JEM Journal of Experimental Medicine

REVIEW

Unfolding innate mechanisms in the cancer microenvironment: The emerging role of the mesenchyme

Vasiliki Koliaraki[1], Ana Henriques[1,2], Alejandro Prados[2], and George Kollias[1,2,3]

Innate mechanisms in the tumor stroma play a crucial role both in the initial rejection of tumors and in cancer promotion. Here, we provide a concise overview of the innate system in cancer and recent advances in the field, including the activation and functions of innate immune cells and the emerging innate properties and modulatory roles of the fibroblastic mesenchyme. Novel insights into the diverse identities and functions of the innate immune and mesenchymal cells in the microenvironment of tumors should lead to improved anticancer therapies.

Introduction

It is now well established that solid tumors are populated by a variety of different cell types, which constitute the tumor microenvironment or stroma and play significant roles in cancer initiation, progression, and metastasis (Hanahan and Coussens, 2012). These include cancer-associated fibroblasts (CAFs) and endothelial and immune cells. The latter are important components of the tumor microenvironment and display both anti- and protumorigenic roles, as they are responsible for the initial immune-mediated rejection of tumors (Gajewski et al., 2013) and chronic inflammation that enables carcinogenesis (Greten and Grivennikov, 2019).

In this context, innate immunity plays a critical role in all aspects of tumorigenesis, including cancer initiation, proliferation, angiogenesis, and immunosuppression. Supporting the antitumor properties of immune cells and alleviating immunosuppression has been of particular interest as a therapeutic target in recent years with the development of immunotherapies (Mellman et al., 2011). However, it is now known that immunotherapeutic regimes are efficient only in a subset of patients, and development of resistance is common (Chen and Mellman, 2017). Innate immunity plays an important role also in this setting, as well as in the acquisition of resistance to other anticancer therapies. It is thus of great importance to better understand the cellular and molecular mechanisms underlying its functions in cancer and how it can be manipulated for therapeutic purposes.

In this review, we provide a concise overview of the recent literature on the relationship between the innate stroma and cancer, including innate immune cell types, the stimuli that lead to their recruitment and activation, and their functions. We focus on recent data highlighting the innate properties of mesenchymal cells and the heterogeneity of the innate tumor microenvironment. Finally, we briefly discuss the potential manipulation of innate mechanisms as a strategy for anticancer therapy.

Innate immune cells in cancer

Innate immunity is mediated by myeloid cells, including macrophages, neutrophils, myeloid-derived suppressor cells (MDSCs), and dendritic cells (DCs), as well as innate lymphoid cells (ILCs).

Macrophages are the most abundant myeloid cells in the tumor, and together with neutrophils, they can be found in different polarization states, originally designated as antitumorigenic M1/N1 and protumorigenic M2/N2, depending on the cancer type, tumor stage, and microenvironmental milieu (Noy and Pollard, 2014; Shaul and Fridlender, 2019), although recent studies have shown that at least macrophage activation actually presents a continuum of functional differentiation states (Azizi et al., 2018; Chung et al., 2017; Müller et al., 2017b; Wagner et al., 2019). Tumor-associated macrophages (TAMs) and tumor-associated neutrophils (TANs) are considered mostly protumorigenic and have been associated with poor prognosis, while the neutrophil/leukocyte ratio has been proposed as a biomarker in cancer (Shen et al., 2014; Templeton et al., 2014; Zhang et al., 2012). MDSCs are immature myeloid cells that display immunosuppressive functions against T and natural

[1]Institute for Fundamental Biomedical Research, Biomedical Sciences Research Center "Alexander Fleming", Vari, Greece; [2]Institute for Bioinnovation, Biomedical Sciences Research Center "Alexander Fleming", Vari, Greece; [3]Department of Physiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece.

Correspondence to George Kollias: kollias@fleming.gr; Vasiliki Koliaraki: koliaraki@fleming.gr.

killer (NK) cells (Gabrilovich, 2017). They are divided in monocytic and polymorphonuclear MDSCs, which represent the majority of MDSCs in cancer (Peranzoni et al., 2010), and are considered by many as the TANs (Shaul and Fridlender, 2019). Their presence in human cancer is associated with tumor progression, metastasis, and recurrence (Zhang et al., 2016). DCs are antigen-presenting cells that act as a bridge between innate and adaptive immunity. Properly activated DCs are able to prime T cells and thus their presence correlates with increased patient survival (Broz et al., 2014; Böttcher and Reis E Sousa, 2018). After tumor establishment, DCs are considered dysfunctional and become tolerogenic, as they fail to elicit efficient antitumor immune responses (Scarlett et al., 2012; Demoulin et al., 2013).

ILCs have emerged as a novel cell group with potent immunomodulatory activities. They are considered as the innate counterpart of T cells and include four subsets: NK cells and ILC1s, ILC2s, and ILC3s as the equivalents to the T helper cell subsets (Chiossone et al., 2018). NK cells are cytotoxic, display antitumor properties, and are associated with good prognosis (Cerwenka and Lanier, 2016; Iannello et al., 2016), while the role of the other ILC populations is not clearly understood and seems to vary greatly depending on the cytokine composition of the tumor microenvironment (Chiossone et al., 2018; Simoni et al., 2017; Wagner and Koyasu, 2019).

Innate immune recruitment and activation in the tumor microenvironment

Recruitment of innate immune cells in tumors

Innate cells in tumors can originate either from the bone marrow or through the proliferation and activation of resident immune cells. Myeloid cells, and especially macrophages and neutrophils, are recruited and infiltrate the tumor site through chemoattractants, mainly cytokines, chemokines, and growth factors that are produced by both cancer cells and the surrounding stroma, including CAFs (Fig. 1; Shalapour and Karin, 2019). Genetic deletion, cell-specific ablation, or chemical inhibition of their respective receptors, as reported for example for CCR2, CCR5, CXCR2, and CSFR1, results in reduced macrophage and neutrophil/MDSC infiltration and reduced inflammation and tumorigenesis in animal models of cancer (Ijichi et al., 2011; Jamieson et al., 2012; Katoh et al., 2013; Pyonteck et al., 2013).

Innate immune sensing and activation

Both recruited and resident myeloid cells are influenced by tumor-specific signals to undergo "reprogramming" or activation (Fig. 1). This innate immune activation usually occurs in response to pathogen-associated molecular patterns or damage-associated molecular patterns (DAMPs) that act through their binding to pattern recognition receptors (PRRs) and downstream activation of adapter molecules and intracellular signaling pathways to induce the expression of cytokines, chemokines, and type I IFNs, as well as immunoregulatory molecules, such as MHC class II, CD40, CD80, and CD86 on DCs (Rakoff-Nahoum and Medzhitov, 2009). In cancer, PRR activation usually occurs by tumor-specific endogenous molecules, which are the result of genetic and epigenetic changes in tumor cells, can resemble DAMPs, and act as neoantigens (Woo et al., 2015). These are either expressed by tumor cells or are more frequently released upon cell death. Cancer cell death is commonly induced by therapeutics and is referred to as immunogenic cell death, as it can lead to antitumor immune responses (Galluzzi et al., 2017). Major DAMPs in this case include the translocation of calreticulin to the cell surface, the secretion of ATP, and the release of high-mobility group box 1 (HMGB1) protein (Elliott et al., 2009; Garg et al., 2012; He et al., 2017; Obeid et al., 2007).

An important source of innate signals and DAMPs is the extracellular matrix (ECM), which is composed of structural and matricellular proteins, including collagens, glycoproteins, glycosaminoglycans, and proteoglycans, and is capable of modulating differentiation, migration, infiltration, and polarization of immune cells. In addition, cleavage of matrisome proteins generates various bioactive peptides, called matrikines, which act as chemokines, cytokines, or DAMPs (Eble and Niland, 2019; Frevert et al., 2018). A representative example is versican, which interacts with TLR2/6 to activate macrophages, leading to cytokine production and increased metastatic potential in a Lewis lung carcinoma model (Kim et al., 2009). Versikine, a versican-derived matrikine, promotes differentiation of DCs, which are critical for antitumor immunity (Hope et al., 2016, 2017). Besides these mechanisms, the ECM also modulates innate immune migration and function through mechanical forces (Huse, 2017).

Nucleic acids derived from tumor cells can also trigger innate immune responses. In this case, necrotic or apoptotic cancer cells are phagocytosed by macrophages and/or DCs, and the released tumor DNA can induce intracellular DNA recognition mechanisms. In recent years, the stimulator of IFN genes (STING) has been recognized as an important innate immune cytoplasmic DNA sensor that senses cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) and, through IFN regulatory factor 3 (IRF3) activation and type I IFN production, leads to antitumor immune responses (Corrales et al., 2015, 2016; Woo et al., 2014). Type I IFNs, in general, are considered crucial for the activation, migration, and cross-presentation of DCs (Diamond et al., 2011; Fuertes et al., 2011), activation of NK cells (Müller et al., 2017a), and polarization of neutrophils to an antitumor phenotype (Jablonska et al., 2010; Wu et al., 2015).

Importantly, activation of PRRs can also be mediated by microbiota, at least in organs that are in direct contact with them, such as the intestine. Excellent recent reviews describe how microbes influence tumorigenesis and response to therapy (Dzutsev et al., 2017; Helmink et al., 2019).

Other soluble mediators, such as cytokines and growth factors, produced by either cancer cells or the stroma, including CAFs, also influence the activation of innate cells. The cytokines IL-4 and IL-13, produced by immune cells, and CAF-secreted chitinase-3-like-1 (Chi3L1) are important for the differentiation of macrophages toward a tumor-promoting phenotype (Cohen et al., 2017; DeNardo et al., 2009). IL-10 and TGF-β also affect macrophage, neutrophil, and DC activation and functions (Ruffell et al., 2014). TGF-β specifically promotes myeloid cell survival and protumorigenic, immunosuppressive lineage commitment (Fridlender et al., 2009; Gao et al., 2017; Gonzalez-Junca et al., 2019). In addition to TAM recruitment, CSF1, along

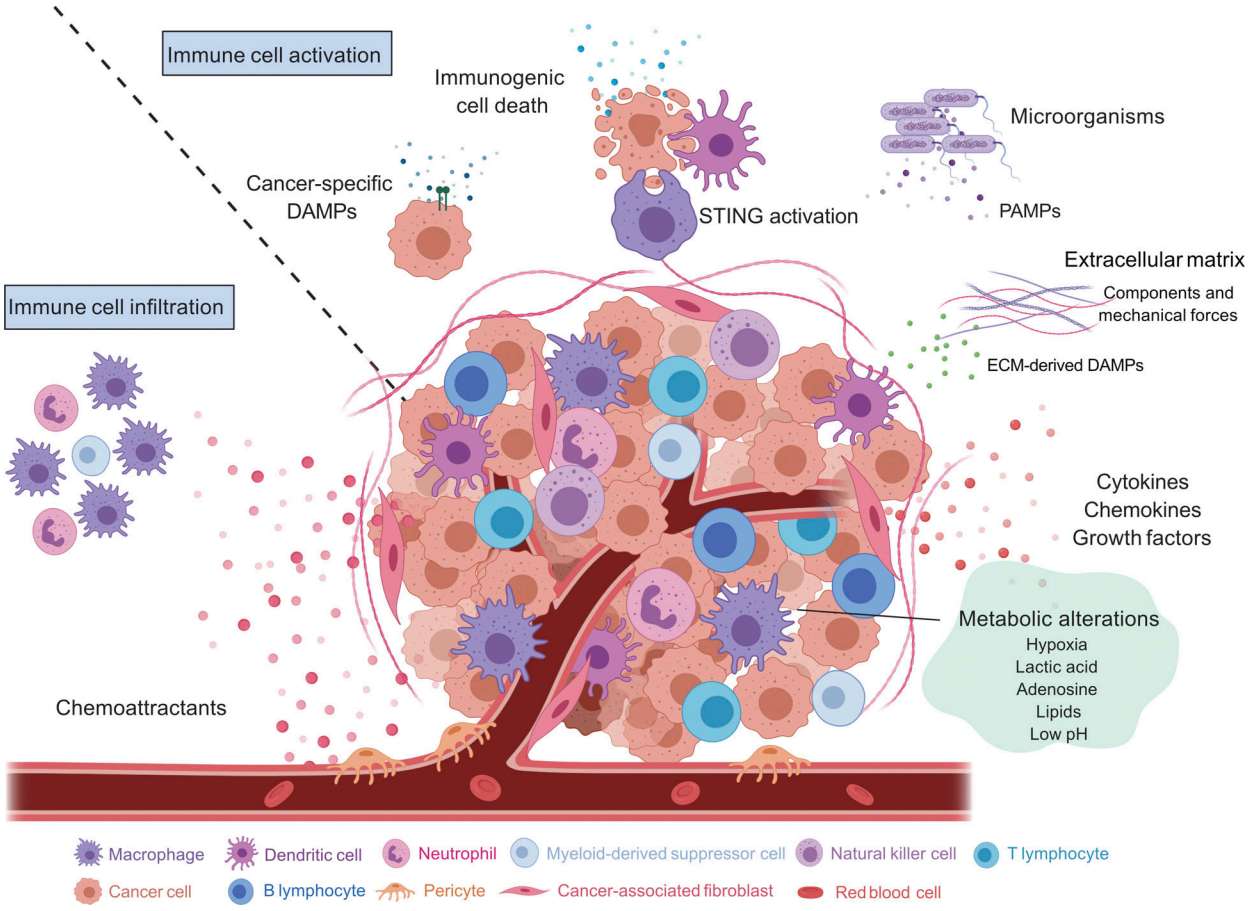

Figure 1. **Innate immune recruitment and activation in the tumor microenvironment.** Cytokines, chemokines, and growth factors produced by cancer cells and the surrounding stroma lead to innate immune infiltration in tumors. DAMPs, uniquely expressed by cancer cells, secreted after cell death or found in the ECM, DNA from apoptotic cells, microorganisms, cytokines, growth factors, and metabolic alterations can trigger activation of nnate immune cells in the tumor stroma. PAMP, pathogen-associated molecular pattern; STING, stimulator of IFN genes.

with CSF2 and CSF3, drives the survival and differentiation of macrophages and granulocytes and the expansion and activation of MDSCs (Gabrilovich et al., 2012; Hagemann et al., 2006; Strauss et al., 2015), while CSF2 and FMS-like tyrosine kinase 3 ligand (Flt3L) play an important role in DC differentiation (Liu et al., 2009). MDSC generation is in general induced by the continuous presence of proinflammatory signals that drive myelopoiesis but are not adequate for complete differentiation to activated neutrophils and monocytes. NKG2D ligands originating from tumor cells after DNA damage response, along with cytokines like IL-12, IL-18, and IL-15 and the cell surface adhesion molecule LFA-1, lead to activation of NK cells (Lakshmikanth et al., 2009; Soriani et al., 2009). ILC1s are also activated in IL-15–enriched environments, while TGF-β–rich environments convert NK cells into ILC1-like cells with a reduced ability to control tumor growth and metastasis (Dadi et al., 2016; Gao et al., 2017). IL-12 and IL-33 play an important role in ILC3 and ILC2 activation, respectively (Jovanovic et al., 2014; Trabanelli et al., 2017).

Finally, besides soluble mediators, metabolic alterations triggered by the tumor microenvironment also play an important role in myeloid cell activation and effector properties (Buck et al., 2017). For example, hypoxia and lactic acid regulate macrophage function while, along with the accumulation of adenosine and lipids and decreased pH, lead to impaired antigen presentation and suppressed DC-mediated antitumor responses (Colegio et al., 2014; Cubillos-Ruiz et al., 2015; Herber et al., 2010; Veglia et al., 2017). Increased uptake of lipids by MDSCs also leads to an increase in their immunosuppressive capacity (Al-Khami et al., 2017).

Functions of innate immune responses in cancer

Innate immunity and antitumor effects

Innate immunity plays a crucial role in limiting initial cancer growth through either direct cytotoxicity against cancer cells or support of antitumor immune responses mediated predominantly by ILCs and DCs (Fig. 2).

NK cells are able to recognize and eliminate nascent transformed cells through expression of perforin and granzyme, as well as death ligands, such as TNF-regulated apoptosis-inducing ligand (TRAIL) and Fas ligand (Finnberg et al., 2008; Glasner et al., 2018; Smyth et al., 2000), while ILC1s also express granzyme under specific conditions (Dadi et al., 2016). Both NK cells and ILC1s activated in IL-15–rich environments produce TNF, IFN-γ, or CSF2, which have antitumor activity by modulating

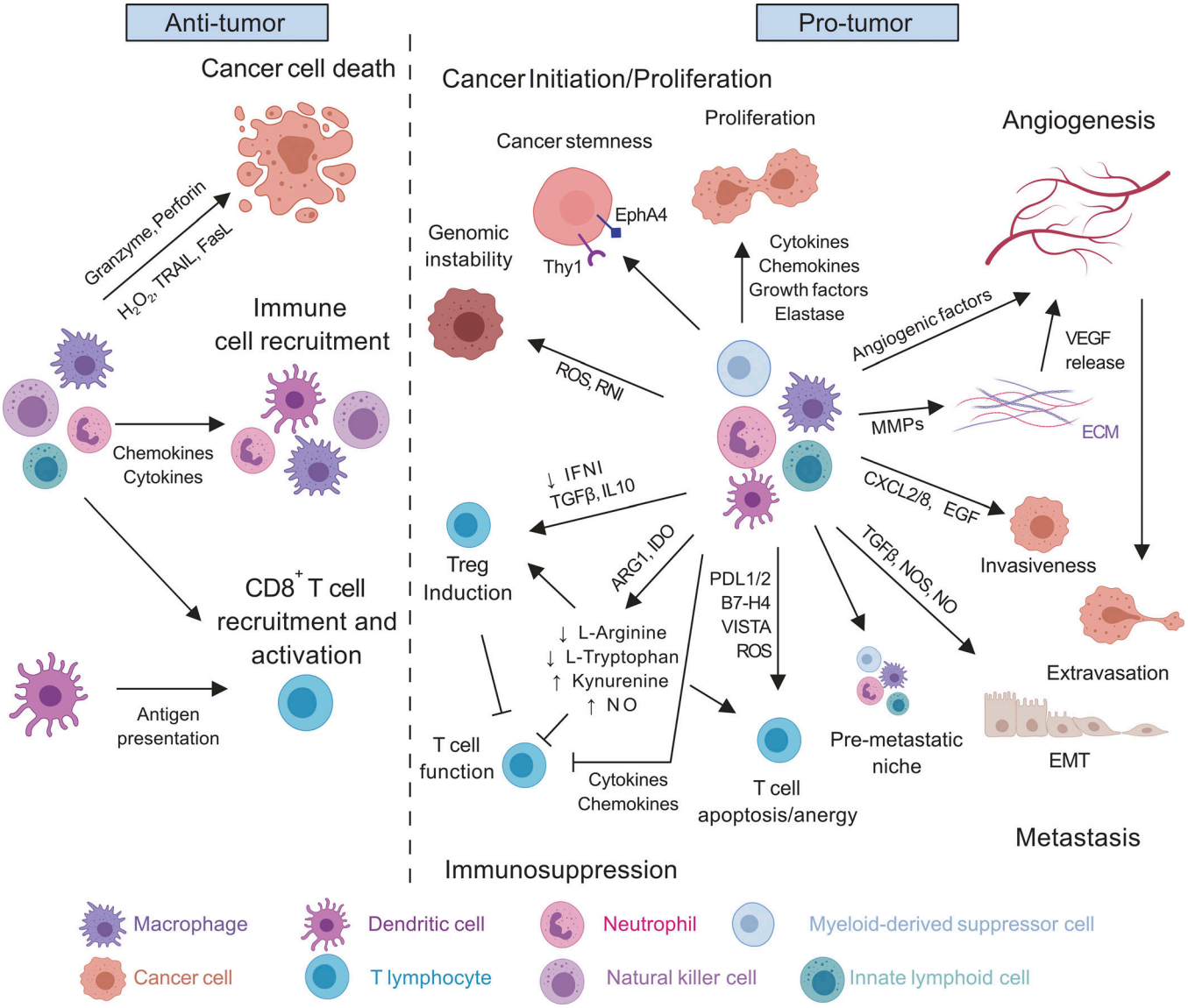

Figure 2. **Innate immune functions in the tumor stroma.** Antitumor functions include direct cancer cell killing and immunomodulation, including immune cell recruitment and activation of $CD8^+$ cytotoxic T cells. Tumor-promoting functions include the promotion of cancer initiation and cancer cell proliferation, remodeling of the ECM, induction of angiogenesis and metastasis, and support of immunosuppression in the tumor microenvironment. EMT, epithelial-to-mesenchymal transition; NO, nitric oxide; NOS, nitric oxide synthase; RNI, ROS and nitrogen intermediate; TRAIL, TNF-regulated apoptosis-inducing ligand.

leukocyte function (Dadi et al., 2016). NK cells also express chemokines, such as CCL5 and XCL1, that recruit DCs into the tumor (Böttcher et al., 2018). ILC3s, similarly to NK cells and ILC1s, contribute to antitumor immunity by releasing TNF, IL-8, and IL-2 after IL-12 stimulation and promoting leukocyte recruitment and proliferation (Carrega et al., 2015; Eisenring et al., 2010).

DCs activated by DAMPs are able to efficiently present tumor antigens to naive antigen-specific T cells, leading to their priming and generation of cytotoxic effector $CD8^+$ T cells (Broz et al., 2014; Roberts et al., 2016; Salmon et al., 2016). This is mediated through expression of MHC class II, CD40, CD80, and CD86 and production of proinflammatory cytokines and chemokines that are crucial for the recruitment and function of $CD8^+$ T cells, NK cells, and ILCs in tumors, as well as type I IFNs, which serve as a link between innate and adaptive immune responses (Mikucki et al., 2015; Ruffell et al., 2014; Tesone et al., 2013; Wendel et al., 2008).

Finally, both macrophages and neutrophils can also have antitumor functions. IFN-γ–activated M1 macrophages can directly kill tumor cells as well as recruit and activate cytotoxic $CD8^+$ and NK cells (Hanna et al., 2015). TANs have been shown to recognize tumor cells through Cathepsin G or in an antibody-dependent manner and produce H_2O_2 (Granot et al., 2011), TNF-regulated apoptosis-inducing ligand (TRAIL), chemokines, IL-6, and IFN-γ as well as express costimulatory molecules, especially during the early stages of cancer (Eruslanov et al., 2014; Granot, 2019).

Regulation of adaptive responses: Immunosuppression

Despite their antitumor functions, innate cells and especially myeloid cells are considered protumorigenic once the tumor is

established (Gajewski et al., 2013). This reversal is mediated by either a phenotypic switch or an inhibition of their functions, orchestrated by signals originating either from cancer cells or the cancer-"educated" stroma. Typical examples are macrophages and neutrophils that acquire protumorigenic roles and DCs, which are considered dysfunctional due to impaired activation (Demoulin et al., 2013). This most commonly leads to overexpression of proinflammatory molecules that results in increased tumor-promoting inflammation and modulation of adaptive immune responses driving immunosuppression. The effect of innate immune cells on immunosuppression is extensively studied and involves the production of immunosuppressive effectors, induction of regulatory T cells (T reg cells), metabolic starvation of T cells, and expression of immune checkpoint proteins (Fig. 2).

The production of immunosuppressive effectors involves molecules produced primarily by TAMs and TANs/MDSCs, such as IL-6, IL-10, TGF-β, PGE2, COX2, inducible nitric oxide synthase, CD40, and galectin 1. TAMs and TANs/MDSCs also produce ROS, which induce T cell apoptosis, reduction of TCR-ζ chain expression, and production of peroxynitrite, leading to impaired T cell signaling and anergy (Gabrilovich, 2017; Mantovani et al., 2017). ILC2s also have an immunosuppressive role through the production of amphiregulin and type 2 cytokines, such as IL-4, IL-5, IL-9, and IL-13 (Jovanovic et al., 2014; Trabanelli et al., 2017). Defective activation of DCs results in reduced type I IFN production along with lower costimulatory molecule expression, thus generating a tolerogenic phenotype (Sisirak et al., 2012).

Impaired IFN production by DCs, along with IL-10 and TGF-β produced by TAMs and TANs, is also involved in increased T reg cell expansion (Batlle and Massagué, 2019; Shalapour and Karin, 2019; Sisirak et al., 2012). Other important mediators that promote the recruitment or induction of T reg cells are inducible T cell costimulatory ligand (ICOSL) and OX40L produced by DCs (Aspord et al., 2013; Conrad et al., 2012; Faget et al., 2013), CCL22 produced by TAMs, and CCL17 produced by TANs (Maolake et al., 2017; Mishalian et al., 2014).

Metabolic starvation involves the expression of enzymes that catabolize essential metabolites or the release of toxic metabolites by TAMs, TANs/MDSCs, and DCs. The most important enzymes are arginase 1 (ARG1) and indoleamine 2,3-dioxygenase (IDO). ARG1 converts L-arginine into L-ornithine and urea, thus limiting the availability of L-arginine, which is necessary for T cell proliferation and function (Geiger et al., 2016; Rodriguez et al., 2007). ARG1 is also the substrate of nitric oxide synthase 2 (NOS2) and leads to production of nitric oxide, which suppresses T cell functions (Caldwell et al., 2018; Molon et al., 2011). IDO expressed by MDSCs and DCs catabolizes L-tryptophan into *N*-formylkynurenin, thus depleting tryptophan and leading to cell cycle arrest and anergy in T cells, as well as T reg cell differentiation. IDO activity also leads to TGF and 3-hydroxykynurenine, which inhibits T and NK cell survival and proliferation and drives differentiation to T reg cells (Munn and Mellor, 2016; Pallotta et al., 2011).

TAMs, MDSCs, and DCs additionally up-regulate programmed death ligand 1 (PD-L1) and PD-L2, which provide a negative costimulatory signal to T cells and promote T cell anergy and apoptosis (Lu et al., 2016; Salmon et al., 2016; Wang et al., 2017). In addition, B7-H4 and V-domain Ig suppressor of T cell activation expression also have similar effects (Wang et al., 2011; 2016b).

Tumor initiation and proliferation

Cancer cell proliferation is a hallmark of cancer, and deregulated cell proliferation is a prerequisite for neoplastic cell transformation. Production of ROS and nitrogen intermediates by TAMs and TANs/MDSCs promotes tumor initiation through their contribution to genetic instability in preneoplastic cells (Canli et al., 2017). Innate myeloid cells also produce proinflammatory cytokines and growth factors, such as IL-6, IL-11, IL-1β, and EGF, which play an important role in both the initiation and progression of tumorigenesis, especially in inflammation-induced cancer (Greten and Grivennikov, 2019). IL-6 and IL-11 in particular have been shown to promote cancer cell proliferation and survival and inhibit their apoptosis through activation of the downstream STAT3 signaling pathway in tumors (Johnson et al., 2018). TANs can also promote cancer cell growth and proliferation through production of elastase through activation of phosphoinositide 3-kinase (PI3K) and/or MAPK signaling pathways (Gong et al., 2013; Houghton et al., 2010; Lerman et al., 2017). ILC3s have been shown to induce abnormal epithelial proliferation in a IL-22–dependent manner (Kirchberger et al., 2013; Fig. 2).

Both TAMs and MDSCs can also affect cancer stem cells (CSCs). TAMs are important components of the CSC niche and have been found to directly interact with CSCs through binding to Thy1 and ephrin type-A4 (EphA4) receptors (Lu et al., 2014), while MDSCs have been shown to enhance stemness and epithelial-to-mesenchymal transition of CSCs through regulation of C-terminal–binding protein-2 (CtBP2; Cui et al., 2013; Panni et al., 2014).

Angiogenesis

Angiogenesis is crucial for tumor progression, as it is both a source of nutrients and oxygen and the route of waste disposal and metastatic dissemination. Infiltrating TAMs and TANs/MDSCs promote angiogenesis through the production of proangiogenic factors, such as VEGF-A, VEGF-C, EGF, FGF, TGF-β, CCL2, CXCL8, CXCL12, IL-8, and TNF (Bruno et al., 2014). TGF-β–rich environments convert NK cells into ILC1-like cells, which can also secrete proangiogenic factors (Gao et al., 2017). TAMs and TANs/MDSCs also affect angiogenesis through the production of matrix metalloproteinases (MMPs), and in particular MMP9, which mediates the release of VEGF-A from the ECM (Deryugina et al., 2014; Kuang et al., 2011). TANs and MDSCs also produce prokineticin1/Bv8, which promotes angiogenesis through MAPK activation in endothelial cells (Shojaei et al., 2007, 2008). Interestingly, lipocalin expressed by TAMs in response to sphingosine 1-phosphate (S1P) was shown to promote endothelial proliferation, leading to subsequent lymphagiogenesis and metastasis in mice (Jung et al., 2016; Fig. 2).

Metastasis

The ability of cancer cells to metastasize is a hallmark of cancer and defines disease progression and patient survival. Innate

immune cells, especially macrophages and neutrophils/MDSCs, have been implicated in the promotion of metastasis (Swierczak and Pollard, 2019; Fig. 2). As mentioned above, both TAMs and TANs/MDSCs promote angiogenesis and tumor cell intravasation, which are necessary for the initial steps of metastasis (Arwert et al., 2018; Bald et al., 2014; Harney et al., 2015), while chemokines, such as CXCL2 and CXCL8, and growth factors, such as EGF, increase the invasiveness of cancer cells (DeNardo et al., 2009). Inflammation-activated neutrophils have been shown to drive dormant cancer cell awakening through the formation of neutrophil extracellular traps, which cleave laminin and activate integrin α3β1 signaling (Albrengues et al., 2018). Both TAMs and MDSCs also promote epithelial-to-mesenchymal transition through TGF-β, nitric oxide, and nitric oxide synthase (NOS) production (Ouzounova et al., 2017). In addition, they can increase tumor-cell dissemination through the production of proteolytic enzymes such as MMPs that are responsible for the digestion and remodeling of the ECM, a key player in metastasis (Bausch et al., 2011; Kai et al., 2019; Yang et al., 2008).

Besides these effects on primary tumors, innate immune cells are also found in premetastatic sites, where they play an important role in cancer dissemination, survival, and growth through a variety of mechanisms, including angiogenesis (Mazzieri et al., 2011), extravasation of cancer cells (Qian and Deng, 2009; Srivastava et al., 2014), support of the survival and proliferation of metastatic cancer cells (Coffelt et al., 2015; Liang et al., 2018; Steele et al., 2016; Wculek and Malanchi, 2015), and immunosuppression (Kitamura et al., 2018). Notably, low-level generalized inflammation also affects metastasis, as shown for the increased lung metastasis associated with obesity-induced neutrophilia (Quail et al., 2017; Fig. 2).

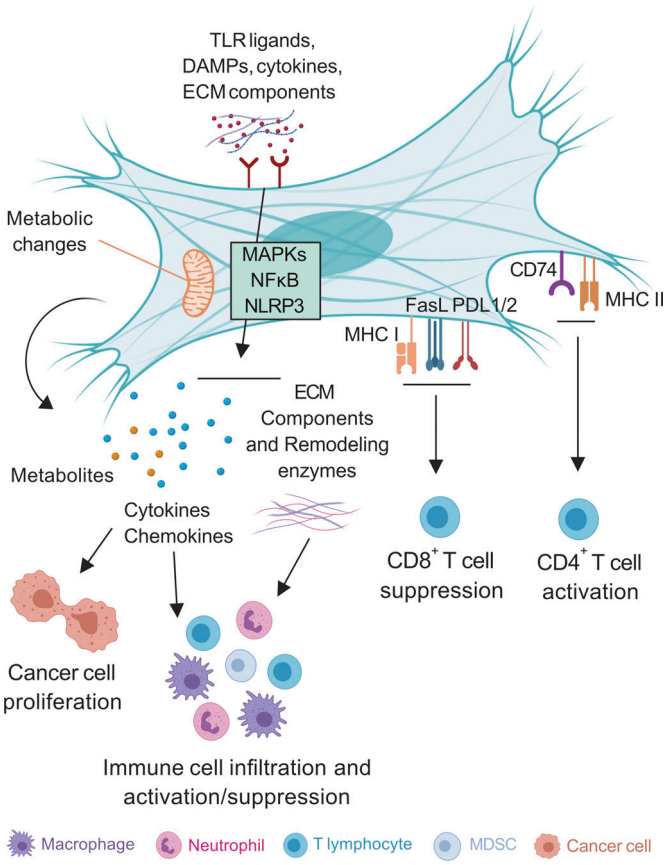

Figure 3. **Innate immune properties of CAFs in the tumor microenvironment.** CAFs express innate immune recognition and cytokine receptors and respond to secrete cytokines, chemokines, and ECM-remodeling enzymes through pathways such as NF-κB, MAPKs, and the inflammasome. They express MHC class I and II molecules, allowing them to act as antigen-presenting cells and leading to the modulation of T cell responses. They also exhibit metabolic changes that modulate both cancer cell proliferation and immune responses.

Innate functions of fibroblastic mesenchymal cells in cancer

Mesenchymal cells in tumors or CAFs are a heterogenous stromal population present in most solid tumors. CAFs contribute to a variety of protumorigenic functions, such as tumor growth, angiogenesis, immunoregulation, ECM remodelling, cancer stemness, invasion, metastasis, and chemoresistance, in an organ-specific manner and have been associated with poor prognosis (Kalluri, 2016; Öhlund et al., 2014; Turley et al., 2015). In the last decade, their immunomodulatory roles have been of particular interest and have been recently reviewed (Monteran and Erez, 2019). Here, we will focus on their functions in innate immune sensing and response in the tumor microenvironment (Fig. 3).

CAFs originate from different cell types, but resident mesenchymal cells are considered the major source (Kalluri, 2016). TGF-β plays a crucial role in their activation and differentiation to myofibroblastic CAFs and the concomitant production of effector molecules, including chemokines, cytokines, growth factors, ECM components, and remodeling enzymes. TGF-β specificity and function on mesenchymal cells is regulated by its availability, which depends on the location of mesenchymal cells, as well as its efficient release from the ECM that is mediated both by proteolysis and mechanical tension (Batlle and Massagué, 2019; Öhlund et al., 2017; Pickup et al., 2013). Notably, a TGF-β signature in mesenchymal cells has been correlated with poor prognosis, immune cell exclusion, and resistance to immunotherapy (Calon et al., 2015; Mariathasan et al., 2018; Tauriello et al., 2018). Besides TGF-β, a variety of stimuli, including innate signals, have been shown to induce their activation.

The activation of CAFs by DAMPs is indicative of their ability to respond to innate immune stimuli. IL-1a is an important such danger signal that is released by cancer cells and promotes the activation of inflammatory CAFs in pancreatic ductal adenocarcinoma (PDAC) through the JAK/STAT pathway. Notably, IL-1a is antagonized by TGF-β toward the differentiation of myofibroblastic CAFs (Biffi et al., 2019). IL-1β has also been shown to induce proinflammatory gene expression that affects tumorigenesis (Erez et al., 2010). Recently, breast cancer CAFs were shown to sense DAMPs through the NLRP3 inflammasome and in response induce proinflammatory gene expression and IL-1β release that promoted tumor growth and metastasis (Ershaid et al., 2019). Interestingly, ECM matricellular proteins and matrikines that can activate innate immunity could also induce CAF activation and immunoregulation (Eble and Niland,

2019). One such example is osteopontin, which activates fibroblasts in breast cancer to promote inflammation and tumor growth (Sharon et al., 2015).

In addition, CAFs express innate recognition (TLRs) and respond to the relevant stimuli by secreting cytokines, chemokines, MMPs, and ECM components. The prognostic value of these expression patterns seems to be organ and cancer-type specific; TLR7 and TLR9 expression in CAFs is associated with enhanced survival in breast and esophageal squamous cell cancer (González-Reyes et al., 2010; Ni et al., 2015; Sheyhidin et al., 2011), while TLR4 and TLR9 expression in colorectal and hepatocellular carcinoma CAFs, respectively, is associated with poor prognosis (Eiró et al., 2013, 2014). We recently provided direct evidence for a pathophysiological role of innate sensing by CAFs in intestinal cancer (Koliaraki et al., 2019). We showed that deletion of either myeloid differentiation primary response 88 (MyD88) or TLR4 in intestinal mesenchymal cells and CAFs is sufficient to reduce tumorigenesis in the $Apc^{min/+}$ model of intestinal cancer, similarly to MyD88's complete deletion (Rakoff-Nahoum and Medzhitov, 2007). Activation of CAFs by TLR4/MyD88-mediated signals resulted in the production of effector cytokines and chemokines capable of affecting both tumor proliferation and the immune microenvironment to promote intestinal cancer.

Besides TLR4, TLR9 activation has also been shown to induce pancreatic stellate cells to become fibrogenic and secrete chemokines that promote epithelial cell proliferation and immunesuppressive effects in PDAC (Zambirinis et al., 2015). Interestingly, it has recently been shown, using single-cell transcriptomics and functional assays, that there is an inflammatory CAF subtype in both human and mouse PDAC tumors (Elyada et al., 2019; Öhlund et al., 2017). In addition, a new population of CAFs termed "antigen-presenting" CAFs has been identified that expresses MHC class II and CD74 and may thus be able to present antigens to $CD4^+$ T cells, albeit in the absence of costimulation, and modulate the immune response in PDAC, although formal proof of this immunosuppressive mechanism of CAFs is still pending (Elyada et al., 2019). CAFs have also recently been shown to be able to sample, process, and cross-present antigens, killing $CD8^+$ T cells in an antigen-specific, antigen-dependent manner via PD-L2 and Fas ligand (Lakins et al., 2018).

Most of the innate CAF responses described above are mediated through the induction of an inflammatory and immunosuppressive gene expression profile. Besides these mechanisms, CAFs are the main producers of both ECM components and remodeling enzymes and can thus modulate immune cell trafficking by altering the biochemical and biophysical properties of the ECM also in response to innate stimuli (Chakravarthy et al., 2018; Eble and Niland, 2019; Kalluri, 2016). Additionally, CAFs undergo metabolic changes that involve the activation of aerobic glycolysis and production of metabolites, such as pyruvate, lactate, ketone bodies, and fatty acids, which in turn support cancer cell proliferation and the promotion of an immunosuppressive milieu (Singer et al., 2018; Wu et al., 2017). This property is commonly induced by stress factors produced by cancer cells and TGF-β leading to loss of caveolin-1 (CAV1), although innate immune signals could also play a role.

The above studies indicate that innate recognition mechanisms are present in CAFs, which respond by secreting mediators capable of shaping the tumor microenvironment, thus contributing to the recruitment of both innate and adaptive immune cells and the establishment of a proinflammatory and immunosuppressive milieu.

Heterogeneity of the innate tumor microenvironment

The expansion of single-cell methodologies, either at the transcriptomics level using single-cell RNA sequencing or using proteomics with mass cytometry, has enabled the in-depth characterization of immune infiltrates in disease, including cancer (Papalexi and Satija, 2018). Single-cell RNA sequencing has identified unprecedented heterogeneity in tumor cell types, referring both to cancer cells and the tumor microenvironment, including immune cells, CAFs, and endothelial cells (Elyada et al., 2019; Lambrechts et al., 2018; Li et al., 2017a; Puram et al., 2017; Tirosh et al., 2016). As mentioned above, CAFs were recently shown to be divided into myofibroblastic, inflammatory, and antigen-presenting populations in PDAC (Elyada et al., 2019). Accordingly, in breast cancer, two of four CAF subtypes identified by FACS analysis were described as myofibroblastic and showed immunoregulatory activity through different mechanisms (Costa et al., 2018). Studies in lung and renal cancer have revealed a vast heterogeneity in TAMs, with previously undescribed populations and distinct gene expression signatures, which is interestingly conserved between mice and humans (Chevrier et al., 2017; Zilionis et al., 2019). In addition, Cassetta et al. (2019) identified transcriptional diversity among TAMs, monocytes, and macrophages, which was further affected by the tumor location and stage. Similar experiments in gliomas and breast cancer have also shown variability in tumor cell composition between patients and correlation with immunosuppression, as well as TAM populations that simultaneously express M1 and M2 signatures, suggesting plasticity and the presence of different intermediate activation states (Azizi et al., 2018; Chung et al., 2017; Müller et al., 2017b; Wagner et al., 2019). In lung adenocarcinoma, single-cell analysis has revealed alterations in the immune landscape even in the early stages, with changes in myeloid cell subsets, including depletion of $CD141^+$ DCs, reduced and impaired NK cells, and enrichment of PPAR-γ^{hi} macrophages, which correspond to impaired antitumor T cell immunity (Lavin et al., 2017). Further analysis at the single-cell level is expected to lead to the identification of more specialized distinct stromal subpopulations and characterization of their origin, activation trajectories, and potential plasticity while aiding in the characterization of the molecular mechanisms underlying their functions, which is especially relevant for low-abundant populations, such as MDSCs (Valdes-Mora et al., 2018).

Therapeutic potential of targeting the innate system in cancer

The prognostic relevance of innate cells, along with their important functions in tumor initiation, progression, and especially immunosuppression, has led to the development of multiple therapeutic strategies. Approaches to manipulate the innate immune responses have been extensively reviewed recently (Cassetta and Pollard, 2018; Chiossone et al., 2018;

Mantovani et al., 2017; Shaul and Fridlender, 2019). Briefly, the most promising approaches (accompanied by representative references) include (i) the depletion of innate immune cells, especially TAMs and TANs/MDSCs (Qin et al., 2014; Ries et al., 2014); (ii) the inhibition of innate immune cell recruitment by targeting the chemoattractants responsible for immune cell infiltration in the tumors (Halama et al., 2016; Li et al., 2017b); (iii) the reprogramming of innate cells toward an antitumor phenotype (Panni et al., 2019; Ring et al., 2017); (iv) the targeting of effector molecules, usually secreted by innate immune cells or activated by innate immune pathways, such as IL-6, IDO, VEGF, neutrophil elastase, and cyclooxygenase-2 (COX2)/prostaglandin E2 (PGE2; Incio et al., 2018); and (v) therapeutic strategies aiming at manipulating NK cell antitumor functions (Hodgins et al., 2019). Many of these therapeutic approaches have shown efficacy in preclinical settings and/or clinical trials either alone or in combination with other anticancer drugs (DeNardo et al., 2011; Nawa et al., 2012; Salvagno et al., 2019; Wang et al., 2016a; Weizman et al., 2014). Of particular interest is the combination of checkpoint inhibition with TAM/TAN manipulation, which by reducing immunosuppression could increase efficacy of checkpoint immunotherapy (Highfill et al., 2014; Kim et al., 2014; Zhu et al., 2017).

CAFs have also been proposed as promising targets for cancer therapy using similar approaches, including cell ablation, targeting of the mechanisms that drive their activation, inhibition of secreted effector mediators, and their potential reprograming. Additional strategies for the manipulation of the ECM and the targeting of matrikines have also been proposed as therapeutics for cancer and for the improvement of drug delivery (Kobayashi et al., 2019; Monboisse et al., 2014; Öhlund et al., 2014). New findings pointing toward an innate role for CAFs, along with their immunomodulatory properties, suggest new potential anticancer therapeutic targets, while novel CAF-specific innate mechanisms and their relationship with corresponding functions in innate immune cells should be taken into account when predicting compensatory responses and potential combinatorial strategies.

Conclusions and future perspectives

Innate immune cells play an important and dual role in carcinogenesis, as they are found to both support initial rejection of tumors and promote tumor initiation, growth, and metastasis following immune evasion and depending on context. Their protumorigenic properties are mediated by signals from the growing tumor and the evolving tumor-educated stroma, which drive their activation, resulting in immunosuppression, increased proliferation, and angiogenesis. Besides immune cells, mesenchymal non-hematopoietic cells in the tumor microenvironment, specifically CAFs, are also able to respond to innate stimuli and affect cancer outcome. A better understanding of the cellular players and their identities, developmental trajectories, and potential plasticity, as well as the molecular mechanisms underlying innate functions in the tumor microenvironment, remains to be exploited and should be important in the design of new or improved immune-targeting therapies. Future studies should address the allocation of functions to specific cell populations within tumors and the identification of potential compensatory mechanisms between the plethora of cell states that mediate innate functions.

Acknowledgments

Figures were prepared using BioRender (https://biorender.com/).

This work was supported by a Stavros Niarchos Foundation grant to the Biomedical Sciences Research Center "Alexander Fleming" as part of the foundation's initiative to support the Greek research center ecosystem and the European Research Council (FP7 Advanced MCs-inTEST grant 340217 to G. Kollias).

Author contributions: V. Koliaraki, A. Henriques, A. Prados, and G. Kollias wrote the manuscript and prepared the figures. V. Koliaraki and G. Kollias designed and revised the manuscript.

Disclosures: The authors declare no competing interests exist.

Submitted: 16 September 2019
Revised: 9 December 2019
Accepted: 22 January 2020

References

Al-Khami, A.A., L. Zheng, L. Del Valle, F. Hossain, D. Wyczechowska, J. Zabaleta, M.D. Sanchez, M.J. Dean, P.C. Rodriguez, and A.C. Ochoa. 2017. Exogenous lipid uptake induces metabolic and functional reprogramming of tumor-associated myeloid-derived suppressor cells. *OncoImmunology*. 6:e1344804. https://doi.org/10.1080/2162402X.2017.1344804

Albrengues, J., M.A. Shields, D. Ng, C.G. Park, A. Ambrico, M.E. Poindexter, P. Upadhyay, D.L. Uyeminami, A. Pommier, V. Küttner, et al. 2018. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. *Science*. 361:eaao4227. https://doi.org/10.1126/science.aao4227

Arwert, E.N., A.S. Harney, D. Entenberg, Y. Wang, E. Sahai, J.W. Pollard, and J.S. Condeelis. 2018. A Unidirectional Transition from Migratory to Perivascular Macrophage Is Required for Tumor Cell Intravasation. *Cell Reports*. 23:1239–1248. https://doi.org/10.1016/j.celrep.2018.04.007

Aspord, C., M.T. Leccia, J. Charles, and J. Plumas. 2013. Plasmacytoid dendritic cells support melanoma progression by promoting Th2 and regulatory immunity through OX40L and ICOSL. *Cancer Immunol. Res.* 1:402–415. https://doi.org/10.1158/2326-6066.CIR-13-0114-T

Azizi, E., A.J. Carr, G. Plitas, A.E. Cornish, C. Konopacki, S. Prabhakaran, J. Nainys, K. Wu, V. Kiseliovas, M. Setty, et al. 2018. Single-Cell Map of Diverse Immune Phenotypes in the Breast Tumor Microenvironment. *Cell*. 174:1293–1308.e36. https://doi.org/10.1016/j.cell.2018.05.060

Bald, T., T. Quast, J. Landsberg, M. Rogava, N. Glodde, D. Lopez-Ramos, J. Kohlmeyer, S. Riesenberg, D. van den Boorn-Konijnenberg, C. Hömig-Hölzel, et al. 2014. Ultraviolet-radiation-induced inflammation promotes angiotropism and metastasis in melanoma. *Nature*. 507:109–113. https://doi.org/10.1038/nature13111

Batlle, E., and J. Massagué. 2019. Transforming Growth Factor-β Signaling in Immunity and Cancer. *Immunity*. 50:924–940. https://doi.org/10.1016/j.immuni.2019.03.024

Bausch, D., T. Pausch, T. Krauss, U.T. Hopt, C. Fernandez-del-Castillo, A.L. Warshaw, S.P. Thayer, and T. Keck. 2011. Neutrophil granulocyte derived MMP-9 is a VEGF independent functional component of the angiogenic switch in pancreatic ductal adenocarcinoma. *Angiogenesis*. 14:235–243. https://doi.org/10.1007/s10456-011-9207-3

Biffi, G., T.E. Oni, B. Spielman, Y. Hao, E. Elyada, Y. Park, J. Preall, and D.A. Tuveson. 2019. IL1-Induced JAK/STAT Signaling Is Antagonized by TGFβ to Shape CAF Heterogeneity in Pancreatic Ductal Adenocarcinoma. *Cancer Discov.* 9:282–301. https://doi.org/10.1158/2159-8290.CD-18-0710

Böttcher, J.P., and C. Reis E Sousa. 2018. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. *Trends Cancer*. 4:784–792. https://doi.org/10.1016/j.trecan.2018.09.001

Böttcher, J.P., E. Bonavita, P. Chakravarty, H. Blees, M. Cabeza-Cabrerizo, S. Sammicheli, N.C. Rogers, E. Sahai, S. Zelenay, and C. Reis e Sousa. 2018. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. *Cell.* 172:1022–1037.e14. https://doi.org/10.1016/j.cell.2018.01.004

Broz, M.L., M. Binnewies, B. Boldajipour, A.E. Nelson, J.L. Pollack, D.J. Erle, A. Barczak, M.D. Rosenblum, A. Daud, D.L. Barber, et al. 2014. Dissecting the Tumor Myeloid Compartment Reveals Rare Activating Antigen-Presenting Cells Critical for T Cell Immunity. *Cancer Cell.* 26:938. https://doi.org/10.1016/j.ccell.2014.11.010

Bruno, A., A. Pagani, L. Pulze, A. Albini, K. Dallaglio, D.M. Noonan, and L. Mortara. 2014. Orchestration of angiogenesis by immune cells. *Front. Oncol.* 4:131. https://doi.org/10.3389/fonc.2014.00131

Buck, M.D., R.T. Sowell, S.M. Kaech, and E.L. Pearce. 2017. Metabolic Instruction of Immunity. *Cell.* 169:570–586. https://doi.org/10.1016/j.cell.2017.04.004

Caldwell, R.W., P.C. Rodriguez, H.A. Toque, S.P. Narayanan, and R.B. Caldwell. 2018. Arginase: A Multifaceted Enzyme Important in Health and Disease. *Physiol. Rev.* 98:641–665. https://doi.org/10.1152/physrev.00037.2016

Calon, A., E. Lonardo, A. Berenguer-Llergo, E. Espinet, X. Hernando-Momblona, M. Iglesias, M. Sevillano, S. Palomo-Ponce, D.V. Tauriello, D. Byrom, et al. 2015. Stromal gene expression defines poor-prognosis subtypes in colorectal cancer. *Nat. Genet.* 47:320–329. https://doi.org/10.1038/ng.3225

Canli, Ö., A.M. Nicolas, J. Gupta, F. Finkelmeier, O. Goncharova, M. Pesic, T. Neumann, D. Horst, M. Löwer, U. Sahin, and F.R. Greten. 2017. Myeloid Cell-Derived Reactive Oxygen Species Induce Epithelial Mutagenesis. *Cancer Cell.* 32:869–883.e5. https://doi.org/10.1016/j.ccell.2017.11.004

Carrega, P., F. Loiacono, E. Di Carlo, A. Scaramuccia, M. Mora, R. Conte, R. Benelli, G.M. Spaggiari, C. Cantoni, S. Campana, et al. 2015. NCR(+)ILC3 concentrate in human lung cancer and associate with intratumoral lymphoid structures. *Nat. Commun.* 6:8280. https://doi.org/10.1038/ncomms9280

Cassetta, L., and J.W. Pollard. 2018. Targeting macrophages: therapeutic approaches in cancer. *Nat. Rev. Drug Discov.* 17:887–904. https://doi.org/10.1038/nrd.2018.169

Cassetta, L., S. Fragkogianni, A.H. Sims, A. Swierczak, L.M. Forrester, H. Zhang, D.Y.H. Soong, T. Cotechini, P. Anur, E.Y. Lin, et al. 2019. Human Tumor-Associated Macrophage and Monocyte Transcriptional Landscapes Reveal Cancer-Specific Reprogramming, Biomarkers, and Therapeutic Targets. *Cancer Cell.* 35:588–602.e10. https://doi.org/10.1016/j.ccell.2019.02.009

Cerwenka, A., and L.L. Lanier. 2016. Natural killer cell memory in infection, inflammation and cancer. *Nat. Rev. Immunol.* 16:112–123. https://doi.org/10.1038/nri.2015.9

Chakravarthy, A., L. Khan, N.P. Bensler, P. Bose, and D.D. De Carvalho. 2018. TGF-β-associated extracellular matrix genes link cancer-associated fibroblasts to immune evasion and immunotherapy failure. *Nat. Commun.* 9:4692. https://doi.org/10.1038/s41467-018-06654-8

Chen, D.S., and I. Mellman. 2017. Elements of cancer immunity and the cancer-immune set point. *Nature.* 541:321–330. https://doi.org/10.1038/nature21349

Chevrier, S., J.H. Levine, V.R.T. Zanotelli, K. Silina, D. Schulz, M. Bacac, C.H. Ries, L. Ailles, M.A.S. Jewett, H. Moch, et al. 2017. An Immune Atlas of Clear Cell Renal Cell Carcinoma. *Cell.* 169:736–749.e18. https://doi.org/10.1016/j.cell.2017.04.016

Chiossone, L., P.Y. Dumas, M. Vienne, and E. Vivier. 2018. Natural killer cells and other innate lymphoid cells in cancer. *Nat. Rev. Immunol.* 18:671–688. https://doi.org/10.1038/s41577-018-0061-z

Chung, W., H.H. Eum, H.O. Lee, K.M. Lee, H.B. Lee, K.T. Kim, H.S. Ryu, S. Kim, J.E. Lee, Y.H. Park, et al. 2017. Single-cell RNA-seq enables comprehensive tumour and immune cell profiling in primary breast cancer. *Nat. Commun.* 8:15081. https://doi.org/10.1038/ncomms15081

Coffelt, S.B., K. Kersten, C.W. Doornebal, J. Weiden, K. Vrijland, C.S. Hau, N.J.M. Verstegen, M. Ciampricotti, L.J.A.C. Hawinkels, J. Jonkers, and K.E. de Visser. 2015. IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. *Nature.* 522:345–348. https://doi.org/10.1038/nature14282

Cohen, N., O. Shani, Y. Raz, Y. Sharon, D. Hoffman, L. Abramovitz, and N. Erez. 2017. Fibroblasts drive an immunosuppressive and growth-promoting microenvironment in breast cancer via secretion of Chitinase 3-like 1. *Oncogene.* 36:4457–4468. https://doi.org/10.1038/onc.2017.65

Colegio, O.R., N.Q. Chu, A.L. Szabo, T. Chu, A.M. Rhebergen, V. Jairam, N. Cyrus, C.E. Brokowski, S.C. Eisenbarth, G.M. Phillips, et al. 2014. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature.* 513:559–563. https://doi.org/10.1038/nature13490

Conrad, C., J. Gregorio, Y.H. Wang, T. Ito, S. Meller, S. Hanabuchi, S. Anderson, N. Atkinson, P.T. Ramirez, Y.J. Liu, et al. 2012. Plasmacytoid dendritic cells promote immunosuppression in ovarian cancer via ICOS costimulation of Foxp3(+) T-regulatory cells. *Cancer Res.* 72:5240–5249. https://doi.org/10.1158/0008-5472.CAN-12-2271

Corrales, L., L.H. Glickman, S.M. McWhirter, D.B. Kanne, K.E. Sivick, G.E. Katibah, S.R. Woo, E. Lemmens, T. Banda, J.J. Leong, et al. 2015. Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity. *Cell Reports.* 11:1018–1030. https://doi.org/10.1016/j.celrep.2015.04.031

Corrales, L., S.M. McWhirter, T.W. Dubensky Jr., and T.F. Gajewski. 2016. The host STING pathway at the interface of cancer and immunity. *J. Clin. Invest.* 126:2404–2411. https://doi.org/10.1172/JCI86892

Costa, A., Y. Kieffer, A. Scholer-Dahirel, F. Pelon, B. Bourachot, M. Cardon, P. Sirven, I. Magagna, L. Fuhrmann, C. Bernard, et al. 2018. Fibroblast Heterogeneity and Immunosuppressive Environment in Human Breast Cancer. *Cancer Cell.* 33:463–479.e10. https://doi.org/10.1016/j.ccell.2018.01.011

Cubillos-Ruiz, J.R., P.C. Silberman, M.R. Rutkowski, S. Chopra, A. Perales-Puchalt, M. Song, S. Zhang, S.E. Bettigole, D. Gupta, K. Holcomb, et al. 2015. ER Stress Sensor XBP1 Controls Anti-tumor Immunity by Disrupting Dendritic Cell Homeostasis. *Cell.* 161:1527–1538. https://doi.org/10.1016/j.cell.2015.05.025

Cui, T.X., I. Kryczek, L. Zhao, E. Zhao, R. Kuick, M.H. Roh, L. Vatan, W. Szeliga, Y. Mao, D.G. Thomas, et al. 2013. Myeloid-derived suppressor cells enhance stemness of cancer cells by inducing microRNA101 and suppressing the corepressor CtBP2. *Immunity.* 39:611–621. https://doi.org/10.1016/j.immuni.2013.08.025

Dadi, S., S. Chhangawala, B.M. Whitlock, R.A. Franklin, C.T. Luo, S.A. Oh, A. Toure, Y. Pritykin, M. Huse, C.S. Leslie, and M.O. Li. 2016. Cancer Immunosurveillance by Tissue-Resident Innate Lymphoid Cells and Innate-like T Cells. *Cell.* 164:365–377. https://doi.org/10.1016/j.cell.2016.01.002

Demoulin, S., M. Herfs, P. Delvenne, and P. Hubert. 2013. Tumor microenvironment converts plasmacytoid dendritic cells into immunosuppressive/tolerogenic cells: insight into the molecular mechanisms. *J. Leukoc. Biol.* 93:343–352. https://doi.org/10.1189/jlb.0812397

DeNardo, D.G., J.B. Barreto, P. Andreu, L. Vasquez, D. Tawfik, N. Kolhatkar, and L.M. Coussens. 2009. CD4(+) T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. *Cancer Cell.* 16:91–102. https://doi.org/10.1016/j.ccr.2009.06.018

DeNardo, D.G., D.J. Brennan, E. Rexhepaj, B. Ruffell, S.L. Shiao, S.F. Madden, W.M. Gallagher, N. Wadhwani, S.D. Keil, S.A. Junaid, et al. 2011. Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discov.* 1:54–67. https://doi.org/10.1158/2159-8274.CD-10-0028

Deryugina, E.I., E. Zajac, A. Juncker-Jensen, T.A. Kupriyanova, L. Welter, and J.P. Quigley. 2014. Tissue-infiltrating neutrophils constitute the major in vivo source of angiogenesis-inducing MMP-9 in the tumor microenvironment. *Neoplasia.* 16:771–788. https://doi.org/10.1016/j.neo.2014.08.013

Diamond, M.S., M. Kinder, H. Matsushita, M. Mashayekhi, G.P. Dunn, J.M. Archambault, H. Lee, C.D. Arthur, J.M. White, U. Kalinke, et al. 2011. Type I interferon is selectively required by dendritic cells for immune rejection of tumors. *J. Exp. Med.* 208:1989–2003. https://doi.org/10.1084/jem.20101158

Dzutsev, A., J.H. Badger, E. Perez-Chanona, S. Roy, R. Salcedo, C.K. Smith, and G. Trinchieri. 2017. Microbes and Cancer. *Annu. Rev. Immunol.* 35:199–228. https://doi.org/10.1146/annurev-immunol-051116-052133

Eble, J.A., and S. Niland. 2019. The extracellular matrix in tumor progression and metastasis. *Clin. Exp. Metastasis.* 36:171–198. https://doi.org/10.1007/s10585-019-09966-1

Eiró, N., L. González, L.O. González, B. Fernandez-Garcia, A. Andicoechea, E. Barbón, J.L. García-Muñiz, and F.J. Vizoso. 2013. Toll-like receptor-4 expression by stromal fibroblasts is associated with poor prognosis in colorectal cancer. *J. Immunother.* 36:342–349. https://doi.org/10.1097/CJI.0b013e31829d85e6

Eiró, N., A. Altadill, L.M. Juárez, M. Rodríguez, L.O. González, S. Atienza, S. Bermúdez, B. Fernandez-Garcia, M.F. Fresno-Forcelledo, L. Rodrigo, and F.J. Vizoso. 2014. Toll-like receptors 3, 4 and 9 in hepatocellular carcinoma: Relationship with clinicopathological characteristics and prognosis. *Hepatol. Res.* 44:769–778. https://doi.org/10.1111/hepr.12180

Eisenring, M., J. vom Berg, G. Kristiansen, E. Saller, and B. Becher. 2010. IL-12 initiates tumor rejection via lymphoid tissue-inducer cells bearing the natural cytotoxicity receptor NKp46. *Nat. Immunol.* 11:1030–1038. https://doi.org/10.1038/ni.1947

Elliott, M.R., F.B. Chekeni, P.C. Trampont, E.R. Lazarowski, A. Kadl, S.F. Walk, D. Park, R.I. Woodson, M. Ostankovich, P. Sharma, et al. 2009. Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. *Nature.* 461:282–286. https://doi.org/10.1038/nature08296

Elyada, E., M. Bolisetty, P. Laise, W.F. Flynn, E.T. Courtois, R.A. Burkhart, J.A. Teinor, P. Belleau, G. Biffi, M.S. Lucito, et al. 2019. Cross-species single-cell analysis of pancreatic ductal adenocarcinoma reveals antigen-presenting cancer-associated fibroblasts. *Cancer Discov.* 9:1102–1123. https://doi.org/10.1158/2159-8290.CD-19-0094

Erez, N., M. Truitt, P. Olson, S.T. Arron, and D. Hanahan. 2010. Cancer-Associated Fibroblasts Are Activated in Incipient Neoplasia to Orchestrate Tumor-Promoting Inflammation in an NF-kappaB-Dependent Manner. *Cancer Cell.* 17:135–147. https://doi.org/10.1016/j.ccr.2009.12.041

Ershaid, N., Y. Sharon, H. Doron, Y. Raz, O. Shani, N. Cohen, L. Monteran, L. Leider-Trejo, A. Ben-Shmuel, M. Yassin, et al. 2019. NLRP3 inflammasome in fibroblasts links tissue damage with inflammation in breast cancer progression and metastasis. *Nat. Commun.* 10:4375. https://doi.org/10.1038/s41467-019-12370-8

Eruslanov, E.B., P.S. Bhojnagarwala, J.G. Quatromoni, T.L. Stephen, A. Ranganathan, C. Deshpande, T. Akimova, A. Vachani, L. Litzky, W.W. Hancock, et al. 2014. Tumor-associated neutrophils stimulate T cell responses in early-stage human lung cancer. *J. Clin. Invest.* 124:5466–5480. https://doi.org/10.1172/JCI77053

Faget, J., V. Sisirak, J.Y. Blay, C. Caux, N. Bendriss-Vermare, and C. Ménétrier-Caux. 2013. ICOS is associated with poor prognosis in breast cancer as it promotes the amplification of immunosuppressive CD4$^+$ T cells by plasmacytoid dendritic cells. *OncoImmunology.* 2:e23185. https://doi.org/10.4161/onci.23185

Finnberg, N., A.J. Klein-Szanto, and W.S. El-Deiry. 2008. TRAIL-R deficiency in mice promotes susceptibility to chronic inflammation and tumorigenesis. *J. Clin. Invest.* 118:111–123. https://doi.org/10.1172/JCI29900

Frevert, C.W., J. Felgenhauer, M. Wygrecka, M.V. Nastase, and L. Schaefer. 2018. Danger-Associated Molecular Patterns Derived From the Extracellular Matrix Provide Temporal Control of Innate Immunity. *J. Histochem. Cytochem.* 66:213–227. https://doi.org/10.1369/0022155417740880

Fridlender, Z.G., J. Sun, S. Kim, V. Kapoor, G. Cheng, L. Ling, G.S. Worthen, and S.M. Albelda. 2009. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. *Cancer Cell.* 16:183–194. https://doi.org/10.1016/j.ccr.2009.06.017

Fuertes, M.B., A.K. Kacha, J. Kline, S.-R. Woo, D.M. Kranz, K.M. Murphy, and T.F. Gajewski. 2011. Host type I IFN signals are required for antitumor CD8+ T cell responses through CD8{alpha}+ dendritic cells. *J. Exp. Med.* 208:2005–2016. https://doi.org/10.1084/jem.20101159

Gabrilovich, D.I. 2017. Myeloid-Derived Suppressor Cells. *Cancer Immunol. Res.* 5:3–8. https://doi.org/10.1158/2326-6066.CIR-16-0297

Gabrilovich, D.I., S. Ostrand-Rosenberg, and V. Bronte. 2012. Coordinated regulation of myeloid cells by tumours. *Nat. Rev. Immunol.* 12:253–268. https://doi.org/10.1038/nri3175

Gajewski, T.F., H. Schreiber, and Y.X. Fu. 2013. Innate and adaptive immune cells in the tumor microenvironment. *Nat. Immunol.* 14:1014–1022. https://doi.org/10.1038/ni.2703

Galluzzi, L., A. Buqué, O. Kepp, L. Zitvogel, and G. Kroemer. 2017. Immunogenic cell death in cancer and infectious disease. *Nat. Rev. Immunol.* 17:97–111. https://doi.org/10.1038/nri.2016.107

Gao, Y., F. Souza-Fonseca-Guimaraes, T. Bald, S.S. Ng, A. Young, S.F. Ngiow, J. Rautela, J. Straube, N. Waddell, S.J. Blake, et al. 2017. Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells. *Nat. Immunol.* 18:1004–1015. https://doi.org/10.1038/ni.3800

Garg, A.D., D.V. Krysko, T. Verfaillie, A. Kaczmarek, G.B. Ferreira, T. Marysael, N. Rubio, M. Firczuk, C. Mathieu, A.J. Roebroek, et al. 2012. A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death. *EMBO J.* 31:1062–1079. https://doi.org/10.1038/emboj.2011.497

Geiger, R., J.C. Rieckmann, T. Wolf, C. Basso, Y. Feng, T. Fuhrer, M. Kogadeeva, P. Picotti, F. Meissner, M. Mann, et al. 2016. L-Arginine Modulates T Cell Metabolism and Enhances Survival and Anti-tumor Activity. *Cell.* 167:829–842.e13. https://doi.org/10.1016/j.cell.2016.09.031

Glasner, A., A. Levi, J. Enk, B. Isaacson, S. Viukov, S. Orlanski, A. Scope, T. Neuman, C.D. Enk, J.H. Hanna, et al. 2018. NKp46 Receptor-Mediated Interferon-γ Production by Natural Killer Cells Increases Fibronectin 1 to Alter Tumor Architecture and Control Metastasis. *Immunity.* 48:396–398. https://doi.org/10.1016/j.immuni.2018.01.010

Gong, L., A.M. Cumpian, M.S. Caetano, C.E. Ochoa, M.M. De la Garza, D.J. Lapid, S.G. Mirabolfathinejad, B.F. Dickey, Q. Zhou, and S.J. Moghaddam. 2013. Promoting effect of neutrophils on lung tumorigenesis is mediated by CXCR2 and neutrophil elastase. *Mol. Cancer.* 12:154. https://doi.org/10.1186/1476-4598-12-154

Gonzalez-Junca, A., K.E. Driscoll, I. Pellicciotta, S. Du, C.H. Lo, R. Roy, R. Parry, I. Tenvooren, D.M. Marquez, M.H. Spitzer, and M.H. Barcellos-Hoff. 2019. Autocrine TGFβ Is a Survival Factor for Monocytes and Drives Immunosuppressive Lineage Commitment. *Cancer Immunol. Res.* 7:306–320. https://doi.org/10.1158/2326-6066.CIR-18-0310

González-Reyes, S., L. Marín, L. González, L.O. González, J.M. del Casar, M.L. Lamelas, J.M. González-Quintana, and F.J. Vizoso. 2010. Study of TLR3, TLR4 and TLR9 in breast carcinomas and their association with metastasis. *BMC Cancer.* 10:665. https://doi.org/10.1186/1471-2407-10-665

Granot, Z. 2019. Neutrophils as a Therapeutic Target in Cancer. *Front. Immunol.* 10:1710. https://doi.org/10.3389/fimmu.2019.01710

Granot, Z., E. Henke, E.A. Comen, T.A. King, L. Norton, and R. Benezra. 2011. Tumor entrained neutrophils inhibit seeding in the premetastatic lung. *Cancer Cell.* 20:300–314. https://doi.org/10.1016/j.ccr.2011.08.012

Greten, F.R., and S.I. Grivennikov. 2019. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity.* 51:27–41. https://doi.org/10.1016/j.immuni.2019.06.025

Hagemann, T., J. Wilson, F. Burke, H. Kulbe, N.F. Li, A. Plüddemann, K. Charles, S. Gordon, and F.R. Balkwill. 2006. Ovarian cancer cells polarize macrophages toward a tumor-associated phenotype. *J. Immunol.* 176:5023–5032. https://doi.org/10.4049/jimmunol.176.8.5023

Halama, N., I. Zoernig, A. Berthel, C. Kahlert, F. Klupp, M. Suarez-Carmona, T. Suetterlin, K. Brand, J. Krauss, F. Lasitschka, et al. 2016. Tumoral Immune Cell Exploitation in Colorectal Cancer Metastases Can Be Targeted Effectively by Anti-CCR5 Therapy in Cancer Patients. *Cancer Cell.* 29:587–601. https://doi.org/10.1016/j.ccell.2016.03.005

Hanahan, D., and L.M. Coussens. 2012. Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell.* 21:309–322. https://doi.org/10.1016/j.ccr.2012.02.022

Hanna, R.N., C. Cekic, D. Sag, R. Tacke, G.D. Thomas, H. Nowyhed, E. Herrley, N. Rasquinha, S. McArdle, R. Wu, et al. 2015. Patrolling monocytes control tumor metastasis to the lung. *Science.* 350:985–990. https://doi.org/10.1126/science.aac9407

Harney, A.S., E.N. Arwert, D. Entenberg, Y. Wang, P. Guo, B.Z. Qian, M.H. Oktay, J.W. Pollard, J.G. Jones, and J.S. Condeelis. 2015. Real-Time Imaging Reveals Local, Transient Vascular Permeability, and Tumor Cell Intravasation Stimulated by TIE2hi Macrophage-Derived VEGFA. *Cancer Discov.* 5:932–943. https://doi.org/10.1158/2159-8290.CD-15-0012

He, S.J., J. Cheng, X. Feng, Y. Yu, L. Tian, and Q. Huang. 2017. The dual role and therapeutic potential of high-mobility group box 1 in cancer. *Oncotarget.* 8:64534–64550.

Helmink, B.A., M.A.W. Khan, A. Hermann, V. Gopalakrishnan, and J.A. Wargo. 2019. The microbiome, cancer, and cancer therapy. *Nat. Med.* 25:377–388. https://doi.org/10.1038/s41591-019-0377-7

Herber, D.L., W. Cao, Y. Nefedova, S.V. Novitskiy, S. Nagaraj, V.A. Tyurin, A. Corzo, H.I. Cho, E. Celis, B. Lennox, et al. 2010. Lipid accumulation and dendritic cell dysfunction in cancer. *Nat. Med.* 16:880–886. https://doi.org/10.1038/nm.2172

Highfill, S.L., Y. Cui, A.J. Giles, J.P. Smith, H. Zhang, E. Morse, R.N. Kaplan, and C.L. Mackall. 2014. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. *Sci. Transl. Med.* 6:237ra67. https://doi.org/10.1126/scitranslmed.3007974

Hodgins, J.J., S.T. Khan, M.M. Park, R.C. Auer, and M. Ardolino. 2019. Killers 2.0: NK cell therapies at the forefront of cancer control. *J. Clin. Invest.* 129:3499–3510. https://doi.org/10.1172/JCI129338

Hope, C., S. Foulcer, J. Jagodinsky, S.X. Chen, J.L. Jensen, S. Patel, C. Leith, I. Maroulakou, N. Callander, S. Miyamoto, et al. 2016. Immunoregulatory roles of versican proteolysis in the myeloma microenvironment. *Blood.* 128:680–685. https://doi.org/10.1182/blood-2016-03-705780

Hope, C., P.B. Emmerich, A. Papadas, A. Pagenkopf, K.A. Matkowskyj, D.R. Van De Hey, S.N. Payne, L. Clipson, N.S. Callander, P. Hematti, et al. 2017. Versican-Derived Matrikines Regulate Batf3-Dendritic Cell Differentiation and Promote T Cell Infiltration in Colorectal Cancer. *J. Immunol.* 199:1933–1941. https://doi.org/10.4049/jimmunol.1700529

Houghton, A.M., D.M. Rzymkiewicz, H. Ji, A.D. Gregory, E.E. Egea, H.E. Metz, D.B. Stolz, S.R. Land, L.A. Marconcini, C.R. Kliment, et al. 2010.

Neutrophil elastase-mediated degradation of IRS-1 accelerates lung tumor growth. *Nat. Med.* 16:219–223. https://doi.org/10.1038/nm.2084

Huse, M. 2017. Mechanical forces in the immune system. *Nat. Rev. Immunol.* 17:679–690. https://doi.org/10.1038/nri.2017.74

Iannello, A., T.W. Thompson, M. Ardolino, A. Marcus, and D.H. Raulet. 2016. Immunosurveillance and immunotherapy of tumors by innate immune cells. *Curr. Opin. Immunol.* 38:52–58. https://doi.org/10.1016/j.coi.2015.11.001

Ijichi, H., A. Chytil, A.E. Gorska, M.E. Aakre, B. Bierie, M. Tada, D. Mohri, K. Miyabayashi, Y. Asaoka, S. Maeda, et al. 2011. Inhibiting Cxcr2 disrupts tumor-stromal interactions and improves survival in a mouse model of pancreatic ductal adenocarcinoma. *J. Clin. Invest.* 121:4106–4117. https://doi.org/10.1172/JCI42754

Incio, J., J.A. Ligibel, D.T. McManus, P. Suboj, K. Jung, K. Kawaguchi, M. Pinter, S. Babykutty, S.M. Chin, T.D. Vardam, et al. 2018. Obesity promotes resistance to anti-VEGF therapy in breast cancer by up-regulating IL-6 and potentially FGF-2. *Sci. Transl. Med.* 10:eaag0945. https://doi.org/10.1126/scitranslmed.aag0945

Jablonska, J., S. Leschner, K. Westphal, S. Lienenklaus, and S. Weiss. 2010. Neutrophils responsive to endogenous IFN-beta regulate tumor angiogenesis and growth in a mouse tumor model. *J. Clin. Invest.* 120: 1151–1164. https://doi.org/10.1172/JCI37223

Jamieson, T., M. Clarke, C.W. Steele, M.S. Samuel, J. Neumann, A. Jung, D. Huels, M.F. Olson, S. Das, R.J. Nibbs, and O.J. Sansom. 2012. Inhibition of CXCR2 profoundly suppresses inflammation-driven and spontaneous tumorigenesis. *J. Clin. Invest.* 122:3127–3144. https://doi.org/10.1172/JCI61067

Johnson, D.E., R.A. O'Keefe, and J.R. Grandis. 2018. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat. Rev. Clin. Oncol.* 15:234–248. https://doi.org/10.1038/nrclinonc.2018.8

Jovanovic, I.P., N.N. Pejnovic, G.D. Radosavljevic, J.M. Pantic, M.Z. Milovanovic, N.N. Arsenijevic, and M.L. Lukic. 2014. Interleukin-33/ST2 axis promotes breast cancer growth and metastases by facilitating intratumoral accumulation of immunosuppressive and innate lymphoid cells. *Int. J. Cancer.* 134:1669–1682. https://doi.org/10.1002/ijc.28481

Jung, M., B. Ören, J. Mora, C. Mertens, S. Dziumbla, R. Popp, A. Weigert, N. Grossmann, I. Fleming, and B. Brüne. 2016. Lipocalin 2 from macrophages stimulated by tumor cell-derived sphingosine 1-phosphate promotes lymphangiogenesis and tumor metastasis. *Sci. Signal.* 9: ra64. https://doi.org/10.1126/scisignal.aaf3241

Kai, F., A.P. Drain, and V.M. Weaver. 2019. The Extracellular Matrix Modulates the Metastatic Journey. *Dev. Cell.* 49:332–346. https://doi.org/10.1016/j.devcel.2019.03.026

Kalluri, R. 2016. The biology and function of fibroblasts in cancer. *Nat. Rev. Cancer.* 16:582–598. https://doi.org/10.1038/nrc.2016.73

Katoh, H., D. Wang, T. Daikoku, H. Sun, S.K. Dey, and R.N. Dubois. 2013. CXCR2-expressing myeloid-derived suppressor cells are essential to promote colitis-associated tumorigenesis. *Cancer Cell.* 24:631–644. https://doi.org/10.1016/j.ccr.2013.10.009

Kim, S., H. Takahashi, W.W. Lin, P. Descargues, S. Grivennikov, Y. Kim, J.L. Luo, and M. Karin. 2009. Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis. *Nature.* 457:102–106. https://doi.org/10.1038/nature07623

Kim, K., A.D. Skora, Z. Li, Q. Liu, A.J. Tam, R.L. Blosser, L.A. Diaz Jr., N. Papadopoulos, K.W. Kinzler, B. Vogelstein, and S. Zhou. 2014. Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. *Proc. Natl. Acad. Sci. USA.* 111: 11774–11779. https://doi.org/10.1073/pnas.1410626111

Kirchberger, S., D.J. Royston, O. Boulard, E. Thornton, F. Franchini, R.L. Szabady, O. Harrison, and F. Powrie. 2013. Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model. *J. Exp. Med.* 210:917–931. https://doi.org/10.1084/jem.20122308

Kitamura, T., D. Doughty-Shenton, L. Cassetta, S. Fragkogianni, D. Brownlie, Y. Kato, N. Carragher, and J.W. Pollard. 2018. Monocytes Differentiate to Immune Suppressive Precursors of Metastasis-Associated Macrophages in Mouse Models of Metastatic Breast Cancer. *Front. Immunol.* 8: 2004. https://doi.org/10.3389/fimmu.2017.02004

Kobayashi, H., A. Enomoto, S.L. Woods, A.D. Burt, M. Takahashi, and D.L. Worthley. 2019. Cancer-associated fibroblasts in gastrointestinal cancer. *Nat. Rev. Gastroenterol. Hepatol.* 16:282–295. https://doi.org/10.1038/s41575-019-0115-0

Koliaraki, V., N. Chalkidi, A. Henriques, C. Tzaferis, A. Polykratis, A. Waisman, W. Muller, D.J. Hackam, M. Pasparakis, and G. Kollias. 2019. Innate Sensing through Mesenchymal TLR4/MyD88 Signals Promotes Spontaneous Intestinal Tumorigenesis. *Cell Reports.* 26:536–545.e4. https://doi.org/10.1016/j.celrep.2018.12.072

Kuang, D.M., Q. Zhao, Y. Wu, C. Peng, J. Wang, Z. Xu, X.Y. Yin, and L. Zheng. 2011. Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. *J. Hepatol.* 54:948–955. https://doi.org/10.1016/j.jhep.2010.08.041

Lakins, M.A., E. Ghorani, H. Munir, C.P. Martins, and J.D. Shields. 2018. Cancer-associated fibroblasts induce antigen-specific deletion of CD8 + T Cells to protect tumour cells. *Nat. Commun.* 9:948. https://doi.org/10.1038/s41467-018-03347-0

Lakshmikanth, T., S. Burke, T.H. Ali, S. Kimpfler, F. Ursini, L. Ruggeri, M. Capanni, V. Umansky, A. Paschen, A. Sucker, et al. 2009. NCRs and DNAM-1 mediate NK cell recognition and lysis of human and mouse melanoma cell lines in vitro and in vivo. *J. Clin. Invest.* 119:1251–1263. https://doi.org/10.1172/JCI36022

Lambrechts, D., E. Wauters, B. Boeckx, S. Aibar, D. Nittner, O. Burton, A. Bassez, H. Decaluwé, A. Pircher, K. Van den Eynde, et al. 2018. Phenotype molding of stromal cells in the lung tumor microenvironment. *Nat. Med.* 24:1277–1289. https://doi.org/10.1038/s41591-018-0096-5

Lavin, Y., S. Kobayashi, A. Leader, E.D. Amir, N. Elefant, C. Bigenwald, R. Remark, R. Sweeney, C.D. Becker, J.H. Levine, et al. 2017. Innate Immune Landscape in Early Lung Adenocarcinoma by Paired Single-Cell Analyses. *Cell.* 169:750–765.e17. https://doi.org/10.1016/j.cell.2017.04.014

Lerman, I., M.L. Garcia-Hernandez, J. Rangel-Moreno, L. Chiriboga, C. Pan, K.L. Nastiuk, J.J. Krolewski, A. Sen, and S.R. Hammes. 2017. Infiltrating Myeloid Cells Exert Protumorigenic Actions via Neutrophil Elastase. *Mol. Cancer Res.* 15:1138–1152. https://doi.org/10.1158/1541-7786.MCR-17-0003

Li, H., E.T. Courtois, D. Sengupta, Y. Tan, K.H. Chen, J.J.L. Goh, S.L. Kong, C. Chua, L.K. Hon, W.S. Tan, et al. 2017a. Reference component analysis of single-cell transcriptomes elucidates cellular heterogeneity in human colorectal tumors. *Nat. Genet.* 49:708–718. https://doi.org/10.1038/ng.3818

Li, X., W. Yao, Y. Yuan, P. Chen, B. Li, J. Li, R. Chu, H. Song, D. Xie, X. Jiang, and H. Wang. 2017b. Targeting of tumour-infiltrating macrophages via CCL2/CCR2 signalling as a therapeutic strategy against hepatocellular carcinoma. *Gut.* 66:157–167. https://doi.org/10.1136/gutjnl-2015-310514

Liang, W., Q. Li, and N. Ferrara. 2018. Metastatic growth instructed by neutrophil-derived transferrin. *Proc. Natl. Acad. Sci. USA.* 115: 11060–11065. https://doi.org/10.1073/pnas.1811717115

Liu, K., G.D. Victora, T.A. Schwickert, P. Guermonprez, M.M. Meredith, K. Yao, F.F. Chu, G.J. Randolph, A.Y. Rudensky, and M. Nussenzweig. 2009. In vivo analysis of dendritic cell development and homeostasis. *Science.* 324:392–397.

Lu, H., K.R. Clauser, W.L. Tam, J. Fröse, X. Ye, E.N. Eaton, F. Reinhardt, V.S. Donnenberg, R. Bhargava, S.A. Carr, and R.A. Weinberg. 2014. A breast cancer stem cell niche supported by juxtacrine signalling from monocytes and macrophages. *Nat. Cell Biol.* 16:1105–1117. https://doi.org/10.1038/ncb3041

Lu, C., P.S. Redd, J.R. Lee, N. Savage, and K. Liu. 2016. The expression profiles and regulation of PD-L1 in tumor-induced myeloid-derived suppressor cells. *OncoImmunology.* 5:e1247135. https://doi.org/10.1080/2162402X.2016.1247135

Mantovani, A., F. Marchesi, A. Malesci, L. Laghi, and P. Allavena. 2017. Tumour-associated macrophages as treatment targets in oncology. *Nat. Rev. Clin. Oncol.* 14:399–416. https://doi.org/10.1038/nrclinonc.2016.217

Maolake, A., K. Izumi, K. Shigehara, A. Natsagdorj, H. Iwamoto, S. Kadomoto, Y. Takezawa, K. Machioka, K. Narimoto, M. Namiki, et al. 2017. Tumor-associated macrophages promote prostate cancer migration through activation of the CCL22-CCR4 axis. *Oncotarget.* 8:9739–9751. https://doi.org/10.18632/oncotarget.14185

Mariathasan, S., S.J. Turley, D. Nickles, A. Castiglioni, K. Yuen, Y. Wang, E.E. Kadel III, H. Koeppen, J.L. Astarita, R. Cubas, et al. 2018. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature.* 554:544–548. https://doi.org/10.1038/nature25501

Mazzieri, R., F. Pucci, D. Moi, E. Zonari, A. Ranghetti, A. Berti, L.S. Politi, B. Gentner, J.L. Brown, L. Naldini, and M. De Palma. 2011. Targeting the ANG2/TIE2 axis inhibits tumor growth and metastasis by impairing angiogenesis and disabling rebounds of proangiogenic myeloid cells. *Cancer Cell.* 19:512–526. https://doi.org/10.1016/j.ccr.2011.02.005

Mellman, I., G. Coukos, and G. Dranoff. 2011. Cancer immunotherapy comes of age. *Nature.* 480:480–489. https://doi.org/10.1038/nature10673

Mikucki, M.E., D.T. Fisher, J. Matsuzaki, J.J. Skitzki, N.B. Gaulin, J.B. Muhitch, A.W. Ku, J.G. Frelinger, K. Odunsi, T.F. Gajewski, et al. 2015. Non-redundant requirement for CXCR3 signalling during tumoricidal T-cell trafficking across tumour vascular checkpoints. *Nat. Commun.* 6: 7458. https://doi.org/10.1038/ncomms8458

Mishalian, I., R. Bayuh, E. Eruslanov, J. Michaeli, L. Levy, L. Zolotarov, S. Singhal, S.M. Albelda, Z. Granot, and Z.G. Fridlender. 2014. Neutrophils recruit regulatory T-cells into tumors via secretion of CCL17--a new mechanism of impaired antitumor immunity. *Int. J. Cancer.* 135: 1178–1186. https://doi.org/10.1002/ijc.28770

Molon, B., S. Ugel, F. Del Pozzo, C. Soldani, S. Zilio, D. Avella, A. De Palma, P. Mauri, A. Monegal, M. Rescigno, et al. 2011. Chemokine nitration prevents intratumoral infiltration of antigen-specific T cells. *J. Exp. Med.* 208:1949–1962. https://doi.org/10.1084/jem.20101956

Monboisse, J.C., J.B. Oudart, L. Ramont, S. Brassart-Pasco, and F.X. Maquart. 2014. Matrikines from basement membrane collagens: a new anti-cancer strategy. *Biochim. Biophys. Acta.* 1840:2589–2598. https://doi.org/10.1016/j.bbagen.2013.12.029

Monteran, L., and N. Erez. 2019. The Dark Side of Fibroblasts: Cancer-Associated Fibroblasts as Mediators of Immunosuppression in the Tumor Microenvironment. *Front. Immunol.* 10:1835. https://doi.org/10.3389/fimmu.2019.01835

Müller, L., P. Aigner, and D. Stoiber. 2017a. Type I Interferons and Natural Killer Cell Regulation in Cancer. *Front. Immunol.* 8:304. https://doi.org/10.3389/fimmu.2017.00304

Müller, S., G. Kohanbash, S.J. Liu, B. Alvarado, D. Carrera, A. Bhaduri, P.B. Watchmaker, G. Yagnik, E. Di Lullo, M. Malatesta, et al. 2017b. Single-cell profiling of human gliomas reveals macrophage ontogeny as a basis for regional differences in macrophage activation in the tumor microenvironment. *Genome Biol.* 18:234. https://doi.org/10.1186/s13059-017-1362-4

Munn, D.H., and A.L. Mellor. 2016. IDO in the Tumor Microenvironment: Inflammation, Counter-Regulation, and Tolerance. *Trends Immunol.* 37: 193–207. https://doi.org/10.1016/j.it.2016.01.002

Nawa, M., S. Osada, K. Morimitsu, K. Nonaka, M. Futamura, Y. Kawaguchi, and K. Yoshida. 2012. Growth effect of neutrophil elastase on breast cancer: favorable action of sivelestat and application to anti-HER2 therapy. *Anticancer Res.* 32:13–19.

Ni, Y.H., L. Ding, D.Y. Zhang, Y.Y. Hou, X. Huang, and Q. Hu. 2015. Distinct expression patterns of Toll-like receptor 7 in tumour cells and fibroblast-like cells in oral squamous cell carcinoma. *Histopathology.* 67: 730–739. https://doi.org/10.1111/his.12703

Noy, R., and J.W. Pollard. 2014. Tumor-associated macrophages: from mechanisms to therapy. *Immunity.* 41:49–61. https://doi.org/10.1016/j.immuni.2014.06.010

Obeid, M., A. Tesniere, F. Ghiringhelli, G.M. Fimia, L. Apetoh, J.L. Perfettini, M. Castedo, G. Mignot, T. Panaretakis, N. Casares, et al. 2007. Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat. Med.* 13:54–61. https://doi.org/10.1038/nm1523

Öhlund, D., E. Elyada, and D. Tuveson. 2014. Fibroblast heterogeneity in the cancer wound. *J. Exp. Med.* 211:1503–1523. https://doi.org/10.1084/jem.20140692

Öhlund, D., A. Handly-Santana, G. Biffi, E. Elyada, A.S. Almeida, M. Ponz-Sarvise, V. Corbo, T.E. Oni, S.A. Hearn, E.J. Lee, et al. 2017. Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. *J. Exp. Med.* 214:579–596. https://doi.org/10.1084/jem.20162024

Ouzounova, M., E. Lee, R. Piranlioglu, A. El Andaloussi, R. Kolhe, M.F. Demirci, D. Marasco, I. Asm, A. Chadli, K.A. Hassan, et al. 2017. Monocytic and granulocytic myeloid derived suppressor cells differentially regulate spatiotemporal tumour plasticity during metastatic cascade. *Nat. Commun.* 8:14979. https://doi.org/10.1038/ncomms14979

Pallotta, M.T., C. Orabona, C. Volpi, C. Vacca, M.L. Belladonna, R. Bianchi, G. Servillo, C. Brunacci, M. Calvitti, S. Bicciato, et al. 2011. Indoleamine 2,3-dioxygenase is a signaling protein in long-term tolerance by dendritic cells. *Nat. Immunol.* 12:870–878. https://doi.org/10.1038/ni.2077

Panni, R.Z., D.E. Sanford, B.A. Belt, J.B. Mitchem, L.A. Worley, B.D. Goetz, P. Mukherjee, A. Wang-Gillam, D.C. Link, D.G. Denardo, et al. 2014. Tumor-induced STAT3 activation in monocytic myeloid-derived suppressor cells enhances stemness and mesenchymal properties in human pancreatic cancer. *Cancer Immunol. Immunother.* 63:513–528. https://doi.org/10.1007/s00262-014-1527-x

Panni, R.Z., J.M. Herndon, C. Zuo, S. Hegde, G.D. Hogg, B.L. Knolhoff, M.A. Breden, X. Li, V.E. Krisnawan, S.Q. Khan, et al. 2019. Agonism of CD11b reprograms innate immunity to sensitize pancreatic cancer to immunotherapies. *Sci. Transl. Med.* 11:eaau9240. https://doi.org/10.1126/scitranslmed.aau9240

Papalexi, E., and R. Satija. 2018. Single-cell RNA sequencing to explore immune cell heterogeneity. *Nat. Rev. Immunol.* 18:35–45. https://doi.org/10.1038/nri.2017.76

Peranzoni, E., S. Zilio, I. Marigo, L. Dolcetti, P. Zanovello, S. Mandruzzato, and V. Bronte. 2010. Myeloid-derived suppressor cell heterogeneity and subset definition. *Curr. Opin. Immunol.* 22:238–244. https://doi.org/10.1016/j.coi.2010.01.021

Pickup, M., S. Novitskiy, and H.L. Moses. 2013. The roles of TGFβ in the tumour microenvironment. *Nat. Rev. Cancer.* 13:788–799. https://doi.org/10.1038/nrc3603

Puram, S.V., I. Tirosh, A.S. Parikh, A.P. Patel, K. Yizhak, S. Gillespie, C. Rodman, C.L. Luo, E.A. Mroz, K.S. Emerick, et al. 2017. Single-Cell Transcriptomic Analysis of Primary and Metastatic Tumor Ecosystems in Head and Neck Cancer. *Cell.* 171:1611–1624.e24. https://doi.org/10.1016/j.cell.2017.10.044

Pyonteck, S.M., L. Akkari, A.J. Schuhmacher, R.L. Bowman, L. Sevenich, D.F. Quail, O.C. Olson, M.L. Quick, J.T. Huse, V. Teijeiro, et al. 2013. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. *Nat. Med.* 19:1264–1272. https://doi.org/10.1038/nm.3337

Qian, B., and Y. Deng. J.H. Im, R.J. Muschel, Y. Zou, J. Li, R.A. Lang, and J.W. Pollard. 2009. A distinct macrophage population mediates metastatic breast cancer cell extravasation, establishment and growth. *PLoS One.* 4: e6562.

Qin, H., B. Lerman, I. Sakamaki, G. Wei, S.C. Cha, S.S. Rao, J. Qian, Y. Hailemichael, R. Nurieva, K.C. Dwyer, et al. 2014. Generation of a new therapeutic peptide that depletes myeloid-derived suppressor cells in tumor-bearing mice. *Nat. Med.* 20:676–681. https://doi.org/10.1038/nm.3560

Quail, D.F., O.C. Olson, P. Bhardwaj, L.A. Walsh, L. Akkari, M.L. Quick, I.C. Chen, N. Wendel, N. Ben-Chetrit, J. Walker, et al. 2017. Obesity alters the lung myeloid cell landscape to enhance breast cancer metastasis through IL5 and GM-CSF. *Nat. Cell Biol.* 19:974–987. https://doi.org/10.1038/ncb3578

Rakoff-Nahoum, S., and R. Medzhitov. 2007. Regulation of spontaneous intestinal tumorigenesis through the adaptor protein MyD88. *Science.* 317: 124–127. https://doi.org/10.1126/science.1140488

Rakoff-Nahoum, S., and R. Medzhitov. 2009. Toll-like receptors and cancer. *Nat. Rev. Cancer.* 9:57–63. https://doi.org/10.1038/nrc2541

Ries, C.H., M.A. Cannarile, S. Hoves, J. Benz, K. Wartha, V. Runza, F. Rey-Giraud, L.P. Pradel, F. Feuerhake, I. Klaman, et al. 2014. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. *Cancer Cell.* 25:846–859. https://doi.org/10.1016/j.ccr.2014.05.016

Ring, N.G., D. Herndler-Brandstetter, K. Weiskopf, L. Shan, J.P. Volkmer, B.M. George, M. Lietzenmayer, K.M. McKenna, T.J. Naik, A. McCarty, et al. 2017. Anti-SIRPα antibody immunotherapy enhances neutrophil and macrophage antitumor activity. *Proc. Natl. Acad. Sci. USA.* 114: E10578–E10585. https://doi.org/10.1073/pnas.1710877114

Roberts, E.W., M.L. Broz, M. Binnewies, M.B. Headley, A.E. Nelson, D.M. Wolf, T. Kaisho, D. Bogunovic, N. Bhardwaj, and M.F. Krummel. 2016. Critical Role for CD103(+)/CD141(+) Dendritic Cells Bearing CCR7 for Tumor Antigen Trafficking and Priming of T Cell Immunity in Melanoma. *Cancer Cell.* 30:324–336. https://doi.org/10.1016/j.ccell.2016.06.003

Rodriguez, P.C., D.G. Quiceno, and A.C. Ochoa. 2007. L-arginine availability regulates T-lymphocyte cell-cycle progression. *Blood.* 109:1568–1573. https://doi.org/10.1182/blood-2006-06-031856

Ruffell, B., D. Chang-Strachan, V. Chan, A. Rosenbusch, C.M. Ho, N. Pryer, D. Daniel, E.S. Hwang, H.S. Rugo, and L.M. Coussens. 2014. Macrophage IL-10 blocks CD8+ T cell-dependent responses to chemotherapy by suppressing IL-12 expression in intratumoral dendritic cells. *Cancer Cell.* 26:623–637. https://doi.org/10.1016/j.ccell.2014.09.006

Salmon, H., J. Idoyaga, A. Rahman, M. Leboeuf, R. Remark, S. Jordan, M. Casanova-Acebes, M. Khudoynazarova, J. Agudo, N. Tung, 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.* 44:924–938. https://doi.org/10.1016/j.immuni.2016.03.012

Salvagno, C., M. Ciampricotti, S. Tuit, C.S. Hau, A. van Weverwijk, S.B. Coffelt, K. Kersten, K. Vrijland, K. Kos, T. Ulas, et al. 2019. Therapeutic targeting of macrophages enhances chemotherapy efficacy by unleashing type I interferon response. *Nat. Cell Biol.* 21:511–521. https://doi.org/10.1038/s41556-019-0298-1

Scarlett, U.K., M.R. Rutkowski, A.M. Rauwerdink, J. Fields, X. Escovar-Fadul, J. Baird, J.R. Cubillos-Ruiz, A.C. Jacobs, J.L. Gonzalez, J. Weaver, et al. 2012. Ovarian cancer progression is controlled by phenotypic changes in dendritic cells. *J. Exp. Med.* 209:495–506. https://doi.org/10.1084/jem.20111413

Shalapour, S., and M. Karin. 2019. Pas de Deux: Control of Anti-tumor Immunity by Cancer-Associated Inflammation. *Immunity.* 51:15–26. https://doi.org/10.1016/j.immuni.2019.06.021

Sharon, Y., Y. Raz, N. Cohen, A. Ben-Shmuel, H. Schwartz, T. Geiger, and N. Erez. 2015. Tumor-derived osteopontin reprograms normal mammary fibroblasts to promote inflammation and tumor growth in breast cancer. *Cancer Res.* 75:963–973. https://doi.org/10.1158/0008-5472.CAN-14-1990

Shaul, M.E., and Z.G. Fridlender. 2019. Tumour-associated neutrophils in patients with cancer. *Nat. Rev. Clin. Oncol.* 16:601–620. https://doi.org/10.1038/s41571-019-0222-4

Shen, M., P. Hu, F. Donskov, G. Wang, Q. Liu, and J. Du. 2014. Tumor-associated neutrophils as a new prognostic factor in cancer: a systematic review and meta-analysis. *PLoS One.* 9:e98259. https://doi.org/10.1371/journal.pone.0098259

Sheyhidin, I., G. Nabi, A. Hasim, R.P. Zhang, J. Ainiwaer, H. Ma, and H. Wang. 2011. Overexpression of TLR3, TLR4, TLR7 and TLR9 in esophageal squamous cell carcinoma. *World J. Gastroenterol.* 17:3745–3751. https://doi.org/10.3748/wjg.v17.i32.3745

Shojaei, F., X. Wu, C. Zhong, L. Yu, X.H. Liang, J. Yao, D. Blanchard, C. Bais, F.V. Peale, N. van Bruggen, et al. 2007. Bv8 regulates myeloid-cell-dependent tumour angiogenesis. *Nature.* 450:825–831. https://doi.org/10.1038/nature06348

Shojaei, F., M. Singh, J.D. Thompson, and N. Ferrara. 2008. Role of Bv8 in neutrophil-dependent angiogenesis in a transgenic model of cancer progression. *Proc. Natl. Acad. Sci. USA.* 105:2640–2645. https://doi.org/10.1073/pnas.0712185105

Simoni, Y., M. Fehlings, H.N. Kløverpris, N. McGovern, S.L. Koo, C.Y. Loh, S. Lim, A. Kurioka, J.R. Fergusson, C.L. Tang, et al. 2017. Human Innate Lymphoid Cell Subsets Possess Tissue-Type Based Heterogeneity in Phenotype and Frequency. *Immunity.* 46:148–161. https://doi.org/10.1016/j.immuni.2016.11.005

Singer, K., W.C. Cheng, M. Kreutz, P.C. Ho, and P.J. Siska. 2018. Immunometabolism in cancer at a glance. *Dis. Model. Mech.* 11:dmm034272. https://doi.org/10.1242/dmm.034272

Sisirak, V., J. Faget, M. Gobert, N. Goutagny, N. Vey, I. Treilleux, S. Renaudineau, G. Poyet, S.I. Labidi-Galy, S. Goddard-Leon, 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.* 72:5188–5197. https://doi.org/10.1158/0008-5472.CAN-11-3468

Smyth, M.J., K.Y. Thia, S.E. Street, D. MacGregor, D.I. Godfrey, and J.A. Trapani. 2000. Perforin-mediated cytotoxicity is critical for surveillance of spontaneous lymphoma. *J. Exp. Med.* 192:755–760. https://doi.org/10.1084/jem.192.5.755

Soriani, A., A. Zingoni, C. Cerboni, M.L. Iannitto, M.R. Ricciardi, V. Di Gialleonardo, M. Cippitelli, C. Fionda, M.T. Petrucci, A. Guarini, et al. 2009. ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. *Blood.* 113:3503–3511. https://doi.org/10.1182/blood-2008-08-173914

Srivastava, K., J. Hu, C. Korn, S. Savant, M. Teichert, S.S. Kapel, M. Jugold, E. Besemfelder, M. Thomas, M. Pasparakis, and H.G. Augustin. 2014. Postsurgical adjuvant tumor therapy by combining anti-angiopoietin-2 and metronomic chemotherapy limits metastatic growth. *Cancer Cell.* 26:880–895. https://doi.org/10.1016/j.ccell.2014.11.005

Steele, C.W., S.A. Karim, J.D.G. Leach, P. Bailey, R. Upstill-Goddard, L. Rishi, M. Foth, S. Bryson, K. McDaid, Z. Wilson, et al. 2016. CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. *Cancer Cell.* 29:832–845. https://doi.org/10.1016/j.ccell.2016.04.014

Strauss, L., S. Sangaletti, F.M. Consonni, G. Szebeni, S. Morlacchi, M.G. Totaro, C. Porta, A. Anselmo, S. Tartari, A. Doni, et al. 2015. RORC1 Regulates Tumor-Promoting "Emergency" Granulo-Monocytopoiesis. *Cancer Cell.* 28:253–269. https://doi.org/10.1016/j.ccell.2015.07.006

Swierczak, A., and J.W. Pollard. 2019. Myeloid Cells in Metastasis. *Cold Spring Harb. Perspect. Med.*:a038026. https://doi.org/10.1101/cshperspect.a038026

Tauriello, D.V.F., S. Palomo-Ponce, D. Stork, A. Berenguer-Llergo, J. Badia-Ramentol, M. Iglesias, M. Sevillano, S. Ibiza, A. Cañellas, X. Hernando-Momblona, et al. 2018. TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis. *Nature.* 554:538–543. https://doi.org/10.1038/nature25492

Templeton, A.J., M.G. McNamara, B. Šeruga, F.E. Vera-Badillo, P. Aneja, A. Ocaña, R. Leibowitz-Amit, G. Sonpavde, J.J. Knox, B. Tran, et al. 2014. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J. Natl. Cancer Inst.* 106:dju124. https://doi.org/10.1093/jnci/dju124

Tesone, A.J., N. Svoronos, M.J. Allegrezza, and J.R. Conejo-Garcia. 2013. Pathological mobilization and activities of dendritic cells in tumor-bearing hosts: challenges and opportunities for immunotherapy of cancer. *Front. Immunol.* 4:435. https://doi.org/10.3389/fimmu.2013.00435

Tirosh, I., B. Izar, S.M. Prakadan, M.H. Wadsworth II, D. Treacy, J.J. Trombetta, A. Rotem, C. Rodman, C. Lian, G. Murphy, et al. 2016. Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. *Science.* 352:189–196. https://doi.org/10.1126/science.aad0501

Trabanelli, S., M.F. Chevalier, A. Martinez-Usatorre, A. Gomez-Cadena, B. Salomé, M. Lecciso, V. Salvestrini, G. Verdeil, J. Racle, C. Papayannidis, et al. 2017. Tumour-derived PGD2 and NKp30-B7H6 engagement drives an immunosuppressive ILC2-MDSC axis. *Nat. Commun.* 8:593. https://doi.org/10.1038/s41467-017-00678-2

Turley, S.J., V. Cremasco, and J.L. Astarita. 2015. Immunological hallmarks of stromal cells in the tumour microenvironment. *Nat. Rev. Immunol.* 15:669–682. https://doi.org/10.1038/nri3902

Valdes-Mora, F., K. Handler, A.M.K. Law, R. Salomon, S.R. Oakes, C.J. Ormandy, and D. Gallego-Ortega. 2018. Single-Cell Transcriptomics in Cancer Immunobiology: The Future of Precision Oncology. *Front. Immunol.* 9:2582. https://doi.org/10.3389/fimmu.2018.02582

Veglia, F., V.A. Tyurin, D. Mohammadyani, M. Blasi, E.K. Duperret, L. Donthireddy, A. Hashimoto, A. Kapralov, A. Amoscato, R. Angelini, et al. 2017. Lipid bodies containing oxidatively truncated lipids block antigen cross-presentation by dendritic cells in cancer. *Nat. Commun.* 8:2122. https://doi.org/10.1038/s41467-017-02186-9

Wagner, M., and S. Koyasu. 2019. Cancer Immunoediting by Innate Lymphoid Cells. *Trends Immunol.* 40:415–430. https://doi.org/10.1016/j.it.2019.03.004

Wagner, J., M.A. Rapsomaniki, S. Chevrier, T. Anzeneder, C. Langwieder, A. Dykgers, M. Rees, A. Ramaswamy, S. Muenst, S.D. Soysal, et al. 2019. A Single-Cell Atlas of the Tumor and Immune Ecosystem of Human Breast Cancer. *Cell.* 177:1330–1345.e18. https://doi.org/10.1016/j.cell.2019.03.005

Wang, L., R. Rubinstein, J.L. Lines, A. Wasiuk, C. Ahonen, Y. Guo, L.F. Lu, D. Gondek, Y. Wang, R.A. Fava, et al. 2011. VISTA, a novel mouse Ig superfamily ligand that negatively regulates T cell responses. *J. Exp. Med.* 208:577–592. https://doi.org/10.1084/jem.20100619

Wang, J., W. Hu, K. Wang, J. Yu, B. Luo, G. Luo, W. Wang, H. Wang, J. Li, and J. Wen. 2016a. Repertaxin, an inhibitor of the chemokine receptors CXCR1 and CXCR2, inhibits malignant behavior of human gastric cancer MKN45 cells in vitro and in vivo and enhances efficacy of 5-fluorouracil. *Int. J. Oncol.* 48:1341–1352. https://doi.org/10.3892/ijo.2016.3371

Wang, L., X. Heng, Y. Lu, Z. Cai, Q. Yi, and F. Che. 2016b. Could B7-H4 serve as a target to activate anti-cancer immunity? *Int. Immunopharmacol.* 38:97–103. https://doi.org/10.1016/j.intimp.2016.05.020

Wang, T.T., Y.L. Zhao, L.S. Peng, N. Chen, W. Chen, Y.P. Lv, F.Y. Mao, J.Y. Zhang, P. Cheng, Y.S. Teng, et al. 2017. Tumour-activated neutrophils in gastric cancer foster immune suppression and disease progression through GM-CSF-PD-L1 pathway. *Gut.* 66:1900–1911. https://doi.org/10.1136/gutjnl-2016-313075

Wculek, S.K., and I. Malanchi. 2015. Neutrophils support lung colonization of metastasis-initiating breast cancer cells. *Nature.* 528:413–417. https://doi.org/10.1038/nature16140

Weizman, N., Y. Krelin, A. Shabtay-Orbach, M. Amit, Y. Binenbaum, R.J. Wong, and Z. Gil. 2014. Macrophages mediate gemcitabine resistance of pancreatic adenocarcinoma by upregulating cytidine deaminase. *Oncogene.* 33:3812–3819. https://doi.org/10.1038/onc.2013.357

Wendel, M., I.E. Galani, E. Suri-Payer, and A. Cerwenka. 2008. Natural killer cell accumulation in tumors is dependent on IFN-gamma and CXCR3 ligands. *Cancer Res.* 68:8437–8445. https://doi.org/10.1158/0008-5472.CAN-08-1440

Woo, S.R., M.B. Fuertes, L. Corrales, S. Spranger, M.J. Furdyna, M.Y. Leung, R. Duggan, Y. Wang, G.N. Barber, K.A. Fitzgerald, et al. 2014. STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. *Immunity.* 41:830–842. https://doi.org/10.1016/j.immuni.2014.10.017

Woo, S.R., L. Corrales, and T.F. Gajewski. 2015. Innate immune recognition of cancer. *Annu. Rev. Immunol.* 33:445–474. https://doi.org/10.1146/annurev-immunol-032414-112043

Wu, C.F., L. Andzinski, N. Kasnitz, A. Kröger, F. Klawonn, S. Lienenklaus, S. Weiss, and J. Jablonska. 2015. The lack of type I interferon induces

neutrophil-mediated pre-metastatic niche formation in the mouse lung. *Int. J. Cancer.* 137:837–847. https://doi.org/10.1002/ijc.29444

Wu, D., L. Zhuo, and X. Wang. 2017. Metabolic reprogramming of carcinoma-associated fibroblasts and its impact on metabolic heterogeneity of tumors. *Semin. Cell Dev. Biol.* 64:125–131. https://doi.org/10.1016/j.semcdb.2016.11.003

Yang, L., J. Huang, X. Ren, A.E. Gorska, A. Chytil, M. Aakre, D.P. Carbone, L.M. Matrisian, A. Richmond, P.C. Lin, and H.L. Moses. 2008. Abrogation of TGF beta signaling in mammary carcinomas recruits Gr-1+CD11b+ myeloid cells that promote metastasis. *Cancer Cell.* 13: 23–35. https://doi.org/10.1016/j.ccr.2007.12.004

Zambirinis, C.P., E. Levie, S. Nguy, A. Avanzi, R. Barilla, Y. Xu, L. Seifert, D. Daley, S.H. Greco, M. Deutsch, et al. 2015. TLR9 ligation in pancreatic stellate cells promotes tumorigenesis. *J. Exp. Med.* 212:2077–2094. https://doi.org/10.1084/jem.20142162

Zhang, Q.W., L. Liu, C.Y. Gong, H.S. Shi, Y.H. Zeng, X.Z. Wang, Y.W. Zhao, and Y.Q. Wei. 2012. Prognostic significance of tumor-associated macrophages in solid tumor: a meta-analysis of the literature. *PLoS One.* 7:e50946. https://doi.org/10.1371/journal.pone.0050946

Zhang, S., X. Ma, C. Zhu, L. Liu, G. Wang, and X. Yuan. 2016. The Role of Myeloid-Derived Suppressor Cells in Patients with Solid Tumors: A Meta-Analysis. *PLoS One.* 11:e0164514. https://doi.org/10.1371/journal.pone.0164514

Zhu, Y., J.M. Herndon, D.K. Sojka, K.W. Kim, B.L. Knolhoff, C. Zuo, D.R. Cullinan, J. Luo, A.R. Bearden, K.J. Lavine, et al. 2017. Tissue-Resident Macrophages in Pancreatic Ductal Adenocarcinoma Originate from Embryonic Hematopoiesis and Promote Tumor Progression. *Immunity.* 47:597. https://doi.org/10.1016/j.immuni.2017.08.018

Zilionis, R., C. Engblom, C. Pfirschke, V. Savova, D. Zemmour, H.D. Saatcioglu, I. Krishnan, G. Maroni, C.V. Meyerovitz, C.M. Kerwin, et al. 2019. Single-Cell Transcriptomics of Human and Mouse Lung Cancers Reveals Conserved Myeloid Populations across Individuals and Species. *Immunity.* 50:1317–1334.e10. https://doi.org/10.1016/j.immuni.2019.03.009