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Tumor Associated Immune Dysfunction: Immune Cells Involved and Suggested Therapies

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors designed the study and wrote the protocol. Author WHT wrote the first draft of the manuscript. Author IHAY managed the literature searches. Both authors read and approved the final manuscript.

Review Article

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ABSTRACT

The improvement in the understanding of cancer immunology did not lead to a successful immunotherapeutic strategy. Cancer immunotherapy faces different obstacles including low immunogenicity, production of immunosuppressive agents, and the peripheral tolerance which is used by cancer cells to avoid recognition and destruction by effective cells in the immune system. The establishment and maintenance of immune tolerance is a result of a contribution of various immune cells. This review discusses the role of immune cells that support tumor growth and suggests some immunotherapeutic strategies that may increase tumor immunogenicity and improve immunotherapy. However, a careful preclinical and clinical evaluation is essential before considering these strategies as therapeutic options.

Keywords: Cancer immune evasion; peripheral tolerance; cancer immunotherapy.

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1. INTRODUCTION

Although tumors express highly immunogenic epitopes, there are several problems with the host immune response that cause the failure to reduce tumor burden [1]. Due to their self-derived nature, tumor cells can use peripheral tolerance as an evasive mechanism to avoid recognition and destruction by immune cells [2]. Tumor outgrowth is a direct result of the failure of the tumors to initiate effective immune response [3]. Additionally, the antitumor immune response leads to the emergence of cancer cells with low immunogenicity which enhances immune evasion [4]. Solid tumors are characterized by an abundance of infiltrating immune cells that mediates different immune effects [5]. Tumor growth, invasion, and progression are results of a chronic inflammatory microenvironment created by pro-tumoral and anti-tumoral effects of infiltrating immune cells [6].

Although different mechanism have been suggested to account for the immune dysfunction in tumor-bearing hosts, an important role is a result of the contribution of various immune cells including CD4+ CD25+ T regulatory cells (Tregs), myeloid-derived suppressor cells (MDSCs), tumor associated macrophages (TAM), natural killer T (NKT) cells, and some dendritic cell (DC) subpopulation. These cells work in concert to maintain peripheral tolerance which supports tumor growth [7-9].

Increasing cancer immunogenicity is a realistic goal that can be achieved using different mechanisms. This review summarizes the main immunological players that support immune evasion in cancer and suggests some immunotherapeutic targets that can increase tumor immunogenicity.

2. CELLS INVOLVED IN IMMUNE EVASION OF CANCER

2.1 Regulatory T lymphocytes (Tregs)

One of the main mechanisms exploited by tumors to avoid immune response is mediated by Tregs. In addition to the co expression of CD4+ and CD25+, the forkhead/winged helix transcription factor (FOXP3) has been detected as an essential regulatory gene for the development and activation of Tregs [10,11]. High levels of Tregs were detected in the peripheral blood and tumors of human patients, and in many cases, a correlation was observed between poor disease outcome and elevated Treg levels [12]. Previous studies showed that depletion of Tregs caused regression in mouse sarcoma induced by methylcholanthrene [13]. Context-dependent adaptation was observed in the diverse functions of Tregs. Tregs involved in the regulation of Th1 showed high expression of the transcriptional factor T-bet [14]. On the other hand, Treg expression of interferon regulatory factor (IRF) [4] was essential for the differentiation of Th2 [15] and the expression of signal transducer and activator of transcription (STAT)3 was involved in the differentiation of Th-17 T cells [16]. Additionally, visceral adipose tissue-associated Tregs highly express peroxisome proliferator-activator receptor (PPAR)-γ which is essential for adipocyte differentiation [17]. A variety of immune response inhibitions is associated with Tregs *in vitro* and *in vivo* [2]. Experimental studies showed that Tregs inhibit the immune system by producing immunosuppressive cytokines IL-10 [18] and TGF-β [19,20]. Additionally, Tregs can modulate the function of dendritic cells to cause immunsupression [21].The link between Tregs and carcinogenesis of different tumors is well documented. Such link was observed in different cancers including pancreatic, breast, cervical, and endometrial cancers [22-25]. Additionally, Tregs expressing the chemokine CCL28 and the vascular endothelial growth

factor (VEGF)A play an important role in the angiogenesis promotion [13]. Promotion of breast cancer metastasis was also observed in Tregs expressing receptor activator of nuclear factor kappa-B ligand (RANKL) [26].

2.2 Myeloid Derived Suppressor Cells (MDSCs)

During tumor progression, the number of Gr-1+CD11b (Mac-1) + MDSCs increase in bone marrow, circulation, and peripheral lymphoid organs [27]. The contribution of these cells in tumor-induced immune dysfunction involve different mechanisms including INF-γ-dependent production of nitric oxide [28], secretion of TGF-β22, IL-4/IL-13-dependent arginase production which cause depletion in arginin [29] and production of reactive oxygen species [30]. Additionally, MDSCs can stimulate the development of CD4+ CD25+ FOXP3+ Tregs *in vivo* [31]. Also MDSCs can cause nitration of TCR-CD8 complex which block peptide-MHC-TCR binding causing CD8+ T-cell tolerance [32]. Additionally, MDSCs is associated with high IL-6 production which is a key cytokine in the stimulation of cancer cell proliferation and inhibition of tumor apoptosis through the activation of signal transducer and activator of transcription 3 (Stat3) [33]. Other effects of IL-6 include T cell subset differentiation [34], induction of angiogenesis[35], and carcinogen associated liver cancer development [36]. Another cytokine associated with MDSCs is IL-1β which activates the transcription factor NF-$_k$B. Stat-3 and NF-$_k$B which are essential transcription factors involved in cancer progression [37]. Inhibition of effector T cells and suppression of antigen presentation were also suggested as possible mechanisms for MDSCs to suppress anti-tumor immunity [38]. Additionally, MDSCs can promote tumor progression by stimulating angiongenesis [39]. Furthermore, these cells may differentiate into tumor associated macrophages (TAM) that produce different cytokines to inhibit T cell function and antigen presentation [40]. Also MDSCs can migrate to distant tissues and induce local angiogenesis which leads to the formation of premetaststic niche for survivals and spread of new metastatic tumor cells[41]. The resistance of tumors to antiangigenic and immune therapies is directly associated with the effects of MDSCs [42,43].

2.3 Tumor Associated Macrophages (TAMs)

Studies on various tumors showed a correlation between the increase in the number of macrophages in the tumor and poor prognosis [44]. The presence of macrophages was observed in the stromal compartments of different solid tumors including breast, pancreatic, ovarian, and hepatocellular [45-47].

Inhibitory effects on anti-tumor responses were reported for TAMs. IL-12 secretion by macrophages is inhibited by IL-10 produced by MDSC. Such inhibition stimulates the development of tumor-promoting macrophage response [48]. Although recent studies reported the presence of a spectrum of intermediate macrophages phenotypes [49,50], oxygen availability and tumor progression lead to the formation of two main groups of TAMs [51]. Type 1 macrophages (M1) develop during the early stage of tumor development. These cells are characterized by low expression of arginase and IL-10 and high expression of IL-12 and MHCII [52]. M1 cells exhibit high antitumor activity and their presence is associated with high concentration of INF-γ [53]. Additionally, they produce pro-inflammatory cytokines such as CXCL19 and CXCL10 which cause Th1, Th17 and NK cells development and differentiation [16].

Tumor progression and hypoxia formation induce the development type 2 macrophages (M2). M2 cells express CCL17, CCL22, and CCL24 cytokines leading to Th2 and Tregdevelopment and recruitment [51]. These cells are normally produced in response to the release IL-4 or IL-13 and characterized by low capabilities of antigen presentation and co-stimulation in addition to the production of immunosuppressive cytokines [54]. Preclinical and clinical observation showed that M2 cells are involved in tumor progression, metastasis, angiogenesis, and immune suppression of pancreatic, breast, colorectal, and ovarian cancers [55-57].

2.4 Natural Killer Cells (NKCs)

These cells are the main subset of innate lymphoid cells and involved in complex regulatory functions [58]. The main role of natural killer cells is to identify and kill cells lacking MHC1 molecules [59]. Although multiple subsets of NK cells were identified [60], there are two main types of these cells. About 95% of NK cells are characterized as $CD56^{dim}$ CD16+ and have high productivity of granzyme and perforin. These cells are also associated with cytotoxicity. On the other hand, the remaining 5% are $CD56^{bright}$ CD16− and exhibit lower cytotoxicity and higher productivity of cytokines compared with $CD56^{dim}$ CD16+ NK cells [60]. NK cells have an important role in the modulation of adaptive antitumor T cell immune response by producing interferon-γ(IFN-γ) and tumor necrosis factor α (TNFα) [61].

Natural killer T (NKT) cells express markers for both T and NK cells. They express either αβ or γδ TCR with various NK cells marks, like CD16, CD56, CD69, and CD161 [62]. Activated NKT cells produce RANTES that cause the recruitment of F4/80+ antigen presenting cells in addition to the generation of CD8+ Tregs that are involved in induction of tumor associated immune tolerance [63]. Experimental studies showed that CD4+ NKT produce IL-13 which down-regulate immunosurveillance of tumor [64]and cause MDSCs activation to produce TGF-β which cause suppression of CD8+ cytotoxic T cells [65]. Recent studies showed that the functional maturation of NK cells can be disturbed by tumor growth through interrupting of IL-15 signaling pathway. However further studies are needed to fully understand the basis of NK defects in tumor [66].

2.5 Dendritic Cells(DCs)

Haematopoietic stem cells in the bone marrow contain progenitor cells that produce dendritic cells. Immature dendritic cells reach peripheral tissues through circulation where they sample antigens of different sources and start differentiation process [67].

Tumor microenvironment contains factors that hamper normal dendritic cells differentiation causing the accumulation of immature dendritic cells (iDCs). Limited antigen- presenting capacity was observed in tumor associated dendritic cells [68]. Various abnormalities were observed in iDCs including low IL-12 production [69], inhibition of endocytic activity [70], suppression of MHC class I antigen processing machinery [71] and abnormal motility [72]. Immature DCs (iDCs) lack the ability to provide costimulatory signals during T cell activation leading to the induction of T-cell tolerance [73] and can be stimulated by tumor cells to produce TGF-β which induce the proliferation of Tregs [74]. Also iDCs expressing the enzyme indoleamine 2,3-dioxygenase showed the ability to induce suppression of T- cell proliferation [75]. Additionally, accumulation of intra-tumoral dendritic cells supports tumor progression by promoting the appearance of Tregs and myeloid-derived suppressor cells together with stimulation of neoangiogenesis and metastasis [76]. These evidences were

supported by the presence of high levels of tumor-infiltrating iDCs in patients with head and neck, lung, breast, and esophageal cancers [77].

3. IMMUNOTHERAPEUTIC STRATEGIES TO BREAK IMMUNE EVASION

3.1 Activation of Antitumor CD8+ Cytotoxic T lymphocytes (CD8+/CTL):

Stimulation of CD8+/CTL to kill cancer cells is a promising target for effective immunotherapy. Different mechanisms were investigated to reach this target including the use of recombinant molecule (HER2-Fc) composed of the immunogenic sequence of the human tumor-associated antigen HER2 and the Fc domain of a human IgG1 to activate dendritic cells which in turn leads to stimulation of HER2-specific CD8(+) T cells [78]. Peptide vaccines consisting of multiple peptides derived from distinct tumor-associated antigens was also used to activate CD8+/CTL and promising results were achieved against multiple myeloma antigens [79]. Recently, experimental data showed that Neem Leaf Glycoprotein can cause activation, expansion, and recruitment of CD8+/CTL into established tumors to induce significant tumor cell lysis [80].

It seems logical to assume that a combination of the previously mentioned methods can produce a potent antitumor CD8+/CTL.

3.2 Temporal Inactivation of Tregs

Previous studies reported a variety of immune response inhibitions associated with Tregs *in vitro* and *in vivo* [2]. Tumor cells can use this inhibition as an evasive mechanism to avoid recognition and destruction by immune cells. Thus temporal depletion of Tregs can be used to initiate immune response against cancer cells without permanent inactivation of the immune tolerance mechanisms. Tregs were inactivated using anti-CD25 antibodies and this treatment showed promising result to inhibit neuroblastoma tumors in mice [81]. Inactivation of Tregs can also be achieved by targeting the forkhead/winged helix transcription factor (FOXP3) using FOXP3-interacting KRAB domain–containing protein which has the ability to link FOXP3 with the chromatin-remodeling scaffold protein KAP1 [82].

3.3 Inactivation of STAT3 Signaling Pathway

Signal transducer and activator of transcription (STAT3) is one of the mediators of tumor associated immune evasion. Tumor-dependent production of different factors such as IL-10, IL-6, and CSF leads to the activation of STAT3 [83]. Activation of STAT3 supports tumor development by inducing systemic accumulation of MDSCs and inhibition of DC differentiation [84]. Inactivation of STAT3 is an attractive target to augment antitumor immune response by the activation of DCs and inhibition of Tregs [85]. Inactivation of STAT3 can be achieved by different mechanisms such as modulating upstream regulators, regulating RNA, and targeting STAT3 protein [86].

3.4 The Use of Bacteria to Enhance Antitumor Immune Response

One of the interesting immunotherapeutic strategies is the use of bacteria to enhance tumor immunogenicity. Different bacterial strains were used to target the hypoxic regions in tumor core. Among these bacteria, *Clostridium novyi-NT* showed promising results and triggered an inflammatory response mediated by different cytokines such as IL-6, MIP-2, G-CSF,

TIMP-1, and KC. This immune response attracts many inflammatory cells including neutrophils, monocytes, and lymphocytes that work together to destroy tumor cells [87]. Genetically modified *S. typhimurium* expressing LIGHT which is a cytokine promoting tumor rejection was used to target primary and metastatic tumors. This treatment exhibited high ability to inhibit growth of primary tumors and pulmonary metastases in various cancers [88]. The use of bacteria to enhance antitumor immune response seems to be a promising strategy for developing efficient therapy. The efficiency of this therapeutic option can be improved by combining bacterial therapy with other treatments.

3.5 Cellular Immunotherapy

Cellular immunotherapy for cancer is considered as an important therapeutic option and different studies reported promising results for such therapy. Sipuleucel-T cells are antigen-presenting cells that were used to treat prostate cancer as autologous immunotherapy without any side effect that usually associated with chemotherapy [89]. Due to its high efficiency; this therapeutic option was approved in 2010 by the United States Food and Drug Administration [90]. In another studies, lympho-depleting treatment followed by administration of tumor-infiltrating T- lymphocytes caused tumor regression in metastatic melanoma patients [91]. Additionally, chimeric antigen receptor-modified T cells showed promising results to treat chronic and acute lymphocytic leukemia patients [92,93]. Combination of activated natural killer cells with chemotherapy or radiotherapy resulted in an improvement in the survival of patients previously exposed to surgical resection of primary lung carcinoma [94]. Another combination consisting of activated lymphocytes and dendritic cells was well tolerated and showed high tumor response in malignant melanoma and advanced pancreatic carcinoma patients [95,96]. Significant additive effect of activated T cells on chemotherapy was observed in carcinoma patients [97]. Furthermore, adoptive T cell therapy caused an increase in the number of T cells subsets and a decrease in regulatory T cells. This action suggests a potential therapy for treating restored and imbalanced immune status in cancer patients [90]. An interesting cellular immunotherapeutic option is the development of artificial antigen-presenting cells which reduce the problems associated with natural antigen-presenting cells. These artificial cells exhibited high potential to improve clinical response in cancer patients [98]. Cellular immunotherapy is a realistic option that can be used to treat different cancers alone or in combination with other therapies.

4. CONCLUSION

Immune evasion in cancer is a complex process and resulted from the activation of different immune cells. Breaking immune evasion is a promising strategy to increase cancer immunogenicity and improve immunotherapy. A combination of different immunotherapeutic strategies could be the solution of immune evasion. However, a balance must be maintained between breaking immune evasion and the initiation of autoimmunity.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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