Innate Immunity and Cancer Pathophysiology

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Abstract

Chronic inflammation increases the risk of several cancers, including gastric, colon, and hepatic cancers. Conversely, tumors, similar to tissue injury, trigger an inflammatory response coordinated by the innate immune system. Cellular and molecular mediators of inflammation modulate tumor growth directly and by influencing the adaptive immune response. Depending on the balance of immune cell types and signals within the tumor microenvironment, inflammation can support or restrain the tumor. Adding to the complexity, research from the past two decades has revealed that innate immune cells are highly heterogeneous and plastic, with variable phenotypes depending on tumor type, stage, and treatment. The field is now on the cusp of being able to harness this wealth of data to (*a*) classify tumors on the basis of their immune makeup, with implications for prognosis, treatment choice, and clinical outcome, and (*b*) design therapeutic strategies that activate antitumor immune responses by targeting innate immune cells.

INTRODUCTION

Tumor development elicits a host response that resembles inflammation and is similarly coordinated by the innate immune system. Cellular and extracellular components engaged in this process shape tumor growth and progression by modifying the abundance and functions of one another, interacting with cancer cells, and modulating the adaptive immune response. Inflammation is a plastic process and ultimately, whether inflammation promotes or inhibits cancer, depends on the balance of a complex and still incompletely understood cellular and molecular circuit (**Figure 1**).

One of the earliest indications of a connection between immunity and cancer was the detection of immune cells in histological sections of tumors (1). Another clue came from clinical practice. In the nineteenth century, the German physicians Wilhelm Busch and Friedrich Fehleisen independently recognized that patients could experience cancer regression after contracting postoperative infections (2). This observation was further expanded upon by William B. Coley, an American surgeon, who in the 1890s began inoculating patients with bacteria, with the idea that the response to the pathogen could clear both the infection and the cancer. Eventually, he settled on Coley's toxins, a formulation comprising heat-killed, gram-positive *Streptococcus pyogenes* and gram-negative *Serratia marcescens* bacteria. The therapy had severe side effects and required daily inoculations, and beneficial responses were limited mostly to sarcoma, a rare cancer. However, Coley's was the first concerted and broadly recognized effort to elicit an immune response against cancer (3, 4).
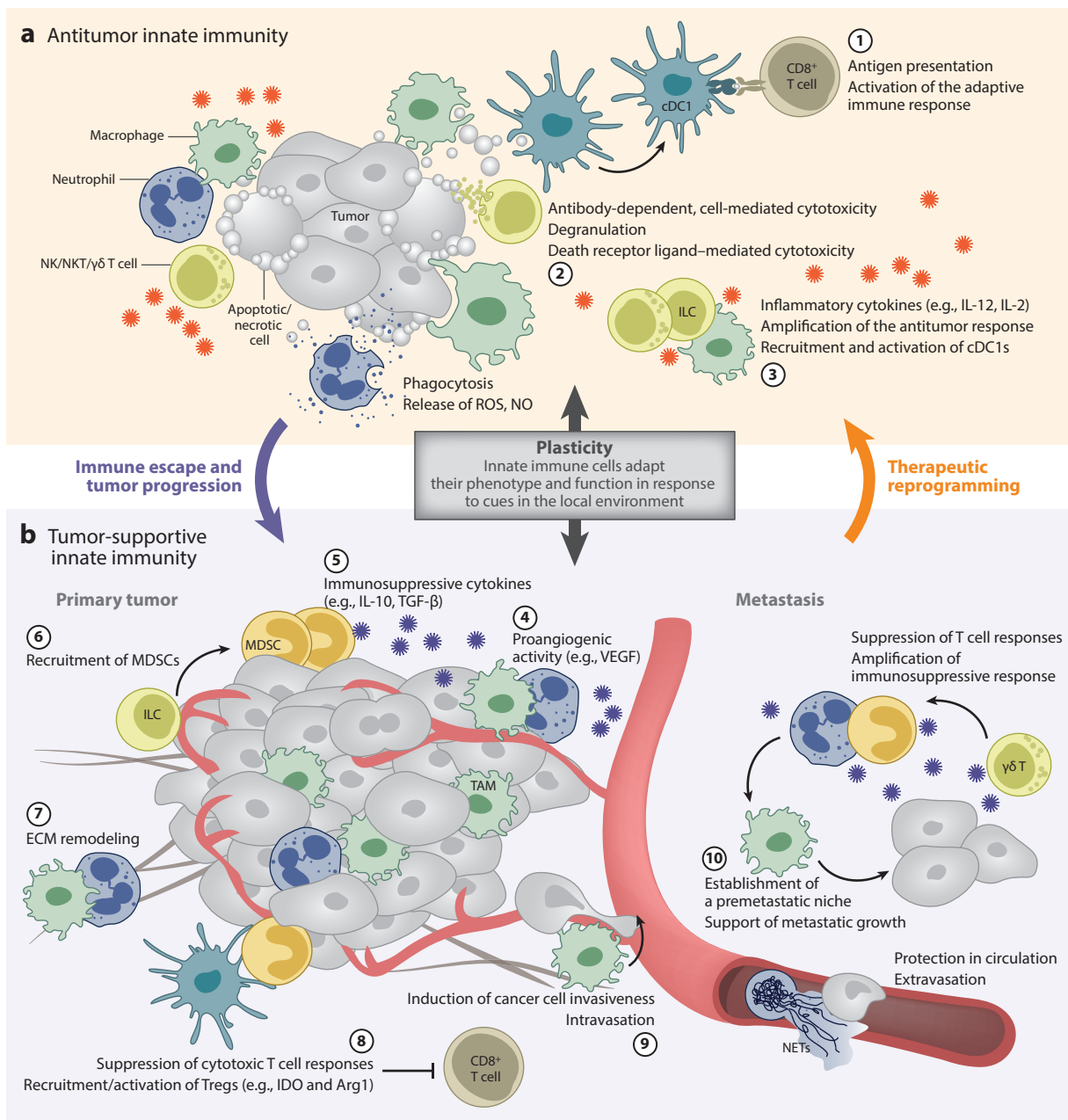
Early research focused mostly on inducing inflammation to elicit anticancer immunity, yet the possibility that inflammation could also drive cancer was already suggested in 1828 by Jean-Nicolas Marjolin, a French surgeon, who reported the occurrence of squamous cell carcinoma in chronically inflamed wounds (5). In 1863, the German pathologist Rudolf Virchow proposed that cancer originates at sites of chronic inflammation (1). Starting in the 1990s, seminal work using genetically engineered mouse models demonstrated that innate immune cells such as neutrophils, macrophages, and mast cells contribute to cancer progression (6–13).

During the past decade, the clinical success of cancer immunotherapy has sparked renewed interest in the role of innate immunity in cancer. Although most approved strategies are aimed at boosting tumor-specific cytotoxic T cell responses, strategies to engage the innate immune system in anticancer responses are being developed. Moreover, sophisticated techniques to resolve gene expression and proteomic profiles at the single-cell level have allowed researchers to classify cancers on the basis of their immune makeup: the type of immune cells present in the tumor, their phenotypes, and their location within the microenvironment. These studies have also highlighted the plasticity of innate immune cells, that is, how their phenotype and function change in response to the microenvironment. Along with its genotype, the cancer immune makeup is refining our capacity to predict clinical outcome. Here, we review the contrasting roles of innate immunity in cancer and discuss the clinical implications of these findings.

INFLAMMATION AND CANCER ARE HIGHLY INTERCONNECTED

Inflammation is a biological reaction the body mounts in response to infections, wounds, and chemical exposure to restore homeostasis and prevent loss of tissue function (14, 15). The cells and molecules responsible for triggering and coordinating inflammation compose the innate immune system. Tissue-resident macrophages and mast cells are the first to recognize the insult. They secrete a variety of soluble mediators, cytokines, and chemokines to recruit other innate immune cells to the infection (or injury) site. Neutrophils are the first cells to respond to such signals, becoming activated and killing invading bacteria (16, 17). If this acute inflammatory response is not able to eliminate the insult, macrophages and T cells are next attracted to and activated by increased expression of chemokines, growth factors, and cytokines. This process is followed

by a resolution and repair phase in which the local release of signals [e.g., resolvins, protectins, and transforming growth factor β (TGF-β)] inhibits further neutrophil recruitment (18). Instead, monocytes are attracted to the site, where they differentiate into macrophages, remove dead cells, and initiate tissue repair mechanisms. This orchestrated immune response mediates neutralization of the offending agent. However, when the body is unable to resolve this acute inflammatory

a Antitumor innate immunity

Macrophage
Neutrophil
NK/NKT/γδ T cell
Tumor
Apoptotic/ necrotic cell
cDC1
CD8⁺ T cell

① Antigen presentation
Activation of the adaptive immune response

② Antibody-dependent, cell-mediated cytotoxicity
Degranulation
Death receptor ligand–mediated cytotoxicity

ILC
③ Inflammatory cytokines (e.g., IL-12, IL-2)
Amplification of the antitumor response
Recruitment and activation of cDC1s

Phagocytosis
Release of ROS, NO

Immune escape and tumor progression

Plasticity
Innate immune cells adapt their phenotype and function in response to cues in the local environment

Therapeutic reprogramming

b Tumor-supportive innate immunity

Primary tumor

⑤ Immunosuppressive cytokines (e.g., IL-10, TGF-β)
④ Proangiogenic activity (e.g., VEGF)
⑥ Recruitment of MDSCs
MDSC
ILC
TAM
⑦ ECM remodeling

Metastasis

Suppression of T cell responses
Amplification of immunosuppressive response
γδ T

⑩ Establishment of a premetastatic niche
Support of metastatic growth

Protection in circulation
Extravasation
NETs

Induction of cancer cell invasiveness
Intravasation
⑨

⑧ Suppression of cytotoxic T cell responses
Recruitment/activation of Tregs (e.g., IDO and Arg1)
CD8⁺ T cell

(*Caption appears on following page*)

Plasticity of the innate immune system. The components of the innate immune system are not inherently tumor supportive or tumor opposing. Rather, cells of the innate immune system are highly plastic and their phenotype and activity depend on the balance of signals within the tumor. (*a*) The antitumorigenic functions of the innate immune system include ((1)) antigen presentation and activation of the adaptive response, ((2)) direct killing of cancer cells, and ((3)) amplification of the antitumor immune response through cytokine secretion. (*b*) During tumor progression, signals from tumor cells and other cells in the microenvironment can polarize innate immune cells toward supporting the tumor, for example, through ((4)) angiogenesis, ((7)) ECM remodeling, ((5)(6)(8)) immunosuppression, and ((9)(10)) prometastatic activities. Thus, because of plasticity, the innate immune system has tumor-promoting potential. However, plasticity also affords us the opportunity to therapeutically reprogram the innate immune system to fight the tumor. Abbreviations: cDC, conventional dendritic cell; ECM, extracellular matrix; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; ILC, innate lymphoid cell; MDSC, myeloid-derived suppressor cell; NET, neutrophil extracellular trap; NK, natural killer; NKT, natural killer T; NO, nitric oxide; ROS, reactive oxygen species; TAM, tumor-associated macrophage; TGF, transforming growth factor; Treg, T regulatory cell; VEGF, vascular endothelial growth factor.

response, the result is chronic inflammation (19). In 1986, Dvorak (20) published an essay where he drew a parallel between tumors and "wounds that do not heal." He argued that tumors invoke an inflammatory wound-healing response similar to the one described above, creating favorable conditions for survival and growth (**Figure 2**).

Epidemiological data support the notion that chronic inflammation drives tumor development. Patients displaying elevated levels of circulating inflammatory markers (e.g., C-reactive protein) at routine checkups have more than twice the risk of developing cancer within 1 year compared with those with normal levels (21). A 2018 study estimated that 42% of adult cancers in the United States are caused by modifiable risk factors (22), all of which cause either local or systemic inflammation. For example, cigarette smoking accounts for 19% of cancers, obesity is linked to 7.8%, alcohol intake explains 5.6% of cases, and chronic infections are the cause of 3.3% of cancers in the United States and 13% of cases worldwide (23).

Local inflammation can promote cancer development and progression within the same tissue or organ site (24, 25). Several infections can result in cancer: *Helicobacter pylori*–induced gastritis can progress to gastric cancers, chronic hepatitis B or C virus infections can lead to liver cancers, and unresolved infection with human papillomavirus can result in cervical cancers. Besides direct carcinogenic mechanisms associated with the infectious agents, the persistent inflammatory environment resulting from the failure to clear the infection contributes to the development of these cancers (26). Chronic inflammatory diseases in the absence of infections can also forge a local microenvironment that is primed for tumor development. For instance, inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, increase the risk of developing colorectal cancer (27). Similarly, chronic pancreatitis carries an elevated risk of developing pancreatic cancer (28). Last, environmental factors can predispose patients to and promote cancer by causing local inflammation. Most notably, exposure to particulate or tobacco smoke has a well-defined relationship with chronic obstructive pulmonary disease development, which increases the risk of lung cancer (29).

In addition to changing the local inflammatory microenvironment, some insults, such as tobacco smoke and obesity, drive systemic inflammation. As a result, levels of circulating proinflammatory mediators are chronically elevated, leading to an increased risk of developing cancer in several organs (30). For instance, in a mouse model of diet-induced obesity, high levels of serum interleukin (IL)-5 and granulocyte macrophage colony–stimulating factor (GM-CSF) cause lung inflammation and subsequent metastasis at this site (31). Consistent with inflammation's pro-tumorigenic role, long-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with lower cancer incidence (32), including a notable decline in the incidence of lung cancer in chronic smokers (33). Moreover, a phase III trial (CANTOS; NCT01327846) of an
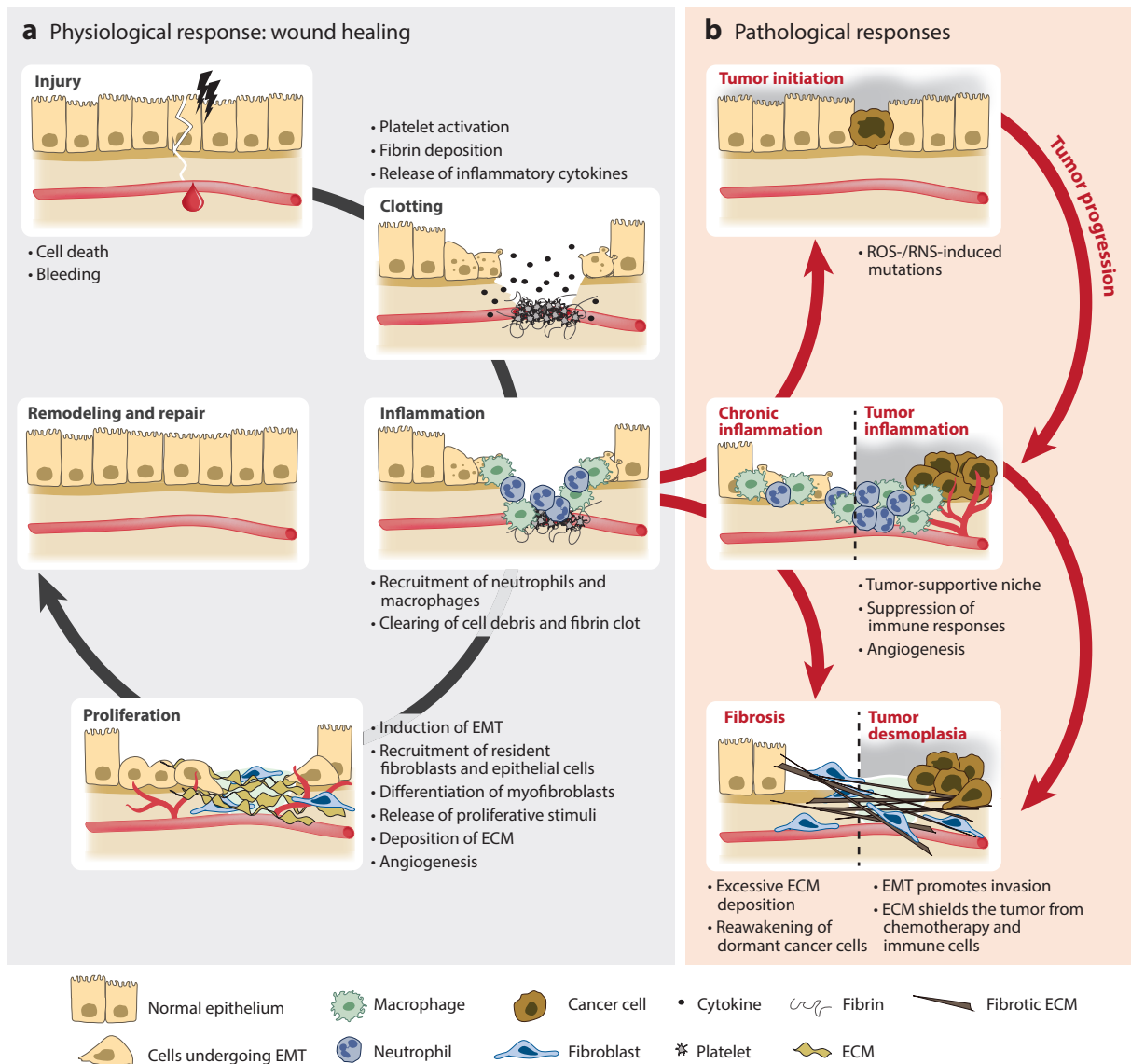
a Physiological response: wound healing

Injury
- Cell death
- Bleeding

- Platelet activation
- Fibrin deposition
- Release of inflammatory cytokines

Clotting

Remodeling and repair

Inflammation
- Recruitment of neutrophils and macrophages
- Clearing of cell debris and fibrin clot

Proliferation
- Induction of EMT
- Recruitment of resident fibroblasts and epithelial cells
- Differentiation of myofibroblasts
- Release of proliferative stimuli
- Deposition of ECM
- Angiogenesis

b Pathological responses

Tumor initiation
- ROS-/RNS-induced mutations

Tumor progression

Chronic inflammation | **Tumor inflammation**
- Tumor-supportive niche
- Suppression of immune responses
- Angiogenesis

Fibrosis | **Tumor desmoplasia**
- Excessive ECM deposition
- Reawakening of dormant cancer cells
- EMT promotes invasion
- ECM shields the tumor from chemotherapy and immune cells

Legend:
- Normal epithelium
- Cells undergoing EMT
- Macrophage
- Neutrophil
- Cancer cell
- Fibroblast
- Cytokine
- Platelet
- Fibrin
- ECM
- Fibrotic ECM

Figure 2

Aberrant wound-healing response, fibrosis, and cancer. Partly owing to the activation of the innate immune system, features of the tumor microenvironment resemble an aberrant wound-healing response. (*a*) Wound healing consists of overlapping phases. Injury of adult tissue results in local hemorrhage, immediately followed by clotting. A temporary matrix of fibrin is deposited locally, which serves as a scaffold for migrating immune cells, epithelial cells, fibroblasts, and endothelial cells. During wound healing, neutrophils and macrophages kill bacteria, degrade the fibrin clot, and remove cellular debris. Neutrophils also secrete mediators such as TNF-α, IL-1β, and IL-6, amplifying the innate response. Macrophages produce VEGF and other growth factors, such as TGF-β, that stimulate the next phase: migration and proliferation of cells within the wound. In this phase, blood supply is restored, new connective tissue is produced, and the wound reepithelializes. Last, during the repair phase, the ECM is remodeled and new blood vessels are culled. (*b*) Failure to clear the rich inflammatory infiltrate results in chronic inflammation. The persistence of inflammatory cells results in the accumulation of toxic compounds such as ROS and RNS, as well as cytokines, which support tumor initiation and progression and sustain myofibroblast activation and fibrosis. Inflammation, fibrosis, and cancer are tightly linked in a vicious cycle, in which each can trigger and aggravate the other. Abbreviations: ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; IL, interleukin; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

inhibitory antibody targeting the proinflammatory molecule IL-1β for atherosclerosis also found that it significantly reduced lung cancer incidence (34), whereas a subsequent trial testing the anti-IL-1β antibody together with chemotherapy in established lung cancer found no effect (35). However, not all chronic inflammatory diseases increase the risk of cancer. For instance, psoriasis and rheumatoid arthritis do not appear to promote cancer, although it is possible that the drugs used to control these inflammatory diseases also modify cancer risk.

Cancers not directly associated with inflammation still recruit innate immune cells, release cytokines, and exhibit angiogenesis and tissue remodeling—essentially driving the establishment of tumor-intrinsic inflammation (36) (**Figure 3a**). NSAIDs can also reduce mortality from some of these cancer types (e.g., prostate and brain cancers) (32, 37).

Drivers of tumor-intrinsic inflammation include genetic and epigenetic alterations in tumor suppressor genes and oncogenes. The tumor suppressor *TP53* is a good example. In several cancer models and in clinical studies, immune cells are attracted to the primary tumor in response to P53 loss. For instance, in prostate cancer, loss of P53 triggers C-X-C motif chemokine ligand 17 (CXCL17) upregulation and the subsequent recruitment of immunosuppressive innate immune cells in the tumor microenvironment (TME) (38). Beyond this local effect, P53 loss in breast cancer stimulates tumor-associated macrophages (TAMs) to release high levels of IL-1β, driving systemic inflammation and ultimately supporting metastasis (39).

Another important cause of tumor-intrinsic inflammation is necrotic cell death. Necrotic cell death occurs when, for example, rapidly growing tumors outpace the blood supply, resulting in hypoxia and necrosis. Necrotic cells release potent danger-associated molecular patterns (DAMPs), endogenous danger signals recognized by innate immune system cells via germline-encoded pattern recognition receptors (PRRs) [e.g., Toll-like receptors (TLRs)] (40). DAMP sensing increases phagocytosis of the necrotic debris and amplifies the inflammatory response so antigen-presenting cells [e.g., dendritic cells (DCs) and macrophages] can activate the adaptive immune response. High mobility group box 1 (HMGB1) is a nuclear non-histone-binding protein that serves as a DAMP by signaling through TLR3, TLR4, and TLR9, as well as the scavenger receptor RAGE (receptor for advanced glycation end products) (**Figure 3b**). HMGB1 binding to its receptors ultimately leads to inflammatory cell recruitment and induces the release of proinflammatory cytokines (41, 42). DAMPs are also important in eliciting the antigen-specific adaptive immune response evoked by immunogenic cell death of tumor cells. This unique form of cell death is defined by its ability to elicit protective immunity and is caused primarily by cytotoxic agents such as anthracyclines and radiotherapy. Following immunogenic cell death, the chronic exposure of DCs to DAMPs, particularly calreticulin, ATP, and HMGB1, favors DC maturation and priming of protective T cell responses that can kill tumor cells and establish antitumor immunological memory (43). Supporting the importance of this mechanism for antitumor immunity, germline mutations in PRRs affect cancer risk and response to therapy. For example, patients with breast cancer who carry a *TLR4* allele displaying reduced binding to HMGB1 relapse faster after chemotherapy (41).

In summary, inflammation is a hallmark of cancer, whether it originated before or is driven by the cancer.

INNATE IMMUNE CELLS IN THE TUMOR ARE HETEROGENEOUS AND PLASTIC

The innate immune system comprises immune cells of either myeloid or lymphoid lineage and several classes of proteins, including cytokines, chemokines, receptors, and proteins of the complement system. These components are not inherently tumor supportive or tumor opposing. Rather, their activity depends on the relative abundance of each cell type in the specific tissue,
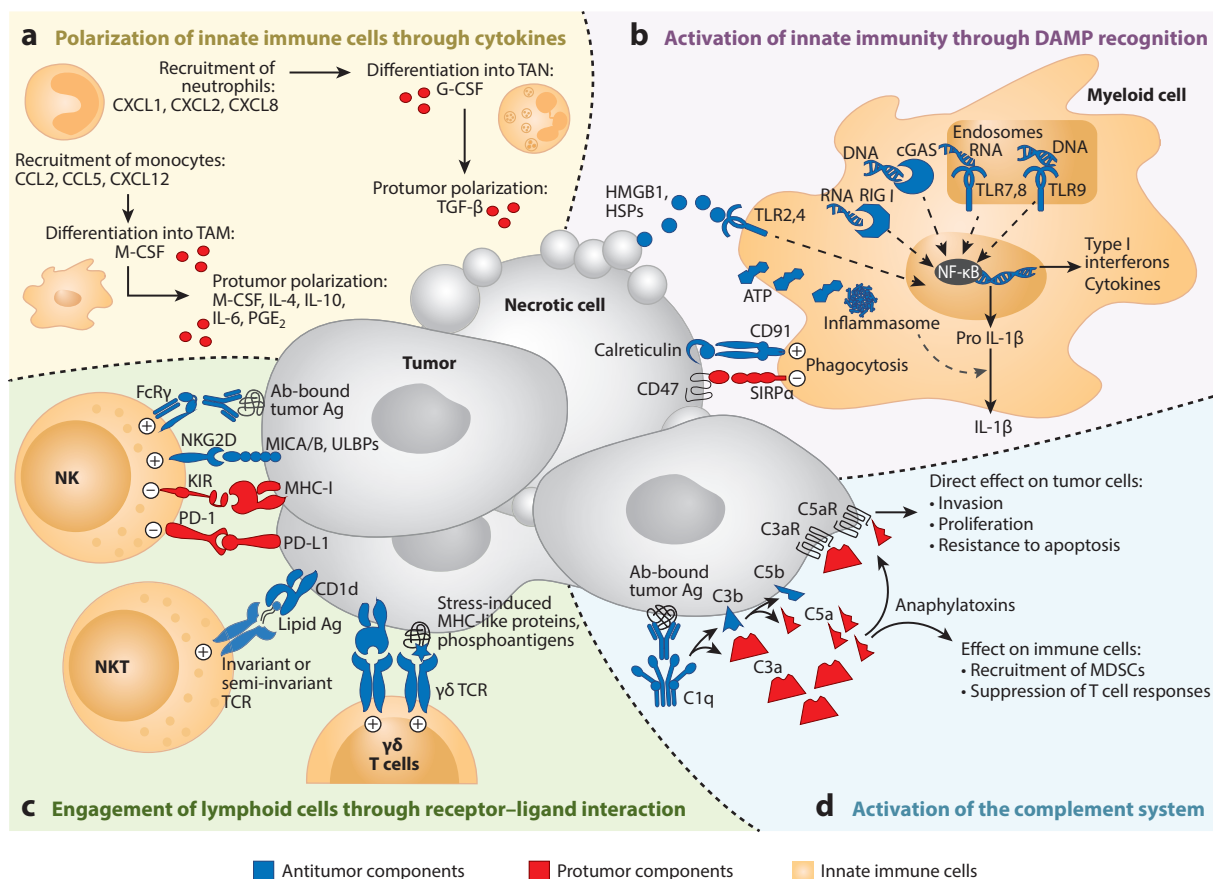
Figure 3

Interactions between cancer and the innate immune system. Cellular and molecular components of innate immunity interact with cancer cells through a variety of mechanisms that can support or restrain tumor growth. (*a*) By virtue of the high degree of plasticity of innate immune cells, cytokines secreted in the tumor microenvironment can polarize innate immune cells toward tumor-supportive phenotypes. (*b*) Necrotic cells release DAMPs, endogenous "danger signals" recognized by PRRs (e.g., TLRs), on innate immune cells. DAMP sensing increases phagocytosis of the necrotic debris and amplifies the inflammatory response, leading to activation of the adaptive immune response. Opposite mechanisms also exist. For example, the binding of CD47 to SIRPα helps cancer cells escape phagocytosis by transmitting a "don't eat me" signal. (*c*) ILCs, NK cells, and unconventional T lymphocytes (γδ T cells and NKT cells) can directly eliminate tumor cells by releasing cytotoxic granules or engaging death receptors. In NK cells, this cytotoxic activity is regulated by cancer cell ligands that bind either activating or inhibitory surface receptors. Unconventional T lymphocytes recognize cancer cells through their TCR. The γδ TCR allows for non-MHC-restricted recognition of, for example, phosphoantigens. The invariant or semi-invariant TCR on NKT cells binds lipid antigens presented on the nonpolymorphic MHC-I-like molecule CD1d. (*d*) The complement system can mediate tumor cell lysis and phagocytosis by immune cells, for example, by binding anticancer antibodies on the surface of cancer cells. By contrast, cleavage products of complement activation (C3a and C5a) can support tumor growth, either by directly affecting cancer cells or by recruiting immunosuppressive cells. Abbreviations: DAMP, danger-associated molecular pattern; G-CSF, granulocyte colony–stimulating factor; HSP, heat shock protein; IL, interleukin; ILC, innate lymphoid cell; M-CSF, macrophage colony–stimulating factor; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer; NKT, natural killer T; PGE$_2$, prostaglandin E2; PRR, pattern recognition receptor; SIRPα, signal-regulatory protein α; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; TCR, T cell receptor; TGF, transforming growth factor; TLR, Toll-like receptor.

the balance of signals within the TME, and the tumor progression stage (**Figure 1**). For instance, lung cancer cells engineered to express a strong antigen are rejected by cytotoxic T cells in the lung, but expression of the same antigen and a similar genetic makeup in pancreatic cancer cells instead exacerbate the disease, as this site has fewer DCs capable of activating T cells (44). In addition, the phenotype and function of innate immune cells are plastic and change as their local environment changes. We present key findings that illustrate this context dependence of innate immune cell types and how it affects cancer.

Myeloid Cells Modulate Tumor-Associated Inflammation

Myeloid cells comprise heterogeneous cell populations derived from a common myeloid progenitor in the bone marrow. These cells are recruited to the tumor and can regulate the tumorigenic process, from initiation to invasion and metastasis. The most well-studied myeloid cells are macrophages/monocytes, neutrophils, myeloid-derived suppressor cells (MDSCs), and DCs.

Macrophages and monocytes. Macrophages are large phagocytic cells critical for host defense, especially against bacteria, but also necessary for tissue homeostasis (e.g., by clearing cell debris and dysfunctional cells). Tissue-resident macrophages originate from cells seeded to tissues during embryogenesis, but macrophages can also expand from bone marrow–derived blood monocytes, which are recruited in large numbers in response to injury or infection (45).

Macrophages and their monocytic precursors constitute the largest fraction of leukocytes in most solid tumors and are critical drivers of cancer-associated inflammation (46, 47). Activated inflammatory macrophages produce potentially mutagenic reactive nitrogen species (RNS) and reactive oxygen species (ROS) and secrete cytokines, including tumor necrosis factor α (TNF-α) and interleukins (e.g., IL-1β, IL-6, IL-12), providing fertile soil for initiation and progression of chronic inflammation-associated cancers. In a model of colitis-associated cancer, constitutive genetic inactivation of the canonical nuclear factor κB (NF-κB) pathway, a master regulatory pathway of inflammation, specifically in myeloid cells (macrophages and neutrophils), results in downregulated inflammatory cytokine secretion and reduced tumor incidence (12). Furthermore, when stimulated by interferon-γ (IFN-γ) and TLR ligands, macrophages can directly kill tumor cells by generating nitric oxide (NO) (48). However, as the tumor progresses, cues in the microenvironment drive TAMs to become tumor supportive. Early findings showed that this phenotypic shift could occur in response to IL-4/IL-13 derived from, for example, T lymphocytes (49). Yet other cytokines (e.g., IL-10 and TGF-β), tumor cell-derived metabolic products, hypoxia, and immune complexes can also induce protumorigenic polarization of TAMs (50–52). Much of the early literature on macrophages categorized antitumorigenic macrophages as classically activated/M1 and protumorigenic macrophages as alternatively activated/M2. This dichotomy reconciled the antithetical roles that macrophages display in cancer, but it is now clear that a spectrum of phenotypes exists beyond the two extremes. Accordingly, the field has moved away from the binary nomenclature, favoring a more precise definition of populations based on how the cells are isolated and which markers define them (53). In 2018, high-dimensional profiling techniques such as single-cell RNA sequencing and mass cytometry have allowed the field to granularly characterize the heterogeneous macrophage populations in tumors and map their plastic evolution during disease progression or treatment (54).

The ability of TAMs to directly sustain tumor progression has been widely documented and reviewed (e.g., 47). In brief, TAMs are key players driving the acquisition of a tumor vasculature, the so-called angiogenetic switch. Tie2+ monocyte-derived macrophages are an essential source of vascular endothelial growth factor (VEGF) and support angiogenesis in several mouse models

(13). In addition, intravital imaging of mammary tumors showed that perivascular TAMs help cancer cells enter blood vessels (55). But TAMs can also promote invasion by remodeling the extracellular matrix (ECM) through expression of proteases such as matrix metalloproteinases (MMPs) and by promoting the epithelial–mesenchymal transition of cancer cells (9, 56). At the metastatic site, macrophages can help cancer cells adapt to the new environment. For instance, in the lungs, α4 integrin on macrophages can serve as a receptor for vascular cell adhesion molecule 1 (VCAM-1) expressed on breast cancer cells and can activate prosurvival signaling (57). In addition, both monocytes (or monocytic MDSCs; see below) and macrophages reinforce the immunosuppressive TME by secreting cytokines (e.g., IL-10 and TGF-β), which inhibit the antitumor immune response (58).

A clinically relevant aspect of macrophage biology is its profound effect on treatment outcome. Depending on the treatment and their phenotype, TAMs can either contribute to or interfere with the therapeutic mechanism (59). For instance, in mice, macrophages capture therapeutic anti-programmed cell death protein 1 (PD-1) monoclonal antibodies (mAbs) from the surface of T cells, the intended target, thus blunting therapeutic efficacy (60). However, PD-1 is also expressed on TAMs, and PD-1 blockade in *NOD scid gamma* mice, which lack T, B, and natural killer (NK) cells, leads to a TAM-dependent decrease in tumor burden, suggesting that TAMs can be pharmacologically reeducated (61) and again highlighting the plasticity of these innate immune cells. Indeed, a colony stimulating factor 1 receptor (CSF-1R) inhibitor causes tumor regression in a mouse model of glioma by repolarizing macrophages rather than by simply depleting them (62). This inherent plasticity of macrophages represents both an obstacle to untangling their complex biology and an opportunity for therapeutic targeting.

Neutrophils. Neutrophils are some of the first immune cells to be recruited to damaged tissues. They can eliminate pathogens by phagocytosis, by the release of antibacterial proteins and proteases, and by the formation of neutrophil extracellular traps (NETs) (63). Granulocyte colony–stimulating factor (G-CSF) and other cytokines that promote the differentiation and release of neutrophils from the bone marrow are often elevated locally in the tumor and systemically in patients with cancer, leading to the mobilization of high numbers of both mature and immature neutrophils (39). High levels of tumor-associated neutrophils and neutrophils in blood (neutrophilia), high neutrophil-to-lymphocyte ratios, or both are associated with poor prognosis in cancer (46, 64, 65). Like macrophages, neutrophils also have pro- or antitumor activities (66), depending on context. Yet the stimuli leading to these opposite activities are much less defined than they are for macrophages.

Tumor-associated neutrophils can support cancer cell proliferation, angiogenesis, and immunosuppression in the TME (67). However, by harnessing their plasticity, they can become antitumor through TGF-β blockade (68). Similarly, IFN-β suppresses genes encoding homing and angiogenic factors in neutrophils, delaying tumor growth in mouse models of melanoma and fibrosarcoma (69).

Early research showed that neutrophils from tumor-bearing animals could increase the invasive potential of cancer cells (70). For example, UV-damaged keratinocytes release HMGB1, resulting in a neutrophilic inflammatory response in the skin. In turn, neutrophil-derived TNF-α increases melanoma cells' migration along blood vessels and consequently lung metastasis (71). Besides aiding cancer cells to escape the primary tumor, neutrophils can assist cancer cells in leaving blood vessels, for example, by tethering cancer cells to liver sinusoids (72). During early stages of tumor progression, neutrophils are mobilized and accumulate at metastatic sites, where they help establish a premetastatic niche before cancer cells infiltrate (73–75). In the lungs of mouse mammary tumor virus–polyoma middle T antigen (MMTV-PyMT) tumor-bearing mice,

neutrophil-derived leukotrienes support the preferential expansion of a highly metastatic subpopulation of cancer cells, and targeting this mechanism is sufficient to decrease metastasis (76). Last, at both the primary and metastatic sites, neutrophils (or the possible overlapping cell population sometimes termed polymorphonuclear MDSCs; see below) can drive immunosuppression (77). Contrasting these findings, in experimental metastasis models, neutrophils activated by inflammatory stimuli inhibit liver metastasis by releasing cytotoxic NO, and thrombospondin-1 released by neutrophils in the lung establishes a metastasis-resistant niche (78, 79).

In the last decade, neutrophil-expelled NETs were found to promote metastasis. NETs are extracellular networks comprising chromatin and granule-derived antimicrobial peptides and proteases, such as neutrophil elastase, cathepsin G, myeloperoxidase, and MMP9. NETs were first described as contributors to the innate immune response, with the ability to immobilize and eliminate large pathogens that could not be engulfed by phagocytosis (80). However, since the first report in 2013, NETs have been found to be associated with tumor progression both in animal models of cancer and in patients with cancer, including breast, ovarian, colorectal, or lung cancer (81–83). NETs can promote metastasis through multiple means. Our group and others reported that NETs can be chemotactic for metastatic cancer cells (82, 84). NET-associated DNA was later shown to serve as a chemotactic factor for cancer cells expressing the transmembrane protein CCDC25, which upon sensing DNA enhances cell motility and facilitates metastasis to the liver (85). Besides increasing cancer cell migration/invasion, NETs can also trap cancer cells in the vasculature and facilitate extravasation (81). The presence of an early-stage ovarian tumor in the abdominal cavity induces neutrophils to accumulate in the omentum and release NETs in response to cell-derived factors (IL-8, G-CSF, CXCL1, and CXCL2), promoting the formation of a favorable premetastatic niche (83). Furthermore, we have shown that in the lungs NET-associated proteases can induce cell proliferation through ECM remodeling (86). Specifically, neutrophil elastase and MMP9 cleave the basement membrane protein laminin, producing a cryptic epitope that activates integrin signaling and reawakens dormant cancer cells. Last, NETs may physically shield cancer cells from cytotoxic immune cells (87). Based on these diverse prometastatic mechanisms, inhibiting NETs is thus a potential therapeutic strategy. Notably, targeting NETs in vivo with DNase I particles or a PAD4 inhibitor reduces metastatic burden in breast and ovarian cancers and inhibits the NET-activated awakening of dormant cancer cells (83, 84, 86).

Immature myeloid cells and myeloid-derived suppressor cells. MDSCs are a heterogeneous population of immature myeloid cells that greatly expand during pathological conditions such as cancer. They are usually divided into two groups on the basis of surface marker expression: monocytic MDSCs (M-MDSCs) and granulocytic or polymorphonuclear MDSCs (PMN-MDSCs). Morphologically and phenotypically, M-MDSCs and PMN-MDSCs are difficult to distinguish from monocytes and neutrophils, respectively, but they are functionally defined by their ability to restrain T cell activities. MDSCs expand in response to stem cell factors and cytokines such as GM-CSF, G-CSF, M-CSF, IL-6, and VEGF. However, the immunosuppressive activity of MDSCs also requires activation by IL-4, IL-13, or TGF-β (88).

Unlike classical monocytes and neutrophils, MDSCs express high levels of molecules that inhibit T cell responses, including ʟ-arginase, inducible nitric oxide synthase (iNOS), TGF-β, IL-10, cyclooxygenase-2 (COX2), and indoleamine 2,3-dioxygenase (IDO). ʟ-Arginase and IDO are important suppressing factors that catabolize essential metabolites and produce toxic metabolites that accumulate in the TME, inhibiting T cell proliferation (89). NO production suppresses T cell function by inhibiting major histocompatibility complex (MHC) class II expression or inducing T cell apoptosis (90). Moreover, MDSCs have a dormant metabolic

phenotype characterized by repressed glycolysis, which they can pass on to T cells by transferring the metabolite methylglyoxal, ultimately causing metabolic and functional paralysis of activated CD8$^+$ T cells (91). A preclinical study found that depleting MDSCs after primary tumor resection delayed lung metastasis and extended survival, implicating them in metastatic progression as well. In this setting, low-dose adjuvant epigenetic therapy (5-azacytidine and entinostat) decreases MDSC trafficking, reducing metastasis (92). Consistent with the ability of MDSCs to repress T cell function, MDSC level is negatively associated with patient responses to immunotherapy, including to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1 inhibition (93, 94). Targeting MDSCs may therefore represent an attractive therapeutic opportunity, but with the caveat that there is currently no clear method to distinguish MDSCs from neutrophils and monocytes—cell types with many complex functions.

Dendritic cells. DCs are innate immune cells with a crucial role in bridging innate and adaptive immunity. DCs constantly scan their surroundings and detect antigens, danger signals, and invading pathogens. Once they take up antigens, they migrate to lymphoid tissues (thymus, spleen, and lymph node), where they present antigens via MHC class I and II complexes to stimulate antigen-reactive effector immune cells, primarily T cells and B cells (95). Traditionally, DCs have been divided into two major populations: conventional (or myeloid) DCs (cDCs) and plasmacytoid DCs (pDCs) (96).

cDCs are professional antigen-presenting cells, further classified as cDC1s and cDC2s, priming CD8$^+$ or CD4$^+$ T cells, respectively. They have the ability to cross-present, that is, present tumor-derived MHC-I antigens to CD8$^+$ T cells. In humans, cDC1s express CD141 and BDCA3. In mouse, the development of these cross-presenting DCs depends on the transcription factors *Batf3* and *Irf8*, and tumor growth is increased in both *Batf3*$^{-/-}$ and *Irf8*$^{-/-}$ mice (97, 98). In lymphoid tissues, cDC1s are CD8α$^+$, while in the periphery, they are identified by the expression of integrin αE, also known as CD103. Though they are a relatively rare population (often <1% of tumor-infiltrating immune cells), CD103$^+$ DCs play a prominent role in recruiting and activating cytotoxic T cells. As antigen-presenting cells, cDC1s influence the breadth of the immune response (i.e., how many antigens are targeted). Adoptive cellular therapy with T cells expressing FMS-like tyrosine kinase 3 ligand (FLT3L), a DC growth factor, leads to cDC1-dependent expansion of the antitumor T cell repertoire (99). In a model of melanoma, CD103$^+$ DCs were necessary for recruiting effector T cells intratumorally through CXCL9/CXCL10 expression (100). Accordingly, ablating CD103$^+$ DCs thwarts tumor rejection after adoptive transfer of activated tumor-specific T cells in combination with immune checkpoint blockade (98, 101). cDC1s also influence chemotherapy response. For example, in the MMTV-PyMT model of breast cancer, macrophages inhibit the secretion of IL-12 by CD103$^+$ DCs and ablating macrophages restores DCs' IL-12 production, increases T cell influx, and improves outcome (58). Exposure to chronic stress can inhibit the immunostimulatory activity of DCs, compromising the response to lung and colon cancers in mice. Stress elevates glucocorticoid levels, which repress the response to the important proinflammatory type I IFN cytokines in tumor-infiltrating DCs and curtail the immune response (102).

In contrast to cDCs, pDCs have limited antigen-presenting ability but are immunomodulatory via, for example, the production of type I IFNs (103). pDCs are largely immunoinhibitory in cancer, and pDC recruitment is associated with poor prognosis in several tumors, including ovarian and breast cancers (104, 105). However, OX40$^+$ pDCs from patients with head and neck cancer can stimulate tumor-specific T cell responses (106). Dysfunction of pDCs or their acquisition of immunosuppressive properties is a result of, for example, tumor-derived IL-10, TGF-β, and TNF-α, which directly suppress pDCs' IFN-α production (107, 108). In addition,

by expressing IDO and inducible T cell costimulator ligand (ICOSL), pDCs support tolerogenic regulatory T cell expansion (109, 110).

DCs can tune the response between immune control or immune tolerance, whereby the tumor is recognized but not attacked. For instance, in inflammatory conditions, cDC2s activate antitumor CD4$^+$ T cells, whereas in noninflamed lymph nodes, they induce ineffective priming of CD4$^+$ cells and a tolerogenic response (111). Single-cell RNA sequencing (scRNA-Seq) of murine and human lung cancers revealed that upon antigen uptake, cDCs in the TME activate a transcriptional program that limits their immunostimulatory function and T cell priming. IL-4 signaling drives this program and IL-4 blockade abolishes its effects, supporting the notion that the cytokine milieu serves as a rheostat for DC activation and determines the outcome of the immune response (112).

Lymphoid Cells and Lymphocytes Straddle Immunomodulation and Effector Functions

Innate lymphoid cells (ILCs) and unconventional T lymphocytes [γδ T cells and natural killer T (NKT) cells] share attributes of innate and adaptive immunity. Besides contributing to cytokine secretion in the TME, they display effector functions, such as cytotoxic killing of cancer cells.

Innate lymphoid cells. ILCs have a lymphoid progenitor in common with T cells. However, they lack antigen-specific receptors, and their cytotoxic activity is instead regulated by soluble ligands that bind either activating or inhibitory surface receptors (**Figure 3***c*). On the basis of their cytokine production pattern and the transcription factors required for their development, ILCs are categorized into five major groups: natural killer (NK) cells, group 1 ILCs (ILC1s), group 2 ILCs (ILC2s), group 3 ILCs (ILC3s), and lymphoid tissue–inducer cells (113, 114).

Like other immune cells, tissue type and cytokine milieu strongly influence whether ILCs are protumor or antitumor. For instance, administering IL-33 to 4T1 breast cancer–bearing mice results in accelerated tumor progression mediated by the accumulation of MDSCs and IL-13 producing ILC2s (115). In contrast, in pancreatic adenocarcinoma, IL-33-dependent expansion of ILC2s leads to therapeutic tumor immunity by recruiting CD103$^+$ DCs and activating CD8$^+$ T cells (116). IL-33 also triggers ILC1-dependent antitumor activity. In a mouse model of metastatic melanoma, IL-33 triggers ILC1 expansion and IL-5 upregulation in the lung, which in turn suppress lung metastasis via a mechanism that depends on eosinophil recruitment (117). ILC1s can also exert immune surveillance of early-stage tumors. In the MMTV-PyMT model of breast cancer, tumor initiation triggers an IL-15-dependent expansion of tissue-resident ILC1-like cells with cytotoxic activity against cancer (118). However, an ILC1-like phenotype can also curb antitumor immunity. For example, owing to the plasticity of NK cells, TGF-β can convert them into ILC1s, resulting in a decreased ability to restrain tumor growth (119, 120). Contrasting roles have been reported for ILC3s as well. In a murine model of melanoma, expression of C-C motif chemokine ligand 21 (CCL21) recruits C-C chemokine receptor 7$^+$ (CCR7$^+$) ILC3s with lymphoid tissue–inducing ability, which promotes the formation of lymphoid stroma and the establishment of an immunosuppressive, protumorigenic milieu (121). In contrast, ILC3s from human lung cancer specimens can be polarized toward an inflammatory phenotype, which correlates with better clinical outcome. Interaction with tumor cells or tumor-associated fibroblasts triggers these ILC3s to produce inflammatory (TNF-α, IL-22) and chemotactic (IL-8, IL-2) cytokines, activating the endothelium and potentially recruiting antitumor leukocytes (122).

Natural killer cells. The role of NK cells in cancer was recognized decades before that of the other ILCs, when in 1980 Talmadge et al. (123) showed that tumor cells transplanted to *beige* mice, which are deficient in NK cell activity, grew faster than those transplanted to control mice.

In humans, the presence of NK cell infiltrate or overexpression of NK-activating ligands by cancer cells correlates with better prognosis (124). In contrast, NK cell dysfunction, measured by flow cytometry analysis of cell surface receptor expression and functional assays, predicts metastatic progression (125, 126).

NK cells can directly eliminate tumor cells by releasing cytotoxic granules or engaging death receptors (127). MHC-I molecules, expressed by most cells, serve as ligands for inhibitory receptors on NK cells, protecting healthy cells from being targeted. Cancer cells often lose MHC-I, especially when subjected to selective pressure by cytotoxic T cells, which rely on MHC-I to recognize their target. In such cases, the ability of NK cells to kill MHC-I-negative cells is an important fail-safe mechanism against immune escape (128). However, MHC-I downregulation is not the only signal that targets cancer cells for NK killing. Cancer cells also present ligands for NK cell–activating receptors (129). For instance, activating the DNA damage response in transformed cells leads to increased expression of ligands for the NK cell–activating receptor NKG2D (130). Genetic models lacking NK cell–activating receptors display impaired tumor immunosurveillance, supporting their important role in making cancer cells susceptible to NK killing. For instance, crossing NKG2D-deficient mice with a transgenic model of prostate cancer or a transgenic model of B cell lymphoma leads to the development of highly malignant, early-arising cancer (131). Similarly, genetically ablating the natural cytotoxicity receptor NKp46 increases lung metastasis following transplantation of B16F10.9 melanoma or Lewis lung carcinoma cells (132). Under selective pressure, cancer cells can lose NK cell–activating ligand expression, leading to immune escape (e.g., 131, 133).

Besides directly killing tumor cells, NK cells also amplify the antitumor immune response by secreting FLT3L, CCL5, and X-C motif chemokine ligand 1/2 (XCL1/2), which recruit cDC1s to the TME (134, 135). Activating cDC1s in turn can potentiate the NK cell response to the tumor. For instance, in the lungs of tumor-bearing mice, cDC1-derived IL-12 suppresses metastasis via an NK cell– and IFN-γ-dependent mechanism (136).

Similar to cytotoxic T cells, activated NK cells are also susceptible to so-called functional exhaustion, a state of decreased effector function. The activating cytokine IL-15 induces expression of the intracellular inhibitory molecule cytokine-inducible SH2-containing protein (CIS), which ultimately renders NK cells unresponsive to IL-15 in a negative feedback loop (137). In preclinical mouse models of metastasis, lung NK cells are activated by IL-12 but are also induced to upregulate checkpoint inhibitory receptors [e.g., PD-1, lymphocyte activating 3 (Lag-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT)] (138). TIGIT expression was detected on tumor-infiltrating NK cells from patients with colon cancer and in several mouse models of cancer and was associated with dysfunction and reduced antitumor potential of these cells (139). In addition, NK cell activity is also restricted by modulated interleukin signaling. For instance, IL-1R8 negatively regulates IL receptor and TLR downstream signaling. IL-1R8-deficient mice display enhanced NK cell maturation and effector functions and are protected from liver cancer development and metastasis in the liver and lungs (140).

Unconventional T cells. Unconventional T cells consist mainly of γδ T cells and NKT cells and have unique effector and modulatory roles in shaping tumor immunity.

γδ T cells. γδ T cells compose 0.5–5% of all circulating T cells in healthy individuals and are most abundant in the gut mucosa. Instead of the classical T cell receptor (TCR) with α and β chains, these cells have a distinct TCR consisting of γ and δ chains. This TCR confers non-MHC-restricted antigen recognition (**Figure 3c**). The presence of intratumoral γδ T cells is associated with a favorable prognosis across many cancer types (46). Accordingly, in vitro studies have shown

that γδ T cells can kill cancer cells via the granzyme-perforin pathway (141), expression of the death receptor ligand TRAIL (TNF-related apoptosis-inducing ligand) (142), and TNF-α and IFN-γ secretion (143). γδ T cells also induce enhanced cytotoxic activation of NK cells by engaging the costimulatory molecule 4–1BB (144). However, like other innate immune cells, γδ T cells are plastic and can acquire a protumorigenic phenotype in response to soluble cues. Stimulation with IL-1β, IL-6, and IL-23 induces γδ T cell enrichment, producing the major immunosuppressive cytokine IL-17, with effects ranging from angiogenesis to immune escape (77, 145, 146). In pancreatic cancer, intratumoral γδ T cells express high levels of exhaustion-inducing ligands, leading to a curtailed adaptive response (146). In a mouse model of breast cancer, γδ T cell–secreted IL-17 and IL-1β stimulate neutrophil expansion and polarization (77). These neutrophils suppress CD8$^+$ T cell function, which in turn facilitates the establishment of metastasis.

Natural killer T cells. NKT cells are a small subset of T lymphocytes that recognize lipid antigens presented on the nonpolymorphic MHC-I-like molecule CD1d. This family is subdivided into type I NKT cells or iNKT cells, presenting a semi-invariant TCR, and type II NKT cells, with a variable TCR (**Figure 3c**). Most studies have found that type I and type II NKT cells play contrasting roles in cancer immunity, with the former promoting and the latter suppressing antitumor responses.

Much like NK cells, iNKT cells can directly kill cancer cells through non-antigen-specific cytotoxic mechanisms (147). iNKT cells can also target other cells expressing CD1d in the TME, including TAMs (148). In addition, iNKT cells support the efficient cross-priming of cytotoxic T cells by inducing DC maturation. For instance, iNKT stimulation with α-galactosylceramide, a high-affinity ligand for CD1d, leads to the upregulation of costimulatory molecules on DCs via CD40–CD40L interaction (149). DCs cross-primed by iNKT cells uniquely recruit T cells via the CCL17–CCR4 axis, potentiating antitumor immunity (150). Last, iNKT cell activation directly boosts cytotoxic cells, as exhausted NK cells and T cells can be rescued via iNKT cell–dependent production of IL-21, IL-12, and IL-2 (151). Conversely, an elegant genetic approach comparing CD1d-deficient mice (lacking all NKT cells) to Jα18$^{-/-}$ mice (deficient in iNKT cells only) showed that type II NKT cells suppress antitumor immunity in several mouse models (152). In fact, type I and type II NKT cells can be mutually antagonistic: When stimulated by specific ligands, type II NKT cells suppress the proliferation and cytokine production of type I NKT cells (153).

The Complement System Bridges Innate and Adaptive Immunity

The complement system is a central part of the humoral arm of innate immunity. It comprises more than 50 plasma proteins, regulators, and receptors that serve as a first defense against pathogens and unwanted host molecules, besides mediating the effects of antibodies involved in a variety of activities, from regulating cytotoxicity to adaptive immunity and tissue homeostasis (154, 155). The complement system is activated by three major pathways (the classical, alternative, and lectin pathways) that converge to cleave C3 into C3b. C3b binds to the surface of cells and marks them for phagocytosis by macrophages or neutrophils. After C3 is activated, C5 is cleaved and initiates assembly of the membrane attack complex, which accumulates on cell membranes and induces cell lysis. Furthermore, the cleavage products of C3 and C5 (C3a and C5a) are chemokines with important inflammatory and chemoattractant functions (**Figure 3d**).

The complement system's activation can induce tumor cell lysis and phagocytosis by immune cells. In fact, the complement system mediates tumor cytolysis induced by rituximab, a chimeric anti-CD20 mAb developed to treat B cell lymphomas (156). Chemotherapy-induced immunogenic cell death (in breast cancer) activates signaling through the complement system, leading

to a switch in B cell phenotype, which ultimately boosts antitumor immunity by increasing the ratio of effector T cells to regulatory T cells (157). However, in some settings, components of the complement system impair antitumor immunity instead. C5a generation suppresses CD8$^+$ T cell responses by recruiting regulatory T cells and MDSCs and producing immunosuppressive molecules [e.g., L-arginase, IL-10, IL-6, CTLA-4, and programmed death ligand-1 (PD-L1)] (158, 159). Furthermore, C3a and C5a change the TME by recruiting TAMs, decreasing NK cell infiltration, and promoting NET formation (160–162). Another complement factor, iC3b, promotes IL-10 and TGF-β2 expression and MDSC generation (163, 164) to induce immunosuppression. Last, genetically or pharmacologically ablating the long pentraxin 3 (PTX3), which restrains complement activation, results in increased susceptibility to mesenchymal or epithelial carcinogenesis due to unleashing macrophage-mediated inflammation (165).

THE TUMOR MICROENVIRONMENT MODULATES INNATE IMMUNITY

Besides cancer cells and immune cells in the TME, innate immune cell plasticity can be triggered by other cellular and noncellular components, including the ECM, fibroblasts, and the microbiome.

Extracellular Matrix

The ECM is a three-dimensional scaffold of extracellular macromolecules, proteins, and polysaccharides that provides structural and biochemical support to cells. Several cell types, including fibroblasts, immune cells, and cancer cells, cooperate to produce, assemble, and modify the ECM.

Tumor progression is often accompanied by the deposition of a tumor-specific ECM, a matrix typically stiffer and more fibrotic than regular ECM characterized by higher levels of remodeled and cross-linked proteins (166). The tumor-specific ECM can augment many hallmarks of cancer, such as resistance to cell death (167), induction of angiogenesis (168), and metastasis (169). In addition, the ECM modulates immune cell activation, polarization, and survival (170). A first layer of regulation comes from the physical and mechanical properties of the ECM. In human breast cancers, more aggressive subtypes display stiffer ECM and higher TGF-β, coinciding with higher macrophage infiltration, especially at the invasive front (171). Moreover, ECM stiffness and density regulate several immunoregulatory genes in macrophages. For example, when macrophage-like RAW 264.7 cells are cultured on high-density collagen matrix, their ability to inhibit T cell proliferation increases, whereas their ability to attract cytotoxic CD8$^+$ T cells decreases (172). As a second layer of regulation, ECM components can be functional ligands of receptors on innate immune cells. As do many human tumors, Lewis lung carcinoma cells overexpress the matrix proteoglycan versican, which signals through TLR2 and stimulates macrophages to produce TNF-α, ultimately sustaining metastatic spread in mice (173). Collagen activates the immune-inhibitory receptor leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1), and overexpression of collagen by tumor cells impairs NK cell cytotoxic activity through LAIR-1 signaling (174).

Matrix remodeling is a third layer of the ECM-mediated regulation of innate immune cells. Enzymes such as MMPs or members of ADAM (a disintegrin and metalloproteinase) and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) families cleave ECM proteins, producing peptide fragments, called matrikines, with immunomodulatory activity. For example, versikine, derived from versican proteolysis, enhances the differentiation of cross-presenting cDC1s from the bone marrow–derived precursor, thus promoting T cell antitumor immunity (175).

Fibroblasts

Within the TME, fibroblasts are a major producer of ECM and soluble factors. Normal fibroblasts can suppress tumor initiation and progression via direct cell–cell contact, secreting soluble factors and maintaining ECM integrity. However, with tumor progression, fibroblasts' tumor-suppressive functions are lost. The transformation of normal fibroblasts into cancer-associated fibroblasts (CAFs) triggers a range of tumor-supportive signals. As reviewed elsewhere, CAFs promote tumor growth by multiple mechanisms (176). One such mechanism is to drive an immunosuppressive microenvironment by secreting cytokines and chemokines that regulate the recruitment and functional differentiation of tumor-infiltrating immune cells. For instance, CAF-produced IL-6 and GM-CSF induce monocyte differentiation toward alternatively activated macrophage (M2)-like TAMs and promote metastasis in a mouse model of colon cancer (177). Human colorectal cancer–derived CAFs can attract monocytes by secreting IL-8 and subsequently enhance the protumor polarization of macrophages, and these macrophages in turn suppress NK cell cytotoxicity and activation (178). Tumor-derived CSF-1 can repress CAFs' expression of chemokines that attract PMN-MDSCs. Therefore, an unwanted effect of CSF-1R inhibitors, used to block recruitment of macrophages into tumors, is the expression of PMN-MDSC-recruiting cytokines by CAFs, resulting in PMN-MDSC accumulation and thus reducing the therapeutic benefit of CSF-1R inhibitors (179). Furthermore, CAFs induce infiltration of IDO-producing DCs, PD-L1[+] neutrophils, and regulatory T cells while decreasing the infiltration and abrogating the functions of NK cells (180–183). In pancreatic adenocarcinoma, besides inflammatory fibroblasts ($\alpha SMA^{low} IL-6^{high}$) with a secretory phenotype and myofibroblasts ($FAP^+ \alpha SMA^{high}$) that secrete ECM, a novel population of CAFs expresses MHC-II and CD74, adding a potential immunomodulatory role as antigen-presenting cells (184). FAP[+] fibroblasts inhibit immunological control of tumors: CXCL12 derived from FAP[+] CAFs can be captured on the surface of cancer cells and mediates the exclusion of cytotoxic lymphocytes from the tumor bed (185, 186). Inhibiting CXCR4, the receptor for CXCL12, sensitizes the tumors to checkpoint inhibition and in patients with cancer produces an integrated response, recruiting adaptive and innate immune cells (185, 187).

Microbiome

As exemplified by Coley's toxin, bacterial components can activate immunity and restrict cancer development. Microbes within a human organism interact with the host at numerous sites, such as skin and mucosal surfaces. These microbes are not inert but regulate innate and adaptive immunity, thus exerting a major influence on health and disease (188). Dysbiosis—a disruption in the homeostasis of microbial communities—has been linked to carcinogenesis. Indeed, large case control studies have demonstrated that prolonged antibiotic use is an independent risk factor for cancer occurrence (189). Besides antibiotics, eating a high-fat diet also induces changes in the intestinal microbiome, favoring tumor progression in gastrointestinal cancers (190).

Microbiota can promote distinct inflammatory responses, thereby indirectly supporting tumor development. For instance, in a mouse model of colorectal cancer, erosion of the intestinal epithelial barrier favors entry of microbial products into the TME of early-stage lesions. This entry leads to the activation of IL-23-producing myeloid cells and enrichment of tumor-promoting cytokines, including IL-17 and IL-6 (191). Immunoregulatory effects of the intestinal microbiota, however, extend beyond the local environment, because other organs, such as the liver, can be exposed to the gut microbiome and its metabolites through the circulation. In mouse models of liver cancer, bile acids metabolized by gram-positive bacteria in the gut circulate back to the liver and downregulate expression of CXCL16 on endothelial cells, inhibiting the CXCL16-mediated recruitment of NKT cells and tumor control (192).

Besides the gut, bacteria and even yeast can reside within the TME of other tissues (e.g., lung and pancreas) (145, 193, 194). In a genetically engineered mouse model, lung cancer development is decreased in germ-free or antibiotic-treated mice versus specific pathogen-free mice (145). At the molecular level, the lung microbiota activates myeloid cells to release IL-1β and IL-23, thereby inducing IL-17 production from γδ T cells and ultimately inflammation and tumor cell proliferation (145). Analogously, the pancreas microbiota generates a tolerogenic environment by inducing an immunosuppressive phenotype in macrophages and monocytes in a TLR signaling-dependent fashion (193).

Aside from contributing to cancer development, pioneering studies of mice revealed that response to immunotherapy in mouse models of melanoma depends on the composition of the intestinal microbiota. Modifying the microbiome, for example, by administering specific bacteria or performing fecal transplant, resensitizes nonresponders, leading to increased DC function and enhanced CD8$^+$ T cell priming (195, 196). These findings spurred clinical trials in which patients with previously immunotherapy-refractory melanoma experienced partial and complete tumor regression when the treatment was repeated after fecal transplant from responsive patients (197, 198). Further studies are needed to define the distinct mechanisms responsible for the microbiota's effect on antitumor immunity, as well as to define more scalable treatment options to modulate the microbiome.

MULTIDIMENSIONAL APPROACHES TO STUDYING INNATE IMMUNE CELLS IN THE TUMOR MICROENVIRONMENT

Although the first decades of TME research, including on innate immune cells, relied heavily on mouse genetics and cell biology to dissect the role of single-cell types or pathways, recent advances have also been made using system-level approaches. The field has benefitted from omics analyses, which produce large-scale biological data sets capturing, for example, the entire complexity of a sample's mRNAs, proteins, or lipids. Initially focused on cancer cells, these approaches have now been extended to study the complexity of the immune infiltrate: the relative abundance of cell populations, diversity of phenotypes, and activation status. A crucial advance was the development of deconvolution techniques capable of estimating the abundance of different immune cell types in a sample from bulk transcriptomics data (199). An early large-scale analysis applied one such computational tool, CIBERSORT (**https://cibersort.stanford.edu/**), to data from more than 27,000 patients across 25 cancers and revealed that intratumoral neutrophils are the leukocyte population most significantly associated with an adverse prognosis (46). Another group used RNA-Seq and flow cytometry to identify immune subtypes of triple-negative breast cancer (TNBC) from mouse models and clinical data sets. Focusing on two myeloid compartments, the group discovered that tumors with a macrophage-enriched microenvironment respond to checkpoint blockade, especially upon macrophage depletion. In contrast, the absence of immune infiltrate or the local and systemic accumulation of neutrophils correlates with a lack of immunotherapy response (200).

Additional improvements in high-throughput techniques have led to characterizing the TME at single-cell resolution: capturing the heterogeneity within one cell type, including innate immune cells. Compared with scRNA-Seq, which informs on thousands of genes per cell, single-cell proteomics protocols are not yet quite as powerful. Immune cells have historically been cataloged by extracellular markers; however, techniques such as mass cytometry, which can probe tens of protein markers, including intracellular markers, have proven particularly informative in the field of cancer immunology. Integrating these approaches in multi-omics studies that yield single-cell-level measurements for both proteins and transcripts promises to further amplify our ability to characterize the TME. Paired scRNA-Seq and mass cytometry of the immune compartment in

early-stage lung tumor specimens revealed that cross-presenting CD141^{+} DCs (cDC1s) and NK cells are already depleted in early lesions compared with normal lungs. Stressing the importance of the single-cell resolution, this approach showed that macrophages were as abundant as in normal tissue but had a more protumorigenic phenotype in tumors, with high expressions of IL-6 and the immunosuppression-associated transcription factor peroxisome proliferator-activated receptor γ (PPARγ) and low expression of the costimulatory molecule CD86 (201). Later, the same research group used scRNA-Seq to discover a cluster of DCs that had gone undetected by bulk methods, named mature DCs enriched in immunoregulatory molecules (mregDCs). The transcriptional program associated with mregDCs is activated upon antigen uptake and, depending on IL-4 signaling, can either enhance or inhibit DC immunostimulatory activity, making it an attractive candidate for clinical intervention (112).

Immunophenotyping tumors is further aided by topological techniques that collect complex data on tumor tissue sections, thus preserving spatial information. A major advantage of this analysis is that it can be applied to archival tissues, such that immune phenotype can be retrospectively correlated with outcome. For instance, a highly multiplexed version of traditional immunohistochemistry techniques was optimized to probe 12-antibody biomarker panels for lymphoid and myeloid cells on specimens from patients with pancreatic ductal adenocarcinoma. Analyzing the leukocyte infiltrates in intratumoral regions revealed that therapeutic response to neoadjuvant GVAX therapy correlates with a rich myeloid infiltrate but not with lymphoid infiltrate (202). Methods that further increase multiplexing or dimensionality are also available. A good example is multiplexed ion beam imaging by time of flight (MIBI-TOF), a method that leverages mass spectrometry to image at subcellular resolution large samples (up to 1 mm^2) labeled with isotope-conjugated antibodies. By integrating this technique with sophisticated digital segmentation of the images, one group spatially located 36 proteins and reconstructed the microenvironmental architecture of TNBC samples. One important takeaway from the study is that tumors with equally abundant immune infiltrates can vary dramatically in the compartmentalization between tumor cells and immune cells (203). A similar conclusion was reached in another TNBC study, in which researchers identified four immune subtypes on the basis of the spatial distribution of CD8^{+} T cells and gene expression profiles from laser capture microdissection of stroma and epithelium. The subtype associated with the poorest outcome had unexpectedly high infiltration of CD8^{+} T cells, but these were restricted to the stroma and accompanied by elevated levels of IL-17-producing cells and neutrophils (204).

As the field moves forward, we must integrate immune phenotyping obtained from multidimensional approaches with the other parameters that guide decision-making in the clinic to improve outcomes. Initiatives such as The Human Tumor Atlas Network (**https://humantumoratlas.org/**), which will link multiparametric analysis of tumor samples with patients' clinical information, promise to greatly accelerate progress (205).

INNATE IMMUNE CELLS CAN BE TARGETED FOR CANCER THERAPY

Immunotherapies boost the immune system's ability to fight diseases such as cancer. They include antibody-based approaches, adoptive cellular therapies (including engineered immune cells), cancer vaccines, cytokine therapy, and small molecules targeting signaling pathways in immune cells. Although the approach of activating the immune system traces back to Coley's work more than 100 years ago, it took off in earnest with the approval of immune checkpoint inhibitors targeting CTLA-4 by the US Food & Drug Administration in 2011 (206). Most approved immunotherapies activate adaptive immune cells (i.e., B cells and CD4^{+} and CD8^{+} T cells), which are excellent targets because of their memory function. Nonetheless, innate immune cells can greatly influence

adaptive immune responses. This potential is demonstrated by *Bacillus* Calmette-Guérin (BCG), a vaccine containing an attenuated *Mycobacterium* strain that has been used to treat nonmuscle invasive bladder cancer for over 40 years. Intravesical administration of BCG activates innate immune cells through PRR signaling and subsequently leads to potent cytotoxic responses against the tumor (207). Approaches to reprogram, deplete, or reduce the recruitment of innate immune cells with immunosuppressive functions are therefore areas of active investigation.

Macrophages: Removed or Reprogrammed

One strategy to target macrophages is to block their recruitment to tumors. CCL2 and the cytokine CSF-1 promote tumor infiltration of monocytes and their maturation to TAMs. Genetically ablating CCL2 or CSF-1 in mouse models limits tumor progression (11, 208). Several antibodies (carlumab, RG7155, AMG 820) and small molecules (PF-04136309, PLX3397) targeting CCL2 and CSF-1, or their receptors CCR2 and CSF-1R, have been studied in clinical trials. CCL2 inhibition correlates with reduced tumor progression and metastasis in mouse models of breast cancer (209). In a phase II study, carlumab (CNTO 888, a humanized antibody that binds CCL2) did not show antitumor activity as a single agent in metastatic castration-resistant prostate cancer (210). In contrast, the CCR2 small inhibitor PF-04136309 combined with the chemotherapeutic regime FOLFIRINOX resulted in an objective tumor response in 16 of 33 patients with pancreatic cancer (211). However, results of randomized, double-blind trials targeting CCR2 have not yet been reported. PLX3397 (pexidartinib), a CSF-1R inhibitor, was tested in phase I and II trials in advanced tenosynovial giant cell tumors, where it was well tolerated, and 12 of 23 patients showed an antitumor response after treatment (212). Yet when PLX3397 was tested in a phase II study of patients with recurrent glioblastoma, it showed no efficacy (213). The antibody RG7155 (emactuzumab) blocks CSF-1R dimerization and showed promising results in a phase I trial: 86% of the 28 patients achieved an objective response and 7% achieved a complete response (214). AMG 820, an anti-CSF-1R antibody, was tested in combination with pembrolizumab in patients with colorectal, pancreatic, and non–small cell lung cancers. The combination therapy showed on-target pharmacodynamic effects, such as CSF-1 accumulation in the serum, and had an acceptable safety profile, but no efficient antitumor responses were observed (215).

A recent study took advantage of myeloid cells' propensity to home to metastatic niches and genetically manipulated myeloid cells to deliver IL-12. Upon homing to the metastatic niches, these IL-12 genetically engineered myeloid cells (IL-12-GEMys) elicited a strong antitumor immune response by activating endogenous T and NK cells and modulating the metastatic TME, resulting in greatly reduced lung and liver metastasis in mice (216).

Strategies exploiting the plasticity of macrophages—attempting to reprogram or repolarize them from protumor to antitumor—are also being explored (45). Repolarizing macrophages theoretically has the advantage of leading to the activation of cytotoxic effector immune cells (e.g., NK and T cells) by producing cytokines (including TNF-α, IL-6, and IL-12). The most straightforward method to repolarize macrophages toward an antitumor phenotype is by activating PRRs, such as TLRs. Synthetic ligands for diverse PRRs, many initially developed as vaccine adjuvants, are now being tested as cancer immunotherapies (217). Topical administration of the TLR7 ligand imiquimod has antitumor activity in superficial basal cell carcinoma and breast cancer skin metastasis (218, 219). The TLR9 ligand IMO-2055 combined with targeted and antiangiogenic therapy in patients with non–small cell lung cancer showed good tolerability and possible antitumor activity (220). Motolimod, a small molecule targeting TLR8, is in clinical trials for advanced cancers (221). We are exploring how the combination of monophosphoryl lipid A (MPLA; a TLR4 agonist) with IFN-γ can reprogram TAMs to upregulate TNF-α, IL-12, and iNOS expression;

decrease CD206 expression; and activate T cells in mouse models of breast and ovarian cancers. The result is significantly reduced primary tumor growth and metastasis (48).

COX2 inhibitors, histone deacetylase (HDAC) inhibitors, phosphoinositide 3-kinase γ (PI3Kγ) inhibitors, and stimulator of interferon genes (STING) agonists are also used to reprogram TAMs. COX2 inhibition increases TNF-α, IL-12, and iNOS expression, shifting the macrophages to an antitumor phenotype (222, 223). In a phase I clinical trial for the treatment of docetaxel-resistant prostate cancer, patients treated with a COX2 inhibitor (celecoxib) and an epidermal growth factor receptor inhibitor (gefitinib) showed reduced tumor growth and invasion (224). HDAC inhibitors modify the epigenetic profile of monocytes and macrophages, resulting in altered gene expression and polarization toward an antitumor phenotype. In a mouse model of breast cancer, the HDAC inhibitor TMP195 induced the recruitment and differentiation of monocytes and macrophages into highly phagocytic and immunostimulatory cells, resulting in reduced tumor burden and metastasis and increased response to chemotherapy and immunotherapy with anti-PD-1 antibodies (225). In mouse models of head and neck squamous cell carcinoma and breast cancer, selective inactivation of PI3Kγ in macrophages promoted an immunostimulatory transcriptional program in TAMs and in turn restored CD8$^+$ T cell activation and cytotoxicity, leading to increased survival (226). A PI3Kγ inhibitor IPI-549 (eganelisib) is currently being tested in multiple phase I/II clinical trials (NCT03719326, NCT03980041, NCT03961698, NCT03795610). Finally, targeting STING-induced TAM repolarization in vitro increased IFN-γ, iNOS, and IL-12 production and led to promising results in mouse models (227). Different STING ligands are currently in clinical trials as sensitizers for multiple immunotherapies (228).

Dendritic Cells: Boosting Presentation of Tumor Antigens

DC-based therapies utilize patient-derived DCs, which are generally produced by isolating circulating DCs or monocytes from the patient's blood. Monocytes are then differentiated into monocyte-derived DCs by culturing them with GM-CSF and IL-4, and these DCs are further matured with a cocktail of substances [e.g., IL-6, TNF-α, IL-1β, prostaglandin E2, and polyinosinic:polycytidylic acid] (229). Maturation—involving enhanced expression of MHC-I, MHC-II, and costimulatory molecules and increased cytokine production—is essential, as incompletely matured DCs can induce tolerance rather than immunity (230). DCs have also been engineered by gene-editing technologies, including RNA interference, viral transduction, and clustered regularly interspaced short palindromic repeats–caspase 9 (CRISPR-Cas9), to promote their maturation (231, 232). Sipuleucel-T, a DC-based therapy approved in 2010 for castration-resistant prostate cancer (233), consists of matured and tumor antigen–loaded patient-derived DCs. Patients with melanoma have also been treated with ex vivo–activated cDCs loaded with the tumor-associated antigens of tyrosinase and glycoprotein 100 (gp100) (234).

Various approaches have also been used to boost cDC mobilization to tumors, for example, administering FLT3L (235) or modifying DC activities within the TME. The latter approaches include using TLR ligands, such as intratumoral injection of TriMix mRNA (three mRNA molecules encoding for CD70, CD40L, and constitutively active TLR4) (236), oncolytic viruses (237), self-replicating IL-12 RNA encapsulated in oncolytic nanoparticles (238), CD40-TLR4 agonists (239), and STING agonists (240). Such approaches have resulted in lasting systemic antigen-specific T cell immunity and tumor regression in many preclinical models of melanoma, breast carcinoma, colon cancer, and lung cancer, among others (236, 238–240).

Natural Killer Cells: A New Frontier of Cytotoxic Immunotherapy

Approaches such as immunomodulatory cytokines, mAbs, and adoptive transfer of engineered NK cells have been investigated to engage NK cell function to treat cancer. The most prominent

cytokines used in NK cell activation are IL-2 and IL-15, which induce the expansion and increased cytotoxicity of NK cells (241). IL-2 treatment, the first approved immunotherapy, was approved to treat patients with metastatic renal cell carcinoma and melanoma (242). Moreover, the adoptive transfer of autologous or allogeneic NK cells is also used to improve NK cell tumor surveillance. mAbs have been designed to either block the interaction between the inhibitory NK cell receptor and its corresponding ligand on the cancer cells or engage activating receptors on NK cells. For example, lirilumab targets the inhibitory killer cell immunoglobulin-like receptor and is in clinical trials for treating acute myeloid leukemia, multiple myeloma, lymphoma, chronic lymphocytic leukemia, and Hodgkin lymphoma (243). Another inhibitory receptor on NK cells, NKG2A, can be targeted by monalizumab, resulting in both enhanced NK cell activation and T cell function (244, 245). Recombinant reagents that increase the specificity and efficacy of NK cell activation—named bispecific and trispecific killer cell engagers (BiKEs and TriKEs)—are also in development. BiKEs bind to a surface tumor antigen (e.g., the highly expressed CD30 on Hodgkin lymphoma) and to an NK cell receptor (e.g., CD16) to trigger NK cell–mediated toxicity of the cancer cells (246). A TriKE has been designed to target CD33-positive hematological malignancies: It engages CD33 on the cancer cells; contains a CD16-heavy chain to activate NK cells; and contains an IL-15 molecule to drive NK cell priming, expansion, and survival. This TriKE is currently in phase I clinical trials (NCT03214666) (247). NK cells have also been engineered to contain chimeric antigen receptors (CARs), which enables them to be directed against specific targets (248), much like similarly engineered CAR-T cells. Adaptive transfer with CAR-NK cells has shown promising results in preclinical models of B cell lymphoma and is currently being evaluated in a phase I/II study (249).

Neutrophils: An Underrated Target

There are currently no approved therapeutics to inhibit neutrophil activity in cancer. However, strategies to limit neutrophils' protumorigenic functions are being tested in early-stage trials. These strategies include blocking CXC chemokine receptor 2 (CXCR2), which is critical for neutrophil recruitment (250). The CXCR2 antagonist AZD5069 markedly reduced neutrophils in a phase II clinical trial in patients with asthma and is now being evaluated in patients with advanced tumors (NCT02583477, NCT02499328, NCT03177187). In addition, the small-molecule inhibitor reparixin, a noncompetitive CXCR1/CXCR2 antagonist, was safe and tolerable in a phase Ib trial for HER-2-negative metastatic breast cancer (NCT02001974) (251). Neutrophils and granulocytic MDSCs can suppress anticancer immune responses, in part via arginase-1 activity (252). The combination of arginase-1 inhibitors with various chemotherapies or anti-PD-1 is in phase I/II clinical trials (NCT02903914, NCT03361228, NCT03314935).

CONCLUSION

Inflammation is an integral part of cancer pathology. Inflammation can favor cancer development, and cancer in turn elicits an inflammatory response. In fact, even cancers that are considered immunologically cold for lack of an adaptive immune response are often populated by innate immune cells. As described above, targeting the innate immune system therefore offers opportunities to prevent cancer development, stratify patients for specific treatments, and elicit an antitumor immune response.

Some chronic inflammatory conditions are well known to favor cancer development, but more research is needed to identify opportunities to interrupt the signaling that supports tumorigenesis and prevent tumor progression. In addition, we are just starting to appreciate how genetic [e.g., polymorphisms in immune-related genes (41)] and environmental [e.g., diet (31, 190), stress (102)] factors influence the immune system and contribute to tipping the scale toward tumorigenesis.

Technological advances now allow us to profile the composition and phenotype of the tumor and systemic immune microenvironment. Soon, we should be able to harness this knowledge to better identify patients at high risk of recurrence and to assign patients to the therapy from which they are most likely to benefit (39, 200, 202, 204).

From a therapeutic standpoint, targeting inflammatory cells provides an opportunity to influence cancer growth and improve adaptive immune responses. The outcome of the inflammatory response is highly context dependent. In fact, almost universally, components of the immune system display both protumor and antitumor functions. This duality implies that the innate immune system has an inherent degree of plasticity that can be leveraged. More work needs to be done to define which molecular players reprogram inflammatory cells to an antitumor phenotype. Moreover, as innate immune cells influence both one another and adaptive immune cells, understanding the hierarchy of signals that can switch an immunosuppressive microenvironment to an inflammatory one can allow us to act on the upstream components.

DISCLOSURE STATEMENT

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LITERATURE CITED

1. Virchow R. 1989 (1858). Cellular pathology. As based upon physiological and pathological histology. Lecture XVI–Atheromatous affection of arteries. *Nutr. Rev.* 47:23–25
2. Oelschlaeger TA. 2010. Bacteria as tumor therapeutics? *Bioeng. Bugs* 1:146–47
3. Coley WB. 1991 (1893). The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. *Clin. Orthop. Relat. Res.* 262:3–11
4. Starnes CO. 1992. Coley's toxins in perspective. *Nature* 357:11–12
5. Balkwill F, Mantovani A. 2001. Inflammation and cancer: back to Virchow? *Lancet* 357:539–45
6. Starkey JR, Crowle PK, Taubenberger S. 1988. Mast-cell-deficient W/Wᵛ mice exhibit a decreased rate of tumor angiogenesis. *Int. J. Cancer* 42:48–52
7. Coussens LM, Raymond WW, Bergers G, Laig-Webster M, Behrendtsen O, et al. 1999. Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. *Genes Dev.* 13:1382–97
8. Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, et al. 2000. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat. Cell Biol.* 2:737–44
9. Coussens LM, Tinkle CL, Hanahan D, Werb Z. 2000. MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell* 103:481–90
10. Lin EY, Nguyen AV, Russell RG, Pollard JW. 2001. Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. *J. Exp. Med.* 193:727–40
11. Lin EY, Li JF, Gnatovskiy L, Deng Y, Zhu L, et al. 2006. Macrophages regulate the angiogenic switch in a mouse model of breast cancer. *Cancer Res.* 66:11238–46

12. Greten FR, Eckmann L, Greten TF, Park JM, Li ZW, et al. 2004. IKKβ links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* 118:285–96

13. De Palma M, Venneri MA, Galli R, Sergi Sergi L, Politi LS, et al. 2005. Tie2 identifies a hematopoietic lineage of proangiogenic monocytes required for tumor vessel formation and a mesenchymal population of pericyte progenitors. *Cancer Cell* 8:211–26

14. Netea MG, Balkwill F, Chonchol M, Cominelli F, Donath MY, et al. 2017. A guiding map for inflammation. *Nat. Immunol.* 18:826–31

15. Hossain M, Kubes P. 2019. Innate immune cells orchestrate the repair of sterile injury in the liver and beyond. *Eur. J. Immunol.* 49:831–41

16. Wang J. 2018. Neutrophils in tissue injury and repair. *Cell Tissue Res.* 371:531–39

17. Castanheira FVS, Kubes P. 2019. Neutrophils and NETs in modulating acute and chronic inflammation. *Blood* 133:2178–85

18. Headland SE, Norling LV. 2015. The resolution of inflammation: principles and challenges. *Semin. Immunol.* 27:149–60

19. Nathan C, Ding A. 2010. Nonresolving inflammation. *Cell* 140:871–82

20. Dvorak HF. 1986. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N. Engl. J. Med.* 315:1650–59

21. Watson J, Salisbury C, Banks J, Whiting P, Hamilton W. 2019. Predictive value of inflammatory markers for cancer diagnosis in primary care: a prospective cohort study using electronic health records. *Br. J. Cancer* 120:1045–51

22. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, et al. 2018. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J. Clin.* 68:31–54

23. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. 2020. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob. Health* 8:e180–90

24. Grivennikov SI, Greten FR, Karin M. 2010. Immunity, inflammation, and cancer. *Cell* 140:883–99

25. Mantovani A, Allavena P, Sica A, Balkwill F. 2008. Cancer-related inflammation. *Nature* 454:436–44

26. Moore PS, Chang Y. 2010. Why do viruses cause cancer? Highlights of the first century of human tumour virology. *Nat. Rev. Cancer* 10:878–89

27. Kappelman MD, Farkas DK, Long MD, Erichsen R, Sandler RS, et al. 2014. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. *Clin. Gastroenterol. Hepatol.* 12:265–73.e1

28. Vujasinovic M, Dugic A, Maisonneuve P, Aljic A, Berggren R, et al. 2020. Risk of developing pancreatic cancer in patients with chronic pancreatitis. *J. Clin. Med.* 9:3720

29. Mouronte-Roibás C, Leiro-Fernández V, Fernández-Villar A, Botana-Rial M, Ramos-Hernández C, Ruano-Ravina A. 2016. COPD, emphysema and the onset of lung cancer. A systematic review. *Cancer Lett.* 382:240–44

30. Iyengar NM, Hudis CA, Dannenberg AJ. 2015. Obesity and cancer: local and systemic mechanisms. *Annu. Rev. Med.* 66:297–309

31. Quail DF, Olson OC, Bhardwaj P, Walsh LA, Akkari L, et al. 2017. Obesity alters the lung myeloid cell landscape to enhance breast cancer metastasis through IL5 and GM-CSF. *Nat. Cell Biol.* 19:974–87

32. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. 2011. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 377:31–41

33. McCormack VA, Hung RJ, Brenner DR, Bickeboller H, Rosenberger A, et al. 2011. Aspirin and NSAID use and lung cancer risk: a pooled analysis in the International Lung Cancer Consortium (ILCCO). *Cancer Causes Control* 22:1709–20

34. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, et al. 2017. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* 390:1833–42

35. Novartis. 2021. *Novartis provides update on phase III study evaluating canakinumab (ACZ885) as second or third-line treatment in combination with chemotherapy in non-small cell lung cancer*. Media Release. Mar. 9. **https://www.novartis.com/news/media-releases/novartis-provides-update-phase-iii-study-evaluating-canakinumab-acz885-second-or-third-line-treatment-combination-chemotherapy-non-small-cell-lung-cancer**

36. Wellenstein MD, de Visser KE. 2018. Cancer-cell-intrinsic mechanisms shaping the tumor immune landscape. *Immunity* 48:399–416

37. Burn J, Gerdes A-M, Macrae F, Mecklin J-P, Moeslein G, et al. 2011. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 378:2081–87

38. Bezzi M, Seitzer N, Ishikawa T, Reschke M, Chen M, et al. 2018. Diverse genetic-driven immune landscapes dictate tumor progression through distinct mechanisms. *Nat. Med.* 24:165–75

39. Wellenstein MD, Coffelt SB, Duits DEM, van Miltenburg MH, Slagter M, et al. 2019. Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis. *Nature* 572:538–42

40. Hernandez C, Huebener P, Schwabe RF. 2016. Damage-associated molecular patterns in cancer: a double-edged sword. *Oncogene* 35:5931–41

41. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, et al. 2007. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat. Med.* 13:1050–59

42. He SJ, Cheng J, Feng X, Yu Y, Tian L, Huang Q. 2017. The dual role and therapeutic potential of high-mobility group box 1 in cancer. *Oncotarget* 8:64534–50

43. Pitt JM, Kroemer G, Zitvogel L. 2017. Immunogenic and non-immunogenic cell death in the tumor microenvironment. *Adv. Exp. Med. Biol.* 1036:65–79

44. Hegde S, Krisnawan VE, Herzog BH, Zuo C, Breden MA, et al. 2020. Dendritic cell paucity leads to dysfunctional immune surveillance in pancreatic cancer. *Cancer Cell* 37:289–307.e9

45. Wynn TA, Chawla A, Pollard JW. 2013. Macrophage biology in development, homeostasis and disease. *Nature* 496:445–55

46. Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, et al. 2015. The prognostic landscape of genes and infiltrating immune cells across human cancers. *Nat. Med.* 21:938–45

47. Noy R, Pollard JW. 2014. Tumor-associated macrophages: from mechanisms to therapy. *Immunity* 41:49–61

48. Sun L, Kees T, Santos Almeida A, Liu B, He X-Y, et al. 2021. Activating a collaborative innate-adaptive immune response to control metastasis. *Cancer Cell* 39(10):1361–74.e9

49. DeNardo DG, Barreto JB, Andreu P, Vasquez L, Tawfik D, et al. 2009. CD4+ T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. *Cancer Cell* 16:91–102

50. Colegio OR, Chu N-Q, Szabo AL, Chu T, Rhebergen AM, et al. 2014. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature* 513:559–63

51. Andreu P, Johansson M, Affara NI, Pucci F, Tan T, et al. 2010. FcRγ activation regulates inflammation-associated squamous carcinogenesis. *Cancer Cell* 17:121–34

52. Imtiyaz HZ, Williams EP, Hickey MM, Patel SA, Durham AC, et al. 2010. Hypoxia-inducible factor 2α regulates macrophage function in mouse models of acute and tumor inflammation. *J. Clin. Investig.* 120:2699–714

53. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, et al. 2014. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity* 41:14–20

54. Gubin MM, Esaulova E, Ward JP, Malkova ON, Runci D, et al. 2018. High-dimensional analysis delineates myeloid and lymphoid compartment remodeling during successful immune-checkpoint cancer therapy. *Cell* 175:1014–30.e19

55. Wyckoff JB, Wang Y, Lin EY, Li JF, Goswami S, et al. 2007. Direct visualization of macrophage-assisted tumor cell intravasation in mammary tumors. *Cancer Res.* 67:2649–56

56. Su S, Liu Q, Chen J, Chen J, Chen F, et al. 2014. A positive feedback loop between mesenchymal-like cancer cells and macrophages is essential to breast cancer metastasis. *Cancer Cell* 25:605–20

57. Chen Q, Zhang XH, Massague J. 2011. Macrophage binding to receptor VCAM-1 transmits survival signals in breast cancer cells that invade the lungs. *Cancer Cell* 20:538–49

58. Ruffell B, Chang-Strachan D, Chan V, Rosenbusch A, Ho CM, et al. 2014. Macrophage IL-10 blocks CD8^{+} T cell-dependent responses to chemotherapy by suppressing IL-12 expression in intratumoral dendritic cells. *Cancer Cell* 26:623–37

59. Mantovani A, Allavena P. 2015. The interaction of anticancer therapies with tumor-associated macrophages. *J. Exp. Med.* 212:435–45

60. Arlauckas SP, Garris CS, Kohler RH, Kitaoka M, Cuccarese MF, et al. 2017. In vivo imaging reveals a tumor-associated macrophage-mediated resistance pathway in anti-PD-1 therapy. *Sci. Transl. Med.* 9:eaal3604

61. Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, et al. 2017. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. *Nature* 545:495–99

62. Pyonteck SM, Akkari L, Schuhmacher AJ, Bowman RL, Sevenich L, et al. 2013. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. *Nat. Med.* 19:1264–72

63. Liew PX, Kubes P. 2019. The neutrophil's role during health and disease. *Physiol. Rev.* 99:1223–48

64. Keizman D, Ish-Shalom M, Huang P, Eisenberger MA, Pili R, et al. 2012. The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. *Eur. J. Cancer* 48:202–8

65. Donskov F. 2013. Immunomonitoring and prognostic relevance of neutrophils in clinical trials. *Semin. Cancer Biol.* 23:200–7

66. Jablonska J, Leschner S, Westphal K, Lienenklaus S, Weiss S. 2010. Neutrophils responsive to endogenous IFN-β regulate tumor angiogenesis and growth in a mouse tumor model. *J. Clin. Investig.* 120:1151–64

67. Coffelt SB, Wellenstein MD, de Visser KE. 2016. Neutrophils in cancer: neutral no more. *Nat. Rev. Cancer* 16:431–46

68. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, et al. 2009. Polarization of tumor-associated neutrophil phenotype by TGF-β: "N1" versus "N2" TAN. *Cancer Cell* 16:183–94

69. Jablonska J, Leschner S, Westphal K, Lienenklaus S, Weiss S. 2010. Neutrophils responsive to endogenous IFN-β regulate tumor angiogenesis and growth in a mouse tumor model. *J. Clin. Investig.* 120:1151–64

70. Welch DR, Schissel DJ, Howrey RP, Aeed PA. 1989. Tumor-elicited polymorphonuclear cells, in contrast to "normal" circulating polymorphonuclear cells, stimulate invasive and metastatic potentials of rat mammary adenocarcinoma cells. *PNAS* 86:5859–63

71. Bald T, Quast T, Landsberg J, Rogava M, Glodde N, et al. 2014. Ultraviolet-radiation-induced inflammation promotes angiotropism and metastasis in melanoma. *Nature* 507:109–13

72. Spicer JD, McDonald B, Cools-Lartigue JJ, Chow SC, Giannias B, et al. 2012. Neutrophils promote liver metastasis via Mac-1-mediated interactions with circulating tumor cells. *Cancer Res.* 72:3919–27

73. Yan HH, Pickup M, Pang Y, Gorska AE, Li Z, et al. 2010. Gr-1+CD11b+ myeloid cells tip the balance of immune protection to tumor promotion in the premetastatic lung. *Cancer Res.* 70:6139–49

74. Kowanetz M, Wu X, Lee J, Tan M, Hagenbeek T, et al. 2010. Granulocyte-colony stimulating factor promotes lung metastasis through mobilization of Ly6G+Ly6C+ granulocytes. *PNAS* 107:21248–55

75. Patel S, Fu S, Mastio J, Dominguez GA, Purohit A, et al. 2018. Unique pattern of neutrophil migration and function during tumor progression. *Nat. Immunol.* 19:1236–47

76. Wculek SK, Malanchi I. 2015. Neutrophils support lung colonization of metastasis-initiating breast cancer cells. *Nature* 528:413–17

77. Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, et al. 2015. IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. *Nature* 522:345–48

78. Catena R, Bhattacharya N, El Rayes T, Wang S, Choi H, et al. 2013. Bone marrow–derived Gr1^{+} cells can generate a metastasis-resistant microenvironment via induced secretion of thrombospondin-1. *Cancer Discov.* 3:578–89

79. Finisguerra V, Di Conza G, Di Matteo M, Serneels J, Costa S, et al. 2015. MET is required for the recruitment of anti-tumoural neutrophils. *Nature* 522:349–53

80. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, et al. 2004. Neutrophil extracellular traps kill bacteria. *Science* 303:1532–35

81. Cools-Lartigue J, Spicer J, McDonald B, Gowing S, Chow S, et al. 2013. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. *J. Clin. Investig.* 123:3446–58

82. Tohme S, Yazdani HO, Al-Khafaji AB, Chidi AP, Loughran P, et al. 2016. Neutrophil extracellular traps promote the development and progression of liver metastases after surgical stress. *Cancer Res.* 76:1367–80

83. Lee W, Ko SY, Mohamed MS, Kenny HA, Lengyel E, Naora H. 2019. Neutrophils facilitate ovarian cancer premetastatic niche formation in the omentum. *J. Exp. Med.* 216:176–94

84. Park J, Wysocki RW, Amoozgar Z, Maiorino L, Fein MR, et al. 2016. Cancer cells induce metastasis-supporting neutrophil extracellular DNA traps. *Sci. Transl. Med.* 8:361ra138

85. Yang L, Liu Q, Zhang X, Liu X, Zhou B, et al. 2020. DNA of neutrophil extracellular traps promotes cancer metastasis via CCDC25. *Nature* 583:133–38

86. Albrengues J, Shields MA, Ng D, Park CG, Ambrico A, et al. 2018. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. *Science* 361:eaao4227

87. Teijeira A, Garasa S, Gato M, Alfaro C, Migueliz I, et al. 2020. CXCR1 and CXCR2 chemokine receptor agonists produced by tumors induce neutrophil extracellular traps that interfere with immune cytotoxicity. *Immunity* 52:856–71.e8

88. Veglia F, Perego M, Gabrilovich D. 2018. Myeloid-derived suppressor cells coming of age. *Nat. Immunol.* 19:108–19

89. Geiger R, Rieckmann JC, Wolf T, Basso C, Feng Y, et al. 2016. L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell* 167:829–42.e13

90. Harari O, Liao JK. 2004. Inhibition of MHC II gene transcription by nitric oxide and antioxidants. *Curr. Pharm. Des.* 10:893–98

91. Baumann T, Dunkel A, Schmid C, Schmitt S, Hiltensperger M, et al. 2020. Regulatory myeloid cells paralyze T cells through cell-cell transfer of the metabolite methylglyoxal. *Nat. Immunol.* 21:555–66

92. Lu Z, Zou J, Li S, Topper MJ, Tao Y, et al. 2020. Epigenetic therapy inhibits metastases by disrupting premetastatic niches. *Nature* 579:284–90

93. Meyer C, Cagnon L, Costa-Nunes CM, Baumgaertner P, Montandon N, et al. 2014. Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab. *Cancer Immunol. Immunother.* 63:247–57

94. Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, et al. 2014. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. *Sci. Transl. Med.* 6:237ra67

95. Steinman RM. 1991. The dendritic cell system and its role in immunogenicity. *Annu. Rev. Immunol.* 9:271–96

96. Villadangos JA, Schnorrer P. 2007. Intrinsic and cooperative antigen-presenting functions of dendritic-cell subsets in vivo. *Nat. Rev. Immunol.* 7:543–55

97. Hildner K, Edelson BT, Purtha WE, Diamond M, Matsushita H, et al. 2008. *Batf3* deficiency reveals a critical role for CD8α+ dendritic cells in cytotoxic T cell immunity. *Science* 322:1097–100

98. Broz ML, Binnewies M, Boldajipour B, Nelson AE, Pollack JL, et al. 2014. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. *Cancer Cell* 26:638–52

99. Lai J, Mardiana S, House IG, Sek K, Henderson MA, et al. 2020. Adoptive cellular therapy with T cells expressing the dendritic cell growth factor Flt3L drives epitope spreading and antitumor immunity. *Nat. Immunol.* 21:914–26

100. Spranger S, Dai D, Horton B, Gajewski TF. 2017. Tumor-residing Batf3 dendritic cells are required for effector T cell trafficking and adoptive T cell therapy. *Cancer Cell* 31:711–23.e4

101. Salmon H, Idoyaga J, Rahman A, Leboeuf M, Remark R, et al. 2016. Expansion and activation of CD103+ dendritic cell progenitors at the tumor site enhances tumor responses to therapeutic PD-L1 and BRAF inhibition. *Immunity* 44:924–38

102. Yang H, Xia L, Chen J, Zhang S, Martin V, et al. 2019. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. *Nat. Med.* 25:1428–41

103. Swiecki M, Colonna M. 2015. The multifaceted biology of plasmacytoid dendritic cells. *Nat. Rev. Immunol.* 15:471–85

104. Treilleux I, Blay J-Y, Bendriss-Vermare N, Ray-Coquard I, Bachelot T, et al. 2004. Dendritic cell infiltration and prognosis of early stage breast cancer. *Clin. Cancer Res.* 10:7466–74

105. Labidi-Galy SI, Treilleux I, Goddard-Leon S, Combes JD, Blay J-Y, et al. 2012. Plasmacytoid dendritic cells infiltrating ovarian cancer are associated with poor prognosis. *Oncoimmunology* 1:380–82

106. Poropatich K, Dominguez D, Chan W-C, Andrade J, Zha Y, et al. 2020. OX40^{+} plasmacytoid dendritic cells in the tumor microenvironment promote antitumor immunity. *J. Clin. Investig.* 130:3528–42

107. Sisirak V, Faget J, Gobert M, Goutagny N, Vey N, et al. 2012. Impaired IFN-α production by plasmacytoid dendritic cells favors regulatory T-cell expansion that may contribute to breast cancer progression. *Cancer Res.* 72:5188–97

108. Terra M, Oberkampf M, Fayolle C, Rosenbaum P, Guillerey C, et al. 2018. Tumor-derived TGFβ alters the ability of plasmacytoid dendritic cells to respond to innate immune signaling. *Cancer Res.* 78:3014–26

109. Chen W, Liang X, Peterson AJ, Munn DH, Blazar BR. 2008. The indoleamine 2,3-dioxygenase pathway is essential for human plasmacytoid dendritic cell-induced adaptive T regulatory cell generation. *J. Immunol.* 181:5396–404

110. Conrad C, Gregorio J, Wang YH, Ito T, Meller S, et al. 2012. Plasmacytoid dendritic cells promote immunosuppression in ovarian cancer via ICOS costimulation of Foxp3^{+} T-regulatory cells. *Cancer Res.* 72:5240–49

111. Binnewies M, Mujal AM, Pollack JL, Combes AJ, Hardison EA, et al. 2019. Unleashing type-2 dendritic cells to drive protective antitumor CD4^{+} T cell immunity. *Cell* 177:556–71.e16

112. Maier B, Leader AM, Chen ST, Tung N, Chang C, et al. 2020. A conserved dendritic-cell regulatory program limits antitumour immunity. *Nature* 580:257–62

113. Lu T, Ramakrishnan R, Altiok S, Youn J-I, Cheng P, et al. 2011. Tumor-infiltrating myeloid cells induce tumor cell resistance to cytotoxic T cells in mice. *J. Clin. Investig.* 121:4015–29

114. Vivier E, Artis D, Colonna M, Diefenbach A, Di Santo JP, et al. 2018. Innate lymphoid cells: 10 years on. *Cell* 174:1054–66

115. Jovanovic IP, Pejnovic NN, Radosavljevic GD, Pantic JM, Milovanovic MZ, et al. 2014. Interleukin-33/ST2 axis promotes breast cancer growth and metastases by facilitating intratumoral accumulation of immunosuppressive and innate lymphoid cells. *Int. J. Cancer* 134:1669–82

116. Moral JA, Leung J, Rojas LA, Ruan J, Zhao J, et al. 2020. ILC2s amplify PD-1 blockade by activating tissue-specific cancer immunity. *Nature* 579:130–35

117. Ikutani M, Yanagibashi T, Ogasawara M, Tsuneyama K, Yamamoto S, et al. 2012. Identification of innate IL-5-producing cells and their role in lung eosinophil regulation and antitumor immunity. *J. Immunol.* 188:703–13

118. Dadi S, Chhangawala S, Whitlock BM, Franklin RA, Luo CT, et al. 2016. Cancer immunosurveillance by tissue-resident innate lymphoid cells and innate-like T cells. *Cell* 164:365–77

119. Gao Y, Souza-Fonseca-Guimaraes F, Bald T, Ng SS, Young A, et al. 2017. Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells. *Nat. Immunol.* 18:1004–15

120. Cortez VS, Ulland TK, Cervantes-Barragan L, Bando JK, Robinette ML, et al. 2017. SMAD4 impedes the conversion of NK cells into ILC1-like cells by curtailing non-canonical TGF-β signaling. *Nat. Immunol.* 18:995–1003

121. Shields JD, Kourtis IC, Tomei AA, Roberts JM, Swartz MA. 2010. Induction of lymphoidlike stroma and immune escape by tumors that express the chemokine CCL21. *Science* 328:749–52

122. Carrega P, Loiacono F, Di Carlo E, Scaramuccia A, Mora M, et al. 2015. NCR[+]ILC3 concentrate in human lung cancer and associate with intratumoral lymphoid structures. *Nat. Commun.* 6:8280

123. Talmadge JE, Meyers KM, Prieur DJ, Starkey JR. 1980. Role of NK cells in tumour growth and metastasis in *beige* mice. *Nature* 284:622–24

124. Coca S, Perez-Piqueras J, Martinez D, Colmenarejo A, Saez MA, et al. 1997. The prognostic significance of intratumoral natural killer cells in patients with colorectal carcinoma. *Cancer* 79:2320–28

125. Mastaglio S, Wong E, Perera T, Ripley J, Blombery P, et al. 2018. Natural killer receptor ligand expression on acute myeloid leukemia impacts survival and relapse after chemotherapy. *Blood Adv.* 2:335–46

126. Stringaris K, Sekine T, Khoder A, Alsuliman A, Razzaghi B, et al. 2014. Leukemia-induced phenotypic and functional defects in natural killer cells predict failure to achieve remission in acute myeloid leukemia. *Haematologica* 99:836–47

127. van den Broek MF, Kägi D, Zinkernagel RM, Hengartner H. 1995. Perforin dependence of natural killer cell-mediated tumor control in vivo. *Eur. J. Immunol.* 25:3514–16

128. Kärre K, Ljunggren HG, Piontek G, Kiessling R. 1986. Selective rejection of H-2-deficient lymphoma variants suggests alternative immune defence strategy. *Nature* 319:675–78

129. Diefenbach A, Jensen ER, Jamieson AM, Raulet DH. 2001. Rae1 and H60 ligands of the NKG2D receptor stimulate tumour immunity. *Nature* 413:165–71

130. Gasser S, Orsulic S, Brown EJ, Raulet DH. 2005. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. *Nature* 436:1186–90

131. Guerra N, Tan YX, Joncker NT, Choy A, Gallardo F, et al. 2008. NKG2D-deficient mice are defective in tumor surveillance in models of spontaneous malignancy. *Immunity* 28:571–80

132. Glasner A, Ghadially H, Gur C, Stanietsky N, Tsukerman P, et al. 2012. Recognition and prevention of tumor metastasis by the NK receptor NKp46/NCR1. *J. Immunol.* 188:2509–15

133. Costello RT, Sivori S, Marcenaro E, Lafage-Pochitaloff M, Mozziconacci MJ, et al. 2002. Defective expression and function of natural killer cell-triggering receptors in patients with acute myeloid leukemia. *Blood* 99:3661–67

134. Barry KC, Hsu J, Broz ML, Cueto FJ, Binnewies M, et al. 2018. A natural killer–dendritic cell axis defines checkpoint therapy–responsive tumor microenvironments. *Nat. Med.* 24:1178–91

135. Bottcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, et al. 2018. NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control. *Cell* 172:1022–37.e14

136. Mittal D, Vijayan D, Putz EM, Aguilera AR, Markey KA, et al. 2017. Interleukin-12 from CD103^{+} Batf3-dependent dendritic cells required for NK-cell suppression of metastasis. *Cancer Immunol. Res.* 5:1098–108

137. Delconte RB, Kolesnik TB, Dagley LF, Rautela J, Shi W, et al. 2016. CIS is a potent checkpoint in NK cell–mediated tumor immunity. *Nat. Immunol.* 17:816–24

138. Ohs I, Ducimetière L, Marinho J, Kulig P, Becher B, Tugues S. 2017. Restoration of natural killer cell antimetastatic activity by IL12 and checkpoint blockade. *Cancer Res.* 77:7059–71

139. Zhang Q, Bi J, Zheng X, Chen Y, Wang H, et al. 2018. Blockade of the checkpoint receptor TIGIT prevents NK cell exhaustion and elicits potent anti-tumor immunity. *Nat. Immunol.* 19:723–32

140. Molgora M, Bonavita E, Ponzetta A, Riva F, Barbagallo M, et al. 2017. IL-1R8 is a checkpoint in NK cells regulating anti-tumour and anti-viral activity. *Nature* 551:110–14

141. Niu C, Jin H, Li M, Xu J, Xu D, et al. 2015. In vitro analysis of the proliferative capacity and cytotoxic effects of ex vivo induced natural killer cells, cytokine-induced killer cells, and gamma-delta T cells. *BMC Immunol.* 16:61

142. Dokouhaki P, Schuh NW, Joe B, Allen CA, Der SD, et al. 2013. NKG2D regulates production of soluble TRAIL by ex vivo expanded human γδ T cells. *Eur. J. Immunol.* 43:3175–82

143. Gao Y, Yang W, Pan M, Scully E, Girardi M, et al. 2003. γδ T cells provide an early source of interferon γ in tumor immunity. *J. Exp. Med.* 198:433–42

144. Maniar A, Zhang X, Lin W, Gastman BR, Pauza CD, et al. 2010. Human γδ T lymphocytes induce robust NK cell–mediated antitumor cytotoxicity through CD137 engagement. *Blood* 116:1726–33

145. Jin C, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, et al. 2019. Commensal microbiota promote lung cancer development via γδ T cells. *Cell* 176:998–1013.e16

146. Daley D, Zambirinis CP, Seifert L, Akkad N, Mohan N, et al. 2016. γδ T cells support pancreatic oncogenesis by restraining αβ T cell activation. *Cell* 166:1485–99.e15

147. Cui J, Shin T, Kawano T, Sato H, Kondo E, et al. 1997. Requirement for V$_\alpha$14 NKT cells in IL-12-mediated rejection of tumors. *Science* 278:1623–26

148. De Santo C, Arscott R, Booth S, Karydis I, Jones M, et al. 2010. Invariant NKT cells modulate the suppressive activity of IL-10-secreting neutrophils differentiated with serum amyloid A. *Nat. Immunol.* 11:1039–46

149. Hermans IF, Silk JD, Gileadi U, Salio M, Mathew B, et al. 2003. NKT cells enhance CD4^{+} and CD8^{+} T cell responses to soluble antigen in vivo through direct interaction with dendritic cells. *J. Immunol.* 171:5140–47

150. Semmling V, Lukacs-Kornek V, Thaiss CA, Quast T, Hochheiser K, et al. 2010. Alternative cross-priming through CCL17-CCR4-mediated attraction of CTLs toward NKT cell–licensed DCs. *Nat. Immunol.* 11:313–20

151. Bae E-A, Seo H, Kim B-S, Choi J, Jeon I, et al. 2018. Activation of NKT cells in an anti-PD-1-resistant tumor model enhances antitumor immunity by reinvigorating exhausted CD8 T cells. *Cancer Res.* 78:5315–26

152. Terabe M, Swann J, Ambrosino E, Sinha P, Takaku S, et al. 2005. A nonclassical non-Vα14Jα18 CD1d-restricted (type II) NKT cell is sufficient for down-regulation of tumor immunosurveillance. *J. Exp. Med.* 202:1627–33

153. Ambrosino E, Terabe M, Halder RC, Peng J, Takaku S, et al. 2007. Cross-regulation between type I and type II NKT cells in regulating tumor immunity: a new immunoregulatory axis. *J. Immunol.* 179:5126–36

154. Merle NS, Church SE, Fremeaux-Bacchi V, Roumenina LT. 2015. Complement system part I – molecular mechanisms of activation and regulation. *Front. Immunol.* 6:262

155. Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT. 2015. Complement system part II: role in immunity. *Front. Immunol.* 6:257

156. Kennedy AD, Beum PV, Solga MD, DiLillo DJ, Lindorfer MA, et al. 2004. Rituximab infusion promotes rapid complement depletion and acute CD20 loss in chronic lymphocytic leukemia. *J. Immunol.* 172:3280–88

157. Lu Y, Zhao Q, Liao JY, Song E, Xia Q, et al. 2020. Complement signals determine opposite effects of B cells in chemotherapy-induced immunity. *Cell* 180:1081–97.e24

158. Corrales L, Ajona D, Rafail S, Lasarte JJ, Riezu-Boj JI, et al. 2012. Anaphylatoxin C5a creates a favorable microenvironment for lung cancer progression. *J. Immunol.* 189:4674–83

159. An LL, Gorman JV, Stephens G, Swerdlow B, Warrener P, et al. 2016. Complement C5a induces PD-L1 expression and acts in synergy with LPS through Erk1/2 and JNK signaling pathways. *Sci. Rep.* 6:33346

160. Janelle V, Langlois M-P, Tarrab E, Lapierre P, Poliquin L, Lamarre A. 2014. Transient complement inhibition promotes a tumor-specific immune response through the implication of natural killer cells. *Cancer Immunol. Res.* 2:200–6

161. Medler TR, Murugan D, Horton W, Kumar S, Cotechini T, et al. 2018. Complement C5a fosters squamous carcinogenesis and limits T cell response to chemotherapy. *Cancer Cell* 34:561–78.e6

162. Guglietta S, Chiavelli A, Zagato E, Krieg C, Gandini S, et al. 2016. Coagulation induced by C3aR-dependent NETosis drives protumorigenic neutrophils during small intestinal tumorigenesis. *Nat. Commun.* 7:11037

163. Sohn J-H, Bora PS, Suk H-J, Molina H, Kaplan HJ, Bora NS. 2003. Tolerance is dependent on complement C3 fragment iC3b binding to antigen-presenting cells. *Nat. Med.* 9:206–12

164. Hsieh C-C, Chou H-S, Yang H-R, Lin F, Bhatt S, et al. 2013. The role of complement component 3 (C3) in differentiation of myeloid-derived suppressor cells. *Blood* 121:1760–68

165. Bonavita E, Gentile S, Rubino M, Maina V, Papait R, et al. 2015. PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. *Cell* 160:700–14

166. Pickup MW, Mouw JK, Weaver VM. 2014. The extracellular matrix modulates the hallmarks of cancer. *EMBO Rep.* 15:1243–53

167. Reginato MJ, Mills KR, Paulus JK, Lynch DK, Sgroi DC, et al. 2003. Integrins and EGFR coordinately regulate the pro-apoptotic protein Bim to prevent anoikis. *Nat. Cell Biol.* 5:733–40

168. Mammoto A, Connor KM, Mammoto T, Yung CW, Huh D, et al. 2009. A mechanosensitive transcriptional mechanism that controls angiogenesis. *Nature* 457:1103–8

169. Leight JL, Wozniak MA, Chen S, Lynch ML, Chen CS. 2012. Matrix rigidity regulates a switch between TGF-β1–induced apoptosis and epithelial–mesenchymal transition. *Mol. Biol. Cell* 23:781–91

170. Sorokin L. 2010. The impact of the extracellular matrix on inflammation. *Nat. Rev. Immunol.* 10:712–23

171. Acerbi I, Cassereau L, Dean I, Shi Q, Au A, et al. 2015. Human breast cancer invasion and aggression correlates with ECM stiffening and immune cell infiltration. *Integr. Biol.* 7:1120–34

172. Larsen AMH, Kuczek DE, Kalvisa A, Siersbæk MS, Thorseth M-L, et al. 2020. Collagen density modulates the immunosuppressive functions of macrophages. *J. Immunol.* 205:1461–72

173. Kim S, Takahashi H, Lin W-W, Descargues P, Grivennikov S, et al. 2009. Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis. *Nature* 457:102–6

174. Rygiel TP, Stolte EH, de Ruiter T, van de Weijer ML, Meyaard L. 2011. Tumor-expressed collagens can modulate immune cell function through the inhibitory collagen receptor LAIR-1. *Mol. Immunol.* 49:402–6

175. Hope C, Emmerich PB, Papadas A, Pagenkopf A, Matkowskyj KA, et al. 2017. Versican-derived matrikines regulate Batf3-dendritic cell differentiation and promote T cell infiltration in colorectal cancer. *J. Immunol.* 199:1933–41

176. Kalluri R. 2016. The biology and function of fibroblasts in cancer. *Nat. Rev. Cancer* 16:582–98

177. Cho H, Seo Y, Loke KM, Kim S-W, Oh S-M, et al. 2018. Cancer-stimulated CAFs enhance monocyte differentiation and protumoral TAM activation via IL6 and GM-CSF secretion. *Clin. Cancer Res.* 24:5407–21

178. Zhang R, Qi F, Zhao F, Li G, Shao S, et al. 2019. Cancer-associated fibroblasts enhance tumor-associated macrophages enrichment and suppress NK cells function in colorectal cancer. *Cell Death Dis.* 10:273

179. Kumar V, Donthireddy L, Marvel D, Condamine T, Wang F, et al. 2017. Cancer-associated fibroblasts neutralize the anti-tumor effect of CSF1 receptor blockade by inducing PMN-MDSC infiltration of tumors. *Cancer Cell* 32:654–68.e5

180. Balsamo M, Scordamaglia F, Pietra G, Manzini C, et al. 2009. Melanoma-associated fibroblasts modulate NK cell phenotype and antitumor cytotoxicity. *PNAS* 106:20847–52

181. Cheng J-T, Deng Y-N, Yi H-M, Wang G-Y, Fu B-S, et al. 2016. Hepatic carcinoma-associated fibroblasts induce IDO-producing regulatory dendritic cells through IL-6-mediated STAT3 activation. *Oncogenesis* 5:e198

182. Cheng Y, Li H, Deng Y, Tai Y, Zeng K, et al. 2018. Cancer-associated fibroblasts induce PDL1+ neutrophils through the IL6-STAT3 pathway that foster immune suppression in hepatocellular carcinoma. *Cell Death Dis.* 9:422

183. Kato T, Noma K, Ohara T, Kashima H, Katsura Y, et al. 2018. Cancer-associated fibroblasts affect intratumoral CD8^{+} and FoxP3^{+} T cells via IL6 in the tumor microenvironment. *Clin. Cancer Res.* 24:4820–33

184. Elyada E, Bolisetty M, Laise P, Flynn WF, Courtois ET, et al. 2019. Cross-species single-cell analysis of pancreatic ductal adenocarcinoma reveals antigen-presenting cancer-associated fibroblasts. *Cancer Discov.* 9:1102–23

185. Feig C, Jones JO, Kraman M, Wells RJB, Deonarine A, et al. 2013. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti–PD-L1 immunotherapy in pancreatic cancer. *PNAS* 110:20212–17

186. Wang Z, Yan R, Li J, Gao Y, Moresco P, et al. 2020. Pancreatic cancer cells assemble a CXCL12-keratin 19 coating to resist immunotherapy. bioRxiv 776419. **https://doi.org/10.1101/776419**

187. Biasci D, Smoragiewicz M, Connell CM, Wang Z, Gao Y, et al. 2020. CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response. *PNAS* 117:28960–70

188. Honda K, Littman DR. 2016. The microbiota in adaptive immune homeostasis and disease. *Nature* 535:75–84

189. Petrelli F, Ghidini M, Ghidini A, Perego G, Cabiddu M, et al. 2019. Use of antibiotics and risk of cancer: a systematic review and meta-analysis of observational studies. *Cancers* 11:1174

190. Schulz MD, Atay C, Heringer J, Romrig FK, Schwitalla S, et al. 2014. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature* 514:508–12

191. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, et al. 2012. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature* 491:254–58

192. Ma C, Han M, Heinrich B, Fu Q, Zhang Q, et al. 2018. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science* 360:eaan5931

193. Pushalkar S, Hundeyin M, Daley D, Zambirinis CP, Kurz E, et al. 2018. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. *Cancer Discov.* 8:403–16

194. Aykut B, Pushalkar S, Chen R, Li Q, Abengozar R, et al. 2019. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. *Nature* 574:264–67

195. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, et al. 2015. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 350:1084–89

196. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, et al. 2015. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 350:1079–84

197. Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, et al. 2021. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 371:602–9

198. Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin JM, et al. 2021. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. *Science* 371:595–602

199. Finotello F, Trajanoski Z. 2018. Quantifying tumor-infiltrating immune cells from transcriptomics data. *Cancer Immunol. Immunother.* 67:1031–40

200. Kim IS, Gao Y, Welte T, Wang H, Liu J, et al. 2019. Immuno-subtyping of breast cancer reveals distinct myeloid cell profiles and immunotherapy resistance mechanisms. *Nat. Cell Biol.* 21:1113–26

201. Lavin Y, Kobayashi S, Leader A, Amir ED, Elefant N, et al. 2017. Innate immune landscape in early lung adenocarcinoma by paired single-cell analyses. *Cell* 169:750–65.e17

202. Tsujikawa T, Kumar S, Borkar RN, Azimi V, Thibault G, et al. 2017. Quantitative multiplex immunohistochemistry reveals myeloid-inflamed tumor-immune complexity associated with poor prognosis. *Cell Rep.* 19:203–17

203. Keren L, Bosse M, Marquez D, Angoshtari R, Jain S, et al. 2018. A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging. *Cell* 174:1373–87.e19

204. Gruosso T, Gigoux M, Manem VSK, Bertos N, et al. 2019. Spatially distinct tumor immune microenvironments stratify triple-negative breast cancers. *J. Clin. Investig.* 129:1785–800

205. Rozenblatt-Rosen O, Regev A, Oberdoerffer P, Nawy T, Hupalowska A, et al. 2020. The Human Tumor Atlas Network: charting tumor transitions across space and time at single-cell resolution. *Cell* 181:236–49

206. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, et al. 2010. Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* 363:711–23

207. van Puffelen JH, Keating ST, Oosterwijk E, van der Heijden AG, Netea MG, et al. 2020. Trained immunity as a molecular mechanism for BCG immunotherapy in bladder cancer. *Nat. Rev. Urol.* 17:513–25

208. Kubota Y, Takubo K, Shimizu T, Ohno H, Kishi K, et al. 2009. M-CSF inhibition selectively targets pathological angiogenesis and lymphangiogenesis. *J. Exp. Med.* 206:1089–102

209. Li M, Knight DA, Snyder LA, Smyth MJ, Stewart TJ. 2013. A role for CCL2 in both tumor progression and immunosurveillance. *Oncoimmunology* 2:e25474

210. Pienta KJ, Machiels JP, Schrijvers D, Alekseev B, Shkolnik M, et al. 2013. Phase 2 study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. *Investig. New Drugs* 31:760–68

211. Nywening TM, Wang-Gillam A, Sanford DE, Belt BA, Panni RZ, et al. 2016. Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. *Lancet Oncol.* 17:651–62

212. Tap WD, Wainberg ZA, Anthony SP, Ibrahim PN, Zhang C, et al. 2015. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N. Engl. J. Med.* 373:428–37

213. Butowski N, Colman H, De Groot JF, Omuro AM, Nayak L, et al. 2016. Orally administered colony stimulating factor 1 receptor inhibitor PLX3397 in recurrent glioblastoma: an Ivy Foundation Early Phase Clinical Trials Consortium phase II study. *Neuro-Oncology* 18:557–64

214. Cassier PA, Italiano A, Gomez-Roca CA, Le Tourneau C, Toulmonde M, et al. 2015. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. *Lancet Oncol.* 16:949–56

215. Razak AR, Cleary JM, Moreno V, Boyer M, Calvo Aller E, et al. 2020. Safety and efficacy of AMG 820, an anti-colony-stimulating factor 1 receptor antibody, in combination with pembrolizumab in adults with advanced solid tumors. *J. Immunother. Cancer* 8:e001006

216. Kaczanowska S, Beury DW, Gopalan V, Tycko AK, Qin H, et al. 2021. Genetically engineered myeloid cells rebalance the core immune-suppression program in metastasis. *Cell* 184(8):2033–52.e21

217. Aleynick M, Svensson-Arvelund J, Flowers CR, Marabelle A, Brody JD. 2019. Pathogen molecular pattern receptor agonists: treating cancer by mimicking infection. *Clin. Cancer Res.* 25:6283–94

218. Smith M, García-Martínez E, Pitter MR, Fucikova J, Spisek R, et al. 2018. Trial Watch: Toll-like receptor agonists in cancer immunotherapy. *Oncoimmunology* 7:e1526250

219. Adams S, Kozhaya L, Martiniuk F, Meng TC, Chiriboga L, et al. 2012. Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer. *Clin. Cancer Res.* 18:6748–57

220. Smith DA, Conkling P, Richards DA, Nemunaitis JJ, Boyd TE, et al. 2014. Antitumor activity and safety of combination therapy with the Toll-like receptor 9 agonist IMO-2055, erlotinib, and bevacizumab in advanced or metastatic non-small cell lung cancer patients who have progressed following chemotherapy. *Cancer Immunol. Immunother.* 63:787–96

221. Dietsch GN. 2016. Motolimod effectively drives immune activation in advanced cancer patients. *Oncoimmunology* 5:e1126037

222. Na YR, Yoon YN, Son D, Jung D, Gu GJ, Seok SH. 2015. Consistent inhibition of cyclooxygenase drives macrophages towards the inflammatory phenotype. *PLOS ONE* 10:e0118203

223. Nakanishi Y, Nakatsuji M, Seno H, Ishizu S, Akitake-Kawano R, et al. 2011. COX-2 inhibition alters the phenotype of tumor-associated macrophages from M2 to M1 in $Apc^{Min/+}$ mouse polyps. *Carcinogenesis* 32:1333–39

224. Lin J-Z, Hameed I, Xu Z, Yu Y, Ren Z-Y, Zhu JG. 2018. Efficacy of gefitinib-celecoxib combination therapy in docetaxel-resistant prostate cancer. *Oncol. Rep.* 40:2242–50

225. Guerriero JL, Sotayo A, Ponichtera HE, Castrillon JA, Pourzia AL, et al. 2017. Class IIa HDAC inhibition reduces breast tumours and metastases through anti-tumour macrophages. *Nature* 543:428–32

226. Kaneda MM, Messer KS, Ralainirina N, Li H, Leem CJ, et al. 2016. PI3Kγ is a molecular switch that controls immune suppression. *Nature* 539:437–42

227. Downey CM, Aghaei M, Schwendener RA, Jirik FR. 2014. DMXAA causes tumor site-specific vascular disruption in murine non-small cell lung cancer, and like the endogenous non-canonical cyclic dinucleotide STING agonist, 2′3′-cGAMP, induces M2 macrophage repolarization. *PLOS ONE* 9:e99988

228. Li A, Yi M, Qin S, Song Y, Chu Q, Wu K. 2019. Activating cGAS-STING pathway for the optimal effect of cancer immunotherapy. *J. Hematol. Oncol.* 12:35

229. Anguille S, Smits EL, Bryant C, Van Acker HH, Goossens H, et al. 2015. Dendritic cells as pharmacological tools for cancer immunotherapy. *Pharmacol. Rev.* 67:731–53

230. Dhodapkar MV, Steinman RM, Krasovsky J, Munz C, Bhardwaj N. 2001. Antigen-specific inhibition of effector T cell function in humans after injection of immature dendritic cells. *J. Exp. Med.* 193:233–38

231. Kim JH, Kang TH, Noh KH, Kim S-H, Lee Y-H, et al. 2010. Enhancement of DC vaccine potency by activating the PI3K/AKT pathway with a small interfering RNA targeting PTEN. *Immunol. Lett.* 134:47–54

232. Theisen DJ, Davidson JT 4th, Briseno CG, Gargaro M, Lauron EJ, et al. 2018. WDFY4 is required for cross-presentation in response to viral and tumor antigens. *Science* 362:694–99

233. Handy CE, Antonarakis ES. 2018. Sipuleucel-T for the treatment of prostate cancer: novel insights and future directions. *Future Oncol.* 14:907–17

234. Schreibelt G, Bol KF, Westdorp H, Wimmers F, Aarntzen EH, et al. 2016. Effective clinical responses in metastatic melanoma patients after vaccination with primary myeloid dendritic cells. *Clin. Cancer Res.* 22:2155–66

235. Hammerich L, Marron TU, Upadhyay R, Svensson-Arvelund J, Dhainaut M, et al. 2019. Systemic clinical tumor regressions and potentiation of PD1 blockade with in situ vaccination. *Nat. Med.* 25:814–24

236. Van Lint S, Renmans D, Broos K, Goethals L, Maenhout S, et al. 2016. Intratumoral delivery of TriMix mRNA results in T-cell activation by cross-presenting dendritic cells. *Cancer Immunol. Res.* 4:146–56

237. Ylosmaki E, Cerullo V. 2020. Design and application of oncolytic viruses for cancer immunotherapy. *Curr. Opin. Biotechnol.* 65:25–36

238. Li Y, Su Z, Zhao W, Zhang X, Momin N, Zhang C, et al. 2020. Multifunctional oncolytic nanoparticles deliver self-replicating IL-12 RNA to eliminate established tumors and prime systemic immunity. *Nat. Cancer* 1:882–93

239. Khalil DN, Suek N, Campesato LF, Budhu S, Redmond D, et al. 2019. In situ vaccination with defined factors overcomes T cell exhaustion in distant tumors. *J. Clin. Investig.* 129:3435–47

240. Corrales L, Glickman LH, McWhirter SM, Kanne DB, Sivick KE, et al. 2015. Direct activation of STING in the tumor microenvironment leads to potent and systemic tumor regression and immunity. *Cell Rep.* 11:1018–30

241. Muntasell A, Ochoa MC, Cordeiro L, Berraondo P, López-Díaz de Cerio A, et al. 2017. Targeting NK-cell checkpoints for cancer immunotherapy. *Curr. Opin. Immunol.* 45:73–81

242. Amin A, White RL Jr. 2013. High-dose interleukin-2: Is it still indicated for melanoma and RCC in an era of targeted therapies? *Oncology* 27:680–91

243. Romagné F, André P, Spee P, Zahn S, Anfossi N, et al. 2009. Preclinical characterization of 1-7F9, a novel human anti-KIR receptor therapeutic antibody that augments natural killer-mediated killing of tumor cells. *Blood* 114:2667–77

244. Mamessier E, Sylvain A, Thibult ML, Houvenaeghel G, Jacquemier J, et al. 2011. Human breast cancer cells enhance self tolerance by promoting evasion from NK cell antitumor immunity. *J. Clin. Investig.* 121:3609–22

245. van Hall T, Andre P, Horowitz A, Ruan DF, Borst L, et al. 2019. Monalizumab: inhibiting the novel immune checkpoint NKG2A. *J. Immunother. Cancer* 7:263

246. Rothe A, Sasse S, Topp MS, Eichenauer DA, Hummel H, et al. 2015. A phase 1 study of the bispecific anti-CD30/CD16A antibody construct AFM13 in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 125:4024–31

247. Vallera DA, Felices M, McElmurry R, McCullar V, Zhou X, et al. 2016. IL15 trispecific killer engagers (TriKE) make natural killer cells specific to CD33^{+} targets while also inducing persistence, in vivo expansion, and enhanced function. *Clin Cancer Res* 22:3440–50

248. Lin C, Zhang J. 2018. Reformation in chimeric antigen receptor based cancer immunotherapy: redirecting natural killer cell. *Biochim. Biophys. Acta Rev. Cancer* 1869:200–15

249. Liu E, Marin D, Banerjee P, Macapinlac HA, Thompson P, et al. 2020. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N. Engl. J. Med.* 382:545–53

250. Martin C, Burdon PC, Bridger G, Gutierrez-Ramos JC, Williams TJ, Rankin SM. 2003. Chemokines acting via CXCR2 and CXCR4 control the release of neutrophils from the bone marrow and their return following senescence. *Immunity* 19:583–93

251. Schott AF, Goldstein LJ, Cristofanilli M, Ruffini PA, McCanna S, et al. 2017. Phase Ib pilot study to evaluate reparixin in combination with weekly paclitaxel in patients with HER-2–negative metastatic breast cancer. *Clin. Cancer Res.* 23:5358–65

252. Steggerda SM, Bennett MK, Chen J, Emberley E, Huang T, et al. 2017. Inhibition of arginase by CB-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironment. *J. Immunother. Cancer* 5:101