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REVIEW

Metabolic reprogramming of myeloid-derived suppressor cells: An innovative approach confronting challenges

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Abstract

Immune cells such as T cells, macrophages, dendritic cells, and other immunoregulatory cells undergo metabolic reprogramming in cancer and inflammation-derived microenvironment to meet specific physiologic and functional demands. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that are characterized by immunosuppressive activity, which plays a key role in host immune homeostasis. In this review, we have discussed the core metabolic pathways, including glycolysis, lipid and fatty acid biosynthesis, and amino acid metabolism in the MDSCs under various pathologic situations. Metabolic reprogramming is a determinant of the phenotype and functions of MDSCs, and is therefore a novel therapeutic possibility in various diseases.

KEYWORDS
MDSCs, metabolic reprogramming, immune homeostasis, microenvironment

Abbreviations: 2-DG, 2-deoxy-dglucose; A2BR, A2B adenosine receptor; AMP, adenosine 5′-monophosphate; AMPK, AMP-activated protein kinase; ApoE, apolipoprotein E; Arg, arginase; ATRA, all-trans retinoic acid; Cat2, cationic amino acid transporter 2; CGD, chronic granulomatous disease; CHOP, CEBP-homologous protein; COX-2, cyclooxygenase-2; CPT, carnitine palmitoyltransferase; DCs, dendritic cells; ECAR, extra-cellular acidification rates; ERK1/2, extracellular signal-regulated kinase 1/2; FAO, fatty acid β-oxidation; FATP, fatty acid transport proteins; f-MDSCs, fibrocytic MDSCs; GLUTs, glucose transporters; GR, glucocorticoid receptor; GVHD, graft-versus-host disease; HADHA, 3-hydroxyacyl-coa dehydrogenase; HIFs, hyvpoxia inducible factors; IMH, immune-mediated hepatic injury; LLC, Lewis lung carcinoma; L-NAME, N(G)-nitro-L-arginine methyl ester; L-NMMA, NG-monomethyl-L-arginine; LSC, leukemia stem cells; LXR, liver-X receptor; MDSCs, myeloid-derived suppressor cells; MIF, migration inhibitory factor; M-MDSCs, monocytic MDSCs; mTOR, mammalian target of rapamycin; nNOS, neuronal NOS; NOHA, N-hydroxy-L-arginine; NOX, NADPH oxidase; Nrf2, nuclear factor (erythroid-derived2)-like; OXPHOS, oxidative phosphorylation; PMN-MDSCs, polymorphonuclear MDSCs; PNT, peroxynitrite; PPARs, peroxisome proliferator-activator receptors; PPP, pentose phosphate pathway; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SIRT1, Sirtuin 1; SREBPs, sterol-regulatory element binding proteins; TAM, tumor-associated macrophage; TCA, tricarboxylic acid; TDO, tryptophan-2, 3-dioxygenase 2; TGM, transglutaminase; TIPE2, TNF-α-induced protein 8-like 2; T-MDSCs, tumor-infiltrating MDSCs; TME, tumor microenvironment; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor; α-KG, α-ketoglutarate

1 | INTRODUCTION

Cells need adequate energy and nutrients to survive and proliferate. Immune cells often undergo metabolic reprogramming to adapt to pathologic microenvironments associated with cancer, inflammation, and autoimmune diseases and elicit an immune response. Cancer cells depend on glycolysis rather than oxidative phosphorylation (OXPHOS) for energy production, a phenomenon known as the "Warburg effect."[1–3] The accumulation of lactate in the tumor microenvironment (TME) as a result of excessive glycolysis creates an acidic milieu, which in turn induces metabolic adaptations in the other cells. For instance, T cells are known to be the most characteristic examples of metabolic reprogramming. Tumor-infiltrating T cells switch to glycolysis and glutaminolysis and show a corresponding decrease in OXPHOS and fatty acid β-oxidation (FAO).[4,5] In graft-versus-host disease (GVHD), a typical representative of inflammatory microenvironment, allogeneic effector T cells exhibit elevated glycolysis mediating tissue injury and oxidative stress,[6] whereas the immunosuppressive regulatory T cells (Tregs) show a marked increase in FAO and OXPHOS.[7,8]

Recent studies show that myeloid immune cells exhibit metabolic plasticity in different microenvironments. The M1 macrophages primarily rely on glycolysis rather than OXPHOS to achieve phagocytic activity and produce proinflammatory cytokines.[9–12] In contrast, the anti-inflammatory M2 macrophages display high rates of mitochondrial biogenesis and FAO in response to type 2 cytokines (IL-4).[13] Likewise, dendritic cells (DCs) depend on OXPHOS in the resting state and on glycolysis when acting as APCs. Neutrophil progenitors also undergo a metabolic shift toward OXPHOS during differentiation.[14] However, the fully differentiated circulating neutrophils harbor very few mitochondria and mainly depend on glycolysis for ATP synthesis.[15,16] The tumor-associated neutrophils are classified into antitumor (N1) and protumor effects (N2) with the metabolic preference of glycolytic and oxidative types, respectively.[17]

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that rapidly differentiate and expand in response to pathogenic infections, cancer, inflammation, trauma, autoimmune disease, and so on.[18–21] Murine MDSCs are characterized by the coexpression of CD11b and Gr1, and are classified into the $CD11b^{+}Ly6G^{+}Ly6C^{lo}$ granulocytic/polymorphonuclear (PMN-MDSCs) and $CD11b^{+}Ly6G^{lo}Ly6C^{hi}$ monocytic (M-MDSCs) subtypes.[22] Human PMN-MDSCs and M-MDSCs are characterized as $CD33^{+}CD14^{-}HLA^{-}DR^{lo}$ plus $CD15^{+}$ or $CD66b^{+}$ and $CD33^{+}CD14^{+}$ $HLA^{-}DR^{lo}CD15^{-}$, respectively.[19,22] The pathologic microenvironment is complex mixture of cytokines contributing to MDSC expansion, differentiation, and recruitment such as G-CSF, GM-CSF, vascular endothelial growth factor (VEGF), proinflammatory proteins (S100A8 and S100A9), and inflammatory mediators (IL-1β and IL-6).[19,23] MDSCs mediate immune responses by expressing enzymes (arginase [Arg], IDO, and NOS), releasing reactive oxygen species (ROS), regulating immunosuppressive cells such as Tregs and secreting cytokines (e.g., IL-6, IL-10, TGF-β, etc.).[20,24–26]

M-MDSCs and PMN-MDSCs share the same morphologic and phenotypic features with monocyte and neutrophils separately but have different biologic signatures.[27–30] Studies on global proteome dynamics and post-translational modifications have shown that MDSCs differentially expressed a core of kinases, which controlled lineage-specific (PI3K-AKT and SRC kinases) and cancer-induced (ERK and PKC kinases) protein,[31] which constitute a distinct myeloid population characterized by a unique "kinase signature."[32] Therefore, MDSCs established a remarkable diversity of metabolic pathways attributed to various microenvironments. In this review, we have summarized the reprogramming of glycolysis, lipid and fatty acid metabolism, amino acid metabolism and other metabolic pathways in MDSCs adapting to different microenvironments (Fig. 1 and Table 1).

2 | GLUCOSE METABOLISM

The survival and immunosuppressive function of MDSCs depend on the generation of ATP via 3 integrated metabolic pathways—glycolysis, tricarboxylic acid (TCA) cycle, and OXPHOS. Aerobic glycolysis produces 30–36% of the cellular ATP by converting pyruvate into acetyl-CoA, which is then fed into the TCA cycle and generates electrons for mitochondrial OXPHOS. Under hypoxic conditions, pyruvate is usually converted into lactate and expelled from the cells, a process known as anaerobic glycolysis that rapidly provides energy during stressful conditions.[33–35]

MDSCs constitute an integral part of the TME and support tumor cell growth.[36,37] As TME is hypoxic and nutrient deficient especially glucose, not only tumor cells and infiltrating T cells but also MDSCs engage in glycolysis for their energy needs. The acidic TME resulting from the high levels of lactate produced by tumor cells facilitates tumor invasion and metastasis by increasing MDSCs infiltration and inhibiting the NK cells.[38] Studies revealed that the suppressive function of MDSCs is positively correlated with glycolytic rate in solid tumor-bearing mice models.[34] The $GLUT3^{hi}$ $CD205^{+}$ PMN-MDSCs, which are particularly sensitive to glucose deprivation, showed massive accumulation in the spleen and liver of 4T1 tumor-bearing mice.[39] Chornoguz et al.[40] hypothesized that MDSCs adopt a higher rate of glycolysis to resist Fas- and Caspase-mediated apoptosis, which prolong MDSCs survival in the TME.

The rapid proliferation of tumor cells and infiltration of inflammatory cells create a hypoxic TME. Hypoxia inducible factor (HIF) is a key transcriptional factor that regulates the expression of glycolytic enzymes and thus shapes the fate of MDSCs.[41–43] Corzo et al.[43] showed that HIF1α drive MDSCs differentiation into a tumor-associated macrophage (TAM)-like phenotype that suppresses T cells. Sirtuin 1 (SIRT1) plays an important role in metabolic and immune pathways by deacetylating downstream targets like HIF1α.[44] SIRT1-deficient MDSCs switch to the proinflammatory M1 lineage with lower suppressive function and glycolytic activation.[45,46] Furthermore, Noman et al.[43,47] reported that HIF1α increases the expression of membrane-bound PD-L1 on MDSCs and mediates apoptosis of T cells expressing PD-1, which points to a link between immune checkpoint activation and metabolic reprogramming of MDSCs. HIF1α also mod-

TABLE 1 Metabolic profile of MDSCs in various pathologic environments

Metabolic pathways	Disease	Microenvironment	Molecular mechanism	Outcomes	Reference
Glycolysis	Infection (*Leishmania donovani*)	Infectious stress (with myelopoiesis)	HIF1α→anaerobic glycolysis	Obtain immunosuppressive function	48,49
	Tumor	Hypoxia	HIF1α→glycolytic enzyme	Differentiate into TAM-like phenotype	41–43
			HIF1α→expression of PD-L1	Enhance T cell apoptosis	43,57
			SIRT1→HIF1α	Promote MDSCs differentiation	45,46
			STAT3-NOX subunit→ROS production through PPP	Large amount of ROS to suppress T cells	60
		Glucose deficiency	Up-regulate GLUT expression	Enhance glycolysis rate and survival time	39
			Loss of c-Rel	Decrease mitochondrial respiration and enhances glycolysis	53
			Inhibit mTOR→reduce the glycolysis rate	Enhance suppressive function	26
		Tumor-derived inflammatory cytokines	Up-regulate TIPE2→PPP	Promote ROS production	61
		Oxidative stress	Nrf2 signal→up-regulate PPP key enzymes	Protect cell from chemical or oxidative stress	62
	IMH	Inappropriate immune activation	Activate of GRs and further regulate HIF1α	Suppress T cells	50
			Inhibit mTOR→lower glycolysis activity	Enhance immune regulatory ability	54
	Maternal-fetal tolerance	Hypoxia	HIF deficiency	Impair suppressive activity	51
	Chronic inflammation	Inflammatory environment	Fas-Caspase network	Resist apoptosis	40
	CGD	Inflammatory environment	NOX2 subunits defection	Control infection	59
FAO	Tumor	Hypoxia	Regulate FAO key enzyme (CPT1, HADHA)	Immunosuppressive ability	79
		Lipid accumulation	PPARγ regulate neutral lipid signaling	Development, suppressive function and transendothelial migration of MDSCs	75
			PUFAs→ROS production	Enhance the induction rate and ability of MDSCs	65
			Lipid-pegylated liposomes i.v.→enhanced B7-H3 expression	Increase number and suppressive ability	69

(Continues)

TABLE 1 (Continued)

Metabolic pathways	Disease	Microenvironment	Molecular mechanism	Outcomes	Reference
			FATP2 overexpression→fatty acid uptake	Promote PEG2 synthesis	70
		Oxidative stress	PGE2-COX2	Mediate MDSC regulatory function	80,81
Arginine	Tumor	Hypoxia	Cat2→increases L-arginine uptake	Arginine starvation→T cell cycle dysfunction	90
			AMPK/mTOR/HIF1α up-regulate Arg	Recruit other immune cells to to strengthen their immune responses	42,50,54,92
			NO production	Increases apoptosis of T cells by impairing IL-2R signaling	94,95
			NO+superoxide anion→PNT and ROS production	Inhibits CD8+ T cell activation and proliferation, nitration of CCL2	97–100
		Tumor-derived cytokines (MIF)	CXCR2→stimulate Arg1 reproduction	suppress T cells	91
	Transplantation	Danger signals (IL-13, LPS and ATP)	Inflammasome formation in MDSCs	Inactivate Arg1 and thus impair suppressive ability	93
Glutamine	Tumor	Glutamine competition	Modulate AMPK pathway	Immunosuppressive ability	109
		Hypoxia	Glutathione biosynthesis and regulate TGM	Protect tumor progression and metastasis	110,111
Cystine	Tumor	Nutrient competition	Acute consumption of cystine	Cystine exahaustion→abrogation of APC function	115–117
Tryptophan	Tumor	Nutrient competition	IDO, TDO	Tryptophan deprivation	120,121
	Transplantation	Transplantation rejection	IDO	Produce N-formylkynurenine→T cell cycle arrest	119
	Allogeneic pregnancy	Maternal immune system			123
Extracellular adenosine	Tumor	Hypoxia	Adenosine (tumor derived)→A2BR	Become an immunosuppressive and proangiogenic phenotype	127–129
			TGFβ-mTOR-HIF1α/AMPK→ectonucleotidases (CD39, CD73)	Hydrolyze extracellular ADP/ATP	130
			Adenosine (autocrine manner)→CD73	Exacerbate immune suppression	123,131,132

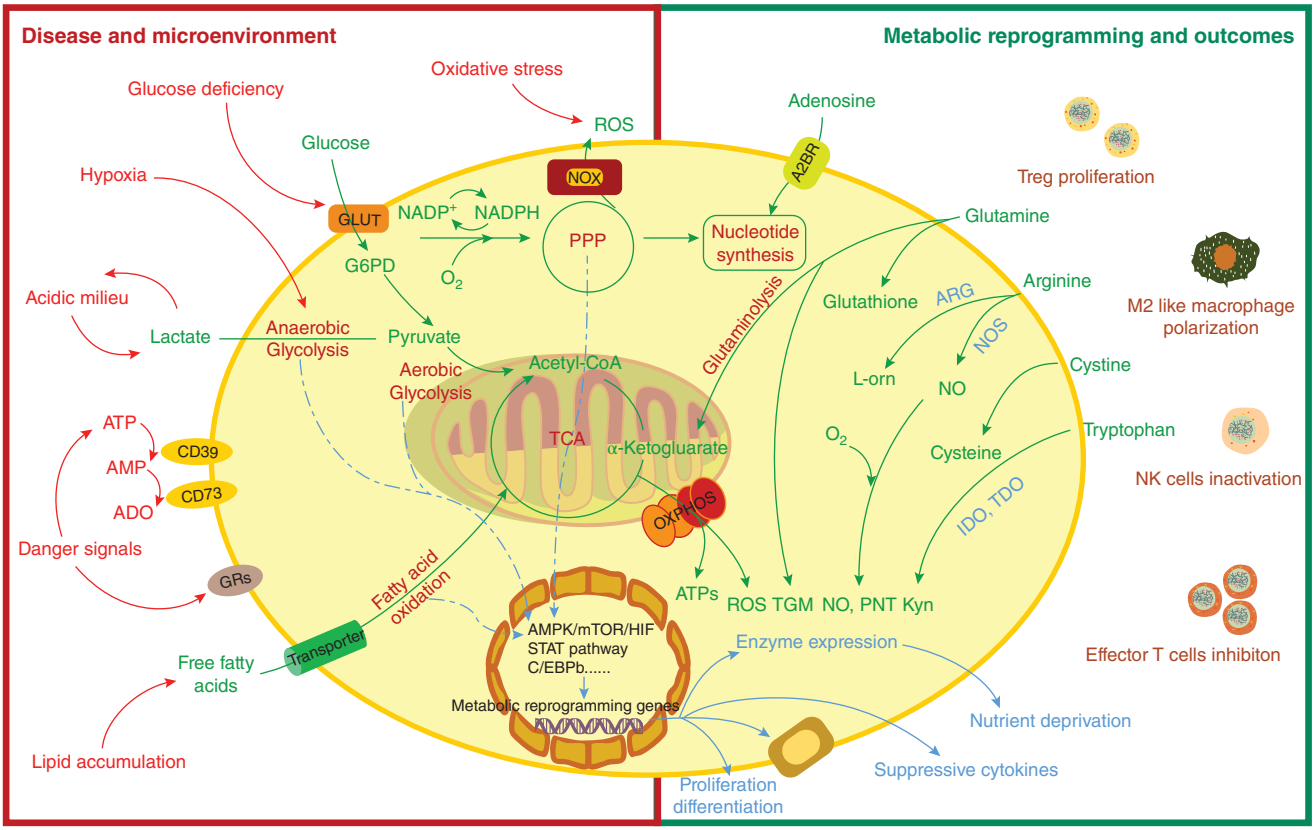

FIGURE 1 Metabolic reprogramming of MDSCs in various pathologic conditions. During pathologic stresses, immature myeloid cells differentiate into immunosuppressive MDSCs accompanying with metabolic reprogramming. Left panel: hypoxic stress and acidic microenvironment accompanies cancer, infection and abnormal placentation, which triggers the hypoxia-signaling cascade in MDSCs. The local cytokine milieu during autoimmune disorders and graft rejection alters the suppressive function of MDSCs. Aberrant content of energy-supplying substance such as glucose and fatty acid change the metabolic phenotype of MDSCs, which further bring about functional alteration. Central part: MDSCs receive extracellular stimuli and transduce signals for metabolic reprogrammings such as changes in glycolysis, fatty acid oxidation, and amino acid metabolism. These metabolic alterations manipulate the expansion, differentiation, and function of MDSCs. Right panel: regulating key metabolic enzymes to induce nutrition deprivation or release immunosuppressive factors are the main ways of MDSCs to fulfill their function. MDSCs can suppress T cells and NK cells and promote Treg cells. From what are discussed above, it is imperative that metabolic intervention can be targeted to regulate immune responses

ulates MDSC metabolism in infectious diseases and immunologic disorders. For instance, splenic myeloid cells switch to anaerobic glycolysis in a HIF1α-dependent manner and attain the MDSCs-like immunosuppressive phenotype when confronting extramedullary myelopoiesis following *Leishmania donovani* infection.[48,49] Furthermore, Lu et al.[50] found that the activation of glucocorticoid receptors (GRs) on MDSCs down-regulate HIF1α expression and HIF1α-dependent glycolysis, and promote their immunosuppressive activity in immune-mediated hepatic injury (IMH). MDSCs also accumulate in the hypoxic placenta, and their immunomodulatory activity may be crucial for maternal–fetal tolerance. Mice with HIF-deficient myeloid cells have increased abortion rate due to the impaired immunosuppressive activity and high apoptosis of MDSCs in the pregnant uterus.[51]

Besides HIF, there are other signaling pathways mediating glucose metabolism as well as glycolysis-dependent immunosuppressive functions in MDSCs. The glycolysis activator AMP-activated protein kinase (AMPK) is closely associated with HIF1α and bridges CEBPβ signaling and the JAK-STAT pathway. Loss of c-Rel, a myeloid and lymphoid-specific transcription factor of the NF-B family,[52] in MDSCs selectively turns on the antitumoral gene signature, decreases mitochondrial respiration, and enhances glycolysis compared to the wild-type cells.[53] Furthermore, inhibition of the mammalian target of rapamycin (mTOR) in 3LL tumor-bearing mice by rapamycin significantly reduced the glycolysis rate contributing to enhancing suppressive function of tumor-infiltrating MDSCs (T-MDSCs).[26] Moreover, Chen et al.[54] showed that inhibiting mTOR with rapamycin and mTOR-deficient MDSCs became a powerful immune modulators with lower glycolytic activity by targeting the HIF1a-dependent glycolytic pathway in IMH.

Pentose phosphate pathway (PPP) is a branch of glycolysis that provides energy and intermediates for biosynthetic pathways.[55] PPP consists of both oxidative and nonoxidative phases. During the oxidative phase, PPP generates cytosolic NADPH through NADPH oxidase (NOX) family, which is a main source of ROS.[15] The nonoxidative phase contributes to the pool of glycolytic precursors, and thus acts as a bridge for the central metabolic pathways in MDSCs. Myeloid cells, especially neutrophils and neutrophilic granulocytes, primarily rely on

PPP to generate ROS due to their low mitochondrial load.[56] ROS is one of the metabolites of PPP and essential for the microbicidal activity of myeloid cells.[57,58] NOX subunits are frequently mutated and inactive in hereditary chronic granulomatous disease (CGD) patients with low-level ROS production and release, which increases the risk of lethal infections.[59]

The PMN-MDSCs display higher NOX activity in response to environmental stress compared with the M-MDSCs, and thus release a far greater amount of ROS to suppress T cells. A substantial increase in ROS levels was observed in the MDSCs of head and neck cancer patients and 7 tumor models and associated with increased activity of NOX2 subunits, especially the STAT3-controlled $p47^{phox}$ and $gp91^{phox}$.[60] In addition, tumor-derived inflammatory cytokines up-regulate TNF-α-induced protein 8-like 2 (TIPE2) in MDSCs and promote ROS production through $p47^{phox}$.[61] Furthermore, the PPP enzymes are overexpressed in nuclear factor erythroid-derived2 (Nrf2)-activated MDSCs, which protects cells from chemical or oxidative stress and inflammation.[62]

Taken together, glycolysis is a major driver of the immunosuppressive activity in MDSCs, and glycolytic metabolites can be potentially targeted to control the fate and activities of MDSCs.

3 | LIPID METABOLISM

Lipid metabolism comprises of cytosolic fatty-acid synthesis and FAO in the mitochondria. Fatty-acid synthesis is ATP-dependent and is initiated with the carboxylation of acetyl-CoA to malonyl CoA by acetyl-CoA carboxylase 1.[63] Lipids are transported from the cytosol to the mitochondria by carnitine palmitoyltransferase (CPT), and subsequently oxidized to acetyl-CoA that is then fed into the TCA cycle and OXPHOS chain.[63] FAO is a crucial factor in regulation of MDSCs function. Polyunsaturated fatty acids (PUFAs) promote expansion of MDSCs from hematopoietic progenitors in vitro.[64] Tumor-bearing mice fed with PUFA-enriched diets show greater tumor load due to the expansion of MDSCs with elevated ROS production, which is driven by the STAT3/$p47^{phox}$ axis.[65] PUFAs can abrogate LPS-induced maturation of DCs and maintain the myeloid progenitors in a MDSC-like state, thereby suppressing adaptive immunity.[66–68] In addition, intravenous injection of pegylated liposomes encapsulated with specific lipids increased the number of MDSC-like cells with enhanced B7-H3 and iNOS expression in the spleen.[69]

The immunosuppressive ability of MDSCs in the TME of tumor-bearing mice correlates with the in situ accumulation of lipids.[70,71] G-CSF or GM-CSF increase MDSCs function through STAT3 and STAT5 signaling following enhanced lipid uptake in the TME.[72,73] Peroxisome proliferator-activator receptors (PPARs) are activated upon sensing fatty acids and relay the signals to downstream transcription factors regulating lipid metabolism.[74] PPARγ activation and the metabolism of neutral lipids affect the development, suppressive function and trans-endothelial migration of MDSCs.[75] Exogenous fatty acid uptake is mediated by fatty acid transport proteins (FATP) and SLC27A. FATP2 overexpression enhanced the function of PMN-MDSCs in both cancer patients and mouse models by promoting cellular arachidonic acid uptake and subsequent PGE2 synthesis.[71] Liver-X receptors (LXR) are members of the nuclear hormone receptor family that transcriptionally activate apolipoprotein E (ApoE). Treating high-metabolic-demand MDSCs with LXR agonists could promote apoptosis and induce dysfunction in MDSCs by potentially mediating lipoprotein metabolism.[76,77] The PMN-MDSCs infiltrating in solid tumors show increased number of mitochondria, oxygen consumption rate and expression levels of FAO cycle enzymes such as CPT1 and 3-hydroxyacyl-coa dehydrogenase (HADHA) compared with the peripheral cells.[73,78] Mitochondria is another major source of ROS in MDSCs.[79] PGE2/cyclooxygenase-2 (COX2) signaling is the common link between FAO and ROS generation, which correlates with the recruitment and differentiation of MDSCs in the TME.[80,81]

Though the exact relationship between FAO and the immunosuppressive ability of MDSCs remains to be clarified, there is considerable evidence that the reprogramming of lipid metabolism in MDSCs determines their phenotype and function.

4 | AMINO ACIDS METABOLISM

Amino acids are indispensable for normal cellular function and survival. The MDSCs with higher metabolic rates can compete with NK cells and CTLs for essential amino acids such as arginine, tryptophan, and cysteine, which limit their survival and induce apoptosis.[82]

4.1 | Arginine

Arginine metabolism plays an important role in regulating innate and adaptive immune responses, and determining the immunologic fate of MDSCs. Breakdown of arginine into L-ornithine and urea by Arg1 leads to arginine starvation, whereas NOS-mediated metabolism generates citrulline and NO resulting in nitrosative stress.[82,83] Arginine deprivation leads to T-cell dysfunction via CD3ζ down-regulation and cell cycle blockade at the G0–G1 phase.[84] Also, lacking Arg results in a decreased initiation of global protein synthesis.[85,86] In addition, MDSCs can steer DCs toward an IDO1-dependent immunosuppressive phenotype via the Arg1 pathway.[87] Cancer cells trigger Arg1 expression in MDSCs, which endows these cells with the ability to induce anergy of NK cells and expansion of natural Treg cells.[88]

Massive consumption of arginine through Arg1 was one of the initially reported immunosuppressive pathways in MDSCs. The hypoxic conditions in the TME markedly increase the expression of Arg1 in T-MDSCs.[87,89] The cationic amino acid transporter 2 (Cat2) is up-regulated in MDSCs that are recruited to inflamed and tumor sites, which increases L-arginine uptake.[90] Otvos et al.[91] found that glioblastoma stem cells secrete macrophage migration inhibitory factor (MIF) that stimulates Arg1 production in MDSCs in a CXCR2-dependent manner. The AMPK/mTOR/HIF1α pathway drives the immunosuppressive function of MDSCs in hypoxic conditions by enhancing the activity of Arg1.[42,50,54,92] The inflammasome triggered by danger sig-

nals including IL-13, LPS, and ATP during allogeneic hemopoietic stem cell transplantation can inactivate Arg1 and thus impair the suppressive phenotype of MDSCs.[93]

Neuronal NOS (nNOS), eNOS, and iNOS metabolize arginine into NO, which has direct apoptotic effects. M-MDSCs-derived NO increases apoptosis of T cells by impairing IL-2R signaling through Jak-3, STAT5, ERK, and AKT.[94,95] High intracellular levels of NO inhibit protein synthesis, DNA damage response, and cell proliferation, and enhance mitochondrial ROS production, such as superoxide and hydrogen peroxide, in MDSCs via NOX subunits ($p22^{phox}$, $p47^{phox}$ and $gp91^{phox}$).[96,97] Furthermore, NO can react with superoxide anion to produce peroxynitrite (PNT) in a NADPH oxidase ($gp91^{phox}$)-dependent manner.[98] PNT inhibits $CD8^+$ T cell activation and proliferation by promoting impairment of tyrosine phosphorylation and inducing apoptosis in cancer.[99,100] Furthermore, PNT induces nitration of chemokines such as CCL2, which inhibits the recruitment of tumor-infiltrating lymphocytes into the inner core of solid tumors.[97] MDSCs also induce graft tolerance by producing iNOS that impairs the function of $CD4^+$ T cells.[24,25] In fact, coexpression of Arg1 and NOS effectively inhibits T cells, and iNOS can only produce PNT in MDSCs in the presence of Arg1.[101] Simultaneous coinhibition of Arg1 and NOS significantly reduced graft survival in vivo compared with that of either alone.[82,102,103] However, Zhang et al.[104] showed that the up-regulation of Arg1 inhibited NOS activity, which aggravated asthma and vascular dysfunction. Enhancing the function of MDSCs by a GR agonist increased iNOS levels but suppressed Arg1.[50] Furthermore, Arg1 can reciprocally induce NOS uncoupling by substrate depletion, which subsequently leads to less NO but more superoxide.[105,106]

4.2 | Glutamine

Glutamine is the most abundant nonessential amino acid in the blood, and the precursor of nucleotide synthesis. During glucose exhaustion in pathophysiologic conditions, glutamine is converted into glutamate and thereafter to α-ketoglutarate (α-KG), which becomes a source of carbon for TCA cycle in the MDSCs. This progress is called anaplerosis, which enables cells to regenerate TCA cycle intermediates for biosynthesis pathways.[107] The differentiation of immature myeloid cells to MDSCs is closely associated with glutamine synthesis.[108] Glutaminolysis provides the intermediates and energy for the development of MDSCs. Apart from competing with antitumor cells for glutamine, MDSCs partially oxidize L-glutamine in an AMPK-dependent manner, which increases immunosuppression and creates favorable conditions for tumor progression.[109] MDSCs were shown to increase glutamine biosynthesis and transglutaminase (TGM) activity in a murine model of metastatic mammary tumors.[110] Consistent with this, c et al.[111] found that TGM expression in MDSCs was correlated to the metastasis and multi-drug resistance of breast cancer.

4.3 | Cysteine

Cysteine is essential for metabolic homeostasis and normal cellular function. T cells cannot take up cysteine nor convert the intracellular methionine into cysteine.[112] In that event, APCs such as macrophages or DCs can convert extracellular cystine into cysteine and taken up by the T cells.[113,114] In contrast to APCs, MDSCs can only import cystine but not export cysteine due to the absence of transporter. As a result, MDSCs lead to sequester cystine from macrophages and DC and create cysteine starvation in the microenvironment.[115] Therefore, T cells do not obtain the cysteine they need for activation and proliferation,[116] and the exhaustion of cysteine reduces glutathione levels in T cells increasing their susceptibility to ROS-mediated oxidative injury.[117]

4.4 | Tryptophan

Tryptophan is required for protein synthesis and other cellular activities. It is metabolized by IDO and TRP-2, 3-dioxygenase 2 (TDO) into kynurenine. Tryptophan is particularly essential for the active cycling of T cells, and its depletion leads to cell cycle arrest at mid-G1 phase and apoptosis. Inhibition of T cells through IDO-mediated tryptophan deprivation is a key mechanism employed by immunosuppressive myeloid cells.[87,118] IDO-expressing MDSCs are increased in tumors and during acute GVHD, and suppress T cell proliferation through the rapid and selective degradation of tryptophan.[119,120] Yu et al.[121] detected IDO^{high} MDSCs in the primary tumors and peripheral blood of cancer patients, and found that these cells promoted Tregs recruitment and metastasis in a STAT3-dependent manner. IDO also protects the allogeneic fetus from rejection, indicating a significant immunomodulatory role.[122] Joo et al.[119] showed that MDSCs treated with G-CSF suppressed acute GVHD in an IDO-dependent manner in murine models. Furthermore, Zoso et al.[123] have identified and characterized a novel population of fibrocytic MDSCs (f-MDSCs) in human umbilical cord blood, which likely originates from the precursor cells in the presence of multiple cytokines. The f-MDSCs can only exert a strong protolerogenic function by releasing IDO when in direct contact with activated T cells.[123]

5 | EXTRACELLULAR ADENOSINE

The A_{2B} adenosine receptor ($A_{2B}R$) is a regulator of nucleotide metabolism and intercellular network.[124] It is activated by high levels of extracellular adenosine induced by pathologic conditions such as inflammation, traumatic stress, transplantation, and so on.[124–126] In addition, the adenosine released by tumor cells enhance the immunosuppressive ability of intra-tumoral MDSCs via $A_{2B}R$.[127] A recent study showed that stimulation of adenosine receptors can disrupt DCs differentiation and turn into a distinct cell population with immunosuppressive and proangiogenic phenotypes as the MDSCs in TME.[128]

TABLE 2 Therapies targeting on MDSCs metabolism

Metabolic pathways	Intervention Strategy	Mechanism in MDSCs	Outcome and Result	Disease	Reference
Glycolysis	2-DG treatment, GLUT3 knockdown or ketogenic diet	Reduce glucose uptake	Decrease MDSCs frequency and improve antitumor immune response	Breast cancer and pancreatic cancer model	39
	Inhibition of c-Rel	Turn on antitumoral gene signatures, enhance glycolysis	Block the generation of MDSCs, reduce suppressive activity	Murine melanoma and lymphoma model	53
	anti-PD-L1	Blockade of PD-L1 and HIF1a	Abrogate the suppressive activity of MDSCs	Murine melanoma model	43,47
	mTOR inhibitor (Rapamycin)	Down-regulating glycolysis	Lead to M-MDSCs dysfunction	LLC	26,137
			Up-regulate PMN-MDSCs suppressive ability	IMH, GVHD	54,89
	Nrf2 activator	Decrease ROS through NOX subunits	Attenuate MDSCs suppressive ability	Sepsis	138
FAO	Blockade of FATP2	Reduce fatty acid uptake and ROS production	Block ROS-mediated immunosuppressive function in MDSCs and enhance anti-PD-L1 immunotherapy	Murine melanoma and lung cancer model, cancer patients	139
	Fatty acid translocase depletion	Inhibit the activation of oxidative metabolism	Deprive T-MDSCs of suppressive function	LLC and colon cancer model	140
	COX-2 inhibitors PGE2 retardants	Reduce chemokine CCL2	Block MDSCs development and accumulation	Murine mesothelioma and glioma model	81,145
	Etomoxir	Inhibitor of the fatty acid oxidation	Decrease MDSCs ability to block T cell proliferation	*Murine* LLC, colon adenocarcinoma model	73,141
	LXR agonists	Activate LXR/ApoE	Reduces abundance and regulates immune suppression	Murine non-small cell lung cancer model	76,77
	mTORC1 activation	Facilitate SREBPs production	Enhance fatty acid synthase	Correct gene function	92
	mTORC2 inhibition	Restrict the activity of ATP citrate lyase	MDSCs deactivation	Breast cancer cell line	142
	Blockade of TIPE2	Reduce ROS production	Abrogate MDSCs immunosuppressive function	*Murine* LLC and melanoma model, lung cancer patients	61,144
Arginine	Blockade of CAT2	Decrease arginine absorption	Inhibit suppressive function of MDSCs	Murine prostate inflammation and cancer models	90
	NOHA or Nor-NOHA	inhibitors of ARG1 activity		LLC	146
	L-NMMA, L-NAME	A transcriptional down-regulator of NOS		*Murine* colon carcinoma and lymphoma model, bladder cancer patients	95,147
	Rapamycin (mTOR inhibitor)	Induce NOS2 expression and NO production		IMH, GVHD	54
	CEBPβ/STAT3 disruption	Regulate key metabolic enzymes expression and functional proteins production	Promote MDSCs differentiation, depletion MDSCs	Murine spontaneous medulloblastoma model	148,149
Glutamine	ATRAs	Regulate glutathione synthase and production	Induce MDSCs differentiation	*Murine* colon carcinoma and lymphoma model, renal carcinoma and acute promyelocytic leukemia patients	151
Nucleotide	Metformin (hypoglycemic agent)	Target on AMPK/HIF1α→down-regulate the expression and activity of CD39 and CD73	Block the suppressive function of MDSCs	ovarian cancer	158
Vitamin	Vitamin D3	Affect NO production	Reduce suppressive function of MDSCs	Head and neck squamous cell carcinoma, chronic lymphocytic leukemia patients	152–154
	Vitamin E			Murine cervical cancer model	155,156

Furthermore, tumor growth was far slower in the $A_{2B}R$ knockout mice, which significantly prolonged their survival mainly due to inactivated MDSCs.[127,129] Li et al.[130] showed that TGFβ-mTOR-HIF1α signaling induced the expression of surface ectonucleotidases (CD39 and CD73) that hydrolyze extracellular ADP/ATP into adenosine in the MDSCs of patients with non-small cell lung cancer, thereby inducing the immunosuppressive and chemo-protective effects of MDSCs. Moreover, MDSCs can secrete adenosine in tumor lesions and exacerbate immune suppression in an autocrine manner via a CD73-dependent pathway.[131] These mechanisms were also verified in Lewis lung carcinoma (LLC)[124,132] and melanoma[129] models.

6 | THERAPEUTIC APPLICATIONS TARGET ON MDSCS METABOLISM

Therapeutic approaches targeting MDSCs have mainly focused on regulating their accumulation, mobilization, differentiation, and function. MDSCs can be eliminated from the TME by chemotherapeutic drugs like 5-fluorouracil,[133] as well inhibitors of GM-CSF, G-CSF, VEGF, IL1β, and so on.[134,135] In addition, blocking the chemokine receptor such as CXCR2 inhibited MDSCs recruitment to the tumor site.[136] More recently, the aberrant metabolic phenotype of MDSCs has gained attention as a promising therapeutic target (Table 2).

Reducing glucose uptake by 2-deoxy-dglucose (2-DG) or down-regulating GLUT expression induce apoptosis in the MDSCs and inhibit tumor progression.[39] The ketogenic diet can lower lactate production in glycolytic tumors, resulting in fewer MDSCs and stronger antitumor immune response.[38] In addition, the proglycolytic transcription factor c-Rel is an established therapeutic target in cancer.[53] Pharmacologic modulation of GR regulates HIF1α and HIF1α-dependent glycolysis in MDSCs and promotes immunosuppression in autoimmune hepatitis.[50] In addition, activation of HIF1α-dependent pathways in MDSCs is crucial for maintaining pregnancy.[51] PD-L1 blockade along with inhibition of HIF1α can abrogate the suppressive activity of MDSCs.[43,47] SIRT1- and HIF1α-associated signals are significantly correlated with the activity of mTOR. However, as mTOR plays distinct roles in different MDSC subsets and diseases, the therapeutic application of rapamycin is ambiguous.[26,54,89,137] Nrf2 activators can decrease PPP-driven ROS production in MDSCs, thereby enhancing T cell function and inhibiting tumor growth.[138]

MDSCs treated with the PUFA linoleic acid exhibit a stronger inhibitory effect than the saturated fatty acid palmitic acid.[70] Pharmaceutic blockade of FATP2 by lipofermata reduced arachidonic acid uptake and PGE2 expression in MDSCs.[139] Genetic ablation of the fatty acid translocase CD36 also mitigated oxidative metabolism in the T-MDSCs through STAT3 and STAT5 signaling.[140] The FAO inhibitor etomoxir markedly decreased the ability of MDSCs to block T cells proliferation.[73,141] LXR/ApoE activation and the ensuing lipoprotein metabolism further reduces the abundance and immunosuppressive function of MDSCs, resulting in tumor regression.[76,77] Activation of mTORC1 facilitates the production of sterol-regulatory element binding proteins (SREBPs), which stimulates the expression of sterol and fatty acid synthase.[92] mTORC2 regulates lipid metabolism in breast tumors by restricting the activity of ATP citrate lyase, which can be targeted to attenuate the immunosuppressive capacity of MDSCs.[142] The production of mitochondrial ROS in MDSCs is dependent on COX2 activity, and blocking TIPE2 or COX2 abrogated the inhibitory function of MDSCs by reducing ROS generation.[61,143,144] Moreover, silencing the PGE2/COX2 pathway down-regulated chemokine CCL2 and inhibited MDSCs accumulation in TME.[81,145]

MDSCs affects other immune cells mainly by competing for essential amino acids. Arginine catabolism plays a key regulatory role in immune recognition. CAT2 blockade and the subsequent decrease in arginine absorption can reverse the immunosuppressive activity of MDSCs.[90] The Arg1 inhibitor N-hydroxy-L-arginine (NOHA) reversed T cell dysfunction both in vitro and in tumor-bearing mice, and led to an anti-tumor response.[146] Likewise, the NOS inhibitor NG-monomethyl-L-arginine (L-NMMA) and N (G)-nitro-L-arginine methyl ester (L-NAME) can increase the number of $CD8^+$ T cells and NK cells while decreasing Treg and MDSCs accumulation.[95,147] Furthermore, down-regulating mTOR in $CD11b^+Gr\text{-}1^+$ MDSCs induced iNOS expression and increased NO production, which mediated a protective effect in IMH.[54] Direct and indirect inhibition of CEBPβ or STAT3 also reduces iNOS and Arg1 levels in T-MDSCs.[148,149]

Glutamine is essential for the continued growth and survival of some cancer cell lines, and limiting its levels through competitive utilization is a promising anticancer therapeutic strategy.[150] All-trans retinoic acids (ATRAs) up-regulate glutathione synthase in the MDSCs though ERK1/2 activation. MDSCs derived from cancer patients and tumor-bearing mice rapidly differentiate into DCs/macrophages in the presence of ATRAs.[151]

Along with the above-mentioned major metabolic pathways, there are other metabolic routes affect the biochemical processes in MDSCs. Vitamin and its analogs affect the differentiation and development of MDSCs from primitive myeloid cells.[152] Vitamin D3 may have a prodifferentiation effect on myeloid cells, which is similar to that seen with ATRA-treated cells,[152–154] whereas vitamin E exerts its functions by neutralizing MDSC-derived NO.[155,156] All 8 isomers of vitamin E exhibit strong antitumor, antioxidant, and proapoptotic effects, especially a-tocopherol succinate.[155,156] Kang et al.[157] found that α-tocopherol succinate could reduce immunosuppression by MDSCs via a NO-dependent mechanism. MDSC-mediated immunosuppression was reversed in ovarian cancer patients by metformin treatment, which inhibited adenosine enzymes by activating AMPKα and blocking the HIF1α pathway.[158]

7 | CONCLUDING REMARKS

MDSCs are a group of highly heterogenetic and immunosuppressive cells that are the result of aberrant myelopoiesis during pathologic conditions. As metabolic reprogramming become a key driver of the immunosuppressive function of MDSCs, we reviewed the different biologic characteristics of MDSCs under various pathophysiologic microenvironments (Table 1). Meanwhile, metabolic intervention

in MDSCs become a novel therapeutic strategy for a wide range of diseases (Table 2). As MDSCs exhibit remarkable phenotypic and functional plasticity, their metabolic characteristics can be potentially classified into specific signatures.

AUTHORSHIP

X.L. studied and wrote the manuscript. Y.L. helped to create the tables. Q.X. helped to search the literatures. P.Q., H.H., and Y.L. discussed and revised the manuscript.

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DISCLOSURES

The authors declared no conflicts of interest.

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