumed to operate in the mucosal setting.

Epithelial cells are a key component of mucosal immunity. While not traditionally regarded as immune cells, these cells are linked by tight junctions that provide a physical barrier excluding bacteria from the systemic environment, and they secrete proteins that inhibit

the growth of bacteria and reduce bacterial attachment to the epithelial surface, thereby promoting bacterial excretion from the gastrointestinal tract. Epithelial cells also bear toll-like receptors (TLRs), described earlier in this chapter, that recognize pathogen-associated molecular patterns (PAMPs) that are unique to bacteria or viruses. Engagement of TLRs causes epithelial cells to secrete products with antimicrobial and pro-inflammatory activity, such as alpha- and beta- defensins, which can disrupt bacterial cell walls.

It is the task of the immune system to protect the host against invading pathogens and thereby to prevent infectious disease [4]. A plethora of pathogens exists (i.e. viruses, bacteria, fungi, parasites and helminths) that have exploited strategies to circumvent an attack by the immune system. Conversely, the immune system has evolved to provide appropriate defence mechanisms at various levels of 'unspecific' (innate) and 'specific' (adaptive) immune responses. In many instances, an appropriate immune response to an infectious agent requires reciprocal interactions between components of the innate and adaptive immune systems.

The various microorganisms have developed different strategies to invade their host. Viruses make use of the host cell's machinery for replication and are thus intracellular pathogens. Helminths, the other extreme, are multicellular organisms that cannot live within host cells but rather behave as extracellular pathogens. In between are bacteria, fungi and protozoa, which, depending on the species, live within or outside host cells.

While the components of the innate immune system are appropriate as a first line of defence, the adaptive (or specific) immune system is activated if the invading microorganism cannot be eliminated, or at least be neutralized, by the abovementioned non-specific effector mechanisms. Two major features characterize the adaptive immune system. Firstly, the immune response is antigen-specific; specificity is made possible through the usage of clonally distributed antigen receptors, i.e. surface Ig on antibody-producing B lymphocytes and T cell receptors (TCRs) on the surface of T lymphocytes. Secondly, the specific immune system develops memory. This allows the rapid response of antigen-specific effector cells upon second encounter of the relevant antigen. The underlying general principle of vaccination is the stimulation of specific immunity with long-lasting memory by harmless components of an infectious agent or by attenuated strains. This endows the host with the capacity to combat the homologous pathogen with high efficiency and thus prevents disease outbreak.

Autoimmunity

Autoimmunity can be broadly defined as a specific immune effector response against self components that inflicts harm on the host. The self-damaging response is often of inflammatory nature, but other effector mechanisms, e.g., complement activation by autoantibodies bound to self structures, can also be the major cause of pathology [1]. Autoimmunity should be distinguished from autoreactivity, the latter denoting the presence of self-specific antigen receptors and antibodies in the body that remain without harmful consequences. The manifestations of autoimmunity are called autoimmune diseases (AIDs), which represent a rather large assemblage of different illnesses with distinct symptoms, locations and pathomechanisms. The only commonality of AIDs on which most participants of the field agree is that the pathology is the consequence of a failure in one or another mechanism of self tolerance. Therefore, autoimmunity can be regarded as the down-side of self tolerance, as well as the most likely selective pressure that has driven self-non-self discrimination. In this context, the frequency of AIDs in the population (up to 5%) may reflect the limit of natural selection, i.e., that the latter cannot operate to perfection, only to adequacy defined as the level of harm that no longer threatens the procreation of the species.

Naturally, many of the diseases now known or assumed to be of autoimmune origin, particularly the more frequent ones, have been known since ancient times, and a large body of information has been gathered on their symptoms and pathology. But that an immune response against self components can be the cause of disease was first recognized at the beginning of the twentieth century. The advent of immunobiology ('the immunological revolution') was an important impetus also for autoimmunity research, and thus a large number of diseases have been added to the list of AIDs from the 1950s on.

Any human body ("self") exists within a hostile environment including microbes ("non-self") and multicellular organisms ("non-self") [5]. The external microbial environment and internal opportunistic germs, as well as even benign tumors, are not those places where any

human body can know who to trust out here to survive. Fortunately, we have our immune system, which has evolutionarily known how to recognize "non-self," "self," and even "former self." To understand, it is necessary to define the "non-self" and "self" at the molecular level in detail.

An antigen is a substance containing such information about "non-self," "self," and/ or "former self," which can trigger immune responses in the body to induce a very long and even lifelong memory to the event if it occurs. T-cell receptor (TCR) and B-cell receptor (BCR) can recognize antigens. Antigens of "self" are named autoantigens (or self- antigens), whereas tumor antigens present in fact "former self." In the enlarged sense, it is currently estimated that the "universe of antigens" make up about 1018 molecules in the environment. The antigens may be divided into complete and incomplete antigens.

Any antigen as an immunogen may trigger an immune response, i.e. the interaction of many cell types of the immune system, which leads to the formation of new cell types destroying the antigen-containing pathogen and commonly keeping a memory about this event for a long time. Naturally, vaccines contain only immunogens. An antigen as a tolerogen triggers immune tolerance, another type of interaction of cells of the immune system. Alternatively, it results in the "specific immunological silence" when none is killed and no tissues are damaged.

The immune system is delegated to defend the body from attacks from outside or inside [6]. Many diseases can affect immune system reducing its ability to defend self or inducing an abnormal response against external or internal antigens. Rare diseases affecting immune system present some issue in common with other rare diseases and some peculiarities due to the huge variability in the disease's expression. However, a correct estimation of the epidemiology of rare disorders is necessary for evaluating the prognosis and the responses to new therapies, for planning proper public health services, and finally to establish fair and sustainable prices for innovative medicines.

Respiratory tract

The nasopharyngeal mucous membranes, which comprise the largest mucosal epithelial surface of the body, line the entry of the respiratory tract and are in continual contact with the external environment [7]. Pathogens and toxins encounter this thin, specialized mucosal epithelium upon inhalation, and this epithelium is the site of initial host–pathogen interactions with cellular and secretory components of the respiratory system. Adequate surface protection, (prevention of invasion), depends on intimate cooperation between natural nonspecific defense mechanisms and acquired specific immunity.

Nonspecific and specific immune responses provide important mechanisms for host resistance to pathogens in the lungs. These responses occur largely within the airways, in relation to mucosal surfaces of the airways, adluminally in the pulmonary parenchyma, or in discrete lymph nodes associated with the respiratory tract.

Immunological mechanisms of host resistance may be associated with cells or their secretory products. Various enzymes, cytokines, or antibodies may alter the pathogenesis of and/or provide nonspecific resistance to an agent introduced through the respiratory tract. Nonspecific cellular resistance is often mediated by neutrophil or macrophage phagocytosis of a pathogen. Macrophages previously activated because of a specific or nonspecific stimulus can protect against an unrelated foreign agent.

Skin

Although not classified as a mucosal tissue per se, the skin possesses a number of immunological features that are similar to MALT (Mucosal Associated Lymphoid Tissue); appreciably the shared need to maintain tissue homeostasis, while at the same time promoting effective immunity [2]. In contrast, the skin has unique qualities, which are borne out of its distinct biological function and anatomical location. Importantly, the skin is considered the largest organ of the body and provides a robust barrier to the external environment, effectively preventing pathogen entry through a combination of structural and immunological features. In addition, the skin is able to respond to injury (following cuts and abrasions) in both a wound-healing and an immunological capacity. Wounded skin is an easy conduit for

pathogens to enter the body and therefore effective immune defences are in place to combat such adverse events. The constant exposure to environmental toxins, solar radiation, a range of pathogens and the daily instances of wounding, makethe skin a unique organ that has evolved its own identifiable immune system.

Structurally, the skin is composed of two main layers, the outermost epidermis and the inner dermis, separated by a basement membrane. The epidermisis mucht hinner than the dermis and largely comprises specialized squamous epithelial cells called keratinocytes that form the durable outer layers of the skin. Keratinocytes produce large quantities of the protein keratin, which is the main constituent of nails and hair and also forms the tough, watertight surface of the skin, the stratum corneum.As well as keratinocytes, the epidermis contains specialized DCs called Langerhan's cells (LCs), which act as sentinels in the skin by detecting the presence of potentially harmful foreign substances, and intra-epidermal lymphocytes (equivalent to intraepithelial lymphocytes in MALT). The dermis is much thicker than the epidermis and contains more complex structures such as sweat glands, sebaceous glands, hair follicles, blood vessels and nerve endings. The dermis mainly consists of dermal fibroblasts and contains many more immune cells than the epidermis, such as T cells, dermal DCs, NK cells, mast cells and macrophages. Throughout the dermis post-capillary venules (equivalent to high endothelial venules in other tissues) act as the main sites of leukocyte entry into the dermis and can influence the extent of inflammatory cell infiltration through the expression of cell-adhesion molecules and chemokines. Below the dermis is a thick subcutaneous layer called the hypodermis, which is connected to the dermis by collagen and elastin fibres. The hypodermis consists mostly of fat cells known as adipocytes, which collect fat and effectively act as energy reserves.

Science

The fundamental observation that led to the development of immunology as a scientific discipline was that an individual might become resistant for life to a certain disease after having contracted it only once [8]. The term immunity, derived from the Latin "immunis" (exempt), was adopted to designate this naturally acquired protection against diseases such as measles or smallpox.

The emergence of immunology as a discipline was closely tied to the development of microbiology. The work of Pasteur, Koch, Metchnikoff, and many other pioneers of the golden age of microbiology resulted in the rapid identification of new infectious agents. This was closely followed by the discovery that infectious diseases could be prevented by exposure to killed or attenuated organisms, or to compounds extracted from the infectious agents. The impact of immunization against infectious diseases such as tetanus, measles, mumps, poliomyelitis, and smallpox, to name just a few examples, can be grasped when we reflect on the fact that these diseases, which were significant causes of mortality and morbidity, are now either extinct or very rarely seen. Indeed, it is fair to state that the impact of vaccination and sanitation on the welfare and life expectancy of humans has had no parallel in any other developments of medical science.

Evolution has fostered the development of defenses against infection [9]. The skin is an effective, if passive, barrier against most bacteria and viral infections. Surface responses that help resist infection include sweating and desquamation, cilia movement in the respiratory tract, and production of mucus along interior epithelial surfaces. Mucous membranes have antibacterial properties; stomach acid, saliva, and tears help to resist infection. In the gut, entrenched but friendly bacteria compete with pathogens, limiting opportunities for the pathogens to establish themselves. For pathogens that manage to penetrate skin or mucous membranes, the immune system provides two more levels of defense. The first comes from the innate immune system. Injury to cells triggers a nonspecific inflammatory reaction, which is a cascade of events involving chemical and cellular responses to the local injury. The inflammatory reaction recruits a variety of blood cells, including mast cells, phagocytes, neutrophils, and others that play various roles in the host response. The innate immune system also activates the adaptive immune system, which allows a specific response to infectious agents. This system produces antibodies that are designed to attach to specific sites on the pathogen or its toxins, neutralizing the threat. Specialized B-cell lymphocytes work in conjunction with helper T cells to produce antibodies. These cells also record the antigenic pattern that stimulated their response, enabling a faster and more effective response if the antigen is encountered again. This antigenic memory is what is commonly referred to as immunity to an infectious agent. Immunity occurs naturally after an infection, but it can also be stimulated by vaccination, which is intended to provoke

an immunogenic reaction without causing an initial pathogenic infection. Immunity can vary in duration from a relatively short period to lifetime protection.

The sophistication of host defenses implies that humans have always had to reckon with infectious disease. The balance between host and pathogen, however, is readily tipped by changing social conditions. For example, human invasions or migrations sometimes brought immunologically naive populations into contact with diseases to which they had not previously been exposed. Urbanization during the Middle Ages brought on the conditions that fostered spread of the plague. Europeans brought with them to the New World a host of infections, such as smallpox, measles, typhus, and cholera, which had catastrophic consequences for natives of the Western Hemisphere. Europeans had adapted to these agents, but the newly exposed natives of the Americas had no natural defenses. Conversely, some speculate that syphilis was prevalent in the Americas but unknown in Europe until after Columbus' first voyage to the New World.

Carcinogenic agents

It is from many of the considerations as well as the presumed critical nature of the adduct in the carcinogenic process that a working hypothesis has evolved which postulates that the extent of the formation of DNA adducts and their persistence in the DNA should correlate with the biological effect of the agent [10]. In accord with this hypothesis, several studies have correlated the persistence of DNA adducts occurring during chemical carcinogenesis with the high incidence of neoplasms in specific tissues.

Despite these and other exceptions to the working hypothesis, our knowledge of the persistence of covalent adducts of DNA and carcinogenic chemicals in tissues has been utilized in attempts to quantitate the exposure of humans to carcinogenic chemicals and relate the potential risk of neoplastic development to such exposure. The occurrence of adducts of benzo(a)pyrene throughout the tissues of exposed animals at unexpectedly similar levels further supports the rationale for the investigation of persistent DNA adducts as well as carcinogen-protein adducts in the human. Immunological and highly sensitive chromatographic technologies have been used to demonstrate the presence of persistent DNA adducts of several carcinogenic species. The detection of DNA adducts of carcinogenic polycyclic aromatic hydrocarbons has been demonstrated at relatively high levels in tissues, especially in blood cells of smokers and foundry workers, compared with nonexposed individuals. As expected, a variety of adducts are found in both normal individuals and those potentially exposed to specific carcinogenic agents. In addition to DNA adducts, adducts of specific carcinogens with serum proteins have been demonstrated.

Vaccines

Vaccines are by far the most successful life-saving medical developments in modern times [11]. Very successful vaccines have been developed with little knowledge of either the pathogen or the human immune system. Due to better understanding of the complex biology of viruses, bacteria, and the immune system and because of technological advances in biotechnology, vaccines are now available against a large assortment of microorganisms. Yet despite our advanced knowledge, no vaccine is available to protect against notorious infectious life-threatening diseases like AIDS, TBC, and malaria. Decades of research have not delivered a vaccine against respiratory syncytial virus (RSV), which is a major cause of pneumonia and bronchiolitis in infants and the elderly. The low-hanging fruit of the easy targets has been picked and this early success strengthened the hope and belief that infectious diseases would be held in check and could be eradicated given enough effort. Eradication has only been achieved for smallpox and is being pursued for other viruses like polio. However, this early optimism has disappeared. Even infectious diseases that are kept in check with effective vaccines still pose a threat because continuous evolution of microbial reservoirs can cause a return of the disease because of mismatch with the vaccine. Such recurrent update of the vaccine strain is common practice for influenza virus which is continuously sampled around the globe in order to select the matching vaccine for next year's epidemic.

Aging population demographics, combined with suboptimal vaccine responses in the elderly, make the improvement of vaccination strategies in the elderly a developing public health issue [12]. The immune system changes with age, with innate and adaptive cell components becoming increasingly dysfunctional. As such, vaccine responses in the elderly are impaired in ways that differ depending on the

type of vaccine (e.g., live attenuated, polysaccharide, conjugate, or subunit) and the mediators of protection (e.g. antibody and/or T cell). The rapidly progressing field of systems biology has been shown to be useful in predicting immunogenicity and offering insights into potential mechanisms of protection in young adults. Future application of systems biology to vaccination in the elderly may help to identify gene signatures that predict suboptimal responses and help to identify more accurate correlates of protection. Moreover, the identification of specific defects may be used to target novel vaccination strategies that improve efficacy in elderly populations.

Vaccines are effective in preventing viral attack by artificially creating an immune response that recognizes the real virus if later exposed and mounts a defense [13]. There are several problems. Vaccines are not available for all types of viruses. For those without vaccines, the cost of making them is prohibitive in many cases, or the present technology has not been able to design a vaccine, or at least one that is not toxic to humans.

Some vaccines are difficult to create, as in the case of HIV, which attacks the immune system. It is very hard to find a stimulant to the immune system for a disease that feeds off that very immune system. For other agents, like influenza (the flu), the virus mutates, or changes, so rapidly that the vaccine that worked last year won't work this year. Scientists spend a great deal of time trying to predict what strains of fl u will be prevalent next year so they can design an effective vaccine combination.

But that investigation takes time, not to mention the time required to create the vaccine, which, even in the case of flu, can take a year to produce sufficient quantity for inoculation. And, since the main medium to culture a vaccine is eggs, it takes a lot of eggs for an adequate vaccine supply.

Conclusion

Since its beginning, immunology has evolved under the wings of microbiology. The scientific cognition that the immune response to microorganisms is only one of the immune responses, and that this response can be caused in almost every organic macromolecule under certain conditions, has stimulated the development of immunology as an independent scientific discipline. Modern immunology encompasses a large number of disciplines that study the structures and physiological functions of the immune system, immunity to infections, conditions of immune hypersensitivity (allergy), immunological deficiencies (immunodeficiencies), immune responses to transplantation and tumor, autoimmune diseases, as well as numerous immunodiagnostic procedures.

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