CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Muscling In on Cancer

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Hippocrates is reported to have said, "Walking is man's best medicine." Regular exercise, including daily brisk walking, is associated with a lower risk of several cancers and with lower risks of tumor recurrence and death among survivors, particularly of colorectal and breast cancers. Data suggest a potential dose-dependent benefit of exercise against colon cancer and possibly postmenopausal breast cancer. People with the highest exercise loads have a 40% lower cancer-related mortality than the general population.[1] But all these findings are ones of association: persons who exercise may engage in other healthy behaviors or have better access to medical services, leading one to wonder whether exposure to exercise has antitumorigenic effects. If it does, what are the mechanisms involved? A study conducted by Pedersen and colleagues in a mouse model provides some clues.[2]

Several indirect mechanisms may mediate exercise benefits against cancer. Exercise decreases the expression of oncogenes, reduces circulating sex hormones, induces antioxidant defense pathways, and helps combat several metabolic conditions, such as adiposity, chronic inflammation, and insulin resistance — all factors that have been associated with some types of cancer. Exercise also induces more direct effects. For example, during an acute bout of exertion, contracting muscle fibers release proteins — the so-called myokines — into the bloodstream; these myokines have beneficial effects on many organ systems, such as increasing insulin sensitivity. Some myokines also have antiproliferative effects: they can induce apoptosis in the cells of some tumors.[3,4]

A myokine that is behind some of the systemic benefits of exercise is interleukin-6, and the study by Pedersen and colleagues has shown its antitumorigenic effects. Using a model of voluntary (wheel) running in mice, the authors found that exercise training for 6 weeks reduced the incidence and rate of growth of several types of tumors (melanoma and liver and lung cancers). The suppressed growth rate was associated with a greater number of certain types of lymphocytes, including natural killer cells, that were present in these tumors. This phenomenon was mediated by the coupled effect of exercise-induced release into the bloodstream of interleukin-6 from working muscles and epinephrine from the adrenal glands, which resulted in an epinephrine-dependent mobilization of interleukin-6–sensitive natural killer cells that then migrated into tumors (Fig. 1). However, injection of interleukin-6 alone failed to induce the infiltration of natural killer cells into tumors or a reduction in tumor growth. This latter finding provides support for the beneficial effects of muscle-derived interleukin-6 in the exercise milieu. The role of interleukin-6 in cancer is, however, complex; tumor-derived interleukin-6 has a protumorigenic effect.[5]

Natural killer cells, a critical component of innate immune defense, are being evaluated as antitumor cell therapy in several clinical trials. Such cells participate in the first phase of surveillance against nascent tumors by destroying proliferating tumor cells and priming the environment for adaptive immunity.[6] Pedersen et al. found that exercise did not enhance natural killer cell cytotoxicity but instead prepared the tumor environment for the infiltration and accumulation of these cells by enhancing the expression of ligands for natural killer cell–activating receptors on the surface of tumor cells.

The finding that contracting muscle fibers

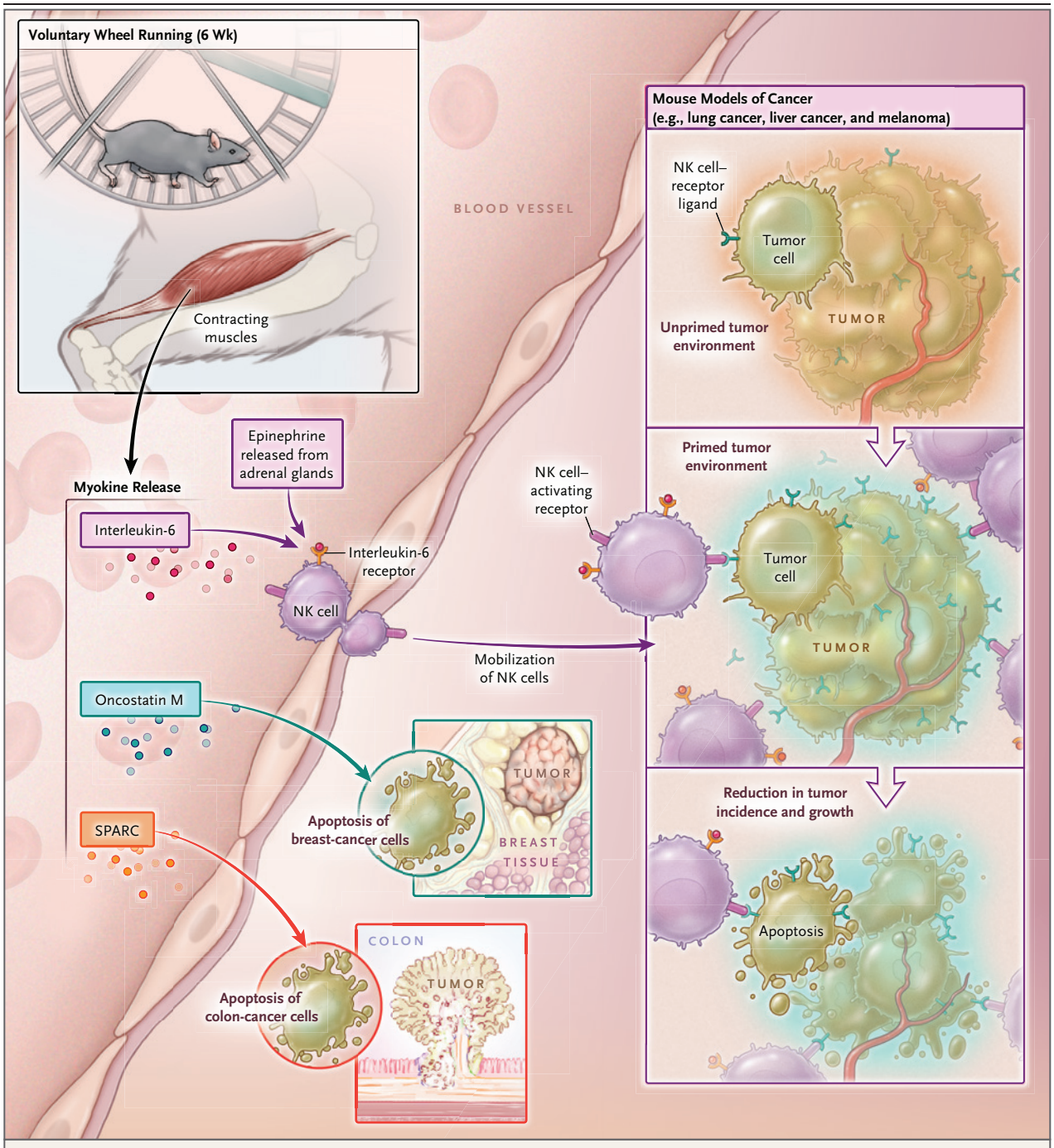

Figure 1. Anticancer Effects of Myokines.

Contracting muscle fibers release myokines, such as oncostatin M and SPARC (also known as osteonectin), into the bloodstream, which can induce apoptosis in breast-cancer and colon-cancer cells, respectively. Recent data from a study by Pedersen and colleagues[2] in mouse models of melanoma and liver and lung cancers support the antitumorigenic effects of another myokine, interleukin-6, which has elevated levels after exercise. The coupled action of interleukin-6 and epinephrine in the blood results in the increased mobilization of natural killer (NK) lymphocytes, which migrate into tumors and destroy tumor cells. Exercise training seems to prepare the tumor environment for the action of these cells by enhancing the expression of ligands for receptors of NK cells.

synthesize anticancer myokines is tantalizing. However, the work of Pedersen and colleagues must be replicated by others and tested for its relevance to the human condition before experimental strategies involving exercise would be warranted.

Disclosure forms provided by the authors are available at NEJM.org.

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DOI: 10.1056/NEJMcibr1606456