STAR REVIEW

Immunosuppression associated with chronic inflammation in the tumor microenvironment

Dingzhi Wang¹ and Raymond N.DuBois¹,²,³,*

¹Laboratory for Inflammation and Cancer, The Biodesign Institute and ²Department of Chemistry and Biochemistry, Arizona State University, PO Box 875001, 1001 S. McAllister Ave., Tempe, AZ 85287, USA and ³Department of Research and Division of Gastroenterology, Mayo Clinic, Scottsdale, AZ 85259, USA

*To whom correspondence should be addressed. Tel: +1 480 965 1228; Fax: +1 480 727 9550; Email: duboisrn@asu.edu

Abstract

Chronic inflammation contributes to cancer development via multiple mechanisms. One potential mechanism is that chronic inflammation can generate an immunosuppressive microenvironment that allows advantages for tumor formation and progression. The immunosuppressive environment in certain chronic inflammatory diseases and solid cancers is characterized by accumulation of proinflammatory mediators, infiltration of immune suppressor cells and activation of immune checkpoint pathways in effector T cells. In this review, we highlight recent advances in our understanding of how immunosuppression contributes to cancer and how proinflammatory mediators induce the immunosuppressive microenvironment via induction of immunosuppressive cells and activation of immune checkpoint pathways.

Introduction

Inflammation is typically referred to as either acute or chronic. Acute inflammation caused by physical or chemical injury or by an infectious agent is meant to provide an early beneficial response that helps eliminate pathogens and necrotic cells as well as initiates the healing process at the site of tissue injury. This inflammatory process is self-limiting and resolves after tissue repair or elimination of pathogens. During the resolution of inflammation, the levels of proinflammatory mediators and infiltrated immune cells decline and resolvins are produced. Resolvins are generated from eicosapentaenoic acid and docosahexaenoic acid via cyclooxygenase (COX) pathway and exhibit both anti-inflammatory and proresolving actions. By contrast, chronic inflammation caused by infectious or autoimmune diseases is a prolonged abnormal immune response that is not terminated by the normal feedback mechanisms. Clinical and epidemiologic evidence indicates that chronic inflammation is a risk factor for several gastrointestinal malignancies, including esophageal, gastric, hepatic, pancreatic and colorectal cancer (CRC). For example, it has been long known that patients with persistent hepatitis B infection, Helicobacter pylori infection or autoimmune disorders such as inflammatory bowel diseases (IBD) face an increased lifetime risk of developing liver, gastric and CRC. For example, more than 20% of patients with ulcerative colitis were reported to develop colitis-associated CRC within 30 years of diagnosis (1). It has been estimated that chronic inflammation contributes to the development of ~15–20% of malignancies worldwide (2). The observation that non-steroidal anti-inflammatory drugs have beneficial effects on reducing the incidence, metastasis and mortality of various solid tumors (3–6) supports the concept that chronic inflammation promotes tumor initiation, growth and progression.

It is generally thought that chronic inflammation promotes tumor initiation, progression and metastasis by providing a tumor-supporting microenvironment. In addition, tumors are referred to as ‘wounds that do not heal’ and chronic inflammation is clearly found in the tumor microenvironment that is probably initiated by the presence of malignant cells. The common pathological features of chronic inflammatory diseases and solid cancers include elevation of proinflammatory mediators such as cytokines, chemokines and prostaglandins; massive infiltration of deregulated immune cells and recruitment of endothelial cells and fibroblasts (7–9). The proinflammatory mediators orchestrate crosstalk between various cells to create a tumor-supporting microenvironment, including...
For example, a recent study showed that COX-2-derived pros-
expression of chemokines that are responsible for recruitment
factor (inducible nitric oxide synthase and vascular endothelial growth
ligand 8 (CXCL8), tumor necrosis factor-
matory genes such as IL-1, IL-6, IL-8 [C-X-C motif chemokine
and cancer activates NF-
rection leading to the dedifferentiation of non-stem tumor epi-
phages, dendritic cells (DCs) and granulocytes, expan-
sion of MDSCs disrupts the normal homeostasis by interrupting
matured of macrophages, DCs and granulocytes.

Several animal studies demonstrate that MDSCs are a targ-
ateable link between chronic inflammation and cancer (Figure 1). Depletion of MDSCs during colonic inflammation attenuated col-
tis-associated tumorigenesis in a mouse model of IBD-associated
carcinogenesis (31). By contrast, transfer of MDSCs promoted chronic inflammation in the colon and colitis-associated tumor
formation, growth and progression via suppression of colonic
CD8+ T-cell cytotoxicity against tumor cells (18). These findings suggest that chronic inflammation might promote tumor ini-
tiation and progression by induction of immunosuppression
via MDSCs. Moreover, proinflammatory mediators induce MDSC
expansion and recruitment (Figure 1). For example, IL-1β, IL-6 and
PGE2 have been shown to induce MDSC accumulation and activa-
(32,33). Moreover, a chemokine receptor, CXCR2, is required for infiltration of MDSCs from the circulatory system to inflamed
colonic mucosa and colitis-associated tumors in a mouse model of colitis-associated tumorigenesis (18). Similarly, CXCL8-
overexpressing transgenic mice exacerbated inflammation and
promoted inflammation-associated tumorigenesis with more infiltration of MDSCs into colonic and gastric mucosa in mouse
models of colitis-associated carcinogenesis and H. feliis-induced
gastritis (34). CXCL8 is one of the CXCR2 ligands. Stomach-specific
overexpression of IL-1β in mice resulted in spontaneous gastric
inflammation and cancer with infiltration of MDSCs into the
stomach (35). Collectively, these results suggest that proinflam-
atory mediators promote chronic inflammation and inflamma-
tion-associated tumorigenesis via MDSCs. However, it is unclear
why MDSCs in a chronic inflammatory environment do not func-
tion as immunosuppressive cells.

Regulatory T cells (Tregs) can also serve as immune sup-
pressor cells and are mainly a subset of CD4+ T cells that
express high levels of CD25 and Foxp3. Tregs are essential for
maintaining self-tolerance and suppressing immune responses by regulating the activity of other immune cells in prevention and control of autoimmune diseases (Figure 2). The functions of Tregs are dependent on both cell–cell contact and secretion of immunosuppressive cytokines IL-10 and transforming growth factor (TGF)-β (36). In contrast to MDSCs, Tregs play a key role in prevention and control of IBD and gastritis (Figure 2). In IBD patients, reduction of Tregs and elevation of Th17 cells were observed in the peripheral blood and proinflammatory cytokines such as IL-17α, IL-1β, and IL-6 were elevated in intestinal mucosa (37). It is unclear whether IL-1β and/or IL-6 regulate the ratio between Tregs and Th17 cells in IBD. In H. pylori-infected patients, the numbers of Tregs in gastric mucosa or peripheral blood are negatively correlated with the level of inflammation (38). Moreover, in vivo studies have demonstrated that Tregs function as immunosuppressive cells in IBD, H. pylori-associated gastritis, and autoimmune gastritis. Transfer of Tregs completely prevented and ameliorated inflammation in a murine T-cell transfer model of colitis (39). Transfer of iTregs that were induced by treatment of naive T cells with TGF-β1 and IL-2 in vitro into mice with the late stages of autoimmune gastritis suppressed disease progression (40). By contrast, depletion of Tregs exacerbated gastric inflammation and elevated proinflammatory cytokine expression in H. pylori-infected mice (41). These studies suggest that Tregs play a key role in the prevention of autoimmune responses and H. pylori-associated gastritis. However, the function of Tregs in connecting chronic inflammation to cancer remains unknown. Emerging evidence revealed that Tregs which expanded in intestinal adenomas no longer produced IL-10 and instead switched to production of IL-17 in vivo (42). The number of IL-17-producing Tregs was found to be significantly increased in inflamed mucosa of IBD patients compared with healthy individuals and associated with colitis-associated tumorigenesis (43, 44), suggesting that proinflammatory mediators produced by chronic inflammation may convert Tregs to IL-17-producing Tregs (Figure 2). Indeed, IL-1β–IL-1R1 signaling induced the conversion of IL-17-producing Tregs from Tregs (45, 46). Since IL-17-producing Tregs lose their anti-inflammatory function and promote CRC development (47), it is conceivable that IL-17-producing Tregs induced by proinflammatory cytokines are a
potential cellular link between chronic inflammation and carcinogenesis (Figure 2). A recent observation that transient depletion of Tregs during inflammation inhibited colitis-associated tumorigenesis in vivo (48) supports this hypothesis.

**Inflammation and immune checkpoint molecules**

T-cell activation requires antigen-specific TCR stimulation and activation of an antigen-independent costimulatory receptor (CD28). On the other hand, coinhibitory signals suppress antigen-specific T-cell responses. The costimulatory receptor and coinhibitory receptors control the balance of T-cell activation and tolerance (Figure 3). Therefore, autoimmune conditions may occur when this balance is disturbed. Programmed death (PD)-1 and cytotoxic T-lymphocyte-associated antigen (CTLA)-4 are the coinhibitory receptors and are mainly expressed on T cells. Although both PD-1 and CTLA-4 function as negative regulators, they play a non-redundant role in inhibition of immune responses. Interaction of PD-1 with its ligands, PD-L1 and PD-L2, inhibits effector T-cell activation and proliferation. Although both CTLA-4 and CD28 bind to same ligands, CD80 (B7-1) and CD86 (B7-2), which are expressed in antigen-presenting cells (APCs), CTLA-4 has higher affinity and avidity for B7-1 and B7-2 than CD28. Therefore, binding of CTLA-4 with its ligands, B7-1 and B7-2, suppresses the early activation and survival of naive and memory T cells by competing with CD28 binding.

Data from animal studies suggest that the coinhibitory signals play a key role in controlling the progress of immune response and reducing the risk for development of chronic inflammation (Figure 3). Deletion of PD-1 in neonatal thymectomized mice led to autoimmune gastritis and hepatitis (49,50). Blockage PD-1/PD-L1 signaling resulted in CD8+ T-cell-mediated intestinal inflammation by elimination of CD8+ T-cell tolerance to intestinal self-antigens (51). Cytokines such as IL-2, IL-7, IL-15 and IL-21 induce the expression of PD-1 in peripheral T cells and its ligands in peripheral monocytes/macrophages (52). The role of PD-1 signaling in connecting inflammation to cancer is unknown. One observation that elevation of PD-L1 expression in intestinal epithelial cells of IBD patients and in gastric epithelial cells of H. pylori-infected patients (53,54) may support the idea that PD-1 signaling may mediate the contribution of chronic inflammation to carcinogenesis by preventing transformed epithelial cells from CD8+ T-cell attack. Further studies are needed to test this hypothesis.

CTLA-4 is minimally expressed on resting T cells and is induced after T-cell activation. In acute infections, CTLA-4 is transiently induced and binds to B7-1 and B7-2, competing with CD28 binding following T-cell activation, which in turn attenuates the T-cell response by counteracting CD28-mediated costimulatory signals. By contrast, CTLA-4 is constitutively expressed in T cells during chronic infections and cancer because of chronic antigen exposure. CTLA-4 is also constitutively expressed on antigen-experienced memory CD4+ and CD8+ T cells as well as Tregs. Similarly, B7-1 is not expressed on resting APCs and is induced after APC activation. By contrast, B7-2 is constitutively expressed on resting APCs and its expression is further induced after APC activation. Inhibition of CTLA-4 signaling by its antibody, ipilimumab, induces bowel inflammation in patients with melanoma (55), suggesting that this signaling is important for maintenance of immune homeostasis in gut (Figure 3). However, the role of CTLA-4 in H. pylori-associated gastritis is not clear because the results from mouse models of H. pylori-associated gastritis are controversial. One report showed that blockade of CTLA-4 accelerated gastric inflammation induced by H. pylori infection (56), whereas another study showed that CTLA-4 blockade reduced H. pylori-induced gastric inflammation (57). The reason for this discrepancy is not known. Further work is necessary to clarify the role of CTLA-4 in autoimmune gastritis and H. pylori-induced gastritis.

Since Tregs constitutively express CTLA-4 (58,59), loss of CTLA-4 in Tregs led to fatal systemic autoimmune disease (60). Moreover, deletion of B7 in mice expressing a soluble B7-2 Ig Fc chimeric protein resulted in more severe colitis with reduction of Tregs (61). Blockage of CTLA-4 by its antibody abrogated the effect of Tregs on prevention of colitis in vivo (58,59). These

Figure 3. The role of checkpoint pathways in chronic inflammation and cancer.
results demonstrate that CTLA-4 is required for Treg development and function in control of colitis. Collectively, these results suggest that checkpoint signaling is important for prevention and control of chronic inflammation. The question is whether the checkpoint pathways are involved in contribution of chronic inflammation to carcinogenesis.

Tumor microenvironment

Similar to chronic inflammation, malignant cells secrete pro-inflammatory mediators such as cytokines, chemokines and eicosanoids that recruit and reprogram various types of pro-inflammatory leukocytes and other cells to establish a more tumor-supportive microenvironment. The tumor microenvironment not only allows tumor cells to evade from host immunosurveillance but also supports tumor growth, progression and spread by inducing angiogenesis and formation of cancer-like stem cells. Cancer immune evasion involves a shift from Th1 to Th2 immune responses, a defective APC function, impaired cytotoxic activity of CD8+ T cells and natural killer (NK) cells and enhancement of immunosuppressive cells such as MDSCs and Tregs. Here, we focus on the multipronged immunosuppressive network that develops in the tumor microenvironment.

Myeloid-derived suppressor cells

In healthy individuals, immature myeloid cells differentiate into mature myeloid cells including macrophages, DCs and granulocytes. However, this normal physiological process is interrupted in cancer patients (Figure 1). In general, there are small numbers of MDSCs in the circulation (3–5%) of healthy individuals, but their numbers are significantly increased in blood and tumor tissues of patients with cancer (Figure 1). The levels of MDSCs in the blood and/or tumor tissue are positively correlated with clinical cancer stage, metastatic tumor burden or poor survival in patients with colon, esophageal, gastric or pancreatic cancers (62–68).

MDSCs have been shown to contribute to cancer immune evasion by suppressing effector T-cell activation, proliferation, trafficking and viability; inhibiting NKs; and promoting activation and expansion of Tregs cells (69). In addition, new evidence reveals novel mechanisms by which MDSCs promote cancer progression and metastasis by directly targeting cancer stem-like cells and tumor cells (Figure 1). MDSCs directly enhanced cancer stem-like cell formation and protected proliferating tumor cells from senescence without involvement of T cells and NKs in vivo (70,71). In tumor implantation models, inhibition of CXCR2 by its antagonist reduced MDSCs abundance in breast tumors (72). Similarly, knockdown of CXCL1/2, ligands of CXCR2, in a breast cancer cell line is associated with reduction of myeloid cells in the tumor (73). These results suggest that CXCR2 is required for infiltration of MDSCs into tumor sites.

Proinflammatory proteins S100A8/9 have been shown to promote tumor growth by induction of MDSC accumulation and inhibition of MDSC differentiation (74). In addition, IL-1β, IL-6 and PGE2 secreted from tumor cells and/or their stromal cells also induce MDSC accumulation and/or activation in the tumor microenvironment (32,33) (Figure 1). IL-1β and IL-6 promote the expansion of MDSCs by induction of myelopoiesis and inhibition of the differentiation of mature myeloid cells via STAT3 (75). Furthermore, IL-1β activated MDSCs via an IL-1R1–NF-κB pathway in gastric inflammation and cancer (35), whereas IL-6 activated breast cancer-infiltrating MDSCs via a STAT3–NF-κB–IDO pathway (76). Other cytokines and growth factors such as interferon γ, IL-4, IL-13 and TGF-β mainly secreted following tumor cell death, and T cells have been shown to activate MDSCs via STAT3 (75). In addition, miR-155 and miR-21 may mediate the effects of granulocyte-macrophage colony-stimulating factor and IL-6 on induction of MDSCs from mouse bone marrow cells (77).

In addition to proinflammatory cytokines, inflammatory PGE2 also plays a central role in regulation of MDSC accumulation and activation (Figure 1). PGE2 promoted tumor growth via inducing the differentiation of MDSCs from bone marrow myeloid progenitor cells, whereas inhibition of PGE2 signaling by deletion of prostaglandin E2 receptor (EP2) or its antagonists blocked this differentiation in mice implanted with 4T1 mammary carcinoma (78). PGE2 has been shown to convert DCs to MDSCs in vitro (79). PGE2 directly activated MDSC-mediated T-cell suppression by induction of arginase I expression via the EP4 receptor (80). Reduction of PGE2 leaves in mesothelioma-bearing mice by celecoxib treatment suppressed MDSC accumulation and activation (81). Inhibition of tumor-derived PGE2 by silencing COX-2 in 4T1 cancer cells reduced the accumulation of MDSCs in the spleen (82). One potential mechanism responsible for PGE2 induction of MDSC accumulation could be that PGE2 induces chemokines that attract MDSCs into the tumor microenvironment from the circulation. Indeed, deletion of COX-2 or treatment with non-steroidal anti-inflammatory drugs inhibits gliomasogenesis by reducing infiltration of MDSCs into tumor microenvironment via CCL2 in vivo (83). PGE2 has also shown to induce CXCR2 ligand expression in inflamed colonic mucosa and colitis-associated tumors from azoxymethane/dextran sodium sulfate-treated mice as well as intestinal mucosa and tumors from Apcmin/+ mice (18), suggesting that PGE2 induces an infiltration of MDSCs into sites of inflammation and in solid tumors through induction of CXCR2 ligands. Further studies are needed to test this hypothesis.

Regulatory T cells

In contrast to autoimmune diseases, Tregs are thought to contribute to cancer-induced immunosuppression by suppressing effector T cells, NKs and DCs. The frequency of Tregs is elevated in the peripheral blood and at the tumor sites of patients with esophageal cancer, gastric cancer or CRC (84–86) and tumor-infiltrating Tregs correlate with poor prognosis in esophageal, gastric and ovarian cancers (87,88). In tumor-bearing mice, depletion of Tregs resulted in regression of many tumors, including CRC, by evoking immunosurveillance, whereas adoptive transfer of Tregs suppressed CD8+ T-cell cytotoxicity against tumor (89–93). These findings indicate that Tregs promote tumor escape from cytotoxic immune responses (Figure 2).

Tumor-infiltrated Tregs include infiltration of thymus-derived CD4+CD25FoxP3+ T cells, local expansion of Tregs and local differentiation from CD4+ T cells. CCL2 has been shown to recruit Tregs into tumors via its receptor,CCR4 (87,94). Treatment with CCR4 antagonists enhanced the efficacy of cancer vaccines against tumor growth by reduction of infiltration of Tregs (95). Moreover, CCL17 and CCL22 are correlated with Treg infiltration in gastric cancer (85). In addition, CCL5 secreted from CRC is not only required for infiltration of Tregs into tumors but also enhances cytotoxicity of Tregs against CD8+ T cells via induction of TGF-β in vivo (96). Neutralization of CCL5 inhibited the infiltration of Tregs into tumors (97). These studies suggest that chemokines such as CCL5, CCL17 and/or CCL22 mediate the trafficking of Tregs into tumor microenvironment (Figure 2). In addition to infiltration of Tregs into tumors, TGF-β-secreting DCs in tumor microenvironment induces Tregs proliferation (88). In vitro studies further revealed that TGF-β secreted from tumor cells converts CD4+CD25+ T cells into Tregs (99) (Figure 2). Treatment of patients with melanoma or renal cell carcinoma (RCC) with IL-2 increased Tregs in blood and/or tumors (100,101). By contrast, anti-VEGF-A
treatment reduced peripheral Treg proliferation in CRC patients and CRC-bearing mice (102). Similarly, PGE\(_2\) secreted from mature DCs attracted Tregs via CCL2 (103). PGE\(_2\) can also directly enhance the differentiation of naïve CD4\(^+\) T cells into Tregs in vitro and induce Treg activation in lung cancer in vivo (104,105) (Figure 2). Deletion of mPges-1 gene suppressed AOM-induced colon carcinogenesis accompanied with reduced frequency of Tregs in the draining mesenteric lymph nodes and lowered serum PGE\(_2\) levels (106). In addition, treatment with an EP4 antagonist resulted in a decreased number of Tregs in lymph nodes and the skin after ultraviolet irradiation (107). These results indicate that PGE\(_2\) may enhance tumor growth via Tregs. Although the role of Tregs in the tumor microenvironment is well established, their role in connecting chronic inflammation to cancer is not known.

### Immune checkpoint molecules

Besides the role of MDSCs and Tregs in tumor-induced immunosuppression, malignant cells can also escape from immunosurveillance by directly impairing cytotoxic activity and proliferation of CD8\(^+\) T cells through PD-1 and CTLA-4 receptors (Figure 3). PD-1 is transiently induced in activated T cells (108) and its expression is maintained in tumor-infiltrating effector T cells (109–111). PD-L1 expression is elevated in various human cancers, including lung, colon, head and neck, and ovarian cancers as well as melanomas (112–114), and its expression is associated with poor prognosis among patients with esophageal, colon, ovarian or RCC (115–118). Although transgenic mice with PD-L1 expression driven by the keratin-14 promoter did not develop skin cancer spontaneously, these mice were much more sensitive to carcinogen-induced skin cancer formation (119). These findings suggest that PD-1 signaling plays an important role in tumor-induced immune evasion and that PD-1 and PD-L1 are promising immunotherapeutic targets for cancer patients (Figure 3). Indeed, recent clinical trials have demonstrated that blockage of PD-1 signaling by anti-PD-1 or anti-PD-L1 antibodies are benefits for patients with advanced melanoma, RCC or non-small cell lung cancer (NSCLC) (120).

Emerging evidence further revealed that oncogenes, tumor suppressive genes and proinflammatory cytokines regulate PD-L1 expression. Elevated PD-L1 expression is associated with epidermal growth factor receptor mutations in both human and mouse NSCLC (121,122). Although previous studies reveal that PD-L1 is expressed in immune cells, recent studies show that it is also aberrantly expressed in cancer cells. High levels of PD-L1 on cancer cells are one potential mechanism underlying tumor evasion from immunosurveillance. In vitro studies demonstrated that loss of phosphatase and tensin homolog resulted in induction of PD-L1 expression in glioma and CRC cells (117,123) and overexpression of mutated epidermal growth factor receptor led to induction of PD-L1 in immortalized bronchial epithelial cells (121). Interferon \(\gamma\) is also able to induce PD-L1 expression in lung, ovarian and colon cancer cell lines (112). In addition, Toll-like receptor 4 signaling induced PD-L1 expression via mitogen-activated protein kinase pathways in bladder cells (124). However, little information of PD-L2 expression in human cancer is available.

Little is known about how oncogenes, tumor suppressive genes and proinflammatory mediators regulate CTLA-4 and its ligands. Similar to antibodies against PD-1 and its ligands, the antibodies against CTLA-4, including ipilimumab and tremelimumab, have been evaluated in multiple clinical trials and demonstrated significant promise in treatment of advanced melanoma, NSCLC, RCC and prostate cancer (120) (Figure 3). Ipilimumab is the first immune checkpoint-blocking antibody approved by Food and Drug Administration in 2011 for patients with metastatic melanoma. Although immunotherapies with these immune checkpoint antibodies against PD-1, PD-L1 and CTLA-4 offer great promise for treatment of many malignancies, the objective response rate of these antibodies is less than 30% in patients with melanoma, RCC and NSCLC and few responses observed in patients with colorectal, pancreatic, gastric or breast cancer (120). These agents seem more effective when the mutational burden is high in the primary cancer or when T cells have infiltrated into the tumor microenvironment.

### Conclusion and perspective

The standard treatment such as chemotherapy and radiotherapy for advanced malignancies has improved over the past decades, but clinical outcomes have not improved as much as we would like because these therapies target tumor cells and are associated with numerous side effects. Immunotherapy with immune checkpoint inhibitors is a promising approach for cancer treatment. However, the success rates are somewhat limited because of an immunosuppressive tumor microenvironment. A growing body of evidence supports the hypothesis that effective therapies should include elimination of tumor cells, subverting tumor-induced immunosuppression by targeting immunosuppressive cells and reactivation of tumor-inhibited effector T cells by checkpoint inhibitors. Inhibition of an immunosuppressive tumor microenvironment by targeting immunosuppressive cells would facilitate antitumor immune responses and enhance antitumor effects of chemotherapeutic agents. Targeting MDSCs and Tregs by inactivation or depletion is not feasible now because we lack specific surface markers of these cells. However, recent in vivo studies showed that inhibition of tumor-infiltrating MDSCs by targeting CXCR2 enhanced anti-PD-1 efficacy in rhabdomyosarcoma in vivo (125) and improved the efficacy of chemotherapy in a spontaneous mouse model of prostate cancer (71). These findings suggest that inhibition of MDSC trafficking into the tumor microenvironment by targeting CXCR2 should not only enhance efficacy of immune checkpoint inhibitors or chemotherapeutic agents but also have benefits for cancer patients who did not originally respond to checkpoint inhibitor treatment. Finally, rational design of combination strategies relies on better understanding of the complexity of the immunosuppressive mechanisms in each cancer type and an accounting for individual variation.

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