Running to Outcompete Metastasis

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The role of exercise in cancer progression is an emerging field of research, with intriguing evidence for physical activity playing an inhibitory role in cancer onset. In their recent publication, Sheinboim and colleagues demonstrate the impact of physical exercise on melanoma primary tumor growth and metastasis. They establish that physical exercise decreases metastatic spread, using both human epidemiologic data and *in vivo* models of melanoma metastasis. Systemic metabolic reprogramming of organs, induced by exercise, leads to a decrease in melanoma growth and progression as healthy organs are able to outcompete melanoma cells for nutrients. Exercise led to systemic metabolic changes in carbohydrate metabolism, glycolysis, and oxidative phosphorylation as well as mitochondrial biogenesis. Interestingly, the "metabolic shield" created by exercise could be reversed using the mTOR inhibitor rapamycin. This study highlights the importance of metabolic plasticity in metastasis and uncovers a direct link between systemic metabolic reprogramming and mTOR signaling. Overall, the study by Sheinboim and colleagues provides a more detailed understanding of the metastatic requirements in the context of energy and nutrient availability and the impact of exercise on cancer progression, highlighting novel opportunities for therapeutic intervention.

See related article by Sheinboim et al., p. 4164

According to the NIH, 39% of women and men will be diagnosed with cancer (NIH, 2015–2017 data). Such a devastating statistic raises the question of how our lifestyle and environment can affect cancer incidence and progression and what can be done to prevent or delay cancer onset. Two major components of our daily lifestyle are our diet and physical exercise. While many dietary changes have been implemented in the context of cancer (1), the World Health Organization states that "there has been no improvement in global levels of physical activity since 2001." This highlights that our society has gotten more sedentary and that more than a quarter of adults are insufficiently physically active (2). In the recent years, the correlation of physical activity and cancer has been extensively studied (2–4). A large epidemiologic study on 1.44 million participants showed that moderate/vigorous leisure time activity is associated with a significantly lower risk of cancer incidence and mortality (5). Other epidemiologic and animal studies have demonstrated that physical exercise can inhibit several cancer hallmarks, such as sustained proliferative signaling, evasion of growth suppression, replicative immortality, increased angiogenesis, and resistance to cell death (3). Yet our knowledge of specific mechanisms through which exercise is able to impact cancer progression and metastasis remains limited.

Metastasis is a tightly regulated process that allows cancer cells to disseminate from a primary tumor to colonize distant organs. It is now widely accepted that during this process cancer cells experience high levels of stress (oxidative stress, shear stress, nutrient availability, interactions with the immune system). To successfully survive these stresses and metastasize, cancer cells adapt to their microenvironment through a process known as metabolic plasticity. Because metastases are the main cause of solid tumor-related deaths and physical activity is associated with lower risk for cancer mortality, a key question is whether exercise can attenuate the development of metastases. Most studies linking metastasis and physical exercise are interventional studies on mice, as not a lot of epidemiologic human data are available on metastatic status of patients and their matched physical activity. In this issue of *Cancer Research*, Sheinboim and colleagues analyze a 20-year-long prospective cohort of 2,734 participants that were initially cancer free to demonstrate that high intensity exercise significantly reduces the incidence of highly metastatic cancer (73% reduction; ref. 6). This epidemiologic study illustrates the unique and significant interaction between metastasis and physical exercise. Despite emerging epidemiologic data on the benefits of exercise and reduced cancer risk, little is known about the underlying mechanisms of how exercise can affect cancer incidence and progression. Some scientific reports have made a connection between exercise metabolism and the activity of the immune system in the context of cancer, demonstrating a reduction in primary tumor growth following exercise (7–9). Specifically, it has been shown that depletion of cytotoxic $CD8^+$ T cells abolishes the anticancer effects of exercise (9). Yet many key questions still remain: Is the effect of exercise on cancer due to a systemic metabolic change? How long does it last? Is it possible to use physical exercise as a preventive measure against metastasis?

To explore the molecular changes that occur in internal organs following exercise, Sheinboim and colleagues established an *in vivo* mouse exercise model and performed comparative proteomics analyses of host organs with the highest frequency of metastasis: lungs, lymph nodes, and liver. They showed that with exercise, healthy organs significantly shifted their metabolism, resulting in a higher nutrient demand. These metabolic changes were systemic and were identified to be part of carbohydrate metabolism, glycolysis, oxidative phosphorylation, and mitochondrial biogenesis. This supports recently published data showing that exercise induces a very specific metabolic signature in the host organs, causing metabolic rewiring between sedentary and active mice (4). Others have also shown that this metabolic shift (mainly related to carbohydrate consumption) can be traced in plasma (4, 9). In addition, it has been shown that the time of day and the duration of the physical activity are determinants of the metabolic changes that are induced in the organs. Some metabolites, such as 2-hydroxybutyrate, are known to be time-dependent "exerkines" or circulating exercise-induced factors (4). In their study, Sheinboim and colleagues show that exercise creates a new microenvironment throughout the body that demands more nutrients.

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To evaluate the potential protective role of exercise-induced increased metabolic activity on metastatic host organs, the authors established three metastatic melanoma models using subdermal, intracarotid, or intrasplenic injection of melanoma cells derived from *Ret* transgenic mice. As shown by others (8–10) and in accordance with the human data (5), they found that exercise significantly reduces primary tumor growth. This was explained by the fact that there was a strong reduction of melanoma cell proliferation *in vivo*. In addition, they showed that, independent of the primary tumor, exercise significantly reduced metastatic frequency, cell dissemination, and survival. This reduction in melanoma cell proliferation and survival was also found *ex vivo* in *in vitro* cocultures of host organ cells extracted from exercised mice and melanoma cells. Put together, these results demonstrate that exercise reduces primary melanoma growth and metastatic dissemination. The creation of what the authors define as "a metabolic shield" via the reprogramming of key metabolic characteristics of these organs under exercise results in a tumor microenvironment that outcompetes melanoma cells for nutrients, leading to an environment hostile to tumor cell colonization. Further in the study, Sheinboim and colleagues showed that the exercise-induced metabolic shield present in the stroma of metastatic host organs could be reversed using rapamycin, an mTOR inhibitor. This demonstrates that exercise effects are reversible and rely on a specific link between signaling and metabolism. Interestingly, this suggests that specific molecules are able to recapitulate the metabolic shift induced by exercise and may represent potential adjuvant therapies to generate an unfavorable microenvironment for tumor development and dissemination.

The study of the impact of physical activity on cancer is a growing scientific research area, with multiple studies focused on metastasis (3, 6). While the link between exercise and cancer progression has to be explored in further detail, it is clear that daily exercise has a significant impact on cancer progression. The study by Sheinboim and colleagues gives us a better understanding of metastatic events in the context of exercise and the systemic impact of exercise on metastatic dissemination, but it is still necessary to assess how each component of the microenvironment contributes to the antimetastatic effect of exercise and how this can be translated into the clinic. Deeper mechanistic insights into the metabolic balance and impact of physical activity on metabolic requirements of metastasizing cell could enable scenarios in which host organs are able to outcompete cancer cells. Exercise-oncology, which combines exercise and oncological treatments in patients, is a novel evolving field that needs more attention and could lead to optimization of existing and novel therapies to improve treatment of patients with cancer.

Authors' Disclosures

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