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Control of tumor-associated macrophage responses by nutrient acquisition and metabolism

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Summary

Metazoan tissue specification is associated with integration of macrophage lineage cells in sub-tissular niches to promote tissue development and homeostasis. Oncogenic transformation, most prevalently of epithelial cell lineages, results in maladaptation of resident tissue macrophage differentiation pathways to generate parenchymal and interstitial tumor-associated macrophages that largely foster cancer progression. In addition to growth factors, nutrients that can be consumed, stored, recycled or converted to signaling molecules, have emerged as crucial regulators of macrophage responses in tumor. Here we review how nutrient acquisition through plasma membrane transporters and engulfment pathways control tumor-associated macrophage differentiation and function. We also discuss how nutrient metabolism regulates tumor-associated macrophages, and how these processes may be targeted for cancer therapy.

eTOC Blurb

Oncogenic transformation drives maladaptation of resident tissue macrophage differentiation pathways to generate tumor-associated macrophages (TAMs) that largely promote cancer progression. Zhang, Ji, and Li review how metabolism controls TAM development and function. They discuss how nutrients acquired through plasma membrane transporters and engulfment pathways are metabolized to control TAMs, and how these processes may be targeted for cancer therapy.

Introduction

Metazoan is characterized by cell differentiation and organization as tissues. The tissue mass is composed mostly of parenchymal cells that execute tissue-specific functions, such as

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epithelial cells that make up all body surfaces and many internal glands to mediate filtration, absorption, excretion, secretion and barrier protective functions. The interstitial part of tissue consists of endothelial cells, fibroblasts, nerves and acellular extracellular matrix (ECM) with infrastructural functions that are largely tissue-agnostic. Cells of the hematopoietic lineage including macrophages are further recruited, with resident tissue macrophages (RTMs) adapted to sub-tissular parenchymal and interstitial niches, promoting tissue development and homeostasis aside from the classical roles of macrophages in host defense against infections[1–9]. Parenchymal cells, particularly those of the epithelium lineages, have a high turn-over rate, and are susceptible to cell transformation[10], accounting for 80–90% human malignancies (https://training.seer.cancer.gov/disease/categories/classification.html). The macrophage compartment in the tumor tissue can as well undergo dynamic remodeling with tumor-associated macrophages (TAMs) making up to 50% of the tumor mass[11–14].

Tumors are fast growing and metabolically demanding tissues and rewiring of metabolic pathways in genetically altered cancer cells has been well documented[15]. Acquisition of nutrients delivered systematically and generated locally by highly adaptable TAMs constitutes another major facet of the metabolic network in the tumor microenvironment[16–21]. Of note, in addition to transporter-mediated nutrient uptake, TAMs are highly capable of scavenging nutrients through engulfment that can be further associated with their detoxification function, befitting the professional phagocyte identity of macrophages. In this review, we will discuss TAM responses from the perspective of cancer as a tissue-level disease with a focus on how nutrient uptake and metabolism regulate TAM differentiation and function.

TAMs as maladapted RTMs

RTMs and TAMs in healthy and tumorous epithelial tissues have been extensively profiled showing cross-tissue transcriptome similarities of macrophage subsets associated with parenchymal and interstitial localizations[22–26], suggesting that there are unique features related to tissue architecture to regulate the differentiation and function of parenchymal RTMs or TAMs (pRTMs, pTAMs), and interstitial RTMs or TAMs (iRTMs, iTAMs) (Figure 1A).

The sub-tissular dichotomous differentiation phenotypes of RTMs and TAMs are best demonstrated in mouse mammary gland, where macrophages are dynamically regulated in response to tissue remodeling during development, reproduction cycle as well as sporadic tumor growth driven by oncogenic cell transformation. In healthy mammary gland, iRTMs numerically dominate, while pRTMs are locally enriched alongside epithelial mammary gland branches[27]. iRTMs are initially derived from fetal liver monocytes and are largely maintained by self-renewal throughout the postnatal development[28]. The interstitial region is highly enriched for ECM compared to the mammary gland ductal structure formed by layers of epithelial cells. Depletion of macrophages by administration of an inhibitor against colony stimulating factor 1 receptor (CSF1R) causes increased level of interstitial ECM proteins, including collagen and Hyaluronic acid (HA)[29]. The respective scavenger receptors for collagen and HA are mannose receptor C-type 1 (Mrc1) and lymphatic vessel endothelial hyaluronan receptor 1 (Lyve1)[30,31], markers for iRTMs[22,23]. Although Mrc1

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and Lyve1 expression largely overlaps, Mrc1 is more broadly expressed in iRTMs. Of note, $Mrc1^{+}Lyve1^{-}$ iRTMs are enriched in interstitial regions close to the mammary gland epithelium[29], where iRTMs may interact with the Notch receptor ligand delta-like 1 (Dll1) expressed by epithelial stem cells[32] to suppress Lyve1 expression[33]. These findings imply further heterogeneity of interstitial niches governing the differentiation of iRTM subsets and suggest prominent functions of iRTMs in ECM remodeling.

Localized between luminal and basal layers of ductal epithelium, the embryonic monocyte-derived pRTMs are a rare population in virgin mammary gland[27]. However, during pregnancy and lactation, pRTMs are differentiated from circulating monocytes, and undergo massive expansion to accommodate the expanded epithelium[27], which is likely because local proliferation of pRTMs is outpaced by the expanding parenchyma niche, causing the *de novo* pRTM differentiation from monocytes. Short term depletion of pRTMs results in the accumulation of apoptotic alveolar cells and enlargement of mammary gland lumen during post-lactation involution, indicating a critical scavenger function of pRTMs and its role in tissue remodeling. Together, these studies reveal that iRTMs and pRTMs are differentiated in distinct sub-tissular niches of the mammary gland to fulfill specialized functions during development and the reproductive cycle.

Before the characterization of mammary tissue iRTMs and pRTMs, the dichotomous differentiation of macrophages had been revealed in a transgenic model of mammary tumors driven by the polyoma middle T (PyMT) oncoprotein[34]. Unlike in healthy mammary gland of young mice, circulating monocytes contribute to not only the highly expanded vascular cell adhesion molecule 1 $(Vcam1)^{+}$ TAMs but also $Mrc1^{+}$ mammary tissue macrophages in PyMT mammary tumors[34], which are localized in the intratumor parenchymal and peritumor interstitial regions, respectively[35], and herein renamed as pTAMs and iTAMs. These findings suggest that the interstitial niche for macrophages undergoes remodeling during tumor progression, which is in line with the observation that iTAMs at various stages of tumor progression are transcriptionally deviated from iRTMs in mammary tissue[22]. Phenotypically similar iTAMs that express the ECM scavenge receptors MRC1 and LYVE1 as well as the folate receptor beta (FOLR2) are also present in human breast tumors[22], which are distinct from pTAMs that express high levels of the lipid endocytosis receptor triggering receptor expressed on myeloid cells 2 (TREM2)[22]. Of note, Trem2 is highly induced in pTAMs from PyMT tumors, and is only minimally expressed in pRTMs from healthy lactating mammary glands (our unpublished observation), suggesting phenotypical adaptation of pTAMs in the tumor microenvironment. Interestingly, Trem2 is also induced in macrophages associated with neuronal and metabolic disorders[36–40]. As damage occurs in diseased tissues, it is conceivable that Trem2 is induced in macrophages to facilitate the clearance of tissue damage-associated lipids. Thus, pTAM differentiation is not only specified by ‘hard-wired’ signals associated with an expanding parenchymal epithelial niche similar to that of pRTM, but also regulated by ‘on-demand’ signals such as damage-associated molecules present in tumorous tissues.

Tissue-level specification of macrophage differentiation underscores the importance of using autochthonous tumor models such as transgenic cancer models to study TAM responses (Figure 1D). Yet, transplantation tumor models have been widely used in the

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field. Although these models could recapitulate some aspects of TAM responses including Trem2 expression[41], they fall short in reproducing critical aspects of human cancer patient TAM biology. For instance, transplanted cancer cells, even through the orthotopic route, often fail to be integrated to the endogenous tissue that provides critical signals for TAM differentiation[42]. In addition, most of the commonly used murine cancer cell lines of epithelial origin show a mesenchymal phenotype[43], and will not provide the same niche signal for pTAM differentiation. It is also important to note that human cancers are genetically heterogeneous, driving distinct immune responses in tumor[44]. In some cases, oncogenic events may disrupt or alter the tissue niche specifying the differentiation of TAMs as maladapted RTMs, causing TAM depletion or acquisition of a distinct differentiation pathway, and will also be better defined in autochthonous tumor models. Therefore, in order to best recapitulate human TAM biology, it is crucial to use autochthonous tumor models to preserve tissue-level regulation of macrophage responses in cancer.

Macronutrient uptake and metabolism in control of TAM responses

In addition to growth factor signals that drive tissue niche-associated TAM differentiation, nutrients delivered systemically through circulation and generated locally in the tumor tissue affect the metabolic and functional states of TAMs (Figure 1B and 1C). Nutrient control of TAM responses is affected by several factors including the tumor tissue origin, cancer cell oncogenomic profiles and stages of tumor progression, while tumor model choice is another confounding factor. In this section, we will discuss how TAM differentiation and function are regulated by macronutrients acquired through plasma membrane transporters (Figure 2).

Carbohydrate serves as a major energy and carbon source. Glucose as the most abundant monosaccharide undergoes glycolysis to generate adenosine triphosphate (ATP) and carbon intermediates to support TAM metabolism[45]. *In vivo* glucose uptake assays showed that $CD11b^+$ myeloid cells including $F4/80^+$ TAMs have the highest capacity to take up glucose in transplantation tumor models[46]. Consistent with this observation, histological analysis showed that glucose transporter 1 (GLUT1) is highly expressed in TAMs localized in hypoxic regions of both transplanted and autochthonous murine breast tumor tissues[47]. In human hepatocellular carcinoma (HCC) samples, high GLUT1 expression is also observed in TAMs compared to macrophages in nontumor regions[48]. In an orthotopic murine pancreatic ductal adenocarcinoma (PDAC) transplantation tumor model, lysozyme M-cre ($LysM^{cre}$)-mediated GLUT1 depletion in TAMs suppresses tumor development through natural killer (NK) cell- and $CD8^+$ T cell-dependent mechanisms[49]. Although this study cannot directly prove that TAM glucose uptake promote cancer progression as $LysM^{cre}$ can also target neutrophils, it suggests that the immunosuppressive function of TAMs is dependent on GLUT1.

Glucose metabolism initiates with a multi-step process of glycolysis (Figure 2A). Glycolytic activities and mRNA expressions of glycolytic enzymes including glucose 6-phosphate isomerase (GPI), phosphofructokinase-B1 (PFKB1), aldolase-A (ALDOA), phosphoglycerate kinase (PGK), and pyruvate kinase-M2 (PKM2) are increased in peritoneal macrophages following transplantation of PDAC tumors[49]. In addition, TAMs from PyMT tumors express high levels of hexokinase-2 (HK2) and PFKL[50]. Furthermore,

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high glycolytic activities are observed in $CD14^+$ monocytes/macrophages from both tumor parenchymal and peritumoral regions of human HCC samples[51,52]. Enhanced glycolysis in TAMs may be induced by cancer cell-derived factors, as both human and murine macrophages cultured with cancer cells or cancer cell-derived supernatant display enhanced glycolytic activities in several settings[50,53,54]. More mechanistical studies should be performed to further clarify how TAM glycolysis is induced in the afore-described tumor models, and whether glycolysis is differently regulated in pTAMs and iTAMs. It is also important to note that lower level of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) activity is observed in TAMs from human colon tumors than colonic RTMs[55]. Although lack of analysis of the whole glycolytic pathway, this study suggests that TAM glucose metabolism varies in different tumor models.

6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) catalyzes the conversion of fructose-6-phosphate (F6P) to fructose-2,6-bisphosphate (F2,6BP) that functions as a potent allosteric activator of the glycolytic enzyme 6-phosphofructokinase-1 (PFK-1). Inhibition of PFKFB3 impairs the production of C-X-C motif chemokine ligand 2 (CXCL2) and CXCL8[51] as well as expression of programmed death-ligand 1 (PD-L1)[52] in HCC supernatant-treated human monocytes *in vitro*, which has been associated with activation of nuclear factor κ B (NF-κB) signaling[51,52]. Glycolysis-dependent PD-L1 expression in human HCC TAMs has also been shown to be dependent on PKM2[56], which may be mediated by the stabilization of hypoxia-inducible factor-1α (HIF)-1α[57]. These observations suggest that TAM glycolysis may promote the immunosuppressive function of TAMs through the induction of chemokine and PD-L1 expression by modulating TAM signaling (Figure 2B). The signaling regulation function of glycolysis in T cells has recently been shown to be rooted in glycolytic ATP production[58,59]. Whether such mechanisms operate in TAMs is also open for investigation.

The end-product of glycolysis, pyruvate, has distinct metabolic fates under different conditions. The tumor parenchyma has often low oxygen levels. In this case, pyruvate in pTAMs is predicted to be mainly reduced by lactate dehydrogenase (LDH) to generate lactate in the cytosol, rather than enter mitochondrion to fuel tricarboxylic acid (TCA) cycle or replenish TCA cycle metabolites mediated by pyruvate dehydrogenase (PDH) or pyruvate carboxylase (PC), respectively. Under hypoxic conditions, HIF-1α-induced PDH kinase 1 (PDK1) phosphorylates and inactivates PDH, and thus promotes shunting of pyruvate to the lactate pathway. Indeed, increased PDK1 expression was observed in TAMs from human HCC samples[51,52]. In addition, PC expression is diminished in TAMs from both mouse and human melanomas, and pharmaceutic activation of PC in TAMs suppresses mouse melanoma progression[60]. These studies imply that mitochondrial pyruvate metabolism is attenuated in TAMs, and lactate generation may be the dominant metabolic fate of pyruvate. Indeed, increased LDH-A expression was observed in TAMs from both human and murine cancers[49,51,52]. In addition, primary human macrophage co-cultured with MCF-7 cancer cells upregulated LDH-A[61], suggesting that cancer cell-derived factors could also promote pyruvate to lactate conversion. Depletion of LDH-A prevents lactate production in TAMs, decreases expression of PD-L1 and the proangiogenic vascular endothelial growth factor-α (VEGF)-α, and inhibits tumor progression in a K-Ras-mediated lung cancer model[62].

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Lactate can be exported or imported via monocarboxylate transporters (MCTs) belonging to the SLC16A family[63]. MCT1 and MCT2 can transport molecules with one carboxylate such as lactate, pyruvate and ketone bodies bidirectionally dependent on the concentration gradient of substrates, while MCT3 and MCT4 are efficient lactate exporters[63]. Histological analysis showed that MCT1 and MCT4 expression is positively associated with CD163-expressing TAMs in tumors from human breast cancer[64] and oral squamous cell carcinoma[65], respectively, but their function remains to be determined. Aside from its metabolic function, lactate can act as a signaling molecule sensed by membrane receptors expressed on TAMs. G protein-coupled receptor 132 (GPR132) is a pH-sensing GPCR, and lactate activation of GPR132 triggers TAM expression of a number of chemokines including C-C motif ligand 17 (CCL17) and CCL22 to promote breast cancer metastasis[66]. In addition, the odorant receptor Olfr78 in TAMs can work together with GPR132 to sense lactate and promote tumor growth and metastasis in a lung transplantation tumor model[67]. Tumor-derived lactate has also been shown to promote VEGF-α expression in TAMs via HIF-1α[68]. Furthermore, lactate can modify histone and regulate gene expression through lactylation[69]. Those findings suggest that lactate may directly regulate TAM signaling and gene expression to promote tumor development.

In addition to glucose catabolism, the metabolic intermediates of glycolysis can be shunted towards a number of anabolic pathways (Figure 2A). Of note, G6P can go through the pentose phosphate pathway (PPP) to generate nicotinamide adenine dinucleotide phosphate (NADPH) as well as ribose 5-phosphate, which is the precursor for *de novo* purine and pyrimidine nucleotide biosynthesis. Single-cell RNA-sequencing (scRNA-seq) studies revealed that the terminal differentiated $Trem2^{+}$ TAMs exhibit high purine metabolism than other macrophages in an MC38 liver metastasis model, and high purine metabolism in TAMs is associated with poor clinical outcomes[70], but whether the PPP pathway supports the tumor-promoting function of TAMs remains to be determined.

F6P together with glutamine can be shunted to the hexosamine biosynthesis pathway (HBP) and form uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc), which acts as glycosyl donors in glycosylation reactions including O-linked-N-acetylglucosaminylation (O-GlcNAcylation) mediated by O-GlcNAc transferase (OGT). In a B16 transplantation tumor model, $MHC\text{-}II^{low}$ TAMs have high OGT expression. O-GlcNAcylation of the protease capthepsin B maintains its high expression and promotes lung cancer metastasis and chemoresistance[71]. TAMs under hyperglycemia conditions promote tumor progression in an MC38 transplantation tumor model, which is also likely dependent on O-GlcNAcylation as glutamine antagonist or the HBP inhibitor 6-Diazo-5-oxo-L-norleucine (DON) can rescue the tumor phenotype[72]. Of note, in a transplantation mammary tumor model, the cellular UDP-GlcNAc level is associated with the immunosuppressive function of TAMs, which may be dependent on glycosylation of the transcription factor signal transducer and activator of transcription 6 (STAT6)[73], implying a signaling function of glycosylation in control of TAM responses (Figure 2B).

Another glycolytic intermediate dihydroxyacetone phosphate (DHAP) can be converted to glycerol 3-phosphate (G3P) by glycerol-3-phosphate dehydrogenase (GPD1). G3P can be further catalyzed by G3P acyltransferases (GPATs) to form phosphatidic acid, which

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is essential for triacylglycerol (TAG) biogenesis, and the TAG metabolic pathway has an important function in TAMs (see below).

The glycolytic intermediate 3-phosphoglycerate (3-PG) can be catalyzed by phosphoglycerate dehydrogenase (PHGDH) and phosphoserine aminotransferase (PSAT) to form serine and participate in the one-carbon metabolism pathway. Compared to RTMs, TAMs from human lung carcinoma have elevated activities of the serine/glycine one-carbon metabolism pathway[74]. In a B16-F10 transplantation tumor model, LysM^{cre}-mediated PSAT1 depletion diminishes the TAM population, and suppresses tumor growth[74], suggesting that the *de novo* serine synthesis pathway is critical to support TAM responses.

The mitochondrial TCA cycle serves as a hub to connect several metabolic pathways including glucose metabolism (Figure 2A). Completion of the TCA cycle produces NADH and flavin adenine dinucleotide ($FADH_2$) that are mostly oxidized through the electron transport chain (ETC) with the built-up proton gradient driving mitochondrial ATP production through the process of oxidative phosphorylation (OXPHOS)[75]. As the tumor microenvironment is relatively hypoxic, the oxygen level may not be high enough to support a robust ETC flow in TAMs[76]. Yet, in an MC38 transplantation tumor model, the abundance of TCA cycle metabolites increases in TAMs during tumor progression[77], suggesting that high TCA flow in TAMs may provide metabolite intermediates to support metabolic events other than OXPHOS. Itaconate is derived from cis-aconitate by aconitate decarboxylase 1 (ACOD1), best known as immune-responsive gene 1 protein (IRG1). IRG1 expression and itaconate production in peritoneal macrophages are elevated following peritoneal tumor inoculation[78], which is in line with the observation that IRG1 expression in monocytes from human peritoneal tumor ascites is increased[78]. Knockdown of IRG1 in peritoneal macrophages reduces the tumor burden[78], supporting a pro-tumor function of TAM-produced itaconate. Moreover, elevated IRG1 expression is observed in TAMs isolated from GL261 glioma-bearing mice, and IRG1-deficient TAMs from late-stage glioblastoma express high levels of transcripts that encode proteins involved in antigen presentation and inflammatory responses[79]. As itaconate can function as an anti-inflammatory metabolite by inhibiting succinate dehydrogenase (SDH) activity to prevent mitochondrial reactive oxygen species (mROS) production[80], future studies will reveal whether similar mechanisms operate in TAMs to promote tumor development (Figure 2B). Succinate is another metabolite with important immunomodulatory functions. Cancer cell-derived succinate activates succinate receptor SUCNR1 to trigger tumorigenic TAM signaling via the PI3K-HIF-1α axis[81]. In addition, intracellular succinate promotes IL-1β production by stabilizing HIF-1α[82], and enhances mROS production by fueling TCA cycle and ETC through SDH[83] in macrophages, but its function in TAMs remains to be clarified. Thus, TAMs exhibit enhanced glucose consumption to support several metabolic pathways and regulate cell signaling, which appears to promote the immunosuppressive function of TAMs.

Lipid droplet formation in TAMs occurs in several human and murine malignancies[84–89], suggesting that TAMs actively acquire and/or synthesize lipid, but have low lipid degradation activity. This is likely because mitochondrion-driven fatty acid oxidation (FAO) is not robust in the low-oxygen tumor microenvironment. CD36, also known as fatty acid translocase, is a member of class B scavenger receptor family and can directly import

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multiple substrates including long-chain fatty acids (LCFAs)[90]. CD36-mediated lipid uptake promotes TAM differentiation and supports tumor growth[84]. In a murine liver metastasis model, macrophages in the liver can also take up tumor microvesicles via CD36, which may contribute to the establishment of a premetastatic niche[91]. Cytosolic citrate can be converted to acetyl-CoA by ATP citrate synthase (ACLY), which is critical for *de novo* fatty acid synthesis[92]. In MC38 and 3LLR transplantation tumor models, $LysM^{cre}$-mediated ACLY depletion does not affect tumor growth, and only slightly affects TAM phenotypes[93]. Those observations suggest that fatty acid uptake but not citrate-mediated *de novo* fatty acid synthesis supports the tumor-promoting function of TAMs (Figure 2A).

The imported cytoplasmic LCFAs bind to fatty acid-binding proteins (FABPs) that facilitate LCFA transportation to subcellular compartments[94]. Epidermal FABP (E-FABP, or FABP5) and adipocyte/macrophage FABP (A-FABP, or FABP4) are highly expressed in macrophages, but they appear to have distinct functions in control of murine breast cancer growth and metastasis[95,96]. FABP5 suppresses E0771 breast cancer growth and metastasis through mechanisms that are dependent on TAM expression of interferon-β (IFN-β), and the frequency of FABP5-expressing TAMs is negatively associated with human breast cancer progression[95]. On the contrary, FABP4 promotes E0771 and PyMT breast cancer progression and metastasis through mechanisms that are dependent on TAM expression of interleukin-6 (IL-6)[96]. Whether the opposing functions of FABP4 and FABP5 are caused by their distinct roles in different subsets of pTAMs and iTAMs is unknown. The underlying mechanisms by which FABPs regulate cytokine expression are also open for future investigation.

Peroxisome proliferator-activated receptors (PPARs) including PPAR-α, PPAR-β/δ and PPAR-γ are a group of nuclear receptor proteins that bind to cytosolic lipid ligands (Figure 2B). Once activated, PPARs enter the nucleus and form heterodimers with retinoid-X receptor (RXR) to induce expression of target genes including those involved in lipid catabolism. Caspase 1 in TAMs could cleave PPAR-γ to inhibit FAO, and caspase 1 deficiency decreases lipid accumulation in TAMs resulting in diminished PyMT mammary tumor growth[87]. As caspase 1 is produced as a latent enzyme, and can be activated by the inflammasome pathway, whether and how inflammasome is induced in TAMs to regulate lipid metabolism remain to be determined.

As a major component of lipid droplet, TAG can be broken down into diacylglycerols (DAGs) by adipose triglyceride lipase (ATGL), hydrolyzed into monoacylglycerols (MAGs) by hormone sensitive lipase (HSL), and further catalyzed into free fatty acids and glycerol by monoacylglycerol lipase (MGLL). Low MGLL expression is detected in TAMs, and overexpression of MGLL prevents lipid accumulation in TAMs, causing $CD8^+$ T cell-dependent tumor suppression in an MC38 transplantation tumor model[85]. MGLL promotes the degradation of 2-arachidonoylglycerol (2-AG), a ligand for cannabinoid receptor 2 (CB2), and thereby reverses the CB2-mediated immunosuppression in TAMs[85]. MAGs can be converted to DAG and TAG by acyltransferases with diglyceride acyltransferase (DGAT) catalyzing the formation of TAG from DAG (Figure 2A). DGAT1-mediated TAG synthesis enhances the production of proinflammatory mediators including prostaglandins E2 (PGE2) and IL-1β in macrophages[97]. As PGE2 inhibits anti-tumor immune responses

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(see below), the DGAT pathway in TAMs may have pro-tumor functions. Indeed, liposome-mediated delivery of a DGAT inhibitor to phagocytes suppresses MCA205 fibrosarcoma tumor development, which is associated with reduced lipid droplet formation and increased $CD8^+$ T cell proliferation in tumor[86]. Together, these findings demonstrate an important function for TAG biosynthesis in promoting the immunosuppressive function of TAMs.

A number of lipids and lipid derivatives function as important signaling molecules (Figure 2). Membrane phospholipids can release arachidonic acids to generate PGE2 catalyzed by cyclooxygenase (COX) enzymes COX1 or COX2 and PGE synthase (PGES). PGE2 binds to PGE2 receptors, and thereby activates the downstream cAMP and Ca^{2+}-mediated signaling pathways. Expression of genes in the arachidonic acid-PGE2 pathway is positively associated with $TREM2^+$ pTAMs in human esophageal squamous cell carcinoma (ESCC)[98]. In addition, COX2 is highly induced in myeloid cells infiltrating the transplanted SW780 bladder tumors[99], and in $CD68^+$ macrophages infiltrating human melanoma[100]. Administration of microsomal PGES-1 (mPGES-1) and COX2 inhibitors or overexpression of the PGE2-degrading enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH) diminishes PGE2 production and inhibits PD-L1 expression in myeloid lineage cells *in vitro*[101]. In a macrophage T cell co-culture system, PGE2 produced by macrophages attenuates $CD4^+$ T cell proliferation[102], but the *in vivo* function of TAM-produced PGE2 remains to be determined. Furthermore, mPGES-1 is barely detectable in TAMs from human neuroblastoma tumors[103], suggesting that the COX/mPGES-1/PGE2 pathway may only be important in some tumor types. In addition to PGE2, arachidonic acids can be catalyzed by lipoxygenase such as 5-lipoxygenase (5-LO) to generate leukotrienes. 5-LO expression in TAMs from mouse and human primary breast tumors is lower than that in monocyte-derived macrophages generated *in vitro*, and 5-LO downregulation is dependent on apoptotic cell engulfment, which may inhibit T cell recruitment and thus exert an immunosuppressive function[104]. However, high expression of 5-LO and production of leukotriene B_4 (LTB_4) in alveolar macrophages promote HCC metastasis in lung[105]. Thus, macrophage production of leukotrienes may have opposing functions in control of tumor development. Aside from phospholipid-derived signaling molecules, cholesterol can be processed to generate vitamin D. Vitamin D binds to vitamin D receptor (VDR) and forms a heterodimer with RXR to control target gene expression. Inhibition of vitamin D-VDR binding in TAMs suppresses tumor progression in a transplantation breast cancer model[106], but the underlying mechanisms remain to be determined.

Ketone bodies including acetone, acetoacetate and β-hydroxybutyrate (BHB) are derived from fatty acids and can be converted to acetyl-CoA and fuel the TCA cycle. Ketogenic diets containing BHB target intestinal epithelial cells to suppress colorectal cancer (CRC) development[107]. BHB has also been shown to inhibit inflammatory responses triggered by the NLRP3 inflammasome in macrophage[108], while hepatocyte-produced acetoacetate can be oxidized in macrophages to inhibit the high-fat diet (HFD)-induced liver fibrosis[109]. Of note, BHB can bind to GPR109a and function as a signaling metabolite in macrophages[110], which promotes tissue repair in injury models including ischemic strokes[111], alcohol-induced liver injury[112], and DSS-induced colitis[113]. Nonetheless, the functions of ketone bodies in control of TAM responses have yet to be revealed.

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Amino acids are a special class of macronutrients that are used for protein biosynthesis and are converted to other metabolite for cellular regulation. Some cytosolic amino acids can also function as signaling molecules, notably, participating in the activation of the metabolic regulator mammalian target of rapamycin complex 1 (mTORC1) through a lysosomal Rag GTPase-mediated nutrient-sensing pathway[114] (Figure 2B). Branched-chain amino acids (valine, leucine, isoleucine) and aromatic amino acids are taken up by the heterodimer amino acid transporter CD98 composed of the heavy chain SLC3A2 and the light chain SLC7A5[115]. As leucine is one of the most critical amino acids that activates mTORC1[116], pharmaceutical inhibition of SLC7A5 diminishes mTORC1-mediated glycolysis and inflammatory cytokine production in activated macrophages *in vitro*[117]. Nonetheless, a role for CD98-mediated leucine uptake in control of mTORC1 signaling and metabolism in TAMs remains to be determined.

Tryptophan can also be imported through CD98, and further catabolized to kynurenine, with indoleamine 2,3-dioxygenase (IDO) being the rate-limiting enzyme (Figure 2). Depletion of tryptophan by IDO1-expressing human monocyte-derived macrophages suppresses T cell proliferation and activation *in vitro*[118]. Macrophage expression of IDO1 has also been shown to promote immune tolerance to apoptotic cells[119]. Nonetheless, whether the IDO1-meidated tryptophan catabolism non-redundantly contributes to the immunosuppressive function of TAMs remains to be determined. Cancer cells can also express IDO and produce kynurenine to activate aryl hydrocarbon receptor (AhR) in TAMs[120]. Kynurenine activation of AhR induces Kruppel-like factor 4 (KLF4) expression, but suppresses NF-κB activation, and AhR-deficient TAMs are poorly recruited to tumor, resulting in impaired growth of GL261 glioma cells[120]. Another study revealed that IDO-overexpressing B16 melanoma display an immunosuppressive phenotype, which is in part dependent on the kynurenine-AhR-mediated regulatory T (Treg) cell-TAM interplay[121]. Furthermore, tryptophan can be degraded by microbiota and generate indole-containing metabolites to activate AhR in TAMs, which promotes PDAC tumor progression by suppressing intra-tumoral $CD8^+$ T cell function[122]. Interleukin-4-induced-1 (IL4I1), an L-amino-acid oxidase, has recently been identified as a potent activator of the AhR pathway by promoting tryptophan catabolism to indole metabolites and kynurenic acid (Figure 2)[123]. scRNA-seq analyses revealed that an enriched $IL4I1^+IDO1^+PD\text{-}L1^+$ TAM subset is associated with T cell dysfunction in a number of human tumors[24]. Although the *in vivo* function of IL4I1 in TAMs has yet to be determined, those findings reveal an alternative metabolic pathway that may account for the immunosuppressive function of tryptophan catabolism. In addition to AhR, kynurenine can bind to the cell surface receptor GPR35[124]. $LysM^{cre}$-mediated GPR35 depletion suppresses tumor development in both genetic and carcinogen-induced CRC models in part mediated by attenuated tumor angiogenesis[125]. These studies suggest that tryptophan metabolites may be sensed by both intracellular and plasma membrane-localized receptors in TAMs to promote tumor development.

Positively charged amino acids including arginine are taken up by cationic amino acid transporters (CATs) SLC7A1–4[126]. Arginases including arginase 1 (Arg1) convert arginine to urea and ornithine as part of the urea cycle for nitrogen excretion. Ornithine can also be catalyzed by ornithine decarboxylase (ODC) to form putrescine, which is the precursor for polyamine biosynthesis (Figure 2A). Polyamines including spermidine and spermine

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promote cell proliferation and maintain tissue homeostasis[127]. Arg1 is highly expressed in TAMs[128], which is in part dependent on HIF-1α signaling, lactate, and granulocyte macrophage colony-stimulating factor (GM-CSF)[129 68,130,131]. Uptake of the metabolite creatine through the creatine transporter Slc6a8 has also been shown to sustain Arg1 expression in macrophages[132], but its role in TAMs is undefined. Arg1-expressing myeloid cells from transplanted Lewis lung carcinoma (LLC) tumors inhibit T cell proliferation in an *in vitro* culture system[133,134]. SLC7A2-mediated arginine uptake in tumor myeloid cells also suppresses T cell proliferation *ex vivo*[135]. Those observations suggest that the Arg1-mediated arginine consumption in TAMs may have an immunosuppressive function. In a number of transplantation tumor models, pharmaceutical inhibition of arginase by CB-1158 enhances arginine concentration and cytotoxic immune cell infiltration and inhibits tumor development[136]. Moreover, LysM^{cre}-mediated Arg1 deletion suppresses murine PDAC progression, which is associated with increased cytotoxic CD8^{+} T cell infiltration and activation[137]. The TAM regulation function of Arg1 may also act through polyamine. For instance, the arginine-polyamine pathway is induced in tumor-infiltrating myeloid cells to promote their survival, and depletion of polyamine prolongs mouse survival in transplantation models of brain tumor[138,139]. These findings suggest a tumor-promoting role of myeloid Arg1, but its specific function in TAMs remains to be determined.

Glutamine is an important non-essential amino aid that can be converted to glutamate by glutaminase (GLS). Conversely, glutamate can generate glutamine via glutamine synthetase (GS). Pharmaceutical inhibition of GLS by JHU083 suppresses transplanted 4T1 tumor progression and reprograms TAMs to a pro-inflammatory state associated with high expression of tumor necrosis factor-α (TNF-α) and co-stimulatory molecules[140], but it was unknown whether such reprograming was due to the blockade of GLS in TAMs. Of note, LysM^{cre}-mediated GLS depletion attenuates macrophage engulfment of apoptotic cells[141], and the impaired efferocytosis may account for the inflammatory phenotype of TAMs, as efferocytosis is largely anti-inflammatory (see below). CSF1R^{cre}-mediated depletion of GS does not affect primary LLC tumor growth, but impairs cancer cell metastasis, which was associated with high abundance of glutamate and succinate under the condition of GS inhibition in macrophages with succinate mainly derived from glucose, but not glutamine[142]. These observations suggest that glutamine/glutamate metabolism may interact with glucose metabolism to regulate macrophage responses, but the exact functions of such metabolic crosstalk in TAMs remain to be investigated.

Engulfment-mediated nutrient acquisition in control of TAM responses

Macrophages can manifest robust engulfment activity to support their scavenger function and provide an alternative route of nutrient acquisition. The transcription factor PU.1 specifies a core macrophage gene expression program including those involved in macrophage phagocytosis such as tyrosine-protein kinase Mer (MerTK) for efferocytosis and CD64 (FCγR1A) for antibody-dependent phagocytosis[143,144]. In addition, specialized scavenger receptor gene expression programs support discrete engulfment activity of macrophage subsets, including ECM scavenger receptors Mrc1 and Lyve1 for iTAMs, and the lipid scavenger receptor Trem2 for pTAMs. While interactions between scavenger receptors and their ligands trigger intracellular receptor signaling to promote phagocytosis

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and regulate inflammatory responses, the engulfed cargo generates nutrients that can be further metabolized and engaged in cell signaling (Figure 3).

A major scavenger function of RTM is apoptotic cell clearance, or efferocytosis. A number of receptors can mediate efferocytosis, including Tyro3, Axl and MerTK that are receptor tyrosine kinases sharing similar structures with two immunoglobulin-like repeats and two fibronectin type III repeats in the extracellular domain[145]. Upon ligand binding and receptor dimerization, autophosphorylation of intracellular kinase domain activates signaling and gene transcription programs that promote membrane and cytoskeleton remodeling in support of efferocytosis[146]. MerTK is indispensable for apoptotic cell clearance in mice[147], while Tyro3, Axl and MerTK collectively promote efferocytosis and suppress autoimmunity[148]. In a PyMT transgenic mammary tumor model, impaired clearance of apoptotic cells in mice on a MerTK-deficient background is associated with defective expression of anti-inflammatory cytokines and diminished cancer cell metastasis to lung[149]. Whether the tumor phenotype can be attributed to the depletion of MerTK in TAMs remains to be determined, as epithelial (cancer) cells can express MerTK and engulf apoptotic cells[150]. Nonetheless, in a CT26 transplantation tumor model, radiation-triggered tumor therapy is potentiated in MerTK-deficient recipient mice[151], and MerTK deficiency inhibits the development of Starry-sky B-cell lymphoma, where MerTK expression is highly restricted in TAMs[152]. These findings support a critical function for MerTK-mediated TAM efferocytosis in fostering cancer progression.

The T-cell immunoglobulin and mucin domain-containing protein (TIM) family receptors can also mediate clearance of apoptotic cells with TIM-4 being the major family member expressed on antigen presentation cells (APCs) including RTMs in liver, heart, intestine, adipose tissue and the peritoneal cavity[153–157]. In patients with metastatic non-small cell lung cancer (NSCLC) to serous body cavities, the frequency of TIM-4-expressing cavity-resident macrophages is inversely associated with the frequency of $CD8^+$ T cells that express the ectonucleotide triphosphate diphosphohydrolase CD39[158]. Importantly, anti-TIM-4 synergizes with anti-PD-1 to revive T cell responses and suppress peritoneal cancer cell metastasis in a murine model[158]. Loss of peritoneal TIM-4^+ TAMs is also associated with elevated T cell immunity and tumor inhibition for ID8 ovarian cancer cell line injected into mouse peritoneal cavity[159]. These observations further support an important function of TAM efferocytosis in promoting tumor development.

The metabolic outcome of macrophage efferocytosis has started to be revealed. Engulfment of apoptotic cells and their processing in the lysosome drastically increases the intracellular lipid level (Figure 3). High amounts of free intracellular cholesterol activate the transcription factor liver X receptor (LXR) that enhances expression of ATP-binding cassette transporter A1 (ABCA1) to promote cholesterol efflux, and MerTK to support continuous efferocytosis[160]. Activation of PPAR-δ, another lipid-sensing transcription factor, enables cellular adaptation to efferocytosis-derived lipids by promoting fatty acid metabolism[161,162]. Mice deficient in LXR or PPAR-δ accumulate dead cells in many tissues due to failure of efferocytosis, revealing a critical role of lipid signaling and metabolism in sustaining efferocytosis[163]. In addition, LXR and PPAR-δ induce expression of anti-inflammatory cytokines including transforming growth factor-β1 (TGF-β1) and IL-10[162], promoting the

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resolution of inflammation. In support of a critical role of apoptotic cell-derived lipids in metabolic reprogramming of macrophage, depletion of lysosomal lipidase lipidase A (LIPA) and phospholipase A2 group 15 (PLA2G15) that hydrolyze cholesteryl esters and phospholipids, respectively, impairs activation of LXR and PPAR-δ[164,165]. Inhibition of Niemann-Pick disease type C1 (NPC1)-mediated sterol transport from lysosome to cytosol as well prevents activation of LXR during efferocytosis[166]. Diminished expression of proinflammatory cytokines IL-1β and IL-6 during efferocytosis has also been shown to be mediated by the Rac GTPase-dependent import of polyamine through pinocytosis[139], but the molecular mechanisms and functions of this non-selective liquid phase engulfment pathway need to be further characterized in macrophages.

Lysosomal clearance of apoptotic cell DNA proceeds with DNA degradation and nucleoside export via equilibrative nucleoside transporter 3 (ENT3) (Figure 3), which is critical for the maintenance of an anti-inflammatory state of macrophage, as depletion of lysosomal DNase II triggers expression of the proinflammatory cytokine TNF-α in part through unmethylated CpG DNA-induced activation of toll-like receptor 9 (TLR9)[167,168]. Furthermore, efferocytosis generates short peptides and free amino acids that are exported from lysosome to cytosol[169]. Among all amino acids, arginine is the most upregulated amino acid following engulfment of apoptotic cells[170]. Efferocytosis-derived arginine and ornithine can further boost efferocytosis through the stabilization of mRNA encoding the GTP-exchange factor (GEF) Dbl and activation of the small GTPase Rac1, following their conversion to putrescine by Arg1 and ODC[170] (Figure 3). Thus, apoptotic cell-derived lipids and amino acids can be sensed and metabolized to sustain efferocytosis.

The afore-discussed metabolic outcomes of macrophage efferocytosis have yet to be directly evaluated in TAMs. It also remains to be determined whether efferocytosis is differentially regulated in iTAMs and pTAMs, and how cancer cell transformation mechanisms and tumor microenvironment signals affect TAM efferocytosis. Furthermore, the functional role of apoptotic cell clearance by TAMs can be modulated by phagolysosome cargo sorting with the LC3-associated phagocytosis promoting tumor immune tolerance[171]. How different apoptotic cell scavenge receptors engage different phagolysosome pathways to impact TAM function warrants further investigation.

The endocytosis receptor Mrc1 marks iRTMs and iTAMs[34,172], and mediates internalization of the ECM protein collagen[173–175] (Figure 3). In a lung tumor model, $Mrc1^+$ iTAMs display a matrix catabolism transcriptome signature[175], suggesting that collagens can be effectively engulfed and proteolyzed by iTAMs. Indeed, $Mrc1^+$ iTAMs are localized at the peripheral collagen-rich tumor region[131,176], and function to remodel the collagen matrix, which promotes cancer cell invasion and metastasis[176,177]. iTAMs can also express Lyve1, an endocytosis receptor for the ECM molecule HA[30] (Figure 3). Notably, Lyve1 expression marks a subset of iRTMs localized in close proximity to the blood vasculature across tissues[178]. In a PyMT transgenic mammary tumor model, depletion of $Lyve1^+$ iTAMs inhibits tumor development in association with disruption of a proangiogenic niche[179].

The metabolic outcome of Mrc1- and Lyve1-mediated ECM scavenging is poorly understood. Engulfment and proteolysis of ECM proteins in the lysosome generate high

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amounts of amino acids that may activate the metabolic regulator mTORC1 (Figure 3). In support of the hypothesis, iTAMs are metabolically more active with a larger cell size than pTAMs[22]. Interestingly, LysM^{cre}-mediated Raptor knockout promotes the accumulation of immune suppressive lung interstitial macrophages and Lewis lung cancer metastasis[180]. As mentioned above, cytosolic amino acids acquired through plasma membrane amino acid transporters can be sensed by Rag GTPases to promote mTORC1 signaling. However, mTORC1 activation by the lysosome-derived amino acids appears to be Rag GTPase-independent[181,182]. Future studies will reveal such mechanisms and define how the lysosome-derived amino acids from scavenged ECMs regulate iTAM differentiation and function.

Trem2 is a scavenger receptor of the immunoglobulin superfamily and can recognize endogenous phospholipids as its ligands[183–185] (Figure 3). Trem2^{+} macrophages are present in damaged tissues[39], and accumulate high levels of lipids in association with enrichment of a lipid metabolism gene expression signature[186]. In a murine model of diet-induced non-alcoholic steatohepatitis (NASH), the interstitial region-localized Kupffer cells and monocyte-derived macrophages upregulate Trem2[187], suggesting that Trem2 is induced in diverse populations of macrophages to clear damage-associated lipids. In contrast to NASH, Trem2 expression is limited to pTAMs in tumor, implying that damage-associated lipids are predominantly released by cancer cells in the tumor parenchyma. In transplantation tumor models, ablation of Trem2 or treatment with a Trem2 blocking antibody alters the TAM phenotype and synergizes with anti-PD-1 to revive anti-tumor T cell responses[41,188,189]. In a lung cancer model, Trem2 deficiency triggers NK cell-mediated suppression of tumor growth[190]. Collectively, these studies demonstrate a critical role for Trem2 in mediating the immunosuppressive function of TAMs.

The metabolic outcome of Trem2-mediated lipid scavenging in macrophages has started to be revealed. Trem2-deficient microglial fail to upregulate lipid metabolism, which can be rescued by an agonist for the lipid-sensing transcription factor LXR[40], suggesting that lipids scavenged by Trem2 are important signaling molecules. However, Trem2 ligands in the tumor microenvironment need be further characterized to understand their function in nutrient metabolism and signaling in TAMs. In addition to Trem2, a number of other lipid scavenger receptors including macrophage receptor with collagenous structure (Marco) and macrophage-inducible C-type lectin (Mincle) have been reported to control TAM responses (Figure 3). Marco-dependent lipid uptake in TAMs is associated with induction of an LXR gene expression program that tracks with short disease-free survival in prostate cancer patients with Marco targetable for cancer therapy in preclinical models[191]. Furthermore, Mincle-mediated lipid uptake supports the pro-tumor function of TAMs through the induction of an X-box binding protein 1 (XBP1)-mediated endoplasmic reticulum (ER) stress response[192]. Thus, blockade of the lipid scavenger function of TAMs may provide novel therapeutic strategies to inhibit their pro-tumor functions.

Iron is a trace element nutrient that primarily utilized by erythrocytes, but equally critical in all other cell types[193]. In addition to SLC39A8 and SLC39A14 transporter-mediated uptake of free iron, iron can be acquired through efferocytosis or endocytosis via specific receptors for ion in complex forms including that bound to transferrin, lipocalin, and heme[194,195]

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(Figure 3). Iron can be used as a metabolic cofactor, stored in macrophages in the form of a ferritin complex, or released through the transporter ferroportin (FPN)[196]. In models of microbial infection and tissue damage, iron-sequestering and iron-donating macrophage phenotypes have been observed at inflammatory and resolving phases of immune responses, respectively[197,198]. Iron metabolism in TAMs has also important functions in control of cancer progression. High level of iron accumulation in TAMs at the tumor edge, likely iTAMs, is associated with a pro-inflammatory phenotype and predicts favorable outcomes in multiple cancer types[199–201]. Yet, an iron-secreting and anti-inflammatory phenotype was observed in TAMs at the tumor core, likely pTAMs[202], and loading TAMs with iron repolarizes them to a pro-inflammatory phenotype and diminishes tumor growth[203]. Furthermore, LysM^{cre}-mediated knockout of low-density lipoprotein (LDL) receptor related protein 1 (LRP1 or CD91), the endocytic receptor for heme, promotes TAM infiltration to the tumor parenchyma and angiogenesis in an implanted mouse pancreatic adenocarcinoma model[204].

The metabolic outcome of engulfment-mediated ion uptake in TAMs has also started to be elucidated. TAMs at the tumor margin express high level of heme oxygenase 1 (HO-1) that degrades intracellular heme exported out of the lysosome via heme-responsive gene 1 protein homolog (HRG1)[205]. LysM^{cre}-mediated depletion of HO-1 triggers an immunostimulatory phenotype, suppresses angiogenesis in a transplantation model of sarcoma[205], inhibits cancer cell dissemination in a model of melanoma lung metastasis[205] and enhances anti-tumor vaccine efficacy in a subcutaneous thymoma model[206]. Thus, the TAM regulation phenotype of iron is dependent on iron metabolic pathways. While iron level modulates TAM polarization, iron metabolism crosstalk between TAMs and cancer cells may also be critical to regulate tumor growth. In a prostate tumor model, the anti-tumor effect of an iron-chelating reagent is negatively associated with infiltration of iron-laden TAMs[207], suggesting that TAMs maintain local iron homeostasis. In breast tumor models, TAMs at the tumor periphery express high levels of the iron carrier lipocalin 2 (Lcn2), that promotes iron transfer to cancer cells in an *in vitro* coculture system and cancer progression *in vivo*[208,209]. Leptomeningeal metastasis cancer cells also secret Lcn2 and express its receptor SLC22A17 to compete with macrophages for iron acquisition in the nutrient sparse subarachnoid space[210]. Therefore, iron is a limiting micronutrient in the tumor microenvironment, and TAMs can recycle iron to support cancer cell growth.

Concluding remarks

TAMs are maladapted RTMs with sub-tissular niche factors including the dynamically fluctuating nutrient source being a critical regulator of TAM differentiation and function. While the plasma membrane transporter-mediated uptake of glucose appears to majorly support the bioenergetic and biosynthetic needs of TAMs, lipids acquired via transporters or scavenger receptors are mostly stored in lipid droplets as a likely means to detoxify inflammatory lipids produced in the tumor tissue. A number of metabolites generated in glucose and lipid metabolism pathways as well as those converted from amino acids can also act as signaling molecules to promote scavenger and anti-inflammation functions of TAMs. Aside from nutrient consumption, storage and conversion to signaling molecules in TAMs, nutrients acquired through engulfment can be further exchanged with neighboring

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cells including cancer cells as a likely means to support their metabolic needs. Collectively, the nutrient acquisition and metabolism pathways appear to enable the tumor-promoting activities of TAMs as maladaptation of the tissue maintenance programs of RTMs. Nonetheless, the definitive functions of many nutrient acquisition and metabolism pathways in TAMs, including their differential regulation in pTAM and iTAM subsets, remain to be investigated, as autochthonous tumor models that recapitulate the tissue architecture associated with cell transformation have yet to be used in most studies. Of note, in a transgenic model of breast cancer, the immunosuppressive function of pTAMs is associated with their ability to present tumor-associated antigens to $CD8^+$ T cells and induce T cell exhaustion[211]. Whether such a tolerogenic function of pTAMs is metabolically regulated is open for investigation.

The pro-tumor activities of TAMs hamper patient responses to conventional chemotherapy and radiotherapy as well as immunotherapy. Notably, blockade of efferocytosis by anti-Mertk enhances TAM uptake of the endogenously produced immune stimulant 2'3-cyclic GMP-AMP (cGAMP) that activates stimulator of interferon genes (STING) signaling and synergizes with immune checkpoint inhibitors to suppress tumor growth[212]. Depletion of the potassium channel Kir2.1 in TAMs also diminishes efferocytosis, which promotes the accumulation of intratumoral cGAMP and the induction of type I IFN production leading to enhanced anti-tumor $CD8^+$ T cell responses[213]. Administration of the immune stimulant unmethylated CpG oligonucleotides also reprograms lipid metabolism in TAMs and facilitates phagocytic clearance of cancer cells both *in vitro* and *in vivo* regardless of their expression of the 'don't eat me' signal CD47[214]. Furthermore, TAMs may inhibit tumor growth by competing with cancer cells or other crucial stromal cells such as the endothelium for essential nutrients[47,210]. Reprograming TAMs by disengaging the tissue-supporting role and promoting the nutrient-competing function may as well represent a new cancer therapy approach. Considering the diverse cell transformation mechanisms and heterogenous immune profiles in tumors of different tissue origin, the functions of TAMs can thus be contextual. A deep understanding of nutrient acquisition and metabolism pathways in TAMs and their metabolic interaction with other components in the tumor microenvironment will help guide the development of mechanism-based cancer therapies by targeting the highly adaptable innate immune cell lineage.

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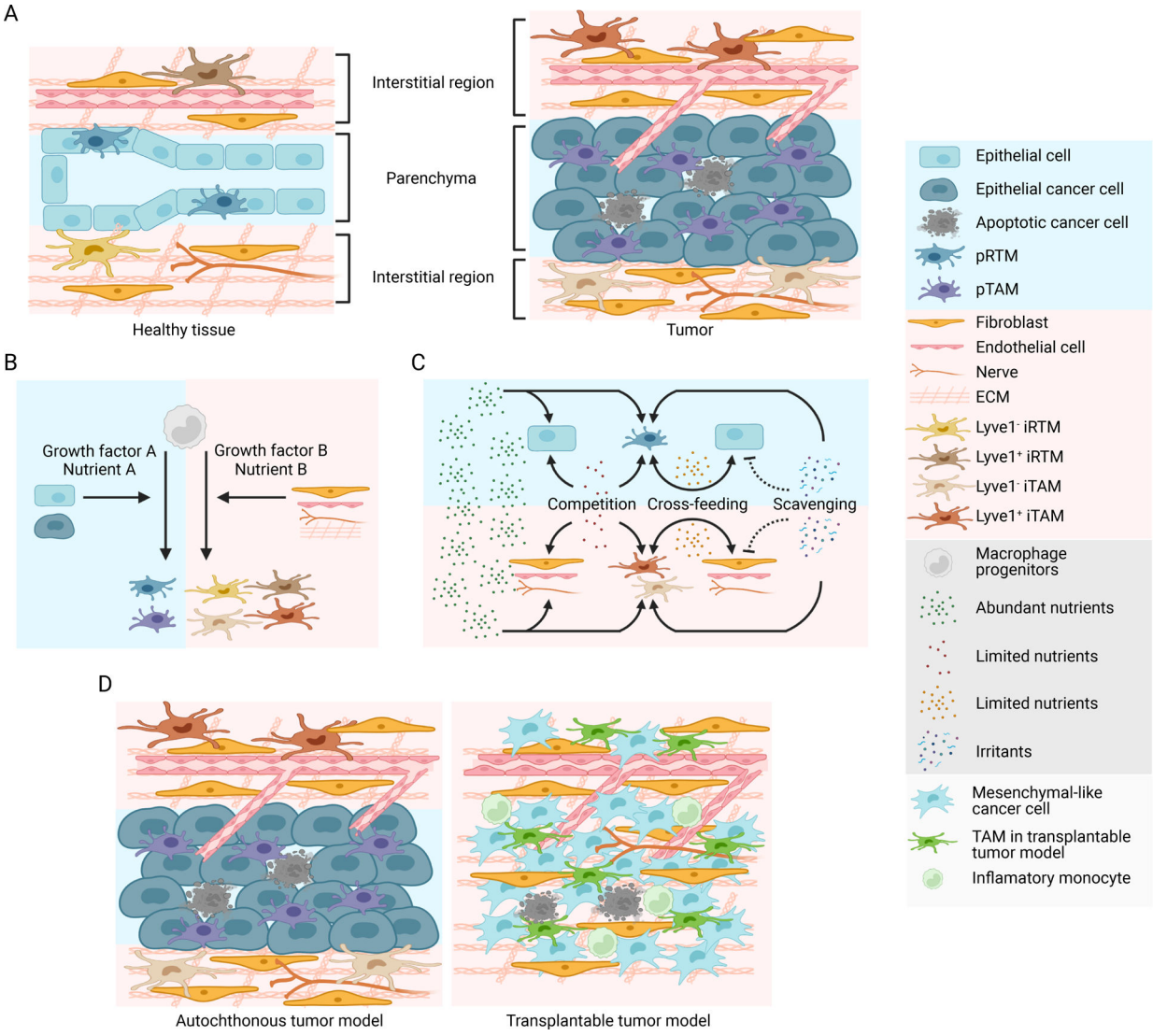

Figure 1. TAM subsets and metabolic crosstalk in the tumor microenvironment

A) A simplified schematic depicting healthy and tumorous epithelial tissues with phenotypically distinct resident tissue macrophages (RTMs) and tumor-associated macrophages (TAMs) localized in sub-tissular interstitial and parenchymal niches. Epithelial cell transformation is associated with expansion and phenotypic adaptation of cancer cell-associated parenchymal TAMs (pTAMs), while interstitial TAMs (iTAMs) with or without expression of the scavenger receptor Lyve1 are also adapted in interstitial regions composed predominantly of fibroblasts, endothelial cells, nerves, and acellular extracellular matrix (ECM).

B) RTM and TAM differentiation from macrophage progenitors is driven by tissue niche factors, including growth factors and nutrients as discussed in[1] for RTMs. The parenchymal and interstitial niche factors regulate differentiation of pRTMs/pTAMs and iRTMs/iTAMs, respectively.

C) Modes of metabolic crosstalk between TAMs, cancer cells and other cell types in the tumor microenvironment. Abundant nutrients are taken up by all cell types with no

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restriction, while limited nutrients can be cross-fed or competed between TAMs, cancer cells, and other cell types in the tumor stroma, promoting or inhibiting tumor growth, respectively. TAMs can also scavenge irritants that otherwise impair tumor tissue fitness and suppress tumor development.

D) A number of animal models have been used to study TAM responses in epithelial cancers. Autochthonous murine tumor models involve transformation of endogenous epithelial lineage cells, and preserve the parenchymal and interstitial tissue architecture with pTAMs and iTAMs differentiated in distinct sub-tissular niches. Transplantable murine tumor models involve inoculation of cancer cell lines propagated *in vitro* into target tissues, which fails to recapitulate the tumor tissue architecture. In addition, many cancer cell lines derived from epithelial tumors acquire mesenchymal phenotype during *in vitro* propagation. TAM responses in these models are often associated with acute influx of a large number of inflammatory monocytes with TAM differentiation poorly resembling that induced in human tumor.

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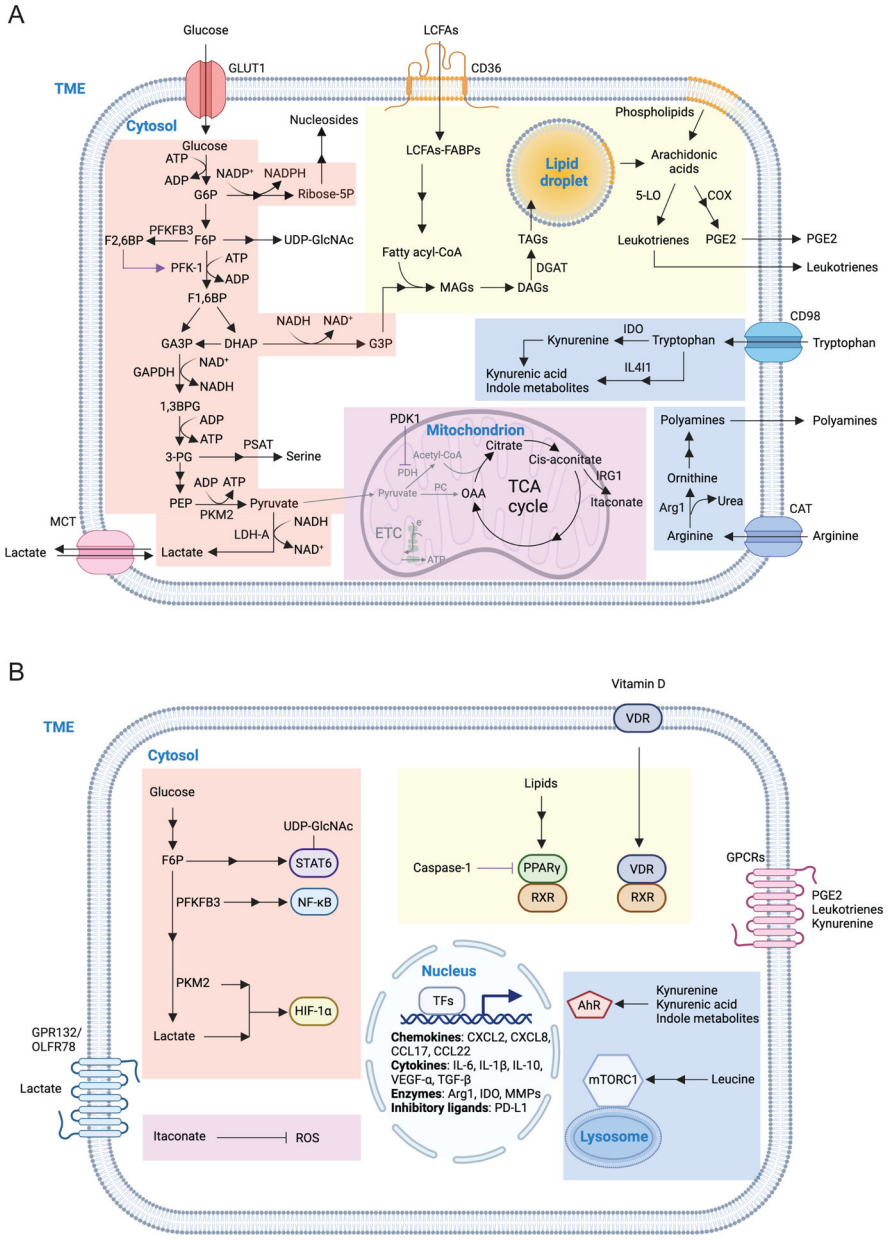

Figure 2. Macronutrient uptake and metabolism control of TAM responses

A) Macronutrients including glucose, lipids and amino acids are taken up by tumor-associated macrophages (TAMs) in the tumor microenvironment (TME) and are catabolized or converted to biosynthetic intermediates or signaling metabolites to regulate TAM responses. Glucose acquired through glucose transporter 1 (GLUT1) undergoes glycolysis to produce adenosine triphosphate (ATP) and generates metabolic intermediates to support several biosynthetic pathways. Pyruvate is the end-product of glycolysis, and is mainly reduced to lactate in the cytosol, rather than enter the mitochondrion to complete the tricarboxylic acid (TCA) cycle as a likely consequence of low oxygen level in the TME. Instead, itaconate can be converted from the TCA intermediate cis-aconitate with tumor-promoting functions. Long-chain fatty acids (LCFAs) are acquired via CD36-mediated

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lipid uptake and contribute to lipogenesis and lipid droplet formation in TAMs, while prostaglandin E2 (PGE2) and leukotrienes are converted from phospholipids, and act as bioactive signaling lipids. Amino acids arginine and tryptophan acquired from plasma membrane transporters can also be converted to bioactive metabolites to regulate tumor progression.

B) Signaling functions of metabolites in TAMs. Metabolites of the glycolytic pathway can promote activation of transcription factors including signal transducer and activator of transcription 6 (STAT6), nuclear factor kappa B (NF-κB), and hypoxia-inducible factor 1-alpha (HIF-1α). In addition, lactate can be sensed by the G protein-coupled receptors (GPCRs) GPR132 and OLFR78, while the TCA cycle metabolite itaconate suppresses the generation of reactive oxygen species (ROS). Lipid-sensing peroxisome proliferator-activated receptor-γ (PPAR-γ) is subject to caspase-1-mediated cleavage to prevent fatty acid oxidation, while lipid-derived metabolites including vitamin D, PGE2, and leukotrienes can bind to vitamin D receptor (VDR) and GPCR family members to induce cellular signaling. Moreover, cytosolic amino acids such as leucine promotes activation of the metabolic regulator mammalian target of rapamycin complex 1 (mTORC1), while the tryptophan metabolites kynurenine, kynurenic acid, and indole metabolites are sensed by aryl hydrocarbon receptor (AhR) and GPCR family member to regulate TAM responses. 1,3BPG, 1,3-bisphosphoglycerate; 3-PG, 3-phosphoglycerate; 5-LO, 5-lipoxygenase; α-KG, alpha-ketoglutarate; ADP, adenosine diphosphate; Arg1, arginase 1; CAT, cationic amino acid transporter; CCL, chemokine (C-C motif) ligand; COX, cyclooxygenase; CXCL, chemokine (C-X-C motif) ligand; DAGs, diacylglycerols; DGAT, diglyceride acyltransferase; DHAP, dihydroxyacetone phosphate; ETC, electron transport chain; F1,6BP, fructose-1,6-bisphosphate; F2,6BP, fructose-2,6-bisphosphate; F6P, fructose 6-phosphate; FABPs, fatty acid-binding proteins; G3P, glycerol 3-phosphate; G6P, glucose 6-phosphate; GA3P, glyceraldehyde 3-phosphate; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; IL, interleukin; IL4I1, interleukin-4 induced 1; IRG1, immune-responsive gene 1; LDH-A, lactate dehydrogenase-A; MAGs, monoacylglycerols; MCT, monocarboxylate transporter; MGLL, monoacylglycerol lipase; MMPs, matrix metalloproteinase; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; OAA, oxaloacetate; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase kinase 1; PD-L1, programmed death-ligand 1; PEP, phosphoenolpyruvate; PFK-1, 6-phosphofructokinase-1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PKM2, pyruvate kinase M2; PSAT, phosphoserine aminotransferase; Ribose-5P, ribose 5-phosphate; RXR, retinoid-X receptor; TAGs, triacylglycerols; TFs, transcription factors; TGF-β, transforming growth factor-beta; UDP-GlcNAc, uridine diphosphate-N-acetylglucosamine; VEGF-α, vascular endothelial growth factor-alpha.

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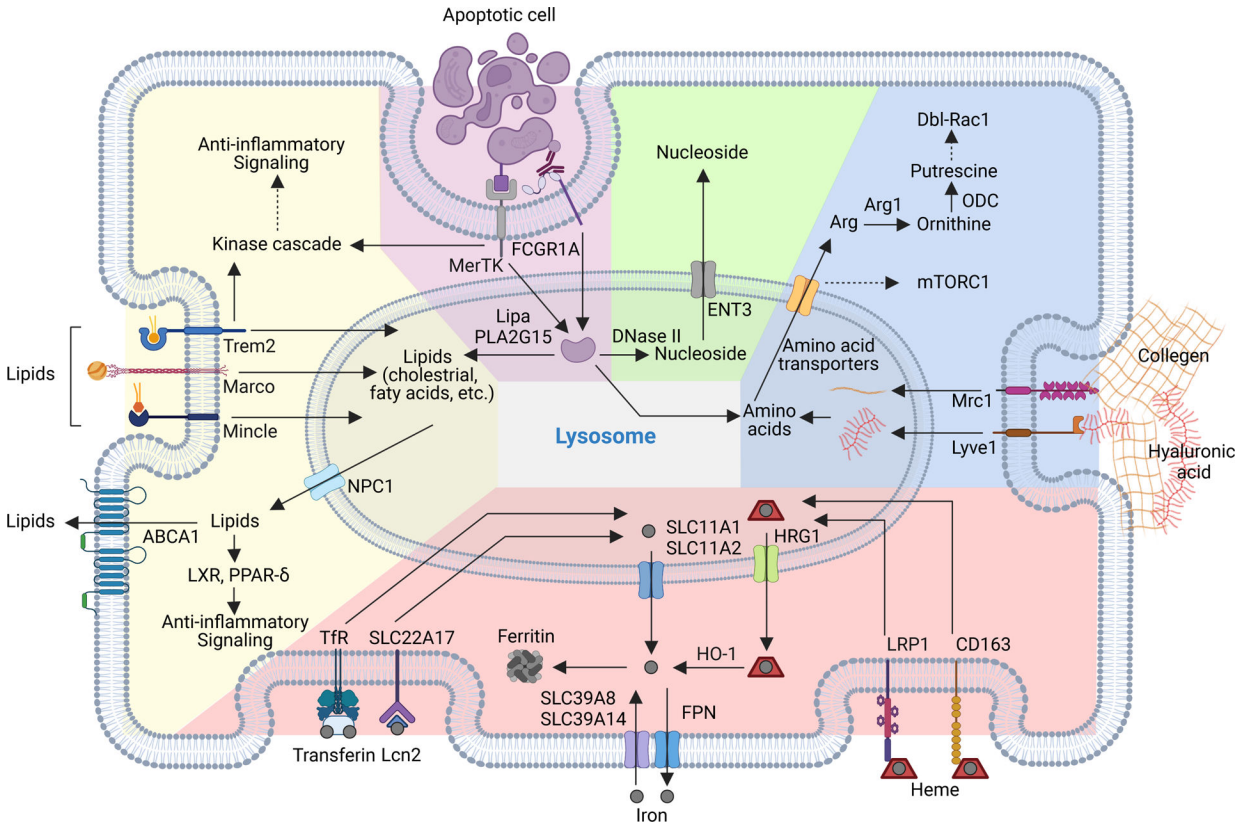

Figure 3. Engulfment-mediated nutrient acquisition control of TAM responses

Apoptotic cell as well as lipids, extracellular matrix (ECM) proteins and iron complexes can be phagocytosed or endocytosed in tumor-associated macrophages (TAMs), and nutrients are further generated in the lysosome and exported to the cytosol to support metabolism and signaling responses. Upon ligand binding, efferocytosis receptors such as MER proto-oncogene, tyrosine kinase (MerTK) or lipid-scavenging receptors such as triggering receptor expressed on myeloid cells 2 (Trem2) can activate intracellular kinase signaling cascades and induce expression of anti-inflammatory mediators. The recycled lipids can also induce anti-inflammatory signaling or exported outside of TAMs to promote cross-feeding. Degradation of apoptotic bodies and ECM proteins generate amino acids in the lysosome and may activate the metabolic regulator mammalian target of rapamycin complex 1 (mTORC1). Arginine is a major amino acid generated from ECM degradation and can activate Rac1 through its downstream metabolites. Engulfed apoptotic cells also contain nucleic acids, proper degradation of which is critical to prevent activation of nucleic acid-innate immune sensing pathways. TAMs can either uptake or release iron in both free and complex forms and regulate iron metabolism through competition or crossfeeding in tumor.

ABCA1, ATP Binding cassette subfamily A member 1; CD163, CD163 molecule; DNase II, deoxyribonuclease 2, lysosomal; ENT3, equilibrative nucleoside transporter 3; FPN1, ferroportin 1; SLC39A8, solute carrier family 39 member 8; HO-1, heme oxygenase 1; HRG1, heme-responsive gene 1 protein homolog; FCGR1A, Fc gamma receptor Ia; Lcn2, lipocalin 2; LIPA, lipase A, lysosomal acid type A; LRP1, LDL receptor

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related protein 1; Lyve1, lymphatic vessel endothelial hyaluronan receptor 1; Marco, macrophage receptor with collagenous structure; Mertk, MER proto-Oncogene, tyrosine kinase; Mincle, macrophage-inducible C-type lectin; Mrc1, mannose receptor C-type 1; NPC1, NPC intracellular cholesterol transporter 1; PLA2G15, phospholipase A2 group XV; SLC11A1, solute carrier family 11 member 1; SLC11A2, solute carrier family 11 member 2; SLC22A17, solute carrier family 22 member 17; SLC39A14, solute carrier family 39 member 14; TfR, transferrin receptor; Trem2, triggering receptor expressed on myeloid cells 2.