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Cancer Immunotherapy: Beyond Checkpoint Blockade

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Abstract

Blocking antibodies to the immune checkpoint receptors or their ligands have revolutionized the treatment of diverse malignancies. Many tumors are recognized by adaptive immunity, but these adaptive responses can be inhibited by immunosuppressive mechanisms within the tumor, often through pathways outside of the currently targeted checkpoints. For this reason, only a minority of cancer patients achieve durable responses to current immunotherapies. Multiple novel approaches strive to expand immunotherapy's reach. These may include targeting alterative immune checkpoints. However, many investigational strategies look beyond checkpoint blockade. These include cellular therapies to bypass endogenous immunity and efforts to stimulate new adaptive antitumor responses using vaccines, adjuvants, and combinations with cytotoxic therapy, as well as strategies to inhibit innate immune suppression and modulate metabolism within the tumor microenvironment. The challenge for immunotherapy going forward will be to select rational strategies for overcoming barriers to effective antitumor responses from the myriad possible targets.

INTRODUCTION

Immunotherapy has been an important component of cancer treatment for decades, but recent advances have shifted immunotherapy to the forefront of oncology (Baumeister et al. 2016, Dougan & Dranoff 2009, Postow et al. 2015, Topalian et al. 2015). Monoclonal antibodies that block immune regulatory checkpoint receptors or their ligands have fundamentally changed treatment for a wide range of cancers (Postow et al. 2015, Topalian et al. 2015). The first of these antibodies approved was ipilimumab, which targets cytotoxic T lymphocyte antigen 4 (CTLA-4), and it was shortly followed by several antibodies that block either programmed cell death protein 1 (PD-1) or its ligand, PD-L1 (Baumeister et al. 2016, Postow et al. 2015, Topalian et al. 2015). We have learned several important lessons from the success of checkpoint blockade. Many human tumors are recognized by adaptive immunity, eliciting $CD4^+$ and $CD8^+$ T cell responses that target mutated proteins within the tumor (neoantigens); indeed, the success of checkpoint blockade is correlated with neoantigen frequency (Schumacher & Schreiber 2015, Tran et al. 2017). These adaptive responses are often inhibited by active immune suppression within the tumor. Relieving immunosuppression with antibodies to CTLA-4 or PD-1/PD-L1 can activate preexisting T cell immunity to elicit robust antitumor responses (Postow et al. 2015, Topalian et al. 2015).

Effective antitumor responses to checkpoint blockade require some cooperation from the tumor cells themselves, as cytotoxicity from $CD8^+$ T cells depends on tumor cell–intrinsic expression of antigenic peptides in the context of major histocompatibility complex (MHC) class I. Both primary and secondary resistance to checkpoint blockade are associated with defects in class I antigen presentation, including monoallelic loss of MHC class I and loss of β2m (Sade-Feldman et al. 2017, Zaretsky et al. 2016). Similarly, resistance is also related to defects in interferon gamma (IFNγ) receptor signaling (Gao et al. 2016, Zaretsky et al. 2016). Many of these findings in patients validate a wide body of preclinical data from immunocompetent, syngeneic mouse models that were the foundation for subsequent clinical trials (Curran et al. 2010, Dunn et al. 2004, van Elsas et al. 1999, Zang & Allison 2007).

Prior to checkpoint blockade, several immunotherapies were already in widespread clinical use (Dougan & Dranoff 2009). Passive transfer of antitumor antibodies has substantial activity against B cell lymphoma and is an important component of the treatment of HER2/neu-positive breast cancer and of colon cancer (Dougan & Dranoff 2009). These antibodies likely exert part of their therapeutic effect through the induction of antitumor immune responses by engagement of Fcγ receptors on phagocytic or natural killer (NK) cells (Dougan & Dranoff 2009), and further efforts to improve these effects through a variety of antitumor antibody strategies are underway. Bone marrow transplant also acts partly as an immunotherapy, with donor-derived lymphocytes recognizing and rejecting host tumor cells (Dougan & Dranoff 2009). The vaccines to HBV (hepatitis B virus) and HPV (human papilloma virus) are effective at preventing malignancies by generating protective immunity to tumor promoting viruses, although neither vaccine is effective against established tumors (Dougan & Dranoff 2009). Broad immune stimulation with cytokines such as IL-2 or immune adjuvants such as imiquimod or BCG (Bacille Calmette–Guérin) have also found success in a more limited range of cancers (Dougan & Dranoff 2009), and this approach is now being revisited, as we discuss below.

Despite the clinical efficacy of checkpoint blockade, most cancer patients still do not derive durable benefits from these therapies (Mellman et al. 2016). Many important tumor types are unresponsive or minimally responsive to checkpoint blockade, including pancreatic cancer, most colorectal tumors, and tumors of the breast and prostate (Mellman et al. 2016). Even in responsive tumors such as melanoma or lung cancer, only a fraction of patients will achieve durable remissions (Garon et al. 2015, Hodi et al. 2010, Larkin et al. 2015, Mellman et al. 2016). The goal of the

next phase of cancer immunotherapy is to expand the range of responsive tumors and to improve responses in susceptible tumor types (Mellman et al. 2016). Some of these tumors may ultimately respond to blockade of alternative checkpoint receptors (Baumeister et al. 2016, Mellman et al. 2016). We have learned from our experience with antibodies to PD-1/PD-L1 and CTLA-4 that response to blockade of one pathway does not preclude response to another (Baumeister et al. 2016). Animal models suggest that tumors often activate multiple immunosuppressive receptor pathways (Baumeister et al. 2016). Additional checkpoint receptors under active investigation as immunotherapy targets include LAG-3, TIM-3, TIGIT, VISTA, and BTLA, among others (Baumeister et al. 2016).

The impressive success of PD-1/PD-L1 blockade, coupled with its relatively favorable safety profile, has led to its widespread adoption in next-generation clinical trials. The great majority of investigational strategies discussed below are combinations using anti-PD-1 as a backbone. Many strategies seek to build upon successful antitumor responses elicited by PD-1 blockade to broaden their scope or enhance their durability; similarly, many trials include PD-1 blockade to ensure that immune suppression by PD-1 does not block antitumor responses initiated by the investigational treatment. The discussion below highlights the novel approaches under investigation grouped mechanistically, looking beyond the considerable contribution of checkpoint blockade (**Figure 1**).

STIMULATION OF INNATE AND ADAPTIVE ANTITUMOR RESPONSES

Priming of Naïve T Cells

The remarkable response to single-agent checkpoint blockade indicates that a significant fraction of cancer patients harbor preexisting antitumor T cells that, presumably, underwent priming and expansion as the tumor developed. Nevertheless, not all patients have endogenously generated antitumor T cells; therefore, stimulating T cell responses de novo is an important consideration for extending the benefits of immunotherapy to a wider population. For optimal T cell priming, we must consider both the source of antigens, as well as the quality and activation state of dendritic cells (DCs). Vaccination approaches have taken two broad forms: systemic vaccines and in situ vaccines.

Systemic Vaccines

Most vaccine efforts either have used single (or a small number of) antigens in the form of synthetic long peptides or DC-associated peptides or have used highly complex mixtures in the form of irradiated tumor cells or tumor cell lysate (Wong et al. 2016). Neither approach has been particularly successful, possibly because the single antigens targeted were not tumor-essential genes and the complex mixtures contained low representation of any particular antigen. Autologous tumor cell–based vaccines secreting GM-CSF showed promise (Dranoff et al. 1997, Soiffer et al. 1998), but attempts to use allogeneic tumor cell lines in the same fashion were less successful. Early approaches were also focused on antigens that are present across many patients. These shared antigens, or self-antigens, tended to be tissue restricted and aberrantly expressed by cancer cells, making them moderately specific to cancer type. However, self-tolerance limits the magnitude of T cell responses capable of being generated to self-antigens (Hacohen et al. 2013). Cancer-mutated neoantigens can generate very strong $CD4^+$ and $CD8^+$ T cell responses. Vaccines containing 2–10 neoantigen peptides have been shown to provide long-lasting tumor control in mice, and early clinical work has been promising (Kreiter et al. 2015, Ott et al. 2017). This strategy may benefit

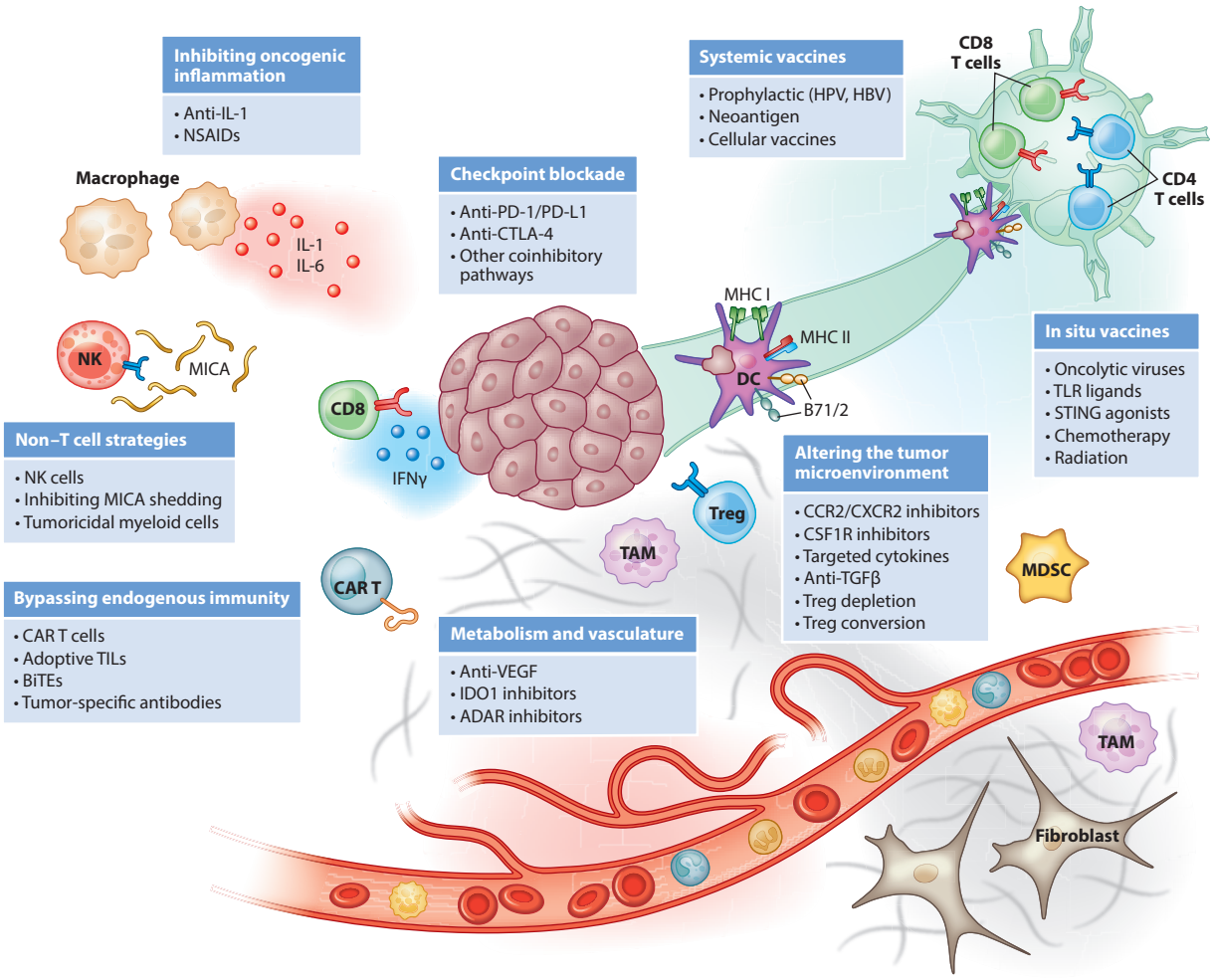

Figure 1

Moving beyond checkpoint blockade to enhance antitumor immunity. Building on the success of checkpoint blockade, multiple investigational strategies aim to overcome the immunosuppressive pathways that protect tumors from productive antitumor immunity. These strategies include both systemic and in situ vaccines to activate naïve T cells, prophylactic vaccines, and efforts to block oncogenic innate inflammation. The tumor microenvironment is being targeted through multiple mechanisms to reduce the number of regulatory adaptive and innate cells, block immunosuppressive metabolites and cytokines, and disrupt tumor vasculature. Several strategies seek to activate tumoricidal macrophages or NK cells. Tumors can be directly targeted by therapeutic antibodies, and adoptive cellular therapies endeavor to bypass endogenous responses either through ex vivo expansion of antitumor T cells or through infusion of gene-modified T cells, such as CAR T cells that directly recognize tumor-expressed targets. Abbreviations: ADAR, adenosine deaminase acting on RNA; BiTE, bispecific T cell engager; CAR, chimeric antigen receptor; DC, dendritic cell; HBV, hepatitis B virus; HPV, human papilloma virus; IDO1, indoleamine 2,3-dioxygenase 1; IFN, interferon; IL, interleukin; MICA, MHC class I chain–related protein A; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer; NSAID, nonsteroidal anti-inflammatory drug; STING, stimulator of interferon genes; TAM, tumor-associated macrophage; TIL, tumor-infiltrating lymphocyte; TLR, Toll-like receptor; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

from targeting multiple proteins simultaneously, limiting the effect of antigen loss; however, these multivalent neoantigen vaccines must be tailor-made to each patient and rely on the existence of high-quality neoantigens.

Scalable production pipelines for neoantigen-based vaccines are a major hurdle, with both peptide- and RNA-based platforms being considered (Kreiter et al. 2015, Ott et al. 2017). Inclusion of adjuvants is a major consideration, and such pipelines must determine whether stimulating multiple Toll-like receptors (TLRs) or targeting neoantigens to cross-presenting DCs can be achieved in a clinically safe and effective manner. Although the recent interest in neoantigen targets has, to some extent, eclipsed research on other antigens, it remains unknown whether a mixture of self- and neoantigens may be more effective than neoantigens alone, particularly in low–mutation burden tumors (Lawrence et al. 2013). Indeed, the fact that vitiligo correlates with the efficacy of checkpoint blockade in humans suggests that T cell responses to shared melanocyte antigens may be contributing to the antitumor response (Teulings et al. 2015).

Autologous tumor cells or lysates, when combined with DC maturation and recruitment factors, are also promising vaccine candidates (Ali et al. 2014, Bencherif et al. 2015, Wong et al. 2016). Freeze-dried lysates combined into injectable biomaterials impregnated with GM-CSF are currently in clinical trials. Tumor cells fused with DCs are also performing well in early stage clinical trials, particularly in hematologic malignancies (Pyzer et al. 2014, Rosenblatt et al. 2013).

In Situ Vaccines

Systemic vaccines require knowledge of the antigens of interest, or at a minimum, cumbersome preparation of tumor cell lysates. Perhaps the simplest and most effective vaccination strategies involve direct delivery of immune stimulatory agents to the tumor microenvironment. These so-called in situ vaccines operate under the idea that induction of tumor cell death releases tumor antigens, which are phagocytosed and presented by local DCs that become activated and prime naïve T cells in the draining lymph node (Sagiv-Barfi et al. 2018). Successful in situ vaccines require both a means of tumor cell death and a source of adjuvant. Presumably, some spontaneous version of this process is responsible for the tumor antigen–specific responses unleashed by checkpoint blockade, providing a proof-of-principle for this approach.

Oncolytic viruses are generally DNA viruses that have been engineered to selectively infect highly replicative tumor cells and cause lytic cell death (Kaufman et al. 2015, Kohlhapp & Kaufman 2016). Viral nucleic acids naturally engage TLRs (usually 3, 7, 8 or 9) and RIG-I and may also bind to cGAS to activate the STING (stimulator of interferon genes) pathway (Ablasser et al. 2013, Chan & Gack 2016). Thus, oncolytic viruses simultaneously cause tumor cell death and induce DC activation. T-Vec (talimogene laherparepvec), the first oncolytic virus approved by the US Food and Drug Administration, also encodes GM-CSF (Andtbacka et al. 2015). Currently, oncolytic viruses must be injected locally into accessible tumors and are most effective at clearing the injected lesion. Identification of additional cytokines or chemokines that can be encoded in the viral genome to elicit more robust DC recruitment and activation would be desirable. Ultimately, oncolytic viruses must induce T cell responses capable of clearing noninjected, usually visceral, tumors (Kaufman et al. 2016). Combination of T-Vec with CTLA-4 blockade is more effective than either therapy alone, suggesting that T cell dysfunction still occurs in T-Vec-treated patients and that supporting effector T cells offer a nonredundant avenue for combination therapy (Chesney et al. 2017).

In addition to viruses, local injection of TLR agonists, STING agonists, or other innate immune receptor ligands can potently activate local DCs, leading to both DC maturation and production of type I and type II IFNs. These agents do not induce tumor cell death on their own

and thus may be more effective when combined with local radiation (Gandhi et al. 2015, Ngwa et al. 2018). Radiation itself has pleiotropic effects on the tumor microenvironment (Sridharan & Schoenfeld 2015), including induction of MHC expression on tumor cells and upregulation of costimulatory ligands on DCs. At the same time, radiation induces production of myeloid cell–attracting chemokines such as CCL2 that can establish an immunosuppressive microenvironment (Kalbasi et al. 2017). For these reasons, radiation alone can occasionally result in T cell priming and induction of effective systemic antitumor immunity, also known as the abscopal effect. Abscopal effects are very rare and are only slightly increased in patients receiving checkpoint blockade, suggesting that additional factors limit the use of radiation as a local vaccine (Postow et al. 2012). The combination of local injection of adjuvants, particularly STING agonists, TGF-β blockade, checkpoint blockade, or agonistic anti-CD40, synergizes with radiation in mouse models, and clinical trials using these approaches are underway (Corrales et al. 2015, Dovedi et al. 2016, Twyman-Saint Victor et al. 2015, Vanpouille-Box et al. 2015).

Local therapy requires accessible lesions, and thus far, it has primarily been attempted in melanoma, lymphoma, Merkel cell carcinoma, and head and neck cancers. Radiation can be targeted more easily to visceral tumors; however, strategies for delivery of immune stimulatory agents directly to tumors are needed. Both nanoparticles and antibody-drug conjugates are being explored (Dougan & Dougan 2017, Goldberg 2015). Another attractive option may be image-guided or surgical injection of TLR or STING agonists, enabling treatment of visceral tumors in inaccessible locations.

Tumor cell death may be achieved in multiple ways, as evidenced by the numerous modalities already in use as cancer therapies. Through their induction of cell death and release of tumor antigens, chemotherapies and targeted therapies may contribute to priming of naïve T cells and therefore synergize with immunotherapies such as checkpoint blockade (Pitt et al. 2017). This concept, however, comes with several caveats. First, immune cells share many features with tumor cells, notably, rapid proliferation and reliance on signaling via NF-κB and MAPK pathways. Most currently approved chemotherapies and targeted therapies were tested in xenograft models with human tumors implanted into immunodeficient mice; thus, effects of these agents on the antitumor immune response are only now being explored (Pfirschke et al. 2016, Tyler et al. 2017). Secondly, the manner in which tumor cells die is critical, and chemotherapies that induce the release of tumor cell–derived ATP, HMGB1, or a surface display of calreticulin are more capable of activating local DCs (Ma et al. 2013, Michaud et al. 2011, Obeid et al. 2007, Pfirschke et al. 2016, Yamazaki et al. 2014). The concept of immunogenic cell death was first proposed by Zitvogel and Kroemer (Casares et al. 2005) and has led to detailed analyses of the effect of chemotherapies on antigen presentation and T cell priming.

In humans, combination of immunotherapy with chemotherapy or targeted therapies has resulted in increased response rates and significant but tolerable toxicities. Empirical combinations of these classes of agents will not necessarily yield synergistic or even additive effects if the cancer-directed agent has off-target consequences on the ensuing immune response; thus, careful assessment of dose and schedule may be required to optimize the therapeutic benefits of these combinations. In non-small-cell lung cancer (NSCLC), carboplatin and pemetrexed combined with PD-1 blockade resulted in higher rates of tumor response and increased overall survival in treatment of naïve patients, regardless of mutational burden or pretreatment tumor PD-L1 expression (Gandhi et al. 2018, Langer et al. 2016). In metastatic melanoma, nearly half of patients cotreated with fotemustine and ipilimumab experienced disease control, albeit with significant grade 3–4 toxicities (Di Giacomo et al. 2012). Targeted therapies, such as BRAF inhibitors, where the mutant target protein is not expressed in lymphocytes, may be more amenable to combination with immunotherapies, although analysis of patients treated sequentially suggests that the two

pathways share a common responder population (Johnson et al. 2017). Late-stage clinical trials of concurrent checkpoint blockade with combined BRAF and MEK inhibitors are underway.

Antibody-Mediated Tumor Cell Death

The Fc portion of antibodies bound to tumor cells can be recognized by Fc receptors on NK cells, macrophages, and even granulocytes, resulting in tumor cell death by cytotoxicity, phagocytosis, exposure to reactive oxygen species, or complement fixation (DiLillo & Ravetch 2015, Lu et al. 2018). All of these processes release tumor antigens in an inflammatory fashion, thereby leading to priming of adaptive immunity. Antibodies to CD47 may assist in this process by blocking CD47 on tumor cells binding to SIRP1α on macrophages to send a "don't eat me" signal (McCracken et al. 2015, Weiskopf et al. 2013). The efficacy of CD47 blockade as a single agent is complicated by the high abundance of CD47 on red blood cells and the fact that near-100% receptor occupancy is required for efficacy (Ingram et al. 2017). Nevertheless, the combination of CD47 blockade with antibodies targeting other tumor-specific proteins may enhance the efficacy of tumor-specific antibodies by engaging macrophage-mediated uptake (Chao et al. 2010). Furthermore, anti-CD47 may be useful in combination with checkpoint blockade (Liu et al. 2015, Sockolosky et al. 2016).

Augmentation of Effector T Cells

T cells express both coinhibitory and costimulatory receptors, and augmentation of the latter represents an important avenue for future therapies. Most costimulatory receptors are members of the TNFR (tumor necrosis factor receptor) superfamily and operate via NF-κB signaling. Augmentation of canonical or noncanonical NF-κB signaling in immune cells mimics costimulatory signaling and augmentation of antitumor immunity (Clancy-Thompson et al. 2018, Dougan et al. 2010). Antagonists of cIAP1/2 enhance NF-κB2 signaling in multiple immune cell types and are currently in phase II trials in combination with PD-1 blockade (Beug et al. 2017, Chesi et al. 2016, Dougan & Dougan 2018). Agonistic antibodies have been more difficult to develop, given that the degree of signaling desired must be carefully titrated. Nevertheless, agonistic antibodies to CD40, OX40, 4–1BB, GITR, ICOS, and others are in clinical trials and have been fairly well tolerated (Melero et al. 2013). $CD4^+$, $CD8^+$, and NK cells express costimulatory ligands, offering the hope that NK cells may be engaged by these antibodies as well. Agonistic anti-CD40 activates myeloid cells, induces production of IFNγ, and can lead to tumoricidal macrophages in pancreatic cancer, in addition to augmenting T cell priming (Beatty et al. 2011, Byrne & Vonderheide 2016, Long et al. 2016).

ALTERING THE TUMOR MICROENVIRONMENT

Myeloid cells come in many different varieties as defined by their surface receptor profiles and production of cytokines, enzymes, and metabolites. Although neutrophils, monocytes, and macrophages can be clearly defined into subsets in healthy tissues, cancer alters the phenotype of each of these cell types into more plastic but, broadly speaking, immunosuppressive phenotypes (Gabrilovich 2017). Cancer-associated myeloid cells are generated by chronically augmented myelopoiesis, with many tumors secreting G-CSF, IL-3, GM-CSF, and RAGE ligands that act on the precursors in the bone marrow (Engblom et al. 2017). Recruitment of myeloid cells is driven by a variety of chemokines, also produced by malignant cells and tumor-associated fibroblasts. Tumor-associated myeloid cells have multiple inhibitory functions, from direct suppression of effector T cell proliferation to consumption of key metabolites (cysteine, arginine, and tryptophan),

production of reactive oxygen and nitrogen species, and activation of regulatory T cells. High tumor density of myeloid cells has been significantly associated with resistance to chemotherapy and worse clinical outcomes in most tumors, including colorectal, breast, ovarian, NSCLC, melanoma, Hodgkin's lymphoma, and multiple myeloma. Significant pharmaceutical effort has focused on myeloid cell inhibition or depletion, with a growing effort to reprogram myeloid cells into tumoricidal macrophages or DCs with increased antigen-presenting function.

Although embryonically derived tissue-resident macrophages can expand in certain tumor types (Zhu et al. 2017), most myeloid cells in tumors are short-lived and are sustained by continual recruitment from the circulation (Franklin et al. 2014). CCR2 and CXCR2 are the major chemokine receptors on monocytes and neutrophils responsible for their trafficking into tissues, and blocking either of these receptors has demonstrated efficacy in mouse models and preliminary evidence of activity in human clinical trials (Nywening et al. 2016, 2017; Sanford et al. 2013). Macrophages require CSF-1R signaling for survival, and blocking this receptor leads to loss of intratumoral macrophages and improved antitumor responses in early-phase trials of pancreatic cancer and reprogramming of microglial cells in glioblastoma (Pyonteck et al. 2013, Zhu et al. 2014).

Myeloid cell reprogramming is an attractive option to repurpose these abundant cells for therapeutic benefit. Targeting the IRE-1/XBP-1 axis of the unfolded protein response in ovarian cancer models leads to reinvigorated DCs capable of priming T cell responses (Cubillos-Ruiz et al. 2015). Agonistic antibodies to CD40 have also been shown to induce IFNγ production, leading to reprogrammed myeloid cells in pancreatic cancer that can cause tumor regressions in mice and clinical responses in humans (Beatty et al. 2011). Other strategies to reprogram myeloid cells include stimulation with TLR ligands, antagonizing the MerTK pathway, targeting arginase activity, and delivery of cytokines such as IFNα, IL-12, or IFNγ (Akalu et al. 2017, Dougan et al. 2018, Kerkar et al. 2011).

Cytokines are the quintessential immune modulators. They generally act in autocrine or paracrine fashion and have short half-lives (Dranoff 2004). Although cytokines such as IL-12 or GM-CSF have extraordinary potency when given locally, their systemic administration has comparatively little effect on tumor burden. Systemic IL-12 in humans leads to dose-limiting toxicities including lymphopenias and elevated transaminases that can be fatal (Del Vecchio et al. 2007). IFNγ is slightly better tolerated than IL-12 but leads to severe lymphopenias and a compensatory production of indoleamine 2,3-dioxygenase (IDO) (de Metz et al. 1999). IFNα produces response rates of 5–30% in patients with metastatic melanoma but is not well tolerated (Nicholas & Lesinski 2011). A high-dose bolus of IL-2 is curative in a small fraction of patients with renal cell carcinoma and melanoma, although determining the maximum IL-2 a patient can tolerate is difficult, and fatal toxicities have been observed (Dranoff 2004, Letourneau et al. 2010, Zhu et al. 2015). An engineered version of IL-2 with reduced binding to CD25 and increased serum half-life has been developed by Nektar Therapeutics and is currently in clinical trials in combination with PD-1 blockade (Charych et al. 2016). TNF-α has high systemic toxicity but can be administered to isolated limbs containing melanoma or sarcoma with reasonable safety and high rates of complete response (Lienard et al. 1992). Systemic versions of IL-15, IL-18, and IL-10 have all demonstrated acceptable safety profiles in phase I trials, although it is not yet clear that they will be effective at tumor control in humans (Conlon et al. 2015, Naing et al. 2016, Robertson et al. 2006, Rosario et al. 2016). Overall, systemic administration of defined cytokines is associated with significant side effects caused by overwhelming immune activation. Furthermore, the therapeutic benefits for cancer patients have been relatively modest, perhaps due to an inability to pharmacologically mimic the localized nature of cytokine signaling. Targeted delivery of cytokines using nanoparticles or antibody-drug conjugates are appealing strategies. Other options include stimulating recruitment and differentiation of particular cell types that can serve as local

sources of cytokine and chemokine production. CD103$^+$ DCs, for example, cross-present tumor antigens and secrete both IL-12 and CCL4, which are useful for recruitment and differentiation of effector T cells.

Immunosuppression is conferred not only by myeloid cells but also by Foxp3$^+$ CD4$^+$ regulatory T cells (Tregs). Tregs exert inhibitory effects through a variety of pathways including sequestration of IL-2, production of adenosine and IL-10, direct inhibition of T cell proliferation, and removal of costimulatory ligands from activated DCs (Bauer et al. 2014, Chao & Savage 2018). Global loss of Tregs leads to overt autoimmunity in both mice and humans; therefore, efforts to target Tregs have focused on discriminating total versus tumor-specific Foxp3$^+$ cells. One distinction is the surface expression of CTLA-4, which is several logs higher on intratumoral Tregs than on those in peripheral blood. Indeed, the efficacy of anti-CTLA-4 therapy in murine models relies on the Fc domain, and several groups have reported that depletion of intratumoral Tregs may be the mechanism of action of CTLA-4–directed therapies (Bulliard et al. 2013, Marabelle et al. 2013, Simpson et al. 2013). Conversion of Tregs into effector CD4$^+$ T cells is another attractive strategy and may be achievable by targeting Helios, a transcription factor involved in stability of the Treg lineage (Nakagawa et al. 2016).

Cancer-associated fibroblasts (CAFs) secrete several factors that negatively impact the immunological tumor microenvironment, including CXCL12, a T cell–repulsive chemokine, and CCL5, CCL2, and CCL17, chemokines that actively recruit immunosuppressive myeloid cells (Jiang et al. 2017). Inflammatory cytokines IL-1, IL-6, IL-13, IL-23, TSLP, and TGF-β secreted by CAFs can polarize CD4$^+$ T cell responses away from IFNγ production (De Monte et al. 2011, Wang et al. 2014). CAF-derived TGF-β plays a critical role in excluding CD8$^+$ T cells from the tumor interior, and simultaneous blockade of TGF-β and PD-L1 facilitates T cell entry into tumors and immune-mediated regressions (Mariathasan et al. 2018, Tauriello et al. 2018).

TARGETING IMMUNOSUPPRESSIVE METABOLISM

The metabolic microenvironment of tumors is hypoxemic and immunosuppressive. Many tumors overexpress the enzyme IDO1, which catalyzes the conversion of L-tryptophan to *N*-formylkynurenine, which then spontaneously degrades into several products including L-kynurenine (Hornyak et al. 2018, Terness et al. 2002). Although depletion of tryptophan, an essential amino acid, likely has some suppressive effects on activated immune cells, L-kynurenine is directly immunosuppressive (Terness et al. 2002). IDO1 is induced by IFNγ, similar to PD-L1, suggesting a role in maintaining immune homeostasis (Munn et al. 1998). Inhibition of IDO1 in tumors enhances T cell responses in mouse models and synergizes with other immunotherapies (Wainwright et al. 2014). IDO1 inhibitors are now in late-stage clinical development for a variety of cancer indications, although some of these trials were recently stopped due to reported lack of efficacy (Hornyak et al. 2018).

Hypoxia within tumors activates HIF1α, which in turn induces the expression of vascular endothelial growth factor (VEGF) in addition to other angiogenic cytokines (Ott et al. 2015). The vasculature grown under these circumstances is difficult for immune cells to traffic through, and VEGF also has direct immunosuppressive roles, promoting the formation of Tregs and immunosuppressive myeloid cells (Facciabene et al. 2011, Gabrilovich et al. 1998, Ghiringhelli et al. 2005, Huang et al. 2007, Terme et al. 2013). Combination treatment with anti-VEGF and immunotherapy is effective in animal models (Li et al. 2006), and clinical trials combining anti-VEGF with checkpoint blockade have shown promising early results (Hodi et al. 2014).

HIF1α also induces several receptors and enzymes involved in the production and downstream signaling of extracellular adenosine, including CD39, CD73, A2AR, and A2BR (Vijayan

et al. 2017). CD39 catalyzes the formation of AMP from ATP, and CD73 produces adenosine from AMP (Vijayan et al. 2017). A2AR is a widely expressed adenosine receptor that has marked immunosuppressive activity in T cells and promotes the production of suppressive myeloid cells (Cekic et al. 2014, Mittal et al. 2016, Ohta et al. 2006, Vijayan et al. 2017, Young et al. 2016). Several therapeutic strategies targeting A2AR, CD73, and CD39 or combinations of these pathways have shown impressive synergy with other immunotherapies in mice (Beavis et al. 2017, Mittal et al. 2014). Multiple clinical trials are now underway in patients using single agents, as well as combinations with checkpoint blockade (Vijayan et al. 2017).

BYPASSING ENDOGENOUS IMMUNITY

The generation of tumor-specific T cells is a multistep, stochastic process. Not only must tumor cells express proteins that can be recognized as foreign, but these proteins must also be processed and presented on the MHC. This not only requires that the antigenic peptides bind to MHC class I or class II but also requires, for class I presentation, that the tumor cell itself express all of the components of the class I antigen processing and presentation machinery. This creates multiple avenues for potential tumor cell escape, including loss of MHC class I or β2m, as discussed above (Sade-Feldman et al. 2017, Zaretsky et al. 2016). The development of immunotherapies that can bypass endogenous, spontaneous T cell responses is thus of considerable interest.

Chimeric antigen receptor (CAR) T cells recognize tumor antigens independent of MHC presentation through the expression of a CAR that fuses an antibody-binding domain [single-chain (sc)Fv] to the signaling domain of CD3ζ linked to a costimulatory domain (e.g., CD28 and or 4–1BB) (Brown et al. 2016; Grupp et al. 2013; Lim & June 2017; Maude et al. 2014, 2018; Neelapu et al. 2017; Park et al. 2018; Schuster et al. 2017). Autologous T cells are isolated from the patient, genetically modified to express the CAR construct, expanded, and returned to the patient as therapy (Brown et al. 2016; Grupp et al. 2013; Lim & June 2017; Maude et al. 2014, 2018; Neelapu et al. 2017; Park et al. 2018; Schuster et al. 2017). To date, approved CAR products target CD19, the B cell costimulatory receptor, which is widely expressed on B cell leukemias and lymphomas (Maude et al. 2018, Neelapu et al. 2017). CAR T therapy targeting CD19 is highly effective even in otherwise refractory disease and can induce durable remissions (Park et al. 2018). Therapeutic success is at the expense of B cell aplasia, a tolerable side effect, due to CD19 expression on all normal B cells; this side effect may also have a benefit by reducing the likelihood of anti-CAR antibodies (Grupp et al. 2013; Lim & June 2017; Maude et al. 2014, 2018; Neelapu et al. 2017; Park et al. 2018; Schuster et al. 2017). Relapse from CAR T therapy often occurs through deletion of the CAR-binding epitope, underscoring that the mechanism of action is through direct recognition of tumor cells expressing CD19 (Maude et al. 2014). Next-generation CAR targets include CD22, a B cell regulatory receptor expressed by many B cell malignancies (Fry et al. 2018). Antibody-secreting plasma cells downregulate CD19, and the plasma cell malignancy multiple myeloma is typically resistant to CD19-targeted CARs, although repopulating myeloma stem cells after autologous bone marrow transplant may retain low-level CD19 expression (Garfall et al. 2015). Multiple myeloma often expresses the growth factor receptors BCMA and TACI. BCMA is now being investigated as a CAR target (Ali et al. 2016). BCMA and TACI can also be targeted by an alternative chimeric receptor strategy that substitutes their shared ligand APRIL (a proliferation-inducing ligand) for the scFv domain of the standard CAR, enabling simultaneous recognition of both receptors, potentially broadening therapeutic responses and reducing the likelihood of escape through antigen loss (Lee et al. 2018). Bispecific T cell engagers (BiTEs) have some conceptual similarities to CAR T cells (Kantarjian et al. 2017). Blinatumomab, the only currently approved BiTE, fuses the antigen-binding domains of antibodies to CD3 and CD19 to

create a small protein capable of linking CD19-expressing tumors to polyclonal T cells, leading to T cell activation (Kantarjian et al. 2017). BiTEs require prolonged infusions, and blinatumomab is primarily used as bridging therapy because it is shelf-ready but rarely induces durable remission (Kantarjian et al. 2017).

The success of CAR T cells has taught us that tumors can be rejected through recognition of a single high-quality antigen. Such antigens must be highly and uniformly expressed and restricted to the tumor or shared with a nonessential or replaceable tissue. For CAR T cells, antigens must also be expressed on the tumor cell surface. These are challenges for CAR T cells directed at epithelial tumors. In addition, CAR T cell expansion in vivo requires lymphodepletion, a standard part of treatment for hematologic malignancies, but one that is not a component of standard care for many epithelial tumors. A further barrier for targeting epithelial tumors is that most preclinical CAR T cell models use xenotransplanted mice; since these mice lack host expression of the target antigen, toxicities related to target expression on normal cells cannot be fully assessed.

One method to target intracellular antigens is to transduce autologous T cells with a complete T cell receptor that recognizes a tumor antigen in the context of MHC. This treatment is necessarily MHC restricted, reducing its broad applicability (Robbins et al. 2011, 2015; Stromnes et al. 2015). Alternatively, since many patients develop spontaneous antitumor responses that are simply insufficient to clear established tumors, autologous tumor-infiltrating lymphocytes (TILs) can be expanded ex vivo in culture and then infused after lymphodepletion (Goff et al. 2016, Tran et al. 2014). This strategy has been highly successful in select patients and can similarly lead to durable responses (Goff et al. 2016, Tran et al. 2014). Infusion of lipid-specific invariant (i)NKT cells similarly expanded ex vivo has shown some antitumor activity in models; an advantage of this approach is that iNKT cells recognize a nonpolymorphic MHC homolog, CD1d, although the responses to this strategy have not been as dramatic as those observed with expanded TILs (Payne et al. 2014).

STRATEGIES NOT PREDICATED ON ACTIVATING T CELLS

Tumor cells' loss of MHC class I renders them invisible to $CD8^+$ T cells, and this is a common explanation for acquired resistance to immunotherapy (Rooney et al. 2015, Sharma et al. 2017). The solution to this dilemma is not immediately obvious. Other types of immune cells could, in theory, be mobilized for tumor cell destruction. Although NK cells can identify and destroy MHC-negative virally infected cells, they are typically poor mediators of antitumor immunity due to several factors, including their lack of abundance in most solid tumors. Tumor cells express the NK cell–activating ligand MICA (MHC class I chain–related protein A) but shed this ligand to produce soluble decoy MICA that distracts NK cells from attacking the tumor (Jinushi et al. 2006, 2008). NK cell killing could be enhanced by blocking MICA shedding or by Fc receptor engagement by antibodies bound to the tumor cell surface (Ferrari de Andrade et al. 2018). Other tumor-targeting antibodies might also promote destruction of MHC class I–deficient escape variants.

As discussed above, strategies targeting myeloid cells may have some benefit, and macrophages in particular can be tumoricidal in some cases. Neutrophils, eosinophils, and mast cells all produce reactive oxygen species and proteases that are good at destroying tissue, yet how to harness this destructive prowess for control of tumor growth has not yet been elucidated.

MANIPULATION OF THE MICROBIOME

Immune responses are influenced not only by individual genetics but also by interactions with the environment. Infection history and, in particular, chronic infections likely influence subsequent immune responses. The microbiome comprises the complex ecosystem of microorganisms that

live on and within us, with most of the organisms and the diversity in the gut. Variation in the microbiome, including the metabolic pathways that are active, likely has a strong influence on systemic immune responses (Schirmer et al. 2016). In cancer, the importance of the microbiome has been clearly established in animal models, where response to checkpoint blockade is dependent on the microbiome (Sivan et al. 2015, Vetizou et al. 2015), and experiments to establish whether the microbiome correlates with immunotherapy response in patients have shown similar results (Gopalakrishnan et al. 2018, Matson et al. 2018, Routy et al. 2018).

INTERFERING WITH TUMOR-PROMOTING INFLAMMATION

Although activation of adaptive immunity can have a substantial antitumor effect, the interplay between cancer and innate immunity is more complex (Dougan & Dranoff 2009, Taniguchi & Karin 2018). Chronic inflammation is a risk factor for many human malignancies, whether caused by infection, such as with HBV and hepatocellular carcinoma, or by autoimmunity, such as with colorectal cancer (CRC) and ulcerative colitis (Dougan & Dranoff 2009, Taniguchi & Karin 2018). Based on animal models and analyses of patients, the mechanistic link between chronic inflammation and cancer appears to involve the elaboration of innate inflammatory cytokines or prostaglandins that activate the transcription factor NF-κB (Taniguchi & Karin 2018).

Prostaglandin (PG)E2 plays an important role in the development of CRC (Chan et al. 2012). Aspirin, an inhibitor of the enzyme required for PGE2 production (cyclooxygenase), is associated with a reduction in the risk of colon polyp formation and incident CRC (Chan et al. 2004, 2005, 2007). This protection is also observed after colorectal tumor formation, with aspirin use correlated with improved overall survival in patients with stage I–III CRC (Chan et al. 2009). Remarkably, this finding persists even among patients treated with adjuvant chemotherapy (Ng et al. 2015). Mechanistic studies have linked this protective effect to a reduction in PGE2 in the tumor microenvironment, depriving the tumor of an important growth and survival factor (Chan et al. 2012).

Although exposure to carcinogens in cigarette smoke plays a central role in lung cancer development, increasing evidence implicates chronic inflammation as an additional causative factor. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial published in 2017 (Ridker et al. 2017) examined the effect of canakinumab, a monoclonal antibody against IL-1β, on cardiovascular outcomes in patients who had a myocardial infarction and high circulating markers of inflammation. The primary outcome of the trial was positive, but in an important secondary analysis, the authors found an unanticipated 70% reduction in incident lung cancers and associated mortality (Ridker et al. 2017). Whether this is a direct effect of IL-1β on tumorigenesis is presently unknown, but innate inflammation has been directly implicated in tumorigenesis in animal models (Dougan et al. 2011).

TOXICITIES

With the exception of neoantigen vaccines and other immune therapies directly targeting mutated proteins, immunotherapy alters normal immune regulatory and effector networks, shifting the balance between tolerance and immune-mediated rejection. At present, most immunotherapies are delivered systemically, leading to a breakdown in tolerance and a series of inflammatory toxicities termed immune-mediated adverse events (imAEs) (Brahmer et al. 2018, Dougan 2017, Sznol et al. 2017). In many ways, these toxicities resemble sporadic autoimmune diseases (Dougan 2017). Although any organ system of the body can be targeted, the most common sites for imAEs are barrier organs, including the gastrointestinal mucosa and liver, the lungs, and the skin (Brahmer et al. 2018, Dougan 2017, Sznol et al. 2017). Endocrine organs can also be targeted, with patients

developing hypophysitis, thyroiditis, and in rare cases diabetes, among other endocrinopathies (Brahmer et al. 2018, Dougan 2017, Sznol et al. 2017).

Immune toxicities represent an important limitation to immunotherapy, particularly in the setting of combination blockade of both PD-1 and CTLA-4, where severe toxicities leading to treatment discontinuation occur in nearly half of patients (Brahmer et al. 2018, Dougan 2017, Larkin et al. 2015, Schadendorf et al. 2017). Currently we cannot predict who will develop imAEs, although CTLA-4 blockade is considerably more toxic than blockade of either PD-1 or PD-L1 (Brahmer et al. 2018, Dougan 2017, Sznol et al. 2017).

The link between toxicity and antitumor responses is presently unclear, although at least some toxicities (such as vitiligo in melanoma) are associated with improved overall survival (Teulings et al. 2015). Most severe imAEs can be successfully treated with systemic corticosteroids, although whether this treatment reduces the efficacy of the antitumor response is unknown (Brahmer et al. 2018, Dougan 2017, Horvat et al. 2015). Animal models demonstrate a reduction in antitumor responses with corticosteroids. Retrospective analyses in patients have shown mixed findings, likely related to the specifics of the analyses (Faje et al. 2018, Horvat et al. 2015). In a large retrospective cohort consisting of patients on anti-CTLA-4 immunotherapy that compared patients who received corticosteroids to those who did not, overall survival was statistically indistinguishable, indicating that corticosteroids do not completely abolish productive antitumor responses (Horvat et al. 2015). However, this analysis compared two very different populations, as corticosteroid treatment was used specifically to treat severe toxicities (Dougan 2017, Horvat et al. 2015). In an analysis of patients who developed hypophysitis on ipilimumab for melanoma, high-dose corticosteroids were associated with a significant reduction in overall survival compared to low-dose therapy. Intriguingly, patients who received low-dose steroids had an overall survival substantially higher than what is observed for patients who do not develop hypophysitis, while patients on high-dose steroids were more similar to patients without this toxicity (Faje et al. 2018). This finding suggests that corticosteroids may mitigate improvements in antitumor responses that would otherwise be correlated with toxicity.

Inflammatory toxicities are likely to become more clinically important as additional combination immunotherapies are used. Strategies to treat or prevent toxicities that do not inhibit antitumor responses may thus become a critical factor in optimizing immunotherapy's reach.

CONCLUSION

The challenge for immunotherapy going forward will be to select rational strategies for overcoming barriers to effective antitumor responses from the myriad possible targets and combinations of targets. These barriers likely differ among cancer types, and thus effective immunotherapy may be somewhat specific to tumor type. The immune system has a dual role in tumor development. Failure of adaptive immunity allows nascent tumors to escape, while innate inflammation can drive tumor growth and proliferation. Similarly, many critical immune effector pathways, such as IFNγ, induce regulatory countermeasures that are immunosuppressive, such as PD-L1. This balance is hardwired into the immune system. Finding ways to effectively perturb it while avoiding immune toxicities is central to expanding immunotherapy's considerable promise.

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