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Mini-review

Metabolic changes in tumor cells and tumor-associated macrophages: A mutual relationship

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ABSTRACT

In order to adapt to the reduced availability of nutrients and oxygen in the tumor microenvironment and the increased requirements of energy and building blocks necessary for maintaining their high proliferation rate, malignant cells undergo metabolic changes that result in an increased production of lactate, nitric oxide, reactive oxygen species, prostaglandins and other byproducts of arachidonic acid metabolism that influence both the composition of the inflammatory microenvironment and the function of the tumor-associated macrophages (TAMs). In response to cues present in the TME, among which products of altered tumor cell metabolism, TAMs are also required to reprogram their metabolism, with activation of glycolysis, fatty acid synthesis and altered nitrogen cycle metabolism. These changes result in functional reprogramming of TAMs which includes changes in the production of cytokines and angiogenetic factors, and contribute to the tumor progression and metastasis. Understanding the metabolic changes governing the intricate relationship between the tumor cells and the TAMs represents an essential step towards developing novel therapeutic approaches targeting the metabolic reprogramming of the immune cells to potentiate their tumoricidal potential and to circumvent therapy resistance.

Introduction

Tumor microenvironment (TME) consists of a complex mixture of malignantly transformed cells, immune cells, and stromal cells which fulfill different functions. Some of these cells, including the dendritic cells (DC), $CD8^+$ and $CD4^+$ T-lymphocytes, natural killer (NK) cells, are activated in order to contain the tumor and prevent immune evasion and progression of the disease. Other immune cells such as tolerogenic DC's, regulatory T-cells (Treg), myeloid derived suppressor cells (MDSC), tumor-associated neutrophils and tumor associated macrophages (TAM), on the other hand, promote tumor growth, progression, invasion, angiogenesis and suppress the antitumoral immune responses [1].

During the last decades, it has become clear that in many tumors a proinflammatory TME promotes cancer development, progression and metastasis [2–5]. Moreover, the composition of the

Abbreviations: TME, tumor microenvironment; DC, dendritic cells; NK, natural killer; Treg, regulatory T-cells; MDSC, myeloid derived suppressor cells; TAM, tumor associated macrophages; RNS, reactive nitrogen species; OXPHOS, oxidative phosphorylation; ATP, adenosine triphosphate; NAD, nicotinamide adenine dinucleotide; NADH, reduced form of nicotinamide adenine dinucleotide; GLUT1, glucose transporter 1; MCT1, monocaroxylic acid transporter 1; MCT4, monocaroxylic acid transporter 4; CAIX, carbonic anhydrase IX; VEGF, vascular endothelial growth factor; PPP, pentose phosphate pathway; FA, fatty acid; TCA, tricarboxylic acid; acetyl CoA, acetyl coenzyme A; $FADH_2$, flavin adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; NO, nitric oxide; HETE, hydroxiepoxyeicosatetraenoic acid; COX, cyclooxygenase; LO, lipoxygenase; PPARs, peroxisome proliferator-activated receptors; SREBP1, sterol regulatory element binding protein 1; TLR4, toll like receptor 4; PGE2, prostaglandin E2; LPS, lipopolysaccharide; TNF, tumor necrosis factor; IL, interleukin; FAO, fatty acid oxidation; PDK4, pyruvate dehydrogenase kinase 4; IFN, interferon; HK2, hexokinase-2; PI3K, phosphatidyl-inositol-3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; PDCA, pancreatic ductal adenocarcinoma; ETM, epithelial-to-mesenchymal; 2DG, 2-deoxiglucose; REDD1, regulated in development and in DNA damage response 1; E-FABP, epithelial fatty acid binding proteins; iNOS, inducible nitric oxide synthase; ARG1, arginase; G6P, glucose-6-phosphate; F6P, fructose-6-phosphate; F1,6P, fructose-1,6-diphosphate; G3P, Glucose-3-phosphate; TG, Triglycerides; αKG, α-ketoglutarate; Gln, Glutamine.

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inflammatory TME correlates with the clinical outcome. In many types of cancer a TME enriched in T-lymphocytes has been associated with a more favorable prognosis, whereas an abundant infiltration with TAMs has been associated with a poor outcome [6–11]. TAMs are one of the most prominent components in the TME. They are characterized by a high functional plasticity [12,13]. Once monocytes are recruited at the tumor site, they undergo reprogramming into TAMs, leading to gain of protumoral functions such as supporting the tumor growth, promoting angiogenesis, tumor invasion and metastases and suppressing T-cells that are responsible for the antitumoral responses. The functional reprogramming of the TAMs is a complex process that has not yet been elucidated. However, emerging evidence suggest that both the tumor cells and the TAMs undergo changes in their cellular metabolism that shapes their functional phenotype in a mutual fashion, with the nature of this relationship orchestrating the complex process of tumor progression. This review focuses on the metabolic changes that are responsible for the cross-talk between the tumor cells and the TAM.

Tumor cell metabolism shapes the inflammatory TME

During the tumor development, the TME changes continuously in parallel with the growth of the tumor. These changes shape on the one hand its cellular content through the release of various recruitment factors resulting in accumulation of specific types of immune cells into the TME, and on the other hand influence the function of these immune cells and the complex relationship between these cells and the tumor cells [14–16]. The TME is typically characterized by hypoxia and a lack of blood bourn nutrients, while being enriched in protons, reactive nitrogen species (RNS) and other byproducts released from the activated tumor cell metabolism.

Tumor cells need to adapt their metabolism in order to survive in this unfavorable, nutrients- and oxygen-deprived TME, and to respond to the increased energy demands required by their high proliferation rate (Fig. 1) [2]. These metabolic changes have been observed and described almost one century ago by Otto Warburg and are now referred to as the “Warburg effect” [17]. In conditions characterized by sufficient availability of oxygen and nutrients, particularly glucose, normal cells burn glucose by using the oxidative phosphorylation (OXPHOS) that takes place in the mitochondria as the main source of energy [18,19]. In hypoxic conditions, the cellular metabolism shifts towards anaerobic glycolysis to produce energy, a process that is far less efficient in terms of adenosine triphosphate (ATP) production than OXPHOS. Warburg effect refers to the phenomenon through which cancer cells shift their energy metabolism towards glycolysis, even in normoxic conditions. In this process, which takes place in the cytosol, cells use the glucose to form pyruvate and ATP. Though this pathway seems relatively inefficient in terms of energy metabolism, resulting in generation of only 2 molecules of ATP per each molecule of glucose, as compared to 36 molecules of ATP per molecule of glucose generated through OXPHOS, it also results in generation of nicotinamide adenine dinucleotide (NAD) in its reduced form NADH. NADH is a key cofactor used by several enzymes that direct intermediate products to biosynthetic pathways and enable anabolic growth. The tumor cell metabolism is therefore characterized by an increased glucose consumption, reflected by the upregulation of the glucose transporter (GLUT1) at the surface of the tumor cells, their increased glucose uptake and oxygen consumption [20,21].

The capacity of tumor cells to mount glucose metabolism has also been used for diagnostic purposes, as it represents the physiologic principle of the functional fluorodeoxyglucose - positron

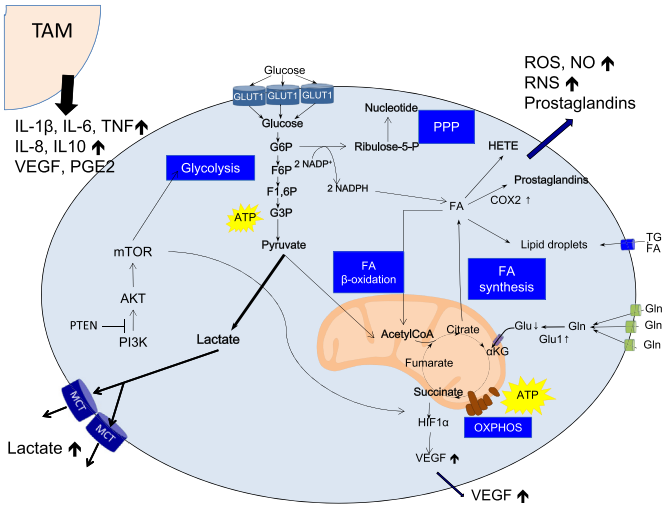

Fig. 1. Changes in tumor cell metabolism that shape the inflammatory tumor microenvironment. In order to respond to the reduced availability of nutrients and oxygen which typically characterize the tumor microenvironment and to match the requirements of energy and building blocks necessary for maintaining a high proliferation rate, malignant cells undergo metabolic changes including increased uptake of glucose through upregulation of glucose transporters (GLUT1), activation of glycolysis which results in increased production of lactate, increased fatty acids (FA) uptake and synthesis and increased uptake of glutamine to fuel the TCA cycle. This process results in increased production of lactate, NO, ROS, RNS and prostaglandins and other byproducts of arachidonic acid metabolism that influence the spatial architecture of the inflammatory microenvironment and the function of the tumor-associated macrophages.

emission tomography imaging technique. As a result of the increased glycolysis, the pyruvate is reduced to lactate. This results in production of high amounts of lactate that are released in the TME and cause local acidification, while the pH within the cancer cells remains normal. The latter may be explained by the upregulation of lactate and protons efflux channels in these cells. In several tumor types, besides evidence of increased glycolysis and expression of GLUT1 in the tumor cells, an increased expression of different proteins such as monocaroxylic acid transporter 1 (MCT1), monocaroxylic acid transporter 4 (MCT4), carbonic anhydrase IX (CAIX) involved in the lactate and H^+ trafficking has been found [22]. The significant reduction of the pH in the TME result in a cytotoxic environment for cells, including the immune cells that are recruited and activated to eliminate the tumor and to limit its progression, that are not equipped to survive in these conditions. This confers a survival advantage to the cancer cells while limiting the number and the functional capacity of the immune cells to elicit antitumoral responses and thus influencing the spatial structure of the TME [15]. In addition to that, waste products of the tumor metabolism such as lactic acid have been shown to shape the functional phenotype of the immune cells towards more tolerogenic phenotypes and conferring them with protumorigenic and proangiogenic properties [23,24]. In a murine model of Lewis lung carcinoma, Colegio et al. showed that, in normoxic conditions, lactate induced an increased expression of *Vegf* and Arg*1* and differentiation of TAMs into a protumoral phenotype [23]. This effect was mediated through stabilization of HIF1alpha transcription factor, similarly to the induction of vascular endothelial growth factor (VEGF) in hypoxic conditions, a process that has been associated with increased angiogenesis and expansion of the MDSC population in malignant tumors [25,26].

Changes in tumor cell metabolism are not limited to the glucose metabolism. Through its different intermediate metabolites, glycolysis is directly interconnected with other intracellular metabolic pathways. This includes the pentose phosphate pathway

(PPP) through the intermediate glucose-6-phosphate, the amino acid metabolism by the intermediate 3-phosphoglycerate, and to the fatty acid (FA) metabolism by pyruvate into the tricarboxylic acid (TCA) cycle [27].

Pyruvate is converted into acetyl coenzyme A (acetyl CoA) which is directed into the mitochondrion where it enters the TCA cycle to generate the NADH and flavin adenine dinucleotide ($FADH_2$) which donate electrons to the electron transport chain in the mitochondrial OXPHOS to generate ATP that is highly required by the proliferating cells [28]. Interestingly, when pyruvate availability becomes limited, the cell can use other metabolites to fuel the TCA cycle. As such, FAs can be converted into acetyl CoA to enter the TCA cycle by forming citrate and glutamate that is converted into α-ketoglutarate. Upon increased nutrient diversion to the TCA cycle, intermediates of the TCA such as citrate can also be used for production of lipids and amino acids [27,29].

Through glucose-6-phosphate glycolysis is linked to the PPP that takes place in the cytosol and leads to production of nucleotide and amino acid precursors as well as nicotinamide adenine dinucleotide phosphate (NADPH), which is necessary for the production of reactive oxygen species (ROS) and nitric oxide (NO) and for FA synthesis [27,30].

In addition to glucose and glutamine, cancer cells can use FAs as an important source of energy. The β-oxidation of the FAs in the mitochondrion generates large amounts of acetyl CoA, NADH and $FADH_2$, electron carriers that can be further used to generate high amounts of ATP in the TCA cycle [27,31]. Changes in lipid metabolism have been increasingly recognized as important ways of communication between the cancer cells and the surrounding stromal and immune cells [32]. On the one hand, cancer cells thrive on rich sources of free FAs such as adipose tissue, as reflected by the FA exchange between metastases of ovarian carcinoma in omental adipose tissue and between adipocytes and metastatic prostate cancer cells [33,34]. On the other hand, the FAs can be used by the cancer cells to produce other bioactive lipids and mediators that in term, can influence the function of other cells in a paracrine fashion [32].

Malignant tumors have been associated with an increased metabolism of arachidonic acid, a precursor for eicosanoids such as leukotrienes, prostaglandins, thromboxane hydroxiepoxyeicosatetraenoic acid (HETE), FAs, as well as other cyclooxygenases (COX) and lipoxygenases (LO) products. Eicosanoids are expressed in higher levels in malignant tumors and can be produced by cancer cells, but also by stromal cells and immune cells including myeloid-derived cells in the TME and therefore are likely involved in the cross-talk between these cells [35]. Through binding to their receptors which include peroxisome proliferator-activated receptors (PPARs), sterol regulatory element binding protein 1 (SREBP1), Toll like receptor 4 (TLR4), and G protein-coupled receptors eicosanoids can influence the functions of immune cells to induce immunosuppression. In this respect, prostaglandin E2 (PGE2), which has been detected at high levels in cancers associated with inflammation, has been shown to promote differentiation of monocytes into TAMs with immunosuppressive phenotype in cervical cancer and to induce activation of MDSCs in breast cancer [36–38]. Furthermore, LO isoform 5-LO could be involved in recruitment and expansion of immune cell populations within the tumors [39,40].

In a recent study, we compared the transcriptome of thyroid cancer-induced macrophages with the transcriptome of 29 different macrophage transcription profiles (see Xue et al. [41]). We found that the transcriptome of the thyroid cancer-induced macrophages after 4-h of co-culture were characterized by gene modules similar to those found in macrophages stimulated by FAs (linoleic, oleic, lauric acid), lipopolysaccharide (LPS), or a combination of tumor necrosis factor (TNF), PGE and Pam2Cys whereas the transcriptome of thyroid cancer-induced macrophages after 24 h co-culture resembled the gene modules found after interleukin 4 (IL-4) stimulation in combination with inflammatory genes stimulated by palmitic acid [24,41]. In line with this, Schumann et al. found that TAMs isolated from ovarian carcinoma patients showed an up-regulation of the vast majority of direct PPARβ/δ target genes in the TAMs compared to the monocyte-derived macrophages and suggest that this may reflect a pro-tumorigenic polarization of the TAMs [42]. Lipidomic analysis of the TAMs revealed that this up-regulation of PPARβ/δ target genes was due to high concentrations in the tumor ascites of polyunsaturated FA, especially linoleic acid and arachidonic acid, which accumulate in highly stable lipid droplets in TAMs and provide a source of PPARβ/δ ligands to TAMs, contributing to a stable up-regulation of PPARβ/δ target genes. These genes include pyruvate dehydrogenase kinase 4 (PDK4), which, interestingly, shifts glucose catabolism towards aerobic glycolysis, rendering TAMs less dependent on oxygen and thereby enabling them to cope with hypoxic conditions in the TME [43].

Taken together, these findings highlight the important role of tumor metabolic reprogramming and tumor-related metabolites in defining the inflammatory TME, which in term promotes the tumor progression.

Metabolic reprogramming of TAMs shapes their functional phenotype

TAMs are one of the most abundant components of TME, and are involved in multiple processes leading to local growth and progression of the primary tumor and promotion of metastasis. Once monocytes are recruited to the TME, these immune cells need to undergo metabolic adaptations in order to survive in the harsh tumor milieu (Fig. 2). These metabolic adaptations result in significant changes in the functional phenotypes of the TAMs. In previous literature, TAMs functional phenotype has often been defined either as M1-like TAMs (similar to the interferon-γ (IFN-γ), TNF–α or TLR4 activation status, also known as “activated”) or as M2-like TAMs (similar to the IL-4 and IL-13 activation status, also known as “alternatively activated”). M1-like TAMs have classically been regarded as tumor suppressors and M2-like TAMs as tumor promoters [44]. More recently, it has become clear however that such a dichotomous model does not accurately reflect the large variety of functional phenotypes of activated macrophages. Large-scale transcriptomic studies have shown that there is a broad heterogeneity of macrophage populations, depending on the cues that they are exposed to [41]. Moreover, tumors may contain distinct subpopulations of TAMs in different tumor regions, displaying either a more M1-like or M2-like phenotype [45,46]. To define their activation status, it has recently proposed to use a nomenclature based on the source of macrophages, the activators, and markers to describe macrophage activation [47]. However, because most of the previous literature used the M1/M2 nomenclature and the metabolic profile of non-M1/M2 is largely unexplored, we will use the M1/M2 nomenclature henceforth in this review, but we will mention also the source, the activators, and the markers of the macrophages used in different studies if this information is available.

In general, the metabolic profile of LPS/IFN-γ -activated macrophages is characterized by an enhanced glycolysis, PPP and FA synthesis, and a truncated TCA cycle leading to an accumulation of succinate and citrate. In contrast, the metabolism of IL-4/IL-13-activated macrophages is characterized by OXPHOS, a decreased glycolysis and PPP, and FA oxidation (FAO) [48]. Furthermore, IL-4/IL-13-activated macrophages in murine models upregulate arginase 1 [49–51]. Nevertheless, little is known on the metabolic

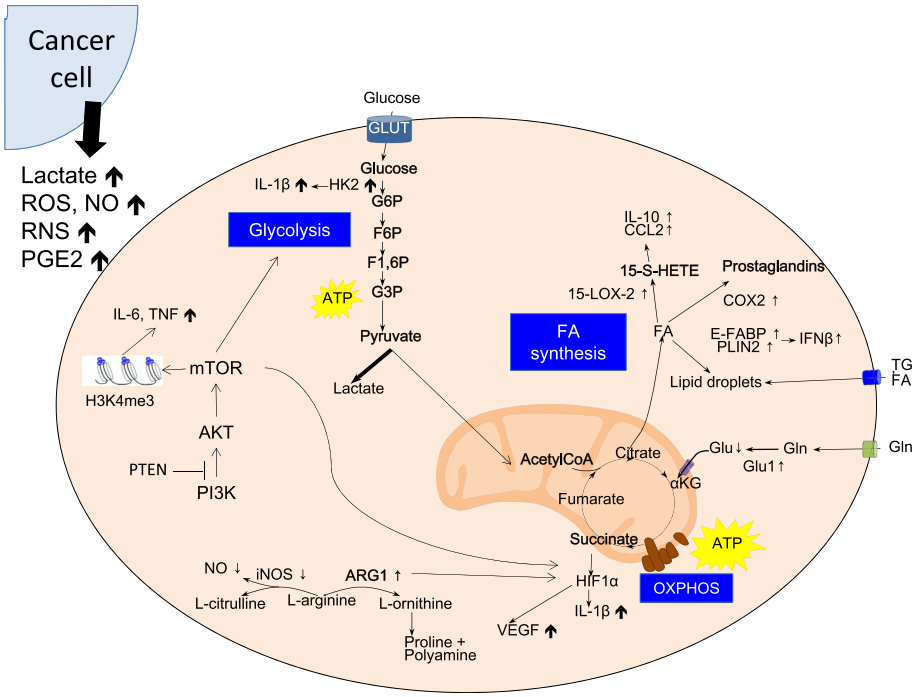

Fig. 2. Metabolic reprogramming of TAMs shapes their functional phenotype. In response to different cues present in the TME, among which products of altered tumor cell metabolism, TAMs undergo metabolic reprogramming, including activation of glycolysis, alterations in their TCA cycle with subsequent use of alternative metabolites (such as glutamine) to fuel the TCA cycle, FA synthesis and altered nitrogen cycle metabolism. These changes result in functional reprogramming of TAMs which include changes in the production of cytokines and angiogenetic factors, and contribute to the tumor growth, suppression of other immune cells and tumor progression and metastasis.

reprogramming of the TAMs and its role in modulating the functional phenotype of these cells in the context of cancer development and progression.

Glucose metabolism of the TAMs

Recent literature suggests that, in the TME, TAMs are forced to compete with cancer cells for nutrients, particularly glucose and therefore undergo changes in their glucose metabolism, in a similar fashion as the tumor cells do. Several studies indicate that TAMs have an activated aerobic glycolysis, which also contributes to their functional reprogramming.

Comparing the proteome of bone marrow-derived macrophages stimulated with tumor extract with the naive bone marrow-derived macrophages, Liu et al. have shown that tumor extract-stimulated bone marrow-derived macrophages depict a molecular signature characterized by up-regulated glycolysis. Furthermore, stimulation of these cells and of primary TAMs from MMTV-PyMT mice with tumor extract solution from a breast cancer patient showed increased expression of hexokinase-2 (HK2), which is a key glycolytic enzyme, and its downstream products PDKL and ENO1 [52]. Accordingly, using a two-wells co-culture model of thyroid cancer cell lines and monocytes from healthy volunteers, we have found that macrophages that were obtained either by co-culture with thyroid cancer cells or those that were stimulated with thyroid carcinoma-conditioned medium displayed a distinct metabolic transcriptomic signature with increased glycolysis and activation of protein kinase B/mammalian target of rapamycin (AKT1/mTOR) pathway, an essential regulator of cell metabolism. These thyroid cancer-induced macrophages also had a pro-inflammatory phenotype which could be partially abrogated by blocking the lactate receptor, confirming the paracrine effects of tumor-derived lactate in modulating the function of TAMs as described by Colegio et al. Immunohistochemistry analysis also showed increased expression of glycolytic enzymes and lactate receptor in TAMs from thyroid cancer tissue samples. Interestingly, in this study, the pro-inflammatory phenotype of the thyroid cancer-induced macrophages was associated with epigenetic changes that could be abrogated by treatment with an mTOR inhibitor, linking the immune cell metabolism with its functional capacity to produce pro-inflammatory cytokines [24].

Changes in TAMs cell metabolism have also been linked to promotion of invasion and metastasis [53,54]. Penny et al. showed that tumor-conditioned medium differentiated from human peripheral blood monocytes co-cultured with pancreatic ductal adenocarcinoma (PDCA) cell lines displayed a pro-metastatic phenotype, promoted vascular network formation, increased extravasation of tumor cells out of blood vessels and induced higher level of epithelial-to-mesenchymal (ETM) transition as compared to macrophages differentiated through co-culture with normal pancreatic cells. The PDCA-induced macrophages also showed an increased glycolysis; inhibition of glycolysis using a HK2 competitive inhibitor 2-deoxiglucose (2DG) abrogated the functional phenotype of these cells [53]. Interestingly, it has been shown that 2DG inhibits the IL-1β production by LPS-stimulated macrophages, but not the production of TNF-α or IL-6, by decreasing the succinate level in the macrophages [55]. Furthermore, in several in vitro and in vivo studies, 2DG suppressed the viability, proliferation and motility of cancer cells when combined with other targeted therapy, and it is being used in clinical trials for cancer treatment [56–64].

It has been previously shown that TAMs can promote angiogenesis and metastasis. However, it has only recently been shown that changes in the TAMs cell metabolism play an important role in the functional reprogramming towards a proangiogenic, pro-metastatic phenotype. In solid tumors, hypoxia is one of the most important factors that determine the vascular architecture of the tumor. Particularly in the hypoxic niches of the tumor TAMs

become pro-angiogenic and pro-invasive. Wenes at al has investigated recently the role of the hypoxic macrophage metabolism in the morphogenesis of blood vessel and metastasis using a comprehensive approach, which included gene-targeting methods, metabolic assays, bone marrow transplantation and pharmacological interventions [54]. The study revealed that in hypoxic conditions, TAMs up-regulate their REDD1 (regulated in development and in DNA damage response 1), which inhibits mTOR, and subsequently inhibited the glycolysis. This was associated with an increased angiogenic response and formation of aberrant leaky vessels. On the other hand, REDD1-deficient TAMs are able to outcompete the neighboring endothelial cells for glucose through activation of mTOR and increased glycolysis, which is associated with normalization of vascular structure, less leakage of tumor cells into the blood vessels and less metastases [54]. This observation is of great relevance as it does not only give mechanistic insight in the process of angiogenesis, but can have implications for therapy as well. Many malignant tumors are being treated with mTOR inhibitors and the results of Wenes et al. suggest that the favorable effect of these medications could be hampered by their effects on the TAMs metabolism through subsequent changes in their functional phenotype.

Lipid metabolism of the TAMs

Besides glucose metabolism, TAMs undergo also changes in lipid metabolism including enhanced FA biosynthesis, uptake and storage, which have been associated with functional reprogramming, although the mechanisms remain largely unknown. Several studies also indicated that TAMs show changes in the metabolism of arachidonic acid. By RNA-expression profiling of macrophages of in the TME of lung cancer in an immunocompetent orthotopic mouse model, Pokzobutt et al. showed increased expression of multiple genes involved in lipid metabolism and lipid signaling in distinct populations of macrophages. In particular, increased expression of *Cox2* and an increased PGE2 production in vitro was found in macrophages infiltrating tumor-bearing lungs compared with the macrophages from naïve lungs. This suggests that upon cancer development, not only cancer cells but also immune cells are able to increase their prostaglandin synthesis, resulting in a cumulative increased prostaglandin production as it has been described in lung tumors [65]. Previously it was shown that IL-1β-induced infiltration with COX2 expressing macrophages is associated with tumor angiogenesis and tumor growth in a murine lung cancer model [66]. Furthermore, COX2 expression was shown in TAMs from human melanoma, but not in the macrophages from normal epidermis adjacent to the lesions. COX2 expression was induced in macrophages upon direct co-culture with F10-M2 murine melanoma cells in vitro [67]. Furthermore, TAMs isolated from human renal cell carcinoma show an increased metabolism of arachidonic acid mediated by 15-LO2 dependent pathways. These TAMs showed an increased activity of 15-L02, an increased secretion the arachidonic acid metabolite, 15(S)-HETE, and have an increased production of the immunosuppressive CCL2 and IL-10 through a 15-LO2-dependent mechanism. This suggests that changes in their cellular lipid metabolism directly affect the function of TAM in the TME [68].

Lipid loading of macrophages has been associated with increased tumoricidal and inflammatory capacity. Schlager et al. has shown that an increased intracellular lipid content was associated with an increased cytotoxic activity of murine peritoneal macrophages, particularly in those that were artificially enriched with polyunsaturated FAs in contrast with those enriched in cholesterol. The cytotoxic activity of the macrophages was also dependent on the type of FA with which the cells were artificially enriched. As such, macrophages enriched with unsaturated FA linolenic acid (18:3), but not those enriched with the saturated FA stearic acid (18:0), were cytotoxic against P815 tumor cells [69]. In line with this, TAMs from a mouse mammary adenocarcinoma model, particularly the M1-like ($MHCII^{+}CD11c^{+}$) population, expressed high levels of epithelial fatty acid binding proteins (E-FABP), an intracellular lipid chaperone, which improved their antitumoral activity by mounting the production of IFN-β) through up-regulation of lipid droplet formation in response to malignancy. This promoted further recruitment of other tumoricidal immune cells, especially NK cells, in the TME [70,71]. In human breast tumors E-FABP expression was also reduced in stroma of invasive tumors as compared to normal stroma, and E-FABP expression of TAMs decreased in parallel with the disease progression [71]. Furthermore, stimulating macrophages with the E-FABP activator EI-05 enhanced lipid droplet formation and IFN-β production, and in vivo administration of the activator in a murine mammary tumor model significantly inhibited tumor growth [70].

In conclusion, in response to microenvironmental cues, macrophages can alter their lipid profile and the production of lipid products, which may contribute to the pro-tumorigenic profile of TAMs. On the other hand, especially unsaturated FAs seem to increase the cytotoxic activity of TAMs. Further studies are needed to unravel the lipid metabolism of TAMs and its related functional consequences.

Amino acids metabolism in TAMs

Several studies report on possible implications of amino acids metabolism for the functional reprogramming of the TAMs. However, the majority of these studies are observational and only scarce mechanistic insight is available.

TAMs, particularly the M2-like, pro-tumorigenic TAMs show an increased use of glutamine. This is associated with high levels of Uridine diphosphate *N*-acetylglucosamine intermediates, which are required for *N*-glycosylation of M2-associated receptors. Consequently, blocking the *N*-glycosylation and deprivation of glutamine impairs the M2 polarization, with concomitant down-regulating effect on the TCA cycle [72]. Also TAMs isolated from with glioblastomas and TAMs exposed to glioblastoma cell lines show increased expression of genes related to glutamate transport and metabolism, which may be of relevance because the glioblastoma TME contains large amounts of glutamate [73].

L-arginine metabolism has also been linked to the function of TAMs. In macrophages, L-arginine can be used either for the NO synthesis or through the arginase pathway. The pro-inflammatory M1-like macrophages are characterized by a more pronounced NO synthesis pathway. Arginine is converted into NO and L-citrulline by the inducible nitric oxide synthase (iNOS). The produced NO subsequently suppresses OXPHOS through the inhibition of enzymes involved in the TCA and electron transport chain and upregulates glycolysis [74,75]. On the other hand, M2 macrophages are characterized by the expression of the urea cycles enzyme arginase (ARG1), which hydrolyzes arginine to ornithine and urea and limits arginine availability for NO synthesis [76,77]. Furthermore, the produced ornithine can be directed into downstream pathways of polyamine and proline synthesis, which are necessary for cell proliferation, tissue remodeling and collagen synthesis [50,51,76].

TAMs isolated from murine mammary and human ovarian tumors TAMs show low cytotoxic properties in association with a reduced NO production and a low iNOS mRNA expression and protein levels in mammary tumor-bearing mice [78,79].

TAMs from various murine tumor models show elevated Arg*1* expression [23,80–82]. ARG1 has long been recognized as a marker

of M2 macrophages. Nonetheless, the function of macrophage-derived ARG1 particularly in the context of malignancy is not well known. Both hypoxia and lactate have been shown to be able to increase the expression of Arg*1* gene [23]. In a murine model of lung cancer, Colegio et al. showed that $Arg1^{fl/fl}$ X $Lysm^{cre/wt}$ mice, whose macrophages are deficient in ARG1, develop significantly smaller tumors than the wild-type mice [23]. Interestingly, in the same study TAMs were showed to have increased expression of all enzymes from the urea nitrogen cycle, which was even higher than in the tumor cells. Furthermore, L-arginine-derived metabolites, cysteine and tryptophan metabolism are important mediators of the immunosuppressive activity of MDSCs [83]. These findings suggest that urea nitrogen cycle may play an important role in the function of TAMs, however further studies are required in order to understand the underlying mechanisms.

Potential therapeutic implications

Therapeutic targeting of both the immune cells and the cancer cells metabolism could have important therapeutic implications. Several of the classical and new anti-tumoral therapeutic interventions potentially induce metabolic changes in the tumor microenvironment that can impact on the recruitment and function of the immune cells. In this respect, hypoxia-induced recruitment of myeloid cells can contribute to the resistance to conventional treatment with anti-angiogenic drugs through induction of vessel formation through alternative routes [84,85]. Similarly, the acidification of the tumor microenvironment, mainly due to increased production of lactate, has also been found to induce resistance to chemotherapy and immunotherapy [86]. Conversely, ketogenic diets that result in reduced lactate production could lead to a reduced lactate-mediated immunosuppression in the tumor microenvironment and improved anti-tumoral immune responses [87,88]. Therefore, targeting the metabolic pathways in tumor cells and in immune cells in combination with conventional targeted therapy could represent a novel approach to circumvent therapy resistance and/or to synergistically enhance the therapeutic effects. An example of such combination is represented by the treatment with anti-glycolytic agents which has been shown to increase the cytotoxicity of sorafenib [61,63,89] in hepatocellular carcinoma. Furthermore, mTOR inhibition has been reported to increase the immunotherapeutic activity of a CD40 agonist in a mouse model of renal cell carcinoma [90]. On the other hand, modulation of TAMs metabolism through REDD1-induced mTOR inhibition and reduction of glucose uptake and glycolysis may be another mechanism through which abnormal tumor angiogenesis and treatment failure can occur in patients treated with mTOR-targeting drugs [54]. Metformin, a drug widely used for treatment of diabetes, has been shown to influence the functional polarization of tumor-educated macrophages by inhibiting the M2-like reprogramming [91–93], thereby suggesting that metformin could be a potentially promising addition to the multi-targeted armamentarium for cancer therapy. Its potential beneficial effects may also include antiproliferative effects. Furthermore, checkpoint blockade antibodies, which are increasingly being used for treatment of different cancers, have also being shown to influence the glucose metabolism in tumors, by reducing the tumor cell glycolysis and glucose consumption, thereby improving the glucose availability required for the metabolic fitness and antitumoral function of immune cells, specifically the tumor infiltrating $CD8^+$ T lymphocytes [94].

These therapeutic implications are not limited to modulation of glucose metabolism. Atorvastatin, a frequently prescribed HMG-Coa reductase and cholesterol synthesis inhibitor, promotes M2-like functional reprogramming of TAMs in a murine model of pancreatic cancer thereby reducing the effects of the chemotherapeutic agent gemcitabine [95]. Altogether, these findings support the concept of metabolic interplay in the TME as a driver of cancer progression and response to therapy.

Concluding remarks

The role of metabolic reprogramming of both the tumor cells and the immune cells present in the TME has increasingly been recognized as a crucial pathway contributing to the complex dialog between these cells. However, the mechanistic insight of the molecular pathways leading to these changes is still limited. This partially precludes at this point therapeutic interventions targeting the metabolic pathways.

Despite these limitations, one can envisage the targeting of cellular metabolism as a therapeutic approach in malignancies. On the one hand, inhibition and modulation of cancer cell metabolism is an approach that has been long sought, and it starts to bear fruits by the use of glycolysis inhibitors such as mTOR inhibitors. On the other hand, it can also be suggested that understanding the particularities of cellular metabolism of pro-tumorigenic TAMs would enable additional treatments. Targeting specifically the TAMs can be achieved by the progress in liposome and nanoparticle drug-delivery systems. Furthermore, combined therapy between recently discovered immunotherapeutic agents (e.g. anti-PD1/PDL1, anti-CTLA4) and inhibitors of cellular metabolism can also be envisaged.

To achieve however the aim of specific metabolic targeting of immune cells in cancer, outstanding questions still need to be addressed. Among them, several important questions are: the specificity of cellular metabolism of macrophages in the primary and metastatic tumors, assessment of the potential existence of subpopulations of TAMs using single-cell technologies, identification of the main enzymatic pathways responsible for these changes and which can be targeted. Only when the answers to these questions will be available will we be able to fulfil the therapeutic potential of targeting the cellular metabolism of immune cells in cancer.

Conflict of interest

The authors have no conflict of interest.

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