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The Regulatory Mechanisms of Lactate: Insights into Metabolic Homeostasis, Immune Modulation, and Tumor Microenvironment

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Abstract. Lactate was long regarded as a harmful byproduct of anaerobic respiration, but with recent in-depth research, its multiple key roles in the human body have been revealed. This article systematically reviews the metabolic regulation mechanisms, immune functions of lactate, and its role in cancer. In terms of metabolism, lactate can participate in energy supplementation through lactate shuttles and mitochondrial oxidation, regulate gluconeogenesis, fatty acid metabolism, and cellular redox balance. In cancer cells, lactate is produced in large quantities through aerobic glycolysis to provide energy for their proliferation, and related molecules such as LDH and MCTs may become targets for cancer treatment. In terms of immunity, lactate is not only a marker for disease diagnosis and prognosiscorrelated, but also can bidirectionally regulate inflammatory responses—inhibiting acute inflammation and promoting chronic inflammation. It can also shape the tumour immunosuppressive microenvironment by affecting macrophages, NK cells, etc. Although breakthroughs have been made in lactate research, issues such as the mechanism of its bidirectional regulation of inflammation and the location of specific reactions remain to be resolved. In the future, research on lactate is expected to provide new directions for the diagnosis and treatment of diseases such as cancer, especially targeting lactate metabolism in the tumor microenvironment to break immunosuppression.

Keywords: Lactate; Metabolism; Immunity; Cancer.

1. Introduction

Lactic acid, or lactate, was first discovered its presence in sour milk in the 1780s by Karl Wilhelm Scheele as the result of fermentation and later found in human blood by Johann Joseph Scherer in 1843 [1], Lactic acid was considered a hypoxic byproduct of anaerobic respiration, which introduces detrimental effects to the human body such as cramps in strenuous exercises as Louis Pasteur found in his observations on lactic acid and exercises [2]. It was not until the 1920s that Otto Warburg discovered that tumor cells, while taking up large amounts of oxygen and glucose, did not undergo aerobic respiration but instead fermented the glucose into lactic acid in a process now identified as aerobic glycolysis [3]. Due to the tumor cells showing an inclination towards aerobic glycolysis over aerobic respiration, scientists have been able to deduce that lactic acid has a role in our body.

Lactic acid has become a popular research subject in various fields, including immunology and cancer research. In all the research, two major fields stood as the most prevalent research topics: lactic acid and its role in metabolism, and its effects on the body's immune system. The former focuses on how lactic acid is produced, cleared, and how it affects numerous metabolic reactions, regulating them through a system known as lactic acid homeostasis [4,5]. Lactic acid's core functions in metabolism include regulating energy metabolism through promoting TCA cycles and acting as a supplementary energy provision where glucose and oxygen levels are lacking, such as the brain [6]. It is also a signaling molecule for the regulation of metabolic processes, such as redox. The latter then focuses more on its interactions with the immune system and the diseases that come with it, specifically cancer, as it produces relatively large amounts of lactic acid using aerobic glycolysis. It focuses on how traits of lactic acid, such as being a product of anaerobic respiration and glycolysis, and being acidic, can alter the behavior of certain enzymes and other cells. Lactic acid's core functions in immunity include its ability to regulate inflammation through signaling and affecting immune cells' activities, which can be used in both physiological and pathological cases. Whilst groundbreaking achievements have been made in recent years, such as the discovery of lactate's ability to promote

modifications of histone lysine residues (known as lactylation), there are questions yet to be answered relating to the function of lactic acid, such as how it regulates its dual functions of promoting and inhibiting inflammatory responses.

2. Lactic Acid in Regulation of Metabolism

2.1 Lactic Acid Production and Removal

2.1.1 Lactate Production

Lactic acid production in the physiological setting is triggered when there is a lack of oxygen and ATP supply in the cell to meet its demand, which often occurs in the case of strenuous exercise and in an infection [4,5]. It is the end product of glycolysis under hypoxic conditions. When a cell is in hypoxia, the glycolysis pathway is activated, creating lactic acid, in order to compensate for the loss of ATP production as the TCA cycle is blocked. This process, while releasing ATP, will cause lactic acid to accumulate. It is also produced excessively in cells without mitochondria, as they cannot perform aerobic respiration or OXYPHOS and therefore have to use anaerobic glycolysis, creating large amounts of lactate.

In the pathological setting, lactate is seen in tissues in hypoxia due to their reliance on anaerobic glycolysis as their energy source. Impaired ability in TCA cycles or OXYPHOS, more notable in impaired mitochondria, also induces an increase in lactate levels in the cell and in its surroundings [7]. It is also predominantly seen in cancer cells, which intriguingly undergo glycolysis and create large amounts of lactate even in the presence of oxygen. This is coined as aerobic glycolysis, which happens due to the tumor cell's metabolic reprogramming, resulting in an inhibition of the regular OXYPHOS, resulting in its reliance on lactate for energy. Another reason for the occurrence is the large energy requirement for the proliferating cells, which results in the lack of ATP, so glycolysis is highly vigorous, which would mean that lactate levels would stay higher compared to cells in a resting state [8]. In cancer cells, glutamine can be metabolized into lactate by being converted into the TCA cycle and into pyruvate in the cytoplasm, which is converted into lactate. This mechanism is also used in supporting the acidic microenvironment in the tumor tissue [9,10,11].

2.1.2 Lactate Removal

The removal of lactate is crucial to maintaining the body's homeostasis, as increased levels of lactate can have deleterious effects on the system. As it is acidic, it lowers the pH of the blood and cells as it accumulates, which can alter enzymes, cells, and other metabolic reactions, which may disrupt the system. Building lactate can cause muscle soreness and disorders in the nervous system if not alleviated [12]. The building of lactate in tumour cells specifically can cause the microenvironment of the tumor cell to shift to being acidic, which could deform proteins related to immunity.

A newly formed theory of how lactate levels are regulated is the lactate shuttle: the shuttling of lactate through intracellular and intercellular membranes, resulting in lactate migration [13]. This theory that lactate is shuttled between cells is based on the unclear site of the oxidation of lactate into pyruvate, and how skeletal and cardiac muscles experience increased lactate/pyruvate ratios in exponents during and after exercise, which needs to be removed from the muscles [13]. Moreover, it is recorded that lactate can enter the mitochondria and oxidize without having to be converted into pyruvate first in the cytoplasm [13], proving the need for such a shuttling theory. Therefore, the theory was made that lactate can be shuttled between cells to be removed. The theory proposes that when the cell accepts the lactate and transfers it into the mitochondria, it will be oxidized by a mitochondrial lactate oxidation complex into pyruvate [13]. However, controversies are still directed to this theory, as none of the transporters that were mentioned were found. Some experimental studies have shown that isolated mouse mitochondria have failed to oxidize lactate, further adding doubts to the theory.

2.1.3 Lactate Level Regulation

The lactate levels are regulated through a series of metabolic reactions. In the cell, excess lactate is converted into pyruvate by LDH and sent into the TCA cycle to utilize the energy in the lactate and also to sustain the cycle. They could also be transported in the blood by monocarboxylate transporters (MCTs) into the blood into high-energy requirement organs such as the heart, the liver, and the kidneys, and sent into the TCA cycle there [8]. When blood and liver cell lactate levels increase, it also activates gluconeogenesis in the liver, where it will convert the lactate back to glucose and send it to the blood to raise glucose consumption in energy metabolism [14].

2.1.4 Lactate Production and Regulation in Cancer Cells

As partially mentioned above, cancer cells undergo more vigorous glycolysis, creating more lactate in the process. Aerobic glycolysis, as a fast ATP production process, is utilized by cancer cells to mass-produce energy for proliferation. Its advantage over aerobic respiration is that it produces ATP faster. As it does so, it lowers the consumption of oxygen while maintaining a high glucose intake. Apart from this, it is shown in studies in mouse fibroblasts that the high lactate levels also improve the mitochondrial respiration, coupling its efficiency [15]. Studies have shown that pyruvate-induced gluconeogenesis does not prevent glucose deprivation-induced cell death, which suggests that glucose is not the only substrate for respiration systems in cancer cells [16]. Researchers have used isotope tracing on 13-lactate and 13-glucose and found that TCA metabolites are more often marked by 13-lactate than 13-glucose, which indicates that lactate can be used as a carbon supply to the TCA cycle, which can provide more energy for the cancer cells to proliferate [17].

An example would be in hepatocellular carcinoma (HCC), in which the hepatocarcinogenesis is closely associated with the production of lactate in the proliferating cell by the Warburg effect, as they undergo glycolysis even under aerobic conditions, under the work of Lactate Dehydrogenase (LDH) [18]. LDHA was found to be highly expressed in tumor cells. MYC, a lactate-acid metabolism regulator gene, is found in HCC cells, and it signals the upregulation of LDHA, which enhances glycolysis in the proliferating cell [18]. The MCTs that are associated with lactate mainly come as MCT-1 and MCT-4, the former being an importer of lactate and the latter an exporter. MCT-1 is shown to inhibit tumor growth, glucose metabolism, and lactate export. MCT-4 is shown to promote tumor progression and is highly expressed in HCC [18]. These factors make room for utilization as they have strong connections to the development and proliferation of tumor cells and could potentially be targets for clinical work.

2.2 Lactate's Role in the Regulation of Metabolic Processes

2.2.1 Energy Regulation

Lactate can fill gaps in energy deficiency by serving as a supplementary energy source. This is especially crucial in energy regulations in organs that require large amounts of energy to function, namely skeletal muscles during strenuous exercise, the brain, heart, and liver. Circulating lactate has been identified as the supplementary source of glucose for parts of the brain during vigorous exercise, in which blood glucose levels are insufficient to sustain such vigorous activity [6]. Studies have found that brain slices in the absence of glucose were still able to perform synaptic transmissions by utilizing lactate [19]. Further studies showed that energy balance in neurons was destroyed when the lactate shuttling of the tissue was inhibited, indicating that lactate is responsible for regulating energy in neurons instead of glucose [20,21]. Lactate also regulates energy production by inhibiting glycolysis based on assessments of endogenous and exogenous lactate accumulation levels through a product feedback loop [22].

Lactate shuttles across the cells can include the infamous Cori cycle, which presents a model for lactate shuttles across skeletal muscles and liver cells, which encourages energy regulation in between cells, benefiting areas in need of energy and areas that have excess lactate [8]. This is essential for the tumor microenvironment as energy-rich lactate can be used as a substrate for ATP synthesis and gluconeogenesis, both of which are crucial for cell sustainment in hypoxic and normoxic

environments, which are prevalent in tumor cells [8]. As hypoxic environments are found more frequently in tumor cells stationed away from the blood vessels, they would use LDH-A to create lactate and transport it to normoxic cells, where the extra lactate can be converted into pyruvate for ATP [8]. This system is regulated by MCT1 and MCT4, in which the former controls the uptake of lactate in normoxic cells and the latter the production of lactate in hypoxic cells. This effect highlights how cancer cells work with each other within a tumor microenvironment and between tumors [8].

2.2.2 Regulation of Metabolism

Lactate can also contribute to regulating multiple metabolic processes. Fatty acid metabolism boasts progression, tumorigenesis, and treatment resistance by enhancing a cell's synthesis, storage, and catabolism of lipids [23,24]. Lactate contributes directly to fatty acid metabolism through supplying the raw materials that are required for fatty acid synthesis, acetyl coenzyme A, or Acetyl-CoA, while also triggering activity of critical enzymes during fatty acid synthesis, namely acetyl coenzyme A carboxylase, or ACC [8]. This helps accelerate fatty acid synthesis in the cytoplasm, which is shown to correlate with the invasiveness of the cancer and its resistance to chemical therapy. Lactate, as the favored energy source in the liver and in the heart, inhibits lipolysis and stops free fatty acids from entering the mitochondria as it attends OXYPHOS [25,26]. However, in cancer cells, studies have shown that it instead promotes extracellular lipolysis and the release of free fatty acids. These together bring about immunotherapy resistance in the cancer cells. These show conflicting roles that lactate plays in normal cells and proliferating cells. The signalling behind this is not yet clear to this day and is for future experiments to clarify.

New experiments led to a hypothesis on the mechanism of biological regulation of mitotic actions of cells controlled by lactate accumulation, the end product of glycolysis. Lactate can bind with zinc to form an inhibitory effect on the active site of cysteine protease SENP1 [27]. The inhibition of SENP1 can result in the stabilization of PTM of Anaphase-Promoting Complex subunit 4 (APC4), which allows the alteration of APC/C to permit UBE2C binding with the complex [27]. Binding APC/C with UBE2C would result in mostly the metabolic degradation of securin, which results in the breakage of the two sister chromosomes during anaphase, and also the degradation of Cyclin B1, which is involved in the exit of mitosis. This links lactate directly to the mitosis regulatory process and shows its direct influence over the metabolism of mitosis. In addition, these lactate remodeling processes regarding APC/C can signal the cell's nutrient-replete anabolism to regulate the cell undergoing mitosis [27]. However, this mechanism could be detrimental as the elevation of lactate levels can drive the depletion or deformation of other cell cycle regulators, which is contradictory to its original function [27].

2.2.3 Regulating Redox Patterns

Lactate also helps sustain glycolysis through maintaining the NAD^+ and NADH balance. Glycolysis breaks glucose down to pyruvate, creating 2 NADH in the process. Building NADH levels in a cell will inhibit glycolysis, so it needs to be converted. By converting pyruvate to lactate, it consumes NADH and converts it back to NAD^+, maintaining the ability to undergo glycolysis in proliferating cells [28]. The ability to maintain the balance of these two substances also prevents the detrimental effects of disruptions in this system. When NAD^+/NADH ratio, cells will enter an oxidation state, which will result in more active substances being produced, accelerating the aging of the cell, and increasing risk of cardiovascular diseases, while on the other hand, high NADH ratios will bring the cell into a high state, which could cause the cell to accept more electrons, which can result in the inhibition of glycolysis and the ability of the cell to prevent oxidative stress reduced [29,30]. Also, as lactate supports the balance of NAD^+/NADH level, it also controls the redox patterns in the cell, as NAD^+ favors oxidative reactions and NADH favors reducing reactions. When cells undergo active aerobic glycolysis, the cell needs more oxidation support from NAD^+; lactate provides it through limited mitochondrial respiration. When this happens, cells will undergo glycolysis, which further amplifies the NAD^+/NADH ratio, which triggers the PDH response, which oxidizes pyruvate

back to lactate to regulate this pattern [31]. These contributions ultimately buffer the redox patterns in the cell.

It is also found that proliferative cells accumulate lactate to initiate the mitotic process. This shows how lactate acts as a signalling molecule for the mitosis reactions to happen, as the lactate's control of flux in anabolic and energetic reactions is used in the growth phase of the cell to create the necessary materials for mitosis [27].

3. Lactate and Immunity

3.1 Lactate's Regulation of Immunity and Marker Functions

3.1.1 Marker in Diagnostic and Prognostic Uses

Lactate is often used as a diagnostic and prognostic marker of diseases and infections. This is due to lactate levels rising, often symbolizing cell necrosis and the lactate accumulation in infected and dying cells [32,33]. As lactate was seen to be the marker of diseases, it can also indicate a sign of recovery as lactate levels are expected to decrease through body regulation when the issue that causes hyperlactatemia is fixed. In treatments for patients in critical states, lactate is often the key indicator for sepsis and trauma, and whether they have recovered [34]. As the recovery of a patient to normal lactate levels is highly linked to its overall recovery, irregularly high lactate levels in blood are linked to morbidity and mortality, with its functions on its connections with mortality critical at the time of presentation, as it can assess the risks the patient is at. As an example, patients presenting at a lactate concentration of 4.0 mol/dL or greater have an 18.8% mortality rate, while patients at less than 2.5 mol/dL have their risks down to 5.4% [15]. The inability to clear lactate also signals mortality, as patients failing to regulate lactate levels for more than 48 hours have their survival rate reduced [35].

Lactate, as it plays a key role in inflammation, can also be used as a marker for any inflammatory responses, whether diseased or not. This includes all proliferating cells, including cancer, as their microenvironment will be filled with lactate. Therefore, through monitoring lactate levels, lactate can help clinics understand whether diseased inflammations and possibly cancer are in the body, and also provide some information on the properties of the disease. As an example, patients with metastatic colorectal cancer would have higher lactate levels in the serum than those without any systemic disease [36].Recent studies on markers of lactate have shown progress as Li and Ai had developed a fluorescent indicator for lactate, named FiLa. As the previous detectors of lactate have multiple undesirable drawbacks, FiLa was a necessary development. The lactate tracers used to have a relatively small dynamic range. Also, prior prototypes show undesired reliance on calcium ions, which could cause issues in physiological usage. In addition, the affinity of these trackers was not suitable for physiological purposes as they were relatively low [37]. This development provides solutions for the issues above, which are more suitable for tracking in mammalian bodies. It was proven successful in mouse models [37].

3.1.2 Inflammation

Inflammatory responses are triggered in a variety of acute and chronic diseases and are a widespread mechanism that is involved in almost all body organs. Lactate has several functions in inflammatory responses. It provides energy that is used in inflammatory injuries and immune energy regulation. In addition, accumulation of lactate triggers a series of cell signalling pathways that can control and regulate inflammatory responses as well as tumour immune resistance, although the mechanism of regulation is not yet fully clear. These functions of lactate have been notably found to be irrelevant to its nature of acidifying its environment [8]. Also, acute inflammatory responses have been generally noted as an occurrence performed by the host's defensive system, but unrestrained proliferation of acute inflammatory responses would lead to necrosis and prolonged disease. Lactate was shown to be effective at inhibiting acute inflammatory actions [8].

In acute inflammations, lactate significantly reduces the production of inflammatory cytokines [38] and delays upregulations of inflammatory responses induced by LPS molecules [8]. Inflammatory

cytokines, including tumour necrosis factor alpha and interleukin 6, initiate, amplify, and sustain inflammation. By reducing the production of these, lactate inhibits further inflammation from happening. Lactate also reduces the accumulation, activation, and translocation of NF-κB, which is a signalling molecule that upregulates inflammation. Inflammatory responses induced by LPS molecules can be further deterred by the lack of NF-κB present, as it is reliant on NF-κB for signalling [39].

In chronic inflammations, lactate is shown to behave in contrast to that of acute inflammations - instead of inhibiting it, it enhances it. Lactate inhibits T cells from migrating and therefore traps T cells near the inflammation site [40]. Without the decrease of the T cells in the inflammation site, the production of the inflammatory cytokines will increase, and the cell lysis will decrease in the inflammation site, therefore prolonging the chronic inflammation [41,42].

D-Lactate, a stereoisomer molecule of lactate, was shown to be able to contribute to diseases involved with obesity, as when inhibited, it was proven to lower hepatic inflammation and fibrosis in metabolic dysfunction-associated fatty liver diseases, in short as MAFLD, and in metabolic dysfunction-associated steatohepatitis, in short, MASH [43]. The effect of D-lactate was shown to contribute to lipogenesis and glucogenesis, which both contribute to more energy in the cells, resulting in higher obesity rates and therefore more risks to MAFLD and MASH. In the study conducted by Fang et al., substrate traps of microbial D-lactate in the guts, its main source, raise the triggers for inflammation and fibrosis during MAFLD and MASH, resulting in less proliferating cells and therefore less severe conditions in mice [43].

3.2 Cancer-related Mechanisms

3.2.1 Provide Energy

As mentioned above, aerobic glycolysis is the main metabolic method for obtaining energy in cancer cells, in which lactate is formed. As lactate can be recycled and converted into pyruvate, lactate forms a key function in preserving the ability of the cell to undergo glycolysis repeatedly, even in aerobic surroundings, as well as maintaining the TCA cycle [44]. Utilization of lactate in the TCA cycle can capitalize on its metastatic capabilities, as research has found in mice xenografts [45].

Recent studies have concluded that lactate and its metabolic properties have different characteristics between stem cells and differentiated cells. In cancerous stem cells (CSCs), it was shown that they had a high NAD+/NADH ratio compared to cancerous differentiated cells (CDCs) [46]. However, the production of lactate was lower in CSCs than in CDCs; therefore, CDCs have more accumulated lactate levels and higher glycolytic rates [47]. This indicated that in CSCs, the mitochondria contributed more extensively to the NAD+/NADH ratio than the pyruvate-lactate change. It could also indicate that CSCs would direct the intermediates of glycolysis to anabolic processes to meet the requirements of proliferation in cancer cells instead of lactate [46]. It was also found that lactate significantly promotes the creation of CSCs as it inhibits the differentiation of cells while inducing the dedifferentiation of cells [46].

3.2.2 Invasion and Immunosuppression

Proliferating cancer cells can benefit from utilizing lactate to increase their invasiveness, such as the proliferation of cancer-associated fibroblasts (CAFs) [47]. In the case of CAFs, it contains COX-2 that synthesizes type I collagen. Type I collagen is a main contributor to the basal membrane remodeling in cancer cells [48], which can increase their invasiveness [49]. Another example is that lactate promotes matrix metalloproteinases expression, which degrades glycoprotein and collagen, and also acts as a collagenase to promote tumor invasion [50].

Lactate can regulate the functions of lymphocytes and macrophages to achieve immunosuppression. Tissues in hypoxia secrete more chemokines, which will attract macrophages to hypoxic areas, which in turn affect the local immune response. Triggering the tumor antigen repeatedly and activating the immune system may lead to exhaustion or remodeling of the immune effector cells in the tumor tissue, disabling the cells from performing their original functions [8].

Tumor-associated macrophages (TAMs) can utilize the hypoxic tumor microenvironment and lactate levels to activate the MAPK signaling cascade to promote tumor immunity [51,52]. M1-like macrophages in the tumor microenvironment can inhibit tumor cell growth stages' progression. M1 macrophage polarization is generally considered a positive clinical prognosis of cancer cells, while M2-polarized macrophages were shown in experiments to positively correlate with tumor growth and its occurrence [53-57]. The acidic tumor microenvironment contains more M2 macrophages than M1 macrophages, as lactate promotes M2 macrophage polarization by activating the ERK/STAT3 signaling pathway, which signals the polarization of M2 macrophages. By inhibiting ERK/STAT3 signaling pathways, it is shown that reduced tumor growth is achieved by reduced M2 macrophage production controlled by lactate [58].

Lactate can affect the immune system to help cancer cells evade detection and suppress the immune system. Firstly, lactate diminishes the effectiveness of Natural Killer cells (NKcs) to tumors [59]. Lactate can downregulate NKp46, CD25, and NKG2D, which consequently decreases the activation of NKcs [59]. Also, lactate can decrease the production of cytotoxic factors that are produced by the expression of nuclear factor of T cells (NFAT) through suppressing this expression by acidification [60].

However, lactate can also function as an anti-tumor molecule as it can trigger an immune response that is anti-tumor when lactate is administered into the body containing a tumor in mice during an investigation by Feng et al. It was shown that lactate treatment in mice successfully promotes the antitumor immunity by promoting the stemness of tumor-infiltrating CD8+ T-Cells. In this lactate treatment, the salt used was sodium lactate, which indicates that it can neutralize some of the acidic tumor microenvironment that lactic acid creates, enabling $CD8^+$ T-Cells to survive and perform their function of anti-tumor immune response [61].

4. Conclusion

Contrary to prior perceptions, lactate is not merely a byproduct of anaerobic glycolysis with deleterious effects to the human body, but a key metabolic carrier, energy supplement, signalling molecule, and immune system regulator. Through its ability to regulate energy and redox patterns, lactate controls the body's metabolism and acts as an emergency supply of energy for cells in short supply of glucose. It can regulate the body's fatty acid metabolism rates, including its transport and its formation. It plays an important role in the body's immune responses, including being a marker of proliferation and areas of disease, showing breaches of the immune system, and regulating inflammatory responses, effectively inhibiting some and promoting others.

Lactate plays an important role in the tumour microenvironment, as it can provide it with energy to sustain the vigorous proliferation that cancer cells undergo to develop the tumour. The effect that high concentration of lactate brings to the tumour microenvironment is crucial to its ability to evade the immune system's detection and remain unharmed when the immune system attacks the tumor tissue. Its immunosuppression role denies the immune system from performing its regulatory actions on cancer cells.

While the research on lactate functions has found groundbreaking progress, a lot of mystery surrounding this molecule is yet to be unveiled. This includes clarifications on methods of its interactions with other molecules as they perform specific functions. Key regulatory patterns of lactate are not yet determined, as well as the areas where specific reactions happen, such as the conversion of lactate to pyruvate. The reasons behind its regulatory patterns are not yet clear.

Lactate, as interest in it has boomed over the last years, shows increasing potential of resolving mysteries and issues that have troubled human scientists for decades. Its close relations with cancer were seen as a breakthrough point – its functions of immunosuppression may be the key to resolving the issue of cancer, as removing lactate in the tumor microenvironment may result in the tumors losing their ability to evade immunity.

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