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Cancer Immunology and Immunodeficiency

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TUMOR IMMUNOLOGY

The immune system has an important part in the defense mechanism against infections and foreign intruders, in addition to preserving the health status of the body. The immune system also plays a major role in the host response to neoplasia. Several effective antitumor mechanisms have been described, but the clear role of the immune system in preventing the formation of tumors and in wiping out any cancerous cells that may rise remains questionable, and it is no longer clear whether antitumor immune responses function in immune surveillance. Therefore, the role of the immune system in stopping cancer may be limited. However, there is no doubt that the immune reactions mounted against tumors often grow, and can be studied and detected in experimental and clinical settings. These responses are elucidated as interactions between immunity and tumor cells in various natural and induced ways, which ultimately leads to tumor regression. As we learn more about the relationships between cancer and the immune system, we stumble upon opportunities for new immunotherapeutic and diagnostic approaches. In this chapter, a brief overview of cancer immunology and the major concepts required to understand the complex reaction between the immune system and cancer development is presented [1-7].

There are some key points to highlight: (1) Tumor cells often express new antigens usually

called “neo-antigens” which are potential targets for immune recognition. (2) Despite this fact, the immune system is regularly unsuccessful in removing tumors or stopping their development. (3) Several ways might be possible for adjusting anti-tumor immune reactions to make them more effective, in diagnostic and treatment approaches [8].

Immune responses also can be classified to innate or adaptive immunity. Innate responses refer to a wide variety of non-antigen-specific Adaptive immunity refers to antigen-specific responses, including the development of immunologic memory and the magnification of effector functions. Innate responses refer to a range of non-antigen-specific mechanisms, which are present at all times. The generation of specific cytotoxic T cells (CTL) directed to a tumor-associated antigen represents an example of an adaptive immune response. On the other hand, an innate antitumor response is represented by the attack on tumor cells by natural killer (NK) cells. Both innate and adaptive immune responses can apply powerful antitumor activity [9,10].

NEOPLASIA

A tumor is formed by the abnormal proliferation of cells, through modifications in the normal growth control. Examples illustrated are when cells which do not normally divide (e.g. muscle cells) start proliferating, or cells that usually proliferate (e.g. hemopoietic cells) start proliferating uncontrollably. If the growth manner of the tumor remains localized (one location), it can be managed surgically (if accessible). These kinds of tumors are referred to as “benign”; which are relatively harmless. However, if tumor cells start growing in an invasive way; intruding into neighboring normal tissue, they are referred to as “malignant”; which possess the “metastasis” feature of leaving the original site and proliferating in a new location.

It is crucial to understand and bring together two conflicting properties of tumors, which are their “monoclonal origin” and “heterogeneity”. While tumors are almost habitually of monoclonal origin, mutation and chromosomal instability usually generate a significant degree of heterogeneity within tumor populations. This fact has important implications in the diagnosis and treatment of cancers [11,12].

NATURAL HISTORY OF NEOPLASIA

Three major factors are known to induce tumor formation, in addition to other unknown etiologies, but whatever the cause was; the consequence is uncontrolled overgrowth. This usually results from an abnormally high expression of genes which stimulate cell proliferation (oncogenes), or a defective expression of genes which normally regulate proliferation (tumor suppressor genes) [13].

Chemical Carcinogens

Numerous natural and manufactured compounds which are present in food and environment are capable of stimulating the formation of tumors (e.g. tobacco and char) [14].

Radiation

X-rays, gamma rays and ultraviolet (UV) radiation can all induce the appearance of tumors by changing the gene expression. We are exposed to these radiations through sunlight (UV), normal background radiation (gamma rays), and clinical sources [15,16].

Viruses

Many existing viruses carry oncogenes; which can induce neoplastic transformation of the infected cell. These genes can be expressed during a viral infection, and sometimes integrated into the host genome, and stay dormant until expressed again later [17].

T LYMPHOCYTES AND ANTITUMOR IMMUNITY

T lymphocytes play an essential part in the induction of immune responses, by acting as helper cells in the generation of humoral and cellular immune responses, and as effector cells in cellular responses. T-lymphocyte precursors mature into functional T lymphocytes in the thymus, where they acquire the knowledge to distinguish antigen in the setting of the major histocompatibility complex (MHC) molecules. Most T lymphocytes with the ability of responding to the self are terminated during thymic development. T lymphocytes can be notable from other types of lymphocytes by their biologic activities and by the expression of unique cell surface clusters of differentiation, including the T-cell antigen receptor and CD3 marker. The expression of lymphocyte cell surface molecules can be quantified by flow cytometry with fluorochrome-labeled monoclonal antibodies that can bind these molecules specifically. There are two major subsets of T lymphocytes: T helper cells, which express the CD4 cell surface marker, and T cytotoxic cells, which express the CD8 marker. CD4 T lymphocytes provide help to B lymphocytes, resulting in antibody production, and can also act as helper cells for other T lymphocytes. The majority of the helping activity of T lymphocytes is affected by the production of cytokines, as interleukin-2 (IL-2). The CD8 T-lymphocyte subset includes cells that are cytotoxic (i.e., can kill target cells directly) [18-20].

A major biologic function of CTLs is the lysis of virus-infected cells. However, CTLs can directly facilitate the lysis of tumor cells, probably by identifying distinctive antigens presented by tumor cells. CTLs can kill tumor cells by signaling the induction of apoptosis in the target cells, and by the secretion of perforin, a pore-forming protein. T cells also can contribute to antitumor immune responses by producing cytokines such as tumor necrosis factor-α (TNF-α), which induce tumor cell lysis and can improve other antitumor cell effector responses [21].

T lymphocytes identify specific antigens by interactions that involve the T-cell antigen receptor. In terms of its general configuration and molecular organization, the T-cell antigen receptor is significant of the antibody molecule. Nevertheless, there are chief variances between the antigen receptor molecules on B lymphocytes and those on T lymphocytes; for one, the T-cell receptor is not secreted. Also, the B-cell antigen receptor interacts with antigen in a different mode than the

T-cell receptor; the T-cell antigen receptor can detect the antigen only when it is presented to it in association with self MHC molecules, on the surface of an antigen-presenting cell. The B-cell antigen receptor can bind antigen directly, and consequently is not limited in this way [22].

B LYMPHOCYTES AND ANTIBODIES

The production of antitumor cell antibodies does not play a dominant role in host antitumor immune responses, but monoclonal antibodies that are responsive to tumor-associated antigens show usefulness in antitumor therapy, or for tumor detection. Immunotoxin-conjugated monoclonal antibodies focused on antigens expressed by human ovarian adenocarcinoma result in tumor cell killing in experimental animal systems. Numerous difficulties had to be overcome before monoclonal antibodies were of useful clinical application, particularly the group of host immune responses fixed to foreign antigens on monoclonal antibodies of murine origin. Since most monoclonal antibodies are of murine and not human origin, the host's immune system can detect and respond to murine monoclonal antibodies. The preparation of humanized murine monoclonal antibodies (i.e., genetically engineered monoclonal antibodies consisting of human constant regions with specific antigen-reactive murine variable regions) has eased many of the complications related to the administration of murine monoclonal antibodies. Monoclonal antibody-based mediators are being utilized more and more in antitumor therapies [23,24].

MACROPHAGES, MONOCYTES, AND DENDRITIC CELLS

Monocyte/macrophages play important roles in immune responses. Macrophages, which form an important part of innate immune responses, also play a key role in the generation of adaptive, antigen-specific, lymphocyte-mediated immune responses, because they can act as active antigen-presenting cells. Helper/inducer (CD4) T lymphocytes, carrying a T-cell receptor of appropriate antigen and self-specificity, can be activated by antigen-presenting macrophages that show processed antigen joint with self MHC molecules (MHC class II molecules). Antigen presenting cells also deliver key costimulatory signals that are important for the initiation of T-lymphocyte activation. In addition to becoming antigen-presenting cells, macrophages can ingest and kill microorganisms, and can act as cytotoxic, antitumor killer cells. Also, macrophages and monocytes produce various cytokines, including IL-1, IL-6, IL-10, TNF and chemokines (RANTES, MIP1α, MIP1βIL-8), which are involved in both innate and adaptive immune reactions, and which can have straight biologic effects on tumor cells, both as growth-inducing and growth-inhibiting factors [25].

Mature dendritic cells also are very effective antigen-presenting cells for T cells. As a matter of fact, dendritic cells found in lymphoid tissue are the most powerful stimulators of naive T cells. Mature dendritic cells express very high levels of MHC class I and class II molecules, along with high levels of cell surface lymphocyte stimulatory molecules and adhesion molecules. Furthermore, dendritic cells secrete chemotactic factors (chemokines) that recruit T cells. Collectively, these

characteristics elucidate their capability to turn as highly efficient antigen-presenting cells for T lymphocytes [26-28].

NATURAL KILLER CELLS (NK), AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY

NK cells have typically large granular lymphocyte morphologic characteristics. NK cells do not express the CD3–T-cell receptor complex, but they express some markers that are shared with T lymphocytes or other types of lymphocytes, additionally to other NK-associated markers. NK cells can lyse target cells, including tumor cells, unrestricted by the expression of antigen on the target cell. Hence, NK cells are effector cells in an innate kind of immune response, and they play a dynamic role in the nonspecific killing of tumor cells or virus-infected cells. NK cells represent an innate form of immunity that does not need an adaptive memory answer for biologic purpose, but NK responses can be increased by cytokines, such as IL-2. NK cells can be moved to kill target cells that do not express MHC class I molecules. MHC class I molecules, which normally are expressed on all nucleated cells, show endogenously synthesized antigens to CD8+ CTLs. Many viruses disrupt CTLs by down-regulating the expression of MHC class I molecules, successfully hiding such virus-infected cells from T-cell attacks. Nevertheless, NK cells can detect and kill such MHC class I-negative cells. Thus, NK cells offer an essential role in the detection of virus infected host cells that have avoided T-cell immunity [29,30].

The cells that can influence antibody-dependent cellular cytotoxicity (ADCC) are NK-like cells. ADCC can result in the lysis of tumor cell targets *in vitro*. Though the mechanisms of tumor cell killing in ADCC are poorly understand, close cellular contact seems to be required between the ADCC effector cell and the target cell [30].

CYTOKINES, LYMPHOKINES, AND IMMUNE MEDIATORS

Cytokines are soluble mediator molecules that stimulate, augment, or affect immune responses. Cytokines are heterogenous which include various molecular super-families, classically have several and laid off biologic actions, are secreted by numerous types of cells, and play serious parts, not only in immune reactions but also in biologic mechanisms outside of the immune response, such as hematopoiesis. Most cytokines are small or medium secreted proteins, which are produced transitorily and locally, and interact with precise cellular receptors, resulting in signal transduction followed by changes in cellular physiological proliferation or differentiation in the target cell [31].

Despite the fact that many cytokines are heterogeneous and share little structural or amino acid homology, some cytokines seem to have evolved from common ancestors (precursors/mother cells), and are classified accordingly into the members of cytokine superfamily. Cytokine super-families include the hematopoietins (IL-2, IL4, IL-6, and related cytokines, interferons), the TNF-like cytokines (TNF-α, lymphotoxin and related molecules), chemokines (IL-8, RANTES, and related cytokines), and the IL-1-like cytokines (IL-1α, IL-1α, IL-1RA, IL-18) [32].

IL-2 stimulates T-lymphocyte proliferation, and is secreted mostly by activated T lymphocytes. T lymphocytes secrete IL-2, express the IL-2 receptor, and respond to IL-2 by proliferating. Much of the helper action of T lymphocytes is mediated by IL-2. IL-2 interacts with specific IL-2 receptors on the surface of the target cell; the high-affinity IL-2 receptor is composed of three polypeptides, the CD25α, CD122β, and CD132γ chains, when it becomes unassociated can have a lower binding affinity for IL-2. T-cell activation causes an increased number of the high affinity receptors for IL-2 on the surface of these cells. IL-2 has other biologic activities, including the induction of B-lymphocyte activation and maturation, and monocyte and NK-cell activation [33].

B-lymphocyte activation and differentiation to immunoglobulin-secreting plasma cells are enhanced by cytokines that are produced by helper T lymphocytes or monocytes. Numerous cytokines, originally described as B-cell-stimulating factors, IL-4, IL-5, and IL-6, have extra biologic activities. For example, IL-6, a factor that can induce B-lymphocyte differentiation to immunoglobulin-secreting cells, is a pleiotropic cytokine10 with biologic activities that include the induction of cytotoxic T-lymphocyte differentiation, the induction of acute-phase reactant production by hepatocytes, and activity as a colony-stimulating factor for hematopoietic stem cells. IL-6 is produced primarily by activated monocytes and macrophages and T lymphocytes. IL-6 interacts with a specific receptor complex composed of two molecules: CD126 (IL-6R) and CD130 (gp130). The CD126 molecule is essential for effective binding of IL-6 to the receptor complex, while the CD130 molecule is responsible for signal transduction. Both of these receptor molecules must be expressed for effective IL-6 signaling. There are several IL-6-like cytokines, including IL-11, Oncostatin-M, leukemia-inhibitory factor (LIF), and ciliary neurotropic factor (CNTF). Remarkably, several types of tumor cells produce IL-6, and IL-6 has been suggested to act as an autocrine and paracrine growth factor for different types of neoplasms. However, IL-6 may be an effective antitumor agent because of its capability to improve antitumor T-cell-mediated immune receptiveness [34,35].

IL-3, a cytokine which can improve the early differentiation of hematopoietic cells, have a title role in immunotherapy because of its capability to induce hematopoietic differentiation in people experiencing destructive chemotherapeutic treatment or bone marrow transplantation [36]. IL-10 is an immune-inhibitory cytokine [37]. IL-12 is a recently described as a T-cell-stimulating and NK-stimulating cytokine, which is thought to be responsible in the induction of type 1, or TH1, immune responses [38]. TNF-α is a cytokine that can be cytotoxic for tumor cells, enhance immune cell-mediated cellular cytotoxicity, activate macrophages and induce monokine secretion. Other biologic activities of TNF-α include the induction of cachexia, inflammation, and fever. This cytokine is an important arbitrator of endotoxin shock [39].

There are three types of interferons: interferon-α (IFN-α), interferon-β (IFN-β), and interferon-γ (IFN-γ). Interferons, which form a family of molecules within the hematopoietin superfamily, are cytokines that can restrict viral production in infected cells and can have countless effects on the immune system. For example, IFN-γ, a T-lymphocyte-produced cytokine, can affect immune

system function by increasing the induction of MHC molecules expression, enhancing the activity of antigen-presenting cells, and in that way enhancing T-lymphocyte activation [40].

Current research has provided the necessary information regarding the biologic activities of cytokines, these factors have appeared to be extraordinarily pleiotropic, with a puzzling array of biologic activities, some of which occur outside of the immune system. Nonetheless, the recognition of two types of helper T cells, the type 1 (TH1) and type 2 (TH2) subsets of CD4+ helper T cells, has brought a degree of understanding to this confusing situation. This is because the difference between these helper cell subdivisions is based on the pattern of cytokines produced by these subdivisions; TH1 and TH2 subdivisions control the nature of an immune response by secreting characteristic and equally antagonistic sets of cytokines. TH1 clones produce IL-2 and IFN-γ, while TH2 clones produce IL-4, IL-5, IL-6, and IL-10. TH1 responses are characterized by enhanced cell-mediated immune and inflammatory responses, including increased macrophage activation and enhanced T-cell proliferation and activation. TH2 responses are conquered by enhanced humoral responses, including increased B-cell activation and antibody production. Most immune responses involve both TH1 and TH2 responses, although some responses are dominated by either a TH1 or TH2 response configuration. The pattern of cytokines produced by TH1 or TH2 cells controls the type of immune response perceived. For example, IL-10 inhibits the production of IFN-γ and other cytokines by human peripheral blood mononuclear cells (PBMC), as well as suppressing the release of cytokines (IL-1, IL-6, IL-8, and TNF-α) by activated monocytes. Also, IL-10 down-regulates class II MHC expression on monocytes, resulting in a strong reduction in the antigen-presenting capacity of these cells, and acts as a direct B-cell stimulatory factor. However, IL-2 is a potent stimulator of IFN-γ, and induces a TH1-type immune response. Because some cytokines have direct or indirect antitumor or immune-enhancing effects, several of these factors have been used in the experimental treatment of cancer [41,42].

The precise roles of cytokines in antitumor immune responses have not been understood completely. Because cytokines are pleiotropic, they may apply antitumor effects through many different direct or indirect mechanisms. It is possible that a single cytokine could improve tumor growth directly by acting as a growth factor while enhancing immune responses directed at the tumor. However, the potential of cytokines to enhance antitumor immune responses has been utilized in different approaches for the experimental management of cancer. These include the enhancement of cytokine production induced nonspecifically by exposure to biologic response modifiers or antigens; direct treatment with recombinant cytokines; the use of adoptive immunotherapy, in which patient peripheral blood cells or tumor-infiltrating lymphocytes (TIL) are exposed to cytokines and activated ex vivo, generating activated cells with antitumor effects that can then be re-injected back into the patient; and gene therapy-based approaches in which tumor cells are transduced with a cytokine gene, the expression of which will presumably enhance antitumor immune responses, or even by the modulation of local cytokine production induced by

drugs. Also, it is essential to note that the antitumor effects of cytokines might be controlled by soluble receptors or blocking factors [43,44].

Cytokines also can have growth-enhancing effects for tumor cells, by which cytokines can perform autocrine or paracrine growth factor effects for human cancer cells, including tumor cells of non-lymphoid origin. As an example, IL-6, which is produced by various types of human tumor cells, can act as an autocrine growth factor for human myeloma, Kaposi sarcoma, and renal carcinoma. Excitingly, new studies show that vIL-6, the viral homologue of human IL-6 that is encoded by HHV-8, may act as a paracrine growth factor for multiple myeloma cells and in Castleman diseases in HIV-negative subjects, as well as for Kaposi sarcoma, in both HIV-positive and HIV-negative people [45].

Evidently, cytokines represent a promising great potential value in the fight against cancer and may also play important parts in the pathogenesis of different cancer types by acting as tumorgrowth enhancing factors. Due to their several and conflicting biological effects, an extensive understanding of cytokine biology is essential for the successful utilization in cancer therapy.

CYTOKINES AND THE PATHOGENESIS OF CANCER

Tumor development has been related to error expression or mutation of various genes: oncogene overexpression, amplification, or mutation; tumor suppressor gene (antioncogene) expression or mutation; or cytokines and growth factors and the cellular receptors for these molecules. Destabilization of host antitumor immune reactions also may play a role in the development of cancer.

As a strong examples, cytokines and several growth factors may play important roles in the development and metastasis of ovarian cancer; additionally, epithelial ovarian cancer may be a cytokine-driven disease. Cytokines, including IL-1 and IL-6, enhance the proliferation of ovarian cancer cells, and numerous cytokines are produced by ovarian cancer cells, including macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1, IL-6, and TNF-α. Many ovarian cancer cells produce both M-CSF and the M-CSF receptor. Levels of fms messenger RNA associated strongly with ovarian tumors of high histologic grade and advanced clinical stage, and were correlated with a poor clinical prognosis. Moreover, raised plasma levels of M-CSF were seen in 70-80% of patients with ovarian cancer. Because M-CSF-stimulated macrophages might produce other cytokines, such as IL-1 or IL-6, that can stimulate tumor cell growth further, M-CSF could act as both an autocrine and paracrine tumor stimulatory factor and as a factor that can adjust the host environment, resulting in enhanced tumor cell growth [46,47].

Tumor-Specific Antigens (TSA) and Tumor-Associated Antigens (TAA)

It is well known that tumors express cell surface antigens which are not expressed on normal

progenitor cells before neoplastic transformation. These antigens have been classified depending on their nature and distribution:

1. Chemical or radiation-induced tumors each generally express a unique neo-antigen different from other tumors induced by the same or different agent. These are called Tumor-Specific Transplantation Antigens (TSTA) [48].

2. Tumors brought by the same virus express antigens shared between different tumors. These consist of membrane-expressed virally encoded antigens, and have been termed Tumor-Associated Transplantation Antigens (TATA) [49].

3. Onco-fetal antigens: These are TATAs which are more or less selectively expressed on tumors, but are also shared with some normal fetal or embryonic tissues. Examples include carcinoembryonic antigen (CEA, shared with healthy fetal gut tissue), and alpha-fetoprotein (AFP, also present in the serum of healthy infants, but decreasing by one year of age) [50].

Immunological Surveillance

This terms means that the cell-mediated immune response (CMI) is intended to detect and destroy newly emerging neoplastic cells as a consequence of the new antigens they tend to express. Nevertheless, substantial experimental data has failed to support this idea. It is important to note that immunocompromised patients do not generally align with this theory. The tumors which are usually found in immunosuppressed subjects are caused more often my viruses, since the defective immune system was not able to mount a normal immune response against the viral infection. Hence, the prominence of the acquired immune system in sustaining natural protection against cancer is greatly questionable, while natural killer (NK) cells are still considered the players of this role. However, there has been significant concentration on using those antitumor immune responses which are known to occur, and direct them toward more effective cancer treatment [51,52].

Factors Limiting Antitumor Immune Reactions

In normal settings, if tumors express antigens which are recognized by the immune system, why are they not normally removed? Several detailed mechanisms have been shown to add to the capacity of tumors to remain growing despite the established existence of a possibly damaging immune response.

Tolerance

A condition of immunological tolerance which might be indorsed by the presence of high levels of tumor antigens, predominantly in soluble forms which may be shed into the serum [53].

Immunomodulation

When a membrane antigen on a normal or neoplastic cell binds to an antibody, it results in the disappearance of the antigen from the cell surface by endocytosis o shedding. Once a tumor cell

has lost its antigen, it becomes invisible to the immune system and almost impossible to detect [54].

Immunoselection

A population of cells within the tumor might have lost a TATA or a TSTA antigen through a mutation; which will have an advantage against an effective immune response, and these cells with a mutation tend to progressively take over the population. This process highly depends on the presence of heterogeneity in a tumor cell population [55].

ENHANCING ANTIBODIES AND IMMUNOSTIMULATION

Enhancing Antibodies

Most nucleated cells (other than lymphocytes, a key exclusion) are fairly resistant to complement-mediated lysis, and demolition of grafted tissue is mainly the role of cell-mediated immunity. Nevertheless, if antibodies exist which can bind to neoantigens, they may efficiently "hide" these antigens which might then serve as targets for T-cell-mediated attack, and therefore "improve" the existence of such cells [56].

Immuno-Stimulation

Antibodies binding to tumor cells might sometimes motivate cell growth, probably through the generation of receptor-mediated proliferative signals [57].

Blocking Factors

Soluble factors have been described to be present in the serum of tumor patients and mammals, which can constrain a current immune response from affecting the tumor. The best described "blocking factors" often consist of circulating antigen-antibody complexes containing tumor antigens, which may blind or divert the immune response in mechanisms that are still poorly understood [58].

Immunosuppression

Tumor-bearing hosts (patients or animals) often show a considerable level of immunosuppression, caused directly or indirectly by inhibitory cytokines and other substances secreted by the tumor (e.g. Hodgkin's lymphoma) [59].

Concomitant Immunity

A host having an increasingly growing tumor may reject a new inoculum of the same tumor at a different site; this rejection is a manifestation of "concomitant immunity", an immune rejection response happening at one site, co-existing with the advanced growth of an antigenically equal tumor elsewhere in the organism. This phenomenon exemplifies the prominence of tumor mass in forming the final consequence of an encounter between a tumor and the immune system; a small

concentration of tumor cells is more susceptible to immune killing than a large well-vascularized tumor [60].

APPLICATIONS OF IMMUNOLOGICAL PRINCIPLES TO CANCER

Immunodiagnosis

Tumor-associated antigens in serum

Testing of TSTA/TATA in serum to detect the presence of tumors which are undetectable by conventional approaches, or to measure the general tumor mass and its response to therapy. Assays for determining serum levels of CEA and PSA ("prostate specific antigen"), for example, are commonly used for both screening and evaluation of the success of therapy [61].

Antibody-based therapy

Use of radioactively labeled antibodies to TSTA, to permit finding and localization of invisible metastases. While the use of radiolabeled antibodies for such purposes has been suggested and studied for years, it has not yet developed to routine clinical application [62].

Immunotherapy

Humoral

Several types of monoclonal antibodies which target tumor antigens have been FDA-approved for therapy, which currently makes up the most extensively used method of immunotherapy. Many are used as unconjugated "bare" antibodies, and their efficiency comes from their capability to target tumor cells for destruction by inducing complement and opsonization, or by helping as antagonists for cell surface receptors vital for cell proliferation or angiogenesis. Several years of research have been dedicated to the prospective use of anti-tumor antibodies conjugated with toxins, or highly radioactive isotopes, which work as target agents to bring these toxins to tumor cells [63].

Cell-mediated (Lymphokine-Activated Killer [LAK] cells)

Lymphocytes removed from a cancer patient can be treated *in vitro* with lymphokines (e.g. IL-2), and the resulting "activated" cells are reinjected into the patient, in hopes that T-cells present in the transfused cell population will attack the tumor cell. These lymphocytes can be either obtained from the patient's blood (which might contain some tumor-specific T-cells), or removed from a surgically excised tumor ("tumor-infiltrating leukocytes" or "TILs"), probably containing of a more greatly enriched tumor-specific population. Results in humans have not been as positive as in experimental animals, but efforts continue to develop this approach into an effective therapeutic approach [64].

CONCLUSIONS

Many mechanisms of the immune system can apply active antitumor responses, including

direct cytotoxicity directed against tumor cells along with the production of cytotoxic or immune-enhancing cytokines. The mis-regulated expression of various genes, including overexpression of oncogenes, mutation or loss of anti-oncogenes, and overproduction of growth factor and cytokines, may be responsible in the development and progression of some cancers. Alteration of the environment and antitumor immune responses may also pay to the development and growth of malignancies. Understanding the exact strategies that are involved in the development and growth of cancer will provide chances for the lucid design of effective antitumor immunotherapy.

Several forms of experimental immunotherapy for cancers have been studied, including biologic response modifiers and cytokines. Preliminary studies show that immune enhancement and antitumor effects that lead to tumor elimination are more likely to happen when reasonably high concentrations of cytokines are brought into direct contact with tumors and when the tumor burden is kept to the minimal, such as in an adjuvant location or when treatment is combined with cytotoxic chemotherapy. In recent years, great advances have been made in the development of suitable forms of monoclonal antibodies, directed to cell-surface molecules expressed on tumor cells. This has resulted in a regeneration of monoclonal antibody-based therapies for several forms of human cancer. Adoptive immunotherapy also has produced new prospects for the use of immunotherapy in patients with different cancers. Of pronounced long-term significance, gene therapy presents promising novel and targeted therapeutic methods depending on an increased understanding of the molecular and cellular biology of cancer and anticancer immune responses, while important hands-on difficulties will need to be resolved before gene therapy for cancer can be effective and widespread.

Immunologic therapy of several types of cancer currently remains experimental. Immunological therapies seem to expand what can be achieved with ideal chemotherapy and therefore could deliver an incremental development in patient management over current standards when outcomes of presently continuing studies establish conclusive treatments as a standard of care. Undoubtedly, we are in an age of fast scientific and technological progress, which is resulting in the growth and testing of several cytokine-based and immune-based therapies for cancers.

Immunodeficiency

Congenital immunodeficiencies are usually uncommon, however they illustrate many of the key features of the development and function of the immune system. The ACQUIRED immunodeficiencies, mostly those of iatrogenic origin, are more common and are of extensive medical importance, powering ongoing studies for more effective and selective immunosuppressive drugs.

The critical significance of the immune system to our daily health becomes especially clear when the consequences of deficiencies are illustrated within the immune function. These immunodeficiencies can be categorized into two major groups:

1. Congenital ("Primary") Immunodeficiencies Patients are born with these diseases, which are the result either of hereditary or developmental defects [65].

2. Acquired ("Secondary") Immunodeficiencies are acquired as secondary outcomes of various environmental disease states, due to the disease pathogenesis or the therapy used to treat them [66].

Immunodeficiency is classified depending on which of the three sections of the immune system is affected, that is whether they represent defects in in the AFFERENT, CENTRAL or EFFERENT section. The Afferent part represents antigen processing carried out by macrophages and associated cells, the Central part involves the triggering and proliferation of clonally committed T-cells and B-cells, and the Efferent part is involves various effector T-cells (Tc , Treg) and the biological mechanisms of antibody binding (which may include complement fixation, phagocytosis and allergic responses). Herein, we present only a few examples of immunodefciencies, taking into consideration that these examples are intended only as illustrations of the importance of different elements in the immune system. This list is far from complete, and the discussion of each example will cover only some limited features [67].

Congenital Deficiencies of the Efferent Part

Chronic granulomatous disease

Syndrome: Granulocytes and monocytes perform their normal functions of phagocytosis, but are incapable of killing the organism they engulf due to a deficiency of the enzyme NADPH oxidase, essential to produce the "oxidative burst". Patients are susceptible to numerous microorganisms which are normally of low virulence, mainly with Staphylococcus aureus and gram-negative bacteria.

Inheritance: This disorder can be caused by several different genetic defects, one of which is controlled by an X-linked gene; symptoms appear at about two years of age [68].

Complement deficiencies

A variety of genetic deficiencies of complement components are known, some may have very mild consequences, but they are often associated with different degrees of increased susceptibility to bacterial infections. Interestingly, deficiencies of some of the early complement components also appear to be related with an increased susceptibility to development of lupus and other autoimmune diseases, emphasizing the importance of the early components of complement in the normal process of removal of immune complexes [69].

Congenital Deficiencies of the Central Part

The congenital defects of T-cell and B-cell lineages are the most biologically interesting and educational among immunodeficiencies, though the clinically important types are extremely rare.

X-linked infantile hypogammaglobulinemia (Bruton's syndrome)

Syndrome: Extreme susceptibility to bacterial infections (more than to viruses or fungi) starting at ~4-6 months of age.

Serum IgG is extremely low, other Ig isotypes are absent.

B-cells (membrane Ig-bearing) are absent, but CR-bearing pre-B-cells may be present.

Defective Ig heavy chain gene rearrangements; D/J rearrangement may occur, but no V/D/J.

T-cell numbers and function are normal.

No follicles or germinal centers, or plasma cells.

Inheritance: X-linked recessive gene, incidence ~1 in 105. This gene has been identified as encoding a tyrosine kinase ("Bruton's Tyrosine Kinase", or BTK) which is expressed selectively in evolving B-cells.

Treatment: Includes chronic treatment with gamma-globulin (intravenous IgG for passive immunization) and antibiotics.

This genetic flaw prevents B-cell precursors from developing into functional B-cells; replacement therapy with human IgG is very effective. Patients suffering from this condition have a higher survival rate past their fourth decade since the development of IV-Ig. Nevertheless, live vaccines are dangerous for these patients and should be evaded [70].

Congenital thymic aplasia (Digeorge syndrome)

Syndrome: Hypocalcemic tetany is evident within 24 hrs of birth (due to a deficiency of PTH, or parathyroid hormone, which is normally produced by the parathyroid and regulates potassium and calcium metabolism).

Repeated infections with viruses and fungi, (also bacteria); Candida and Pneumocystis carinii are common pathogens.

No functional thymus (hypoplasia or aplasia).

Few or no T-cells.

B-cells present, but with variable function (serum Ig levels are also variable).

Primary follicles present in lymphoid tissues but without germinal centers, and empty thymus-dependent areas.

Inheritance: This disease is most commonly sporadic (not inherited) due to de novo deletion of a region of chromosome 22q1. This deletion results in a developmental defect of the 3rd and 4th pharyngeal pouches which give rise to both the thymus and parathyroid. It is often linked with malformations of the heart and face, DiGeorge is considered as one manifestation of the

larger complex of diseases collectively known as cardiovelofacial syndrome. The occurrence of the deletion is ~1 in 104, the appearance of severe immunodeficiency is less common.

Treatment: Fetal thymus transplant might be a valuable treatment option; the transplant should not contain lymphocytes, only a small amount of thymic epithelium. Any therapy must consider the danger of Graft versus host disease reaction; for this reason one must not use adult thymus tissue, and any transfused blood must be first X-irradiated. No live vaccines should be given.

This disease is the result of the absence of T-cell development through failure to provide an appropriate environment for differentiation. The patient's lymphocytes themselves (pre-T cells) are perfectly capable of developing into mature cells, and if the appropriate environment is provided (by a thymic transplant) they will colonize it and develop normally [71].

Severe combined immunodeficiency (SCID)

Syndrome: Devastating infections in first year of life.

No functional T- or B-cells (abnormal B-cells may be present).

Thymus and peripheral lymphoid tissues extremely depleted of lymphocytes.

Inheritance: Several different known genetic defects can cause this disease, including both X-linked and autosomal recessive forms, with an overall frequency around 1 in 106.

Treatment: The only successful treatment is replacement of the hemopoietic stem cells by bone marrow transplant.

Prevention of Graft versus host disease is a key to success.

This genetic defect is expressed in the common lymphocyte precursor of T and B-cells indicated in the diagram above, and prevents their further development. If a source of competent stem cells is provided (e.g. by bone marrow transplantation), they will colonize the thymus and peripheral lymphoid tissues in a normal fashion [72].

Selective Iga deficiency

Syndrome Very low serum levels of IgA (<0.05 mg/ml), normal levels of other isotypes.

Normal cell-mediated immunity.

Increased susceptibility to viral and bacterial pulmonary infections, even though it may often be asymptomatic. Can also be associated with autoimmune or allergic states.

Inheritance: Genetic poorly understood; frequency up to 1 in 300.

Treatment: No specific treatment other than antibiotic therapy. IgA should not be administered, as it can trigger an anti-IgA autoimmune or allergic responses. This is the most common of several

isotype-specific Ig deficiencies; it is not known whether it is a defect in the precursors of IgA-producing cells, or in the mechanism by which their differentiation is controlled [73].

Acquired Immunodeficiencies

Secondary to disease

- Many infectious diseases result in more or less general immunosuppression. In the case of Human Immunodeficiency Virus (HIV), the agent which causes Acquired Immunodeficiency Disease (AIDS), its pathogenicity is due to a direct outcome of extreme deterioration of the immune system responses [74].

- Malignancies can often result in immunosuppression, either by largely interfering with normal physiological functions, or through the production of factors which explicitly inhibit immune functions [75].

- Renal failure can cause the loss of large amounts of serum immunoglobulins into the urine, resulting in humoral immunodeficiency [76].

- Enteropathies can lead to loss of immunoglobulin through the intestines, with similar results.

Iatrogenic (Due to a treatment)

This category includes the most common immunodeficiency conditions which most physicians will encounter. They are the result of various forms of therapy which have either as their goal or as a major side effect the suppression of immune receptiveness [77].

Increased susceptibility to infections is an important consequence of immunosuppression, and well-adjusted against the therapeutic benefits of a particular treatment. Some therapeutic treatments which can have this result are:

1. Corticosteroids: Prednisone is widely used for both its anti-inflammatory effect and immunosuppressive capability; lymphocytes are generally very sensitive to steroids [78].

2. Cytotoxic drugs: Many anti-tumor drugs (such as azathioprine and cyclophosphamide) are strongly immunosuppressive, and may also be used deliberately for this purpose. Susceptibility to infections might consequently be a main side effect of anti-tumor treatment, in a patient who may already be immunosuppressed by the presence of the tumor itself [79].

3. Anti-Lymphocyte Antibodies: Sera from horses immunized with human thymocytes contain effective anti-T-cell antibodies, and have been used extensively since the 1950's to inhibit rejection of transplanted organs; such preparations are known as Antilymphocyte Serum (ALS) or Anti-Lymphocyte Globulin (ALG). Their use is inadequate now, due to the increasing availability of more selective monoclonal antibodies and the development of new classes of immunosuppressive drugs (such as cyclosporin and FK-506) [80].

4. Ionizing Radiation: X-rays or gamma-rays, often used in tumor therapy, also destroy healthy in the way. While ionizing radiation commonly kills proliferating cells in a highly selective manner (which is the basis for its anti-tumor effectiveness), inactive lymphocytes are remarkably sensitive to such radiation [81].

Cyclosporin A and FK506 (Tacrolimus)

Since the early 1980's Cyclosporin A, a fungal peptide, and FK506, a bacterial macrolide, have been a noteworthy effective immunosuppressive agents in human transplantation. They inhibit T-cell function to a greater degree than B-cells or phagocytic cells, selectively blocking TH cell function by interfering with the production of and response to IL-2, but without killing the cells. While they are less effective in inhibiting established immune responses, however they have been enormously beneficial in prolonging kidney, liver and heart transplants. Their molecular target, nevertheless, is not limited to cells of the immune system, and they exhibit a group of often serious side effects, including nephrotoxicity. Although they have not completely substituted steroids and cytotoxic drugs in clinical immunosuppressive therapy, cyclosporin and FK506 have indorsed the use of lower doses of these drugs, resulting in lesser extreme generalized immunosuppression and other side effects in the management of transplant recipients [82].

References

1. Barthel D, Seliger B. "Tumor Immunology Meets Oncology (TIMO) VIII" from May 4 to 5, 2012, in Halle/Saale, Germany.Cancer Immunol Immunother. 2013; 62: 197-202.
2. Bruttel VS, Wischhusen J. Cancer stem cell immunology: key to understanding tumorigenesis and tumor immune escape?Front Immunol. 2014; 5: 360.
3. Iranzo J, Villoslada P. Autoimmunity and tumor immunology: two facets of a probabilistic immune system.BMC Syst Biol. 2014; 8: 120.
4. Ogino S, Galon J, Fuchs CS, Dranoff G. Cancer immunology--analysis of host and tumor factors for personalized medicine.Nat Rev Clin Oncol. 2011; 8: 711-719.
5. Raval RR, Sharabi AB, Walker AJ, Drake CG, Sharma P. Tumor immunology and cancer immunotherapy: summary of the 2013 SITC primer.J Immunother Cancer. 2014; 2: 14.
6. Tiwari M. From tumor immunology to cancer immunotherapy: miles to go.J Cancer Res Ther. 2010; 6: 427-431.
7. Zindl CL, Chaplin DD. Immunology. Tumor immune evasion.Science. 2010; 328: 697-698.
8. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy.Science. 2015; 348: 69-74.
9. Poletaev A, Boura P. The immune system, natural autoantibodies and general homeostasis in health and disease.Hippokratia. 2011; 15: 295-298.
10. Dudley DJ. The immune system in health and disease.Baillieres Clin Obstet Gynaecol. 1992; 6: 393-416.
11. O'Hare MJ. Teratomas, neoplasia and differentiation: a biological overview. I. The natural history of teratomas.Invest Cell Pathol. 1978; 1: 39-63.
12. Salmon SE. Neoplastic proliferation and natural history of B-cell neoplasia.Recent Results Cancer Res. 1978; 64: 277-283.
13. Pitot HC. The natural history of neoplasia. Newer insights into an old problem.Am J Pathol. 1977; 89: 402-411.
14. Shubik P. Chemical carcinogens and human cancer.Cancer Lett. 1995; 93: 3-7.
15. Osterlind A. Cancer and UV-radiation.Pharmacol Toxicol. 1993; 72 Suppl 1: 67-68.
16. Rass K, Reichrath J. UV damage and DNA repair in malignant melanoma and nonmelanoma skin cancer.Adv Exp Med Biol. 2008; 624: 162-178.

17. Post A. Environmental exposure to bacteria and viruses may provide oncolytic protection against cancers, and declining exposure to infections may contribute to a rising incidence of cancer. Med Hypotheses. 2007; 68: 558-561.

18. Shimizu K, Miyao Y, Okamoto Y, Matsui Y, Ushio Y, et al. The antitumor efficacy of lymphokine-activated killer (LAK) cells and gamma interferon production induced in vitro from peripheral blood lymphocytes of patients with malignant gliomas. Nihon Gan Chiryo Gakkai Shi. 1986; 21: 760-766.

19. Chen J, Niu H, He W, Ba D. Antitumor activity of expanded human tumor-infiltrating gammadelta T lymphocytes.Int Arch Allergy Immunol. 2001; 125: 256-263.

20. Bronte V, Kasic T, Gri G, Gallana K, Borsellino G. Boosting antitumor responses of T lymphocytes infiltrating human prostate cancers.J Exp Med. 2005; 201: 1257-1268.

21. Gervais A, Bouet-Toussaint F, Toutirais O, De La Pintiere CT, Genetet N. Ex vivo expansion of antitumor cytotoxic lymphocytes with tumor-associated antigen-loaded dendritic cells.Anticancer Res. 2005; 25: 2177-2185.

22. Uenaka A, Nakayama E. [Tumor specific antigen and cytotoxic T lymphocytes].Nihon Rinsho. 2005; 63 Suppl 4: 568-573.

23. Bohn J, Roggenbuck D, Settmacher U, Döcke W, Volk HD. Binding of natural human IgM auto-antibodies to human tumor cell lines and stimulated normal T lymphocytes.Immunol Lett. 1994; 39: 187-194.

24. Li Y, JM Ashby, O Eremin. In vitro primary immunization of B lymphocytes for producing human monoclonal antibodies against tumor-associated antigens. Hum Antibodies Hybridomas. 1993; 4: 26-30.

25. Gough MJ, Melcher AA, Ahmed A, Crittenden MR, Riddle DS. Macrophages orchestrate the immune response to tumor cell death. Cancer Res. 2001; 61: 7240-7247.

26. Gulubova MV, Ananiev JR, Vlaykova TI, Yovchev Y, Tsoneva V. Role of dendritic cells in progression and clinical outcome of colon cancer.Int J Colorectal Dis. 2012; 27: 159-169.

27. Engleman EG. Dendritic cells: potential role in cancer therapy.Cytotechnology. 1997; 25: 1-8.

28. Manickam A, Sivanandham M, Tourkova IL. Immunological role of dendritic cells in cervical cancer.Adv Exp Med Biol. 2007; 601: 155-162.

29. Szabó B, Tóth FD, Váczi L, Kiss J, Réthy A, et al. Cytotoxicity of lymphocytes and antibodies against autologous tumor cells in patients with myeloid leukaemias and preleukaemic disorders. III. Stage-dependence of oncovirus-specific immune response. Acta Microbiol Hung. 1986; 33: 103-110.

30. Jewett A, Tseng HC, Arasteh A, Saadat S, Christensen RE. Natural killer cells preferentially target cancer stem cells; role of monocytes in protection against NK cell mediated lysis of cancer stem cells.Curr Drug Deliv. 2012; 9: 5-16.

31. Wilson J, Balkwill F. The role of cytokines in the epithelial cancer microenvironment.Semin Cancer Biol. 2002; 12: 113-120.

32. Oppenheim J, Fujiwara H. The role of cytokines in cancer.Cytokine Growth Factor Rev. 1996; 7: 279-288.

33. Mantovani G, Coiana A, Massidda A, Proto E, Floris C. Role of interleukin-2 (IL-2) in cancer-related immune deficiency: in vitro response to IL-2, production of IL-2, and IL-2 receptor expression in patients with advanced cancer.Cancer Detect Prev. 1988; 12: 149-159.

34. Chang KT, Huang CY, Tsai CM, Chiu CH, Lok YY. Role of IL-6 in neuroendocrine differentiation and chemosensitivity of non-small cell lung cancer.Am J Physiol Lung Cell Mol Physiol. 2005; 289: L438-445.

35. Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer.Eur J Cancer. 2005; 41: 2502-2512.

36. Dentelli P, Rosso A, Calvi C, Ghiringhello B, Garbarino G. IL-3 affects endothelial cell-mediated smooth muscle cell recruitment by increasing TGF beta activity: potential role in tumor vessel stabilization.Oncogene. 2004; 23: 1681-1692.

37. Cassatella MA, Meda L, Bonora S, Ceska M, Constantin G. Interleukin 10 (IL-10) inhibits the release of proinflammatory cytokines from human polymorphonuclear leukocytes. Evidence for an autocrine role of tumor necrosis factor and IL-1 beta in mediating the production of IL-8 triggered by lipopolysaccharide. J Exp Med. 1993; 178: 2207-2211.

38. Uekusa Y, Gao P, Yamaguchi N, Tomura M, Mukai T. A role for endogenous IL-12 in tumor immunity: IL-12 is required for the acquisition of tumor-migratory capacity by T cells and the development of T cell-accepting capacity in tumor masses.J Leukoc Biol. 2002; 72: 864-873.

39. Foa R, Massaia M, Cardona S, Tos AG, Bianchi A. Production of tumor necrosis factor-alpha by B-cell chronic lymphocytic leukemia cells: a possible regulatory role of TNF in the progression of the disease.Blood. 1990; 76: 393-400.

40. Aggarwal BB, Pandita R. Both type I and type II interferons down-regulate human tumor necrosis factor receptors in human hepatocellular carcinoma cell line Hep G2. Role of protein kinase C.FEBS Lett. 1994; 337: 99-102.

41. Berger A. Th1 and Th2 responses: what are they?BMJ. 2000; 321: 424.

42. Lappin MB, Campbell JD. The Th1-Th2 classification of cellular immune responses: concepts, current thinking and applications in haematological malignancy. Blood Rev. 2000; 14: 228-239.

43. Lo CH, Chang CM, Tang SW, Pan WY, Fang CC. Differential antitumor effect of interleukin-12 family cytokines on orthotopic hepatocellular carcinoma.J Gene Med. 2010; 12: 423-434.

44. Okadome M, Saito T, Kinoshita H, Kobayashi H, Kamura T, et al. An attempt to generate an antitumor effect in the regional lymph nodes against endometrial cancer cells by inducing antitumor cytokines. Cancer Lett. 1996; 104: 55-61.

45. Suthaus J, Stuhlmann-Laeisz C, Tompkins VS, Rosean TR, Klapper W. HHV-8-encoded viral IL-6 collaborates with mouse IL-6 in the development of multicentric Castleman disease in mice.Blood. 2012; 119: 5173-5181.

46. Yu JH, Kim H. Oxidative stress and cytokines in the pathogenesis of pancreatic cancer.J Cancer Prev. 2014; 19: 97-102.

47. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy.Nat Rev Cancer. 2004; 4: 11-22.

48. Shiroki K, Shimojo H, Maeta Y, Hamada C. Tumor-specific transplantation and surface antigen in cells transformed by the adenovirus 12 DNA fragments.Virology. 1979; 99: 188-191.

49. Parmiani G, Meschini A, Invernizzi G, Carbone G. Tumor-associated transplantation antigen distinct from H-2k-like antigens on a BALB/c (H-2d) fibrosarcoma.J Natl Cancer Inst. 1978; 61: 1229-1234.

50. Coggin JH Jr. Oncofetal antigens.Nature. 1986; 319: 428.

51. Salomon JC. [Immunological surveillance and spontaneous carcinogenesis].Ann Inst Pasteur (Paris). 1972; 122: 669-675.

52. Doherty PC, Knowles BB, Wettstein PJ. Immunological surveillance of tumors in the context of major histocompatibility complex restriction of T cell function.Adv Cancer Res. 1984; 42: 1-65.

53. Rosic-Kablar S, Chan K, Reis MD, Dubé ID, Hough MR. Induction of tolerance to immunogenic tumor antigens associated with lymphomagenesis in HOX11 transgenic mice.Proc Natl Acad Sci U S A. 2000; 97: 13300-13305.

54. Prehn RT. Immunomodulation of tumor growth.Am J Pathol. 1974; 77: 119-122.

55. Scholler PM, Zeller WJ, Rössler W, Lenhard V, Weber E. [Effect of immunomodulation following allogeneic blood transfusion on tumor neogenesis and growth--experimental studies in rats].Arch Geschwulstforsch. 1987; 57: 81-90.

56. Klapper LN, Waterman H, Sela M, Yarden Y. Tumor-inhibitory antibodies to HER-2/ErbB-2 may act by recruiting c-Cbl and enhancing ubiquitination of HER-2.Cancer Res. 2000; 60: 3384-3388.

57. Seki T, Morimura S, Ohba H, Tang Y, Shigematsu T. Immunostimulation-mediated antitumor activity by preconditioning with rice-shochu distillation residue against implanted tumor in mice.Nutr Cancer. 2008; 60: 776-783.

58. Hellström KE, Hellström I, Snyder HW Jr, Balint JP, Jones FR. Blocking (suppressor) factors, immune complexes, and extracorporeal immunoadsorption in tumor immunity.Contemp Top Immunobiol. 1985; 15: 213-238.

59. Umansky V. Immunosuppression in the tumor microenvironment: where are we standing?Semin Cancer Biol. 2012; 22: 273-274.

60. Gorelik E. Concomitant tumor immunity and the resistance to a second tumor challenge.Adv Cancer Res. 1983; 39: 71-120.

61. Chen Y, Zhou Y, Qiu S, Wang K, Liu S, et al. Autoantibodies to tumor-associated antigens combined with abnormal alpha-fetoprotein enhance immunodiagnosis of hepatocellular carcinoma. Cancer Lett. 2010; 289: 32-39.

62. Liu D, Liu F, Liu Z, Wang L, Zhang N. Tumor specific delivery and therapy by double-targeted nanostructured lipid carriers with anti-VEGFR-2 antibody.Mol Pharm. 2011; 8: 2291-2301.

63. Ophir R, Pecht M, Keisari Y, Rashid G, Lourie S, et al. Thymic humoral factor-gamma 2 (THF-gamma 2) immunotherapy reduces the metastatic load and restores immunocompetence in 3LL tumor-bearing mice receiving anticancer chemotherapy. Immunopharmacol Immunotoxicol. 1996; 18: 209-236.

64. Schirrmacher V. [Tumor cell immunogenicity and T-cell-mediated antitumor immune reactions. Modulation and application to immunotherapy].Arzneimittelforschung. 1987; 37: 259-262.

65. Hayakawa H. [Congenital immunodeficiency diseases and infection (author's transl)].Rinsho Byori. 1978; 26: 328-331.

66. Schuurman HJ, Krone WJ, Broekhuizen R, van Baarlen J, van Veen P, et al. The thymus in acquired immune deficiency syndrome. Comparison with other types of immunodeficiency diseases, and presence of components of human immunodeficiency virus type 1. Am J Pathol. 1989; 134: 1329-1338.

67. Sapin MR. [Immune system and immunodeficiency].Klin Med (Mosk). 1999; 77: 5-11.

68. Kang EM, Marciano BE, DeRavin S, Zarember KA, Holland SM. Chronic granulomatous disease: overview and hematopoietic stem cell transplantation.J Allergy Clin Immunol. 2011; 127: 1319-1326.

69. Jesus AA, Liphaus BL, Silva CA, Bando SY, Andrade LE. Complement and antibody primary immunodeficiency in juvenile systemic lupus erythematosus patients.Lupus. 2011; 20: 1275-1284.

70. SÅ,omka A. [Bruton's syndrome in an 8-year-old boy].Pneumonol Pol. 1990; 58: 129-132.

71. Shuib S, Abdul Latif Z, Abidin NZ, Akmal SN, Zakaria Z. Inherited t(9;22) as the cause of DiGeorge syndrome: a case report.Malays J Pathol. 2009; 31: 133-136.

72. de Pagter AP, Bredius RG, Kuijpers TW, Tramper J, van der Burg M. Overview of 15-year severe combined immunodeficiency in the Netherlands: towards newborn blood spot screening.Eur J Pediatr. 2015;.

73. Norris CR, Gershwin LJ. Gershwin. Evaluation of systemic and secretory IgA concentrations and immunohistochemical stains for IgA-containing B cells in mucosal tissues of an Irish setter with selective IgA deficiency. J Am Anim Hosp Assoc. 2003; 39: 247-250.

74. Bozzette SA, Phillips B, Asch S, Gifford AL, Lenert L, et al. Quality Enhancement Research Initiative for human immunodeficiency virus/acquired immunodeficiency syndrome: framework and plan. HIV-QUERI Executive Committee. Med Care. 2000; 38: I60-169.

75. Behrend M, Kolditz M, Kliem V, Oldhafer KJ, Brunkhorst R. Malignancies in patients under long-term immunosuppression after kidney transplantation.Transplant Proc. 1997; 29: 834-835.

76. Ibrahim F, Naftalin C, Cheserem E, Roe J, Campbell LJ. Immunodeficiency and renal impairment are risk factors for HIV-associated acute renal failure.AIDS. 2010; 24: 2239-2244.

77. Miranda RN, Loo E, Medeiros LJ. Iatrogenic immunodeficiency-associated classical hodgkin lymphoma: clinicopathologic features of 54 cases reported in the literature. Am J Surg Pathol. 2013; 37: 1895-1897.

78. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. The National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia. N Engl J Med. 1990; 323: 1500-1504.

79. Dukor P, Dietrich FM. Characteristic features of immunosuppression by steroids and cytotoxic drugs.Int Arch Allergy Appl Immunol. 1968; 34: 32-48.

80. Searles RP, Williams RC Jr. Anti-lymphocyte antibodies in the pathogenesis of SLE.Clin Exp Rheumatol. 1986; 4: 175-182.

81. P205. Ionizing radiation throughout the duration of immunosuppression therapy in Crohn's disease: should it remain a concern? J Crohns Colitis. 2015; 9 Suppl 1: S178.

82. Gajjar NA, Kobashigawa J, Laks H, Fishbein M. FK506 vs. cyclosporin: pathologic findings in 1067 endomyocardial biopsies.J Heart Lung Transplant. 2001; 20: 229.