Harnessing the antitumor potential of macrophages for cancer immunotherapy

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Abbreviations: ANG2, angiopoietin 2; CCl4, carbon tetrachloride; CSF1R, colony stimulating factor 1 receptor; ECM, extracellular matrix; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LDL, low density lipoprotein; LRP, LDL-receptor related protein; mAb, monoclonal antibody; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NOD, nucleotide-binding oligomerization domain; PDA, pancreatic ductal adenocarcinoma; SIRPα, signal regulatory protein α; TLR, toll-like receptor; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor

Macrophages constitute a dominant fraction of the population of immune cells that infiltrate developing tumors. Recruited by tumor-derived signals, tumor-infiltrating macrophages are key orchestrators of a microenvironment that supports tumor progression. However, the phenotype of macrophages is pliable and, if instructed properly, macrophages can mediate robust antitumor functions through their ability to eliminate malignant cells, inhibit angiogenesis, and deplete fibrosis. While much effort has focused on strategies to block the tumor-supporting activity of macrophages, emerging approaches designed to instruct macrophages with antitumor properties are demonstrating promise and may offer a novel strategy for cancer immunotherapy.

Introduction

Macrophages are key determinants of the biology of developing tumors. The impact of macrophages on tumor biology is largely instructed by a dynamic network of signals present within their surrounding microenvironment. These signals produce a heterogeneous population of macrophages which are commonly described based on their similarity to an M1 (classically activated) or M2 (alternatively activated) phenotype. M1 macrophages are characterized by an interleukin (IL)-12highIL-10low cytokine production profile and are activated by interferon (IFN)γ, toll-like receptor (TLR) ligands, nucleotide-binding oligomerization domain (NOD)-specific agonists, and pro-inflammatory cytokines such as tumor necrosis factor α (TNFα). Conversely, M2 macrophages are associated with a IL-12lowIL-10high cytokine production profile and are induced by stimulation with IL-4 and IL-13.1 M1 and M2 macrophages represent the extremes of a spectrum of macrophage phenotypes that can be observed within tumors.

Within most solid malignancies, macrophages are polarized by the tumor microenvironment toward an M2 phenotype.2 These macrophages, in turn, foster a microenvironment that supports many of the hallmarks of cancer that have been enumerated by Hanahan and Weinberg. Namely, macrophages can promote tumor angiogenesis,11,12 provide growth factors that sustain the proliferation and survival of malignant cells, facilitate invasion and metastasis, and protect developing tumors from the pressures imposed by adaptive immunosurveillance.3 In most solid malignancies, an increased density of tumor-infiltrating macrophages portends a poor prognosis.4 Further, macrophages are fundamental to chronic inflammatory processes that are often associated with malignancy.5 Thus, macrophages play a critical role in defining tumor biology.

The identification of macrophages as significant supporters of tumor progression has generated interest in the identification of strategies to block macrophage infiltration into tumor tissue, to suppress the tumor-promoting functions of macrophages, or to selectively deplete macrophages.6 However, macrophage biology is pliable such that under the appropriate conditions, macrophages can acquire potent antitumor properties. As such, shifting the phenotype of tumor-infiltrating macrophages toward an M1 phenotype has been shown to inhibit tumor progression in preclinical and clinical studies. To this end, macrophages can be polarized to eliminate tumor cells,7-10 to inhibit tumor-induced angiogenesis,11,12 and to deplete tumor-associated stromal fibrosis.13 These observations provide the basis for studies investigating strategies that exploit the antitumor potential of macrophages. Here, we review recent advances on the preclinical and clinical evaluation of therapeutic approaches designed to “educate” macrophages with tumor-suppressing properties and to exploit their tropism for malignant lesions.

Tumor Biology

It has long been recognized that microbial products (e.g., TLR ligands and NOD specific agonists) as well as pro-inflammatory
cytokines (e.g., IFNγ and TNFα) can induce macrophages with antitumor properties. Liposomal encapsulation has been explored as a means to specifically deliver these activating signals to macrophages in vivo. For example, systemic administration of liposomes containing NOD2 agonists (e.g., muramylpeptide) was found to provide alveolar macrophages with tumoricidal properties capable of eradicating established spontaneous pulmonary and lymph node metastases. In a Phase I clinical trial, the intravenous delivery of liposomes encapsulated with muramyl tripeptide phosphatidylethanolamine induced circulating monocytes with tumoricidal properties. In a randomized phase III study, this approach in combination with chemotherapy was found to improve the overall survival of patients with osteosarcoma. These clinical data demonstrate the potential benefit that can be achieved by selectively activating macrophages with antitumor properties in vivo.

Macrophages are actively recruited to neoplastic lesions by chemokines that are produced by both malignant and non-malignant cells within the tumor microenvironment. The phenotype of tumor-infiltrating macrophages depends on signals received within the blood stream (prior to infiltration), as well as on cues provided by the tumor microenvironment. To polarize tumor-infiltrating macrophages with antitumor properties, activation signals can be delivered either locally or systemically. For example, the intravesical administration of bacillus Calmette-Guérin (an attenuated strain of Mycobacterium bovis) for the treatment of bladder carcinoma can activate macrophages via TLR2 with pro-inflammatory and tumoricidal properties. In addition, the systemic delivery of an agonist monoclonal antibody (mAb) specific for CD40, a member of the TNF receptor superfamily that is expressed on macrophages as well as on many other hematopoietic and non-hematopoietic cells, has demonstrated potent macrophage-dependent antitumor activity in a clinically relevant mouse model of pancreatic ductal adenocarcinoma (PDA) and in patients with advanced PDA. In these studies, the administration of CD40-targeting mAbs was observed to induce a rapid systemic inflammatory response marked by high levels of IFNγ and TNFα, which may have sculpted tumor-infiltrating macrophages with tumoricidal properties.

Similarly, the systemic administration of Listeria monocytogenes, a gram-positive facultative intracellular bacterium, has been shown to exert antitumor activity in preclinical and clinical studies. This antitumor activity produced by the administration of Listeria may be due, at least in part, to its ability to activate macrophages with tumoricidal properties. Thus, tumor-infiltrating macrophages can be polarized with an antitumor phenotype.

Macrophages have been shown to eliminate malignant cells through the production of soluble factors (e.g., nitric oxide and TNFα) that can induce tumor cell apoptosis. Macrophages can also eliminate cancer tumor cells through phagocytosis, based on their recognition of “eat-me” molecules present on tumor cells. To improve the overall survival of patients with osteosarcoma. These clinical data demonstrate the potential benefit that can be achieved by selectively activating macrophages with antitumor properties in vivo.

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Pro-phagocytic signals encountered by macrophages are balanced by “don’t eat-me” signals, which allow cancer cells to evade engulfment by macrophages (Fig. 1). CD47 is an integrin-associated protein that is expressed on the surface of normal cells and interacts with signal regulatory protein α (SIRPα) on macrophages to inhibit phagocytosis. In essence, CD47 is a marker of “self” that is recognized by the innate immune system. For example, CD47-SIRPα interactions prevent macrophages from clearing healthy red blood cells. Similarly, CD47 is upregulated on circulating hematopoietic stem cells in response to mobilizing cytokines and inflammatory stimuli in order to allow these cells to avoid elimination by macrophages.

To evade recognition by macrophages, tumor cells also express increased amounts of CD47 on their surface. This was first observed in myeloid leukemia, a setting in which CD47...
is commonly overexpressed and correlates with increased pathogenicity.\(^{33,34}\) Similar findings have now been reported for many solid tumors.\(^7\) This suggests that the interaction between CD47 on malignant cells and SIRP\(\alpha\) on macrophages is a critical determinant of the outcome of innate cancer immunosurveillance. Blocking this interaction has been shown to restore macrophage-dependent Fc gamma receptor-mediated phagocytosis.\(^{30}\) In addition, CD47-SIRP\(\alpha\) can control calreticulin-LRP mediated phagocytosis.\(^{28,29}\) However, because CD47 allows for distinguishing self from non-self, strategies that interfere with CD47-SIRP\(\alpha\) interactions may be complicated by anemia as a result of the macrophage-dependent clearance of red blood cells, as demonstrated in preclinical studies. However, the limitations observed with CD47-blocking antibodies can be circumvented using SIRP\(\alpha\) variants engineered to exhibit high affinity for CD47. In xenograft tumor models, the systemic administration of such SIRP\(\alpha\) variants enhances the recognition and phagocytosis of cancer cells by macrophages, hence prolonging the overall survival of tumor-bearing mice when used in combination with monoclonal antibodies.\(^{10}\) These observations suggest that the innate immunosurveillance mediated by macrophages is regulated by a balance between “eat-me” and “don’t eat-me” signals present on the surface of tumor cells.

**Angiogenesis**

Macrophages are important orchestrators of angiogenesis within the tumor microenvironment. Their presence within human tumors correlates with microvessel density,\(^{35,36}\) and in preclinical models, macrophages are observed to infiltrate premalignant lesions just prior to an “angiogenic switch,” in which the necessary pro-angiogenic signals are established to drive the transition to malignancy.\(^{37}\) Moreover, the elimination of macrophages is associated with a reduction in vascular density.\(^{37}\) Thus, macrophages can be instructed by developing tumors to promote angiogenesis.

Hypoxia is a common feature of solid malignancies. Within the tumor microenvironment, tumor-associated macrophages respond to hypoxia by producing cytokines including IL-1\(\beta\), which can drive the infiltration of macrophages into neoplastic lesions in an IL-1R dependent manner. This is important for the subsequent recruitment of endothelial cells from neighboring tissues, which in turn can provide macrophages with pro-angiogenic properties.\(^{38}\) Endothelial cells generate an instructive niche that serves to differentiate and polarize macrophages. For example, TIE2\(^+\) monocytes, which express the angiopoietin (ANG) tyrosine kinase receptor TEK (best known as TIE2), are a subpopulation of peripheral blood monocytes that are recruited by tumors to promote angiogenesis.\(^{39}\) In response to ANG2 produced by activated endothelial cells, TIE2\(^+\) monocytes acquire a pro-angiogenic phenotype marked by a decreased capacity to produce IL-12 and TNF\(\alpha\).\(^{40,41}\) However, in the presence of anti-angiogenic therapeutics, which normalize the tumor vasculature, tumor-infiltrating macrophages can be reprogrammed toward an M1 phenotype.\(^{42}\) These findings suggest the importance of the cross-talk between endothelial cells and macrophages in defining both macrophage phenotype and angiogenesis within the tumor microenvironment.

Macrophages are important contributors to a balance of pro- and anti-angiogenic signals that define the extent of angiogenesis observed within tumors (Fig. 2). Tumor-associated macrophages responding to hypoxia can release matrix metalloproteinase 9 (MMP9), which mobilizes VEGF for the activation of endothelial cells. In contrast, macrophages responding to anti-angiogenic signals such as interferon-\(\gamma\) (IFN\(\gamma\)) and granulocyte macrophage colony-stimulating factor (GM-CSF) acquire an anti-angiogenic phenotype and produce IL-12 as well as a soluble variant of the VEGF receptor 1 (sVEGFR1), which blocks VEGF activity.

![Figure 2](image.png)

**Figure 2**. Macrophages can shape the balance of pro- and anti-angiogenic signals within the tumor microenvironment. Tumor-infiltrating macrophages responding to pro-angiogenic signals such as interleukin (IL)-1\(\beta\), IL-4, angiopoietin 2 (ANG2), and hypoxia acquire a pro-angiogenic phenotype and secrete vascular endothelial growth factor (VEGF), as well as matrix metalloproteinase 9 (MMP9), which mobilizes VEGF for the activation of endothelial cells. In contrast, macrophages responding to anti-angiogenic signals such as interferon-\(\gamma\) (IFN\(\gamma\)) and granulocyte macrophage colony-stimulating factor (GM-CSF) acquire an anti-angiogenic phenotype and produce IL-12 as well as a soluble variant of the VEGF receptor 1 (sVEGFR1), which blocks VEGF activity.
been demonstrated that TLR4 signaling in the absence of IFNγ activates the mammalian target of rapamycin (mTOR) signaling pathway in macrophages, leading to increased secretion of IL-10 and limited production of IL-12. When mTOR signaling is inhibited with rapamycin, the response of macrophages to TLR4 signaling is shifted toward an M1 phenotype with an increase in macrophage production of IL-12 and a decrease in the release of IL-10. In a xenograft model of hepatocarcinoma, rapamycin was found to inhibit tumor growth and angiogenesis in a macrophage-dependent manner. These findings suggest that disrupting key signaling pathways that define macrophage phenotype can shift the behavior of macrophages from pro- to anti-angiogenic.

The production of IL-12 by macrophages is an important regulator of tumor angiogenesis. The systemic or local administration of IL-12 to tumor-bearing mice can modulate the function of tumor capillaries leading to ischemic-hemorrhagic necrosis. However, IL-12 does not directly alter endothelial cell function but rather appears to activate lymphocytes to produce soluble factors that can arrest the growth of endothelial cells and inhibit angiogenesis. Guiducci et al. showed that combining CpG oligodeoxynucleotides (a TLR9 ligand) with an antibody specific for the IL-10 receptor shifted tumor-infiltrating macrophages from an M2 to M1 phenotype, resulting in increased production of IL-12 and a rapid debulking of large tumors that was associated with a diffuse hemorrhagic necrosis. These findings demonstrate that macrophages, when properly instructed, can mediate potent antitumor activity by targeting the tumor-associated vasculature.

**Figure 3.** The phenotype of tumor-infiltrating macrophages is a critical determinant of tumor-associated stromal fibrosis. Systemic inflammation induced with an agonist CD40-specific monoclonal antibody (mAb) shifts the phenotype of tumor-infiltrating macrophages from pro- to anti-fibrotic. ECM, extracellular matrix.

Tumor-Associated Fibrosis

Macrophages are important mediators of wound healing and repair. In wound healing studies, macrophages are observed to regulate angiogenesis as well as the deposition of collagen by myofibroblasts. During the early phases of wound healing, tissue-resident macrophages and infiltrating monocytes are polarized toward an M1 phenotype in response to injury or infection. However, after this initial inflammatory response, these macrophages shift toward an M2 phenotype and produce anti-inflammatory cytokines as part of the normal wound healing process. This transition in macrophage behavior alters the phenotype of neighboring fibroblasts and induces their differentiation into myofibroblasts, which are capable of producing extracellular matrix (ECM) proteins, such as collagen. The intercellular communications and the consequent matrix remodeling that are normally observed during wound healing are also seen in the tumor microenvironment. For this reason, tumors have often been referred to as “wounds that never heal.”

In fibrotic disorders, macrophages are recognized for their capacity to both promote and inhibit ECM accumulation. For example, in a carbon tetrachloride (CCl4)-induced liver injury model, macrophages are necessary for both the development as well as the spontaneous resolution of hepatic fibrosis. In these studies, the depletion of macrophages was found to prevent the generation of mature, cross-linked collagen in the liver. In contrast, the ability of macrophages to secrete MMP13 (best known as collagenase 3), a member of the MMP family of neutral endopeptidases, was determined to be necessary for the resolution of hepatic fibrosis induced by CCl4. In an effort to understand the mechanism driving the distinct functional outcomes of macrophage activation, Ramachandran et al. found that macrophages involved in resolving CCl4-induced hepatic fibrosis are recruited from the peripheral blood and display a gene signature profile that is distinct from that of macrophages promoting fibrosis. In this study, the macrophages that were responsible for fibrosis resolution showed a marked increase in the expression of several MMPs, including MMP13 as well as MMP2, 9 and 12. These restorative macrophages were also found to express elevated levels of genes involved in phagocytosis, which were necessary for accelerating fibrosis resolution. Consistent with the existence of pro- and anti-fibrotic macrophages, in vitro studies have revealed that the expression pattern of MMPs can differ markedly between M1 and M2 macrophages. Thus, macrophages can be programmed with either pro- or anti-fibrotic properties.

In cancer, macrophages can promote fibrosis by recruiting fibroblasts through the production of chemokines, and by producing growth factors such as transforming growth factor β1 (TGFβ1), which can stimulate the differentiation of fibroblasts into myofibroblasts and hence promote collagen deposition. Through the production of tissue inhibitors of metalloproteinases, macrophages can also block ECM degradation. These pro-fibrotic activities of tumor-associated macrophages support the production and persistence of the ECM that surrounds neoplastic lesions. In this regard, developing tumors often establish a microenvironment that is characterized as a dense desmoplastic stromal reaction marked by a robust infiltration of macrophages. This collagen-rich...
microenvironment can inhibit the diffusion of therapeutics.\textsuperscript{57-59} In preclinical models of PDA, disrupting this fibrotic reaction has been shown to improve the delivery of chemotherapy, resulting in enhanced efficacy.\textsuperscript{59-61} These findings illustrate the potential benefit from derailing the signaling network that supports tumor-associated fibrosis.

The ability of macrophages to inhibit fibrosis and deplete fibrosis seen in other diseases suggests the possibility that macrophages might be stimulated to resolve tumor-associated fibrosis. However, little is known about the role of macrophages in regulating cancer-associated fibrosis. In PDA, both macrophages and fibrosis are common features of the tumor microenvironment. This microenvironment, though, is not well reproduced in transplantable mouse models of PDA and therefore, could not be properly studied until recently, when a genetically engineered mouse model of PDA was developed. These mice spontaneously develop pancreatic neoplasms accompanied by a desmoplastic stromal reaction that is indistinguishable from that observed in PDA patients.\textsuperscript{62} In this preclinical model, macrophages responding to a single administration of an agonist CD40-specific mAb were observed to rapidly infiltrate the tumor microenvironment and facilitate the depletion of collagen, leading to tumor regression.\textsuperscript{7} While collagen depletion in this model was found to be focal and transient, the repeated administration of a fully human agonist CD40-targeting antibody in combination with gemcitabine-based chemotherapy to patients with advanced PDA induced clinical responses with each cycle of treatment.\textsuperscript{63} Consistent with a role for macrophages in mediating the antitumor activity of CD40-targeting antibodies, a biopsy of a regressing tumor lesion demonstrated an impressive macrophage infiltrate with an absence of viable tumor cells.\textsuperscript{7} As the tumor microenvironment in PDA is often described as fibrotic, these findings suggest the potential of macrophages induced with anti-stromal properties to impact tumor-associated fibrosis (Fig. 3). However, further studies are needed to understand the full capacity of macrophages to regulate fibrosis associated with cancer.

**Cancer Immunosurveillance**

Oncogenesis and tumor progression are contingent on the capacity of malignant cells to evade elimination by the immune system. In this regard, macrophages can be fundamental in establishing a microenvironment that is unfavorable to adaptive immunosurveillance. For example, macrophages responding to neoplastic lesions can express amino acid-metabolizing enzymes such as indoleamine 2,3-dioxygenase 1 (IDO1), nitric oxide synthase 2 (NOS2) and arginase, which generate metabolites that inhibit T-cell responses.\textsuperscript{64} Tumor-associated macrophages can also produce reactive oxygen species and reactive nitrogen species, which disrupt the proper binding of the T-cell receptor (TCR) to MHC-peptide complexes present on antigen-presenting and cancer cells. In addition, through the production of immunosuppressive soluble factors such as prostaglandin E\textsubscript{2} (PGE\textsubscript{2}), TGF\textbeta1 and...
IL-10, as well as through the expression of immune checkpoint molecules such as CD174 (best known as PD-L1) and galectin 9, macrophages can suppress T-cell activation and even induce T-cell exhaustion.\textsuperscript{2,65} Thus, macrophages represent a major obstacle to T cell-based immunotherapy.

Strategies to reverse the immunosuppressive behavior of macrophages may offer a novel approach for restoring productive antitumor T-cell immunity in cancer. For example, signaling through the colony stimulating factor 1 receptor (CSF1R) was recently shown to be critical for defining the phenotype of tumor-infiltrating macrophages as either pro- or antitumor. In a mouse model of glioma, CSF1R inhibition was found to induce a shift in the genetic signature and phenotype of tumor-infiltrating macrophages from pro- to antitumor, prolonging the survival of tumor-bearing mice.\textsuperscript{66} Blocking the CSF1R has also been shown to promote immunosurveillance by CD8\textsuperscript{+} T cells when combined with chemotherapy in a mouse model of breast carcinoma.\textsuperscript{67} These findings suggest that reprogramming macrophages in vivo may support the development of a productive antitumor T cell-mediated immune response.

With an improved understanding of the genetic signatures that define pro- vs. antitumor macrophages, novel strategies to reprogram macrophages with properties supportive of antitumor T-cell immunity are now being explored. One such approach involves the use of microRNAs, short non-coding RNAs that can inhibit the expression of a panel of target genes. miR-125b is a microRNA that is enriched in macrophages. The overexpression of miR-125b in macrophages was found to increase the expression of the IFN\textgamma{} receptor, allowing macrophages to respond to IFN\textgamma{} with increased levels of co-stimulatory molecules and hence with an improved ability to induce T-cell activation.\textsuperscript{68} miR-155 is another microRNA that is upregulated in macrophages responding to inflammatory stimuli.\textsuperscript{69} Using a bioinformatics approach, Martinez-Nunez et al. found that miR-155 downregulates the IL-13 receptor \alpha{}1 (IL-13R\alpha{}1), a component of the IL-4 receptor, hence inhibiting IL-4/IL-13 signaling.\textsuperscript{70} In a mouse model of breast cancer, the knockdown of miR-155 accelerated tumor growth, a process that was associated with the skewing of tumor-infiltrating macrophages toward a pro-tumor phenotype.\textsuperscript{71} Taken together, these findings suggest that augmenting the expression of distinct microRNAs to re-direct the biology of tumor-infiltrating macrophages toward an antitumor phenotype may support the development of antitumor T-cell immunity (Fig. 4).

While microRNAs can be critical in directing macrophages toward an antitumor phenotype, they can also be involved in polarizing macrophages with a pro-tumor phenotype. For example, macrophages responding to macrophage colony-stimulating factor express high levels of the miRNA let-7c, which inhibits the production of molecules associated with antitumor T-cell immunity, including IL-12, and enhances the production of arginase which can promote tumor growth by suppressing T cell immunosurveillance.\textsuperscript{64,72} An understanding of the complexity by which microRNAs regulate the biology of macrophages is beginning to emerge, and is revealing that multiple microRNAs can act to polarize macrophages with either pro- or antitumor properties.\textsuperscript{73,74} It is likely that a balance in the expression of various microRNAs that are regulated by microenvironmental factors is critical for defining the polarization status of macrophages.

MicroRNAs can also be involved in the differentiation of macrophages during tumor-induced myelopoiesis. In particular, miR-142–3p, which is generally downregulated in tumor-recruited myeloid cells, has recently been demonstrated to be an important regulator of T-cell immunity. Reduced levels of miR-142–3p have been found to support the differentiation of macrophages with immunosuppressive properties, whereas the constitutive expression of miR-142–3p in myeloid cells inhibits macrophage differentiation by skewing tumor-induced myelopoiesis toward the granulocyte lineage, resulting in improved T-cell activation.\textsuperscript{75} Intriguingly, Sonda et al. used bone marrow chimera studies in a mouse model of fibrosarcoma to show that constitutive expression of miR-142–3p in bone marrow cells can enhance the efficacy of adoptive therapy with tumor-specific T cells. These findings point to the potential of strategies designed to reprogram macrophages for enhancing T-cell immunotherapy.

Concluding Remarks

Macrophages are attractive targets for cancer immunotherapy because of their unique ability to regulate key elements of oncogenesis and tumor progression, including cancer cell viability and invasiveness, angiogenesis, and fibrosis. Because the activity of macrophages is dependent on microenvironmental signals, it is likely that many anticancer therapies that are designed to target malignant cells also impact the biology of macrophages. For example, chemotherapies and radiotherapies-induced death of tumor cells is known to induce the recruitment of macrophages to the tumor microenvironment.\textsuperscript{67,76} Similarly, targeted anticancer therapeutics that are currently being explored in the clinic, such as specific inhibitors of JAK/STAT, NOTCH, and PI3K/AKT1 signaling, may also exert off-target effects in normal cells such as macrophages. Thus, targeting these signaling pathways may have an important impact on macrophage activity, which may either enhance or hinder therapeutic responses. As a result, it will be critical to understand the role of conventional and experimental therapies in shaping macrophage behavior.

Macrophages are commonly recognized as obstacles to many forms of anticancer therapy. However, if instructed properly, macrophages may mediate robust antitumor effects. For example, macrophages can reduce tumor-associated fibrosis, which is a key barrier against the delivery of chemotherapy.\textsuperscript{7} Thus, providing macrophages with anti-fibrotic properties may hold promise for facilitating the delivery of chemotherapies to neoplastic lesions. Because macrophages can rapidly debulk tumors, they may also be useful in downsizing tumors that were initially considered borderline for surgical resection. In addition, blocking CD47-SIRP\alpha{} signaling may prime macrophages for enhancing antibody-based immunotherapies, as it facilitates the Fc receptor-mediated phagocytosis of antibody-coated cancer cells. Finally, shifting the phenotype of tumor-promoting macrophages may reverse many of the immunosuppressive mechanisms established within the tumor microenvironment and thus enhance the efficacy of T cell-based therapeutic approaches.
In summary, strategies to tame macrophages and instruct them with antitumor properties hold promise. Further studies are needed to improve our understanding of the intricate link between macrophage activity and tumor viability, angiogenesis and fibrosis. This knowledge is expected to facilitate the development of novel approaches to harness macrophages for debulking tumors as well as for enhancing the efficacy of conventional and experimental forms of cancer therapy.

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No potential conflicts of interest were disclosed.

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