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Journal of Clinical & Cellular Immunology

Review Article

An Overview of the Immune System: What the Physician Should Know

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ABSTRACT

The immune response system contributes to the body's defence against infection, toxic or allergenic substances and is concerned with the recognition of tumour cells. In responding to a challenge the immune system is able to distinguish the body's own cells and components (self) *via* the major histocompatibility complex (HLA-DR) class 1 from cells that are foreign (non-self). The abnormalities of the immune response is demonstrated in the immunodeficiency diseases (congenital and acquired), the hypersensitivity reactions that may be involved in producing autoimmune diseases and the switching-off of T cell function by cancer cells. The genetic regulations of the immune system have major implications in clinical medicine as to the understanding of autoimmune disease and the idiotypic network that militates against autoimmune response and excessive immune responses. The relationship between immune function and tumour cells is highly complex but crucial to the understanding of both tumour rejection and progression mechanisms. The improved knowledge of the immune system has expanded the role of immunotherapy and vaccine therapy in oncology. The article reviewed the essential immune mechanisms in health and disease, and the clinical implications.

Keywords: Antigen; Tumour; Immune response; Autoimmunity; Immunotherapy, Hypersensitivity

INTRODUCTION

The body's first line of defence against the environment (innate immunity) comprises a layer of epithelial cells which line all external surfaces. Once, this has been breached, the role of the immune system and inflammation is to limit the damage, eliminate the foreign substance and promote repair [1,2]. Antigens are substances that induce an immune response, and proteins are the most antigenic material, followed by carbohydrates and lipids which are weakly antigenic. A large molecule, such as protein, may have several different sites (epitopes) to which dissimilar clones of immunologically competent cells respond. Some foreign proteins possess epitopes similar to those on self-proteins, accounting for some cases of auto-immunity *i.e.* the environmental aetiology of autoimmune disease. Immunological tolerance, the state of specific un-reactivity to the body's own tissue is thought to be acquired during fetal life when the immune system has not reached immunological maturity. Therefore, the body does not mount significant antibodies against its own tissues. Nevertheless, clones of cells which can produce 'autoantibody' ('forbidden clones') are thought to be produced throughout life and are either suppressed by large amounts of 'self' antigen or by antigen-specific T suppressor cells. 'Autoantibodies' are produced to a wide variety of antigens in autoimmune disease. These autoantibodies may be organ-specific, e.g. intrinsic factor antibodies in pernicious anaemia, thyroid antibodies in Hashimoto's disease, or non-organ specific, e.g. antinuclear factor in Systemic Lupus Erythematosus (SLE). Autoimmune disease states are thought to arise when this system of mopping up forbidden clones breaks down [3]. The body can react to an antigen by producing antibody (humoral immunity) or specific T lymphocytes (cellular immunity). Antibodies belong to the class of serum proteins known as immunoglobulins. The T lymphocytes can be directly cytotoxic (T cytotoxic cells), or may produce cytokines (T helper cells) which are short-lived 'hormones' that acts on other cells to enhance or suppress their activity. Interleukins (lymphocyte activating factors) are specific lymphokines active between cells of the immune system and affect antibody production. The role of complement a multi-molecular activation system of plasma proteins dependent in

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Received: 01-Oct-2023, Manuscript No. JCCI-23-27270; **Editor assigned:** 03-Oct-2023, PreQC No. JCCI-23-27270 (PQ); **Reviewed:** 17-Oct-2023, QC No. JCCI-23-27270; **Revised:** 04-Jan-2025, Manuscript No. JCCI-23-27270 (R); **Published:** 11-Jan-2025, DOI: 10.35248/2155-9899.25.16.750

Citation: Weledji EP (2025) An Overview of the Immune System: What the Physician Should Know. J Clin Cell Immunol. 16:750.

part on the sequential activation of a series of proteolytic zymogens is to promote inflammation, phagocytosis of antigens and immune complexes by macrophages (opsonization), and, lysis when activation is at or near the surface of a target cell. Abnormalities of the immune response are seen in the immunodeficiency diseases and the hypersensitivity reactions. Immunodeficiency may be inherited or may occur as a result of infection or drug therapy. It includes defects in antibody production (hypo- or agammaglobinaemia, selective IgA deficiency), complement fixation (C1 esterase inhibitor (hereditary angioedema), C1q (discoid lupus erythematosus), C1q, C1r, C4 or C2 (immune complex vasculitis), C3 or C3b inhibitor (Kline-felter's syndrome), C5, C6, C7 or C8 (recurrent Neisseria); T lymphocyte function, Thymic aplasia, purine nucleoside phosphorylase deficiency, ataxia telangiectasia, Wiskott-Aldrich syndrome, Bloom's syndrome, Severe Combined Immunodeficiency (SCID)); and phagocyte functioning (Job's syndrome, Chronic Granulomatous Disease (CGD), Chediak-Higashi syndrome, Myeloperoxidase deficiency) [5]. Immunological priming can lead, on further exposure to antigen, to either secondary boosting of the immune response or to an excessive damaging inflammatory reaction (antibody and cellular immune response) termed hypersensitivity. The implications of the immune response in health and the inflammatory (hypersensitivity) reactions (type I anaphylactic, type II-cytotoxic, type III-immune complex mediated, type IV-cell mediated/delayed, type V-stimulating antibody, and type VI-antibody-dependent cell mediated cytotoxicity) in disease are elucidated. The proliferation of normal cells is carefully regulated but tumour cells have undergone mutations which makes them capable of uncontrolled growth. The immunological mechanisms involved in cancer growth are highly complex and the understanding of the relationship between immune function and tumour cells is important [6].

LITERATURE REVIEW

The immune system

The primary lymphoid organs include the bone marrow and the thymus. They create special immune system cells called lymphocytes. Secondary lymphoid organs include the lymph nodes, the spleen, the tonsils and Mucosally Associated Lymphoid Tissue (MALT). MALT is present in the gut, pharynx, bronchi, breast tissue, genitourinary system and the salivary and lacrimal glands. Lymphoid organs appear early in gestation. The thymus appears first, producing cells at 8 weeks which become immunocompetent at 11 weeks. The total population of lymphoid tissue is completed by 16 weeks of gestation. The bone marrow gives rise to the cells of the blood (the haemopoietic system). Some of these cells are involved in the recognition of antigen and mounting of an immune response (lymphocytes), while others are involved in elimination (e.g. macrophages and granulocytes). The thymus is derived from the third and fourth pharyngeal pouches, thus giving it an epithelial framework. It becomes populated by T lymphoblasts produced in the bone marrow, matures in the thymus generating large numbers of specific T lymphocytes. Thymus output is essential during early life to establish immune competence and homeostasis but is dispensable thereafter [1,7]. The tissue cells of the mononuclear phagocyte system are derived from blood monocytes and constitute approximately 5% of the total number of leucocytes. They are large and possess a bean-shaped nucleus. They have abundant cytoplasm containing lysosomes, rough endoplasmic reticulum and other organelles, rendering them capable of division and longevity. Immunoglobulin (IgG, IgE) and complement (C3,C5) receptors on their cell surface allow them to bind immune complexes. They can be divided depending on their function into antigen presenting cells, macrophages, multinucleate giant cells and sinus-lining histiocytes. Within the immune system the Antigen Presenting Cells (APC) are of particular importance. They are involved in interactions between T cells and B cells as a result of their ability to bind antigen-antibody complexes on their surface. The presentation of partially degraded antigen-antibody complexes or free antigen to T and B lymphocytes is important in humoral immunity. Tissue histiocytes are related cells, pinocytotic and facultative phagocytes found in most organs, particularly lining sinusoidal spaces in the spleen, lymph node and liver. The engulfment and digestion of cell debris and foreign material is important in non-specific immunity [8-10].

Lymphocytes are distributed in all organs, tissues, interstitial fluids except the brain. Lymphocytes account for up to 45% of the circulating blood leucocytes. They are divided into T lymphocytes (thymus-derived T cells)-70% of total lymphocytes, B lymphocytes cells derived from the bursa of Fabricius (in birds)-20% of total, and 'Null' Cells (10% of total). T cells are mainly involved with cell mediated immunity whilst B cells are involved in humoral immunity. Immunological memory is carried by long-living T and B cells. The T lymphocytes migrate from the bone marrow to the thymus where they are processed by the thymic epithelial cell hormone, which transforms them into immunocompetent cells. They are activated to form 'blast' cells by specific antigens and non-specific mitogens such as phytohaemoglutinin (PHA). The activation involves macrophages (antigen-presenting cells), which process and present the antigen to the lymphocytes. T-lymphocytes live for months or years and are divided into subsets depending on their role in the immune response, either regulating antibody production through the secretion of interleukins (T Helper (TH) or T suppressor cells (Ts), directly cytotoxic (T cytotoxic (Tc) or taking part in delayed hypersensitivity reactions (T Delayed hypersensitivity cells (TD)). Following the T cell interaction with antigen in association with the HLA glycoprotein (the T cell receptor complex), non-specific lymphokines and interleukins are released which amplify the immunological response. For example many bacteria and protozoa can survive within phagocytic cells (macrophages). These cells may be activated by Macrophage-Activation Factor (MAF) from specifically sensitized T lymphocytes, causing release of intracellular lysosomal enzymes and destruction of the infecting agents. T lymphocytes are the most potent mediators of adaptive anti-tumour immune response. The T cell mediated immunity can be transferred by giving T cells to a genetically compatible individual. In addition, the transfer factor, a soluble extract of T cells, can transfer some T cell functions which is

applied in immunotherapy for cancer or infection [1,2]. It is important to note that T cells have proteins on them that turn on an immune response for an example when an infection is present, and other proteins that turn it off. These are called checkpoint proteins because if T cells are active for too long, or react to things they shouldn't, they can start to destroy healthy cells and tissues [11]. B lymphocytes are derived from the bone marrow, are thought to be processed in the fetal liver and spleen and the adult bone marrow in (mammals), and live for days or weeks. Although B cells and T cells are fundamentally similar, they differ in their surface receptors and markers (Table 1). They use antigen receptors to recognize foreign material, and both undergo a first stage of proliferation in one organ while simultaneously inducing specificity through rearrangement of their antigen-receptor genes. They then undergo a second antigen-driven proliferation at another site, usually a secondary lymphoid organ. Finally, they produce a functional cell, B cells giving rise to immunoglobulin-secreting plasma cells and T cells to functional cytotoxic T cells and helper T cells. Although antibody synthesis is inhibited by Ts cells, TH and B cell interaction is essential for an optimal humoral response to most antigens. The Human Immunodeficiency Virus (HIV) is an RNA retrovirus that infects human T lymphocytes. The suppressed cellular immunity manifesting as AIDS allows the development of malignancies (Kaposi's sarcoma, lymphoma) and opportunistic infections (pneumocystis jiroveci pneumonia, cryptosporidium, Cytomegalovirus (CMV), herpes simplex (SV), disseminated tuberculosis and candida 5-10 years later [12]. B cell and T cell hyperplasia is the basis of lymphomagenesis with T-cell lymphomas being worse than B-cell lymphomas. The combination of recurrent P. falciparum malaria and Epstein-Barr virus (EBV) infection very early in childhood cause B cell hyperplasia which is an essential component of Burkitt's lymphomagenesis. This EBV-associated lymphoma was one of the first tumours shown to have chromosomal translocation (chromosome 14) that activates an oncogene (c-MYC). The transformation of these cells compromises host defence and evolves mechanisms to escape immune surveillance. Thus, Burkitt's lymphoma patients do not usually exhibit the B-symptoms (fever, night sweats, and weight loss) [13,14] . HIV-associated Burkitt's lymphoma is associated with EBV in approximately 40% of cases. T cell hyperplasia is mainly caused by infection with the HTLV-1 virus which may give rise to adult T-cell lymphoma/leukaemia [15]. The 'Null' cells originate from the bone marrow but are lymphocytes that do not possess the phenotype surface markers of either T or B cells. Some may be identical to 'killer' (k) cells, which have cytotoxic properties against target cells coated with antibody, and some may be 'Natural Killer' (NK) cells, which are thought to lyse certain tumour cells [16].

Table 1: Receptors and surface antigens present on T and B lymphocytes.

	T-lymphocytes	B-lymphocytes	Comments
Receptors complement			
C3b	-	+	Receptors mainly for IgM but also for IgA, IgG and IgE present on 60-65% of all circulating T-lymphocytes
C4b	-	+	
Immunoglobulin	-	+	
Sheep erythrocyte (E receptor)	+	-	
Surface antigens/markers			
1a	+	-	Present on circulating lymphocytes and involved in cell-cell cooperation circulating T lymphocytes T helper/inducer cells T suppressor cells T cytotoxic cells/ suppressor cells
Immunoglobulin	-	+	
CD3 (T3)	+	-	
CD4 (T4)	+	-	
CD5 (T5)	+	-	
CD8 (T8)	+	-	

Polymorphonuclear granulocytes (neutrophils) originate from bone marrow derived myeloid cells, and circulate in the bloodstream. Neutrophils live for 6-20 h and constitute approximately 60% of the total number of leucocytes. They bear surface receptors for IgA, IgG and complement components. Neutrophils play a primary role in non-specific immunity by engulfing and digesting microorganisms, and their absence usually proves fatal [17]. Mast cells are present in the skin and mucosal surfaces, and basophils circulate in the blood, where they constitute 0.5 to 2% of the circulating leucocytes. Although direct proof of common origin is lacking both mast cells and basophils are involved in type 1 immediate hypersensitivity

reactions, when they release inflammatory mediators following allergen binding to IgE on their surface. They also bear receptors for complement components. Circulating basophils show an increase in allergic disease states and are seen in secretions of patients with allergic rhinitis. Eosinophil granulocytes originate from myeloid precursors in the bone marrow and circulate in the bloodstream, where they constitute 2-5% of the total number of leucocytes, although they may account for up to 20% in individuals with immediate sensitivity diseases or helminth infestation. They live for 6-20 h and bear receptors for IgG and complement components. Thus their primary activities are to engulf and digest immune-complexes important against helminth infection, and the release of enzymes that are able to inactivate biologically active substances such as histamine in type I hypersensitivity reactions [18].

Immunoglobulins

The basic Immunoglobulin molecule (Ig) comprises four protein molecules, two heavy chains and two light chains, with a variable Fab end (antigen binding end) and Fc (the constant end) that determines the properties of the molecule. There are five classes of immunoglobulin, IgG, IgM, IgA, and IgD, each having a specialized function determined by its heavy chain. Following gene rearrangement, antigen activated B cells differentiate into plasma cells, which are designed for high protein production and secretion. Initially, the splicing of variable region genes onto the new heavy chain gene leads to the production of IgM. This immunoglobulin is expressed on the surface of the developing B cells and acts as a trigger to further cell proliferation. Subsequently 'gene switching' leads to the production of IgG and the other immunoglobulins. IgG is the most abundant. Immunoglobulin in the blood. IgM is a pentamer and is the first to be produced in an immune response. IgA is a dimer and is secreted by mucosal plasma cells. It passes through the epithelium and resides in the gut ready to deal with ingested antigens. On passage through the epithelium, a polypeptide secretory component is attached to the immunoglobulin which helps prevent digestion by the gut enzymes. IgE binds to specific regions of mast cells which recognize the Fc region of the immunoglobulin molecule. This immunoglobulin is important in combating helminth infections and also plays a role in hypersensitivity reactions [19].

DISCUSSION

Specificity and antigen receptor rearrangement (Diversity)

The complex and diverse immune system is genetically regulated by somatic generation of variations on the basis of a limited number of germ-line genes. Each germline cell in the body contains genes for immunoglobulin and also a T cell receptor. The genes are divided into sections designated V (variable), D (diversity), J (joining) and C (constant). The V, D and J regions contain different versions of the same genes. Gene rearrangement occurs during the lymphocyte development. A single gene from each section is selected while the other genes are eliminated. The new V, D, J sequence is spliced onto the heavy chain gene. Since these joins are random, this process generates considerable diversity. This diversity is even greater in the case of the heavy chain genes in which the Variable Heavy (VH) genes combine with a D gene which comprises a hypervariable region which in turn recombines with one of a cluster of J gene. Further variation occurs by the association of different light chains with the heavy chains, and possibly by changes of the arranged immunoglobulin genes by somatic mutations in the course of B cell ontogeny, and the arrangement of the α and β chains of the T cell receptor. It should be noted that this rearrangement is random and does not require the presence of antigen. Antigen-driven proliferation occurs in the secondary lymphoid organs where the lymphocyte and its progeny are specific for a single epitope on an antigen. Throughout life a person is exposed to a wide variety of antigens and consequently produces antibodies with a corresponding wide range of specificities. Of some 10^{20} immunoglobulin molecules in the circulation there are an estimated 10^5-10^8 different specificities.

The lymph node ensures thorough mixing of antigen, immunocompetent cells band immunoglobulins. The constant slow flow of lymph from the tissues back to the blood ensures that antigenic sampling by the immune system can be easily carried out. The sampling occurs in the lymph node sinuses, which are lined by histiocytes capable of trapping antigen, particularly when coated with antibody. Simultaneously blood carrying lymphocytes arrives at the node. The peripheral blood contains 2×10^9 lymphocytes/ml, 70% of which are T cells. The cells continuously recirculate from the blood to the lymph node, to the thoracic duct and back to the blood. Antigen carried in the lymph is highly likely to meet its specific lymphocyte, because the two flows meet in the lymph node. The post-capillary venules in the lymph node are lined by cuboidal epithelial cells and are the site of lymphocyte emigration from the cardiovascular to the lymphatic system. The mixing of lymphocytes with antigen leads to a second phase of proliferation and differentiation. Proliferation and differentiation of the B cells occurs in the germinal centre. Firstly, plasma cells are produced that migrate to the medulla, where they secrete large amounts of specific immunoglobulin. Secondly, memory B cells are produced ready to confront the antigen on subsequent exposure. The secondary immune response is characterized by the rapid production of IgG, because the clone of specific B cells has multiplied and the immunoglobulin genes have already switched from IgM to IgG transcription. T cells migrating through the node will proliferate and differentiate as well, but around the blood vessels of the paracortex. The specific T cells produced, un-stimulated lymphocytes, immunoglobulin leaves the lymph node at the medulla, return via the thoracic duct to the bloodstream and ultimately arrives at the tissue from which the lymph was draining. In most cases, antigens are stopped at the lymph node and prevented from further progress through the body. In some overwhelming infections, however, organisms will elude the first line of defence, enter the bloodstream and then the lymphoid tissue of the spleen becomes very important. The spleen is essentially an enlarged lymph node with a very similar arrangement. The splenic lymphoid t issue (the white pulp)

consists of aggregates of T cells and B cells arranged around the arterioles. The spleen has two main roles: Mounting immunological reactions to blood-borne antigens in the systemic circulation and the removal of abnormal red blood cells. Mucosa-associated lymphoid tissue, which is present beneath the mucosa, from the tonsils to the anus, is responsible for generating immune response to gut contents. Similar lymphoid aggregates can also be found in the respiratory tract. There are B and T cell areas similar to those found in the lymph node, but the B cells have a tendency to infiltrate the epithelium possibly as a way of sampling the antigens in the lumen as particularly seen with the secretory IgA antibodies from Peyer's patches (Gut Associated Lymphoid Tissues (GALT)) in the terminal ileum [1].

Elimination of the antigen

The foreign organism is eliminated by the immune system in conjunction with elements of the inflammatory process. The precise reaction varies according to the nature of the pathogen. If the whole cell is recognized as foreign, immunoglobulins will be directed against it and will bind to cell surface antigens. The binding of antibodies and antigens activates the complement system. Complement is a series of nine plasma proteins which become bound to antigen-antibody complexes in a specific sequence (cascade). The binding or fixation of complement results in either the lysis or engulfment by phagocytes of the antigen via the classical or alternative pathways respectively. In the classical pathway, if the binding is on the surface of a bacteria cell wall the final protein product, C9, is able to punch a hole in the membrane and lyse the cell. In the alternative pathway, complement has more important function in aiding the phagocytosis of material in a process of opsonization. Phagocytes, both macrophages and granulocytes, have receptors for the Fc component of immunoglobulin and the C3b component of complement. The presence of both of these proteins will render it liable to phagocytosis. In promoting the elimination of the pathogen, the T helper cells have a role in the B cell germinal centre reaction, and for stimulating monocytes to differentiate into macrophages. Cytotoxic T cells are able to kill other cells directly. When a cell becomes infected by a virus, components of the virus are expressed on the surface of the cell in association with the Human Leucocyte Antigen (HLA). The receptors on the cytotoxic T cell recognizes the virus on the HLA molecule and is stimulated to secrete perforins, which punch holes in the membrane similar to those produced by complement C9. The helper or cytotoxic functions are determined by the CD4 or CD8 molecules expressed near the T cell receptor [1,2,4].

Hypersensitivity (inflammatory reactions)

Six types of hypersensitivity have been described. Types I, II, II and V are mediated by antibody and type IV and VI by cellular mechanisms. In practice, these reactions may not necessarily occur singly. For example type II-VI may be involved in producing autoimmune diseases. Type I reaction (reaginic/anaphylactic/immediate hypersensitivity) is an allergic reaction produced within 30 min of exposure to a specific antigen e.g. house dust,, pollens, animal danders or moulds in certain genetically predisposed individuals who are said to be a topic. Prausnitz and Kustner in 1921, showed that the passive transfer of a serum factor (reagin) from an allergic person to the skin of a normal person could produce an immediate wheal and flare reaction in the latter in response to the allergen. The mechanism entails the allergen stimulating B cells to produce specific IgE, with the aid of T helper cells. This IgE, which is allergen-specific, binds to mast cells via their Fc receptor. On subsequent exposure, the allergen cross-links the surface bound IgE on the sensitized mast cell that triggers the mast cell to degranulate and release inflammatory mediators (histamine, prostaglandins, slow reacting substance (leukotriene SRS-A)) aimed at destroying the noxious substance. In type II reactions (cytotoxic/membrane reactions), antibodies (IgG or IgM) are produced against antigens on the patient's own cells. These antibodies interacting via their Fc regions and fixing complement as well as the effector cell can lead to autoimmune diseases, e.g. autoimmune anaemia. Antibodies can also 'block' a receptor site preventing its normal function e.g. insulin-resistant diabetes antibodies, or the IgG autoantibodies against the gastric acid-secretory parietal cells (intrinsic factor antibodies) found in pernicious anaemia. In type III reactions (immune complex mediated hypersensitivity) there is a hypersensitivity reaction to the immune complexes when not removed by the reticuloendothelial system but deposited in the tissues. Complement is activated and results in inflammatory reactions leading to cellular damage. The soluble complexes are formed when the antigen is in excess as by injecting large amounts of heterogenic serum into the circulation causing 'serum sickness' or the precipitation by insoluble complexes when the antibody and antigen are equivalent or in an excess of antibody causing an 'arthus reaction' (a red, oedematous area at site of injection within 4-12 h). Complexes are deposited in the bronchial walls in pulmonary asperigillosis, in the vessels in erythema nodosum. Immune complex formation with a self-antigen occurs in the autoimmune disease such as Systemic Lupus Erythematosus (SLE); low-grade persistent infection with a weak antibody response to a microbial antigen occurs with viral hepatitis B or staphylococcal infective endocarditis and repeated inhalation of an environmental antigen, e.g. moulds or animal antigen can produce an extensive allergic alveolitis such as farmer's lung disease with the antibodies being IgG. Type IV reactions (cell-mediated/delayed hypersensitivity) reactions) take more than 12 h to develop and can be produced in several ways. The cell recruitment is initially neutrophil in nature (within a few hours) and is followed by lymphocytes and macrophage infiltration (24-48 h). Type IV reactions can be transferred from one animal to another by certain types of lymphocytes but not by serum. The reaction is mediated by a) T delayed hypersensitivity cells (TD) that have become sensitized to a particular antigen previously and release lymphokines (MAF, MIF, Interferon) and interleukins (IL-1,-2,-3); b) T cytotoxic cells (Tc), which directly damage infected target cells, e.g. virus-infected cells, allogenic cells or host cells in graft-versus host disease. Thus, type IV reactions are seen in association with viral infections and the intracellular bacterial infections-tuberculosis, leprosy and brucellosis and cause severe tissue damage. They are also implicated in autoimmune diseases such as Hashimoto's thyroiditis and homograft rejection. Type V reaction stimulating

antibody reaction) is an IgG directed against cell surface antigens that stimulate some cells instead of killing them. This is seen in the pathogenesis of neonatal hyperthyroidism as IgG stimulating antibodies directed against thyroid cells would be capable of crossing the placenta, or Graves' disease (hyperthyroidism) in adults where serum IgG behave like TSH and binds to the thyroid TSH receptor producing excessive stimulation of thyroid hormone production. Interestingly, Graves' disease is associated with other autoimmune disorders such as pernicious anaemia and myasthenia gravis. Type VI reaction (Antibody-Dependent, Cell-mediated Cytotoxicity (ADCC) entails killer lymphocytes (K cells) which lyse target cells coated with antibody. Being activated by antigen-antibody complexes, the K cells interact with the Fc region of cell-bound antibody, and destroy the target cells by the release of proteolytic enzymes. Type VI reactions are also involved in autoimmune diseases, tumour rejection and defence against helminthic parasites. Immuno-pharmacology includes the role of anti-inflammatory (e.g. corticosteroids), immunosuppressive drugs (e.g. corticosteroids, cyclosporine and tracolimus against T cells) and anti-lymphocytic sera in dampening these hypersensitivity reactions and the prevention of transplant/graft rejection [1-4].

Tumour immunology

The immunological mechanisms involved in cancer growth are highly complex, including tissue-resident and blood-derived cells. Tumour-infiltrating immune cells plays a key role against cancer. However, malignant cells are capable of evading the immune response and establishing a very complex balance in which different immune subtypes may drive tumour progression, metastases and resistance to therapy. Cancer cells make high levels of proteins that can switch off the checkpoint proteins in T cells and the T cells can no longer recognise and kill cancer cells. Drugs or antibodies-3 that block checkpoint proteins (checkpoint inhibitors) would prevent the switching-off action of the cancer cells and the T cells can then find and attack the cancer cells. The checkpoint proteins CTLA-4 (cytotoxic T lymphocyte associated protein 4) and PD-1 (programmed cell death protein 1) are found on T cells. PD-L1 is on cancer cells. The checkpoint inhibitors are used in immunotherapy of cancers but since they boost all the immune cells, and not the ones that target cancer, the overactive T cells can cause possible side effects such as fatigue, nausea, skin rash, pruritus, anorexia, diarrhoea and breathlessness and dry cough from inflammation of the lungs. They also cause, liver, kidney and thyroid dysfunction [11]. The human immune system mounts natural endogenous response to highly immunogenic tumour cells through a series of steps, including the presenting of tumour antigens to T cells *via* Antigen-Presenting Cells (APCs), priming and activation of T cells in the lymph nodes, trafficking and infiltration of T-cells into tumour beds, recognition of cancer cells by T cells, development of antigen-specific effector and memory T cells, and humoral immunity, allowing effector T cells and other endogenous immune cells as well as tumour-effective antibodies to tumour to eliminate cancer cells. Monoclonal antibodies made from hybridoma cells by recombinant DNA technology are routinely used in several fields including infections, and. targeted cancer therapy. They may also help turn the immune system against cancer *i.e.* immunotherapy by marking cancer cells for better recognition and destruction. An example is rituximab, which binds to the CD20 on B cells and some types of cancer cells such as lymphomas, causing the immune system to kill them. Other monoclonal antibodies such as blinatumomab bring T cells close to leukaemia cancer cells by binding to both CD19 protein on the surface of leukaemia cells, and CD3, a protein on the surface of T cells which would facilitate the response and killing of the leukaemia cells by the T cells.

Innate immune response to tumour cells

Cancer cells can alter the steady state activity of al myeloid cells present in the tumour microenvironment by secreting IL-6 or Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), that induce the recruitment of immature myeloid cells to tumour cells, as well as cell proliferation. Natural Killer Cells (NKL) can kill target cells without the need for prior activation. As many neoplastic cells lose the expression of MHC-I during malignant transformation which at normal levels inhibit NK cells, they continue to express ligands (e.g. glycolipid) that activate NK cells. This recognition mechanism further leads to the progression of anti-tumour immune response through the production of interferon-λ which activate a number of interferon-λ signalling pathways which enhances the killing of a proportion of the tumour, induces the production of chemokines that further recruits more cells in the innate immune system, activates macrophages that express tumoricidal products (reactive oxygen and nitrogen metabolites) and Tumour Necrosis Factor (TNF) that activates endothelial cells and coagulation leading to tumour necrosis and directly stimulating apoptosis. Moreover, the cytokines, IL-12. IL-15, and the type 1 interferons stimulate NK cells, which leads to proliferation and increased cytotoxic activity.

Adaptive immune response to tumour cells

Cytotoxic T Lymphocytes (CTLs) are the primary mechanism of tumour cell killing in adaptive immune response, which in many cases, requires the participation of APCs to present the relevant tumour antigen to the CTLs. MHC-I and-II molecules must be present to stimulate the production CTLs. Typically, MHC-I APCs such as Dendritic Cells (DC), present antigen (tumour-derived peptides) to $CD8^+$ T cells in the context of co-stimulation through CD80, CD70, and 4-1BB, as well as through Dendritic Cells (DC)-derived cytokines such as IL-12, type 1 interferon, and IL-15. $CD8^+$ CTLs have been demonstrated in numerous different types of solid tumours in vivo and have been shown to cause tumour cell destruction *in vitro*. $CD4^+$ T helper cells release cytokines, leading to the anti-tumour immune reaction. The Th 1-polarized $CD4^+$ T cells secrete IL-2. TNF-α, anf IFN-λ, which promote the development of $CD8^+$ CTLs and the activation of macrophage cytotoxic activity. In addition, they can up-regulate antigen processing and the expression of MHC-I and-II molecules in professional APCs such as macrophages and DCs. In contrast, Th2 polarized $CD4^+$ T cells release cytokines IL-4,-5,-6,-10 and -13, resulting in T-cell-mediated cytotoxicity, enhance humoral immunity, and regulate

the tumor-promoting activities of macrophages. In addition to the effector mechanism mediated by CTLs, the host immune system can generate specific antibodies against cancer antigens, which exert cytotoxic effect against the antigen-bearing tumour cells. Rather than recognizing only protein-derived antigens by T cell antigen receptors, antibodies can bind to multiple types of tumour antigens including polysaccharides, lipids and proteins. This enhances anti-tumour ability by broadening the number of tumour antigens that can be exploited for cytotoxic reactions. Mechanisms of antibodies mediated tumour cytotoxicity include antibody-dependent cell-mediated cytotoxicity (Type VI hypersensitivity reaction) and complement-mediated cytotoxicity. Cancer vaccines against the tumour. Associated antigens may stimulate the immune system so that it recognizes the cancer cells as foreign and attacks the cells. Cancer vaccines are made with cells from the patient's own tumour, modified in the laboratory and then returned to stop, destroy or delay the growth of cancer. Combination of whole cell vaccine GVAX and mesothelin-secreting vaccine CRS-207 demonstrated an overall survival benefit in metastatic refractory pancreatic cancer patients. Anti-Gal is the most abundant natural antibody in humans, comprising about 1% of immunoglobulins. The anti-Gal ligand is a carbohydrate antigen called α-gal epitopes which is exploited in cancer vaccines to increase the immunogenicity of Antigen-Presenting Cells (APCs). As cancer cells or Pancreatic Ductal Adenocarcinoma Cells (PDAC) tumour lysates are processed to express α-gal epitopes vaccination with these components results in *in vivo* opsonisation by anti-Gal IgG in PDAC patients. The Fc portion of the vaccine bound anti-Gal interacts with Fc receptors of APCs, inducing uptake of the vaccine components, transport of the vaccine tumour membranes to draining lymph nodes, and processing and presentation of Tumour-Associated Antigens (TAAs). It also elicited strong antibody production against multiple TAAs contained in pancreatic ductal adenocarcinoma cells and induce activation of multiple tumour-specific T cell. Murine dendritic cell, loaded with pancreatic tumour-specific glycoepitope C-ter-J28^{+}, induces efficient anticancer adaptive immunity and represents a potential adjuvant therapy for patients afflicted with PDAC.

CONCLUSION

The immune system is complex, dynamic and integrated in function so as to fight against foreign substances (antigen) such as infection and cancer. The results of the response are not only to eliminate the foreign material through humeral (antibodies) and cell -mediated mechanisms, but, to confer protection against future contact with the antigen through memory B and T cell formation, and that forms the basis of passive and active immunity (vaccinations). The improving knowledge of the immune system has expanded the role of immunotherapy and vaccine therapy in oncology. However, the immunodeficiency diseases, autoimmune disease and the hypersensitivity reactions remain the major short-comings of the immune response.

REFERENCES

1. Chaplin DD. Overview of the immune response. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S3-S23.
2. Bonilla FA, Oettgen HC. Adaptive immunity. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S33-S40.
3. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med. 2015;278(4):369-395.
4. Sjöberg AP, Trouw LA, Blom AM. Complement activation and inhibition: a delicate balance. Trends Immunol. 2009;30(2):83-90.
5. Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S182-S194.
6. Melvold RW,Sticca RP. Basic and tumour immunology: a review. Surg Oncol Clin. 2007;16(4):711-735.
7. Thapa P, Farber DL. The Role of the Thymus in the Immune Response. Thorac Surg Clin. 2019;29(2):123-131.
8. Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature. 2007;449(7164):819-826.
9. Benoit M, Desnues B, Mege JL. Macrophage polarization in bacterial infections. J Immunol. 2008;181(6):3733-3739.
10. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003;3(1):23-35.
11. Gaikwad S, Agrawal MY, Kaushik I, Ramachandran S, Srivastava SK. Immune checkpoint proteins: Signaling mechanisms and molecular interactions in cancer immunotherapy. Semin Cancer Biol. 2022;86(Pt 3):137-150.
12. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983;220(4599):868-871.
13. Shindiaina P, Ahmed EH, Mozhenkova A, Abebe T, Baiocchi RA. Immunology of EBV-related lymphoproliferative disease in HIV-positive individuals. Front Oncol. 2020;10:1723.
14. Weledji EP, Ngowe MN, Abba JS. Burkitt's lymphoma masquerading as appendicitis--two case reports and review of the literature. World J Surg Oncol. 2014;12:187.
15. Gallo RC, Salahuddin SZ, Popovic M. Human T-lymphotropic retrovirus, HTLV III, isolated from AIDS. Science. 1983;220:868-870.
16. Kennedy AD, DeLeo FR. Neutrophil apoptosis and the resolution of infection. Immunol Res. 2009;43(1-3):25-61.
17. Minai-Fleminger Y, Levi-Schaffer F. Mast cells and eosinophils: the two key effector cells in allergic inflammation. Inflamm Res. 2009;58(10):631-638.
18. Schroeder HW, Cavacini L. Structure and function of immunoglobulins. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S41-S52.
19. Chaudhuri J, Basu U, Zarrin A, Yan C, Franco S, Perlot T, et al. Evolution of the immunoglobulin heavy chain class switch recombination mechanism. Adv Immunol. 2007:94:157-214.