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REVIEW

The roles of lactate and the interplay with m^{6}A modification in diseases

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Abstract Lactate exhibits various biological functions, including the mediation of histone and non-histone lactylation to regulate gene transcription, influencing the activity of T lymphocytes, NK cells, and macrophages in immune suppression, activating G protein-coupled receptor 81 for signal transduction, and serving as an energy substrate. The m^{6}A modification represents the most prevalent post-transcriptional epigenetic alteration. It is regulated by m^{6}A-related regulatory enzymes (including methyltransferases, demethylases, and recognition proteins) that control the transcription, splicing, stability, and translation of downstream target RNAs. Lactate-mediated lactylation at histone H3K18 can modulate downstream target m^{6}A modifications by enhancing the transcriptional expression levels of m^{6}A-related regulatory enzymes. These enzymes play a crucial role in the progression of diseases such as cancer, fibrosis (in both liver and lung), myocardial ischemia, cerebral hemorrhage, and sepsis. Furthermore, m^{6}A-related regulatory enzymes are also subject to lactylation by lactate. In turn, these regulatory enzymes can influence key glycolytic pathway enzymes or modify lactate transporter MCT4 via m^{6}A alterations to impact lactate levels and subsequently affect lactylation processes.

Keywords Lactate · M^{6}A modification · Lactylation · Glycolysis

Abbreviations

m^{6}A	N6-Methyladenosine
m^{6}A-REE	M^{6}A-related regulatory enzymes
LDH	Lactate dehydrogenase
TCA	Tricarboxylic acid cycle
MCT	Monocarboxylate transporters
PDH	Pyruvate dehydrogenase
HMGB1	High mobility group protein 1
CBP	CREB binding protein
HBO1	Histone acetyltransferase binding to ORC1
KAT8	Lysine acetyltransferase 8
SIRT	Silent information regulator proteins
HDAC	Histone deacetylases
Brg1	Brahma-related gene 1

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GPR81	G protein-coupled receptor 1
MTC	Methyltransferase complex
METTL	Methyltransferase-like
WTAP	Wilms' tumor 1-associated protein
FTO	Fat mass and obesity-associated gene
YTHD	YTH domain
m^6A-RRE	M^6A related regulatory enzymes
JAK	Janus kinase
STAT	Signal transducer and activator of transcription
CDK2	Cyclin-dependent kinase 2
PER1	Period circadian protein homolog 1
TP53	Tumor protein 53
NREP	Neurofilament protein
FDX1	Ferredoxin 1
GLUT1	Glucose transporter 1
mTORC1	Mechanistic target of rapamycin complex1
AMPK	AMP-activated protein kinase
PGK1	Phosphoglycerate kinase1
KCNK6	Potassium channel subfamily K member 6
5-FU	5-Fluorouracil
FOXP3	Forkhead box protein P3
GLUD1	Glutamate dehydrogenase 1
PDK1	Pyruvate dehydrogenase kinase Isozyme 1
ALDOA	Aldolase A
ICH	Intracerebral hemorrhage

In the past, lactate was regarded as the terminal product of glycolysis and considered a waste byproduct produced when the demand for ATP surpasses the available oxygen supply (Joshua and Sven 2020). However, lactate is now recognized as not only an energy substrate but also a signaling molecule that participates in the regulation of cellular metabolic activities (Joshua and Sven 2020; Brooks 2018). Lactate accumulation can promote metabolic reprogramming and immune evasion in tumor cells, thereby contributing to tumor resistance (Lihua et al. 2022). Moreover, elevated lactate levels can induce phenotypic changes in macrophages, subsequently modulating inflammatory processes (Yunda et al. 2024). Interestingly, recent studies have revealed that lactate can also act as a protein modification substrate, playing a crucial role in regulating the tumor microenvironment and inflammatory responses by mediating histone or non-histone lactylation (Certo et al. 2022; Xiaoning et al. 2024). N6-Methyladenosine (m^6A) modification is the most common post-transcriptional modification of mRNA in eukaryotic cells,It plays a crucial role in regulating gene expression, RNA stability, and translation efficiency, and is dynamically controlled by m^6A-related regulatory enzymes (m^6A-REE) (Erdem and Yang 2023). However, the upstream regulatory mechanisms governing m^6A-RRE mediated m^6A modification remain inadequately understood. Recent studies have suggested that the activation of lactate dehydrogenase (LDH) induced by lactate accumulation may serve as a potential upstream regulatory mechanism influencing m^6A-RRE mediated m^6A modification in both tumors and sepsis (Jia et al. 2022; Dan et al. 2024). Notably, some studies have indicated that m^6A-RRE can also modulate the m^6A modification of key enzymes involved in glycolysis, further regulating lactate levels (Chen et al. 2021), (Kai et al. 2024). These findings imply that the interplay between lactate and m^6A modification plays a significant role in the pathogenesis of diseases. This paper primarily aims to summarize the functions of lactate and investigate the reciprocal regulation between lactate and m^6A modification across different disease contexts.

Lactate metabolism

The body primarily obtains energy through glycolysis and oxidative phosphorylation, with lactate acting as the final product of glycolysis (Joshua and Sven 2020). The traditional understanding is that lactate in cells primarily originates from anaerobic glycolysis: glucose undergoes a series of catalytic reactions to be converted into pyruvate, which is then directly reduced to lactate by lactate dehydrogenase LDH (Fig. 1) (Brooks 2018; Fantin et al. 2006). Currently, it is believed that cells can obtain energy through the glycolytic pathway and produce lactate in aerobic conditions,this phenomenon was first discovered in cancer cells by Warburg (known as the "Warburg effect") (Warburg 1925). Additionally, increasing evidences suggest that the "Warburg effect" not only exists in cancer cells but has also been observed in immune cells (Zoé et al. 2023; Benjamin et al. 2017; Michelangelo et al. 2020; Eva et al. 2022). In addition, in cancer cells, glutamine enters the tricarboxylic

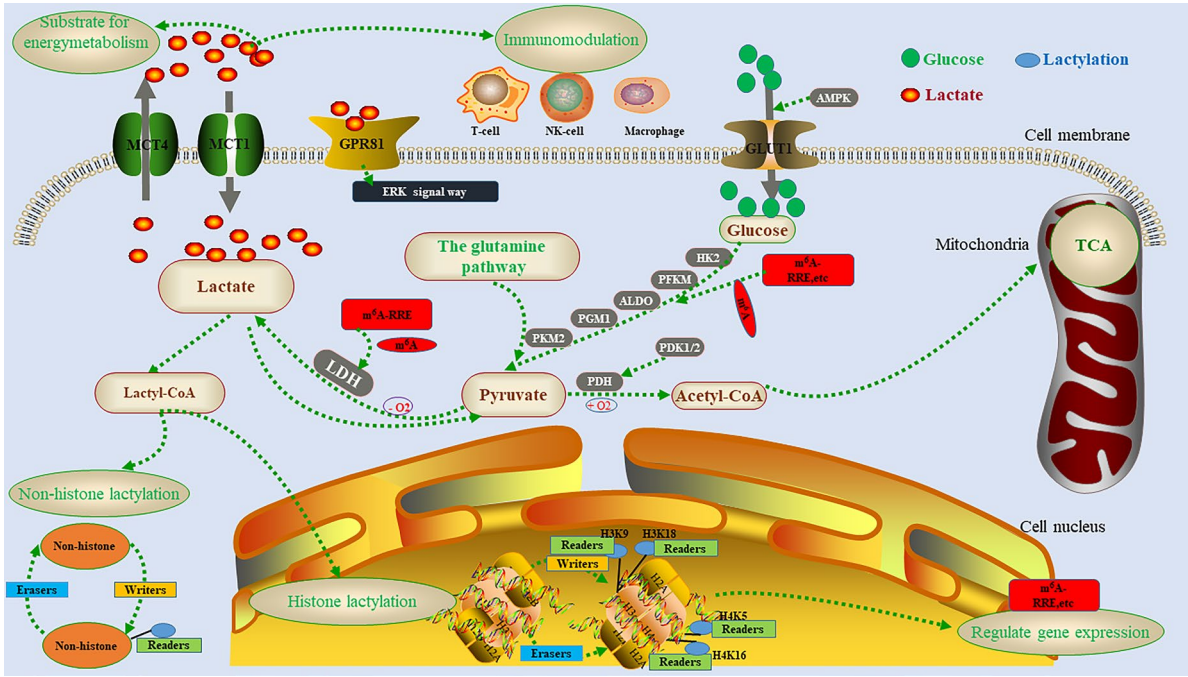

Fig. 1 Extracellular glucose enters the cell through the action of GLUT1, which is regulated by AMPK. Subsequently, a series of enzymes including HK2, PFKM, ALDO, PGM1, and PKM2 work together to produce pyruvate. Pyruvate is then converted into lactate by LDH. Furthermore, pyruvate participates in the TCA cycle with the assistance of PDH and PDK1/2. MCT1 facilitates the transport of extracellular lactate into the cell while MCT4 is responsible for exporting intracellular lactate from the cell. Lactate plays a role in promoting lactyl-CoA production and contributes to histone or non-histone lactylation under the writers, erasers or readers. Additionally, lactate activates the GPR81 receptor, can be involved in immune regulation and serves as a substrate for energy metabolism

acid cycle (TCA) cycle via enzymes such as glutaminase, where it is converted into nicotinamide adenine dinucleotide phosphate hydrogen and pyruvate,the resulting carbon provides a carbon skeleton for the production of lactate (Ralph et al. 2007; Zacharias et al. 2023). Lactate is transported across the plasma membrane by monocarboxylate transporters (MCT), with MCT1 primarily responsible for uptake and MCT4 for export (Alpaslan et al. 2019). Extracellular lactate can enter target cells through intercellular shuttling via MCT1 (Tomoya et al. 2024; Valéry et al. 2019). The transport direction of lactate is influenced by its concentration gradient (Alpaslan et al. 2019). Lactate is primarily eliminated through oxidation to pyruvate (Mithileshkumar et al. 2016),Pyruvate subsequently employs pyruvate dehydrogenase (PDH) to translocate into the mitochondria, where it undergoes metabolism via TCA cycle (Mithileshkumar et al. 2016). Furthermore, lactate can be converted into glucose through the gluconeogenesis pathway,it also promotes the production of lactyl-CoA, which plays a role in the lactylation of histone and non-histone protein (Xiaolu et al. 2022), (Chi-An et al. 1985).

Main functions of lactate

Mediating lactylation

Lactylation is a recently discovered post-translational modification induced by lactate, which was first identified in histone by Zhang et al. (Zhang et al. 2019). Histone is primarily composed of H1, H2A, H2B, H3, and H4 subunits (The 8-mer made of 2 molecules each of H2A, H2B, H3, and H4 is the core component of the nucleosome), and various acyl groups can be linked to the amino and carboxyl terminal amino acid residues of these subunits. Lactate covalently binds to the lysine (K) residues of histone in a concentration-dependent manner, resulting in their

lactylation (Martín et al. 2019). The most common modification site is H3K18, where a lactate group is added at the K18 site of histone H3, thereby altering the function and regulatory processes of this histone in the cells (Jingyu et al. 2024). Interestingly, lactylation also exists on non-histone proteins (Dominique et al. 2019). For example, a study has found that the abnormal increase in blood lactate levels in sepsis patients can lactacylate the high mobility group protein 1(HMGB1) in macrophages, promoting exosome secretion and release, disrupting endothelial integrity, and leading to endothelial barrier dysfunction (Kun et al. 2021).

Lactylation has been shown to be regulated by lactate levels (Erika et al. 2020). And this process necessitates the involvement of specific lactate dehydrogenase "Writers" and lactate dehydrogenase "Erasers" for regulation (Table 1) (Yang et al. 2022; Cui et al. 2021). A study has demonstrated that knockdown of p300 in mouse bone marrow-derived macrophages significantly impairs lactate-induced histone lactylation (Cui et al. 2021). And, overexpression of p300 in HEK293T cells leads to an increase in histone H3K18 lactylation levels (Zhang et al. 2019). Another study indicated that the p300/ CREB binding protein (CBP) inhibitor C646 antagonized lactate-induced lactylation of non-histone protein HMGB1 in RAW 264.7 cells, and knockdown of p300 or CBP also significantly inhibited this phenomenon (Yang et al. 2022). These findings suggest that p300 and CBP play a role as "Writers" in the process of lactylation. Additionally, new evidences confirm that histone acetyltransferase binding to ORC1(HBO1), YiaC, and lysine acetyltransferase 8 (KAT8) can act as "Writers" to catalyze the addition of lactate to lysine, affecting the activity of metabolic enzymes, promoting translational extension, and protein synthesis,HBO1 seems to preferentially promote H3K9 lactylation (Ziping et al. 2024; Hanyang et al. 2022; Bingteng et al. 2024). These findings provide new insights into the regulation of protein lactylation by p300, CBP, YiaC, HBO1 and KAT8 in different biological environments,however, further research is needed to determine whether they act independently or synergistically. Class I histone deacetylases (HDAC1-3) and silent information regulator proteins (SIRT1-3) are particularly effective in deacylation modification (Carlos et al. 2022). Interestingly, in vitro experiments have demonstrated that HDAC1 and HDAC3 function as "Erasers" by reducing the lactylation level of H4K5 in HeLa cells (Carlos et al. 2022). Zhao et al. further validated the specific delactylation enzyme activity of HDAC1 and HDAC3 through overexpression and knockdown experiments in cells in 2022 (Moreno-Yruela et al. 2022). Additionally, Zessin et al. discovered potential delactylation enzyme activity for HDAC6 and HDAC8 in the same year (Zessin et al. 2022). Subsequently, SIRT2 and SIRT3 were also identified as potential delactylation enzymes, with SIRT3 demonstrating a higher activity towards H4K16 (Zu et al. 2022; Jin et al. 2023). Lactylation requires specific "Readers" for recognition (Xinglin et al. 2024). A study on induced pluripotent stem cell reprogramming conducted a proteomic analysis during an immunoprecipitation experiment targeting H3K18 lactylation in embryonic stem cells, revealing the selective recruitment of Brahma-related gene 1 (Brg1) (Xinglin et al. 2024). Both H3K18 lactylation and Brg1 were enriched at the promoters of genes linked to pluripotency and epithelial connectivity

Table 1 Enzymes associated with m^6A and lactylation

Classification	m^6A modification Gene (Function)	Lactylation Gene (Function)
Writers	METTL3/METTL14/WTAP/VIRMA/KIAA1429/ METTL16/ ZC3H13 (Catalyze m6A modification) (Bokar et al. 1994), (Śledź and Jinek 2016)	p300/CBP/YiaC/KAT8 (Promotes histone or non-histone Lactylation) (Yang et al. 2022), (Ziping et al. 2024), (Hanyang et al. 2022), (Bingteng et al. 2024)
Erasers	FTO/ALKBH5/ALKBH3 (Mediate m^6A demethylation modification as demethylases) (Sarah Kassem et al. 2022)	HDAC1-3/ HDAC6/ HDAC8/ SIRT2/ SIRT3 (Promotes histone or non-histone de-lactylation as de-lactate enzymes) (Moreno-Yruela et al. 2022), (Zessin et al. 2022), (Zu et al. 2022), (Jin et al. 2023)
Readers	YTH domain/ IGF2BPs /EIF3 (Identify m^6A modification sites and promote RNA translation, degradation, etc.) (Tingting et al. 2014), (Peter et al. 2002), (Hailing et al. 2017), (Alarcón et al. 2015)	Brg1 (Identify m^6A lactylation sites) (Xinglin et al. 2024)

(Xinglin et al. 2024). Thus, Brg1 is proposed as a "Reader" for histone lactylation. In summary, these findings indicate that lactylation can be regulated by both lactylation enzymes and de-lactylation enzymes, functioning under the influence of corresponding recognition enzymes. However, it is important to note that these regulatory enzymes exhibit a lack of specificity.

Participation in immune regulation

Immune cells can rapidly activate in response to tissue damage, microbial infections, or cellular stress, activating inflammation pathways and eliminating threats (Rathinam and Chan 2018). Immune evasion plays a crucial role in the development of cancer within the tumor microenvironment (Tay et al. 2023). Lactate has been identified as an important factor in promoting tumor growth by exerting immunosuppressive effects, including inducing, recruiting, and regulating immune suppressor cells (Tay et al. 2023). A study has demonstrated that lactate can inhibit the function of T lymphocytes and NK cells, thus facilitating tumor immune evasion (Brand et al. 2016). Lactate can enter the cytoplasm of CD8 + T lymphocytes, leading to a decrease in intracellular PH and inhibiting the proliferation and cytotoxic function of these cells (Apostolova and Pearce 2022). A high lactate microenvironment can also impair NK cell stability and effectiveness (Brand et al. 2016). Concentrations above 20 mM can induce apoptosis in both T lymphocyte and NK cells (Brand et al. 2016). Additionally, lactate can regulate macrophage metabolic reprogramming, suppressing M1 (pro-inflammatory)50 macrophage activation and M2 (anti-inflammatory) polarization, thereby influencing tumor progression and inflammation development (Bangjun et al. 2024). Additionally, lactate can activate the immune escape mechanism in cancer cells through autocrine signaling by stimulating the G protein-coupled receptor 81 (GPR81) on the cell membrane (Brown and Ganapathy 2020).

Involvement in signal transduction

GPR81 is a selective lactate-sensitive receptor expressed in brain, fat, cancer, and retinal cells (Brown and Ganapathy 2019). Lactate activates GPR81 to transmit signaling molecules and perform biological functions (Certo et al. 2022). For instance, it promotes the dephosphorylation of extracellular signal-regulated kinase (ERK) and enhances cell apoptosis in ischemic brain injury (Shen et al. 2014). In cancer cells relying on lactate as their primary energy source due to the "Warburg effect", the absence of GPR81 impairs mitochondrial function and significantly reduces tumor growth (Roland et al. 2014). Lactate inhibits Yes-related protein (YAP) and NF-κB activation via GPR81-mediated signaling, reducing macrophage pro-inflammatory responses to LPS stimulation (Yang et al. 2020). These findings indicate that GPR81 is a key target for lactate-regulated signaling, significantly influencing tumor growth and inflammation regulation.

As an energy metabolic substrate

Lactate can function as an energy substrate, capable of uncoupling mitochondrial energy production driven by carbohydrates from glycolysis (Joshua and Sven 2020). When blood glucose levels are low, lactate acts as an energy supplement to meet the excitatory activities of the brain (Brooks 2018; Dienel 2019). A study has shown that in the absence of glucose, lactate also participates in synaptic transmission activities in the brain (Schurr et al. 1988). Moreover, research has confirmed that when the shuttling of lactate in the hypothalamic ventricular membrane-neuroglial cells is inhibited, the energy balance of the pre-agouti-related peptide neurons is disrupted (Lhomme et al. 2021). This indicates that lactate may be a primary energy substrate in specific environments.

m^6A modification

Common epigenetic modifications mainly consist of DNA methylation, histone modification, non-coding RNA, RNA methylation modification, and chromatin remodeling (Jonas et al. 2023). In mammals, m^6A modification is the most prevalent epigenetic alteration in mRNA, which can impact gene transcription, splicing, stability, and translation (Zhigalova et al. 2024; Meyer et al. 2015; Molinie et al. 2016). The dynamic regulation of m^6A modification is carried out by methyltransferases (Writers) (Bokar et al. 1994; Śledź and Jinek 2016) and demethylases (Erasers) (Karthiya and Khandelia 2020). Under the action of enzymes (Readers) that can recognize the RNA

base sites with m^6A modifications, the fate of the target RNA is regulated (Shi et al. 2021), (Huang et al. 2018), (Meyer et al. 2015).

The occurrence of m^6A depends on the catalytic action of the methyltransferase complex (MTC), which is mainly composed of methyltransferase-like protein 3 (METTL3), methyltransferase-like protein 14 (METTL14), Wilms' tumor 1-associated protein (WTAP), Vir-like m^6A methyltransferase-associated (VIRMA/KIAA1429), and RNA binding motif protein 15 (RBM15) (Bokar et al. 1994; Śledź and Jinek 2016). METTL3 is the core component of MTC, containing an S-adenosylmethionine (SAM) binding domain that catalyzes the transfer of the methyl group from SAM to the adenine base in RNA (Stephanie et al. 2021). METTL14 and METTL3 form a stable complex in a 1:1 ratio to stabilize the structure of MTC (Wang et al. 2016). This complex is recruited and guided to nuclear speckles by the action of WTAP and RBM15 to jointly promote the installation of m6A methylation (Schöller et al. 2018; Patil et al. 2016). In addition, VIRMA/KIAA1429, zinc finger CCCH-type containing 13 (ZC3H13), and methyltransferase-like protein 16 (METTL16) play a significant role in the complex recruitment and promotion of MTC complex formation in this regulatory process (Yue et al. 2018), (Knuckles et al. 2018), (Warda et al. 2017).

Currently, the identified demethylases mainly include fat mass and obesity-associated gene (FTO), AlkB homolog 5 (ALKBH5), and ALKBH3. FTO is the first identified enzyme capable of catalyzing m6A demethylation, and its dysregulation plays an important role in diseases such as cancer by affecting demethylation modifications (Sarah Kassem et al. 2022). ALKBH5 catalyzes m6A demethylation in a manner dependent on Fe (II) and α-ketoglutarate (Aik et al. 2014). In addition, new research has reported the demethylation function of ALKBH3 (Mohua et al. 2018). However, there is currently limited research on this topic.

The proteins that recognize "Readers" can be categorized into direct and indirect "Readers". Direct "Readers" primarily consist of proteins containing the YTH domain, which binds to regions on RNA where m^6A has occurred. In the mammalian genome, there are three types of YTH domain proteins: YTHDC1, YTHDC2, and the YTHDF protein family (Tingting et al. 2014; Peter et al. 2002). YTHDC1 mainly functions in the nucleus, YTHDC2 has roles in both the nucleus and cytoplasm, and the YTHDF family primarily operates in the cytoplasm (Hailing et al. 2017; Magdalena Natalia et al. 2017). YTHDC1 promotes RNA splicing and export by recruiting mRNA splicing factors (Woodcock et al. 2020). YTHDC2 has an RNA helicase domain and interacts with RNA helicases that regulate translation to promote the translation of target RNA (Phillip et al. 2017). YTHDF1 enhances mRNA translation and protein synthesis by recruiting initiation factors (Wang et al. 2015), YTHDF2 promotes the cleavage of bound mRNA, leading to transcript degradation (Park et al. 2019), while YHTDF3 enhances the functions of both YHTDF1 and YHTDF2 by binding to them respectively (Lasman et al. 2020). Indirect readers such as IGF2BPs, EIF3, and members of heterogeneous nuclear ribonucleoprotein (HNRNP) family also play important roles in improving mRNA stability and efficiency of translation initiation complex formation (Alarcón et al. 2015; Müller et al. 2019; Lee et al. 2016).

The interplay between lactate and m^6A modification

Lactate mediates the regulation of m^6A by histone or non-histone protein lactylating

An increase in lactate levels can induce histone lactylation, regulating m^6A-RRE activity to modulate m^6A of downstream targets involved in disease progression (Fig. 2) (Yu et al. 2021; Xue et al. 2024). Lactate-induced H3K18 lactylation upregulates METTL3 in infiltrating myeloid cells within tumors,METTL3 further modifies the oncogene janus kinase 1 (Jak1) via m^6A, facilitating tumor immune evasion (Jia et al. 2022). H3K18 lactylation is enriched in the METTL3 promoter region, enhancing its transcription,inhibiting p300 enzyme reduces both lactylation and METTL3 levels (Jia et al. 2022). Additionally, lactate promotes similar mechanisms to enrich H3K18 lactylation in the FTO promoter region, leading to increased FTO expression (Xue et al. 2024). This affects endothelial cell vascular permeability by regulating cyclin-dependent kinase 2 (CDK2) mRNA stability through YTHDF2 (Xue et al. 2024). Furthermore, H3K18 lactylation directly

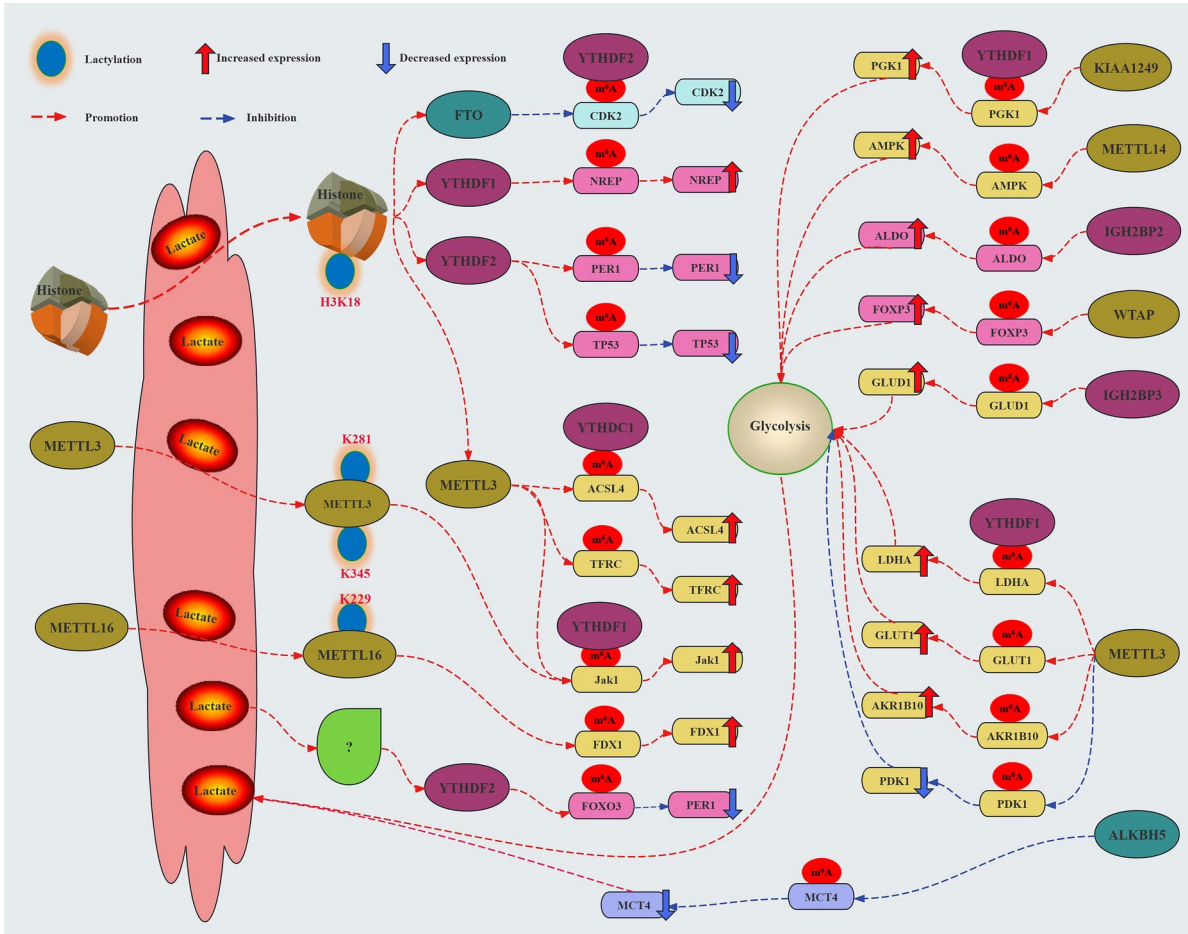

Fig. 2 Lactate regulates m^{6}A-RRE (METTL3, YTHDF2, YTFDF1 and FTO) by lactylating histone H3K18, thereby mediating the modification of downstream target m^{6}A to affect the expression level of target gene. Additionally, it mediates m^{6}A modification of target genes through non-histone METTL3 (K281, K345) and METTL16 (K229) lactylation. Furthermore, lactate also regulates YTHDF2-mediated FOXO3 mRNA-m^{6}A through an unknown mechanism. In turn, these regulatory enzymes can influence key glycolytic pathway enzymes or modify MCT4 lactate transporter via m^{6}A alterations to impact lactate level

regulates YTHDF2 expression to enhance recognition and degradation of m^{6}A-modified period circadian protein homolog 1 (PER1) and tumor protein 53 (TP53) mRNAs, thereby accelerating tumor progression (Yu et al. 2021). Elevated H3K18 lactylation also boosts YTHDF1 transcription, which mediates m^{6}A modification of neurofilament protein (NREP) and increases transforming growth factor-β1 secretion, promoting fibroblast transformation into myofibroblasts (Wang et al. 2024). These findings indicate that H3K18 is a key site for regulating m^{6}A modification via lactate-induced histone lactylation. This mechanism primarily enhances expression regulation of m^{6}A-RRE targets and influences various biological processes. However, specific regulatory mechanisms require further investigation.

It's worth mentioning that lactate also presents a show by mediating the lactylation of non-histone protein (Ning et al. 2022). In the study on colon cancer invasive myeloid cells, lactate enhanced transcription by mediating the lactylation of METTL3 at K281 and K345 residues (Jia et al. 2022). The lactylation of METTL3 enhanced both its enzymatic activity and expression levels and targeted the m^{6}A modification of Jak1 mRNA, promoting colon cancer development (Jia et al. 2022). Furthermore, lactate enhances

the lactylation of METTL16 at the K229 site, boosting its transcription and enzymatic activity (Lianhui et al. 2023). This upregulates METTL16 expression and function, mediating ferredoxin 1 (FDX1) mRNA-m^{6}A involvement in gastric tumorigenesis (Lianhui et al. 2023). These findings suggest that non-histone lactylation may influence the expression and function of the protein itself,however, specific regulatory mechanisms are not yet clear.

m^{6}A modification regulates lactate levels by controlling glycolytic pathways

Glycolysis serves as the primary energy metabolic process in cancer cells, and m^{6}A has the ability to influence lactate levels by regulating key glycolytic enzymes, thereby activating related signaling pathways (Fig. 2) (Chen et al. 2021; Kun et al. 2022). For instance, METTL3 mediates the LDHA mRNA-m^{6}A through YTHDF1, enhancing LDHA expression to trigger glycolysis (Kun et al. 2022),this catalyzes the conversion of pyruvate to lactate and increases the resistance of rectal cancer cells to 5-fluorouracil (Kun et al. 2022). Additionally, METTL3 regulates glucose transporter 1 (GLUT1) mRNA-m^{6}A to promote glucose uptake and lactate production, leading to the activation of mechanistic target of rapamycin complex1 (mTORC1) signaling and the development of colorectal cancer (Chen et al. 2021). A study has shown that METTL14 promotes lactate levels in the promotion of cervical cancer by regulating glycolytic pathways through AMP-activated protein kinase (AMPK) (Bingyu et al. 2024). Phosphoglycerate kinase1 (PGK1) is a key enzyme in regulating glycolytic pathways, and KIAA1429 promotes aerobic glycolysis and inhibits ferroptosis in oral squamous cell carcinoma by mediating the stability of PGK1 mRNA through YTHDF1 (Ke et al. 2023). Unexpectedly, in one study, overexpression of METTL3 increased the expression of mature miR-27b-3p through m^{6}A modification, inhibiting the expression of glycolytic regulatory enzyme PDK1, thereby suppressing aerobic glycolysis and lactate levels in gliomas (Cijie et al. 2023). These results indicate that key enzymes in the glycolytic pathway are important regulatory targets for m^{6}A in regulating lactate levels. Moreover, under different disease conditions, m^{6}A may promote or inhibit glycolytic pathways.

m^{6}A modification regulates lactate levels by modulating lactate transporters

MCT4 is a crucial enzyme that facilitates lactate transport across the cell membrane (Nathalie et al. 2023). Inhibiting MCT4 can reduce lactate excretion within the cell (Nathalie et al. 2023). A study has shown that the knockout of ALKBH5 mediates the regulation of MCT4 through m^{6}A modification, significantly reducing the growth of melanoma in mice and extending the survival period of mice during immunotherapy (Li et al. 2020). ALKBH5 targets MCT4 mRNA-m^{6}A, further affecting mRNA stability, increasing lactate levels, and affecting tumor growth (Li et al. 2020). However, there is currently less research on this topic, and more evidences are needed to further understand the relationship between them.

The role of lactate in crosstalk with m^{6}A in diseases

Lactate interacts with various m^{6}A-RREs to mediate the m^{6}A of downstream target genes, playing roles in cancer, fibrosis (lung, liver), myocardial ischemia, intracerebral hemorrhage**,** and sepsis (Table 2) (Wang et al. 2024), (Jia et al. 2022), (Yongqiang et al. 2024), (Gui-E et al. 2024), (Zhang et al. 2023a), (Dan et al. 2024).

Tumors

Colon cancer and Colorectal cancer

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway is a key regulator of the tumor microenvironment, and its dysregulation can induce immune evasion and drug resistance in tumor cells (Nauf and Athina-Myrto 2023). In colon cancer-infiltrating myeloid cells, accumulated lactate induces the upregulation of METTL3 in the tumor microenvironment through H3K18 lactylation (Jia et al. 2022). METTL3 mediates YTHDF1/Jak1 mRNA-m^{6}A, enhancing the translation efficiency of JAK1 protein and subsequent STAT3 phosphorylation, promoting tumor progression (Jia et al. 2022). Interestingly, two lactylation modification sites, K281 and K345, located within the zinc finger

Table 2 The role of lactate in crosstalk with m^6A in diseases

Disease type	The level of lactate	m^6A-RRE involved in diseases	Target	Possible mechanism	Reference
Tumors					
Colon cancers	Increased	METTL3/YTHDF1	*Jak1*	Lactate induces METTL3 upregulation through H3K18 or METTL3 lactylation to mediate Jak1 mRNA-m^6A and promote tumor development	Jia et al. 2022)
		WTAP	FOXP3	WTAP promotes tumor development by promoting glycolysis and increasing lactate levels through FOXP3 mRNA- m^6A	Yu et al. 2022)
Colorectal cancers	Increased	METTL3/YTHDF1	LDHA	METTL3/YTHDF1 mediates m^6A modification of LDHA mRNA to promote glycolysis and increase lactate levels	Kun et al. 2022)
Gastric cancer	Increased	METTL16	*FDX1*	Copper ions cooperate with lactate to promote the lactylation of METTL16, and up-regulate the level of FDX1 mRNA-m^6A to induce cuproptosis	Lianhui et al. 2023)
Ocular melanoma	Increased	YTHDF2	PER1/ TP53	H3K18 lactylation accelerates tumor development by promoting YTHDF2 expression, recognizing and promoting degradation of m^6A modified PER1 and TP53 mRNAs	Yu et al. 2021)
		ALKBH5	MCT4	ALKBH5 regulates m^6A modification of Mct4 mRNA to increase lactate levels	Li et al. 2020)
Cervical cancer	Increased	IGF2BP3	GLUD1	IGF2BP3 promotes lactate levels by stabilizing the mRNA of GLUD1 gene through m^6A modification	Tiantian et al. 2023)

Table 2 (continued)

Disease type	The level of lactate	m^6A-RRE involved in diseases	Target	Possible mechanism	Reference
		METTL14	AMPK	METTL14 promotes cervical cancer by regulating the glycolytic pathway through AMPK and increasing lactate levels	Bingyu et al. 2024)
Glioma	Increased	METTL3	PDK1	Overexpression of METTL3 inhibits the expression of PDK1 through m^6A modification to further inhibit aerobic glycolysis and lactate levels	Cijie et al. 2023)
Oral squamous cell carcinoma	Increased	KIAA1429/ YTHDF1	PGK1	KIAA1429/YTHDF1 mediates PGK1 mRNA stability to promote aerobic glycolysis and inhibit ferroptosis	Ke et al. 2023)
Cholangiocarcinoma	Increased	METTL3	AKR1B10	METTL3 regulates the m^6A of AKR1B10 to promote glycolysis and increase lactate levels to promote tumor development	Jingli et al. 2022)
Non-small cell lung cancer	Increased	YTHDF2	FOXO3	Lactate influences YTHDF2-mediated m^6A modification of FOXO3 to promote tumor progression through an unknown mechanism	Wei et al. 2024)
Hepatic fibrosis	Increased	IGF2BP2	*ALDOA*	IGF2BP2 mediates m^6A modification of ALDOA, promoting increased lactate levels and further promoting H3K18 lactylation to accelerate the development of fibrosis	Yongqiang et al. 2024)
Idiopathic pulmonary fibrosis	Increased	YTHDF1	*NREP*	Lactate promotes YTHDF1 transcription by regulating H3K18 lactylation, and promotes fibrosis through YTHDF1/m^6A/NREP pathway	Wang et al. 2024)

Table 2 (continued)

Disease type	The level of lactate	m^6A-RRE involved in diseases	Target	Possible mechanism	Reference
Myocardial ischemia	Increased	YTHDF2	-	Lactate level mediates H3K18 lactylation to promote YTHDF2 expression and promote ferroptosis	Gui-E et al. 2024)
Cerebral hemorrhage	Increased	METTL3	TFRC	The up-regulation of METTL3 lactate level enhances the stability and expression level of METTL3 protein, thereby regulating the m^6A level of TFRC mRNA to inhibit ferroptosis	Zhang et al. 2023a)
Sepsis	Increased	METTL3	ACLS4	Lactate regulates the m^6A level by promoting P300-mediated H3K18 lactylation and the binding of METTL3 promoter sites, and promotes the stable upregulation of ACSL4 mRNA, thus promoting ferroptosis	Dan et al. 2024)

domain of METTL3, enhance the capture of m^6A on Jak1 mRNA (Jia et al. 2022). Potassium channel subfamily K member 6 (KCNK6) enhances potassium channel activity and triggers NOD-like receptor protein 3 (NLRP3) inflammasome activation (Anke et al. 2018). In a study investigating inflammation-associated colorectal cancer, it was found that METTL3-mediated m^6A modification increases the stability of KCNK6 in a YTHDF2-dependent manner (Yuan et al. 2024). During this process, histone lactylation promotes the transcription of YTHDF2, thereby reinforcing the regulatory mechanism (Yuan et al. 2024). Consequently, it appears that in colorectal cancer, lactate-induced histone lactylation may serve as an upstream mechanism regulating downstream target mRNA-m^6A modifications.

Chemotherapy resistance to 5-fluorouracil (5-FU) is a major obstacle to the treatment efficiency of colorectal cancer patients. LDHA is involved in glycolysis and plays an important role in the mechanism of colon adenocarcinoma resistance to 5-FU by mediating lactate production (Aldona 2021; Maosha et al. 2023).A study has found that METTL3 mediates the recruitment of YTHDF1 to LDHA mRNA with m^6A modification, triggering translation and promoting the expression of LDHA (Kun et al. 2022). Inhibition or knockdown of METTL3 can suppress glycolysis, reduce the production of lactate in colorectal cancer cells, and restore the chemosensitivity of 5-FU-resistant colon adenocarcinoma cells (Kun et al. 2022). A study shows that WTAP confers glycolytic activity to colon adenocarcinoma through forkhead box protein P3 (FOXP3) mRNA-m^6A and the upregulation of SMARCE1, promoting tumor malignant development (Yu et al. 2022). In this case, lactate levels may rise due to m^6A modification's regulation of the glycolytic pathway. However, there is currently no direct evidence that the abnormal lactate levels would promote histone or non-histone protein lactylation, which in turn would regulate m^6A modification. The network relationship between these processes remains unclear and requires further investigation.

Gastric cancer

High concentrations of copper ions have been proven to induce a form of cell death known as cuproptosis, which is a potential cancer treatment method, with FDX1 being an important regulatory gene (Qianwen and Tonggang 2023). Gastric cancer cells exhibit high levels of copper ions and lactate (Lianhui et al. 2023). METTL16 is an atypical methyltransferase with elevated expression in gastric cancer cells,moreover, copper ions synergize with lactate to promote the lactylation of METTL16 at the K229 site, increasing the level of FDX1 mRNA-m6A, ultimately affecting copper-induced cell death (Lianhui et al. 2023). These findings reveal the significant role of non-histone METTL16 lactylation in tumor cuproptosis, but further research is needed to fully understand the synergistic mechanism involving copper ions.

Ocular Melanoma

PER1 and TP53 are closely related to the occurrence of tumors. Studies have found that histone H3K18 lactylation promotes the expression of YTHDF2, which further recognizes the m^6A-modified PER1 and TP53 mRNA and promotes their degradation, thereby accelerating the tumorigenesis of ocular melanoma (Yu et al. 2021). Additionally, in animal models, ALKBH5 was found to target the regulation of MCT4 mRNA-m^6A modification, further affecting mRNA stability and increasing lactate levels to affect tumor development (Li et al. 2020). The results presented above indicate that lactate not only mediates histone lactylation to regulate the function of m^6A modification in melanoma, but also is subject to regulation by m^6A modification in reverse.

Others

In other cancer-related studies, the interplay between lactate and m^6A also plays a significant role (Simona et al. 2016). For instance, IGF2BP3 stabilizes the mRNA of GLS and glutamate dehydrogenase 1 (GLUD1) genes through m^6A modification, promoting lactate production and mediating the immune escape of cervical cancer cells (Tiantian et al. 2023). Studies have shown that METTL14 promotes the occurrence of cervical cancer by regulating glycolytic pathways to increase lactate levels through AMPK (Bingyu et al. 2024). Pyruvate dehydrogenase kinase Isozyme 1 (PDK1), a key enzyme in the migration and differentiation of glioma cells, promotes glycolysis under mild hypoxia (Simona et al. 2016), and the overexpression of METTL3 increases the expression of mature miR-27b-3p through m^6A modification, suppressing the expression of PDK1, thereby inhibiting aerobic glycolysis and lactate levels in gliomas (Cijie et al. 2023). PGK1 is a key enzyme in regulating glycolytic pathways, and KIAA1429 promotes aerobic glycolysis in oral squamous cell carcinoma and inhibits ferroptosis by mediating the stability of PGK1 mRNA through YTHDF1 (Ke et al. 2023). Additionally, Aldose reductase 1B10 (AKR1B10) has been proven to play an important role in promoting glycolysis, and studies have found that elevated expression of METTL3 regulates AKR1B10 mRNA-m^6A, promoting tumor growth and glycolysis in cholangiocarcinoma (Jingli et al. 2022). Overexpression of METTL3 promotes the proliferation, migration, invasion, glucose uptake, and lactate production of cancer cells, while knockdown of METTL3 has the opposite effect (Jingli et al. 2022). Interestingly, another study found that lactate affected the m^6A modification mediated by YTHDF2 of forkhead box protein O3 (FOXO3), participating in the cisplatin resistance of non-small cell lung cancer through an unknown mechanism (Wei et al. 2024). In summary, the studies on these tumors indicate that m^6A modification primarily mediates the regulation of key enzymes in the glycolytic pathway, thereby controlling lactate levels. However, further research is necessary to explore the relationship between the produced lactate and histone or non-histone lactylation.

Liver fibrosis and idiopathic pulmonary fibrosis

IGF2BP2 is a recently discovered m^6A-binding protein that has been shown to enhance mRNA stability and translation (Nils et al. 2016). In a mouse model of liver fibrosis, the expression of IGF2BP2 is increased, and inhibiting its expression suppresses the progression of liver fibrosis,IGF2BP2 regulates the m^6A of the key glycolytic target aldolase A (ALDOA) mRNA, upregulating the expression of ALDOA, promoting the increase of lactate levels; and further promoting histone H3K18 lactylation to accelerate the development of liver fibrosis (Yongqiang et al. 2024). In a mouse model of arsenic-induced

idiopathic pulmonary fibrosis, the increased lactate in lung tissue promotes the transcription of YTHDF1 by regulating histone H3K18 lactylation, promotes the activation of the YTHDF1/NREP mRNA-m^{6}A pathway, and increases the secretion level of TGF-β1, promoting the transformation of fibroblasts into myofibroblasts, ultimately leading to pulmonary fibrosis (Wang et al. 2024). The results demonstrate that elevated lactate levels have a promoting effect on these types of fibroses and have a regulatory relationship with m^{6}A. Although the mechanisms are not yet fully understood, they highlight the potential for IGF2BP2 and YTHDF1 as therapeutic targets.

Myocardial ischemia

Myocardial ischemia–reperfusion (I/R) injury can promote the death of myocardial cells. YTHDF2 has been shown to be upregulated in myocardial cells in a mouse I/R model, and silencing endogenous YTHDF2 can inhibit ferroptosis in myocardial cells, eliminate heart dysfunction, and reduce the infarct area (Ping et al. 2023). In recent years, the relationship between lactate accumulation and oxidative metabolism as well as glycolysis in ischemic myocardium has gained recognition (Joshua and Sven 2020). Lactate levels are elevated in ischemic myocardial cells, contributing to an increased myocardial lactate burden (Gui-E et al. 2024). Swimming exercise has been shown to reduce lactate levels in mouse cardiac tissue and decrease the lactate modification of histone H3K18,This process downregulates YTHDF2, thereby preventing myocardial ischemia–reperfusion injury (Gui-E et al. 2024). Lactate levels are influenced by the balance between glycolysis and oxidative phosphorylation (Joshua and Sven 2020). Endurance exercise can enhance its metabolism by modulating mitochondrial fusion and fission processes while increasing mitochondrial abundance (Glancy et al. 2021). Consequently, despite the higher glycolytic rate induced by exercise training, pyruvate can be rapidly oxidized within mitochondria, resulting in a reduction of intracellular lactate accumulation (Glancy et al. 2021). Targeted regulation of lactate metabolism within the myocardium may aid the heart's adaptation to endurance exercise as well as I/R-induced cardiac remodeling. Furthermore, inhibiting YTHDF2 expression through reduced histone lactate modification could represent a potential therapeutic strategy for cardiovascular diseases.

Intracerebral hemorrhage

Intracerebral hemorrhage is a type of bleeding caused by increased vascular fragility and rupture within the non-traumatic brain parenchyma, and its progression is driven by METTL3 (Lei et al. 2024). Research has demonstrated that in the PC12 cell model of intracerebral hemorrhage (ICH) treated with heme, ferroptosis is activated and lactate levels increase (Zhang et al. 2023a). Lactate promotes the upregulation of METTL3 lactylation, thereby enhancing the stability and expression level of METTL3 protein in heme-treated PC12 cells (Zhang et al. 2023a). Conversely, silencing METTL3 modulates the m^{6}A modification of transferrin receptor (TFRC) mRNA, which inhibits the involvement of ferroptosis in ICH progression (Zhang et al. 2023a). This suggests that lactate exacerbates cellular damage and that non-histone METTL3 lactylation serves as a significant regulatory mechanism. However, a study has indicated that within both the core and penumbra regions of cerebral hemorrhage, there is an accumulation of lactate,notably, while its concentration decreases in the core region following treatment with dahuangsu, it increases in the penumbra region (Yue et al. 2020). Lactate appears to facilitate phagocytosis, proliferation, cell survival, and migration of microglia, that collectively promote recovery from ICH (Yue et al. 2020). The aforementioned evidence underscores the complexity surrounding lactate's role in ICH. Its impact on ICH outcomes varies depending on disease stage. Therefore, targeted regulation at different stages may represent a promising therapeutic strategy for future interventions.

Sepsis

Elevated lactate levels are an important biomarker of sepsis and are closely related to sepsis-associated mortality (Jiri et al. 2023). In the early stages of sepsis, activated immune cells enhance lactate production through aerobic glycolysis (Chu et al. 2021). Elevated levels of lactate can facilitate the progression of sepsis by inhibiting SIRT1 activity and recruiting CBP/p300 to promote HMGB1 lactate modification (Yang et al. 2022). Peripheral blood mononuclear cells from patients experiencing septic shock exhibit significantly increased H3K18 lactylation, with this upregulation showing a positive correlation with

procalcitonin levels (Chu et al. 2021). These findings suggest that the role of lactylation in sepsis is becoming increasingly evident. Furthermore, A previous study has indicated that METTL3-mediated m^6A modification may exacerbate lung injury associated with sepsis (Zhang et al. 2023b). In a cecal ligation and puncture induced sepsis-associated lung injury mouse model, increased lactate levels in lung tissue, lactate promotes the binding of p300-mediated H3K18 lactylation to the METTL3 promoter site to regulate m^6A modification levels, and METTL3 mediates the YTHDC1-dependent pathway to regulate m^6A enrichment in long-chain acyl-CoA synthetase 4 (ACSL4), promoting its mRNA stability and upregulating ACSL4, thereby promoting ferroptosis (Dan et al. 2024). Knocking down or targeting the inhibition of METTL3 can effectively inhibit the ferroptosis induced by suppurative hyperlactemia in alveolar epithelial cells and alleviate lung injury in septic mice (Dan et al. 2024). The evidence presented above indicates that lactate associates with m^6A through lactate modification and contributes to the pathophysiology of sepsis. Targeting METTL3 and regulating lactate modification may represent a novel therapeutic strategy for patients suffering from sepsis.

Prospective

In conclusion, lactate primarily interacts with the m^6A through lactylation, glycolytic pathways, and lactate transporters. Lactate-induced lactylation of histone or non-histone can regulate downstream targets by influencing the transcription and activity of m^6A-RRE. In turn, m^6A-RRE-mediated m^6A modifications can affect key enzymes in the glycolytic pathway or MCT, impacting lactate levels and further modulating lactylation.

In tumors, the interplay between lactate and m^6A modification significantly contributes to tumor progression. Targeted inhibition of lactylation seems to be a good strategy for tumor treatment. However, there seem to be conflicting views on tumor treatment. In a previous study, it was mentioned that inducing copper-dependent cell death in tumor cells is currently considered a strategy for tumor treatment, and METTL3 lactylation increases copper-dependent cell death (Lianhui et al. 2023). In this case, it seems that promoting lactylation levels is more beneficial. Therefore, lactylation in tumors seems to be a double-edged sword, and the complex mechanisms between them need to be further explored. In sepsis, although guidelines suggest that lactate levels should be used as a marker of severity or prognosis in sepsis patients, it has always been controversial because in actual clinical practice, some severe sepsis patients may not have elevated lactate levels. A previous study mentioned that lactate can induce the increased lactylation level of ALDO (a key regulator of glycolysis), inhibit the expression of ALDO, and thus provide negative feedback to reduce lactate production (Ning et al. 2022). Does this negative feedback mechanism exist in these patients? In this case, if it could be further proved that lactylation is upregulated universally in sepsis, lactylation level seems to be more meaningful than lactate as a diagnostic and prognostic marker in sepsis.

However, several issues remain unresolved. First, there is a shortage of specific lactylation regulatory enzymes. For instance, in tumors, the lactylation enzyme P300 regulates histone lactylation levels but also influences acetylation (Hogg et al. 2021). Inhibiting acetylation can hinder m^6A-RRE-mediated m^6A modification (Zhuang et al. 2023), making it challenging to determine if changes in m^6A modification are primarily due to lactylation. Second, the mechanisms by which lactylation alters histone or non-histone protein activity and function are unclear. Third, the relationship between lactate and lactylation warrants further investigation. Currently, it is believed that lactylation depends on lactate levels,however, defining these levels in various disease contexts poses challenges. Some severe sepsis patients may not exhibit elevated lactate levels, leaving questions about their lactylation status and underlying regulatory mechanisms unanswered. In summary, while the significance of lactylation is evident, clear evidence establishing causality between lactylation and m^6A modification as well as specific phenotypes still requires further elucidation.

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