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Tumor Immunology: Uncovering Relationship Between Cancer and Immune System

Yorran Hardman Araújo Montenegro[1]*, Anderson dos Santos Ramos[2] and Geilza Carla de Lima Silva[3]

[1]Department of Biological Sciences at the State University of Paraíba, Laboratory of Genetics and Molecular Biology (LGBM), Brazil
[2]Department of Cellular and Molecular Biology, Federal University of Paraíba, Laboratory of Molecular Biology Applied to Health, Brazil
[3]Department of Applied Biology to Health, Laboratory of Immunopathology Keizo Asami (LIKA), Federal University of Pernambuco (UFPE), Brazil

Abstract

Cancer is a heterogeneous disease, the result of the specific combination of genetic and epigenetic changes in somatic cells, occurring as a cumulative process throughout the life of the human organism. The immune system is specialized to act in defense of our body, with potential of specific destruction without toxicity to the normal tissue. In the tumor context, this system acts both by actions of recognition and inhibition of development, as well as in tumor control through the interaction with cells that promote oncogenesis. As criteria to perform a systematic review of the literature understanding the relevance of the systemic-immune interaction and cancer, we select articles in the English language, with a descriptive an/or experimental design. Recognition of a tumor can be accomplished by identifying oncofetal antigens, proteins with altered structural conformation, abnormal expression of surface carbohydrates, as well as increased expression of proteins found in normal cells. In view of this recognition, antitumor responses may be cellular and/or humoral in nature, where cells of the immune system act by means of cytotoxic activity, or by releasing effector molecules. Like all immunological efforts, tumor cells are able to bypass the immune system through mutations in key molecules, loss of antigenicity and immunogenicity, changes in carbohydrate patterns, immunosuppressive activity of the tumor microenvironment, among others. Understanding the relationships between immune cells and cancer cells is essential for understanding the dynamics of cancer.

Keywords: Anti-tumor response; Immune avoidance; Tumor recognition; Tumor microenvironment; Immunomodulation

Introduction

Cancer is a heterogeneous disease, resulting from the specific combination of genetic and epigenetic changes in somatic cells, occurring as a cumulative process throughout the life of the human organism. The immune system, for another hand, is specialized to act in defense of our body with potential for specific destruction, without toxicity to the normal tissue. In the tumor context, this system acts both by actions of recognition and inhibition of development, as well as in tumor control through the interaction with cells that promote oncogenesis. The oncogenesis processes are independent of the immune response against the tumor. However, in recent years, there have been discoveries regarding the use of molecular mechanisms that mediates tumor "leakage" of immunological surveillance by gradually increasing the concentration of immunosuppressed factors in the tumor microenvironment, indicating the regulation of the active role in the development of cancer [1]. Observing the relevance of the systemic-immune interaction and cancer, this work objective to carry out a systematic literature review, through a bibliographical survey on the mechanisms of tumor recognition by the human organism, the possible antitumor responses conceived by the immune system, besides of avoidance strategies by cancer cells.

Literature Review

Tumor recognition

Cancer is a disease that results from alterations in the cell cycle, where a disordered growth of fined cells occurs due to the activation of specific oncogenes and/or inhibition of tumor suppressor genes, through a cumulative process. The process of interaction of cancer with the immune system occurs by the suppressor activity of immune-responses or exaggerated activation of some molecular pathways, also used to negatively control the pathogens, where they induce the immunological homeostasis or, in some cases, cause an escape of the detection of activity tumor [2].

The development of cancer occurs through a gradual transformation with somatic changes, evolving a normal state to pre-cancer and finally, cancer cells. It should be borne in mind that the cell growth checkpoints are primarily responsible for not suppressing the tumor when there are changes in some of its components, such as mutations in proteins analysis. These modifications lead to malignant transformation through two distinct phases: (i) initiation, involving changes in the cellular genome, but not, *per se*, malignant transformation. Malignant transformation requires the second step: (ii) promotion. The promotion results from cumulative changes in DNA, which in turn affect proto-oncogenes, tumor suppressor genes or apoptosis genes; resulting in irregular cell growth [3].

These modifications in the cellular phenotype drive the cells to malignancy, and this process leaves molecular "traces", which can be recognized by the human organism as foreign or non-self. These changes can manifest themselves in different ways and this recognition is carried out by the immune system. One of the mechanisms of tumor recognition is through the expression of oncofetal antigens, product of the expression of oncofetal genes. The expression of these proteins

***Corresponding author:** Yorran Hardman Araújo Montenegro, Graduate Student, Department of Biological Sciences (Bachelors) at the State University of Paraíba, Laboratory of Genetics and Molecular Biology (LGBM), Brazil, Tel: +55 83 3315-3300; E-mail: Yorran_Montenegro@icloud.com

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occurs at a specific stage of gestation and then declines [4]. These are immunogenic and not expressed in adult tissues or newborn babies. Thus, when they are reactivated in adulthood, the immune system can detect that these proteins are being expressed at an inopportune time. It is observed an intrinsic relationship between the expression of the protein and the pathogen of malignant neoplasms, mainly solid [5].

In addition to the expression of oncofetal genes, gene or chromosomal mutations can lead to changes in the morphological conformation of some proteins, resulting in the recognition of a structurally different molecule through the immune system [6]. Chronic myeloid leukemia (AML), for example, is characterized by the formation of the Philadelphia chromosome, responsible for 90% of the cases. This chromosome is formed by the (9;22) translocation, where the fusion between the ABL tyrosine kinase gene on chromosome 9 and the BCR tyrosine kinase gene on chromosome 22 results in the formation of the BCR-ABL oncogene. The BCR-ABL oncogene exists in three different forms (p210, p185 and p230), where each form has distinct structural domains, producing a distinct type of leukemia. Tumorigenic potential of BCR-ABL lies in the fact that this fusion gene leads to the production and activation of other kinase signaling molecules [7].

Another form of tumor recognition is through the differential expression of genes that determine the architecture of the cell surface carbohydrates. Dramatic alterations in the antigenic profile of the tumor cell surface modify the anchoring of carbohydrate-binding proteins (used to discriminate between normal and malignant adult cells) [8]. Among these changes, the increase in sialylation and fucosylation, which are more common in carcinogenesis and progression, as well as prognosis of cancer, is highlighted. In addition to the increase in carbohydrate expression, some of these molecules may be lost on the cell surface, leading to the formation of differentiated neo-antigens or epitopes, not normally found in healthy cells. Thus, changes in the expression of enzymes involved in the glycosylation process of lipids and proteins may contribute to the detection of tumor cells part of the immune system [9].

Some proteins are expressed both in normal cells and in cancer cells, is important for the functioning of basic cellular activities. However, in some tumors, these proteins may present with greater expression, if compared to normal conditions. These quantitative protein profiles are also used in the differentiation between normal and tumor cells. As an example, we have the HER-2 protein receptor in breast tumors. After signaling, the presence of cancer cells, the immune response occurs through the interpretation of all these chemical signals. Thus, the immune response depends on its own endogenous factors and manifests itself as a process of linked events.

Anti-tumor response

The immune system, upon perceiving the presence of tumor cells, can emit a cellular and/or humoral immune response. In this way, immune cells and molecules produced by them work by means of several signaling pathways, pleiotropic or redundant, aiming to eradicate the malignity of the human organism.

Macrophages, potent phagocytes of the innate component of the immune system, act in the primary defense against tumorigenesis, either directly destroying tumor cells or by producing antitumor mediators, as well as removing apoptotic cells and avoiding autoimmunity reactions [10]. Taking into account recent data, tumor-associated macrophages (TAMs) have two phenotypes (M1 and M2), where M1 macrophages produce IL-12 and IL-10 cytokines contributing to tumor growth control and, in turn, M2 macrophages present a pro-tumor profile, inducing by various mechanisms, tumor progression [3]. The presence of the latter has been associated with a poor prognosis in most cases and have been shown to adopt anti-inflammatory phenotypes, promoting angiogenesis, extracellular matrix remodeling, tumor growth and metastasis [11].

Although we do not have so much detail about the role of neutrophils in the context of cancer, such phagocytic cells, the most abundant of all white blood cells, play important roles in the antitumor response, either directly or antibody-dependent cytotoxicity, as well as through activation of other cell types, including T cells and dendritic cells [12]. Recently, in a study by Takeshima it was seen that neutrophils induced by radiation (RT-Ns) acquired greater antitumor activity, producing molecules that damage the tumor cells. In this study, it was shown that they also possessed the ability to modulate a tumor-specific T cell-mediated anti-tumor response.

Active immunological responses against tumors are dependent on efficient presentation of tumor antigens and co-stimulatory signals through antigen presenting cells (APCs), which include macrophages, B cells, dendritic cells (DCs) and, in the case of the skin, Langerhans cells [13]. Among these, DCs are central cells in inducing an antitumor response, because of their unique ability to mediate primary T cell immune responses, as seen by Brian, who verified that CD103+ intratumorally DCs were identified as active in the tumor microenvironment, effecting antigen processing and robustly stimulating the effector response of cytotoxic T lymphocytes (CTLs) to tumor cells.

CD8+ T-cells are perhaps the most potent arm of the immune system capable of killing tumor cells by recognition of MHC-I peptide tumor epitopes. When active, they perform direct cytolytic effect against the tumor cell in response to secretion of elevated levels of IFNγ, TNFα, perforins and granzymes [14]. Responses generated by tumor-specific CD8+ T-cells are often insufficient for tumor eradication without help of CD4+ T-cells.

CD4+ T-cells, on the other hand, present a certain singularity, since they are the only ones that express the surface marker of CD4 cells. This subset of lymphocytes is quite diverse and its subpopulations exert a variety of functions, such as assisting CD8+ T cells and B-cells to induce their function of cytotoxicity and antibody production, respectively [15].

In cancer, the role of Th1 response, a subtype of CD4+ T-cells, is already better understood, since such cells directly regulate antitumor programs not only by the secretion of high levels of IFN-γ and TNF-α capable of positively regulating the presentation of MHC class I molecules, as well as APCs, collaborating with the cell death functions of CD8+ T-cells and regulating the length and magnitude of CTLs responses. In addition, in an indirect action, these cells can activate and expand CTLs that kill the tumor through perforin and granzyme molecules [16].

With respect to humoral immunity, tumor cells may undergo cytokine action and the complement system. Immune cells release the so-called cytokines, substances directly related to differentiation, maturation and activation of immune cells. In a study conducted by the team of Raja [17], it was observed that factors derived from the tumor microenvironment, be these cytokines and/or chemokines, an implicit relation with tumor progression. According to the researchers, the quantitative and qualitative changes in the cytokine profile could

be associated with cell dedifferentiation, conferring an increase in the malignant phenotype.

As part of the immune system, the complement system consists of a set of more than 50 proteins that act as the first line of defense against infections of bacteria, viruses and parasites, organizing the immune response by recruiting immune cells to the site of infection and direct cell lysis. Generally, this system is known as a mechanism of protection against the formation of tumors in humans but is often limited by several mechanisms of resistance that interfere with its cytotoxic action. Its activation triggers several biological effects, among them the induction of pro-inflammatory conditions that affect the cell surface molecules of leukocytes and endothelial cells. This pro-inflammatory condition may aid in the mobilization of the immune system and, consequently, in the identification of tumor cells [18].

Despite all the mechanisms of antitumor response carried out by the immune system, the tumor cells find escape mechanisms of the immune defenses and manage to acquire a resistant phenotype, culminating in a faster tumor progression. These mechanisms of resistance are associated with micro-environmental pressures that select existing mutations. Thus, it is important to understand these evasion mechanisms to devise more effective therapeutic strategies.

Evasion of the immune system

The hallmarks of cancer comprise six biological capabilities acquired during development of human tumors: proliferative signaling, evading growth suppressors, resisting cells death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [19]. These processes are established with the help of extracellular vesicles that differ in the biological sign unleashed by molecular in the stroma and the neighborhood cells, implicating in induction of angiogenesis, control of cellular invasion, initiation of pre-mstastic niches, maintenance of inflammation, and evasion of immune system [20].

A question that still presents gaps involving the formation of tumors surrounds in the role that the immune system plays in the resistance or eradication of the formation and progression of neoplasms [21]. Tumor cells can sometimes escape the immune system by using effector mechanisms capable of nullifying or deceiving immune-vigilance, one of those strategies call hallmarks.

Presentation of tumor antigens to CD8+ T-cells by MHC class I molecules is crucial for immune responses against cancer, while downward modulation of the antigen processing machinery that affects the MHC-I pathway, making it defective, is one of the strategies used by cancers in immunological circumvention. As a result of down-regulation in antigenic expression, a higher incidence of tumor and metastasis is verified, because CTLs become unable to recognize target antigens in tumor cells.

MHC class I transcription promoter (CITA), NLRC5 (nucleotide binding domain and leucine-rich repeats containing (NLR), caspase activation domain and recruitment domain (CARD) 5), is a co-activator Key transcript of MHC class I genes. Recent genetic studies have revealed that NLRC5 is one of the primary targets for cancer immune evasion mechanisms. Genetic and epigenetic changes in NLRC5 associated with its sub-expression are related to the insufficient activation of CD8+ T-cells, which in turn induce inefficient responses on tumor cells [22]. Thus, NLRC5 is a new biomarker in the prognosis and promising therapeutic target in cancer.

Several tumor cells have the ability to adapt to immune pressure through loss of antigenicity and immunogenicity, as well as through their ability to establish an immunosuppressive microenvironment. In recent studies, it has been noted that tumor cells do not adequately express co-stimulatory molecules as a result of mutations and selection, rendering such cells incapable of expressing immunogenic proteins and thus may induce anergy and tolerance over T cells, or reduction of apoptosis receptors [21].

Significant efforts in understanding and modulating the immune response in cancer have been observed in recent years. In this context, immunosuppressive cells, including regulatory T-cells (Tregs) and myelogenous line derived suppressor cells (MDSCs), have been targeted for their proposed functions in suppressing tumor-specific immune responses and in establishing an immunosuppressive tumor microenvironment capable of promoting immune evasion [23].

Several studies have identified subgroups of Treg suppressors in the peripheral blood of cancer patients. However, direct insights into Tregs suppressor roles within the tumor microenvironment (TME) are limited. Treg FoxP3+/- (tumor infiltrating agents), isolated subsets of primary tumors of patients with colorectal cancer (CRC) exerted a potent suppressive function mediated by TGF-β and IL-10, as well as up-regulated CTLA-4 (CD152) and ICOS (CD278) [24]. Cytokines present in the tumor microenvironment can act as trophic factors on tumor cells, thus inducing growth and progression, either by inducing angiogenesis or by chemotaxis of inflammatory and stromal cells into the tumor bed, maintaining a nourished environment and accelerating its growth progression [25]. In contrast to the inflammatory repertoire, tumor growth is induced by the production of cytokines such as IL-6, IL-1, TNF-a, and pro-angiogenic molecules such as VEGF, PIGF, TGF-b, among others.

Numerous strategies to avoid recognition and destruction by the immune system are adopted by several types of cancer. In this context, we can speculate that tumor cells may evolve strategies to avoid blockage of the production of important cytokines in tumor progression events. Once the "dialogue" between malignant cells and their tumor microenvironment is established, cancer seeks to achieve a cooperative interaction. By positively regulating the cytotoxic T lymphocytes associated with antigen-4 (CTLA-4), and the programmed cell death protein 1 (PD1), tumor cells are shown to be effective in blocking anti-tumor immune responses. The expression by tumor cells of inhibitors of programmed cell death (PD)-L1/B7H1 was observed to cause deletion or anergy in reactive tumor cells [26]. Therefore, the immunosuppressive function of the PD-1/PD-L1 immune checkpoint pathway has been shown to be a promising oncological target in a variety of cancers.

A recent study by Kataoka [27] the role of the genetic mechanism resulting from structural variations which commonly affects the 3' region of the *PD-L1* gene, has been uncovered, resulting in the immune escape. Disruption of Pd-11β-UTR in mice allowed immune evasion of tumor cells with high PD-L1 expression *in vivo,* which is effectively inhibited by PD-1/PD-L1 blockade. Therefore, it is suggested that PD-L1 3'-UTR cleavage may serve as a genetic marker to identify cancers that actively cheat antitumor immunity through overexpression of PD-L1.

It is not surprising that there is a wide range of effector mechanisms used by cancer to escape the antitumor components of the immune system. Antigenic masking is an example whereby tumor cells "cheat" the immune system by deposition of sialic acid, aberrantly expressed by tumor cells [28].

The advances in glycobiology and immunology, a gradual process in the research on sialic acid has brought strong evidence about its action on immune escape. Such a biomolecule, when present excessively in the tumor microenvironment, acts a) by preventing physical interaction with receptors and immune ligands on the surface of tumor cells, including antigens; b) disguising them as self (own); c) deactivating the main mechanisms of death of the immune system; d) and positively modulating the functions of local immune cells and systemically forming the ligands for immunosuppressive receptors [29].

Sialic acid has been shown to promote Treg expression exemplified in murine melanoma (B16) cancer model. Isogenic B16 cell lines with high or low expression of sialic acids were generated by removal of the SLC35A1 sialic acid transporter. The growth of B16 tumors, observed *in vivo*, showed delay due to the low levels of sialic acid induced by the absence of its transporter. In contrast, tumor growth was significant because of the high levels of sialic acid provided by its transporter. An important observation was that in tumors with low levels of sialic acid more effector T cells and a decreased number of regulatory T cells were detected at the tumor site [30]. Factors that promote tolerance and immune shunting are significant contributors to immune avoidance during tumorigenesis.

CD4+ T cells in immunotherapy

CD4+ T cells play a central role in the immunotherapy. These cells are crucial for the activation and regulatory process of the host defense against infections and for adequate functions of the cytotoxic CD8+. The role difference between CD4+ T cells and CD8+ cytotoxic cells been on the recognize antigens, respectively, in MHC class II and MHC class I.

CD4+ T cells need an effector for the consolidation of your immunologic potential against the tumor progression. Once effected, there an induction of delayed-type hypersensitivity-like reactions and an attraction of inflammatory cells (macrophages, granulocytes, eosinophil, and NK cells) in or around the tumor [31]. As helpers, they provide cytokines and stimulation for the differentiation of the CD8+ populations, augmenting the priming, persistence, and cytotoxic effectors [32].

The potential use for this knowledge for the clinical trials as well established in recent years. The potential to cure metastatic solid tumors by manipulating T-cells responses was established in humans by IL-2 treatment for metastatic melanoma and renal cell carcinoma, using the infusion of tumor-specific T-cells; one promising strategy call tumor-infiltrating lymphocytes (TILs), once the T cells grown from resected metastatic tumor deposits, has resulted in high response rates, reproducible and durable responses in metastatic melanomas [33].

Strategies used by these clinical trials depend directly on the CD4+ CD25+FoxP3+ T Regulatory Cells on synergy with IL-2-critical for the establishment and maintenance of immunological tolerance to Self-Antigens. Elpek [34] reported the use of inducible costimulatory receptor 4-1BB in response to IL-2 via novel form of ligand (4-IBBL) was effective in expanding the Treg cells population *ex vivo*, and with cooperation with expanded cells up-regulation CD25 and membranous TGF-β, suppressed T cell proliferation and prevented the rejection of allogeneic islets upon adoptive transfer. This revel as an important mechanism to homeostasis following antigenic challenge, as reported for the researches.

Another hand, another strategy, Pallandre reported the foxp3 transference in murine CD4+CD25- T lymphocytes, resulting in the acquisition of suppressive function. To understand this mechanism, the researchers showed that CD28 activation in CD+CD25- T lymphocytes lead to STAT3 Tyr705 phosphorylation, demonstrated neutralization during naïve peripheral conversion into Treg through costimulation with TCR\CD28 and TGF-β, decreasing FoxP3 expression, prevented acquisition of suppressive functions and restore the ability of the converted lymphocytes to produce IL-2 and IFN-γ. Differences between the murine CD4+CD25+ was observed, especially in suppressive functions, obtaining a failed control to an occurrence of acute graft-vs-host disease. In a TIL, was demonstrated the critical importance of STAT3 in the molecular pathway for FOXP3 expression.

Sun [35] observed the CD4+CD25+FoxP3+ T cells in the draining LN lymphocytes and reported the high level showed a strong inhibitory effect on the proliferation of CD4+CD25- T cells and the production of IFN-γ by CD4+CD25- T cells, demonstrating a potential mechanism for the inflammatory occurrence. Pallandre defended that STAT3 – influence on the suppressive functions of CD4+CD25+ T cells – activation is associated to T cells-tolerance induced by repetitive Ag stimulation, offering an opportunity to develop target therapies to reverse established tolerance.

Immunotherapy in the context of cancer

Immunotherapy has emerged recently in the cancer context through the holistic understanding of the function of the immune system to inhibit or supporting tumor progression, resulting in the development of several therapeutic approaches against cancer, some tested in preclinical animal models and in contexts clinical [36]. Among them, the most successful protocols are: 1) immunological checkpoint inhibitors based on the use of monoclonal antibodies; 2) adoptive cell therapy; and 2) immunomodulation via cytokines.

The role of immunotherapy is to stimulate and enhance host immune responses against tumor cells and, at the same time, inhibit polarized immune elements in promoting tumorigenesis. A relevant fact is that without been observed failures during clinical intervention based on conventional therapies, such as chemotherapy, because the high toxicity ultimately affects also healthy cells of the host, in addition to the plasticity of the cells within the tumor microenvironment.

The use of monoclonal antibodies (mAbs) in anti-cancer therapy has shown promise, once administered to the patient, selectively and efficiently, targets a particular protein involved in some way with tumor proliferation. Antibodies are also being used to increase the strength of the immune response.

In 1996, Leach, Krummel and Allison mAbs [37] demonstrated that CTLA-4 blockers to inhibit tumor progression in animal models. The CTLA-4 and PD-1 pathways are critical for the regulation of the immune response, acting as an immunological checkpoint whose primary function is to prevent the autoimmune response by activating routes that aim to "brake" the immune response [38]. The mAbs that have been approved for clinical use target PD-1, PD-L1 or CTLA-4, which block T-cell "brakes", with the consequent increase in the immune response against tumor cells.

The activated T cells and tumor cells expressing the CTLA-4 receptor as an immunosuppressive mechanism to acquire protection against autoimmunity; and avoid elimination [39]. The antagonism of these receptors showed antitumor benefit. For example, Ipilimumab and Tremelimumab are mAbs that block the binding of CTLA-4, allowing the persistent activation of T cells [40].

Discussion

In a physiological context, the PD1 is expressed on activated T and B cells and, when bound to PD-L1, it becomes disabled, inhibiting signaling pathways that normally lead to the effector response of cytotoxic T lymphocytes [41]. Tumor cells tend to overexpress PD1 (PD-L1/2) linkers, allowing them to deactivate this response. In the scenario represented by the PD-1 pathway, current immune therapies are based on the use of anti-PD-1, such as Nivolumab and Pembrolizumab, whose clinical efficacy has already been demonstrated in the fight against melanoma and other tumors [42] they bind to PD-1 blocking binding of PD-L1 (and -2) and resulting in the cytotoxic activity of CD8 + T lymphocytes and therefore, the restoration and augmentation of the immune response antitumor [43].

The adoptive cell therapy (ACT) is a type of immunotherapy aims to induce tumor regression from the antitumor activity of autologous T cells, preferably TILs whose populations are usually mixtures of CD4 + and CD8 + lymphocytes [44], which are subsequently harvested, manipulated, expanded *in vitro* and transferred to the host [45]. In addition, the goal of *in vitro* expansion and alteration is to release T cells from the influence of tumor immunosuppressive mechanisms, increasing their numbers and inducing a more efficient antitumor response [46]. The use of modified T lymphocytes expressing the T cell receptor (TCR) or the chimeric antigen receptor (CAR) against targets such as MART-1 and gp100 is shown to be very promising in melanoma therapy [44].

The oncolytic viruses are an emerging class of therapy for cancer which relies on the use of genetically modified viruses do not show virulence against normal cells, but with efficiency and lyse tumor cells invade. The lysis of tumor cells, due to viral action, induces the release of tumor-specific antigens that are capable of inducing a new attack by an immune system [47]. Recent studies have reported therapeutic benefits in the application of oncolytic virus approved by the FDA in 2015 to treat advanced melanoma. It is a simplex-1 herpes virus (HSV-1) called "T-VEC", modified to express the stimulating factor granulocyte-macrophage colonies (GM-CSF) that widely induces the proliferation of immune cells [48].

Another immunotherapeutic forward approach to cancer is based on the use cytokine, messenger molecules produced by immune cells which have autocrine roles and paracrine, so that work by increasing or suppressing innate and adaptive immune responses [49], and such features explored in cancer therapy. Thus, the application of interleukin-2 (IL-2) was one of the first treatment within the immunotherapy approved for use against cancer and, together with interferon alpha (IFN-α), consist of administered cytokines treatment options for against melanoma and renal cell carcinoma [50-55].

Conclusion and Final Considerations

In view of the complexity of the interactions between the immune system and cancer, understanding the forms of tumor recognition, antitumor responses and their evasion mechanisms becomes essential for understanding the dynamics of this pathology, as well as providing conditions to develop therapeutic strategies based on in this interaction. Many tumors are responsive to conventional cytotoxic therapies but are well controlled by immunomodulatory drugs. This fact underscores the importance of scientific research in the field of cancer immunology, whose objective is to elucidate the main relationships between immunological cells and tumor cells, enabling the synthesis of new drugs and, consequently, improving the quality of life of patients with cancer.

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