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Exploring the Potential of Glycolytic Modulation in Myeloid-Derived Suppressor Cells for Immunotherapy and Disease Management

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Abbreviations
2-DG, 2-deoxy-D-glucose; 3-BrPA, 3-Bromopyruvate; AG, aerobic glycolysis; AML, acute myeloid leukemia; AMPK, adenosine monophosphate-activated protein kinase; AR, adrenergic receptor; ARG1, arginase-1; ATP,

ABSTRACT

Recent advancements in various technologies have shed light on the critical role of metabolism in immune cells, paving the way for innovative disease treatment strategies through immunometabolism modulation. This review emphasizes the glucose metabolism of myeloid-derived suppressor cells (MDSCs), an emerging pivotal immunosuppressive factor especially within the tumor microenvironment. MDSCs, an immature and heterogeneous myeloid cell population, act as a double-edged sword by exacerbating tumors or mitigating inflammatory diseases through their immune-suppressive functions. Numerous recent studies have centered on glycolysis of MDSC, investigating the regulation of altered glycolytic pathways to manage diseases. However, the specific changes in MDSC glycolysis and their exact functions continue to be areas of ongoing discussion yet. In this paper, we review a range of current findings, including the latest research on the alteration of glycolysis in MDSCs, the consequential functional alterations in these cells, and the outcomes of attempts to modulate MDSC functions by regulating glycolysis. Ultimately, we will provide insights into whether these research efforts could be translated into clinical applications.

Keywords: Glycolysis; Immunomodulation; Metabolic reprogramming; Myeloid-derived suppressor cell

INTRODUCTION

Myeloid-derived suppressor cells (MDSCs), constituting a heterogeneous immature myeloid cells, have been identified to execute diverse functions in various contexts, from well-established subjects like cancer and inflammatory diseases to bacteria and virus infections, diabetes, and even during pregnancy (1). Their role has been particularly accentuated in the sphere of cancer research, attributed largely to their capacity to inhibit immune responses against tumor cells—including T cells and NK cells—within the tumor microenvironment (TME). With the expanding emphasis on tumor immunotherapy in recent scientific dialogues, the significance of MDSCs has been concurrently emphasized. While chimeric Ag receptor-T cells have shown remarkable success in treating hematological malignancies, their application in solid tumors has encountered impediments, partially owing to the TME, where anti-tumoral immune responses are suppressed, thereby posing challenges to the utility of chimeric Ag receptor-T cells (2). Moreover, although immune checkpoint inhibitors

adenosine triphosphate; BM, bone marrow; COX-2, cyclooxygenase-2; EV, extracellular vesicle; GLUT, glucose transporter; HIF, hypoxia-inducible factor; ICI, immune checkpoint inhibitor; IDO, indoleamine-2,3-dioxygenase; IMH, immune-mediated hepatitis; iNOS, inducible nitric oxide synthase; KO, knockout; MDSC, myeloid-derived suppressor cell; mMDSC, monocytic myeloid-derived suppressor cell; mTOR, mammalian target of rapamycin; NK, natural killer; NO, nitric oxide; OXPHOS, oxidative phosphorylation; PBMC, peripheral blood mononuclear cell; PD-L1, programmed death-ligand 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; pmnMDSC, polymorphonuclear myeloid-derived suppressor cell; ROS, reactive oxygen species; SC, subcutaneous; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TCA, tricarboxylic acid; TLR2, toll-like receptor 2; TME, tumor microenvironment; Treg, regulatory T cell.

Conflict of Interest

The authors declare no potential conflicts of interest.

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(ICIs) demonstrate efficacy across numerous malignancies, not all patients respond due to issues such as the development of resistance and subsequent loss of therapeutic response. One contributory factor to this limitation is the presence of MDSCs which exhibit immunosuppression against immune cells within the TME, thereby mitigating the impact of ICI. This is often accompanied by an associated increase in circulating MDSCs in patients receiving ICI (3,4). Therefore, research into MDSCs continues, with various therapeutic strategies targeting MDSCs under development and numerous ongoing clinical trials (5,6).

Beyond the well-established immunosuppressive role in tumor progression, MDSCs perform various functions in various other diseases. Although it is evident that MDSCs enhance tumor progression by suppressing immune responses, the role of MDSCs in other diseases is not as well-defined and often subject to debate (7). In systemic lupus erythematosus, MDSCs initially exhibit an immunosuppressive role, curbing overactive immune responses through mechanisms such as arginase-1 (ARG1) expression and inducible nitric oxide synthase (iNOS) activity (8,9). However, in certain contexts, MDSCs can exacerbate inflammation by promoting Th17 cell differentiation (10). This dual behavior extends to diseases like rheumatoid arthritis and inflammatory bowel disease, where MDSCs are known to both alleviate and exacerbate inflammation, contingent on the disease phase and the specific milieu (11-14). Particularly noteworthy is that MDSCs can enhance the transition from chronic inflammation to colitis-associated cancer in the advanced stages of inflammatory bowel disease (15). This indicates that while MDSCs have potential therapeutic benefits in moderating autoimmune disorders, their role is significantly influenced by the local tissue context and disease state. The multifaceted roles of MDSCs underscore their potential as targets for therapeutic intervention. By enhancing regulatory functions of MDSCs, there may be opportunities to develop treatments that more effectively manage inflammatory diseases. Nonetheless, the challenge lies in understanding and manipulating complex functions of MDSCs within the dynamically changing environments of these diseases.

The concept of immunometabolism, despite being a topic of research for an extensive period (16), has gained renewed interest owing to developments in diverse technologies (17). Notably, it has been discovered that metabolites can also regulate intracellular signaling pathways and perform as cellular immunological mediators (18). Consequently, there is growing interest in using metabolic processes to manage diseases that involve immune cells. Especially within immunometabolism, glucose metabolism has been highlighted for its pivotal role in the activation and differentiation of immune cells, prompting extensive research into modulating glycolysis to regulate the immune cells (19,20).

In this review, we systematically explore the differences in glycolysis between MDSCs and normal myeloid cells across various diseases, and aim to identify the intracellular signaling pathways that mediate these changes. We will compile findings from preclinical studies that investigated the impacts of modulating MDSCs by targeting glycolysis. Additionally, we will discuss projections for developing therapeutic strategies that target glycolysis in MDSCs, providing a foundation for future research and discussions in this area.

MDSC

Characteristics

Even before the term "MDSC" was firmly established in 2007 (21), multiple reports had surfaced regarding the presence of immature myeloid cells with immunosuppressive capabilities against T cells (22,23). After specifying MDSCs, numerous studies have undertaken to understand these immunosuppressive cells. They have been identified to emerge due to various factors, including tumors, inflammations, infections, pregnancy, heart failure, and diabetes (1).

Bone marrow (BM) progenitor cells are induced to differentiate into MDSCs through tumor-derived cytokines including GM-CSF, other CSFs, VEGF, IL-6, IL-1β, and other inflammatory cytokines (24). Transcription factors such as CCAAT-enhancer-binding proteins and signal transducer and activator of transcription 3 (STAT3) are known to regulate MDSC development (25). MDSCs migrate in an immature state to the blood, subsequently moving to secondary lymphoid organs and, finally, to the TME. Their migration involves chemokine-receptor axis such as CCL2/CCL12-CCR2, CCL3/4/5-CCR5, CCL15-CCR1, and CX3CL1/CCL26-CX3CR1 (26). Once in the tumor, MDSCs can polarize toward tumor-associated macrophage (TAM) or tumor-associated neutrophil and contribute to establishing the immunosuppressive environment of the TME (27).

MDSCs can be broadly categorized into two subtypes: monocytic MDSC (mMDSC), bearing resemblance to monocytes, and polymorphonuclear MDSC (pmnMDSC), similar to polymorphonuclear cells. As heterogeneous cells, mMDSC and pmnMDSC exhibit distinct characteristics. MDSCs are defined in mice and humans using various markers like pmnMDSC, $CD11b^{+}Ly6G^{+}Ly6C^{int}$; mMDSC, $CD11b^{+}Ly6G^{-}Ly6C^{hi}$ for mice, and pmnMDSC, $CD11b^{+}CD14^{-}CD15^{+}$(or $CD66b^{+}$); mMDSC, $CD11b^{+}CD14^{+}CD15^{-}HLA\text{-}DR^{lo/-}$ for humans. Additionally, early MDSCs, which are specific to humans, have been identified and are defined as Lin^{-}(CD3/14/15/19/56)$HLA\text{-}DR^{-}CD33^{+}$ (28).

Function

MDSCs exhibit immunosuppressive functions within the TME through direct cell-to-cell contact with immune cells, indirect methods, such as immunosuppressive cytokines, ROS, nitric oxide (NO), exosomes, and by regulating T cell metabolism through mechanisms involving ARG1, indoleamine-2,3-dioxygenase (IDO), etc. MDSCs suppress T cell and NK cell functions while enhancing immunosuppressive Treg, consequently inhibiting anti-tumor immune responses or alleviating inflammatory conditions in inflammatory diseases (29). Recent research has unveiled that MDSCs can modulate systemic immune function by manifesting immunosuppressive capabilities of lymphocytes right from the lymphoid organ (30). While both mMDSCs and pmnMDSCs suppress the immune response, mMDSCs are observed to have a higher immunosuppressive capability. pmnMDSCs conduct immune suppression via ROS-mediated suppression, whereas mMDSCs demonstrate immune suppression through NO, IL-10, and TGF-β (31). Notably, MDSCs possess plasticity between subtypes, as evidenced by Youn et al., revealing that mMDSC can differentiate into pmnMDSC (32).

Metabolic characteristics of MDSC

Immune cells have distinct metabolic profiles. Naïve T cells and Tregs primarily use oxidative phosphorylation (OXPHOS) to produce ATP, while activated T cells ramp up glycolysis following increased glucose uptake (33). MDSCs are highly metabolically active,

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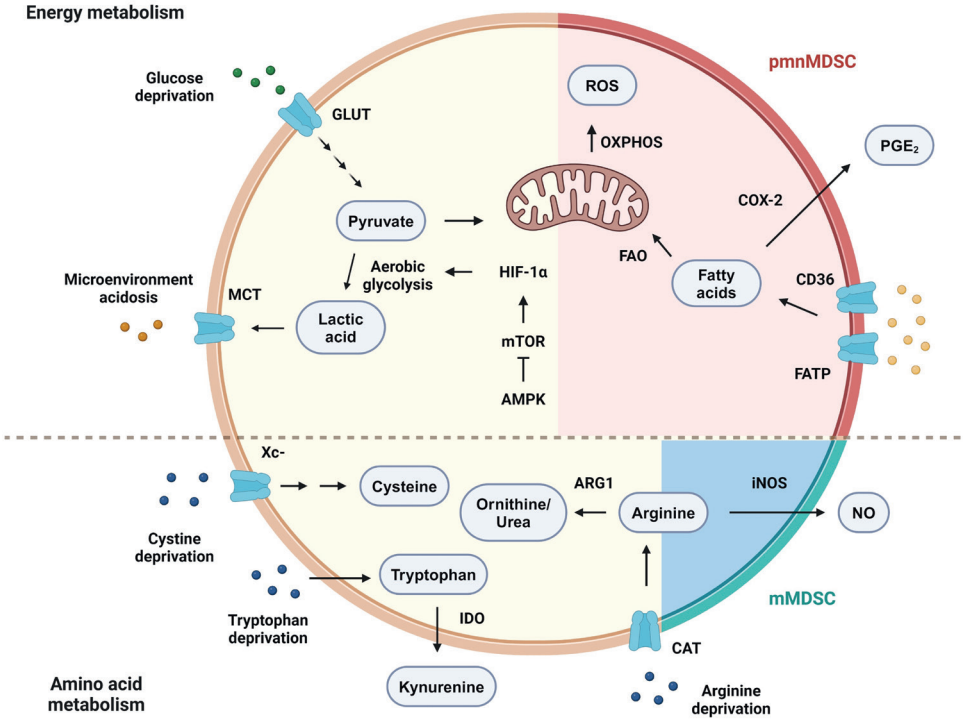

Figure 1. Metabolic pathways related to immunosuppressive function in MDSCs. The red shaded area represents metabolic pathways activated in pmnMDSCs. The green shaded area represents metabolic pathways activated in mMDSCs. The yellow shaded area indicates metabolic pathways commonly activated across MDSC subtypes.
CAT, cationic amino acid transporter; FAO, fatty acid oxidation; FATP, fatty acid transport protein; MCT, monocarboxylate transporter; Xc-, cystine/glutamate transporter.
The figure was created with BioRender.com.

consuming large amounts of glucose and fatty acids as energy sources within the TME (31). Consequently, MDSCs contribute to nutrient depletion in the TME, leading to T cell anergy (34). Moreover, MDSCs convert fatty acids into immunosuppressive prostaglandin E_2 (PGE_2) via cyclooxygenase-2 (COX-2) expression (35). Beyond energy metabolism, MDSCs also deplete amino acids crucial for T cell function, such as arginine, tryptophan, and cysteine (29). Upon cellular uptake, arginine is metabolized by iNOS or ARG1. MDSCs predominantly use ARG, depleting arginine in the TME. mMDSCs express iNOS, which produces NO that suppresses T cell function (36). Reports also indicate increased expression of IDO in MDSCs, which depletes the essential amino acid tryptophan for effector T cells, converting it to kynurenine, which activates Treg differentiation (37). MDSCs also deplete cysteine, essential for T cell activation, highlighting their role in immune suppression (**Fig. 1**) (38).

GLYCOLYSIS

Glycolysis initiates with the uptake of extracellular glucose through the glucose transporter (GLUT). Once inside the cytosol, glucose immediately undergoes phosphorylation by hexokinase to form glucose-6-phosphate. Subsequently, through several steps, a single molecule of glucose is metabolized to yield two molecules of pyruvate. This sequence of metabolic reactions from glucose to pyruvate defines 'glycolysis.' In most normal cells, pyruvate is then converted into acetyl-CoA, feeding into the tricarboxylic acid (TCA) cycle and, ultimately, through OXPHOS, serves as a highly efficient source for ATP production.

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In conditions such as insufficient oxygen supply in mammalian muscles, akin to an oxygen-deprived environment, pyruvate is converted into lactate. This process, known as 'anaerobic glycolysis,' is characterized by a lower ATP yield rate. However, in tumor cells, a phenomenon occurs whereby pyruvate is converted into lactate in the presence of oxygen, a process known as 'aerobic glycolysis' or the Warburg effect. Since Otto Warburg's initial studies, extensive research has been conducted on this atypical metabolic pathway. While aerobic glycolysis is less efficient in ATP production, it compensates with rapid ATP generation at the expense of increased glucose consumption and the production of metabolic intermediates for other biosynthetic pathways. This advantage explains why aerobic glycolysis is not exclusive to tumor cells but also prevalent in rapidly proliferating cells and activated immune cells.

Activated immune cells undergo a process called metabolic reprogramming which involves changes in the cellular metabolism. This change in metabolism allows the cells to meet the increased metabolic demand and adapt to different environments (39). Metabolic reprogramming is caused by a variety of factors, which includes cytokines and Ags. This process is crucial for immune cells to properly function since it allows them to give off an effective immune response. For example, myeloid immune cells express metabolic plasticity (40,41). Macrophages can be categorized into two groups, known as the M1 and M2 subtypes. According to organ context and microenvironment, monocytes can differentiate into M1 or M2 macrophage, with each subtype performing contrasting roles (42). M1 macrophages, known for producing pro-inflammatory cytokines, inducing Th1 response, and having phagocytic activity, primarily depend on glycolysis for their energy needs. In contrast, M2 macrophages, which produce anti-inflammatory cytokines, induce Th2 response, and support angiogenesis, rely on OXPHOS and fatty acid oxidation. Nonetheless, recent studies show that M2 differentiation relies on hypoxia-inducible factor (HIF)-1α-dependent glycolysis, indicating the potential importance of glycolysis in M2 macrophage polarization (41). In terms of arginine metabolism, M1 macrophages convert arginine to NO by iNOS, which suppresses T cells, while M2 macrophage metabolize arginine using ARG1 to produce putrescine and other polyamines, supporting the M2-oriented environment (43).

GLYCOLYTIC PATHWAY IN MDSC

Extensive research has been conducted on the energy metabolism of MDSCs. It has been established that MDSCs exhibit increased glycolytic activity compared to normal myeloid cells (44,45). These cells consume substantial amounts of glucose, and multiple studies have noted an increase in GLUT expression within MDSCs (45,46). In studies quantifying intracellular constituents, it was found through liquid chromatography–mass spectrometry assessments that MDSCs exhibit markedly elevated glucose concentrations internally, in contrast to the levels identified within myeloid precursor cells (46). This insight not only underlines the metabolic alterations inherent to MDSCs but also highlights potential therapeutic intersections by manipulating such metabolic dependencies.

MDSCs are heavily reliant on glycolysis, and thus, inhibiting this pathway can modulate both the generation and function of MDSCs. The hyperactivation of glycolysis in MDSCs not only contributes to glucose deprivation but also fosters an immunosuppressive environment within the TME. While all MDSCs commonly activate glycolytic pathways, the metabolic processes following glycolysis, such as aerobic glycolysis and OXPHOS, vary according to the subtype of MDSC.

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pmnMDSCs metabolize post-glycolytic pyruvate through both aerobic glycolysis and OXPHOS (45,47,48). In contrast, mMDSCs generally favor aerobic glycolysis over OXPHOS. Inhibition of aerobic glycolysis in mMDSCs can lead to reduced immunosuppressive function or increased apoptosis of mMDSCs (49,50). The lactic acid produced via aerobic glycolysis leads to acidification of TME and immunosuppression (51). Additionally, lactate produced by tumor cells through the Warburg effect enhances the immunosuppressive capabilities of MDSCs (52). Consequently, strategies targeting aerobic glycolysis and OXPHOS are under investigation, along with approaches targeting whole glycolysis metabolism.

On another front, hyperglycemic conditions, as seen in diabetic patients, have been associated with an increase in MDSCs. Observations across both type 1 and type 2 diabetes indicate that rather than disease etiology or mechanisms, it is the hyperglycemic environment and glycolysis reliance that promote MDSC proliferation (53).

ADENOSINE MONOPHOSPHATE-ACTIVATED PROTEIN KINASE (AMPK)/MTOR/HIF-1A PATHWAY IN MDSC

In the realm of MDSCs, the signaling pathways related to aerobic glycolysis notably include the mTOR and the transcription factor HIF-1α. mTOR, a serine/threonine protein kinase, is integral for sensing various cellular conditions, such as nutrient availability, oxygen levels, and energy status, subsequently promoting cellular growth through protein synthesis (54). Excessively activated in tumor cells, mTOR fosters cell cycle progression and proliferation. It also enhances the expression of HIF-1α, which becomes stabilized under hypoxia and activates aerobic glycolysis by inducing related gene expression (55). This phenomenon is particularly evident in immune cells stimulated within the hypoxic TME, where HIF-1α plays a crucial role in promoting tumor growth through immune suppression. AMPK is known to suppress the actions of mTOR, leading to the suppression of HIF-1α and aerobic glycolysis (56). Significant research has delved into the role of the AMPK-mTOR-HIF-1α interaction in MDSCs, especially concerning glycolysis.

In the context of disease models, insights emerge on how mTOR modulation impacts function of MDSCs and disease outcomes. Extensive research indicates that reducing mTOR activity directly enhances the immunosuppressive capabilities of pmnMDSCs. For instance, in an acute kidney injury model, rapamycin-induced mTOR suppression increased recruitment of pmnMDSCs to injured kidneys, and the adoptive transfer of rapamycin-treated MDSC enhanced renal function, reduced histologic damage, and diminished T cell infiltration (57). Fascinatingly, in an acute graft-versus-host disease mouse model, mice deficient in mTOR exhibited a notable alleviation of acute graft-versus-host disease symptoms, attributed to the heightened functional proficiency of pmnMDSCs and increased chemokine expression level (58). Similarly, human pmnMDSCs treated with rapamycin increased their immunosuppressive capacity against PBMCs, a regulation attributed to the STAT3-CCAAT-enhancer-binding proteins β pathway (58). Distinct scenarios in various disease models further illustrate the mTOR pathway's influence. In diabetic mice, a marked increase in MDSCs accompanies mTOR activation. Treatment with the mTOR inhibitor INK128 revealed a subtype-specific shift within MDSCs in the BM and spleen, increasing pmnMDSCs and decreasing mMDSCs (59). Similar dynamics were observed in tuberculosis, systemic lupus erythematosus, and in the context of a cardiac allograft model, where mTOR modulation by treatment such as rapamycin or INK128 significantly affected MDSC

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populations and functions, influencing disease progression or therapy responses (60-62). In pregnant mice, myeloid-specific *Hif1a* knockout (KO) reduced the abundance of MDSCs and their immunosuppressive activity, correlating with an increased abortion rate (63).

In cancer scenarios, such as in patients with non-small cell lung cancer, increased ectonucleotidase expression (CD39 and CD73) on MDSCs was identified, driven by TGF-β/mTOR/HIF-1α activation signaling. This change expanded the immunosuppressive function of MDSCs against T cells and NK cells (64). Also, suppressing HIF-1α *in vivo* within mouse BM hindered MDSC migration due to the inhibition of CXCR4 expression in tumor bearing mice (65). In pancreatic ductal adenocarcinoma, radiotherapy-induced lactate abundance in the TME seemed to activate a mTOR/HIF-1α/STAT3 pathway in MDSCs, and subsequently immunosuppressive function of MDCS was increased, granting radioresistance to the cancer cells (66). Research also highlights that aerobic glycolysis, essential for mMDSC survival, is activated by HIF-1α during the differentiation of myeloid progenitor cells induced by CSFs (36,67). HIF-1α's direct action on the PD-L1 promoter in hypoxic conditions enhances its expression, increasing the immunosuppressive capacity of MDSCs on T cells (68). Corzo et al. (69) reported diminished T cell suppression in *Hif1a* KO mice, linked to reduced ARG1 and iNOS expression in MDSCs. Additionally, the absence of HIF-1α impaired the differentiation of mMDSCs into TAMs in the TME.

The function of AMPK on MDSCs varies depending on the context. Trillo-Tinoco et al. (70) reported that inhibition of AMPK reduced the immunosuppressive capabilities of MDSCs and suppressed tumor growth in tumor-bearing mice. Similarly, activation of AMPK in MDSCs lead to their expansion, activation, and differentiation into M2 macrophages (71). Conversely, treatment with AMPK activators has been shown to inhibit MDSC migration, reduce MDSC populations in tumor and spleen, and decrease the immunosuppressive function of MDSCs in tumor-bearing mice (72). Treatment with phenformin led to an increased ROS production in pmnMDSCs, exceeding the toxic threshold and causing deleterious effects, which selectively reduced pmnMDSC populations (73). Additionally, administration of metformin in tumor-bearing mice reduced pmnMDSCs in tumor and shifted TAMs from an M2-like to an M1-like phenotype (74).

Metformin is recognized for its AMPK activating feature that followed by inhibition of the mTOR/HIF-1α axis of MDSC. Experimental insights reveal that metformin's role extends beyond glucose regulation, impacting immune responses in cancer. *In vitro* induction of MDSCs using THP-1 cells demonstrated that metformin treatment reduces the fraction of $CD68^{+}CD33^{+}$ and $CD68^{+}ARG1^{+}$ MDSCs, attributed to AMPK activation and subsequent mTOR inhibition. Parallel studies in a mouse colorectal cancer model have reinforced these findings, where metformin administration resulted in the MDSC reduction, manifesting in decreased colonic tumor sizes (75). Metformin showed similar promise in studies involving ovarian cancer patients. *Ex vivo* metformin treatment of MDSCs from patients showed activation of AMPK and inhibition of HIF-1α, paralleled by reduced expression of CD39 and CD73, marking a decrease in their immunosuppressive function. Clinically, these molecular alterations have profound implications, as evidenced by extended survival durations of ovarian cancer patients receiving metformin (76).

The interplay between mTOR, HIF-1α, and glycolysis in MDSCs appears to be complex and context-dependent, influenced by the heterogeneity among MDSC subtypes and their varying preferences for OXPHOS and aerobic glycolysis. For instance, *Mtor* KO resulted in decreased

T cell suppression by mMDSCs, while increasing the suppressive capabilities of pmnMDSCs. When these effects were combined, the overall immunosuppressive effect of total MDSCs on T cells was enhanced (58). Additionally, there are numerous conflicting reports about AMPK in the immunosuppressive functions of MDSCs. This is thought to be due to AMPK affecting various downstream signaling pathways beyond mTOR/HIF-1α (77). Moving forward, this review will explore the nuanced shifts in MDSC glycolysis across various diseases and explore cutting-edge experimental outcomes targeting these changes.

GLYCOLYSIS OF MDSC IN TUMOR

In the TME, not only cancer cells exhibit the well-known Warburg effect, consuming excessive glucose, but MDSCs also display a similar increase in glucose consumption and glycolysis. This metabolic shift contributes to an immunosuppressive milieu in the TME by starving immune cells of glucose (78). Furthermore, the byproducts of increased glycolysis in MDSCs influence both the cells themselves and the surrounding environment (**Table 1**).

Enhanced aerobic glycolysis or OXPHOS

Internally, MDSCs undergo significant metabolic reprogramming during differentiation process. When BM cells are induced into MDSCs *in vitro* using IL-6 and GM-CSF, there is a notable increase in glucose uptake, fueling aerobic glycolysis (44). In tumor-bearing mouse models, MDSCs within the tumor context exhibit elevated aerobic glycolysis compared to splenic monocytes and neutrophils, particularly when they are in co-culture with cancer cells or stimulated by GM-CSF. This surge in glycolysis helps mitigating ROS production, protecting MDSCs from ROS-induced apoptosis and boosting the levels of an antioxidant, phosphoenolpyruvate, within MDSCs (45).

Externally, although cancer cells are known to produce lactate in abundance via the Warburg effect, immune cells within the TME, including MDSCs, also generate lactate, affecting surrounding immune cells (79). Seth et al. (80) demonstrated that deleting lactate dehydrogenase A in myeloid cells, which converts pyruvate to lactate, suppressed tumor growth and influenced T cell activity, leading to increased numbers of $CD3^+$ T cells and activated $CD8^+$ T cells producing IL-17 and IFN-γ. This finding indicates that lactate production by myeloid cells in the TME, not just by cancer cells, fosters an immunosuppressive atmosphere.

In their study, Mohammadpour et al. (81) explored the relationship between β_2-adrenergic signaling and glycolysis in MDSCs within the TME. They found that the high concentration of norepinephrine in the TME activates β_2-adrenergic signaling in MDSCs. This activation results

Table 1. Changes in glycolysis of MDSC compared to normal cell

Host	Disease/model	Control	MDSC subtype	Glycolysis	Ref
Mouse	Esophageal squamous cell carcinoma	Neutrophil	pmnMDSC	Aerobic glycolysis↑; OXPHOS↑	(47)
Mouse	Breast tumor	Neutrophil and monocyte	Total MDSC	Aerobic glycolysis↑; OXPHOS↑	(45)
Mouse	Sjögren syndrome-like NOD mice	PBMC	Total MDSC	Aerobic glycolysis↑	(84)
Mouse	Concanavalin-A induced immune-mediated hepatitis	Normal liver $CD11b^+Gr\text{-}1^+$ cell	Total MDSC	Aerobic glycolysis↑	(85)
Mouse	*Staphylococcus aureus* chronic infection	Neutrophil	pmnMDSC	Aerobic glycolysis↑; OXPHOS↑	(48)
Mouse	*Ex vivo* induced MDSC	Bone marrow cell	Total MDSC	Glycolysis↑	(44)
Human	*Ex vivo* induced MDSC Hepatocellular carcinoma	Monocyte	Total MDSC	Aerobic glycolysis↓; OXPHOS↓	(82)

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in MDSC's increased OXPHOS, reduced aerobic glycolysis, and enhanced COX-2 expression and PGE_2 production, thereby intensifying the immunosuppressive function of MDSCs.

Reduced glycolysis

Conversely, an opposite result suggests a decrease in glycolytic activity in MDSCs compared to PBMCs, as seen in human stromal cell-induced MDSCs, which show downregulated expression of glycolysis-related genes and suppressed OXPHOS and aerobic glycolysis (82). Methylglyoxal, a byproduct of glycolysis or degradation of acetone and threonine, is detoxified by glutathione due to its cytotoxicity and is known to increase under high glucose conditions, such as in diabetes (83). Baumann et al. (82) identified elevated levels of methylglyoxal in MDSCs, which impair immune function by suppressing T cells, suggesting its potential role as a specific marker for human MDSCs. They discovered that in MDSCs, methylglyoxal is produced from acetyl-CoA and glycine by the semicarbazide-sensitive amine oxidase. Notably, while methylglyoxal accumulates specifically in MDSCs, it was also found to build up in T cells when they were co-cultured with MDSCs, hinting at a transfer of methylglyoxal from MDSCs to T cells. This transfer depletes L-arginine, a critical molecule for T cell function, thus suppressing the immune response of the T cells.

Adjusting MDSC function through modulation of glycolysis

While numerous studies generally report an increase in glycolysis within MDSCs, contrasting results have also emerged, contingent on experimental conditions and the selection of control groups (44,45,82,84,85). This inconsistency is particularly notable since MDSCs are immature cells, allowing for a range of potential control groups, including BM myeloid progenitor cells and mature myeloid cells. The same diversity in outcomes extends to studies manipulating glycolysis to regulate MDSC differentiation and function (**Table 2**). Indeed, many investigations have reported that impeding glycolysis inhibits MDSC differentiation and suppresses their immunosuppressive functions (45,49,86). Particularly, an analysis of the subsequent papers indicates that the responses to modulating aerobic glycolysis and OXPHOS differ depending on the subtype of MDSC. First, the following experimental findings highlight a proportional relationship between aerobic glycolysis and immunosuppressive function in mMDSCs. Acute myeloid leukemia (AML) was shown to influence immune regulation by increasing the differentiation of human monocytes into $CD14^+HLA\text{-}DR^{lo}$ mMDSCs through extracellular vesicles (EVs). These vesicles not only induced MDSC-specific phenotypes but also upregulated immunosuppressive proteins like IDO. Notably, AML-EVs enhanced aerobic glycolysis evidenced by increased expression of glycolysis-related genes, glucose consumption, lactate production, and a decreased oxygen consumption rate/extracellular acidification rate ratio, a process controlled by the protein kinase B (AKT)/mTOR pathway. This metabolic reprogramming proved particularly vulnerable to glycolysis inhibition, suggesting potential therapeutic avenues (87). The role of mTOR in regulating aerobic glycolysis within mMDSCs was further emphasized by a study showing that mTOR inhibition by rapamycin decreased aerobic glycolysis and the immunosuppressive capacity of tumor-infiltrating mMDSCs in 3LL tumor-bearing mice (50). The critical involvement of mTOR in mMDSC differentiation from myeloid precursors was demonstrated through mTOR inhibition and KO models, which suppressed aerobic glycolysis and mMDSC differentiation (49). In addition, *Candida tropicalis* was found to promote colorectal tumorigenesis by stimulating aerobic glycolysis in MDSCs, enhancing their immunosuppressive capacity. The study also revealed that NO, which is known to be generated from mMDSCs, further amplifies aerobic glycolysis in a positive feedback loop. Modulating this pathway using specific iNOS inhibitors such as *S*-methylisothiourea

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hemisulfate salt or NO donors such as *S*-nitroso-*N*-acetylpenicillamine highlighted the crucial role of glycolytic control in cancer progression (88).

Secondly, subsequent papers have directed their experimental focus towards the glycolysis of pmnMDSCs. These studies reveal that both aerobic glycolysis and OXPHOS play crucial roles in determining the immunosuppressive capabilities and survival of pmnMDSCs. Huang et al. reported that in a tumor mouse model, mitochondria-targeted atovaquone effectively inhibited OXPHOS in pmnMDSCs, triggering their apoptosis. This, in turn, reduced MDSC population in the TME, enhanced $CD4^+$ T cell tumor infiltration, and reinforced anti-tumor activities (47). Fu et al. (34) further subdivided pmnMDSCs in a breast cancer mouse model based on the expression of CD205 and toll-like receptor 2 (TLR2), identifying two subsets: $CD205^+$ pmnMDSCs and $TLR2^+$ pmnMDSCs. They found that the surface protein expression

Table 2. The effects of glycolysis modulation on MDSC functionality in diverse diseases and experimental models

Host	Disease/model	MDSC subtype	Method	Glycolysis	MDSC function	Ref
Mouse	Newcastle disease virus treated hepatocarcinoma	Total MDSC	Dichloroacetate	AG↓; OXPHOS↑	IDO1↓; MDSC infiltration to tumor↓; Mouse survival↑	(91)
Mouse	SC tumor	Total MDSC	Enzalutamide	AG↑; OXPHOS↓	Tumor growth↑	(90)
Mouse	*Ex vivo* induced MDSC	Total MDSC	β-AR signaling	AG↓; OXPHOS↑	COX-2↑; Immune suppression↑	(81)
Proportional relationship between MDSC function and glycolysis						
Mouse	Breast tumor	Total MDSC	2-DG	Glycolysis↓	Apoptosis↑; T cell inhibition↓; Tumor growth↓	(45)
Mouse	Colitis-associated colon cancer	Total MDSC	*Candida tropicalis*	AG↑	COX-2, NOX, and iNOS↑; T cell inhibition↑	(88)
Mouse	SC tumor	mMDSC	Rapamycin	AG↓	ARG1, NOS2, and PD-L1↓; T cell inhibition↓; Tumor growth↑	(50)
Mouse	SC tumor	Total MDSC	*Gcn2* KO	OXPHOS↓	CD86, MHCII, and IL-1β↑; PD-L1, IL-4Rα, Nos2, and Arg1↓; T cell inhibition↓	(86)
Mouse	SC tumor	pmnMDSC	Mito-ATO	Glycolysis↓; OXPHOS↓	Apoptosis↑; Tumor growth↓	(47)
Mouse	SC tumor	mMDSC	*Mtor* KO	AG↓	iNOS↓; T cell inhibition↓; Tumor growth↓	(49)
	Alloskin-graft	mMDSC	Rapamycin	AG↓	iNOS↓; T cell inhibition↓; Grafted skin rejection↑	
			Mtor KO			
			Metformin	AG↑	iNOS↑; T cell inhibition↑; Grafted skin rejection↓	
Human	Sjögren's syndrome *MDSCs show pro-inflammatory effect in Sjögren's syndrome	Total MDSC	2-DG	Glycolysis↓	Th1/Th2 ratio↑; Th17/Treg ratio↓	(84)
Human	*Ex vivo* induced MDSC	mMDSC	AML-EV	AG↑	Differentiation of monocyte into mMDSC↑; T cell inhibition↑	(87)
Inverse relationship between MDSC function and glycolysis						
Human	Hepatocellular carcinoma	Total MDSC	Metformin	AG↑; OXPHOS↑	Methylglyoxal↓; T cell inhibition↓	(82)
Mouse	SC tumor	Total MDSC	*Sirt1* KO	AG↑	M1 differentiation↑; T cell inhibition↓	(95)
Mouse	SC tumor	Total MDSC	*Akt1* KO	Glycolysis↑	CD115, PDL1, CD86, TNF-α, and IL-12↑; CD206, IL-1R, CD80, and IL-10↓; T cell inhibition↓; Tumor growth↓; Mouse survival↑	(94)
Mouse	*Ex vivo* induced MDSC	pmnMDSC	3-BrPA	AG↓	Arg1, *Cxcr2*, and *Inos* mRNA↑; PD-L1 and TGF-β↑; $CD4^+$ T cell inhibition↑	(92)
Mouse	Transient middle cerebral artery occlusion	Total MDSC	*Pfkb3* KO	AG↓	M1 maturation↓; Ischemic brain injury↓	(93)
			3PO			
Mouse	LPS-induced IMH	Total MDSC	Dexamethasone	AG↓	T cell inhibition↑; Mouse survival↑	(97)
Mouse	Concanavalin A-induced IMH	Total MDSC	Rapamycin	AG↓	T cell inhibition↑; Mouse survival↑	(85)
			Hif1a KO			

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profile of CD205$^+$ pmnMDSCs was more similar to mMDSCs than to pmnMDSCs and exhibited stronger immunosuppressive capabilities compared to TLR2$^+$ pmnMDSCs. In the TME, *GLUT3* knockdown, glucose deprivation, and 2-Deoxy-D-glucose (2-DG) treatment induced apoptosis in CD205$^+$ pmnMDSCs. In contrast, TLR2$^+$ pmnMDSCs showed less apoptosis upon glucose deprivation and 2-DG treatment.

In the context of MDSC subtypes, the following studies have observed changes in the overall immunosuppressive capabilities of MDSCs resulting from the modulation of glycolysis, regardless of subtype. A strategy targeting hexokinase 2 with 3-bromopyruvate (3-BrPA) in a pancreatic cancer syngeneic mouse model resulted in a notable decrease in tumor MDSCs, accompanied by an increase in CD8$^+$ T cell tumor infiltration (89). Studies have also found that MDSCs within the TME express androgen receptors, and, in a colon cancer model, inhibition of these receptors suppressed OXPHOS, increased aerobic glycolysis, and subsequently enhanced the immunosuppressive ability of MDSCs, promoting tumor progression (90). In mouse models of hepatocellular carcinoma, a combination treatment of oncolytic virus and dichloroacetate, an inhibitor of pyruvate dehydrogenase kinase increased pyruvate dehydrogenase activity, thereby elevating OXPHOS and curtailing aerobic glycolysis. This metabolic shift reduced MDSCs and suppressed tumor growth (91). Unlike normal splenic myeloid cells, suppressing aerobic glycolysis in MDSCs using 2-DG led to an increase in ROS production, causing oxidative stress-induced apoptosis. This effect could be mitigated by treating cells with glycolytic metabolite, phosphoenolpyruvate (45). Furthermore, the KO of general control nonderepressible 2, a protein kinase that plays a role in regulating the cellular response to amino acid availability, in MDSCs reduces OXPHOS without impacting aerobic glycolysis. This metabolic shift results in increased CD86 expression and IL-1β production, and decreased PD-L1 levels, as well as reduced IL-4α and ARG1 expression, ultimately weakening the immunosuppressive function of MDSCs (86).

On the contrary, a few literatures suggest that the inhibition of glycolysis can lead to an increase in immune suppression by MDSCs (92,93). Studies using *Akt1*-deficient mice treated with 2-DG or *Hif1a* KO demonstrate that the suppression of glycolysis in cancer environments enhances the immunosuppressive function of MDSCs. It is proposed that AKT1 blocks HIF-1α and glycolysis; thus, *Akt1* KO increases HIF-1α and glycolysis, impairing MDSC's immunosuppressive function. The simultaneous KO of *Akt1* with *Hif1a* or glycolysis inhibition reverses this, restoring MDSC functionality (94). It has been reported that inhibition of glycolysis in MDSCs leads to the production of methylglyoxal. Treatment with metformin activates aerobic glycolysis in MDSCs, subsequently inhibiting methylglyoxal production. As a result, this treatment also reduces the capacity of MDSCs to suppress CD8$^+$ T cells. This was evident in preclinical studies where inhibiting methylglyoxal, combined with an ICI, enhanced anti-tumor effects (82).

In addition, two studies have delved into the role of mTOR activation and glycolysis in the impaired maturation process of mMDSCs. In a study using diabetic mice, it was observed that the hyperglycemic environment caused mMDSCs to turn into harmful M1 pro-inflammatory macrophages, which impairs wound healing, while treatment with the mTOR inhibitor INK128 under high glucose conditions reduced this differentiation of mMDSCs into M1 macrophages (59). Additionally, in *Sirt1* KO mice, terminal maturation of spleen MDSCs was associated with the loss of immunosuppressive function and tumor repression. This transition to M1 macrophages occurred as aerobic glycolysis was activated through the mTOR-HIF-1α pathway. It led to MDSCs maturing into M1 macrophages and

losing their immunosuppressive properties, ultimately inhibiting tumor growth (95). The varying impacts of glycolysis on M1 macrophage maturation and MDSC immunosuppression may help clarify the inconsistencies seen in how glycolysis activation affects the functional changes of MDSCs.

GLYCOLYSIS OF MDSC IN OTHER DISEASES

Research into the therapeutic effects of modulating glycolysis in MDSCs spans various diseases beyond cancer. In ischemic stroke patients and mouse models, an increase of MDSCs was noted, which contributed to the alleviation of symptoms. Enhanced aerobic glycolysis elevated lactate levels, and lactate subsequently promoted MDSC mTOR signaling, thereby driving their differentiation into M1 macrophages. These immunologically strong mature myeloid cells, in turn, boosted Th1 and Th17 responses. The process was associated with upregulated glycolysis-related gene expression in maturing MDSCs. Remarkably, alleviation of brain injury was achieved through glycolysis inhibition via 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 blockade, which prevented MDSC maturation, enhancing their immunosuppressive function (93). Contrary to the findings mentioned in (89), in a heart allograft mouse model, administration of 3-BrPA, an aerobic glycolysis inhibitor, extended survival times and increased *in vivo* pmnMDSC levels. During MDSC differentiation *ex vivo*, 3-BrPA treatment escalated immunosuppressive factors (iNOS, ARG1, PD-L1, CD155, IL-10, TGF-β) and CXCR2 indicating enhanced migratory function. The adoptive transfer of 3-BrPA-treated MDSCs notably prolonged the survival of heart-allografted mice (92).

In Sjögren's syndrome, MDSCs lose their immunosuppressive ability and instead promote inflammation as the disease progresses. In both human and mouse models, MDSCs demonstrated increased glycolysis via mTOR/HIF-1α pathways. Glycolysis-augmented MDSCs in the Sjögren's syndrome raised the Th17/Treg ratio, mitigated by 2-DG treatment (84). In a mouse model of *Staphylococcus aureus* chronic infection, MDSCs suppressed immune responses, contributing to chronic infection. Splenic pmnMDSCs showed activated aerobic glycolysis and elevated glucose consumption, despite being exposed to low glucose levels due to rapid depletion of glucose. As the majority of glucose in MDSCs metabolized to lactate, carbon for the TCA cycle was primarily sourced from glutamine. Systemic blood glucose levels also diminished with infection. Limited supply of glucose kept MDSCs in an immature state, while ample glucose promoted the terminal maturation of MDSCs (48).

In a *Leishmania donovani* chronic inflammation model, the upregulation of HIF-1α-mediated aerobic glycolysis endowed splenic myeloid cells with MDSC-like functions, steering them towards M2 macrophage differentiation (96). In immunological hepatic injury mouse models, activation of glucocorticoid receptor inhibited HIF-1α and aerobic glycolysis in MDSCs, enhancing their immunosuppressive functions and thereby offering protection from hepatic injury (97). Another study on immune-mediated hepatotoxicity model showed similar results: MDSC immunosuppressive function was reinforced by suppression of mTOR/HIF-1α dependent aerobic glycolysis (85). In patients with acquired aplastic anemia, decreased mMDSC was accompanied by diminished expression of glycolysis-related genes. Similar to the tumor model discussed in (95), treatment with rapamycin led to the inhibition of mTOR, subsequently suppressing the maturation of MDSCs into mature myeloid cells. This restraint on maturation enhanced the immunosuppressive function of MDSCs, providing insights for therapeutic strategy for acquired aplastic anemia (98).

This breadth of research underscores the multifaceted roles of glycolysis in MDSC functions across diverse pathological states, highlighting intricate interplays with immune modulation.

FUTURE PERSPECTIVE AND CONCLUSION

Targeting the glycolysis of MDSCs in therapeutic strategies appears to be promising based on current trends in immunometabolism research. However, regulating the glycolysis of MDSCs to control their function necessitates a thorough understanding the role of glycolysis within MDSCs. The realm of cellular metabolism is inherently complicated, and the situation is further intricate by the fact that MDSCs are a heterogeneous population, making it more difficult to fully understand the metabolism of MDSCs. This complexity is highlighted by conflicting findings in literature, such as varying responses of MDSC immunosuppressive function to 3-BrPA (89,92), discrepancies in reports on glycolysis activity in MDSCs (44,81,82), and inconsistent results concerning MDSC maturation into M1 and M2 subsets due to HIF-1α activation (59,96). As researchers continue to unravel these intricate mechanisms, there's likely to be a surge in targeted therapies that modulate the metabolic pathways of these cells. Despite these challenges, therapeutic strategy targeting glycolysis within MDSCs could be particularly effective, given that many tumors and associated stromal cells (including MDSCs) are known to rely on glycolytic metabolism. One exciting possibility is the use of therapies targeting MDSC glycolysis in combination with other treatments (99). For example, combining glycolysis inhibitors with immunotherapy, chemotherapy, or radiation therapy could enhance the effectiveness of these traditional cancer treatments. This multi-pronged approach might help to overcome treatment resistance, a significant challenge in current cancer therapy protocols. Currently, a clinical trial related to MDSC glycolysis is the investigation of Eganelisib (Phase 1, NCT02637531). Eganelisib functions primarily as a phosphoinositide 3-kinase (PI3K) inhibitor, with the potential to suppress the PI3K/AKT/mTOR pathway (100). By targeting this pathway, the compound is expected to mitigate MDSC-mediated immunosuppression, presenting a promising avenue for enhancing anti-tumor immune responses. The outcomes of this research could significantly influence future strategies, marking a pivotal point in our approach to oncological diseases.

Also, while much of the focus is on cancer, the principles of targeting MDSC metabolism could extend to other conditions, such as autoimmune diseases, infections, and chronic inflammation. By modulating the immune response through metabolic intervention, it might be possible to develop more effective treatments for a variety of challenging diseases. However, due to the unclear roles of MDSCs in diseases other than cancer, further research is required before progressing to clinical studies. In diabetes, however, it is evident that MDSC populations increase—although the function of MDSCs on diabetes and its complications remains controversial (53). Therefore, targeting MDSCs in diabetes-related conditions could be a promising approach for future research.

While promising, strategy targeting glycolysis is not without potential obstacles. Selectively targeting MDSCs' metabolic processes without affecting other cells might be challenging, given that most cells share glycolysis. Additionally, compensatory metabolic mechanisms might arise, contributing to drug resistance.

In conclusion, while targeting MDSC glycolysis is a promising field, actual clinical application will require overcoming significant research and developmental hurdles,

including specificity, resistance, and integration with existing treatment paradigms. Continued research, clinical trials, and technological advancements in monitoring and manipulation at the cellular level will be critical for realizing the full potential of these therapeutic strategies.

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