

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, hypoxia 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

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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-1 β 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 HIF1 α 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 HIF1 α .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 HIF1 α 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. HIF1 α also mod-

TABLE 1 Metabolic profile of MDSCs in various pathologic environments

Metabolic pathways	Disease	Microenvironment	Molecular mechanism	Outcomes	Reference
Glycolysis	Infection (<i>Leishmania donovani</i>)	Infectious stress (with myelopoiesis)	HIF1 α →anaerobic glycolysis	Obtain immunosuppressive function	48,49
	Tumor	Hypoxia	HIF1 α →glycolytic enzyme	Differentiate into TAM-like phenotype	41–43
			HIF1 α →expression of PD-L1	Enhance T cell apoptosis	43,57
			SIRT1→HIF1 α	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
			Up-regulate TIPE2→PPP	Promote ROS production	61
IMH		Tumor-derived inflammatory cytokines	Nrf2 signal→up-regulate PPP key enzymes	Protect cell from chemical or oxidative stress	62
			Activate of GRs and further regulate HIF1 α	Suppress T cells	50
FAO	Tumor	Hypoxia	Inhibit mTOR→lower glycolysis activity	Enhance immune regulatory ability	54
			HIF deficiency	Impair suppressive activity	51
			Fas-Caspase network	Resist apoptosis	40
CGD	Tumor	Inflammatory environment	NOX2 subunits defecton	Control infection	59
			Regulate FAO key enzyme (CPT1, HADHA)	Immunosuppressive ability	79
		Lipid accumulation	PPAR γ 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
Arginine	Tumor	Oxidative stress Hypoxia	PGE2-COX2 Cat2 → increases L-arginine uptake	Mediate MDSC regulatory function Arginine starvation → T cell cycle dysfunction	80,81 90
			AMPK/mTOR/HIF1 α up-regulate Arg	Recruit other immune cells 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 exhaustion → 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
			TGF β -mTOR-HIF1 α /AMPK → ectonucleotidases (CD39, CD73)	Hydrolyze extracellular ADP/ATP	130
			Adenosine (autocrine manner) → CD73	Exacerbate immune suppression	123,131,132

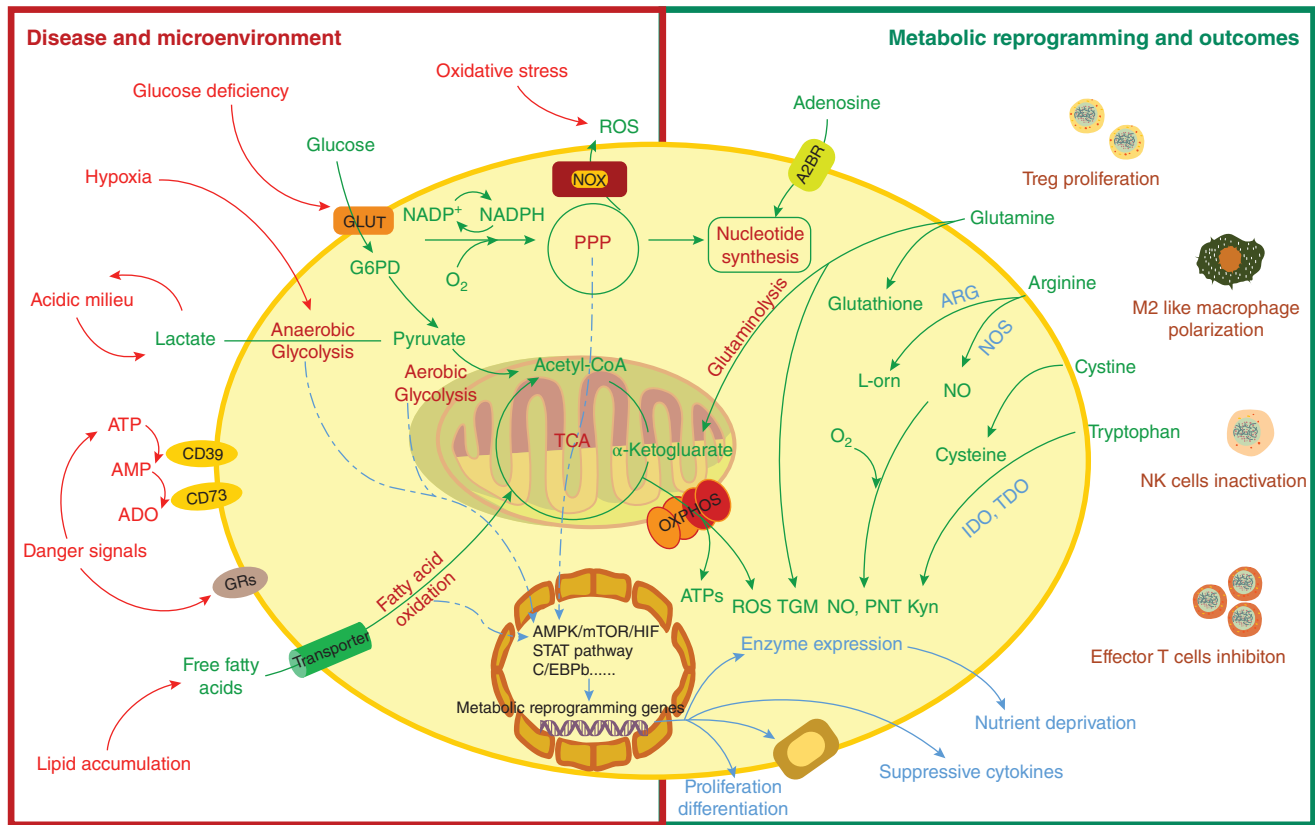


FIGURE 1 Metabolic reprogramming of MDSCs in various pathologic conditions. During pathologic stresses, immature myeloid cells differentiate into immunosuppressive MDSCs accompanying with metabolic reprogramming. Left panel: hypoxic stress and acidic microenvironment accompanies cancer, infection and 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 HIF1 α -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 HIF1 α expression and HIF1 α -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 HIF1 α and bridges CEBP β signaling and the JAK-STAT pathway. Loss of c-Rel, a myeloid and lymphoid-

specific transcription factor of the NF- κ 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 HIF1 α -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 PPAR γ 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 CD3 ζ 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/HIF1 α 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 process 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 HIF1 α	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
	Nrf2 activator	Decrease ROS through NOX subunits	Up-regulate PMN-MDSCs suppressive ability	IMH, GVHD	54,89
FAO	Blockade of FATP2	Reduce fatty acid uptake and ROS production	Attenuate MDSCs suppressive ability	Sepsis	138
	Fatty acid translocase depletion	Inhibit the activation of oxidative metabolism	Block ROS-mediated immunosuppressive function in MDSCs and enhance anti-PD-L1 immunotherapy	Murine melanoma and lung cancer model, cancer patients	139
	COX-2 inhibitors PGE2 retardants	Reduce chemokine CCL2	Deplete T-MDSCs of suppressive function	LLC and colon cancer model	140
	Etomoxir	Inhibitor of the fatty acid oxidation	Block MDSCs development and accumulation	Murine mesothelioma and glioma model	81,145
	LXR agonists	Activate LXR/ApoE	Decrease MDSCs ability to block T cell proliferation	Murine LLC, colon adenocarcinoma model	73,141
	mTORC1 activation	Facilitate SREBPs production	Reduces abundance and regulates immune suppression	Murine non-small cell lung cancer model	76,77
	mTORC2 inhibition	Restrict the activity of ATP citrate lyase	Enhance fatty acid synthase	Correct gene function	92
	Blockade of TIPE2	Reduce ROS production	MDSCs deactivation	Breast cancer cell line	142
Arginine	Blockade of CAT2	Decrease arginine absorption	Abrogate MDSCs immunosuppressive function	Murine LLC and melanoma model, lung cancer patients	61,144
	NOHA or Nor-NOHA	inhibitors of ARG1 activity	Inhibit suppressive function of MDSCs	Murine prostate inflammation and cancer models	90
	L-NMMA, L-NAME	A transcriptional down-regulator of NOS		LLC	146
	Rapamycin (mTOR inhibitor)	Induce NOS2 expression and NO production		Murine colon carcinoma and lymphoma model, bladder cancer patients	95,147
	CEBP β /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	IMH, GVHD	54
Nucleotide	Metformin (hypoglycemic agent)	Target on AMPK/HIF1 α →down-regulate the expression and activity of CD39 and CD73	Block the suppressive function of MDSCs	Murine melanoma and lymphoma model, renal carcinoma and acute promyelocytic leukemia patients	151
Vitamin	Vitamin D3	Affect NO production	Reduce suppressive function of MDSCs	Murine spontaneous medulloblastoma model, ovarian cancer	158
	Vitamin E		Reduce suppressive function of MDSCs	Head and neck squamous cell carcinoma, chronic lymphocytic leukemia patients	152–154
				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 TGF β -mTOR-HIF1 α 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 melanoma¹²⁹ 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, IL1 β , 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 HIF1 α and HIF1 α -dependent glycolysis in MDSCs and promotes immunosuppression in autoimmune hepatitis.⁵⁰ In addition, activation of HIF1 α -dependent pathways in MDSCs is crucial for maintaining pregnancy.⁵¹ PD-L1 blockade along with inhibition of HIF1 α can abrogate the suppressive activity of MDSCs.^{43,47} SIRT1- and HIF1 α -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 Pharmaceutical 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-1⁺ MDSCs induced iNOS expression and increased NO production, which mediated a protective effect in IMH.⁵⁴ Direct and indirect inhibition of CEBP β 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 (ATRA) up-regulate glutathione synthase in the MDSCs through 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 α -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 AMPK α and blocking the HIF1 α pathway.¹⁵⁸

7 | CONCLUDING REMARKS

MDSCs are a group of highly heterogenous 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 pathophysiological 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.

REFERENCES

- DeBerardinis RJ, Lum JJ, Hatzivassiliou G, et al. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab* 2008;7(1):11-20.
- Biswas SK. Metabolic reprogramming of immune cells in cancer progression. *Immunity* 2015;43(3):435-49.
- Sanderson SM, Locasale JW. Revisiting the Warburg effect: some tumors hold their breath. *Cell Metab* 2018;28(5):669-670.
- Dugnani E, Pasquale V, Bordignon C, et al. Integrating T cell metabolism in cancer immunotherapy. *Cancer Lett* 2017;411:12-18.
- Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. *Immunity* 2013;38(4):633-43.
- Assmann JC, Farthing DE, Saito K, et al. Glycolytic metabolism of pathogenic T cells enables early detection of GvHD by 13C-MRI. *Blood* 2020.
- Hippen KL, Aguilar EG, Rhee SY, et al. Distinct regulatory and effector T cell metabolic demands during graft-versus-host disease. *Trends Immunol* 2020;41(1):77-91.
- Nguyen HD, Chatterjee S, Haarberg KM, et al. Metabolic reprogramming of alloantigen-activated T cells after hematopoietic cell transplantation. *J Clin Invest* 2016;126(4):1337-52.
- Kelly B, O'Neill LA. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. *Cell Res* 2015;25(7):771-84.
- Kornberg MD. The immunologic Warburg effect: Evidence and therapeutic opportunities in autoimmunity. *Wiley Interdiscip Rev Syst Biol Med* 2020;12(5):e1486.
- Ip WKE, Hoshi N, Shouval DS, et al. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. *Science* 2017;356(6337):513-519.
- Papathanassiou AE, Ko JH, Imprialou M, et al. BCAT1 controls metabolic reprogramming in activated human macrophages and is associated with inflammatory diseases. *Nat Commun* 2017;8:16040.
- Vats D, Mukundan L, Odegaard JI, et al. Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. *Cell Metab* 2006;4(1):13-24.
- Rice CM, Davies LC, Subleski JJ, et al. Tumour-elicited neutrophils engage mitochondrial metabolism to circumvent nutrient limitations and maintain immune suppression. *Nat Commun* 2018;9(1):5099.
- Injarabian L, Devin A, Ransac S, et al. Neutrophil metabolic shift during their lifecycle: impact on their survival and activation. *Int J Mol Sci* 2019;21(1).
- Maianski NA, Geissler J, Srinivasula SM, et al. Functional characterization of mitochondria in neutrophils: a role restricted to apoptosis. *Cell Death Differ* 2004;11(2):143-53.
- Fridlender ZG, Sun J, Kim S, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. *Cancer Cell* 2009;16(3):183-94.
- Condamine T, Gabrilovich DI. Molecular mechanisms regulating myeloid-derived suppressor cell differentiation and function. *Trends Immunol* 2011;32(1):19-25.
- Talmadge JE, Gabrilovich DI. History of myeloid-derived suppressor cells. *Nat Rev Cancer* 2013;13(10):739-52.
- Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol* 2009;9(3):162-74.
- Koehn BH, Blazar BR. Role of myeloid-derived suppressor cells in allogeneic hematopoietic cell transplantation. *J Leukoc Biol* 2017;102(2):335-341.
- Bronte V, Brandau S, Chen SH, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat Commun* 2016;7:12150.
- Najafi M, Goradel NH, Farhood B, et al. Tumor microenvironment: Interactions and therapy. *J Cell Physiol* 2019;234(5):5700-5721.
- Garcia MR, Ledgerwood L, Yang Y, et al. Monocytic suppressive cells mediate cardiovascular transplantation tolerance in mice. *J Clin Invest* 2010;120(7):2486-96.
- Dugast AS, Haudebourg T, Coulon F, et al. Myeloid-derived suppressor cells accumulate in kidney allograft tolerance and specifically suppress effector T cell expansion. *J Immunol* 2008;180(12):7898-906.
- Deng Y, Yang J, Luo F, Qian J, et al. mTOR-mediated glycolysis contributes to the enhanced suppressive function of murine tumor-infiltrating monocytic myeloid-derived suppressor cells. *Cancer Immunol Immunother* 2018;67(9):1355-1364.
- Yang L, DeBusk LM, Fukuda K, et al. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. *Cancer Cell* 2004;6(4):409-21.
- Di Mitri D, Toso A, Chen JJ, et al. Tumour-infiltrating Gr-1+ myeloid cells antagonize senescence in cancer. *Nature* 2014;515(7525):134-7.
- Nozawa H, Chiu C, Hanahan D. Infiltrating neutrophils mediate the initial angiogenic switch in a mouse model of multistage carcinogenesis. *Proc Natl Acad Sci USA* 2006;103(33):12493-8.
- Shojaei F, Singh M, Thompson JD, et al. Role of Bv8 in neutrophil-dependent angiogenesis in a transgenic model of cancer progression. *Proc Natl Acad Sci USA* 2008;105(7):2640-5.
- Gato-Canas M, Martinez de Morentin X, Blanco-Luquin I, et al. A core of kinase-regulated interactomes defines the neoplastic MDSC lineage. *Oncotarget* 2015;6(29):27160-75.
- Gato M, Blanco-Luquin I, Zudaire M, et al. Drafting the proteome landscape of myeloid-derived suppressor cells. *Proteomics* 2016;16(2):367-378.
- Naifeh J, Varacallo M. Biochemistry, Aerobic glycolysis. *StatPearls*. Treasure Island (FL) 2020.
- Jian SL, Chen WW, Su YC, et al. Glycolysis regulates the expansion of myeloid-derived suppressor cells in tumor-bearing hosts through prevention of ROS-mediated apoptosis. *Cell Death Dis* 2017;8(5):e2779.
- Valentine WN. Introduction to discussion of regulation of erythrocyte glycolysis. *Exp Eye Res* 1971;11(3):273-9.
- Al-Khami AA, Rodriguez PC, Chocac AC. Metabolic reprogramming of myeloid-derived suppressor cells (MDSC) in cancer. *Oncoimmunology* 2016;5(8):e1200771.

37. Sica A, Strauss L. Energy metabolism drives myeloid-derived suppressor cell differentiation and functions in pathology. *J Leukoc Biol* 2017;102(2):325-334.
38. Husain Z, Huang Y, Seth P, et al. Tumor-derived lactate modifies anti-tumor immune response: effect on myeloid-derived suppressor cells and NK cells. *J Immunol* 2013;191(3):1486-95.
39. Fu C, Fu Z, Jiang C, et al. CD205(+) polymorphonuclear myeloid-derived suppressor cells suppress antitumor immunity by overexpressing GLUT3. *Cancer Sci* 2020;112(3):1011-1025.
40. Chornoguz O, Grmai L, Sinha P, et al. Proteomic pathway analysis reveals inflammation increases myeloid-derived suppressor cell resistance to apoptosis. *Mol Cell Proteomics* 2011;10(3):M110002980.
41. Li C, Liu T, Bazhin AV, et al. The sabotaging role of myeloid cells in anti-angiogenic therapy: coordination of angiogenesis and immune suppression by hypoxia. *J Cell Physiol* 2017;232(9):2312-2322.
42. Corcoran SE, O'Neill LA. HIF1alpha and metabolic reprogramming in inflammation. *J Clin Invest* 2016;126(10):3699-3707.
43. Corzo CA, Condamine T, Lu L, et al. HIF-1alpha regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. *J Exp Med* 2010;207(11):2439-53.
44. Cohen HY, Miller C, Bitterman KJ, et al. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. *Science* 2004;305(5682):390-2.
45. Dong L, Bi Y, Jia A, et al. Crucial role of histone deacetylase SIRT1 in myeloid-derived suppressor cell-mediated reprogramming of CD4(+) T-cell differentiation. *Cell Mol Immunol* 2020;17(7):785-787.
46. Liu G, Bi Y, Shen B, et al. SIRT1 limits the function and fate of myeloid-derived suppressor cells in tumors by orchestrating HIF-1alpha-dependent glycolysis. *Cancer Res* 2014;74(3):727-37.
47. Noman MZ, Desantis G, Janji B, et al. PD-L1 is a novel direct target of HIF-1alpha, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. *J Exp Med* 2014;211(5):781-90.
48. Mesquita I, Ferreira C, Moreira D, et al. The absence of HIF-1alpha increases susceptibility to *Leishmania donovani* infection via activation of BNIP3/mTOR/SREBP-1c axis. *Cell Rep* 2020;30(12):4052-4064 e7.
49. Sacks D, Hammami A, Abidin BM, et al. HIF-1 α is a key regulator in potentiating suppressor activity and limiting the microbicidal capacity of MDSC-like cells during visceral leishmaniasis. *PLOS Pathogens* 2017;13(9):e1006616.
50. Lu Y, Liu H, Bi Y, et al. Glucocorticoid receptor promotes the function of myeloid-derived suppressor cells by suppressing HIF1alpha-dependent glycolysis. *Cell Mol Immunol* 2018;15(6):618-629.
51. Kostlin-Gille N, Dietz S, Schwarz J, et al. HIF-1alpha-deficiency in myeloid cells leads to a disturbed accumulation of myeloid derived suppressor cells (MDSC) during pregnancy and to an increased abortion rate in mice. *Front Immunol* 2019;10:161.
52. Grumont RJ, Gerondakis S. The murine c-rel proto-oncogene encodes two mRNAs the expression of which is modulated by lymphoid stimuli. *Oncogene Res* 1990;5(4):245-54.
53. Li T, Li X, Zamani A, et al. c-Rel is a myeloid checkpoint for cancer immunotherapy. *Nat Cancer* 2020;1(5):507-517.
54. Chen X, Zhang Z, Bi Y, et al. mTOR signaling disruption from myeloid-derived suppressive cells protects against immune-mediated hepatic injury through the HIF1alpha-dependent glycolytic pathway. *J Leukoc Biol* 2016;100(6):1349-1362.
55. Adler Lt, Chen C, Koutalos Y. Mitochondria contribute to NADPH generation in mouse rod photoreceptors. *J Biol Chem* 2014;289(3):1519-28.
56. Sieow JL, Gun SY, Wong SC. The sweet surrender: how myeloid cell metabolic plasticity shapes the tumor microenvironment. *Front Cell Dev Biol* 2018;6:168.
57. Kruger NJ, von Schaewen A. The oxidative pentose phosphate pathway: structure and organisation. *Curr Opin Plant Biol* 2003;6(3):236-246.
58. Al-Khami AA, Rodriguez PC, Ochoa AC. Energy metabolic pathways control the fate and function of myeloid immune cells. *J Leukoc Biol* 2017;102(2):369-380.
59. Assari T. Chronic granulomatous disease; fundamental stages in our understanding of CGD. *Med Immunol* 2006;5(1):4.
60. Freerman AJ, Johnson AR, Sacks GN, et al. Metabolic reprogramming of macrophages: glucose transporter 1 (GLUT1)-mediated glucose metabolism drives a proinflammatory phenotype. *J Biol Chem* 2014;289(11):7884-96.
61. Yan D, Wang J, Sun H, et al. TIPE2 specifies the functional polarization of myeloid-derived suppressor cells during tumorigenesis. *J Exp Med* 2020;217(2).
62. Ohl K, Fragoulis A, Klemm P, et al. Nrf2 is a central regulator of metabolic reprogramming of myeloid-derived suppressor cells in steady state and sepsis. *Front Immunol* 2018;9:1552.
63. Yan D, Adeshakin AO, Xu M, et al. Lipid metabolic pathways confer the immunosuppressive function of myeloid-derived suppressor cells in tumor. *Front Immunol* 2019;10:1399.
64. Veglia F, Tyurin V, Kagan V, et al. Abstract 467: Oxidized lipids contribute to the suppression function of myeloid derived suppressor cells in cancer. *Cancer Res* 2015;75(15 Supplement):467-467.
65. Yan D, Yang Q, Shi M, et al. Polyunsaturated fatty acids promote the expansion of myeloid-derived suppressor cells by activating the JAK/STAT3 pathway. *Eur J Immunol* 2013;43(11):2943-55.
66. Obermajer N, Muthuswamy R, Lesnock J, et al. Positive feedback between PGE2 and COX2 redirects the differentiation of human dendritic cells toward stable myeloid-derived suppressor cells. *Blood* 2011;118(20):5498-505.
67. Zeyda M, Szekeres AB, Saemann MD, et al. Suppression of T cell signaling by polyunsaturated fatty acids: selectivity in inhibition of mitogen-activated protein kinase and nuclear factor activation. *J Immunol* 2003;170(12):6033-9.
68. Draper E, Reynolds CM, Canavan M, et al. Omega-3 fatty acids attenuate dendritic cell function via NF-kappaB independent of PPARgamma. *J Nutr Biochem* 2011;22(8):784-90.
69. Yoshida Y, Nagamori T, Ishibazawa E, et al. Contribution of long-chain fatty acid to induction of myeloid-derived suppressor cell (MDSC)-like cells - induction of MDSC by lipid vesicles (liposome). *Immunopharmacol Immunotoxicol* 2020;42(6):614-624.
70. Ramakrishnan R, Tyurin VA, Veglia F, et al. Oxidized lipids block antigen cross-presentation by dendritic cells in cancer. *J Immunol* 2014;192(6):2920-31.
71. Veglia F, Tyurin VA, Blasi M, et al. Fatty acid transport protein 2 reprograms neutrophils in cancer. *Nature* 2019;569(7754):73-78.
72. Abrams SI, Waight JD. Identification of a G-CSF-Granulocytic MDSC axis that promotes tumor progression. *Oncoimmunology* 2012;1(4):550-551.
73. Hossain F, Al-Khami AA, Wyczechowska D, et al. Inhibition of fatty acid oxidation modulates immunosuppressive functions of myeloid-derived suppressor cells and enhances cancer therapies. *Cancer Immunol Res* 2015;3(11):1236-47.
74. Liu Y, Colby JK, Zuo X, et al. The role of PPAR-delta in metabolism, inflammation, and cancer: many characters of a critical transcription factor. *Int J Mol Sci* 2018;19(11).
75. Zhao T, Du H, Blum JS, et al. Critical role of PPAR γ in myeloid-derived suppressor cell-stimulated cancer cell proliferation and metastasis. *Oncotarget* 2016;7(2):1529.
76. Tavazoie MF, Pollack I, Tanqueco R, et al. LXR/ApoE activation restricts innate immune suppression in cancer. *Cell* 2018;172(4):825-840 e18.

77. Liang H, Shen X. LXR activation radiosensitizes non-small cell lung cancer by restricting myeloid-derived suppressor cells. *Biochem Biophys Res Commun* 2020;528(2):330-335.
78. Ochando JC, Chen SH. Myeloid-derived suppressor cells in transplantation and cancer. *Immunol Res* 2012;54(1-3):275-85.
79. West AP, Brodsky IE, Rahner C, et al. TLR signalling augments macrophage bactericidal activity through mitochondrial ROS. *Nature* 2011;472(7344):476-480.
80. Rieser C, Bock G, Klocker H, et al. Prostaglandin E2 and tumor necrosis factor alpha cooperate to activate human dendritic cells: synergistic activation of interleukin 12 production. *J Exp Med* 1997;186(9):1603-8.
81. Veltman JD, Lambers ME, van Nimwegen M, et al. COX-2 inhibition improves immunotherapy and is associated with decreased numbers of myeloid-derived suppressor cells in mesothelioma. Celecoxib influences MDSC function. *BMC Cancer* 2010;10:464.
82. Rodriguez PC, Quiceno DG, Ochoa AC. L-arginine availability regulates T-lymphocyte cell-cycle progression. *Blood* 2007;109(4):1568-73.
83. Raber P, Ochoa AC, Rodriguez PC. Metabolism of L-arginine by myeloid-derived suppressor cells in cancer: mechanisms of T cell suppression and therapeutic perspectives. *Immunol Invest* 2012;41(6-7):614-34.
84. Zea AH, Rodriguez PC, Culotta KS, et al. L-Arginine modulates CD3 ζ expression and T cell function in activated human T lymphocytes. *Cell Immunol* 2004;232(1-2):21-31.
85. Geiger R, Rieckmann JC, Wolf T, et al. L-Arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell* 2016;167(3):829-842 e13.
86. Hernandez CP, Morrow K, Lopez-Barcons LA, et al. Pegylated arginase I: a potential therapeutic approach in T-ALL. *Blood* 2010;115(25):5214-21.
87. Mondanelli G, Bianchi R, Pallotta MT, et al. A relay pathway between arginine and tryptophan metabolism confers immunosuppressive properties on dendritic cells. *Immunity* 2017;46(2):233-244.
88. Lindau D, Gielen P, Kroesen M, et al. The immunosuppressive tumour network: myeloid-derived suppressor cells, regulatory T cells and natural killer T cells. *Immunology* 2013;138(2):105-15.
89. Lin Y, Wang B, Shan W, et al. mTOR inhibitor rapamycin induce polymorphonuclear myeloid-derived suppressor cells mobilization and function in protecting against acute graft-versus-host disease after bone marrow transplantation. *Clin Immunol* 2018;187:122-131.
90. Cimen Bozkus C, Elzey BD, Crist SA, et al. Expression of cationic amino acid transporter 2 is required for myeloid-derived suppressor cell-mediated control of T cell immunity. *J Immunol* 2015;195(11):5237-50.
91. Otvos B, Silver DJ, Mulkearns-Hubert EE, et al. Cancer stem cell-secreted macrophage migration inhibitory factor stimulates myeloid derived suppressor cell function and facilitates glioblastoma immune evasion. *Stem Cells* 2016;34(8):2026-39.
92. Duvel K, Yecies JL, Menon S, et al. Activation of a metabolic gene regulatory network downstream of mTOR complex 1. *Mol Cell* 2010;39(2):171-83.
93. Koehn BH, Saha A, McDonald-Hyman C, et al. Danger-associated extracellular ATP counters MDSC therapeutic efficacy in acute GVHD. *Blood* 2019;134(19):1670-1682.
94. Chicoine LG, Paffett ML, Young TL, et al. Arginase inhibition increases nitric oxide production in bovine pulmonary arterial endothelial cells. *Am J Physiol Lung Cell Mol Physiol* 2004;287(1):L60-L68.
95. Mazzoni A, Bronte V, Visintin A, et al. Myeloid suppressor lines inhibit T cell responses by an NO-dependent mechanism. *J Immunol* 2002;168(2):689-95.
96. Terabe M, Matsui S, Park J-M, et al. Transforming growth factor- β production and myeloid cells are an effector mechanism through which CD1d-restricted T cells block cytotoxic T lymphocyte-mediated tumor immunosurveillance: abrogation prevents tumor recurrence. *J Exp Med* 2003;198(11):1741-1752.
97. Molon B, Ugel S, Del Pozzo F, et al. Chemokine nitration prevents intratumoral infiltration of antigen-specific T cells. *J Exp Med* 2011;208(10):1949-62.
98. Raber PL, Thevenot P, Sierra R, et al. Subpopulations of myeloid-derived suppressor cells impair T cell responses through independent nitric oxide-related pathways. *Int J Cancer* 2014;134(12):2853-64.
99. Brito C, Naviliat M, Tiscornia AC, et al. Peroxynitrite inhibits T lymphocyte activation and proliferation by promoting impairment of tyrosine phosphorylation and peroxynitrite-driven apoptotic death. *J Immunol* 1999;162(6):3356-66.
100. Nagaraj S, Gupta K, Pisarev V, et al. Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer. *Nat Med* 2007;13(7):828-835.
101. Kusmartsev S, Gabrilovich DI. STAT1 signaling regulates tumor-associated macrophage-mediated T cell deletion. *J Immunol* 2005;174(8):4880-4891.
102. Rodriguez PC, Quiceno DG, Zabaleta J, et al. Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. *Cancer Res* 2004;64(16):5839-49.
103. Rodriguez PC, Ochoa AC, Al-Khami AA. Arginine metabolism in myeloid cells shapes innate and adaptive immunity. *Front Immunol* 2017;8:93.
104. Zhang C, Hein TW, Wang W, et al. Upregulation of vascular arginase in hypertension decreases nitric oxide-mediated dilation of coronary arterioles. *Hypertension* 2004;44(6):935-943.
105. Kim JH, Bugaj LJ, Oh YJ, et al. Arginase inhibition restores NOS coupling and reverses endothelial dysfunction and vascular stiffness in old rats. *J Appl Physiol* (1985) 2009;107(4):1249-57.
106. Zou MH, Shi C, Cohen RA. Oxidation of the zinc-thiolate complex and uncoupling of endothelial nitric oxide synthase by peroxynitrite. *J Clin Invest* 2002;109(6):817-26.
107. Owen OE, Kalhan SC, Hanson RW. The key role of anaplerosis and cataplerosis for citric acid cycle function. *J Biol Chem* 2002;277(34):30409-12.
108. Groth C, Weber R, Utikal J, et al. Depletion and maturation of myeloid-derived suppressor cells in murine cancer models. In: Branda S, Dorhoi A, editors. *Myeloid-Derived Suppressor Cells*. New York, NY: Springer US; 2021. p 67-75.
109. Hammami I, Chen J, Murschel F, et al. Immunosuppressive activity enhances central carbon metabolism and bioenergetics in myeloid-derived suppressor cells in vitro models. *BMC Cell Biol* 2012;13:18.
110. Boutte AM, McDonald WH, Shyr Y, et al. Characterization of the MDSC proteome associated with metastatic murine mammary tumors using label-free mass spectrometry and shotgun proteomics. *PLoS One* 2011;6(8):e22446.
111. Verma A, Mehta K. Tissue transglutaminase-mediated chemoresistance in cancer cells. *Drug Resist Updat* 2007;10(4-5):144-51.
112. Srivastava MK, Sinha P, Clements VK, et al. Myeloid-derived suppressor cells inhibit t-cell activation by depleting cystine and cysteine. *Cancer Res* 2009;70(1):68-77.
113. Gmünder H, Eck H-P, Benninghoff B, et al. Macrophages regulate intracellular glutathione levels of lymphocytes. Evidence for an immunoregulatory role of cysteine. *Cell Immunol* 1990;129(1):32-46.
114. Sato H, Watanabe H, Ishii T, et al. Neutral amino acid transport in mouse peritoneal macrophages. *J Biol Chem* 1987;262(27):13015-13019.
115. Sakakura Y, Sato H, Shiiya A, et al. Expression and function of cystine/glutamate transporter in neutrophils. *J Leukoc Biol* 2007;81(4):974-982.

116. Ostrand-Rosenberg S. Myeloid-derived suppressor cells: more mechanisms for inhibiting antitumor immunity. *Cancer Immunol Immunother* 2010;59(10):1593-600.
117. Smyth M. Glutathione modulates activation-dependent proliferation of human peripheral blood lymphocyte populations without regulating their activated function. *J Immunol* 1991;146(6):1921-1927.
118. Grohmann U, Bronte V. Control of immune response by amino acid metabolism. *Immunol Rev* 2010;236:243-64.
119. Joo YD, Lee SM, Lee SW, et al. Granulocyte colony-stimulating factor-induced immature myeloid cells inhibit acute graft-versus-host disease lethality through an indoleamine dioxygenase-independent mechanism. *Immunology* 2009;128(1 Suppl):e632-40.
120. Yang L, Huang J, Ren X, et al. Abrogation of TGF beta signaling in mammary carcinomas recruits Gr-1+CD11b+ myeloid cells that promote metastasis. *Cancer Cell* 2008;13(1):23-35.
121. Yu J, Du W, Yan F, et al. Myeloid-derived suppressor cells suppress antitumor immune responses through IDO expression and correlate with lymph node metastasis in patients with breast cancer. *J Immunol* 2013;190(7):3783-97.
122. Munn DH, Shafizadeh E, Attwood JT, et al. Inhibition of T cell proliferation by macrophage tryptophan catabolism. *J Exp Med* 1999;189(9):1363-72.
123. Zoso A, Mazza EM, Bicciato S, et al. Human fibrocytic myeloid-derived suppressor cells express IDO and promote tolerance via Treg-cell expansion. *Eur J Immunol* 2014;44(11):3307-19.
124. Ryzhov S, Novitskiy SV, Goldstein AE, et al. Adenosinergic regulation of the expansion and immunosuppressive activity of CD11b+Gr1+ cells. *J Immunol* 2011;187(11):6120-9.
125. Thiel M, Caldwell CC, Sitkovsky MV. The critical role of adenosine A2A receptors in downregulation of inflammation and immunity in the pathogenesis of infectious diseases. *Microbes Infect* 2003;5(6):515-26.
126. Hasko G, Csoka B, Nemeth ZH, et al. A(2B) adenosine receptors in immunity and inflammation. *Trends Immunol* 2009;30(6):263-70.
127. Morello S, Miele L. Targeting the adenosine A2b receptor in the tumor microenvironment overcomes local immunosuppression by myeloid-derived suppressor cells. *Oncoimmunology* 2014;3:e27989.
128. Novitskiy SV, Ryzhov S, Zaynagetdinov R, et al. Adenosine receptors in regulation of dendritic cell differentiation and function. *Blood* 2008;112(5):1822-31.
129. Iannone R, Miele L, Maiolino P, et al. Blockade of A2b adenosine receptor reduces tumor growth and immune suppression mediated by myeloid-derived suppressor cells in a mouse model of melanoma. *Neoplasia* 2013;15(12):1400-9.
130. Li J, Wang L, Chen X, et al. CD39/CD73 upregulation on myeloid-derived suppressor cells via TGF-beta-mTOR-HIF-1 signaling in patients with non-small cell lung cancer. *Oncoimmunology* 2017;6(6):e1320011.
131. Ohta A. A metabolic immune checkpoint: adenosine in tumor microenvironment. *Front Immunol* 2016;7:109.
132. Shevchenko I, Bazhin AV, Umansky V. Comment on "Adenosinergic regulation of the expansion and immunosuppressive activity of CD11b(+)Gr1(+) cells". *J Immunol* 2012;188(7):2929-30; author reply 1930.
133. Dumont A, de Rosny C, Kieu TLV, et al. Docosahexaenoic acid inhibits both NLRP3 inflammasome assembly and JNK-mediated mature IL-1 beta secretion in 5-fluorouracil-treated MDSC: implication in cancer treatment. *Cell Death Dis* 2019;10.
134. Liu Q, Wu H, Li Y, et al. Combined blockade of TGF-beta1 and GM-CSF improves chemotherapeutic effects for pancreatic cancer by modulating tumor microenvironment. *Cancer Immunol Immunother* 2020;69(8):1477-1492.
135. Horikawa N, Abiko K, Matsumura N, et al. Anti-VEGF therapy resistance in ovarian cancer is caused by GM-CSF-induced myeloid-derived suppressor cell recruitment. *Br J Cancer* 2020;122(6):778-788.
136. Sun L, Clavijo PE, Robbins Y, et al. Inhibiting myeloid-derived suppressor cell trafficking enhances T cell immunotherapy. *JCI Insight* 2019;4(7).
137. Wu T, Zhao Y, Wang H, et al. mTOR masters monocytic myeloid-derived suppressor cells in mice with allografts or tumors. *Sci Rep* 2016;6:20250.
138. Thimmulappa RK, Fuchs RJ, Malhotra D, et al. Preclinical evaluation of targeting the Nrf2 pathway by triterpenoids (CDDO-Im and CDDO-Me) for protection from LPS-induced inflammatory response and reactive oxygen species in human peripheral blood mononuclear cells and neutrophils. *Antioxid Redox Signal* 2007;9(11):1963-70.
139. Adeshakin AO, Liu W, Adeshakin FO, et al. Regulation of ROS in myeloid-derived suppressor cells through targeting fatty acid transport protein 2 enhanced anti-PD-L1 tumor immunotherapy. *Cell Immunol* 2021;362:104286.
140. Al-Khami AA, Zheng L, Del Valle L, et al. Exogenous lipid uptake induces metabolic and functional reprogramming of tumor-associated myeloid-derived suppressor cells. *Oncoimmunology* 2017;6(10):e1344804.
141. Ben-Meir K, Twaik N, Baniyash M. Plasticity and biological diversity of myeloid derived suppressor cells. *Curr Opin Immunol* 2018;51:154-161.
142. Chen Y, Qian J, He Q, et al. mTOR complex-2 stimulates acetyl-CoA and de novo lipogenesis through ATP citrate lyase in HER2/PIK3CA-hyperactive breast cancer. *Oncotarget* 2016;7(18):25224.
143. Won WJ, Deshane JS, Leavenworth JW, et al. Metabolic and functional reprogramming of myeloid-derived suppressor cells and their therapeutic control in glioblastoma. *Cell Stress* 2019;3(2):47-65.
144. Wang Y, Jia A, Bi Y, et al. Metabolic regulation of myeloid-derived suppressor cell function in cancer. *Cells* 2020;9(4).
145. Fujita M, Kohanbash G, Fellows-Mayle W, et al. COX-2 blockade suppresses gliomagenesis by inhibiting myeloid-derived suppressor cells. *Cancer Res* 2011;71(7):2664-74.
146. Rodriguez PC, Ochoa AC. Arginine regulation by myeloid derived suppressor cells and tolerance in cancer: mechanisms and therapeutic perspectives. *Immunol Rev* 2008;222(1):180-191.
147. Langle YV, Balarino NP, Belgorosky D, et al. Effect of nitric oxide inhibition in Bacillus Calmette-Guerin bladder cancer treatment. *Nitric Oxide* 2020;98:50-59.
148. Marigo I, Bosio E, Solito S, et al. Tumor-induced tolerance and immune suppression depend on the C/EBPbeta transcription factor. *Immunity* 2010;32(6):790-802.
149. Parker KH, Beury DW, et al. Myeloid-derived suppressor cells: critical cells driving immune suppression in the tumor microenvironment. *Adv Cancer Res* 2015;128:95-139.
150. Wise DR, Thompson CB. Glutamine addiction: a new therapeutic target in cancer. *Trends Biochem Sci* 2010;35(8):427-33.
151. Nefedova Y, Fishman M, Sherman S, et al. Mechanism of all-trans retinoic acid effect on tumor-associated myeloid-derived suppressor cells. *Cancer Res* 2007;67(22):11021-11028.
152. Griffin MD, Lutz WH, Phan VA, et al. Potent inhibition of dendritic cell differentiation and maturation by vitamin D analogs. *Biochem Biophys Res Commun* 2000;270(3):701-8.
153. Chen Y, Liu W, Sun T, et al. 1,25-Dihydroxyvitamin D promotes negative feedback regulation of TLR signaling via targeting microRNA-155-SOCS1 in macrophages. *J Immunol* 2013;190(7):3687-95.
154. Wiers KM, Ridley Lathers DM, Wright MA, et al. Vitamin D3 treatment to diminish the levels of immune suppressive CD34+ Cells increases the effectiveness of adoptive immunotherapy. *J Immunother* 2000;23(1):115-124.
155. Constantinou C, Papas A, Constantinou AI. Vitamin E and cancer: an insight into the anticancer activities of vitamin E isomers and analogs. *Int J Cancer* 2008;123(4):739-752.

156. Prasad KN, Kumar B, Yan X-D, et al. α -tocopheryl succinate, the most effective form of vitamin E for adjuvant cancer treatment: a review. *J Am College Nutr* 2003;22(2):108-117.
157. Kang TH, Knoff J, Yeh WH, et al. Treatment of tumors with vitamin E suppresses myeloid derived suppressor cells and enhances CD8+ T cell-mediated antitumor effects. *PLoS One* 2014;9(7):e103562.
158. Li L, Wang L, Li J, et al. Metformin-induced reduction of CD39 and CD73 blocks myeloid-derived suppressor cell activity in patients with ovarian cancer. *Cancer Res* 2018;78(7):1779-1791.

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