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The immune system and its never-ending battle against tumor cells: recognition, elimination, and evasion of the immune response

El sistema inmune y su interminable batalla contra las células tumorales: reconocimiento, eliminación y evasión de la respuesta inmune

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ABSTRACT

Cancer is one of the main causes of death in the world; for this reason, current research focuses on evaluating the mechanisms involved in the development of this disease. Over the years, it has been shown that the immune response (both innate and adaptive) plays a fundamental role in identifying and eliminating tumor cells. However, tumors can evade immune recognition and continue proliferating. In this review, we explain current aspects of the mechanisms used by the immune system to eliminate tumor cells; we also provide a review of the mechanisms mediated by the tumor to evade the immune response.

KEY WORDS: Immune response, cancer, innate immunity, adaptive immunity, evasion mechanisms.

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RESUMEN

El cáncer es una de las principales causas de muerte en el mundo, por ello las investigaciones actuales se centran en evaluar los mecanismos implicados en el desarrollo de esta enfermedad. A lo largo de los años se ha demostrado que la respuesta inmune (tanto innata como adaptativa) juega un papel fundamental en la identificación y eliminación de células tumorales. Sin embargo, los tumores pueden evadir el reconocimiento inmunológico y seguir proliferando. En esta revisión explicamos aspectos actuales sobre los mecanismos usados por el sistema inmune en humanos para eliminar las células tumorales, también hacemos una revisión de los mecanismos mediados por parte del tumor para evadir la respuesta inmune.

PALABRAS CLAVE: Respuesta inmune, cáncer, inmunidad innata, inmunidad adaptativa, mecanismos de evasión.

Introduction

Cancer is one of the main causes of death in the world. In 2020, ten million people died from this disease (Sung *et al*., 2021). The etiology of cancer is complex and depends on a diversity of factors that include aging, lifestyle habits, and genetic aspects, which together can induce permanent (but not lethal) errors in the DNA (Deoxyribonucleic Acid) of the cell, initiating the process of tumor transformation (Wu *et al*., 2016). Tumor cells acquire diverse biological capabilities that help evade cell cycle regulation and allow them to continue proliferating. These capabilities include proliferative signaling, evasion of growth suppressor genes, resistance to cell death, replicative immortality, angiogenesis induction, invasion, metastasis, reprogramming of cellular metabolism, and evasion of destruction by the immune response (Hanahan, 2022).

Tumors are more than masses of transformed cells; they are also composed of other cellular components, including the infiltration of immune cells, that eliminate transformed cells to prevent cancer development (Burnet, 1964). However, tumors have acquired the ability to evade the immune response since they reduce the expression of tumor antigens and MHC (Main Histocompatibility Complex) molecules. Tumors also secrete cytokines that suppress the function of immune cells (Dunn *et al*., 2004[a]; Dunn *et al*., 2004[b]). In this article, we explain current aspects of the mechanisms of tumor elimination mediated by the immune system. On the other hand, we also review the escape mechanisms that the tumor uses to evade the immune response.

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Carcinogenesis process

Carcinogenesis is the process of malignant cell transformation, in which alterations in the DNA and failures in the signaling pathways that control and regulate cell proliferation are observed. Subsequently, cells continue to proliferate, accumulating more mutations and genetic changes. This allows tumor cells to acquire distinctive capabilities known as the hallmarks of cancer, which were first proposed in 2000 and expanded in 2011 (Hanahan & Weinberg, 2000). These hallmarks include the ability to sustain proliferative signaling, evade growth suppressors, resist cell death, enable replicative immortality, induce angiogenesis, activate invasion and metastasis, metabolic reprogramming, induce inflammation, genomic instability, and evasion of immune destruction. Additional emerging characteristics were recently included: unlocking phenotypic plasticity, and non-mutational epigenetic reprogramming. There are also factors, such as polymorphic variability in the microbiomes of the tumor microenvironment, as well as senescent cells, that can modify the capabilities acquired by tumor cells and impact cancer phenotypes (Hanahan, 2022). The characteristics acquired by transformed cells allow them to detach from the tissue and travel through the bloodstream to a secondary organ, where the tumor cell adheres again and begins to proliferate, generating new blood vessels and allowing cancer cells to spread to other parts of the body. This entire process, known as metastasis, is observed in patients in advanced stages of the disease (Lambert *et al*., 2017).

During cancer development, the damage in a cell caused by genetic aspects and lifestyle is required. Those aspects are considered factors that increase the risk of suffering cancer and are classified as non-modifiable and modifiable (Cogliano *et al*., 2011; Wu *et al*., 2018) Non-modifiable risk factors include mutations that occur spontaneously or are inherited in the genome. Spontaneous mutations arise due to random errors in DNA replication during the cell cycle and are acquired at some point in the life of any person (Tomasetti & Vogelstein, 2015). There are also mutations inherited from the parents that are not modifiable and are associated with the development of inherited cancers, which are rare and represent 5 to 10% of all cancers (Fearon, 1997; Lichtenstein *et al*., 2000; Jahn *et al*., 2022; Garutti *et al*., 2023).

On the other hand, modifiable risk factors are related to lifestyle and the environment (diet, physical activity, toxic compounds, sun exposure, and, infections by microbes or viruses) (Wu *et al*., 2018). Those factors are considered modifiable because a healthy lifestyle can reduce the risk of cancer. For example, exposure to ultraviolet radiation is the main risk factor for the development of skin cancer, since it is considered a carcinogen that induces DNA mutations and suppresses the antitumor immune response (Neale *et al*., 2023). It has been reported that people who experience more than 5 episodes of severe sunburn have a 2 times greater risk of developing melanoma, therefore, avoiding exposure to the sun for long periods and using sun protection can reduce the possibility of suffering from this type of cancer (White & Lee, 1994). Infections caused by oncogenic microbes or viruses have been related to the formation of tumors, an example is the persistent infection by the Human Papillomavirus (mainly by genotypes 16 and 18), which is associated with approximately 95-99.7% of the cases of cervical cancer (Bosch *et al*., 1995; Kusakabe *et al*., 2023).

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Role of the immune system in the development of cancer

Tumors are more than clusters of transformed cells; they are also composed of the extra cellular matrix (chemokines, inflammatory cytokines, integrins, matrix metalloproteinases, and other secreted molecules), stromal cells (endothelial cells and fibroblasts), immune cells and other resident cells of the tissue, which together constitute a complex and dynamic ecosystem known as the tumor microenvironment, in which there is an interaction between all its components (Dvorak, 1986; Clemente *et al*., 1996; Chen *et al*., 2017; Ho *et al*., 2022). Depending on the tumor stage, the organ where it formed, the characteristics of the tumor cells and the patient, the components of the tumor microenvironment, and their functional status may vary (de Visser & Joyce, 2023). Immune cells in the tumor microenvironment can be located differently, which affects the communication with the tumor, for example, there are infiltrated tumors in which immune cells are homogeneously distributed throughout the tumor. In other tumors, the immune components are distributed in the periphery without infiltrating the tumor; these are considered immune-excluded tumors. While so-called immune-silent tumors that lack immune cells can also be observed (Anderson & Simon, 2020). Therefore, the interaction between the immune system and the tumor is complex and can have a dual effect, that is, it can suppress tumor development or promote tumorigenesis (Dunn *et al*., 2002; Schreiber & Smyth, 2011; Anderson & Simon, 2020).

The role of the immune response in cancer has been a focus of research since the 1950s; In 1957, Sir Frank Macfarlane Burnet proposed the concept of “immunovigilance,” which explains the ability of the immune system to recognize and eliminate tumor cells. This theory was refuted and resurfaced several times (Burnet 1970). Subsequently, with technological advances, studies were carried out in murine models that made it possible to demonstrate that an immune response in which there is a lack of cells such as lymphocytes (T cells, B cells, and NK cells) or cytokines (a particular case of Interleukin 12 and Interferon- γ) is associated with the development of spontaneous tumors, induced by chemical or infectious agents such as viruses (Nishizuka *et al*., 1965; Burstein & Law, 1971; Sanford *et al*., 1973; Stutman, 1975; Dighe *et al*., 1994; Kaplan *et al*., 1998; Smyth *et al*., 2000[a]; Smyth *et al*., 2000[b]; Girardi *et al*., 2001; Shankaran *et al*, 2001; Street *et al*., 2002). This hypothesis was later evaluated in humans and it was observed that patients suffering from autoimmune diseases or being treated with immunosuppressive drugs have a higher risk of developing cancer (Knuth *et al*., 1984; van der Bruggen *et al*., 1991; Sahin *et al*., 1995). Currently, part of the new therapies against malignant tumors aim to modulate the immune response to eliminate transformed cells effectively (Korman *et al*., 2006). The most promising therapies include immune checkpoint blockade (examples via PD-1/PD-L1, and CTLA-4), administration of cytokines (IL-2, Interleukin-2 and GM-CSF, Colony-Stimulating Factor of Granulocytes and Macrophages), adoptive TILs (Tumorinfiltrating Lymphocytes), and CAR-Ts (Genetically Engineered T cells expressing specific T cell Receptors, TCRs, or Chimeric Antigen Receptors CARs). (Hamdan & Cerullo, 2023). Selection of the best therapeutic option for a patient depends largely on the clinical stage, tumor type, tumor microenvironment, and the response to conventional treatments (chemotherapy or radiotherapy).

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Recognition and elimination of tumor cells by the immune response

The immune system comprises innate immune cells (macrophages, neutrophils, dendritic cells, NK cells, among others) and adaptive immune cells (T lymphocytes and B lymphocytes). The innate immune system provides rapid defense mechanisms against tumors. In contrast, the adaptive immune system responds later, more specifically, which requires time and leads to the generation of immunological memory. Both types of responses are coordinated and work together to prevent the development of cancer (See Figure 1) (Hellstrom *et al*., 1968; Herberman & Holden, 1978; Boon *et al*.,1995; Anichini *et al*., 1999, Girardi *et al*., 2001; Schlosser *et al*., 2019).

Recognition of Tumor Cells

During the process of malignant transformation, changes occur in the expression of antigens that differentiate tumor cells from healthy cells, inducing the recognition by the immune system (Robbins *et al*., 2013). Different types of antigens can be recognized by immune cells. Molecules such as phosphatidylserines or calreticulins are expressed in the tumor cells and act as pro-phagocytic signals (Feng *et al*., 2015; Vallabhapurapu *et al*., 2015).

All the cells that undergo a stress process can suffer a type of death “called immunological death,” in which the cell death is accompanied by the secretion of molecules called Damage-Associated Molecular Patterns (DAMPs). (Galluzzi *et al*., 2020). These molecules can activate the immune system and function as warning molecules for the innate immune cells. DAMPs are identified by PRRs (Pattern Recognition Receptors) expressed in cells such as macrophages, neutrophils, and dendritic cells (Matzinger, 1994; Bluwstein *et al*., 2013; Gong *et al*., 2020).

Tumor cells exhibit high expression of heat shock proteins that can be captured by dendritic cells, processed, and presented to CD8 T cells. An example is the heat shock protein Hsp70 (Tumor-derived Heat Shock Protein (HSP)70) (Noessner *et al*., 2002). On the other hand, it has been reported that HSP70 also mediates the NK cells activation and promotes cytotoxicity *in vitro* (Gross *et al*., 2008).

Due to the number of mutations in the genome of tumor cells, the expression of proteins with a low expression in healthy cells increases. An example is the protein NY-ESO-1 (New York Esophageal Squamous Cell Carcinoma 1) expressed in germ or placental cells, and overexpressed in several types of cancer (melanoma, sarcoma, and some types of lung cancer, breast, ovary, among others) (Jungbluth *et al*., 2001; Satie *et al*., 2002; Woloszynska-Read *et al*., 2008, Thomas *et al*., 2018). Tumor cells also produce new incomplete, non-functional, or defective proteins that are identified by the immune system, these are known as neoantigens and are produced by tumor cells due to genomic mutations, aberrant transcriptomic variants, and post-translational modifications (Yarchoan *et al*., 2017; Smith *et al*., 2019). Neoantigens are widely studied in the design of personalized vaccines (peptide, nucleic acid, and dendritic cell vaccines). The most immunogenic neoantigens are used as targets in adoptive cell therapies that use autologous TILs (Tumor-Infiltrating Lymphocytes) expanded *in vitro* without genetic modifications and genetically

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modified immune cells TCRs (T-Cell Receptor) or CARs (Chimeric Antigen Receptor) (Liu *et al*., 2019; Yamamoto & Restifo, 2019; Paijens *et al*., 2021). Finally, therapies based on antibodies against neoantigens have also been developed for various purposes. For example, antibodies conjugated with drugs directed against a neoantigen are more effective when administered to the tumor site.

Phagocytic cells

Phagocytic cells (monocyte/macrophage, dendritic cell, neutrophil, mast cell, and B cells) are responsible for capturing apoptotic cells and degrading them (Feng *et al*., 2019). For example, macrophages recognize DAMPs in apoptotic transformed cells and engulf them, thus eliminating tumor cell debris. Tumor-Associated Macrophages (TAMs) are composed of two main populations with distinct phenotypes: M1 (classically activated macrophages) and M2 (alternatively activated macrophages) (Mills *et al*., 2000). The polarization to each subtype depends on different stimuli (Shapouri-Moghaddam *et al*., 2018) Stimulation with IFN-γ and/or bacterial lipopolysaccharides drives macrophage polarization to an M1, which has a pro-inflammatory and anti-tumor role due to the high expression of MHC molecules (which increase the presentation of tumor antigens), nitric oxide, reactive oxygen, and nitrogen species. Furthermore, M1 macrophages secrete a great diversity of cytokines such as TNF-α, IL-1α, IL-1β, IL-6, IL-12, IL-18, and IL-23, which modulate the immune response against the tumor (Duan & Luo, 2021). On the other hand, polarization to an M2 (anti-inflammatory) is associated with cytokines such as IL-4 and IL-13, in addition, it participates in tissue remodeling regeneration, and wound healing through the production of arginase/ornithine, EGF, VEGF, and TGF-β. In cancer, M2 promotes tumor growth by downregulating the immune response (Mantovani *et al*., 2013; Mills & Ley, 2014; Duan & Luo, 2021). TAMs are mostly macrophages of the M2 type, for this reason the presence of these cells is associated with tumor progression, poor prognosis, and resistance to immunotherapy (Gao & Wang, 2022).

Another type of phagocytic cell are dendritic cells, which mainly capture tumor antigens, phagocytose them, degrade them, and assemble them into MHC molecules. These cells then travel to the lymph nodes that drain the tumor and present the antigens on the MHC molecules to CD4 T cells (known as helpers for their function in coordinating immune responses) and CD8 T cells (with cytotoxic functions that help destroy tumor cells). This process of antigen presentation allows the activation of T cells and the expansion of clones of antigen-specific CD4 or CD8 T cells (Nussenzweig *et al*., 1980; Albert & Bhardwaj, 1998; Steinman, 2012). Dendritic cells can be classified as conventional or classical (cDC) and plasmacytoid (pDC). The cDCs are also classified into cDC1 and cDC2 (Del Prete *et al*., 2023). cDC1 mainly specializes in the processing and cross-presenting of antigens derived from necrotic and apoptotic tumor cells associated with MHC I molecules to CD8 T cells (See *et al*., 2017). There is a correlation between the proportion of cDC1 in the tumor with survival and response to treatment in cancer patients. Regarding cDC2, these cells present antigens associated with MHC II molecules to CD4 T cells to promote the polarization of T helper cells to a Th1, Th2, and Th17 profile, with different functions in cancer (Plesca *et al*., 2022). A higher frequency of cDC2s correlates with higher CD4 T cell infiltration in melanoma (Binnewies *et al*., 2019). Regarding plasmacytoid dendritic cells, they are the main producers of type I interferons (IFN), cytokines that play an important role in cancer by modulating

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the immune response to eliminate tumor cells (Reizis, 2019). Furthermore, pDCs contribute to the presentation of antigens to CD4 T cells via MHC II molecules (Siegal *et al*., 1999).

Neutrophils are a population of phagocytic cells that represent an important part of the immune cells in the tumor microenvironment of various types of cancer, including colorectal cancer, cervical cancer, and non-small cell lung cancer, among others (Rao *et al*., 2012; Carus *et al*., 2013; Rakaee *et al*., 2016). It is reported that the production of Granulocyte Colony-Stimulating Factor (G-CSF) by tumor cells favors the release of neutrophils into the circulation, increasing their proportions in the blood (Jablonska *et al*., 2017; Furumaya *et al*., 2020). Furthermore, tumor cells can secrete IL-8 and attract neutrophils and other myeloid cells to the tumor microenvironment (Gonzalez-Aparicio & Alfaro, 2020). Tumor-Associated neutrophils can induce direct cytotoxicity and inhibition of metastasis; however, they represent a heterogeneous population of cells that may have both anti- and pro-tumor roles in cancer (Shaul & Fridlende, 2019). In murine models, neutrophils are classified as antitumor neutrophils (N1) or tumor-promoting neutrophils (N2) (Fridlender *et al*., 2009). Three populations of neutrophils classified according to their densities after isolation by centrifugation have been identified in the peripheral blood of cancer patients: High-Density mature neutrophils (HDN), Low-Density mature neutrophils (mature LDN) and Low-Density immature neutrophils (immature LDN) (Sagiv *et al*., 2015; Shaul & Fridlender, 2019). HDNs have an antitumor effect similar to N1, while mature LDNs or immature LDNs have a protumor effect (Sagiv *et al*., 2015). Mast cells are another population of cells that have recently been studied in the context of cancer because of their dual role (pro-tumor or anti-tumor) depending on the type of tumor and location in the tumor microenvironment (Varricchi *et al*., 2017). For example, it has been observed that they have a pro-tumoral role in different types of cancer like gastric, thyroid, pancreatic, bladder, Merkel cell carcinoma, Hodgkin, and non-Hodgkin lymphoma. Mast cells can even be associated with poor prognosis (Agata *et al*., 1996; Yano *et al*; 1999; Beer *et al*., 2008; Melillo *et al*., 2010; Rabenhorst *et al*., 2012; Andersen *et al*., 2016; Rao *et al*., 2016). On the contrary, in breast cancer, mast cells have antitumor functions (Dabiri *et al*., 2004). The antitumor activity of mast cells is mediated by the release of ROS and TNF-α, which have a cytotoxic effect, and the release of heparin and IL-9, which inhibit tumor growth. Furthermore, histamine release contributes to the maturation of dendritic cells (Varricchi *et al*., 2017).

B cells and the role of antibodies in cancer

B lymphocytes are important in cancer as they are antigen-presenting cells to CD4 T cells and antibody-producing cells (Chen & Jensen 2008; DiLillo *et al*., 2010). For a B cell to be activated, it must first recognize the tumor antigen through its BCR; this antigen is then processed and presented to CD4 T cells. This interaction provides the costimulatory signals necessary to complete B cell activation that allows their clonal expansion, generating a population of identical B cells with specificity for the same antigen and capable of producing antibodies. Some activated B cells differentiate into plasma cells, the main producers of antibodies (LeBien & Tedder, 2008).

Antibodies are soluble molecules that recognize and bind to an antigen through a highly specific and complementary chemical interaction between the antigen-binding site molecules (present on the antibody) and the chemical structure of the antigen.

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The functions of antibodies in cancer are diverse. By binding to tumor cells, they allow macrophages and dendritic cells to capture tumor antigens since they induce phagocytosis (Anderson *et al*., 1990; Ravetch & Bolland, 2001; Tan & Long, 2022). They also promote antibody-dependent cellular cytotoxicity (ADCC), a process in which cytotoxic cells such as NK cells (Natural Killer cells) recognize antibodies bound to the tumor, leading to the release of molecules that induce tumor cell death (Titus *et al*., 1987; Sondel & Hank, 2001; Bruhns, 2012).

Antibodies bound to tumor cells also promote the recognition by the complement system, a group of proteins that form a complex attack on the membrane of tumor cells that leads to cell lysis and destruction (Kolev *et al*., 2022). However, the function of antibodies is not always beneficial in cancer since antibodies can bind to various soluble antigens released by tumor cells, which favors the formation of circulating immune complexes that have negative implications (Gunderson & Coussens, 2013; Tan & Long, 2022). In a murine model of squamous cell carcinoma, the accumulation of immune complexes in the stroma of the tumor tissue increases the recruitment of protumoral myeloid cells (Andreu *et al*., 2010).

Cytotoxic lymphocytes and CD4 T cells

In the immune system, we can find two types of cytotoxic cells: Natural Killer (NK) cells and CD8 T cells (counterpart of the adaptive immunity) (West *et al*., 1977). Both cells destroy transformed cells through the secretion of granules with granzymes and perforins, which induce the death of the target cell (Sykulev *et al*., 1996; Barry & Bleackley, 2002).

NK cells belong to the group of innate lymphoid cells and are characterized by the expression of the transcription factor Eomesodermin (EOMES) (Cherrier *et al*., 2018). Unlike CD8 T cells that express antigen-specific clonotypic receptors, NK cells are equipped with an arsenal of germline-encoded activating or inhibitory receptors, which recognize their cognate ligands on healthy, infected, and transformed cells (Karre, 1997; Diefenbach & Raulet, 1999; Bryceson *et al*., 2006; Lanier, 2008). Tumor cells can express molecules recognized by activating receptors, such as MICA (activating ligand for the NKG2D receptor) overexpressed on cells in stress situations. The recognition of MICA by NKGD induces the activation in the NK cell and the secretion of cytotoxic granules. NK cells are also activated in the absence of MHC I molecules (a common mechanism developed by tumors to evade the recognition by CD8 T cells) (Karre, 1997). A great diversity of activation receptors is expressed by the NK cells; among the most studied are the NCRs family members(Natural Cytotoxicity Receptors, such as NKp30, NKp44, and NKp46) and the members of the NKG2 family (NKG2C and NKG2D). The main inhibitory receptors include members of the KIR (Killer Immunoglobulin-like Receptors) family and NKG2A (NKG2 family member) (Nersesian *et al*., 2023). The expression and co-expression of the various receptors are associated with NK cell populations with a different maturation status and functions. In cancer, Tumor-Infiltrating NK cells are associated with a good disease prognosis. Therefore, the modulation of the response mediated by NK cells is an important therapeutic target in cancer. The main strategies include the induction of NK cell activation by administering monoclonal antibodies to increase ADCC, BiKEs (Bispecific Killer Cell Engager), *ex vivo* expanded NK cells, and CAR-NK (Liu *et al*., 2020; Dixon *et al*., 2021).

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Regarding CD8 T cells, they recognize specific tumor antigens presented on MHC I molecules. This presentation occurs in the lymph nodes close to the tumor, and to complete the activation, other costimulatory signals (CD28 or NKG2D) and cytokines produced by the dendritic cell are required. This process induces the proliferation, clonal expansion, and differentiation of naïve CD8 T cells into effector cells, where subsequently, CD8 T cell clones migrate to the tumor microenvironment, recognize the antigen on the tumor cells, and release their cytotoxic granules to eliminate tumor cells. CD8 T cells also produce cytokines such as IFN-γ and TNF-α (Koh *et al*., 2023).

Other cells have cytotoxic functions in cancer; for example, the antitumor function of CD4 T cells depends on their ability to directly activate CD8 T cells and the activation of macrophages and NK cells. On the other hand, a population of cytotoxic CD4 T cells capable of secreting granzymes in a similar way to CD8 T cells is observed in cancer. Another example is the case of B lymphocytes that can directly attack tumor cells using granzyme B and the TRAIL ligand (TNF Related Apoptosis-Inducing Ligand) that will induce tumor cell death by interacting with its cognate molecule (Van-Leeuwen *et al*., 2004; Quezada *et al*., 2010; Janjic *et al*., 2022). Other cells with a cytotoxic function in the tumor microenvironment are macrophages that release reactive oxygen species and reactive nitrogen species that contribute to the destruction of cancer cells.

Mechanisms of evasion of the immune response in cancer

Although the immune system can eliminate tumor cells, it can also edit the tumor by eliminating the most immunogenic clones. Therefore, the less immunogenic tumor cells proliferate without control (Schreiber & Smyth, 2011). This idea is the basis of the cancer immunoediting hypothesis, which consists of three distinct phases: elimination, equilibrium, and escape (Dunn *et al*.; 2002; Dunn *et al*., 2004a; Dunn *et al*., 2004b; Vesely *et al*., 2011). The elimination phase includes the stage in which the immune system eliminates the most immunogenic tumor cells, through the mechanisms described in the previous sections. In the equilibrium phase, the cell variants that survived the elimination by the immune system move to this stage, where adaptive immune cells control the growth of tumor cells and maintain them in a functional state of latency for decades (Aguirre-Ghiso, 2007). While in the escape phase, tumor cells that evaded the elimination phase, because they acquired mechanisms to evade the immune response, begin to proliferate rapidly, forming detectable tumors and advanced stages of the disease (Smyth *et al*., 2006).

A mechanism used by tumors to evade the immune response is the loss of the expression of tumor antigens, which prevents tumor cells from being identified by the immune system. For example, tumors reduce the expression of MHC I molecules, avoiding detection by T cells (as previously described) (Dhatchinamoorthy *et al*., 2021). They also secrete metalloproteases that cleave the activating ligands for NK cells. A clear example is the proteolytic cleavage of MICA, in this way tumor cells escape the elimination mediated by NK cells (Deng *et al*., 2015; Xing & Ferrari de Andrade, 2020). Some tumors secrete cytokines that suppress the immune system and create an immunosuppressive tumor microenvironment for example IL-10 and TGF-β (Transforming Growth Factor-Beta). One of the functions of IL-10 is downregulating the expression of MHC II molecules in antigen-presenting cells, while TGF-β inhibits the activation of T cells and NK cells (Fischer *et al*., 1992; Lazar-Molnar *et al*., 2000). The immunosuppressive tumor microenvironment

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induces the expansion of regulatory T or B cells (variants of CD4 T cells or B cells with the function of inhibiting the activation of other immune cells and their functions) (Mauri & Bosma, 2012; Togashi *et al*., 2019). Another mechanism of evasion of cancer cells is the expression of molecules such as PD-L1 (present in the tumor) that when interacting with its receptor PD-1 (expressed in B lymphocytes, CD8 T cells, CD4 T cells, NK cells, among others) inhibits the function of immune cells (Agata *et al*., 1996; Liu *et al*., 2021). The constant stimulation with this type of inhibitory molecules, together with a suppressive microenvironment, hypoxia, and the presence of tumor antigens, induces a process in CD8 T cells known as exhaustion, in which T cells begin to gradually lose their functions including their cytotoxic effect (Wherry, 2011).

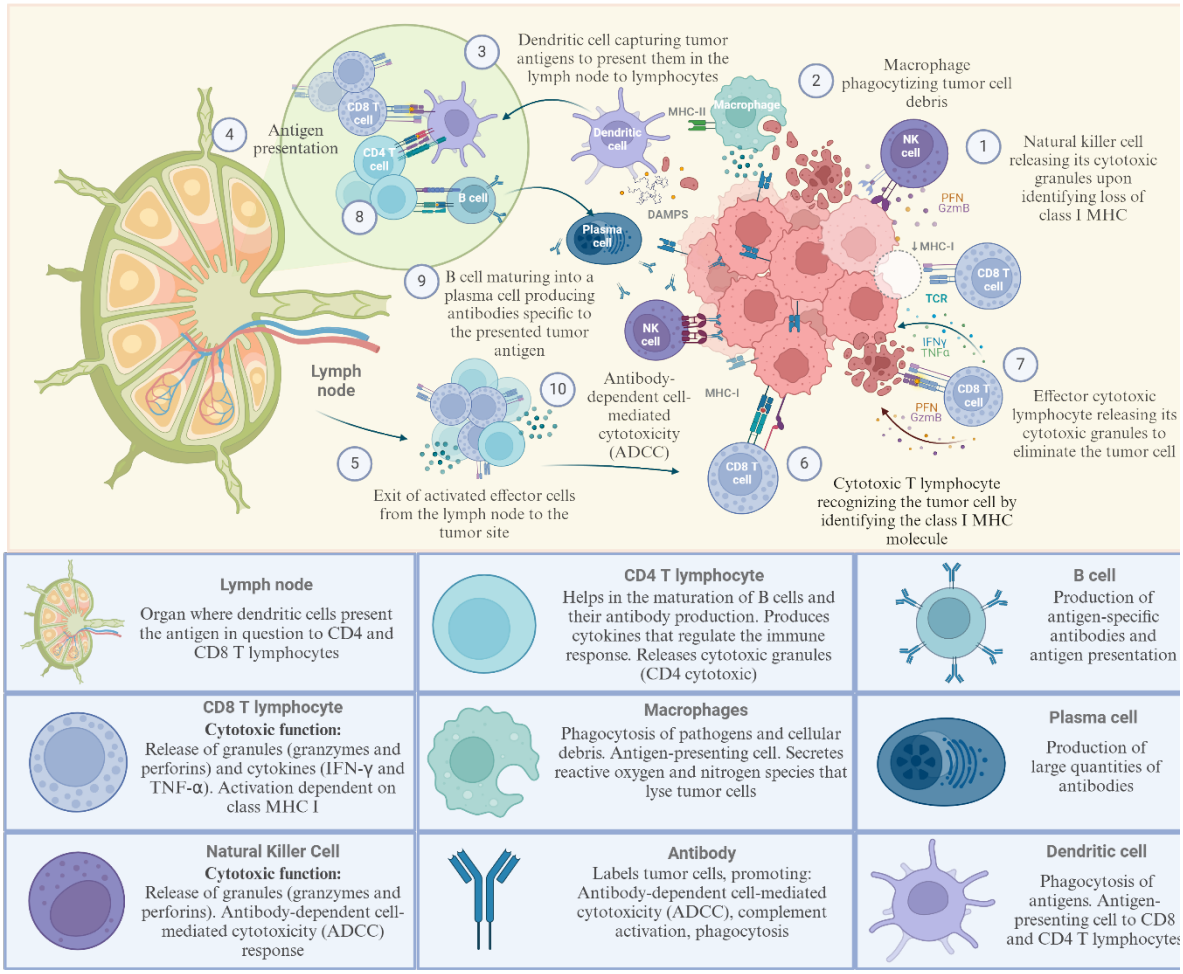

Figure 1. Immune response against cancer.

Different cells and molecules that comprise the immune system, such as macrophages, dendritic cells, NK cells, T cells (CD4 and CD8), and B cells, work together to eliminate tumor cells. Transformed cells express

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molecules called antigens that induce an immune response. (1) Cells of the innate immune system, such as NK cells, release their cytotoxic granules (with granzymes and perforins) upon the recognition of tumor cells. (2) Macrophages identify antigens and phagocytose apoptotic tumor cells and present them in MHC class I and II molecules. (3) Similarly, dendritic cells take up these tumor antigens to present them to CD4 and CD8 T cells in the lymph nodes near the tumor. This process is the union between the innate and adaptive immune systems. (4) Antigen presentation occurs after the TCR recognizes the antigen bound in MHC I or MHC II molecules. (5) This generates the clonal expansion and migration of effector T cells (CD4 or CD8) to the tumor microenvironment. (6) Once in the tumor, CD8 T cells recognize the tumor cell by identifying the MHC I molecule. (7) In this way, the effector lymphocytes are activated and release their cytotoxic granules (with granzymes, perforins) and cytokines (IFN-γ, Interferon-γ, and TNF Tumor Necrosis Factor) to eliminate the tumor cells. (8) B cells identify antigens on tumor cells, phagocytose them, and present them to CD4 T cells. This interaction induces the activation of B cells. (9) Cooperation with CD4 cells helps the maturation of B cells into plasma cells, which produce large amounts of antibodies. (10) Finally, antibodies produced by these cells bind to tumor antigens against which they were generated and allow phagocytosis by phagocytic cells or antibody-mediated cytotoxicity by NK cells.

Image created in Biorender.

Conclusions

The immune system comprises cells and molecules that can prevent cancer development by identifying and destroying tumor cells. However, tumors acquire mutations that induce the secretion of cytokines or expression of immunomodulatory molecules that tumors use in advantage to continue proliferating without being eliminated. Therefore, cancer research has focused on studying the tumor immune evasion mechanisms to understand the interaction between immune cells and transformed cells. This knowledge helps to develop immunotherapies that modify the immune response by reinvigorating or changing the phenotype of immune cells. Together, it helps to have a specific recognition of the tumor cells and a more effective elimination. New research should focus on evaluating changes in the tumor microenvironment regarding the expression profile of inhibition and activation receptors with therapeutic potential and cytokines that allow the activation of cytotoxic cells or polarization to an anti-tumor profile.

Author contribution

Conceptualization of the work: S.I.F., O.L.P.C.; Writing and manuscript preparation: G.A.M.S., S.I.F.; Writing, review, and editing: G.A.M.S., S.I.F., O.L.P.C.; Figure creation and editing: : G.A.M.S., S.I.F., O.L.P.C..

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"The authors declare no conflict of interest".

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