EXERCISE METABOLISM IN 2016

Health benefits of exercise — more than meets the eye!

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Although regular physical activity can prevent or reduce the risk of many age-related diseases, the molecular mechanisms underpinning the protective effects of exercise are largely unknown. In 2016, a series of studies demonstrated that crosstalk between tissues during exercise can protect against metabolic disease, cancer, retinal degeneration and memory loss. These studies provide a molecular basis for the concept of 'exercise as medicine'.

Since ~450 BC, physical activity has been known to be able to prevent chronic disease. Quotes attributed to Hippocrates, the father of Western medicine, include: "Walking is man's best medicine" and "If there is a deficiency in food and exercise the body will fall sick". Now, even short periods of physical inactivity are known to be associated with disruption of metabolic homeostasis, which manifests as decreased insulin sensitivity, reduced postprandial lipid clearance, loss of muscle mass and accumulation of visceral adiposity[1]. These acute changes provide a link between physical inactivity and an increased risk of developing many diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease, cancers such as those of the colon and breast, osteoporosis, osteoarthritis, erectile dysfunction and polycystic ovary syndrome[1,2]. The benefits of physical activity have been attributed to several mechanisms, which include reduced adiposity, increased cardiorespiratory fitness (maximal oxygen consumption (VO_2 max)), reduced levels of circulating lipids and the maintenance of muscle mass. However, in the current millennium, research has shown that, during exercise, proteins, peptides, enzymes and metabolites are released from one organ (mainly contracting skeletal muscle) to affect the metabolism in another organ.

In 2016, this paradigm was strengthened in several important studies. As exercise involves muscle contraction, most emphasis has been placed on the release of proteins from contracting skeletal muscle (so called myokines) that affect metabolic processes in other organs[3]. Exercise is known to improve brain function and cognition. In an elegant and important study, Moon *et al.*[4] initially treated L6 myotubes with the AMP-activated protein kinase (AMPK) agonist 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) in an attempt to model the effects of exercise *in vitro*. Subsequent screening of the culture media for proteins using mass spectrometry revealed the presence of cathepsin B. The investigators validated cathepsin B as a myokine by demonstrating that the levels of this protein increased in the plasma of mice, monkeys and humans during exercise. In humans, plasma levels of cathepsin B correlated with both fitness and memory. Moreover, although running improved memory and increased hippocampal neurogenesis in wild-type mice, no effect was observed in mice deficient in cathepsin B[4]. This study demonstrated that exercise can induce the release of cathepsin B from contacting skeletal muscle to modify memory and brain function (FIG. 1), which validates the hypothesis that exercise is beneficial for delaying dementia in ageing.

Although contracting muscle is undoubtedly an organ capable of releasing important proteins and metabolites during exercise, other organs could have endocrine-like properties during physical activity. In a complex study published in 2016, Mera *et al.*[5] demonstrated that bone can also drive the adaptation to physical exercise via the release of osteocalcin. The investigators demonstrated that circulating levels of undercarboxylated and bioactive osteocalcin markedly increase during exercise. Circulating osteocalcin was then shown not only to increase intramuscular glucose uptake during exercise but also to increase the production and release of the prototypical myokine IL-6, in turn increasing fatty acid availability from adipocytes and glucose production in the liver; findings that support previous studies performed over a decade ago[6,7]. The study by Mera *et al.*[5] is an important addition to the existing model of tissue crosstalk, as it uncovered a bone–muscle–liver and/or adipose tissue axis that regulates nutrient supply and demand during muscle contraction (FIG. 1). Determining precisely how bone senses muscle contraction is the next challenge in further defining this model.

Physical activity can decrease the risk and/or improve the prognosis of a limited number of cancers such as those of the colon, breast and possibly endometrium[2]. Many hypotheses have been proposed as to the mechanism underpinning the beneficial effects of physical activity on carcinogenesis. These hypotheses include: the mechanistic target of rapamycin (mTOR) network hypothesis, in which exercise inhibits carcinogenesis by suppressing

Key advances

- Cathepsin B is a contraction-induced myokine that improves memory function[4]
- Osteocalcin is released from bone during exercise to signal to skeletal muscle to release IL-6, which in turn regulates metabolic homeostasis[5]
- Exercise can reduce tumour growth in a variety of cancers in mice by mobilizing and redistributing natural killer cells[9]
- Exercise prevents the loss of brain-derived neurotrophic factor in the retina after injury to preserve neuronal function[10]

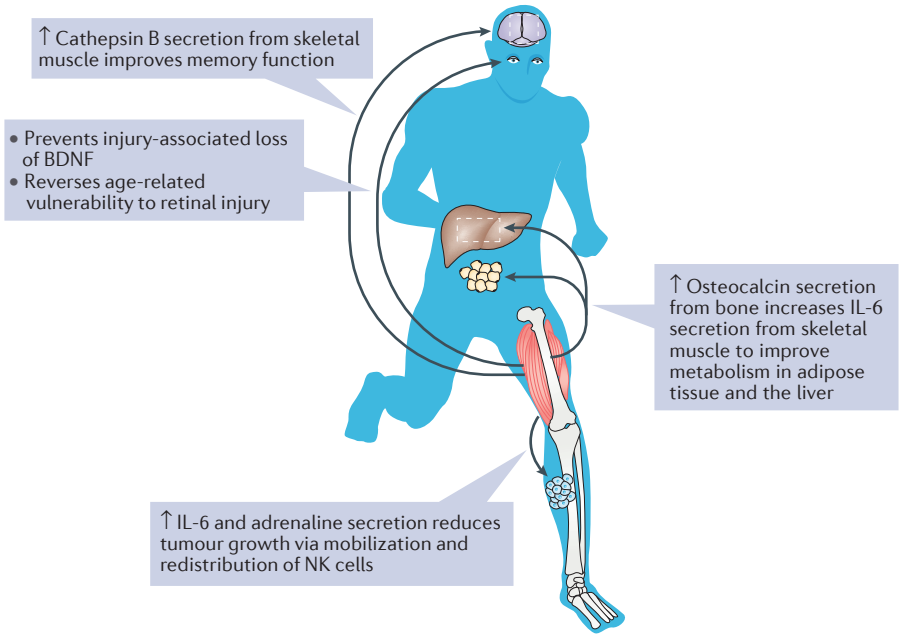

Figure 1 | **The multiple benefits of exercise.** Exercise can reverse age-related vulnerability to retinal injury, increase memory function via the myokine cathepsin B, improve metabolic homeostasis via communication between bone and skeletal muscle, and reduce tumour growth via the mobilization and redistribution of natural killer (NK) cells. BDNF, brain-derived neurotrophic factor.

activation of mTOR signalling in mammary carcinomas; the hormesis hypothesis, in which the carcinogenic response to physical activity is nonlinear and is accounted for by a physiological cellular stress response; and the metabolic reprogramming hypothesis, in which exercise limits the amount of glucose and glutamine available to mammary carcinomas, thereby inducing apoptosis due to reversal of tumour-associated metabolic programming[8]. In an important paper published in 2016, Pedersen *et al.*[9] demonstrated that exercise initiates complex hormonal and immunological responses that inhibit tumour growth in mouse models of cancer. Tumour-bearing mice were randomly assigned to cages with access to either locked or unlocked running wheels. In the latter group, the mice ran considerably longer distances over a 4-week period than mice in the sedentary (locked wheel) group. Importantly, exercise-trained mice exhibited a >60% reduction in tumour incidence and growth across five different cancer models[9]. The investigators demonstrated that, by activating the sympathetic nervous system and increasing the exercise-induced IL-6 response, a specific subset of natural killer (NK) cells were immobilized. These NK cells were subsequently redistributed to the site of tumours to control tumour growth[9] (FIG. 1). This study is important for many reasons. First, if patients with cancer can tolerate physical exercise, clinical oncologists could integrate physical activity into current treatment plans, which could have profound effects on current lifestyle intervention for successful cancer treatment. Second, as with the studies on memory and metabolic homeostasis described earlier[4,5], the study by Pedersen and colleagues provides a molecular basis for the concept of 'exercise as medicine'. Such evidence-based research might have profound public health ramifications that facilitate behavioural modification within patient populations.

Last, in an intriguing study, Chrysostomou *et al.*[10] demonstrated that exercise can reverse age-related vulnerability to retinal damage. Retinal ganglion cells are recognized to be increasingly susceptible to injury with advanced age. As levels of brain-derived neurotrophic factor (BDNF) and AMPK both increase with exercise and are thought to mediate the beneficial effects of exercise, the investigators focused on the role of these two molecules in the protective effects of exercise against retinal injury in mice[10]. The investigators demonstrated that retinal ganglion cells undergo an increase in intra-ocular pressure during exercise, which in turn preserves inner retinal synapses. Moreover, when an injury takes place in sedentary mice, levels of BDNF normally decrease, but this reduction did not occur in exercised mice. However, in mice with *BDNF* haploinsufficiency or when BDNF was pharmacologically blocked, the beneficial effect of exercise was diminished[10]. Interestingly, although BDNF can activate AMPK in skeletal muscle during exercise, the protective effects of BDNF in this model were independent of activation of this important fuel-sensing kinase[10]. Chrysostomou and colleagues justifiably concluded that their data provided new insights into the mechanism underlying exercise-mediated protection of retinal cells (FIG. 1).

In summary, these four important studies published in 2016 provide new insights into the molecular mechanisms underlying the protective effects of exercise against a myriad of diseases including dementia[4], cancer[9], obesity[5] and retinal disease[10]. In addition, by uncovering these mechanisms, the investigators have opened up the field for future identification of therapeutic targets and development of therapies for the treatment of these diseases. However, more importantly, these studies provide additional evidence that 'exercise is medicine'.

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