Reversing T-cell Dysfunction and Exhaustion in Cancer
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Abstract
In the context of chronic antigen exposure in chronic viral infections and cancer, T cells become exhausted/dysfunctional. These exhausted T cells exhibit defective proliferative capacities and cytokine production, but are not totally inert and may exert lytic functions. Importantly, exhausted T cells upregulate multiple inhibitory receptors/immune checkpoints that bind to their ligands expressed by tumor cells and antigen-presenting cells in the tumor microenvironment (TME). Immune checkpoint blockades with anti-CTLA antigen 4 (CTLA-4) and/or anti-programmed death 1 (PD-1) mAbs successfully reinvigorate tumor-infiltrating T lymphocytes and provide persistent clinical benefits to a large number of patients with advanced cancer. This great and long-awaited success for the immunotherapy of cancer has infused considerable enthusiasm in the field of oncology and fostered the development of combinatorial strategies to target the multiple mechanisms of tumor-induced T-cell dysfunction. Here, we review the critical immunoregulatory mechanisms driving T-cell exhaustion in the TME. We also discuss the development of promising combinatorial immunotherapies to counteract the mechanisms of tumor-induced T-cell dysfunction to improve the clinical efficacy of current immune checkpoint blockades. As our understanding of the mechanisms supporting tumor-induced T-cell dysfunction improves based upon preclinical and clinical studies, we expect that novel combinatorial immunotherapies will emerge to improve the clinical outcome of patients with advanced cancers. Clin Cancer Res; 22(8); 1856–64. ©2016 AACR.

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Introduction
T cells recognize tumor antigens (TA) expressed by cancer cells and induce tumor rejection in vivo (1). Although the presence of CD8+ tumor-infiltrating T lymphocytes (TIL) is usually a marker of good clinical outcome in multiple primary solid tumors (2–4), high-frequency TA-specific CD8+ T cells often fail to promote tumor regression in patients with advanced cancer (5). The paradoxical coexistence of TA-specific CD8+ T cells and tumor progression in patients with advanced cancer arises from multiple negative immunoregulatory pathways that impede T-cell–mediated tumor destruction in the tumor microenvironment (TME). The recent successes of immune checkpoint blockade with anti-CTLA antigen 4 (anti-CTLA-4) and anti-programmed death 1 (PD-1) mAbs in multiple cancers illustrate the potency of therapeutic strategies aiming at counteracting these immunoregulatory pathways. Here, we review the findings supporting the potent mechanisms of tumor-induced T-cell dysfunction in the TME, which include chronic T-cell receptor (TCR) activation, inhibitory receptors (IR), soluble mediators, suppressive cells, and metabolic restrictions. We also discuss the rationale for current and future combinatorial therapeutic strategies to improve the clinical efficacy of immune checkpoint blockade for patients with advanced cancer.

T-cell Exhaustion and IRs in Cancer
The concept of T-cell exhaustion was first described in chronic viral infections in mice and was subsequently reported in human chronic viral infections and cancer (6–9). Exhausted T cells progressively lose their functional capacities to proliferate, produce cytokine, and lyse upon chronic antigen exposure. The severity of T-cell exhaustion appears to increase with high antigen load and low CD4 help (10). Gene profiling and phenotypical studies in mice and humans with chronic viral infections and cancer have shown that exhausted T cells upregulate IRs (Fig. 1), including PD-1, CILAT-4, T-cell immunoglobulin, mucin-3 (Tim-3), lymphocyte activation gene 3 (LAG-3), and T-Cell tyrosine-based inhibitory motif (ITIM) domain (TIGIT) (refs.11–15). Interestingly, data in mice and humans have indicated that exhausted CD8+ T cells co-upregulate multiple IRs and that the pattern and number of IRs correlate with variable levels of T-cell dysfunction (9, 12, 16, 17). For example, in patients with advanced melanoma, Tim-3 is coexpressed by a fraction of effector memory and more differentiated PD-1+ TA-specific CD8+ T cells in the periphery and at tumor sites, which exhibit high-level T-cell dysfunction as compared with PD-1+ Tim-3+ and PD-1− Tim-3− CD8+ T cells (16). In contrast, the coexpression of PD-1 and TIGIT by CD8+ TILs in metastatic melanoma did not correlate with lower functional capability as compared with PD-1+ or TIGIT+ CD8+ TILs (13). CD8+ TILs that coexpress multiple IRs including PD-1 and Tim-3 appear to represent an autologous tumor-reactive repertoire, including mutated neoantigen-specific CD8+ T cells, supporting that the upregulation of IRs in the TME occurs upon chronic TCR activation by TAs (18).
T cells that upregulate IRs are not always exhausted/dysfunctional. In healthy donors, circulating PD-1^+CD8^+ T cells represent effector memory cells rather than exhausted T cells (19). In cancer patients, activated and functional CD8^+ T cells can upregulate PD-1 or Tim-3 as observed with circulating PD-1^+ BTLA^+/Tim-3^NY-ESO-1^−specific and PD-1^+Tim-3^Flu^−specific CD8^+ T cells isolated from melanoma patients (16, 17). IRs are upregulated transiently and often sequentially by antigen-specific CD8^+ T cells upon T-cell activation, exposure to common gamma-chain cytokines, or VEGF-A in vitro as shown for PD-1 and Tim-3 (20–22). For example, TA-specific CD8^+ T cells isolated from peripheral blood lymphocytes of patients with advanced melanoma upregulate TIGIT before PD-1 and Tim-3 upon stimulation with cognate antigen, and IR expression further augments upon immune checkpoint blockade in vitro (8, 13, 16). In patients with advanced melanoma, functional TA-specific CD8^+ T cells that have been either primed or expanded in vivo upon immunization with cancer vaccines also upregulate IRs (23). Altogether, these findings support the concept that IR upregulation by TA-specific CD8^+ T cells in the periphery and tumor sites depends on their differentiation and activation status (24).

Although gene profiling of Melan-A/MART-1–specific CD8^+ T cells has suggested that TA-specific CD8^+ T cells in metastatic melanoma and exhausted virus-specific CD8^+ T cells share many common features (25), the pattern of IR expression in patients with advanced melanoma and mice with chronic viral infections is not entirely identical. One example is the upregulation of the BTLA by dysfunctional CD8^+ TA-specific cells in the periphery and at tumor sites, while it is not in exhausted lymphocytic choriomeningitis virus (LCMV)–CD8^+ T cells (12, 17). This observation suggests that the molecular programs driving IR upregulation and T-cell dysfunction in chronic viral infections and cancer may not totally overlap. In particular and aside from T-cell exhaustion, one may wonder whether poor antigen presentation in the TME promotes T hyporesponsiveness as a result of T-cell anergy (26). This question still needs to be thoroughly investigated.
The mechanisms supporting the IR-mediated immunoregulatory effects on T cells are not fully understood. These include (i) the competition with costimulatory receptors for binding to their ligands to impede formation of microclusters and lipid rafts (27); (ii) negative signaling to disrupt T-cell activation through TCR or costimulatory receptors (27, 28); (iii) the upregulation of inhibitory genes such as the upregulation of BATF by PD-1 ligation (29); (iv) IL10 production by antigen-presenting cells (APC) occurring upon TIGIT/CD155 ligation (30); and (v) the imbalance of IR and costimulatory receptor competing for the same ligands as described in CD8⁺ TILs that upregulate TIGIT and downregulate CD226 (13). IRs signal through (i) intracytoplasmic immunoreceptor ITIMs such as PD-1, BTLA, and TIGIT; (ii) immunoreceptor tyrosine-based inhibitory switch motifs such as PD-1, BTLA, and 2B4; or (iii) other specific motifs such as CTLA-4, LAG-3, and Tim-3 (26, 31). There is now ample evidence that dual IR blockade, including PD-1 blockade, is more efficacious than single IR blockade in enhancing TA-specific CD8⁺ T-cell function in vitro and in vivo, as previously shown with dual PD-1/CTLA-4, PD-1/Tim-3, PD-1/LAG-3, and PD-1/TIGIT blockades (13, 14, 16, 17, 32). These observations strongly suggest that these IR pathways are nonredundant. Phenotypical and functional studies to evaluate IR expression by TILs and IR blockades in multiple cancers will help us understanding whether dual IR blockade needs to be tailored to cancer patients in personalized immunotherapy of cancer.

The initial concept of exhaustion is challenged by the observation that CD8⁺ T cells that upregulate multiple IRs are not entirely inert and exhibit functionally capacities. In chronic viral infection, two subsets of PD-1⁺/exhausted CD8⁺ T cells have been reported. TbethighEomeslowPD-1⁺Tc e l l s proliferate, produce cytokines, and convert upon chronic antigen exposure into TbetlowEomeshighPD-1hiCD8⁺ T cells that coexpress multiple IRs, exhibit reduced proliferative and cytokine-producing capacities, but exert lytic functions and accumulate in peripheral tissues (33). PD-1 blockade reinvigorates PD-1⁺/exhausted CD8⁺ T cells with little effect on PD-1⁻/CD8⁺ T cells. In chronic viral infections, T-cell exhaustion occurs in the absence of PD-1 (after genetic deletion), whereas PD-1 preserves exhausted T cells from excessive activation, proliferation, and terminal differentiation (34). Such experimental study suggests that PD-1 expression is dispensable to T-cell exhaustion and plays a critical role in preventing the terminal differentiation of CD8⁺ T cells in the presence of cognate antigens. In mice chronically infected with LCMV, CD8⁺ T cells exhibit an exhausted phenotype that proliferates and controls viral infection after transfer into naïve mice (24). This observation suggests that upon exposure to chronic antigen, exhausted T cells may correspond to effector T cells that stably differentiate into a state that is optimized to limit viral replication without causing overwhelming immunologic pathology. Whether these findings are relevant to CD8⁺ TILs present in the TME remains to be determined.

Each IR interacts with its ligand(s) often expressed by tumor cells and APCs in the TME to impede T-cell survival, expansion, and function (Fig. 1). Therefore, the availability of IR ligands in the TME plays a major role in modulating the negative regulatory effects of the IRs expressed by CD8⁺ TILs. The expression of programmed death ligand 1 (PD-L1) in the TME varies depending on the exposure to inflammatory cytokines such as IFNy produced by CD8⁺ TILs (35). In contrast, the TIGIT ligands CD155 and CD112 are expressed consistently by a large fraction of melanoma cells and APCs in the TME (13). Galectin-9 and CEACAM1 bind to Tim-3 to mediate T-cell inhibition (36, 37). Tim-3 can also bind to phosphatidylinositol expressed by apoptotic cells, and the DNA-binding protein, HMGB1, which is released in the extracellular space upon cell stress (38, 39). V-domain Ig suppressor of T-cell activation (VISTA) is a novel ligand highly expressed by myeloid cells in the TME that decreases T-cell function (40). Its receptor on T cells has not been identified yet. The same IR ligand may bind to both costimulatory receptors and IRs. For example, CTLA-4 competes with CD28 for binding to CD80 and CD86 (41), whereas TIGIT competes with the costimulatory molecule CD226 for binding to the same ligands CD155 and CD112 (30, 42). Also, CD8⁺ TILs in metastatic melanoma upregulate TIGIT, while they downregulate CD226. Therefore, in addition to the TIGIT-mediated T-cell-intrinsic inhibitory effects (43), the downregulation of CD226 expression resulting in the imbalance of TIGIT/CD226 expression by CD8⁺ TILs may contribute to dampening of T-cell responses to tumors in the TME (13). The mechanisms supporting CD226 downregulation in the TME are not fully understood.

Soluble Mediators of T-cell Dysfunction

Some immunoregulatory molecules produced in the TME, contribute to promoting T-cell dysfunction. For example, IL10 is a potent anti-inflammatory molecule produced by innate and adaptive immune cells including T cells, natural killer cells, APCs, as well as tumor cells such as melanoma (44, 45). In cancer immunology, IL10 promotes tumor growth in experimental models and is overexpressed in PD-L1+ melanoma (46, 47). Counteracting IL10 with IL10 blockade in combination with intratumoral injection of CPG reverses tumor-infiltrating dendritic cell dysfunction leading to potent antitumor T-cell responses and tumor regression in mice (48). Strikingly, high-dose IL10 and pegylated IL10 impede tumor regression in animals and enhance the expansion and functions of CD8⁺ TILs that express elevated levels of IL10R (49, 50). Therefore, IL10 may exert two opposite effects on T cells in vivo, depending on the dose of IL10 and state of T-cell activation (50). These conflicting findings have led to the implementation of clinical trials to evaluate the clinical efficacy of either pegylated IL10 or anti-IL10 mAbs together with intratumoral CpG in cancer patients. One major challenge will be to precisely identify the location, schedule, and timing of administration as well as the patient population most likely to respond to each therapy. It should also be noted that IL10R is upregulated by PD-1hiCD8⁺ T cells in the periphery and at tumor sites in patients with advanced melanoma (23). IL10R expression further augments upon PD-1 blockade, suggesting that it is a marker of T-cell activation and that PD-1 blockade may render PD-1hiCD8⁺ T cells more sensitive to endogenous IL10. While IL10 hampers PD-1hiCD8⁺ T-cell survival, IL10 blockade added to PD-1 blockade further enhances the expansion and functions of TA-specific CD8⁺ T cells (23). Such findings strongly support combinatorial therapies with dual PD-1/IL10 blockade in patients with advanced melanoma.

Preclinical data from in vitro and experimental models have shown the immunosuppressive role of adenosine, which is a metabolite produced from ATP by the CD73 ectoenzyme (51).
Downstream of CD73, the ectonucleotidase CD39 hydrolyzes ATP into AMP. CD73 and CD39 are expressed on epithelial cells, endothelial cells, multiple tumor cells, and regulatory T cells (Treg). Adenosine binds to adenosine receptors, which are ubiquitously expressed by a wide variety of immune cells, including T cells, and are further upregulated upon T-cell activation. Adenosine disrupts T-cell effector functions directly through the activation of the adenosine receptor A2AR (52) and indirectly by increasing Treg functions, decreasing APC activation and inducing myeloid-derived suppressor cells (MDSC; ref. 53). A2AR and CD73 inhibitors enhance antitumor T-cell responses in experimental models (54). In addition, dual A2aR/PD-1 blockade enhances IFNγ and granzyme B production by CD8⁺ TILs, reduces tumor growth of CD73⁺ mouse tumors, and increases survival (55). This promising combinatorial therapy is currently being investigated in cancer patients.

Indoleamine 2,3-dioxygenase (IDO) is constitutively expressed by tumor cells and APCs in the TME (56, 57). IDO expression by tumor cells can also be induced by IFNγ-producing CD8⁺ T cells in the TME (58). IDO inhibits T-cell functions through the depletion of the essential amino acid tryptophan and activates Tregs through kynurenine production (59). IDO is involved in the resistance to immune checkpoint blockade with anti–CTLA-4 and anti–PD-1 mAbs (60). Hence, combinatorial therapies with anti–CTLA-4 or anti–PD-1 mAbs and IDO inhibitor induced slow tumor growth and increased survival in mouse tumor models (60, 61). The clinical efficacy of dual IDO/PD-1 blockade has been recently observed in an ongoing trial with epacadostat (IDO inhibitor) in combination with pembrolizumab (anti–PD-1 antibody) with no major adverse events and evidence of significant clinical activity in patients with advanced cancers, including melanoma (62).

Aside from its proangiogenic properties, VEGF-A, produced by tumor cells in the TME, contributes to the induction of an immunosuppressive TME through multiple mechanisms, including the inhibition of dendritic cell maturation, the accumulation of MDSCs, and induction of Tregs in experimental models (63, 64). VEGF-A also enhances the coexpression of multiple IRs, including PD-1, CTLA-4, and Tim-3 involved in CD8⁺ T-cell exhaustion in a VEGF-R2- and NFAT-dependent manner (22). Hence, VEGF-A blockade synergizes with PD-1 blockade to decrease IR expression by CD8⁺ TILs and promote tumor regression in mice transplanted with VEGF-expressing colon cancer. Dual PD-1/VEGF blockade is currently being investigated in multiple clinical trials.

Type I IFNs play an important role in stimulating antigen-specific T-cell responses through dendritic cell polarization, T-cell activation, and differentiation. Paradoxically, experimental evidence suggests that IFNα facilitates viral persistence in chronic viral infections and promotes T-cell exhaustion and that IFNα blockade within the first few days of LCMV infections prevents the occurrence of T-cell exhaustion (65). The mechanisms used by IFNα to induce T-cell dysfunction are not fully understood and may include (i) the production of immunoregulatory molecules involved in T-cell dysfunction such as IL10, PD-L1, and IDO by APCs, and (ii) the induction and maintenance of PD-1 expression on TCR-engaged T cells (66). Interestingly, combinatorial therapy with IFNα and PD-1 blockade augmented the antitumor immunity in tumor-bearing mice (66). Such combinatorial therapy is being evaluated in patients with advanced melanoma (H.M. Zarour; unpublished data).

**Metabolic Checkpoints**

Cancer cells consume nutrients and, in particular, glucose to sustain their proliferation, restricting glucose availability to TILs (67). Glucose deprivation impedes CD8⁺ TIL effector function by limiting aerobic glycolysis, and decreasing mTOR activity and IFNγ production. Immune checkpoint blockades with anti–CTLA-4 or anti–PD-1 mAbs augment the glycolytic capacities and effector functions of TILs in experimental models (68). PD-L1 blockade also acts directly on tumor cells to inhibit mTOR activity, dampening glycolysis in tumors and increasing extracellular glucose availability (68). These observations suggest that immune checkpoint blockades counteract inhibitory signals but also by increasing T-cell metabolic fitness. Interestingly, low-level glycolytic metabolite phosphoenolpyruvate (PEP) has been shown to impede Ca²⁺–NFAT signaling and CD4⁺ TIL activation, while adoptive transfer of CD4⁺ T cells engineered to upregulate PEP improved T-cell function and overall survival in mice with B16 melanoma (69). Also, tumor-induced glucose restriction decreases the expression of methyltransferase EZH2 in T cells, limiting T polyfunctionality and survival via the miRNA–EZH2–Notch signaling pathway (70). Therefore, the therapeutic manipulation of metabolic checkpoints like PEP and EZH2 may represent a promising approach to reverse tumor-induced T-cell dysfunction in the TME.

Hypoxia selectively upregulates PD-L1 on MDSCs via hypoxia-inducible factor-1α (HIF-1α; ref. 71). Blockade of PD-L1 under hypoxia enhanced MDSC-mediated T-cell activation with downregulation of IL10 and IL6 production. These findings suggest that therapy with PD-L1 blockade and HIF-1α inhibitors may prove useful to reverse MDSC-mediated T-cell dysfunction in the TME.

**Regulatory Cells (Tregs and MDSCs)**

Foxp3⁺ Tregs are enriched in the TME upon exposure to multiple tumor-derived factors and exert immunosuppressive effects on effector T cells (72). The role of Tregs in T-cell exhaustion stems from experimental studies showing the synergistic effects of PD-1 blockade and Treg depletion in enhancing virus-specific T-cell function and promoting viral clearance (73). In experimental models, Tregs locally regulate Ag-dependent interactions between CTLs and APCs to induce CTL dysfunction by altering the balance of costimulatory and coinhibitory signals (74). They also produce immunosuppressive molecules, including IL10, TGFβ, IDO, and adenosine to induce T-cell exhaustion (31). Interestingly, activated and highly suppressive Tregs upregulate multiple IRs, including PD-1, CTLA-4, Tim-3, and TIGIT, which often contribute to Treg stability and functions (75–77). They upregulate members of the TNF receptor superfamily (TNFRSF), including GITR and OX40 (78, 79). They also upregulate molecules involved in T-cell dysfunction or trafficking such as CD39, CD73, and CCR4 (80). Hence, targeting CTLA-4, GITR, or CCR4 on Tregs with Fc-engineered antibodies appears to deplete Tregs through antibody-dependent cellular cytotoxicity (ADCC) and contributes to reverse...
Several strategies are currently under investigation in clinical trials together with PD-1 blockade. APCs present in the TME actively contribute to T-cell dysfunction. In particular, tumor-associated macrophages (TAM) and MDSCs impede T-cell functions through the production of immunosuppressive soluble mediators, including arginase, iNOS, TGFβ, and IL10 in the TME. Interestingly, MDSCs can be recruited in the TME by IDO-expressing tumors through Treg activation. In addition, the production of colony-stimulating factor 1 (CSF-1) in tumors recruits myeloid cells such as TAMs and MDSCs, leading to an immune-suppressive tumor milieu, while CSF1 inhibitors can reprogram tumor-infiltrating myeloid cells to enhance T-cell responses against tumors. Therefore, therapies with IDO and CSF-1R inhibitors, which are currently being investigated in clinical trials, may develop into useful approaches to counteract TAM and MDSC-mediated T-cell dysfunction in the TME.

**Genetic and Epigenetic Regulation of T-cell Exhaustion**

In mice with chronic viral infections, CD8⁺ T-cell–exhausted T cells exhibit a gene signature profile that is different from those of effector and memory CD8⁺ T cells, including genes regulating IRs, transcription factors, signaling molecules, chemokine receptors, and metabolism. A number of transcription factors, including Blimp-1, T-bet, Eomes, NEAT-1, and BAFF, are involved in T-cell exhaustion in chronic viral infection in mice and humans. However, these transcription factors also play a role in nonexhausted T cells, suggesting that they act in a context-specific fashion. The transcription factor Maf is overexpressed in exhausted CD8⁺ T cells in mouse and human tissues.

Figure 2. Immunoregulatory pathways in the TME and strategies to reverse tumor-induced T-cell dysfunction.
malignant melanoma and is induced by TGFβ and IL6 [90]. Transduction of murine tumor-specific CD8+ T cells to express Maf partially reproduced the transcriptional program associated with tumor-induced exhaustion.

Several lines of evidence suggest that the epigenetics plays a role in T-cell exhaustion. First, profound and persistent demethylation of the PD-1 locus has been reported in exhausted virus-specific T cells in mice and in humans [91]. Second, epigenetic therapy with a DNA hypomethylating agent upregulates genes related to both innate and adaptive immunity and genes related to immune evasion, including PD-L1 in human cancer cell lines in vitro [92]. Therapies with hypomethylating agents and PD-1 blockade are being evaluated in cancer patients.

**Therapeutic Strategies to Reverse T-cell Exhaustion in Cancer**

Targeted immunotherapies to counteract the mechanisms of tumor-induced T-cell dysfunction have successfully provided persistent clinical benefits to patients with advanced cancer. Most recently, these immunotherapies have focused on immune checkpoint blockade with anti–CTLA-4 and/or PD-1 mAbs, which are beneficial to a growing number of solid and hematologic tumors [93–95]. The precise mechanisms supporting the efficacy of immune checkpoint blockade have not been fully elucidated yet. On the basis of the findings previously discussed in this review, it is likely that immune checkpoint blockades act by blocking T-cell–intrinsic signals, unleashing activating pathways competing for the same ligand, modulate IL10 production by APCs, and/or by metabolically reprogramming the TME. Preexisting TILs, possibly in tumors enriched in neopeptides due to nonsynonymous mutations and/or defective mismatch repair appear to correlate with clinical response to anti–PD-1 mAbs [94, 96, 97]. The great clinical success of immune checkpoint blockade in the clinic has infused considerable enthusiasm in the field of oncology and fostered the development of combinatorial strategies to target the multiple mechanisms of tumors that are spontaneously immunogenic and may be more likely to respond to immune interventions to counteract the mechanisms of tumor-induced T-cell dysfunction; and (ii) the “noninflamed” tumors that lack tumor-infiltrating T cells upon activation of oncogenic pathways, including the β-catenin pathway and PTEN loss/PI3K–AKT pathway; that can be targeted to induce T-cell activation and migration into the tumors [101–103]. As our understanding of the mechanisms supporting tumor-induced T-cell dysfunction improves, novel combinatorial immunotherapies will emerge to counteract these mechanisms in the TME to promote potent T-cell responses to tumors and improve clinical outcomes in patients with advanced cancers. With the improved immunomonitoring of the novel cancer immunotherapies (see review by Hegde and colleagues in this CCR Focus; ref. 104), one major challenge may be to determine for each cancer patient what are the main immunoregulatory and oncogenic pathways driving T-cell exhaustion, T-cell exclusion, and resistance to T-cell–mediated tumor cell death in the TME to elaborate potent personalized combinatorial immunotherapies of cancer.

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