Review

Cancer Research

The Tumor Microenvironment Innately Modulates Cancer Progression

Dominique C. Hinshaw[1] and Lalita A. Shevde[1,2]

Abstract

Cancer development and progression occurs in concert with alterations in the surrounding stroma. Cancer cells can functionally sculpt their microenvironment through the secretion of various cytokines, chemokines, and other factors. This results in a reprogramming of the surrounding cells, enabling them to play a determinative role in tumor survival and progression. Immune cells are important constituents of the tumor stroma and critically take part in this process. Growing evidence suggests that the innate immune cells (macrophages, neutrophils, dendritic cells, innate lymphoid cells, myeloid-derived suppressor cells, and natural killer cells) as well as adaptive immune cells (T cells and B cells) contribute to tumor progression when present in the tumor microenvironment (TME). Cross-talk between cancer cells and the proximal immune cells ultimately results in an environment that fosters tumor growth and metastasis. Understanding the nature of this dialog will allow for improved therapeutics that simultaneously target multiple components of the TME, increasing the likelihood of favorable patient outcomes.

Introduction

The tumor microenvironment (TME) is complex and continuously evolving. In addition to stromal cells, fibroblasts, and endothelial cells, the TME comprises innate and adaptive immune cells. Previous studies have focused predominantly on adaptive immune cells in the context of cancer. T lymphocytes, in particular, have been a target of interest for their potent cytotoxic capabilities, so much so that their differentiation status became a model for other cell types and was coined the "Th1/Th2 paradigm" (1). This dichotomy posits that T cells orchestrate pathogen-dependent immune responses by differential production of cytokines: Th1 cells govern a proinflammatory phenotype and Th2 cells orchestrate an immunosuppressive phenotype. Current TME-targeted treatments have focused predominantly on T cells; prime examples include checkpoint blockade and chimeric antigen receptor (CAR) T-cell therapies. With an expansion of the literature regarding the TME, it is now evident that the innate immune response not only indirectly influences the TME by controlling T-cell fate, but also critically sculpts the TME. These innate immune cell types include macrophages, dendritic cells (DC), neutrophils, myeloid-derived suppressor cells (MDSC), natural killer cells (NK), and innate lymphoid cells (ILC). Mechanistically, cytokines within the TME manipulate immune functions that culminate in muted immune responses that guide tumor progression. It is essential to develop a comprehensive understanding of the innate immune cells and extend this knowledge to current therapies that target dysfunctional cells in the TME. In this review, we summarize the current knowledge on the ability of the TME to co-opt innate immune cells for cancer promotion and clinical strategies targeting these innate immune responses in the context of cancer.

Macrophages

Of all of the innate immune cells, monocyte-derived macrophages (Mφ) best reflect the Th1/Th2 paradigm. Simplistically, Mφs can be polarized into inflammatory M1 (classically activated) or immune-suppressive M2 Mφs (alternatively activated) (2). Mφs modulate immune responses through pathogen phagocytosis and antigen presentation, and also function in wound healing and tissue repair, thus necessitating them for immune homeostasis (3). Mφs are tissue-specific and ubiquitous; they contribute to all stages of wound healing, tissue formation, coagulation, inflammation, and tissue reorganization (4). Mφs first appear in the yolk sac on embryonic day 7, and from there they disseminate to peripheral tissues to establish tissue-resident Mφs, although a majority of adult tissue Mφ populations (including the spleen, lung, and skin), originate in the fetal liver, indicating that the Mφs established by the yolk sac are replaced by those that originate in the fetal liver. Specifically, hematopoietic stem cells colonizing the fetal liver give rise to all hematopoietic lineages, including monocytes (5). In the context of cancer, one form of Mφ recruitment includes recruitment from the bone marrow as monocytes by chemokines (CCL1, CCL2, CCL3, CCL4, CCL5, CCL7, CXCL1, CXCL2, CXCL4, CX3CL1), leading to Mφ differentiation in response to cytokines (CSF-1) that are secreted by many different cell types, including tumor cells, osteoblasts, and uterine epithelial cells (4, 6).

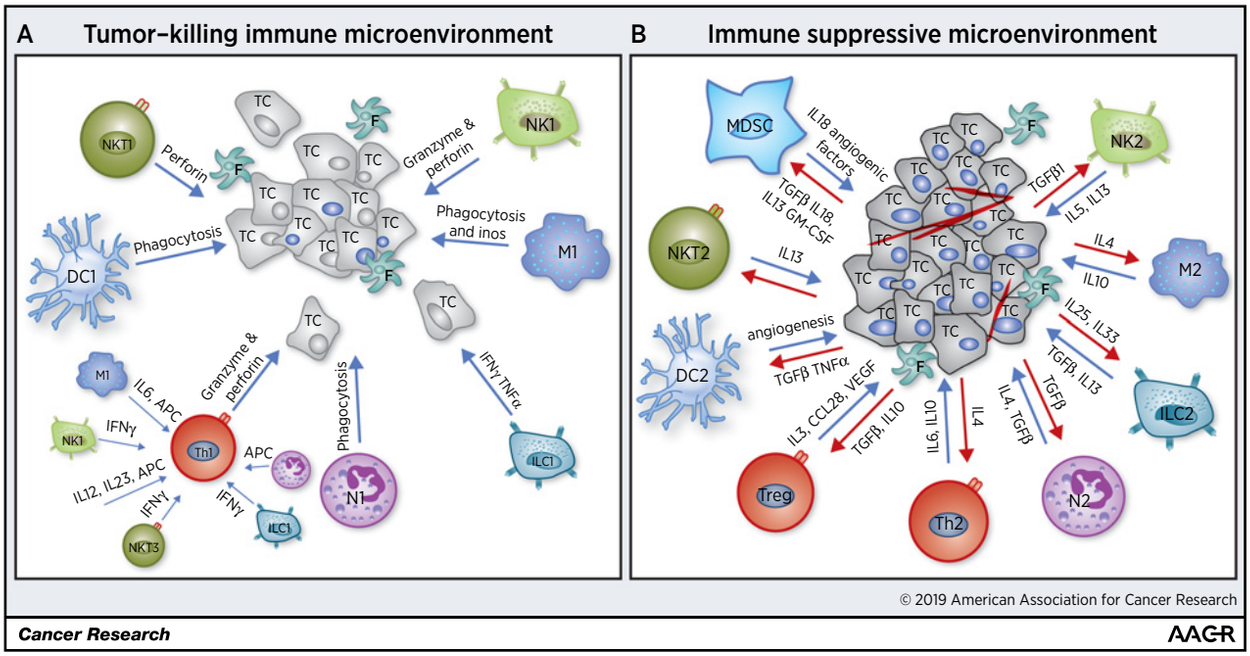
The TME potentiates immune suppressive M2 Mφs through the secretion of cytokines such as IL4 (Fig. 1A and B). Cumulatively, this enables tumor growth and progression as Mφs can make up to 50% of tumor mass (7). High Mφ infiltration of most tumor types including breast cancer, gastric cancer, lung cancer, hepatoma, and other malignancies correlated with a negative prognosis, further establishing their role in cancer progression (8–10). Also,

[1]Department of Pathology, The University of Alabama at Birmingham, Birmingham, Alabama. [2]O'Neal Comprehensive Cancer Center, The University of Alabama at Birmingham, Birmingham, Alabama.

Corresponding Author: Lalita A. Shevde, University of Alabama at Birmingham, Birmingham, AL 35233. Phone: 205-975-6261; Fax: 205-975-6615; E-mail: lsamant@uab.edu

Cancer Res 2019;79:4557–66

doi: 10.1158/0008-5472.CAN-18-3962



Cancer Research AACR

Figure 1.

Cross-talk in the tumor microenvironment. **A,** The impact of inflammatory or tumor-suppressive immune cells on tumor cells in the TME. The bold arrows show the impact that immune cells ideally have on tumor cells (TC). The interactions between NKTs, DCs, T cells, neutrophils, ILCs, Mφ, and NK cells and tumor cells are depicted. Fibroblasts are denoted with the letter "F." **B,** The cross-talk between immune cells in the TME that have been polarized to an immune-suppressive type and the cytokines secreted by the TCs that contribute to this Th2-like polarization.

an aspect of their normal tissue remodeling abilities includes regulation of epithelial cell movement. This function of Mφs is co-opted by tumor cells within the TME; Mφs release factors (e.g., EGF) that promote the movement and invasion of cancer cells (11, 12).

While the M1/M2 classification is a simplified understanding of Mφ phenotype and function, in reality Mφs are plastic in nature and exist in a continuum of functional states (7). M2 Mφs can further be classified into M2a, M2b, M2c, and M2d subsets (Table 1). These subsets are defined on the basis of their different inducers namely: IFNγ, and LPS for M1; IL4, IL10, IL13 for M2a; TLR agonists for M2b; IL10, TNFα, and glucocorticoids for M2c; and TLR and adenosine A2A receptor for M2d (13). Furthermore, these differential Mφ subtypes have different functional roles as outlined in Table 1. Therefore, it is unsurprising that Mφs that exhibit properties of both M1 and M2 exist in distinct proportions in the TME, depending on the tumor type, although the M2 phenotype is typically favored. This poses a conundrum because Mφ-mediated killing of cancer cells is virtually nonexistent in the TME of tumors with high proportions of M2 Mφs. The wound-healing phenotype of M2 Mφs established by the TME enables tumor growth, proliferation, angiogenesis, and epithelial–mesenchymal transition (EMT; ref. 14). There are many aspects of the TME, including cytokines and hypoxia, which orchestrate Mφ polarization and function (Table 1; ref. 15). IL4, commonly present in the TME, initiates STAT6 signaling in Mφs, launching a transcriptional program that directs alternative polarization of Mφs. In a recent publication, Hanna and colleagues have identified that tumor cells engage in a dialog with Mφs via secreted Hedgehog ligands (16). This kindles a feed-forward loop that sustains alternatively polarized Mφs within the TME. Interfering with this cross-talk reprogrammed the TME to be immune reactive and diminished the occurrence of metastasis. Given their role in inducing a premetastatic niche ("a favorable microenvironment for survival and outgrowth of tumor cells induced at distal sites by tumors"; ref. 17), aiding in extravasation of circulating cancer cells, and promoting metastasis (18), Mφs present as prime candidates for therapeutic intervention.

Dendritic cells

DCs bridge the gap between the adaptive and innate immune systems. They initiate pathogen-specific T-cell responses and are therefore important for bolstering protective immunity. It is important to note that B cells and Mφs also perform antigen presentation, albeit with lower activity than that of DCs. To effectively stimulate the adaptive immune response, DCs must recognize, capture, and present antigens, upregulate costimulatory molecules, produce inflammatory cytokines, and then travel to secondary lymphoid organs for antigen presentation to T cells. The inability of DCs to perform these functions greatly hampers the immune response to pathogens, viruses, and tumors. DCs are functionally classified into different subtypes such as classical DCs (cDC), plasmacytoid DCs (pDC), and monocyte-derived inflammatory DCs (moDC). cDCs can be further divided into cDC1 and cDC2. cDC1s develop under the control of the transcription factors IRF8, ID2, and BATF3, and cDC2s develop under the control of transcription factors IRF4, ID2, ZEB, and Notch2/KLF4 (19). These subsets are also functionally distinct: cDC1s are capable of cross-presentation and thus are able to present both

Table 1. Innate immune cells in the tumor microenvironment

Cell type	Normal functions	Stimulatory cytokines in the TME	Cytokine/ chemokine secretion	Human markers	Mouse markers	Effect	Source(s)
MACROPHAGES							
M1	Activate Th1 responses, phagocytosis, type 4 hypersensitivity	IFNγ	IL12, IL23, IL1β, IL6, IL12, IL23, CCL10, CCL11, CCL2–5, CCL8, CCL9	CD64, IDO, SOCS1, CXCL10, CD80, CD86, CD68, MHC-II, IL1R, SOCS3	CXCL9, CXCL10, CXCL11, NOS2	Antitumor	(2, 13, 94)
M2a	Activate Th2 responses, wound healing, allergy	IL4, IL10, IL13, CSF1, CCL2, CCL3, CCL14	IL4, L-arginine, PGE2, IL10, TGFβ, IL1ra, CCL17, CCL22, CCL24	MRC1, TGM2, CD23, CCL22, CD163, IL-1R II	Mrc1, Tgm2, Fizz1, Ym1/2, Arg1, MHC-II, IL1ra	Protumor	(2, 13, 94)
M2b	Th2 activation, immunoregulation	TLR agonists, Immunocomplex	IL1, IL6, IL10, TNFα, CCL1	CD86, MHC-II	CD86, MHC-II	Protumor	(13, 94)
M2c	Tissue repair, immunoregulation, matrix remodeling	IL10, TNFα, Glucocorticoids	TGFβ, IL10, CCR2	CD163, Mrc2	CD163, Mrc1	Protumor	(13, 94)
M2d	Angiogenesis, clearance of apoptotic tissues	TLR, adenosine A2A receptor	TNFα, TGFβ, VEGF-A, IL10, IL12, CCL5, CXCL10, CXCL16	VEGF	VEGF	Protumor	(13, 94)
DCs							
Immature DCs	Recognize antigens, migrate to secondary lymphoid organs, phagocytosis, minimal APC, induce T-cell anergy and promote Th2 and T-reg responses	N/A	N/A	CD11c, HLA-DR, FLT3L	Cd11c, MHCII, FLT3L, CD45	Depends on tumor type	(20, 95)
cDC1	APC to CD8 T cells, cross presentation, secretion of IL12		IL12, TNFα, IFNγ	CD11c, CD141, XCR1, HLA-DR, Necl2, CLEC9A, CD80, CD86, CD40, CCR7, FLT3, TLR3, CD103, CADM1, CD26, BTLA, CD226, CD13 CD33, CXCR3, CXCR4 CLEC9A	CD11c, CD8α (lymphoid), MHCII, Clec9A, CD103 (Non-Lymphoid), DEC205, XCR1, CD80, CD86, CADM1, CD26, CD24	Depends on tumor type	(19, 96–98)
cDC2	APC to CD4 T cells		TGFβ, IL6, IL8, IL1, IL12, IL23, IL10, TNFα	CD11c, HLA-DR, CD1c, CD11b, CD80, CD86, FLT3, CLEC7A, CLEC6A, Dectin 1&2, CD40, CADM1, CD172a, CD2, SIRPA, FceR1, DCIR, CD62L, MHCII, ILT1	CD11c, CD11b, MHCII, CD4 ±, Sirpa+, CD80, CD86, CD172a, CD26	Depends on tumor type	(19, 96–98)
pDCs	Abundant secretory activity (IFN type 1), respond to viral infections		Type 1 IFN, TNF, IL6	CD11c, HLA-DR, CD304, CD303, CD123, FLT3, B220, PDCA1, FceR1, ILT3, ILT7, DR6, CD300A, BTLA, CD62L, CD45RA	CD11c, B220, CD45, Siglec H, CD317, Gr-1, Ly6C	Depends on tumor type	(20, 96–98)
MoDCs	Produce high levels of the pro-inflammatory cytokines TNF, IL6, and IL12		TNFα, IL1, IL12, IL23	CD11c,CD14, Factor XIIIA, HLA-DR, CD62L, CXCR3, CD209, CD1c, CD80, CD86, CD64, MAR-1	CD11c, MHC-II, CD11b, F4/80, Ly6C, CD206, CD115, CD107b, FcεRI, CD80, CD86	Antitumor	(19, 95, 97, 99, 100)
Tolerogenic DCs	Diminished APC, stimulate Th2 responses and Tregs to induce tolerance	PGE2, TGFβ, VEGF, IL10, TNFα	TGFβ	C1QA, C3AR1, CD163, CD300LF, CFH, CSGALNACT1, FcyR11A, FcyR11B, P2RY14, ZBT16	SLAM, PDL1, PDL2, DEC205, IDO	Protumor	(99–101)

(Continued on the following page)

Table 1. Innate immune cells in the tumor microenvironment (Cont'd)

Cell type	Normal functions	Stimulatory cytokines in the TME	Cytokine/ chemokine secretion	Human markers	Mouse markers	Effect	Source(s)
NEUTROPHILS							
N1	Phagocytosis; release of NETs, inflammatory cytokines, toxin and ROS; respiratory burst, promotion of tumor cell apoptosis	N/A	TNFα, IL1, IFNs, MMP-8, Defensins, Along with toxic substances and reactive oxygen species.	TNFα, I-CAM1, FAS, ROS	TNFα, I-CAM1, FAS, ROS	Antitumor	(23, 30, 33)
N2	Support angiogenesis, cancer cell migration and invasion, immune surveillance, and metastasis as well as secrete chemokines, cytokines and ROS/ RNS	TGFβ, Angiotensin II	Oncostatin-M, MMP-9, CXCL1, CXCL8, CCL-3, Neutrophil elastase (NE), CXCL6, Collagenase IV, Heparanase, TGFβ, PGE2	Arginase, CCL2, CCL5	Arginase, CCL2, CCL5	Protumor	(23, 30, 33)
MDSCs							
M-MDSCs	Suppress innate and adaptive immune responses	CSF-1, CCL2, CCL7, HIf1α, CXCL1	NO, CCL3, CCL4, CCL5, Arg1, PGE2, IL4	$CD11b^{+}$, $HLADR^{lo/-}$, $CD14^{+}$	$Cd11b^{+}$, $Ly6C^{hi}$, $CD49d^{+}$	Protumor	(41–43)
PMN-MDSCs	Suppress innate and adaptive immune responses		ROS, Arg1, PGE2, IL4	$CD11b^{+}$, $HLADR^{-}$, $CD15^{+}$, $CD14^{-}$	$Cd11b^{+}$, $Gr\text{-}1^{hi}$, $Ly6G^{+}$, $Ly6C^{lo}$	Protumor	(41–43)
eMDSCs	Suppress innate and adaptive immune responses		N/A	$CD33^{+}$, Lin^{-}, $CD13^{-}$, $CD14^{-}$ $CD3^{-}$, $CD6^{-}$	Not well characterized	Protumor	(42)
NK CELLS							
$CD56^{hi}$ CD16 ± NKs	Produce inflammatory cytokines	TGFβ, PGE2, IDO, IL10	IFNγ, TNFα	CD16±, CD56, NKG2A, CCR7, CXCR, CXCR3	NKp46, NK1.1, CD122	Depends on tumor type	(48, 51)
$CD56^{lo}$ $CD16^{hi}$ NKs	Promote antibody-dependent cellular cytotoxicity, high perforin production, enhanced killing	TGFβ, PGE2, IDO, IL10	IL22, IL10	$CD16^{hi}$, $perforin^{hi}$	Not well characterized	Depends on tumor type	(48, 51)
ILCs							
ILC1 NK Cells	Cytotoxicity, macrophage activation, chronic inflammation, CD8 T-cell activation	N/A	IFNγ, TNFα	CD56, NKp46, NKp44, IL/12RB2, DNAM1	CD56, NKp46, NKp44, IL/ 12RB2, CD161, TIGIT, CTLA-4, CD96, NKG2A	Antitumor	(57, 62)
ILC1 Non-NK	Macrophage activation, chronic inflammation	N/A	IFNγ, TNFα	ICOS, IL1R, IL/12RB2, CCR6	ICOS, IL1R IL/ 12RB2	Antitumor	(57, 62)
ILC2	Stimulate T-cell responses through Th2-related cytokines, promotes skin inflammation	IL33, IL25	IL5, IL13	CD117, CD127, ICOS, CD294, IL1R, ST2, IL17RB, CD161, NKp30, PD1, CRTH2	CD127, ICOS, CD294, IL1R, ST2, IL17RB, Sca1, PD1, CRTH2	Protumor and antitumor	(57, 62)
ILC3	Chronic inflammation, intestinal homeostasis, lymphoid development bacterial immunity,	IL23, IL1β	IL22, IL17, GM-CSF	CD127, CD117, CD25, IL1R, ICOS, IL23R, MHCII, CCR6, NKp44, NKp30, NKp46, CD161	CD127, CD117, CD25, IL1R, ICOS, IL23R, Sca1, MHCII, NKp46, CD161	Protumor	(57, 62)

Abbreviation: N/A, not applicable.

endogenous and exogenous antigens, whereas cDC2s only present exogenous antigens and do not typically perform cross-presentation. cDCs and pDCs are present and active during steady-state conditions, while moDCs tend to only arise during inflammation. DCs specialize in different functions dependent on their stage of maturation and differentiation (Table 1). DCs can localize and acclimate to different tissues such as skin, lung, intestine, and liver and efficiently respond to environmental stimuli (20).

Analogous to Mφs, DCs are plastic in nature and can be stratified into specific subtypes. In the context of cancer, DCs are broadly referred to as tumor-infiltrating dendritic cells (TIDC), which will be the predominant focus of this section. TIDCs can be immunogenic or tolerogenic dependent upon environmental signals. Examples of DCs that contribute to immune suppression include $CD5^{hi}$ cDC2s that stimulate Th2, Th17, and T regulatory responses (19). It is important to note that each of the subtypes

referred to in Table 1 can make up TIDCs that often adopt an immune-suppressive phenotype due to the suppressive nature of the TME.

Tumors classically reprogram their microenvironment to support their survival. In the context of DCs, they do so by secreting cytokines to upregulate transcriptional and metabolic pathways that promote a tolerogenic phenotype, such as those that involve IDO, Arg1, iNOS, and STAT3 (21). These pathways trigger alterations in DC metabolism, metabolite production, energetic shifts, and/or alterations of chromatin accessibility (22). These modifications impact every aspect of DC functionality, including their abilities to secrete inflammatory cytokines and to prime effector T cells. Generally, DCs patrolling the TME encounter immunesuppressive factors such as VEGF, IL10, TGFβ, prostaglandin E2 (PGE2), and other cytokines (seen in Fig. 1B) that inhibit DC maturation into immunogenic cells and promote their development into a tolerogenic phenotype, not only stunting their Th1-priming capacities, but also affording them the ability to promote Th2 and T regulatory responses (20). Once removed from the TME, these DCs regain their ability to effectively process antigen and prime T cells (23), demonstrating that stimulating DC inflammatory functions in the TME may be an effective therapeutic strategy.

Further complexity regarding DC plasticity arises when considering different tumor types. DCs have been reported to be tumor-promoting in some TMEs, and tumor-suppressive in others. For example, TIDCs correlate with a positive prognosis in endometrial carcinoma, but not in breast cancer (24, 25). This could be indicative of a tumor stage–dependent phenomenon, that is, DCs are tumor suppressive in early stages and become tumor promoting as the tumor progresses. Furthermore, infiltrating TIDC percentages differ among tumor types, suggesting that TMEs vary in their capacities to potently polarize TIDCs to tolerogenic DCs (26). Adding to this complexity, there are discrepancies among DC phenotypes between subtypes of the same tumor type. For example, transcriptomics of triple-negative breast cancers reveals upregulated IFN pathways for all DC subtypes, whereas this is not the case in luminal breast cancer (27). As such, the DC composition and functionality is tremendously influenced by the tumor type or the tumor subtype and its unique TME.

Neutrophils

Neutrophils account for up to 70% of circulating leukocytes and are the first line of defense against pathogens (28). These cells are typically short-lived, persisting up to five days in circulation (29). Upon tissue damage or infection, epithelial cells secrete neutrophil homing chemokines, compelling them to extravasate from circulation and enter the damaged tissue where they secrete inflammatory cytokines, release neutrophil extracellular traps (NET), and phagocytose invading microorganisms (30). NETs are composed of a chromatin backbone as a vehicle for antimicrobial peptides and toxins and are released as a further method of attack, although to the detriment of the neutrophil (31, 32). In the context of cancer, tumor-associated neutrophils (TAN) also follow the Th1/Th2 paradigm and exhibit an N1 (tumor-suppressive) or N2 (tumor-promoting) phenotype (Table 1). The phenotype of neutrophils in the TME depends on the tumor type and the stage of disease progression. Neutrophils are inflammatory during early tumor stages, but as the tumor progresses, they adopt an immunosuppressive phenotype (33). Neutrophils modulate inflammation via production of reactive intermediates (ROS/RNS). They also reconfigure the extracellular matrix through secretion of neutrophil elastase (NE) and matrix metalloproteinases (MMP8/9) in the TME and promote angiogenesis (Oncostatin-M), tumor progression (PGE2), and invasion (through the release of ROS/RNS, NE, MMP-9). NETs are comprised of MMPs, cathepsin G, and NE (34, 35). These proteases degrade proinflammatory cytokines and reposition the TME to enhance tumor progression and aid in metastasis (36).

The plasticity of circulating neutrophils is an important feature in patients with cancer. These neutrophils, called high-density neutrophils (HDN) or low-density neutrophils (LDN), correspond to N1 and N2 phenotypes, respectively. In many cancer types, LDNs, which exhibit a more immature phenotype, predominate in the circulation and may contribute to cancer progression and metastasis (29). A detailed understanding of neutrophils and signals that pivot neutrophils to become immune suppressive holds much promise toward reprogramming the TME. This is important given that they are present in the tumor in large numbers. The unique mechanism of NET-osis (NET formation) may prove to be a promising therapeutic target. While preclinical models demonstrate effectiveness of NET targeting, evidence on the clinical front is awaited.

Myeloid-derived suppressor cells

Another cell type that can be found in the TME includes myeloid-derived suppressor cells (MDSC). Some argue that MDSCs are a subtype of neutrophils (33), as there are several overlapping markers between MDSCs and TANs that make distinguishing between these cell types challenging. It is still debated whether MDSCs represent a separate lineage of cells or are polarized immature neutrophils (37). Despite this quandary, MDSCs are defined as, "a heterogeneous population of cells of myeloid origin that comprise myeloid progenitor cells and immature macrophages, immature granulocytes, and immature dendritic cells" (38). Accordingly, MDSCs and TANs clearly differentiate into distinct cell types even though they both stem from myeloid progenitor cells. Other than being hypodense, MDSCs are divergent from neutrophils in several ways, including reduced expression of CD16 and CD62L, and increased expression of Arg1, CD66B, and CD11b (39, 40). MDSCs can be further categorized into subsets: monocytic MDSCs (M-MDSC), which are distinguished by a $CD11b^{hi}$, $LY6C^{hi}$, and $LY6G^{lo}$ phenotype, polymorphonuclear MDSCs (PMN-MDSC), which display a $CD11b^{hi}$, $LY6C^{lo}$, and $LY6G^{hi}$ phenotype, and early-stage MDSCs (eMDSC) that are $CD13^{-}$ and $CD14^{-}$, and $CD33^{+}$ in humans (41, 42). It is noteworthy that both M-MDSCs and PMN-MDSCs present within the TME have an enhanced suppressive phenotype when compared with MDSCs present within peripheral lymphoid organs, due to increased expression of suppressive molecules by MDSCs in the TME (43).

MDSCs present in the TME contribute to immunosuppression, including T-cell suppression and innate immune regulation, through various mechanisms (Table 1; ref. 43). Furthermore, MDSCs sculpt the primary TME and also initiate formation of the premetastatic niche. In particular, MDSCs enhance tumor cell stemness, increase angiogenesis, and advance the metastatic process by promoting EMT through IL6 secretion (44, 45). MDSCs also are influenced by the TME (Fig. 1B) that further perpetuates their inherent immunosuppressive functions. For example, HIF-1α, a key player in the hypoxic tumor microenvironment, aids in MDSC differentiation to tumor-promoting TAMs (46). Also,

factors in the TME can alter the metabolism of MDSCs toward fatty acid oxidation, prompting an upregulation of Arg1 and NOS2 production (47). The critical role of MDSCs in tumorigenesis, growth, the establishment of the premetastatic niche, and metastatic outgrowth warrants the need to effectively target them by depletion or blockade. Although their critical role in the survival and advancement of tumors is well known, there are currently no FDA-approved drugs or therapies that directly target MDSCs.

Natural killer cells and natural killer T cells

NK cells are circulatory, innate lymphoid cells recognized for their cytotoxic effector functions. Classically, there are two subsets of NKs defined by their expression of CD16 and CD56 levels: namely, $CD56^{hi}$ $CD16^{\pm}$ and $CD56^{lo}$ $CD16^{hi}$ (48). $CD56^{hi}$ $CD16^{\pm}$ NKs secrete inflammatory cytokines, whereas $CD56^{lo}$ $CD16^{hi}$ NKs specialize in cytotoxic functions and cell-mediated killing. Within the cancer framework, these cells are extremely efficient in eliminating malignant cells and limiting tumor metastases (49). Their significance in tumor surveillance is illustrated by a correlation between low NK-cell activity and increased cancer risk (50). NKs employ death receptor–mediated apoptosis and perforin/granzyme-mediated cytotoxicity to target tumor cells and limit primary tumor growth (51). While NKs characteristically destroy circulating tumor cells, they are much less efficient at cell killing within the TME. Tumors deploy many mechanisms to evade destruction by NKs, including coating themselves in collagen to engage inhibitory NK receptors and utilizing platelets as a shield to avoid NK detection (52). Within the TME, both NK subsets exhibit reduced inflammatory cytokine production and reduced or no cytotoxicity and both subsets will be referred to collectively as tumor-infiltrating natural killer cells (TINK). Many cytokines commonly present in the TME diminish NK effector functions (Table 1). These cytokines can stunt the cytotoxicity of TINKs (Fig. 1B), which not only display diminished cytotoxicity, but also contribute to arresting the proliferation and expansion of T cells, enhancing their immune-suppressive properties (these cells are often referred to as NKregs as well). Future efforts for developing therapeutic approaches could consider augmentation of cytotoxic NKs and/or targeting of TINKs. It is tempting to speculate that administration of NKs may enable a cancer-preventative approach, or at the very least, a metastasis-preventative approach as NKs are extremely efficient at targeting circulating cancer cells.

Also prevalent in the TME are natural killer T cells (NKT), which are CD1d restricted, innate-like T lymphocytes that, like T cells, possess a T-cell receptor, and like NKs, respond quickly to antigenic exposure (53). Also, like T cells, overstimulation of NKTs can render them anergic. There are two major types of NKTs, type 1 NKTs (NKTI) and type II (NKTII) cells, which are characterized by their distinct T-cell repertoires. While NKTIs express the Va14Ja18 invariant TCR alpha chain, the T-cell repertoire of NKTIIs is less defined (54). Both types can be dissected into further subsets that reflect the T-cell subsets that play inflammatory or immune-suppressive roles in the context of the TME. Specifically, NKTIs can be divided into Th1-like, Th2-like, Th17-like, Treg-like, and T follicular helper (TFH)-like NKTs; and NKTIIs can be divided into Th1-like and Th2-like NKTs. Furthermore, NKTs are reported to switch back and forth between inflammatory and immune-suppressive subsets in response to their environment. In particular, NKTIs are typically antitumor, whereas NKTIIs are predominantly protumor. NKTIs have been reported to prevent metastatic breast cancer (55) in mouse models. However, NKTIIs have been reported to support MDSCs in a B-cell lymphoma mouse model (54, 56). As such, targeting NKTIIs and supplementation with NKTIs may provide an exciting therapeutic approach.

Innate lymphoid cells

Another crucial component of the TME is the ILCs that have characteristics similar to those of NK cells. ILCs share a common lymphoid progenitor with B and T cells, but lack B- and T-cell receptors and are thus classified as innate immune cells (57). ILCs contribute to T-cell polarization through antigen presentation and cytokine secretion (58). There are three types of ILCs (ILC1, ILC2, and ILC3) classified on the basis of their production of Th1, Th2, and Th17-based cytokines and distinct transcription factors. (59). ILC1s tend to exhibit antitumor functions through cytokine production (mainly IFNγ). Furthermore, ILC1s can be divided into NK ILC1s and non-NK ILC1s based on their expression or lack thereof of the NK-specific transcription factor, Eomesodermin. Importantly, NK ILCs can be distinguished from conventional NKs by differences in transcriptional regulation, phenotype, and localization as described by Seillet and colleagues (60). While ILC2s can functionally either promote or antagonize tumor growth depending on the tumor type (Fig. 1), ILC3s are classically protumorigenic. ILC polarization is determined by the composition of each specific TME (Table 1). As such, ILCs are differentially associated with different tumor types, likely because different tumor types have distinct TME compositions; for example, ILC2s are typically found in the TME of breast and gastric cancer, ILC3s are implicated in colon cancer (61, 62), and ILC1s prevent melanoma growth through the production of inflammatory cytokines (63, 64). ILC3s may differentiate into ILC1s upon IL12 stimulation, and ILC1s may differentiate into ILC3s upon stimulation by retinoic acid and IL23 (62). The conversion of ILC1 to ILC3 stunts their ability to aggressively target the tumor. This plasticity offers an attractive opportunity for therapeutically reprogramming ILC3s to ILC1s.

Immune cells and other components of the microenvironment

While the importance of direct interactions between tumor cells and immune cells is clear, it is also noteworthy to mention that immune cell interactions with other components in the TME can impact tumor fate. For example, it has been reported that the extracellular matrix can play both supportive and inhibitory roles to the adaptive immune response by providing migratory pathways that allow T cells to invade the tissue or by directly inhibiting T-cell proliferation, respectively (65). Also, lymphatic vessels can regulate the immune microenvironment. Lymphatic vessels have been linked to providing nutrients to tumors through increased angiogenesis. They may also serve as migratory highways for immune cells (66), and lymphatic endothelial cells have also been reported to directly regulate DC activation (67). Immune cells also interact with stromal cells, including cancer-associated fibroblasts (CAF). CAFs exhibit wound-healing properties and have been implicated as contributors to tumor proliferation, invasion, and metastasis. CAFs may secrete immune-suppressive cytokines that polarize Mφs to the M2 phenotype and contribute to $CD8^{+}$ T-cell exhaustion and deletion (68).

These observations indicate a complex series of interactions between immune cell types and nontumor cells within the TME that clearly impact tumor progression, invasion, and metastasis. Therefore, not only should therapy designs consider tumor–

immune cell cross-talk and tumor–stromal cross-talk, but also stromal–immune cell cross-talk as it contributes significantly to tumor development.

Current and future therapeutics

The tumor masterfully controls its surrounding environment to promote its establishment, growth, survival, and spread. One of the chief ways it does this is through reprogramming innate immune cells to foster tumor growth and survival, leaving the patient with a weakened defense and often a worse prognosis. This is a potential Achilles heel of the tumor; as such, reprogramming the innate immune system is a potentially important approach to improve patient outcomes.

Macrophage therapies

Previous clinical trials targeting Mφs in the TME have been unsuccessful. Many prior trials involved the activation and injection of Mφs into patients with cancer using various activation methods such as IFNγ, mifamurtide, and LPS, but none of these methods were therapeutically efficacious (69–71). There have been some promising clinical trials utilizing anti-M-CSFR antibodies. One such example includes the administration of RG7155, an anti-M-CSFR antibody, to diffuse-type giant cell tumor (Dt-GCT) patients. This strategy led to decreased TAM infiltration and overall positive patient responses (72). It is noteworthy that anti-M-CSFR antibodies have yet to be successful in glioblastoma models, and there is still work to be done on this front. Ongoing clinical trials that target Mφ receptor, CSF-1R, and the CCL2–CCR2 signaling axis ablate tumor-infiltrating Mφs and show promise in advanced solid tumors (73). Moreover, the efficacy of CSF-1R inhibition is vastly improved when combined with receptor tyrosine kinase inhibitors. In addition to targeting CSF-1R and the CCL2–CCR2 signaling axis, there are ongoing clinical trials targeting CXCL12/CXCR4, CD40, and angiopoietin1/2 (74). Treatment with IFNα has yielded favorable outcomes in patients with melanoma. IFNα promotes an inflammatory environment, stimulates Mφs toward an M1 type, and has been demonstrated to reduce tumor growth and diminish metastasis (75).

DC therapies

Targeting DC activation via DC vaccination is another therapeutic option. An important consideration in using DC vaccinations as cancer treatment is the method of priming DCs with tumor antigen. Options including priming with whole tumor cells, tumor cell lysate, apoptotic bodies, exosomes, or DNA or RNA need to be considered when designing an effective DC vaccine (76–78). Thus far, whole-cell vaccines seem to be the most promising. Several DC vaccination trials are currently ongoing (clinicaltrials.gov). One trial (NCT01204684) involves enrichment of DCs from patients with glioma, pulsation with tumor lysate, and autologous intradermal injection. In their phase I clinical trial, Hus and colleagues primed DCs from patients with B-cell chronic lymphocytic lymphoma with tumor lysates and autologously vaccinated patients with these primed DCs (79). This strategy resulted in an increase in cytotoxic T-cell response. An example of a successful DC-based therapy for prostate cancer is Provenge. The regimen for Provenge therapy involves harvesting monocytes from prostate cancer patients, differentiating and activating them *in vivo* with PAP antigen, and introducing them back into the patient. This therapy has achieved significant success marked by diminished tumor burden in patients with prostate cancer. A new DC vaccine targeting glioblastoma is DCVax-L that includes autologous DCs loaded with glioblastoma tumor lysate. This vaccine has been tested in a phase III clinical trial for glioblastoma, and overall patient survival was shown to increase by 6 months (80).

Despite success with DC vaccinations, there are challenges associated with them, including high cost, the absence of universal vaccine, the need for massive amounts of DCs, and issues with polarizing conventional DCs *in vitro*. Previous attempts at DC vaccinations focused on moDCs that are rare and do not functionally resemble cross-presenting DCs *in vivo* (81). It is now recognized that cDCs comprise the DC subtype that is most likely to come into contact with cancer cells in the TME and mount the ensuing immune response. While cDCs are challenging to isolate, a cDC vaccine for melanoma has been reported to elicit a cytotoxic T-cell response making them functionally more relevant (82). Further work is required to standardize methods to effectively isolate cDCs for antigen loading and DC vaccination. A new focus for DC therapy involves directly targeting them *in vivo*. *In vivo* delivery of antibodies to cDC1 receptors conjugated to tumor antigens results in better DC activity and a higher rate of primed T cells. This is expected to reduce treatment costs due to the universality of the therapy and improve therapeutic effectiveness because DCs *in vivo* are already at the tumor site (in contrast to direct tumor injections that are not always possible or effective depending on tumor type). Combining this approach with immune checkpoint inhibitor blockade therapy will allow for rapid, effective T-cell priming without T-cell exhaustion.

Neutrophil therapies

There are ongoing efforts to target neutrophils in the TME. Preclinical models have yielded optimistic success in reducing neutrophil number by squelching G-MCSF from the TME. Reparixin is a noncompetitive allosteric inhibitor of CXCR1 and CXCR2 (83) and targets neutrophil maturation to inhibit the immunosuppressive impact of tumor-induced N2 neutrophils. Reparixin is currently in one phase I and two phase II clinical trials for metastatic breast cancer. Targeting neutrophil polarization is another enticing therapeutic option through TGFβ inhibitors (84). While there are currently many clinical trials that use TGFβ inhibitors, off-target effects, and cytotoxicity have been reported (85).

MDSC therapies

There are currently several ongoing clinical trials that target MDSCs in different cancer types including leukemia, melanoma, glioblastoma, and breast cancer (86). These trials utilize different mechanisms of indirectly impacting MDSC function, including targeting Arg1, iNOS, and STAT3 activities, metabolism through CD36, and trafficking through CXCR2 (86). MDSC depletion is another tested avenue for cancer therapeutics. There has been some success in triggering MDSC apoptosis with gemcitabine and 5-fluorouracil, correlating with diminished tumor growth. Docetaxel, doxorubicin, paclitaxel, and tyrosine kinase inhibitors have also been demonstrated to reduce the numbers and effectiveness of MDSCs in the TME (86). There also are therapies targeting MDSCs in combination with immune checkpoint inhibitors. A phase I/II clinical trial in patients with renal cell

carcinoma using atezolizumab and a histone deacetylase inhibitor shows promise (NCT03024437). Also, a phase II clinical trial in patients with melanoma combines ipilimumab and ATRA, which blocks retinoic acid signal transduction, leading to the differentiation of MDSCs into Mφs and DCs (NCT02403778). ATRA alone also leads to a reduction of MDSC frequencies in small-cell lung cancer (87, 88). While these trials show moderate yet encouraging success, off-target effects of these drugs may contribute to diminished therapeutic efficacy.

NK-cell therapies

Multiple enduring clinical trials aim to stimulate the immune system with NK-cell therapy. For example, there is a phase I trial targeting advanced biliary tract cancer via allogeneic NK injection (NCT03358849). Yang and colleagues pioneered allogeneic NK-cell therapy by activating allogeneic NKs with IL2, followed by administration to patients with advanced lymphoma (89). The results revealed diminished T-reg and MDSC populations and increased expression of NKG2D on cytotoxic T cells (90). NK-cell therapy in combination with chemotherapy for small-cell lung cancer (NCT03410368) is also an effective strategy (91). Also, the use of CAR-NK cells, genetically engineered cells that directly target tumor-specific antigens in an HLA-unrestricted manner, has shown favorable outcomes in preclinical studies for B-cell malignancies, ovarian, breast, prostate, and colon cancers (92). All of these approaches have exhibited varying degrees of positive outcomes, but they also are limited by toxicity and detrimental side effects, high cost, and low efficacy (51, 93). In contrast, there have been few successful clinical trials for ILC therapy in cancer.

Conclusion

Each of the therapeutic approaches discussed in this review has focused on targeting one aspect of the immune system. While some of these treatments yield positive outcomes, a more definitive and likely more effective approach involves altering multiple facets of the TME through a strong inflammatory response by promoting the inflammatory innate immune cells. There are multiple strategies that target immune-suppressive cells, but unfortunately many of these responses are important for self-tolerance mechanisms and aid in protection against autoimmunity. Targeting immune-suppressive cells cannot focus on a global depletion of all innate cells in the TME as this could cause dire effects in the host. The solution must be an intricate combination that involves selective inhibition or depletion of robust tumor-suppressive cytokines and cell types in addition to bolstering the inflammatory phenotype of immune cells.

Disclosure of Potential Conflicts of Interest

L.A. Shevde is a consultant/advisory board member for NIH and CDMRP. No potential conflicts of interest were disclosed by the other author.

Acknowledgments

We acknowledge funding from the Department of Defense (W81XWH-14-1-0516 and W81XWH-18-1-0036), NCI R01CA169202, and The Breast Cancer Research Foundation of Alabama (BCRFA; to L.A. Shevde). We would also like to acknowledge Will Jackson who contributed to figure development and conceptualization of this work, Dr. Rajeev Samant, Dr. Ann Hanna, Brandon Metge, and Sarah Bailey for editorial suggestions, and the UAB O'Neal Comprehensive Cancer Center (P30CA013148).

Received December 27, 2018; revised February 28, 2019; accepted May 21, 2019; published first July 26, 2019.

References

1. McGuirk P, Mills KH.Pathogen-specific regulatory T cells provoke a shift in the Th1/Th2 paradigm in immunity to infectious diseases. Trends Immunol 2002;23:450–5.
2. Yang L, Zhang Y. Tumor-associated macrophages: from basic research to clinical application. J Hematol Oncol 2017;10:58.
3. Chen H, Shi R, Luo B, Yang X, Qiu L, Xiong J, et al. Macrophage peroxisome proliferator-activated receptor gamma deficiency delays skin wound healing through impairing apoptotic cell clearance in mice. Cell Death Dis 2015;6:e1597.
4. Peiseler M, Kubes P.Macrophages play an essential role in trauma-induced sterile inflammation and tissue repair. Eur J Trauma Emerg Surg 2018;44:335–49.
5. Varol C, Mildner A, Jung S. Macrophages: development and tissue specialization. Annu Rev Immunol 2015;33:643–75.
6. Qin L, Wu YL, Toneff MJ, Li D, Liao L, Gao X, et al. NCOA1 Directly Targets M-CSF1 expression to promote breast cancer metastasis. Cancer Res 2014;74:3477–88.
7. Kim J, Bae JS.Tumor-associated macrophages and neutrophils in tumor microenvironment. Mediators Inflamm 2016;2016:6058147.
8. Cardoso AP, Pinto ML, Pinto AT, Oliveira MI, Pinto MT, Gonçalves R, et al. Macrophages stimulate gastric and colorectal cancer invasion through EGFR Y(1086), c-Src, Erk1/2 and Akt phosphorylation and smallGTPase activity. Oncogene 2014;33:2123–33.
9. Wang N, Liu W, Zheng Y, Wang S, Yang B, Li M, et al. CXCL1 derived from tumor-associated macrophages promotes breast cancer metastasis via activating NF-kappaB/SOX4 signaling. Cell Death Dis 2018;9:880.
10. Zhao X, Qu J, Sun Y, Wang J, Liu X, Wang F, et al. Prognostic significance of tumor-associated macrophages in breast cancer: a meta-analysis of the literature. Oncotarget 2017;8:30576–86.
11. Goswami S, Sahai E, Wyckoff JB, Cammer M, Cox D, Pixley FJ, et al. Macrophages promote the invasion of breast carcinoma cells via a colony-stimulating factor-1/epidermal growth factor paracrine loop. Cancer Res 2005;65:5278–83.
12. Wyckoff J, Wang W, Lin EY, Wang Y, Pixley F, Stanley ER, et al. A paracrine loop between tumor cells and macrophages is required for tumor cell migration in mammary tumors. Cancer Res 2004;64:7022–9.
13. Funes SC, Rios M, Escobar-Vera J, Kalergis AM. Implications of macrophage polarization in autoimmunity. Immunology 2018;154:186–95.
14. Zheng X, Turkowski K, Mora J, Brüne B, Seeger W, Weigert A, et al. Redirecting tumor-associated macrophages to become tumoricidal effectors as a novel strategy for cancer therapy. Oncotarget 2017;8:48436–52.
15. Petrova V, Annicchiarico-Petruzzelli M, Melino G, Ivano Amelio I. The hypoxic tumour microenvironment. Oncogenesis 2018;7:10.
16. Hanna A, Metge BJ, Bailey SK, Chen D, Chandrashekar DS, Varambally S, et al. Inhibition of Hedgehog signaling reprograms the dysfunctional immune microenvironment in breast cancer. Oncoimmunology 2019;8:1548241.
17. Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, et al. Pre-metastatic niches: organ-specific homes for metastases. Nat Rev Cancer 2017;17:302–17.
18. Doak GR, Schwertfeger KL, Wood DK. Distant Relations: Macrophage Functions in the Metastatic Niche. Trends Cancer 2018;4:445–59.
19. Collin M, Bigley V. Human dendritic cell subsets: an update. Immunology 2018;154:3–20.
20. Motta JM, Rumjanek VM.Sensitivity of Dendritic Cells to Microenvironment Signals. J Immunol Res 2016;2016:4753607.
21. Sumpter TL, Dangi A, Matta BM, Huang C, Stolz DB, Vodovotz Y, et al. Hepatic stellate cells undermine the allostimulatory function of liver myeloid dendritic cells via STAT3-dependent induction of IDO. J Immunol 2012;189:3848–58.

22. Basit F, Mathan T, Sancho D, de Vries IJM. Human dendritic cell subsets undergo distinct metabolic reprogramming for immune response. Front Immunol 2018;9:2489.
23. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer Cell 2009;16:183–94.
24. Chaput N, Conforti R, Viaud S, Spatz A, Zitvogel L. The Janus face of dendritic cells in cancer. Oncogene 2008;27:5920–31.
25. Aspord C, Pedroza-Gonzalez A, Gallegos M, Tindle S, Burton EC, Su D, et al. Breast cancer instructs dendritic cells to prime interleukin 13-secreting CD4+ T cells that facilitate tumor development. J Exp Med 2007;204:1037–47.
26. Tran Janco JM, Lamichhane P, Karyampudi L, Knutson KL. Tumor-infiltrating dendritic cells in cancer pathogenesis. J Immunol 2015; 194:2985–91.
27. Michea P, Noël F, Zakine E, Czerwinska U, Sirven P, Abouzid O, et al. Adjustment of dendritic cells to the breast-cancer microenvironment is subset specific. Nat Immunol 2018;19:885–97.
28. Wang J, Jia Y, Wang N, Zhang X, Tan B, Zhang G, et al. The clinical significance of tumor-infiltrating neutrophils and neutrophil-to-CD8+ lymphocyte ratio in patients with resectable esophageal squamous cell carcinoma. J Transl Med 2014;12:7.
29. Deniset JF, Kubes P.Recent advances in understanding neutrophils. F1000Res 2016;5:2912.
30. Uribe-Querol E, Rosales C.Neutrophils in cancer: two sides of the same coin. J Immunol Res 2015;2015:983698.
31. Cools-Lartigue J, Spicer J, Najmeh S, Ferri L. Neutrophil extracellular traps in cancer progression. Cell Mol Life Sci 2014;71:4179–94.
32. Jin W, Xu HX, Zhang SR, Li H, Wang WQ, Gao HL, et al. Tumor-infiltrating NETs predict postsurgical survival in patients with pancreatic ductal adenocarcinoma. Ann Surg Oncol 2018;26:635–43.
33. Fridlender ZG, Albelda SM. Tumor-associated neutrophils: friend or foe? Carcinogenesis 2012;33:949–55.
34. Demers M, Wong SL, Martinod K, Gallant M, Cabral JE, Wang Y, et al. Priming of neutrophils toward NETosis promotes tumor growth. Oncoimmunology 2016;5:e1134073.
35. He M, Peng A, Huang XZ, Shi DC, Wang JC, Zhao Q, et al. Peritumoral stromal neutrophils are essential for c-Met-elicited metastasis in human hepatocellular carcinoma. Oncoimmunology 2016;5:e1219828.
36. Schauer C, Janko C, Munoz LE, Zhao Y, Kienhöfer D, Frey B, et al. Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. Nat Med 2014;20:511–7.
37. Pillay J, Tak T, Kamp VM, Koenderman L. Immune suppression by neutrophils and granulocytic myeloid-derived suppressor cells: similarities and differences. Cell Mol Life Sci 2013;70:3813–27.
38. Gabrilovich DI, Nagaraj S.Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009;9:162–74.
39. Rodriguez PC, Ernstoff MS, Hernandez C, Atkins M, Zabaleta J, Sierra R, et al. Arginase I-producing myeloid-derived suppressor cells in renal cell carcinoma are a subpopulation of activated granulocytes. Cancer Res 2009;69:1553–60.
40. Youn JI, Collazo M, Shalova IN, Biswas SK, Gabrilovich DI. Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. J Leukoc Biol 2012;91:167–81.
41. Gabrilovich DI,Ostrand-Rosenberg S., Bronte V.Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 2012;12:253–68.
42. Bronte V, Brandau S, Chen SH, Colombo MP, Frey AB, Greten TF, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun 2016;7:12150.
43. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The nature of myeloid-derived suppressor cells in the tumor microenvironment. Trends Immunol 2016;37:208–20.
44. Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. Regulation of tumor metastasis by myeloid-derived suppressor cells. Annu Rev Med 2015;66:97–110.
45. Condamine T, Dominguez GA, Youn JI, Kossenkov AV, Mony S, Alicea-Torres K, et al. Lectin-type oxidized LDL receptor-1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients. Sci Immunol 2016;1:aaf8943.
46. Corzo CA, Condamine T, Lu L, Cotter MJ, Youn JI, Cheng P, et al. HIF-1alpha regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. J Exp Med 2010;207: 2439–53.
47. Hossain F, Al-Khami AA, Wyczechowska D, Hernandez C, Zheng L, Reiss K, et al. Inhibition of fatty acid oxidation modulates immunosuppressive functions of myeloid-derived suppressor cells and enhances cancer therapies. Cancer Immunol Res 2015;3:1236–47.
48. Stabile H, Fionda C, Gismondi A, Santoni A. Role of distinct natural killer cell subsets in anticancer response. Front Immunol 2017;8:293.
49. Glasner A, Levi A, Enk J, Isaacson B, Viukov S, Orlanski S, et al. NKp46 receptor-mediated interferon-gamma production by natural killer cells increases fibronectin 1 to alter tumor architecture and control metastasis. Immunity 2018;48:396–398.
50. Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. Lancet 2000;356: 1795–9.
51. Langers I, Renoux VM, Thiry M, Delvenne P, Jacobs N, et al. Natural killer cells: role in local tumor growth and metastasis. Biologics 2012; 6:73–82.
52. Maurer S, Kropp KN, Klein G, Steinle A, Haen SP, Walz JS, et al. Platelet-mediated shedding of NKG2D ligands impairs NK cell immune-surveillance of tumor cells. Oncoimmunology 2018;7:e1364827.
53. Nair S, Dhodapkar MV.Natural killer T cells in cancer immunotherapy. Front Immunol 2017;8:1178.
54. Krijgsman D, Hokland M, Kuppen PJK. The role of natural killer T cells in cancer-a phenotypical and functional approach. Front Immunol 2018;9: 367.
55. Gebremeskel S, Clattenburg DR, Slauenwhite D, Lobert L, Johnston B. Natural killer T cell activation overcomes immunosuppression to enhance clearance of postsurgical breast cancer metastasis in mice. Oncoimmunology 2015;4:e995562.
56. Renukaradhya GJ, Khan MA, Vieira M, Du W, Gervay-Hague J, Brutkiewicz RR. Type I NKT cells protect (and type II NKT cells suppress) the host's innate antitumor immune response to a B-cell lymphoma. Blood 2008; 111:5637–45.
57. Flores-Borja F, Irshad S, Gordon P, Wong F, Sheriff I, Tutt A, et al. Crosstalk between innate lymphoid cells and other immune cells in the tumor microenvironment. J Immunol Res 2016;2016:7803091.
58. von Burg N, Chappaz S, Baerenwaldt A, Horvath E, Bose Dasgupta S, Ashok D, et al. Activated group 3 innate lymphoid cells promote T-cell-mediated immune responses. Proc Natl Acad Sci U S A 2014;111: 12835–40.
59. Kyoizumi S, Kubo Y, Kajimura J, Yoshida K, Hayashi T, Nakachi K, et al. Fate decision between group 3 innate lymphoid and conventional nk cell lineages by Notch signaling in human circulating hematopoietic progenitors. J Immunol 2017;199:2777–93.
60. Seillet C, Belz GT, Huntington ND. Development, homeostasis, and heterogeneity of NK cells and ILC1. Curr Top Microbiol Immunol 2016;395:37–61.
61. Jovanovic IP, Pejnovic NN, Radosavljevic GD, Pantic JM, Milovanovic MZ, Arsenijevic NN, et al. Interleukin-33/ST2 axis promotes breast cancer growth and metastases by facilitating intratumoral accumulation of immunosuppressive and innate lymphoid cells. Int J Cancer 2014;134: 1669–82.
62. van Beek JJP, Martens AWJ, Bakdash G, de Vries IJM. Innate lymphoid cells in tumor immunity. Biomedicines 2016;4. doi: 10.3390/biomedicines4010007.
63. Fuchs A, Vermi W, Lee JS, Lonardi S, Gilfillan S, Newberry RD, et al. Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN-gamma-producing cells. Immunity 2013;38: 769–81.
64. Mattner J, Wirtz S.Friend or foe? The ambiguous role of innate lymphoid cells in cancer development. Trends Immunol 2017;38:29–38.
65. Pickup MW, Mouw JK, Weaver VM. The extracellular matrix modulates the hallmarks of cancer. EMBO Rep 2014;15:1243–53.
66. Lund AW, Wagner M, Fankhauser M, Steinskog ES, Broggi MA, Spranger S, et al. Lymphatic vessels regulate immune microenvironments in human and murine melanoma. J Clin Invest 2016;126: 3389–402.
67. Podgrabinska S, Kamalu O, Mayer L, Shimaoka M, Snoeck H, Randolph GJ, et al. Inflamed lymphatic endothelium suppresses dendritic cell

maturation and function via Mac-1/ICAM-1-dependent mechanism. J Immunol 2009;183:1767–79.
68. Lakins MA, Ghorani E, Munir H, Martins CP, Shields JD. Cancer-associated fibroblasts induce antigen-specific deletion of CD8 (+) T cells to protect tumour cells. Nat Commun 2018;9:948.
69. Faradji A, Bohbot A, Frost H, Schmitt-Goguel M, Siffert JC, Dufour P, et al. Phase I study of liposomal MTP-PE-activated autologous monocytes administered intraperitoneally to patients with peritoneal carcinomatosis. J Clin Oncol 1991;9:1251–60.
70. Hennemann B, Beckmann G, Eichelmann A, Rehm A, Andreesen R. Phase I trial of adoptive immunotherapy of cancer patients using monocyte-derived macrophages activated with interferon gamma and lipopolysaccharide. Cancer Immunol Immunother 1998;45:250–6.
71. Stevenson HC, Keenan AM, Woodhouse C, Ottow RT, Miller P, Steller EP, et al. Fate of gamma-interferon-activated killer blood monocytes adoptively transferred into the abdominal cavity of patients with peritoneal carcinomatosis. Cancer Res 1987;47:6100–3.
72. Ries CH, Cannarile MA, Hoves S, Benz J, Wartha K, Runza V, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer Cell 2014;25:846–59.
73. Ostuni R, Kratochvill F, Murray PJ, Natoli G. Macrophages and cancer: from mechanisms to therapeutic implications. Trends Immunol 2015;36:229–39.
74. Quail DF, Joyce JA. Molecular pathways: deciphering mechanisms of resistance to macrophage-targeted therapies. Clin Cancer Res 2017;23:876–884.
75. De Palma M, Mazzieri R, Politi LS, Pucci F, Zonari E, Sitia G, et al. Tumor-targeted interferon-alpha delivery by Tie2-expressing monocytes inhibits tumor growth and metastasis. Cancer Cell 2008;14:299–311.
76. Boczkowski D, Nair SK, Snyder D, Gilboa E. Dendritic cells pulsed with RNA are potent antigen-presenting cells *in vitro* and *in vivo*. J Exp Med 1996;184:465–72.
77. Cao J, Jin Y, Li W, Zhang B, He Y, Liu H, et al. DNA vaccines targeting the encoded antigens to dendritic cells induce potent antitumor immunity in mice. BMC Immunol 2013;14:39.
78. Hamilton DH, Litzinger MT, Jales A, Huang B, Fernando RI, Hodge JW, et al. Immunological targeting of tumor cells undergoing an epithelial-mesenchymal transition via a recombinant brachyury-yeast vaccine. Oncotarget 2013;4:1777–90.
79. Hus I, Rolinski J, Tabarkiewicz J, Wojas K, Bojarska-Junak A, Greiner J, et al. Allogeneic dendritic cells pulsed with tumor lysates or apoptotic bodies as immunotherapy for patients with early-stage B-cell chronic lymphocytic leukemia. Leukemia 2005;19:1621–7.
80. van Willigen WW, Bloemendal M, Gerritsen WR, Schreibelt G, de Vries IJM, Bol KF. Dendritic cell cancer therapy: vaccinating the right patient at the right time. Front Immunol 2018;9:2265.
81. Saxena M, Bhardwaj N.Re-emergence of dendritic cell vaccines for cancer treatment. Trends Cancer 2018;4:119–137.
82. Lesterhuis WJ, Aarntzen EH, De Vries IJ, Schuurhuis DH, Figdor CG, Adema GJ, et al. Dendritic cell vaccines in melanoma: from promise to proof? Crit Rev Oncol Hematol 2008;66:118–34.
83. Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. Mol Cancer 2017;16:137.
84. Colak S,Ten Dijke P.Targeting TGF-beta signaling in cancer. Trends Cancer 2017;3:56–71.
85. Connolly EC, Freimuth J, Akhurst RJ. Complexities of TGF-beta targeted cancer therapy. Int J Biol Sci 2012;8:964–78.
86. Fleming V, Hu X, Weber R, Nagibin V, Groth C, Altevogt P, et al. Targeting myeloid-derived suppressor cells to bypass tumor-induced immunosuppression. Front Immunol 2018;9:398.
87. Iclozan C, Antonia S, Chiappori A, Chen DT, Gabrilovich D. Therapeutic regulation of myeloid-derived suppressor cells and immune response to cancer vaccine in patients with extensive stage small cell lung cancer. Cancer Immunol Immunother 2013;62:909–18.
88. Weber R, Fleming V, Hu X, Nagibin V, Groth C, Altevogt P, et al. Myeloid-derived suppressor cells hinder the anti-cancer activity of immune checkpoint inhibitors. Front Immunol 2018;9:1310.
89. Yang Y, Lim O, Kim TM, Ahn YO, Choi H, Chung H, et al. Phase I Study of random healthy donor-derived allogeneic natural killer cell therapy in patients with malignant lymphoma or advanced solid tumors. Cancer Immunol Res 2016;4:215–24.
90. Veluchamy JP, Kok N, van der Vliet HJ, Verheul HMW, de Gruijl TD, Spanholtz J. The rise of allogeneic natural killer cells as a platform for cancer immunotherapy: recent innovations and future developments. Front Immunol 2017;8:631.
91. Tang X, Yang L, Li Z, Nalin AP, Dai H, Xu T, et al. First-in-man clinical trial of CAR NK-92 cells: safety test of CD33-CAR NK-92 cells in patients with relapsed and refractory acute myeloid leukemia. Am J Cancer Res 2018;8:1083–9.
92. Rezvani K, Rouce R, Liu E, Shpall E. Engineering natural killer cells for cancer immunotherapy. Mol Ther 2017;25:1769–81.
93. Bolourian A, Mojtahedi Z.Possible damage to immune-privileged sites in natural killer cell therapy in cancer patients: side effects of natural killer cell therapy. Immunotherapy 2017;9:281–288.
94. Roszer TUnderstanding the mysterious M2 macrophage through activation markers and effector mechanisms. Mediators Inflamm 2015;2015:816460.
95. Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. Annu Rev Immunol 2003;21:685–711.
96. Ma DY, Clark EA.The role of CD40 and CD154/CD40L in dendritic cells. Semin Immunol 2009;21:265–72.
97. Conejo-Garcia JR, Rutkowski MR, Cubillos-Ruiz JR. State-of-the-art of regulatory dendritic cells in cancer. Pharmacol Ther 2016;164:97–104.
98. Guilliams M, Dutertre CA, Scott CL, McGovern N, Sichien D, Chakarov S, et al. Unsupervised high-dimensional analysis aligns dendritic cells across tissues and species. Immunity 2016;45:669–684.
99. Collin M, McGovern N, Haniffa M. Human dendritic cell subsets. Immunology 2013;140:22–30.
100. Chen K, Wang JM, Yuan R, Yi X, Li L, Gong W, et al. Tissue-resident dendritic cells and diseases involving dendritic cell malfunction. Int Immunopharmacol 2016;34:1–15.
101. Gueguen C, Bouley J, Moussu H, Luce S, Duchateau M, Chamot-Rooke J, et al. Changes in markers associated with dendritic cells driving the differentiation of either TH2 cells or regulatory T cells correlate with clinical benefit during allergen immunotherapy. J Allergy Clin Immunol 2016;137:545–58.