Tumor-Associated Macrophages and Their Functional Transformation in the Hypoxic Tumor Microenvironment

Zicong He and Shuixing Zhang*

Department of Radiology, First Affiliated Hospital of Jinan University, Guangzhou, China

Tumor-associated macrophages (TAMs) are some of the most abundant immune cells within tumors and perform a broad repertoire of functions via diverse phenotypes. On the basis of their functional differences in tumor growth, TAMs are usually categorized into two subsets of M1 and M2. It is well established that the tumor microenvironment (TME) is characterized by hypoxia along with tumor progression. TAMs adopt an M1-like pro-inflammatory phenotype at the early phases of oncogenesis and mediate immune response that inhibits tumor growth. As tumors progress, anabatic hypoxia of the TME gradually induces the M2-like functional transformation of TAMs by means of direct effects, metabolic influence, lactic acidosis, angiogenesis, remodeled stroma, and then urges them to participate in immunosuppression, angiogenesis and other tumor-supporting procedure. Therefore, thorough comprehension of internal mechanism of this TAM functional transformation in the hypoxic TME is of the essence, and might provide some novel insights in hypoxic tumor immunotherapeutic strategies.

Keywords: tumor hypoxia, hypoxic tumor microenvironment, tumor-associated macrophages, macrophage polarization, macrophage functional transformation

INTRODUCTION

The tumor microenvironment (TME) is now recognized as a major contributor to cancer progression. Hypoxia, resulting from an imbalance between oxygen supply and consumption (1), is an intrinsic property of the TME. The rapid proliferation of cells in the tumor mass necessitates extensive vascularization to sustain an adequate oxygen supply; however, tumor vessels are usually immature, disorganized, and hyperpermeable (2), leading to intratumoral oxygen deprivation. Cancer cells adapt to the resultant hypoxic microenvironment mainly via the hypoxia-inducible factor (HIF) signaling pathway, which regulates the expression of genes that contribute to immune evasion and malignant progression (3, 4). However, such inhospitable conditions are not favorable for infiltrating immune cells and promote their immunosuppressive functions (5).

Macrophages, which originate from circulating bone marrow-derived monocytic precursors, are among the most abundant immune cells within tumors and can be polarized into different phenotypes, each of which is associated with different and diverse functions (6, 7). According to their functional differences, these tumor-associated macrophages (TAMs) can be broadly...
categorized into two subsets, namely, M1 (pro-inflammatory and anti-tumor) and M2 (anti-inflammatory and pro-tumor) (8). M1-like TAMs are activated by IFN-γ, lipopolysaccharide, IL-1β, TNF, and/or GM-CSF and can recognize and destroy malignant cells via phagocytosis and cytotoxicity, in addition to producing pro-inflammatory cytokines that stimulate anti-tumor immunity (9–11). In contrast, M2-like TAMs are induced by Th2 cytokines such as IL-4, IL-10, IL-13, and/or M-CSF, and can favor tumor growth and promote TME remodeling by producing growth factors, immunosuppressive factors, pro-angiogenic molecules, and proteases (9, 12–14). However, this simplified distinction of M1/M2 polarization cannot strictly delineate the phenotypic and functional boundaries of TAMs as these cells are both highly dynamic and heterogeneous within and across tumors (15). TAMs have an extraordinary degree of plasticity, which enables them to finely modulate themselves in response to microenvironmental changes and thereby orchestrate various aspects of the TME (7, 15). Hypoxia is a microenvironmental cue that induces the tumor-supporting transformation of TAMs, an effect that is associated with disease progression and resistance to therapy (16). This highlights the need to integrate TAM-related hypoxic stress into tumor immunotherapy.

Here, we review the known mechanistic effects of a hypoxic TME on TAM functional transformation (Figure 1) and provide insights into immunotherapeutic strategies targeting hypoxic macrophages.

**PRO-TUMOR TRANSFORMATION OF TAMs IN THE HYPOXIC TME**

**Hypoxia-Driven TAM Recruitment**

Due to unbalanced growth and a disorganized microvasculature, there is significant heterogeneity in oxygen content in a tumor mass. The hypoxic condition induces the production of a broad array of migratory stimulating factors, such as VEGF, CCL2, CCL5, CSF-1, EMAP-II, endothelin-2, SEMA3A, oncostatin M, and eotaxin, in tumor cells and the stroma within oxygen-deprived regions (17–24), resulting in macrophage recruitment and entrapment (25). When macrophages are recruited in hypoxic tumor areas, their polarization can be altered to an M2-like pro-tumor phenotype via the activity of the above-mentioned hypoxic tumor cell-derived cytokines (20, 24). A recent study revealed that neuropilin-1 (NRP-1) expression is significantly upregulated in hypoxic areas and induces pro-tumor phenotypes in recruited macrophages (26). Consequently, there is a greater abundance of M2-like TAMs at the invasive margin of tumors, where the hypoxic status is more severe, compared with that at the tumor center (27).

**Direct Effects of Hypoxia**

Hypoxia may also direct TAM polarization by affecting gene expression profiles. HIFs are key hypoxia-responsive transcription factors, the expression of which is upregulated in...
Macrophages (28). Two isoforms of HIF—HIF-1 and HIF-2—elicit overlapping but sometimes opposing effects on macrophage transcriptional profiles, which endow macrophages with plasticity and shape their versatile phenotypes (29, 30). HIF activity in macrophages is dependent on the type of cytokine stimulus (31), with HIF-1α reported to be activated by Th1 cytokines and HIF-2α by Th2 cytokines. Additionally, HIF-1α and HIF-2α, via the regulation of respectively the inducible nitric oxide (NO) synthase and the arginase 1 genes, coordinate the regulation of NO availability to guide macrophage functional phenotypes (31). HIF-1α and HIF-2α are known to participate in the inflammatory function of macrophages. Macrophages sense changes in oxygen concentrations and then mediate IFN-γ production via HIF-1α, thereby enhancing their phagocytic functions and antigen presentation abilities (32). Meanwhile, HIF-1α promotes the production of inflammatory molecules in a TLR4-dependent fashion, including granule proteases, antimicrobial peptides, TNF-α, IL-1, IL-4, IL-6, and IL-12, thereby regulating the killing capacity of macrophages (33, 34). In vitro findings indicated that the absence of HIF-1α in macrophages leads to reduced ARG1 expression and the consequent suppression of T-cell activation (35). Additionally, there is evidence to indicate that HIF-1α affects the inflammatory function of macrophages by regulating their glycolytic capacity under hypoxic conditions (36). The contributions of HIF-2α to pro-inflammatory cytokine expression in hypoxic macrophages have also been documented (37). However, unlike HIF-1α, the regulation of inflammation by HIF-2α involves neither the production of NO nor the expression of costimulatory molecules (33, 37). Furthermore, HIF-1α and HIF-2α were found to exert antagonistic functions in angiogenesis. The role of HIF-1α as a positive regulator of macrophage-derived VEGF is well established (38). The knockout of HIF-1α in TAMs can attenuate their pro-angiogenic responses (39). In contrast, HIF-2α upregulates the production of soluble VEGF receptor 1 (sVEGFR-1) by macrophages (40, 41). sVEGFR-1 is an alternatively spliced variant of the membrane-bound VEGFR-1 expressed on endothelial cells and acts as a negative regulator of VEGF in tumor angiogenesis (40). Furthermore, HIF-1α was recently reported to upregulate the expression of PD-L1 in tumor-infiltrating macrophages, thereby promoting the establishment of an immunosuppressive TME (42). A recent study found that macrophage-derived HIF-2α regulates the expression of the serine protease inhibitor Kunitz type 1 (SPINT1), which contributes to the tumor-suppressive functions of TAMs in breast cancer development (43). Nonetheless, the latest evidence from single-cell RNA sequencing revealed that macrophages within both tumors and normal tissues do not show defined M1 or M2 polarization signature gene expression (44). The multifarious functional phenotypes of TAMs in hypoxic tumors might not be entirely dependent on gene expression profiles, but may also be influenced by the local environment.

At the early stages of oncogenesis, infiltrating macrophages adopt an M1-like phenotype that promotes the destruction of tumor cells and the inhibition of angiogenesis, concomitant with the activation of the inflammatory response (45). However, chronic inflammation resulting from M1-like TAM activity can accelerate genomic instability in malignant cells and serve as a driver of tumor progression (46, 47). As tumors progress, increasing levels of hypoxia lead to reduced secretion of pro-inflammatory mediators (e.g., IL-1β, TNF-α, and CCL17) by M1-polarized macrophages and facilitates macrophage differentiation toward the M2-like phenotype (48). Although hypoxia does not directly alter the relative abundance of macrophage subsets, it induces a pro-tumor gene expression profile in the M2-like macrophage subset (49), including the expression of growth factors (e.g., FGF2, PDGF, and VEGF) (50, 51), angiogenic molecules (e.g., VEGF, FGFR2, CXCL8, and IL-8) (52), angiogenic modulators (e.g., COX2 and iNOS) (52), and matrix metalloproteinases (e.g., MMP2, MMP7, and MMP9) (53, 54). Furthermore, hypoxia can reportedly promote an increase in CCL20 expression in TAMs through the ERK/NF-κB pathway, leading to the accumulation of CCR6+ Foxp3+ T regulatory cells (Tregs) (55). Although TAMs show no differences in M1 and M2 polarization capacity, they tend to exert M2-like pro-tumor functions in the hypoxic TME (35).

**Metabolic Influence of Hypoxia**

Hypoxia is known as a metabolic cue that shapes macrophage functional phenotypes within the TME. M1-like macrophages usually employ glycolytic metabolism for their energy supply and have a robust capacity for reactive oxygen species (ROS) production; in contrast, M2-like macrophages generally utilize oxidative phosphorylation to fuel their longer-term tissue repair functions (56). The crucial role of HIF-1α in regulating the glycolytic capacity of macrophages, as well as their survival and function, in the hypoxic TME has been documented (36). The expression of the glycolytic enzyme phosphoglycerate kinase (PGK) and glucose transporter 1 (GLUT-1) is markedly reduced in macrophages with deletion of myeloid HIF-1α, as is the cellular ATP pool, which leads to an impaired inflammatory response (33, 36). There is some evidence to suggest that pro-inflammatory macrophages redirect pyruvate away from pyruvate dehydrogenase (PDH) in a NO-dependent and HIF-1α-independent manner, thereby promoting their metabolic reprogramming (57). Pyruvate dehydrogenase kinase, isozyme 1 (PDK1), induced by HIF-1α in mildly hypoxic condition, has been found to regulate glycolytic reprogramming of macrophages through the redirection of pyruvate flux into lactate, while leaving cytochrome c oxidase activity unaffected (58). Such active glycolysis promotes the redistribution of intracellular ATP, and plays an essential role in macrophage migratory capacity (58). However, long-term hypoxia in tumors still exerts a negative influence on TAM metabolism. Mammalian target of rapamycin (mTOR) functions as an integrative rheostat that couples cellular activation to nutrient sensing and metabolic status (59, 60). Hypoxia drives the upregulation of regulated in development and DNA damage response 1 (REDD1), an inhibitor of mTOR, which strongly hinders glycolysis in TAMs and reduces their metabolic competition with endothelial cells (61, 62). Such a
REDD1/mTOR metabolic shift in TAMs culminates in endothelial cell hyperactivation, with the consequent formation of an abnormal vascular network (61, 62). A significant reduction in microRNA-30c levels is also observed in hypoxic TAMs, which impairs both mTOR activity and glycolysis, thereby inhibiting TAM M1-like polarization (63). BMAL1 is known as a molecular clock that regulates mitochondrial metabolism under metabolic stress in macrophages. A recent study found that BMAL1/HIF-1α cross-talk regulates macrophage energy metabolism, while metabolic dysregulation due to aberrant HIF-1α activation in TAMs contributes to an immunosuppressive TME (64).

Iron is an essential nutrient for malignant cell growth and proliferation and also contributes to both tumor progression and metastasis (65). Most iron is recycled and released to tissues by macrophages via erythropagocytosis (66). M2-like TAMs exhibit a gene expression profile associated with iron efflux (increased ferroportin levels and reduced ferritin levels), whereas M1-like TAMs favor iron retention (67, 68). Tumor hypoxia supports such an iron-donor phenotype by upregulating solute carrier family 40, member 1 (SLC40A1) and lipocalin 2 (LCN2) expression in TAMs, resulting in increased iron availability in the TME and improved iron uptake by malignant cells (69–71).

**Lactic Acidosis After Hypoxia**

It is well established that the hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Meanwhile, such fermentative metabolism occurs in highly glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72). Hypoxic TME is characterized by acidosis. Hypoxic tumor cells mainly obtain energy via anaerobic glycolysis, leading to increased concentrations of lactic acid (72).

Moreover, the activation of acid-sensing ion channels (ASICs) was identified as an important mediator of the endocytic functions of macrophages as well as their maturation (82). Recently, lactic acid was shown to be capable of skewing the macrophage phenotype toward the M2-like state via monocarboxylate channel transporter (MCT)/HIF-1α signaling (83). Lactate-derived histone lysine lactylation, a recently identified epigenetic modification, was demonstrated to induce the expression of M2-associated genes, including ARG1 (84). Moreover, the most recent evidence has indicated that tumor-released succinate can activate succinate receptor 1 (SUCNR1) signaling to polarize TAMs toward tumor-supporting phenotypes through a SUCNR1-activated PI3K/HIF-1α axis (85).

**Angiogenesis in Hypoxic Areas**

Hypoxia in the TME induces angiogenesis to meet the oxygen and nutrient needs of proliferating tumor cells. TAMs accumulate and transition into proangiogenic phenotypes in perivascular areas (86), especially those that are poorly vascularized (87). TIE2, an angiopoietin (ANG) receptor expressed by TAMs, is upregulated under hypoxic conditions and, together with ANG-2, enhances the pro-tumor functions of TAMs (88, 89). Compared with TIE2+ TAMs, TIE2− TAMs within the same tumor express higher levels of pro-angiogenic genes, including MMP9, VEGFA, COX2, WNT5A, and PDGFβ (90, 91). ANG-2 expression is known to be increased in hypoxic regions and serves as a chemotactant for macrophages (89). ANG-2, secreted from tumor and vasculature cells, can enhance IL-10 and mannose receptor expression, while decreasing that of TNF-α and IL-12, thereby weakening TAM anti-tumor activity under hypoxic conditions (88, 89).

The secretion of macrophage-derived VEGF-A is also markedly increased by HIF-1α at hypoxic sites, thereby enhancing tumor angiogenesis (92, 93). In contrast, under the regulation of HIF-2α, hypoxic TAMs generate high levels of sVEGFR-1, which selectively neutralizes VEGF activity and diminishes tumor angiogenesis (40, 41). This antagonistic effect of HIF-1α and HIF-2α on angiogenesis was suggested to facilitate the redistribution of the vascular network in hypoxic tumors to meet their growth and metabolic requirements. Of note, HIF-2α is also highly expressed in normoxic macrophages, leading to enhanced transcription of proangiogenic genes (52).

Neoangiogenesis can provide oxygen and nutrients to hypoxic areas, but can also result in erythrocyte extravasation and hemolysis. The release of heme and iron from hemolytic red blood cells can help convert M2-like TAMs into proinflammatory M1-like TAMs that display tumor-killing activity (94).

**Hypoxia-Remodeled Stromal Components**

Stromal fibrosis is a commonly occurring event in the hypoxic TME. Cancer-associated fibroblasts (CAFs) are considered to be the dominant component of fibrotic stroma and can be activated by tumor hypoxia through several mechanisms (95). These activated fibroblasts have been found to overexpress numerous pro-inflammatory cytokines (e.g., CCL2, CCL5, IL-4, IL-6, IL-8,
GM-CSF, CXCL8, and CXCL14) that regulate TAM recruitment, differentiation, and activation (96). CAF-derived CXCL14 has been demonstrated to affect macrophage recruitment in tumors via NOS1-derived NO signaling. CAFs have also been reported to impair the maturation and differentiation of recruited macrophages, locking them in a suppressive state, through the induction of STAT3 phosphorylation (97, 98). In vitro observations have indicated that CAF might drive myeloid cells toward immunosuppressive differentiation via the production of IL-4, IL-6, and IL-8 (99).

Extensive lymphocyte subpopulations also constitute a major fraction of tumor stroma. These lymphocytes in the hypoxic TME engage the tumor-supporting activities of TAMs via a large array of cytokines. For instance, Th2 lymphocyte-derived IL-4 and IL-13 can enhance epidermal growth factor expression in TAMs, which promotes tumor cell metastasis, as well as the suppressive activity of TAMs, which blunts CD8+ T-cell responses to therapy (100, 101). Moreover, there is evidence showing that hypoxia can upregulate the expression of forkhead box P3 (FOXP3), a transcripational activator of Tregs, through an HIF-1α-dependent mechanism (102), while FOXP3+ Tregs drive TAMs toward an immunosuppressive phenotype (103, 104).

Extracellular matrix (ECM), which serves as a structural scaffold for immune cell infiltration in the TME, is extensively remodeled under tumor hypoxia (105). Hyaluronic acid (HA), a primary ECM component, is associated with macrophage trafficking and tumor neovascularization (106). Hypoxia enhances the endogenous production of HA by tumor cells (107). Pro-angiogenic M2-like TAMs preferentially traffic to HA-rich areas in the TME (106). Tumor-derived HA has also been identified to trigger the transient, early activation of monocytes, thereby promoting M2-like immunosuppressive phenotypes among TAMs (108). Another study reported that periostin and collagen, both fibrosis-associated ECM components, respectively facilitated TAM recruitment via integrin binding (109) and promoted their M2-like polarization (110).

Cellular debris resulting from cell death is prevalent within hypoxic regions of tumors. The release of high mobility group protein B1 (HMGB1) was demonstrated to drive IL-10 production in TAMs selectively through the receptor for advanced glycation end products (RAGE), leading to an IL-10-rich milieu within the tumor (111). The recognition of apoptotic cells is also thought to suppress macrophage activation potential (112). TAMs can recognize dying tumor cells through the MER tyrosine-protein kinase (MERTK) receptor and upregulate the expression of wound-healing factors such as TGF-β, IL-10, and ARG1 that suppress anti-tumor immunity (113).

Research attention has increasingly focused on exosomes released by hypoxic tumor cells. Hypoxia can stimulate tumor cells to produce higher numbers of exosomes (114). Exosomes in hypoxic tumor areas contain large amounts of chemokines and immunomodulatory proteins, including CSF-1, CCL2, FTH, FTL, and TGF-β, which promote the differentiation of infiltrating myeloid cells toward an M2-like macrophage lineage (115). Exosomal miR-301a-3p derived from hypoxic pancreatic cancer cells was reported to promote M2-like macrophage polarization by activating the PTEN/P13K/γ pathway (116). MiR-7a, another exosomal miRNA derived from hypoxic tumor cells, was shown to suppress several target genes of the insulin pathway, such as INS-1 and IGFR1, and thus trigger M2-like TAM polarization (117), similar to that seen for miR940 from exosomes derived from ovarian epithelial carcinoma cells (118). Recently, exosomal lncRNA BCRT1 was demonstrated to promote M2-like phenotype polarization and enhance macrophage-induced tumor progression (119). Additionally, miR-1246 in hypoxic glioma-derived exosomes was shown to mediate H-GDE-induced M2-like macrophage polarization by targeting TERF2IP via activating and inhibiting the STAT3 and NF-kB signaling pathways, respectively (120). Hypoxic stress was also demonstrated to suppress miR101 expression, which resulted in an increase in TAM-derived IL-1α and IL-6, which, in turn, promoted lung tumor cell growth (121).

Epithelial to mesenchymal transition (EMT) is also a common phenomenon associated with stroma remodeling in hypoxic tumors, helping to foster an immunosuppressive TME and facilitating tumor progression and metastasis (122, 123). A significant correlation has been confirmed to exist between EMT and TAM infiltration in hypoxic tumor tissues (124). Zinc finger E-box binding homeobox 1 (ZEB1) plays a critical role in the EMT program by restraining epithelial differentiation via the inhibition of members of the microRNA-200 family (125). The high expression of ZEB1 in hypoxic regions has a positive relationship with M2-like TAM abundance, i.e., it recruits M2-like TAMs by activating CCL8 transcription (126). Moreover, high HIF-1α expression under hypoxic conditions leads to increased secretion of the cytokine IL-1β by M2 TAMs, which, in turn, enhances EMT progression (127).

**IMMUNOTHERAPEUTIC STRATEGIES TARGETING HYPOXIC TAMs**

Substantial evidence supports that the hypoxia-induced immunosuppressive TME elicits a more aggressive tumor phenotype and promotes resistance to treatment (128). Several studies have reported that TAM polarization might counterproductively be skewed towards an M2-like pro-tumor phenotype after chemotherapy and radiotherapy, which contributes to tumor revascularization and relapse, while increasing levels of hypoxia after therapy could further enhance the tumor-supporting functions of TAMs (129, 130). This highlights the potential of TAMs as immunotherapeutic targets for hypoxic tumors. Macrophage-centered therapeutic strategies for treating hypoxic tumors should focus on improving the hypoxic status of the TME, inhibiting the tumor-promoting functions of M2-like TAMs, or reactivating the anti-tumor activity of M1-like TAMs.

**Improving the Hypoxic Status of the TME**

As described above, the hypoxic TME is responsible for the pro-tumor transformation of TAMs. Redressing hypoxia in the TME
may be beneficial for reversing the malignant TAM phenotypes and improving responses to immunotherapy. Oxygen delivery to hypoxic areas via nanomaterials may be an attractive means for achieving this. Various strategies for delivering O2 to the hypoxic TME have been reported, such as using certain oxygen carriers for transporting O2 to tumor sites or generating O2 from endogenous hydrogen peroxide in situ using nanocatalysts (131–134). Recently, a TAM-targeted biomimetic nano red blood cell system was designed for precise O2 delivery and M2-like TAM depletion within the TME (135). This nanosystem alleviated tumor hypoxia and markedly enhanced chemoimmunotherapeutic effects. Normalization of the tumor vasculature represents another possible approach for directly alleviating tumor hypoxia. Vessel normalization is now thought to be beneficial for tumor immune reprogramming (136). As is generally acknowledged, a wide spectrum of highly expressed pro-angiogenic proteins are responsible for the abnormal vasculature networks found in hypoxic tumors. Scheduling a proper dose of anti-angiogenic drugs that block these pro-angiogenic proteins or their receptors, such as VEGF/VEGFR, could help restore functional vessels, thus alleviating tumor hypoxia (137). Low-dose anti-VEGFR2 therapy has been reported to improve the perfusion of hypoxic tumors and promote an immunosuppressive-to-immunostimulatory TAM phenotype conversion (138). Counterintuitively, monotherapy with anti-angiogenic drugs at high doses might be counterproductive owing to the associated excessive pruning of tumor vessels (137). Modification of the HIF signaling pathway might be another way of alleviating hypoxia in the TME. Vorinostat (suberoylanilide hydroxamic acid, SAHA) is a histone deacytelase inhibitor that has been approved by the United States Food and Drug Administration (FDA) and has been demonstrated to negatively regulate the expression and function of HIF-1α through the inhibition of an eIF3G-dependent translation mechanism (139). Meanwhile, topoetan, a FDA-approved topoisomerase I inhibitor, has been shown to inhibit HIF-1α protein accumulation through a DNA damage-independent mechanism and thus delay both angiogenesis and tumor growth (140).

### Inhibiting the Tumor-Promoting Functions of M2-like TAMs

The depletion of M2-like TAMs represents a possible therapeutic approach for lessening pro-tumor functions. Liposomal clodronate treatment was shown to attenuate lung cancer progression through depleting TAMs (141). Additionally, trabectedin (ET-743), originally developed as an anti-proliferative agent for soft tissue sarcoma and relapsed ovarian cancer, was reported to activate the extrinsic apoptotic pathway via TRAIL receptors, followed by TAM depletion in tumors (142). However, anti-cancer therapy with trabectedin might elicit undesirable effects on monocyte/macrophage-mediated host defenses because of the indiscriminate depletion of macrophages (142). As a consequence, molecular-targeting has emerged as a promising direction for M2-like TAM depletion. Cieslewicz and colleagues constructed an M2-targeting fusion peptide to selectively exhaust M2-like TAMs, thereby reducing systemic damage (143).

Because macrophages are recruited and entrapped in hypoxic areas of tumors by tumor- and stroma-derived chemoattractants, preventing macrophage recruitment via pharmacological modulation may be another effective treatment method for inhibiting the pro-tumor functions of TAMs. Several antibodies selectively targeting chemoattractant receptors, including CCL2R, VEGFR2, and CSF-1R, have been shown to reduce macrophage infiltration and suppress tumor growth (144–146). Accordingly, interfering pharmacologically with other macrophage chemoattractants, such as CXCL12 and CCL5, as a means of inhibiting tumor growth merits further investigation (147, 148).

### Reactivating the Anti-Tumor Activity of M1-like TAMs

As mentioned above, M1-like TAMs possess anti-tumor activity, such as the ability to inhibit tumor angiogenesis as well as the activation of inflammatory responses. This suggests that repolarizing TAMs to an M1-like phenotype may be an additional supplement to the arsenal of anti-cancer therapies. One study found that zoledronic acid, a nitrogen-containing bisphosphonate used for the treatment of cancer patients with bone metastases, could convert the TAM phenotype from M2-like to M1-like by targeting the mevalonate pathway (149). Additionally, M2-like TAMs activated using CD40 agonists can reportedly reacquire antigen-presenting capabilities and become tumoricidal, resulting in the reestablishment of tumor immune surveillance and the short-term reduction of tumor volume (150). Meanwhile, it has been shown that Toll-like receptor 3 (TLR3) signaling can transform tumor-supporting TAMs into tumor suppressors by rapidly inducing the production of pro-inflammatory cytokines (151). Furthermore, there is evidence to support that the structural and functional restoration of the tumor vasculature might restore the anti-tumor functions of TAMs. It has been demonstrated that histidine-rich glycoprotein (HRG) can downregulate placental growth factor (PIGF) levels, leading to the restoration of tumor vessel functionality and TAM repolarization (152). CSF-1R inhibition has also been reported to alter TAM polarization in combination with glioma-secreted factors, including GM-CSF and IFN-γ (20). Anti-CD47-elicited antibody-dependent cellular phagocytosis might also lead to the skewing of TAM polarization toward an M1-like phenotype (153). Recent studies have found that PI3Kγ signaling represents a crucial mediator of the switching between immunostimulatory and immunosuppressive macrophage phenotypes. The selective inactivation of PI3Kγ can stimulate and prolong NF-κB activation while inhibiting that of C/EBPβ, thereby restoring the pro-inflammatory functions of macrophages (154). However, whether the anti-tumor functions of repolarized TAMs will be overridden by the hypoxic TME remains unclear and warrants further investigation.

### CONCLUDING REMARKS

Hypoxia is a critical modulator of tumor immunity. TAMs, an important component of tumor immunity, are recruited into the
hypoxic regions of tumors, where they acquire a pro-tumor phenotype following direct or indirect stimulation by the hypoxic TME. TAMs subsequently become important contributors to tumor immune escape, angiogenesis, matrix remodeling, metabolic changes, and treatment resistance through a vast array of pathophysiological processes. Although hypoxia-modified gene expression profiles endow TAMs with plasticity and versatility, the interaction with the hypoxic TME finally defines their specific functions. Consequently, a close characterization of the cross-talk between the TAM functional state and other components of the TME might offer significant insight into the development of new treatment regimens. Alleviating hypoxia in the TME and the phenotypic conversion of TAMs might be the focus of future efforts for cancer immunotherapy.

REFERENCES

1. Petrova V, Annicchiarico-Petruzzelli M, Melino G, Amelio I. The Hypoxic Tumour Microenvironment. Oncogenesis (2018) 7:10. doi: 10.1038/s41389-017-0011-9
2. Siemann DW. The Unique Characteristics of Tumor Vasculature and Preclinical Evidence for Its Selective Disruption by Tumor-Vascular Disrupting Agents. Cancer Treat Rev (2011) 37:63–74. doi: 10.1016/j.ctrv.2010.05.001
3. Schito L, Semenza GL. Hypoxia-Inducible Factors: Master Regulators of Tumor Microenvironment. Cells (2020) 9:992. doi: 10.3390/cells9040992
4. Gordon S, Martinez FO, Gordon S. The M1 and M2 Paradigm of Macrophage Activation: Mechanism and Functions. Immunity (2010) 32:593–604. doi: 10.1016/j.immuni.2010.05.007
5. Poh AR, Ernst M. Targeting Macrophages in Cancer: From Bench to Bedside. Front Oncol (2018) 8:49. doi: 10.3389/fonc.2018.00049
6. Rhee I. Diverse Macrophage Polarization in Tumor Microenvironment. Arch Pharm Res (2016) 39:1588–96. doi: 10.1007/s12272-016-0620-y
7. Martinez FO, Gordon S. The M1 and M2 Paradigm of Macrophage Activation: Time for Reassessment. F1000Prime Rep (2014) 6:13. doi: 10.12703/P6-13
8. Crusz SM, Balkwill FR. Inflammation and Cancer: Advances and New Agents. Nat Rev Clin Oncol (2015) 12:584–96. doi: 10.1038/nrclinonc.2015.105
9. Mantovani A, Allavena P. The Interaction of Anticancer Therapies With Tumor-Associated Macrophages. J Exp Med (2015) 212:435–45. doi: 10.1084/jem.201502925
10. Coussens LM, Zitvogel L, Palucka AK. Neutralizing Tumor-Promoting Chronic Inflammation: A Magic Bullet? Sci (N Y NY) (2013) 339:286–91. doi: 10.1126/science.1232227
11. Coussens LM, Zitvogel L, Palucka AK. Neutralizing Tumor-Promoting Chronic Inflammation: A Magic Bullet? Sci (N Y NY) (2013) 339:286–91. doi: 10.1126/science.1232227
12. Mantovani A, Marches I, Maleri A, Laghi L, Allavena P. Tumour-Associated Macrophages as Treatment Targets in Oncology. Nat Rev Oncol (2017) 14:399–416. doi: 10.1038/nrclinonc.2016.217
13. Cassetta L, Pollard JW. Targeting Macrophages: Therapeutic Approaches in Cancer. Nat Rev Drug Discov (2018) 17:887–904. doi: 10.1038/nrd.2018.169
14. Vitale I, Manic G, Coussens LM, Kroemer G, Galluzzi L. Macrophages and Metabolism in the Tumor Microenvironment. Cell Metab (2019) 30:36–50. doi: 10.1016/j.cmet.2019.06.001
15. Henze AT, Mazzone M. The Impact of Hypoxia on Tumor-Associated Macrophages. J Clin Invest (2016) 126:3672–9. doi: 10.1172/JCI84427

AUTHOR CONTRIBUTIONS

Conceptualization, ZH. Investigation and Resources, ZH. Writing - Original Draft Preparation, ZH. Writing - Review and Editing, SZ. Visualization, ZH. Graphics, ZH. Supervision, SZ. and Project Administration, SZ. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the National Natural Science Foundation of China (81871323, 81801665, 81901709) and the Natural Science Foundation of Guangdong Province (2018B030311024, 2019A1515010198).
in Primary Macrophages Experiencing Hypoxia. Blood (2009) 114:844–59. doi: 10.1182/blood-2008-12-195941

30. Tausendschon M, Rehli M, Dehne N, Schmidl C, Doring C, Hansmann ML, et al. Genome-Wide Identification of Hypoxia-Inducible Factor-1 and -2 Binding Sites in Hypoxic Human Macrophages Alternately Activated by IL-10. Biochem Biophys Acta (2015) 1849:10–22. doi: 10.1016/j.bbamcr.2014.10.006

31. Takeda N, O’Dea EL, Doedens A, Kim JW, Weidemann A, Stockmann C, et al. Differential Activation and Antagonistic Function of HIF-Alpha Isoforms in Macrophages Are Essential for NO Homeostasis. Genes Dev (2010) 24:491–501. doi: 10.1101/gad.1881410

32. Acosta-Iborra B, Elorza A, Olazabal IM, Martin-Cofreces NB, Martin-Puig S, Miro M, et al. Macrophage Oxygen Sensing Modulates Antibody Presentation and Phagocytic Functions Involving IFN-Gamma Production Through the HIF-1 Alpha Transcription Factor. J Immunol (2009) 182:3155–64. doi: 10.4049/jimmunol.0801710

33. Peyssonaux C, Datta V, Cramer T, Doedens A, Theodorakis EA, Gallo RL, et al. HIF-1alpha Expression Regulates the Bacterial Cidal Activity of Phagocytes. J Clin Invest (2005) 115:1806–15. doi: 10.1172/JCI23865

34. Peyssonaux C, Cejudo-Martin P, Doedens A, Zinkernagel AS, Johnson RS, Nizet V. Cutting Edge: Essential Role of Hypoxia Inducible Factor-1alpha in Development of Lipopolysaccharide-Induced Sepsis. J Immunol (2007) 178:7516–9. doi: 10.4049/jimmunol.178.12.7516

35. Doedens AL, Stockmann C, Rubinstein MP, Liao D, Zhang N, DeNardo DG, et al. Macrophage Expression of Hypoxia-Inducible Factor-1 Alpha Suppresses T-Cell Function and Promotes Tumor Progression. Cancer Res (2010) 70:7465–75. doi: 10.1158/0008-5472.CAN-10-1439

36. Cramer T, Yamaniushi Y, Clausen BE, Förster I, Pavlinski R, Mackman N, et al. HIF-1alpha is Essential for Myeloid Cell-Mediated Inflammation. Cell (2003) 112:645–57. doi: 10.1016/S0092-8674(03)00154-5

37. Imtiyaz HZ, Williams EP, Hickey MM, Patel SA, Durham AC, Yuan LJ, et al. Hypoxia-Inducible Factor 2alpha Regulates Macrophage Function in Mouse Models of Acute and Tumor Inflammation. J Clin Invest (2010) 120:2699–714. doi: 10.1172/JCI39506

38. Choi SM, Oh H, Park H. Microarray Analyses of Hypoxia-Regulated Genes in an Aryl Hydrocarbon Receptor Nuclear Translocator (Aran)-Dependent Manner. FEBs J (2008) 275:5618–34. doi: 10.1111/j.1742-4658.2008.06686.x

39. Werno C, Menrad H, Weigert A, Dehne N, Goerdt S, Schledzewski K, et al. Knockout of HIF-1alpha in Tumor-Associated Macrophages Enhances M2 Polarization and Attenuates Their Pro-Angiogenic Responses. Carcinogenesis (2010) 31:1863–72. doi: 10.1093/carcin/bgp088

40. Eubank TD, Roa JM, Liu H, O’Neill T, Marsh CB. Opposing Roles for HIF-1alpha and HIF-2alpha in the Regulation of Angiogenesis by Mononuclear Phagocytes. Blood (2001) 97:323–32. doi: 10.1182/blood.2001-0261792

41. Roa JM, Sumner LA, Evans R, Phillips GS, Marsh CB, Eubank TD. Hypoxia-Inducible Factor-2alpha Regulates GM-CSF-Derived Soluble Vascular Endothelial Growth Factor Receptor 1 Production From Macrophages and Inhibits Tumor Growth and Angiogenesis. J Immunol (2011) 187:1970–6. doi: 10.4049/jimmunol.1100841

42. Noman MZ, Desantis G, Janji B, Hasimmi M, Karray S, Hasmim M, et al. PD-L1 Is a Novel Direct Target of HIF-1alpha in Early-Stage Lung Adenocarcinomas Harboring EGFR Mutations. Oncogene (2011) 30:11783–93. doi: 10.1038/onc.2011.423

43. He D, Wang D, Lu P, Yang N, Xue Z, Zhu X, et al. Nitric Oxide Orchestrates Metabolic Rewiring in M1 Macrophages by Targeting Aconitase 2 and Pyruvate Dehydrogenase. Nat Commun (2020) 11:6998. doi: 10.1038/s41467-020-14433-7

44. Zhihua Y, Yulin T, Yibo W, Wei D, Yin C, Jiahao X, et al. Hypoxia Decreases Pyruvate Dehydrogenase Activity in Tumor-Associated Macrophages Enhances M2 Macrophage Metabolism Controls Tumor Blood Vessel Morphogenesis and Inhibits Malignant Behavior in Cancer Cells. OncoLett (2019) 18:5871–8. doi: 10.3892/onc.2019.10956

45. Ke X, Chen C, Song Y, Cai Q, Li J, Tang Y, et al. Hypoxia Modifies the Polarization of Macrophages and Their Inflammatory Microenvironment, and Inhibits Malignant Behavior in Cancer Cells. OncoLett (2019) 18:5871–8. doi: 10.3892/onc.2019.10956

46. Alexander RK, Liou YH, Knudsen NH, Starost KA, Xu C, Hyde AL, et al. Benmall Integrates Mitochondrial Metabolism and Macrophage Activation. Elife (2020) 9:e54090. doi: 10.7554/elife.54090

47. Torti SV, Torti FM. Iron and Cancer: More to be Mined. Nat Rev Cancer (2013) 13:342–55. doi: 10.1038/nrc3495
66. Beaumont C, Delaby C. Recycling Iron in Normal and Pathological States. *Semin Hematol* (2009) 46:328–38. doi: 10.1053/j.seminhematol.2009.06.004
67. Recalcati S, Locati M, Marini A, Santambrogio P, Zaninotto F, De Pizzol M, et al. Differential Regulation of Iron Homeostasis During Human Macrophage Polarization. *Eur J Immunol* (2010) 40:824–35. doi: 10.1002/eji.200939889
68. Corna G, Campana L, Pignatti E, Castiglioni A, Tagliafico E, Bosurgi L, et al. Polarization Dictates Iron Handling by Inflammatory and Alternatively Activated Macrophages. *Haematologica* (2010) 95:1814–22. doi: 10.3324/haematol.2010.023879
69. Mertens C, Akam EA, Rehwald C, Brune B, Tomat E, Jung M. Intracellular Iron Chelation Modulates the Macrophage Iron Phenotype With Consequences on Tumor Progression. *PloS One* (2016) 11:e0166164. doi: 10.1371/journal.pone.0166164
70. Oren B, Urosevic J, Mertens C, Mora J, Guiu M, Gomis RR, et al. Differential Regulation of Iron Homeostasis During Human Macrophage Polarization. *Eur J Immunol* (2010) 40:824–35. doi: 10.1002/eji.200939889
71. Pillai SR, Damaghi M, Marunaka Y, Spugnini EP, Fais S, Gillies RJ. Causes, Consequences, and Therapy of Tumors Acidosis. *Cancer Metastasis Rev* (2016) 35:205–22. doi: 10.1007/s10555-015-09792-7
72. Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, et al. Functional Polarization of Tumor-Associated Macrophages by Tumor-Derived Lactic Acid. *Nature* (2014) 513:559–63. doi: 10.1038/nature13490
73. Zhao Y, Wang DG, Xu T, Liu P, Cao WW, Wang YH, et al. Bladder Cancer Cells Re-Educate TAMs Through Lactate Shuttling in the Microfluidic Cancer Microenvironment. *Oncoimmunology* (2018) 7:e1408751. doi: 10.1080/2162402X.2017.1408751
74. Pillai L, Adams C, Beuvillain C, Preisser L, Blanchard S, Pignon P, et al. Lactic Acidosis Together With GM-CSF and M-CSF Induces Human Macrophages Toward an Inflammatory Proinflammatory Phenotype. *Cancer Immunol Res* (2020) 8:838–93. doi: 10.1158/2326-6066.CIR-18-0749
75. Shan T, Chen S, Chen X, Wu T, Yang Y, Li S, et al. M2-TAM Subsets Altered by Lactic Acid Promote T-cell Apoptosis Through the PD-L1–PD-1 Pathway. *Oncol Rep* (2020) 44:1885–94. doi: 10.3829/ior.2020.7767
76. Bohn T, Rapp S, Luther N, Klein M, Bruehl TJ, Kojima N, et al. Tumor Immunoenvasation via Acidosis-Dependent Induction of Regulatory Tumor-Associated Macrophages. *Nat Immunol* (2018) 19:1319–29. doi: 10.1038/s41590-018-0226-8
77. El-Kenawi A, Gatenbe C, Robertson-Tessi M, Bravo R, Dhillon J, Balagurunathan Y, et al. Acidification Promotes Tumor Progression by Altering Macrophage Phenotype in Prostate Cancer. *Br J Cancer* (2019) 121:556–66. doi: 10.1038/s41416-019-0542-2
78. Liu N, Luo J, Kuang D, Xu S, Duan X, Yia Y, et al. Lactate Inhibits ATP6V0d2 Expression in Tumor-Associated Macrophages to Promote HIF-2alpha-Mediated Tumor Progression. *J Clin Invest* (2019) 129:631–46. doi: 10.1172/JCI132027
79. Zhao Y, Zhao B, Wang X, Guan G, Xin Y, Sun YD, et al. Macrophage Transcription Modulation Induced by Hypoxia and Lactate. *Exp Ther Med* (2019) 18:4811–9. doi: 10.3892/etm.2019.9164
80. Chen P, Zuo H, Xiong H, Kolar MJ, Chu Q, Saghatelian A, et al. Gpr132 Sensing of Lactate Mediates Tumor-Macrophage Interplay to Promote Breast Cancer Metastasis. *Proc Natl Acad Sci USA* (2017) 114:580–5. doi: 10.1073/pnas.1614035114
81. Ni L, Fang P, Hu ZL, Zhou HY, Chen JG, Wang F, et al. Identification and Function of Acid-Sensing Ion Channels in RAW 264.7 Macrophage Cells. *Curr Med Sci* (2018) 38:436–42. doi: 10.1007/s11596-018-1897-y
82. Zhang L, Li S. Lactic Acid Promotes Macrophage Polarization Through MCT-HIF-1alpha Signaling in Gastric Cancer. *Exp Cell Res* (2020) 388:111846. doi: 10.1016/j.yexcr.2020.111846
83. Zhang D, Yang Z, Huang H, Zhou G, Cui C, Weng Y, et al. Metabolic Regulation of Gene Expression by Histone Lysylation. *Nature* (2019) 574:575–80. doi: 10.1038/s41586-019-1678-1
84. Wu JY, Huang TW, Hsieh YT, Wang YF, Yen CC, Lee GL, et al. Cancer-Derived Succinate Promotes Macrophage Polarization and Cancer Metastasis via Succinate Receptor. *Mol Cell* (2020) 77:213–27 e5. doi: 10.1016/j.molcel.2019.10.023
85. Lewis CE, Harney AS, Pollard JW. The Multifacted Role of Perivascular Macrophages in Tumors. *Cancer Cell* (2016) 30:365. doi: 10.1016/j.ccell.2016.07.009
86. Lewis JS, Landers RJ, Underwood JC, Harris AL, Lewis CE. Expression of Vascular Endothelial Growth Factor by Macrophages is Up-Regulated in Poorly Vascularized Areas of Breast Carcinomas. *J Pathol* (2000) 192:150–8. doi: 10.1002/1096-9896(200009)9999:9-Aid-path687-3.0.CO;2-g
87. Lewis CE, De Palma M, Naldini L. Tie-2 Expressing Monocytes and Tumor Angiogenesis: Regulation by Hypoxia and Angiopoietin-2. *Cancer Res* (2007) 67:8429–32. doi: 10.1158/0008-5472.CAN-07-1684
88. Kalluri R. The Biology and Function of Fibroblasts in Cancer. *Nat Rev Cancer* (2016) 16:582–9. doi: 10.1038/nrcan.2016.73
89. Mace TA, Ameen Z, Collins A, Wojcik S, Mair M, Young GS, et al. Pancreatic Cancer-Associated Stellate Cells Promote Differentiation of Myeloid-Derived Suppressor Cells in a STAT3-Dependent Manner. *Cancer Res* (2013) 73:3007–18. doi: 10.1158/0008-5472.CAN-12-4601
90. Shiao SL, Ruffell B, DeNardo DG, Faddegon BA, Park CC, Coussens LM. CD45 Phosphatase Inhibits STAT3 Transcription Factor Activity in Myeloid-Derived Suppressor Cells in a STAT3-Dependent Manner. *Cancer Immunol Res* (2015) 3:518. doi: 10.1158/2326-6066.CIR-14-0232
91. Shiao SL, Ruffell B, DeNardo DG, Faddegon BA, Park CC, Coussens LM. CD45+ T Cells Regulate Pulmonary Metastasis of Mammary Carcinomas by Enhancing Proinflammatory Properties of Macrophages. *Cancer Cell* (2009) 16:91–102. doi: 10.1016/j.ccr.2009.06.018
92. DeNardo DG, Barreto JB, Andreu P, Vasquez L, Tawfik D, Kolhatkar N, et al. CD45+ T Cells and Macrophages Limit Efficacy of Radiotherapy. *Cancer Immunol Res* (2015) 3:518–25. doi: 10.1158/2326-6066.CIR-14-0232
93. Ben-Shoshan J, Mayes-Auslander S, Mor A, Keren G, George J. Hypoxia Controls CD4+CD25+ Regulatory T-Cell Homeostasis. *Via Hypoxia-Inducible Factor-alfa Eur J Immunol* (2008) 38:2412–8. doi: 10.1002/eji.200838318
94. Kryczek I, Zou L, Rodriguez P, Zhu G, Wei S, Mottram P, et al. B7-H4 Expression Identifies a Novel Suppressive Macrophage Population in
Human Ovarian Carcinoma. *J Exp Med* (2006) 203:871–81. doi: 10.1084/jem.20050930

104. Parkickz D, Wei S, Zhu G, Myers L, Mottram P, Cheng P, et al. Relationship Between B7-H4, Regulatory T Cells, and Patient Outcome in Human Ovarian Carcinoma. *Cancer Res* (2007) 67:8900–5. doi: 10.1158/0008-5472.CAN-07-1866

105. Xu S, Xu H, Wang W, Li S, Li H, Li T, et al. The Role of Collagen in Cancer: From Bench to Bedside. *J Transl Med* (2019) 17:309. doi: 10.1186/s12967-019-2058-1

106. Kobayashi N, Miyoshi S, Mikami T, Koyama H, Kitazawa M, Takeoka M, et al. Hyaluronan Deficiency in Tumor Stroma Impairs Macrophage Trafficking and Tumor Neovascularization. *Cancer Res* (2010) 70:7073–8. doi: 10.1158/0008-5472.CAN-09-4667

107. Chen JE, Lumibao J, Blazek A, Gaskins HR, Harley B. Hypoxia Activates Enhanced Invasive Potential and Endogenous Hyaluronic Acid Production by Glioblastoma Cells. *Biomater Sci* (2018) 6:685–62. doi: 10.1039/c7bm01195d

108. Kuang DM, Wu Y, Chen N, Cheng J, Zhuang SM, Zheng L. Tumor-Derived Hyaluronan Induces Formation of Immunosuppressive Macrophages Through Transient Early Activation of Monocytes. *Blood* (2007) 110:587–95. doi: 10.1182/blood-2007-01-068031

109. Zhou W, Ke SQ, Huang Z, Flavahan W, Fang X, Paul J, et al. Periostin Secreted by Glioblastoma Stem Cells Recruits M2 Tumor-Associated Macrophages and Promotes Malignant Growth. *Nat Cell Biol* (2015) 17:170–82. doi: 10.1038/ncb3090

110. Stahl M, Schupp J, Jager B, Schmid M, Zissel G, Muller-Quernheim J, et al. Hyaluronan Induces Formation of Immunosuppressive Macrophages and Inhibiting microRNAs. *Nat Cell Biol* (2009) 11:1487–95. doi: 10.1038/ncb1998

111. Chen XJ, Deng YR, Wang ZC, Wei WF, Zhu CF, Zhang YM, et al. Hypoxia-Induced ZEB1 Promotes Cervical Cancer Progression via CCL8-Dependent Tumor-Associated Macrophage Recruitment. *Cell Death Dis* (2019) 10:508. doi: 10.1038/s41419-017-481-1

112. Yang B, Chen Y, Shi J. Nanocatalytic Medicine. *Sci Rep* (2013) 123:3231. doi: 10.1038/srep03231

113. Cook RS, Jacobsen KM, Wolford AM, De Ryckere D, Stanford J, Prieto AL, et al. Hyaluronan Depletion in Tumor Stroma Impairs Macrophage Recruitment and Tumor Progression. *Cancer Res* (2006) 203:871

114. Wu Q, Li J, Zou S, Zhu S, Wang L, et al. Exosomes From the Tumour-Adipoocyte Interplay Stimulate Beige/Brown Differentiation and Reprogram Metabolism in Stromal Adipocytes to Promote Tumour Progression. *Cell Death Dis* (2017) 8:1587–604. doi: 10.7150/thno.62572

115. Chen X, Ying X, Wang X, Wu X, Zhu Q, Chen W, et al. Hypoxia-Inducible Factor-1α/Interleukin-1β Signaling Enhances Hepatoma Epithelial-Mesenchymal Transition Through Macropores in a Hypoxic-Indifferent Microenvironment. *Hepatology* (2018) 67:1872–89. doi: 10.1002/hep.29681

116. Wilson WR, Hay MP. Targeting Hypoxia in Cancer Therapy. *Nat Rev Cancer* (2011) 11:393–410. doi: 10.1038/nrc3064

117. Hughes R, Qian BZ, Rowan C, Muthana M, Keldikoglou I, Olson OC, et al. Perivascular M2 Macrophages Stimulate Tumor Relapse After Chemotherapy. *Cancer Res* (2015) 75:3479–91. doi: 10.1158/0008-5472.CAN-14-3587

118. Chen X, Ying X, Wang X, Wu X, Zhu Q, Chen W, et al. Hypoxia-Inducible Factor-1α/Interleukin-1β Signaling Enhances Hepatoma Epithelial-Mesenchymal Transition Through Macropores in a Hypoxic-Indifferent Microenvironment. *Hepatology* (2018) 67:1872–89. doi: 10.1002/hep.29681

119. Li J, Xu P, Wu D, Guan M, Weng X, Lu Y, et al. Hypoxic Stress Suppresses Lung Tumor-Secreted Exosomal mir101 to Activate Macrophages and Induce Inflammation. *Cell Death Dis* (2021) 12:776. doi: 10.1038/s41419-021-04030-x

120. Huang Y, Yuan J, Righi E, Kamoun WS, Ancukiewicz M, Nezivar J, et al. Vascular Normalizing Doses of Antiangiogenic Treatment Reprogram Tumor Immunosuppressive Microenvironment and Enhance Immunotherapy. *Proc Natl Acad Sci USA* (2012) 109:17561–6. doi: 10.1073/pnas.1215397109

Frontiers in Immunology | www.frontiersin.org September 2021 | Volume 12 | Article 741305

10
139. Hutt DM, Roth DM, Vignaud H, Callin C, Boucheareil M. The Histone Deacetylase Inhibitor, Vorinostat, Represses Hypoxia Inducible Factor 1 Alpha Expression Through Translational Inhibition. PloS One (2014) 9: e106224. doi: 10.1371/journal.pone.0106224

140. Rapisarda A, Zalek I, Hollingshead M, Braunschweig T, Uranchimeg R, Bonomi CA, et al. Schedule-Dependent Inhibition of Hypoxia-Inducible Factor-α-Helicase Protein Accumulation, Angiogenesis, and Tumor Growth by Topotecan in U251-HRE Glioblastoma Xenografts. Cancer Res (2004) 64:8485–8. doi: 10.1158/0008-5472.Can-04-2116

141. Fritz JM, Tennis MA, Orlicky DJ, Lin H, Ju C, Redente EF, et al. Depletion of Tumor-Associated Macrophages Slows the Growth of Chemically Induced Mouse Lung Adenocarcinomas. Front Immunol (2014) 5:587. doi: 10.3389/fimmu.2014.00587

142. Germano G, Frapolli R, Belgiovine C, Anselmo A, Pesce S, Liguori M, et al. Role of Macrophage Targeting in the Antitumor Activity of Trabectedin. Cancer Cell (2013) 23:249–62. doi: 10.1016/j.ccr.2013.01.008

143. Cieslewicz M, Tang J, Yu JL, Cao H, Zavaljevski M, Motoyama K, et al. Targeted Delivery of Proapoptotic Peptides to Tumor-Associated Macrophages Improves Survival. Proc Natl Acad Sci USA (2013) 110:15919–24. doi: 10.1073/pnas.1312197110

144. Gazzaniga S, Bravo AI, Guglielmotti A, van Rooijen N, Maschi F, Vecchi A, et al. Deacetylase Inhibitor, Vorinostat, Represses Hypoxia Inducible Factor 1 Expression Through Translational Inhibition. PloS One (2014) 9: e106224. doi: 10.1371/journal.pone.0106224

145. Dineen SP, Lynn KD, Holloway SE, Miller AF, Sullivan JP, Shames DS, et al. Vascular Endothelial Growth Factor Receptor 2 Mediates Macrophage Infiltration Into Orthotopic Pancreatic Tumors in Mice. Cancer Res (2008) 68:4340–6. doi: 10.1158/0008-5472.Can-07-6705

146. Mok S, Koya RC, Tsui C, Xu J, Robert L, Wu L, et al. Inhibition of CSF-1 Receptor Improves the Antitumor Efficacy of Adoptive Cell Transfer Immunotherapy. Cancer Res (2014) 74:153–61. doi: 10.1158/0008-5472.CAN-13-1816

147. Halama N, Zoernig I, Berthel A, Kahlert C, Klupp F, Suarez-Carmona M, et al. Tumoral Immune Cell Exploitation in Colorectal Cancer Metastases Can Be Targeted Effectively by Anti-CCR5 Therapy in Cancer Patients. Cancer Cell (2016) 29:587–601. doi: 10.1016/j.ccell.2016.03.005

148. Welford AF, Bizziato D, Coiffet SB, Nucera S, Fisher M, Pucci F, et al. TIE2-Expressing Macrophages Limit the Therapeutic Efficacy of the Vascular-Disrupting Agent Combretastatin A4 Phosphate in Mice. J Clin Invest (2011) 121:1969–73. doi: 10.1172/jci44562

149. Coscia M, Quagli e D, Iezzi M, Curcio C, Pantaleoni F, Riganti C, et al. Zoledronic Acid Repolarizes Tumor-Associated Macrophages and Inhibits Mammary Carcinogenesis by Targeting the Mevalonate Pathway. J Cell Mol Med (2010) 14:2803–15. doi: 10.1111/j.1582-4934.2009.00926.x

150. Beatty GL, Chio roean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, et al. CD40 Agonists Alter Tumor Stroma and Show Efficacy Against Pancreatic Carcinoma in Mice and Humans. Sci (N Y NY) (2011) 331:1612–6. doi: 10.1126/science.1198443

151. Shime H, Matsumoto M, Oshiumi H, Tanaka S, Nakane A, Iwakura Y, et al. Toll-Like Receptor 3 Signaling Converts Tumor-Supporting Myeloid Cells to Tumoricidal Effectors. Proc Natl Acad Sci USA (2012) 109:20666–71. doi: 10.1073/pnas.1113099109

152. Rolny C, Maizone M, Tugues S, Laoui D, Johansson I, Coulon C, et al. HRG Reduces Angiogenesis and Tumor Growth in Human Breast Cancer Xenografts. Cancer Res (2010) 70:5075–8. doi: 10.1158/0008-5472.CAN-09-3126

153. Sockolosky JT, Dougan M, Ingram JR, Ho CC, Kauke MJ, Almo SC, et al. Targeted Delivery of Proapoptotic Peptides to Tumor-Associated Macrophages Improves Survival. Proc Natl Acad Sci USA (2013) 110:15919–24. doi: 10.1073/pnas.1312197110

154. Canedo MM, Messer KS, Ralainirina N, Li H, Leem CJ, Gorjestani S, et al. PI3Kδ Is a Molecular Switch That Controls Immune Suppression. Nature (2016) 539:437–42. doi: 10.1038/nature19834

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 He and Zhang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.