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New Insights Into the Immunomodulatory Effects of Exercise and Potential Impact on Tumorigenesis

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Exercise immunology has been a very lively field of research for the last few decades. Studies have focused on the apparent immunosuppressive effects of excessive exercise in elite athletes and the proposed immune-boosting effects of more moderate exercise in previously inactive individuals. Exercise studies with immunologic outcomes are less common in cancer populations, and the results of such studies have been inconclusive. This is likely due to small sample sizes, the use of different exercise regimens, heterogeneous patient populations, and differences between studies with regard to the immune markers under investigation and/or the assaying techniques used. In this review, Koelwyn and colleagues provide an overview of key studies in the field and a framework that highlights the critical steps at which exercise could modulate tumorigenesis; the framework can thus serve as a roadmap for future research.[1]

The authors propose a number of mechanisms by which exercise training can modulate the systemic host milieu, with particular reference to the inflammation-immune axis. However, the extent to which exercise per se, as opposed to exercise-induced changes in body composition, accounts for

such changes remains unclear. A secondary analysis of data from early-stage breast cancer survivors who underwent a combined aerobic exercise and hypocaloric diet intervention suggests that weight loss (perhaps reflecting a reduction in body fat stores), rather than exercise per se, could be a more pronounced determinant of the observed changes in the systemic host milieu.[2] This is consistent with recent data from the SHAPE-2 trial, which show that the reduction in body fat stores resulting from an exercise program has a greater impact on circulating sex hormones (implicated in breast cancer) than exercise per se in overweight, insufficiently active postmenopausal women.[3] The independent effects of different doses of exercise on the inflammation-immune axis, as opposed to the effects of exercise-induced body composition changes, need to be more clearly delineated in future research.

With regard to exercise-induced changes in immune surveillance, Koelwyn et al cite studies in healthy populations that have reported acute and long-term changes in the number of circulating cells in specific immune cell populations and in the functioning of these cells. They show that data from the limited number of studies that have investigated the long-term effects of exercise on natural killer (NK) cell function in cancer patients are equivocal; this may be a reflection of the aforementioned methodologic differences between studies, not least of which are differences in the method of analysis (eg, chromium release assay vs flow cytometry). Additionally, immune cell function has typically been studied using in vitro techniques—and the in vitro environment is somewhat different from the in vivo environment, where different components of the innate and acquired immune system operate in concert. A key question is whether the acute effects of frequent exposure to exercise-induced demargination of leukocytes (eg, NK cells) from the blood vessel walls to the wider circulation, leading to a boost in the number of circulating cells but not necessarily to enhanced cellular function,[4] confers anticancer effects through multiple transient periods of augmented surveillance.

The authors then provide a compelling discussion of how changes in the tumor microenvironment could be influenced by exercise. This relatively unexplored area of research in human cancer patients clearly offers much potential for improving our understanding of how the immune system could be implicated in reported associations between physical activity and postdiagnosis survival. Preclinical animal studies demonstrate the impact of the tumor microenvironment on tumor-associated macrophages and neutrophils—and in particular, the role of tumor hypoxic regions in the conversion of these innate immune effector cells from antitumorigenic to immunosuppressive, protumorigenic phenotypes. Furthermore, murine studies suggest that exercise has the potential to attenuate the protumorigenic effects of hypoxic regions on infiltrating innate immune cells (perhaps by promoting microvascular changes), thereby retarding tumor progression. In the absence of human clinical studies, observational data provide indirect evidence of inhibited tumor progression in physically active men with clinically localized prostate cancer,[5] and of more regularly shaped blood vessels in the prostate tumors of men who engaged in brisk-pace walking before diagnosis,[6] which is consistent with this hypothesis. A limited number of investigations have focused on exercise as a modulator of the adaptive immune response in cancer, and further studies of exercise-induced changes in intratumoral dendritic cell antigen recognition and intratumoral T-cell phenotype and function are clearly warranted.

In conclusion, this insightful overview of current evidence shows how exercise at the right dosage could provide a potent stimulus for acute changes and long-term adaptations in numerous biological pathways that influence tumorigenesis. Sallis[7] pondered: “If we had a pill that conferred all the confirmed health benefits of exercise, would we not do everything humanly possible to see to it that everyone had access to this wonder drug? Would it not be the most prescribed pill in the history of mankind?” Over the last 10 years, since the seminal publication of Holmes et al in the *Journal of the American Medical Association*,[8] a growing body of observational evidence has provided further support for an inverse association between postdiagnosis physical activity and disease recurrence, cancer-specific mortality, and/or overall mortality in cancer survivors. A deeper understanding of how exercise modulates the biological pathways of tumor progression would provide a more solid foundation for public health interventions aimed at primary and secondary cancer prevention, and could also inform novel pharmacologic therapies designed to target the same pathways.

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