

Review

Metabolic regulatory crosstalk between tumor microenvironment and tumor-associated macrophages

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Abstract

Macrophages phagocytize pathogens to initiate innate immunity and products from the tumor microenvironment (TME) to mediate tumor immunity. The loss of tumor-associated macrophage (TAM)-mediated immune responses results in immune suppression. To reverse this immune disorder, the regulatory mechanism of TAMs in the TME needs to be clarified. Immune molecules (cytokines and chemokines) from TAMs and the TME have been widely accepted as mutual mediators of signal transduction in the past few decades. Recently, researchers have tried to seek the intrinsic mechanism of TAM phenotypic and functional changes through metabolic connections. Numerous metabolites derived from the TME have been identified that induce the cell–cell crosstalk with TAMs. The bulk tumor cells, immune cells, and stromal cells produce metabolites in the TME that are involved in the metabolic regulation of TAMs. Meanwhile, some products from TAMs regulate the biological functions of the tumor as well. Here, we review the recent reports demonstrating the metabolic regulation between TME and TAMs.

Key words: Tumor-associated macrophage; tumor microenvironment; metabolism; tumor immunotherapy

Introduction

Macrophages that reside within the tumor microenvironment (TME) are known as tumor-associated macrophages (TAMs). As the predominant infiltrated immune cells in the TME [1-3], TAMs have been extensively studied for their pro-tumoral activities, such as tumor initiation, angiogenesis, metastasis, drug-resistance, and antitumor immunosuppression [4]. To mirror the Th1/2 immune response, canonical concepts suggest that there are two distinct states of polarized activation in macrophages, namely classical (M1, induced by lipopolysaccharide and IFN- γ) and alternative (M2, induced by IL-4 or IL-13) [5]. M1 and M2 macrophages have different transcriptional profiles, such as cytokines, chemokines, metabolic pathways. Studies have indicated that TAMs predominantly have an M2-like phenotype, which

manifests as an immunosuppressive state and pro-tumoral progression [6]. Hence, targeting M2-like TAMs and depleting them in the TME or reversing the M2-like TAMs into an M1-like phenotype, which directly boosts their cytotoxicity and indirectly stimulates cytotoxic T cells to eliminate tumor cells, is a potential strategy for antitumor immunotherapy [7, 8]. Numerous mechanisms underlying the role of TAMs in tumor immunosuppression have been elucidated, and novel therapeutic agents based on these new targets have been subjected to clinical trials in recent years [8, 9]. In addition, some recent reports focused on phagocytosis, the primordial function of macrophages, to reactivate antitumor immunity by targeting CD47/SIRP α [10], PD-1/PD-L1 [11], and CD24/Siglec-10 [12] pathways. All of these strategies have moved TAMs to the forefront of tumor

immunotherapy.

In addition to the cytokine and chemokine regulatory mechanisms, metabolic regulation between the TME and TAMs has also been widely studied. All members of the TME rely on nutrients for their survival, maintenance, and proliferation. Meanwhile, the competition and symbiosis between TAMs and other members of the TME form a crosstalk mechanism linked by metabolites. Excessive metabolites uptake or secretion reprograms the phenotype and function of such components and interferes with tumor outcomes. Therefore, clarifying the metabolic regulatory mechanisms would help elucidate the landscape of metabolite connections between the TME and TAMs and promote metabolic immunotherapy targeting TAMs. Some excellent reviews have focused on TAM metabolism and the metabolic crosstalk between tumor cells and TAMs [13-15]. However, other than tumor cells, the metabolic regulation of immune and stromal cells in TME also needs to be concerned, especially the interaction with TAMs. Besides, the metabolism pattern of TAMs affects the outcome of cancer. This review discusses the metabolic crosstalk from TME to TAMs based on different cell types and from TAMs to TME by diverse oncobiological functions.

Metabolic crosstalk: from TME to TAMs

TAMs and other TME members make up the tumor ecosystem, suggesting that there are some interactions between them through cytokines, chemokines, and other factors [16]. Most often, all members of the TME consume oxygen and nutrients from the host for their phenotypic and functional performance [17, 18]. Thus, metabolites are accumulated in the TME and recycled from cell to cell. In particular, as messengers for cell-cell contact, the metabolites, which are derived from the TME (tumor cells, T cells, mast cells, cancer-associated fibroblasts, adipocytes, except TAMs), are ingested by TAMs to change their phenotype and function. In turn, TAMs promote tumor progression via metabolic reprogramming, which is triggered by the metabolites that are shuttled in the TME. Moreover, blockade of the metabolic pathways in the TME and TAMs is being used for drug discovery and tumor therapy [8, 19]. Next, we describe the recent findings regarding metabolic crosstalk between the TME and TAMs (Figure 1).

Tumor cells

The bulk of cells in the TME are tumor cells. Tumor cells possess the self-serving characteristic of educating the TME to provide pro-tumoral conditions. Numerous tumor cells deprive glucose

from the TME for their progression [20]. Thereby, other cells, including TAMs, have no alternative but mainly rely on oxidative phosphorylation (OXPHOS) to produce energy for cellular processes [21]. However, most tumor cells do not fully transmit glucose into the mitochondrial tricarboxylic acid (TCA) cycle to generate ATP (adenosine triphosphate) efficiently, but instead use glucose in aerobic glycolysis, which is termed the “Warburg Effect” [22]. Thus, tumor cells produce a large amount of lactic acid through aerobic glycolysis and release the redundant lactic acid into the extracellular microenvironment via monocarboxylate transporter 4 (MCT4) [23].

Reports indicate that lactic acid-treatment suppresses TNF secretion in human monocytes through glycolysis inhibition [24]. Furthermore, lactic acid is reportedly the messenger between tumor cells and TAMs. In addition, tumor cell-derived lactic acid induces the expression of vascular endothelial growth factor (VEGF) and the M2-like polarization of TAMs, which is mediated by hypoxia-inducible factor 1 α (HIF1 α) [25]. Moreover, a recent study demonstrated that lactic acid induces M2-like gene activation in macrophages through histone lactylation [26]. Besides, extracellular acidosis is involved in tumor progression via the stimulation of autophagy and immunosuppression [23], which was also found to promote tumor progression by increasing tumor-promoting macrophages in prostate cancer [27]. Regarding the underlying mechanism, tumor acidosis is sensed by G protein-coupled receptors (GPCRs) in TAMs. It induces transcriptional repressor ICER (inducible cyclic AMP (cAMP) early repressor) expression to enhance pro-tumoral macrophage polarization, especially in tumors with a high glycolytic rate, such as melanoma [28]. It is noteworthy that tumor-derived lactic acid was found to be dispensable for the induction of ICER expression in TAMs in this study [28], which means that other organic acids and hydrogen ions together, with or without lactic acid, contribute to prime TAMs for tumor growth.

Interestingly, the restricted OXPHOS in tumor cells is accompanied by glutamine consumption to fuel the TCA cycle. Glutamine is converted to α -ketoglutarate by glutamate dehydrogenase or aminotransferases [29]. One study has reported that intracellular α -ketoglutarate leads to the M2-like activation of macrophages via FAO (fatty acid oxidation) and Jmjd3-dependent epigenetic reprogramming of M2 genes [30]. However, more research is needed to elucidate the mechanism of α -ketoglutarate shuttling between tumor cells and TAMs. Succinate, the downstream product of

α -ketoglutarate, is an intermediate of the TCA cycle in mitochondria, and its levels are mainly controlled by succinate dehydrogenase (SDH), which is regarded as a tumor suppressor [31]. Inherited or somatic mutations and the inhibition of SDH result in tumor formation, which importantly causes the accumulation of succinate in tumor cells [32]. Nevertheless, the excessive uptake of glutamine by tumor cells induces glutamine-based anaplerosis, and the γ -aminobutyric acid shunting pathway also increases succinate levels [33]. The tumor-derived succinate is taken up through succinate receptor (SUCNR1) and results in the polarization of TAMs into a pro-tumoral form via the SUCNR1/PI3K/HIF1 α signaling pathway to enhance tumor metastasis, which can also be mediated by autocrine succinate [34]. These studies suggest that serum succinate could be a potential clinical biomarker.

ATP has long been known as the energy molecule. Hypoxia and chemotherapy lead to the accumulation of abundant ATP in the TME [35],

which is primarily derived from tumor cells via ATP-binding cassette (ABC) transporters [36], pannexin 1 [37], or connexins [38]. The extracellular ATP triggers the P2 purinergic receptors (P2XRs and P2YRs) in tumor cells for its growth or inhibition [39]. In most cases, ATP is unstable in biological fluids and is rapidly degraded to adenosine, which is abundantly accumulated in extracellular fluids of solid tumors for tumor immunosuppression [40]. This biological process is mediated through the ectonucleotidases CD39, which converts ATP into ADP/AMP, and CD73, degrading AMP into adenosine [41]. One study reported that adenosine induces TAMs to express CD39 and CD73 for tumor immune escape [42]. Moreover, adenosine receptors (A1R, A2AR, A2BR, and A3R) have been found to sense adenosine for tumor growth, survival, metastasis, and immunosuppression [38]. Furthermore, reports suggest that CD39/CD73 and adenosine receptors are mainly induced and regulated by HIF1 α [43-45]. Furthermore, A2AR and

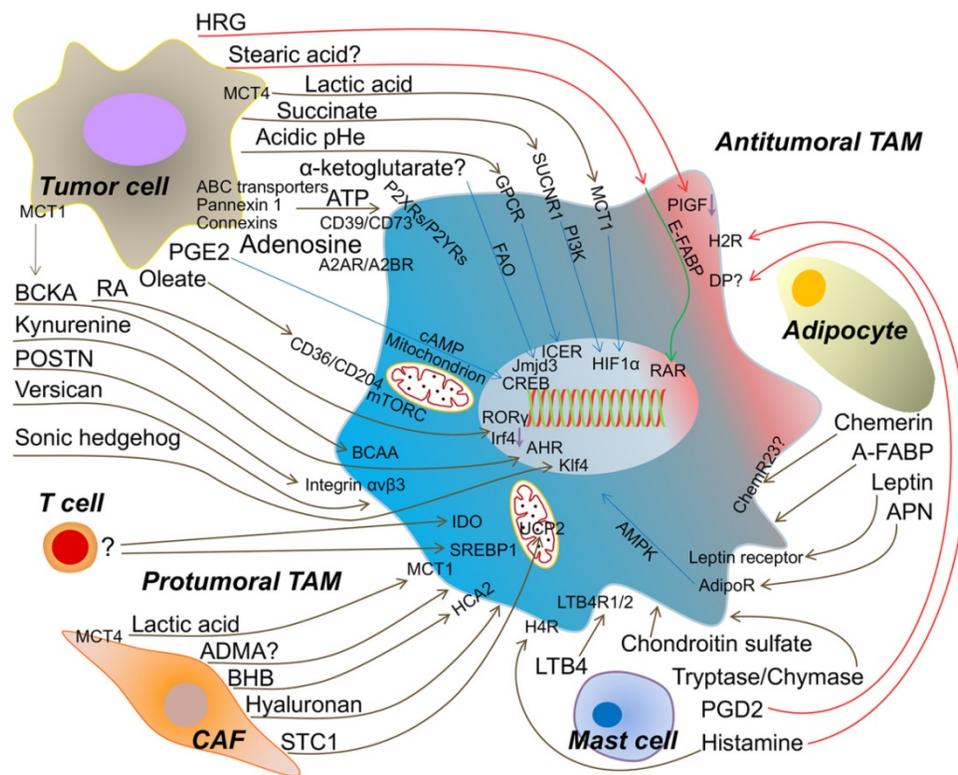


Figure 1. The metabolic crosstalk: from TME to TAMs. Tumor cell-derived lactic acid, succinate, α -ketoglutarate, ATP/Adenosine, PGE2 (prostaglandin E2), oleate, Retinoic acid (RA), BCKA (branched-chain ketoacids), kynurenine, POSTN (periostin), versican, sonic hedgehog and the extracellular acidosis promote the protumoral TAM formation to accelerate tumor progression. Artificially increasing HRG (histidine-rich glycoprotein) or stearic acid expression from tumor cell induce the antitumoral TAM. Metabolites from T cell to TAM are rarely identified, but activated T cell enhances IDO and SREBP1 (sterol regulatory element-binding protein 1) in TAM to facilitate tumor growth. CAF (cancer-associated fibroblast)-produced lactic acid, ADMA (asymmetric dimethyl arginine), BHB (beta-hydroxybutyrate), hyaluronan and STC1 (stanniocalcin-1) assist TAM to be protumoral. Mast cell-released LTB4 (leukotriene B4), chondroitin sulfate and trypsin/chymase guide TAM toward into tumor promoting. However, PGD2 (prostaglandin D2) from mast cell may bind DP (PGD2 receptors) on TAM and skews TAM to be antitumoral. Histamine triggers H4R (histamine H4-receptor) on macrophage into protumoral TAM, but H2R (histamine H2-receptor) into antitumoral TAM. Adipocyte-derived APN (adiponectin), leptin and A-FABP (adipose fatty acid binding protein) induce the protumoral TAM. Chemerin from adipocyte causing the phenotypic change of TAM is tumor context dependent. MCT1/4 (monocarboxylate transporter 1/4); SUCNR1 (succinate receptor1); GPCR (G protein-coupled receptors); FAO (fatty acid oxidation); P2XRs/P2YRs (P2 purinergic receptors); A2AR/A2BR (adenosine receptors); BCAA (branched-chain amino acid); HCA2 (hydroxycarboxylic acid receptor 2); LTB4R1/2 (leukotriene B4 receptor 1/2); AdipoR (adiponectin receptor); ChemR23 (chemokine-like receptor 1, CMKLR1); PIGF (placental growth factor); E-FABP (epidermal fatty acid binding protein); ICER (inducible cyclic AMP (cAMP) early repressor); CREB (cyclic AMP-responsive element binding); AHR (aryl hydrocarbon receptor); RAR (retinoic acid receptor); UCP2 (uncoupling protein 2).

A2BR were reportedly to be expressed on macrophages and stimulated by adenosine, inducing M2-like TAM polarization [38, 41]. Additionally, A2AR depletion on myeloid cells, especially macrophages, slows melanoma growth and reduces metastasis by relieving T and NK cell suppression [46]. Studies have recently revealed that ectonucleotidases, adenosine receptors, and the adenosinergic pathway are potential targets to enhance antitumor immunity [38, 40], which would accelerate drug discovery in this field.

Prostaglandin E2 (PGE2), a prostanoid lipid, is associated with tumor progression [47] and is synthesized by tumor cyclooxygenase to mediate tumor immune escape [48]. Reports suggested that PGE2 induces M2 polarization in macrophages through the cyclic AMP-responsive element binding (CREB) pathway [49, 50]. Furthermore, PD-L1 expression in TAMs can be regulated by PGE2 levels [51]. Recently, one study clarified that PGE2 modulates mitochondrial membrane potential to regulate M2-like gene expression in the nucleus [52]. Thereby, PGE2 from tumor cells polarizes TAMs through cAMP and mitochondrial signaling.

Fatty acids are reportedly enriched in the TME and mainly tumor cell-derived [53]. A recent paper indicated that long-chain fatty acids, exemplified by oleate, are scavenged by CD36/204, facilitate mitochondrial respiration in TAMs, and polarize immune-suppressive TAMs through mTORC signaling [54]. Thus, tumor lipid metabolites orchestrate a TAM phenotype, and this might explain why a lipid droplet-rich TME is associated with more infiltrating TAMs. Nevertheless, researchers revealed that free fatty acids, particularly stearic acid, facilitate the inflammatory functions of CD11c⁺ macrophages via activation of the nuclear retinoic acid receptor and the cytosolic expression of epidermal fatty acid-binding proteins (E-FABP) in obesity models [55]. Therefore, whether various categories of fatty acids have different effects on TAM polarization needs more clarification.

Retinoic acid (RA) is a metabolite of vitamin A that has an established role in organ development [56], cancer therapy [57], and immune homeostasis [58]. *In vitro*, RA-treated head and neck squamous cell carcinoma cells fail to activate macrophages by decreasing VEGF and IL-8 secretion [59]. In addition, the clinical use of available all-trans-retinoic acid (ATRA) abrogates the pro-tumorigenic phenotype of TAMs in prostate cancer by suppressing the activation of NF- κ B p50 [60] and reduces osteosarcoma metastasis by downregulating MMP12 (matrix metalloproteinase 12) secretion from M2-type TAMs [61]. Further, ATRA could prevent osteosarcoma

initiation and stemness by inhibiting M2-like TAMs [62]. However, retinoic-acid-related orphan receptor (RORC1/ROR γ), one of the retinoid nuclear receptors, has been found to prevent myeloid-derived suppressor cells (MDSCs) from undergoing apoptosis, and to promote M2-like TAM differentiation in the TME [63]. Moreover, a recent study indicated that tumor cell-derived RA promotes TAMs and suppresses immunostimulatory dendritic cell differentiation from monocytes [64]. Combined with the RA mechanism in treating acute promyelocytic leukemia, the concept of differentiation therapy, and hence, RA from tumor cells, seems more like an immunosuppressant to mediate TAM formation in the TME.

Nevertheless, the effects of other tumor cell-derived metabolites on TAMs have been investigated. Branched-chain ketoacids, which are excreted from glioblastoma cells via monocarboxylate transporter 1 (MCT1), are taken up by TAMs and re-purposed to form branched-chain amino acids, which reduces phagocytosis by TAMs and mediates tumor immunosuppression [65]. Moreover, a recent study revealed that glioblastoma cell-derived kynurenine activates AHR (aryl hydrocarbon receptor) in TAMs to modulate TAM recruitment and T cell dysfunction [66]. With respect to glioblastoma, researchers found that periostin (POSTN) from glioma stem cells (GSCs) recruits monocyte-derived macrophages from the peripheral blood through integrin α v β 3 to induce an M2 phenotype, and POSTN knockdown in GSCs inhibits tumor growth [67]. One report revealed that bladder tumor cell-derived versican drives lung metastasis in a TAM dependent manner [68]; however, the mechanism underlying CCL2 expression in TAMs via versican warrants additional investigation. Another recent study reported that tumor cell-derived sonic hedgehog triggers hedgehog signaling in TAMs for M2 polarization and impedes CD8⁺ T cell recruitment by hindering CXCL9 and CXCL10 production by TAMs, which is mediated by Kruppel-like factor 4 (Klf4) [69]. Meanwhile, some tumor metabolites can re-educate TAMs to induce antitumor activity. HRG (histidine-rich glycoprotein) levels are decreased in the TME, and researchers have increased tumor levels by using a genetic gain-of-function strategy to find that HRG derived from these tumor cells inhibits tumor growth and metastasis by inducing macrophage polarization and vessel normalization through the downregulation of PIGF (placental growth factor), suggesting that HRG contributes to the skewing of TAMs to an antitumor polarization phenotype [70].

T cells

T cell-based immune-checkpoint inhibitors have resulted in tremendous achievements [71]. Given that T cells are the cytotoxic cells of the antitumor immune response, their persistent survival, and the production of toxicity factors are critical to eliminate tumor cells and surveil tumor initiation and recurrence. All of these functions are based on metabolic support [72]. The naïve T cells mainly use the OXPHOS pathway to produce ATP [73]. When activated by immunological signals, the metabolic model switches to be glycolysis-dependent [74]. In the TME, glucose, oxygen, and other essential metabolites are deprived by tumor cells. T cells must thus adapt to the hypoxic and nutrient-deficient conditions, which becomes tumor immunosuppressive. Thus, the TME reprograms T cell metabolism into weak glycolysis and OXPHOS, accompanying the decrease in IFN- γ and perforin/granzyme B secretion [72]. However, the impact of T cell-derived metabolites on TAMs has not received much research attention with respect to the TME. One report indicated that tumor-infiltrating CD69⁺-activated T cells increase IDO (indoleamine 2,3-dioxygenase) expression in TAMs, but the metabolic mediator has not been identified [75]. Another group revealed that CD8 T cell-derived IFN- γ could block sterol regulatory element-binding protein 1 (SREBP1)-mediated fatty acid metabolism in TAMs [76]. In summary, cytokine/chemokine crosstalk is common between T cells and TAMs, but metabolites are also important.

Mast cells

Mast cells are derived from bone marrow precursors and reside in peripheral tissues after maturation; further, they play the role of sentinels to recruit an immune army during infection, especially in allergic responses [77]. To date, the beneficial effects of mast cells on both the tumor and the host have been reported [78, 79]. A recent report found that IL-33-mediated mast cell activation in gastric cancer enhances TAM infiltration and tumorigenesis through CSF2, CCL3, and IL-6 secretion [80]. Other than cytokines and chemokines, mast cells also secrete distinct biogenic amines, eicosanoids, and proteoglycans when they are activated, which are either pro- or anti-tumoral. Theoharis C. Theoharides proposed M1- and M2-type mast cells according to their different effects on the tumor [78]. Moreover, some of these molecules have been studied on TAMs.

Histamine, one of the biogenic amines from mast cells, combined with IL-2, increases Th1 immune responses in patients with stage IV melanoma [81]. Later clinical data suggested that histamine with IL-2 does not change the number of intratumoral

macrophages [82]. With respect to the mechanism, histamine can interact with the H₂-receptor on macrophages to inhibit ROS production, which relieves NK and T cell inhibition to favor tumor inhibition [83]. Further, histamine deficiency causes a high incidence of colon and skin carcinogenesis via abnormal myeloid differentiation [84]. Moreover, macrophages also express other histamine receptors, including H_{1/4}-receptor, and the H₄-receptor is required to induce histamine-mediated chemotaxis and phagocytic activity [85]. Further, H₄-receptor knockout mice show suppressed mammary tumor growth and metastasis through a reduction in CD4 T and Treg cells and an increase in NK cells in tumor-draining lymph nodes; besides, stimulation of the H₄-receptor increases Treg numbers, enhances IL-10 expression, and decreases IFN- γ [86]. Moreover, the same group recently found that histamine has an antitumor effect, with increased cytotoxic lymphocyte infiltration, in H₄-receptor knockout mice [87]. Thus, the specific histamine receptor that induces the antitumor immune response is still unknown. Histamine is generated by histidine decarboxylase (HDC), and HDC-knockout mice fail to form M1-like macrophages [88]. To date, although no systematic study has revealed the phenotypic and functional effect of histamine on TAMs, we speculate that histamine could polarize M1-like TAMs, based on these data combined with results of a previous report [89].

Activated mast cells can produce three eicosanoids, prostaglandin D₂ (PGD₂), leukotriene B₄ (LTB₄), and LTC₄ [90]. These three eicosanoids are produced *de novo* from arachidonic acid derived from nuclear membrane phospholipids via cytosolic phospholipase A₂. Prostaglandin H₂ (PGH₂) is generated from arachidonic acid by prostaglandin H synthase 1/2 (PGHS1/2, also called cyclooxygenase 1/2) and then is converted to PGD₂ by hematopoietic prostaglandin D₂ synthase (H-PGDS, in leukocytes) or lipocalin prostaglandin D₂ synthase (L-PGDS, in the central nervous system). PGD₂ has been found to induce leukocyte chemotaxis via PGD₂ receptors (DP) in Th₂ cells [91]. Enhancing the PGD₂/DP pathway results in a suppressive effect on tumor growth by modulating tumor hyperpermeability and angiogenesis [92]. Moreover, decreasing PGD₂ through H-PGDS deficiency increases tumor growth, and mast cell-derived PGD₂ reduces tumor expansion [93]. These findings suggest that the PGD₂/DP pathway favors the inhibition of tumor progression. Although many studies mentioned PGD₂ in the TME [94], DP expression and the regulation of PGD₂ biosynthesis in TAMs are yet to be identified. Mast cell-derived leukotrienes are potent pro-inflammatory

lipid mediators implicated in cancers, which require 5-lipoxygenase (5-LOX) for their production. Generally, 5-LOX plays a pro-carcinogenic role [95], whereas its repression in TAMs also promotes tumor progression [96]. Thus, the effect of the 5-LOX pathway on tumors is diverse and might depend on the metabolites from 5-LOX. LTB₄, one of several leukotrienes derived from mast cells, binds to two GPCR LTB₄Rs (LTB₄R1 with high affinity and LTB₄R2 with low affinity [47]) and favors murine melanoma growth [97]. Elevated TAMs can be attracted to the TME inducing immunosuppression via LTB₄ [98]. The addition of LTC₄ has no remarkably increasing effect on the tumoricidal function of TAMs [99]. Leukotrienes and the expression of their receptors, especially LTB₄, are increased in some human cancers, including colon, prostate, and pancreatic cancer [47]. Except with respect to chemotaxis functions, other mechanisms of leukotriene-mediated TAM polarization are comparatively less well known.

For proteoglycans, mast cell-derived heparin has been reported to increase angiogenesis [100]. However, the interaction between heparin and TAMs has not been elucidated. Chondroitin sulfate, another proteoglycan from mast cells, is associated with decreased T cells and increases in TAM infiltration in the TME [68, 101]. However, the use of chondroitinase gene therapy to digest chondroitin sulfate increases CD206 (a marker of M2-like macrophages) expression after spinal cord contusion injury [102]. These data suggest that chondroitin sulfate deficiency might favor wound healing. Thus, further clarification of the mechanism underlying the effect of mast cell-derived proteoglycans on TAMs might explain the different functional changes. Mast cells are typically characterized by protease storage and secretion, including tryptase and chymase [103]. The expression of these two enzymes correlates with tumor progression [104]. These enzymes' primary function is to degrade the extracellular matrix, which might indirectly mediate the immune response in the TME. However, fewer studies have mentioned the impact on TAMs.

In general, mast cells were known to produce chemotactic materials. These chemoattractants induce immune responses in the TME, and especially, TAMs have been overlooked. Increasing research findings indicate that the number of immune cells in the TME is not the crucial factor with respect to tumor elimination, and increasing the tumoricidal immune cells by regulating these metabolites might be the future task, for instance, by reversing the M2-like phenotype of TAMs to generate antitumor M1-like macrophages with these mast cell-derived

metabolites.

Cancer-associated fibroblasts

The tumor stroma constructs the framework of a solid tumor. Cancer-associated fibroblasts (CAFs), which can be derived from endothelial cells, pericytes, adipocytes, and mesenchymal stem cells [105], are the dominant component of the tumor stroma and have been suggested to boost tumor progression and metastasis [106, 107]. A variety of makers have been used to identify CAFs, such as α -SMA (smooth muscle actin), FSP1 (fibroblast specific protein 1), NG2 (neuron-glial antigen-2), and CD90, among others [105]. To date, CAFs cannot be identified with a single marker, even in the same tumor. In line with this, CD10⁺GPR77⁺ CAFs have been found to promote tumor formation and chemoresistance by sustaining tumor stemness [108]. Studies have indicated that fibroblast activation protein and microRNAs can reprogram normal fibroblasts into CAFs [109]. Moreover, CAFs and TAMs are often used together to assess tumor progression [110].

In recent years, some discoveries in CAF metabolism have been made. Michael P. Lisanti's group has presented many studies on metabolism in CAFs, and they termed this new paradigm "The Reverse Warburg Effect" [111], which is characterized by increased lactate and pyruvate secretion from CAFs to fuel tumor cells [112]. As in the tumor cells, they found that lactate is released from CAFs via MCT4 [113, 114]. Even though no study has determined whether lactate from CAFs differentially affects TAMs than that from tumor cells, we believe that CAF-derived lactate polarizes M2-like TAMs, as previously mentioned herein. Moreover, they found that the loss of caveolin-1 (Cav-1) in CAFs is associated with tumor progression [115]. Asymmetric dimethyl arginine (ADMA) and beta-hydroxybutyrate (BHB), which are markers of oxidative stress and mitochondrial dysfunction, are profoundly upregulated in Cav-1-knockout CAFs [116]. Interestingly, endogenous ADMA has been demonstrated to inhibit nitric oxide synthase activity, probably inducing immune-suppressive TAMs in the TME [117]; however, more evidence is needed to indicate if ADMA can be taken up into TAMs. Furthermore, BHB, a ketone body produced by β -oxidation, also induces anti-inflammatory macrophages through HCA2 (hydroxycarboxylic acid receptor 2) [118]. Therefore, ADMA and BHB from CAFs might be conducive to TAM polarization, but the two metabolites' primary source needs to be fully elucidated.

Additionally, other CAF-specific metabolites have been found to affect TAMs. It has been found a

high level of hyaluronan in the TME predicts poor prognosis for tumor patients [119]. Nobutaka Kobayashi and co-workers found that TAMs preferentially traffic to hyaluronan-enriched areas, and genetic disruption of the hyaluronan synthase 2 (*Has2*) gene in fibroblasts impairs TAM recruitment and reduces tumor angiogenesis and lymphangiogenesis, which indicates that CAF secretion of hyaluronan results in TAM pro-tumoral activities [120]. Besides, stanniocalcin-1 (STC1), which is secreted by CAFs, is recognized as a mediator of colorectal cancer growth and metastasis [121]. The previous studies suggested that STC1 is an anti-inflammatory protein, especially for macrophages, which is mediated by inducing mitochondrial UCP2 (uncoupling protein 2) to suppress superoxide generation [122]. Thus, STC1 might inhibit the antitumor chemokine expression in TAMs to impede antitumor T cell infiltration. In summary, very few studies have been performed to assess CAF metabolites' effect on TAMs, except for some specific metabolites.

Adipocytes

Besides CAFs, as another type of stromal cell, adipocytes, also called cancer-associated adipocytes (CAAs), are through to promote tumor growth and metastasis by secreting inflammatory factors and metabolites in the TME [123], especially in breast cancer [124]. CAAs have been reported to increase tumor growth and vascularization through TAMs [125]. Meanwhile, the impact of metabolites from CAAs on TAMs has been studied. For example, adiponectin (APN), one such adipokine, is produced by adipocytes and has antitumor activities [126] and pro-tumoral activities [127]. In response to APN, macrophages are mainly characterized by their anti-inflammatory effect [128] and M2-like phenotype, specifically, negatively regulating the growth of macrophage progenitors [129], inhibiting the production of CXCR3 ligands to reduce T cell migration [130], and decreasing the production of pro-inflammatory cytokines by suppressing I κ B, JNK, p38, and STAT3 phosphorylation [131, 132]. Likewise, full-length APN was reported to induce M2 macrophage polarization via AMPK and shift macrophage metabolism to OXPHOS [133]. Moreover, in the TME, APN deficiency induces TAM polarization to an M1-like phenotype to favor an antitumor immune response for tumor inhibition [134]. In mechanistic terms, APN might trigger downstream signaling of adiponectin receptors (AdipoRs) to polarize M2-like TAMs, such as AdipoR1 [135, 136], AdipoR2 [136, 137], C1qRp [129], and calreticulin receptor [138], among others.

AdipoR1/2 probably mediates this on TAMs, which is suggested by the observation that AdipoR1/2 expression on dendritic cells mediates T cell energy and tolerance in breast cancer [139].

Leptin, another adipokine, was also found to shape the TME and contribute to tumor development [140]. In macrophages, leptin induces some inflammatory mediators' production, including TNF- α , IL-6, and leukotriene B4 [141]. Moreover, leptin modulates cellular lipid metabolism and storage by enhancing ADRP (adipose differentiation-related protein) accumulation within macrophages via the PI3K/mTOR pathway [141]. Although the phenotypic changes in TAMs mediated by leptin have not been revealed, leptin-mediated macrophage chemotaxis and activation were demonstrated through the leptin receptor, which was found to require JAK/STAT, MAPK, and PI3K pathways [142]. This indicates that leptin might mediate the link between CAAs and M2-like macrophages in high-fat diet-induced obesity-associated tumor metastasis [143].

Chemerin, a novel adipokine, regulates adipogenesis and adipocyte metabolism in an autocrine and paracrine manner [144] and was found to be a potent chemoattractant for macrophages that functions in a ChemR23-dependent manner [145]. ChemR23, also known as chemokine-like receptor 1 (CMKLR1), is downregulated in mouse M1-like macrophages but upregulated in mouse M2-like macrophages [146]. However, subsequent research suggested that human M1-like macrophages express ChemR23 but human M2-like macrophages do not [147]. In DSS-induced colitis, chemerin aggravates mucosal damage and increases pro-inflammatory cytokines by suppressing M2-like macrophage polarization [148]. This suggests that the mechanism of chemerin-induced inflammation is intricate. In the TME, chemerin has been reported to inhibit tumor growth by increasing NK cell infiltration and reducing MDSC accumulation [149]. Furthermore, chemerin-deficient (*Rarres2*^{-/-}) mice show significantly increased TAM numbers in the hepatocellular carcinoma TME [150]. Moreover, tumor cells favor CMKLR1 expression in macrophages, and chemerin enhances pro-inflammatory gene expression in TAMs [151]. This reveals that chemerin might skew TAMs to have an antitumor effect. However, chemerin is downregulated in most tumor tissues, including melanoma, acute myeloid leukemia, breast cancer, and adrenocortical carcinoma [152], indicating that chemerin downregulation can induce tumor immune escape. Thus, the re-introduction of chemerin into the TME might represent a therapeutic strategy [153]. Meanwhile, chemerin is elevated in colorectal cancer, gastric cancer, glioblastoma, hepatocellular carcinoma, and

others [152]. Therefore, the effect of treating tumors with chemerin could be tumor context-dependent, and further study is warranted. In addition, recent research indicated that circulating adipose fatty acid binding protein (A-FABP) is mainly derived from CAAs, and elevated circulating A-FABP is associated with obesity-associated tumor development [154]. However, the impact of A-FABP on TAMs is still elusive, since CD11b⁺F4/80⁺MHCII⁻Ly6C⁻ TAMs produce A-FABP as well [155]. Together, the metabolite-mediated interaction between CAAs and TAMs is complicated, and further studies are urgently needed.

Although cellular metabolism in the TME is different from that in normal host cells, all cells share the same metabolic pathways [156]. It is difficult to find some specific metabolites from one component of the TME, but it is feasible to analyze the quantity of various metabolites based on corresponding key metabolic enzymes' expression. In general, the quantity of metabolites in early tumor patients is relatively small. Thereby, the diagnostic validity of metabolic tumor markers is limited to advanced and metabolically hyperactive tumors. TAMs are surrounded by the bulk of tumor cells and other components in the TME in either early- or late-stage tumors. Even slight changes in TME metabolic secretions could shape the immune phenotype of TAMs. However, it is a technical challenge to detect changes in local TME metabolites directly.

Metabolic crosstalk: from TAMs to TME

Metabolites from the TME affect the polarization of TAMs to induce tumor progression and inhibition. In turn, TAMs regulate the TME as well, such as via known cytokines and vesicles. As mentioned previously herein, tumor tissues are hypoxic, and tumor cells mainly use aerobic glycolysis to generate energy. TAMs have a direct impact on tumor cell metabolism. A recent study reported that TAMs make non-small cell lung cancer (NSCLC) cells more glycolytic through TNF- α secretion and promote enhanced hypoxia through AMP-activated protein kinase and PGC-1 α activation. Moreover, the depletion of TAMs increases T cell infiltration and PD-L1 expression in tumor cells, which is beneficial for the PD-L1 blockade in NSCLC [157]. Another recent study suggested that enhanced aerobic glycolysis and decreased apoptosis in breast cancer cells are mediated by TAM-derived extracellular vesicle-packaged HIF-1 α -stabilizing long noncoding RNA, which is upregulated by lactate in the TME [158]. An additional recent report focused on clear cell renal cell carcinoma, which highly relies on glutamine, and found that glutamine-deprived TAMs

secrete IL-23 to decrease survival and enhance the immunosuppressive function of Tregs [159]. In addition to the altered tumor cell metabolism mediated by TAM-derived cytokines and vesicles, metabolites from TAMs extensively regulate the tumor immune microenvironment, metastasis, angiogenesis, and drug-resistance (Figure 2).

First, some secreted molecules from TAMs can shape their immune phenotype. Reducing circulating cholesterol levels has been considered a useful strategy to treat breast cancer [160]. One study recently suggested that membrane cholesterol efflux in TAMs is increased by ovarian cancer cell-derived hyaluronic acid. On the one hand, these TAM-derived cholesterols promote tumor growth, whereas, on the other hand, high cholesterol efflux disrupts lipid rafts in TAMs and results in TAM reprogramming toward a tumor-promoting phenotype [161]. The cholesterol efflux in TAMs has a positive correlation with tumor burden. The genetic deletion of ABCA1 and/or ABCG1 revert the tumor-promoting functions of TAMs and reduces tumor growth. Activated macrophages could produce itaconic acid [162], which is regulated by immune-responsive gene 1 (Irg1) and an essential regulator of macrophage metabolism and inflammation [163]. Interestingly, itaconic acid acts as a metabolic brake in activated macrophages to avoid hyperinflammatory reactions. In mechanistic terms, itaconic acid inhibits succinate dehydrogenase to reprogram immune responses in macrophages [164] and activates the anti-inflammatory transcription factor Nrf2 via KEAP1 alkylation [165]. Importantly, itaconic acid, a key anti-inflammatory metabolite in macrophages, is the most highly upregulated metabolite of TAMs in a peritoneal tumor model and mediates tumor growth. Correspondingly, the genetic downregulation of Irg1 remarkably reduces peritoneal tumors [166]. FABPs are known as the carrier of free fatty acids that regulate lipid metabolism and inflammation in the host cells. The tissue distributions and ligand-binding specificities of a series of FABPs have been elucidated [167]. In tumors, one report found that F4/80⁺CD11b⁺MHCII⁺CD11c⁺ TAMs highly express E-FABP, which promotes the recruitment of T and NK cells to mediate antitumor effects through IFN- β production [168]. However, the same group later found that F4/80⁺CD11b⁺MHCII⁻CD11c⁻ TAMs express adipocyte/macrophage FABP (A-FABP) and promote tumor progression through NF- κ B-miR-29b-regulated IL-6 production [155]. Therefore, TAMs expressing FABPs represent a double-edged sword for tumor immune surveillance. Moreover, the marker of M2-like TAMs is arginase 1 (Arg1), which depletes arginine to form urea and ornithine [169]. Another

result of L-arginine metabolism is the generation of creatine. In addition to ATP, earlier reports indicated that creatine, another direct energy molecule, is likely an antitumor molecule [170]. However, a recent study suggested that creatine uptake via Slc6a8 skews the alternative macrophage polarization by suppressing IFN- γ -STAT1 signaling and promoting ATP-dependent SWI-SNF-mediated chromatin remodeling [171]. Creatine is highly needed in muscle, liver, and brain tissues [172]. Thus, it is assumed that the TME, especially tumors initiated from these organs, maintains high creatine amounts. However, the crosstalk between creatine in the TME and TAMs is not understood. Meanwhile, arginine-generated ornithine is the precursor of polyamines and proline, TAM-derived ornithine might be beneficial for tumor cells and their proliferation [173]. Additionally, T cell immune responses are affected by TAM metabolites [174]. Early research reported that arginine consumption via Arg1 suppresses T cell receptor expression and T cell cytotoxicity [175, 176]. Later, a study found that arginine is critical for T cell survival and antitumor T cell immunity [177]. This is one of the metabolic reasons why increased TAM accumulation in tumor tissues hinders the antitumor T cell immune

response. Furthermore, the 15-lipoxygenase-2 (15-LOX2) pathway enhances eicosanoid production in renal cell carcinoma TAMs, which increases the expression of FOXP3 and CTLA-4 in T lymphocytes to mediate immunosuppression [178]. Tumor-repopulating cell-derived kynurenine, the downstream metabolite of tryptophan via IDO catalysis, upregulates PD-1 expression in CD8 T cells by activating the transcriptional factor AhR [179]. This study indicated that metabolites from IDO signaling modulate T cell immunosuppression. It should be noted that IDO is also overexpressed in TAMs [180]. In addition, TAM-derived kynurenine might similarly induce immunosuppressive T cells.

Metabolites from TAMs contribute to tumor invasion and metastasis. TAM-secreted microvesicle-packaged microRNAs have been found to promote breast cancer cell invasion [181]. Osteopontin from TAMs induces bladder cancer metastasis through the osteopontin-CD44-TIAM1 (T cell lymphoma invasion and metastasis 1)-Rac1 pathway [182]. The blockade of this pathway disrupts the initial steps in bladder cancer metastasis. Furthermore, monocyte-derived TAMs upregulate collagenous extracellular matrix, such as collagen types I, VI, and XIV, for tumor

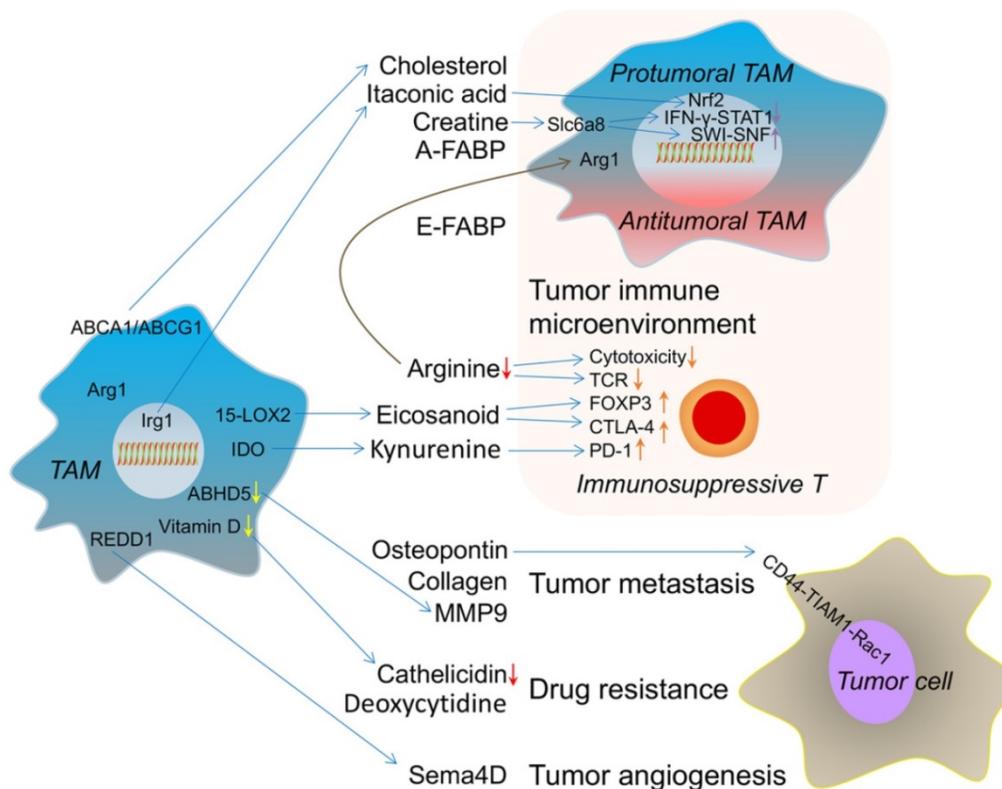


Figure 2. The metabolic crosstalk: from TAMs to TME. TAM-derived cholesterol, itaconic acid, creatine and A-FABP switch its own phenotype into protumoral TAM. E-FABP (epidermal fatty acid binding protein) from TAM induces the antitumoral TAM formation. TAM-caused arginine consumption, eicosanoid and kynurenine accumulation result in immunosuppressive T cell. These effects reflect the immune microenvironment changes induced by metabolites from TAM. TAM-produced osteopontin, collagen and MMP9 (matrix metalloproteinase 9) promote tumor metastasis. Lower vitamin D-caused decreased cathelicidin in TAM and TAM-released deoxycytidine induce drug resistance. REDD1 (regulated in development and DNA damage response 1)-dependent Sema4D (semaphorin 4D) secretion from TAM accelerates tumor angiogenesis. ABHD5 (abhydrolase domain-containing 5); 15-LOX2 (15-lipoxygenase-2); Irg1 (immune-responsive gene 1).

invasion [183]. MMP9 has been involved in tumor lung-specific metastasis [184]. Recently, researchers found that ABHD5 (abhydrolase domain-containing 5) deficiency in TAMs induces the NF- κ B p65-dependent production of MMP, which indicates that low-level triglyceride hydrolysis-mediated MMP is one of the mediators of tumor metastasis from TAMs [185].

Moreover, TAMs influence tumor angiogenesis. An earlier study found that high TAM numbers are associated with human breast tumor angiogenesis [186]. In terms of the mechanism, cytokines and chemokines are the predominant pro-angiogenic factors produced by TAMs [187]. Besides, MMPs [188] and cathepsins [189] from TAMs have been suggested to support tumor angiogenesis through extracellular matrix degradation. Semaphorin 4D, a ligand of plexin B1 on endothelial cells, is mainly derived from TAMs in the TME and promotes tumor angiogenesis and vessel maturation [190]. Subsequent research also found that TAMs enhance the abnormal vessel formation that occurs through REDD1 (regulated in development and DNA damage response 1)-mediated mTOR inhibition, and REDD1-deficient TAMs deprive glucose from endothelial cells, with consequent formation of an organized tumor vasculature to prevent metastasis [191]. However, the metabolic derivatives of REDD1-deficient TAMs are still unknown.

In principle, macrophages can kill tumor cells via antibody-dependent cellular cytotoxicity (ADCC). For example, the M1-like macrophages target proliferating high-grade B cell lymphoma cells by releasing cathelicidin in a vitamin D-dependent manner. Instead, tumor-educated M2-like TAMs downregulate vitamin D metabolism and produce less cathelicidin resulting in failed cytotoxicity [192]. This phenomenon suggests that reduced cathelicidin from TAMs mediates ADCC resistance. Another recent report found that TAMs release deoxycytidine, based on liquid chromatography coupled tandem mass spectrometry metabolomics, which induces gemcitabine resistance by competitively inhibiting gemcitabine uptake in pancreatic ductal adenocarcinoma [193]. Using the colony-stimulating factor receptor 1 (CSFR1) inhibitor AZD7507, depleting TAMs prolongs survival in an autochthonous pancreatic cancer model. In summary, metabolites from TAMs affect multiple biological functions of the TME, especially remodeling the tumor immune microenvironment. With the clinical application of immunotherapy, an evaluation of metabolic flux in TAMs might guide tumor immunotherapy and elucidate the mechanism underlying drug-resistance and tumor

immunotherapy progression.

Conclusions and Perspectives

Outstanding achievements have been made with respect to tumor immunotherapy; however, we still cannot completely overcome tumors. Chimeric antigen receptor (CAR)-T therapy effectively saves patients from refractory B cell malignancies, especially acute lymphoblastic leukemia (ALL), but the macrophage-involved cytokine-release syndrome (CRS) and neurotoxicity after CAR-T injection are associated with life-threatening consequences [194, 195]. Some cytokines from macrophages have been identified in CAR-T-mediated CRS and neurotoxicity, such as IL-1 and IL-6. However, no metabolites have been clarified in this field. Meanwhile, even after receiving immune-checkpoint inhibitors, a so-called hyperprogressive phenomenon is observed in the clinic [196]. The mechanism of hyperprogression in immunotherapy has puzzled clinical immunologists. We might consider that the phenotype of TAMs becomes tumoricidal after immunotherapy, but little is known about the metabolic changes in these cells. An analysis of unique shuttling metabolites between TAMs and the TME might help us understand hyperprogression in immunotherapy.

Even though the M1/2 classification is useful to analyze macrophages *in vitro*, this oversimplification cannot convey the heterogeneity of TAMs *in vivo*. Recent studies have indicated that TAM subsets cannot be explained by the M1/2-associated genes [197-199]. Using single-cell RNA sequencing and/or mass cytometry, the immune landscape of the TME has been revealed in human clear cell renal cell carcinoma [200], breast cancer [201], hepatocellular carcinoma [199], brain cancer [202], and colon cancer [203]. Thus, combined with metabolomics, the subtype classification of TAMs will more abundantly reflect the heterogeneity of TAMs in the TME, and novel metabolic targets might be discovered.

Abbreviations

TME: tumor microenvironment; TAM: tumor-associated macrophage; IFN- γ : interferon- γ ; SIRP α : signal regulatory protein α ; OXPHOS: oxidative phosphorylation; TCA: tricarboxylic acid; ATP: adenosine triphosphate; MCT1: monocarboxylate transporter 1; MCT4: monocarboxylate transporter 4; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; HIF1 α : hypoxia-inducible factor 1 α ; GPCRs: G protein-coupled receptors; ICER: inducible cyclic AMP (cAMP) early repressor; FAO: fatty acid oxidation; SDH: succinate dehydrogenase; SUCNR1: succinate receptor; P2XRs and P2YRs: P2 purinergic receptors; PGE2: prostaglandin E2; CREB:

cyclic AMP-responsive element binding; mTOR: mammalian target of rapamycin; RA: retinoic acid; ATRA: all trans-retinoic acid; MMP12: matrix metalloproteinase 12; RORC1/ROR γ : retinoic-acid-related orphan receptor; MDSCs: myeloid-derived suppressor cells; AHR: aryl hydrocarbon receptor; POSTN: periostin; GSCs: glioma stem cells; Klf4: Kruppel-like factor 4; HRG: histidine-rich glycoprotein; PIGF: placental growth factor;IDO: indoleamine 2,3-dioxygenase; SREBP1: sterol regulatory element-binding protein 1; HDC: histidine decarboxylase; PGD2: prostaglandin D2; LTB4: leukotriene B4; LTC4: leukotriene C4; PGH2: prostaglandin H2; H-PGDS: hematopoietic prostaglandin D2 synthase; L-PGDS: lipocalin prostaglandin D2 synthase; 5-LOX: 5-lipoxygenase; CAFs: cancer-associated fibroblasts; α -SMA: smooth muscle actin; FSP1: fibroblast specific protein 1; NG2: neuron-glia antigen-2; Cav-1: caveolin-1; ADMA: asymmetric dimethyl arginine; BHB: beta-hydroxybutyrate; HCA2: hydroxycarboxylic acid receptor 2; STC1: stanniocalcin-1; UCP2: uncoupling protein 2; CAAs: cancer-associated adipocytes; APN: adiponectin; AdipoRs: adiponectin receptors; ADRP: adipose differentiation-related protein; CMKLR1: chemokine-like receptor 1; A-FABP: adipose fatty acid binding protein; NSCLC: non-small cell lung cancer; Arg1: arginase 1; TIAM1: T cell lymphoma invasion and metastasis 1; ABHD5: abhydrolase domain-containing 5; REDD1: regulated in development and DNA damage response 1; ADCC: antibody-dependent cellular cytotoxicity; CSFR1: colony stimulating factor receptor 1; CAR: chimeric antigen receptor; ALL: acute lymphoblastic leukemia; CRS: cytokine-release syndrome.

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Competing Interests

The authors have declared that no competing interest exists.

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