Letter to the Editor

Immunological and physiological changes of exercise-released lactate on tumors: an important and new research window

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Dear Editor-in-Chief

With the alarming rise in cancer cases, which is now recognized as the leading cause of death, the importance of exercise in cancer management is gaining significant recognition (Ahmadi Hekmatikar et al., 2023). In a study titled "Exerkines in health, resilience, and disease," Chow et al. (2022) shed light on the crucial role of exerkines in relation to various diseases, highlighting the positive impact of exercise, particularly in cancer (Chow et al., 2022). However, Brooks et al. (2022), in a letter to the editor addressing the aforementioned study by Chow et al., noted that lactate, a notable myokine and exerkine, was not mentioned. They emphasized the pivotal role of lactate as an important secretory product of exercise (Brooks et al., 2022). In this regard, our recent study, which was published in the journal Support Care Cancer (Ahmadi Hekmatikar, 2023), presented a critique of the article by Depenbusch et al. 2023. We highlighted that lactate, an important myokine secreted during exercise, can potentially pose a risk to tumors (Depenbusch et al., 2023). Our study emphasized that lactate may contribute to tumor angiogenesis and immunosuppression. Therefore, caution should be exercised when designing exercise programs for cancer patients (Ahmadi Hekmatikar, 2023) In a previous study published in support Care Cancer (Lavín-Pérez et al., 2023), we found that moderate-intensity physical activity does not negatively impact the immunological changes in breast cancer patients. However, upon further examination of the role of lactate, it became evident that more research is needed. Our study aims to provide researchers with a detailed exploration of the role of lactate in cancer, offering a valuable perspective for future investigations.

Lactate and immune checkpoint: lactate leads to immune system suppression (How)

One of the most crucial treatment strategies currently pursued by oncology researchers is immune checkpoint blockade (Sharma et al., 2023). Within the tumor microenvironment, PD-1 and its ligand PD-L1 play a crucial role in tumor progression and survival by evading immune surveillance aimed at neutralizing the tumor (Keir et al., 2008). In the cancer immune cycle, the immune checkpoint PD-1 and its ligand PD-L1 collaborate to facilitate immune escape and promote tumor progression (Keir et al., 2008). In this context, a study revealed that lactate can enhance the expression of PD-L1 on tumor cells, suggesting that lactate may have a protective effect against tumors by increasing PD-L1 expression (Feng et al., 2017). Furthermore, another study strongly emphasized that the lactate-induced activation of the PD-1/PD-L1 pathway can induce immunosuppression by promoting lymphocyte apoptosis in AKI (Xu et al., 2021). Additionally, it has been discovered that lactate metabolism is essential for the function of anti-tumor immune cells (Ahmadi Hekmatikar et al., 2023; Heuser et al., 2023). There are two main perspectives regarding the role of lactate in immune evasion. The first perspective suggests that lactate, by increasing PD-L1 expression, contributes to immune evasion and facilitates tumor growth. The second perspective proposes that lactate derived from the tumor inhibits the proliferation of human T lymphocytes (Ahmadi Hekmatikar et al., 2019; Heuser et al., 2023; Rami et al., 2023; Tayebi et al., 2020).

Lactate and tumor angiogenesis

One characteristic of cancerous tumors is their ability to induce angiogenesis in their surrounding environment, facilitating their growth and metastasis to other parts of the body (Bokhari & Hamar, 2023). This angiogenesis is triggered by an upregulation in the expression of the vascular endothelial growth factor (VEGF) gene (Bokhari & Hamar, 2023). While it is known that tumors promote angiogenesis through the establishment of signaling cascades in their vicinity, a more co-

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-mprehensive examination of this topic reveals the involvement of lactate in tumor angiogenesis (Pérez-Tomás & Pérez-Guillén, 2020). Lactate appears to play a role in enhancing the expression of VEGF, potentially explaining the association between lactate and tumor angiogenesis (Ahmadi Hekmatikar, 2024; Ahmadi Hekmatikar & Moqhadasi, 2024; Pérez-Tomás & Pérez-Guillén, 2020).

Why exercise?

The first perspective

One of the fundamental characteristics of exercise is the elevation of blood lactate levels during physical exercise (Ahmadi Hekmatikar et al., 2024; Brooks, 2018). It was previously believed that lactate production occurred as a consequence of oxygen deprivation in skeletal muscle contractions. However, it is now understood that lactate is continually generated and utilized in various cells even under fully aerobic conditions. In fact, lactate, as a metabolic byproduct of glycolysis and a substrate for downstream pathways like mitochondrial respiration, can be considered an interface between glycolytic and aerobic pathways (Brooks, 2018). In a study titled "Physiological Significance of Elevated Levels of Lactate by Exercise Training in the Brain and Body," it was discovered that exercise can increase lactate levels in the bloodstream. Moreover, this rise in lactate was found to have implications for angiogenesis. Physical exercise stimulates the production of vascular endothelial growth factor (VEGF) and promotes angiogenesis through the lactate receptor known as HCAR1 (Lee et al., 2023).

The second perspective

Drawing from previous research, oncology and exercise physiology researchers are striving to establish appropriate physical exercise strategies for individuals with cancer, recognizing that physical exercise is a cost-free intervention that can play a significant role in disease management (Ahmadi Hekmatikar et al., 2023; Chow et al., 2022; Depenbusch et al., 2023; Lavín-Pérez et al., 2023). The importance of physical exercise during cancer is underscored by its potential to mitigate fatigue, alleviate side effects of treatment and medication, and address general physiological mechanisms. However, the tumor microenvironment operates in a sophisticated and intricate manner, necessitating a deep exploration of its underlying mechanisms to develop tailored exercise regimens. Oncology researchers are placing their focus on immunotherapy, as enhancing the performance of tumor-specific immune cells holds promise for researchers. In a meta-analysis study, we asserted that physical exercise does not suppress tumor-specific immune cells, yet it does not significantly increase their levels either (Lavín-Pérez et al., 2023). Furthermore, we reported in another study that low-intensity physical exercise during cancers, viewed through the lens of "exerkines and cancer management," can be beneficial. However, caution must be exercised with moderate to high-intensity exercise, as it may contribute to disease progression. One aspect we emphasized was the significance of lactate (Ahmadi Hekmatikar et al., 2023). Lastly, in our study titled "Correspondence: Work Smart or Work Hard in Patients with Metastatic Breast Cancer: Emphasizing the Importance of Immunological and Lactate Changes," we highlighted that physical exercise induces lactate secretion, and the detrimental impact of lactate on tumors has been identified. Consequently, physical exercise recommendations should be approached with caution (Ahmadi Hekmatikar, 2023).

Low-intensity, moderate and high-intensity exercise

The American College of Sports Medicine recommends low-intensity exercise (20-40% VO_2max, 35-45% HRmax) for beginners. Studies show lactate levels typically increase by 1-2 mmol after such activity. However, responses vary based on fitness level, glycogen stores, and oxygen availability. Moderate exercise (40-60% VO_2max, 55-70% HRmax) can elevate lactate by 2-6.5 mmol (Zinman et al., 2003). Some studies also report lactate reduction after prolonged training. Lactate monitoring during moderate-intensity exercise provides insights into physiological adaptation (Andersen et al., 2023; Andersson et al., 2021; Falz et al., 2019; Wiecek et al., 2017; Yuxin et al., 2021). High-intensity exercise (≥64% VO_2max) leads to greater lactate accumulation (4.5-13.2 mmol). Trained individuals may experience lower increases compared to untrained counterparts. Long-term high-intensity training may reduce resting lactate levels. Resting lactate levels in cancer patients can be significantly elevated, but post-exercise lactate increases are generally lower than in healthy individuals. Exercise interventions may help regulate lactate metabolism and reduce fatigue in cancer patients. However, responses vary based on training intensity and individual health conditions. Overall, lactate dynamics depend on exercise intensity, fitness level, and metabolic factors. Further research is needed to optimize exercise prescriptions for different populations, including cancer patients (Andersen et al., 2023; Andersson et al., 2021; Falz et al., 2019; Wiecek et al., 2017; Yuxin et al., 2021).

Conclusion and research gap

In our study, we have demonstrated the detrimental effects of lactate on tumors. Additionally, we have taken a more specialized approach by examining the relationship between lactate and exercise. It is evident that physical exercise leads to increased lactate levels and angiogenesis. Therefore, we strongly recommend that in order to develop appropriate physical exercise strategies for cancer patients, it is crucial to delve into the deeper and more fundamental mechanisms underlying the interaction between exercise and cancer, rather than solely focusing on surf-

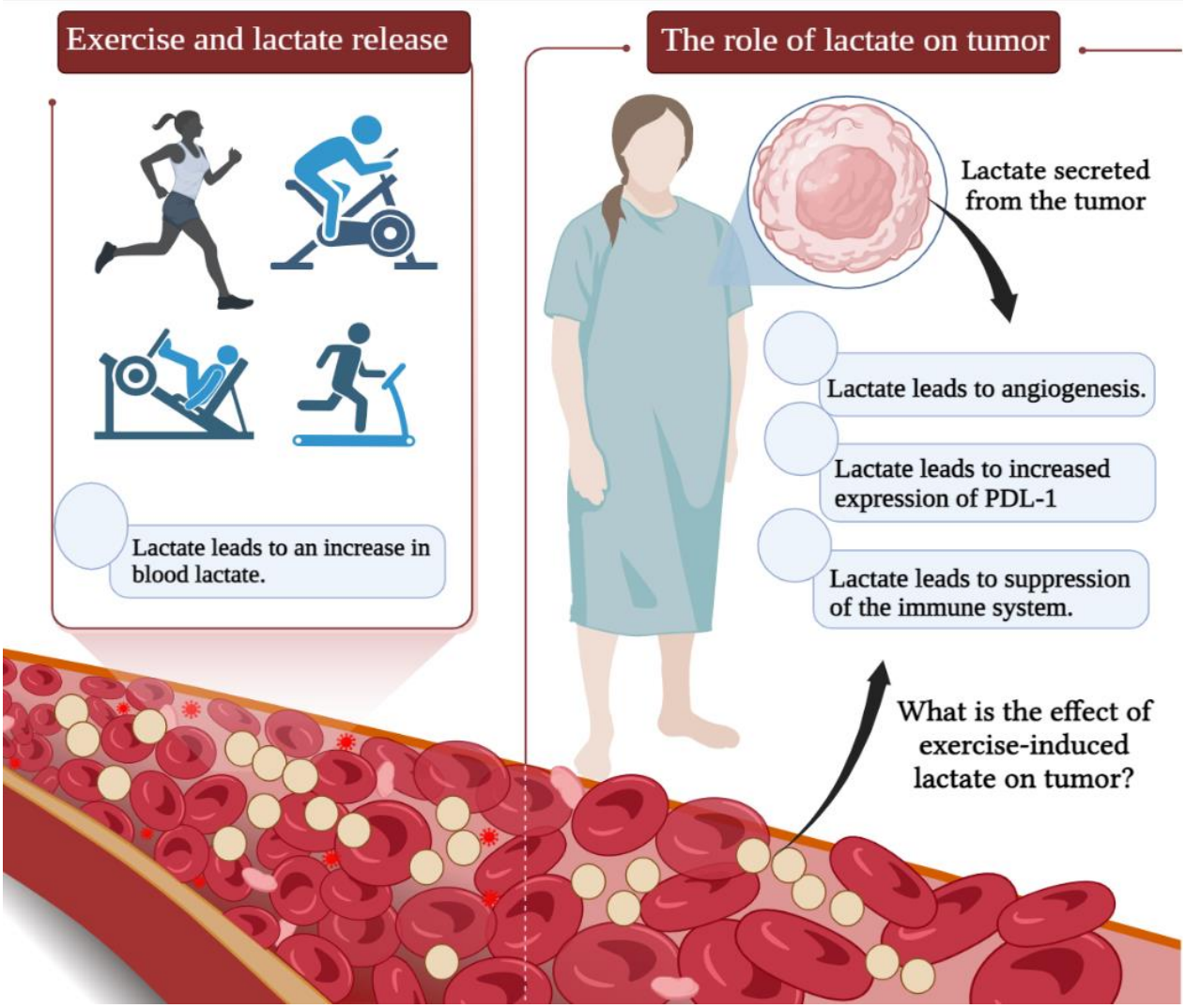

Figure 1. Research prospects for the future.

-ace level mechanisms. Considering that immunotherapy is a key focus of cancer treatment for oncology researchers, the role of lactate secreted during exercise becomes particularly significant. It has been established that lactate can negatively impact the immune system's performance in two ways: 1) by increasing the expression of anti-PD-L1, allowing tumors to evade immune surveillance, and 2) by directly suppressing T cells. Furthermore, lactate can also contribute to angiogenesis and facilitate tumor growth (See figure 1). Therefore, our study has opened a specialized and important avenue in the field of sports oncology, presenting these significant hypotheses that can guide future research and aid in developing more effective training strategies:

1. Can physical exercise -induced elevation of lactate contribute to tumor growth?

2. Can physical exercise -induced elevation of lactate impact the expression of PD-L1 in tumors?

3. Can physical exercise-induced elevation of lactate affect tumor -specific immune cells?

4. Can physical exercise -induced elevation of lactate lead to tumor angiogenesis?

5. What intensity of physical exercise can be effective for cancer patients, considering lactate and its relationship with tumors?

By addressing these questions, we can gain valuable insights and uncover numerous aspects through this newly opened window.

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