Metabolic reprogramming of myeloid-derived suppressor cells in colorectal cancer: Mechanistic insights and immunometabolic targeted rehabilitation (Review)

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Abstract. Metabolic reprogramming of myeloid-derived suppressor cells (MDSCs) plays a role in immunotherapy resistance in colorectal cancer (CRC). This metabolic reprogramming appears to be coordinated by oncogenic mutations (such as adenomatous polyposis coli, KRAS and TP53) through a proposed self-reinforcing 'mutation-metabolism-suppression' axis. In the present review, four core metabolic pillars sustaining MDSC pathogenicity and the epimetabolic regulation that durably locks them into a suppressive state were examined. Furthermore, two emerging dimensions were highlighted: The spatial metabolic antagonism through which MDSCs may construct a metabolically hostile zone to limit the functional activity of tertiary lymphoid structures, and the remote manipulation of MDSC function by gut and intratumoral microbiota-derived metabolites. To transcend the limitations of non-specific myeloid depletion, immunometabolic rehabilitation is proposed as a potentially transformative framework targeting intrinsic metabolic vulnerabilities to functionally reprogram MDSCs from an immunosuppressive to a homeostatic or immunostimulatory phenotype. By integrating emerging spatial omics for precise target validation, artificial intelligence-guided rational drug design and microbiome modulation, this paradigm provides a strategic roadmap for next-generation precision immunotherapy, aiming to achieve durable responses across both microsatellite stable and microsatellite instability-high CRC.

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Abbreviations: AI, artificial intelligence; AOR, arginine/ornithine ratio; APC, adenomatous polyposis coli; ARG1, arginase 1; C/EBPβ, CCAAT/enhancer-binding protein β; CPT1A, carnitine palmitoyltransferase 1A; CRC, colorectal cancer; FAO, fatty acid oxidation; GLS, glutaminase; HIF-1α, hypoxia inducible factor-1α; HK2, hexokinase 2; ICI, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; IMC, imaging mass cytometry; LDHA, lactate dehydrogenase A; MCT, monocarboxylate transporter; MDSC, myeloid-derived suppressor cell; MFA, metabolic flux analysis; MSI-H, microsatellite instability-high; MSS, microsatellite stable; MYC, myelocytomatosis oncogene; OXPHOS, oxidative phosphorylation; PGE2, prostaglandin E2; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding proteins; STAT3, signal transducer and activator of transcription 3; TME, tumor microenvironment; TLS, tertiary lymphoid structure

Key words: colorectal cancer, myeloid-derived suppressor cells, immunometabolism, metabolic reprogramming, spatial omics, immunotherapy resistance, histone lactylation, tertiary lymphoid structures, tumor microenvironment

Contents

1. Introduction
2. Multidimensional metabolic landscape of MDSCs in CRC
3. Metabolic-driven immunosuppression: From biochemical barriers to spatial exclusion
4. Regulatory networks: The 'mutation-metabolism-suppression' axis in CRC
5. Emerging technologies: From descriptive profiling to spatial functional validation
6. MDSC metabolic signatures as precision biomarkers in CRC
7. Immunometabolic rehabilitation: Reprogramming MDSC metabolism to restore immunity
8. Challenges, bottlenecks and future directions
9. Conclusions

1. Introduction

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide. GLOBOCAN 2022 estimated 1,926,425 new cases (9.6% of all cancers) and 904,019 deaths (9.3% of all cancer mortalities) globally, ranking third in incidence and second in mortality among all malignancies (1). Although immune checkpoint inhibitors (ICIs) have transformed oncology, their clinical benefit is largely confined to the microsatellite instability-high (MSI-H) subtype, which accounts for approximately 15% of all colorectal cancers (2). The majority of CRCs, classified as microsatellite stable (MSS), exhibit poor responsiveness to immunotherapy, a resistance intimately linked to the profoundly immunosuppressive tumor microenvironment (TME), in which myeloid-derived suppressor cells (MDSCs) have emerged as key orchestrators (3,4) (Fig. 1).

Emerging evidence has suggested that the immunosuppressive identity of MDSCs is not merely a fixed phenotypic state but a functional output of deep metabolic reprogramming (5-7). In the hypoxic, nutrient-deprived TME, MDSC metabolism has emerged as a key 'immunometabolic checkpoint' that determines the amount and potency of immunosuppressive mediators [such as arginase 1 (ARG1), inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), prostaglandin E_2 (PGE_2) and programmed death-ligand 1 (PD-L1)] and the construction of the immune evasion barrier (8,9). This recognition has catalyzed a paradigm shift: MDSC metabolism is increasingly viewed as a key determinant of immunosuppression, a pathogenic metabolic state that represents a therapeutic vulnerability.

The metabolic identity of MDSCs appears to be associated with oncogenic mutations through a 'mutation-metabolism-suppression' regulatory axis. Driver mutations in adenomatous polyposis coli (APC) (10), KRAS (11) and TP53 (12) converge on master metabolic transcription factors, hypoxia inducible factor-1α (HIF-1α), myelocytomatosis oncogene e(MYC), signal transducer and activator of transcription 3 (STAT3), CCAAT/enhancer-binding protein β (C/EBPβ) and sterol regulatory element-binding proteins (SREBP), to influence MDSC metabolism toward glycolysis, lipid oxidation and glutamine addiction. These metabolic adaptations not only fuel the production of immunosuppressive effectors but also establish epimetabolic memory through histone lactylation that durably locks MDSCs into a suppressive state (13,14). Concurrently, two emerging dimensions, the spatial metabolic antagonism through which MDSCs may limit the functional activity of tertiary lymphoid structures (TLSs) (15,16) and the remote manipulation of MDSC metabolic fitness by gut and intratumoral microbiota-derived metabolites, extend their immunosuppressive reach beyond individual cell interactions (17,18).

In the present review, the metabolic heterogeneity of MDSCs in CRC and the regulatory networks that govern their pathogenicity will be discussed. Central to the present review, the 'immunometabolic rehabilitation' framework is proposed as a potentially transformative therapeutic framework, one that shifts clinical focus from non-specific myeloid depletion to precise functional reprogramming by targeting intrinsic metabolic vulnerabilities such as glycolysis, fatty acid oxidation (FAO) and glutaminolysis. By severing the metabolic link between oncogenic mutations and immune evasion, this paradigm offers a strategic roadmap for next-generation precision immunotherapy in CRC.

Review methodology. The present narrative review was informed by a systematic literature search of PubMed, Web of Science and Scopus databases, covering publications up to July 2026. Search terms included combinations of the following keywords: 'myeloid-derived suppressor cells', 'MDSCs', 'colorectal cancer', 'CRC', 'metabolism', 'glycolysis', 'fatty acid oxidation', 'lipid metabolism', 'amino acid metabolism', 'glutamine metabolism', 'mitochondrial dynamics', 'immunometabolism', 'lactate', 'arginine', 'arginase', 'indoleamine 2,3-dioxygenase', 'immunotherapy', 'immune checkpoint inhibitors', 'tumor microenvironment' and 'tertiary lymphoid structures'.

Peer-reviewed original research articles, high-quality reviews and clinical trial reports were prioritized. Studies directly examining MDSC metabolism in CRC contexts (Tier 1 evidence) were included, while also incorporating mechanistic insights from other tumor types and inflammatory settings where CRC-specific data were limited (Tier 2 evidence). Studies were excluded if they did not address MDSC biology, lacked relevance to metabolism or immunosuppression or were published as conference abstracts without full peer review.

Throughout the present review, a three-tier evidence classification framework was applied to distinguish: i) Tier 1 mechanisms directly demonstrated in CRC-MDSCs; ii) tier 2 findings extrapolated from other tumor types or inflammatory settings; and iii) Tier 3 hypotheses and integrative frameworks proposed by the authors. This approach is intended to provide readers with a transparent assessment of the strength and source of evidence underlying each mechanistic conclusion.

2. Multidimensional metabolic landscape of MDSCs in CRC

In the CRC microenvironment, the pathological activation of MDSCs manifests as bioenergetic rewiring (19). By integrating single-cell metabolic profiling with functional metabolomics, four core metabolic pillars can be delineated: Aerobic glycolysis (20), lipid metabolism (21), amino acid scavenging (22) and mitochondrial dynamics (23). Each represents a distinct yet interdependent vulnerability underpinning MDSC pathogenicity. These metabolic programs are further reinforced by epimetabolic regulation and exhibit subset-specific heterogeneity (Fig. 2).

Aerobic glycolysis and the lactate-epigenetic axis. Under the drive of HIF-1α, MDSCs upregulate glycolytic flux through key enzymes including hexokinase 2 (HK2), pyruvate kinase M2 (PKM2) and lactate dehydrogenase A (LDHA). A key regulatory node in this pathway is the conformational switch of PKM2: Its transition from an active tetrameric form to a less active dimeric form redirects glycolytic intermediates into the pentose phosphate pathway, enhancing antioxidant defense through NADPH generation, while dimeric PKM2 translocates to the nucleus where it functions as a transcriptional

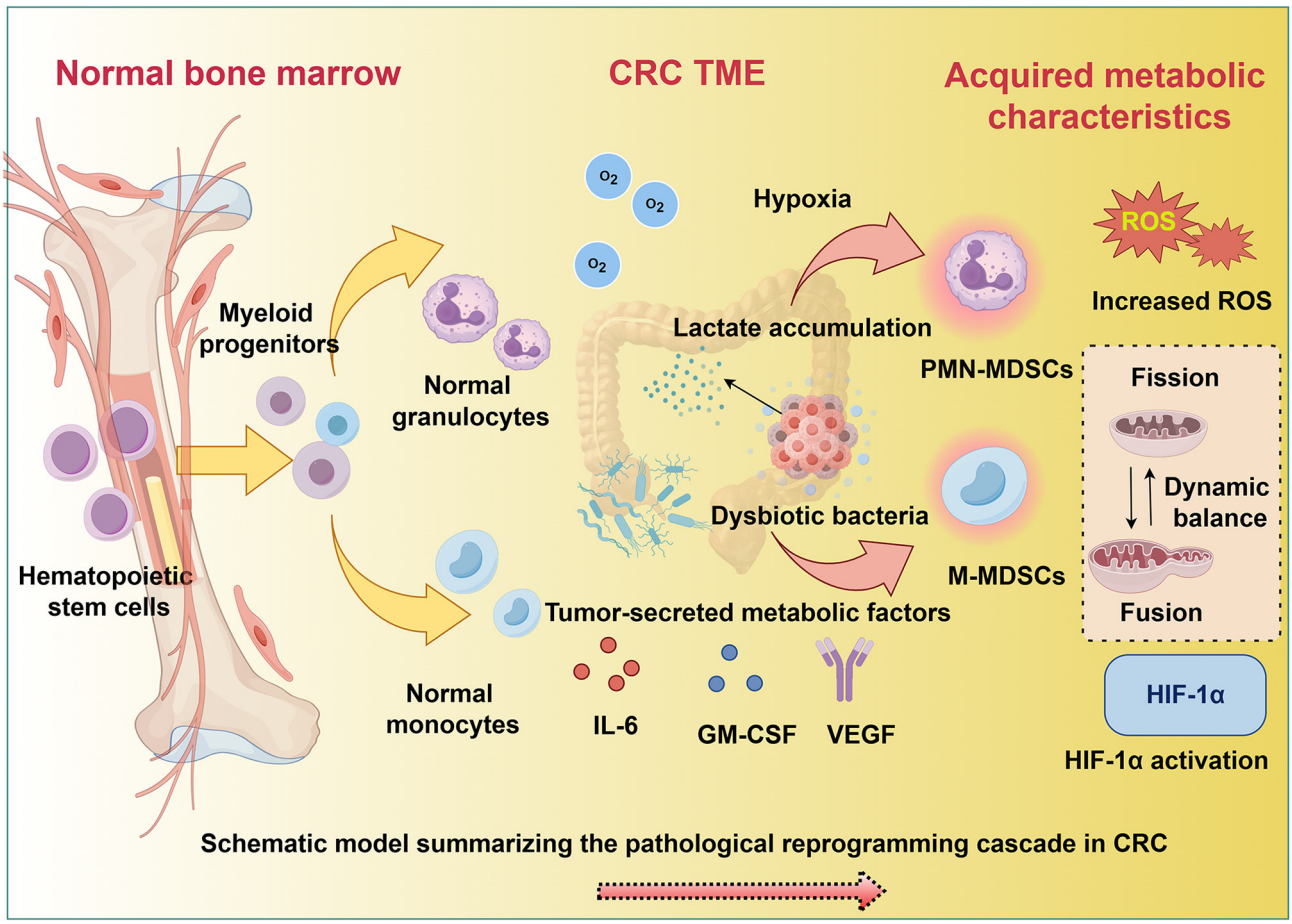


Figure 1. Pathological reprogramming and metabolic adaptation of MDSCs in the CRC TME. Schematic representation of the lineage commitment and functional divergence of M-MDSC and PMN-MDSC myeloid-derived suppressor cells driven by the CRC microenvironment. Normal myelopoiesis is diverted by a multifactorial network of microenvironmental stressors, including localized hypoxia, lactate accumulation, gut dysbiosis (such as *Fusobacterium nucleatum*) and tumor-derived soluble mediators (IL-6, GM-CSF and VEGF). In response to these TME-derived signals, tumor-infiltrating M-MDSCs and PMN-MDSCs acquire distinct functional and metabolic signatures, marked by sustained HIF-1α activation, elevated ROS production, and altered mitochondrial dynamics and quality control (fission/fusion). Solid lines denote pathways experimentally validated with direct evidence in CRC-MDSC models (Tier 1); dashed lines represent proposed mechanisms, systemic signaling extrapolations, or hypothetical models requiring further validation (Tiers 2 and 3). CRC, colorectal cancer; GM-CSF, granulocyte-macrophage colony-stimulating factor; M-MDSC, monocytic myeloid-derived suppressor cells; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cells; ROS, reactive oxygen species; HIF-1α, hypoxia inducible factor-1α; TME, tumor microenvironment.

coactivator promoting c-Myc and other proliferative genes (24). This hyper-glycolytic state leads to massive lactate accumulation, actively exported via monocarboxylate transporter (MCT) 4. Rather than serving as mere metabolic waste, extracellular lactate engages the G protein-coupled receptor (GPR) 81 receptor on MDSCs, triggering STAT3 activation that directly drives ARG1 and PD-L1 transcription, establishing a feed-forward immunometabolic loop in which lactate reinforces the suppressive identity of the cells that generate it (25). The disruption of local lactate gradients further causes intracellular lactate buildup in neighboring T cells via MCT1-mediated uptake, inhibiting NAD^+ regeneration and paralyzing effector activation. Critically, this lactate-driven transcriptional activation is reinforced by epimetabolic regulation that translates glycolytic output into durable transcriptional memory. Glycolysis-derived lactate drives histone lactylation, specifically H3K18 lactylation (H3K18la), which upregulates tet methylcytosine dioxygenase 2 (TET2) to demethylate the ARG1 promoter, locking MDSCs into a suppressive state through an 'epigenetic memory' that persists beyond the initial metabolic stimulus (20). Beyond lactylation, acetyl-CoA produced via ATP citrate lyase serves as the acetyl donor for histone acetyltransferases, while sirtuins (SIRT) 1 and SIRT3 mediate deacetylation, together modulating genes involved in MDSC expansion (26). The tricarboxylic acid (TCA) cycle metabolites succinate and fumarate act as competitive analogues of α-ketoglutarate (α-KG) and inhibit α-KG-dependent dioxygenases, including TET2 and Jumonji domain-containing histone demethylases (27). As these enzymes normally remove DNA and histone methylation marks, their inhibition leads to accumulation of 5-methylcytosine (5mC) and repressive histone modifications such as H3K9me3 and H3K27me3, while reducing 5-hydroxymethylcytosine (5hmC) and preventing the removal of repressive marks. This broadly remodels the DNA and histone methylation landscape, promoting a closed chromatin state that stabilizes the expression of immunosuppressive genes such as ARG1, iNOS, and PD-L1. Together, these epimetabolic mechanisms transform transient glycolytic fluxes into stable functional identities, explaining why MDSCs maintain their suppressive phenotype even when the initial metabolic cues fluctuate (28).

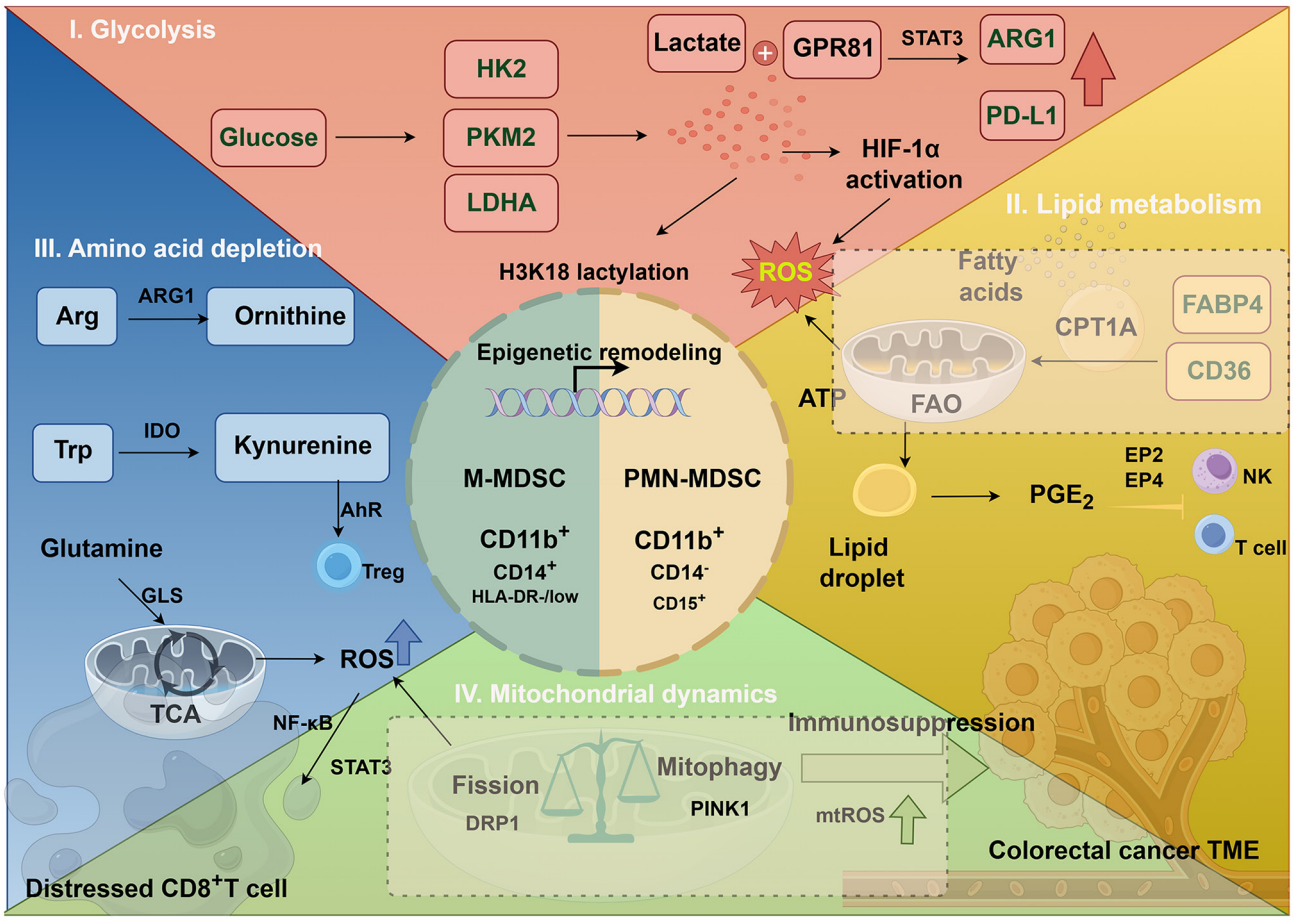


Figure 2. Integrated metabolic networks modulating MDSC accumulation and immunosuppressive function. Schematic diagram detailing the four major metabolic axes that support MDSC function and recruitment within the CRC TME: (I) Glycolytic pathways and lactate signaling, where glycolytic flux and elevated extracellular lactate drive HIF-1α activation and upregulate immunosuppressive effectors (such as ARG1 and PD-L1); (II) Lipid metabolism, mediated by fatty acid uptake (CD36 and FABP4) and FAO (via CPT1A) to support cell survival and ROS generation; (III) Amino acid catabolism, characterized by local depletion of L-arginine (via ARG1), tryptophan (via IDO1), and glutamine (via GLS), generating suppressive metabolites such as kynurenine; and (IV) Mitochondrial dynamics and quality control, balancing DRP1-mediated fission and PINK1-mediated selective mitophagy to maintain metabolic fitness and sustain ROS generation. Central panels depict key phenotypical markers of human M-MDSCs and PMN-MDSCs, alongside epigenetically driven reprogramming (such as H3K18 lactylation). Downstream metabolic outputs, including ROS and PGE_2, collectively suppress effector $CD8^+$ T cell and NK cell responses. Solid lines represent pathways experimentally validated in CRC-MDSC models (Tier 1); dashed lines denote proposed mechanisms, cross-disease extrapolations, or hypothetical models requiring further validation (Tiers 2 and 3). HIF-1α, hypoxia inducible factor-1α; NK, natural killer; CRC, colorectal cancer; ROS, reactive oxygen species; MDSC, myeloid-derived suppressor; ARG1, arginine 1; PGE_2, prostaglandin E_2; M-MDSC, monocytic myeloid-derived suppressor cells; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cells; HK, hexokinase 2; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; GPR81, G protein-coupled receptor 81; PINK1, PTEN-induced kinase 1; FABP4, fatty acid-binding protein 4; PD-L1, programmed death-ligand 1; HLA-DR, human leukocyte antigen-DR isotype; DRP1, dynamin-related protein 1; FAO, fatty acid oxidation; GLS, glutaminase; IDO, indoleamine 2,3-dioxygenase; Treg, regulatory T cell; AhR, aryl hydrocarbon receptor; EP2, prostaglandin E_2 receptor 2; EP4, prostaglandin E_2 receptor 4; CPT1A, carnitine palmitoyltransferase 1A; TCA, tricarboxylic acid cycle; mtROS, mitochondrial ROS.

Lipid metabolism: FAO, lipid droplets and PGE_2 synthesis. While glycolysis provides the signaling infrastructure and epimetabolic locking mechanism, lipid metabolism supplies the energetic fuel. CRC-infiltrating G-MDSCs exhibit enhanced lipid uptake and utilization, initiated by the upregulation of fatty acid transporters CD36 and fatty acid-binding protein 4 (FABP4), which efficiently internalize extracellular lipids. Within the cytoplasm, carnitine palmitoyltransferase 1A (CPT1A) shuttles long-chain fatty acids into mitochondria for β-oxidation, generating high-energy phosphates and fueling sustained ROS production (29). Excess lipids are sequestered in perilipin 2 (PLIN2)-coated lipid droplets, which serve dual functions: They supply substrates for continued FAO and fuel the synthesis of PGE_2. PGE_2 subsequently acts through prostaglandin E_2 receptor (EP)2/EP4 receptors to dampen natural killer (NK) and T cell cytotoxicity while promoting regulatory T cell (Treg) expansion (30,31).

Amino acid scavenging: Arginine, tryptophan and glutamine addiction. MDSCs construct a formidable 'amino acid desert' through the high expression of ARG1 and indoleamine 2,3-dioxygenase (IDO). ARG1 rapidly depletes L-arginine, directly downregulating the CD3ζ chain in T cells and impairing T cell receptor (TCR) signaling from its metabolic foundation, while IDO degrades tryptophan into immunosuppressive kynurenines that bind to the aryl hydrocarbon receptor (AhR), inducing T cell cycle arrest and promoting Treg differentiation (27). Paradoxically, while starving effector cells of essential nutrients, MDSCs themselves display a glutamine addiction. Utilizing glutaminase (GLS), they convert

glutamine to glutamate and α-ketoglutarate, feeding the TCA cycle and supporting mitochondrial ROS (mtROS) production (28,32). Glutamine-derived carbons also fuel glutathione synthesis, endowing MDSCs with a robust antioxidant defense system that ensures their survival amid the notable oxidative stress they themselves generate (33).

Mitochondrial dynamics and quality control. MDSC mitochondria function as dynamic immunometabolic hubs rather than static ATP factories (34). This dynamism is maintained through continuous mitochondrial fission and fusion, which allow rapid adaptation to the hypoxic, nutrient-deprived TME and support sustained oxidative phosphorylation. This enhanced respiration generates elevated levels of mtROS, which act as retrograde signals activating NF-κB and STAT3 pathways, further reinforcing the immunosuppressive transcriptional program (35). To sustain this metabolically demanding state without succumbing to apoptosis, MDSCs rely on a delicate mitochondrial quality control system: Dynamin-related protein 1-mediated mitochondrial fission ensures the segregation of damaged organelles, while selective mitophagy, coordinated by PTEN-induced kinase 1 (PINK1)/Parkin and mitophagy receptors such as BCL2 interacting protein 3 and NIX, clears dysfunctional mitochondria, maintaining a healthy network capable of supporting persistent immunosuppressive output (36).

Metabolic heterogeneity across MDSC subsets. These four core metabolic programs do not operate uniformly but exhibit lineage-specific patterns (28). Granulocytic MDSCs (termed PMN-MDSCs in humans and G-MDSCs in murine models) preferentially upregulate FAO, mitochondrial respiration and ROS production pathways, with elevated expression of CPT1A, CD36 and NADPH oxidase subunits, positioning them as 'lipid-burning' cells whose suppressive activity is intimately tied to mitochondrial integrity and oxidative output (30). M-MDSCs, by contrast, are enriched for glycolytic enzymes including HK2, PKM2 and LDHA, as well as iNOS and amino acid catabolic pathways such as ARG1, IDO and GLS, positioning them as 'glucose-avid and amino acid-scavenging' cells that dominate nutrient-depleted microregions. It should be noted that distinguishing human PMN-MDSCs from conventional neutrophils and M-MDSCs from monocytes is technically challenging, as these populations share overlapping surface markers. Definitive identification typically requires functional validation (such as suppression of T cell proliferation) in addition to phenotypic characterization. This technical limitation should be considered when interpreting studies based solely on surface marker expression. Early stage-MDSCs, as the common upstream precursor, exhibit a more plastic metabolic profile driven by JAK/STAT signaling, with STAT3 hyperactivation, often resulting from the loss of negative regulators such as suppressor of cytokine signaling 3 (SOCS3), biasing their differentiation toward both G-MDSC and M-MDSC fates (36,37). This subset-specific metabolic heterogeneity carries direct therapeutic implications: FAO inhibitors may preferentially target the lipid-burning G-MDSC compartment, while glycolytic or glutaminolysis blockade may more effectively neutralize the glucose-avid M-MDSC population, underscoring the need for precision-targeted rather than blanket metabolic interventions (Table I).

3. Metabolic-driven immunosuppression: From biochemical barriers to spatial exclusion

The four aforementioned metabolic pillars converge on a final common pathway of T cell dysfunction, yet each imposes a mechanistically distinct mode of metabolic constraint that collectively ensures the completeness of immune evasion (28,37).

Arginine depletion and T cell metabolic exhaustion. The amino acid scavenging systems directly convert MDSC glutamine addiction into T cell starvation. ARG1 hydrolyzes L-arginine, downregulating the CD3ζ chain and impairing TCR signaling from its metabolic foundation (26). The resulting arginine starvation activates the general control nonderepressible 2 kinase pathway in T cells, triggering a stress response that halts proliferation. Simultaneously, iNOS-generated nitric oxide reacts with superoxide to form peroxynitrite, nitrating both TCR and major histocompatibility complex molecules and rendering T cells unresponsive to antigen stimulation. IDO further compounds nutrient stress by degrading tryptophan into kynurenines, which engage the AhR to induce T cell cycle arrest and Treg differentiation (33). Metabolic quantification reveals that MDSC-enriched tumor regions can reduce extracellular arginine concentrations by >90% relative to normal tissue, effectively starving infiltrating T cells (28).

Lactate accumulation blunts T cell effector function. Lactate accumulation, the direct output of the glycolytic pillar, exerts immunosuppressive effects beyond MDSC autocrine signaling. Extracellular lactate concentrations in the CRC TME reach 10-30 mM, compared with 1.5-3 mM in normal tissues (24-26). This lactate gradient curtails T cell fitness through multiple mechanisms: Intracellular acidification via MCT1-mediated uptake inhibits glycolysis in T cells by suppressing phosphofructokinase activity, lactate competitively inhibits lactate dehydrogenase in T cells, disrupting their own glycolytic flux essential for effector function and lactate directly suppresses TCR signaling by inhibiting nuclear factor of activated T cells translocation. Simultaneously, the acidic microenvironment impairs NK cell cytotoxicity and promotes M2 macrophage polarization. This lactate-driven T cell paralysis is self-reinforcing, the more lactate MDSCs produce, the more effectively they blunt the effector function of the T cells that could eliminate them (38).

ROS-mediated oxidative stress and T cell trafficking blockade. The oxidative arm of MDSC-mediated immunosuppression originates directly from the mitochondrial FAO and oxidative phosphorylation (OXPHOS) pathways. G-MDSCs leverage their enhanced β-oxidation to fuel NADPH oxidase-driven superoxide production (30). This oxidative pressure not only directly induces effector cell apoptosis through mitochondrial membrane depolarization but also nitrates chemokines such as C-C motif chemokine ligand 2 and C-X-C motif chemokine ligand (CXCL) 10 via peroxynitrite, creating chemically modified chemokine gradients that fail to guide T cell migration into

Table I. Metabolic heterogeneity and proposed biomarkers of MDSCs in colorectal cancer.

Proposed metabolic phenotype	Predominant subset	Core regulatory transcription factors	Key enzymes and transporters	Core immunosuppressive mechanisms	Potential candidate biomarkers (detectable)	Validation status
Hyper-glycolytic	Predominantly M-MDSC	HIF-1α and STAT3	HK2, PKM2, LDHA and MCT4	Lactate accumulation induces T cell paralysis; histone lactylation maintains the MDSC suppressive epigenetic memory	Elevated serum HK2 and LDHA activity; increased circulating lactate concentrations	Correlative evidence (Tier 2) requires prospective validation
Hyper-lipid-oxidative	Predominantly G-MDSC	SREBP-1 and NF-κB	CD36, CPT1A and FABP4	FAO drives massive ROS production (blocking T cell homing); PGE_2 synthesis promotes Treg expansion	High CD36 expression on peripheral blood G-MDSCs; elevated serum CPT1A levels	Preclinical (Tier 2) clinical assays not standardized
Hyper-amino-acid-consuming	M-MDSC/ G-MDSC	C/EBPβ and MYC	ARG1, IDO and GLS	Deprivation of microenvironmental arginine/ tryptophan, triggering T cell metabolic exhaustion and cell cycle arrest	Decreased plasma arginine concentrations; reduced AOR	Correlative evidence (Tier 2) proposed as surrogate marker of systemic MDSC burden

This classification represents a heuristic, hypothesis-generating framework that has not been validated by systematic clustering analysis in patient cohorts. The proposed phenotypes and their associated biomarkers require prospective validation in independent colorectal cancer patient populations. AOR, arginine/ornithine ratio; ARG1, arginase 1; CPT1A, carnitine palmitoyltransferase 1A; FAO, fatty acid oxidation; GLS, glutaminase; HIF-1α, hypoxia-inducible factor-1α; HK2, hexokinase 2; ICI, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; LDHA, lactate dehydrogenase A; MCT, monocarboxylate transporter; MDSC, myeloid-derived suppressor cell; phosphorylation; PGE_2, prostaglandin E_2; ROS, reactive oxygen species; M-MDSC, monocytic myeloid-derived suppressor cells; G-MDSCs, granulocytic MDSCs; C/EBPβ, CCAAT/enhancer-binding protein β; SREBP, sterol regulatory element-binding proteins; FABP4, fatty acid-binding protein 4; Treg, regulatory T cell.

the tumor core (39). Clinically, elevated ROS levels in MDSCs associate with lymph node metastasis and reduced $CD8^+$ T cell density in tumor invasive margins. This ROS-mediated chemokine inactivation represents a spatially targeted mode of immunosuppression, MDSCs generate an oxidative shield that excludes T cells from tumor regions even when chemotactic signals are abundant (34,40).

Lipid-derived PGE_2 fosters an immunosuppressive microenvironment. The lipid metabolic pillar generates a second class of immunosuppressive mediators. PGE_2, synthesized from arachidonic acid released from PLIN2-coated lipid droplets via cyclooxygenase-2 (COX-2), acts through EP2 and EP4 receptors on multiple immune cell types (31). In T cells, PGE_2 suppresses IL-2 production and cytotoxicity; in NK cells, it inhibits activating receptor signaling, and in dendritic cells, it impairs antigen presentation and promotes a tolerogenic phenotype. PGE_2 also synergizes with TGF-β to expand Treg populations, creating a microenvironment enriched in suppressive regulatory cells. The dectin-1 receptor on MDSCs upregulates PGE_2 synthesis, and blocking this pathway suppresses colorectal tumorigenesis. This lipid-to-PGE_2 axis illustrates how metabolic substrates stored in lipid droplets are directly channeled into paracrine signals that suppress antitumor immunity (32,41).

Hypothetical spatial metabolic barrier: A proposed model of MDSC-mediated siege of tertiary lymphoid structures. An emerging and conceptually notable dimension of MDSC-mediated immunosuppression involves their spatial relationship with TLSs. TLSs are ectopic lymphoid aggregates that serve as local sites for adaptive antitumor immunity and are associated with improved ICI responses in CRC. MDSCs may construct a metabolically hostile zone around TLSs, a region potentially defined by high lactate, depleted arginine and reactive nitrogen species, that may physically and chemically limit the activity of effector lymphocytes generated within these lymphoid structures (42). It is important to note that this model is currently supported primarily by indirect evidence from cervical cancer (15) and renal cell carcinoma (16) (Tier 2), rather than direct spatial metabolomic studies in CRC (Tier 1). This hypothesis, while conceptually compelling and consistent with known MDSC metabolic activities, requires direct experimental validation using emerging spatial metabolomic technologies in CRC tissues (Fig. 3).

Having delineated how each metabolic pillar translates into a specific immunosuppressive mechanism, from arginine depletion to spatial TLS exclusion, a fundamental question arises: What drives this metabolic rewiring in the first place? The answer lies in a hierarchical regulatory framework that integrates oncogenic mutations, master transcription factors and microenvironmental inputs to wire MDSC metabolism toward immunosuppression.

4. Regulatory networks: The 'mutation-metabolism-suppression' axis in CRC

The metabolic landscape of MDSCs appears to be shaped by both tumor-intrinsic and microenvironmental inputs. In the present section, available evidence is integrated to propose a 'mutation-metabolism-suppression' axis, a conceptual framework that links oncogenic mutations to MDSC metabolic reprogramming and subsequent immunosuppression. It is important to note that this framework synthesizes findings from multiple experimental systems, including CRC tissues (Tier 1), murine CRC models (Tier 1) and extrapolated evidence from other tumor types (Tier 2). The complete pathway has not been demonstrated in a single experimental system, and several links remain hypothetical (Tier 3). This framework is presented as an organizing principle to guide future investigation rather than as a fully established mechanistic pathway.

APC/Wnt activation drives the glycolysis-lactate-MDSC loop. APC loss-of-function mutations, the most common initiating mutation in CRC, leads to aberrant stabilization of β-catenin and constitutive activation of Wnt/β-catenin signaling (10). Activated Wnt/β-catenin directly upregulates PKM2 and LDHA in tumor cells, driving a hyper-glycolytic state that generates massive lactate (43). This lactate is exported via MCT4 and acts on MDSCs through two complementary pathways: Extracellular lactate engages GPR81, triggering STAT3 activation that transactivates ARG1 and PD-L1; concurrently, lactate uptake via MCT1 fuels H3K18la, epigenetically locking the ARG1 promoter in an open configuration (20). At the transcriptional level, HIF-1α and STAT3 cooperate to upregulate HK2, PKM2 and LDHA in MDSCs themselves, converting them into lactate-producing factories that perpetuate the immunosuppressive milieu. SREBP-1, activated by mTORC1 downstream of Wnt, further promotes *de novo* lipogenesis and lipid droplet formation in M-MDSCs. The initial steps of this cascade, Wnt/β-catenin activation and upregulation of glycolytic enzymes in tumor cells, are well established in CRC (Tier 1). However, the subsequent effects on MDSC metabolic reprogramming are primarily supported by studies in other tumor types or *in vitro* systems (Tier 2), and direct demonstration of this cascade in CRC-MDSCs is limited. This is therefore presented as a plausible model requiring experimental confirmation in CRC-MDSC contexts (44).

KRAS/BRAF mutations drive glutamine-fueled MDSC differentiation. KRAS mutations, occurring in ~48.9% of CRCs, drive persistent activation of the MAPK and PI3K/AKT pathways (11). Mutant KRAS upregulates MYC, which directly transactivates GLS and the mitochondrial glutamate transporter solute carrier family 25 member 22. The resulting metabolic intermediates, α-ketoglutarate and glutamate, act as paracrine signaling molecules that activate C/EBPβ within myeloid precursors, driving their differentiation toward suppressive PMN-MDSCs characterized by elevated ARG1 and iNOS expression (45). Concurrently, mutant KRAS upregulates granulocyte-macrophage colony-stimulating factor (GM-CSF) secretion via STAT3, and GM-CSF signaling in myeloid progenitors activates STAT5, which cooperates with C/EBPβ to reinforce the PMN-MDSC transcriptional program. This establishes a direct mechanistic conduit from oncogenic signaling to myeloid-mediated immune evasion, with this regulatory cascade ultimately enhancing MDSC suppressive function through glutamine-fueled differentiation and arginine catabolism (46).

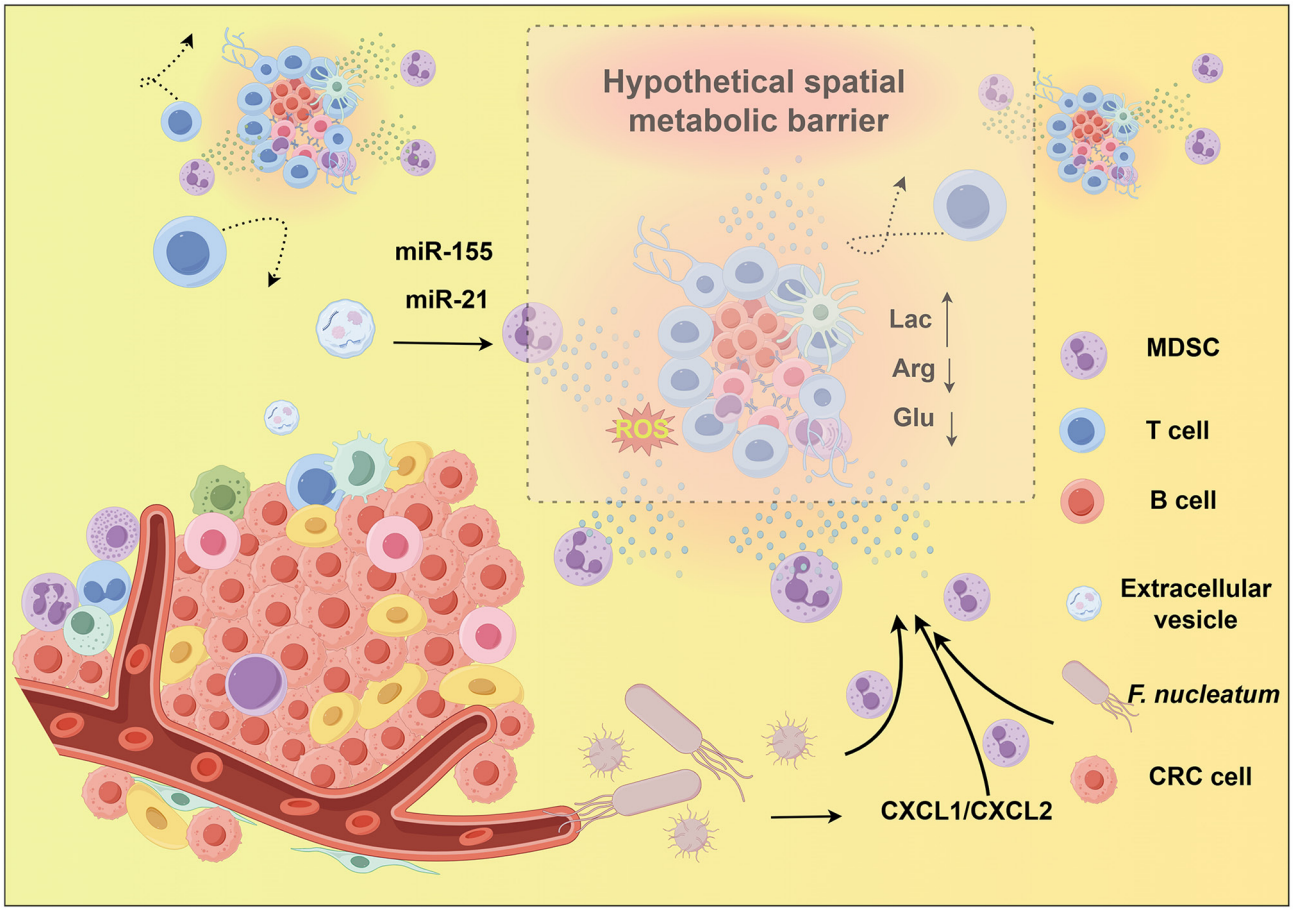


Figure 3. Hypothetical spatial model of MDSC-mediated metabolic barrier and TLS 'metabolic siege' in CRC. Schematic representation of a proposed spatial model depicting how metabolic heterogeneity and regional immunosuppression may structure the CRC tumor microenvironment. Within the primary tumor niche, local drivers including gut pathobionts (such as *F. nucleatum* via CXCL1/CXCL2 chemokines), tumor-derived extracellular vesicles (carrying miR-155/miR-21) and hypoxia promote MDSC recruitment and accumulation. At the invasive margin and peritumoral zones, MDSCs are hypothesized to physically and chemically construct a spatial metabolic barrier around TLSs. This regional barrier, characterized by localized lactate accumulation alongside severe depletion of arginine and glucose (Lac↑, Arg↓ and Glu↓) is proposed to impair lymphocyte infiltration and blunt T cell and B cell effector functions. While local chemokinetic recruitment and MDSC suppressive factors are established in CRC, the specific spatial 'TLS metabolic siege' architecture represents an integrative hypothesis derived from cross-disease extrapolations and awaits direct validation via spatial metabolomics and transcriptomics in human CRC tissues. Solid lines indicate pathways experimentally validated in CRC models (Tier 1); dashed lines and shaded borders denote proposed spatial mechanisms and hypothetical models requiring further validation (Tiers 2 and 3). MDSC, myeloid-derived suppressor cells; CRC, colorectal cancer; TLS, tertiary lymphoid structure; *F. nucleatum*, Fusobacterium nucleatum, CXCL, C-X-C motif chemokine ligand.

TP53 loss remodels mitochondrial metabolism in MDSCs. TP53 mutations, present in ~50% of advanced CRCs, dismantle key metabolic checkpoints that extend beyond tumor cells to the myeloid compartment (12). Mutant p53 upregulates the mevalonate pathway, increasing secretion of geranylgeranyl pyrophosphate, which activates NF-κB signaling in MDSCs and induces CPT1A expression, promoting FAO (47). Simultaneously, p53-deficient tumor cells release extracellular vesicles enriched with various microRNAs (miRNAs) implicated in immune modulation, including miR-1246, which reprograms macrophages toward an anti-inflammatory, tumor-supportive phenotype (48), and miR-145, which promotes M2-like macrophage polarization by targeting HDAC11 (49). Other p53-regulated miRNAs such as miR-34a and exosomal miR-203a-3p have also been implicated in modulating the immune microenvironment in colorectal cancer (50). While these miRNAs have been studied in CRC, their specific role in MDSC metabolic reprogramming via SOCS3 suppression is primarily supported by evidence from other tumor types and requires direct validation in CRC-MDSCs (Tier 2) (51). This regulatory cascade ultimately enhances MDSC suppressive function through mitochondrial remodeling and oxidative metabolism.

Master metabolic transcription factors as integrative hubs. Converging on these mutation-driven pathways, a network of master metabolic transcription factors translates oncogenic signals into MDSC metabolic identity. HIF-1α orchestrates the hypoxic response, coordinately upregulating HK2, PKM2, LDHA and MCT4. MYC, activated by KRAS-driven MAPK and Wnt/β-catenin, drives glutamine uptake through transactivation of GLS and solute carrier family 1 member 5. STAT3 functions as the central immunometabolic integrator downstream of GPR81, GM-CSF and IL-6 receptors, simultaneously transactivating ARG1, PD-L1 and CPT1A. C/EBPβ, activated by KRAS-derived metabolic intermediates, directs myeloid differentiation toward the PMN-MDSC lineage (52). SREBP-1 and SREBP-2, activated by mTORC1, drive the lipogenic

program that provides lipid substrates for FAO and PGE_2 synthesis. Together, this transcription factor network converts diverse upstream genetic lesions into a convergent metabolic phenotype, the metabolic hallmarks that define MDSC immunosuppressive identity, ultimately enhancing their suppressive function through coordinated metabolic reprogramming (53).

Microenvironmental and microbiota-derived distal regulators. Beyond cell-intrinsic genetic alterations, tumor-derived extracellular vesicles transfer miR-21, miR-155 and glycolytic enzymes directly into the MDSC cytosol, remotely reprogramming their metabolic circuitry (54,55). Specifically, miR-21 and miR-155 synergistically target PTEN and SHIP-1, respectively, to activate PI3K/AKT and STAT3 signaling, thereby driving a glycolytic shift in MDSCs (56). In parallel, tumor-derived exosomes can deliver PKM2 to myeloid cells, including MDSCs and macrophages (57), increasing glycolytic flux and lactate production, and thereby reinforcing their immunosuppressive or tumor-supportive phenotype (Tier 2). In the gut, microbial metabolites such as 4-hydroxybenzeneacetic acid activate the JAK2/STAT3 pathway, which upregulates C-X-C motif chemokine ligand 3 transcription, thereby recruiting PMN-MDSCs to the CRC microenvironment (18). Bile acids, through Takeda G protein-coupled receptor 5 receptor activation, promote MDSC infiltration in liver metastases. Within the tumor itself, intratumoral *Fusobacterium nucleatum* establishes a bidirectional reinforcement loop with MDSCs: The immunosuppressive TME provides a permissive niche for bacterial colonization, while *F. nucleatum* upregulates autophagy in cancer cells via toll-like receptor 4-myeloid differentiation primary response 88 signaling, conferring resistance to MDSC-derived ROS (58). Through these diverse distal inputs, MDSC metabolic identity is continuously reinforced by signals originating far beyond the tumor genome, and this remote regulatory network ultimately enhances MDSC suppressive function through sustained metabolic rewiring (59).

The 'mutation-metabolism-suppression' axis constitutes a self-reinforcing regulatory circuit: Oncogenic mutations activate master transcription factors, which rewire MDSC metabolism, which directly generates the immunosuppressive effector molecules that incapacitate antitumor immunity. Critically testing these mechanistic models, particularly the spatial dimension of MDSC-mediated immune exclusion, requires technologies that can resolve metabolic fluxes and metabolite distributions within native tissue contexts.

5. Emerging technologies: From descriptive profiling to spatial functional validation

Key questions emerge from the aforementioned mechanistic framework outlined: Whether MDSCs truly construct metabolically hostile zones around tertiary lymphoid structures, and how oncogenic signals are quantitatively transduced into specific metabolic fluxes, have traditionally been constrained by the limitations of bulk analytical approaches. Standard metabolomics (60), flow cytometry (61) and even single-cell transcriptomics (62) either average metabolic signals across heterogeneous populations or detect only transcriptional proxies of enzymatic activity rather than metabolic fluxes themselves, inevitably erasing the tissue context in which MDSC metabolic phenotypes operate. A suite of emerging technologies is now poised to overcome these constraints, enabling the transition from descriptive metabolic profiling to spatially resolved, dynamically quantified and functionally validated MDSC metabolism.

Decoding metabolic dynamics and single-cell heterogeneity. To transition from observing 'what is present' to quantifying 'how active a pathway is', metabolic flux analysis (MFA) serves as the gold standard (62,63). By combining stable isotope tracing (such as ^{13}C-glucose and ^{13}C-glutamine) with mass spectrometry, MFA tracks the flow and rate of labeled carbon atoms through metabolic networks. Rather than relying on static enzyme expression, MFA directly quantifies the rate at which ^{13}C-glucose channels into lactate via PKM2/LDHA or ^{13}C-palmitate enters mitochondrial β-oxidation via CPT1A (64). Recent applications of MFA in murine MDSC models have confirmed their intense carbon-sink behavior, directly explaining how MDSCs deplete microenvironmental nutrients to precipitate effector cell starvation. In a dynamic metabolic flux analysis of *in vitro* matured murine bone marrow-derived MDSCs, glycolytic flux contributed up to 95% of the global ATP turnover rate, with most glucose-derived carbon entering the TCA cycle; the model further suggested that MDSCs reduce the availability of carbon sources in the tumor periphery, which could explain the dysfunction and death of immune effector cells (65). In parallel, tumor-infiltrating MDSCs increase fatty acid uptake and activate FAO, accompanied by increased mitochondrial mass, upregulation of key FAO enzymes, and elevated oxygen consumption rate (66). MDSCs also compete with antigen-presenting cells for extracellular cystine and do not export cysteine, thereby depriving T cells of the cysteine required for activation and function (67).

Simultaneously, single-cell metabolomics is emerging to overcome the fundamental limitations of single cell RNA-sequencing, which relies on transcriptomic proxies rather than actual metabolic outputs (68,69). Utilizing high-resolution mass spectrometry and label-free dynamic analysis platforms, this technology captures the authentic metabolic fingerprints of individual cells (70). In the future, this technology may allow for the direct validation of whether high CPT1A mRNA expression in G-MDSCs truly translates into enhanced FAO flux, and whether ARG1 and iNOS expression in M-MDSCs function synergistically or exclusively at the single-cell level. However, application of single-cell metabolomics to CRC MDSCs remains technically challenging and is yet to be demonstrated.

High-dimensional spatial mapping of MDSC-associated metabolic gradients. The hypothesis that MDSCs construct a physical and chemical barrier around TLSs requires high-dimensional spatial validation. Spatial multi-omics integration, driven by algorithms such as SpatialMETA, co-registers spatial transcriptomics with spatial metabolomics/proteomics onto the exact same tissue coordinates (71). This breakthrough enables researchers to simultaneously visualize the molecular hierarchy within the same tissue voxel: Identifying cells actively transcribing arginase (ARG1 mRNA), mapping the precise regions where arginine is depleted (metabolite phenotype) and observing the consequent physical exclusion of T cells.

This spatial landscape is further illuminated by imaging mass cytometry (IMC) (72) and multiplexed ion beam imaging (73). Utilizing metal-isotope-labeled antibodies, IMC enables the simultaneous detection of >40 markers at subcellular resolution. By co-staining ARG1, iNOS, PD-L1, CD8 and hypoxia markers (such as carbonic anhydrase IX) in CRC tissues, researchers could potentially compute a proposed 'spatial suppression index' to map the exact density gradient of $CD8^+$ T cell decline within defined radii of MDSCs, although this approach remains to be validated in CRC tissues.

For real-time, *in vivo* visualization, live-cell metabolic imaging offers unprecedented temporal resolution. Label-free multi-modal non-linear optical imaging, such as stimulated Raman scattering microscopy, can track lipid droplets without fluorescent tags, verifying the FAO-preference of G-MDSCs (74). Concurrently, fluorescence lifetime imaging microscopy exploits the autofluorescence lifetime of NAD(P)H to differentiate between glycolysis (short-lifetime free NADH) and OXPHOS (long-lifetime enzyme-bound NADH), providing a direct window into the dynamic metabolic rewiring of MDSCs within living tumor tissue (75,76).

It is important to acknowledge that while these technologies hold promise, their application to CRC MDSC research is still in early stages. The proposed applications such as the 'spatial suppression index' or real-time metabolic imaging of MDSC-TLS interactions require substantial technical refinement and validation before they can be routinely applied in clinical or translational research settings. Furthermore, the cost, complexity and expertise required for these platforms limit their current accessibility.

Functional validation and unbiased target discovery. Moving beyond observational data, functionally validating the myriad of proposed metabolic targets (such as PKM2, CPT1A and GLS) necessitates advanced *ex vivo* models. Patient-derived organoid (PDO)-immune cell co-cultures successfully reconstruct the complex, patient-specific TME (77). By co-culturing autologous MDSCs and T cells with CRC organoids, researchers can perform precise 'metabolic interference experiments' to confirm whether targeting specific metabolic nodes reverses MDSC-mediated immunosuppression without compromising normal cellular networks.

Finally, while current research focuses on well-characterized targets such as ARG1 or CPT1A, CRISPR-Cas9 metabolic gene screening offers an unbiased approach to uncovering novel vulnerabilities (78). Utilizing lentiviral single guide RNA libraries targeting comprehensive metabolic gene sets (such as all fatty acid metabolism enzymes, including long-chain acyl-CoA synthetase and fatty acid desaturase families) within MDSC-T cell co-culture systems, this high-throughput screening platform can identify previously uncharacterized metabolic dependencies that maintain MDSC suppressive function, driving the discovery of next-generation immunometabolic therapeutic targets (79,80) (Table II).

6. MDSC metabolic signatures as precision biomarkers in CRC

MDSC metabolic enzymes as candidate biomarkers. The metabolic identity of MDSCs provides a rich source of candidate biomarkers. Glycolytic enzymes, serum HK2, LDHA activity and circulating lactate concentrations, may reflect the glycolytic pillar of MDSC activation. Notably, elevated serum LDHA and lactate have been implicated as prognostic markers in several malignancies, including CRC and pancreatic cancer, and have been suggested to associate with MDSC abundance and immunosuppressive activity (81). However, while these associations are suggestive, their specific utility as predictive biomarkers for ICI response in CRC remains to be prospectively validated, particularly given that the majority of evidence to date derives from correlative studies or extrapolation from other tumor types. Lipid metabolism markers, membrane CD36 expression on circulating G-MDSCs and serum CPT1A levels, may reflect the FAO activity of these cells. Elevated CD36 expression on peripheral blood G-MDSCs has been suggested to identify patients with a 'high FAO' MDSC phenotype that may preferentially benefit from FAO-targeted therapy (82). Amino acid metabolism markers, plasma arginine concentration, the arginine/ornithine ratio (AOR) reflecting ARG1 activity and serum GLS levels, provide complementary readouts of MDSC-mediated nutrient depletion. A low plasma AOR has been proposed as a surrogate marker of systemic MDSC burden. These metabolic markers can be measured using clinically available assays, ELISA for enzyme concentrations, colorimetric assays for metabolite levels and flow cytometry for transporter expression, facilitating their translation into routine practice (27,83). However, it should be noted that with the exception of correlative studies linking serum lactate and LDHA to MDSC abundance in CRC cohorts (84,85), the clinical utility of these biomarkers as predictive or prognostic tools has not been prospectively validated.

Furthermore, given the phenotypic overlap and dynamic plasticity of these cells, circulating MDSCs detected in peripheral blood may not perfectly mirror the metabolic state of tumor-infiltrating MDSCs adapted to a hypoxic and lactate-rich microenvironment. Future biomarker development must address this spatial translation gap.

MDSC metabolic phenotypes and clinical stratification. Based on the four metabolic pillars, the present study proposed a heuristic classification of MDSC metabolic phenotypes, hyper-glycolytic, hyper-lipid-oxidative and hyper-amino-acid-consuming as an exploratory framework (82,83). It is important to emphasize that this classification has not been validated by systematic clustering analysis in patient cohorts and should be considered a hypothesis-generating framework requiring prospective validation. It is plausible, based on indirect evidence, that different CRC molecular backgrounds may preferentially associate with distinct MDSC metabolic phenotypes. For example, consensus molecular subtype 4 tumors, which are characterized by high glycolytic activity and G-MDSC infiltration, may be enriched for a hyper-glycolytic MDSC phenotype (86); KRAS-mutant tumors, with their upregulated lipid metabolism, may favor a hyper-lipid-oxidative phenotype (87); and TP53-mutant tumors, which exhibit metabolic dysregulation, may associate with a hyper-amino-acid-consuming phenotype (88). However, these associations are currently speculative and based on circumstantial evidence; systematic

Table II. Emerging technologies for the functional and spatial validation of MDSC immunometabolism.

Technology	Core principle	Key advantage over traditional methods	Current/proposed application in MDSC immunometabolism	Application status
Metabolic flux analysis	Traces stable isotopes (such as ^{13}C-glucose and ^{13}C-glutamine) using mass spectrometry to map metabolic networks	Shifts from static metabolite concentrations to quantifying dynamic metabolic flux rates	Directly measuring the rate at which MDSCs consume microenvironmental nutrients (acting as 'carbon sinks') to starve T cells	Demonstrated in murine MDSC models; requires validation in CRC-MDSCs
Single-cell metabolomics	Utilizes high-resolution MS and label-free systems to capture metabolic fingerprints of individual cells	Captures true metabolic outputs, overcoming the reliance on mRNA proxies seen in scRNA-seq	Validating whether high CPT1A or ARG1 transcript levels in specific MDSC subsets truly translate into enhanced FAO or amino acid catabolism	Technically feasible but not yet applied to CRC-MDSC; proposed/future application
Spatial multi-omics integration	Co-registers spatial transcriptomics with spatial metabolomics onto the exact same tissue coordinates (SpatialMETA)	Provides a systemic 3D landscape integrating gene expression and metabolite distribution	Visualizing the 'metabolic no-man's land' around TLSs by mapping *ARG1* transcription, arginine depletion and T cell exclusion simultaneously	Proposed conceptual framework; awaiting experimental confirmation in CRC
Imaging mass cytometry/ MIBI	Uses metal-isotope-labeled antibodies and MS scanning for highly multiplexed tissue imaging	Enables simultaneous detection of 40+ markers at subcellular resolution within intact tissue.	Mapping the spatial distribution of MDSCs (ARG1/ iNOS^{+}) and calculating the 'spatial suppression index' gradient of CD8^{+} T cells.	Demonstrated in other tumor types; requires validation in CRC tissues
Live-cell metabolic imaging (SRS/FLIM)	Employs label-free multi-modal non-linear optical imaging to track endogenous molecules based on structural or fluorescence lifetime differences	Allows for real-time, *in vivo* spatiotemporal tracking without the need for fluorescent tags	Directly observing lipid droplet accumulation (FAO) via SRS, or mapping glycolysis/OXPHOS shifts in MDSCs via NAD(P)H FLIM	Technically feasible but requires validation in CRC-MDSC models
PDO-immune cell co-cultures	Co-cultivates patient-derived tumor organoids with autologous immune cells (MDSCs/T cells)	Preserves patient-specific genetic backgrounds and 3D tumor architecture for functional testing	Conducting precise *ex vivo* 'metabolic interference experiments' to validate the efficacy of metabolic inhibitors in restoring T cell function	Emerging application; requires standardization for CRC-MDSC studies
CRISPR-Cas9 metabolic gene screening	Utilizes lentiviral sgRNA libraries to systematically knock out specific metabolic gene sets	Enables unbiased, high-throughput discovery of novel functional nodes rather than relying on known targets	Identifying previously uncharacterized metabolic dependencies (specific lipid synthesis enzymes) required for MDSC suppressive function	Preclinical; proposed for MDSC-T cell co-culture systems

MDSC, myeloid-derived suppressor cell; CRC, colorectal cancer; sgRNA, single guide RNA; FAO, fatty acid oxidation; OXPHOS, oxidative phosphorylation; ARG1, arginine 1; iNOS, inducible nitric oxide synthase; SRS, stimulated Raman scattering; MIBI, multiplexed ion beam imaging; PDO, patient-derived organoid. scRNA-seq, single cell RNA-sequencing; MS, mass spectrometry. FLIM, fluorescence lifetime imaging microscopy.

metabolic profiling of MDSCs stratified by CRC molecular subtypes is needed to validate or refute these hypotheses. CMS1 (MSI-H subtype) typically displays low MDSC infiltration, but a specific PMN-MDSC subpopulation regulated by H3K18la at the C-X-C motif chemokine receptor 2 (CXCR2) promoter has been identified as driving acquired resistance to programmed cell death protein 1 (PD-1) blockade, representing a metabolically 'sleeper' population that undermines durable responses (20). These proposed phenotypes provide a hypothesis-generating framework for precision patient stratification, patients with a predominant 'hyper-glycolytic' MDSC phenotype may benefit most from MCT4 or HK2 inhibitors, while those with a 'hyper-lipid-oxidative' signature may respond preferentially to CPT1A blockade, although these predictions require systematic validation (89,90).

MDSC metabolic features predict immunotherapy response. The predictive value of MDSC metabolic features for immunotherapy response has been demonstrated in clinical cohorts. A high pretreatment circulating MDSC/$CD8^+$ T cell ratio has been associated with diminished clinical benefit from pembrolizumab in CRC cohorts, while a lower ratio is associated with favorable response (91,92). Adding metabolic parameters (such as serum lactate and the AOR) may have the potential to improve predictive accuracy beyond cell counts alone, although this remains to be validated in prospective cohorts with appropriate statistical power. Currently, no established thresholds, sensitivity/specificity or area under the curve/receiver operating characteristic data are available for these candidate markers in patients with CRC receiving ICI therapy. Mechanistically, high ARG1 expression by MDSCs depletes microenvironmental arginine, rendering T cells metabolically starved. This explains why CEA decline is not always associated with clinical benefit, even when tumor burden decreases, MDSC-imposed metabolic constraints can prevent effective antitumor immunity. While incorporating MDSC metabolic markers into ICI response prediction models represents a promising direction, this approach remains exploratory. Future studies should prospectively evaluate whether the addition of metabolic parameters improves predictive accuracy, with appropriate statistical validation including cohort-specific effect estimates and discrimination statistics (82,93).

Several limitations must be acknowledged regarding the clinical translation of MDSC metabolic biomarkers. First, the majority of reported associations are correlative and derived from small retrospective cohorts; prospective validation in large, independent patient populations is lacking. Second, circulating metabolite levels may be influenced by multiple confounding factors, including tumor burden, systemic inflammation, nutritional status and treatment history (94), which must be carefully controlled. Third, standardized assay protocols and clinically meaningful cutoff values have not been established for most candidate markers. Fourth, the specificity of these biomarkers for MDSC metabolism, as opposed to tumor cell metabolism or other immune cell activity, requires rigorous demonstration through MDSC-specific metabolic profiling. Until these challenges are addressed, the proposed metabolic signatures should be considered exploratory research tools rather than clinically validated biomarkers.

7. Immunometabolic rehabilitation: Reprogramming MDSC metabolism to restore immunity

From depletion to functional reversal. Traditional MDSC-targeted strategies, depletion via low-dose chemotherapy and recruitment blockade via colony-stimulating factor 1 receptor/CXCR2 inhibitors operate fundamentally as 'subtractive' approaches: They aim to eliminate MDSCs from the TME or prevent their arrival (95). These strategies are inherently limited by compensatory expansion of alternative MDSC subsets and systemic toxicity. Additionally, they overlook a key biological reality: MDSCs are not obligate immunosuppressors but plastic cells whose functional identity is dynamically maintained by specific metabolic programs (96). This insight opens a fundamentally different therapeutic avenue: Not eliminating these cells but functionally reversing them (Table III).

This approach is termed 'immunometabolic rehabilitation'. Its core principle is functional reversal rather than physical ablation, severing the metabolic lifelines that sustain MDSC suppressive identity while simultaneously activating differentiation pathways that redirect these cells into non-suppressive or even immunostimulatory myeloid effectors (97). Since the suppressive phenotype of MDSCs is maintained by glycolysis, FAO and glutaminolysis, it is pharmacologically reversible; interrupting these metabolic programs unmasks latent immunostimulatory potential. This rehabilitative strategy offers a key advantage: Preservation of tissue homeostasis. Unlike depletion, which indiscriminately removes myeloid cells essential for wound healing, pathogen clearance and homeostatic phagocytosis, immunometabolic rehabilitation dismantles immunosuppression while leaving the host immunologically competent. Conceptually, it transforms MDSCs from a predominantly suppressive to a homeostatic or immunostimulatory immune phenotype, a paradigm shift from subtraction to conversion (Fig. 4).

Glycolysis-lactate axis rehabilitation. Disrupting the glycolytic addiction of MDSCs represents a frontline rehabilitative strategy. HK2 inhibitors such as 2-deoxy-D-glucose block glucose utilization. Notably, inhibition of HK2 with 3-bromopyruvate (3-BrPA) has been reported to promote MDSC differentiation and enhance, rather than reduce, immunosuppressive function (98), highlighting that metabolic reprogramming is not a simple 'nutrient cut-off' and requires target-specific approaches when considering glycolytic inhibition as a rehabilitative strategy. Consequently 3-BrPA is not recommended as a prototypical rehabilitative agent in the proposed framework.

Simultaneously, MCT1 inhibitors, such as AZD3965, block lactate uptake via MCT1, thereby reducing intracellular lactate signaling and disrupting the lactate-GPR81-STAT3 feed-forward loop (99). However, MCT4-mediated lactate export may compensate for MCT1 blockade, as AZD3965 has limited activity against MCT4. Selective MCT4 blockade, either through small-molecule MCT4 inhibitors (such as VB-62176) (100) or dual MCT1/MCT4 inhibitors (such as syrosingopine) (101), represents a mechanistically distinct approach from isolated MCT1 inhibition. Crucially, as demonstrated by Babl *et al* (100), MCT4-specific blockade has been functionally validated in 3D human CRC tumor

Table III. Targeted strategies and translational landscape of 'immunometabolic rehabilitation' in CRC.

Metabolic intervention dimension	Targeted molecules/ pathways	Representative agents (preclinical/clinical)	Core 'immunometabolic rehabilitation' mechanisms	Evidence level/ clinical status	Caveats/limitations	(Refs.)
Blockade of glycolysis-lactate axis	HK2, MCT1 and MCT4	2-DG, 3-BrPA (not recommended), AZD3965 (MCT1 inhibitor) and selective MCT4 inhibitors	Blocks glucose utilization; inhibits lactate efflux, disrupting the 'lactate-STAT3' feed-forward loop and reversing epigenetic locking.	Preclinical (validated in 3D CRC models and extrapolated from solid tumors) + early clinical (MCT1/AZD3965)	2-DG is non-selective; affects multiple cell types. AZD3965 is MCT1-selective. MCT4-specific blockade overcomes compensatory export in CRC; lineage-specific MDSC targeting requires further prospective validation	(98-101)
Rewiring of lipid metabolism	CPT1, CD36 and COX-2	Etomoxir, CD36 blocking antibodies, COX-2 inhibitors (e.g., celecoxib)	Deprives G-MDSCs of energetic fuel, reducing ROS-mediated oxidative stress; severs the PGE_2 immunosuppressive network.	Preclinical	Etomoxir affects FAO in tumor cells, T cells and other immune populations; MDSC-specific mechanism requires lineage-restricted genetic deletion studies	(102,103,114)
Restoration of amino acid homeostasis	ARG1, GLS and IDO	CB-1158, CB-839 and JHU083	Replenishes microenvironmental nutrients, relieving T cell proliferation suppression; drives MDSC mitochondrial metabolic collapse.	Preclinical + Phase I/II (CB-1158: modest activity in MSS CRC; Phase I/II trials NCT02903914 and NCT03314935)	CB-1158 shows modest activity in MSS CRC (PR + SD: 27%); recent PDO studies suggest limited efficacy. Requires further validation	(77,104-107)
Mitochondrial reprogramming and differentiation	AMPK and PI3Kγ	Metformin, IPI-549 and ATRA	Drives terminal differentiation of MDSCs, reprogramming them into mature, immunostimulatory myeloid cells with robust antitumor activity.	Preclinical + approved (Metformin for T2DM; ATRA for APL)	Systemic metabolic effects; MDSC-specific contribution requires functional validation in CRC patient samples	(108-110)
Combination strategies (clinical)	Multi-targeted TKIs and ICIs	Zanzalintinib + atezolizumab (STELLAR-303); mFOLFOX6/bevacizumab/ atezolizumab (COMMIT)	Demonstrates clinical efficacy; potential MDSC modulation through VEGF inhibition and TME remodeling	Phase III (STELLAR-303: OS, 10.9 vs. 9.4 months; HR, 0.80; COMMIT: PFS, 24.5 vs. 5.3 months; HR, 0.439)	Clinical efficacy does not by itself validate MDSC metabolic reprogramming as the mechanism. Mechanistic attribution requires correlative MDSC biomarker analysis and functional validation in trial participants	(111,112)

Evidence levels: Preclinical/Phase I/Phase I/II/Phase II/Phase III/Approved. HK2, hexokinase 2, MCT, monocarboxylate transporter; 3-BrPA, 3-bromopyruvate; 2-DG, 2-deoxy-D-glucose; CPT1, carnitine palmitoyltransferase I; COX-2, cyclooxygenase-2, ROS, reactive oxygen species; ARG1, arginine 1; TME, tumor microenvironment; GLS, glutaminase; IDO, indoleamine 2,3-dioxygenase; TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; APL, acute promyelocytic leukemia; T2DM, type 2 diabetes mellitus; OS, overall survival; PFS, progression free survival; HR, hazard ratio.

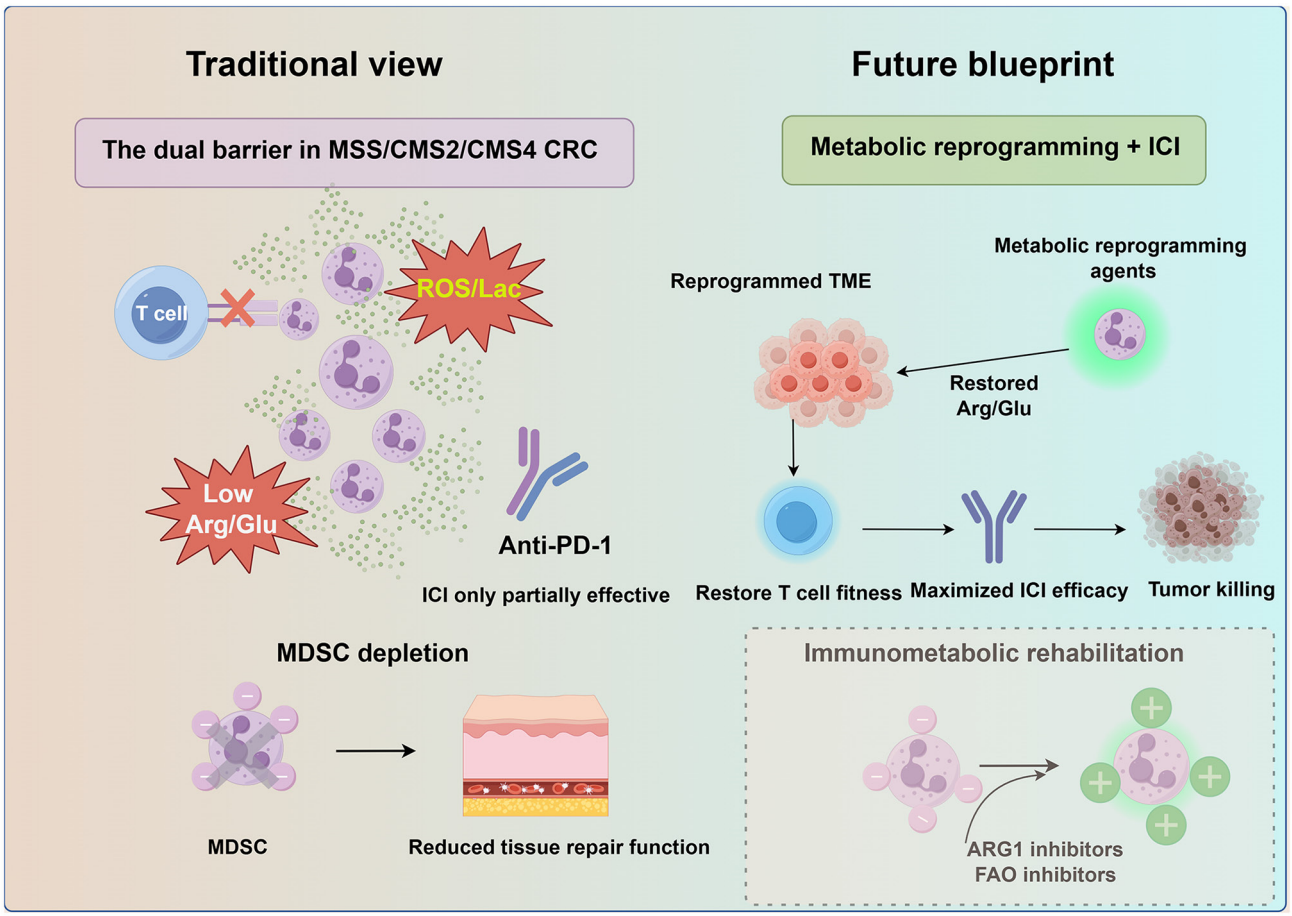


Figure 4. Conceptual transition from broad MDSC depletion to immunometabolic rehabilitation in CRC. Schematic illustration contrasting the traditional paradigm of immunosuppression with the proposed model of immunometabolic rehabilitation. (Left) In the traditional view, MDSC-derived metabolic suppressive factors (such as ROS, lactate accumulation and local depletion of arginine/glucose) form a dual metabolic wall that limits effective T cell fitness and diminishes the efficacy of ICIs. Systemic depletion of MDSCs risks impairing essential tissue repair and homeostatic functions. (Right) The proposed 'immunometabolic rehabilitation' framework utilizes targeted metabolic modulators (such as ARG1 inhibitors, FAO inhibitors or monocarboxylate transporter blockers) to functionally convert suppressive MDSCs into non-suppressive or homeostatic phenotypes rather than destroying them. This metabolic reprogramming aims to dismantle the microenvironmental barrier, restore T cell fitness and synergize with ICIs. Demonstrated clinical efficacy of combination regimens (including in trials such as STELLAR-303 or COMMIT) reflects overall antitumor activity; attributing these benefits directly to MDSC-specific metabolic reprogramming represents an exploratory scientific model requiring further mechanistic validation in patient cohorts. Solid lines denote pathways experimentally validated in CRC models (Tier 1); dashed lines represent proposed therapeutic mechanisms and hypothetical models requiring further confirmation (Tiers 2 and 3). MDSC, myeloid-derived suppressor cells; ICI, immune checkpoint inhibitors; ARG1, arginine 1; ROS, reactive oxygen species; FAO, fatty acid oxidation; CRC, colorectal cancer; TME, tumor microenvironment; PD-1, programmed cell death protein 1; MSS, microsatellite stable; CMS, consensus molecular subtype.

models to overcome compensatory lactate export, reverse lactic-acid-driven immunosuppression and boost immune checkpoint blockade efficacy (Tier 1), with additional mechanistic rationale extrapolated from preclinical models across other solid tumors (Tier 2). Furthermore, by reducing extracellular lactate availability, MCT inhibition diminishes the substrate for H3K18la, potentially reversing the epigenetic locking of ARG1 expression. Preclinical CRC models demonstrate that MCT blockade can synergize with anti-PD-1 therapy; however, as these studies involve systemic administration, the relative contribution of MDSC-specific vs. tumor cell-intrinsic or T cell-intrinsic effects remains to be definitively disentangled through lineage-restricted genetic deletion studies.

Lipid metabolism rehabilitation. For 'lipid-burning' G-MDSCs, pharmacological blockade of FAO with CPT1 inhibitors such as etomoxir has been demonstrated to reduce ROS production and MDSC suppressive function *in vitro*. However, etomoxir also affects FAO in tumor cells, T cells and other immune populations. The *in vivo* antitumor efficacy of etomoxir or other FAO inhibitors cannot therefore be interpreted as establishing MDSC-specific mechanism without appropriate controls, including myeloid-specific genetic deletion of CPT1A (or other FAO enzymes) or purified MDSC transfer experiments (102). Blocking lipid uptake via CD36 neutralizing antibodies or inhibiting PGE_2 synthesis through COX-2 blockade further attenuates the immunosuppressive lipid network. The combination of CPT1 inhibition with ICIs has demonstrated enhanced antitumor efficacy compared with either agent alone in preclinical CRC models (103).

Amino acid metabolism rehabilitation. ARG1 inhibitors such as CB-1158 (numidargistat) replenish microenvironmental arginine and restore T cell proliferation in preclinical models (104). In clinical evaluation, a phase I/II study

(NCT02903914) evaluated CB-1158 as a single agent and in combination with pembrolizumab in advanced solid tumors, including MSS CRC. Preliminary phase I data demonstrated modest activity (partial response + stable disease: 27% in MSS CRC), indicating that ARG inhibition requires further refinement (105). However, recent PDO studies suggest limited efficacy in MSS CRC, with CB-1158 failing to enhance T cell recognition or cytotoxicity. Thus, while ARG inhibition remains a biologically rational strategy, its clinical utility in CRC requires further investigation (77,104,105). Glutaminase antagonists (CB-839 and the TME-activated prodrug JHU083) simultaneously dismantle MDSC mitochondrial respiration while promoting a shift toward a helper T cell phenotype (106). IDO inhibitors, when combined with ICIs, have demonstrated potential in reversing tryptophan-mediated immune tolerance in CRC models (107).

Mitochondrial reprogramming and differentiation therapy. The most transformative application of immunometabolic rehabilitation lies in actively driving MDSC differentiation into mature, non-suppressive myeloid cells. Metformin inhibits mitochondrial complex I and activates AMPK, promoting MDSC differentiation toward an antitumor phenotype. PI3Kγ inhibition with IPI-549 reduces ROS and ARG1 expression, shifting MDSCs toward an immunostimulatory state (108,109). All-trans retinoic acid fosters MDSC maturation and decreases circulating MDSC levels in patients with CRC (110). Collectively, these interventions embody the core principle of rehabilitation: The functional identity of MDSCs is not fixed but can be therapeutically redirected by altering their metabolic wiring.

Combination strategies and clinical validation. The integration of metabolic rehabilitation with ICIs is supported by recent phase III trials. The STELLAR-303 phase III trial demonstrated a significant overall survival (OS) benefit for zanzalintinib-atezolizumab over regorafenib in refractory MSS mCRC [median OS, 10.9 vs. 9.4 months; hazard ratio (HR), 0.80; 95% CI, 0.69-0.93; P=0.0045]. While this represents the first immunotherapy-based regimen to indicate an OS benefit in this historically refractory population, the trial results do not by themselves validate MDSC metabolic reprogramming as the underlying mechanism. The observed benefit may be mediated through multiple pathways, including VEGF inhibition, reduced MDSC mobilization and direct effects on tumor cells, and future mechanistic studies are needed to establish causality (111). In the MSI-H setting, the phase III COMMIT trial (NRG-GI004/SWOG-S1610; n=168) demonstrated that mFOLFOX6/bevacizumab/atezolizumab significantly improved progression free survival (PFS) compared with atezolizumab monotherapy in first-line deficient mismatch repair/MSI-H mCRC (median PFS, 24.5 vs. 5.3 months; HR, 0.439; 95% CI, 0.23-0.84; P=0.0103; prespecified primary endpoint). However, the trial was not designed to establish MDSC-specific metabolic reprogramming as the mechanism of action (112).

A key distinction must be made throughout this section: Demonstrating clinical efficacy of a combination regimen does not equate to proving that the benefit is mediated through MDSC-specific metabolic reprogramming. Establishing the latter requires: i) Correlative analyses of MDSC metabolic markers with clinical response in trial participants; ii) functional validation of MDSC suppression reversal in patient samples; and iii) evidence that metabolic changes in MDSCs precede or correlate with T cell reinvigoration. Unless such evidence is available, clinical trial results should be cited as supportive of the therapeutic potential of combination strategies rather than as direct validation of the immunometabolic rehabilitation framework.

8. Challenges, bottlenecks and future directions

Current bottlenecks in clinical translation. Several challenges hinder the translation of immunometabolic rehabilitation into clinical practice. The safety and selectivity of metabolic inhibitors remain primary concerns, glycolysis and FAO are essential for normal tissues, and achieving a therapeutic window that preferentially targets MDSCs while sparing normal myelopoiesis requires careful optimization. A distinction must be maintained throughout the present section: Observing antitumor responses following systemic metabolic inhibition does not establish MDSC-specific mechanism. Strong mechanistic evidence for MDSC-specific metabolic targeting requires: i) Lineage-restricted genetic perturbation (such as myeloid-specific deletion of CPT1A, GLS or HK2); ii) purified MDSC-subset experiments demonstrating functional reversal of T cell suppression; iii) metabolic-flux measurements confirming target engagement in MDSCs; iv) rescue experiments restoring the metabolic pathway to confirm specificity; and v) correlative evidence linking MDSC metabolic changes to T cell reinvigoration *in vivo*. The majority of studies cited in the present section provide correlative or indirect evidence; the field is still evolving toward the aforementioned rigorous experimental standards. To address this, future efforts should prioritize the development of tumor-targeted delivery systems that confine metabolic inhibitors to the TME, minimizing systemic exposure (113). Nanoparticle-based formulations engineered to accumulate in tumor tissues via the enhanced permeability and retention effect or functionalized with ligands recognizing MDSC surface receptors (such as CD33 and CD36), could selectively deliver FAO inhibitors or MCT blockers to intratumoral MDSCs while largely sparing normal myeloid cells (114). Antibody-drug conjugates targeting MDSC-enriched markers represent another promising avenue, coupling metabolic inhibitors to monoclonal antibodies that recognize MDSC-expressed antigens for cell-specific payload delivery. Such targeted strategies could substantially widen the therapeutic index of metabolic inhibitors (115). Subtype-specific considerations further complicate translation: G-MDSCs and M-MDSCs exhibit distinct metabolic dependencies, and a one-size-fits-all metabolic inhibitor approach may inadvertently promote compensatory expansion of the non-targeted subset. The absence of validated companion biomarkers to prospectively identify patients likely to benefit from specific metabolic interventions represents another critical gap.

Spatial metabolomics to decode MDSC-TLS interactions. Beyond these translational hurdles, however, lies a more fundamental obstacle: Several core mechanistic hypotheses

central to immunometabolic rehabilitation, most notably the proposed 'metabolic siege' of tertiary lymphoid structures remain experimentally unvalidated. Resolving these spatial mechanistic questions is not merely an academic exercise; it is a prerequisite for the rational design of spatially targeted interventions. This is where emerging technologies become indispensable.

A key direction is the application of spatial metabolomics (matrix-assisted laser desorption ionization-MSI and desorption electrospray ionization-MSI) integrated with imaging mass cytometry to experimentally validate the proposed MDSC-TLS 'metabolic siege' model (116). These technologies can map the precise metabolic gradients, lactate enrichment, arginine depletion, reactive nitrogen species accumulation, that demarcate MDSC-enriched zones from TLS-containing regions (117). Resolving this spatial architecture will inform whether metabolic rehabilitation can re-open TLS conduits for effector cell trafficking into the tumor core.

Microbiome-metabolism-MDSC axis as a therapeutic target. While spatial metabolomics addresses the local metabolic architecture within tumor tissue, a complementary dimension of MDSC regulation operates systemically: The gut and intratumoral microbiota. These microbial communities continuously release metabolites that enter the circulation and reach the TME, where they shape MDSC recruitment and metabolic function. Targeting this microbiome-MDSC axis represents a fundamentally distinct strategy from direct metabolic inhibition, one that aims to dismantle the microbial inputs that sustain MDSC pathogenicity from the top down.

Interventional strategies including dietary modifications that alter microbial metabolite profiles, precision antibiotics targeting *F. nucleatum* (118) and fecal microbiota transplantation (119) may indirectly reprogram MDSC metabolism by manipulating the microbial inputs that sustain their suppressive phenotype. Dietary interventions, for instance, can shift the gut microbiome composition toward a profile less permissive for MDSC recruitment, reducing systemic levels of MDSC-promoting metabolites such as 4-hydroxybenzeneacetic acid. Precision antibiotics offer a more targeted approach by selectively eliminating intratumoral *F. nucleatum*, which drives MDSC recruitment and confers ROS resistance to tumor cells (18,120,121). As demonstrated in recent work from the present authors (122), disrupting the pathogen-tumor symbiosis through the elimination of intratumoral *F. nucleatum* using protein-supported copper single-atom nanozymes successfully restores tumor cell sensitivity to ROS (tumor growth inhibition up to 82.97%). This example highlights the potential of combining precision pathogen clearance with MDSC-targeted immunometabolic rehabilitation. The combination of targeted antibiotic therapy with MDSC metabolic inhibitors represents a particularly attractive strategy. Fecal microbiota transplantation from healthy donors may restore a homeostatic microbiome that no longer sustains pathological MDSC activation. Clinical trials integrating these microbiome-directed interventions with metabolic rehabilitation and ICIs warrant exploration (123).

Artificial intelligence (AI)-guided precision immunometabolic rehabilitation. The complexity of MDSC metabolic networks spanning four interconnected pillars, multiple subsets and dynamic microenvironmental influences necessitates computational approaches for rational therapeutic design. Machine learning algorithms trained on integrated multi-omics datasets (metabolomics, transcriptomics and spatial proteomics) could predict optimal metabolic intervention combinations for individual patients based on the tumor mutational profile, MDSC metabolic subtype and microbiome composition (124). Beyond patient stratification, AI is poised to revolutionize the discovery and screening of novel immunometabolic therapeutics. Deep learning and generative AI can accelerate high-throughput virtual screening and *de novo* drug design by targeting specific MDSC metabolic vulnerabilities. A key application lies in the identification of allosteric regulatory sites on metabolic enzymes, pockets topographically distinct from the active site that permit selective, non-competitive inhibition. By integrating AI-driven structural biology (such as AlphaFold-based platforms), these elusive allosteric pockets can be systematically mapped, enabling the rapid screening of billion-scale compound libraries to discover inhibitors that selectively target MDSC isoforms while sparing their counterparts in normal immune cells, a key requirement for minimizing systemic toxicity (125). Furthermore, AI-based network pharmacology can accelerate drug repurposing efforts by identifying unexpected immunometabolic rehabilitative properties of existing FDA-approved drugs. Such AI-driven precision approaches may ultimately guide both the development of next-generation drugs and the personalized deployment of immunometabolic rehabilitation, maximizing therapeutic efficacy while minimizing toxicity (126).

9. Conclusions

MDSCs appear to serve as key gatekeepers of immune evasion in CRC, with evidence supporting a 'mutation-metabolism-suppression' axis as an integrative framework. Driver mutations in APC, KRAS and TP53 converge on master transcription factors: HIF-1α, MYC, STAT3, C/EBPβ and SREBP to influence MDSC metabolism toward glycolysis, FAO and amino acid scavenging. These metabolic adaptations construct biochemical and spatial barriers: Arginine depletion drives T cell metabolic exhaustion, lactate accumulation paralyzes effector function, ROS creates chemokine-inactivating oxidative shields and lipid-derived PGE_2 fosters a suppressive microenvironment. Spatially, we hypothesize that MDSCs may limit the functional activity of TLSs by constructing metabolically hostile zones that may restrict effector lymphocyte activity a model that awaits experimental confirmation.

To overcome these barriers, a paradigm shift is proposed from non-specific myeloid ablation to immunometabolic rehabilitation, a framework that severs the metabolic lifelines sustaining MDSC pathogenicity and reprograms these cells from a predominantly suppressive to a potentially homeostatic or supportive immune phenotype. By dismantling the metabolic link between oncogenic mutations and immune evasion through glycolysis-lactate axis disruption, lipid metabolism rewiring, amino acid pathway restoration

and mitochondrial reprogramming, this approach achieves immunosuppression reversal without the collateral damage of myeloid ablation. Integration of metabolic rehabilitation with ICIs, pathogen-directed interventions and fecal microbiota transplantation guided by CMS subtype, metabolic biomarker signatures and AI-driven precision algorithms offers a comprehensive strategy for breaking immune tolerance across both MSS and MSI-H CRC. The coming decade may witness the maturation of immunometabolic rehabilitation from mechanistic concept to clinical reality, provided that ongoing challenges in target validation, drug specificity, and biomarker development are successfully addressed. The proposed framework should therefore be viewed as a hypothesis-driven roadmap to guide future investigation rather than as an established therapeutic paradigm.

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Authors' contributions

LXZ wrote the initial draft of the manuscript. GJJ interpreted literature data to design the key mechanistic diagrams. FHG and YQD contributed to the study design and final manuscript preparation. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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