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Advances in the Regulation of Histone Lactate Modification in Gastrointestinal Malignant Tumor

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Abstract

In recent years, gastrointestinal malignancies have ranked as the primary cause of cancer-related deaths across the globe. Despite remarkable progress in medical technology and treatment modalities, the majority of patients still experience local relapse and distant metastasis.It remains imperative to carry out in-depth investigations into the mechanisms underlying the occurrence and develpment of gastriointestinal tumours. Metabolic reprogramming represent one of the pivotal hallmarks of malignancy. Notably, histone lactylation, serving as an innovative post-translational modification has established a connection between epigenetics and metabolic reprogramming for the first time. Therefore, this review is going to scrutinize the advancements of histone lactonisation in gastrointestinal malignancies. An profound exploration into the regulatory mechanisms of histone lactylation in gastrointestinal malignancies will not only facilitate a more comprehensive understanding of the epigenetic background of gastrointestinal tumours, but also hold significant implications for the development of novel diagnostic tools, therapeutic strategies and prognostic assessment systems.

Keywords: Histone; Lactate Modification; Tumor; Immune

Introduction

Gastrointestinal (GI) malignancies have emerged as a leading global health concern. Comprising a diverse array of tumours originating from the esophagus, stomach, intesines, and colorectal cancers, these malignancies pose complex diagnostic,therapeutic, and prognostic dilemmas. In spite of the remarkable progress achieved in unstanding the fundamental biology of GI tumours, the quest for novel diagnostic and therapeutic targets remains as a crucial subject in the dimain of contemporary tumour research.

Histone lactylation modification (HLM) was first reported as a novel epigenetic modification in 2019 [1]. The modification pertains to the covalent binding of lactate groups to histone lysine residues. This modification is intimately associated with the cellular metabolic state, especially within the microenvironment characterized by hypoxia and elevated glycolytic activity. Lactylation modifications assume a significant part in diverse biological processes, including cell proliferation, metastasis, and immune escape. This is achieved by exerting an impact on chromatin structure and gene expression patterns.

With the intensification of epigenetic research, the function of lactylation modification in tumorigenesis has progressively drawn increasing attention. Studies have shown that lactation not only plays a pivotal role in the metabolic reprogramming of cancer but also strongly associated with treatment resistance in tumours [2-4]. The study of this modification provides a theoretical basis and technical support for the exploration of new biomarkers and targeted therapeutic strategies. Therefore, further elucidation of the regulatory mechanism underlying lactate modification is poised to offer novel insights and practical solutions for the early diagnosis, targeted therapy and overcoming drug resistance in cancer.

Mechanisms of Histone Lactate Modification

Biochemical Process of Histone Lactate Modification

In normal cells, lactate is normally a by-product of the glycolytic process, especially under conditions of hypoxia or high energy demand. The cell produces lactate by anaerobic glycolysis to maintain energy supply. In tumour cells, however, the Warburg effect (i.e. glycolysis even under aerobic conditions) leads to excessive accumulation of lactate [5-8]（Figure 1). Accumulation of lactate is not only a result of metabolic reprogramming of tumour cells, but also a manifestation of adaptive survival of tumour cells in a hypoxic microenvironment. Recent studies have shown that intracellular lactate accumulation can be converted to lactate coenzyme A to modify histones and directly affect the regulation of chromatin gene expression [9]. This suggests that lactate-induced lysine lactylation (Kla) may be an important bridge between metabolic reprogramming and epigenetics.

Histone lactate modification is an important post-translational modification involving the covalent attachment of lactate groups to histone lysine residues [10]. This process is not only closely related to the regulation of gene expression, but also plays a role in the regulation of cellular metabolism, tumourigenesis and other physiological processes. The biochemical process of lactate modification is mainly based on specific enzyme catalysis and is closely related to the metabolic state of the cell, especially under the high metabolic demand or hypoxia of tumour cells, the increased level of lactate modification has significant biological significance. Histone lactylation is a post-translational modification that occurs at lysine sites on histones. Specific enzymes, called 'writers' and 'erasers', catalyse the addition or removal of lactate groups at the target lysine site [11]. The 'writing' process of lactate modification is mainly catalysed by an enzyme called p300. p300 is a transcriptional co-activator with histone acetyltransferase (HAT) activity, capable of catalysing the covalent attachment of lactate groups to lysine residues of histones by binding to lactate molecules. Relatively little has been reported about lactating writers, erasers and readers, with the exception of p300 (the first lactating writer found to date) [12]. The 'writing' function of p300 in lactonisation and acetylation suggests that different forms of the epigenetic code may share enzymes, and therefore enzymes with writing, erasing and reading roles in other epigenetic marks may have similar functions in lactonisation.

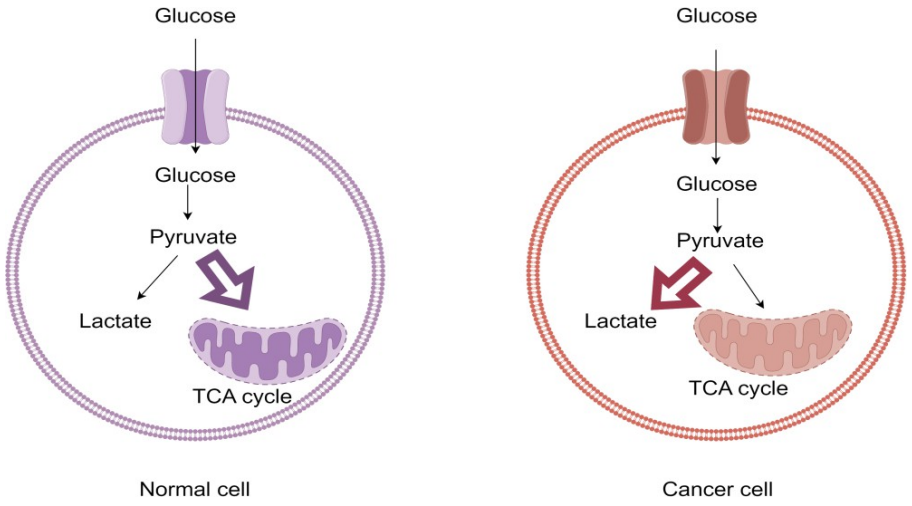

Figure 1: Warburg effect in normal cell and cancer cell

Regulators of Histone Lactylation Modifications

The occurrence of histone lactylation modifications is closely linked to lactate production. Overall, it was found that exposure to substances or conditions that increase cellular lactate levels, such as glucose supplementation, the glycolysis-promoting inhibitor fisetinone, hypoxia and M1-polarised macrophages, increased histone lactation in human cell lines [2]. Histone lactylation is also regulated by a number of enzymes. These enzymes act as regulators in the 'writing' and 'un-writing' of lactate modifications and are closely linked to the metabolic state of the cell, the supply of oxygen and the characteristics of the tumour microenvironment.

First, as a major histone acetyltransferase, p300 can catalyse lactylation modifications in addition to acetylation [13]. It has been shown that p300 alters the modification state of histones and thus affects gene expression by binding to lactic acid and forming a stable lactylated moiety, thereby adding lactic acid to histone lysine residues. Similar to p300, CBP (CREB binding protein) has histone acetyltransferase activity and catalyses lactate modification. Because of their sequence homology and functional overlap, the histone acetyltransferases CBP and p300 are often studied together and referred to as the CBP/p300 complex [14]. They therefore work synergistically in the process of lactate modification, regulating cellular metabolism and gene expression (Fig.2).

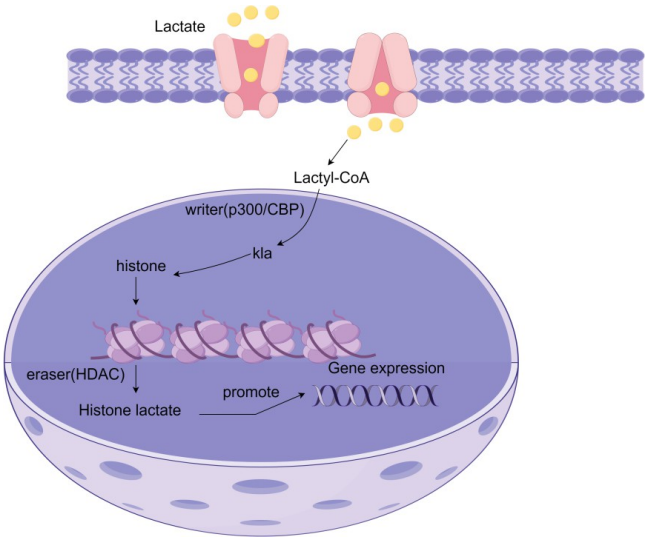

Figure 2: Mechanism of histone lactate

However, lactate modification is not a static process. HDAC (histone deacetylase)-like enzymes play an important role in the reversal of lactylation modifications [15]. HDAC enzymes are involved in the 'de-writing' process of lactate modification by removing lactate groups. It has been shown that deacetylases such as HDAC1 and HDAC2 are able to catalyse the removal of the lactate moiety by binding to lactated histones, thereby restoring the histones to their normal state. This process not only regulates the dynamic balance of lactation changes, but also has a profound effect on the transcriptional activity of cells.

In addition, lactate levels change the tumour microenvironment play an important role in regulating changes in lactation. Tumour cells accumulate lactate through anaerobic glycolysis under high metabolic demand, and the concentration of lactate in the tumour microenvironment has a direct effect on the occurrence of lactation changes [16]. In tumour cells, elevated levels of lactate not only promote the activity of enzymes such as p300, but may also influence the extent of lactate modification by altering local pH or regulating relevant signalling pathways through activation of lactate receptors [17]. Thus, changes in lactate levels play an important role in the metabolic and epigenetic regulation of tumour cells.

In summary, the regulators of lactation changes include a variety of enzyme systems as well as metabolic states in the tumour microenvironment. These regulatory factors affect biological processes such as gene expression, metabolic reprogramming, proliferation and metastasis of tumour cells by regulating the dynamic process of lactation modification. Therefore, studying the regulatory mechanisms of lactation changes, and in particular the role of these regulators.It will help to elucidate the molecular mechanisms of tumourigenesis and development and provide new targets for tumour therapy.

The Role of Histone Lactylation Modifications in Gastrointestinal Malignancies

Promote Tumour Cell Proliferation

In recent years, the function of histone lactate modification, as a novel type of post-translational modification, in the proliferation and growth of tumour cells has attracted growing concern..It indicates that this is primarily attributed to the elevated glycolysis, which exerts an impact on the alterations in lactate levels. Subsequently, these changes in lactate levels, due to histone lactylation modifications, influence the rapid proliferation of tumour cells. Consequently, diverse factors capable of influencing glycolysis can indirectly affect the variation in lactate levels, such as hypoxia, enzymes involved in the glycolytic process, and substrates, among others. In colorectal [18] and oesophageal [19] cancers, hypoxia has been shown to lead to lactate accumulation in tumour cells. This, in turn, influences the lactate modification of histones and facilitates tumour cell proliferation. However, the histone modification sites differ between the two malignancies. In colorectal cancer, the modification site is H3K18la, while in oesophageal cancer, it promotes H3K9 lactylation. Recent studies have demonstrated that multiple mechanisms exist which can impact histone lactylation in CRC. For instance, the m5C methyltransferase NSUN2 can trigger metabolic reprogramming. It enhances glucose metabolism by regulating the expression of ENO1 in an m5C-dependent manner, thereby resulting in increased lactate production within CRC cells. Meanwhile, the lactate accumulated by CRC cells undergoes lactation through histone H3K18 lactylation (H3K18la). This lactylation activates NSUN2 transcription and induces lactation at the Lys356 (K356) residue of NSUN2, thus forming the NSUN2/YBX1/m5C-ENO1 positive feedback loop that drives CRC progression [20]. Furthermore, G protein-coupled receptor 37 (GPR37) accelerates colorectal cancer liver metastasis by facilitating glycolysis and histone lactylation through the Hippo pathway [21]. Additionally, lipopolysaccharide (LPS) derived from intestinal bacteria upregulates the expression of LINC00152 by increasing H4K8 lactylation modification, which subsequently promotesthe invasion and migrationof tumour cells [22].

In tumour cells, lactylation modifications make it easier for certain transcription factors to bind to the promoter regions of target genes by altering the charge state and chromatin structure of histones, which in turn activates transcription of these genes.Specifically, this applies to cell cycle regulatory genes like cyclin D1, CDK4, and CDK6.Moreover, histone lactylation modifications contribute to the survival of tumour cells within an adverse environment by influencing genes related to DNA repair

and anti-apoptosis [23, 24].

The promoting effect of lactylation modifications on tumour cell proliferation is not limited to their direct regulation of the cell cycle. As a metabolite, lactate can trigger metabolic reprogramming in tumour cells. By increasing the accumulation of lactic acid, tumour cells are able to maintain a high level of glycolysis and acquire sufficient energy to sustain their rapid proliferation, even under hypoxic conditions. Lactylation modification not only promotes tumour cell proliferation by regulating gene expression, but also equips tumour cells with the requisite energy and synthetic materials by optimizing metabolic pathways.

In addition, histone lactylation modifications play an important role in the interaction of tumour cells with the surrounding microenvironment. During rapid tumour proliferation, cells need to maintain activity under high metabolic stress, and histone lactonisation modifications enable tumour cells to adapt more efficiently to hypoxic and nutrient-poor environments by regulating cellular metabolism and gene expression. This metabolic adaptability allows tumour cells to continue to proliferate in a hostile microenvironment, accelerating tumour growth and progression.

Overall, lactylation modifications fuel the rapid proliferation of tumour cells under high metabolic demands. They do so by enhancing the expression of genes related to the cell cycle and proliferation. Meanwhile, these modifications optimize the metabolic pathways of the cells, ensuring that they remain active within the hypoxic and nutrient-poor tumour microenvironment. This modification serves as a significant driver for tumour proliferation and lays the essential biological foundation for tumour initiation and progression.

Regulating the Tumour Microenvironment

Histone lactylation modifications not only directly regulate tumour cell proliferation, but also are of great significance in shaping and regulating the tumour microenvironment [25]. Lactate, as one of the products of tumour cell metabolism, can accumulate in the tumour microenvironment and regulate immune cell function and tumour angiogenesis through lactate modifications [26]. In particular, in response to lactation changes， the increased accumulation of immunosuppressive cell populations in tumours, such as M2-type macrophages, alters the immune profile of the tumour microenvironment. Thereby,it promots tumour growth and dissemination [27].

M2 macrophages represent a crucial immunosuppressive cell type within the tumour microenvironment and their role in tumour progression is by no means negligible. M2-type macrophages inhibit the anti-tumour immune response and promote tumour cell growth and metastasis through the secretion of various cytokines, including IL-10 and TGF-β, among others [28]. It has been discovered that lactylation modifications can induce the aggregation of M2-type macrophages and enhance their immunosuppressive function by increasing lactate accumulation in the tumour microenvironment [29]. Lactate serves not only as a signalling molecule for M2-type macrophage activation, but also augments its immunosuppressive effects by altering the metabolic state of macrophages [30]. Thus, lactylation modifications contribute to immune escape mechanisms in the tumour microenvironment by modulating the function of immune cells.

In addition to regulatory effects on immune cells, lactylation modifications play a crucial part in tumour angiogenesis. Rapid tumour growth requires new blood vessels to supply oxygen and nutrients.

Lacylation promotes the expression of angiogenic factors like VEGF through the regulation of related transcription factors such as HIF-1α. VEGF not only facilitates tumour vessel growth, but also plays a significant role in tumour cell invasion and metastasis [31]. Lactylation modification propels tumour angiogenesis and metastasis by increasing the expression of these key factors.

Lactylation changes may also influence the interaction between tumour cells and surrounding cells by regulating the acidic pH in the tumour microenvironment [32]. The accumulation of lactic acid reduces the pH of the tumour microenvironment. This

acidic environment not only intensifies tumour cell invasiveness, but may also enhance the effects of lactic acidification changes on tumour cell function by altering cell membrane permeability [33]. Lactose modification exerts a profound impact on the process of tumour growth, proliferation, and metastasis by regulating immune cell function, angiogenesis, as well as cell--to-cell interactions in the tumour microenvironment.

Taken together, lactylation changes further shape the tumour microenvironment by altering the immune cell composition within it, facilitating angiogenesis and potentially altering pH. Through these multiple mechanisms, histone lactylation modification promotes tumour growth and metastasis, thus emerging an important regulator of tumour progression that cannot be ignored.

Impact of Tumour Immune Escape Mechanisms

Tumour immune escape is a crucial mechanisms that enables tumour cells to survive and proliferate despite host immune surveillance. Under normal circumstances, the immune system identifies and eliminates tumour cells via mechanisms involving T cells and natural killer (NK) cells. CD8+ T cells, which are part of the adaptive immune system,serve as key immune surveillance cells. Nevertheless, tumour cells elude these immune responses through diverse mechanisms, resulting in sustained growth and metastasis. Through modifying histone lactylation, tumour cells are able to inhibit the activity of CD8+ T cells and NK cells.This results in the reduction of the recognition and elimination of tumour cells by the immune system, thereby further strengthening the immune escape of tumour cells [26, 34, 35]. Moreover, histone lactylation modifications contribute to immune escape by influencing the expression of immune checkpoint molecules (such as PD-L1) on the surface of tumour cells. For instance, Research has found that in gastric cancer [36], CAF may reduce the effectiveness of PD-1/PD-L1 blocking immunotherapy through LOX-induced glycolysis and lactate accumulation.Moreover， STAT5 promotes PD-L1 expression by facilitating histone lactylation, which triggers immunosuppression in acute myeloid leukaemia [37]. In non-small cell lung cancer, H3K18la promotes immune escape in NSCLC cells by activating the POM121/MYC/PD-L1 pathway [38].

Histone lactylation modifications can also contribute to the production of substantial amounts of lactic acid by tumour cells via inducing metabolic changes within them [39]. For example, in pancreatic ductal adenocarcinoma (PDAC), H3K18la activates the transcription of TTK and BUB1B, which subsequently increase P300 expression. This, in turn, boost glycolysis and forms a feedback loop [40]. Lactic acid, as a metabolic waste product, is capable of directly inhibiting the function of immune cells. It suppresses the function of immune cells like CD8+ T cells and NK cells by reducing the pH of the tumour microenvironment. These immune cells are inactivated in an acidic environment and are unable to effectively recognize and kill tumour cells. Lactic acid has been shown to modulate the activity of the immune checkpoint pathway through the action of the lactate receptor, enabling tumour cells to suppress the activity of CD8+ T cells. This mechanism is especially prominent in tumours of the digestive tract, such as stomach [36, 41], colon [42, 43] and oesophageal [44] cancers. By means of modifying histone lactylation, tumour cells acquire a favourable position in the immune escape process and avoid immune surveillance attacks.

In conclusion, the role of lactylation modifications in tumour immune escape is achieved through multiple mechanisms, including alteration of the acidic state of the tumour microenvironment, inhibition of immune cell function and enhancement of immune escape pathway activity.

Research Progress and Challenges

Recent studies have highlighted the critical role of lactation changes in malignant tumours, particularly in the regulation of tumour metabolism and immune escape. Lactylation modification promotes the survival and proliferation of tumour cells in hypoxic or nutrient-poor environments by regulating metabolic pathways like glycolysis and fatty acid metabolism. Besides functioning as an energy source, lactic acid regulates immune cell function by influencing the tumour microenvironment and facili-

tating tumour cells to evade host immune surveillance. This mechanism contributes to tumour initiation and progression. Lactylation modifications are closely associated with tumour resistance to radiotherapy. Several studies have demonstrated that the application of etodolac in bowel cancer can effectively increase the sensitivity of cancer cells to radiotherapy, thus improving the effectiveness of treatment [45].

Although the role of lactylation modification in cancer is gradually being understood, its molecular mechanism remains incompletely clear. Specifically, how lactate modulates diversemetabolic pathways and the precise relationship between lactate and tumour immune escape still await thorough investigation. While the acetyltransferase p300 is thought to mediate protein lactylation, the cellular concentration of the proposed lactyl donor, lactyl-coenzyme A, is approximately 1,000 times lower than the cellular concentration of acetyl-coenzyme A. This raises doubts as to whether p300 is truly a lactate transferase. Recently, it has been suggested that alanyl-tRNA synthetase 1 (AARS1) functions as a bona fide lactate transferase, directly utilizing lactate and ATP to catalyse protein lactylation. AARS1 has been identified as a Hippo target gene and forms a positive feedback loop with YAP-TEAD to promote the proliferation of gastric cancer (GC) cells [46]. Although the interaction of AARS1 with YAP-TEAD1 and the revealed mechanism of lactoylation have uncovered a new pathway for converting intracellular lactate into a signal for cell proliferation, its clinical relevance in other malignancies remains to be investigated. On the other hand, the development of effective lactylation modification inhibitors and their translation into clinical applications are also significant topics in current research. How to precisely regulate the level of lactylation changes and rationally employ these inhibitors in clinical treatment remains an urgent challenge for future cancer therapy.

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