مجلة الدراسات التربوية والعلمية - كلية التربية - الجامعة العراقية
العدد الخامس والعشرون - المجلد الخامس - علوم الحياة - آذار 2025 م
doi.org/10.52866/esj.2025.05.25.13

Description of molecular immunology and its application (a Review article)

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Abstract :

Effective innate and adaptive immune responses are largely dependent on the anatomical arrangement of the immune system's cells and tissues. In addition to allowing a small number of lymphocytes specific for any antigen to locate and respond to that antigen efficiently, regardless of where the antigen is introduced in the body, this organization enables the quick delivery of innate immune cells, such as neutrophils and monocytes, to infection sites. Both innate and adaptive immunity rely on phagocytes (including neutrophils and macrophages), mast cells, basophils, eosinophils, dendritic cells, innate lymphoid cells (ILCs), natural killer (NK) cells, and lymphocytes to carry out the bulk of their effector tasks. The CD nomenclature is used to designate the many surface molecules that are differently expressed on different immune cell types and subsets. With their characteristic multilobed segmented nucleus and profusion of cytoplasmic lysosomal granules, neutrophils—the most prevalent blood leukocyte—are quickly drawn to infection and tissue damage areas to carry out phagocytic and microbial killing tasks. In addition to being sentinel cells that identify pathogens and notify the immune system, tissue resident macrophages can carry out other specific tasks in various tissues, including the liver, spleen, and lung. Circulating phagocytes known as monocytes are drawn to tissue infection and injury sites, where they quickly develop into macrophages that consume and eliminate bacteria and dead host cells. They also release cytokines and chemokines that encourage the recruitment of leukocytes from the blood and start the healing process of injured tissues. Many of the methods previously outlined are employed in clinical laboratories to assess patients' immune system health. The most popular laboratory techniques for identifying immunologic abnormalities will be outlined below. Molecular genetic analysis and other highly specialized testing are frequently performed in response to anomalies discovered by these methods.

key words: Cytokines, DNA sequencing, Peptides, Antibodies.

وصف علم المناعة الجزيئية وتطبيقاته (مقالة مراجعة)

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مستخلص:

تعتمد الاستجابات المناعية الفطرية والتكيفية الفعّالة إلى حد كبير على الترتيب التشريحي لخلايا وأنسجة الجهاز المناعي. بالإضافة إلى السماح لعدد صغير من الخلايا الليمفاوية الخاصة بأي مستضد بتحديد موقع هذا المستضد والاستجابة له بكفاءة، بغض النظر عن مكان إدخال المستضد في الجسم، فإن هذا التنظيم يمكّن من التوصيل السريع للخلايا المناعية الفطرية، مثل الخلايا المتعادلة والوحيدات، إلى مواقع العدوى. تعتمد كل من المناعة الفطرية والتكيفية على الخلايا البلعمية (بما في ذلك الخلايا المتعادلة والبلعميات)، والخلايا البدينة، والخلايا القاعدية، والخلايا الحمضية، والخلايا الشجيرية، والخلايا الليمفاوية الفطرية (ILCs)، والخلايا القاتلة الطبيعية (NK)، والخلايا الليمفاوية لتنفيذ الجزء الأكبر من مهامها المؤثرة. تُستخدم تسمية CD لتعيين العديد من الجزيئات السطحية التي يتم التعبير عنها بشكل مختلف في أنواع الخلايا المناعية المختلفة والمجموعات الفرعية. بفضل نواتها المتعددة الفصوص والمجزأة ووفرة حبيبات الليزوزوم السيتوبلازمية، تنجذب العدلات - وهي أكثر خلايا الدم البيضاء انتشاراً - بسرعة إلى مناطق العدوى وتلف الأنسجة للقيام بمهام البلعمة وقتل الميكروبات. وبالإضافة إلى كونها خلايا حارسة تحدد مسببات الأمراض وتنبه الجهاز المناعي، فإن الخلايا البلعمية المقيمة في الأنسجة قادرة على القيام بمهام محددة أخرى في أنسجة مختلفة، بما في ذلك الكبد والطحال والرئة. تنجذب الخلايا البلعمية الدائرية المعروفة باسم الخلايا الوحيدة إلى مواقع العدوى والإصابة في الأنسجة، حيث تتطور بسرعة إلى خلايا بلعمية تستهلك وتقضي على البكتيريا وخلايا المضيف الميتة. كما أنها تطلق السيتوكينات والكيموكينات التي تشجع على تجنيد الكريات البيضاء من الدم وتبدأ عملية شفاء الأنسجة المصابة. يتم استخدام العديد من الطرق الموضحة سابقًا في المختبرات السريرية لتقييم صحة الجهاز المناعي للمرضى. سيتم توضيح أكثر التقنيات المعملية شيوعًا لتحديد التشوهات المناعية أدناه. في كثير من الأحيان يتم إجراء التحليل الجيني الجزيئي وغيره من الاختبارات المتخصصة للغاية استجابةً للتشوهات التي يتم اكتشافها من خلال هذه الأساليب.

الكلمات المفتاحية : السيتوكينات، تسلسل الحمض النووي، الببتيدات، الأجسام المضادة.

Introduction

The Latin word immunitas, which described the protection from prosecution provided to Roman senators while they were in office, is where the word immunity originates. Immunity has traditionally meant defense against illness, particularly infectious sickness. The immune response is the collective and coordinated reaction of the immune system's cells and molecules, which are responsible for immunity, to the introduction of foreign substances (1). Defense against infectious germs is the immune system's physiological role, but immune responses can also be triggered by noninfectious external substances and by the byproducts of our own damaged and malignant (tumor) cells. Furthermore, in some circumstances, the same systems that typically shield people against infection and the removal of unwanted substances can also result in tissue damage and illness. Even self-molecules can trigger immunological reactions (also known as autoimmune reactions) in certain circumstances. Therefore, independent of the physiological or pathologic ramifications of such a reaction, a more encompassing definition of the immune response is a reaction to microorganisms and to molecules that are identified as alien or aberrant. Immunology is the study of the immune system's reaction to microorganisms and other foreign macromolecules, as well as the cellular and molecular processes that follow (2).

The earliest obvious instance of this manipulation in history, and still one of the most spectacular, was Edward Jenner's successful smallpox vaccination. English doctor Jenner was aware of a finding in rural England that milkmaids who had recovered from cowpox did not get smallpox, which is more dangerous. This finding led him to inject the substance from a cowpox pustule into an 8-year-old boy's elbow. This youngster later had a purposeful smallpox vaccination, but the illness did not manifest. Jenner's seminal vaccination treatise (3). A century later, Louis Pasteur and Robert Koch's work solidified the concepts of infectious illnesses and immunization. Due to these developments, the process of generating immunity became widely accepted, and vaccination is still the best way to avoid illnesses. The World

Health Organization's 1980 declaration that smallpox was the first illness to be completely eliminated globally by vaccination was a powerful example of the significance of immunology. Both the COVID-19 pandemic, which began in 2019 and was caused by the coronavirus SARS-CoV-2, and the AIDS (acquired immunodeficiency syndrome) epidemic, which began in the 1980s and was caused by HIV (human immunodeficiency virus), have tragically and dramatically brought attention to the importance of the immune system. Both have had a terrible effect on society and have resulted in significant morbidity and numerous fatalities. One of the top priorities is the creation of potent vaccinations against both illnesses (4).

History of molecular immunology

Since the 1960s, there has been a significant shift in our understanding of the immune system and how it functions. Thanks to advancements in cell culture techniques (including the production of monoclonal antibodies), immunochemistry, recombinant DNA methodology, next-generation DNA sequencing, x-ray crystallography, and the creation of genetically altered animals (particularly transgenic and knockout mice), immunology has transformed from a primarily descriptive science to one in which a variety of immune phenomena can be explained in structural and biochemical terms. Some of the most important advancements in immunology have taken place during the 1990s, including the discovery of therapies that target different elements of the immune system. These therapies, which have their roots in fundamental science, are having a major impact on how inflammatory diseases and cancer develop in people (3). Some historians believe that the first recorded reference of immunity occurred during an epidemic in Athens in the fifth century BC that Thucydides called the "plague" (although this was probably not the bubonic plague as we know it today). The concept of protective immunity may have existed even before the ancient Chinese technique of making children immune to smallpox by having them inhale powders made from the skin lesions of patients recovering from the illness. The experimental field of modern immunology

explains immunologic processes by use of experimental data and the conclusions drawn from them. Our ability to alter immune system function under closely watched conditions has been crucial to immunology's development as an experimental discipline.(5) .

Immune Response Genes

The Major Histocompatibility Complex (MHC) was only known to play a part in transplant rejection for over two decades after its discovery. Since transplantation is not a natural occurrence, immunologists found this puzzling. If a gene's sole purpose was to promote the rejection of foreign tissue grafts, there was no reason for it to be retained through evolution. It was shown in the 1960s and 1970s that MHC genes are essential for every immunological response to protein antigens. Inbred strains of a single species (mice or guinea pigs) varied in their capacity to produce antibodies against certain basic synthetic polypeptides, and responsiveness was inherited as a dominant Mendelian characteristic, according to research by Baruj Benacerraf, Hugh McDevitt, and associates(6). The MHC included all of the pertinent genes, which were referred to as immune response (Ir) genes. The capacity of Ir genes to bind and display peptides produced from different protein antigens varies, indicating that they are indeed class II MHC genes that encode class II MHC molecules. Helper T cells may identify peptide-MHC complexes that are formed when responder strains that are able to mount immunological responses to a specific polypeptide antigen acquire MHC alleles whose products can bind peptides produced from these antigens. After that, these T cells aid B cells in the production of antibodies (7). Nonresponder strains are unable to produce helper T cells or antigen-specific antibodies because they contain MHC molecules that are unable to bind peptides produced from the polypeptide antigen. Later research also revealed that the inheritance of certain MHC alleles was linked to a number of autoimmune illnesses, putting these genes at the core of the systems governing immune responses. More thorough examinations of MHC genes and proteins were prompted by these investigations. In addition to other nonpolymorphic genes whose products are important in antigen presentation, the MHC locus contains two types of

polymorphic MHC genes, the class I and class II MHC genes, which encode two sets of structurally different but homologous proteins (Fig. 1) . Variations in a gene among members of an outbred population are referred to as polymorphism. Peptide antigens are shown by class I and class II MHC molecules so that CD8 + and CD4 + T lymphocytes may recognize them, respectively. Peptides necessary for T cell identification are absent from the nonpolymorphic molecules encoded in the MHC (8).

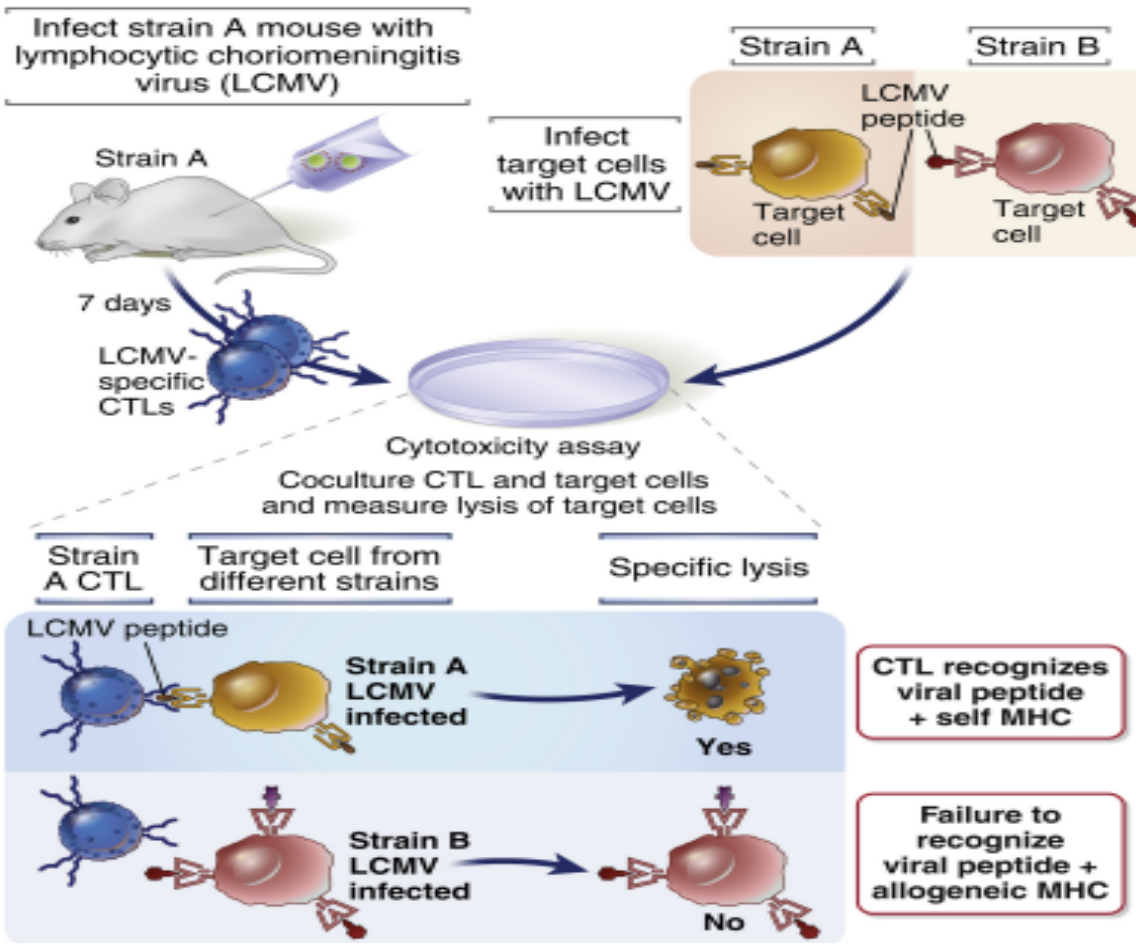

Figure 1 Experimental demonstration of the phenomenon of major histocompatibility complex (MHC) restriction of T lymphocytes. Virus-specific cytotoxic T lymphocytes (CTLs) generated from virus-infected strain A mice kill only syngeneic (strain A) target cells infected with that virus. The CTLs do not kill infected strain B targets (which express different MHC alleles than does strain A). By use of congenic mouse strains that differ only at class I MHC loci, it has been proved that recognition of antigen by CD8 + CTLs is self class I MHC restricted. LCMV, Lymphocytic choriomeningitis virus.

The most polymorphic genes found in any mammalian genome are class I and class II MHC genes. One noteworthy finding from research on human MHC genes is the surprising degree of variation. Within the populace, It is believed that there are about 14,000 distinct HLA alleles with varying amino acid sequences, with over 3500 variations for the HLA-B locus alone. Gene recombination does not cause the changes in MHC molecules that cause the polymorphism; rather, they are the consequence of inheritance of different DNA sequences. distinct members of a population may exhibit distinct peptides from the same protein antigen because different MHC alleles' products bind and show different peptides (9).

Binding of Peptides to MHC Molecules

The ability of proteins' peptides to be displayed by MHC molecules is what makes them immunogenic. Since then, a lot of work has been done to understand the molecular basis of peptide-MHC interactions and the properties of peptides that enable them to bind to MHC molecules. The functional tests of helper T cells and CTLs reacting to APCs treated with various peptides were the original basis for these investigations (10). Using techniques like equilibrium dialysis and gel filtration, the direct binding of MHC molecules and peptides has been investigated with pure MHC molecules and peptides that have been radioactively or fluorescently tagged in solution. The way that peptides sit in the clefts of MHC molecules and the residues of each that contribute to this binding have been definitively determined by X-ray crystallographic study of peptide-MHC complexes. Computer algorithms that can predict which peptides of a given protein are most likely to bind to MHC molecules have been developed using this knowledge. Theoretically, vaccinations targeting altered tumor proteins or microbial proteins may be created using this knowledge (11).

Processing of Protein Antigens

Protein antigens found in the cytosol or internalized from the external environment are transformed into peptides by the antigen processing pathways, which then load the peptides onto MHC molecules so that T cells can see them.

Antigen processing mechanisms have developed to produce peptides with the structural properties needed to attach to MHC molecules and to locate these peptides in the same cellular region as freshly generated MHC proteins when peptide-binding clefts are available (12). The production and assembly of MHC molecules depend on peptide binding, which takes place prior to cell surface expression. Indeed, as was previously stated, the assembly and surface expression of stable class I and class II MHC molecules depend on peptide association. Proteases break down cytosolic proteins to produce peptides that are shown on class I MHC molecules, while lysosomes (also known as late endosomes) break down extracellular environment-ingested proteins that are trapped in vesicles to produce peptides that are shown on class II MHC molecules (13).

Self Versus Nonself

The immune system's primary role is thought to be discriminating between the self and the nonself. Invaders are attacking us all the time. Because our bodies provide a wealth of nutrition, warmth, and shelter from the elements, they are ideal places for creatures to thrive and live. In essence, the immune system consists of a number of barriers designed to prevent and restrict the entry of pathogens, as well as to combat and eliminate them after they have entered the body. The immune system is beautifully crafted to identify these intruders as "foreign." The capacity of our immune system to differentiate between the cells that belong to our body (the self) and those that it perceives as alien (the nonself) is actually the primary characteristic that makes it so successful (14).Every single one of our cells has unique tags, or molecular identifiers, that identify it as "self." These indicators are crucial, because they not only define our individuality but also set us apart from one another. The immune system will react to almost anything that detects as "nonself." Immune components work together to fight disease-causing organisms through a complex network of cellular connections and molecular communication. An antigen is any component of the foreign agent (virus, parasite, bacterium, etc.) that can be uniquely identified. Any material or physical structure that the immune system can identify

is known as an antigen. The two main categories of antigens are proteins and carbohydrates, Nucleic acids and lipids. An antigen can become immunogenic and cause complete immune activation if it is heavy and complicated. Maintaining functional protection requires the capacity to discriminate between our own cells and the external environment. The loss of this function causes our immune system to react aggressively against our own tissues, such as when "self" tissue is seen as alien. This is the case with autoimmunity, when clinical illness results from the breakdown of the self (15).The immune system keeps its response under check. While a reaction that is overly forceful may result in the deliberate killing of bystander tissues, a response that is too minimal is ineffectual. Both situations have the potential to cause clinical illness and are equally destructive. Numerous elements govern the management of immune function and overall immuno-homeostasis, including both environmental stimuli and hereditary components. When the foreign material (the antigen or the pathogen) is gone, the responses must be specific and quick to downregulate, and their length and strength must be adequate to defend against invasive infections. Hypersensitivity is the clinical condition that results from improperly controlled immune responses; it is characterized by excessive or inappropriate reactions that cause illness. Depending on whatever part of the immune system is dysregulated, hypersensitivity can manifest itself in a variety of ways (16).

Role of Epigenetic Changes and MicroRNAs in Lymphocyte Development

Numerous nuclear processes in the development of lymphocytes are controlled by epigenetic mechanisms. The term "epigenetics" describes how processes other than modifications to the coding sequences themselves regulate gene expression and phenotypes. Antigen receptor gene rearrangement processes in developing lymphocytes are also regulated by epigenetic mechanisms. Chromatin is made up of DNA that is firmly attached to histones and nonhistone proteins in chromosomes. A protein core of histone octamers is looped around DNA in chromatin to create structures known as nucleosomes, which can be tightly packed

or well separated from neighboring nucleosomes (17). Therefore, chromatin can exist as either densely packed heterochromatin, where genes are kept in a quiet condition, or as relatively loosely packed structures termed euchromatin, where genes can be accessible by transcription factors and are transcribed. distinct cells have distinct chromosomal structural arrangements, which can make some genes accessible to transcription factors while preventing transcription factors from binding to those same genes in other cells (18). By altering the promoter and enhancer regions of genes, epigenetic processes control the accessibility and activity of genes. Among these modifications are : The silencing of gene expression by noncoding RNAs; the active remodeling of chromatin by protein machines called remodeling complexes that can also either enhance or suppress gene expression; the methylation of DNA on specific cytosine residues that generally silences genes; and post-translational modifications of the histone tails of nucleosomes (such as acetylation, methylation, and ubiquitination) that can make genes either active or inactive depending on the histone modified and the type of modification. Epigenetic processes control certain essential aspects of lymphocyte development(19).

Antigen Receptor Gene Rearrangement and Expression

A variety of adaptive immune repertoires are produced by the rearrangement of antigen receptor genes, which is a crucial step in lymphocyte development. Every B or T cell clone produces an antigen receptor with a distinct antigen-binding structure, as we covered in earlier chapters. Any given person may have between 107 and 109 distinct B and T cell clones, each with its own receptor. Each person's capacity to produce these enormous and varied lymphocyte repertoires has developed to the point where a relatively small number of genes may produce a huge variety of unique Ig and TCR molecules, Each has the ability to attach to a distinct antigen. Through a process of gene rearrangement, immature T cells in the thymus and immature B cells in the bone marrow create functional antigen receptor genes (20). Numerous variable region-encoding exons are produced as a result of the random recombination of antigen re-

ceptor gene segments and the introduction of nucleotide sequence variants at the joints. The presence of antigens has no bearing on or effect on the DNA rearrangement processes that result in the synthesis of antigen receptors. In other words, different antigen receptors are produced and expressed before to encountering antigens, as suggested by the clonal selection theory (21).

Rearrangement of Antigen Receptor Genes in B and T Lymphocytes

The genes that encode diverse antigen receptors of individual B and T lymphocytes are generated by the recombination of different variable (V) region gene segments with diversity (D) and joining (J) gene segments. This specialized process of site-specific gene rearrangement is called V(D) J recombination. Elucidation of the mechanisms of antigen receptor gene rearrangement, and therefore of the underlying basis for the generation of lymphocyte diversity, represents one of the landmark achievements of modern immunology (22). The first insights into how millions of different antigen receptors could be generated from a limited amount of coding DNA in the genome came from analyses of the amino acid sequences of Ig molecules. These analyses showed that the polypeptide chains of many different antibodies of the same isotype shared identical sequences at their C-terminal ends (corresponding to the constant domains of antibody heavy and light chains) but differed considerably in the sequences at their N-terminal ends that correspond to the variable domains of antibodies(23).

Immunologic tolerance

T and B lymphocyte populations exhibit tolerance in a number of ways. Before we talk about the particular processes of tolerance in these cells, it is crucial to understand the broad concepts. High-affinity receptor-expressing lymphocytes for self-antigens are eliminated and rendered inactive by the processes of tolerance. Every person inherits almost identical parts of the antigen receptor gene, which recombine and are expressed in lymphocytes as the cells develop from precursor cells. What is foreign or self for each individual has no bearing on the random specificities of the receptors generat-

ed by the recombined genes.It should come as no surprise that while creating a vast and varied repertoire, Each person may have some developing T and B cells that have receptors that can identify normal substances in that person (self antigens) (24). As a result, there is a chance that lymphocytes will react negatively to the person's cells and tissues, leading to illness. Such responses are prevented by immunologic tolerance mechanisms. Antigen-specific tolerance arises from individual lymphocyte clones' identification of antigens. Therapeutic immunosuppression, on the other hand, targets lymphocytes with a variety of specificities. The capacity to develop tolerance in animals by exposing them to specific antigens under varied settings and then analyzing the survival and functions of the lymphocytes that had encountered the antigens were the major advancements that made it possible for immunologists to research tolerance (25). The 1950s, It was demonstrated by Peter Medawar and associates that newborn mice of one strain exposed to cells from different strains lost their ability to respond to skin grafts from the donor strain. Subsequent research revealed that tolerance might be developed to proteins and other antigens in addition to invading cells. Depending on a variety of conditions, including exposure to the antigen during lymphocyte development and detection by certain lymphocytes with or without innate immune responses, every antigen can be either an immunogen or a tolerogen. Later in the chapter, these aspects are covered. It is possible to establish self-tolerance in mature lymphocytes in peripheral locations (peripheral tolerance) or in immature self-reactive lymphocytes in the generative lymphoid organs (central tolerance).The generative lymphoid organs (the bone marrow for B lymphocytes and the thymus for T cells, also known as main or central lymphoid organs) produce self antigens, and central tolerance makes sure that the repertoire of mature naïve lymphocytes is unable to react to them. Central tolerance is not flawless, though, and healthy people have a large number of self-reactive lymphocytes that have fully matured. Peripheral tolerance mechanisms are therefore required to stop these potentially harmful cells from activating (26).

Roles of Regulatory T Cells in Self-Tolerance and Autoimmunity

Convincing evidence of the role Tregs play in immune system homeostasis and self-tolerance has been provided by the identification of the genetic basis of IPEX syndrome and the related illness in mice brought on by mutations in the foxp3 gene.There are several attempts to find flaws in Treg generation or function in more prevalent autoimmune and inflammatory human illnesses including multiple sclerosis (MS), type 1 diabetes, and inflammatory bowel disease (IBD), as well as in allergy disorders.The pathophysiology of these disorders may be influenced by Treg defects or effector cell resistance to Treg suppression (27).However, because it is difficult to define and quantify functioning Tregs in people, it has proven difficult to firmly demonstrate the significance of Treg abnormalities in these prevalent disorders. In order to regulate pathologic immune responses, Tregs may also be cultivated and then reinjected into patients. Treg transfer is now being used in clinical studies to treat autoimmune and other inflammatory diseases, graft-versus-host disease, and transplant rejection. Clinical experiments are also being conducted to increase these cells in patients by giving them cytokine IL-2 in dosages or forms that selectively bind to CD25, activating Tregs in the process. Apart from their significance in managing autoimmunity, Other functions of tregs have been demonstrated. Numerous tissues include subpopulations of Tregs with distinct transcriptional profiles, which seem to carry out tasks that are particularly advantageous for that tissues. Skin, muscle, and organs like the lung include tregs that support tissue healing as well as the growth and differentiation of stem cells, which aids in reestablishing tissue integrity following the resolution of inflammatory responses. Adipose tissue Tregs regulate the metabolism of fat. Additionally, Tregs help to inhibit inflammatory reactions to commensal microorganisms, maintain fetal tolerance, and avoid fetal rejection (28).

Clinical Diagnostic Applications

Many immunologic procedures, which are employed in both clinical and research contexts, rely on the usage of antibodies. Furthermore, a number of contemporary molecular biol-

ogy methods have yielded priceless insights into the immune system and are currently being used to the diagnostic analysis of immunologic disease characteristics. Numerous techniques, including Transgenic Mice and Gene Targeting, Measurement of Antigen-Antibody Interactions, Assays for Cellular Immunity, Immunofluorescence and Immunohistochemistry, Labeling and Detection of Antigens in Cells and Tissues, Western Blotting, Immunoprecipitation and Immuno-Affinity Chromatography, Protein Identification and Purification, and Antigen Quantification by Immunoassays (29, 30).

Conclusions

Our understanding of the role of immune cells in the pathophysiology of pulmonary diseases has been enhanced by recent advances in molecular immunology. T cells and T cell subsets, including T rags and NK cells, are key players in the activation of regulatory pathways in a number of lung diseases and, crucially, in host defense. T cells, as key regulators of the interaction between innate and adaptive immune responses, may offer promising targets for future therapeutic options in pulmonary diseases.

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