OncoImmunology 4:7, e1016700; July 2015; © 2015 Taylor & Francis Group, LLC

Reprogramming the tumor microenvironment: tumor-induced immunosuppressive factors paralyze T cells

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Keywords: immunosuppression, immunotherapy, immunosuppressive factors, T cells, tumor microenvironment

Abbreviations: 1MT, 1-methyltryptophan; COX2, cyclooxygenase-2; Gal1, galectin-1; GM-CSF, granulocyte macrophage colony-stimulating factor; GPI, glycosylphosphatidylinositol; HDACi, histone deacetylase inhibitor; HLA, human leukocyte antigen; IDO, indoleamine-2,3- dioxygenase; IL-10, interleukin-10; IMC, immature myeloid cell; iNOS, inducible nitric-oxide synthase; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility; MICA, MHC class I related molecule A; MICB, MHC class I related molecule B; NO, nitric oxide; PD-1, program death receptor-1; PD-L1, programmed death ligand 1; PGE2, prostaglandin E2; SOCS, suppressor of cytokine signaling; STAT3, signal transducer and activator of transcription 3; SVV, survivin; TCR, T-cell receptor; TGF-β, transforming growth factor β; TRAIL, TNF-related apoptosis-inducing ligand; PARP, poly ADP-ribose polymerase; RCAS1, receptor-binding cancer antigen expressed on Siso cells 1; RCC, renal cell carcinoma; VCAM-1, vascular cell adhesion molecule-1; XIAP, X-linked inhibitor of apoptosis protein.

It has become evident that tumor-induced immunosuppressive factors in the tumor microenvironment play a major role in suppressing normal functions of effector T cells. These factors serve as hurdles that limit the therapeutic potential of cancer immunotherapies. This review focuses on illustrating the molecular mechanisms of immunosuppression in the tumor microenvironment, including evasion of T-cell recognition, interference with T-cell trafficking, metabolism, and functions, induction of resistance to T-cell killing, and apoptosis of T cells. A better understanding of these mechanisms may help in the development of strategies to enhance the effectiveness of cancer immunotherapies.

Introduction

Significance of studying the tumor microenvironment

Cancer represents a challenging disease for which the development of innovative treatments is desperately needed to improve the quality of life and survival of patients. Immunotherapy, particularly T cell-mediated therapy, has emerged as a promising cancer therapeutic strategy based on its ability to specifically recognize and destroy tumor cells without harming the surrounding normal cells. However, a current limitation of cancer immunotherapy is the presence of various immunosuppressive factors in the tumor microenvironment that pose a formidable barrier to T-cell infiltration and function. The tumor microenvironment contains a network of immunosuppressive factors that are capable of inhibiting T-cell function despite the activated immune response against the tumor achieved through immunotherapy. Tumor cells have the ability to reprogram the tumor microenvironment and form a strong immunosuppressive network to limit the ability of T cells to eradicate tumor cells. Thus, to improve cancer immunotherapy a better understanding of the tumor microenvironment and tumor-induced immunosuppressive mechanisms is essential for the development of molecular interventions that can be used in conjunction with various cancer immunotherapies to enhance therapeutic effects and specificities.

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Submitted: 12/19/2014; Revised: 02/02/2015; Accepted: 02/03/2015
http://dx.doi.org/10.1080/2162402X.2015.1016700

Overview of immune-related aspects of the tumor microenvironment

The tumor microenvironment consists of cellular components of the tumor, the surrounding extracellular matrix, and interstitial fluid. These factors interact with each other, contributing to the hallmarks of cancer,[1] and have a significant influence on immune responses against the tumor. The cellular components in the tumor include tumor cells themselves, associated stromal cells such as fibroblasts, endothelial cells, and infiltrating immune cells. The infiltrating immune cells play an essential role in immune responses against cancer. For example, particular subsets of immune cells such as cytotoxic T lymphocytes and natural killer (NK) cells inhibit tumor growth. Other infiltrating immune cells may either assist in tumor growth (e.g., tumor-associated macrophages, neutrophils, and mast cells) or inhibit immune reactions against tumor cells (e.g., regulatory T cells and myeloid-derived suppressor cells [MDSCs]). These tumor and non-tumor cells express molecules on their cell surfaces and secrete extracellular matrix components, growth factors, cytokines, chemokines, proteases, other enzymes, and metabolites

that may affect the effectiveness of tumor immunotherapy.[2] Other characteristics of the tumor microenvironment may significantly influence T-cell immune responses against cancers. For example, hypoxia has been shown to inhibit T-cell receptor (TCR) and CD28-mediated activation of T lymphocytes, in addition to indirectly recruiting regulatory T cells,[3] which may suppress T-cell immune responses. In addition, low extracellular pH,[4] low glucose concentration,[5] and aberrant vasculature may affect T-cell trafficking, infiltration, and function.[5] This is a dynamic relationship in which the tumor shapes its microenvironment, influencing T-cell activity, while a balance between pro- and anti-malignancy factors in the microenvironment regulate the growth of the tumor.

Focus on tumor escape of T-cell attack

Increasing evidence suggests that despite our ability to effectively generate potent tumor-specific effector T cells through active immunization or adoptive T-cell transfer, cancer cells may possess, or develop over time, several strategies to successfully evade immune attack mediated by T cells. For instance, tumor cells can activate antiapoptotic pathways or inhibit proapoptosis signaling to resist killing mediated by tumor-specific $CD8^+$ T cells.[6,7] Alternatively, tumor cells and other cell types involved or recruited in the tumor microenvironment can inhibit T-cell proliferation, cause dysfunction of T cells, and induce apoptosis of T cells.[6,8-10] This review will focus on the different mechanisms by which tumor cells manipulate the microenvironment to hinder effector T cell infiltration and function. More specifically, we will summarize several key factors present in the tumor microenvironment that contribute to tumor evasion of T-cell attack (as summarized in **Fig. 1**) and discuss strategies to block these molecular targets, which will allow for better efficacy of immunotherapeutic treatment for the control of cancer.

Molecular Mechanisms of Immune Evasion by Tumors

Evading recognition by T cells

MHC class I: antigen complex

Although tumor antigen-specific T cells can access tumors, they are unable to target them for destruction if they cannot recognize the tumor cells as their target. Tumors can evade detection by the immunosurveillance system through alteration of their major histocompatibility complex (MHC) Class I/tumor antigenic peptide complexes and antigen presentation machinery (for review, see ref. 11[11]). It has been shown that epigenetic silencing and subsequent transcriptional repression of MHC class I genes lead to loss of function of MHC class I molecules or loss of the MHC class I molecules themselves (for review, see ref. 12[12]). Genetic alterations of human leukocyte antigen (HLA), including mutations leading to HLA total losses, haplotype losses, allelic losses, and downregulation of specific loci, may result in reduced or complete loss of MHC class I molecules on the tumor cell surfaces (for review, see ref. 13[13]). A variety of altered human MHC class I genes have been identified in human tumors, including ovarian, cervical, breast, skin, esophageal, and colorectal cancers (for review, see ref 12, 14[12,14]). Studies have shown that mutations at the β-2 microglobulin locus contribute to loss of function of MHC class I molecules on the cell surface.[15-18] Tumors may also alter their antigen processing and presentation machinery,[19] thus preventing tumor antigens from being presented on surface MHC I molecules. These alterations occur in the transporter associated with antigen processing (TAP[20]), subunits of the immunoproteosome (LMP-2, LMP-7,[20] PA28[21]), tapasin, calreticulin, and calnexin,[22] which have been found in many human cancers (for review, see ref. 11[11]). Mutations in

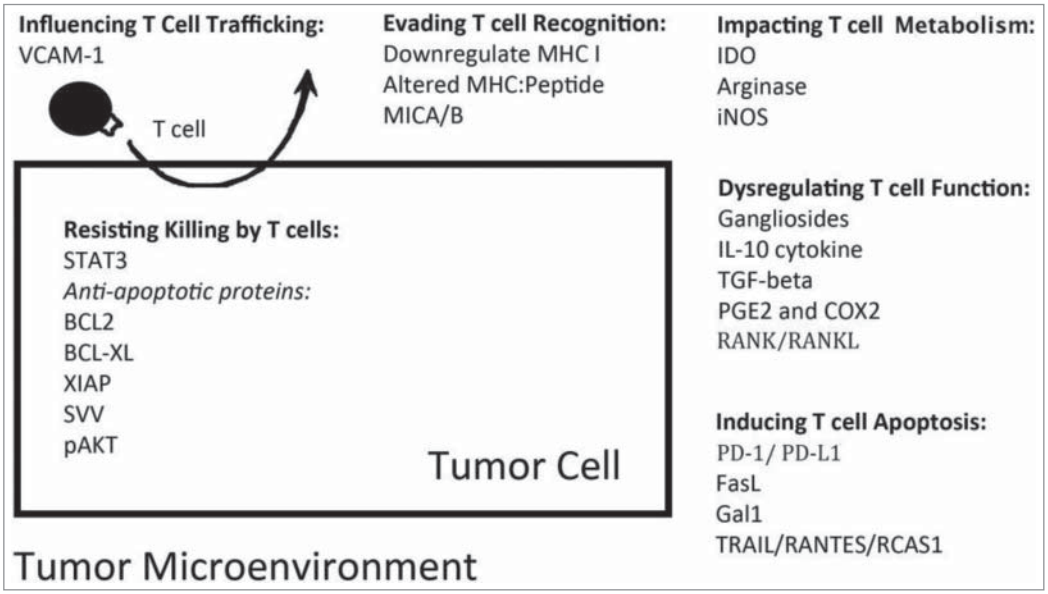

Figure 1. Factors contributing to tumor immune evasion in the tumor microenvironment. Tumor cells can influence T-cell trafficking by upregulating adhesion molecules that prevent T cells from infiltrating the tumor.[45] In addition, tumors can evade T-cell recognition through alteration of their MHC Class I/ tumor antigenic peptide complexes and antigen presentation machinery.[11] Tumor cells utilize a number of altered metabolic pathways to contribute to an unfavorable environment for T-cell expansion.[55,79] Another mechanism used by tumors to dysregulate T-cell function[98,118,146,167, 175] or induce T-cell apoptosis[10,201,204,209] is the production and secretion of immunosuppressive factors into the microenvironment. Finally, tumors can prolong their survival by overexpressing various antiapoptotic proteins.[177]

tumor antigenic peptides may also result in a change in avidity of peptides to their MHC Class I molecules, rendering T cells unable to recognize tumor antigens. For instance, mutations in antigenic epitopes, or antigenic drift, enable the tumor to evade host immunity.[23] These antigen presentation machinery deficiencies may be reversed by treatment with interferon gamma (IFN-γ).[24]

Soluble and exosomal NKG2D ligands

Another way that tumors can evade immune recognition is through the shedding of NKG2D ligands, including major histocompatibility complex class I-related molecules A and B (MICA and MICB) and UL16-binding proteins. NKG2D ligands are glycoproteins that share a common MHC class I-related α1α2 superdomain and bind to the membrane through either transmembrane domains or glycosylphosphatidylinositol (GPI) anchors.[25] In their membrane-bound form, NKG2D ligands are upregulated in tumors in response to infection, malignant transformation, or other cellular stresses through various pathways, resulting in enhanced activation of NK cells and $CD8^+$ T cells as well as subsequent cytotoxic effects against NKG2D-ligand expressing cells (for review, see ref. 25-27[25-27]). However, tumors can shed NKG2D ligand into the tumor microenvironment through tumor cell death, secretion of exosomes, or proteolysis by matrix metalloproteinases.[26,28-35] These soluble or exosomal NKG2D ligands can bind to NKG2D receptors on T cells and induce the internalization and degradation of NKG2D in $CD8^+$ T cells infiltrating the tumor.[26,33, 36] The degradation of NKG2D in T cells ultimately results in decreased activation of $CD8^+$ T cells upon contact with tumor cells, contributing to tumor immune evasion.[34,37] In some human cancers, serum MICA (sMICA) and serum MICB (sMICB) are related to disease stage and survival rates, and thus may be used to predict prognosis (for review, see ref. 38[38]). Histone deacetylase inhibitors (HDACis) are being tested as treatments to upregulate MICA/MICB (for review, see ref. 25[25]). Other substances that target the shedding of NKG2DL are also being explored to enhance $CD8^+$ T cell cytotoxic killing of cancer cells.[39]

Influencing T-cell trafficking

Although cytotoxic T cells are likely to play a role in eliminating tumors, failure to access the target tumor tissue presents a critical obstacle. Tumors may influence T-cell trafficking by downregulating adhesion molecules such as ICAM-1/2, VCAM-1, and CD34 in their vessel component to prevent T cells from infiltrating the tumor.[40,41] Tumors may also adversely influence T-cell trafficking by overexpressing vascular cell adhesion molecule-1 (VCAM-1).[42] VCAM-1 is widely known as a cell surface glycoprotein expressed in endothelial cells that mediates leukocyte extravasation to inflammatory sites by binding to α4 integrin on T cells[43] (for review, see ref. 44[44]). Recently, overexpression of VCAM-1 in tumors has been proposed as an important mechanism for tumor metastasis and immune escape.[45] A study led by Lin et al. demonstrated that introducing VCAM-1 into a murine cancer cell line could render the tumor highly resistant to T-cell infiltration and killing.[42] Tumors expressing VCAM-1 with mutated amino acids at sites required for interaction with α4β1 integrins completely lost the immune resistance conferred by VCAM-1.[42] This interaction between VCAM-1 and α4 integrin is thought to promote T-cell migration away from the tumor, thus reducing infiltration of $CD8^+$ T cells. Aberrant expression of VCAM-1 on tumors is not only found in preclinical models, but also in human tumors. For example, human renal cell carcinomas (RCCs) are highly positive for VCAM-1 expression.[46] VCAM-1 may also be associated with tumor stage and overall survival of patients with RCC.[47,48] Interestingly, the only RCC that responded to immunotherapy in one clinical trial was negative for VCAM-1.[46] Thus, VCAM-1 expression may serve as an indicator for the outcome of immunotherapy.

Affecting T-cell metabolism

IDO

Tumor cells use a number of altered metabolic pathways to contribute to an unfavorable environment for T-cell expansion. For instance, indoleamine-2,3- dioxygenase (IDO) is a heme-containing enzyme that is overexpressed in tumors[49] and overexpression of IDO has been correlated with poor prognosis of several types of cancer[50-54](for review, see ref. 55[55]). In addition, IDO overexpression has been found in stromal immune cells, especially in certain sets of dendritic cells and MDSCs,[49,56] where it reduces the levels of tryptophan, an essential nutrient for T cells. This function has multiple effects on T-cell mediated clearance of tumor cells. T cells are very sensitive to tryptophan shortage, therefore deprivation of tryptophan ultimately impairs T-cell proliferation in the tumor microenvironment by causing arrest in the G1 phase of the cell cycle.[49,57] Depletion of tryptophan also causes downregulation of TCR ζ-chain in $CD8^+$ T cells, which impairs T-cell function.[58] IDO may convert tryptophan into toxic metabolites, such as kynurenine, that are harmful to T-cell function[59] (for review, see ref. 60[60]) and induce IDO-dependent apoptosis of T cells.[61-63] In addition, tumor-derived IDO has been shown to recruit regulatory T cells into the tumor microenvironment and promote their differentiation from naïve T cells, thus exerting an immunosuppressive effect.[50,58, 64] Although the exact mechanisms that regulate IDO expression in tumor cells remain to be clarified, one study has shown that IDO is under the genetic control of the tumor suppressor gene *Bin1*.[65] Elevated expression of IDO may therefore be related to the loss of *Bin1* in tumors.[66]

Consequently, blocking IDO may allow for effective T-cell immune responses against tumors. Several studies have shown that inhibition of IDO with 1-methyltryptophan (1MT) or other small molecule inhibitors, including thiohydantooin derivatives of tryptophan, or by RNA interference can promote antitumor effects by re-establishing T-cell immunity (for review, see ref. 67[67]).[65, 68] 1MT is anticipated to have no serious side effects since it inhibits IDO while sparing tryptophan dioxygenase, a hepatic enzyme that regulates body tryptophan levels.[69] Design and development of more effective IDO inhibitors is underway (for review, see ref. 60, 67, 70).[60, 67, 70]

Arginase and nitric-oxide synthase

Alteration in the pathway involving the catabolism of L-arginine is linked to the suppression of T-cell expansion. Two important enzymes involved in arginine metabolism are arginase and inducible nitric oxide synthase (iNOS).[9] Arginine is used by iNOS as a precursor for the production of nitric oxide (NO). Therefore, elevated levels of arginase and iNOS deplete arginine, an essential nutrient of T cells, from the tumor microenvironment.[9,71] Various types of tumors exhibit elevated arginase and iNOS levels,[72-76] and MDSCs recruited by tumor cells into the tumor microenvironment[78,79] have been shown to produce arginase.[75, 79, 80] Arginine depletion by increased levels of arginase leads to downregulation of ζ-chains on T-cell receptors[80, 81] and is associated with cell cycle arrest of T cells[72,82] (for review, see ref. 79[79]). Increased iNOS expression by MDSCs, and thus higher levels of NO, may also induce cell cycle arrest of T cells[83] and has been shown to be related to tumor progression and angiogenesis.[84] In addition, increased NO blocks T cell production of IL-2,[85,86] a cytokine that stimulates T-cell proliferation. Consequently, the use of inhibitors against arginase/iNOS, such as N(omega)-Hydroxy-nor-L-arginine (nor-NOHA), N(omega)-Hydroxy-L-arginine (NOHA),[87-89] or the iNOS inhibitor N^G-Monomethyl-L-arginine, monoacetate salt (L-NMMA), has been shown to restore T-cell expansion and block tumor growth in mouse models.[80, 90-93] Blocking NO may also allow for effective antitumor effects. One study showed that NO inhibition using nitroaspirin (NCX-4016) combined with a tumor vaccine improved the number and effector function of T cells, leading to reduced tumor growth and improved survival of mice.[94] Although arginine analogs that block arginase activity are available for investigating this biological pathway,[95,96] none are currently used for clinical studies because of safety concerns associated with disrupting the natural role of arginine in the urea cycle.

Dysregulating the function of T cells

Gangliosides

Tumors are capable of escaping destruction by adopting strategies that impair T-cell function in the microenvironment. One proposed mechanism involves the shedding of gangliosides by tumors. Gangliosides are glycosphingolipids found as clusters on the surface of all mammalian cells that regulate cellular responses such as growth and differentiation (for review, see ref. 97, 98[97,98]). Many tumors, however, express large quantities of gangliosides that are not expressed in their normal tissue origin or overexpress certain gangliosides specific to the tissue that are often shed into the microenvironment. This phenomenon has been observed in several types of human cancers (for review, see ref. 98[98]). The soluble gangliosides shed into the tumor microenvironment can dysregulate T-cell function in multiple ways. For instance, there is evidence that these soluble gangliosides inhibit tumor-specific T-cell proliferation[99,100] and induce T-cell apoptosis.[8,101-103] They may play a role in disrupting cytokine production, including that of IFNγ in T helper 1 cells[104,105] and IL-5 in T helper 2 cells.[106] In addition, soluble gangliosides may skew the T-cell response against tumor antigen toward a Th2 response, which contributes far less than a Th1 response to tumor clearance.[105,107] Furthermore, soluble gangliosides have been shown to disrupt nuclear factor kappa B (NF-B) function in immune cells[108,109] as well as lytic granule trafficking and exocytosis in $CD8^+$ T cells.[110] Thus, gangliosides that are shed into the microenvironment can disrupt the normal functioning of T cells in numerous ways. Therapies targeting the tumor gangliosides GD2, GM3, and GD3 may potentially prevent gangliosides from inducing T-cell dysfunction. For example, an anti-GM2 monoclonal antibody, DMF10.167.4, has been shown to inhibit tumor growth in vitro and in a preclinical model.[111] Antibodies targeting gangliosides GD2, GM3, and GD3 may also serve as promising vaccines,[111-115] (for review, see ref. 116, 117[116,117]). Since gangliosides are expressed on all cells, it is essential that the engineered monoclonal antibodies bind specifically to tumor gangliosides and not to normal tissues (for review, see ref. 116[116]).

Interleukin-10

Another mechanism utilized by tumors to disrupt T-cell function is the production of interleukin-10 (IL-10) and its secretion into the microenvironment. IL-10 is an important cytokine that displays both immunostimulatory and immunosuppressive activities toward various components of the immune system.[118,119] IL-10 mRNA and protein have been found in freshly excised human tumors and cancer cell lines of a variety of origins,[120-124] and IL-10 secreted into the tumor microenvironment can be produced by tumor cells[120] or tumor-associated macrophages.[125] There are several ways in which IL-10 may assist in tumor immune evasion. For instance, IL-10 downregulates HLA class I expression on tumors, thereby facilitating tumor escape from T-cell recognition.[126] In addition, IL-10 has been shown to downregulate immune effector mechanisms, such as $CD8^+$ T-cell mediated tumor cell lysis.[126,127] Furthermore, IL-10 may block T helper 1 cell differentiation and proliferation and suppress production of Th1 cytokines,[128-130] which would negatively impact the proliferation of cytotoxic T cells. IL-10 also serves as an activator of STAT, which in turn inhibits maturation of dendritic cells and immature myeloid cells (IMCs) through STAT3 activation.[131-133] These immature myeloid cells then become MDSCs and exert immunosuppressive effects on $CD8^+$ T-cells through various mechanisms.[134,135] Considering the immunosuppressive functions of IL-10, administration of neutralizing antibodies may provide a promising strategy to target IL-10.[136] In fact, neutralizing antibodies against IL-10 have been shown to significantly restore T-cell proliferation[137,138] and enhance antitumor immune responses. However, given the dual function of IL-10, its knockdown may also diminish immune responses (for review, see ref. 119[119]). Thus, further evaluation of IL-10 blockade as an immunomodulatory approach is required (for review, see ref. 139[139]). Major efforts have also been made to identify inhibitors or inhibition strategies of STAT3, downstream of the IL-10 pathway. For example, suppressor of cytokine signaling (SOCS) has been shown to negatively regulate STAT3 activation.[140,141] In a preclinical study, demethylation followed by pharmacologic inhibitors of SOCS-1 expression resulted in the inhibition of

STAT3 activation and cell proliferation and the stimulation of cell apoptosis in a mouse carcinoma cell line.[140] Although several STAT3 inhibitors are under development, none of them have made it to clinical stage investigation (for review, see ref. 142[142]). With recent advancements of technology, small molecule STAT3 inhibitors such as TW-37 represent potential candidates for further development in clinical trials[143-145] and STAT3 still serves as a promising target for cancer immunotherapy (for review, see ref. 140, 142[140, 142]).

TGF-β

Overexpression of transforming growth factor (TGF)-β, a cytokine known to regulate the growth and activity of T cells, profoundly suppresses T-cell responses (for review see ref. 146[146]). Various types of tumors that produce TGF-β exploit this mechanism to evade immune attack.[147] Overexpression of TGF-β by tumors suppresses T-cell responses through numerous TGF-β signaling pathways. In terms of activation and function, TGF-β cytokines may bind to TGF-β receptors on T cells and inhibit IL-2 production, cytotoxic T lymphocyte activation, clonal expansion of memory CD8+ T cells, and expression of perforin, an essential mediator for CD8+ T cell killing of tumor cells[148,149] (for review, see ref. 150[150]). Another equally important immunosuppressive role of TGF-β is altering the differentiation of Th1 and Th2 cells by inhibiting their lineage specification transcription factors.[151, 152] TGF-β is also involved in inducing the expression of transcription factor FoxP3, which ultimately promotes growth and differentiation of $CD4^+$ $CD25^+$ T regulatory cells.[153-155] These regulatory T cells then secrete TGF-β and other inhibitory cytokines to suppress $CD8^+$ T cell-mediated killing of tumor cells (for review, see ref. 155[155]). TGF-β can also promote the development and maintenance of T helper 17 (Th17) cells, which have been shown to suppress $CD8^+$ T-cell effector functions.[156] The roles of Th17 cells in the tumor microenvironment, however, appear to be double edged. In addition to its role in the procarcinogenic inflammatory response, Th17 cells may also play a role in antitumor immunity, as demonstrated by a number of studies on human cancer and mouse models.[157-161] Nevertheless, inhibiting TGF-β-induced inactivation of T cells may provide protection against tumors.[147] In fact, several agents are being developed in preclinical and clinical settings with this aim. One potential strategy to block TGF-β is the use of antisense gene therapy, which impedes the translation of *TGF-β* mRNA.[162] Other strategies to inhibit TGF-β include monoclonal anti-TGF-β antibodies, small molecule inhibitors of TGF-β, and Smad inhibitors (for review, see ref. 163, 164[163, 164]). Thus, we expect that future endeavors will focus on effective ways to block TGF-β to enhance T-cell responses.

PGE2 and COX2

Numerous tumors, particularly colorectal, pancreatic, lung, and breast cancer, overexpress cyclooxygenase-2 (COX2) enzyme and its metabolite prostaglandin E2 (PGE2), which both contribute to T-cell dysfunction[165,166] (for review, see ref. 167[167]). PGE2 induces the accumulation of MDSCs, which inhibit the activation of $CD4^+$ and $CD8^+$ T cells.[165] The interaction between PGE2 released by tumors and prostaglandin E2 receptor (EP2) on T cells has been shown to alter the cytokine profile of T cells, fueling the Th2-type while reducing Th1-type cytokine levels.[168,169] This cytokine imbalance promotes humoral immune responses that are ineffective in targeting tumors, which requires cellular immune responses established by Th1 cells. *In vivo* studies have shown that PGE2 overexpression results in production of the immunosuppressive cytokine IL-10 and downregulation of the immunostimulatory cytokines IL-12 and IFNγ.[169-172] Further support of the importance of COX2 in inhibiting antitumor immune responses is provided by an *in vivo* study in which COX2 expression was silenced with antisense oligonucleotides or COX2 activity was blocked with a selective COX2 inhibitor.[173] Knockdown/inhibition of COX2 resulted in increased lymphocyte infiltration, increased levels of IL-12 and IFNγ, and decreased levels of IL-10, ultimately reducing tumor burden.[171, 173] Thus, inhibition of COX2 and PGE using COX2 inhibitors may stimulate cellular immunity, resulting in potent antitumor effects.[172]

RANK/RANKL

Receptor activator of NFkB (RANK)[8] is a member of the tumor necrosis factor (TNF) receptor molecular subfamily that is associated with immune cell function. It has been shown that RANK is highly expressed in breast and prostate cancers.[174] The engagement of RANK with RANK ligand (RANKL) expressed on regulatory T cells leads to the expansion of regulatory T cells, one of the major types of immunosuppressive cells in the tumor microenvironment, ultimately forming an immunosuppressive niche that contributes to cancer bone metastasis and disrupts effector T cell function.[175] Since this pathway is important in bone marrow metastasis of prostate cancer in humans and immunosuppression, RANK/RANKL is a clinically validated target.

Resisting killing by T cells

Antiapoptotic proteins

Tumors can prolong their survival by overexpressing antiapoptotic proteins. Well-known antiapoptotic proteins include Bcl-2, Bcl-xL, X-linked inhibitor of apoptosis protein (XIAP), survivin (SVV), and an active form of phospho-Akt (pAkt). Upregulated Bcl-xL has been found in 63% of hepatocellular carcinoma specimens and has been associated with poor survival.[176] High expression of SVV or XIAP (for review, see ref. 177[177]) has also been observed in numerous cancers. Both XIAP and SVV have been shown to be highly expressed in malignant mesotheliomas.[178] XIAP overexpression in renal cell carcinomas was associated with worse prognosis [179] and SVV overexpression was associated with tumor progression, tumor cell resistance to chemotherapy, and tumor recurrence[180] (for review, see[177,181]). In one study, tumor expression of antiapoptotic proteins was linked to tumor immune evasion. Kim et al. developed an HPV-16 E7–expressing tumor capable of escaping attack by E7-specific CD8+ T cells through multiple cycles of *in vivo* immune selection.[182] Further characterization of the tumor revealed increased expression of pAkt, which led to upregulation of antiapoptotic

proteins Bcl-2, Bcl-xL, and XIAP. Tumors can also express activated signal transducer and activator of transcription 3 (STAT3), which is associated with numerous oncogenic signaling pathways and linked to increased proliferation and inhibited apoptosis of tumor cells (for review, see ref. 183[183]). This constantly activated STAT3 pathway in tumor cells has multiple effects. For example, STAT3 signaling pathways upregulate the antiapoptotic protein BCL-X, rendering the tumor cell more resistant to T-cell induced apoptosis.

Inducing apoptosis of T cells

Co-inhibitory molecules

Tumors can evade immune attack by inducing apoptosis of T cells. When induced by oncogenic signals or in response to endogenous antitumor immune responses, tumors upregulate a co-inhibitory molecule, programmed death ligand 1 (PD-L1), which functions as an immune checkpoint signal.[6, 184-187] Binding of PD-L1 to program death receptor-1 (PD-1) on activated T cells[188, 189] results in T-cell anergy or death, thus dampening antitumor activity and promoting tumor growth.[188, 190, 191] Studies have also shown high levels of PD-L1 on tumor-associated myeloid cells in the tumor microenvironment of human cancers, serving as an important immune escape mechanism.[192,193] These discoveries propelled development of the current PD-1/PD-L1 blockade therapeutic strategies, which have been successful in overcoming this tolerance mechanism. Antibody blockade of PD-L1 can protect $CD8^+$ T cells from apoptosis *in vitro* and augment the antitumor effects of adoptively transferred T cells[194] and tumor cell-based vaccines.[195] In addition, clinical trials using anti-PD-1 and anti-PD-L1 antibodies showed durable tumor regression and prolonged stabilization of disease in non-small cell lung cancer, melanoma, and renal cell carcinoma.[185, 196-200] Other novel approaches targeting PD-L1, including interference RNA or small molecules (for review, see ref. 201[201]) and soluble PD-1, which can bind PD-L1 and render it inactive,[202] are under development. Encouraging clinical results using single blocking agents against PD-1 have led to trials exploring the combination of anti–PD-L1 antibody or anti–PD-1 treatment with a granulocyte macrophage colony-stimulating factor (GM-CSF)-secreting allogeneic pancreatic tumor cell vaccine (GVAX) in human patients.[203]

B7-H4 is another co-inhibitory molecule that is expressed on the surface of tumor cells and immunosuppressive tumor-associated macrophages and has been used as a negative prognostic indicator for many human tumors. It has the ability to inhibit T-cell proliferation, cell cycle progression, IL-2 cytokine production, and effector T cell function. The specific receptor of B7-H4 has not yet been identified, necessitating further investigation (for review, see ref. 204[204]). As B7-H4 molecules play such an important role in inhibiting T-cell function, strategies aimed at blocking their activity are currently being developed to improve the efficacy of cancer immunotherapy. The application of monoclonal antibodies that block B7-H4 has been shown to promote T-cell responses,[205] although studies using anti-B7-H4 combined with immunotherapy remain to be tested.

Fas ligand

A wide variety of tumors have been reported to express Fas ligand (FasL/CD95L) (for review, see ref. 10[10]). Upregulation of FasL on tumor cells might be another mechanism that allows tumors to counterattack T cells. FasL is a transmembrane protein belonging to the TNF superfamily and the death receptor subfamily that can trigger apoptotic cell death when bound to its Fas (CD95) receptor. FasL expression and its association with tumor immune escape have been extensively studied. Activated effector T cells upregulate expression of Fas on their surface upon recognition of tumor antigenic peptides.[206] It has been proposed that upregulation of Fas ligand on tumor cells enables the tumors to counterattack T cells.[207-213] When FasL on tumors interacts with the Fas receptor on T cells, FasL delivers death signals to Fas-expressing T cells resulting in apoptosis of tumor-specific effector T cells that have infiltrated the tumor[207,208,213] However, the role of FasL in tumor immune evasion is not entirely clear[10] and several contradictory results have been reported in recent studies.[10,214-217] For instance, FasL expression on tumor cells may confer antitumor and proinflammatory effects.[207,211,217,219] Researchers have therefore hypothesized that other immunosuppressive factors are required in order for FasL to exert its effect.[209,213] As shown in the next section, galectin-1 can help to create an immunosuppressive tumor microenvironment in favor of FasL action. Despite its debatable role in immune counterattack, FasL still presents a potential target for cancer therapy. Strategies to downregulate FasL expression or block FasL on tumors may decrease its binding to Fas on T cells, thus decreasing Fas-mediated apoptosis of T cells. Downregulation of FasL expression using an antisense FasL has been shown to significantly reduce tumor bulk and suppress tumor immune evasion of colon cancers in a preclinical model as a result of increased T-cell infiltration within tumors.[220] Further research is encouraged and indeed necessary to unravel the application of FasL inhibition in cancer therapy.

Galectin-1

Galectin-1 (Gal1) overexpression by tumors contributes to immune evasion by promoting T-cell apoptosis. Gal1 is a β-galactoside-binding protein that is involved in cell–cell adhesion,[221] cell–matrix interactions,[221-223] immune system homeostasis[224,225] and cell growth.[225] It is also associated with angiogenesis,[226,227] transformation,[228] and poor prognosis.[226, 229-231] Studies have shown that Gal1 is overexpressed on tumor cells and secreted at high levels in a wide variety of cancers (for review, see ref. 232, 233[232,233]), in which Gal1 may serve as a negative regulator of immune responses.[234] Gal1 interacts with a receptor on T cells that is yet to be identified, and can induce apoptosis of activated T cells.[215,234] There are contradicting opinions on whether CD45 is the functional Gal1 receptor expressed on T cells.[235-241] Gal1 is a determining factor of tumor cell-induced T-cell apoptosis, as demonstrated by *in vitro* and *in vivo* Gal1 knockdown experiments.[215] Hypoxia, which is commonly present in solid tumors, enhances Gal1 secretion from tumors, further promoting T-cell apoptosis.[242,243] Expression and cell surface/extracellular matrix presentation of Gal1 on

tumor cells contributes to tumor cell-induced T-cell death,[243-245] which requires direct T cell–tumor cell contact.[245] High expression levels of Gal1 by tumor-associated stromal cells[246-249] and tumor-associated blood vessel endothelium[250, 251] enhance this process. Upon encountering its target on T cells, Gal-1 induces the caspase-dependent mitochondrial route of apoptosis involving $p56^{Lck}$ and ZAP70.[235, 245] Furthermore, extracellular Gal1 can regulate the survival of tumor-infiltrating T cells by promoting Fas ligand-induced apoptosis in T cells, thus reinforcing the immunoregulatory effect of Fas ligand.[252] As mentioned previously, Gal1 can help create an immunosuppressive microenvironment in favor of FasL action. Gal1 may suppress IFNγ production and increase IL-10 release from T cells[215 253] or skew the Th1/Th2 cytokine balance toward a more Th2 cytokine profile,[253] thereby further decreasing cellular immunity against tumors. Targeting galectin-1 might promote antitumor responses by improving T-cell infiltration into tumors, reducing T-cell death, and enhancing cellular immunity (for review, see ref. 232[232]). Strategies currently under investigation include Gal-1 neutralizing antibodies,[254, 255] competent inhibitors of Gal1-binding,[256-259] and metabolic modifiers of N-acetyl-D-Lactosamine (LacNAc).

TRAIL, RANTES, RCAS1

Other mechanisms that tumors employ to outmaneuver immune attack by inducing T-cell apoptosis involve TRAIL, RANTES, and RCAS1. TNF-related apoptosis-inducing ligand (TRAIL) is a type II transmembrane protein of the TNF family that can activate apoptosis through the death-signaling receptors DR4 and DR5 and formation of a death-inducing signaling complex[208] (for review, see ref. 209[209]). TRAIL shares significant homology with FasL, which as mentioned above, also belongs to the TNF family and can induce T-cell apoptosis.[207, 211, 214] Moreover, TRAIL seems to suppress cytotoxic T cell responses in a manner similar to that of FasL.[216] Both tumor cell membrane-bound and soluble forms of TRAIL can initiate apoptosis in IL-2–secreting T cells, but not in inactivated T cells.[210] RANTES (also known as CCL5) is a chemokine that can also activate the apoptotic cell death pathway in T cells. RANTES is a strong chemoattractant for $CD8^+$ T cells and can bind to G protein-coupled receptors CCR1, CCR3, CCR4, and CCR5 on T cells.[213] Upon binding to CCR5 on tumor infiltrating T lymphocytes, RANTES activates a CCR5-dependent apoptotic pathway that involves the release of cytochrome-c into the cytosol, activation of caspase-3 and caspase-9 pathways, and cleavage of poly ADP-ribose polymerase (PARP).[206, 260, 261] Hypoxia in the tumor microenvironment can induce strong release of RANTES, which promotes tumor migration.[262, 263] In addition, RANTES in serum is associated with cancer clinical stage and tumor progression in several cancers (for review, see ref 264[264]).[191, 263, 265-267] One study demonstrated that RANTES may induce Fas-mediated apoptosis of cytotoxic T cells,[268] whereas another study found that RANTES is able to enhance regulatory T cell-mediated $CD8^+$ T cell killing.[269] Tumors can also enhance T-cell apoptosis by expressing the membrane ligand receptor-binding cancer antigen expressed on Siso cells 1 (RCAS1), which is secreted by ectodomain shedding.[218, 270] RCAS1 is expressed in a variety of tumors and is related to poor patient survival (for review, see ref. 270, 271[270,271]). Soluble RCAS1 can bind to RCAS1 receptors on activated T cells, initiating cell cycle arrest and thereby suppressing clonal expansion and increasing the destruction of RCAS1 receptor-positive T cells via apoptosis.[217, 218, 272] One study used shRNA to knock down RCAS1 expression, which reduced T-cell apoptosis and partially reversed T-cell function.[273] However, current knowledge of the role of TRAIL, RANTES, and RCAS1 in T-cell apoptosis is very limited and further research is recommended before these 3 factors can be used as immunotherapeutic targets. Future development of new strategies to interfere with their immunosuppressive effects may be helpful as an adjuvant to cancer treatment.

Conclusion

The tumor microenvironment is predominantly infiltrated with immunosuppressive factors that cripple T cell responses against the tumor. These factors are not present in normal tissues, but are components of tumor regulatory pathways in response to inflammatory or infectious etiologies. They are also induced or "hijacked" by tumor cells to act as tumor protectors. Altering these factors may provide effective cancer immunotherapy. For example, PD-1 and PD-L1 have become 2 of the most exciting targets for immune-based cancer therapies.

Despite efforts to understand tumor-induced immunosuppressive factors and their interactions in the tumor microenvironment, our current understanding is insufficient to develop a comprehensive treatment strategy for many cancers. Moreover, targeting one single immunosuppressive factor is often not effective because tumor cells have formed a network of immunosuppressive factors to protect them and have programed the tumor microenvironment to be immune quiescent. Identification of novel and effective molecular targets in the tumor immunosuppressive network and stimulants of T-cell–mediated immunity is desperately needed. Treatment strategies that change the balance of the immune regulatory network and reprogram the tumor microenvironment from an immune quiescent one to an immune active one may render tumors more susceptible to immunotherapies that would be otherwise not be effective as monotherapy. Finally, strategies for targeting the tumor immunosuppressive network as a whole, rather than targeting a single molecular target, should also be established.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Benjamin Yang for his helpful comments and critical review of the manuscript. This review is not intended to be an encyclopedic one, and we apologize to those whose work is not cited.

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