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Review

Cancer and Immunosuppression

Ayşe Yürekli[1], Oytun Erbaş[1,2]

ABSTRACT

Cancer, thought to date back about 120,000 years ago, is described as an uncontrolled and abnormal growth of cells. The degradation of the cell mechanism due to chemical, radiation, or genetic factors is the cause of this uncontrolled development. The immune system helps our bodies combat cancer cells that develop out of control and cause damage to other tissues. However, the immune system's response to antigens is sometimes suppressed. Immunosuppression can be triggered by cellular processes or produced by the use of drugs in certain surgical cases, such as transplantation. The immune system tolerates certain tumors while remaining unprotected due to the suppression of cancer and the inability to completely express the response. In this case, the question arises whether a cure can be discovered by identifying the immune system's response mechanism using immunosuppressive drugs in this manner. In this review, the relationship between immunosuppression and cancer is discussed.

Keywords: Cancer, immunosuppression, tumor.

According to the 2018 data obtained from the World Health Organization (WHO) and the American Cancer Society (ACS) database, there are approximately 22.4 percent male and 18.2 percent female cancer patients in the 0-74 age range. Lung cancer (2.09 million cases), breast cancer (2.09 million cases), and prostate cancer (1.28 million cases) are the most common cancers in 2018. Lung, liver, and stomach cancers are the most lethal cancers.[1] Among many types of cancer, lungs, breast, colorectal, stomach, prostate and liver accounted for about 55% of the global incidence in 2012, and major cancer types were selected.[1] Although the exact mechanism of cancer formation is unknown, it is known that the cells that need apoptosis continue to grow faster and uncontrolled. According to evidence from the human genome project, cancer is genetically inherited and characterized by mutations.[2] The immune system interacts closely with tumors during the entire cancer phase, just as it does with any disease. Immune and cancer cells have a symbiotic relationship that both prevents and promotes tumor growth. This characteristic is now regarded as a distinguishing feature.[2,3] The characteristics of cancer were first identified in 2000. These characteristics are determined to continue proliferative signaling, to resist cell death, to avoid immunosuppression, to activate invasion and metastasis. In 2011, in addition to these features, two key features were added. Reprogramming energy metabolism and preventing immune system destruction are two of them. Immunosuppressive T cells, which is a distinctive feature of cancer, have been in hope for treatment by providing elimination of cancer cells.[4,5] Immunosuppression is linked to the immune system's ability to promote or treat cancer. In animal studies, immunosuppressive drugs and other strategies have been used to develop a specific immune status. Only a few types of cancer have been detected using immunosuppressive drugs, with epithelial-induced cancer accounting for 75% of the cases. Immunosuppressive drugs prevent pediatric patients with all of these complications from growing and developing normally. The current immunosuppressive therapy protocol includes the combined use of prednisone, azathioprine,

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey
[2]Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey

Correspondence: Ayşe Yürekli. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.

E-mail: ayseyurekli3344@gmail.com

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cyclosporin A.[6] Extreme stress is also known to have negative effects on cancer and the immune system. Research by psycho-immunologists showed the effects of β-adrenergic receptors on tumor cells and noradrenaline stimulates tumor development and psychosocial stressors have a direct effect.[7,8] Immunotherapy, which has been developed by reversing the functioning of immunization mechanisms, has been a sign of hope in the treatment of cancer. Immunotherapy has already replaced traditional cancer treatments in many cases. However, it was not considered as a definitive treatment in all tumors, as return rates are between 20-80%, but there has been great progress as long as a return is made.[9]

CANCER

Cancer is defined as the uncontrolled growth of cells with abnormal growth characteristics. Bacteria, viruses, radiation, heredity, environmental factors, eating habits, and chemicals are all factors that can cause it. Studies suggest that cancer is a disease that involves dynamic changes in the genome.[10] Tumor cells are classified as benign or malignant. Benign tumors are defined by the fact that they are limited to the area in which they are found. Malignant tumors are not limited to the area in which they are found; they can also invade lymph tissue or blood vessels. There are several stages to cancer development, and in the human population, four to seven age-related stochastic cancers have been found.[11] Inherited cancer is less common than cancer caused by environmental factors. Hereditary transfer of the disorder in suppressive genes affecting tumor formation and the composition of environmental factors causes predisposition. Even minute changes in tumor cells, such as point mutations, appear to cause noticeable deterioration. Whether genes predispose to certain diseases is still being researched.[10,11] Genetically transmitted to us from our ancestors, this disease has clearly expressed its characteristics with the impact of many environmental factors today and cancer has become one of the most common diseases of the era.[12] In order for cancer cells to grow and multiply, metabolism needs to be reorganized. Glucose intake and lactate fermentation are both increased as a result of altered metabolism. In the presence of mitochondria, this process continues. It can be explained as cancer's tendency to glucose. This event is called the "Warburg Effect". This event, known for more than 90 years, has been studied in more detail over the last 10 years.[13,14] Tumor glycolysis plays an important role in activating the immune avoidance systems and immunosuppressive networks of cancer cells. Recent studies have shown that cancer cells are sensitive to anti-tumor cells. It is thought that metabolism is working together during the reprogramming of metabolism and immune avoidance in the advancement of cancer.[13]

CANCER AND IMMUNE SYSTEM

The body uses the immune system against antigens. The immune system is made up of many cells and proteins. There are two types, namely innate and acquired immunity. The first development of fighting antigens is thanks to innate immunity. Acquired immunity is divided into two categories: humoral and cellular immunity. The organism battles antigens outside the cell in humoral immunity, while intracellular antigens are fought in cellular immunity.[15] Cancerous cells are destroyed by the immune system before they grow and become harmful. Cancer immuno-surveillance is the term for this condition. Inhibition of carcinogenesis and regular cell homeostasis are used to accomplish this goal.[16] In the theory of immune surveillance, tumor cells are no longer passive targets for the immune system. According to studies, the immune system has been suppressed in the prevention of cancer in some cases. The term immune regulation was coined as a result of these two characteristics of the immune system. 3E is the acronym for cancer immuno-surveillance. Elimination, equilibrium, and escape are the steps of these processes. The tumor cell will expand if it passes through these stages.[16] Natural Killer (NK) cells play an important role in the immune system's immune surveillance. NK cells are effector lymphocytes that aid in the removal of tumors. They can do this by using cytolytic granules and death receptors, as well as triggering the production of cytokines, and interacting with and reinforcing immune responses. In the context of hematopoietic stem cell transplantation, NK cells have been shown to display leukemia activity against the vaccine and are important in the clinical efficacy of antibodies.[17] However, adaptive immune effects such as CD4 + auxiliary T cells, CD8 + cytotoxic T cells, and antibodies are particularly expressed in tumor cells. Effective T cells that manage to cross the endotel barrier are directed to the tumor stroma without encountering the target tumor cell. It is quite possible to encounter immunosuppressive signals here.[18] Tumor cells can be totally destroyed at this point, and clonal variants can emerge. Clonal variants reduce their immunogenic properties and

develop resistance by acting immunosuppressive. The theory of immunoediting is described by these events.[19] This interaction between the immune system and the tumor from the early phases of carcinogenesis continues by shaping each other. This process can either result in one side winning, or it can become chronic, with the equilibrium lasting for years.[17,20] Viruses are the most common cause of cancer in people with immunodeficiency. Lymphomas linked to the Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), and tumors linked to the human papillomavirus virus (HPV) have all been reported.[21]

NATURAL IMMUNITY TO CANCER

Natural immunity is the body's first line of defense against any antigen. Innate immune cells include natural killer cells (NK), neutrophils, and macrophages. T cells collaborate with these cells. Furthermore, oncological viruses direct natural immunization, leaving the tumor region defenseless.[22] With an in-depth investigation of cancer immunity, it has been observed that natural immune lymphocytes inhibit tumor development. Recombination activating gene 2 (RAG-2) and lymphocytes expressing antigen receptors have been shown to play a critical role in cancer immunosuppression. It has been observed that mice that do not carry RAG-2 are unable to rearrange lymphocyte antigen receptors. NK and NKT (natural killer T) cells also participate in cancer immuno-surveillance.[23]

ADAPTIVE IMMUNITY AND CANCER

The immune response's kinetic is sensitive to hazard signals. When a danger signal is received, the adaptive immune system can be reinforced. The adaptive immune system's therapeutic contributions to chemotherapy were observed by moving cyclophosphamide and fludarabine to T cells. There is a constant synergy between natural and adaptive immunity. While immunotherapy is expected to enhance this synergy, inflammatory stimuli have been shown to suppress adaptive immunity.[22]

IMMUNOSUPPRESSIVE MECHANISMS

Glucocorticoids, a steroid-based hormone, are used to treat both acute and chronic illnesses. It is the most commonly prescribed anti-inflammatory, immunosuppressive, and anti-allergic medication.[24] In recent studies, it has been observed that glucocorticoids, an immunosuppressive agent, may occur through the release of target cells in leukocytes. However, as a result of immune changes caused by surgical interventions, immunosuppression mechanisms work, and in this case, glucocorticoid release occurs. Adrenaline and noradrenaline released from nerve ends also have immunosuppressive effects. Immunosuppression is formed when these effects interact with receptors on immune cells.[25]

It has been observed that lymphocyte activity can be suppressed by using IL-1 (interleukin-1) and TGF-β (transforming growth factor-beta) secreted by tumors in tumor cyst fluid.[26]

Glioblastoma is known to have some effects on the immune response in the microenvironment. In order to inhibit immunosuppression, there is a tendency for modulator use.[26]

IMMUNOSUPPRESSION CELLULAR MECHANISM IN CANCER

Cancer suppressor cells; Myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg), stromal cells, natural killer T cells (NKT), endothelial cells, and B cells.[27] MDSC consists of an immature myeloid cell population. It is capable of suppressing both innate and acquired immunity. Both anti-tumor and immunotherapy are inhibited by MDSCs. They are activated by the host cells' production of proinflammatory mediators in the tumor microenvironment.[27] According to the results of some experiments on mice, MDSCs nitrate T cell receptors, preventing CD8+ from binding to T cells. The idea emerged that MDSC starved arginine T cells and those COX-2 inhibitors could reduce arginine and weaken tumor growth in mice. However, it has been shown that IL-1 secreted by tumor cells induced MDSC accumulation and polarized its immunity to tumor incentive. Tregs (regulatory T cells) also serve as anti-tumor suppressors, with the primary goal of preventing autoimmunization. It has been concluded that T cells recognize their antigen in FoxP3 (a protein involved in immune system responses) of mice, but the Tregs suppress them. Induced Tregs (iTregs) have been shown to contribute to immune suppression.[28] They express CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed cell death protein 1), which are effector T cells that inhibit tumor growth. It has been detected that these blockage agents can also target Tregs. The anti-tumor event in the

CTLA-4 antibody has been shown to be ineffective. In addition, it has been proven that the immune suppression of Tregs without PD-1 expression is higher.[29] Tumor stroma assists immunosuppression even after tumor cells have been removed. Research conducted in the mice revealed that CD8+ T cells recognize antigen-charged stroma cells, but do not identify cancer cells. The NKT recognizes cancer cells and helps in tumor prevention, while the NKT2 subunit aids in tumor recurrence.[28] The primary component of B cell activation, polyamines, has a major impact on tumor growth rates. Within the tumor microenvironment, the polyamines suppress the immune response, allowing the tumor to evade immune surveillance. Polyamines are used by B cells to activate their suppressive properties as well as to support their metabolism.[30]

MOLECULAR MECHANISMS OF IMMUNOSUPPRESSION IN CANCER

Immunosuppressive molecular mechanisms are nitric oxide synthesis, arginase, indolamine 2,3-dioxygenase (IDO), signal transducer, and activator of transcription (STAT).[16] In the metabolism of arginine, two essential enzymes are arginase and inducible nitric oxide (NO). Arginine is the main nutrient of T cells in the tumor microenvironment. Therefore, an increase in the level of arginase leads to downregulation of T cells in the p chain. Increased nitric oxide inhibits T cells, allowing tumors to grow.[16] IDO is a tryptophan-degrading enzyme that is highly expressed in most cancers. Due to T-cell suppression in tumors, IDO allows tumors to escape. STAT 1 and STAT3, the transcription activators, play a role in tumor development. In humans, STAT 1 has been shown to cause tumors to form spontaneously.[28] STAT 3 is the best way to study immune suppression. In most tumor types, STAT3 is structurally active. STAT3 activation involves phosphorylation of tyrosine. Some mutations provide oncogenic activation for STAT 3. Many receptors (EGFR, HER2, Neu...) partially signal using STAT3. STAT3 activation suppresses the production of cytokines and chemokines, which increase anti-tumor immune responses. Based on this, blocking STAT3 signals results in tumor growth in immune cells.[24]

CANCER IMMUNOTHERAPY

In recent years, cancer treatment has advanced with developing technology. Chemotherapy, surgery, radiation therapy, and immunotherapy are currently being used as treatments, but no definitive solution has yet been discovered. Immunotherapy is a cancer-fighting treatment that helps the immune system. Monoclonal antibodies bind cancer cells and stop uncontrolled growth by changing therapeutic strategies by blocking specific proteins (immune control points). Despite this, not all patients had positive results.[15,31] As a mechanism, anti-tumor immunity is suppressed due to the role of T cells in signaling. The CTLA-4 ligand inhibits stimulating signaling and weakens the response of T-cells. It also serves as a regulatory T-cell. This brings the anti-tumor effects to a halt. At this stage, an immunotherapeutic treatment process is formed using immune suppressive factors.[32] There are three types of immunotherapeutic antigens that stimulate anti-tumor immune responses. Tumor-mutated antigens, tumor-related antigens, and cancer-testis antigens are among them. Tumor-related and cancer-testis antigens are expressed in tumor tissues in various ways. By weakening central tolerance, these cells were able to respond to their own antigens in autoimmunity. Antigen expression in healthy tissues has resulted in side effects. Tumor-mutated antigens (neo-antigens) are tumor-specific because they result from somatic mutation. These antigens are the most promising immunotherapy targets. With the development of next-generation sequencing (NGS) technology, genome scanning can be performed to detect neo-antigens. T cells play the most important role in cancer immune research. The control mechanism is defined by T cells containing antibodies against CTLA-4, PD1, and PD-L1 (programmed death-ligand 1).[33]

Cytotoxic T lymphocytes, against PD-1 programmed to CTLA-4, using blocking antibodies, the latest clinical trial obtained by immune checkpoint therapy has been successful. It was revealed that cancer cells were killed and modified as a result of these processes.[34]

IMMUNOSUPPRESSIVE DRUGS AND CANCER

Immunosuppressive drugs are commonly used after transplantation surgery to suppress immunity continuously or until the body accepts the organ into the tissue. At the same time, in order to treat immunological disorders, it's critical to understand how immunosuppressive drugs work in the immune system.[35] For example, cyclophosphamide is a potent immunosuppressive drug. It is commonly used in blood and bone marrow transplantation.

It was developed to select the cancer cell, but it was found to be inefficient against the cancer cell's phosphamidases. However, the effects of aldehyde dehydrogenase on different cellular expressions, anti-cancer therapeutic index of cyclophosphamide, and on immunosuppressive properties have been found.[36] In the form of solid tumors, cancer-associated fibroblasts (CAFs) are usually the most prominent components of the microenvironment. Tumor cell growth is known to stimulate angiogenesis, which causes inflammation and facilitates cancer. Tumors have an immune evasion and immunosuppressive nature in addition to the inflammatory microenvironment. CAFs play a role in immune regulation by shaping the tumor's microenvironment. To gain immune cells, they infiltrate tumors.[36] In cancer patients with decreased immune cytotoxicity, a lack of T-cell infiltration in the tumor microenvironment indicates adverse effects.[37] In addition, immunosuppressive drugs like prednisone, ATG (Anti-Thymocyte globulin), and azathioprine accelerated metastasis in animals. Based on this, immunosuppression is thought to facilitate the growth and spread of tumors that were previously left undeveloped.[7]

DISCUSSION

Immunosuppressive agents that suppress the function of the immune system are divided into molecular and cellular mechanisms. The immune system in cancer disease is unable to fully fulfill its duties as it encounters suppressive cells and secretions in the tumor microenvironment. While the mechanisms appear to favor the anti-tumor feature, they negatively affect cancer treatment by providing an environment for tumor growth. Patients may die unexpectedly while appearing to be recovering as a result of this negative effect. Recent research has shown that immunotherapeutic methods and immune-suppressing factors can be used in the treatment of cancer. Ongoing studies include immuno-cancer vaccines and immune growth against oncological viruses. Non-toxic agents that control or eliminate immunosuppression in the tumor micro-environment from the formation of tumors are used as control and chemopreventive agents. These agents will help determine how tumors avoid treatment and develop treatment strategies. Although immunologists and oncologists have yet to reach a consensus on this topic, research is ongoing.

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