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An Overview of Advances in Cell-Based Cancer Immunotherapies Based on the Multiple Immune-Cancer Cell Interactions

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Abstract

Tumors have a complex ecosystem in which behavior and fate are determined by the interaction of diverse cancerous and noncancerous cells at local and systemic levels. A number of studies indicate that various immune cells participate in tumor development (Fig. 1). In this review, we will discuss interactions among T lymphocytes (T cells), B cells, natural killer (NK) cells, dendritic cells (DCs), tumor-associated macrophages (TAMs), neutrophils, and myeloid-derived suppressor cells (MDSCs). In addition, we will touch upon attempts to either use or block subsets of immune cells to target cancer.

Keywords

Immunotherapy; Adoptive cell therapy; Immune cells

1 Introduction

Cancer is a complex ecosystem where the interaction of diverse cancer and noncancerous cells collectively determine the overall behavior and subsequent treatment response [1–3]. Many studies indicate that various immune cells (e.g., T cells, B cells, natural killer cells (NK cells), tumor-associated macrophages (TAMs), neutrophils, and dendritic cells (DCs)) have been found in and influence the natural course of tumors. The majority of immune cells reveal subsets that have both anti- and pro-tumorigenic roles in regulating tumor cell proliferation, angiogenesis, and metastasis [4, 5]. The idea of maximizing the antitumor activity and minimizing the tumor-promoting activity of immune cells to target and eliminate tumors has been investigated since the beginning of the twentieth century. An increased understanding of the processes that take place in the tumor immune microenvironment is rapidly advancing the translation toward novel therapeutic strategies in cancer treatment. The progress of antitumor immune responses are coordinated through a set

of defined, as well as yet unknown innate and adaptive immune components, comprised of immune cells [6], cell surface molecules [7], co-stimulatory receptors [8], ligands [6], cytokines, and chemokine signaling pathways (Fig. 1) [6, 9].

The collaboration of innate and adaptive immune cells has a significant impact on tumorigenesis and treatment response via cell-cell physical contacts, the production of cytokines (e.g., IL-6, interferon- α (IFN- α), tumor necrosis factor- α (TNF- α)), and the use of chemokines (e.g., CCL2, CXCL12, CX3C) [5, 6, 10]. Numerous studies on the effects of cytokines and chemokines in the development of primary tumors and metastases have been reported and even translated to adjuvant immunotherapeutic agents (e.g., IL-2, CCL21) [11]. These studies indicate that cytokines and chemokines impart a synergistic effect by attracting relevant subsets of the host immune cells to the site of antigen presentation. Enhancement of exposure of tumor-associated alterations to the host immune system during early tumorigenesis poses a vulnerability to the tumor's continued growth. Shedding malignant cell antigens into the blood system; the lymphatic circulation, including lymph nodes; and the extracellular matrix (ECM) ultimately activates the adaptive immune system [6, 12]. For cancers lacking major histocompatibility complexes-I (MHC-I) on the surface of their malignant cells, the innate immune system recognizes their absence and attacks them in a manner similar to the recognition of nonself pathogens [13]. Thus, it is not surprising to see the growing number of studies revealing that cellular components of both innate and adaptive immunity significantly contribute to disease outcomes [6]. Here, we review the recent findings of cellular components in the human immune system, which indicate promising potential in immunotherapy and perspectives for the continued translation from experimental evidence into clinical practice.

2 T Cells

T cells are involved in many different types of immune responses and are regulated by signals of T cell receptors and co-activating, inhibitory, and cytokine receptors [14]. Different subsets of T cells play crucial roles in mediating tumor growth control. Some T cells, like cytotoxic CD8⁺ T cells and helper CD4⁺ T cells, inhibit tumor growth, while others like regulatory T cells (Treg) support tumor progression, and still others, like T helper 17 (Th17) cells, do both. Helper CD4⁺ T cells can recognize cancer-associated antigens presented on MHC class II molecules on antigen-presenting cells, and mediate antitumor immunity by secretion of IFN and inhibition of angiogenesis [15]. Cytotoxic CD8⁺ T cells express T cell receptors (TCRs) that can bind to MHC class I molecules on cancer cells, subsequently targeting the cells for elimination (Fig. 1) [14]. Tumor-infiltrating CD8⁺ T cells have been shown to slow tumor cell growth and significantly reduce metastasis [5, 16]. Increased infiltration of certain T cell subsets within several types of tumors has a favorable prognosis, particularly when those T cells express memory and activation markers [5, 16, 17]. This finding led to the development of an adoptive cell therapy (ACT) approach, in which tumor-infiltrating lymphocytes (TILs) harvested from the patient are expanded ex vivo and then injected back into the patient (Fig. 1) [18]. Clinical outcomes of these studies are variable and likely impacted by the TIL composition and prior chemotherapy and radiotherapy. Treg cells, through the production of immunosuppressive cytokines (e.g., TGF β and IL-10) and the immune-inhibitory receptor cytotoxic T lymphocyte antigen 4

(CTLA4), negatively modulate T-cell activation, survival, and expansion [19–22]. Depletion of CD25⁺ Treg cells in B16/BL6 syngeneic mouse melanoma models results in improved anti-melanoma CD4⁺ and CD8⁺ T-cell responses and, if completed before tumor engraftment, also results in increased T-cell infiltration and tumor rejection [21, 23]. High numbers of tumor-infiltrating Th17 cells correlate with poor prognosis in colon and pancreatic cancer [24, 25], but improved survival in ovarian cancer [26–28]. These opposing regulatory and inflammatory properties of Th17 cells are thought to be influenced by the stimuli they encounter in different tumor microenvironments [29]. Taken together, the therapeutic value of TILs either alone or in combination with other treatments, such as Treg cell depletion, needs to be further elucidated.

A second form of ACT uses circulating T cells from patients' blood. These peripheral blood T cells can be reprogrammed *ex vivo* with specific antitumor T-cell receptors (TCRs) or chimeric antigen receptors (CARs) (*see* Chapter 1). The usefulness of T cells expressing ectopic TCRs and CARs against B-cell leukemias has been demonstrated in both preclinical and clinical trials (Fig. 1) [30]. In 2017, an autologous CAR T-cell therapy developed for children and young adults with relapsed and/or refractory CD19⁺ acute lymphoblastic leukemia (ALL) was the first CAR-T cell therapy approved by the FDA in the USA. Extending this to solid tumors is still difficult. Some of the challenges that must be overcome include getting enough of the engineered T cells to infiltrate the site of solid tumors, enabling the CAR-T cells to survive in the inhospitable tumor microenvironment, and identifying homogeneously expressed, unique target antigens. One approach that has already emerged in clinical testing for solid tumors is the combination of CAR-T cells with a checkpoint inhibitor antibody (e.g., PD-1, CTLA-4).

3 B Cells

After CD8⁺ T cells, B cells are the second most abundant TIL population in lung cancer and melanoma [31, 32]. Whereas some studies have associated the presence of B cells within solid tumors with poor survival [33, 34], others have associated their presence with improved survival [35–38], suggesting that, like other immune cell types, B cells may have both tumor-inhibitory and tumor-promoting roles. One study showed that the presence of both B cells and T cells in ovarian cancer correlates with a better survival than if only B or T cells are present alone, suggesting important interactive functions [39]. B cells are chiefly known for producing antibodies through which they can influence all immune cells that express Fc receptors, including dendritic cells, granulocytes, NK cells, and myeloid-derived suppressor cells. B cells also interact with other immune cells as potent antigen-presenting cells and through the secretion of cytokines and chemokines [40].

B cells are able to inhibit tumor growth through several mechanisms. Autoantibodies can recognize tumor-associated antigens and discriminate between cancer and control cells [41]. Some autoantibodies are anti-tumorigenic by reducing invasiveness and increasing apoptosis [42]. In ovarian cancer, production of IFN γ , IL12, GM-CSF, and CXCL10 by B cells supports an antitumor response [37]. Cell communication between T and B cells is tightly linked through CD40L-CD40 and CD80-CD28 signaling. The cell surface protein CD40L serves as a crucial co-stimulatory factor for B cell activation by binding CD40, which

promotes B-cell proliferation, germinal center formation, immunoglobulin class switching, somatic hypermutation, plasma cell and memory B-cell formation, and antigen presentation [43–49]. CD40-activated B-cell-based cancer immunotherapy induces effective antitumor immunity in mice and dogs [50].

B cells also perform multiple functions that can promote tumor growth. For example, some autoantibodies have been identified, which are pro-tumorigenic and can help form a pre-metastatic niche [51]. In addition, by production of TNF α and IL-21, tumor cells can induce the conversion of TIL B cells into Breg cells, a poorly defined subset of B cells [52, 53]. Breg cells promote tumor growth through the secretion of IL10 and TGF β [54–56]. Through checkpoint receptors like PD-1, Breg cells inhibit T-cell functions in hepatocellular carcinoma and thyroid cancer [57, 58]. However, at least in melanomas, PD-1 inhibitors maintain activity even in the absence of B cells [59]. Additional pro-tumorigenic roles of B cells include reducing CD8⁺ T-cell and NK cell infiltration [60], the polarization of immunosuppressive macrophages [61, 62], and the induction of cancer cells with stem cell-like properties in melanoma [63]. Future studies will be needed to identify the immunologic conditions that specifically enhance the effects of B cells on antitumor immunity in solid tumors, while avoiding these pro-tumorigenic aspects of their function as a form of cancer immunotherapy.

4 NK Cells

NK cells comprise 5–15% of circulating lymphocytes and are part of the first line of defense against cancer (Fig. 1) [6]. The infiltration of NK cells in the solid tumor microenvironment is a well- documented favorable prognostic sign in cancer patients [64, 65]. NK cells discriminate between cancerous and healthy cells based on a tightly regulated balance of the signaling produced by their activating (e.g., NKG2D) and inhibitory (e.g., KIRs) receptors (Fig. 1) [66]. Activated NK cells can kill tumor cells through various mechanisms, including the release of perforin and granzymes, expression of Fas antigen ligand (FasL) or TNF-related, apoptosis- inducing ligand (TRAIL), secretion of IFN- γ , and by antibody-dependent cellular cytotoxicity (ADCC) (Fig. 1) [67]. Through the production of IFN- γ , NK cells contribute to the activation of cytotoxic CD8⁺ T cells and promote differentiation of CD4⁺ T cells [68]. NK cell-mediated tumor cell lysis may also produce tumor antigens for phagocytic immune cells, which subsequently induce DC activation and maturation, with the ultimate goal of cross priming specific T cells [69].

More than a decade has passed since initial reports established the ability of NK cells to mediate tumor regression in patients with acute myeloid leukemia (AML) [70, 71]. Many discoveries on the pathways that activate and suppress NK cell function, and sensitize tumors to NK cell cytotoxicity, have led to the development of numerous pharmacological and genetic methods to enhance NK cell antitumor immunity (Fig. 1) [72–74]. Genetically modified NK cells and NK cell adoptive transfer therapies have shown promising results and are currently being tested in multiple ongoing phase I/II and III trials (e.g., NCT 03420963, NCT 00328861, NCT 02370017), involving several cancer types (Fig. 1) [66]. So far, the therapeutic exploitation of NK cell-based immunotherapy has achieved only limited clinical success in cancer patients. Further research toward a better understanding of NK cell biology

and their function in cancer is needed to foster the development of novel NK cell-based therapeutic approaches.

5 Dendritic Cells (DCs)

DCs represent the most important subset of antigen-presenting cells that activate innate immune pathways and induce potent adaptive immune responses, and in doing so act as messenger cells between the innate and adaptive immune systems (Fig. 1) [75, 76]. There are many different types of DCs, including myeloid (mDCs), plasmacytoid DCs (pDCs), monocyte-related CD14⁺ DCs, Langerhans cells, and microglia [76]. DCs detect invading pathogens through their expression of a variety of sensors for pathogen-derived components including Toll-like receptors (TLRs) [77], NOD-like receptors (NLRs) [78], RIG-I like helicases [79], and C-type lectin receptors [75, 80, 81]. The DCs are stimulated to mature and migrate to the T-cell zones of lymph nodes, where the resulting peptide-MHC complexes are transported to the plasma membrane [82, 83] and presented to naïve T cells [84–86].

Depending on multiple factors, DCs may either be immune stimulatory or suppressive. In general, mature DCs and mDCs are more immunostimulatory, whereas immature DCs and pDCs are tolerogenic [87]. Mature DCs, expressing co-stimulatory receptors (e.g., CD28), produce IL-12 for optimal T-cell stimulation and can even stimulate B cells [75, 88]. By the production of IL-12, IL-15, and type I IFNs, mature DCs trigger NK cell activation, while NK cells can induce further DC maturation through the secretion of TNF α (Fig. 1) [89]. Given these immune stimulatory functions, it is not surprising that the presence of mature antigen-presenting DCs leading to an enhanced immune response has been correlated with improved survival in many cancer patients [87, 90], including in melanoma [91, 92], breast cancer [93], and gastric cancer [94].

Other studies have shown that increased tumor-infiltrating DCs correlates with worse survival and have linked this to their immunosuppressive functions. For example, worse patient survival has been seen in colorectal cancer, where the DCs were more immature [95] and in breast cancer, where pDCs produced low levels of IFN α and sustained Treg expansion [96]. TGF β , IL-10, and IL2 also induce DCs to stimulate Treg formation [97]. Tumors inhibit DC function and maturation through production of chemokines (e.g., CCL2, CXCL1, CXCL5) [98], by induction of PD-1 expression [99], and/or by induction of TIM-3 expression [100]. In addition, tumor cells induce transcription factors in DCs, like STAT3 [101–103] and FOXO3 [104], that make them immunosuppressive. DCs can suppress T cells both by increasing ROS [105] and by upregulation of arginase I, which depletes arginine, an essential amino acid that T cells cannot produce themselves [106].

DC-based immunotherapy attempts to exploit the ability of DCs to stimulate a T-cell-based antitumor response (Fig. 1). Several studies utilizing established DC-based vaccines for cancer treatment have confirmed their strong potential for clinical benefit [107, 108]. Sipuleucel-T (APC8015), the first and only approved DC vaccine, targets prostate-specific acid phosphatase in human prostate cancer. While effective, it only prolonged the median overall survival of castration-resistant prostate cancer to 25.8 months, compared with 21.7

months in the placebo group [109]. The majority of past melanoma vaccines have been ineffective in clinical trials [110]. Additional DC vaccine combination studies, specifically targeting checkpoint inhibitors, are underway (NCT02677155, NCT01067287, and NCT0144765) with notable preliminary efficacy in preclinical mouse models (Fig. 1) [107]. This is an interesting approach, given the ability of PD-1 expression on DCs to induce tolerogenic effects [99]. A variety of other methods including gene transfer, antigenic pulsing, and DC/tumor cell fusion have also yielded some clinical evidence of antitumor responses [107]. More trials are needed to further evaluate the efficacy of DC vaccines and draw meaningful conclusions on their ability to prevent cancer recurrence.

6 Macrophages

Macrophages are highly heterogeneous with multiple functions, origins, and locations of action within the tumor. Historically, macrophages were predominantly separated into two major groups: a classically activated M1 type that is pro-inflammatory and tumoricidal, and an alternatively activated M2 type that is anti-inflammatory and pro-tumorigenic [111, 112]. M1-polarized macrophages are activated by lipopolysaccharide (LPS) and Th1 cytokines IFN γ and TNF α [113, 114]. M1 macrophages secrete pro-inflammatory cytokines IL-12 and IL-23, they present antigens through MHC class II, and they help CD4⁺ T cells differentiate into Th1 and Th17 cells [112]. M2 macrophages are activated by numerous stimuli, including M-CSF/CSF1 produced by the tumor cells [115], immunoglobulin produced by B cells [61], IL-10 produced by Treg cells [116], IL-4 and IL-13 produced by CD4⁺ Th2 T cells [117–120], and MIF and CXCL12 produced by the monocytes/macrophages themselves [121, 122]. Activated M2 macrophages are anti-inflammatory, have relatively decreased phagocytic activity, stimulate angiogenesis, and help Treg differentiation [123, 124]. However, as the various stimuli for M1 and M2 macrophages do not exist in isolation in vivo, macrophages exist along a spectrum with various expression levels of markers associated with both of these phenotypes [125, 126]. In addition, there is plasticity in the macrophage activation state, with COX2, TLR/Myd88 signaling, and Notch, all favoring an M2 to M1 switch [127–129]. Most tumor-associated macrophages (TAM) lean more toward the so-called M2-like, pro-tumorigenic phenotype [130], and concordantly, high numbers of TAMs are typically considered a poor prognostic factor in breast [131], lung [132, 133], liver [134], gastric [135], and bladder cancer [136].

Differences in the macrophage's developmental origin also impacts on their function. Both macrophages recruited into the tumor that are derived from adult peripheral blood monocytes and tissue resident macrophages that are derived from embryonic macrophages and proliferate in situ, as the tissue develops have been identified in glioblastomas, pancreatic cancers, and lung cancers [137–140]. For pancreatic cancers, the embryonically derived, tissue-resident macrophages were more important in establishing the fibrotic tumor microenvironment, whereas the peripheral blood monocyte-derived macrophages were more important in antigen presentation [140].

TAM function is also dependent on the macrophage's specific location within the tumor, with differences found in invasive, intra-tumoral, stromal, hypoxic, and perivascular regions [126, 141–143]. At the invasive front, macrophages can help invasive potential by the

expression of cathepsins B and S, matrix metalloproteinase 9, and urokinase-type plasminogen activator [117, 144]. Conversely, TAMs at the invasive front of human colon carcinomas express the T-cell co-stimulatory signals CD80 and CD86 [145], which may explain why high macrophage numbers at this location correlate with decreased metastasis and improved survival [142, 146].

TAMs within tumor nests are in close contact with cancer cells and have both tumoricidal and immunosuppressive properties. In prostate cancer, TAMs express NOS2, which has been linked to their cytotoxic potential due to the production of nitric oxide [147]. In line with this, high numbers of TAMs in tumor nests of endometrial or gastric cancer correlate with improved prognosis and reduced recurrence, respectively [148, 149]. However, several cancers, including bladder cancer, breast cancer, non-Hodgkin lymphomas, and acute myeloid leukemia, express high levels of the “don’t eat me” receptor CD47, which associates with poor prognosis [150, 151]. Also, in hepatocellular carcinoma, TAMs localized to the tumor nests preferentially recruit Treg cells through the expression of IL-10 [152]. Although this was not correlated with prognosis, high numbers of nest-located TAMs have been correlated with reduced overall survival in melanoma and breast and esophageal tumors [153–155].

Stromal macrophages have also been shown to both promote and inhibit tumor growth. Macrophage phenotypes can be regulated by extracellular matrix (ECM) components, like fibronectin and laminin-10 [156]. Decellularized human colorectal cancer ECM stimulates macrophages to increase anti-inflammatory cytokines like IL-10 and TGF β and decrease pro-inflammatory cytokines like TNF α and IL-6 [157]. However, the biophysical properties of the ECM also regulates TAM phenotype. Increased substrate stiffness activates TLR4 pathways and pro-inflammatory gene expression [158]. Given these opposing stimuli and phenotypes, it is not surprising that high numbers of stromal TAMs have been correlated with a poor overall survival in breast, esophageal, gastric, pancreatic, oral, and skin tumors [153, 155, 159–162], an improved survival in bladder cancer [163], and no correlation in endometrial, cervical, and lung cancer [147, 164, 165].

Under hypoxia, TAMs increase expression of IL-10, PD-L1, and indoleamine 2,3-dioxygenase (IDO), which suppress T-cell activation [166, 167]. Likewise, high numbers of TAMs in hypoxic regions are associated with increased angiogenesis and metastasis and reduced overall survival in endometrial, breast, and cervical cancer [147, 168, 169]. Perivascular TAMs are also tumor promoting. These TIE2-expressing macrophages help vascularize tumors [170–173], increase lymphovascular invasion [174], and increase metastasis [175, 176].

Given the generally pro-tumorigenic role of TAMs, one therapeutic goal is to eliminate them by targeting their cell surface markers (e.g., CSF1, CSF1R, scavenger receptor A, and CD52), which are being investigated in ongoing clinical trials (i.e., NCT00637390, NCT0073979) (Fig. 1) [114, 177]. Furthermore, trabectedin was shown to decrease the number of TAMs in tumor tissues by inducing the apoptosis of macrophages [178]. Trabectedin was approved by the European commission for use in the treatment of ovarian

cancer and soft tissue sarcomas, and by the FDA for use in unremovable or metastatic liposarcoma or leiomyosarcoma [179].

An alternative approach has been to generate reprogrammed macrophages. One reprogramming scheme is to convert M2 TAMs to M1 TAMs since macrophages exhibit high plasticity [126]. Reprogramming macrophages to an M1 phenotype has been accomplished by *Pseudomonas aeruginosa* mannose-sensitive hemagglutinin [180], various nanoparticles [181–183], CD40 agonists [184], and yeast-derived β -glucan [185–187]. Genetic reprogramming of macrophages and using them as a cell-based delivery system is also being explored in several studies [188–190]. Some approaches that have led to mild to no improvement, include expressing IL-21 to activate T and NK cells, a soluble TGF β receptor to act as a decoy and reduce TGF β signaling, and cytochrome P450 under control of a hypoxia-regulated promoter to locally convert the prodrug cyclophosphamide [189, 190]. Recently, Morrissey et al. have reprogrammed macrophages with a chimeric antigen receptor that triggers phagocytosis using intracellular domains from the engulfment receptors Megf10 and FcR γ [191]. Alternatively, blocking CD47 is another promising avenue being explored to increase macrophage phagocytosis. In combination trials with rituximab in diffuse large B-cell lymphoma, CD47 blockade achieved a 71% objective response rate [192, 193]. Recently, another pathway shown to block TAM phagocytosis is tumor cell expression of CD24, which binds Siglec-10 on TAMs [194]. Genetic ablation of CD24 or Siglec-10, or antibody blockade reduced tumor growth and increased survival in a mouse model. In summary, macrophages perform numerous functions in the development of tumors, and multiple approaches to manipulate them are only beginning to be explored.

7 Neutrophils

Neutrophils are the most abundant white blood cells, representing 50–70% of all leukocytes in humans. They are one of the first responders of inflammatory cells and can quickly migrate toward the site of damaged tissue through the blood vessels following chemotaxis signals, such as IL-8, C5a, and fMLP [195]. Some oncogenes have been shown to produce the CXC chemokine, CXCL8, which recruits neutrophils [196, 197]. Activated neutrophils can also attract and activate other cells of the immune system, including DCs, mast cells, T cells, and macrophages [195]. Patients with various cancer types often exhibit increased numbers of circulating neutrophils, and the ratio of neutrophils to lymphocytes in the peripheral blood has been shown to correlate with better patient outcome in breast cancer [198–200]. Conversely, a meta-analysis of 100 studies comprising over 40,000 patients showed that the neutrophil to lymphocyte ratio correlated with an adverse overall survival in many solid tumors [199], and another meta-analysis of nearly 4000 patients revealed that high numbers of intra-tumoral neutrophils were significantly associated with an unfavorable survival [201].

Early observations from Anton Chekhov, William Coley, and others suggested that the neutrophilic infiltration associated with inflammation to an infection had tumoricidal properties [202]. Neutrophils are an important component of ADCC, particularly immature neutrophils mediated through IgA Fc receptors [203, 204]. Antitumor neutrophils can be recruited and activated by TGF- β -blockade or can be isolated and used from healthy donors

[205, 206]. Similarly, studies of the antitumor response of *Mycobacterium bovis bacillus* Calmette-Guérin (BCG) therapy for bladder cancer revealed that BCG stimulates a massive infiltration of neutrophils into the bladder wall, which express the apoptosis-inducing molecule TNF-related ligand (TRAIL) [207].

Nonetheless, several observations have supported a pro-tumorigenic role for neutrophils [208]. Neutrophils can induce the apoptosis of CD8⁺ T cells in a TNF- α - and nitric oxide (NO)-dependent manner [209]. These neutrophils are expanded and polarized to suppress CD8⁺ T cells by IL-17-producing $\gamma\delta$ T cells, leading to increased breast cancer metastasis in a mouse model [210]. Recently, pro-metastatic neutrophils were found to be stimulated by loss of p53 in cancer cells in 16 distinct mouse models of breast cancer [211]. Loss of p53 stimulated the cancer cells to secrete WNT ligands that stimulated TAMs to secrete IL-1 β and attract neutrophils. In a mouse lung cancer model, elastase released from neutrophil granules was taken up by the tumor cells and stimulated the PDGFR-PI3K pathway [212]. In another mouse lung cancer study, neutrophils were shown to reduce T-cell homing, prevent successful anti-PD1 immunotherapy, and induce the expression of Snail, which accelerated tumor growth [213]. Similarly, patients with lower neutrophil to lymphocyte ratios responded better to PD-1 and PD-L1 inhibitors [214].

Human neutrophils have been shown to induce angiogenesis in multiple ways. CXCL1 is a neutrophil-attracting chemokine that increases angiogenesis via neutrophil production of VEGF-A [215, 216]. A second mechanism by which neutrophils increase angiogenesis is through the release of the matrix metalloproteinase MMP9 [217]. Expression of MMP9 from neutrophils was shown to increase tumor production of VEGF in a mouse pancreatic cancer model and to correlate with neutrophil number and angiogenesis in human hepatocellular carcinoma [218, 219]. A third mechanism neutrophils use to increase angiogenesis is through the production of BV8/prokineticin 2 [220].

Given the multiple pro-tumorigenic roles of neutrophils, eliminating them may offer therapeutic benefit. The CXCR1/CXCR2 antagonist reparixin, IL-23 antagonists, and IL-17 antagonists are all antineutrophil therapies approved for autoimmune diseases that might be of interest to test in the cancer setting [208]. However, there are mixed findings on the effects of neutrophil elimination in cancer. Some studies show that the presence of neutrophils are beneficial to chemotherapy responses, whereas others demonstrate the reverse [221]. Similarly, the use of G-CSF to increase neutrophil numbers and prevent infections during chemotherapy also polarizes neutrophils toward a pro-tumorigenic phenotype. Overall, the various neutrophil subpopulations and behavior of peripheral vs. tumor-infiltrating neutrophils need to be better characterized to design better neutrophil-targeted therapies.

8 Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are distinct from macrophages and neutrophils insofar as they maintain an immature differentiation state due to the chronic inflammatory conditions common in cancers and constitutive activation of STAT-3 [222–224]. Both monocytic and granulocytic lineages contribute to MDSCs and can be identified in humans as HLADR⁺, CD33⁺, CD11b⁺, and

either CD14⁺ or CD33⁺, respectively [225]. Although these surface markers alone cannot distinguish MDSCs from mature monocytes and granulocytes, the expression of other enzymes, cytokines, chemo-attractants, and transcription factors that mediate their immunosuppressive properties can discriminate them [226]. In addition, granulocytic MDSCs are distinguishable by their mononuclear variants, as opposed to the more mature polymorphonuclear forms [227].

The tumor microenvironment helps to recruit and expand MDSCs. Tumor cell production of IDO, CCL26, and CCL2 helps to attract MDSCs [228–231]. CCL26 is induced in hypoxic tumor cells by HIF-1 and binds the MDSC chemokine receptor CX3CR1 [229]. MDSC recruitment is impaired by deficiency of CCL2 in glioblastoma multiforme (GBM) and colorectal cancer mouse models, whereas CCL2 accumulation is a poor prognostic marker in human GBM [228, 230]. Tumor cells continue to drive the formation and expansion of MDSCs through the release of numerous factors, including granulocyte/monocyte-colony-stimulating factor (GM-CSF), G-CSF, M-CSF, PGE2, IL-6, IL-10, IL-1 β , TGF- β , SCF, and VEGF, both as soluble molecules and within extracellular vesicles [232–237]. These stimuli then activate several transcriptional programs in MDSCs that stimulate their immunoregulatory function [222]. Most notably, high dose IL-6 increases STAT3 activation, correlating with MDSC suppressive function and number, and when blocked reduces tumor progression in mice [238–240]. Similarly, blockade of GM-CSF prevents the immunosuppressive features of human MDSCs in vitro [241]. STAT3 is an important MDSC regulatory factor, activating cell survival proteins, cell cycle proteins, NOX2 that suppresses T cells, and calcium binding proteins that suppress DC differentiation [101, 103, 242, 243]. Other STAT proteins that contribute to MDSC activity include STAT1, which increases ROS activity [244, 245], and STAT6, which increases TGF β and ARG1 [246]. A second pathway important in MDSC activity is CK2 phosphorylation and inhibition of Notch [247–249]. Restoration of Notch activity with a CK2 inhibitor decreases MDSCs and reduces tumor growth in a mouse model [248]. Finally, there is some evidence that MDSCs can be generated in tumor-bearing mice, by direct conversion of adoptively transferred NK cells [250].

One of the ways MDSCs support tumor growth is by inhibition of cytotoxic T and NK cells [251]. MDSCs produce cytokines, growth factors, and MMPs that convert naïve CD4⁺ T cells and Th17 cells into Tregs [252–254], as well as shift macrophages to a more M2-like phenotype [255]. Reactive oxygen species (ROS) produced by NOX1–4 in MDSCs trigger NK and T-cell apoptosis [242, 256–258]. In contrast, the ROS do not harm the MDSCs because of buffering by increased Nrf2 and increased phosphoenolpyruvate, due to their relatively high glycolytic metabolism [259, 260]. Rather, ROS prevents MDSC differentiation and increases their recruitment through VEGF receptors [242, 261]. Inhibition of ROS by NOX2 knockout or treatment with catalase limits MDSC immunosuppressive abilities [257]. Reactive nitrogen species (RNS) produced by MDSCs also cause T-cell apoptosis and block T-cell activation through peroxynitrites and nitration of the T-cell receptor [262]. In addition, RNS prevent FcR-mediated NK cell function [263], decrease lymphocyte recruitment by nitration of CCL2 [258], and increase immunosuppressive molecules IDO, IL-10, and ARG1, through induction of COX-2 and HIF-1 [264–266]. By expression of the metalloprotease ADAM17, MDSCs also decrease L-

selectin and reduce T- and B-cell homing and activation in lymph nodes [264, 266]. Consumption of cysteine and arginine by MDSCs reduces T-cell proliferation and TCR ζ expression, as T cells lack the ability to make cysteine themselves [266–268]. Priming of naïve T cells is also inhibited by extracellular adenosine, which is converted from ATP by CD39 and CD73 expressed on the cell surface of MDSCs [269, 270]. Downregulation of CD39 and CD73 by metformin in ovarian cancer can decrease MDSCs, enhance antitumor T cells, and prolong survival [271]. MDSCs also inhibit T cells by overexpression of HIF-1-induced PD-L1 [272] and NK cells by direct cell-cell contact with NKp30 [273].

These direct immunosuppressive properties, as well as a few other functions, help MDSCs promote metastases and establish the pre-metastatic niche. In a breast cancer mouse model, MDSCs are abundant in pre-metastatic lung tissue, and their numbers correlate with the subsequent metastatic cancer burden [274]. MDSCs accumulate in the pre-metastatic niche due to CCL12 [275], lysyl oxidase (LOX) produced by the primary tumor [276], STAT3 [277, 278], prokineticin (Bv8) [279], carbonic anhydrase IX [280, 281], cancer exosomes [237, 282], C5a receptor [283], and calprotectin (S100A8/A9) [284, 285]. Once there, MDSCs promote an immune-permissive environment, induce vascular leakage, remodel the extracellular matrix, produce CCL9 to attract cancer cells, and induce endothelium to upregulate E-selectin to help cancer cells adhere [275, 286–290]. MDSCs further support metastasis by STAT3 induction of VEGF and FGF-2 to increase angiogenesis [291–293], by increasing the number of cancer stem cells in pancreatic and ovarian cancer [294, 295], and by inducing epithelial-mesenchymal transition (EMT) through Cox-2 and NOS2 in a nasopharyngeal carcinoma model [296, 297]. Given these many forms of promoting tumor growth, it is not surprising that a meta-analysis of 16 studies and 1864 patients found that elevated MDSC frequency correlated with shorter overall survival [298].

Several different approaches have been taken to decrease MDSC function. Although perhaps only part of its mechanism of action, gemcitabine was noted to decrease both MDSCs and Tregs in pancreatic cancer [299]. To more directly block MDSC expansion and mobilization, several groups are exploring the therapeutic effects of blocking M-CSF, G-CSF, GM-CSF, SCF, VEGF-A, and IL-6 signaling [253, 300–303]. Unfortunately, STAT3 and MMP inhibitors have had limited efficacy in clinical trials, with severe adverse effects [304, 305]. Combinations being explored include IL-2 and an anti-CD40 antibody, which increases Fas-mediated apoptosis of MDSCs [306] and inhibition of PI3K, which reduces MDSC accumulation in tumor-bearing mice, and prolongs survival when combined with a PD-L1 antibody [307, 308]. In addition, depletion of MDSCs in small cell lung cancer patients was observed when combining a DC vaccine with all-trans retinoic acid (ATRA), an agent known to promote myeloid differentiation and used as differentiation therapy in acute promyelocytic leukemia [309, 310]. In summary, MDSCs play an important role in tumor progression, and several promising approaches to specifically target them, particularly as a combination therapy, are in the early phase of investigation.

9 Summary

A hallmark of solid tumors is their infiltration by immune cells that both inhibit and promote tumor cell growth. Despite a large number of promising immune cell-based therapies, only a

very few products have been approved for clinical use, with a limited number of patients showing substantial benefit from cancer immunotherapies [311]. The major successes have been either by directly programming T cells to attack known tumor constituents or by blocking effectors that might inhibit T cells. However, the majority of patients are either unresponsive or relapse after a variable period of response to the immunotherapy [66, 190, 311, 312]. Often, it is the highly immunogenic tumors that respond, and there may be a role for tumor therapy that spreads immunity after increasing immunogenicity of some of the target cells. This may depend on manipulating the broad variety of immune cell components present in the tumor to enrich for the more tumoricidal subsets. Achieving this goal will require a better understanding of the biological mechanisms that determine the safety, efficacy, and potential of immune cellular components in cancer treatment.

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Fig. 1.

Immune response in antitumor activity. Key cellular components of the innate and adaptive immune system as well as broad defense mechanisms against tumors are shown. Current targeting approaches and/ or ongoing clinical trials are shown in gray boxes. *TAM* (tumor-associated macrophage), *ADCC* (antibody- dependent cellular cytotoxicity), *mAbs* (monoclonal antibodies), *BCR* (B-cell receptor), *TCR* (T-cell receptor), *MHC* (major histocompatibility), *NK* (natural killer), *CTL* (cytotoxic T lymphocyte), *ACT* (adoptive cell transfer), *CAR-T* (chimeric antigen receptor T cell)