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Review Article

Investigating the Dynamic Interplay Between Cellular Immunity and Tumor Cells in the Fight Against Cancer: An Updated Comprehensive Review

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Abstract

The dynamic interplay between cellular immunity and tumor cells is essential in cancer advancement and response to therapy. This updated, comprehensive review examines the intricate relationship between these components, focusing on the function of different subsets of immune cells in both innate and acquired immunity. A literature search was conducted to identify cytokines involved in tumor cell induction, using keywords such as cytokines, tumor cells, immune cells, and cancer. Relevant articles published between 2003 and 2024 were reviewed, and their data were summarized. The review highlights the different roles of immune cell subsets in coordinating immune responses against tumors. Tumor-associated macrophages (TAMs) And Myeloid-derived suppressor cells (MDSCs) often stimulate cancer growth and evasion of the immune system by suppressing effector cells. Eosinophils and natural killer (NK) cells contribute to tumor surveillance and cytotoxicity, while dendritic cells (DCs) recreate paramount function in T-cell activation and antigen presentation. The complement system and neutrophils contribute to immune regulation and tumor-associated inflammation. T lymphocytes, particularly antigen-presenting cells (APCs) and cytotoxic CD8+ T cells are central to acquired immunity and the anti-tumor immune response. This review highlights how cytokines interact with tumor cells and their role in cancer biology, paving the way for identifying improved prognostic and diagnostic factors. The compiled findings discuss valuable cytokines for a more effective diagnosis of tumors and an accurate prognosis prediction.

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1. INTRODUCTION

Bleeding Cancer is a significant public health concern, responsible for numerous deaths and the emergence of new patients every year. In the United States alone, it is estimated that by 2023, nearly 2 million new cancer cases will be diagnosed, and over 500,000 deaths attributed to the disease (1). For many decades, the treatment options for cancer patients have been limited methods to combat and manage the body's effects, including surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy , targeted therapy, and stem cell transplant, tailored to the individual's type and stage (2). In immunotherapy, cytokines improve the body's immune comeback against cancer cells (3). Tumor necrosis factor, interleukins, and interferons are examples of cytokines crucial to immunotherapy. They stimulate immune cells, like T and NK cells, to better identify and combat cancer cells (4). Interleukin-2 (IL-2) is widely used in cancer treatment, enhancing Natural killer (NK) cells and T cell expansion and activation. Interferons, like interferon-alpha (IFN-α) and interferon-gamma (IFN-γ), modulate the immune response against cancer, inhibiting cell growth and enhancing immune system recognition. Tumor necrosis factor (TNF) is another cytokine that can induce tumor cell death and promote an immune response against cancer cells. Immunotherapy aims to bolster the body's natural defenses and improve the ability to fight cancer by harnessing the power of cytokines. Cytokine-based immunotherapies are being studied and developed as potential treatments for various types of cancer, either as standalone therapies or in combine with other approaches like Chimeric Antigen Receptor T-cells (CAR-T cell) therapy (5-7). Despite promising results, there are still significant challenges to overcome in cytokine-induced sensitivity therapies for cancer. One such challenge is the potential for adverse effects like cytokine release syndrome and inflammation (8). Overcoming these challenges is essential for further developing and optimizing cytokine-induced sensitivity therapies. This review offers a comprehensive and critical analysis of the immune system's function in tumor cell susceptibility, encompassing previous research on modifications in immune system cells and the cytokines responsible for inducing tumor cell susceptibility.

2. INNATE IMMUNITY CELLS

2.1. Macrophage

Tumor-associated macrophages (TAMs) are a central part of the tumor microenvironment (TME) and are known to regulate tumor growth and progression (9, 10). Through their multiple interactions with tumor cells, TAMs significantly affect tumor cells' sensitivity to various therapies. These interactions manifest via a mixture of mechanisms, including facilitating an immune response against tumor cells, phagocytosis of tumor cells, antigen presentation to T-cells to promote an immune reaction, and direct induction of cancer cell apoptosis. These interactions result in the decimation of viable tumor cells and the overall improvement of therapy response. In addition, TAMs can alter TME, which increases the efficacy of cancer therapy by promoting immune cell infiltration, enhancing drug delivery to tumor cells, and changing the extracellular matrix to facilitate treatment (11-13). The growing interest in the potential of macrophages to influence the sensitivity of tumor cells to cancer therapies has made them a focus of research in recent years (14).

TAMs have been identified as crucial players in the TME that can influence cancer cell susceptibility through several mechanisms, including activating an immune response against tumor cells. TAMs produce cytokines and chemokines that recruit and activate immune cells, like NK cells and T-cells. This triggers an immune response that leads to increased tumor cell death and decreased tumor growth (15). In addition, TAMs can also modulate TME to improve the efficacy of cancer therapies. For example, they enable the infiltration of cytotoxic T-cells into TME and improve the response of tumor cells to chemotherapy and immunotherapy (16).

TAMs recreate an essential function in TME and exhibit different activation states, namely M1 and M2. The polarization of TAMs may vary within TME in different cancer types (17, 18). M1 macrophages possess tumor-inhibitory properties and have a proinflammatory phenotype. They secrete various cytokines and chemokines, including tumor necrosis factor-alpha (TNF-α), and IFN-γ, interleukin 1β (IL -1β), which stimulate proinflammatory and antitumor responses against tumor cells and infectious agents. On the other hand, M2 macrophages have immunosuppressive effects and promote tumor progression through metabolic reprogramming. They release interleukin-4 (IL -4), interleukin-13 (IL -13), interleukin-10 (IL -10), fibroblast growth factor (FGF), and matrix metalloproteinase-9 (MMP-9) that contribute to immune defense and tumor growth. These factors also recreate paramount role in angiogenesis and extracellular matrix remodeling, both critical processes in tumor progression (13, 19, 20). FGF and MMP-9 play vital roles in promoting tumor growth and metastasis, with FGF driving angiogenesis and MMP-9 degrading the extracellular matrix

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to enable tumor cell invasion and migration. The interaction between these two molecules is critical for tumor progression, demonstrating the importance of targeting both factors in cancer treatment (13). Colony-stimulating factor-1 (CSF-1) and chemokine (C-C motif)-ligand-2 (CCL2) are molecules that can influence the polarization of TAMs in TME. TAMs have different phenotypes, with M1 macrophages having an anti-tumor effect and M2 macrophages promoting tumor growth. Regulating the activation state of TAMs, CSF-1, and CCL2 may affect the balance between pro- and anti-inflammatory responses in TME. Thus, these molecules represent potential targets for immunotherapy approaches to manipulate TME for enhancing anti-tumor immunity (13, 21).

Scientists found that blocking or knocking out the CSF-1 can reduce the density and polarization of macrophages in TME, leading to the inhibition of metastasis. The possibility of targeting CSF-1 in TME through immunomodulation has attracted considerable interest from researchers and clinicians. This approach could improve the efficacy of current cancer treatments and even open new avenues for therapeutic intervention. However, much remains to be done to unlock the full potential of CSF-1 as an effective weapon in the fight against cancer (22, 23). M2-polarized macrophages are known to stimulate tumor growth and suppress anti-tumor immunity. VEGF-A may also modulate the presentation of cytokines, like IL-10 and IL-4, to further promote the recruitment of M2-polarized macrophages in TME **(Fig. 1).**

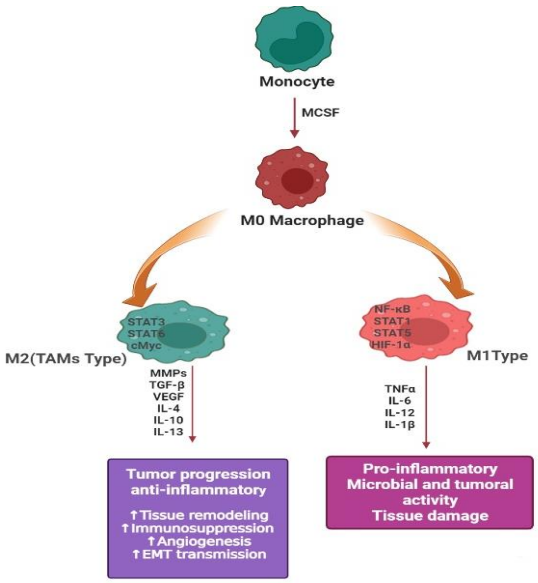

Figure 1. The schematic pattern of macrophage polarization in tumorigenesis. M0 macrophages undergo polarization into the M2 phenotype, promoting VEGF expression, matrix metalloproteinases (MMPs), epithelial-to-mesenchymal transition (EMT), and tissue remodeling.

2.2. Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a multifaceted and complex status of immature myeloid cells that have been shown to recreate a central function in handling immune reactions in TME (24). These cells possess the impressive ability to suppress the activation and function of several immune cells, including T-cells, NK cells, and dendritic cells (DCs), ultimately promoting tumor growth and progression (25). Through their distinct immunomodulatory potential, MDSCs can produce a whole series of reactive oxygen species (ROS) and nitric oxide (NO) that significantly damage immune cells such as T-cells and NK cells, leading to their dysfunction and eventually apoptosis. The interplay between ROS and NO also impedes signaling pathways essential for T-cell activation and expansion effectively suppress the anti-tumor-resistant response (24, 26, 27). Furthermore, these versatile cells are recognized and acknowledged to consume crucial amino acids like arginine and tryptophan, which are critical for T-cell function and proliferation. This marked deficiency in amino acids can profoundly damage T-cell receptor (TCR) signaling, impairing T-cell expansion, differentiation, and cytokine production and culminating in deleterious suppression of anti-tumor immune response (28-30). MDSCs secrete some cytokines, including the enigmatic vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and IL-10, which inhibit immune cell activation. The dualistic nature of IL-10 may impede the maturation and function of DCs necessary for T-cell activation and differentiation. TGF-β can also inhibit activating T-cells and proliferation, leading to the installation of regulatory T-cells (Tregs) and adding another level of suppression to the anti-tumor immune reaction (31, 32). In addition, these MDSCs can promote the proliferation of Tregs, an essential subset of immune cells suppressing the activity of effector T-cells. Tregs can effectively prevent activating T-cells and proliferation, resulting in T-cell apoptosis and further enhancing the suppression of anti-tumor immune reactions (33, 34) **(Fig. 2)**.

Numerous investigations have shown the central function of MDSCs in promoting cancer progression while inhibiting antitumor immunity. These MDSCs are essential mediators in suppressing tumor-specific immune responses through multiple mechanisms. For example, MDSCs in ovarian cancer tissues (OvCA) exhibit abundant expression of CD39 and CD73 ectonucleotidases, which produce immunomodulatory adenosine and inhibit cytotoxic lymphocytes (35, 36). In a study of non-small cell lung cancer (NSCLC) patients, elevated MDSC types were correlated

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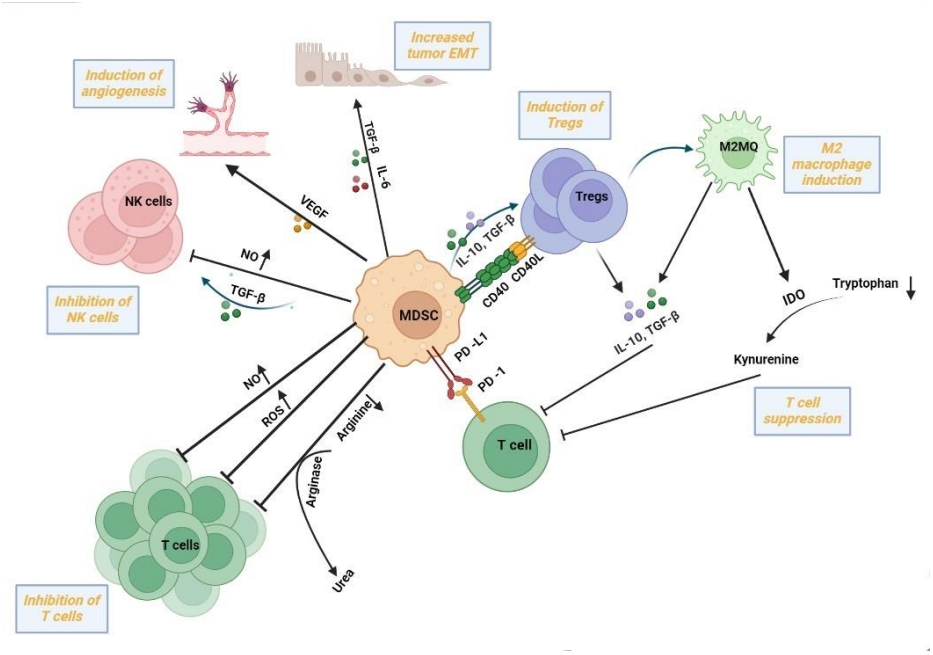

Figure 2. Mechanism of MDSCs in inhibiting the immune system within tumor environment. Myeloid-derived suppressor cells (MDSCs) suppress immune responses by producing arginase, ROS, and NO, which impair T-cell function and deprive essential nutrients. Additionally, MDSCs express immune checkpoint molecules such as PD-L1, which inhibits T-cell function by binding to PD-1. Tregs are also promoted by MDSC-secreted cytokines, further suppressing immune responses. **ROS:** Reactive oxygen species; **NO:** Nitric oxide; **PD -L1:** Programmed cell death ligand 1; **PD -1:** Programmed cell death protein; **Tregs:** Regulatory T cells; **EMT:** Epithelial-mesenchymal transition; **IDO:** Indoleamine 2,3-dioxygenase.

with poorer overall survival (25). In another study in a mouse melanoma model, depletion of MDSCs resulted in enhanced antitumor immunity and survival rate (37). Moreover, research strategies targeting MDSCs have indicated great assurance in preclinical and clinical studies. For instance, all-trans-retinoic acid (ATRA) studies have indicated a significant reduction in MDSC accumulation and improved antitumor immunity in mouse models of breast cancer and melanoma (38, 39). Significant reductions in MDSC levels and improved anti-tumor immune responses were also seen in patients with renal cell carcinoma (RCC) ministered with cabozantinib, which targets MDSC (40).

In addition, MDSCs induce immune evasion and resistance to immunotherapy in cancer patients. These immunosuppressive cells have been shown to promote resistance to checkpoint inhibitor therapy by promoting the manifestation of programmed cell death ligand 1 (PD-L1) on tumor cells, thereby inhibiting T-cell activation (41). Moreover, targeting MDSCs has shown great potential as an impressive strategy for cancer immunotherapy. Preclinical studies have revealed that inhibiting or depleting MDSC function can significantly improve the immune comeback against tumors and enhance the efficacy of immunotherapy in cancer patients (34, 42, 43). Consequently, understanding how MDSCs suppress antitumor immune responses is critical for developing effective immunotherapeutic strategies for treating cancer (44).

2.3. Natural Killer Cells

The human body's NK cells have several mechanisms to recognize and eliminate tumor cells, including recognizing stress-induced molecules such as MICA and MICB on the surface of cancer cells and other tumor-specific antigens (45). Moreover, NK cells use antibody-dependent cellular cytotoxicity (ADCC) to attack tumor cells by recognizing cancer cells coated with antibodies. Interestingly, NK cells can recognize and eliminate malignant cells without prior sensitization, making them a crucial component of the body's immune response (46-48). Cytokines are signaling molecules that can activate NK cells and enhance the antitumor immune response. IFN-γ, and IL-18, IL-12, IL-15, IL-2 are cytokines showing antitumor activity in preclinical models and clinical trials (49, 50).

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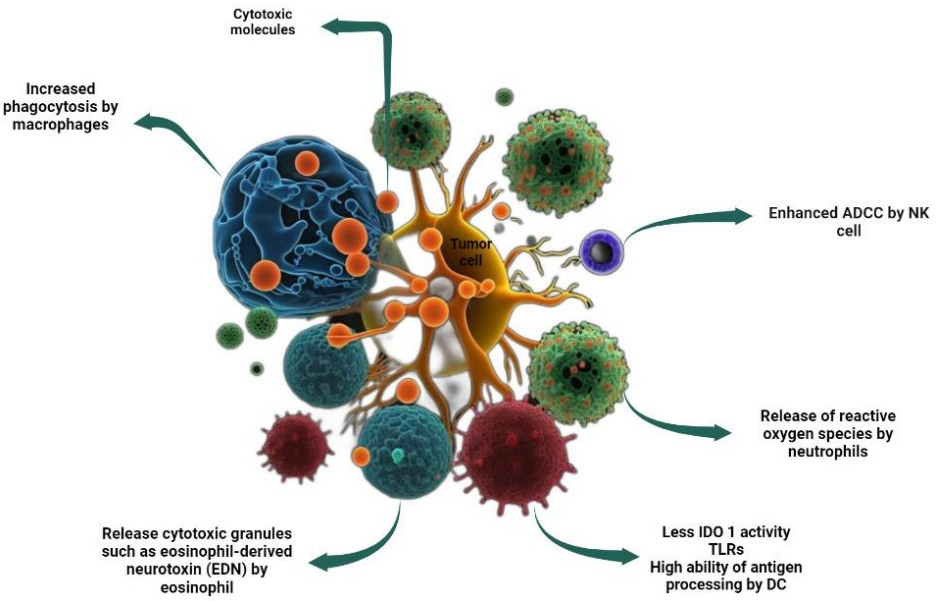

Figure 3. Innate Immune system components in tumor cells. Tumor cell susceptibility is influenced by the innate immune system. The process is mediated by macrophages, natural killer cells, dendritic cells, eosinophils, and neutrophils. Macrophages phagocytose tumor antigens, stimulating an immune response. Cytotoxic molecules released by natural killer cells kill tumor cells directly. The dendritic cells present tumor antigens to the T cells, activating them against the tumor. The eosinophils are also cytotoxic against tumor cells. Neutrophils release reactive oxygen species and other cytotoxic molecules, destroying tumor cells. Innate immune systems play a key role in sensitizing tumor cells and triggering an immune response.

Cytokines like TNF-α and IFN-γ can prompt the upregulation of death receptors like Fas and tumor cells via secretion of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on the surface of tumor cells. This upregulation then triggers the activation of apoptosis pathways, ultimately eradicating malignant cells (51, 52).

The evasion of cancer cells from NK cell-mediated lysis is a complex process. While NK cells comprise activating receptors like NK group 2D (NKG2D) and DNAX Accessory Molecule 1 (DNAM-1), inhibitory receptors expressed in NK cells are CD94/NK group 2A (NKG2A) and killer immunoglobulin-like receptors (KIRs) (53-56). However, tumor cells also employ sophisticated strategies to dodge NK cell-mediated lysis, such as displaying nonclassical human leukocyte antigen (HLA)-G molecules on their surface (57).

NK cells are multifaceted immune cells pivotal in orchestrating a proper immune retort against cancer (58). Moreover, due to their capacity to destroy cancer cells directly, NK cells also influence the activity of other immune cells, such as DCs and T-cells, leading to a coordinated attack against cancer (59-62).

The complexity of NK cells' function in tumor immunity underscores their potential application in cancer immunotherapy. By harnessing their ability to sensitize cancer cells to death and enhance anti-tumor immune response, NK cells offer avenues for developing effective anti-cancer therapies (45, 52, 61).

2.4. Eosinophil

There are few and sometimes conflicting examinations on the function of eosinophils in cancer cells. These investigations suggest that eosinophils play a dual part in tumorigenesis, depending on the context and type of cancer. A study has shown that eosinophils can inhibit the growth of certain types of tumors by increasing the sharpness of cancer cells to immune-mediated killing. The researchers found that eosinophils release cytotoxic granules such as eosinophil-derived neurotoxin (EDN), which can induce apoptosis (programmed cell death) in tumor cells. Eosinophils also increase the expression of MHC class I molecules (MHC-I) on the surface of tumor cells, which helps NK cells and T cells identify and destroy tumor cells (63). However, other studies suggest that eosinophils recreate a function in the development of pancreatic cancer. Researchers found that eosinophils in melanoma cancers are linked to poor prognoses (64). Eosinophils were found

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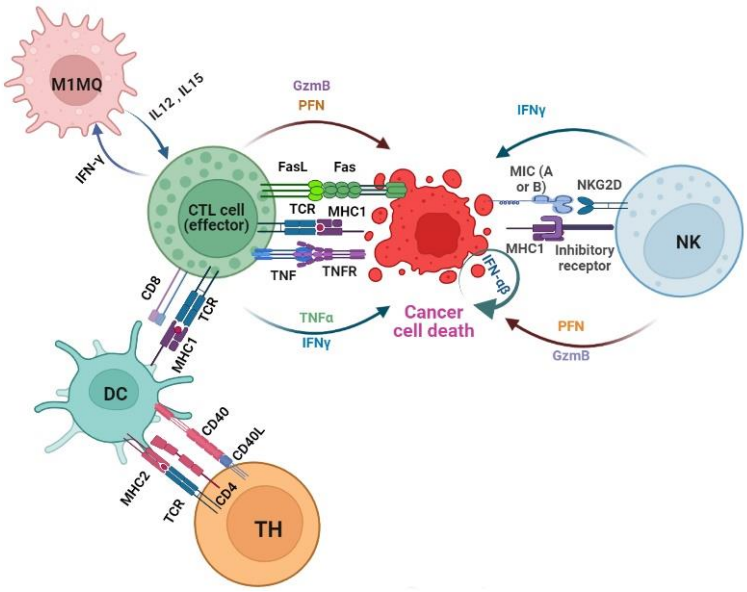

Figure 4. Acquired immune system components in tumor cells. CTLs directly target and kill tumor cells by releasing cytotoxic molecules such as perforin and granzyme. NK cells (natural killer cells) also play a main role in cancer surveillance by identifying and killing cancer cells that have lost their usual cell surface markers or those expressing stress-induced molecules. Similar to CTLs, NK cells kill cancer cells directly by releasing perforin and granzymes. Macrophages also present cancer antigens to CTL cells, triggering a specific immune response. Dendritic cells capture cancer cell antigens, process and present them to CTL cells to trigger an immune response. T helper cells are a type of T-cell that help coordinate the immune response against cancer cells. They release cytokines such as interferon-gamma, which activate other immune cells, including CTL, NK cells, and macrophages, to destroy cancer cells. **PFN:** Perforin; **GzmB;** Granzyme B.

to promote tumor growth by stimulating the construction of new blood vessels (angiogenesis) and inhibiting the activity of T-cells, which are essential for cancer control (65). However, the role of eosinophils needs to be better understood and further investigated.

2.5. Dendritic Cells

DCs are an essential immune system component that plays a critical role in the TME. These cells form a heterogeneous group characterized by a high indication of MHC complexes, adhesion molecules, and costimulatory molecules that enable them to activate and regulate both innate and adaptive immune responses (66, 67).

DCs activate CD8+ T-cells and trigger cytotoxic T lymphocytes (CTLs) response by presenting exogenous antigens on their MHC-I. This process is favored by the uptake of tumor antigens from apoptotic cells (68-70). In addition, DCs also play a decisive role in differentiating naïve T-cells into effector or regulatory T-cells, which could enhance the anti-tumor immune response (71).

DCs can positively and negatively affect tumorigenesis. Research has shown that DCs positively influence anti-tumor immunity by promoting the differentiation of T-cells into effector cells and activating NK cells through the production of cytokines (72). In addition, DCs sensitize tumor cells by increasing the expression of MHC-I molecules on the surface of tumor cells. This increased expression can present tumor antigens to T-cells and increase the susceptibility of tumor cells to recognition and killing by cytotoxic T-cells (73). However, immune tolerance and immunosuppression may also be mediated by DCs' function in the TME. DCs produce immunosuppressive cytokines and express inhibitory molecules such as PD-L1, which repress the activity of T cells (73, 74).

Some immunomodulatory agents can activate DCs, enhancing their ability to present antigens. These agents are referred to as toll-like receptor agonists (TLR). TLR agonists are like a wake-up call for DCs. They stimulate DCs to produce pro-inflammatory cytokines, increase their expression of co-stimulatory molecules, and make them more mobile. In this way, TLR agonists facilitate the migration of DCs to lymph nodes, activating T-cells and initiating an immune response against tumors (75). Researchers found that DCs derived from colon cancer patients have an incredible faculty in another study. They can sensitize tumor cells to chemotherapy, increasing tumor

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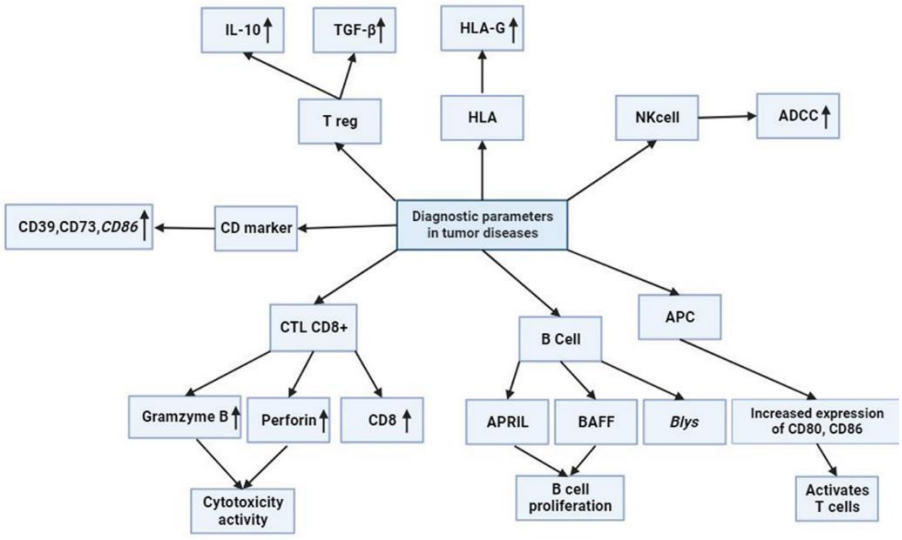

Figure 5. Summary of the possible diagnostic parameters in tumor diseases. IFN-γ: Interferon-gamma; **TNFα:** Tumor necrosis factor α; **HLA:** Human leukocyte antigen; **ADCC:** Antibody-dependent cellular cytotoxicity; **CTL:** Cytotoxic T lymphocytes; **APRIL:** a proliferation-inducing ligand; **BAFF:** B-cell activating factor; **Blys:** B lymphocyte stimulator.

cell death and improving chemotherapy's effectiveness (76). Plasmacytoid dendritic cells (PDCs) are an essential and distinct subset of DCs involved in innate and adaptive immune responses. PDCs possess potent antitumor activity by triggering tumor cell sensitization, which leads to the activating of tumor-specific T cells and subsequent cancer cell destruction (77). PDCs induce tumor cell sensitization by recognizing tumor-associated antigens (TAAs) through the TLR7 and TLR9 signal-guiding pathways. This leads to the generation of type I interferon (IFN I) and increased expression of MHC-I molecules on tumor cells (78, 79). Interestingly, TLR9, a pattern recognition receptor recognizing unmethylated CpG motifs in bacterial and viral DNA, is also expressed by PDCs and can detect CpG motifs in tumor-derived DNA (80-82). Activation of TLR9 signaling in PDCs produces IFN I (83) as well as other cytokines that activate NK cells and CTLs (84). In addition, PDCs can directly induce apoptosis in tumor cells via secretion of TRAIL (85, 86).

Recent studies have shown that PDCs enhance the efficacy of cancer immunotherapies, including immune checkpoint inhibitors (ICI) and chimeric antigen receptor T-cell therapy (CAR). PDCs promote the upregulation of PD -L1 expression on tumor cells, potentially enhancing the efficacy of ICI (87). Moreover, PDCs activate CAR T cells by presenting TAAs and emitting costimulatory signals, ultimately leading to enhanced tumor cell elimination (88).

Interestingly, the use of DCs has been shown to downregulate the expression of indoleamine 2,3-dioxygenase 1 (IDO1) in tumor patients, resulting in a decline in the proportion of T-cells converting to Tregs (**Fig. 3**). In addition, the resulting Tregs are less able to produce IL-10, which suppresses DCs (89, 90).

2.6. Neutrophil

Tumor-associated neutrophils (TANs) are a significant player in the TME and are thought to recreate a multifaceted function in cancer. Studies have shown that TANs produce ROS, causing oxidative stress in cancer cells and leading to their death (91). TANs also release cytotoxic molecules such as granulysin and elastase, which induce apoptosis in tumor cells, potentially sensitizing them to cancer therapy and increasing their efficacy (92, 93).

TANs have been investigated extensively due to their potential to sensitize cancer cells and promote cell death. Nonetheless, their role in cancer therapy remains controversial. Studies have shown that TANs produce pro-tumor cytokines and suppress the immune response against tumors, Advancing tumor expansion and metastasis (94-96). Nevertheless, the role of TANs in cancer therapy remains uncertain and controversial. Some studies suggest that TANs improve the efficacy of cancer therapy, especially radiotherapy. In one study, TANs were shown to be essential in promoting the recruitment of immune cells to the tumor,

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which could improve the immune response against the tumor (97). In addition, TANs produce cytokines and growth factors promoting angiogenesis and proliferation of tumor cells (98).

2.7. Complement system

It has been demonstrated that complement activation increases the efficacy of monoclonal antibody therapy by ADCC and CDC mechanisms against cancer cells (99). In addition, complement activation triggers ICD in tumor cells, releasing TAAs and DAMPs and triggering an adaptive immune response against the tumor (100). In addition, complement activation leads to tumor cell death through MAC and the release of anaphylatoxins such as C3a and C5a, which can induce apoptosis of tumor cells or sensitize them to other forms of therapy (101). Studies have indicated that concentrations of C3, C4, and CH50 complement are lower in tumor patients than in control subjects and that decreased C4 concentrations predict disease severity and prognosis (102).

Complement-based therapies, which include complement inhibitors and complement-activating agents, have been developed for cancer treatment. Complement inhibitors, such as CR1 or CD55, have been shown to decrease complement-mediated lysis of erythrocytes, thereby protecting tumor cells from complement-mediated killing (103). Conversely, monoclonal antibodies against tumor antigens promote CDC and enhance the antitumor immune response as complement-activating agents (104) (**Fig. 3**).

3. ACQUIRED IMMUNITY ELEMENTS

3.1. Antigen-presenting cells

Recent studies have demonstrated the central function of antigen-presenting cells (APCs) in sensitizing tumor cells by presenting TAAs to the immune system (68, 105). Macrophages, B cells, and DCs are among APCs that take up, function, and give these antigens to T-cells in the context of MHC molecules (**Fig. 4**). This complicated process is critical for the activation of T-cells that recognize and efficiently attack tumor cells (106, 107).

Other studies suggest that tumor-infiltrating APCs recreate a vital function in determining the prognosis of cancer patients. In animal models and human clinical trials, APC-based vaccines have been indicated to elicit tumor-specific T-cell responses and improve anti-tumor immunity, providing hope for future treatments (108, 109).

In addition to presenting antigens, APCs provide co-stimulatory signals necessary for T-cell activation. These signals are mediated by molecules such as CD80 and CD86 on the surface of APCs, which interact with receptors on T-cells such as CD28 (110). Optimal activation of these co-stimulatory signals is essential for a robust T-cell response and effective immune-mediated tumor destruction. Research has shown that APCs are critical in sensitizing tumor cells by presenting TAAs to the immune system (111).

3.2. Role of B Cells in Tumor Immunity

B cells, the mysterious and elusive players of the humoral immune system, play an indispensable role in a complex and intricate web of tumor development through various mechanisms (112). These competent cells are responsible for sensing TAAs and processing and presenting them to T-cells in the context of MHC molecules- a truly remarkable feat (113). B cells have also been shown to produce antibodies that can significantly enhance T cell-mediated cytotoxicity against TAAs (114). B cells are unsatisfied with producing antibodies and forming tertiary lymphoid structures (TLS) in the TME, creating an environment that actively promotes immune cell recruitment and activation and further strengthens anti-tumor immunity (115).

Some studies have shown that patients with hematological malignancies such as lymphoma and myeloma and solid tumors such as breast cancer have significantly elevated plasma serum levels of a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF) (116). These cytokines recreate a paramount function in B cell survival, differentiation, and expansion, which makes them indispensable for cancer control. However, the upregulation of these cytokines could be a double-edged sword. They can boost tumor cell growth and survival by supporting the proliferation of regulatory B cells (Bregs) or inhibiting effector B cell function (117). Another cytokine, B-lymphocyte stimulator (BLyS), has also been found to alter in multiple cancers, including lung, prostate, melanoma, and breast (118, 119). Moreover, the Bregs we mentioned earlier can also suppress the proliferation and activation of effector T-cells and promote the proliferation of regulatory T-cells, inhibiting anti-tumor immunity (120). B-Regs belong to a specific subset of cells, namely CD19+/CD24hi/CD38 hi, responsible for activating T-Regs by producing IL10, reducing the function of T helper cells, and generating tolerance (121, 122).

CD40, found on the surface of B cells, has been identified as a potential target for cancer therapy (123). Preclinical research has shown that CD40 agonists induce tumor regression in mouse models of cancer, including melanoma (124), lymphoma (125), and pancreatic cancer (126, 127). In addition, CD40 agonists improve the efficacy of other

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cancer therapies, such as chemotherapy and radiotherapy (128, 129). Clinical trials investigating the security and effectiveness of CD40 agonists in tumor patients have shown inspiring outcomes. For example, a stage I trial of an agonistic CD40 antibody in patients with solid tumors showed that tumor size was decreased in some patients and that the disease remained stable over time (130). Selicrelumab, formerly CP -870,893, is a CD40 agonist that has shown promise in early clinical trials in various solid cancers. In patients with advanced melanoma in a phase I trial, treatment with selicrelumab resulted in an objective response in 15% of patients and stable disease in an additional 40% of patients (128). A landmark Stage I clinical trial in pancreatic cancer patients, selicrelumab was evaluated in combination with chemotherapy and resulted in a remarkable 75% rate of disease control (131). The impressive results have sparked interest in investigating CD40 stimulation as a component of variety therapies. For example, a stage I/ II clinical trial of the combination of selicrelumab with pembrolizumab immune checkpoint inhibitor in patients with advanced solid tumors showed encouraging results, with an objective response rate of 36% (132). Several well-tolerated CD40 antagonist antibodies have been studied in clinical trials and have shown potential anti-tumor activity with or without treatment with an anti-CTLA4 monoclonal antibody (mAb), as seen in patients with melanoma. Combinations with chemotherapy have shown tumor regression in mesothelioma, pancreatic cancer, and other cancers (129).

3.3. Function of T-cells in Cancer Immune Response

The role of T-cells in tumors has been extensively studied with a focus on TFH, Th1, Th22, Th17, and TCD8+ cells (133). T-cells are affected in tumor pathogenesis through several mechanisms, including alteration of Th1/Th2 ratio in favor of Th1 (134). In addition, T-cells produce cytokines such as IL-2 and IFN-γ that stimulate CTL, NK cells, macrophages, and Ig in ADCC (135). In Sufferers with malignancy, an expansion in Th1 cytokines, such as IFN-γ and IL-2, is often followed, while Th2 cytokines, such as IL4, decrease due to an altered Th1/Th2 ratio (136).

Studies have shown that IL-10 levels decrease in patients with malignancy compared to those having cured or controlled tumors, indicating that this cytokine modulates the immune response (137). In addition, immune checkpoint inhibitors, including anti-PD -1 and anti-CTLA-4 antibodies, can help shift the balance toward Th1 dominance by inhibiting the function of Tregs and other immunosuppressive cells (138).

One of the primary mechanisms by which T-cells sensitize tumor cells is the release of cytokines. Cytokines act as messengers between cells and regulate immune responses. IL-2 is an essential cytokine for T-cell stimulation and expansion (139). IL-2 plays an integral part in cancer cell sensitization by promoting surface expression of MHC molecules on tumor cells, thereby increasing their recognition by T cells (140). T cells, powerful immune cells traveling throughout the body, can recognize and destroy malignant cells. They accomplish this task in part by expressing co-stimulatory molecules that interact with receptors on the surface of T-cells and provide an extra kick enhancing T-cell activation. For example, CD80 is a well-known co-stimulatory molecule crucial in sensitizing cancer cells (141, 142). Although co-stimulatory molecules are essential for T-cell functionality, these cells can release cytotoxic molecules that can kill target cells directly. One such molecule is perforin, which creates tiny pits in the target cell membrane through which granzymes enter and initiate cell death in a precise and deadly dance of biological warfare (143) (**Fig. 4**). Research has shown that the infiltration of $CD8^+$ T-cells into a tumor improves prognosis and response to immunotherapy in some cancers, including breast and lung cancers; Tregs expressing the transcription factor Foxp3 are associated with immunosuppression and may slow the antitumor response of other T-cells (144). It has been found that the number of Tregs increases in the TME from various cancers such as colon, breast, lung, and melanoma (145-147). The high number of Tregs in cancer patients has been associated with poor prognosis (148). However, scientists are developing innovative approaches to target Tregs for cancer treatment, including depletion of Tregs, inhibition of Treg function, and even conversion of Tregs into effector T-cells (149).

Helper 22 (Th22) cells are a subset of CD4+ T-cells with a unique cytokine profile distinguished by interleukin-22 (IL-22) and IL-13 production. Growing evidence shows that Th22 cells are critical in developing autoimmune and inflammatory diseases (150), but interestingly, recent studies suggest a possible involvement of Th22 cells in cancer biology.

An experimental study discovered that Th22 cells could sensitize tumor cells to chemotherapy by upregulating the expression of death receptors on the surface of tumor cells. Death receptors, including Fas and TRAIL receptors, have the potential to induce apoptosis in tumor cells when their corresponding ligands are activated (151). In vitro studies have shown that Th22 cells enhance the indication of Fas and TRAIL receptors on tumor cells, inducing cancer cell apoptosis in response to chemotherapy (152). In another

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study, Th22 cells were found to limit tumor growth by secreting IL-22, which can convert MDSCs into APCs (153).

Follicular T helper cells (Tfh) are a distinctive subset of CD4+ T cells with distinct phenotypes and functions. They are characterized by their role in supporting germinal center (GC) B cells during the humoral immune response. Tfh cells secrete cytokines such as IL-4 and interleukin-21 (IL-21), which enhance B-cell differentiation and antibody production (154). An experimental study in a mouse melanoma model revealed that Tfh cells are required to generate a solid antitumor immune response. Tfh cells can promote the maturation of DCs in the TME, which increases CTL activity and cell death (155). In contrast, a clinical study found that Tfh cells were connected with a favorable prognosis in hepatocellular carcinoma patients (HCC). Patients with greater levels of Tfh cells in their tumors had better overall survival and higher levels of tumor-infiltrating lymphocytes (TILs) than those with lower Tfh cells (156).

T helper 17 (Th17) cells are a subset of CD4+ T-cells that produce interleukin-17 (IL-17) and other pro-inflammatory cytokines. Th17 cells have been associated with the pathogenesis of various autoimmune and inflammatory diseases, but their role in cancer is less clear (157). One study found that IL-17, produced by Th17 cells, can increase the sensitivity of tumor cells to chemotherapy by upregulating the expression of death receptors on the surface of tumor cells. The death receptors, including Fas and TRAIL receptors, induce apoptosis in tumor cells when their ligands are activated. It has been found that IL-17 enhances the induction of Fas and TRAIL receptors on cancer cells in vitro, leading to increased apoptosis of tumor cells in response to chemotherapy (158) (**Fig. 4**).

The prognostic value of some CD markers expressed by immune system cells in tumors has been evaluated using flow cytometry. In several cancers, such as colorectal, lung, and melanoma, a high percentage of CD8+ T-cells in tumor tissue has been connected with a favorable prognosis (159, 160). Another example is programmed cell death protein 1 (PD-1), an immune checkpoint protein expressed on activated T-cells. PD-1 suppresses T-cell activity and inhibits antitumor immune responses. The high expression of PD-1 on T-cells in tumor tissue has been associated with poor prognosis in several cancers, including lung cancer, melanoma, and RCC (161, 162). In addition, CD markers such as CD45RO expressed on memory T-cells are associated with favorable prognosis in breast and colorectal cancers (163, 164). It should be noted that the importance of CD markers for prognosis varies by cancer type and disease stage (165, 166). For more details on the diagnostic parameters in tumor diseases, please refer to **Figure 5**.

4. MOLECULAR AND GENETIC MECHANISMS UNDERLYING THE INTERPLAY BETWEEN CELLULAR IMMUNITY AND TUMOR CELLS

The intricate interplay between cellular immunity and tumor cells is fundamental to understanding cancer progression and the efficacy of various therapeutic approaches. This section delves into the molecular and genetic mechanisms that underpin this dynamic interaction, emphasizing the roles of different immune cell subsets and the cytokines they produce.

Genetic studies have been performed on a large scale to evaluate the potential risks of developing tumor diseases (167, 168). The extensive data gathered may allow for utilizing specific laboratory-derived factors and parameters to predict prognosis disease severity and monitor treatment progress. An illustrative example involves identifying specific polymorphisms within genes associated with the immune system, such as chemokines, proinflammatory cytokines, and anti-inflammatory cytokines, which play roles in tumor disease development (169-171). One example is the TNF-a _308G > A polymorphism in the TNF-a gene. This polymorphism increases TNF-a expression, leading to heightened T-cell activation and cytokine production in tumor patients (172).

Another inflammatory cytokine produced by Th1 cells is IFN-γ, which plays a crucial role in B cell activation and promotes isotype switching to Ab IgG. Remarkably, a polymorphism in this cytokine leading to increased expression of IFN-γ may be considered a poor prognostic factor in tumor patients (173). Furthermore, interleukin-10 (IL-10), an immunoregulatory cytokine, significantly impacts the prognosis of cervical cancer. Elevated types of IL-10 in cervical serum and tissues have been linked to poor prognoses for this disease. Particularly intriguing is the rs1800872 polymorphism (c.-592C > A) in the promoter region of the IL-10 gene. This genetic variation affects IL-10 production and expression, potentially influencing the immune response profile in the cervix (174).

Understanding the complicated interplay between tumors and genetic factors is a strenuous task fraught with many obstacles. One of the significant obstacles is tumor heterogeneity, which challenges understanding the mechanisms underlying tumor development, progression, and response to treatment. These limitations significantly affect the efficacy of targeted treatments and compromise treatment outcomes. We must conduct further research in this area to overcome these limitations and gain new insights

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Table 1. An Overview of common polymorphisms concerning tumor prognosis.

Gene	Sequence polymorphism	Chromosome	Cancer models	Effect of polymorphism	Ref
IL-4	−589C>T	5q31	Prostate cancer	Activates B cells, Antibody production (IgE)	(171)
TNF-a	308G>A	6p21.3	Breast cancer	Increased expression of TNF-a and proliferation of tumor cells	(172)
IFNγ	+874A/T	12q24	Breast cancer	Activates B cells	(173)
IL-10	-592C>A	1q31	Cervical cancer	Increased production of IL-10, stimulates antibody production	(174, 175)
IL-8	rs4073	4q13-21	Prostate cancer	Proangiogenic activities, cytokine production	(176)
IL-17A	rs2275913	6p21	Colorectal cancer	Inflammatory cytokine production	(177)
IL-6	rs1800797	7p21	Cervical cancer	NA	(178)
IL-2	330T/G	4q26	Lung Cancer	NA	(179)

N/A: Not Available

into the nature of these diseases. In **Table 1**, we have compiled a list of possible prognostic factors that may be helpful in this context.

5. CONCLUSIONS

The dynamic interplay between cellular immunity and tumor cells is a cornerstone of cancer biology and therapeutic strategies. This comprehensive review has elucidated the multifaceted roles of various immune cell subsets, including TAMs, MDSCs, NKCs, DCs, and T lymphocytes, in shaping the TME and influencing cancer progression and response to therapy. TAMs and MDSCs often contribute to tumor immune evasion through cytokine-mediated suppression of effector cells, while NK cells and eosinophils provide robust cytotoxic responses against tumor cells. DCs are crucial for T-cell activation and antigen presentation, underscoring their potential in enhancing adaptive immunity.

Recent genetic and molecular investigations illuminated the regulatory mechanisms within the TME, revealing that cytokines like TGF-β, VEGF-A, and IL-10 play pivotal roles in immune suppression and tumor promotion. Conversely, cytokines like IL-12 and IFN-γ enhance anti-tumor immunity by triggering cytotoxic T and NK cells. These insights highlight the potential of targeting specific cytokine pathways to modulate the immune response and improve therapeutic outcomes.

Moreover, advancements in single-cell RNA sequencing and genetic profiling have enabled a deeper understanding of the heterogeneity and functional states of immune cells within tumors. These technological advancements are paving the way for personalized cancer immunotherapies that can harness the unique characteristics of an individual's tumor-immune microenvironment. Future research should continue to explore these molecular and genetic mechanisms, aiming to identify novel biomarkers and therapeutic targets that can enhance the efficacy of cancer immunotherapies and improve patient prognosis.

In conclusion, the integration of molecular, genetic, and immunological insights is essential for developing innovative therapeutic strategies that leverage the body's immune system to combat cancer more effectively. Understanding the complex interchanges between tumors and immune cells will be crucial for advancing personalized medicine and achieving better clinical outcomes for cancer patients.

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Conflict of interest

The authors declare no conflict of interest.

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