Glycolysis-driven immunosuppression in gastric cancer: Metabolic crosstalk between tumor cells and the immune microenvironment (Review)

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Abstract. Gastric cancer (GC) remains a major cause of cancer-related mortality worldwide, and only a subset of patients achieves durable benefit from immune checkpoint blockade (ICB). This suggests that non-genomic barriers within the tumor microenvironment (TME) substantially limit antitumor immunity. Increasing evidence indicates that tumor-intrinsic glycolytic reprogramming and lactate accumulation contribute to this immune resistance. Oncogenic signaling, hypoxia-inducible factor-1α (HIF-1α), phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (mTOR) pathways and noncoding RNA networks promote the expression of glycolytic enzymes and lactate transporters, including hexokinase 2, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), pyruvate kinase M2, lactate dehydrogenase A (LDHA) and monocarboxylate transporters, thereby establishing a glycolysis-high, lactate-rich TME. Within this metabolic niche, lactate functions as a bioactive mediator that impairs dendritic cell differentiation and cross-priming, weakens cytotoxic T-cell and natural killer-cell activity,

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Abbreviations: 2-DG, 2-deoxy-D-glucose; AMPK, AMP-activated protein kinase; ARG1, arginase 1; ATP, adenosine triphosphate; CAF, cancer-associated fibroblast; cDC1, conventional type 1 dendritic cell; ceRNA, competitive endogenous RNA; circRNA, circular RNA; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DCA, dichloroacetate; EBV, Epstein-Barr virus; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FA, fatty acid; FAK, focal adhesion kinase; FDG, fluorodeoxyglucose; GC, gastric cancer; GLUT1/3, glucose transporter 1/3; HCAR1/GPR81, hydroxycarboxylic acid receptor 1/G protein-coupled receptor 81; HER2, human epidermal growth factor receptor 2; HIF-1α, hypoxia-inducible factor-1α; HK2, hexokinase 2; ICB, immune checkpoint blockade; IFN-γ, interferon-γ; IL, interleukin; IRF, interferon regulatory factor; LAG-3, lymphocyte activation gene-3; LDHA, lactate dehydrogenase A; lncRNA, long noncoding RNA; MAPK, mitogen-activated protein kinase; MCT1/4, monocarboxylate transporter 1/4; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; miRNA, microRNA; MRC1, mannose receptor C-type 1; MSC, mesenchymal stem/stromal cell; MTV, metabolic tumor volume; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; NAD^+, oxidized nicotinamide adenine dinucleotide; ncRNA, noncoding RNA; NF-κB, nuclear factor κB; NK, natural killer; OXPHOS, oxidative phosphorylation; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PDK, pyruvate dehydrogenase kinase; PER1, period circadian regulator 1; PET/CT, positron emission tomography/computed tomography; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PI3K, phosphoinositide 3-kinase; PKM2, pyruvate kinase M2; ROS, reactive oxygen species; SMYD2, SET and MYND domain-containing protein 2; STAT, signal transducer and activator of transcription; SUVmax, maximum standardized uptake value; TAZ, transcriptional coactivator with PDZ-binding motif; TCA, tricarboxylic acid; TGF-β, transforming growth factor-β; TLG, total lesion glycolysis; TME, tumor microenvironment; Treg, regulatory T cell; VEGFA, vascular endothelial growth factor A; WNT5A, wingless-type MMTV integration site family member 5A; YAP, yes-associated protein; SULmax, maximum standardized uptake value normalized by lean body mass; SULpeak, peak standardized uptake value normalized by lean body mass

Key words: gastric cancer, tumor immunometabolism, glycolysis, lactate, tumor microenvironment, dendritic cells, immune checkpoint blockade, metabolic imaging

and promotes M2-like macrophages and myeloid-derived suppressor cells through hydroxycarboxylic acid receptor 1/G protein-coupled receptor 81-dependent signaling and histone lactylation. Cancer-associated fibroblasts and mesenchymal stem/stromal cells further reinforce this state through glycolysis, lactate shuttling, cytokine secretion, extracellular matrix remodeling and exosome-mediated transfer of glycolysis-promoting noncoding RNAs. These interactions generate spatially organized immunometabolic niches characterized by lactate accumulation, stromal remodeling, abnormal angiogenesis and poor $CD8^+$ T-cell infiltration. The present review summarizes the molecular drivers of glycolytic reprogramming in GC, the mechanisms by which lactate-centered crosstalk reshapes stromal and immune compartments, and emerging therapeutic strategies targeting LDHA/monocarboxylate transporter 4, PFKFB3, HIF-1α/mTOR, epigenetic regulators and repurposed metabolic drugs in combination with programmed death-1/programmed death-ligand 1 blockade. It is also discussed how fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography, radiomics, glycolysis- and lactylation-related gene signatures, exosomal biomarkers and dynamic metabolic monitoring may support patient stratification and response prediction. Viewing selected GC subtypes through a glycolysis-centered immunometabolic framework may help guide the rational integration of metabolic and immune interventions to overcome metabolically protected, ICB-refractory disease.

Contents

1. Introduction

Gastric cancer (GC) ranks as the fifth most frequently diagnosed malignancy and the third leading cause of cancer-related mortality worldwide, with a particularly high incidence in East Asia, where dietary exposures, chronic inflammation and persistent *Helicobacter pylori* infection are prevalent (1,2). Despite advances in surgery, perioperative chemotherapy and targeted therapy, numerous patients still present with advanced disease, and the 5-year survival rate remains unsatisfactory (3,4). Immune checkpoint blockade (ICB) targeting programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1), human epidermal factor receptor 2 (HER2)-directed regimens and fibroblast growth factor receptor 2b-targeted agents have improved outcomes in biomarker-selected subgroups. However, durable benefit remains limited to a minority of patients, indicating that conventional clinicopathologic and genomic classifications do not fully capture key barriers to effective antitumor immunity (5-7).

A major barrier is tumor-intrinsic metabolic reprogramming and its impact on the tumor microenvironment (TME). GC cells preferentially engage aerobic glycolysis, also known as the Warburg effect, converting glucose to lactate even under normoxic conditions. This process supports rapid adenosine triphosphate (ATP) generation and biosynthesis while simultaneously depleting nutrients for effector lymphocytes and acidifying the TME (8-10). Lactate accumulation and low pH impair dendritic cell (DC) differentiation and cross-priming and disrupt cytotoxic T lymphocyte (CTL), natural killer (NK)-cell and regulatory T-cell (Treg) homeostasis, collectively promoting immune escape (11-13). This glycolytic phenotype is reinforced by hypoxia-inducible factor-1α (HIF-1α), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) signaling, chronic *Helicobacter pylori*-driven inflammation and noncoding RNA (ncRNA) networks that upregulate glycolytic enzymes such as hexokinase 2 (HK2), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), pyruvate kinase M2 (PKM2) and lactate dehydrogenase A (LDHA) and couple inflammatory cues to PD-L1 expression (14-17).

These metabolic changes have clear clinical associations. High LDHA and monocarboxylate transporter (MCT)4 expression are associated with deeper invasion, nodal metastasis, immune-excluded histology and increased uptake on fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) (18,19). Diffuse-type and Epstein-Barr virus (EBV)-positive tumors with dense stroma often display enriched glycolytic and lactate-transport signatures, together with poor $CD8^+$ T-cell and DC infiltration. Glycolysis- or lactylation-based transcriptional signatures can further stratify patients into metabolic-immune subgroups with distinct prognosis and differential likelihood of responding to ICB (9,20,21). The surrounding stroma further amplifies this axis: Cancer-associated fibroblasts (CAFs) and mesenchymal stem/stromal cells (MSCs) adopt aerobic glycolysis, export lactate and secrete cytokines such as interleukin (IL)-6 and IL-8. In parallel, ncRNAs, including long noncoding RNAs (lncRNAs), microRNAs (miRNAs or miRs) and circular RNAs (circRNAs), fine-tune glycolytic enzymes and immune checkpoints, linking glucose metabolism to stemness, drug resistance and immune escape (22-25).

From a translational perspective, the glycolysis-lactate axis presents both vulnerabilities and challenges. Lactate is now recognized as a bioactive metabolite that drives histone lactylation, M2-like macrophage polarization, tolerogenic DC differentiation and PD-L1 upregulation through LDHA-dependent flux and MCT-mediated export. High stromal MCT4 or tumor LDHA/glucose transporter (GLUT)3 expression was shown to be associated with adverse outcomes and poor response to PD-1-based immunotherapy (11,12,26,27). Metabolic imaging with ^{18}F-FDG PET/CT and radiomics-derived metrics, such as metabolic tumor volume and total lesion glycolysis, can noninvasively

capture glycolytic burden, reflect immune-cold phenotypes and support response prediction in immunotherapy trials (1,7,28,29).

These findings support a glycolysis-centered but metabolically flexible framework for understanding immune suppression and therapeutic resistance in GC in which glycolytic reprogramming in tumor and stromal compartments establishes a lactate-rich, low-pH niche that impairs DC and T-cell activation. At the same time, ncRNA- and inflammation-dependent programs help stabilize this state and are linked to therapy resistance (17,30,31). The present review focuses on: i) The molecular drivers and landscape of glycolytic reprogramming in GC; ii) how lactate-centered crosstalk reshapes stromal and immune compartments into an immune-refractory TME; and iii) emerging therapeutic strategies that combine metabolic intervention, ICB and metabolic imaging for precision patient stratification.

2. Glycolytic reprogramming in GC: Molecular drivers and metabolic landscape

GC maintains a highly glycolytic state through oncogenic signaling, hypoxia- and inflammation-driven transcriptional programs, ncRNA-mediated regulation and persistent metabolic crosstalk with stromal cells (12,17,32). These convergent inputs increase glucose uptake, accelerate glycolytic flux and promote lactate export, creating a nutrient-competitive, acidified TME that disfavors antitumor immune responses (Fig. 1) (24,33,34).

Oncogenic, hypoxic and inflammatory signals converging on glycolysis. Hypoxia stabilizes HIF-1α, which induces glucose transporters and key glycolytic enzymes, including HK2, PFKFB3, PKM2, LDHA and pyruvate dehydrogenase kinase (PDK)1, thereby diverting pyruvate away from oxidative phosphorylation (OXPHOS) toward lactate production (14,35-37). Coexpression of HIF-1α, GLUT1 and lactate dehydrogenase isoforms was shown to be associated with advanced stage, nodal metastasis and poor survival, while hypoxia-driven mitochondrial dysfunction and reactive oxygen species (ROS) were demonstrated to further reinforce glycolytic dependence (38-40). Oncogenic receptor tyrosine kinase-rat sarcoma (RAS)-mitogen-activated protein kinase (MAPK) and PI3K/AKT/mTOR signaling converge with this hypoxic program by enhancing GLUT trafficking, HK2-mitochondrial association and translation of glycolytic enzymes (17,41,42). Additional regulators, including formyl peptide receptor 3, monoamine oxidase A, mitochondrial creatine kinase and mitochondrial topoisomerase I, promote HK2/LDHA-dependent aerobic glycolysis, epithelialmesenchymal transition (EMT) and peritoneal dissemination. Other glycolysis-associated proteins, such as enolase 1 (ENO1), hexokinase domain containing 1, PDK4 and PKM2, are also frequently upregulated and may represent potential therapeutic targets (43-47).

Systemic, neuroendocrine and circadian cues further shape this metabolic circuitry. Norepinephrine enhances aerobic glycolysis and lactate release and may predict immunotherapy responsiveness in GC, supporting an association between sympathetic stress signaling and glycolytic remodeling (48). Mechanistically, β-adrenergic stimulation may activate cyclic adenosine monophosphate (cAMP)/protein kinase A/cAMP response element-binding protein- and HIF-1α-associated transcriptional programs, thereby increasing the expression of glycolytic enzymes and lactate-handling molecules, including GLUT1, HK2, LDHA and MCTs, and linking sympathetic stress to lactate-rich immunosuppressive niches (34,48). Circadian disruption also intersects with HER2-targeted therapy resistance. In HER2-positive GC, trastuzumab-resistant cells exhibited circadian oscillation of glycolysis regulated by the BMAL1-CLOCK- period circadian regulator 1 (PER1)-HK2 axis, and disruption of PER1 was shown to enhance HK2-dependent glycolytic activity and trastuzumab resistance (49). In this context, the 'metabolic bypass' refers to HK2-driven maintenance of ATP production, biosynthetic precursor supply and redox buffering when HER2-dependent PI3K/AKT and RAS/MAPK growth signaling is pharmacologically inhibited. This interpretation is supported by evidence that MACC1 promotes the Warburg effect through PI3K/AKT pathway activation and thereby contributes to trastuzumab resistance in HER2-positive GC (50). Lactate accumulation and extracellular acidification may further support EMT-like plasticity, stromal remodeling and immune escape; however, direct evidence that lactate accumulation itself induces HER2 protein degradation in GC remains insufficient. Therefore, lactate is discussed here as a downstream mediator of glycolytic adaptation and an immunosuppressive acidic niche rather than as a proven driver of HER2 degradation. Thus, norepinephrine-related adrenergic signaling, circadian PER1-HK2 dysregulation and HK2-dependent glycolytic rewiring may jointly support metabolic plasticity during HER2-targeted therapy resistance, although the precise contribution of lactate-HER2 protein regulation requires further validation.

Helicobacter pylori remodels mitochondrial homeostasis via ATP-dependent Lon protease, while cytotoxin-associated gene A and Toll-like receptor 2/superoxide dismutase 2 signaling promote mitochondrial damage, ROS accumulation and HIF-1α activation. These changes shift tumor cells toward a highly glycolytic and chemoresistant state (16,51-53). EBV-encoded miR-BART6-5p further modulates transforming growth factor-β (TGF-β)/SMAD signaling and may contribute to a virus-associated immunometabolic subtype (16,51-53). Proinflammatory cytokines, including IL-6 and IL-8, activate signal transducer and activator of transcription (STAT3)-mTOR-MYC cascades, upregulating HK2, LDHA and PD-L1 and thereby linking inflammation, glycolysis and immune checkpoint expression (15,54,55). At the immune interface, lactate-rich niches promote M2-like macrophage polarization through MCT-HIF-1α signaling, while M2-derived exosomal metastasis associated lung adenocarcinoma transcript 1 (MALAT1) and claudin-9-mediated PD-L1 lactylation further enhance tumor invasion, $CD8^+$ T-cell suppression and resistance to PD-1/PD-L1 blockade (11,56-58). Representative ncRNAs, shown in Fig. 1, including H19, gastric cancer-associated lncRNA 1 (GLCC1), MALAT1 and Opa interacting protein 5-antisense RNA1 (OIP5-AS1), illustrate how ncRNA-mediated regulation converges on GLUT1/3, HK2, PFKFB3, PKM2, LDHA and MCT4-dependent lactate

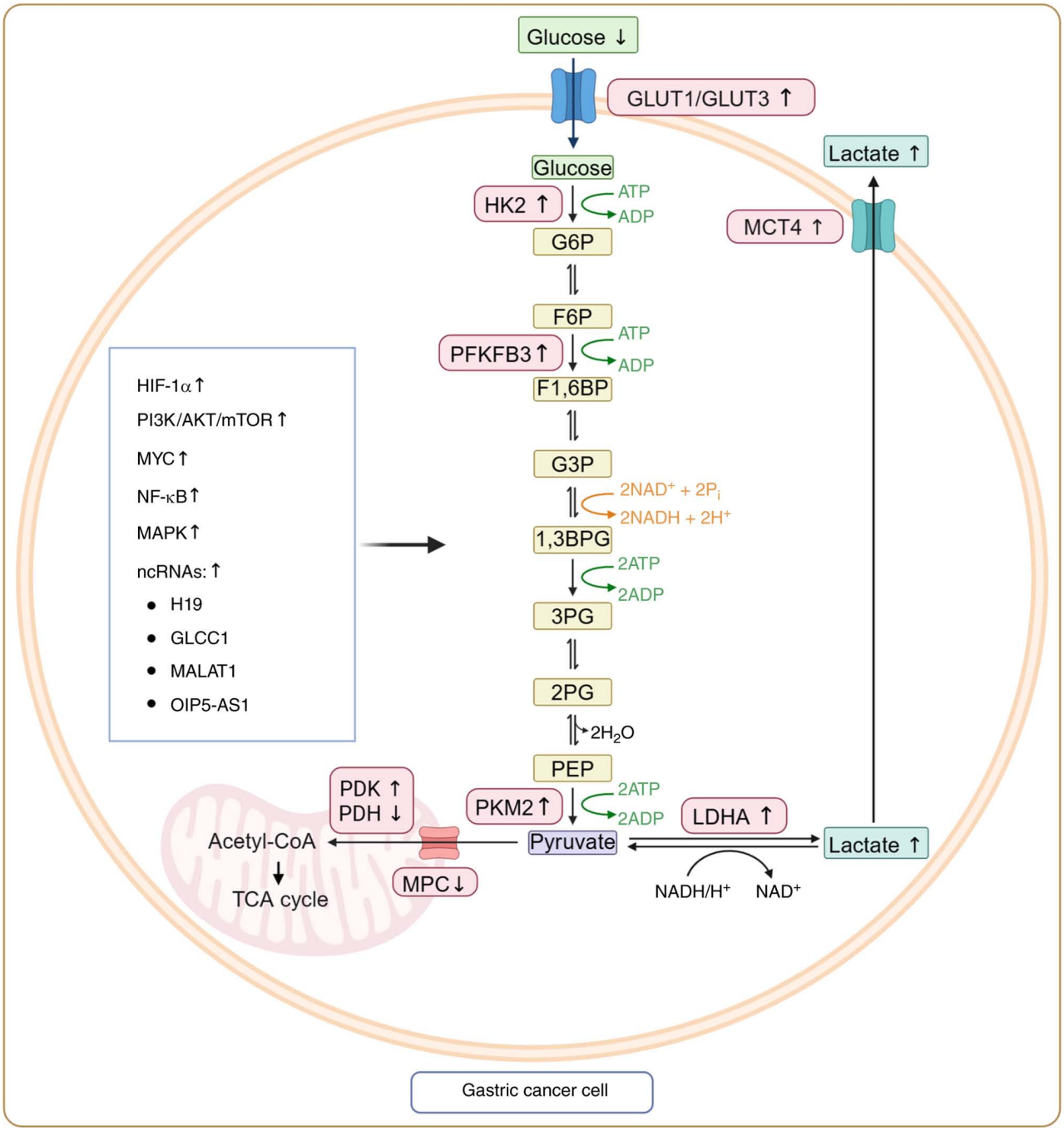

Figure 1. Glycolytic reprogramming in GC. Tumor-intrinsic signaling pathways, including hypoxia-induced HIF-1α, PI3K-AKT-mTOR, MAPK, NF-κB and MYC, and multiple ncRNAs converge to activate glycolysis in GC. Upregulation of GLUT1/3 enhances glucose uptake, while HK2, PFKFB3, PKM2 and LDHA accelerate glycolytic flux and lactate production. Mitochondrial pyruvate oxidation is further inhibited by PDK-mediated PDH suppression. Excess lactate is exported via MCT4, acidifying the tumor microenvironment and initiating downstream immunosuppressive programs. Created with BioRender.com. GC, gastic cancer; HIF-1α, hypoxia-inducible factor-1α; PI3K, phosphoinositide 3-kinase; mTOR, mechanistic target of rapamycin; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; ncRNAs, noncoding RNAs; GLUT1/3, glucose transporter 1/3; HK2, hexokinase 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; PDK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase kinase complex; MCT4, monocarboxylate transporter 4; GLCC1, gastric cancer-associated lncRNA 1; MALAT1, metastasis associated lung adenocarcinoma transcript 1; OIP5-AS1, Opa interacting protein 5-antisense RNA1; TCA, tricarboxylic acid cycle; MPC, mitochrondrial pyruvate carrier; ATP, adenosine triphosphate; NAD^+, oxidized nicotinamide adenine dinucleotide.

export, thereby linking glycolytic enzyme expression to lactate production and immune escape (Fig. 1).

Mechanistically distinct ncRNA networks in glycolytic regulation. ncRNAs, including lncRNAs, miRNAs and circRNAs, constitute a multilayered regulatory system that fine-tunes glycolytic reprogramming in GC. Rather than acting through a single mechanism, these ncRNA classes regulate glucose metabolism at different molecular levels, including chromatin remodeling, RNA-protein interactions, mRNA stability, translational repression and competitive endogenous RNA (ceRNA) networks (17,30,32). This mechanistic diversity

is particularly relevant in GC, where tumor cells, stromal cells and immune cells exchange metabolic signals through soluble mediators and exosome-associated ncRNAs, linking glycolytic flux to immune evasion and therapeutic resistance.

lncRNAs mainly regulate glycolysis by modulating transcriptional, epigenetic and post-transcriptional programs. For example, deleted in lymphocytic leukemia 1 (DLEU1) was shown to promote GC-cell proliferation and glycolysis by recruiting the histone methyltransferase SET and MYND domain-containing protein 2 (SMYD2) to induce H3K4 trimethylation and upregulate apolipoprotein C1, indicating that lncRNAs can remodel chromatin to sustain metabolic gene expression (30). GLCC1 was demonstrated to enhance tumorigenesis by strengthening the interaction between c-Myc and insulin-like growth factor 2 mRNA-binding protein 1, thereby stabilizing glycolysis-related oncogenic programs (59,60). The lncRNA VAL has been shown to promote PKM2 enzymatic activity and facilitate malignant progression, whereas m6A-modified OIP5-AS1 was revealed to enhance glycolysis, tumorigenesis and metastasis by inhibiting Trim21-mediated ubiquitination and degradation of heterogeneous nuclear ribonucleoprotein A1 (32,61,62). These findings suggest that lncRNAs often act as scaffolds or guides for chromatin modifiers and RNA-binding proteins, enabling sustained activation of HK2-, LDHA- and PKM2-centered glycolytic circuits.

miRNAs regulate glycolysis mainly through sequence-specific post-transcriptional repression of metabolic enzymes, transporters or upstream transcription factors. miR-21-5p was shown to promote glycolytic progression by targeting pyruvate dehydrogenase E1 subunit α1, thereby limiting pyruvate entry into mitochondrial oxidative metabolism and favoring lactate production (63). miR-186 was demonstrated to inhibit aerobic glycolysis through HIF-1α regulation, whereas miR-379 was revealed to be associated with reduced glycolytic capacity through enhanced regulation of PKM2 (64,65). miR-148b-5p has also been linked to metabolic remodeling of the immune microenvironment and GC progression (66). Compared with lncRNAs, miRNAs tend to provide more direct and rapidly adjustable control over glycolytic enzymes and signaling nodes, thereby shaping tumor metabolic tone, treatment sensitivity and local immune remodeling.

circRNAs predominantly function as stable ceRNA molecules that sequester miRNAs and derepress glycolysis-promoting targets. circ-NRIP1, circ-0032821 and circ-ATP2B1 have been implicated in hypoxia-induced glucose metabolism, chemoresistance, proliferation, invasion and aerobic glycolysis by buffering specific miRNA axes (20,67,68). Cancer-derived exosomal circ-0038138 was shown to enhance glycolysis, growth and metastasis through the miR-198/enhancer of zeste homolog 2 (EZH2) axis, illustrating how circRNAs can transmit glycolytic traits between tumor cells and the surrounding microenvironment (22). In addition, exosomal circ-ATP8A1 was demonstrated to induce M2 macrophage polarization through the miR-1-3p/STAT6 axis, linking circRNA-mediated metabolic regulation to myeloid immune suppression (69). Thus, circRNAs are not only intracellular ceRNA regulators but also extracellular messengers that disseminate glycolysis-supporting and immunosuppressive programs across the GC TME.

The cellular and spatial context of ncRNA regulation is also important. Tumor-cell-intrinsic ncRNAs, such as H19, DLEU1, GLCC1, VAL and OIP5-AS1, primarily reinforce glycolytic enzyme expression, lactate production, stemness and drug resistance. By contrast, stromal- and immune-cell-associated ncRNAs, including macrophage-derived exosomal MALAT1 and exosomal circ-ATP8A1, reshape macrophage polarization, DC activation and antigen presentation (8,58,69). This compartment-specific regulation helps explain why glycolysis-related ncRNA signatures may reflect not only malignant-cell metabolism but also the metabolic state of CAFs, tumor-associated macrophages (TAMs) and other immune populations. Overall, ncRNA networks provide a molecular bridge between tumor glycolysis, lactate accumulation, PD-L1 regulation, histone lactylation and immune escape. Distinguishing lncRNA-, miRNA- and circRNA-mediated mechanisms may therefore improve the interpretation of glycolysis-related biomarkers and support more precise patient stratification in GC. This cell-type-resolved interpretation is important for bulk GC tissue analyses because glycolysis-related ncRNA signatures may represent mixed signals from malignant epithelial cells, CAFs, TAMs, DCs and exosome-enriched stromal or immune compartments rather than tumor-cell-intrinsic glycolysis alone (8,58,69).

Metabolic heterogeneity and glycolytic immunophenotypes. Despite widespread glycolytic upregulation, GC exhibits marked intra- and intertumoral metabolic heterogeneity. Nuclear magnetic resonance-based metabolomics has identified tumor clusters with distinct patterns of glycolytic intermediates, amino acids and lipid species (70-72). In orthotopic xenograft models, glycolysis-targeted therapy produces heterogeneous reductions in metabolic tumor volume on ^{18}F-FDG PET/CT, underscoring variable glycolytic dependence among lesions and its association with Lauren classification and depth of invasion (39,73-75).

Transcriptomic and multi-omics signatures, including nine-gene glycolysis scores, stratify GC into glycolysis-high and glycolysis-low subgroups with distinct prognostic and immune features (18,21,76). Glycolysis-high tumors are enriched for EMT, angiogenesis and immunosuppressive pathways, exhibit elevated LDHA, HK2, ENO1, PFKFB3 and MCT4, and generally contain fewer cytotoxic T cells and DCs but more Tregs and myeloid-derived suppressor cells (MDSCs) (26,73,77). By contrast, glycolysis-low tumors tend to display more inflamed gene-expression patterns and may respond better to ICB or cytotoxic chemotherapy. Imaging-derived metrics further refine this framework: ^{18}F-FDG PET/CT parameters, such as metabolic tumor volume and total lesion glycolysis, are prognostic markers and associated with HER2 status, c-MET expression and treatment response. Radiomics models integrating textural, metabolic and anatomical features may also predict microvascular invasion, response to neoadjuvant immunochemotherapy and long-term outcomes (28,29,73,78). High stromal or tumor-cell MCT4, together with coexpression of MCT1/MCT4 and mitochondrial markers such as mitochondrially encoded cytochrome *c* oxidase I, identifies subsets with poor prognosis and strong lactate-shuttling capacity. These findings support a

continuum of glycolytic immunophenotypes ranging from hyper-glycolytic, immune-cold tumors to moderately glycolytic, immune-inflamed tumors (21,27,76,79).

Substrate-level heterogeneity adds another layer of complexity. Although glucose is a dominant fuel source, some GC cells can oxidize lactate, glutamine or fatty acids (FAs), enabling metabolic flexibility when glycolysis is pharmacologically inhibited (80-82). Metabolomic analyses in cell lines and patient-derived xenografts show that tumors with robust anaplerotic glutamine use or FA oxidation can partially escape glycolysis blockade. Together with lactate-driven immune suppression, this metabolic flexibility may contribute to incomplete responses to single-agent glycolytic inhibitors (56,70,74,83,84).

Notably, glycolysis-centered immune suppression should be interpreted as part of a broader metabolic network rather than as an isolated pathway. When glycolytic carbon is preferentially diverted toward lactate production, glutamine anaplerosis can replenish tricarboxylic acid-cycle intermediates and support nucleotide synthesis, redox buffering and mitochondrial function, allowing glycolysis-high tumor cells to maintain biosynthetic capacity despite incomplete glucose oxidation (70,74,80-84). FA uptake and FA oxidation may provide an additional survival route under glucose-limited or glycolysis-inhibited conditions, whereas mitochondrial rewiring enables tumor cells to switch between glycolysis, oxidative phosphorylation and substrate oxidation when one pathway is therapeutically restricted (6,80-85). In parallel, stromal metabolism reinforces this flexibility: CAFs and MSCs can export lactate, recycle lactate-derived carbon or provide alanine, glutamine and cytokine signals that sustain tumor anabolism and immune suppression (24,86,87,88,89). Vascular remodeling further closes this loop by maintaining hypoxia, HIF-1α activation, vascular endothelial growth factor A (VEGFA) production and lactate accumulation, thereby linking metabolic plasticity to immune exclusion and reduced T-cell trafficking (14,37-40). Thus, glycolysis-centered immunosuppression in GC is best viewed as a dominant but context-dependent node within an interconnected network involving glutamine metabolism, lipid oxidation, mitochondrial adaptation, stromal nutrient exchange and hypoxia-driven vascular remodeling. This interpretation avoids treating glycolysis as the sole determinant of immune suppression and instead places glycolytic signaling within a plastic metabolic ecosystem in which different GC subtypes may rely on distinct combinations of glucose, glutamine, fatty-acid and mitochondrial pathways.

Crosstalk with stromal and immune compartments. GC frequently develops within a desmoplastic and immunosuppressive stroma in which fibroblasts, MSCs and myeloid cells are metabolically co-opted. GC-associated MSCs secrete IL-8 and related cytokines that activate STAT3/mTOR-c-MYC signaling in tumor cells, thereby upregulating HK2, PD-L1 and other glycolytic drivers; MSC-derived IL-8 has also been shown to promote EMT and stemness (24,55). In turn, GC cells condition MSCs and CAFs to adopt a glycolytic, lactate-exporting phenotype through glucose-6-phosphate dehydrogenase (G6PD)-NF-κB-hepatocyte growth factor signaling. This establishes a tumor-stroma metabolic circuit in which stromal cells support tumor metabolism, while C-X-C motif chemokine receptor (CXCR)2/HK2/PD-L1 signaling in MSCs further links stromal glycolysis to checkpoint expression (86,87).

Myeloid cells integrate metabolic and inflammatory cues from this remodeled stroma. Lactic acid promotes macrophage polarization toward an M2-like phenotype through MCT-HIF-1α signaling and histone lactylation. M2 TAMs secrete exosomal MALAT1 and circ-ATP8A1, which enhance GC-cell glycolysis, invasion and immunoregulatory programming through the miR-1-3p/STAT6 axis and related circuits (58,69,90). DCs exposed to high lactate show impaired activation and antigen presentation, with tumor-derived lactic acid directly modulating DC phenotype and reinforcing a stromal-immune niche that favors tumor survival (11,91).

Endothelial cells and the vasculature also participate in this metabolic network. Radiomics signatures capturing angiogenic and metabolic features on ^{18}F-FDG PET/CT can predict microvascular invasion and survival, and glycolysis-high tumors often exhibit abnormal vasculature and hypoxic, immune-excluded regions that restrict immune-cell trafficking while sustaining HIF-1α-driven glycolysis and lactate production (14,37,38,40). Overall, tumor, stromal and immune cells form an interconnected metabolic network in which glycolysis is both a driver and a consequence of TME remodeling (12,24,81). Key glycolytic drivers, primary metabolic effects, immunologic consequences and supporting references in GC are summarized in Table I.

3. Lactate as a central mediator of immunosuppression

GC is shaped by converging oncogenic, hypoxic and inflammatory signals, reinforced by ncRNAs and stromal-immune crosstalk, which together maintain a high-glycolysis, lactate-producing state and a spectrum of glycolytic immunophenotypes ranging from hyper-glycolytic, immune-excluded tumors to more immune-inflamed lesions (14,21,32). Within this context, lactate has emerged as a multifunctional metabolite. Through MCT1/4-mediated transport, hydroxycarboxylic acid receptor 1 (HCAR1, also known as GPR81) signaling and induction of histone lactylation, lactate creates spatially organized niches in desmoplastic and poorly perfused regions that are acidic, MCT4-high and depleted of effector lymphocytes (Fig. 2) (11,13,77). The major immune-cell consequences of lactate accumulation in the GC TME, including impaired DC activation and migration, reduced $CD8^+$ T-cell interferon-γ (IFN-γ) production and Ca^{2+} flux, weakened B-cell mTOR complex 1 (mTORC1)/OXPHOS activity, reduced NK-cell cytotoxicity and granzyme B/perforin expression, and TAM/MDSC-associated immunosuppressive remodeling are summarized in Fig. 2.

Lactate production and export as a metabolic circuit. GC cells display high lactate-to-pyruvate ratios driven by LDHA activation and MCT1/4 overexpression, which are induced by HIF-1α, MYC, NF-κB and inflammatory cytokines (10,16,18). Lactate export regenerates oxidized nicotinamide adenine dinucleotide (NAD^+), sustains glycolytic flux and acidifies the TME, generating gradients in which $CD8^+$ T cells are scarce, whereas $CD163^+$ TAMs and MDSCs accumulate (1,2,4). To

Table I. Key glycolytic drivers and their immunologic consequences in gastric cancer.

Molecular driver	Primary metabolic effect	Immune consequence	(Refs.)
HK2	Enhances glucose phosphorylation and glycolytic flux	Promotes immunosuppressive metabolite accumulation	(49,81,89)
PFKFB3	Increases fructose-2,6-bisphosphate, accelerates glycolysis	May contribute to lactate-rich metabolic conditions that limit immune-cell function	(95)
PKM2	Regulates pyruvate conversion, supports anabolic metabolism	Supports glycolytic remodeling associated with immune evasion	(32,42,96,127)
LDHA	Converts pyruvate → lactate	Generates acidic TME; inhibits DC/T-cell activation	(46,77,92,94)
MCT4	Exports lactate	Establishes $CD8^+$-poor niches in glycolysis-high tumors	(79,104)
HIF-1α	Transcriptionally activates glycolytic enzymes	Upregulates PD-L1; suppresses CTL infiltration	(35,37,38,40,99)
mTOR	Integrates nutrient signaling to glycolysis	Affects T-cell exhaustion and DC differentiation	(35,42)

Representative glycolysis-associated regulators frequently implicated in gastric cancer and their predominant metabolic effects and reported immunologic consequences in the tumor microenvironment. Immune consequences summarized reflect reported associations in experimental and translational studies and may vary depending on tumor context, cellular compartment and treatment exposure. Only primary research articles directly investigating the corresponding molecular driver or closely related target axis were retained in the supporting-reference column. HK2, hexokinase 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; MCT 4, monocarboxylate transporter 4; HIF-1α, hypoxia-inducible factor-1α; PD-L1, programmed death-ligand 1; CTL, cytotoxic T lymphocyte; mTOR, mechanistic target of rapamycin; DC, dendritic cell.

preserve biosynthetic capacity when carbons are diverted from the tricarboxylic acid (TCA) cycle, GC cells increase glutamine anaplerosis and FA uptake. At the same time, lactate acts as a paracrine signal that conditions stromal and immune cells toward immunoregulatory phenotypes (10,11,92).

Stromal cells contribute to a lactate shuttle. CAFs and MSCs take up extracellular lactate via MCT1, oxidize it and release alanine and glutamine that support tumor anabolism and redox control (24,88,89). Disrupting this circuit by inhibiting LDHA or MCT4 increases intratumoral pH, reduces M2/MDSC abundance and restores CTL infiltration in GC models, highlighting lactate transport as a shared metabolic and immunologic vulnerability (80,93-95).

Direct effects on DCs and T cells. High lactate levels impair monocyte-to-DC differentiation, downregulate CD80/CD86 and suppress IL-12 and type I interferon production through inhibition of NF-κB and interferon regulatory factor (IRF)1. Lactate also reduces the mitochondrial spare respiratory capacity required for antigen processing and cross-presentation (33,96,97). In addition, lactate skews DC programs away from IRF8/basic leucine zipper ATF-like transcription factor 3-dependent cross-priming toward IRF4/Kruppel-like factor 4-associated regulatory states with elevated PD-L1, IL-10 and Treg-recruiting chemokines. Consistently, $MCT4^+$/lactate-rich regions in GC are almost devoid of $CD103^+$ conventional type 1 DCs (cDC1) (1,77,98). Activated $CD8^+$ T cells rely heavily on glycolysis and are therefore highly sensitive to lactate-rich and acidic conditions. In such environments, cytosolic acidification and NAD^+ depletion impair glycolytic enzymes, T-cell receptor-triggered Ca^{2+} flux, proliferation, motility and IFN-γ/granzyme B release (12,13). LDHA silencing or lactic-acid neutralization in GC models was shown to restore T-cell motility and effector function. Lactate may also limit mitochondrial biogenesis and FA oxidation, biasing differentiation toward short-lived effector cells rather than long-lived memory subsets (8,93,94). These findings support lactate as a metabolic checkpoint for antitumor T-cell immunity and position LDHA/MCT4 inhibition as an immune-adjuvant strategy rather than a purely cytotoxic approach (Fig. 2).

Epigenetic and signaling reprogramming of myeloid cells. Lactate directly couples metabolism to gene expression through histone lactylation (13,90). In macrophages, lactate-driven H3K18 lactylation activates arginase 1 (ARG1), VEGFA and mannose receptor C-type 1 (MRC1). Together with HCAR1-mediated HIF-1α stabilization and NF-κB dampening, these changes reinforce an M2-like, pro-angiogenic and IL-10/TGF-β-secreting phenotype (10,57,58). Lactate-conditioned TAMs also upregulate chemokines that attract Tregs and C-C motif chemokine receptor 2-positive monocytes while limiting $CXCR3^+$ effector T-cell infiltration. Lactate-driven histone lactylation may further cooperate with SMYD2/SET domain containing 1A, histone lysine methyltransferase (SETD1A)/p300-dependent methylation and acetylation programs to stabilize these transcriptional circuits (17,30,99).

MDSCs similarly exploit lactate-rich conditions. Lactate has been reported to enhance ARG1 and PD-L1 expression through extracellular signal-regulated kinase (ERK) and STAT3 signaling, thereby promoting T-cell anergy and Treg expansion (97,100). $LDHA^+$/$MCT4^+$ MDSC clusters are

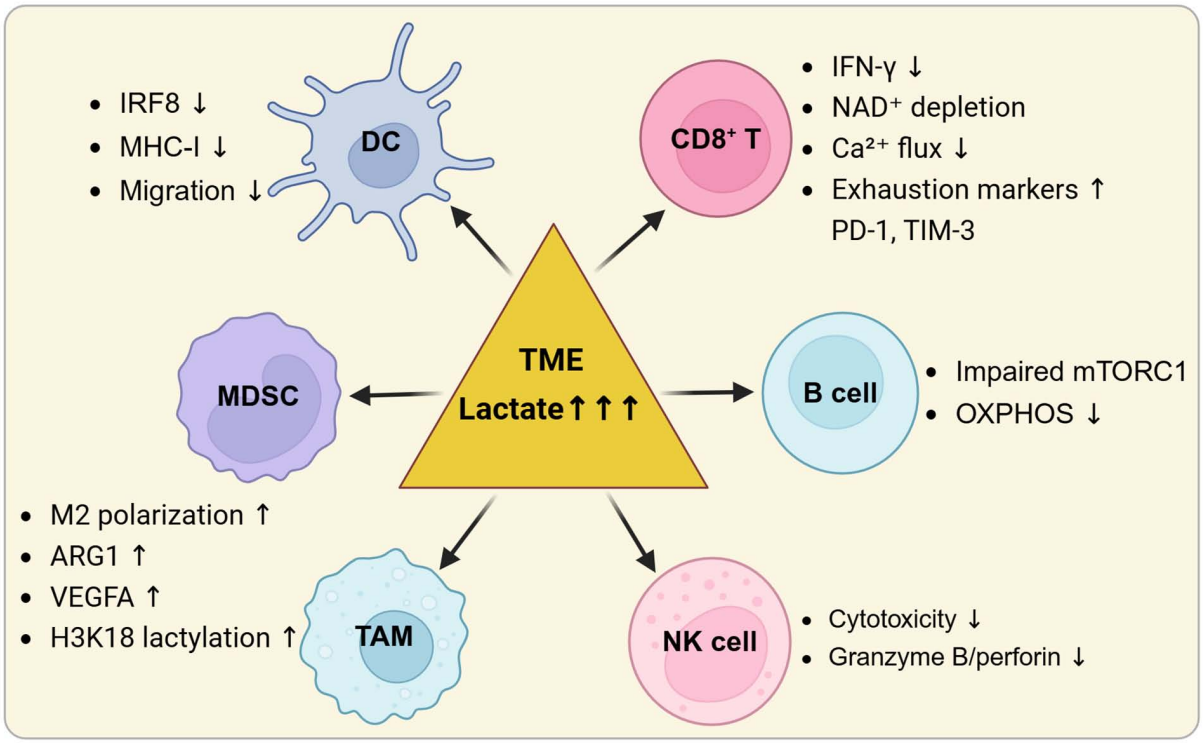

Figure 2. Immune-cell consequences of lactate accumulation in the GC tumor microenvironment. Lactate accumulation in the GC TME impairs DC-associated IRF8 expression, MHC-I expression and migration, suppresses $CD8^+$ T-cell IFN-γ production and Ca^{2+} flux while increasing exhaustion markers, weakens B-cell mTORC1 and OXPHOS activity, reduces NK-cell cytotoxicity and granzyme B/perforin expression, and promotes TAM/MDSC-associated immunosuppressive remodeling, including M2 polarization, ARG1 expression, VEGFA expression and H3K18 lactylation. Created with BioRender.com. GC, gastric cancer; TME, tumor microenvironment; DC, dendritic cell; IRF8, interferon regulatory factor 8; MHC-I, major histocompatibility complex class I; IFN-γ, interferon-γ; mTORC1, mTOR complex 1; OXPHOS, oxidative phosphorylation; NK, natural killer; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; ARG1, arginase 1; VEGFA, vascular endothelial growth factor A; NAD^+, oxidized nicotinamide adenine dinucleotide; PD-1, programmed death-1; TIM-3, T-cell immunoglobulin and mucin domain-3.

associated with immune-excluded histology and shortened survival, and MCT4 inhibition was shown to reduce MDSC infiltration and restore DC maturation in GC models (3,54,94). These lactate-driven changes in TAMs and MDSCs constitute the myeloid-cell component of the immune-cell remodeling summarized in Fig. 2.

Impact on B cells and NK cells. Lactate also dampens humoral and innate immunity. In B cells, low pH and altered NAD^+/NADH ratios impair mTORC1 activity and OXPHOS, reducing major histocompatibility complex (MHC) class II expression and class-switch recombination. These changes may weaken antibody-dependent effector mechanisms in the GC TME (8,100). In NK cells, lactate suppresses ERK/mTORC1 signaling, cytotoxic granule exocytosis, IFN-γ production and immunological synapse formation. Consistently, glycolysis-high, MCT4-high GC specimens often show reduced $CD56^+$ NK-cell infiltration and attenuated B-cell activation signatures (4,19,33,78). Together, these effects on B-cell metabolic activity and NK-cell cytotoxicity are included in the immune-cell consequences of lactate accumulation summarized in Fig. 2.

Lactate and immune checkpoint activation. Lactate provides a mechanistic bridge between metabolic stress and checkpoint dominance. PD-L1 expression in GC was shown to be associated with LDHA/MCT4 and could be induced by histone lactylation at the CD274 promoter, with further amplification through hypoxia-driven HIF-1α binding to PD-L1 regulatory elements (18,35,92). Lactate was also demonstrated to stabilize MYC and increase acetyl-coenzyme A availability, favoring acetylation events that may upregulate additional inhibitory receptors, including T-cell immunoglobulin and mucin domain-3 and lymphocyte activation gene-3 (LAG-3) (3,26). CAF-derived wingless-type MMTV integration site family member 5A (WNT5A) and MSC-derived IL-8 were reported to converge through STAT3/mTOR-MYC signaling to further augment PD-L1, integrating lactate, hypoxia and cytokine signaling into a broader immunosuppressive network (54,55,89).

Functionally, this creates a metabolic-checkpoint interface in which effector T cells encounter both high PD-L1 density and a bioenergetically hostile microenvironment. Even when PD-1/PD-L1 interactions are blocked, residual lactate signaling may sustain other inhibitory receptors and maintain epigenetically imprinted exhaustion programs (3,101). Glycolysis-high GC subtypes often show coelevation of PD-L1, LAG-3, MCT4 and myeloid-suppressive signatures, providing a rationale for combining modulation of lactate metabolism, HCAR1 blockade or targeting of histone lactylation with checkpoint inhibition (21,27). This checkpoint-associated remodeling overlaps with the lactate-driven suppression of T cells and myeloid-cell polarization illustrated in Fig. 2.

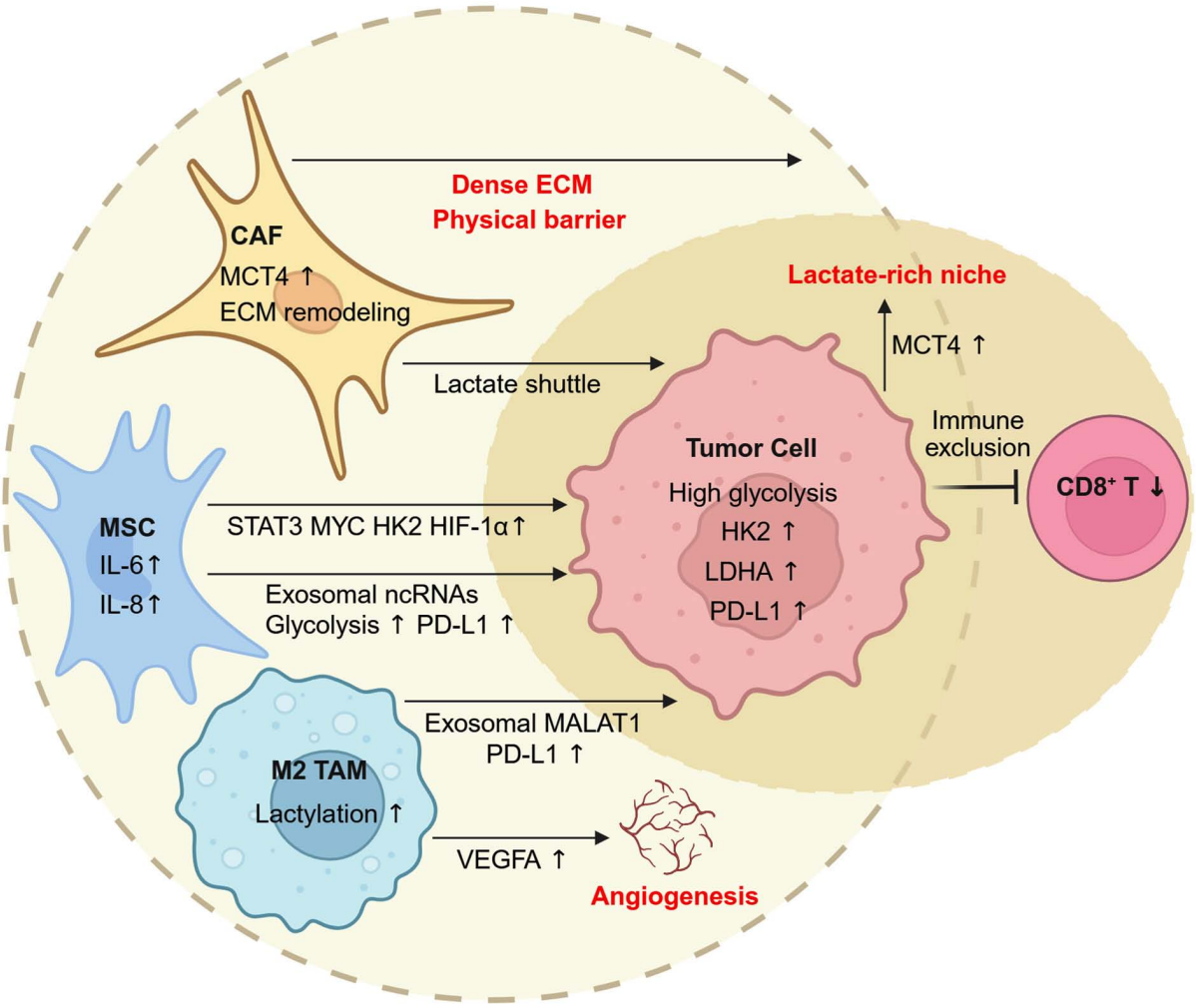

Figure 3. Metabolic and inflammatory crosstalk between tumor, stromal and immune compartments in gastric cancer. CAFs sustain a high-lactate niche through MCT4-dependent export and ECM remodeling, contributing to $CD8^+$ T-cell exclusion. MSCs amplify tumor glycolysis via IL-6/IL-8-STAT3-MYC signaling and deliver glycolysis-promoting or PD-L1-inducing ncRNAs through exosomes. M2-like macrophages reinforce immune suppression by releasing MALAT1-rich vesicles and promoting VEGFA through histone lactylation. These reciprocal interactions generate spatially organized metabolic-immune neighborhoods characteristic of glycolysis-high gastric cancer. Created with BioRender.com. CAFs, cancer-associated fibroblasts; MCT4, monocarboxylate transporter 4; ECM, extracellular matrix; MSCs, MSC, mesenchymal stem/stromal cells; IL, interleukin; STAT3, signal transducer and activator of transcription 3; PD-L1, programmed death-ligand 1; ncRNAs, noncoding RNAs; MALAT1, metastasis associated lung adenocarcinoma transcript 1; VEGFA, vascular endothelial growth factor A; HK2, hexokinase 2; HIF-1α, hypoxia-inducible factor-1α; LDHA, lactate dehydrogenase A; TAM, tumor-associated macrophage.

4. Tumor-stroma-immune crosstalk in metabolic immunosuppression

In GC, lactate functions not only as a metabolic fuel but also as an epigenetic and signaling mediator. It shapes acidic and hypoxic lactate-rich niches that suppress DCs and T cells while skewing macrophages and MDSCs toward tolerogenic, checkpoint-high states (Fig. 2) (1,11,92). Tumor, stromal and immune cells form a metabolically interdependent network that maintains immune-silent metabolic neighborhoods characterized by high MCT4 expression, low pH and enrichment of suppressive myeloid subsets (19,21,73). Within this framework, the LDHA/MCT4/HCAR1 axis and stromal-immune crosstalk emerge as core organizers of glycolysis-driven immune escape and potential targets for immunometabolic intervention (Fig. 3) (20,24,80,95). The stromal, vascular and immune components of this network, including CAF-derived MCT4-dependent lactate export and extracellular matrix (ECM) remodeling, MSC-derived IL-6/IL-8-STAT3/MYC signaling, exosome-mediated ncRNA transfer, M2 TAM-associated lactylation and VEGFA induction, abnormal angiogenesis and $CD8^+$ T-cell exclusion are integrated in Fig. 3. Accordingly, the following section focuses on multicellular feedback loops, stromal-vascular remodeling and spatial immune exclusion, rather than reiterating the direct DC- and T-cell-intrinsic effects of lactate aforementioned.

MSCs and CAFs as metabolic amplifiers. MSCs and CAFs are key stromal amplifiers of metabolic immunosuppression. MSC-derived IL-6 and IL-8 have been shown to activate STAT3/mTOR-MYC signaling in neighboring tumor cells, inducing HK2, PD-L1 and lactate production. Tumor-derived lactate can in turn fuel MSC OXPHOS through MCT1 and be recycled into alanine and glutamine to support tumor anabolism and redox control (25,54,89,102). Single-cell analyses have identified $CXCR2^{high}/HK2^{high}/PD\text{-}L1^{high}$ MSC subsets with strong immunosuppressive potential in glycolysis-high, immune-excluded lesions (24,86,87).

CAFs, driven by TGF-β, WNT5A, hypoxia and mechanical stress, undergo aerobic glycolysis and export lactate through MCT4, thereby supporting oxidative tumor subclones and dampening CTL motility and DC activation (103,104). Hypoxia and lactate further reprogram CAFs into α-smooth muscle actin-positive myofibroblasts expressing C-X-C motif chemokine ligand 12 (CXCL12), VEGFA and TGF-β, which recruit MDSCs and Tregs and promote abnormal angiogenesis (77,105). As discussed below, matrix stiffening further amplifies this process by linking mechanotransduction to CAF glycolytic reprogramming and immune exclusion. Clinically, MCT4-high CAFs and IL-8-rich MSCs are associated with immune exclusion, elevated PD-L1 and reduced response to PD-1 blockade, supporting the role of stromal cells as metabolic amplifiers of glycolysis-driven immunosuppression.

Exosome-mediated metabolic communication. Exosomes provide a major route for long-range transfer of metabolic and immunoregulatory signals (13,22,88). GC-derived exosomes carry glycolysis-enhancing circRNAs and lncRNAs, such as circ-0038138, circ-ATP8A1 and MALAT1, which activate EZH2-, STAT6- or STAT3-dependent pathways in recipient macrophages and fibroblasts, thereby promoting M2 polarization, VEGFA expression and ECM remodeling (99,106). M2 macrophage-derived exosomes enriched in MALAT1 and miR-21 feed back to tumor cells to increase LDHA, HK2 and PD-L1 expression, completing a feed-forward glycolytic loop (58,102).

CAFs and MSCs also release exosomes enriched in PD-L1, glycolytic enzymes and immunoregulatory miRNAs, including miR-155 and miR-23a, which suppress DC antigen presentation and CTL granzyme B secretion (10,55,102). Acidic pH can further imprint exosomal cargo with PD-L1, HIF-1α, LDHA and lactylation-related signatures, facilitating dissemination of metabolic and immunologic messages within the TME (93,99,105). Proteomic and RNA profiling of plasma exosomes has identified stromal-associated proteins, such as integrin-linked kinase and CD14, and ncRNAs as candidate circulating markers of metabolic immunosuppression and ICB response (7,85,107).

Glycolysis, angiogenesis and immune exclusion. Glycolytic reprogramming also contributes to immune exclusion by reshaping the vascular architecture of GC. Hypoxia and oncogenic signaling stabilize HIF-1α, which transcriptionally induces both glycolytic genes and pro-angiogenic mediators, particularly VEGFA. In this setting, HIF-1α links glucose uptake, LDHA-dependent lactate production and MCT-mediated lactate export with VEGFA-driven angiogenesis, thereby coupling lactate-producing metabolism to abnormal vascular remodeling (14,35-38). Although angiogenesis may increase vessel density, the resulting vasculature is often tortuous, leaky and poorly perfused. This leads to heterogeneous oxygen delivery, persistent hypoxia and further activation of HIF-1α-dependent glycolysis, forming a feed-forward loop between hypoxia, glycolysis, lactate accumulation and vascular dysfunction.

At the immune interface, lactate and VEGFA cooperate through several mechanisms. Tumor-derived lactic acid can stabilize HIF-1α in macrophages and induce VEGF and ARG1 expression, thereby polarizing TAMs toward a tumor-promoting, pro-angiogenic and immunosuppressive phenotype (108). Lactate-rich regions may also reinforce HCAR1/GPR81- and MCT-dependent signaling in macrophages and DCs, promoting ARG1, IL-10, TGF-β and VEGFA-associated programs that suppress antigen presentation and favor MDSC/Treg-rich niches (11,13,57,58,90,92,99). In parallel, VEGFA can impair T-cell entry into tumors by inhibiting NF-κB-dependent endothelial activation and reducing leukocyte-endothelial adhesion programs, including intercellular adhesion molecule 1- and VCAM-1-associated trafficking signals (109). Thus, the HIF-1α/VEGFA/lactate network simultaneously sustains hypoxic glycolysis, abnormal angiogenesis, suppressive myeloid polarization and defective T-cell homing.

This metabolic-vascular loop has direct immunologic consequences. Disorganized tumor vessels impair T-cell homing by reducing effective perfusion, limiting endothelial activation and generating hypoxic and acidic barriers that restrict lymphocyte trafficking. At the same time, VEGFA and lactate promote immunosuppressive myeloid-cell recruitment, inhibit DC maturation and favor Treg and MDSC accumulation, thereby converting metabolically active vascular regions into immune-excluded niches. In GC, glycolysis-high tumors frequently display angiogenic signatures, MCT4-rich stromal regions and poor $CD8^+$ T-cell infiltration, supporting the concept that vascular dysfunction is not merely a consequence of tumor growth but also an active mediator of glycolysis-driven immune escape (21,26,73,77). This metabolism-angiogenesis-immunity axis is incorporated into the integrated tumor-stroma-immune network shown in Fig. 3.

Matrix stiffness, yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) signaling and CAF glycolysis. The physical properties of the GC stroma provide another layer of metabolic regulation. In desmoplastic tumors, excessive ECM deposition and collagen crosslinking increase stromal stiffness, which is sensed by CAFs through integrins and focal adhesion complexes (110). Activation of integrin-focal adhesion kinase (FAK)/Src signaling promotes nuclear translocation of YAP/TAZ, allowing mechanotransduction to converge with TGF-β, WNT and hypoxia-dependent pathways (111,112). In this context, YAP/TAZ activation may cooperate with these pathways to enhance glycolytic and immunoregulatory CAF phenotypes, thereby converting mechanical stress into CAF metabolic reprogramming (112). More specifically, YAP/TAZ-TEA domain transcription factor-associated transcriptional programs can promote glycolysis-related gene expression, including glucose transporters and enzymes involved in hexokinase activity, fructose-2,6-bisphosphate production and lactate generation, thereby providing a plausible molecular route by which matrix stiffness may increase CAF glycolytic output and lactate release (113).

This stiffness-driven metabolic state has important consequences for immune exclusion. Glycolytic CAFs release lactate, CXCL12, TGF-β and VEGFA, which reinforce ECM remodeling, abnormal angiogenesis and myeloid-cell recruitment (77,89,105). At the same time, the stiff matrix acts as a physical barrier to T-cell infiltration, while CAF-derived lactate and cytokines create metabolic and immunologic

barriers that suppress DC activation and cytotoxic T-cell function (112,114). Thus, stromal stiffness and CAF glycolysis form a self-reinforcing circuit: Increased matrix rigidity activates mechanotransduction, mechanotransduction promotes glycolytic and immunoregulatory CAF phenotypes, and these CAFs further remodel the matrix and maintain immune exclusion.

This mechanism is particularly relevant for diffuse-type and stroma-rich GC, in which dense ECM, hypoxia, MCT4-high CAFs and poor $CD8^+$ T-cell infiltration often coexist (19,21,27,77). From a therapeutic perspective, disrupting this physical-metabolic coupling may require strategies beyond direct glycolytic inhibition. Agents targeting integrin signaling, FAK/Src activation, YAP/TAZ-dependent transcription, TGF-β signaling or collagen crosslinking may reduce CAF-mediated matrix remodeling and immune exclusion, especially when combined with metabolic intervention and ICB (110,112,114). However, because mechanotransduction pathways also participate in tissue repair and immune-cell trafficking, such strategies require careful dose, timing and patient selection.

Lactate-driven feedback loop and immune remodeling. Central to this ecosystem is a self-reinforcing lactate feedback circuit. Lactate released from tumor and stromal cells engages HCAR1/GPR81 on macrophages and DCs, stabilizing HIF-1α and inducing VEGFA, ARG1, IL-10 and TGF-β, which collectively suppress CTL recruitment and effector function (11,58,90,105). These cytokines, together with prostaglandin E2 and adenosine, feed back through STAT3/mTOR-MYC signaling to enhance glycolytic gene expression and PD-L1 expression in tumor cells (15,25,54,55). Lactate- and CXCL12-activated MDSCs further secrete nitric oxide and ROS that inhibit DC maturation and T-cell proliferation, while CAF-derived WNT5A and MSC-derived IL-8 reinforce this multicellular positive-feedback loop (24,33,89,97,100,103).

Epigenetic decoding of lactate adds durability to these suppressive circuits. Histone lactylation at loci such as ARG1 and MRC1 can lock in M2-like macrophage programs, while similar modifications at immune checkpoint loci may help maintain PD-L1 and LAG-3 expression in tumor cells (13,17,30,99). Lactylation-related gene-expression models show that high lactate signaling coincides with increased M2/MDSC infiltration and reduced cytotoxic T-cell signatures (9,26). Spatial analyses further demonstrate that regions populated by $MCT4^+$ CAFs and $CD163^+$ TAMs are lactate-rich but $CD8^+$-poor, whereas regions with lower lactate burden show partial immune infiltration (1,2,77). In these metabolic dead zones, glucose is largely monopolized by tumor and stromal cells, driving infiltrating lymphocytes toward bioenergetic stress and exhausted or regulatory states (8,12,93). In preclinical GC models, inhibition of LDHA or MCT4 was shown to normalize pH, reduce M2/MDSC signatures and restore T-cell trafficking, indicating that lactate stabilizes both the functional and spatial architecture of the immunosuppressive TME (27,80,95,115).

Integrated therapeutic perspective. Viewing GC as a stromal-metabolic network reframes therapy from single-target inhibition to multi-node modulation. Combinatorial strategies that co-target tumor glycolysis and stromal signaling, such as LDHA/MCT4 inhibition together with IL-8, WNT5A or TGF-β blockade, were revealed to restore $CD8^+$ T-cell infiltration, dismantle M2/MDSC-rich niches and weaken CAF-mediated barriers in preclinical models (18,80,94,104). Re-educating CAFs through inhibition of metabolic epigenetic writers, such as SMYD2 and SETD1A, or through vitamin D analogues may further reduce lactate output and normalize stromal architecture (17,30,99). In parallel, targeting exosome biogenesis, such as through Ras-related protein Rab-27A knockdown or GW4869, or targeting exosomal cargos such as MALAT1 and circ-ATP8A1 may limit long-range dissemination of metabolic and immunoregulatory cues (22,88,102). Co-targeting glycolysis, lactate transport, exosome signaling and stromal reprogramming may therefore help disrupt the lactate-driven feedback loop that maintains the TME in a low-pH, high-PD-L1 and immunotherapy-resistant state, providing a rational route to more durable antitumor immunity in GC (9,19).

5. Therapeutic implications: Targeting the glycolytic-immune axis

A central translational objective in GC is to convert a metabolically cold, immune-excluded TME into one that supports effective T-cell responses. Because glycolysis and lactate accumulation suppress multiple components of antitumor immunity, current strategies emphasize coordinated modulation of metabolism and immunity through enzyme and transporter inhibition, upstream and epigenetic targeting, repurposed metabolic drugs and rational integration with ICB (12,33,116). The goal is not to abolish glycolysis, which would also impair effector lymphocytes, but to reduce glycolytic pressure in tumor and stromal compartments and rebalance nutrients and pH in favor of DC and T-cell function. Such approaches should be guided by glycolysis/lactate-based signatures, ^{18}F-FDG PET-derived metabolic burden and MCT4-high stroma for patient selection (3,117). An overview of this translational framework, linking metabolic targets, metabolic-ICB combination therapy, safety monitoring and biomarker-guided patient stratification, including ^{18}F-FDG PET/CT, radiomics-derived glycolytic features, lactylation-related gene signatures and exosomal ncRNA biomarkers is provided in Fig. 4. Therapeutic strategies, representative agents, proposed mechanisms, expected immunologic benefits, current evidence levels and supporting references are summarized in Table II.

Inhibiting glycolytic enzymes and lactate transporters. Several agents directly reduce glycolytic flux. 2-Deoxy-D-glucose (2-DG) competitively inhibits HK2, lowers ATP levels and can downregulate PD-L1. In GC models, 2-DG combined with pyrolyzed deketene curcumin attenuated tumor glycolysis and limited Treg generation (15,115,118). LDHA inhibitors, such as FX11, oxamate and related analogues, were shown to restore pyruvate oxidation, increase intratumoral pH, enhance CTL/DC activity and reduce invasion and EMT (77,94,95). PFKFB3 inhibitors, including PF-3, 3PO and KAN0438757, were demonstrated to suppress glycolytic flux and normalize tumor vasculature, thereby improving T-cell trafficking and drug delivery (4,80). Additional targets, including PDK1/4,

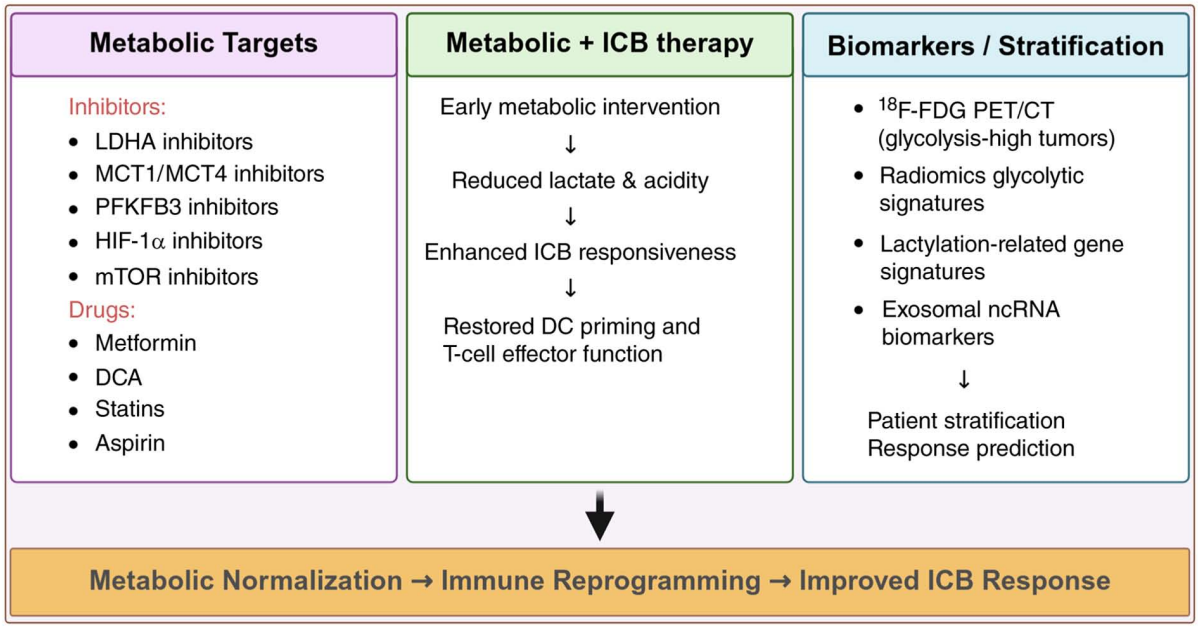

Figure 4. Therapeutic and biomarker-guided strategies targeting glycolytic immunosuppression in gastric cancer. Inhibitors of LDHA, MCT1/4, PFKFB3, HIF-1α and mTOR, as well as repurposed metabolic agents such as metformin, DCA, statins and aspirin, can normalize glycolytic pressure and lactate accumulation. These interventions may enhance dendritic-cell priming, restore T-cell effector function and improve responsiveness to PD-1/PD-L1 blockade in selected metabolic contexts. Metabolic imaging (^{18}F-FDG PET/CT), radiomic glycolysis signatures and lactylation-based transcriptomic classifiers provide complementary tools for selecting glycolysis-high tumors most likely to benefit from immunometabolic combination strategies. Created with BioRender.com. LDHA, lactate dehydrogenase A; MCT1/4, monocarboxylate transporter 1/4; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; HIF-1α, hypoxia-inducible factor-1α; mTOR, mechanistic target of rapamycin; DCA, dichloroacetate; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose; ICB, immune checkpoint blockade; DC, dendritic cell; ncRNA, noncoding RNA.

G6PD, transketolase-like protein 1 and PKM2, weaken the Warburg phenotype, increase radio- and chemosensitivity and reduce redox buffering (96,119).

Lactate transport is a complementary target. MCT1 inhibitors, including AZD3965 and AR-C155858, limit lactate uptake by oxidative tumor cells, whereas MCT4 inhibitors, such as syrosingopine and α-cyano-4-hydroxycinnamate, trap lactate intracellularly, inducing metabolic stress and reducing extracellular acidification (4,18,93). High stromal MCT4, particularly in CAFs and TAMs, has been shown to be associated with poor survival, immune exclusion and peritoneal carcinomatosis (27,79,104). *In vivo*, MCT4 blockade was reported to normalize pH, reduce M2/MDSC signatures and restore T-cell trafficking (80,94,115). Because systemic inhibition of glycolysis or lactate shuttling may also affect highly glycolytic normal tissues and activated lymphocytes, tumor-targeted formulations, including liposomes, nanoparticles and antibody-drug conjugates, as well as intermittent dosing schedules, are being explored to exploit the stronger glycolytic dependence of GC cells while preserving immune-cell fitness (6,9,12,95,100,118).

Targeting upstream signaling and epigenetic regulators. Master regulators link oncogenic signaling, glycolysis and immune evasion. HIF-1α, PI3K/AKT/mTOR and MYC collectively induce GLUT1, HK2, LDHA, PD-L1 as well as other targets (16,35,42,120). Inhibition of HIF-1α, such as with PT2385 or BAY 87-2243, or mTOR, such as with everolimus or rapamycin, was shown to reduce lactate output in GC models, partially normalize metabolic competition between tumor cells and T cells, and improve responses to anti-PD-1 therapy (37,105,121,122). Epigenetic writers such as SMYD2 and SETD1A, together with m6A-modified lncRNAs including OIP5-AS1, were reported to stabilize glycolytic gene expression and immune-cold phenotypes; inhibiting these pathways may lower PD-L1 expression and resensitize tumors to ICB (26,61,123,124). In myeloid cells, modulation of histone lactylation, for example through p300 inhibition or histone deacetylase activation, was shown to partially re-educate M2 macrophages and reverse lactate-imprinted tolerogenic memory, providing another potential route to restore anti-tumor immunity (11,13,58,90). Given the pleiotropic roles of these pathways, most strategies favor short metabolic-priming windows around ICB, with dosing guided by real-time metabolic and immune readouts (1,21,28,82).

Repurposing clinically available metabolic modulators. Several licensed agents exert immunometabolic effects that may be therapeutically useful. Metformin, an AMP-activated protein kinase (AMPK) activator and OXPHOS enhancer, reduces LDHA and MCT4, limits HIF-1α stabilization and can reverse PD-L1 upregulation by restoring the NAD^+/NADH balance (4,9,93). Observational studies in diabetic GC suggest improved outcomes, consistent with combined tumor-intrinsic and immune-related benefits (6,48). Dichloroacetate (DCA) inhibits PDKs, promotes pyruvate entry into the TCA cycle and may improve antigen presentation. In GC models, DCA was shown to enhance 5-fluorouracil efficacy and reverse hypoxia-related resistance through HIF-1α downregulation (36,54,64,125). Aspirin and other nonsteroidal anti-inflammatory drugs can dampen HIF-1α/mTOR signaling, limit HK2 transcription and

Table II. Metabolic-immune therapeutic strategies and clinical relevance in GC.

Strategy	Target/Drug	Mechanism	Expected immunologic benefit	Clinical relevance	(Refs.)
LDHA inhibition	FX11, GNE-140	Reduces lactate production	Restores DC/T-cell activation	Preclinical evidence	(77,94,148)
MCT1/4 blockade	AZD3965, syrosingopine	Blocks lactate shuttle	Disrupts metabolic immune exclusion	Early clinical evidence for MCT1; MCT4 mainly preclinical	(79,104,146,147)
PFKFB3 modulation	PFKFB3-targeting approaches	Reduces glycolytic flux	May reduce glycolysis-high metabolic pressure	Preclinical evidence; GC-specific therapeutic validation remains limited	(95)
HIF-1α/AKT/mTOR-axis targeting	HIF-1α-, AKT- or mTOR-related approaches	Suppresses hypoxia- and growth-factor-driven glycolysis	May reduce PD-L1-linked metabolic remodeling	Preclinical and translational evidence; GC metabolic-ICB efficacy remains unproven	(35,37,38,121,122)
Dichloroacetate	PDH activation	Reduces lactate	Restores T-cell metabolism	Early investigation	(36,125)
Chemoimmunotherapy backbone	PD-1 blockade plus chemotherapy	Provides an established clinical backbone for future metabolic combinations	Supports antitumor immune responses in selected patients	Established first-line clinical evidence in advanced GC/GEJ adenocarcinoma; metabolic add-on remains unproven	(134,143-145)

Representative metabolic intervention strategies targeting glycolysis and lactate handling, together with their proposed mechanisms and potential immunologic benefits when integrated with antitumor immunity. Clinical relevance provides a qualitative summary of the current level of evidence in gastric cancer or related solid tumors. Only primary research articles directly investigating the corresponding target, drug, strategy or chemoimmunotherapy backbone were retained in the supporting-reference column; review articles, guidelines and indirect background references were removed from this column. GC, gastric cancer; LDHA, lactate dehydrogenase A; DC, dendritic cell; MCT1/4, monocarboxylate transporter 1/4; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; HIF-1α, hypoxia-inducible factor-1α; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; PD-L1, programmed death-ligand 1; ICB, immune checkpoint blockade; PDH, pyruvate dehydrogenase kinase complex; PD-1, programmed death-1; GEJ, gastroesophageal junction.

suppress COX-2-mediated immunosuppressive prostaglandins (33,88,96).

Additional candidates include β-blockers, such as propranolol, which may attenuate sympathetic HIF-1α stabilization; statins, which target mevalonate pathways involved in membrane organization and immune regulation; AMPK agonists such as 5-aminoimidazole-4-carboxamide ribonucleotide; proton pump inhibitors such as pantoprazole, which can inhibit PKM2; FA synthase inhibitors such as orlistat; and ketogenic-like diets enriched with omega-3 FAs and medium-chain triglycerides. These interventions can shift metabolic states, increase vulnerability to glycolytic stress and slow GC xenograft growth in experimental settings (126-128). They are best viewed as background modulators that reduce glycolytic pressure, acidosis or redox stress and create a more permissive niche for DCs and CTLs, making them potential partners for PD-1/PD-L1 inhibitors in biomarker-defined GC subsets (Fig. 4) (48,101,118,119,129). The therapeutic strategies targeting glycolytic enzymes, lactate transport, upstream signaling, repurposed metabolic modulators and immunometabolic combination approaches are summarized in Fig. 4.

Risk factor-guided refinement may further improve the rational use of these repurposed agents. *Helicobacter pylori*-positive and chronic inflammation-enriched GC should be regarded as etiologically high-risk and inflammation-associated contexts rather than as established β-blocker-sensitive subtypes. Chronic *Helicobacter pylori* infection induces long-standing gastritis, disrupts local immune responses and increases the risk of gastric adenocarcinoma, particularly in high-incidence regions, supporting its classification as a major risk context for GC (1,2,16,51-53). In this inflammatory background, β-blockers may be most biologically relevant

when tumors show high sympathetic stress-related signaling, β-adrenergic pathway activation or inflammation-associated glycolytic remodeling. This hypothesis is supported by evidence that norepinephrine enhances aerobic glycolysis and lactate release and may act as a predictive factor for immunotherapy in GC (48). However, direct evidence that *Helicobacter pylori*-positive GC is preferentially sensitive to β-adrenergic blockade remains unavailable. Therefore, β-blockers should be considered exploratory metabolic-neuroimmune modulators for adrenergic or inflammation-linked glycolysis-high contexts rather than universal adjuvants for all patients with *Helicobacter pylori*-positive GC.

For statins, the most plausible risk-factor-guided context may involve metabolic syndrome, dysregulated lipid metabolism or cholesterol/mevalonate pathway activation. Metabolic syndrome has been associated with increased GC risk in a large prospective Korean cohort, and hypertriglyceridemia, low high-density lipoprotein cholesterol and hyperglycemia were independently associated with GC risk (130). In parallel, epidemiologic studies suggest that statin exposure is associated with a reduced risk of GC, particularly in selected metabolic backgrounds such as elderly patients with hyperglycemia, although these findings do not prove an immunometabolic treatment effect in established GC (131). Mechanistically, statins inhibit 3-hydroxy-3 methylglutaryl coenzyme A reductase and suppress the mevalonate pathway, which can influence membrane cholesterol availability, lipid raft organization, oncogenic signaling and immune regulation (132). In GC models, disruption of the mevalonate pathway has also been linked to altered tumor growth and progression, supporting the biological plausibility of statin-related metabolic intervention (133). Overall, β-blockers and statins should not be considered universal metabolic adjuvants. Future studies should incorporate *Helicobacter pylori* status, chronic inflammatory background, metabolic syndrome, lipid profiles, adrenergic-pathway activity, cholesterol/mevalonate-pathway activation, glycolysis/lactate signatures and immune contexture to define candidate populations more precisely.

Combination strategies with ICB. Because metabolic inhibition alone rarely yields durable responses, most preclinical studies now evaluate combinations with ICB. In murine GC and colorectal models, dual LDHA/MCT4 blockade plus anti-PD-1 was shown to increase T-cell infiltration, reduce Tregs and prolong survival (27,80,104,115). Co-targeting HIF-1α and PD-1, or combining metformin with anti-PD-1, achieved superior control of hypoxia-driven tumors by lowering lactate, normalizing pH, improving CTL metabolic fitness and attenuating STAT3/MYC signaling and histone lactylation (26,100,105). Early-phase trials, including NCT03721944, NCT05101237 and NCT04772633, are testing MCT1 inhibitors and other metabolic modulators with anti-PD-1/PD-L1 therapy in solid tumors, including GC or gastroesophageal cancers. These studies are expected to clarify whether metabolic modulation can enhance immune activation and whether such combinations have acceptable safety profiles in biomarker-selected populations (Fig. 4) (3,21,134).

Large randomized trials such as CheckMate 649 have established PD-1 plus chemotherapy as a first-line standard in advanced GC (7,135), providing a clinical backbone onto which metabolic agents could theoretically be layered. However, because chemoimmunotherapy already carries substantial immune-related and hematologic toxicity, metabolic-ICB combinations should prioritize glycolysis-high, immune-cold patients, use temporal staggering such as short metabolic priming before or briefly overlapping with ICB, and incorporate de-escalation strategies guided by metabolic imaging and immune biomarkers (5,129,136). The specific safety considerations of these combinations are discussed below as part of the biomarker-guided translational framework shown in Fig. 4.

Emerging biomarkers and dynamic imaging tools. Robust biomarkers are essential for deploying immunometabolic strategies in GC (9,18,33). MCT4 expression, LDHA activity and lactate levels measured by magnetic resonance spectroscopy, together with gene-expression-derived glycolysis scores incorporating HK2, PFKFB3, LDHA, ENO1 and MCT4, are inversely associated with $CD8^+$ T-cell infiltration and ICB benefit and may identify tumors more likely to benefit from metabolic intervention (3,27,137). Circulating exosomal lncRNAs such as H19 and MALAT1, glycolysis-associated circRNAs and serum IL-8 provide minimally invasive indicators of metabolic immunosuppression (55,85,99,138). Integrating tissue biomarkers, exosomal signals and peripheral immune-cell profiles may therefore help define glycolysis-high, lactate-rich and immune-excluded GC subsets before treatment, corresponding to the biomarker-guided stratification module in Fig. 4.

Imaging biomarkers provide complementary, noninvasive information on whole-tumor metabolic burden. Baseline ^{18}F-FDG PET/CT parameters, including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG), can capture glycolytic activity, viable tumor burden and spatial heterogeneity beyond anatomic size alone (1,2,4,28,29). PET/CT-derived volumetric parameters and radiomics features have been associated with survival, c-MET/HER2 status, lymphovascular invasion, response to chemotherapy or ramucirumab-based regimens and outcomes after neoadjuvant immunochemotherapy (4,28,29,73,78). These parameters may therefore serve as baseline tools for selecting patients with FDG-avid, glycolysis-high tumors who are more likely to require metabolic modulation in addition to ICB, as summarized in Fig. 4.

Beyond baseline stratification, dynamic changes in metabolic imaging during treatment may be particularly informative. Early reductions in MTV or TLG after one or two treatment cycles may reflect decreased viable glycolytic tumor burden before conventional CT-based tumor shrinkage becomes apparent. Conversely, persistent or increasing MTV/TLG despite therapy may indicate primary metabolic resistance, inadequate immune infiltration or continued stromal lactate production. In the setting of ICB or chemoimmunotherapy, longitudinal PET/CT may also help distinguish true metabolic response from mixed response, pseudoprogression, hyperprogression or inflammatory immune-cell infiltration, although standardized interpretation criteria for GC immunotherapy remain insufficiently established.

Although GC-specific dynamic PET/CT data during ICB remain limited, primary studies in other solid tumors provide clinically relevant examples supporting this concept.

In previously treated non-small cell lung cancer (NSCLC), Kaira *et al* (139) performed ^{18}F-FDG PET/CT before and 1 month after nivolumab therapy and calculated SUVmax, MTV and TLG; metabolic response at 1 month predicted early therapeutic efficacy and survival more effectively than CT alone. In another prospective NSCLC study, Umeda *et al* (140) performed integrated ^{18}F-FDG PET/magnetic resonance imaging (MRI) before and 2 weeks after nivolumab therapy; early changes in TLG combined with ADC changes distinguished non-progressive disease from progressive disease and were associated with progression-free survival (PFS) and overall survival (OS). In the neoadjuvant setting, Tao *et al* (141) evaluated baseline and preoperative ^{18}F-FDG PET/CT in resectable NSCLC treated with two cycles of sintilimab; percentage changes in maximum and peak standardized uptake values normalized by lean body mass (SULmax and SULpeak), MTV and TLG, and PET Response Criteria in Solid Tumors-based metabolic response were significantly associated with major pathological response, with all partial metabolic responders achieving major pathological response (141). These primary studies support the rationale for prospectively testing serial PET/CT-derived MTV, TLG and metabolic response criteria in GC immunotherapy or chemoimmunotherapy trials, while acknowledging that disease-specific validation in GC remains necessary.

Dynamic metabolic imaging should ideally be interpreted together with immune and liquid-biopsy markers. For example, early decreases in MTV/TLG accompanied by increased peripheral effector T-cell signatures, reduced serum IL-8, declining exosomal glycolytic ncRNAs or reduced lactate-related gene signatures would support effective immunometabolic remodeling. By contrast, persistently high FDG uptake together with MCT4-high stroma, elevated IL-8 or myeloid-suppressive signatures may suggest ongoing lactate-driven immune exclusion and the need for therapeutic adaptation. Artificial-intelligence-assisted radiomics, hyperpolarized ^{13}C MRI, spatial transcriptomics and multiplex immunohistochemistry could further refine this framework by linking whole-body metabolic changes to regional immune architecture (19,20,75,76,142).

Thus, PET/CT and radiomics should not be viewed only as static prognostic tools. In future trials of metabolic intervention plus ICB, serial imaging at baseline, early on-treatment time points and progression should be incorporated to evaluate whether changes in MTV, TLG, SUV-derived heterogeneity and radiomics features can predict response, immune remodeling and resistance earlier than anatomic criteria. Safety and toxicity should be assessed together with clinical symptoms, laboratory parameters and treatment exposure. Such dynamic monitoring may support adaptive treatment strategies, including continuation, escalation, de-escalation or switching of immunometabolic combinations.

Challenges in clinical translation. Despite the strong biologic rationale for combining metabolic intervention with ICB, clinical translation remains challenging. A central concern is therapeutic selectivity. Glycolysis and lactate transport are not unique to malignant cells; activated T cells, DCs, intestinal epithelial cells, hematopoietic progenitors and other proliferating normal tissues also depend on glucose metabolism or lactate handling under stress conditions (12,33,100). Therefore, systemic inhibition of LDHA, MCT1/4, PFKFB3 or upstream glycolytic regulators may impair not only tumor glycolysis but also immune-cell fitness, epithelial repair and bone marrow recovery. Accordingly, early-phase trials should prospectively monitor immune-cell fitness, blood counts, mucosal toxicity, nutritional status and gastrointestinal tolerance when glycolysis- or lactate-transport-targeted agents are combined with chemotherapy and ICB.

Toxicity is especially important when metabolic agents are layered onto chemotherapy plus ICB. Published chemoimmunotherapy trials in advanced GC and gastroesophageal junction (GEJ) adenocarcinoma provide concrete examples of how therapeutic selectivity, patient selection and toxicity monitoring have already been incorporated into clinical study design. In CheckMate 649, nivolumab was combined with fluoropyrimidine- and platinum-based chemotherapy as first-line treatment for previously untreated, unresectable, non-HER2-positive gastric, GEJ or esophageal adenocarcinoma. Therapeutic selectivity was implemented through prespecified PD-L1 combined positive score (CPS) subgroups, with OS and PFS tested primarily in patients with PD-L1 CPS ≥5. This trial demonstrated improved OS and PFS in the CPS ≥5 population, but also showed higher grade 3-4 treatment-related adverse events with nivolumab plus chemotherapy than with chemotherapy alone (59% vs. 44%), most commonly nausea, diarrhea and peripheral neuropathy, although no new safety signals were identified (134).

ATTRACTION-4 provides an Asian population-specific example. This randomized, double-blind phase 3 trial enrolled patients from Japan, South Korea and Taiwan with previously untreated, HER2-negative, unresectable advanced or recurrent GC/GEJ cancer and Eastern Cooperative Oncology Group (ECOG) performance status 0-1, regardless of PD-L1 expression. Nivolumab plus oxaliplatin-based chemotherapy significantly improved PFS but not OS. The most common treatment-related grade 3-4 adverse events were decreased neutrophil count and decreased platelet count, and treatment-related serious adverse events were more frequent with nivolumab plus chemotherapy than with placebo plus chemotherapy (143). In KEYNOTE-859, pembrolizumab plus chemotherapy was evaluated in previously untreated, locally advanced or metastatic HER2-negative gastric/GEJ adenocarcinoma. Patient selection included HER2-negative status and ECOG performance status 0-1, and randomization was stratified by geographical region, PD-L1 status and chemotherapy backbone. Pembrolizumab plus chemotherapy improved OS in the intention-to-treat population and in PD-L1 CPS ≥1 and CPS ≥10 subgroups, while grade 3-5 adverse events included anemia and decreased neutrophil count, and serious treatment-related adverse events occurred in 23% vs. 19% of patients (144). ORIENT-16 further illustrates population- and biomarker-informed selection in Chinese patients with unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma. Sintilimab plus capecitabine and oxaliplatin improved OS both in all randomized patients and in the PD-L1 CPS ≥5 subgroup; grade 3 or higher treatment-related adverse events included decreased platelet count, decreased neutrophil count and anemia (145).

These published trials indicate that chemoimmunotherapy development in GC has already relied on clinically applicable selection variables, including HER2 status, PD-L1 CPS, ECOG performance status, disease setting, geographic or regional population and chemotherapy backbone. They also show that hematologic, gastrointestinal, neurologic and immune-related toxicities must be actively monitored even before adding metabolic inhibitors. Therefore, future metabolic-ICB combinations should not be developed as uniform add-on strategies. Instead, they should build on trial-tested selection variables and add experimental metabolic biomarkers, such as LDHA/MCT4 expression, FDG avidity, MTV/TLG, glycolysis-related gene signatures and exosomal ncRNA markers, only after prospective validation (Fig. 4). By contrast, published clinical data specifically evaluating chemotherapy plus ICB plus LDHA or MCT4 inhibition in GC are not yet available. Therefore, the possibility that LDHA/MCT4 inhibitors could increase myelosuppression, gastrointestinal toxicity or immune-related toxicity should currently be considered a biologically plausible concern rather than an established clinical observation.

Available evidence on lactate-transport or glycolysis-targeted agents further supports cautious clinical translation. The MCT1 inhibitor AZD3965 has entered first-in-human phase I testing in patients with advanced solid tumors or lymphoma, providing initial human safety information for pharmacologic lactate-transport inhibition (146). However, AZD3965 selectively targets MCT1 rather than MCT4, and these data do not establish the safety of combining lactate-transport inhibition with chemotherapy plus ICB in GC. MCT4-targeting approaches remain predominantly preclinical; for example, syrosingopine has been evaluated as a dual MCT1/MCT4 inhibitor that modulates tumor metabolism and extracellular acidification in experimental models (147). Similarly, LDHA inhibitors such as FX11 and oxamate have shown antitumor activity mainly in preclinical studies, and mature clinical toxicity data for LDHA inhibition in GC are lacking (148). Thus, the toxicity of chemotherapy plus ICB plus LDHA/MCT4 inhibition should be prospectively evaluated in early-phase trials rather than inferred from preclinical efficacy alone.

Several strategies may improve the therapeutic window. First, metabolic intervention should be guided by patient selection rather than applied uniformly; patients with glycolysis-high, MCT4-high, FDG-avid and immune-excluded tumors are more rational candidates than those with metabolically inflamed or glycolysis-low tumors (18,21,27,28,29,73,78). Second, intermittent dosing or short metabolic-priming windows before ICB may reduce chronic suppression of effector lymphocytes while transiently lowering lactate burden and improving T-cell infiltration. Third, tumor-targeted delivery systems, pH-responsive formulations and stromal-targeted approaches may help limit systemic exposure. Finally, early-phase trials should prospectively monitor not only tumor response but also neutrophil and lymphocyte dynamics, anemia, mucosal toxicity, nutritional status, liver function, inflammatory cytokines and immune-related adverse events.

Biomarker-integrated toxicity assessment will be essential. Dynamic ^{18}F-FDG PET/CT, circulating lactate-related signatures, exosomal ncRNAs, peripheral immune-cell profiling and serum cytokine panels may help distinguish beneficial metabolic reprogramming from excessive systemic metabolic stress. In this context, the goal of metabolic-ICB combination therapy should not be maximal glycolytic inhibition, but carefully timed and biomarker-guided reduction of tumor- and stroma-derived metabolic pressure while preserving antitumor immune-cell function, as summarized in Fig. 4.

6. Conclusions

Glycolytic reprogramming is a major organizer of immune suppression in selected GC subtypes. Tumor-intrinsic oncogenic signaling, hypoxia, inflammation and ncRNA-mediated regulation enhance glucose uptake, glycolytic flux and lactate export, while stromal cells, CAFs, MSCs and immunosuppressive myeloid populations further amplify this metabolic state. The resulting lactate-rich and acidic TME impairs DC maturation, T-cell effector function and NK-cell activity, promotes M2-like macrophages and MDSCs, and reinforces immune checkpoint activation through signaling and epigenetic mechanisms, including HCAR1/GPR81 signaling and histone lactylation. Together, these processes establish spatially organized immunometabolic niches in which glycolytic stress, abnormal vasculature, stromal stiffness and immune exclusion limit durable responses to ICB.

At the same time, GC should not be viewed as a uniformly glycolysis-dependent disease. Glycolysis-centered immune suppression represents an important but heterogeneous framework that interacts with glutamine metabolism, FA oxidation, mitochondrial rewiring, stromal metabolism and vascular remodeling. Therefore, the concept of glycolysis-driven immunosuppression should be interpreted as a working model for selected glycolysis-dominant, lactate-rich and immune-excluded GC subtypes rather than as a universal explanation for all GC biology. Recognizing this metabolic heterogeneity is essential for translating glycolysis-targeted strategies into rational, biomarker-guided therapeutic combinations.

7. Future perspectives: Roadmap for clinical translation

Future studies should first validate glycolysis- and lactate-centered biomarkers in prospective GC cohorts. Candidate markers include tumor or stromal LDHA and MCT4 expression, glycolysis-related gene signatures, lactylation-related models, exosomal glycolytic ncRNAs, serum inflammatory mediators such as IL-8, and baseline ^{18}F-FDG PET/CT parameters such as SUVmax, MTV and TLG. These markers should be integrated with immune contexture, including $CD8^+$ T-cell infiltration, cDC1 abundance, TAM and MDSC signatures, PD-L1 status and spatial immune exclusion.

Second, clinical development of immunometabolic combinations should move from empiric combinations toward subtype-guided trial design. Patients with FDG-avid, LDHA/MCT4-high, lactate-rich and immune-excluded tumors may be the most rational candidates for metabolic priming combined with ICB. By contrast, tumors with lower

glycolytic burden or stronger dependence on glutamine, lipid or mitochondrial metabolism may require alternative strategies. Risk-factor annotation, including *Helicobacter pylori* status, EBV status, inflammatory background, metabolic comorbidities and sympathetic stress-related signaling, may further refine the use of repurposed agents such as β-blockers, statins, metformin or DCA.

Third, safety and therapeutic window should remain central considerations. Because glycolysis and lactate handling are also required by activated immune cells, intestinal epithelium and hematopoietic progenitors, future trials should avoid indiscriminate metabolic inhibition and instead evaluate intermittent dosing, short metabolic-priming windows, tumor-targeted or pH-responsive delivery systems, and prospective monitoring of myelosuppression, gastrointestinal toxicity, immune-related adverse events, nutritional status and peripheral immune-cell dynamics.

Finally, dynamic monitoring should guide adaptive treatment. Serial ^{18}F-FDG PET/CT, radiomics, circulating exosomal ncRNAs, cytokine profiling and peripheral immune monitoring may help determine whether metabolic intervention reduces tumor glycolytic pressure while preserving immune-cell function. Early changes in MTV, TLG, SUV-derived heterogeneity or glycolysis-related liquid-biopsy markers may provide earlier evidence of response or resistance than anatomic imaging alone. Ultimately, the goal is not maximal suppression of glycolysis, but precise remodeling of tumor- and stroma-derived metabolic barriers to restore immune control in appropriately selected patients.

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Authors' contributions

BZ and LS contributed equally to this work. BZ and LS designed the scope and structure of the review, performed structured literature searches, organized the figures and tables, and drafted the initial manuscript. ZK, CW and BS contributed to structured literature searches, critical synthesis and interpretation of relevant findings, and revision of major sections of the manuscript. FK conceived the review topic, supervised the overall project, critically revised major sections of the manuscript and approved the final version. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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