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Chapter

Role of Macrophages in Solid Tumor Metabolism

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Abstract

Cancer cells undergo several complex processes to grow and evolve. For their survival, they manipulate the entire system and acquire the ability to gain all the energy demands from the host system itself. Tumor associated macrophages (TAMs) are macrophages abundantly present in the tumor micro environment (TME) and essentially plays a critical role in coordination with the tumor cells helping them to progress and metastasize. One of the key hallmarks in tumor cells is elevated metabolic processes such as glycolysis, fatty acid oxidation, mitochondrial oxidation, and amino acid metabolism. Macrophages help cancer cells to achieve this metabolic demand through a series of signaling events including mTOR, Akt, and PI3K pathways. The M2-like phenotype of macrophages leads to the tumorous macrophage phenotype along with the tumor cells to support tumor growth through metabolic dysregulation. Focusing upon the area of macrophage-mediated tumor metabolism in solid tumors has been a new area that provides new effective targets to treat cancer. This chapter discusses the role of macrophages in tumor metabolism and cancer progression. Targeting TAMs in tumor microenvironment through metabolic axis could be a potential therapeutic option to control the solid tumor growth and propagation.

Keywords: macrophages, hypoxia, TME, PD-1, OXPHOS, tumor microenvironment

1. Introduction

The slow pace development of solid tumors inside a human body involves a lot of complex process. It is not only the genetic mutations that play important role but also the so-called tumor microenvironment (TME), which is a silent player enhancing this process. TME has complex players such as the T-cells, dendritic cells, and macrophages in the solid tumor [1]. Among these, macrophages have three types of classification namely tumor-associated macrophages (TAMs), tissue-resident macrophages, and myeloid-derived suppressor cells (MDSCs). The most abundant tumor infiltrating immune cells in the tumor microenvironment are TAMs. These TAMs are classified into two subtypes namely M1 or M2 macrophages. Macrophages have a role in defense as well as homeostasis of cells by acquiring the capacity of phagocytosis. TAMs have reportedly been associated with several functions such as tumor initiation, progression, and metastasis with secretion of supporting factors such as cytokines, growth factors, inflammatory substrates, and proteolytic enzymes. As macrophages are known to be associated with tumor progression, understanding different signaling complexes has been an important field. The major signaling molecules involved are cytokines, growth factors,

chemokines, and transforming growth factors beta, vascular endothelial growth factor, and platelet-derived growth factor. Several murine tumor models have reported TAMs as the major source for tumor-promoting factor like IL-6 [2]. The VEGF-A factor produced via TAMs specifically helps tumor cells with angiogenesis switch providing new blood vessels for tumor progression. TAMs have certain immunosuppressive functions apart from their strong inflammatory properties. Macrophages are poor producers of IL-12 but highly produce IL-10 and TGF-β with the help of STAT-3 activation [3]. The membrane-derived PDL-1 is activated on the surface of TAMs by IL-10 and TNF-A. Thus, PDL-1A has a prominent role in inhibiting the activated T-effector cells via the PD-1 receptor. TAMs are also widely reported to suppress therapeutic conditions such as chemotherapy, irradiation, and angiogenic inhibitors.

TAMs are associated with major metabolic changes associated with solid tumor progression. Macrophages can have a sudden change in their function while having a pathogen attack inside the host. The metabolic network inside a tumor cell has been a rich area of study as to decode the signaling molecules and find novel targets for the cure of cancer. Glycolysis is one such heavily activated pathway acquired by cancer cells to have sufficient energy and other key metabolites to progress and survive. TAMs highly elevate the process of glycolysis through HIF-1 stabilization and Akt/mTOR pathway [4]. Glycolysis in cancer cells also acts as intermediate for other cellular mechanisms such as the pentose phosphate pathway, TCA cycle, lipid metabolism, and amino acid metabolism. TAMs are also associated with increased OXPHOS despite having abrupt TCA cycle. Together with increased glycolytic flux and narrowed pathway of TCA cycle, OXPHOS promotes the accumulation of succinate and citrate in LPS/IFN-Y-activated macrophages. This accumulation of succinate leads to a major change in track of pathways by activating the HIF1-alpha subunit factor, which is otherwise in normal conditions inactivated by prolyl hydrolase enzymatic activity. This enhances production of pyruvate through glycolysis, which leads the macrophages to activate inflammatory cytokine production and the abrupt TCA cycle enhances the anti-microbial activity. Other metabolic functions such as the lipid metabolism are actively supported by the macrophages. These macrophages act as a source for synthesizing lipid mediators and fulfill the energy requirements in solid tumors. Macrophages utilize glycerides in lipoproteins as their major source of free fatty acids. This process is indicated by the increased production of lipoprotein lipase (LPL) in activated macrophages. M2-like macrophages have shown to have elevated consumption of amino acids in the form of glutamine as well as fatty acids [5]. An important mechanism of tumor suppression by macrophages through immunosuppressive phenotype helps solid tumors to evolve and grow. This mode of suppressed immunosurveillance in TAMs is mostly led by non-saturated fatty acid metabolism in macrophages. Mitochondrial respiration takes place with the help of lipid droplets, which regulates the catabolic process of free fatty acids (FFAs). mTOR signaling pathway has been reported to play an important role in suppressed immunosurveillance of TAMs. The mTORC1 responsibly is involved in the regulation of de novo lipid synthesis with the help of sterol-responsive element binding protein transcription factors.

Cancer cells and tumor microenvironment has a co-existing phenomenon which supports their growth and metastasis. As macrophages are one of the major immune cells actively present in the tumor microenvironment, the complex signaling procedure involved between the two is of utmost interest. CSF1 is one such major kind of cytokines that comes into play between TAMs and cancer cells to induce an immunosuppressive function to support tumor growth. The CSF-1 induction recruits the monocyte-derived macrophages toward the tumor surface and polarizes it to a M2-like phenotype, which is coupled to fatty acid oxidation [6]. This leads to the

secretion of variety of immunosuppressive factors such as epidermal growth factor (EGF). Interestingly, the metabolic influence of TAMs on solid tumors is not unidirectional. Under hypoxia or increased lactate levels, TAMs secrete various cytokines associated with metabolic systems such as IL6, TNF, C-C motif chemokine ligand 5 (CCL5), and CCL18 [7]. These chemokines in particular promote metabolic processes like glycolysis as well as key glycolytic enzymes such as hexokinase-II, lactate dehydrogenase A (LDH-A), glucose-6-phosphate dehydrogenase etc. One of the major factors involved in cancer cells is anaerobic glycolysis or the famous Warburg effect. Hypoxia-inducible factor-1A (HIF-1A) is one of the key factors that activates aerobic glycolysis and thus stabilizes the long noncoding RNA from lactate-exposed TAMs to cancer cells. The main players in the immune system against tumors like the helper CD 4+ T-cells, cytotoxic CD 8+ T-cells, and natural killer (NK) cells on activation rely on elevated glycolytic metabolism, which in turn supports the tumor cells for their energy demands. On a similar note, Treg cells rely majorly on oxidative phosphorylation for bioenergetic demands. Interestingly this glucose dependency of both tumor and immune cells mediates the TAMs to limit the glycolytic flux in effector cells. This is mainly done through the expression of CD274, which is also known as PDL-1 and is an immunosuppressive molecule. Moreover, PDL-1 is upregulated in cellular types like TAMs, endothelial cells, and tumor cells due to the release of interferon gamma from effector cells [8]. This interaction delineates the immune effector functions and thus balances the metabolic competition majorly toward tumor progression.

Considering the growing knowledge on TAMs and its interaction toward solid tumors have given a green signal toward immune-based therapies to treat cancer. Majorly focusing on the delineation of M2-like macrophages or their depolarization toward M1-like phenotype TAMs. The inhibitor against CSF1R also holds a strong promise toward the treatment of such diseases. Strategies to shift the balance from M2- to M1-like phenotype macrophages are also being done using inhibitors against VEGF-A. Interestingly, considering the factor of co-interaction of TAMs with cancer cell and modulating their metabolism provide a great area to identify potential targets against these diseases. In line with this notion, inhibitors against MTORC1 surprisingly favor tumor progression as glycolysis gets inhibited in hypoxia-coupled TAMs, which ultimately favors tumor growth. The food and drug administration has approved drugs against PDL-1, which is an immune checkpoint blocker, which in turn simulates the immune system against cancer cells. In this reference, several metabolism-related antibodies can be functioned along with immune stimulators to treat certain types of cancer.

2. Macrophages

A sheer claim lead by Elie Metchnikoff stated that in "cellular (phagocytic) theory of immunity" the portion of white corpuscle holds an important significance in the elements of the immune system as well as protect the individuals from the invasion of pathogenic organisms [9]. Furthermore, macrophages show key role in immune responses and immunity, also the defensive role assigned to them is perfect depiction to execute the phagocytosis of pathogen aggregation. These are also held responsible for regulating lymphocyte activation as well as proliferation. With the help of antigens and allogenic cells, macrophages play an important role in the activation process of T- and B-lymphocytes [10]. Apart from these, macrophages also grant defense mechanism against the tumor cells, but studies conducted in the past several years describe the mechanism of tumor cell killed by macrophages [11]. Tumor-associated macrophages (TAMs) initiate and progress human cancers and angiogenesis and are important part of the tumor

microenvironment. Targeting TAMs for therapeutic strategy to cure cancer is still in doubt [12]. Tumor metastasis is the parent cause of the deaths of cancer patients, adding to statement the intrinsic alterations in the tumor cells, but also implicated the cross-talk between cancer cells along with their altered components of microenvironment [12]. Tumor microenvironments (TME) are produced by TAMs, which further initiate the immune checkpoint and produce cytokines, chemokines, growth factors that are produced in T-cells. By doing this, TAMs have the most important functions in facilitating a metastatic cascade of the cancerous cells. At the same time, these trigger couple of more targets and few checkpoint blockade immunotherapies in order to oppose the tumor progression [13].

The term macrophages is generally defined as large bodies or cells that are instituted in the tissues that are present in the stationary forms. These are also regarded as the exceedingly multifaceted or the most versatile cells whose functions are based on their basic area of occupancy. Apart from this confinement, their pathophysiologic as well as physiologic contexts are considered to be very efficient in various studies [14]. Holding this significance in favor of host defense, also in primitive organisms, these tend to not only function as the recognition of the threats but at the same time engulf along with destroying the threats and in the higher organisms, such as humans. Macrophages have important roles in both immune responses whether adaptive or innate to the pathogens and also tend to serve as the mediators of inflammatory processes [15]. Macrophages are liberated as immature monocytes deriving from the bone marrow and further circulate in the blood stream in order to finally migrate into the tissues and also undergo the final differentiation into the resident macrophages that include kupffer cells in the liver, alveolar macrophages in the lung, and osteoclasts in the bone. It is a well-documented fact that macrophages have immunological and repair functions and are the first ones to arrive at the sites of wounding or infection where they carry out several functions that are assigned to them [16]. For promoting tissue repair, macrophages release proteases, growth factors, and angiogenic factors and for killing pathogens they release reactive oxygen and nitrogen radicals. They also release some chemokines or cytokines to arrange the action and recruitment of other immune cells and present the foreign antigens to cytotoxic T-cells [17]. Usually they are not lethal to cancer cells until they are triggered, for example, interferon gamma (IFN-γ) or lipopolysaccharide (LPS), but once they are triggered, the toxicity of cell is directly exerted toward tumor cells or indirectly via the secretion of factors that promote the anti-tumor functions of other cell types; thus, macrophages have pro- and anti-inflammatory properties, which depend on the signals they receive and the stage of disease they possess, that is the inflammatory balance in the microenvironment. Macrophages have multiple phenotypic expressions, which include removal of debris and tissue remodeling, antigen presentation, regulation of inflammation, target cell cytotoxicity, induction of immunity, thrombosis, and various forms of endocytosis [8].

Well promotion comes that of the tumor-associated macrophages (TAMs), which cover multiple strands of neoplastic tissues that counts in the angiogenesis as well as the vascularization, stroma formation accompanied by dissolution, and modulation that supports tumor cell growth which are a part of important enhancement and inhibition. On being activated TAMs are activated, and further gives rise to neoplastic cell death covering cytotoxicity and apoptosis, or even evokes tumor-destructive reactions led by the alteration of the tumor microvasculature. The primary lesions and metastases are known to group of solid tumors that are contented with the large numbers of tumor well associated of leukocytes. Famous as being the heterogeneous ones in the nature and consisting various as well as variable subsets of t-cells which are mainly the helpers, suppressor and cytotoxic,

b-cells, these are considered to be the natural killer (nk) cells, and hence are termed macrophages. Significance of these macrophages lies in them making up to 80% of the cell mass in breast cancer patients [18]. Due to being heterogeneous in nature, macrophages possess wide range of phenotypes like M1 and M2 based on their environment stimulation. M1 phenotype is related with active microbe killing and M2 phenotype is related with tissue remodeling and angiogenesis. When these monocytes come in contact with tumor-derived anti-inflammatory molecules (i.e., IL-4, IL-10, prostaglandin E2, and transforming growth factor 1), in tumor cells they mature into M2 or polarized macrophages and produce factors that suppress T-cell proliferation and activity, possess poor antigen presenting ability, adapt scavenging for debris, repairing and remodeling of damaged and wound tissues, and promote angiogenesis [19]. In contrast to this, type I or M1 macrophages are immune effector cells that kill microorganisms and tumor cells. They present antigens and produce high levels of immune stimulatory cytokines. The M2 phenotype appears to be that which dominates in tumors, as TAMs show a similar molecular and functional profile that is characterized by low expression of differentiation-associated macrophage antigens such as carboxypeptidase M and CD51, high constitutive expression of interleukin IL-1 and IL-6, and low levels of tumor necrosis factor [20]. Tumor cells, endothelial cells, fibroblasts, and macrophages in human tumors expressed monocyte chemotactic protein (MCP). MCP and chemokines are TAMs derived from monocytes and are recruited largely by CCL2 (chemokine (C–C motif) ligand 2). MCP-1 highly is expressed in a wide range of tumor types such as meningioma, ovarian carcinoma, glioma, and squamous cell carcinoma of uterine cervix and may be the main determinant of the macrophages as suggested by some studies. Other major chemoattractants like vascular endothelial growth factor (VEGF), CCL3, CCL4, CCL5, CCL8, macrophage-colony stimulating factor (M-CSF or CSF-1), macrophage migration inhibition factor (MIF), and macrophage inflammatory protein-1 alpha(MIP-1) are involved in monocyte uptake into tumors and their levels in tumor mass often correlate positively with TAM numbers in human tumors [21].

3. Role of macrophage in tumor progression

As it is becoming clear now, the inflammatory cells survive in the tumor microenvironment and show crucial role in the development of cancer. The best example is TAMs that are important components of the mononuclear leukocyte population of solid tumors and show an indecisive association with tumors. TAMs exhibit several tumorigenesis-promoting functions, which have significant roles in the growth and progression of cancer such as these tend to qualify in providing the cytokines and also when it comes to induce tumor angiogenesis [22]. TAMs produce many types of protein digestive enzymes, growth factors, inflammatory mediators, and cytokines in tumor microenvironment that are the main factors in the metastasis of cancer cells. Not only this, TAMs' function and movement are also regulated in tumor microenvironment by cytokines and hypoxia. Some studies suggest that TAMs come in contact with cancer cells, they alter ECM and promote invasion and metastasis of cancer cell and several studies show the release of natural products by TAMs to inhibit the formation of pro-inflammatory cytokines and growth factors and also correlation with cancer metastasis and poor prognosis in various types of cancers that happen in humans [23]. The tumor in various murine models shows IL-6 (tumor-promoting) as the main source of TAMs, and also that the tumor-related myeloid cell production of IL-6 promotes proliferation in colon cells along with the apoptosis prevention through STAT3 activation. There is a Doppler effect observed in pancreatic cancer, IL-6 derived from myeloid cell initiate tumor

development possess from epithelial precursor lesions through STAT3 [16]. In a specific genetic model of colorectal cancer, initiation of tumor starts with the loss of the adenomatous polyposis coli tumor suppressor gene, which results in the activation of β-catenin and further causes the barrier disruption of the epithelium. It allows the products of microbes to penetrate and moreover causes IL-23 macrophage production. In CD4+ T-cells, IL-23 drives Th17 response through IL-6 and IL-17, which initiate colorectal cancer [24].

The proportion of blood capillaries present in the non-infectious tissues mainly rests in an inactivated state in which angiogenesis transiently gets started in the perfect response in favor of certain stimuli. On the contrary, at the time of tumor initiation, an "angiogenic switch" is almost always initiated as well as turned on, which leads to vascularization of new capillaries from the inactivated state. On comparing the normal vascular network, the network of blood capillaries that are present in the tumors are basically identified by the complex and excessive branching of the blood vessels, which are contorted and also become large vessels, show irregular blood flow, microhemorrhage, and leakiness [25]. Macrophages are very particular to switch this angiogenic, that in the case of tumors mainly goes through production of vascular-endothelial growth factor A (VEGF-A) along with placental growth factor (PlGF). Talking of the specificity the blood vessels present in the tumors lacking myeloid cell-derived VEGF-A were less tortuous then having more pericyte coverage as well as the less vessel length. Above mentioned characteristics are consider successfully that show normal blood vessels. These are further counted upon modifying the bioavailability of VEGF-A in the tumors by matrix metalloproteinases processing. Adding to this fact, antibody-mediated neutralization of angiopoietin 2, the ligand for the Tie2 receptor, or macrophage depletion blocks tumor angiogenesis as well as limits tumor progression in a mouse model of breast cancer [26]. Several studies conducted on the patients having cancer in liver cells showed that the marginal macrophage density is different from the macrophage density present inside the tumor of the liver although they are directly associated along with the vascular invasion, tumor multiplicity, and also fibrous capsule formation. Furthermore, there was an important relationship observed between the density of TAMs as well as in the poor prognosis in those patients. According to Hansen et al., CD64+ macrophages (TAMs) are present in high numbers in tumor biopsies before treatment and thus show a negative relation along with clinical outcomes in the patients with the metastatic melanoma who undergo IL-2 based immunotherapy [27].

4. Tumor microenvironment

Tumor microenvironment (TME) changes continuously during the tumor development in parallel with the tumor growth. These changes on the one hand influence the immune cells' function and the complex relationship between tumor cells and these cells, and on the other hand influence its cellular content through the release of several factors, which leads to the accumulation of specific types of immune cells into the TME. Hypoxia and limitation of blood-borne nutrients are a characteristic feature of TME, while being enriched in reactive nitrogen species (RNS), protons, and other by-products released from the activated tumor cell metabolism [28, 29]. It is therefore important for the tumor cells to acclimatize their metabolism in order to survive in oxygen- and nutrients-deprived TME, and to respond to their increased demands of energy depending on their enhanced proliferation rate. The metabolic changes have been described over a century ago as "Warburg phenomenon" or "aerobic glycolysis," where tumor cells exploit glycolysis in order to provide energy regardless of the

availability of oxygen [30]. Under hypoxic conditions, the cellular metabolism migrates toward anaerobic glycolysis to generate energy, rather than oxidative phosphorylation (OXPHOS), which plays a major role in terms of adenosine triphosphate (ATP) production [31]. As a consequence of the increased rate of glycolysis, the pyruvate is significantly reduced to lactate. This causes upregulated lactate levels that are released in TME by monocarboxylate transporters (MCTs) and that results in reduction in the pH levels and local acidification, while pH within the tumor remains normal [32]. In TME, this significant reduction in the pH levels causes cytotoxic environment for cells, including immune cells such as macrophages that are activated and recruited to restrict the progression of tumor and eliminate the tumor. This provides survival benefit to the cancer cells [29]. Additionally, the toxic waste, for example, lactic acid has been shown to frame and shape the functional phenotype of recruited macrophages toward more tolerogenic phenotypes and conferring them with proangiogenic and pro-tumorigenic properties [33].

5. Metabolic reprogramming of TAMs

TAMs are involved in multiple processes, which result in the promotion and progression of primary tumor facilitating metastasis. The compartment of TAM via an extensive remodeling of energy metabolism evolves over time (i.e., during treatment response and tumor progression) as well as in space (at various tumor sites) [34]. The variations in TAMs in response to the nutritional needs of solid tumor are very dynamic and TME perturbations have a major influence not only on the survival of TAM but also on tumor progression [35] (**Figure 1**).

5.1 Glucose metabolism in macrophages

TAMs majorly support the progression of tumor by (i) indirectly enhancing the nutrients' availability in the TME, (ii) providing signals to tumor cells, and (iii) mediating immunosuppressive functions. "Neoangiogenesis" is the major

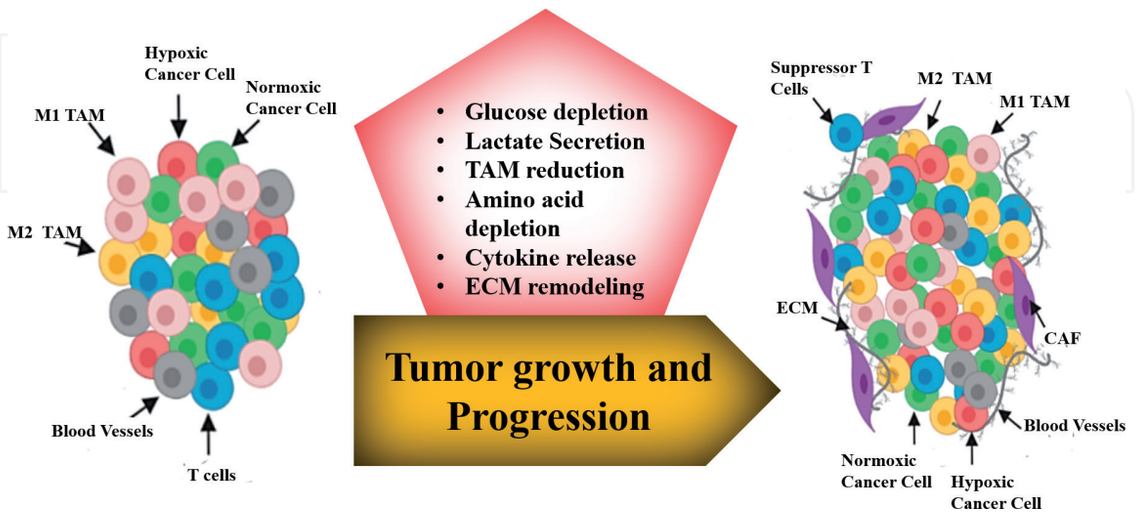


Figure 1.
TAM compartment is highly polarized toward M1-like state. Tumor progression depletes TME for the availability of glucose since it produces significant amount of lactate and polarization toward M2-like state. M2-like TAMs show restricted activity of phagocytes, chemokine, and cytokine secretion that facilitates the neoangiogenesis process, deprive TME of amino acids such as glutamine for T-cell function supporting remodulation of ECM. This metabolic alteration results in tumor growth and progression. (TAM: Tumor-associated macrophages; TME: Tumor microenvironment; ECM: Extracellular matrix).

mechanism of nutritional support to the solid tumor cells by products derived from TAM such as adrenomedullin (AMD), C-X-C motif chemokine ligand 8 (CXCL8), vascular endothelial growth factor A (VEGFA), and CXCL12 [36, 37]. Although the vasculature of tumor is functionally and phenotypically impaired, neoangiogenesis plays a crucial role for the growth of neoplasms in this scenario [38]. TME has been shown to exhibit some degree of hypoxia, which facilitates TAMs' tumor-supporting functions majorly via two mechanisms: First, hypoxic condition supports the upregulation of lipocalin 2 (LCN2), and upregulation of solute carrier family 40 member 1 (SLC40A1 or FPN). This causes the acquisition of an iron donor phenotype by TAMs, therefore enhanced availability of iron in the TME, and thus improved iron uptake by malignant cells and significant proliferation [39]. Wenes et al. investigated the character of metabolically activated hypoxic macrophage in metastasis and the blood vessel morphogenesis. It was observed that hypoxia causes TAMs to upregulate REDD1 (regulated in development and in DNA damage response 1), which causes the inhibition of mTOR, and further glycolysis inhibition. This was linked with an enhanced response to angiogenesis and leaky vessels formation. As a consequence, hypoxic TAMs migrate toward oxidative mode of metabolism coupled with decreased intake of glucose, which causes hyperactivation of endothelial cells and results in metastasis and neoangiogenesis because of the increased availability of glucose in the TME. However, the physiological relevance of such shift in humans has not been proven yet [40]. Under normoxia, TAMs exhibit downregulated activity of succinate dehydrogenase (SDH) and lower glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as compared to normal macrophages, aiding their potential to function on relatively low inputs of nutrients as found in the TME. Interestingly, the activity of GAPDH was observed to be more downregulated in M2-like than M1-like macrophages infiltrating colorectal tumors in humans [41]. In a similar manner, in human gliomas TAMs derived from monocytes showed reduced glucose metabolism than tissue-resident TAMs, which was linked with poor patient survival and escalated immunosuppression in the TME. These observations in TAMs suggest that decreased glycolytic activity elicits progression of tumor via both immunosuppression and nutritional circuitries [42]. Even when a decreased glycolysis metabolism in TAMs spears to favor growth of the tumor in a majority of settings, tissue section analysis and co-culture experiments in TAMs showed that production of lactate by human medullary carcinoma cells causes a shift from OXPHOS to glycolysis, couples to upregulated secretion of interleukin 6 (IL6), lactate and tumor necrosis factor (TNF), ultimately supporting tumor progression [43]. Additionally, proteomic analysis demonstrated that enzymes involved in glycolysis such as hexokinase 2 (HK-II) are increased in TAMs from individuals with pancreatic cancer and macrophages derived from bone marrow exposed to breast carcinoma extracts from individuals suggesting an enhanced rather than decreased capacity in glycolysis [44, 45]. Therefore, glycolysis in TAMs can facilitate tumor progression and growth irrespective of an increased competition for local availability of glucose [44].

Macrophages-mediated metabolic reprogramming in tumor is not only limited to glycolysis. Through the different glycolysis intermediates, glycolysis is directly associated with various other intracellular metabolic pathways. This includes fatty acid (FA) and glutamine metabolism, pentose phosphate pathway (PPP), and amino acid metabolism.

5.2 Fatty acid and glutamine metabolism

M2-like TAMs also display increased consumption of fatty acid and glutamine. The latter represents relatively increased levels of metabolic enzymes and glutamine

transporters expression, observed in both in vitro and in vivo in primary human TAMs [43]. In line with this, another study shows, glutamate ammonia ligase (GLUL) facilitates polarization of M2 by catalytic conversion of glutamate to glutamine, at least in vitro [46]. Therefore, inhibition of GLUL supports the M2-like TAMs repolarization into M1 counterparts along with enhanced flux of glycolysis and availability of succinate, suggesting the role of glutamine metabolism in TAMs regulation. Also, depletion of glutamine restrains polarization of M2-like macrophages in murine as a result of limited availability of a-ketoglutarate for epigenetic reprogramming [47]. A similar outcome ensues *N*-glycosylation inhibition suggesting the limited synthesis of aspartate-dependent UDP-N-acetyl-glucosamine (UDP-GlcNac) [47] and limited glucose-acetyl-CoA, which also plays a crucial role in epigenetic functions [48]. The former is the result of interleukin 4 (IL4)-driven activation of signal transducer and PPARG coactivator 1 beta (PPARGC1B), leading to enhanced epigenetic reprogramming and mitochondrial biogenesis toward fatty acid oxidation (FAO) [49]. Therefore, inhibition of pharmacological FAO reportedly supports repolarization of M1-like and M2-like macrophages [50], while upregulation of fatty acid synthase (FASN) in several subsets of TAM has been shown to favor pulmonary tumorigenesis because of the secretion of colony stimulating factor 1 (CSF1). In such a setting, TAMs have shown to support tumor progression by immunosuppressive cytokine interleukin 10 (IL10) release downstream of peroxisome proliferator-activated receptor delta (PPARD) [50]. The latter observation suggests the crosstalk between immune and metabolic functions in the TME. Some TAMs accumulate intracellular source of lipids in order to support metabolic fitness in tumor [51]. This suggests the alteration in majority of crucial factors involved in lipid metabolism such as monoglyceride lipase (MGLL), abhydrolase domain containing 5 (ABHD5), and acyl-CoA dehydrogenase medium chain (ACADM) [51–53]. Therefore, these observations suggest the major role of TAM metabolism on their ability to influence tumor progression and growth.

5.3 Amino acid metabolism

TAMs, exclusively pro-tumorigenic and M2-like macrophages, exhibit increased utilization of glutamine. This is linked with upregulated levels of intermediates such as uridine diphosphate N-acetylglucosamine, which are needed for N linked glycosylation of M2-like macrophages-associated receptors. Consequently, inhibiting the process of N-glycosylation and glutamine deprivation impairs polarization of M2-like macrophages along with downregulation in the TCA cycle [47]. Additionally, TAM isolated and exposed to glioblastoma cell lines exhibited enhanced gene expression related to metabolism [54]. The metabolism of L-arginine has also been shown to be associated with TAMs function. L-arginine can be used either through arginase metabolic pathway or for the synthesis of NO in macrophages. NO synthesis pathway is the characteristic feature of M1-like macrophages. Arginine is converted to L-citrulline and NO by nitric oxide synthase (iNOS). The NO furthermore downregulates OXPHOS through inhibition of electron transport chain (ETC) and TCA cycle enzymes and increases glycolysis [55, 56]. While on the other hand, expression of arginase (ARG1), enzyme that plays a crucial role in urea cycle, is the characteristic feature of M2-like macrophage, which hydrolyses arginine to urea and ornithine and restricts the availability of arginine for NO synthesis [57, 58]. TAM isolated from human ovarian and murine mammary tumors showed reduced cytotoxic properties linked with a decreased production of NO and a lower expression of iNOS in tumor-bearing mice [59, 60]. Another study demonstrated elevated expression of Arg1 in TAMs isolated from murine models. Lactate and hypoxia have been studied to be able to upregulate Arg1 expression [13]. Colegio et al. in lung cancer murine model

demonstrated that Arg1fl/fl X Lysmcre/wt mice, with deficient ARG1 in macrophages, developed small-sized tumor as compared to the wild-type mice [33]. In the same study, TAMs exhibited upregulated expression of urea cycle. Additionally, metabolites such as tryptophan and cysteine derived from L-arginine are crucial mediators of myeloid-derived suppressor cells (*MDSC*). These findings highlight the role of nitrogen cycle in TAMs' function [61].

6. Signaling cross-talk between macrophages and solid tumor

Colony stimulating factor 1 (CSF1), the major cytokine, plays an important role in the interplay between TAMs and tumor cells [62]. After binding to its cognate receptor, CSF1 facilitates monocyte-derived macrophages' recruitment to tumor bed and M2-like macrophages polarization. This is accompanied with (1) upregulation of FAO [63] and (2) immunosuppressive and pro-tumorigenic factor secretion, such as IL10 [64] and epidermal growth factor (EGF) [65]. Accordingly, inhibition of colony stimulating factor 1 receptor (CSF1R) with monoclonal antibodies or small molecules supports the M1-like TAMs' accumulation [66]. This is accompanied by glycolysis restoration, mediating therapeutic effects in majority of tumor models. CSF1, VEGFA, and IL34 supporting TAMs' growth is sensitive to chemotherapeutic environmental stress, local pH, nutrient availability, and oxygen tension [33, 62]. Therefore, metabolism of lactate is exclusively relevant not only for metabolic symbiosis between normoxic and hypoxic cancer cells but also for the potential of hypoxic cancer cells to decrease TAMs toward poor M2-like glycolytic profile, exhibiting upregulation of FAO, reduced potential for antigen presentation [67]. Additionally, M2 polarization of TAMs-associated melanoma is elicited by a G-protein-coupled receptor (GPCR) signaling mechanism that senses acidification of TME induced by increased glycolysis in cancer cells [68]. Mathematical modeling accompanied with in vivo experiments revealed the potential of TAMs to support the process of neoangiogenesis. This specific metabolic alteration has additional immunological consequences, as VEGFA favors the immunosuppressive receptors' expression [69]. Upregulated activity of lactate in the TME causing hypoxic nature contributes to the arginine catabolism by arginase 1 (ARG1) and ARG2 over nitric oxide synthase 2 (NOS2), causing enhanced secretion of factors supporting tumor such as polyamines and ornithine by TAMs [33, 69]. The levels of ARG1 can be increased in M2-like TAMs by signals induced by apoptotic cancer cells [70], such as FASN-dependent pathway driven by CSF1 [42] and sphingosine-1-phosphate (S1P). Also, lactate contributes polarization of M2-like macrophages in murine breast cancer models by triggering G-protein-coupled receptor 132 (GPR132) signaling. Accordingly, upregulated levels of GPR132 elicit infiltration in breast cancer by monocyte-derived macrophages, which certainly acquire functions supporting tumor phenotype. Another receptor of lactate, hydroxycarboxylic acid receptor 1 (HCAR1), seems to be upregulated in M1-like TAMs [71]. Additionally, cancer cells' metabolic influence on TAMs is not unidirectional. Therefore, when TAMs are exposed to the hypoxic conditions or upregulated lactate levels, they secrete variety of cytokines such as TNF, IL6, C-C motif chemokine ligand 5 (CCL5), and CCL18 [72]. IL6 supports glucose metabolism by mediating 3-phosphoinositide-dependent protein kinase 1 (PDPK1) potential to phosphorylate CCL5, TNF, phosphoglycerate kinase 1 (PGK), and CCL18 enhances pro-glycolytic factors such as PGK1, HXK2, glucose-6-phosphate dehydrogenase (G6PD), lactate dehydrogenase A (LDHA), vascular cell adhesion molecule 1 (VCAM1), pyruvate dehydrogenase (PDH), pyruvate dehydrogenase kinase 1 (PDK1), and GLUT1 [73]. Apart from these findings, Warburg phenomenon is triggered, both in vitro and in vivo, by transfer of long noncoding RNA of hypoxia

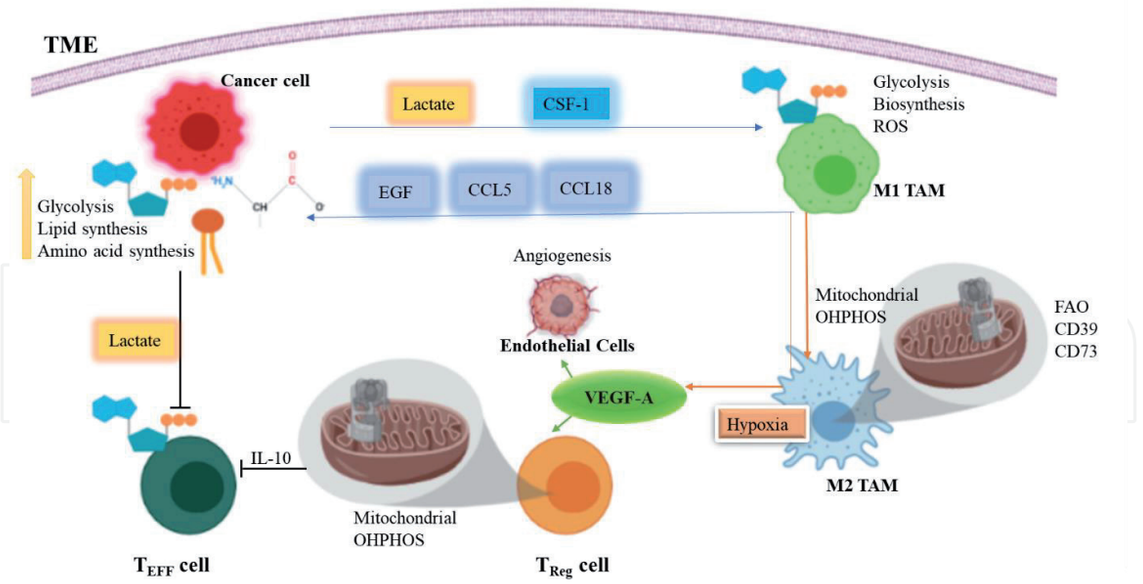


Figure 2.
Metabolic cross-talk signatures between TAMs and cancer cells. As cancer cells begin to proliferate in an uncontrollable manner, they start consuming elevated levels of glucose and other biosynthetic products to progress. This triggers the release of CSF-1 into the tumor microenvironment, which repolarizes the M1-like phenotype macrophages into M2-like macrophages. The M2-like state then releases several chemokines such as EGF, CCL-5, CCL-18, which act as immunosuppressive molecules. The expensive use of lactate by cancer cells delineates the immune function of T effector cells. Moreover, M2-like macrophages upregulated mitochondrial phosphorylation and fatty acid oxidation.

inducible factor 1 subunit alpha (HIF1A) from TAMs exposed to lactate to the tumor cells. Intriguingly, HIF1A have been shown to play a crucial role in exacerbating tumor glycolysis as well as M2 polarization. Furthermore, M2-like TAMs trigger hypoxia in an active manner [37] (**Figure 2**).

7. Therapeutic strategies against macrophages-mediated tumor metabolism

As now it is very evident that TAMs and tumors have very complex interactions between them, which supports the tumor progression, growth, and metastasis, researches across the globe are widely studying this area and finding novel targets against the immune regulators and metabolic mediators in the system. TAMs are the widely found immune cells in the tumor microenvironment and undergo complex processes to support the tumor growth. M2-like TAM phenotype is highly reported from studies to likely support the tumor progression. This conclusion supports the idea of developing antibodies that intervene with the M2 phenotype macrophage function. CCL2 blocking agents have been a promising antibody against cancer metastasis and cancer death. Therefore, strategies to deplete the M2 phenotype into non-tumorous M1 phenotype have been a promising step toward treating cancer. Drugs associated with metabolic blockers also paved a new method for treating cancer. Drugs such as inhibiting HK-II helped in the inhibition of pro-metastatic M2 phenotype of TAMs. Similarly, drugs inhibiting FAO also appear to be a promising field to target pro-tumoral macrophage as well as tumor metabolism. T-cells are the major players contributing toward immune-mediated cell metabolism, which is also approached as an effective target. PD-1 ligation with T-cells helps in the shift in metabolism from glycolysis to FAO, which maintains the longevity of T-cells and impairs their effector function (**Table 1**).

S. No.	Target	Effect	References
1	CCL2	Reduce tumor growth and metastasis in prostate and breast cancer	[74]
2.	CSF1 receptor	Antiangiogenic and antimetastasis effects in melanoma and mammary xenograft	[66]
3.	IL4Rα	Less aggressive skin tumors	[75]
4.	STAT3	Inhibited immunosuppressive cytokine profile of AAMs	[76]
5.	COX2	Suppression of breast cancer metastasis	[77]
6.	HCK	Suppression of AAM polarization, enhanced tumor immunity in colon cancer	[78]

Table 1.
Metabolic targets in tumor-associated macrophages.

Therefore, strategies that target macrophages along with tumor metabolism without encouraging the tumor cell growth have been quite challenging and have provide an effective means to treat the solid tumors.

8. Conclusion

Solid tumors are evolving over the years strongly by acquiring the capability to manipulate the host system to help them attain energy demands to survive and metastasize. One such player helping tumor cells is the macrophages. The polarization of macrophages into tumorous M2 phenotype helps the cancer cells in their glycolytic demands. Metabolic events such as amino acid metabolism and oxidative phosphorylation are triggered in cancer cells. The hypoxia event in cancer cells stimulates the signaling events toward glycolysis increasing glycolytic enzymes such as hexokinase-II, LDH-A, and pyruvate dehydrogenase. Thus, series of research has proved that macrophages has an important role to play in tumor metabolism inside the TME. This kind of immunometabolism has triggered challenges and interest in finding novel targets on this area to cure the disease cancer.

Acknowledgements

We thank our lab members for carefully reading the article and contributing valuable inputs for improving it. V.C., S.R., and D.K. were supported by the Department of Science & Technology-Science and Engineering Research Board (DST-SERB)-funded research grant (ECR/2016/001489), Govt. of India.

DOI: http://dx.doi.org/10.5772/intechopen.93182

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