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The history context and future directions of lactic acid

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Abstract. Lactic acid, initially considered a neglected metabolic waste product, has gradually shown its irreplaceable value in the human body. Up to now, it has become a hot topic of current research. From its first time its discovery in milk to its becoming a product of cellular respiration and metabolism, lactic acid was viewed to be a useless product in metabolism and therefore resulted in the suspension of related research. Later, with the birth of the concept of lactate shuttle between cells, lactate once again showed a very important function in the energy field of physiological research, including the participation of whole-body energy metabolism and the regulation of the cancer microenvironment. However, after some time, the research on lactic acid seems to have stalled again in the role of lactic acid as a small molecule. Not until 2019, the discovery of acetylation of histone extended a new field of lactate research epigenetic modification. This review summarizes the research on various aspects of lactate and highlights the progress and application of lactate in histone modification.

Keywords: lactate metabolism, histone lactylation, lactate and cancer

1. Introduction

Lactate is a small molecule which has been considered as the main metabolic waste in cell respiration for almost half of a century. It was first discovered in 1780 and scientists at that time regarded lactic acid only as the by-product of respiration. Therefore, lactic acid is not given attention until 1923, when an abundant amount of lactic acid is discovered in cancer cells. Nevertheless, although the function of lactic acid is observed, the mechanism in those processes is still not clearly understood. In 2019, research found another important function of lactic acid lactylation plays a vital role in epigenetics modification. This discovery expands the new field of lactate research and lactate receives more and more attention as a tiny molecule in the human body [1]. This paper summarized the research process of lactic acid.

2. The Development of Lactate Research

2.1. Discovery of Lactic Acid

Lactic acid was first discovered in the 18th century by the Swedish scientist Carl Wilhelm Scheele, who isolated it from yoghurt in 1780. However, due to the lack of knowledge and theory, continuing to explore the value of lactic acid at that time was impossible, and the study of lactic acid was out of sight. Only after 28 years, precisely in 1808, did Jöns Jacob Berzelius, an eminent Swedish chemist who had earlier identified the buildup of L-lactic acid post-exercise, make pioneering observations. In this paper, the authors discerned that this acidic compound existed as unbound ions in postmortem bodily fluids

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and subsequently verified its equivalence to Carl Wilhelm Scheele's prior discovery [2]. This milestone revelation signified the initial identification of lactate within a living organism; nevertheless, its exact role and configuration within the human body continue to elude us.

Later, in 1856, Pasteur was invited by local wine merchants to study the problem of alcohol fermentation [3]. He studied the fermentation process of lactic acid by lactic acid bacteria. According to the observation that the concentration of lactic acid in anaerobic conditions was higher than that in aerobic conditions, he concluded that there was a direct relationship between the concentration of lactic acid and the lack of oxygen [4].Karlsson, J, Juhlin-Dannfelt, A. and Jorfeldt, L. In 1978, blood lactate concentrations were measured with fluorescent markers and lactate accumulation and release rates were recorded from leg muscles after exercise and found that lactate was produced in large amounts after exercise. In previous studies, lactic acid has been considered a by-product of metabolism, which will eventually be excreted from the body [5]. Wislicenus reported in 1873 that the characteristics of lactic acid in muscle and milk are different [6], which are now known as L-lactic acid and D-lactic acid, respectively. Since L-lactic acid is the main type of lactic acid that is produced in the human body, the focus of this article is on the role of L-lactic acid in living organisms.

Then, in 1895, the discoverer of glycogen observed that lactic acid was released in the muscles of dead cattle, and he began to study the source of this lactic acid production. Subsequently, Nasse carried out a series of experiments from 1877 to 1899, in which he studied various acids in the human body, including carbonic acid and lactic acid, etc., and finally concluded that lactic acid was derived from glycogen [7]. Later, researchers found that lactic acid is linked to the intensity of human exercise, and after extensive testing, lactic acid is a metabolite of human exercise [8]. After that, with lots of research about lactate, the function of lactic acid in the formation of tumors, metabolic process, and epigenetics are revealed.

2.2. Lactic Acid and Cancer

The study of lactate in cancer began in 1923 with Weggue using Flexner-Jobling carcinoma. By comparing it with normal rat kidney tissue, he found that the glycolysis frequency of cancer cells was abnormally high, and the lactic acid concentration was extremely high, even when oxygen was introduced, it only decreased a little, which was different from normal cells that undergo TCA cycle under aerobic conditions to produce pyruvate and produce lactic acid under anaerobic fermentation. According to his words, 'We regard it as the most important of our findings, that in its metabolism carcinoma tissue does not behave like muscle or Mucor mucedo, but like yeast [9] This was the first time that lactic acid was linked to cancer, and the authors' discovery was named the Warburg effect [10]. Although this is not an authoritative official name, it is widely accepted by the academic community. Later studies on two tumour cells illustrated the extent to which tumour metabolism is now being studied [11], and thus lactate was also considered a new feature of cancer [12].

Another effect of lactate is to ensure the survival of cancer cells. Why do cancer cells have abnormally high rates of glycolysis? The answer has to do with the cancer microenvironment. In the human body, the first cancer cells are separated from the blood vessels by the basement membrane, which means that the cancer cells can only get oxygen and nutrients by spreading. But this spread has a limit distance beyond which cancer cells have to face a hypoxic or even anaerobic environment. Therefore, in this case, those cancer cells that are better able to adapt to the anaerobic environment will have a significant competitive advantage due to the selective pressure. Cancer cells then turn to glycolysis as their main mode of energy supply [13]. Another important role of lactate in cancer tissue is its contribution to the immunity-avoiding process. First, Lactate contributes to the abnormal apoptosis of natural killer (NK) and natural killer T (NKT) cells, at concentrations > 20 mM, both of which exhibit antitumoral activity. This effect helps tumor to escape from the immunity system. Second, lactate blocks interferon (IFN)-γ and interleukin (IL)-4 production by antitumoral NKT cells in the TME (tumor microenvironment), via the inhibition of mTOR signaling, thereby preventing the activation of these immune cells. Third, dendritic cells (DC) are also influenced by the production of lactate. The lactate will prevent the DC from differentiation and increase the tolerogenic to the cancer. Therefore, the antigen

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cannot be presented to active T cells. Fourth, Lactate causes the increase of myeloid-derived suppressor cell levels in the body, which can inhibit both innate and adaptive immunity by preventing the maturation of dendritic cells [14].

Since plenty of research discovered and revealed lactic acid, it has been studied and learned a lot. The presence of lactic acid throughout the body indicates that lactic acid does not exist in the human body merely as a metabolic waste product. In contrast, lactate plays an important role in many body metabolism. Therefore, more and more research about the mechanism of lactic acid as a small molecule in the body has been done.

3. The Role of Lactic Acid as the Molecules in the Body

3.1. Lactic Acid Cell Shuttle

In 1985, Brooks first put forward the function of the lactate shuttle, which also is one of the important functions of lactic acid. It records the concentration of lactate in human arterial and venous blood vessels at different times through the use of isotopic tracers. In Brook's book, the author regarded lactic acid as an energy delivery carrier, indicating that lactic acid is another important biofuel in the human body [15], because in many experimental data, it was found that lactic acid was oxidized in various parts of the body to deliver energy. The rate of glucose reduction decreased, indicating that lactic acid could be used as another energy supply source instead of glucose. In the myocardium, lipid oxidation is usually used to supply capacity, but when oxygen is insufficient, carbohydrate oxidation is used to provide energy. Lactate is the first choice for carbohydrate oxidation; therefore, lactate infusion has also been used to treat myocardial failure. A large number of subsequent research experiments on the lactic acid content in the human body also proved this point [16,17].

3.2. Lactic Acid Supplies the Energy of the Brain

For a long time, the brain model considers glucose as the main energy source in the mature brain [18]. However, the emerging view proposes another metabolic substrate, the lactate. The literature review by Schurr clearly described the absorption of lactate in the brain, revealing that lactate is an energy substrate within the brain [19]. To account for the metabolic process of lactate in the brain, a hypothesis Astrocyte–Neuron Lactate Shuttle (ANLS) is farmed. In this model, glutamate functions as a neurotransmitter to stimulate the take-up of Na+, H+, and release K+ [20]. It will consume ATP increase astrocyte aerobic glycolysis and trigger lactate release.[21] After that, the lactate will transfer into neurons in which lactate is oxidated by the neurons when energy demands increase. Experiments have found that after strenuous exercise, the brain absorbs more lactate, reducing the amount of glucose absorbed, as the lactate level in arterial blood rises and supplies more lactate to the brain. After the end, the lactate concentration in the brain returned to the standard concentration, indicating that the brain absorbed a large amount of lactate to maintain the energy level in the brain.[22]

3.3. Lactic Acid and Diabetes

The abnormal lactate production rate in diabetic patients has attracted people's attention. Recently, Berhane et al. demonstrated that lactate production progressively rises during hyperinsulinemic-euglycemic clamp study, a condition of hyperinsulinemia similar to the early stages in the development of T2DM [23]. If the patients are in high insulin condition, that will activate two rate-limiting enzymes, namely, phosphofructokinase and pyruvate dehydrogenase to enhance the glycolysis. Thus, patients with insulin resistance/diabetes exhibit augmented activity of glycolysis [24]. Therefore, lactate may represent the developing diabetes.

4. Lactylation of Histones

Although lactate has shed its status as a metabolic waste product, and plays a very important role in the human body, such as the immune evasion in tumors, an energy source, and metabolite, its function in physiological reactions in other ways are still unclear. It was not until 2019 that Zhang, D., Tang, Z., and

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Huang published an article [25], in which they first proposed the role of lactylation in epigenetics. Histones are the building blocks of chromosomes that intertwine with DNA to form nucleosomes. Therefore, it has a crucial effect on chromosome regulation. Inspired by other histone acylation modifications, zhang et al. suggested that histones could also be modified by adding lactate groups. By looking at the mass spectra, they found that the mass shift of the residual lysine was the same as that caused by the addition of one lactate group, thus presumed that the change was caused by the lactylation. Subsequent mass spectrometry analysis of HeLa cells and mouse cells revealed 26 and 16 sites of lactylation, respectively. By exposing cells to different concentrations of glucose, they verified that histone lysine lactase modification was dependent on the endogenous lactate concentration in the cell, and subsequently 13C isotope tracers in glucose confirmed that the lactase was derived from glycolysis. They then stimulate macrophages with lipopolysaccharide (LPS) to induce M1 characteristics. They found that the glycolysis rate upregulates when the inflammatory response is activated, and they also observed an increased degree of lactylation.

After the discovery of histone lactylation, the related research and application also began to get attention and many studies have been related to histone or non-histone lactylation. For example, people have found the role of histone lactylation in Alzheimer's disease, lactylation in myocardial repair and other fields. Alzheimer's disease, a common neurodegenerative disease, has been found to have a close relationship with neuromicroglia [26]. However, recent studies have found that histone lactatation is involved in the pathogenesis of Alzheimer's disease. Increased histone lactate was found in Alzheimer's disease (AD) patients and focused on the promoters of genes that control glycolysis, driving these genes to turn on transcription and ultimately leading to microglia dysfunction in AD patients [27]. In addition to modifications on histones, lactylation on other non-histone proteins has profound implications. One report mentions that lactylation has some clinical uses and alleviates heart failure. Studies have found that inhibiting lactate efflux in cardiomyocytes can play a protective role, and lactylation of the α-myosin heavy chain is significantly reduced in the process of myocardial failure, so the use of drugs containing sodium lactate can relieve symptoms [28].

5. Conclusion

Since its first discovery in 1870, the study of lactic acid has been progressing for two centuries. From its initial discovery in vitro, to in vivo studies, to the TCA cycle, intercellular shuttle, the fuel of the body metabolic processes, Warburg effect, signaling molecule in tumors and finally to lactylation, lactic acid plays an important role in many metabolic processes. So far, the study of lactate metabolism continues to expand and exploit the potential for multiple clinical applications. However, the current studies of lactate are most focused on the influence or function of lactate in the body. The mechanism or theory about how lactate functions in the bioprocess is still unclear and incomplete. The discovery of lactylation not only indicates the role of lactate in participating in epigenetics but also provides an entry point for the molecular mechanism by which lactate regulates life activities. For the non-histone proteins, it may be the new sites of lactylation and their roles. For histones, the specific mechanism of the effect of lactylation on gene expression remains to be studied. In the future, studies on the lactylation on histones and even non-histone proteins will provide a basis for explaining the mode of action of lactate, and also provide basis and clues for the precise regulation of lactate and the treatment of related diseases.

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