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Commentary

Exercise and its influence on the tumor microenvironment — the role of muscle-cancer cross talk

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Exercise is increasingly being recognized as an important part of cancer treatment, as it has been shown to alleviate treatment- and disease-related side effects and improve quality of life of patients with cancer [1]. Furthermore, exercise has been linked to a reduced risk of cancer recurrence, particularly in cases of breast and colorectal cancer [2]. In recent years, the question has come to the forefront: "How?" does exercise influences cancer survival, and with it the interest in the underlying physiological mechanisms.

The tumor microenvironment (TME) and its individual composition can be involved in both metastasis formation and the response to treatment and survival of cancer cells, making it an extremely interesting target for therapeutic approaches [3]. Four pathways are currently known to influence the TME: The immune system, vascularization, cancer cell metabolism, and muscle-cancer cross talk [4,5]. All of these pathways can be influenced by exercise through myokines. In the following, we will focus on the last pathway —muscle-cancer cross talk.

Recently, a pilot study by Gunasekara *et al.* [6] demonstrated that an acute endurance training session appears to influence the growth of breast cancer cells. Serum collected before and after one hour of endurance exercise on a bicycle ergometer with an intensity of 50% VO_{2peak} for 20 min and 60% VO_{2peak} for the remaining 40 min was analyzed to assess its effects on breast cancer cell growth *in vitro*. Hormone-independent cells, specifically MDA-MB-231 cells (triple-negative breast cancer cells), were incubated with this serum, and cell vitality and proliferation were evaluated.

Additionally, the chemokine CXCL9 was identified as a promising key element in the pathway of muscle-cancer cross talk using cytokine arrays. The analyses showed that CXCL9 levels decreased following the acute endurance exercise compared to the resting control condition. To investigate whether the reduced cell activity was related to CXCL9 concentration, the CXCL9 signaling pathway was blocked using a CXCR3 antagonist, and cytotoxicity and proliferation assays were repeated with serum before the intervention and with serum plus the inhibitor. The results indicated that inhibition of CXCL9 led to growth-inhibitory effects (**Figures 1A** and **1B**). These findings suggest that serum conditioned by an endurance intervention induces changes in cancer cell growth, possibly mediated through the CXCR3 axis [6].

The chemokine CXCL9 has the property of recruiting and activating immune cells, particularly CD8+ T cells, which play a crucial role in targeted attack and elimination of cancer cells [7]. To our knowledge, direct interactions with cancer cells have not yet been described.

This result highlights the importance of further research into the role of CXCL9 and other possible myokines in cancer biology. Therefore, in a further step, analyses were first conducted using a hormone-

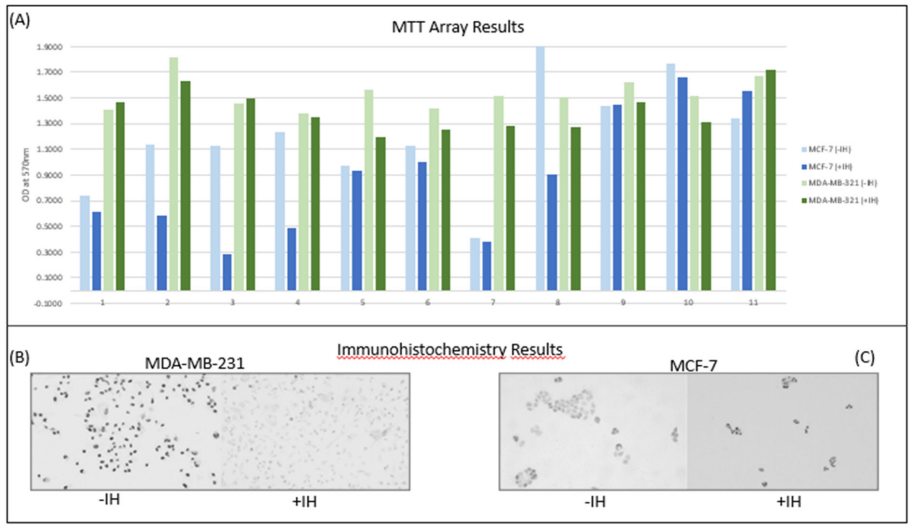

Figure 1. Effects of exercise-conditioned serum on different breast cancer cell lines. (A) Results of the MTT assay with the hormone-independent cell line (MDA-MB-231) and the hormone-dependent cell line (MCF-7), each treated with pre-exercise (-IH) serum and pre-exercise serum plus the CXCR3 pathway inhibitor AMG 497 (+IH). Optical density was measured at 570 nm. **(B)** Results of the immunohistochemistry with the hormone-independent cell line (MDA-MB-231) before and after inhibition of CXCR3. On the left, MDA-MB-231 cells were treated with the conditioned pre-exercise serum (-IH) and Ki-67. The darker appearance of the cells indicates the presence of Ki-67, an indicator of proliferative cells. On the right, cells were treated with the conditioned pre-exercise serum, Ki-67, and CXCR3 inhibitor AMG 486 (+IH). Images were taken at 20x magnification. **(C)** Results of the immunohistochemistry with the hormone-dependent cell line (MCF-7) before and after inhibition of CXCR3. On the left, MCF-7 cells were treated with the conditioned pre-exercise serum (-IH) and Ki-67, with stronger Ki-67 expression visible. On the right, cells were treated with the conditioned pre-exercise serum, Ki-67, and CXCR3 inhibitor AMG 486 (+IH). The darker appearance of the cells indicates the presence of Ki-67, an indicator of proliferative cells. Here a lower number of Ki-67 positive cells was observed. Images were taken at 20x magnification.

dependent breast cancer cell line (MCF-7) to examine whether other cancer cells respond differently to exercise-conditioned serum. The MCF-7 cells were also incubated with serum samples from all subjects under two experimental conditions: without addition (-IH) and with addition of the CXCR3 inhibitor (+IH). The MTT analysis showed a significant decrease in cell viability after CXCR3 inhibition (d= 0,75; p= .032) (**Figure 1A**), while immunohistochemical analysis revealed increased Ki-67 expression under the inhibitor condition (+IH) compared to the control condition (-IH) (**Figure 1C**).

These results suggest that although blockade of the CXCR3 signaling pathway influences metabolic processes, it does not cause clear antiproliferative effects in hormone receptor-positive breast cancer cells. Overall, the study underscores the complex role of the CXCR3 signaling pathway in the TME and provides key points for future research. The effects also appear to be cell type-specific, which should also be taken into account in future studies. Further, in the next step, analyses will be conducted to investigate whether acute strength training has similar effects on reducing cancer cell growth. This would support the hypothesis that exercise could influence the TME in a way that is beneficial for the patient. In future, more complex *in vitro* cancer cell models, which also include extra-cellular matrices and vessels, could be used to identify more complex influences of exercise on tumor growth.

This newly gained insight emphasizes the significance of exercise and its impact on the TME. Exercise could support the immune system's ability to target and eliminate tumor cells, especially in immunoreactive cancers such as triple-negative breast cancer by influencing the TME.

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