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Myeloid metabolism and its role in immunotherapy of cancer

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ABSTRACT

The proper functioning of the immune system requires an adequate balance between myeloid and lymphoid populations. Tumor growth alters this balance, also through the dramatic expansion of immunosuppressive myeloid populations, which block specific immunity, fueling tumor growth and dissemination and limiting the effectiveness of antitumor therapies, including immunotherapy. Tumors alter the expansion and functions of myeloid cells by acting locally in the tumor microenvironment, as well as on myeloid progenitors, through the manipulation of metabolic traits that govern their functions. The understanding of these metabolic alterations and their clinical translation is expected to offer new valid therapeutic options.

INTRODUCTION

Immune functions rely on the availability of energy metabolism, specifically of ATP, which in normoxia is mainly assured by the mitochondrial-dependent oxidative phosphorylation pathway, while in hypoxia is partially compensated by adaptations towards anaerobic pathways, including glycolysis.[1]

Notably, myeloid cells adapt metabolically better than lymphoid cells under oxygen-deficient conditions, thus maintaining their viability and cellular functions.[2] In cancer, this metabolic prerogative favors a reduced infiltration of cytotoxic CD8+T cells, while increasing the frequency and activity of myeloid suppressor cells,[3–5] capable of compromising antitumor immunity and limiting the efficacy of immunotherapy.[6] Strikingly, the trophic action of hypoxia on innate immune cells is reminiscent of early evolutionary steps, during which the basic structure of the eukaryotic cell, as well as early innate defense mechanisms,[7] evolved in low oxygen tension, thus recalling the trophic action of tumor hypoxia on suppressor myeloid cells, as exemplified by the "accumulation" of tumor-associated macrophages (TAMs) in low oxygen regions of solid tumors.[4 5] Beyond these ancient evolutionary roots, metabolic adaptation and functional specialization of myeloid cells occurs throughout the entire life cycle (ontogenesis), including embryonic, fetal, and adult life,[8] tightly depending on the type and integrity of the tissue.[9–11] As such, pathological conditions contribute to dictating the phenotypic heterogeneity and functional inclination of myeloid populations in vivo.[12] Although the functional specialization of different myeloid populations has demonstrated prognostic significance,[6] its regulatory mechanisms and metabolic bases remain partly obscure. The continued and progressive understanding of these mechanisms remains a promising avenue for the generation of new valid therapeutic options.

Ontological origin of myeloid cells

During organogenesis, macrophages originating during fetal development from embryonic progenitors differentiate into self-regenerating subsets of tissue-resident macrophages (TRMs) that seed into all tissues and become essential for tissue growth, homeostasis and repair.[13] In adults, meanwhile, blood monocytes are derived primarily from the bone marrow, with some contribution from splenic hematopoiesis, and orchestrate defense effector and repair functions, also acquiring phenotypic traits of TRMs.[14] Embryonic development is characterized by two distinct waves. The first, primitive wave, originates in the yolk sac by week 3–4 of gestation in humans and gives rise to early myeloid progenitors that seed various tissues and generate the embryonic macrophages developing TRMs, such as microglial cells in the brain, Kupffer cells in liver and Langerhans cells in the skin, independently of hematopoietic stem cells (HSCs).[15] The second, definitive wave, arises in the embryo from self-renewing HSCs located in the aorta-gonad-mesonephros region, which later, during the development, colonize the fetal liver and ultimately the bone marrow, establishing the framework for adult hematopoiesis.[11 16]

Within the definitive hematopoietic pathway, HSCs differentiate into multipotent progenitors that subsequently give rise to common myeloid progenitors (CMPs).

CMPs serve as a critical branch point in hematopoiesis, as they can differentiate into various lineages, including erythrocytes, megakaryocytes, granulocytes, and monocytes/macrophages.[17] Recent advances have refined this classical model in mice by showing that CMPs give rise to both granulocyte-monocyte progenitors (GMPs) and monocyte-dendritic cell progenitors (MDPs), which represent parallel pathways rather than a linear hierarchy. Both GMPs and MDPs can independently generate monocytes, leading to ontogenetically distinct monocyte populations with functional and transcriptional differences.[18] GMPs give rise to granulocytes (such as neutrophils) and a subset of monocytes with pro-inflammatory potential, whereas MDPs produce monocytes as well as monocyte-derived dendritic cells. MDPs further differentiate into common monocyte progenitors (cMoPs), which are now recognized to arise downstream of MDPs, not GMPs, as previously thought. cMoPs are exclusively committed to the monocyte lineage and serve as the principal source of circulating monocytes.[19] Importantly, MDPs exhibit an intermediate expression profile of key transcription factors, such as PU.1 and IRF8, which primes them for bifurcated differentiation into both monocytes and dendritic cells.[20] This transcriptional landscape not only reflects the close ontological relationship between these mature cell types, but also exemplifies the tightly regulated interplay between intrinsic transcriptional programs and extrinsic cytokine signals that orchestrate myeloid lineage commitment.

This differentiation cascade is governed by a tightly regulated network of transcription factors and cytokine signals that dictate lineage commitment and cellular maturation under both homeostatic and pathological conditions. Among the key regulators, PU.1 plays a pivotal role in dictating myeloid-specific genes, while C/EBPα promotes granulocytic differentiation. Additionally, GATA-1 interacts with PU.1 to fine-tune the balance between myeloid and erythroid lineage specification.[19] In this scenario, MafB is crucial for driving terminal differentiation, whereas IRF8 contributes to lineage determination at various developmental stages under homeostatic or pathological conditions.[20] The coordinated expression of these factors, along with dynamic changes in cytokine receptor levels (eg, upregulation of colony-stimulating factor 1 receptor (CSF-1R) during differentiation), orchestrates the transition from progenitor cells to mature.[20]

Extrinsic signals further refine this process; growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), and interleukin-3 (IL-3) provide essential cues for survival, proliferation, and differentiation. Specifically, M-CSF, through its receptor CSF-1R, robustly drives the differentiation of GMPs into monocytes and macrophages, while GM-CSF influences the development of both macrophages and dendritic cells.[21] The precise balance between these cytokines and the intrinsic transcriptional programs ensures the generation of functionally distinct myeloid cell populations that span from embryonic progenitors through adult hematopoiesis.[22]

Monocytes and macrophages

Primitive macrophages that first emerge in the yolk sac are characterized by high expression of markers such as F4/80 and CX3CR1 with relatively low levels of CD11b. They colonize developing tissues and, in several organs, persist in adulthood through self-renewal rather than relying on replenishment from circulating monocytes.[23] Subsequently, definitive hematopoiesis in the fetal liver gives rise to monocytes that further differentiate into tissue-resident macrophages. Fetal liver-derived monocytes often display intermediate levels of F4/80 and increased CD11b expression, a profile that helps distinguish them from their yolk sac-derived counterparts.[10] For instance, in the brain, microglia exhibit high levels of CX3CR1 and Iba1, whereas Kupffer cells in the liver can be identified by markers such as Clec4F and Timd4.[24] In the adult organism, under homeostatic conditions, many tissue macrophage populations are maintained locally through self-renewal.[13] However, in response to inflammatory stimuli or injury, circulating monocytes, typically marked by high CD11b and Ly6C (in mice) or CD14 in humans, are recruited to tissues, where they differentiate into macrophages. These monocyte-derived macrophages generally acquire a distinct marker profile on maturation, such as elevated F4/80 (mouse), CD68 (human), and major histocompatibility complex (MHC)-II expression, which reflects their activated status and functional specialization.[10]

The development and maintenance of macrophages are governed by a network of extrinsic signals and transcriptional programs. Growth factors such as M-CSF/CSF-1 and interleukin-34 (IL-34) are pivotal for macrophage survival and differentiation via their common receptor, CSF-1R. IL-34, in particular, has been implicated in the maintenance of certain tissue-resident populations, notably microglia in the brain.[25] The dual origin of macrophages has profound functional implications.[20] Embryonically derived macrophages often exhibit a more quiescent, homeostatic phenotype, which is essential for tissue development and steady-state maintenance. In contrast, monocyte-derived macrophages tend to be more plastic. Indeed, microenvironmental signals can rapidly induce either a classically activated (pro-inflammatory) phenotype, characterized by markers such as CD86 and iNOS and associated with the promotion of immune responses, or an alternatively activated (anti-inflammatory) phenotype, marked by CD206 and Arg1 and involved in inflammation resolution and tissue repair.[26] In the context of cancer, the tumor microenvironment secretes chemokines and growth factors, such as C-C motif chemokine ligand 2 (CCL2), CSF-1, and GM-CSF, that recruit these bone marrow-derived monocytes and program them into TAMs which support tumorigenesis.[27] This reprogramming is marked by the upregulation of surface markers

like CD206 and CD163 and the increased production of anti-inflammatory cytokines such as IL-10 and Transforming Growth Factor-Beta (TGF-β), with transcription factors like Signal Transducer and Activator of Transcription 3 (STAT3) and Nuclear Factor-kappa B (NF-κB) playing key roles in mediating this shift.[28 29]

Recent studies suggest that alterations in the embryonic hematopoietic niche may predispose certain progenitor cells to expand as myeloid-derived suppressor cells (MDSCs) in adulthood, particularly in the presence of persistent pro-inflammatory signals.[30] As such, cancers alter the myeloid cell pool, also acting on their precursors, skewing GMP differentiation towards the accumulation of immature immunosuppressive MDSCs,[31] thereby contributing to tumor progression.[32] In particular, tumor-derived factors, such as GM-CSF, granulocyte colony-stimulating factor (G-CSF), M-CSF, IL-6, and vascular endothelial growth factor (VEGF), stimulate key molecular pathways that redirect the differentiation of GMPs. Among these, STAT3 and retinoic acid-related orphan receptor C1 (RORC1/RORγ)[33] emerge as central regulators, promoting the survival and proliferation of MDSCs, while preventing their final maturation.[14 33] Understanding the ontogenetic pathways of MDSCs highlights the crucial roles of both the hematopoietic environment, from the embryonic niche to the adult bone marrow, and external signals, such as cytokines and growth factors, in determining cell fate, while the identification of key molecular pathways, particularly STAT3, NF-κB, RORC1/RORγ and CCAAT/enhancer-binding protein beta (C/EBPβ), not only delineates the ontogeny of MDSCs but also provides promising therapeutic targets for inhibiting their expansion and immunosuppressive functions.

Neutrophils

Neutrophils are produced in vast numbers in the bone marrow and are characterized by their short lifespan and rapid response to inflammatory signals. Their development is regulated primarily by G-CSF, which promotes both their proliferation and maturation from the GMP and to the mature neutrophils.[34] Concerning neutrophil origin, the development and utilization of cutting-edge technologies, including high-dimensional analyses, have made it possible to uncover, in humans, novel $CD34^{+}$ and $CD34^{dim/-}CD66b^{-}CD38^{+}CD64^{dim}CD115^{-}$ neutrophil-committed progenitors (NCPs).[35 36] The discovery of these new cell compartments, standing at stages much earlier than the promyelocytes along the neutropoiesis cascade, challenges the vision of $CD45RA^{+}$GMPs as obligatory compartments to generate neutrophils since some NCPs are $CD45RA^{-}$.[37] Consistently, NCPs have been shown to be involved in two maturation pathways[36] whose biological meaning(s) is/are still unknown.

Immunosuppressive polymorphonuclear cells

Polymorphonuclear (PMN)-MDSCs and tumor-associated neutrophils (TANs) are gaining a major interest in cancer research as their frequency in patients often correlates with tumor severity, prognosis, and/or lack of responsiveness to treatment.[38] However, a crucial issue to clarify is the origin of protumor TANs, as we need to understand whether they derive from the attraction to the tumor microenvironment (TME) of circulating normal neutrophils, immature bone marrow/splenic neutrophils, PMN-MDSCs or local tissue neutrophils. An important advance has been the demonstration that, in several human cancers, including head and neck cancer (HNC),[39] non-small cell lung cancer (NSCLC),[39] urological cancer[40] and multiple myeloma,[41] it is the mature fraction of PMN-MDSCs responsible for the immunosuppressive functions attributed to PMN-MDSCs.[42]

Moreover, bulk RNA sequencing experiments examining this PMN-MDSC compartment in patients with NSCLC and HNC, as well as in healthy subjects receiving G-CSF for stem cell mobilization (named G-CSF-treated donors (GDs)), found that all these different PMN-MDSC populations share a common genetic signature.[43] Notably, analysis of the related gene signature by the Gene Ontology term enrichment, has found it to be associated with metabolic processes and response to oxidative stress that typically characterize cancer-associated myeloid cells, including protumor TANs (figure 1).[43]

Functional specializations of myeloid cells

While the adaptation of macrophages to metabolic cues in homeostasis shows largely predictable tissue-specific differentiation, pathological conditions substantially contribute to the differentiation complexity of tissue macrophages.[44] Hence, physiological events (such as ontogenesis) and pathological conditions (including allergic and chronic inflammation, tissue repair, infection and cancer) concur to dictate phenotypic heterogeneity and the functional skewing of macrophage populations in vivo.[26] TRMs have a variety of roles in maintaining tissue homeostasis, extracellular matrix (ECM) remodeling, and inflammation.[10] Across the fat, dermis, heart, lung and mesenteric membranes, it is thought that interstitial TRMs can be subdivided into at least two major subpopulations, $LYVE1^{hi}CX3CR1^{lo}MHC\text{-}II^{lo/int}$ and $LYVE1^{lo}CX3CR1^{hi}MHC\text{-}II^{hi}$ cells, with $LYVE1^{hi}CX3CR1^{lo}MHC\text{-}II^{lo/Int}$ TRMs reported to be involved in ECM remodeling.[45 46] However, it is not fully understood how TRM subsets and monocyte-derived macrophages (MDMs) might be uniquely poised to respond to tissue damage or pathologic conditions. TRMs have been historically linked to host defense/innate immunity and pathogenesis of several devastating chronic inflammatory diseases (eg, atherosclerosis, type 2 diabetes, Alzheimer's disease, and cancer).[20 47–49] However, TRMs have broader, often overlooked functions beyond immunity. They integrate various environmental cues in order to exert supportive activities that help other tissue-resident cells function at a steady state.[44] In addition, TRMs are considered one of the main accessory cells constituting the "minimal necessary tissue unit", alongside

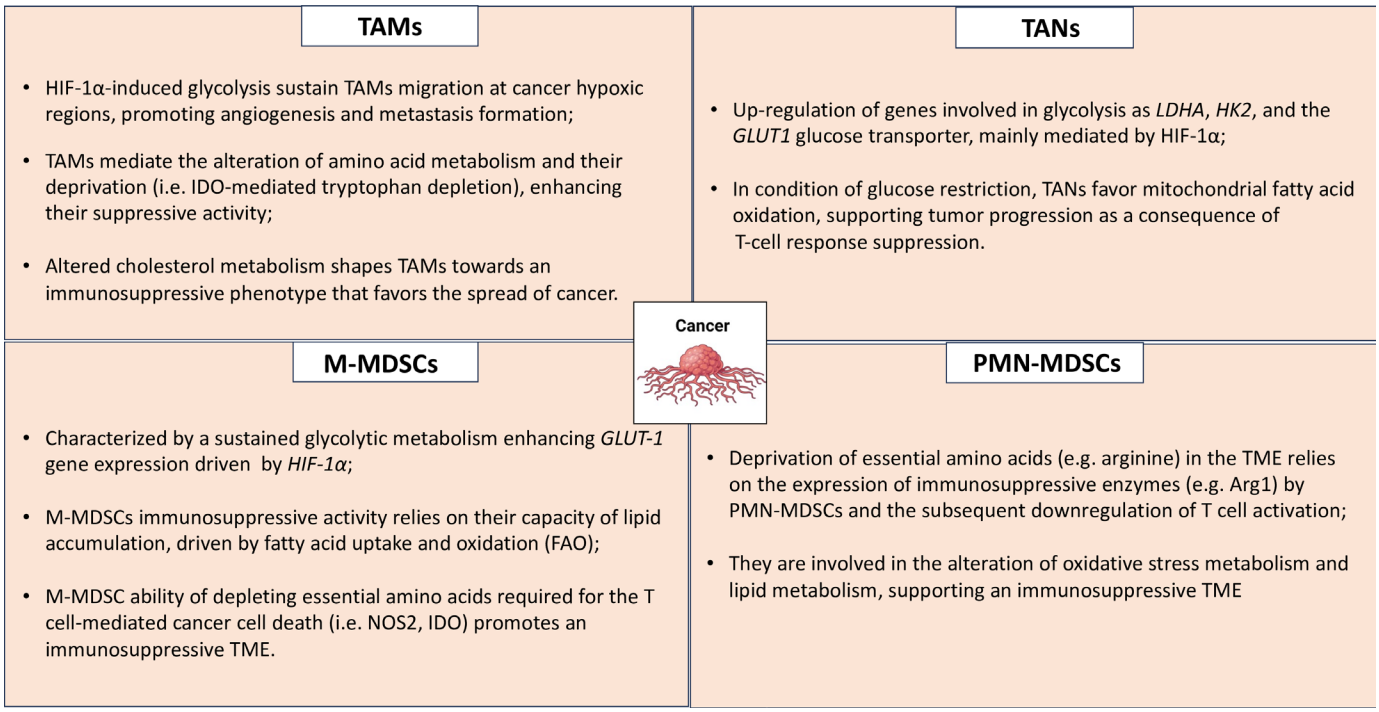

Figure 1 Principal metabolic signatures characterizing myeloid immunosuppression in cancer. Created by BioRender. FAO, fatty acid oxidation; GLUT1, glucose transporter; HIF1α, hypoxia-inducible factor 1 alpha; HK2, hexokinase 2; IDO, indoleamine 2,3-dioxygenase 1; LDHA, lactate dehydrogenase A; M-MDSCs, monocytic-myeloid-derived suppressors; NOS2, nitric oxide synthase; PMN-MDSCs, polymorphonuclear-myeloid derived suppressor cells; TAMs, tumor-associated macrophages; TANs, tumor-associated neutrophils; TME, tumor microenvironment.

endothelial, stromal, and tissue-specific primary cells (eg, hepatocytes in the liver).[44 50]

MDMs are specialized in the elimination of infectious agents, through innate defense mechanisms and the ability to activate adaptive immune response. Furthermore, MDMs play a relevant role in the promotion of wound healing and maintenance of host tissue homeostasis. During inflammation, MDMs may become dominant, and dysregulation of their functional program could fuel non-resolving inflammation and exacerbate tissue damage.[49]

Macrophages exhibit a variety of functions due to their recognized functional plasticity, which has been oversimplified in the "M1/M2 macrophages" nomenclature.[51] The definition of an M1 (classically activated, pro-inflammatory) macrophage is based on macrophages cultured ex vivo in the presence of LPS and interferon (IFN)-γ. In culture, these M1-stimulated macrophages release high amounts of IL-12 and low levels of IL-10. By contrast, the definition of an M2 (alternatively activated, anti-inflammatory) macrophage is based on the ex vivo culture of macrophages in the presence of anti-inflammatory cytokines and products (ie, IL-4, IL-10, IL-13, and glucocorticoid hormones) and usually are associated with an anti-inflammatory profile, releasing high levels of IL-10 and low levels of IL-12.[52] However, these states do not exist in tissues, as macrophages activate and adapt their functional state by perceiving microenvironmental cues through a variety of innate immune receptors, including Fc receptors, complement receptors, and various pattern recognition receptors such as mannose receptor, scavenger receptor, and toll-like receptors.[48] Macrophage functions can also evolve dynamically under the control of cell-intrinsic mechanisms, as observed during the spontaneous recovery of homeostatic functions in macrophages undergoing lipopolysaccharide-mediated tolerance.[53] During tumor development, dynamic adaptation of macrophage functions may also occur in conjunction with the remodeling of tumor microphysiology (with changing oxygen availability, pH, glucose levels, amino acids, lipid metabolism, and inflammatory signals), and as a result of hematopoietic changes (eg, emergency hematopoiesis) that influence the differentiation and availability of myeloid progenitors.[33]

Metabolic traits of myeloid cells in cancer

The high metabolic activity of tumor cells promotes an immunosuppressive TME. Among the diverse myeloid cells populating the TME, MDSCs and TAMs are strong promoters of tumor growth and spread, both sharing immunosuppressive properties.[54] Interestingly, to exert their activity and functions, MDSCs and TAMs undergo metabolic reprogramming, which includes alteration of glucose, lipid, and amino acid metabolism, simultaneously altering the surrounding environment and thus promoting tumor progression.[54]

Glucose metabolism

The aberrant proliferation of tumor cells relies on energy production via aerobic glycolysis, which increases glucose

uptake and, consequently, ATP production.[55] Under the hypoxic condition observed in the TME, the hypoxia-inducing factor-1α (HIF-1α) enhances the glucose transporter and glycolytic enzyme expression while hampering mitochondrial oxygen consumption. This metabolic reprogramming, known as the Warburg effect, deeply affects the tumor immune landscape.[56]

Indeed, increased aerobic glycolysis fosters the differentiation of MDSCs in the bone marrow, while also sustaining their subsequential expansion and activity.[57] Additionally, glycolytic intermediates promote MDSC survival and recruitment in the tumor. For instance, phosphoenolpyruvate protects MDSCs from the reactive oxygen species in the TME,[58] while lactate enhances their infiltration in the tumor, further shaping the immunosuppressive environment.[59] Moreover, in line with the findings of Geeraerts *et al*, lactate functions not merely as a product of glycolysis but also as an alternative carbon source, enhancing oxidative metabolism in specific TAM subsets, while suppressing it in others. This dual role of lactate underscores its critical impact on both the metabolic programming and functional polarization of TAMs within the TME.[60] Notably, MDSCs activation strongly depends on high glucose uptake, exhibiting a metabolic profile resembling the one observed in tumor cells. Numerous studies have shown that activation of HIF-1α in MDSCs is crucial to promote a glycolytic metabolism by upregulating glucose transporter-1 (GLUT-1), accelerating glycolysis and lactate production, which acidifies the TME.[61] Additionally, several other factors can influence MDSCs glycolysis. Nicotinamide adenine dinucleotide (NAD)-dependent deacetylase sirtuin 1 (SIRT1) promotes HIF-1α-induced glycolysis required for MDSCs differentiation, while its deficiency enhances MDSCs immunosuppression in lymphoma and melanoma murine models.[62]

Conversely, AMP-activated protein kinase (AMPK) counteracts glycolysis through the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of the rapamycin (mTOR) pathway, favoring oxidative phosphorylation (OXPHOS).[63] Moreover, Yali *et al* demonstrated that methionine enkephalin, an endogenous neuropeptide, hinders glycolysis through the downregulation of the PI3K-AKT-mTOR pathway, ultimately leading to the inhibition of MDSCs immunosuppressive functions. Of relevance, the interplay between cancer cell metabolism and the functional specialization of macrophages was highlighted by the observation that lactic acid produced by tumor cells, as a by-product of aerobic or anaerobic glycolysis, promotes the polarization of TAMs to acquire tumor-promoting functions.[64] Tumor-promoting, wound-healing macrophages primarily rely on OXPHOS and fatty acid oxidation (FAO) to exert their activity. In contrast, the glucose uptake in TAMs is significantly higher compared with tumor cells and the other immune cells infiltrating the tumor. Strikingly, TAMs in MMTV-PyMT breast cancer and Lewis lung carcinoma exhibit an elevated glycolytic rate dependent on the expression of glycolytic enzymes such as the pyruvate kinase isoform PKM2, hexokinase 2 (HK2) and enolase 1.[65] Moreover, the hypoxic environment of the tumor activates HIF-1α, which in turn promotes the gene expression of crucial players in the glycolytic pathway (ie, pyruvate dehydrogenase kinase 1 (PDK1), phosphoglycerate kinase 1, GLUT1, glucokinase).[66] Interestingly, while TAMs rely on HIF-1α-induced glycolysis to migrate into hypoxic regions of the TME, where they promote angiogenesis and metastatic spread,[65 67] low oxygen concentration increases their CXCL12 receptor (CXCR4) expression in TAMs, supporting their accumulation in hypoxic regions of the tumor.[4]

Lipid metabolism

Emerging evidence indicates that the immunosuppressive functions of MDSCs within the TME rely on lipid accumulation, driven by FAO, which increases mitochondrial mass and the oxygen consumption rate.[68] Previous studies have shown that inhibition of MDSCs FAO hampers their ability to produce immunosuppressive molecules and hinders T-cell suppression, suggesting that FAO upregulation is tightly associated with the immunosuppressive function of MDSCs.[69] Additionally, fatty acid metabolism plays a pivotal role in TAMs polarization.[70 71] For instance, fatty acid accumulation, through the fatty acid transporter CD36, enhances the phosphorylation of STAT6.[72] Moreover, arachidonic acid derivatives, such as prostaglandin E2, upregulate the nuclear accumulation of p50 NF-κB leading to nitric oxide (NO)-mediated immune suppression.[73] Importantly, a study by Clement *et al* suggested that a high-fat diet, characterized by elevated cholesterol and fatty acid content, induces the production of the endocrine factor leptin. Leptin, in turn, drives IFN-γ production in cancer cells, ultimately promoting programmed death-ligand 1 (PD-L1) expression in MDSCs.[74]

Tumor cells secrete inflammatory mediators, such as G-CSF and GM-CSF, that promote STAT3 and STAT5 activation. This signaling cascade induces the uptake of exogenous lipids in MDSCs by upregulating the expression of the fatty acid transporter protein 2, a long-chain fatty acid transporter.[68] Moreover, STAT3 signaling leads to the activation of the proto-oncogene serine/threonine kinase PIM1, whose activity promotes the peroxisome proliferator-activated receptor-γ, ultimately regulating the expression of CD36 and facilitating lipid accumulation in MDSCs.[75] Additional studies suggest the crucial role of the liver X receptor (LXR)/apolipoprotein E (ApoE) axis in regulating MDSC functions. LXR acts as a master regulator of lipid metabolism, controlling the expression of genes involved in cholesterol efflux, FAO and lipid transport. Among its target genes, ApoE binds to LDL receptors to induce lipoprotein transportation, standing out as a crucial factor in lipid redistribution and metabolism.[76] Within the TME, LXR activation enhances ApoE expression, which, in turn, drives lipid accumulation in MDSCs. Studies in B16-F10 melanoma tumor-bearing mice have shown that genetic deletion of ApoE impairs

MDSCs accumulation and diminishes their suppressive activity, effectively restoring T-cell function. Conversely, pharmacological activation of LXR with agonists appears to induce apoptosis in MDSCs, leading to delayed tumor progression. This paradoxical effect suggests that while LXR-driven lipid metabolism supports MDSCs function, excessive activation may push these cells toward metabolic stress and cell death.[77] Of note, tumor cells can also produce hyaluronic acid (HA) that promotes cholesterol efflux from TAMs through the ATP-binding cassette (ABC) transporters ABCA1/ABCG, leading to enhanced IL-4 signaling in macrophages, while hampering IFN-γ-induced gene expression. Consequently, macrophages preferentially differentiate toward a protumoral phenotype, sustaining immune suppression and tumor progression.[78]

In conclusion, targeting metabolic pathways like FAO and LXR/ApoE signaling offers a promising approach to modulate MDSCs and TAMs function, potentially improving cancer immunotherapy outcomes.

Amino acid metabolism

Another crucial metabolic pathway for tumor-associated myeloid cells (TAMCs)-dependent immune suppression is represented by the metabolism of amino acids. Specifically, MDSCs within the TME cause the depletion of amino acids required for the T cell-mediated cancer cell death, thereby contributing to the maintenance of an immunosuppressive microenvironment.[79] Among these, arginine (Arg) is a fundamental constituent of the ζ chain of the T-cell receptor. The production and secretion of inflammatory mediators such as IFN-γ, IL-4 and IL-10 induce the MDSCs to decrease the availability of Arg in the TME.[80] Specifically, IFN-γ-mediated MDSCs activation leads to the upregulation of cationic amino acid transporter 2 enhancing Arg uptake, while IL-4 and IL-10 promote the activity of the enzyme arginase-1, which is responsible for Arg degradation. Consequently, T-cell receptor expression is hindered by the depletion of Arg in the tumor, causing the T cells to fail to recognize tumor antigens.[79 81] In addition, the inducible NO synthase (iNOS) metabolism is also implicated in MDSCs-mediated Arg depletion. Indeed, while Arg1 catalyzes Arg conversion into urea and L-ornithine, studies have demonstrated that iNOS catalyzes the conversion of Arg into NO and L-citrulline.[82 83] Interestingly, PMN-MDSCs rely on Arg1 to promote Arg depletion and the consequential downregulation of T-cell receptor,[84] while in M-MDSCs Arg depletion mainly depends on iNOS activity, which promotes NO production.[85] In addition to Arg, tryptophan (Trp) metabolism plays a crucial role in supporting T-cell proliferation following activation. At the same time, its catabolism sustains the immunosuppressive properties of MDSCs through multiple mechanisms. Within the TME, MDSCs limit Trp availability by upregulating the enzymes indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase (TDO).[86] These enzymes catalyze the first and rate-limiting step of Trp degradation, leading to the production of kynurenine (Kyn), a key immunoregulatory metabolite.[87] Kyn, in turn, activates the aryl hydrocarbon receptor (AhR), which exerts immunomodulatory effects and further induces IDO1 expression, establishing a positive feedback loop that amplifies Trp catabolism.[88] Additionally, kynurenine 3-monooxygenase facilitates the conversion of Kyn into 3-hydroxykynurenine, a precursor essential for the de novo synthesis of NAD+, protecting MDSCs, within the TME, against oxidative stress.[87] Ultimately, the depletion of Trp, caused by MDSCs activity, results in T-cell cycle arrest at the G1 phase, thereby impairing effective T-cell proliferation and reinforcing immune suppression within the tumor.[89]

Another essential pathway involves glutamine (Gln), the second most used carbon source for energy production. A recent study highlighted the centrality of Gln in guiding the MDSCs-mediated immune suppression. In particular, inhibiting the glutaminolysis pathway through a Gln analog causes MDSCs to undergo apoptosis and polarization towards a pro-inflammatory phenotype characterized by an incremented antigen presentation.[90] Accordingly, hampering glutaminase 1 activity, which promotes the production of α-ketoglutarate (α-KG) from Gln, can profoundly affect MDSCs expansion and formation.[91] Moreover, research on immuno-metabolism has identified α-KG as a crucial promoter of the differentiation of anti-inflammatory macrophages. Indeed, α-KG is required for the demethylation of histone H3 at lysine 27 (H3K27), which, when trimethylated, inhibits the transcription of genes related to alternative macrophage activation. Additionally, α-KG stimulates the prolyl hydroxylase enzyme, which post-translationally modifies IKKβ (inhibitor of nuclear factor kappa-B kinase subunit beta), disrupting the NF-κB pathway and limiting the pro-inflammatory functions of macrophages.[92]

Within the TME, featured by nutrient-deprived and hypoxic conditions, neutrophils also undergo a metabolic reprogramming,[93] shifting towards a protumor phenotype characterized by an altered mitochondrial, lipid, and amino acid metabolism, as well as anaerobic glycolysis. In this context, metabolic reprogramming in neutrophils is largely driven by HIF-1α,[94] which ensures that neutrophils continue to perform their functions in an environment with limited nutrient and oxygen availability. For instance, the scRNA TAN subcluster identified by Wang *et al* in pancreatic ductal adenocarcinoma (PDAC) was found to strongly express genes involved in glycolysis such as *LDHA*, *HK2*, and the *GLUT1* glucose transporter, suggesting a switch to glycolysis.[95] In contrast, HIF-1α knockout (KO) in a murine model of PDAC was found to significantly diminish tumor burden and weight, while HIF-1α KO MDSCs recuperated antitumor T-cell responses, ultimately leading to an effective tumor inhibition after radiotherapy.[96] Another example occurs when TANs, by adapting their metabolism to glucose restriction in the TME, use mitochondrial fatty acid oxidation to generate energy and promote tumor progression, suppressing T-cell responses.[97] Lipid metabolism is, in

fact, directly related to the suppressive activity of PMN-MDSCs.[98] Additional studies have shown that selective inhibition of fatty acids can eliminate the suppressive capacity of PMN-MDSCs lead to a notable reduction in tumor growth, especially if combined with immune checkpoint inhibitor (ICI) therapy.[99] Thus, by elucidating the metabolic alterations of PMN-MDSCs, novel therapeutic targets for modulating immune responses and improving cancer treatment outcomes could emerge.

Metabolic pathways of emergency myelopoiesis

Metabolic alterations can influence myeloid functions both locally (ie, TME) and systemically. Our group uncovered the role of rRORC1/RORγ, as orchestrator of emergency protumoral myelopoiesis in cancer.[33] We described that RORC1 induces C/EBPβ as well as the key transcriptional mediators of myeloid progenitor commitment and differentiation to the monocytic/macrophage lineage (IRF8 and PU.1). Furthermore, RORC1 supported tumor-promoting innate immunity by protecting MDSCs from apoptosis, mediating TAM differentiation, and limiting tumor infiltration by mature neutrophils.[33] Accordingly, pharmacological inhibition of RORC1 in the hematopoietic compartment prevented cancer-driven myelopoiesis, resulting in inhibition of tumor growth and metastasis.

Accordingly, we recently demonstrated that RORγ acts as a key sensor of cancer-related lipid disorders and that cancer and hypercholesterolemic diet can independently or cooperatively activate RORγ-dependent expansion of MDSCs and tumor-supportive TAMs, thereby supporting cancer spread.[100] Importantly, genetic or pharmacological inhibition of cholesterol levels prevented MDSC expansion, TAMs accumulation and tumor progression in an RORγ-dependent manner, triggering specific antitumor immunity and enhancing the efficacy of immunotherapy. Since RORγ is a putative interconnector between circadian clocks and metabolism,[101] the temporally resolved pharmacological control of this nuclear receptor appears particularly intriguing.[101]

More recently, it has been shown that a novel population of prometastatic TAMs, endowed with a high rate of heme catabolism, emerges during cancer-induced emergency myelopoiesis, under the control of M-CSF-dependent activation of the transcription factor Nrf2.[102] Of relevance, inhibition of $F4/80^{+}HO\text{-}1^{+}$ TAMs recruitment or myeloid-specific deletion of HO-1 blocks metastasis formation and improves anticancer immune-checkpoint blockers (ie, anti-programmed cell death protein-1 (PD-1)).

Finally, metabolic pathways appear to control the maturation and exit of myeloid progenitors from the bone marrow to the periphery. In this regard, we reported that in myeloid cells, M-CSF increases the levels of nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in the NAD salvage pathway, which acts as a negative regulator of the CXCR4 retention axis of hematopoietic cells in the bone marrow, through an NAD/SIRT1-mediated inactivation of HIF-1α-driven CXCR4 gene transcription.[103] This leads to the mobilization of immature MDSCs and increases their production of suppressive NO. Pharmacological inhibition or myeloid-specific ablation of NAMPT prevented MDSCs mobilization, reactivated specific antitumor immunity, and increased the antitumor activity of ICIs.

MYELOID CELLS METABOLISM AS AN IMMUNOTHERAPEUTIC TARGET IN CANCER

Metabolic myeloid cells reprogramming in the nutrient-deprived TME drives immunosuppression, tumor progression and therapy resistance; thus, targeting these pathways may reprogram them into antitumorigenic phenotypes, boosting immunotherapy efficacy.[104 105]

Glucose metabolism

As compared with naïve myeloid cells, tumor-infiltrating MDSCs and TAMs exhibit increased glycolytic activity, predominantly driven by HIF-1α and PI3K/AKT/mTOR signaling, increasing lactate production and impairing T cells, thus promoting tumor progression and ICIs resistance.[61 106] Preclinical studies show that glycolysis inhibition via 2-deoxy-D-glucose (2-DG), a competitive HK inhibitor, reprograms TAMs by down-regulating *ARG1*, *Fizz*, *Mrc1*, and *VEGF*, inciting their pro-inflammatory metabolic shift.[107] Sasaki *et al* engineered 2-DG-loaded poly (lactic-co-glycolic acid) nanoparticles with potent antitumor activity in hepatocellular carcinoma, promoting CXCL9/CXCL10 production via the AMPK-EZH2-H3K27me3 axis, enhancing T-cell cytotoxicity, and augmenting sorafenib and anti-PD-1 efficacy.[108] Additionally, the monocarboxylate transporter 1 (MCT1) inhibitor, AZD3965, limits lactate export, reducing tumor acidity and improving ICIs response in melanoma and breast cancer.[109] PKM2 regulates PD-L1 expression in TAMs in pancreatic cancer supporting tumor cell proliferation[110] and its lactylation prevents macrophage inflammatory activation.[111] Notably, the PKM2 inhibitor shikonin mitigates chemoresistance in lung, melanoma, and bladder cancers.[112] Dichloroacetate (DCA), a PDK inhibitor, reduces lactate-driven ARG1 expression in macrophages, enhancing T-cell cytotoxicity and boosting Poly(I:C) immunotherapy efficacy.[113] PX-478, a selective HIF-1α inhibitor, disrupts tumor glycolysis, enhancing radiotherapy in prostate cancer, suppressing metastasis in small cell lung cancer, and promoting immunogenic cell death in pancreatic cancer.[114 115] HIF-1α inhibition also triggers a shift from immunosuppressive phenotypes and reduces PD-1/PD-L1 expression.[116]

Clinically, a phase II trial (NCT01386632) is assessing the safety and efficacy of DCA in combination with chemoradiation in advanced head and neck squamous cell carcinoma and glioblastoma (NCT05120284).[117] 2-DG is in phase I trials (NCT00096707, NCT00633087) alone or in combination with docetaxel in advanced solid tumors, though its efficacy in prostate cancer is limited.[118] Additionally, PX-478 (NCT00522652) is undergoing phase I evaluation in solid tumors and lymphoma. AZD3965 has

been assessed in metastatic solid tumors (NCT01791595 results not been reported) and in lymphoma with a moderate DCR.

Tricarboxylic acid cycle and oxidative phosphorylation

Pharmacological inhibition of OXPHOS has been substantiated to undermine the metabolic fitness of immunosuppressive myeloid subsets, thereby potentiating antitumor immune responses.[104]

In mouse models, metformin, an inhibitor of mitochondrial complex I preventing the production of mitochondrial ATP, curbs MDSCs accumulation, unleashing tumor infiltration of CD8+T cells.[119] It also orchestrates the metabolic reprogramming of TAMs, from an anti-inflammatory to a pro-inflammatory phenotype via the AMPK/mTOR/NF-kB signaling axis[120]; interestingly, mannose-modified murine macrophage-derived microparticles loaded with metformin, efficiently target TAMs, inducing the acquisition of pro-inflammatory functions, recruitment of $CD8^+$ T cells and boosting anti-PD-1 efficacy.[121] Additionally, metformin was reported to overcome primary resistance to anti-PD-1 in STK11 mutant non-small cell lung cancer via AXIN1-based STING ubiquitination.[122] CPI-613, a lipoate analog that inhibits pyruvate dehydrogenase (PDH) and α-KG dehydrogenase, has been shown to suppress OXPHOS-dependent MDSCs function, engendering enhanced T-cell activation and restraining tumor growth in melanoma model.[123] Clinical trials are evaluating the therapeutic prowess of OXPHOS inhibitors with immunotherapy. A phase I trial (NCT03291938) of IACS-010759, a selective complex I inhibitor, in patients with advanced solid tumors and with relapsed/refractory acute myeloid leukemia (NCT02882321), showed limited efficacy at tolerated doses, leading to discontinuation.[124]

Amino acid metabolism

Glutamine metabolism targeting with ICIs boosts antitumor immunity by suppressing tumor metabolism and reprogramming T-cell glucose metabolism, epigenetics, and cytotoxicity.[125]

JHU-083, a prodrug of the glutamine antagonist DON (6-diazo-5-oxo-L-norleucine), effectively suppresses murine triple-negative breast cancer progression, especially with immunotherapy, by reducing G-CSF secretion, limiting MDSCs recruitment and fostering a pro-inflammatory TME, characterized by an increased prevalence of pro-inflammatory TAMs.[90 125] It also induces MDSCs apoptosis and reprograms both MDSCs and TAMs into antitumor phenotype. Notably, JHU-083 enhances anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) efficacy in resistant tumors.[125] Interestingly, the novel broad-acting glutamine antagonist DRP-104 (Sirpiglenastat), is under clinical evaluation with atezolizumab (NCT04471415). Preclinical studies show that blocking glutamine metabolism enhances ICIs efficacy. GLS inhibition by CB-839 (telaglenastat) upregulates PD-L1 via glutathione depletion and SERCA inhibition, impairing cytotoxic T cell.[126] Moreover, CB-839 also boosts chimeric-antigen receptor (CAR)-T cell activity and synergizes with ICIs to enhance T cell-mediated melanoma suppression.[127] Additionally, V-9302 amplifies anti-PD-1 efficacy in breast cancer models.[128] Ongoing trials assess CB-839 in various tumors, alone or with PARP inhibitors, chemotherapy, or TKIs. In metastatic renal cell carcinoma, the CANTATA (NCT03428217) and ENTRATA (NCT03163667) studies evaluated CB-839 with cabozantinib, a VEGF receptor inhibitor, and the mTOR inhibitor everolimus, respectively. CANTATA showed no significant differences between cabozantinib alone or in combination therapy, but prior anti-PD-1 or anti-PD-1/CTLA-4 treatment was associated with higher objective response rate (32% and 37% vs 20%) and a 2-month progression-free survival extension, suggesting that targeting glutamine metabolism may overcome immunotherapy resistance.[129] Arg metabolism is another key target. CB-1158, an ARG1 inhibitor, enhances immunotherapy efficacy in preclinical melanoma, colorectal and breast cancer models by mitigating myeloid cell-mediated T-cell suppression.[130] Notably, its administration alone or in combination with chemotherapy, adoptive cell transfer, or ICIs, boosts $CD8^+$ T and natural killer (NK) cell infiltration, restores pro-inflammatory cytokine secretion, and inhibits tumor growth.[130] Similarly, ADI-PEG20, an Arg-depleting enzyme, enhances T-cell infiltration, suppresses regulatory T cells (Tregs), and reduces melanoma growth, both as monotherapy and in combination with anti-PD-1.[131] Clinical trials are evaluating CB-1158 (NCT02903914, NCT03910530, NCT03837509, NCT03361228) and ADI-PEG20 (NCT03254732) in advanced solid tumors.

Trp metabolism via the Kyn pathway is a key immunosuppressive mechanism in the TME, driven by IDO. IDO-mediated Trp depletion results in Kyn accumulation, which activates AhR in TAMs and MDSCs, reinforcing their suppressive activity.[86] Signaling induces TAM polarization towards a tumor-supporting phenotype, MDSC expansion, and T-cell inhibition, making it a promising immunotherapy target.[132] IDO inhibitors (epacadostat, linrodostat, indoximod) have been reported to enhance ICIs efficacy by reducing Kyn accumulation and restoring T-cell responses.[133] In glioblastoma and lung cancer models, IDO blockade limits MDSCs recruitment, shifts TAMs to a pro-inflammatory state and enhances NK and T cell-mediated tumor rejection, with epacadostat showing immune-dependent tumor suppression.[133] While phase I/II trials indicated synergy between IDO inhibitors and anti-PD-1 therapy, the phase III ECHO-301 trial (NCT02752074) of epacadostat with pembrolizumab in metastatic melanoma failed to improve survival, highlighting the need for better patient stratification.[134] Likewise, a phase I trial (NCT02752074) of navoximod with atezolizumab in advanced cancer showed activity but no clear additional benefit.[135] Ongoing trials are investigating alternative IDO-targeting approaches, including dual inhibition of IDO and TDO, and combination therapies with metabolic inhibitors of glycolysis, fatty acid oxidation, or glutaminolysis.[136]

Direct AhR antagonism offers an alternative approach to counteract Kyn-driven immunosuppression. Preclinically, CH-223191, a selective AhR antagonist, disrupts MDSCs-mediated T-cell suppression and promotes a pro-inflammatory TAM phenotype in melanoma models.[137] Similarly, BAY 2416964 restores $CD8^+$ T-cell function and enhances ICIs responses in preclinical lung and breast cancer models.[138] A phase I trial (NCT04069026) is testing BAY 2416964 alone and with pembrolizumab in advanced solid tumors; while another ongoing phase I study (NCT04999202) is assessing IK-175, an oral AhR inhibitor, in advanced urothelial carcinoma showing potential synergy with PD-1 blockade.[139]

Lipid metabolism and cholesterol pathways

Etomoxir, a carnitine palmitoyltransferase-1 (CPT1) inhibitor, reverses immunosuppression and enhances T-cell infiltration in preclinical models; in melanoma, it increases tumor sensitivity to T cell-mediated cytolysis, while in breast and lung cancer models, it reduces

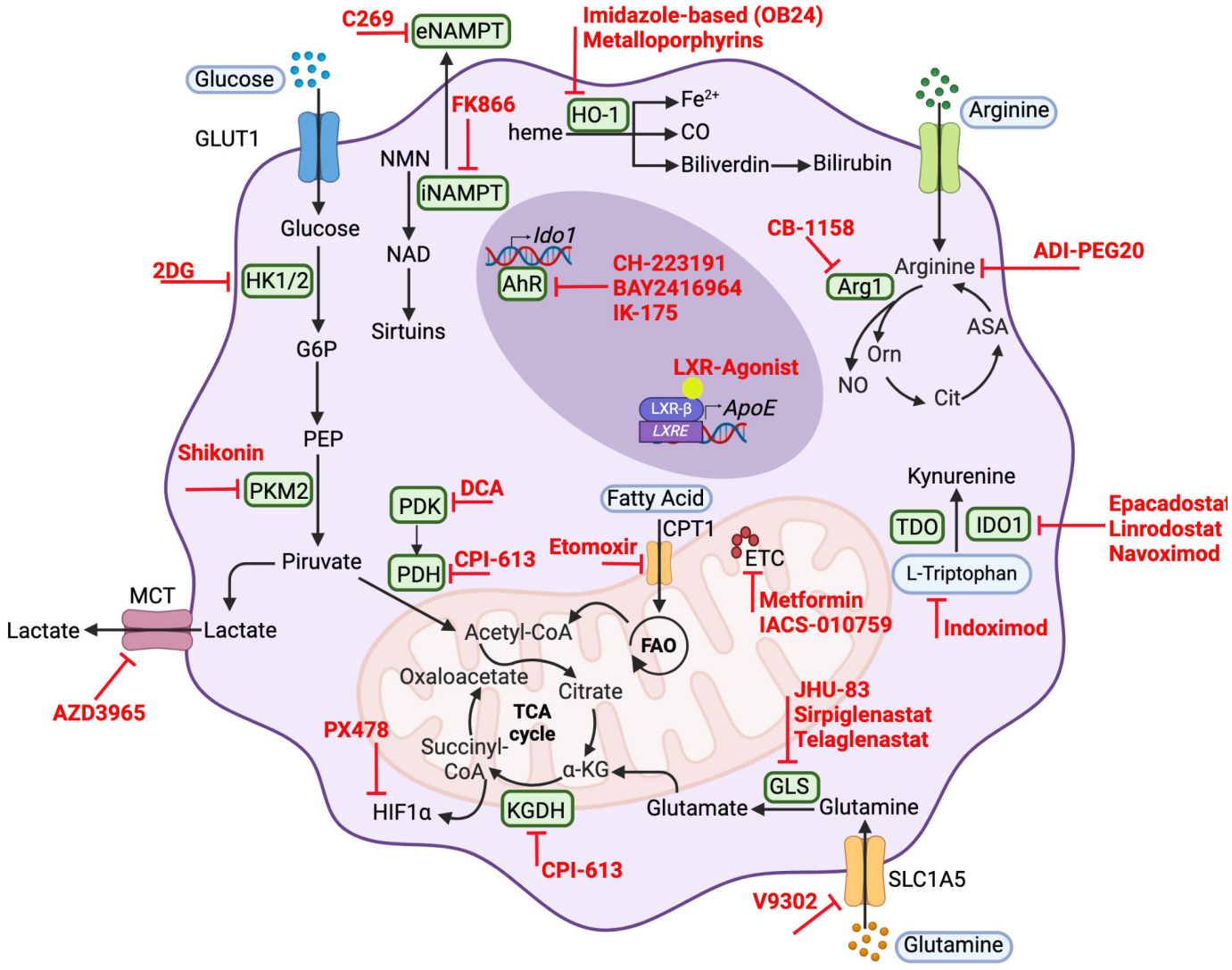

Figure 2 Major metabolic pathways interconnected with myeloid immunosuppression in cancer. The figure also highlights available pharmacological evidence for metabolic reprogramming and reactivation of the antitumor response of myeloid cells. Glycolysis, oxidative phosphorylation, fatty acid oxidation, NAD; heme, lipid and amino acid metabolism are responsible for the immunosuppressive and protumor phenotype of myeloid cells in tumor carriers. Drugs currently used in preclinical and clinical studies are highlighted in red. α-KG, alpha-ketoglutarate; 2-deoxyglucose; ADI-PEG, pegylated arginine deiminase; AhR, aryl hydrocarbon receptor; ApoE, apolipoprotein E; ASA, arginine succinate; Cit, citrulline; CO, carbon monoxide; CPT1, carnitine palmitoyltransferase I; ECT, electron transport chain; eNAMPT, extracellular nicotinamide phosphoribosyltransferase; FAO, fatty acid oxidation; G6P, glucose-6-phosphate; GLS, glutaminase; GLUT1, glucose transporter; HIF-1α, hypoxia-inducible factor 1 alpha; HO-1, heme oxygenase 1; HK1/2, hexokinase 1/2; IDO1, indolamine 2,3-dioxygenase-1; iNAMPT, intracellular nicotinamide phosphoribosyltransferase; KDGH, alpha-ketoglutarate dehydrogenase; LXR, liver X receptor; LXRE, LXR response elements; MCT, monocarboxylate transporter; NAD, nicotinamide adenine dinucleotide; NMN, nicotinamide mononucleotide; NO, nitric oxide; Orn, ornithine; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PEP, phosphoenolpyruvic acid; PKM2, pyruvate kinase M2; TCA, tricarboxylic acid cycle; TDO, tryptophan 2,3-dioxygenase. Created by BioRender.

invasiveness and stemness-related gene expression.[140] Similarly, perhexiline, a prophylactic antianginal drug known to act by inhibiting CPT1 and CPT2,[141] restricts tumor growth and boosts $CD8^+$ T-cell effector function by suppressing oxidative metabolism in MDSCs.[69] In addition, etomoxir prevents peroxisome proliferator-activated receptor gamma coactivator 1-beta upregulation, boosting TAMs pro-inflammatory activity.[142] Additionally, FAO blockade also improves CAR T-cell therapy by enhancing persistence and cytotoxicity in the TME.[143]

Despite metformin is an insulin-sensitizing drug widely prescribed for treating type 2 diabetes mellitus, it has also been reported to alter lipid metabolism.[144] Recent studies highlight metformin's role in enhancing antitumor immunity by modulating TAMs mitochondrial metabolism. In non-alcoholic steatohepatitis-associated hepatocellular carcinoma (HCC) models, metformin reduced tumor growth and increased IFN-γ^+ $CD8^+$ T-cell infiltration, especially with anti-PD-1 therapy.[145] Metformin is under clinical evaluation alone or with carboplatin/paclitaxel for prostate, breast, ovarian, and NSCLC (NCT02640534, NCT02019979, NCT01310231, NCT02312661). Its combination with anti-PD-1 is also being investigated in colorectal cancer, NSCLC, and melanoma (NCT03800602, NCT04114136, NCT03874000, NCT03311308).

LXR agonists have been shown to mitigate MDSCs accumulation, by promoting cholesterol efflux and downregulating immunosuppressive ARG1 and TGF-β.[77] The synthetic LXR agonist RGX-104 reduces intratumoral MDSCs and enhances ICIs responses in melanoma, ovarian cancer, and glioblastoma. In B16F10 models, RGX-104 combined with gp100-specific CTLs or anti-PD-1 improves antitumor efficacy and survival.[77] Clinically, RGX-104 (abequolixron) is under evaluation in a phase I trial (NCT02922764) for advanced solid tumors, exhibiting favorable tolerability and promising immunomodulatory effects.[146]

DISCUSSION

Tumors and immune cells establish a reciprocal relationship that determines clinical outcome.[5 6] In fact, if on the one hand, the immune system affects cancer development and progression through immunosurveillance mechanisms,[147] tumors use metabolic pathways to undermine this ability, creating a microenvironment that is commonly acidic, hypoxic and depleted of critical nutrients essential for immune cells. In this context, tumor metabolism limits immune-mediated tumor destruction by activating multiple resistance mechanisms.

New evidence indicates that the establishment of these tumor-promoting conditions is the result of a multistep process, encompassing initial events originating in the bone marrow and later steps operating in the TME, including: altered differentiation of hematopoietic progenitors toward suppressive myeloid phenotypes and their mobilization to the periphery; their recruitment to both secondary lymphoid organs and tumor tissues; the protumoral diversion of resident and infiltrating myeloid subsets in response to microenvironmental signals. The progression through these steps appears chronologically driven by tumors, through distinct metabolic alterations that act both locally and systemically as true immunological checkpoints, hindering the efficacy of antitumor therapies, including immunotherapy. Ongoing studies are now defining the mechanisms underlying the crucial immunometabolic intersections between cancer and myeloid cells (figure 2), in the distinct phases of differentiation and activation of immune cells. This effort aims to reveal the crucial metabolic nodes of this evil liaison and will likely uncover new and more effective strategies for therapeutic reactivation of antitumor immunity.

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