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Glucose Metabolism: The Metabolic Signature of Tumor Associated Macrophage

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Macrophages exist in most tissues of the body, where they perform various functions at the same time equilibrating with other cells to maintain immune responses in numerous diseases including cancer. Recently, emerging investigations revealed that metabolism profiles control macrophage phenotypes and functions, and in turn, polarization can trigger metabolic shifts in macrophages. Those findings implicate a special role of metabolism in tumor-associated macrophages (TAMs) because of the sophisticated microenvironment in cancer. Glucose is the major energy source of cells, especially for TAMs. However, the complicated association between TAMs and their glucose metabolism is still unclearly illustrated. Here, we review the recent advances in macrophage and glucose metabolism within the tumor microenvironment, and the significant transformations that occur in TAMs during the tumor progression. Additionally, we have also outlined the potential implications for macrophage-based therapies in cancer targeting TAMs.

Keywords: macrophage, glucose metabolism, polarization, cancer, therapy

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INTRODUCTION

Cancer is a major public health burden worldwide, with a significantly high incidence of mortality. The environment around the tumor is called as tumor microenvironment (TME), which assists cancer cells in growth and progression (1). Over the last few years, TME has extensively been studied for the effective treatment of cancer. Though TME has diverse tumor-infiltrating immune cells like the T-cells, regulatory T-cells (Treg), myeloid-derived suppressor cells (MDSC), tumor-associated neutrophils, dendritic cells, and tumor-associated macrophages (TAMs), macrophages are the most abundant (2). A large number of studies suggest that TAMs serve as a key promoter of metastasis in cancer, by releasing extracellular signals, growth factors, proteolytic enzymes, and inhibitory proteins for T cells (3). Thus, targeting TAMs to prevent tumor progression and metastasis has been a hot spot in current cancer research.

Traditionally, macrophages are the large phagocytes that pose various forms in tissues throughout the body (e.g., Kupffer cells in the liver, alveolar macrophages in the lungs, microglia

in the cerebrum) and typically play an important role in homeostatic and immune responses during the disease process (4, 5). Moreover, macrophages are highly plastic and can modify their properties subsequently according to the microenvironment (6). Inactive macrophages (M0) typically represent undifferentiated cells and can reprogram themselves into polarized cells when exposed to certain stimuli. Depending on the cell surface markers, cytokines release, and metabolic signatures, macrophages are conventionally classified into two subtypes, i.e. classically activated pro-inflammatory M1 macrophages, and alternatively activated anti-inflammatory M2 macrophages (5, 7–9).

In recent years, increasing evidence has put forward that TAMs can unanimously adopt distinct metabolic signatures to execute proper effector functions required for the TME (10–13). It has been traditionally assumed that cancer cells primarily metabolize glucose *via* glycolysis to produce sufficient energy and other key metabolites necessary for survival (Warburg effect) (14–17), which essentially perplexes the metabolic profiles of immune cells especially TAMs (18). However, a fresh study astonishingly revealed that TAMs are the main consumer of glucose in cancers rather than cancer cells themselves (19). Yet, how glucose metabolism influences TAMs functions in cancer and vice versa are still obscure. Consequently, the complex correlation between glucose metabolism and TAMs in TME is worthy to investigate adequately. In this review, we have focused on the modifications that consistently occur in glucose metabolism and TAMs in TME, and the potential implications for macrophage-based therapies in cancer.

GLUCOSE METABOLISM PATHWAYS

Glucose traditionally serves as the primary source of energy for supporting the normal functions of the cells including macrophages. After being transported across the plasma membrane, glucose is principally metabolized through three pathways, i.e. glycolysis, pentose phosphate pathway (PPP), and Krebs or Tricarboxylic Acid (TCA) cycle (20, 21). Glycolysis is a metabolic pathway typically takes place in the cytosol, which breaks down glucose into pyruvate in aerobic environment and lactate in anaerobic settings and produces adenosine triphosphate (ATP). Pyruvate produced from aerobic glycolysis further enters the Krebs cycle and is oxidized through a series of reactions called oxidative phosphorylation (OXPHOS) to produce more ATPs. On the other hand, glycolysis also supplies glucose-6-phosphate to the PPP, provoking the production of nicotinamide adenine dinucleotide phosphate (NADPH) and ribose-5-phosphate. Though glycolysis possesses a lower capacity for ATP generation than OXPHOS, (only two ATP per molecule of glucose), it is a more rapid source of energy for macrophages and other cells and contributes metabolic intermediates for biosynthetic pathways to support the synthesis of ribose, amino acids, and fatty acids that are crucial for metabolic adaptation (22, 23). Apart from the above-mentioned three glucose metabolism pathways, glucose can further be metabolized *via* the hexosamine biosynthesis pathway (HBP) (2–5%) and eventually leading to the generation of a donor molecule uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) (24–26).

Macrophages preferentially attach the surface of glucose transporter 1 (GLUT1) to meet their energy requirements (27). Under normal conditions, naïve M0 macrophages get energy by efficiently employing OXPHOS (28). Whereas, polarized macrophages (M1 and M2) rely more on their characteristic metabolic signatures for energy prerequisite within the tissue microenvironment (23).

GLUCOSE METABOLISM AND THE M1 MACROPHAGES

Traditional pro-inflammatory cytokine such as interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), and lipopolysaccharide (LPS) stimulates M0 macrophages to differentiate into classical M1 phenotype (29–31). M1 macrophages exhibit profound inflammatory cytokines secretion (including IL-1β, IL-6, IL-23, TNF-α) and precise antigen presentation (**Table 1**). To uphold dramatic pro-inflammatory functions, M1 macrophages trigger energy expenditure by the magnified aerobic glycolysis and PPP in conjunction with decreased OXPHOS and fatty acid oxidation (FAO). Glycolysis and PPP are fundamental for macrophage functional adjustments and preventing the body from harmful events within an exigent time.

In parallel, glycolytic enzymes are found to have remarkable alternations within the LPS microenvironment (32). Traditionally, glycolysis is mainly regulated by three major enzymes: hexokinase (HK), phosphofructokinase 1 (PFK1), and pyruvate kinase (PK), which catalyze irreversible steps in this process (21). Under LPS stimulation, HK acts as the glucose sensor and mediates the phosphorylation of glucose for subsequent utilization, crucially contributing to the pro-inflammatory cytokine secretion in M1 macrophages (33). Recently, an inducible form of PFK1, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) stepped into research (34, 35). Once PFKFB3 is stimulated with IFN-γ/LPS, it further induces progressive production of fructose 2,6-bisphosphate, and thus, promotes overall glycolysis flux in M1 macrophages to meet its energy demand (36). On the other hand, M1 macrophages significantly upregulate the key metabolic regulator, an isoform 2 of the pyruvate kinase (PKM2) under LPS activation to bind IL-1β promotor region concerning increased inflammatory response (37, 38).

Besides, overexpression of GLUT1 in M1 macrophages promotes glucose metabolism and metabolites production in the PPP, striking a complex pro-inflammatory signature (39). It has been found that long-term glucose exposure reduces the phagocytic ability of M1 macrophages, probably because of impaired glycolytic capacity (40). Interestingly, the constitutive expression of sedoheptulose kinase (CARKL), a carbohydrate

TABLE 1 | The complexity between macrophage phenotypes and glucose metabolism.

	M1 macrophage	M2 macrophage	Tumor-associated Macrophage
Activation stimuli	IFN-γ, LPS, TNF-α	IL-4, IL-13	Tumor microenvironment, such as hypoxia, adenosine
Inflammatory cytokines secretion	IL-1β, IL-6, IL-12, IL-23, TNF-α	IL-1, IL-6, IL-10, TGF-β	Both, mainly anti-inflammatory cytokines
Marker expression	CD68, CD86, CD80, MHC-II, INOS, TLR-4	CD163, CD206, MHC-II, CXCR1, CXCR2, TLR1, TLR8	Both M1 & M2 markers, mainly immunosuppressive molecules
Chemokine secretion	CXCL3, CXCL5, CCL2, CCL3, CCL4, CCL5, CCL8-11	CCL17, CCL18, CCL22, CCL24	CCL1, CCL5, CCL10
Antigen presentation	Yes	No	Yes
Glucose metabolism pattern	Glycolysis, PPP, HBP	OXPHOS, FAO, HBP	OXPHOS & FAO, with increased glycolysis, PPP, HBP
Glucose metabolism enzymes	HK, PFKFB3, PKM2, PDK1	PDK1, CARKL, PFKFB1	both
Signaling pathways	HIF-1α, STAT1, STAT5, IRF3, IRF5, NF-κb	mTORC2, IRF4, STAT3, STAT6	AKT/mTOR, HIF-1α, NF-κb
Functions	Pro-inflammatory, tissue damage	Anti-inflammatory, phagocytosis; tumor formation and progression	M2a, M2b, M2c, M2d and others subtypes; promoting tumor progression; immune suppression; immune scape

kinase-like protein that is involved in the conversion of sedoheptulose into sedoheptulose-7-phosphate, decreases the glycolytic flux of glucose and results in defective M1 polarization (41) These findings portray an interlaced network that pro-inflammatory molecules stimulate glucose metabolism in macrophages. Conversely, glucose uptake in macrophages supervises pro-inflammatory phenotype. The pro-inflammatory environment and increased glucose levels might guide each other in a self-perpetuating cycle, among which hypoxia-induced factor 1 alpha (HIF-1α) (37, 42–44) plays an essential role.

Previously, HBP was identified to promote inflammation in macrophages that associated with O-linked β-N-acetylglucosamine (O-GlcNAc) signaling (45, 46). Nevertheless, a study surprisingly observed a decreased HBP activity and protein O-GlcNAcylation in LPS-stimulated macrophages. Subsequently, they proved that the O-GlcNAcylation of the receptor-interacting serine/threonine-protein kinase 3 contributed to an unexpected inhibitory effect (47). Indeed, Yang et al. observed a similar immunosuppressive role of O-GlcNAc signaling in macrophage activation. Macrophages presented suppressed O-GlcNAc signaling during M1 polarization even though the increased glucose uptake. Therefore, macrophage O-GlcNAc signaling is an important regulator of integrating glucose metabolism and inflammatory response. Taken together, those results indicated that metabolic changes are not just the result of the inflammatory response, but rather a critical modulator of the entire process.

GLUCOSE METABOLISM AND THE M2 MACROPHAGES

Alternatively activated M2 macrophages are primarily induced by IL-4 and IL-13 that are secreted from innate and adaptive immune cells, and are characterized by an anti-inflammatory profile mainly IL-10 and transforming growth factor-beta (TGF-β) (8, 29–31). In contrast to M1 macrophages, M2 macrophages preferentially utilize FAO and OXPHOS to execute cellular behaviors and activities (**Table 1**) (48–50). Although some evidence demonstrated that FAO is typical for M2 polarization, researchers believe that M2 macrophages retain the same dependence on glycolysis and exhibit modest glucose consumption (51, 52). Glucose can fuel fatty acid synthesis to support increased FAO in M2 macrophages, linking glycolysis, fatty acid synthesis, and FAO.

An integrative analysis demonstrated that glucose oxidation, but not that of fatty acids, is necessary for the early differentiation of M2 macrophages and PDK-1 plays an ineffable role in this conversion (53). Glucose uptake was increased over time in macrophages when stimulated by IL-4. This observation pioneeringly spiked interest of glycolysis in M2 macrophages (54). Another point as recognized, CARKL is upregulated in M2 macrophages, which can lead to the production of ribose-5P, enhancing the nonoxidative steps of PPP (41). Moreover, a selective expression of the glycolytic enzyme 6-phosphofructo 2-kinase B1 (PFKFB1), was consistently found in M2 macrophage, it can catabolize fructose-2,6-bisphosphate more efficiently than PFKFB3.

Alluringly, it was found that blocking glycolysis with 2-deoxyglucose (2-DG) diminished the IL-4-induced expression of the M2 phenotype, and the mTORC2 signaling upstream of IRF4 expression played a critical role (54, 55). Interestingly, similar results were acquired from macrophages cultured in a glucose-free medium (55). Depletion of glucose or substitution of glucose with galactose remarkably suppresses glycolysis but does not affect OXPHOS and M2 macrophages activation (51). This phenomenon indicates that glycolysis is not mandatory for M2 activation if OXPHOS is intact, but becomes necessary if OXPHOS is compromised (56). At the same time, HBP was also found dispensable for anti-inflammatory M2-like polarization (57). Thus, glucose looks like energy support for OXPHOS in M2 macrophages, probably triggering a spurt mitochondrial respiratory activity.

GLUCOSE METABOLISM SIGNATURE OF TUMOR-ASSOCIATED MACROPHAGES

As stated earlier, TAMs constitute the largest population of immune cells within the tumor, and are immunosuppressive in nature during tumor progression. Upregulation of the expression of ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD also known as CD39), 5'-nucleotidase Ecto (NT5E also known as CD73) (58, 59), or programmed cell death ligand 1 (PDL-1) (60) were comprehensively detected in TAMs. As cancer cells themselves are typically dependent on glucose, they consume most glucose from the surrounding microenvironment and administrate glycolysis to supply rapidly growing energy requirements. Consequently, TAMs domestically shift toward OXPHOS and FAO metabolism and exhibit functions primarily similar to M2 macrophages in a poor glucose TME to maintain their immunosuppressive roles (61, 62). Wenes et al. recently revealed that in hypoxic conditions of solid tumors, TAMs promoted neoangiogenesis and tumor metastasis by shift towards oxidative metabolism with decreased glycolysis through activation of mTOR signaling pathways (63). In the meanwhile, results showed that enhanced glucose flux through the HBP propelled cancer progression by boosting O-GlcNAcylation in TAMs (64).

However, slightly distinction of environment stimulus can elicit substantially different macrophage phenotypes and metabolism profiles (65, 66). Even though given the same stimuli, macrophages can display differential responsiveness. Considering the complexity of the TME, the plasticity and adaptability of macrophages, it should be noted that such a defined 2D spectrum of M1–M2 polarization adopted from *in-vitro* experiments may not properly map the metabolism signatures of macrophage *in-vivo*, it has to be considered as an extremely dynamic and mixed 3D spectrum. More recently researches revealed that TAMs actually have higher glucose uptake (67) and a high level of glycolytic metabolism similar to M1 macrophages to support their cytokine profiles and functions. Proteomic analyses revealed that glycolytic enzymes including hexokinase 2 are upregulated in macrophages stimulated by tumor extract solution from breast cancer patients (68), consistent with the findings in pancreatic ductal adenocarcinoma (PDAC) (69) and non-medullary thyroid carcinoma (70). Simultaneously, lactic acid released by glycolytic cancer cells into the TME also upregulates HIF-1α expression in TAMs responsible for increased glycolysis and M2-like state (71, 72). Additionally, *in-vivo*, macrophages are capable of repolarization from M2 to dichotomous M1 phenotype, they can co-express both M1 and M2 polarization hallmarks following tumor progression (56). We recently identified a subtype of pro-inflammatory M2-type (CD206+IL-1β+) TAMs characterized as stable mitochondrial respiration, enhanced glycolysis, and elevated O-GlcNAcylation protein levels in hepatocellular carcinoma. This novel subtype of macrophages shares similar cell markers and cellular metabolism with classic M2-like phenotype while playing a pro-inflammatory M1-like function (73). Other researchers too have found such enhanced glycolysis in TAMs and have recognized more subtypes of TAMs in cancer like CD68+ TAM in non-small cell lung cancer (NSCLC) (74), CD169+ macrophages in PADC (75, 76), CD163+ macrophages in epithelial ovarian cancer (77), and PD-1+ macrophages in primary mouse and human cancer (78). Hence, all various phenotypes of TAMs can contribute to the tumor progression, depending on the metabolism balance in TME.

By integrating data from the ImmGen project, Schultze et al. proposed a core signature for human and murine macrophages expanding our understanding (79). Correspondingly, Sarukhan et al. discussed the potential underlying mechanisms regulating TAMs specialization (80). These studies allowed us better understand the heterogeneity of TAMs in tumors. Nevertheless, the question that how glucose metabolism influence macrophages' switch in the tumor microenvironment, involving the recruitment of circulating precursors or the re-education of cells *in situ* still existed. Our group recently identified a novel subtype of CD19+ TAMs in HCC, results showed that glycolysis may be an innate feature that prefers the tumor progression (unpublished data). A recent study also supported that glucose use was modulated by cell-intrinsic programs of cells through mTORC1 signaling in tumor (19). In fact, tumor cells rely more on glucose to support their growth than TAMs, such nutrient competition between tumor cells and immune cells apparently are adverse for the ready proliferation of tumor cells. Additionally, how macrophages glucose metabolism affects other immune cells in tumor is incompletely explored. Hence, more profound work is required to develop the underlying process.

Delightfully, advances in technology for single-cell RNA sequencing (81, 82) and high-dimensional cytometry by fluorescence or mass cytometry (cytometry by time of flight (CyTOF)) (83) significantly promoted the high-dimensional single-cell analyses. In the past few years, numerous profound and novel views of metabolic flux and TAMs have been stated (84, 85). In further study, the complete and elaborate description of TAMs subpopulations landscape remains to establish to explain the macrophages evolution and glucose metabolism.

TARGET GLUCOSE METABOLISM IN MACROPHAGE FOR CANCER THERAPY

Given the important role of TAMs in promoting tumor development and the complex landscape of the macrophages which are heterogeneously evolved under the selective pressure of TME, manipulating macrophages tentatively may serve as a promising approach for controlling tumor progression (**Figure 1A**). Previously, TAMs-targeted antitumor strategies were mainly based on the inhibition of macrophages recruitment (86, 87) or depletion of M2-like TAMs. However, a recent study discovered that interruption of C–C motif chemokine ligand 2 (CCL2) inhibition was associated with increased cancer cell mobility and neovascularization, leading to accelerated metastasis and cancer death (88). Furthermore,

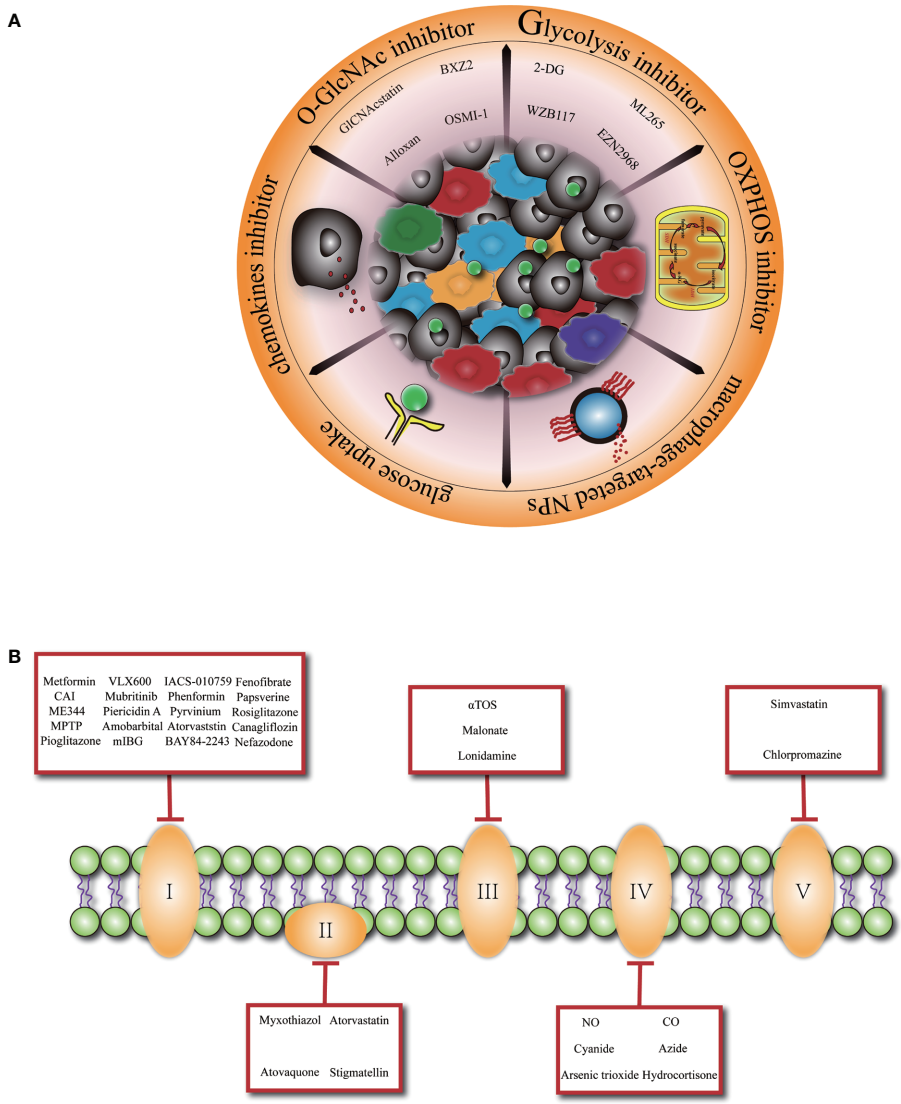

FIGURE 1 | Glucose metabolism basis macrophage-targeted therapy for cancer. **(A)** Overview of promising cancer therapy based on glucose metabolism characteristic in tumor-associated macrophage. 2-DG, 2-deoxyglucose. **(B)** Specific presentation of OXPHOS (oxidative phosphorylation) inhibitors involved mitochondrial complex I, II, III, IV, V. CAI, carboxyamidotriazole; MPTP, 1-methyl 4-phenyl 1,2,3,6 tetrahydropyridine; mIBG2, meta-iodobenzylguanidine; aTOS, a-tocopheryl succinate; NO, nitric oxide; CO, carbon monoxide.

far-ranging macrophage depletion could bring outside effects, such as other immunosuppressive cells' compensation (89–91).

Since macrophages glucose metabolism is inextricably connected to its functionality, metabolic reprogramming of M2-like TAMs toward an anti-tumoral phenotype at the same time rupture cancer cell metabolism might be an elegant way. In the context of a profound relationship between OXPHOS and the differentiation of M2 macrophages especially in TAMs, inhibiting OXPHOS pathway (**Figure 1B**) has been explored as a promising approach to promote TAMs transition to M1 macrophages (92). Blocking the expression of succinate dehydrogenase complex flavoprotein subunit A (SDHA) and oxidative phosphorylation activities of macrophages with dimethyl malonate treatment exhibited markedly delayed tumor growth (93). Similarly, FAO inhibitors are developed to achieve the phenotypic transition of macrophages and inhibit tumor development. Furthermore, researchers have revealed that acriflavine (ACF), a heteroaromatic dye with an antibacterial and antiviral effect, shifted macrophage polarization to an M1-like anti-tumoral phenotype by blocking the HIF-1α pathway and enhancing glucose uptake in PDAC (94). This phenomenon shows that increasing the glucose utilization of TAMs may be a promising direction.

As above mentioned, glycolysis is important in the early differentiation of TAMs, the maintenance of an M2-like profiles

also dependent on a high glycolytic flow. Consequently, glycolysis inhibition (with decreased lactate derived from the tumor) of TAMs is certainly hopeful for cancer therapy. Chitin administration significantly decreased anti-inflammatory M2 macrophage polarization and prevented disease progression in a series of mouse models (95). Also, dichloroacetic acid profoundly prevented macrophage migration in a lung tumor xenograft model by inhibiting macrophages glycolysis (42). Several O-GlcNAcylation inhibitors had been proved to inhibit cancer cell growth (96, 97). Nevertheless, specific targeting of one of the metabolic pathways for macrophages is potentially deflective. Proper adjustment of glucose metabolism in macrophages, instead of a simple one-way increase or decrease, presents a potential therapeutic strategy.

In addition, owing to distinct cell populations of the TME share common metabolic profiles and all metabolic pathways are important for normal cells, sustained modifications of core metabolic pathways may have marginally immunological effects that are difficult to predict. Alternatively, the use of prodrugs that are specifically activated macrophages according to the embellishment of glucose metabolism in TME could be considered for future therapy. For instance, esterase-sensitive motif (ESM) inhibitors were prosperously tested as clinical agents targeting macrophages (98). More than that, with the development of nanotechnology, drug delivery systems based on nanoparticles (NPs) have been in the generation of therapeutic agents for several features, they are avirulent and can easily penetrate physiological barriers with a stable consistency. Glucose-based NPs have been used as biocompatible polymers to re-educate TAMs (99). Meanwhile, ^{18}F-FDG PET (100–102) has been proposed as a non-invasive strategy to detect glucose uptake and orbit underlying macrophage polarization mechanisms. The application of biological or chemical materials in targeted therapy makes it possible for the natural modulation of macrophage glucose metabolism *in-vivo*, favoring an optimal metabolic balance of macrophages to display functions in TME.

CONCLUSION

As previously described, macrophages might respond diversely depending on the heterogeneity in miscellaneous tissue microenvironment and cell subpopulations ongoing changed. Hence, macrophages should be considered as dynamic alternations in the different phases of cancer where they adapt various phenotypes and also metabolic signatures; the enhanced or decreased glucose metabolism of macrophages should also not be taken as favorable or harmful effects for TME. On the other hand, advanced tools such as spatial transcriptomics and multiplex immunohistochemistry need to be developed to dig the association of glucose metabolism and macrophages. Whatever, currently, the most effective strategies to target cancer will have to precisely combine TAM-targeted prodrugs delivery systems with complex cell glucose metabolism pathways and real-time imaging systems in cancer. In summary, depth work is required to probe the macrophage-response specificity, tissue-type sensitivity, and metabolism-pattern availability, especially constricting the gap between research and clinic with the help of precision medicine.

AUTHOR CONTRIBUTIONS

QZ and JW wrote the manuscript. DY, XB, and TL revised the manuscript. QZ and JW contributed equally to this work. All authors contributed to the article and approved the submitted version.

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