INFLAMMATION

Exercise protects against cardiovascular disease by modulating immune cell supply

“physical activity exerts beneficial effects by altering HSPCs via modulation of their niche, leading to a reduction in the systemic supply of inflammatory leukocytes”

The precise mechanisms underlying the cardiovascular benefits of regular physical activity are incompletely understood. In a study published in *Nature Medicine*, Nahrendorf and colleagues now show that habitual voluntary exercise reduces the proliferation of haematopoietic stem and progenitor cells (HSPCs) in mice, which results in a reduced output of inflammatory leukocytes in the circulation, diminished cardiovascular inflammation after myocardial infarction and reduced atherosclerotic plaque inflammation. By contrast, a sedentary lifestyle accelerates the leukocyte supply to atherosclerotic plaques in both mice and patients with atherosclerosis.

“The bone marrow and HSPCs that produce leukocytes are important in cardiovascular health,” explains Nahrendorf. Leukocytosis and chronic inflammation are both associated with increased risk of atherosclerosis. “Likewise, sedentary behaviour associates with increased incidence of myocardial infarction,” he adds. Given that the mechanisms by which physical activity affects the immune and cardiovascular systems are unclear, Nahrendorf and colleagues set out to test how regular exercise influences the production of inflammatory leukocytes, which then

can travel to atherosclerotic plaques or the diseased heart. Previous studies showed that endurance training increased haematopoiesis and cell mobilization from the bone marrow and led to leukocytosis in mice. “Those studies had used forced exercise, which is probably stressful,” points out Nahrendorf. As stress can increase HSPC activity, the researchers used a different protocol whereby running wheels were placed in the cages and mice were free to exercise as desired.

Analysis of the mice after 6 weeks showed that habitual voluntary running increased activity by 20-fold and promoted HSPC quiescence in exercising versus sedentary mice. In addition, compared with sedentary mice, exercising mice had lower levels of HSPC proliferation, less formation of myeloid and lymphoid colonies and fewer HSPCs mobilized to the circulation. The reduction in HSPC proliferation and leukocyte production was regulated by leptin-mediated modulation of haematopoietic niche cells in the bone marrow. Exercise reduced leptin production in adipose tissue, which resulted in decreased leptin levels in blood and the bone marrow. Reduced leptin signalling in leptin receptor-positive stromal cells in the bone marrow led to increased production of quiescence-promoting factors, which in turn reduced HSPC proliferation and leukocyte output. Withdrawal of the running wheel reversed leptin levels, but the effects of exercise on the HSPC epigenetic and transcriptional profiles persisted for several weeks. This short-term memory effect of exercise on haematopoietic cells was mediated by reduced chromatin accessibility in HSPCs in exercising mice compared with sedentary mice.

A reduction in circulating leukocytes might lead to an increased risk of infections, as has been described with acute exercise. However, the research team found that habitual voluntary exercise improved emergency haematopoiesis and improved survival during sepsis in mice. Conversely, the high blood leukocyte levels associated with sedentary behaviour might increase the risk of cardiovascular disease via increased systemic leukocyte supply. Indeed, Nahrendorf and colleagues found that sedentary behaviour accelerated the supply of leukocytes to atherosclerotic plaques in a mouse model of atherosclerosis. By contrast, habitual exercise protected mice from chronic leukocytosis but did not compromise emergency haematopoiesis after acute myocardial infarction. In addition, mice with leptin receptor deficiency had reduced inflammation, improved recovery and reduced heart failure after acute myocardial infarction compared with mice expressing the leptin receptor. Importantly, the associations between a sedentary lifestyle, leptin levels and leukocyte levels were confirmed in two independent cohorts of patients with cardiovascular disease from the CANTOS trial and the Athero-Express study.

Taken together, these results indicate that physical activity exerts beneficial effects by altering HSPCs via modulation of their niche, leading to a reduction in the systemic supply of inflammatory leukocytes. “We plan to next use this set-up for unbiased drug discovery research,” comments Nahrendorf. “Not to find the ‘exercise pill’, but drug targets that help dampen inflammation without jeopardizing our innate immune defences.”

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ORIGINAL ARTICLE Frodermann, V. et al. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nat. Med.* **25**, 1761–1771 (2019)

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