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RUNNING FROM CANCER: A ROLE FOR EXERCISE-MEDIATED CONTROL OF CANCER THROUGH REGULATION OF IMMUNE FUNCTION

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KEY WORDS: Exercise; physical activity; inflammation; NK cells; tumor growth

INTRODUCTION

The benefits of engaging cancer patients in an active lifestyle and exercise training despite their cancer disease are becoming increasingly evident. At present, more than 100 exercise intervention studies in cancer patients have reported favorable effects on both patient-reported outcomes and physical functioning, when exercise is performed during or after anti-neoplastic therapy⁽¹⁾. Moreover, early evidence from observational studies has shown that physical activity reduces the risk of disease recurrence in colorectal, prostate and breast cancer patients (2-4), suggesting that exercise has a direct effect on tumor growth.

In addition to the clinical training intervention studies, a number of preclinical studies have shown that exercise training can directly affect tumor growth. To this end, more than 80 different preclinical studies in rodents have investigated the impact of exercise on tumor incidence and tumor growth, and the vast majority of the studies shows that voluntary wheel running, treadmill running or swimming can reduce tumor growth in rodents⁽⁵⁾. Yet, in order to further elucidate that basis for this training-dependent suppression of tumor growth, understanding of the underlying molecular mechanisms is warranted.

Control of tumor initiation and growth through exercise-dependent regulation of cytotoxic immune cells

We have recently shown that voluntary wheel running in mice could reduce tumor growth with 50-60% across a range of genetic and transplantable murine tumor models⁽⁶⁾. This exercise-dependent suppression of tumor growth was associated with an in-

• 53

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crease in intratumoral immune cell infiltration, in particular of cytotoxic natural killer cells (NK) and T cells. To explore the importance of this enhanced immune cell infiltration, we repeated the voluntary wheel running studies in mice depleted of NK cells or mice lacking T cells. While the more than 50% reduction in tumor growth with wheel running persisted in mice lacking T cells, this exercise-dependent suppression of tumor growth was completely abolished in mice depleted of NK cells. These results highlight the pivotal role of NK cells in driving the exercise-mediated suppression of tumor growth.

We went on to characterize how wheel running regulated intratumoral immune cell infiltration⁽⁶⁾. First, NK cells are mobilized to the circulation through increased blood flow and epinephrine induction during exercise⁽⁷⁾. In line with this, blockade of β -adrenergic signaling during the exercise intervention blunted the exercise-mediated tumor suppression and immune cell infiltration into the tumors of the running mice. In addition, we found that wheel running increased the immunogenic profile of the tumor and redirected trafficking of the mobilized immune cells into the tumors through an IL-6-dependent mechanism. IL-6 is released from contracting muscles during exercise, and this muscle-derived myokine release points to a role for muscle to immune cell cross talk during exercise⁽⁶⁾.

TRANSLABILITY TO CANCER PATIENTS

While this preclinical study was the first to link exercise to cancer control through mobilization of cytotoxic immune cells, it has long been recognized that exercise regulate immune cell mobilization in humans. Based on an extensive amount of studies in humans, a consistent picture of a rapid and general mobilization of NK cells during exercise is evident⁽⁷⁾. While NK cells are the most responsive immune cells to the exercise-dependent mobilization, cytotoxic T cells and to a lesser extent B cells are also mobilized to the circulation during exercise. This exercise-dependent mobilization relies on β -adrenergic signaling, thus the performed exercise must be of an intensity associated with increases in catecholamine levels and heart rate to elicit this response⁽⁷⁾. Once mobilized, these cytotoxic immune cells survey the body for transformed cells as immunological targets.

The consistency of the exercise-dependent mobilization of immune cells, in particular NK cells, is highlighted by the fact that this response is observed across all ages and in both genders, as well as in lean and obese individuals, and trained and inactive people. In fact, any variation in the exercise-dependent NK cell mobilization response is more likely to reflect a barrier in exercise performance than a functional deficit in NK cell mobilization. Despite the general understanding of immune cell mobilization with exercise, very little is known in cancer patients. Only one study has characterized the acute mobilization of NK cells, and finds that breast cancer survivors are able to mobilize NK cells equivalent to that observed in age-matched control subjects⁽⁸⁾. Yet, the study also documented that the rest-

ing levels of NK cells were slightly reduced in the breast cancer survivors due to preceding chemotherapeutic therapy⁽⁸⁾. We have studied immune cell mobilization in patients with cancer in the esophageal-gastric junction receiving neoadjuvant chemotherapy. These patients are generally more fragile and symptom-ridden than the breast cancer survivors, yet our experience shows that these patients can also mobilize large amounts of cytotoxic immune cells. In fact, 35 min of interval-based cycling induced a 3-7 fold increase in circulating NK cells (unpublished data).

MAKING TUMORS MORE IMMUNOGENIC

The clinical potential of exercise-mediated immune cell mobilization is emphasized by the huge focus on cancer immune therapy. Currently, the introduction of immune therapy in cancer therapy is revolutionizing the treatment of cancer patients⁽⁹⁾. Immune check point blockers can relieve the brake that some tumors are placing on cytotoxic immune cells by interfering with the immune check point receptor-ligand interaction (e.g. PD-1 and PD-L1). Clinical insight from the first trials with these drugs shows that the immune check point blockers are most efficient if the tumors are highly immunogenic. Thus, approaches aimed at generating an inflammatory intratumoral environment may promote the efficacy of these drugs. In the tumors from the above-mentioned study⁽⁶⁾, we found that voluntary wheel running delivered such therapeutic adaptations within the tumors, as we observed an exercise-dependent regulation of the expression of various immune check point receptors, chemokines and cytokines, all adding to the observed enhanced immune cell infiltration. Thus, exercise supports cancer patients' immune function and may reinforce the effect of immunotherapeutic strategies. This demonstrates how insight into the mechanistic effects of exercise might govern the use of targeted exercise in combination with conventional treatments. However, this field is only just starting to attract attention and far more research is warranted to fully understand the synergistic effects of exercise and different modalities of anti-cancer therapies.

• 55

CONCLUSION

Our results underline that molecular and systemic changes occurring during exercise can directly target cancer cells, controlling their initiation and progression. Our results demonstrate that an exercise-mediated mobilization and activation of cytotoxic immune cells, in particular NK cells, plays a pivotal role in this control of tumor growth. If these exercise-dependent molecular and immunogenic effects can also regulate direct anti-cancer effects

in cancer patients, incorporation of exercise therapy into standard oncological treatment is highly warranted. Conceptually, this places exercise training within anti-cancer treatment strategies, rather than the current focus of exercise as supportive care and rehabilitation for cancer patients.

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