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REVIEW

Dynamic cross-talk between tumor and immune cells in orchestrating the immunosuppressive network at the tumor microenvironment

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Abstract Accumulating evidence indicates that a dynamic cross-talk between tumors and the immune system can regulate tumor growth and metastasis. Increased understanding of the biochemical nature of tumor antigens and the molecular mechanisms responsible for innate and adaptive immune cell activation has revolutionized the fields of tumor immunology and immunotherapy. Both the protective effects of the immune system against tumor cells (immunosurveillance) and the evasion of tumor cells from immune attack (tumor-immune escape) have led to the concept of cancer immunoediting, a proposal which infers that a bidirectional interaction between tumor and inflammatory/regulatory cells is ultimately responsible for orchestrating the immunosuppressive network at the tumor site. In this context, a major challenge is the potentiation or redirection of tumor antigen-specific immune responses. The success in reaching this goal is highly dependent on an improved understanding of the interactions and mechanisms operating during the different phases of the cancer immunoediting process. In this review, we discuss the multiple defense and counterattack strategies that tumors have devised in order to evade immune attack and to thwart the effectiveness of several immunotherapeutic approaches.

Keywords Inflammation · Immunosuppression · Tumor-immune escape · Tumor immunoediting

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Cancer Immunoediting: dynamic cross-talk between the tumor and immune cells

The "cancer immunoediting" hypothesis, recently put forward by Schreiber et al. [31], has integrated mechanisms of tumor-immune escape with classical immunosurveillance theory. The renaissance of tumor immunosurveillance as part of the new concept of "immunoediting" emerges from the idea that the host's immune system not only protects against tumor development, but can also inadvertently promote tumor growth by selecting tumor escape variants with reduced immunogenicity. It is proposed that the process of cancer immunoediting comprises three phases. The first phase, referred to as "elimination," encompasses our traditional understanding of cancer immunosurveillance, in which cells of the innate and adaptive immune systems recognize and thereby destroy developing tumors, thus protecting the host against cancer. The second phase is "equilibrium," a protracted period in which ongoing tumor growth and immune surveillance enter into a dynamic balance with one another. The third phase is "escape", where tumor variants that can avoid immune-mediated destruction emerge and develop into clinically apparent neoplasms [31].

Certainly, a better understanding of the interactions between tumors and the immune system will lead to novel and more effective cancer immunotherapy strategies. As such, we summarize here the recent findings on different mechanisms leading to tumor-immune escape, including strategies employed by tumor cells that permit them to resist immune-mediated attack, particularly those that specifically thwart or counteract effector T cell responses.

Natural history of the relationship between tumors and the immune system

The first notion of a defense system recognizing tumor cells as foreign was postulated by Paul Ehrlich in the beginning of the last century [32]. In response to his pioneering foresight, the field of tumor antigens has evolved and several new concepts have emerged as central to our current understanding. Among them, we now understand that tumor tissue is not a plain box or static entity containing a fixed pool of different antigens, but it is instead a complex and evolving tissue modulated and sculpted by the cellular microenvironment. Likewise, it is important to recognize that a solid tumor is composed of different cellular compartments, including neoplastic tissue and stromal cells [49], both of which may develop strong interactions with the immune system.

Among the earliest supporters of Ehrlich's hypothesis were Burnet and Thomas who postulated *the theory of tumor-immune surveillance* [11, 131]. Burnet and Thomas proposed that tumors appeared more frequently but were eliminated efficiently by the immune system, even before they were clinically detectable. However, in spite of the presence of an effective immune system, tumors arise and develop from normal tissues and invade surrounding and distant sites, suggesting that malignant cells have the capacity to devise multiple strategies to evade or to counterattack the immune response.

Mechanisms of tumor-immune resistance

Mechanisms used to elude recognition include tumor-induced impairment of antigen presentation, activation of negative costimulatory signals, and elaboration of immunosuppressive factors (Fig. 1). In addition, cancer cells may promote the expansion and/or recruitment of regulatory cell populations that can contribute to the immunosuppressive network; these populations include regulatory T cells (Tregs), myeloid suppressor cells, and distinct subsets of immature and mature regulatory dendritic cells (DCs).

Alterations in the antigen presentation machinery

During the past decades, many laboratory groups participated in the identification and characterization of the structure and the molecular nature of different tumor antigens recognized by T cells [20, 30, 89]. However, to elude immune recognition, tumor cells employ different mechanisms to modify, down-regulate or even lose these antigens completely.

Mechanisms that include down-regulation of antigen expression can vary from decreased expression levels to a complete loss of one or more tumor antigens [107, 118, 124]. For example, the Melan-A/MART-1 antigen characteristic of melanoma can be silenced via its promoter, thus permitting the neoplastic tissue to avoid recognition by specific T cells [62, 113].

Tumors, like viruses, can also undergo "*antigenic drift*" in which the accumulation of point mutations result in cell surface antigens that are no longer recognized by the specific cytotoxic T cells [4].

The endogenous (class-I) antigen presentation machinery (APM) plays a crucial role in the generation of peptides from endogenously synthesized proteins, like tumor antigens, and in their presentation to CTL. Several defects in APM components, including the transporter associated with antigen processing (TAP) and components of the immunoproteosome (LMP-2, LMP-7), have been identified in head and neck, bladder and astrocytic tumors, among others [13, 29, 70, 111]. These findings support the notion that alterations in the APM might account, at least in part, for the resistance of tumor cells to immune recognition.

Also, in order to thwart CTL responses, tumor cells lose MHC molecules or alter their expression, thus rendering the tumor antigens invisible and, therefore resistant to CTLs. In this context, more than 50% of all the tumors show a complete loss of MHC class-I molecules or loss of at least a single allele. Several laboratories demonstrated that different types of tumors, including leukemia and melanoma, decrease the expression of HLA-A and HLA-B alleles [26, 38], and that such down-regulation has important prognostic value [12]. Moreover, complete loss of expression of HLA class I alleles is a phenotype found in many human tumors [53]. The HLA loss could be caused by different mutations involving β_2-microglobulin genes [16]. In addition to the aforementioned HLA abnormalities, the HLA phenotype may be altered by the hemizygous loss of HLA-A, -B and -C alleles, generally caused by the presence of large deletions in chromosome 6 [51] or loss of single HLA alleles [110].

It is clearly established that cells that express lower levels of MHC class I molecules are more susceptible to lysis by NK cells [139]. In addition, expression of non-classical

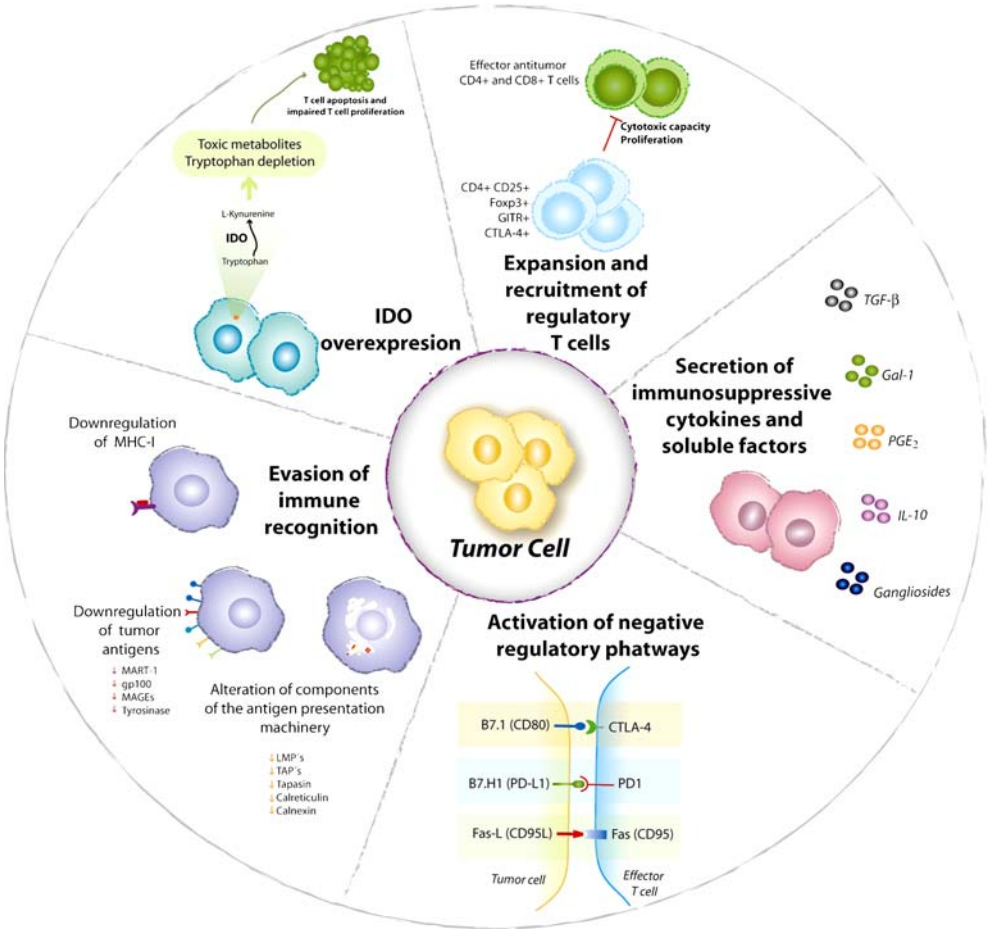

Fig. 1 Immunosuppressive strategies used by tumors to evade immune responses. Tumors employ a plethora of immunosuppressive mechanisms, which may act in concert to counteract effective immune responses. These include tumor-induced impairment of the antigen presentation machinery, activation of negative costimulatory signals in the tumor microenvironment (CTLA-4/B7, PD-1/PD-L1, Fas/ FasL), elaboration of immunosuppressive factors (*IL-10*, *TGF-β*, galectin-1, gangliosides, PGE_2), and overexpression of indoleamine 2,3 dioxygenase (*IDO*). In addition, different regulatory cell populations contribute to this immunosuppressive network including $CD4^+CD25^+$ regulatory T-cells (Tregs) and inducible T regulatory (Tr1) cells which negatively impact on the fate of effector T cells. Abbreviations: *Gal-1* galectin-1, PGE_2 prostaglandin-E_2, *TGF-β* transforming growth factor-*β*, *MHC-I* major histocompatibility complex, *TAP* transporter-associated protein

HLA molecules such as HLA-G and HLA-E, which belong to the group MHC class Ib, also modulate the immune response by inhibiting NK-cell-mediated cytotoxicity [108, 114, 141]. The expression of HLA-G in melanoma cells has been shown to contribute to cell evasion of immune response by hampering NK cell recognition [92], while the expression of HLA-E seems to play a role in the inhibition of NK cell-mediated lysis [1]. HLA-E binds to the leader peptide derived from the polymorphic classical major histocompatibility molecules. This peptide binding is highly specific and stabilizes the HLA-E protein, allowing it to migrate to the cell surface where it can interact with CD94/NKG2A receptors on NK cells. This interaction inhibits NK cell-mediated lysis of cells displaying HLA-E. If the leader peptide is not present in the endoplasmic reticulum, HLA-E is unstable and is degraded before it reaches the cell surface. In damaged cells, such as virally infected or tumor cells, down-regulation of classical HLA molecules (HLA-A, HLA-B and HLA-C) prevents stabilization of HLA-E by the leader peptide. Under these circumstances, HLA-E does not reach the cell surface and the cell is then vulnerable to lysis by NK cells. In addition, even when tumor cells express normal levels of MHC-I molecules and tumor-specific antigens (TSA), the lack of costimulation (B7.1/CD80 and B7.2/CD86) would provide another mechanism by which tumor cells can circumvent the immune system and remain undetectable [34].

Since a number of excellent reviews have been devoted to defects in antigen processing and presentation [29, 70], we will not discuss these mechanisms in detail and instead will focus on active immunosuppressive strategies developed by tumor cells.

Tumor cell resistance to apoptosis

Tumor cells possess a wide variety of mechanisms that permit them to resist CTL-induced apoptosis. Although, a direct role for these mechanisms in tumor-immune escape has only been shown in a few instances, it is likely that resistance to apoptosis is relevant not only for tumorigenesis, but also has influence on mechanisms of immunosurveillance and immunotherapy.

A critical strategy used by tumors to acquire resistance to apoptosis is the over-expression of anti-apoptotic molecules. The anti-apoptotic proteins $FLIP_{L,S}$ interfere with the induction of apoptosis at the level of death receptors (e.g. Fas/CD95) by inhibiting recruitment of caspase-8, but they do not prevent apoptosis induced by perforin/granzyme [47, 60]. Similarly, enhanced Bcl-2 expression correlates with the grade of malignancy of human tumors and protects different tumor types from apoptosis [137], and the anti-apoptotic Bcl-2 family members, Bcl-x_L and Mcl-1 are up-regulated in several types of tumors and can confer resistance to multiple apoptotic stimuli [33]. Furthermore, the IAP family member, survivin, is expressed in a highly tumor-specific manner and can confer resistance to CTL-induced apoptosis [104]. Interestingly, in addition to anti-apoptotic effects associated with the inhibition of the apoptosome formation, survivin also has a role in cell cycle regulation [104].

In addition to blockade of the death receptor pathway, tumor cells can also resist killing by CTLs through direct interference with the perforin/granzyme cytotoxic pathway. In this regard, the serine protease inhibitor PI-9/SPI-6 that inhibits granzyme B is expressed in a variety of human and murine tumors and its overexpression results in resistance of tumor cells to CTLs [6, 76]. Finally, the expression of soluble receptors that act as decoys for death ligands may also interfere with apoptosis induction via death receptors [46]. In this regard, soluble Fas/CD95 and decoy receptor 3 (DcR3) interrupt Fas/CD95-mediated signaling and inhibit FasL-induced cell death [18].

Thus, resistance of tumor cells to the effector mechanisms of CTLs can be generated by inhibition of death receptor or granzyme/perforin pro-apoptotic pathways, leading not only to escape of the tumors from immunosurveillance, but also having a profound influence on the efficacy of immunotherapy strategies.

The immunosuppressive network

IDO (Indoleamine 2,3 dioxygenase)

A connection between elevated urinary tryptophan catabolites and bladder cancer was first reported in 1956 [9]. IDO is a heme-containing enzyme that catalyzes the oxidative breakdown of the essential amino acid tryptophan via the kynurenine pathway. Elevated levels of IDO-generated catabolites have been associated with a number of malignancies, including melanoma and colon and endometrial carcinoma. Although, this phenomenon was initially thought to be a consequence of the antitumor activity of IFN-γ, which stimulates expression of IDO in tumor cells [91], an independent mechanism action has been proposed for IDO, suggesting its participation in tolerance and immunosuppression in tumor-bearing hosts [81]. Specifically, Uyttenhove et al. demonstrated that expression of IDO by immunogenic mouse tumor cells prevents their rejection by pre-immunized mice. This effect was accompanied by diminished accumulation of antigen-specific T cells at the tumor site that was partially reversed by systemic administration of 1-methyl-tryptophan (1-MT), a competitive inhibitor of IDO [132]. Beside these effects of IDO activity within the tumor itself, other findings suggested that IDO might regulate the afferent arm of the antitumor immune response, at tumor-draining lymph nodes (TDLN) [82]. IDO appears to be able to create potent local, and even systemic, immunosuppression, by a mechanism of action that still remains to be clarified. However, there is currently sufficient evidence showing that deprivation of tryptophan favors the induction of apoptosis and cell cycle arrest in effector T cells [82]. On the basis of these findings, it is possible that IDO might render the TDLN a tolerizing microenvironment, and thus contribute to tumor-immune escape. Recently, it has been shown that IDO is under the control of the tumor suppression gene *Bin1* [80].

A number of pharmacological compounds that could potentially function as specific IDO inhibitors are currently available [80, 132]. By potentiating antitumor immune responses in combination with chemotherapy or other immunotherapy strategies, IDO inhibitors may offer a novel possibility of overcoming tumor-immune resistance and of promoting tumor regression. In this regard, Muller et al. have shown that small molecule inhibitors of IDO cooperate with chemotherapeutic agents to elicit regression of established tumors [80].

Expansion of T regulatory cells (Tregs) and secretion of immunosuppressive cytokines

$CD4^+$ $CD25^+$ $FoxP3^+$ Tregs cells were identified by Sakaguchi et al. [117] as a natural occurring $CD4^+$ T cell subset (comprising 5–10% of all peripheral T cells) constitutively expressing CD25 that suppresses T cell responses in vivo [117]. Tregs contribute to the prevention of autoimmune disorders by controlling the activity of autoreactive T lymphocytes and by suppressing the proliferation of antigen-specific effector and bystander T cells [117]. Recent studies

have demonstrated that immunosuppression mediated by Tregs is one of the most critical mechanisms of tumor-immune escape and a major hurdle for successful tumor immunotherapy [146]. By modulating the tumor microenvironment through the secretion of selected chemokines, cancer cells can actively prevent the induction of antitumor immunity through the differentiation, expansion and/or recruitment of Tregs. Indeed, recent work has identified a distinct set of chemokines that drive the recruitment of Tregs, namely thymus and activation-regulated chemokine (TARC or CCL-17) and macrophage-derived chemoattractant (MDC or CCL-22), both chemokines with affinity for the receptor, CCR4, expressed on Tregs [147].

Natural Tregs are found at a higher frequency in peripheral blood of cancer patients compared to healthy donors and have been shown to induce tolerance at the tumor microenvironment, facilitating metastatic spread of cancer cells [56, 68]. When Tregs were depleted in mice, transplantable tumors were efficiently rejected by the host immune system [120]. Interestingly, Dannull et al. recently demonstrated that vaccine-mediated antitumor immunity could be significantly enhanced following depletion of Tregs [23]. In addition, administration of anti-CD25 monoclonal antibody and/or anti-CTLA-4 antibody for a limited period of time also provoked effective tumor-specific immunity against syngeneic tumor cells [90]. Recently, Curiel et al. demonstrated that Tregs confer immune privilege to ovary tumor cells. The authors found that large numbers of $CD4^+$ $CD25^+$ $Foxp3^+$ Tregs in tumors and malignant ascites inversely correlated with the survival of patients with malignant ovarian carcinoma. Interestingly, in this clinical setting, Tregs were recruited to the tumor site under the influence of the chemokine CCL22 produced by tumor cells and macrophages in the tumor microenvironment [14].

In addition to $CD4^+$ $CD25^+$ $FoxP3^+$ Tregs' recent studies highlighted the importance of inducible T regulatory (Tr1) cells and T_H3 cells in suppressing T-cell responses [145]. The immunoregulatory functions of Tr1 and T_H3 cells have been attributed to their capacity to secrete immunosuppressive cytokines such as IL-10 and transforming growth factor-β (TGF-β) [112]. In contrast, naturally occurring Tregs can suppress the effector immune response by cell-cell contact or by release of immunosuppressive factors [147].

In conjunction with the major roles of Tregs and Tr1 cells in suppressing effector T cell responses, it has been postulated that an imbalance in T_H1/T_H2 cytokine production may also be responsible for tumor cell evasion, with a shift toward a T_H2 response and induction of immunosuppressive cytokines including IL-10 and IL-4 [54]. As an example of this phenomenon, low doses of the alkylating agent cyclophosphamide (Cy), induce a T_H2 shift in the cytokine profile of syngeneic lymphoma-bearing rats, which may be in part responsible for its anti-metastatic effect. Such a treatment reduced the splenic production of IL-10, TGF-β and nitric oxide, and restored the lymphoproliferative capacity [71–73]. In broad agreement with early studies of North et al., who showed that Cy favors the elimination of tumor-induced suppressor T cells [88], preliminary evidence in a rat lymphoma model supports the concept that Cy may selectively eliminate $CD4^+CD25^+$ Tregs (Scharovsky et al., unpublished data).

In conclusion, the idea that removal and/or inhibition of $CD4^+CD25^+$ Tregs or inducible Tr1 cells can abrogate immunological unresponsiveness to syngeneic tumors, has established novel strategies of evoking tumor immunity that would boost other cancer immunotherapy strategies.

Tolerogenic dendritic cells (DCs) and myeloid suppressor cells (MSCs) in cancer

Dendritic cells (DCs) are critically important for the generation and maintenance of an anti-tumor immune response [125]. Data from many laboratories obtained during the past few years indicate that defects in DCs are among the main factors responsible for tumor escape. DC abnormalities manifest in several major ways in the tumor microenvironment including: (a) decreased presence of functionally competent DCs, (b) accumulation of immature DCs, and (c) expansion of tolerogenic/regulatory DCs.

Since there are several excellent reviews that have been devoted to the study of DCs in cancer [125], we will only focus here on the role of MSCs in tumor-immune escape. MSCs represent a heterogeneous population of myeloid cells, including immature macrophages, granulocytes, DCs and other myeloid cells at earlier stages of differentiation, which can be identified in mice by expression of CD11b and Gr-1 [63] These cells are capable of inactivating both $CD4^+$ and $CD8^+$ T cells and are responsible for tumor-related immune dysfunction. The number of MSCs in tumor-bearing hosts increases steadily during tumor progression, since the tumor-derived factors that alter myeloid differentiation accumulate in proportion to tumor burden [87, 130]. The functional activity of MSCs involves the inhibition of IFN-γ production by $CD8^+$ T cells in response to peptide epitopes presented by MHC-I molecules on the surface of MSCs [37]. This effect depends on MHC-I expression by MSCs, requires direct cell–cell contact, and is dependent on reactive oxygen species such as hydrogen peroxide [37]. Interestingly, although nitric oxide is required for MSCs-induced T cell inhibition, the enzyme arginase-I mediates the inhibition of allogeneic T cell responses by MSCs [10]. These cells can inhibit cytokine production by T cells and this effect is abrogated by the addition of the hydrogen peroxide scavenger catalase, implicating hydrogen peroxide as a critical effector molecule similarly to the mouse MSCs [10].

Alterations of signal transduction molecules: a mechanism driven by the tumor microenvironment with consequences for tumor-immune escape

Patients in advanced stages of cancer and mice with large transplantable tumors have compromised systemic immune responses with highly decreased delayed-type hypersensitivity (DTH) responses. In this regard, T and NK cells often exhibit alterations in their proliferative and cytotoxic capacities as well as in cytokine secretion [5]. Several observations showing alterations in signal transduction molecules in T and NK cells from both tumor-bearing mice and cancer patients provide a molecular basis to understand this immune dysfunction more completely [78, 138].

Of particular interest is the correlation observed between CD3-ζ expression and the disease stage in cancer patients [75]. Interestingly, evidence has been provided for tumor-induced degradation of the CD3-ζ chain. Tumor cells can induce the activation of intracellular peptidases in T lymphocytes that is responsible for decreased or absent expression of signal transduction molecules, including the CD3-ζ chain in activated T cells [140]. Finally, other mechanisms, including generation of free oxygen radicals and increased arginase activity within the tumor microenvironment, have been proposed to account for decreased CD3-ζ expression in cancer [57, 109]. In this regard, it has been shown that human T cells stimulated and cultured in the absence of L-arginine lose the expression of the CD3-ζ chain and demonstrate impaired proliferation and decreased cytokine production [109]. Therefore, the regulation of L-arginine concentration in the microenvironment could represent an important mechanism via which the expression of CD3-ζ chain is modulated, with critical consequences in TCR-mediated signaling and T cell function.

Recently, aberrant activation of STAT3 (signal transducer and activator of transcription 3) has been proposed as a novel mechanism of tumor-immune escape [136]. It was shown that STAT3 signaling in tumor cells suppresses both, innate and adaptive anti-tumor immune responses, further enhancing tumor progression [59]. Also, inhibition of STAT3 signaling up-regulates the expression of a subset of immunoregulatory genes, including a number of chemokines that promote recruitment of effector T cells [136]. Altogether, these observations suggest that the activation of STAT3 signaling contributes to the establishment of an immunosuppressive tumor microenvironment. Proof-of-concept studies in cell culture and animal models have validated STAT3 protein as a promising molecular target for novel cancer therapies, including small molecule inhibitors of STAT3 signaling [59, 136].

Other observations of tumor-induced alterations of T-cell signal transduction molecules have been provided from metastatic colorectal carcinoma patients who failed to respond to the tumor antigen epithelial mucin-1 (MUC-1) vaccine. These non-responding patients had T cells that lacked NF-κB p65; in contrast to those patients responding to treatment, who showed increased levels of NF-κB and augmented T-cell effector functions [55]. Interestingly, alterations in NF-κB family proteins, specifically the failure of p65 translocation to the nucleus, occur earlier and more frequently than the decrease in CD3-ζ chain and these defects are paralleled by an impaired ability to produce T_H1 cytokines. These initial changes are then followed by a marked decrease in CTL functions [56].

Other immunosuppressive factors in the tumor microenvironment

Other tumor-derived or tumor-induced suppressive factors result in impaired T-cell function [102]. The production of prostaglandin E_2 (PGE_2) by macrophages is enhanced by tumor-derived factors, which induce an immunosuppressive state in glioma-bearing hosts [85]. In addition, RCAS1, a receptor binding cancer antigen that induces cell cycle arrest and apoptosis of effector T cells, has been identified as a tumor evasion mechanism in different tumor types, mainly those of gynecological origin [86].

The Fas (CD95)/FasL (CD95L) counterattack controversy

The Fas-dependent cell death pathway is regulated by cognate interactions between the Fas receptor (CD95) and its ligand FasL (CD95L). Expression of FasL has been reported in different solid tumors, including melanoma and colon carcinoma, and its expression has been shown to confer immune privilege to tumors by delivering death signals to Fas-positive effector T cells [116].

Although, considerable heterogeneity in cell surface expression of FasL has been detected even within a particular tumor cell line [40], and non-specific staining of specific FasL antibodies has been demonstrated [127], it has been shown that FasL-positive tumor cells can kill Fas-positive T cells in vitro, demonstrating functional significance of FasL expression [45].

Several lines of evidence support the involvement of the Fas system in tumor counterattack. Fais et al. demonstrated that purified microvesicle preparations from melanoma cell supernatants are able to induce FasL-mediated apoptosis in Fas-sensitive human T cells, providing evidence of a novel potential mechanism of tumor-immune escape [3]. However, certain experimental evidence seems to contradict the FasL counterattack hypothesis, as a pro-inflammatory function for FasL has been also demonstrated [17, 77]. Also, some results on tumor counterattack are controversial given that many factors may influence FasL activity in vivo, including the different levels and the kinetics of FasL

expression on tumor cells, the release of different types of cytokines, such as TGF-β and IL-10, the levels of hypoxia at the tumor site, the extent of vascularization and the accessibility to immune cell infiltration [119]. A further complicating aspect in tumor-immune escape mediated by FasL is the role of soluble FasL (sFasL) [129], which is derived from cleavage of FasL by MMPs (matrix metalloproteinases), and can also counterattack CTLs, but to a lesser extent than FasL [42]. Thus, the altered expression of FasL and the shedding of sFasL may contribute to immune evasion by allowing tumor cells to escape from CTL-mediated cytotoxicity. Finally, other death factors, such as TNF-α and TRAIL, have been shown to eliminate T cells and might also contribute to suppression of T cell responses [84].

To further elucidate the pathophysiologic relevance of the tumor counterattack hypothesis, it will be essential to use defined experimental systems, in which all the above-mentioned elements are carefully controlled and modulated. These experiments will be critical to determine whether targeting tumor counterattack mechanisms might be beneficial or detrimental for cancer therapy.

Negative regulatory pathways: CTLA-4 and the PD-1/PD-L1 system

Compelling evidence indicates that costimulatory molecules with negative regulatory functions are expressed on the cell surface of tumor cells, effector T cells and Tregs. Undoubtedly, one of the best-studied regulatory signals is mediated by CTLA-4, a ligand for B7 expressed on activated T cells and naturally occurring Tregs [66, 94, 135]. Allison et al. were pioneers in demonstrating that blockade of CTLA-4 signaling might enhance anti-tumor responses [66]. Further studies supported this concept showing that antibody-mediated blockade of CTLA-4 enhances anti-tumor immunity elicited by a GM-CSF-transduced melanoma vaccine [44, 98].

In addition, the interaction between programmed death-1 (PD-1) and programmed death receptor ligand-1 (PD-L1) represents a clear example of how negative costimulatory signals may contribute to create an immunosuppressive microenvironment at the tumor site [144]. PD-L1, engages the inducible inhibitory receptor on activated T cells called PD-1 and induces phosphorylation of an immunoreceptor tyrosine-based inhibitory motif (ITIM) [144]. Dong et al. demonstrated the presence of PD-L1 (also called B7-H1) on the cell surface of a wide range of tumors [28]. The expression of PD-L1 on tumor cells of diverse histological origins suggested that this molecule might contribute to tumor-immune escape. In fact, it has been demonstrated that cancer cell-associated PD-L1 promotes apoptosis of antigen-specific human T cell clones in vitro and in vivo [8]. In addition, blockade of PD-L1 enhances DC-mediated T-cell activation and limited tumor growth, suggesting another potential mechanism by which PD-L1 restrains T cell–mediated anti-tumor immunity [15].

Furthermore, Kryczek et al. recently reported that B7-H4, a B7 family molecule, identifies a novel suppressive macrophage population in human ovarian carcinoma, and that depletion of B7-H4$^+$ tumor macrophages may represent a useful strategy to enhance T cell-mediated immunity in cancer [61].

Thus, blockade of the inhibitory pathways mediated by CTLA-4, PD-L1 or B7-H4 may be complementary approaches to augment tumor-specific T cell-mediated immunity for cancer immunotherapy.

The “sweet escape”: galectins and gangliosides

Galectins are animal lectins defined by their conserved amino acid sequences and affinity for poly-N-acetyllactosamine-containing glycoconjugates [99]. Galectin-1, a proto-type member of this family, has the potential to induce T-cell apoptosis and regulate cytokine secretion, thus inhibiting or skewing T-cell effector functions [99]. Accumulating evidence indicates the expression of galectin-1 in many different tumor types including astrocytoma, melanoma and prostate, breast and colon carcinomas [21]. Interestingly, in most cases a positive correlation exists between the expression of galectin-1 in tumor and stromal cells and the aggressiveness of these tumors [67].

Given the expression of galectin-1 in most malignant tumor types and the ability of this glycan-binding protein to down-modulate T-cell responses, we hypothesized that tumors may contribute to the immunosuppressive and anti-inflammatory microenvironment through the expression of galectin-1. By a combination of in vitro and in vivo experiments using knockdown transfectants, we established a link between galectin-1-mediated immunoregulation and its contribution to tumor-immune escape [115]. Interestingly, we observed a marked reduction of tumor mass (an effect which required intact CD4$^+$ and CD8$^+$ T cell responses) and the generation of a tumor-specific T-cell response following blockade of the inhibitory effects of galectin-1. Our observations suggest that galectin-1 contributes to immune privilege of tumors by modulating survival and effector functions of CD4$^+$ and CD8$^+$ T cells. Recently, Le et al. showed a link between tumor hypoxia and galectin-1 expression in head and neck squamous carcinoma cells [65]. Consistent with our findings, the authors found that galectin-1 expression negatively correlates with the presence of CD3$^+$ T cells in tumor sections [65].

A very recent study conducted by Park et al. in human breast carcinoma demonstrates a tight correlation between galectin-1 expression levels in cancer-associated stromal tissue and various clinicopathologic parameters, including

tumor invasiveness and lymph node metastases [52]. Moreover, we found high expression levels of galectin-1, sensitive to the immunosuppressive cytokine TGF-β, in two mammary adenocarcinoma cell lines and in a lung carcinoma cell line [24]. Accordingly, we proposed that TGF-β1 might trigger a Smad-dependent pathway to control galectin-1 expression, suggesting a possible cross-talk between different immunosuppressive factors in the regulation of tumor-immune escape. Furthermore, results from our laboratory demonstrate that low doses of Cy can modulate the kinetics of galectin-1 expression in tumor cells and its proapoptotic function in a B-cell lymphoma model [103, 143].

Accumulating evidence indicates that galectin-1 critically modulates other T cell functions including sensitization of T cells to FasL-induced cell death [74], inhibition of proximal TCR signaling [19] and suppression of T_H1 and proinflammatory cytokines [101]. Moreover, galectin-1 has been shown to enhance the secretion of IL-10 by activated T cells [134]. In addition, a very recent study demonstrates that Tregs express high levels of galectin-1 and that this protein is critical for the immunosuppressive activity of these cells [39].

The information obtained so far suggests that potent and selective small inhibitors of galectin-1 could be designed that could be used to prevent the immunosuppressive activity of galectin-1. In fact, molecules with such properties have already been developed for galectin-1 and other galectins [2, 100, 123]. However, the possibility to target galectin-1 expression in cancer has been hindered by the limited understanding of the multifunctional modes of action of this protein and its particular biochemical properties. In addition, these limitations are further complicated by the potential compensatory functions of other members of the galectin family.

In this regard, galectin-2, -3 and -9 also regulate T-cell apoptosis and modulate cytokine production in vitro, suggesting potential roles in tumor-immune escape [67, 128]. Interestingly, galectin-3 has been shown to act in a dual manner, either protecting cells from apoptosis or promoting apoptosis depending on whether the protein acts intracellularly [142] or is added exogenously [126]. Yang et al. demonstrated that T-cell transfectants overexpressing galectin-3 display higher growth rates than control transfectants and are protected from apoptosis induced by a variety of agents including Fas ligation and staurosporine [35, 142]. Interestingly, recent findings showed that recombinant galectin-3 can signal apoptosis of human T cells through binding to cell surface glycoconjugates resulting in activation of the mitochondrial pathway, cytochrome c release and caspase-3 activation [35]. Furthermore, Hahn et al. suggested a functional cross-talk between intracellular and extracellular galectins in the regulation of T-cell death; the authors demonstrated that galectin-1-induced cell death is inhibited by intracellular expression of galectin-3 [41].

Interestingly, Demetriou et al. reported that galectin-3 may play a role in restricting TCR complex-initiated signal transduction by forming multivalent complexes with *N*-glycans on the TCR [27]. Thus, galectin-3 may influence T-cell interactions with APC and control T-cell activation by negatively regulating the immunological synapse.

Gangliosides are structurally diverse acidic glycosphingolipids that exist as clusters on the cell surface and contribute to the structure of lipid rafts [122]. They function as signaling intermediates in the regulation of multiple cellular responses by modulating the activities of various receptors [48]. Enhanced production of gangliosides has been observed in different tumor types [106]. Gangliosides can inhibit multiple steps of cellular immune responses, including antigen processing and presentation, T-cell proliferation, and production of cytokines such as IFN-γ [43, 93].

Biswas et al. examined the effect of human renal cell carcinoma (RCC)-derived gangliosides on T-cell apoptosis. Induction of T cell death by tumor-derived gangliosides was partially blocked by anti-GM2, suggesting that GM2 has a role in the T-cell dysfunction observed in RCC patients [7]. In addition, the same group found that gangliosides isolated from RCC induce mitochondrial permeability transition and inhibit the activation of NF-κB, suggesting the possible contribution of these glycosphingolipids to the suppression of the inflammatory response [133]. Interestingly, it has been observed that gangliosides isolated from RCC supernatants from some patients suppressed both T_H1 (IFN-γ) and T_H2 (IL-5) cytokine responses, whereas gangliosides from other tumor types suppressed only T_H1-mediated immune responses [7]. Thus, the cytokine profile of the anti-tumor immune response in cancer patients seems to be, at least partially, influenced by the activity of different gangliosides expressed by tumors.

Immunostimulation: is cancer-associated inflammation a friend or a foe?

The phenomenon of immunostimulation was originally noticed by Richmond Prehn who established in 1971 that a mild immune response against certain tumor types might often stimulate rather than inhibit their development [96]. The findings on human breast cancer published by Stewart et al. confirmed Prehn's postulation [125], as they found that the progression of certain types of human mammary carcinomas at the first stages of tumor evolution is stimulated by a mild inflammatory response.

What is the rationale supporting these findings? Similar to the cross-talk between different immune cell types, cytokines, chemokines and growth factors produced by inflammatory cells and the stroma can act as paracrine growth factors stimulating tumor growth and progression. In fact,

tumors that appeared in cancer-prone mice immunized against a mutant oncoprotein grew faster than in non-immunized animals [121]. Interestingly, it has also been shown that $CD4^+$ T cells can enhance skin cancer progression under certain circumstances [22]. Besides, recent findings support the notion that B lymphocytes are required for establishing chronic inflammatory states that promote de novo carcinogenesis [25]. Related to soluble factors released by immune cells, several publications proposed their association with immunostimulation. IL-10 and its receptor (IL-10R) can stimulate the growth of metastatic cells of a B-cell lymphoma, establishing an autocrine loop [105]. In addition, it has been demonstrated that liver metastases are enhanced in human colorectal carcinomas by increased production of IL-10, induced by carcinoembryonic antigen (CEA) [50]. Also, immune cells can release other type of soluble factors, like those involved in angiogenesis, a critical process for tumor progression [79]. In fact, serum levels of VEGF and/or other angiogenic molecules are positively associated with cancer progression [95]. In contrast, other studies report a critical role for VEGF in the suppression of DC differentiation and maturation [36].

Remarkably, Karin et al. demonstrated that inflammation-induced tumor growth depends on TNF-α production by host hematopoietic cells and NF-κB activation in tumor cells [69]. Inhibition of NF-κB in tumor cells can convert tumor growth into tumor regression [69]. Finally, in very elegant studies, Langowski et al. recently showed that IL-12 promotes infiltration of CTLs and subsequent immunosurveillance, while IL-23, which shares the p40 subunit with IL-12, promotes tumor-associated inflammatory responses mediated by the matrix metalloproteinase MMP-9 and angiogenic factors, but reduces CTL infiltration [64]. Thus, closely related cytokines may positively or negatively influence tumor progression by modulating the magnitude and quality of tumor-associated inflammatory responses.

Concluding remarks and future perspectives

There is currently no doubt concerning the wide variety of mechanisms that tumors employ in order to evade immune attack. These immune escape strategies range from a passive failure to express MHC or resistance to CTL-mediated cytotoxicity to more active strategies involving expression of inhibitory factors and immunosuppressive cytokines (e.g. TGF-β, IL-10, galectin-1, IDO), activation of negative regulatory pathways (e.g CTLA-4, PD-1/PD-L1, B7-H4), acquisition of counterattack mechanisms (FasL, TRAIL) and recruitment of regulatory immune cells ($CD4^+CD25^+FoxP3^+$ Tregs, Tr1 cells, tolerogenic DCs and MSCs). Investigation during the past few years has provided novel insights into the cellular and molecular mechanisms involved in the bidirectional cross-talk between tumor cells and the immune system. Understanding this functional dialogue and the hierarchical status of different tumor-immune escape mechanisms at different stages of tumor progression will guide the design of novel therapeutic strategies aiming to destroy the "tumor fortress". In this regard, it will be of particular interest to investigate the kinetics of the interactions between different inhibitory molecules and endogenous factors that influence the expansion and trafficking of Tregs, Tr1 and tolerogenic DCs within tumor-draining lymph nodes and the tumor surroundings. In addition it will be of critical importance to determine the effectiveness of combined strategies involving blockade of different inhibitory signals (PD-1/PD-L1, IDO, TGF-β, IL-10, VEGF, galectin-1) together with conventional chemotherapy, vaccination or adoptive transfer of effector CTLs. In fact, progress has been made in this direction by evaluating the effects of combined strategies, such as GM-CSF-secreting vaccines plus CTLA-4 blockade or OX-40 costimulation, and chemotherapy plus IDO blockade [58, 83, 97, 135]. The current wealth of available data promises a future scenario in which inhibition of tumor escape strategies and removal of inhibitory signals in the tumor microenvironment will be successful in combination with other therapeutic strategies to overcome immunological tolerance and promote tumor rejection.

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