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Effects of Lactylation in Cancer Progression

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Abstract. Protein lactylation is a newly described post-translational modification (PTM), initiated by the transfer of lactyl group in lactyl-CoA to lysine residues, and can be classified into histone and non-histone lactylation. Lactylation bridges glycolytic metabolism pathways to epigenetic modifications, complementing knowledge in both parts of cancer regulation. Here, we systemically review the recent advances in understanding the effects of lactylation on cancer, including survival, proliferation, metastasis, angiogenesis and vasculogenic mimicry, stemness and immune evasion. We also summarized lactylation-induced resistance mechanisms and emerging therapeutic opportunities, which may contribute to its integration in current therapies as a sensitizer.

Keywords: cancer, lactylation, post-translational modification, resistance

1. Introduction

Lactylation refers to the post-translational modification that attaches lactyl groups to protein residues, and the landmark identification of histone lactylation reported by Zhao's group in 2019 established an independent regulatory layer separate from histone acetylation, opening a new research field of epigenetic modification [1].

Subsequent abundant studies have expanded the scope of lactylation from histone substrates to a wide array of non-histone proteins. As a lysine-specific epigenetic mark, histone lactylation only modifies a restricted set of residues, mainly H3K9/14/18/56 [2] and H4K5/8/12/16 [3]; among these sites, H3K18la is the most well-characterized and frequently overexpressed to accelerate tumor progression, with undiscovered regulatory exceptions remaining to be explored. The dynamic addition and removal of lactyl moieties rely on enzymes originally characterized as acetylation regulators, including p300, KAT2A, HDAC1-3 and sirtuins [4]. After lactate is converted to lactyl-CoA, p300 serves as a master lactyltransferase whose expression positively correlates with global histone lactylation levels [1]. Nuclear ACSS2 activated by EGFR-ERK signaling and GTPSCS separately cooperate with KAT2A and p300 to mediate H3K14la and H3K18la in tumor and glioma cells [5], while class I HDACs exert dual context-dependent catalytic effects, eliminating lactyl groups under low lactate concentrations yet catalyzing lactylation at high lactate levels [6], indicating sophisticated regulatory kinetics requiring further validation. Cellular histone lactylation abundance is collectively shaped by glycolytic reprogramming, metabolite transporters and mitochondrial homeostasis: multiple transcription factors and glycolytic enzymes form positive feedback circuits to boost lactate production and H3K18la [7]; glucose transporters GLUT1/3 and

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lactate transporter MCT1/4 modulate intracellular lactate pools to remodel histone lactylation across multiple tumor types and tumor-associated macrophages [8]. Defective Numb-Parkin mitophagy and ACAT2-MTCH2 axis suppress oxidative phosphorylation and upregulate histone lactylation in prostate cancer [9], whereas direct links between disrupted TCA/oxidative phosphorylation enzymes and tumor histone lactylation have not yet been validated. Beyond histones, non-histone lactylation was first discovered on moesin by Gu et al. [10], and multi-omics approaches now systematically decode the biological functions non-histone lactylation in controlling protein stability, enzymatic activity, conformation and phase separation [11]. Non-histone lactylation shares homologous enzymatic regulators with histone lactylation, like ACAT and KAT [12], and its abundance is also governed by glycolysis, oncogenic signaling and non-coding RNAs [11]; post-translational crosstalk between phosphorylation and lactylation further enriches the complexity of lactylation-mediated cellular regulation [13].

As is the case with other PTMs, lactylation has been linked with the progression of cancer. Protein lactylations are shown to play a role in key cancer functions and hallmarks, including survival, proliferation, angiogenesis, metastasis and stemness of cancer stem cells. While even more complexity could be found and depicted, the extensive researches shed light on carcinogenesis and cancer progression, which hopefully will translate into therapeutic uses.

2. The roles of lactylation in tumor progression

2.1. Survival and proliferation

Lactylation critically facilitates the survival and proliferation of cancer cells via regulating multiple intracellular signaling and metabolic pathways. Histone H3K18la promotes endometrial and breast cancer survival and proliferation by activating the PI3K/AKT signaling axis and forming positive glycolytic feedback loops [14]. In renal cell carcinoma, YTHDC1 K82la-induced phase separation stabilizes BCL2 and E2F2 mRNAs to suppress apoptosis and sustain malignant growth [15]. Additionally, lactylation modulates cancer autophagy to maintain cellular homeostasis and tumor progression: Vps34 lactylation [16], TFEB K91 lactylation [17], and FLCN K523la [18] enhance autophagic activity and oncogenic capacity. Moreover, lactylation drives tumor proliferation across various cancers by targeting diverse signaling cascades including MEK/ERK [19], WNT [5], and MYC [20]-related glycolysis, and mediates intercellular regulatory crosstalk to sustain malignant progression.

2.2. Angiogenesis and vasculogenic mimicry

Angiogenesis, also called neovascularization, is an important part of tumour progression, serving for nutrient supply and spreading of the tumour cells into the body circulation. It has also been reported that cancer growth can be independent of angiogenesis, where vessels can be lined with cancer cells, and this is called vasculogenic mimicry [21].

Although there has not been much evidence, lactylation is shown to promote both angiogenesis and vasculogenic mimicry in different types of cancer. Fan et al. demonstrated a new pro-angiogenic route, where VEGF could stimulate angiogenesis via influencing gene expression instead of directly activating signalling pathways, complementing current knowledge on VEGF-induced angiogenesis. VEGF stimulated LDHA, increasing lactate and H3K9la levels. Analysis of lactylation in gene promoters showed that multiple angiogenic genes are activated by H3K9la, such as PRCP and EGFR. Increased H3K9la is also shown to inhibit HDAC2 expression, unveiling a positive feedback

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pathway regulating angiogenesis [22]. In hepatocellular carcinoma, researchers have used single cell transcriptomics to reveal a complex regulatory network that mediates angiogenesis. H3K18la upregulates GP73 that can stimulate the JAK2/STAT3 pathway, enhancing pro-angiogenic factor expression including CXCL5, MCP-1 and TPO [23]. Non-histone lactylation can also expedite angiogenesis. ASH2L K312la mediated by AARS1 could activate VEGFA expression through methylating H3K4 in the coding region [24]. Moreover, MAPK6P4-activated KLF15 increases LDHA expression, which leads to lactylation of VEGFR2 and VE-cadherin that promotes VM [25]. VE-cadherin and three other vasculogenic molecules, Sema3A, VEGFA and EphA2, can be regulated via HIF-1α Kla-mediated KIAA1199, contributing to both angiogenesis and VM in prostate cancer [26]. To sum up, current studies report that lactylation exerts a promoting effect on angiogenesis and VM in various cancers through multiple mechanisms, involving the regulation of both histone and non-histone proteins and the crosstalk with other PTMs like methylation, collectively advancing tumour progression.

2.3. Metastasis

Tumor metastasis accounts for most cancer-related mortality, relying on cancer cell invasion, migration, epithelial-mesenchymal transition (EMT) and extracellular matrix remodeling [27]. Lactylation extensively regulates metastatic progression through diverse metabolic, transcriptional and non-coding RNA-mediated mechanisms. Aberrant histone lactylation modulates the expression of metastasis-related genes to facilitate tumor invasion and EMT, while multiple lncRNAs mediate H3K14la and H3K18la accumulation to activate metastatic signaling [28]. Lactylation also promotes tumor-derived exosome formation to remodel premetastatic niches and drive organ-specific metastasis [29]. Furthermore, ablation-induced stress and microbial involvement facilitate metastasis via lactylation-dependent glycolytic reprogramming and immune microenvironment remodeling [30]. Nevertheless, current research remains incomplete, as the detailed mechanisms of several lactylation sites, microbial-induced glycolysis, and lactylation-mediated metastatic dormancy and organotropism require further exploration.

2.4. Cancer stemness

Cancer stem cells (CSCs) drive tumor initiation and progression [31], and accumulating evidence confirms protein lactylation sustains CSC self-renewal, tumorigenicity and stemness plasticity. Histone lactylation at H3K9 and H3K18 activates stemness genes through multiple axes including USP4/ANXA2/STAT3 and Hippo-YAP signaling [32]. Glycolytic reprogramming elevates histone lactylation to form positive feedback loops sustaining pluripotency, while tumor microenvironment mesenchymal cells secrete lactate to trigger lactylation-mediated stemness via ANTXR1 and PARP1 modification [33]. Lactylation also competes with ubiquitination or SUMOylation [34] to stabilize oncogenic proteins, and drives tumor phenotypic transdifferentiation such as prostate neuroendocrine conversion by opening chromatin for stemness gene transcription [35]. Reciprocally, lactylated proteins reinforce glycolysis to maintain stemness [36]. Nevertheless, the detailed crosstalk between stromal cells and CSCs, as well as universal glycolysis-lactylation feedback circuits across tumors remain insufficiently characterized and demand further multi-model validations.

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2.5. Immune evasion

The tumor microenvironment (TME) contains diverse immune and stromal cells that jointly regulate anti-tumor immune responses, and protein lactylation serves as a critical epigenetic mechanism driving TME immunosuppression across multiple cell types. In T cells, histone lactylation directly impairs CD8+ cytotoxic T cell function: H3K18la induces circATXN7 expression to trigger T cell apoptosis in colorectal cancer [37] and elevates Nur77 to disable TCR activation in small cell lung cancer [38]. It also enhances the immunosuppressive capacity of Tregs by activating the NF-κB p65/TNFR2 axis to secrete IL-10 and TGF-β in malignant pleural effusion [39]. Additionally, tumor lactylation upregulates immune checkpoints including PD-L1 and B7-H3 via distinct histone lactylation modifications, ultimately inducing CD8+ T cell exhaustion and immune escape [40]. Lactylation dominates macrophage M2 polarization: H3K18la promotes M2 marker expression and suppresses anti-tumor T cell responses in lung adenocarcinoma and glioblastoma [41], while H3K18la-mediated NUPR1 activation drives immunosuppressive macrophage phenotypes in hepatocellular carcinoma [42]. For neutrophils, lactylation upregulates ARG1 to mediate immunosuppression, and TAM-derived H3K18la further promotes neutrophil chemotaxis to aggravate immune dysfunction [43, 44]). Moreover, lactylation remodels stromal cell functions: CAF-derived lactate induces H3K18la to activate the ASPM/SRC/STAT3/PD-L1 axis for immune escape (40898336 [45]), and lactylated Mettl16 in tumor-associated Schwann cells inhibits CD8+ T cell activity in pancreatic cancer [46]. Lactylation also impairs NK cell activity and induces immunosuppressive FOXP3+ NKT cells, comprehensively shaping an overall immunosuppressive TME [47].

2.6. Therapeutic resistance

2.6.1. Chemoresistance

Lactylation exerts divergent effects on cancer drug resistance across tumor subtypes. In glioblastoma, H3K9la reduces temozolomide sensitivity by repressing MLH1 via LUC7L2 transcriptional inhibition [48]. Lactylation of homologous recombination proteins RAD51 and NBS1 facilitates DNA damage repair to drive cisplatin and chemotherapy resistance [49]. Conversely, HDAC2-mediated Mettl3 delactylation confers chemoresistance in triple-negative breast cancer by impairing m6A modification [50]. Blocking MCT4 elevates H3K9la in pancreatic cancer, upregulating ACSL4 and triggering ferroptosis to suppress tumor progression [51]. Such discrepancies reflect context-dependent functions of lactylation, and MCT transporters are key confounding factors altering lactate pools and downstream lactylation signaling.

2.6.2. Immune resistance

Lactylation remodels the immunosuppressive TME to drive tumor immunotherapy resistance. In PDAC, lactate uptake induces high Kla in TAMs; ENSA K63la activates SRC/STAT3-CCL2 signaling to blunt anti-PD-1 efficacy [52]. Concerning NSCLC, APOC2 K70la fuels Treg expansion and suppresses CD8+ T cells, correlating with poor clinical response to immunotherapy [53]. In ICC, AKT-activated PCK1 boosts SPRING K82la to block ferroptosis and confer chemo-immunotherapy resistance [54]. In serine/glycine-deprived CRC, HIF-1α-driven lactate triggers GCN5-dependent PD-L1 lactylation to stabilize PD-L1 and evade immune surveillance [55].

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However, current studies mainly focus on PD-1/PD-L1 blockade, while mechanisms for other immune checkpoint inhibitors remain underexplored.

2.6.3. Radiotherapy resistance

Radiation therapy is increasingly recognized as an important constituent of anti-cancer therapies, assisting in resolving diseases perioperatively. Sometimes cancer cells develop resistance against radiation, rendering the treatment ineffective. Recent studies have provided a novel perspective of understanding radiation therapy resistance by looking into lactylation. As is previously indicated, H3K18la enriched at USP4 promoter can activate its transcription, and USP4 promotes radioresistance of GSCs by preventing ANXA2 degradation and allowing STAT3 signaling to maintain GSC survival and self-renewal [32]. Likewise, MCM7 also facilitate radioresistance by promoting CSC maintenance, and the overexpression of MCM7 is triggered by H3K18la as well [56]. Furthermore, in a subgroup of glioblastoma overexpressing ALDH1A3, lactate production is increased. Interestingly, this is not only because of an intrinsic high ALDH1A3 level, but also due to ALDH1A3-PKM2 interactions that lead to tetramerization of the latter enzyme, thus enhancing its activity [57]. Abundant intracellular lactate causes an increase in XRCC1 lactylation at multiple sites, among which K247la facilitates its nuclear translocation and allows endurance of CIT by elevated DNA repair [57]. Briefly, protein lactylation drives radioresistance by different routes like maintaining CSCs and strengthening DNA repair mechanisms. These studies could provide valuable opinions for resensitizing tumors to radiotherapy.

2.6.4. Targeted therapy resistance

Lactylation widely mediates acquired resistance to multiple targeted therapies across diverse malignancies. For unresectable HCC, lactylation confers lenvatinib resistance via two NRF2 antioxidant cascades: IGF2BP3 K76la stabilizes PCK2 and NRF2 mRNA to boost serine-derived SAM and m6A modification, forming a reinforcing antioxidant feedback loop [58], meanwhile H3K18la upregulates HECTD2 to degrade KEAP1 and sustain NRF2 activity [59]. For regorafenib resistance in HCC, ZNF207 elevates LDHA to induce PRDX1 K67la, which interacts with NRF2 to facilitate its nuclear translocation, repress ferroptosis and sustain drug tolerance [60]. In EGFR-TKI-resistant NSCLC, NNMT reduces histone methylation to upregulate LDHA and H3K18la; H3K18la reciprocally transactivates NNMT, establishing a vicious cycle supporting tumor growth [61]. H3K18la also drives bevacizumab resistance in colorectal cancer by activating RUBCNL transcription, which binds BECN1 to boost autophagy and enable hypoxic survival [62]. Moreover, H4K12la mediates resistance to PARP inhibitor niraparib: H4K12 lactylation opens chromatin at a niraparib-associated super-enhancer, recruits MYC and upregulates RAD23A to strengthen nucleotide excision repair [63]. Collectively, lactylation orchestrates targeted therapy resistance by regulating antioxidant defense, autophagy, DNA damage repair and oncogenic survival signals, offering promising therapeutic targets to reverse clinical drug resistance.

2.7. Lactylation and strategies of cancer treatment

Given the oncogenic function of lactylation, multiple lactylation-targeted therapeutic strategies have been proposed. First, suppressing glycolysis with LDHA, HK enzyme inhibitors only serve research verification without clinical translation; blocking glycolysis upstream via SRSF10 inhibitor 1C8 restores tumor sensitivity to anti-PD-1 therapy [64]. Lactate shuttle blockers including crizotinib,

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dracorhodin perchlorate and AZD0095 limit lactate transport to relieve drug resistance [65]. Second, lactyltransferases and delactylases represent valuable targets: GCN5 inhibitor MB-3 curbs cisplatin resistance in ovarian cancer [49], while SIRT3 inhibitor honokiol enhances NK cell cytotoxicity through ROCK1 delactylation [66]. Clinically available HDAC inhibitor vorinostat blocks HDAC1 K412la to trigger ferroptosis [67]. Third, subtype-specific lactylation blockers cover small molecules, neutralizing antibodies and peptides: irinotecan inhibits BLM K24la to restore chemosensitivity [68], anti-APOC2 K70la antibody reverses immunoresistance [53], and peptide antagonists competitively block MRE11, ENSA and XLF lactylation [69]. Notably, SIRT3 inhibitor AGK2 suppresses Mettl16 delactylation to sensitize gastric cancer to cuproptosis, revealing context-dependent dual roles of lactylation across tumor types [70]. Overall, lactylation-targeted interventions effectively reverse cancer drug resistance; future work will focus on combination therapies, lactylated protein degradation and nanoparticle delivery systems.

3. Conclusion and future perspectives

Since histone lactylation was identified, its deposition and removal mechanisms, as well as downstream molecular crosstalk within tumor cells and the tumor microenvironment, have been extensively characterized. This PTM links cancer cell metabolism to epigenetic regulation, offering novel insights into how metabolic reprogramming—particularly the Warburg effect—drives malignant phenotypes. Collectively, existing evidence outlines an intricate lactylation regulatory network that facilitates cancer cell survival, stemness, invasion, metastasis, angiogenesis, vasculogenic mimicry and therapeutic resistance. Targeted therapies against lactylation have been developed to curb tumor progression, yet inconsistent experimental observations remain unresolved. Key gaps include unconfirmed writers and erasers of lactylation, undefined conditions enabling acetyltransferases to function as lactyltransferases, and insufficient data on lactylations' impacts on NK/NKT cells and tumor radioresistance. Future multi-omics and AI-aided research will clarify crosstalk between lactylation and other histone PTMs. Large-cohort biomarker validation, clinical trials and nanomedicine translational work are required to advance lactylation-based cancer diagnosis and treatment.

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