

Review

Exercise sustains the hallmarks of health

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Abstract

Exercise has long been known for its active role in improving physical fitness and sustaining health. Regular moderate-intensity exercise improves all aspects of human health and is widely accepted as a preventative and therapeutic strategy for various diseases. It is well-documented that exercise maintains and restores homeostasis at the organismal, tissue, cellular, and molecular levels to stimulate positive physiological adaptations that consequently protect against various pathological conditions. Here we mainly summarize how moderate-intensity exercise affects the major hallmarks of health, including the integrity of barriers, containment of local perturbations, recycling and turnover, integration of circuitries, rhythmic oscillations, homeostatic resilience, hormetic regulation, as well as repair and regeneration. Furthermore, we summarize the current understanding of the mechanisms responsible for beneficial adaptations in response to exercise. This review aimed at providing a comprehensive summary of the vital biological mechanisms through which moderate-intensity exercise maintains health and opens a window for its application in other health interventions. We hope that continuing investigation in this field will further increase our understanding of the processes involved in the positive role of moderate-intensity exercise and thus get us closer to the identification of new therapeutics that improve quality of life.

Keywords: Beneficial effects of exercise; Exercise-related physiological adaptations; Hallmarks of health; Moderate-intensity exercise; Therapeutic exercise

1. Introduction

While modernization has contributed to increased population longevity, it has also witnessed a continuous rise in non-communicable diseases such as obesity, hypertension, type 2 diabetes, cancer, *etc.* Non-communicable diseases are now considered “the number one killer” globally, as they lead

to more than 80% of deaths in certain countries.^{1,2} The prevalence of non-communicable diseases can be at least partly attributed to insufficient physical activity or exercise.³ According to data from the World Health Organization, in 2016, more than one-quarter of adults worldwide were physically inactive.⁴ The worldwide pandemic of physical inactivity should be a public health priority. It is well-known that a healthy lifestyle is associated with a significantly lower risk of total mortality and a longer life expectancy.⁵ Together with a healthy and adequate dietary pattern, exercise represents a promising strategy for reducing the risk of chronic metabolic and

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inflammatory diseases, such as those related to obesity. In general, physical activity is defined as any movement requiring energy, such as walking, manual labor, or housework. By contrast, exercise refers to a routine of physical activity that is planned and structured with the aim of improving physical fitness.⁶ In this review, we use the term “regular exercise” to refer to regular moderate-intensity exercise at a <70% maximal oxygen uptake (VO_{2max}).

It has been strongly recommended that children and adults should limit the amount of sedentary time, which is associated with adverse health outcomes, including all-cause mortality and the incidence of cardiovascular disease, cancer, and type 2 diabetes. Replacing sedentary behavior with physical activity of any intensity (including light intensity) is beneficial for health. For substantial health benefits, World Health Organization recommends adults should undertake at least 150–300 min of moderate-intensity or 75–150 min of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity.⁷ Adults are recommended to increase moderate-intensity aerobic physical activity to more than 300 min, or perform more than 150 min of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity for additional health benefits. Adults are also recommended to do muscle-strengthening activities that involve all major muscle groups for 2 or more days a week at a moderate or greater intensity.⁷ Next to aerobic activities, adults aged 65 years and older are recommended to do multicomponent physical activity that includes functional balance and strength training at a moderate or higher intensity for at least 3 days a week.⁷

There is evidence showing that 30 metabolic equivalent task-h of pre-pregnancy is associated with a 12% reduction in the relative risk of gestational diabetes mellitus, and 7 h of physical activity per week before and during pregnancy is associated with a 30% reduction and 37% reduction of risk, respectively.⁸ Additionally, 500 metabolic equivalent task-min/week of aerobic physical activity, which is equivalent to 150 min of moderate-intensity or 75 min of vigorous-intensity physical activity weekly, led to a 14% risk reduction in all-cause mortality in patients with cardiovascular disease and a 7% risk reduction in healthy adults.⁹ And children and adolescents aged 5–17 years performed an average of 60 min of moderate-to-vigorous intensity physical activity per day, which was associated with multiple beneficial health outcomes including cardiorespiratory fitness, muscular fitness, bone health, and cardiometabolic health.¹⁰

A large body of studies supports the notion that regular exercise plays an important role in reducing the risk of cardiovascular disease^{11,12} and improving the health outcomes of patients with multiple other pathologies, including obesity, type 2 diabetes, multiple sclerosis, stroke, age-related sarcopenia, and some types of cancer.^{13–18} The epidemiological studies report that a higher level of physical activity is associated with lower mortality risk in individuals with or without cardiovascular disease, yet the benefits of physical activity with

respect to mortality appear to be greater in people with cardiovascular disease as compared to those without cardiovascular disease.⁹ Moreover, regular physical activity or exercise is associated with a reduced risk of adverse health outcomes generally (e.g., disability levels, mortality) and with better survival.^{19–21} Exercise could partially reverse chronic conditions and multimorbidity related to low physical activity and can be employed as a preventive approach to improve quality of life.^{22,23} Furthermore, greater amounts and higher intensities of physical activity, as well as distinct types of physical activity (e.g., aerobic, muscle and bone-strengthening activities), are associated with multiple beneficial health outcomes (e.g., cardiorespiratory fitness, muscular fitness, bone health, and cardiometabolic health) for children and adolescents aged 5–17 years.¹⁰

Regular moderate-intensity types of exercise, such as strength, endurance, balance, flexibility, and coordination, benefit all aspects of human health and are widely accepted as a therapeutic and preventative strategy for various diseases, including cardiovascular diseases (e.g., cardiomyopathy, cardiac ischemia/reperfusion injury, heart failure), metabolic diseases (e.g., hyperlipidemia, metabolic syndrome, type 2 diabetes), neurological diseases (e.g., Parkinson’s disease, multiple sclerosis), and pulmonary diseases, *etc.*^{24,25} However, if physical exercise undercuts a minimum intensity level, no significant changes in body homeostasis are to be expected. In untrained individuals, sudden bouts of vigorous-intensity exercise can lead to adverse cardiovascular events and prolonged intense exercise may increase the incidence of infarction.²⁶ Therefore, the intensity and mode of exercise are of critical importance for producing positive effects on health.

The biology of exercise is complex and involves adaptive responses in multiple organ systems. Movement and physical activity is an evolutionary survival advantage that turns skeletal muscle into a systemic modulator to meet energy demand.²⁷ Exercise is a dynamic energy-demanding activity that not only involves the cardiovascular, respiratory, and musculoskeletal systems but also affects the immunological and endocrine systems. Despite broad investigation into the efficacy of exercise, the underlying mechanisms of its benefits remain elusive. Although quite a few papers have summarized the psychosocial and biological responses to exercise, most of them are focused on specific diseases or organ systems. To our knowledge, few studies report exercise-induced changes from the perspective of the overall “organization” of organisms as well as the underlying mechanisms.

In a recent paper, two of the co-authors of this study proposed 8 hallmarks of health: integrity of barriers, containment of local perturbations, recycling and turnover, integration of circuitries, rhythmic oscillations, homeostatic resilience, hormonal regulation, as well as repair and regeneration.²⁸ Although more investigations are needed, a wealth of evidence indicates that exercise can affect most of these hallmarks (Fig. 1). This review aimed to provide a comprehensive summary of the vital biological changes through which exercise produces beneficial effects on health. In addition, this review summarizes the mechanisms through which exercise

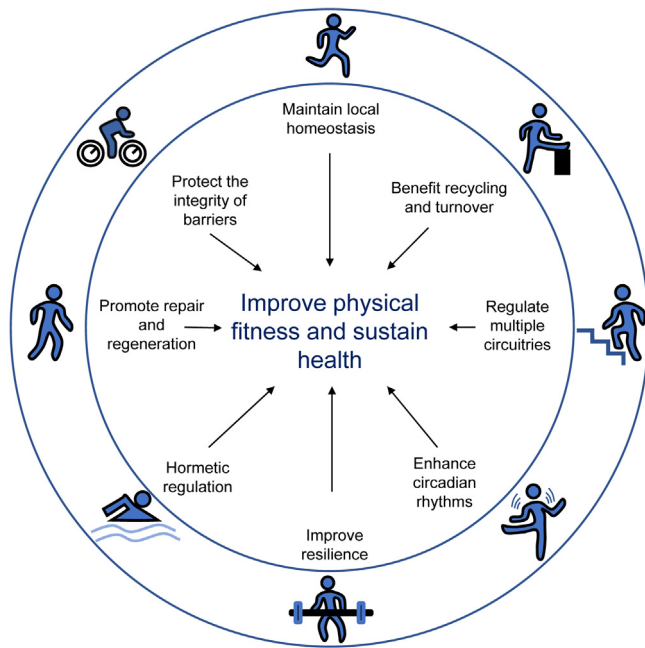


Fig. 1. Summary of the main regulatory mechanisms by which exercise sustains health. Exercise impacts the major hallmarks of health, including the integrity of barriers, containment of local perturbations, recycling and turnover, integration of circuitries, rhythmic oscillations, homeostatic resilience, hormetic regulation, as well as repair and regeneration.

interventions are effective in preventing diseases, specifically age-related diseases (Alzheimer's disease, Parkinson's disease), type 2 diabetes, cardiovascular diseases (cardiomyopathy, cardiac ischemia/reperfusion injury, and heart failure), and certain cancers (breast and colorectal cancer). For better reading comprehension, we have included [Supplementary Table 1](#), which details exercise protocols in animal studies, [Table 1](#), which details exercise protocols in human studies, and [Table 2](#), which summarizes the evidence based on the randomized control trials cited in this review.

2. Exercise protects the integrity of barriers

Human health is linked to the integrity of barriers at the level of organelles (mitochondria and nuclei), cell membranes, internal barriers (blood–brain), and barriers against the external (intestinal, respiratory, and cutaneous) environment. Exercise confers health benefits partly by regulating the integrity of these barriers, as explained below ([Fig. 2](#)).

2.1. Exercise maintains mitochondrial integrity

Mitochondrial health is of vital importance for cellular function in various tissues and, as a result, contributes to overall vitality in health and disease. Mitochondria generate cellular ATP and, thus, are key actors in whole-body energy regulation. During exercise, there is a greater demand for ATP, which is mediated by increasing mitochondrial biogenesis and enhancing mitochondrial function.²⁹ The effects of exercise on mitochondria have been intensively studied, with muscle mitochondria being the most well-studied. Exercise

training upregulates skeletal muscle sirtuins (SIRT1), which contribute to mitochondrial biogenesis and maintenance of the antioxidant system. Specifically, acute exercise (a single bout of exercise) activates SIRT1 in skeletal muscle, while several sessions of high-intensity interval training (HIIT) and aerobic or resistance exercise training activate SIRT1 and SIRT3.³⁰

Importantly, aerobic exercise causes significant changes in mitochondrial content and quality that are good for metabolic health.³¹ For example, the number of myonuclei is increased in rats in response to resistance training, and this increase can be retained for a long-term detraining period. When re-subjected to resistance training, the newly acquired myonuclei contribute to a greater degree of muscle hypertrophy and mitochondrial biogenesis.³² Taken together, these results provide further support for the assertion that exposing young muscles to resistance exercise training may help to restore age-related muscle loss associated with mitochondrial dysfunction in later life.³²

Mitochondria are also involved in calcium metabolism, contribute to the formation of intracellular reactive oxygen species (ROS), and play a leading role in the initiation of apoptosis; therefore, they are essential to maintaining cellular homeostasis and act as important signaling organelles in different tissues. Exercise may decisively influence all these mitochondrial functions.

The mitochondrial membranes represent the battleground on which opposing signals fight to determine the cell's fate. The unique lipid composition and structure of mitochondrial membranes are critical for the proper functioning of mitochondria. Quality control of mitochondrial protein synthesis plays an important role in maintaining mitochondrial integrity.³³ In particular, mitochondrial membrane permeabilization, a tightly regulated process, has been described as an essential feature of cell death.³⁴ Acute exercise, as an allostatic stimulus, causes a temporary alteration of the interaction between mitochondria and other organelles, such as the endoplasmic reticulum (ER), due to the upregulation of regulated in development and DNA damage responses 1.³⁵

The beneficial effects of exercise on health are at least partly due to the improvement of mitochondrial membrane structure and, thus, mitochondrial function. It is reported that endurance-trained athletes (e.g., cross-country and soccer players) show a higher density of mitochondrial cristae, which is related to oxygen consumption and oxidative capacity.³⁶ Both 17-week voluntary wheel running exercise and 8-week endurance training (treadmill running) confer protection against non-alcoholic steatohepatitis-induced alterations in rat mitochondrial membrane composition, as revealed by the increased ratio of phosphatidylcholine to phosphatidylethanolamine,³⁷ because the ratio is a key regulator of membrane integrity.³⁸ More recent studies indicate that 8-week endurance training could inhibit non-alcoholic steatohepatitis-induced mitochondrial permeability transition pore opening, indicating decreased mitochondrial membrane permeability.³⁹ Seven days of treadmill exercise can prevent mitochondrial outer membrane permeabilization in the rat model of cerebral ischemic injury by increasing caveolin-1 expression, thus inhibiting excessive cytochrome C release from mitochondria,⁴⁰

Table 1
The detailed exercise protocols in human studies cited in this review.

Reference	Exercise protocol	Subject	Effect	Mechanism
51	120 min cycling at 60% VO_{2max} , which is determined by an incremental ride to exhaustion on a cycle ergometer	Human	Increase fatty acid transport	Increase FAT/CD36 and FABPpm
61	1 h of treadmill running at 80% VO_{2max} , 0% grade	Human	Increase small intestinal permeability	/
62	A standard marathon (42.16 km)	Human	Increase intestinal permeability	/
64	Two 1-h-long bouts of submaximal treadmill exercise at 65% VO_{2max}	Human	Increase gut barrier permeability	/
95	45 min cycling (start with 30 min cycling at 65% of HR_{max} and progressed by 5% every other week until intensity reached 75% of HR_{max}), twice per week for 12 weeks	Human (65–86 years old)	Attenuate skin aging and enhance mitochondrial biogenesis	Increase IL-15 level
116	12 weeks combined endurance (20 min treadmill walking at 70%–80% heart rate reserve) and resistance exercise (8 sets of exercises, 2 sets at 70%–80% of one-repetition maximum, 30 min), 3 days/week	Human (65–80 years old)	Reduced systemic inflammation	Reductions in $CD14^+CD16^+$ monocytes
126	1-h cycling at 70% of VO_{2max}	Human	Increased levels of inflammatory gene	/
138	Three 30-min bouts of cycling exercise at –5%, +5%, or +15% of lactate threshold	Human	Augment cytotoxicity against tumor cells	Enhanced NK cell activity
188	Marathon (a 42.2-km running race)	Athlete	Increased plasma level of GDF15	Changes in circulating immune cells levels
190	1 h cycling exercise at 67% of VO_{2max}	Human	Increased plasma level of GDF15	/
234	Maximal exercise test, start cycling with a 75 W load for 3 min (warm-up stage) followed by increments of 25 W every 3 min until volitional exhaustion	Human	Significant modulation of clock genes in effector-memory $CD4^+$ T cells	/
322	3 months of moderate exercise involving a combination of treadmill or cycling, each exercise session included 10 min warm-up and cool-down steps at 50%–60% of HR_{max} , along with 40 min of the prescribed exercise program at 65%–80% of HR_{max} , 3 times/week	Obese human subject ($30 \text{ kg/m}^2 \leq \text{BMI} < 40 \text{ kg/m}^2$)	Alleviate obesity-related ER stress	Downregulate GRP78 signaling

Note: / stands for unknown.

Abbreviations: BMI = body mass index; ER = endoplasmic reticulum; FABPpm = plasma membrane fatty acid-binding protein; FAT = fatty acid translocase; GDF15 = growth differentiation factor-15; GRP78 = glucose-regulated protein 78; HR_{max} = maximal heart rate; IL-15 = interleukin-15; NK cell = natural killer cell; VO_{2max} = maximal oxygen uptake; W = watt.

reducing mitochondrial damage, and protecting mitochondrial integrity. In addition, 12 weeks of moderate-intensity treadmill exercise exerts cardioprotection in diabetic mice by down-regulating mammalian sterile 20-like kinase 1, which enhances mitochondrial membrane potential.⁴¹

2.2. Exercise and the sarcoplasmic reticulum (SR)

The SR is a structure involved in Ca^{2+} mobilization for muscle contraction. Disruption of the SR is implicated in muscular dystrophy, cardiomyopathy, sarcopenia due to aging, and neurodegenerative diseases.⁴² Exercise decreases lipid peroxidation and calpain activity in the SR, thereby preventing heat stress.⁴³

2.3. Exercise and nuclear envelope (NE) integrity

The double membrane structure of the NE serves as a barrier that separates the genome from the cytoplasm in

eukaryotic cells. Disruption of the NE and exposure of chromatin endanger cell viability and induce genome instability. Thus, the integrity of NE is critical for cell survival. The NE homeostasis is maintained through a balance between the various forces imposed upon the nuclei, which can be disrupted under certain conditions (e.g., alterations in the expression of lamins, migration and invasion, micronuclei, telomere fusion, heterochromatin modulation, virus infection, the loss of ATR, retinoblastoma protein or p53) resulting in transient NE collapse.⁴⁴

Few studies have focused on the role of exercise on NE integrity. The NE provides a semi-permeable barrier, with its structural integrity being maintained partly by the intermediate filament proteins called lamins (A, B, and C), which are encoded by the *LMNA* gene. Six weeks of moderate exercise attenuates dilated cardiomyopathy development in heterozygous *LMNA* knockout (*LMNA*^{+/-}) mice whose cardiomyocytes

Table 2
Effects of exercise on health outcomes in humans with different conditions.

Reference	Design	Participant condition	No. of participants	Age (year; mean \pm SD)	Intervention	Outcome
57	RCT	Woman living in a nursing home support center; capacity to practice exercise without causing harm to themselves with approval of the medical department	25 (C = 12; I = 13)	C = 82.0 \pm 7.5; I = 83.5 \pm 7.3	14 weeks of combined resistance (e.g., front squat, bench over row, standing reverse fly, <i>etc.</i>) and aerobic exercise training (e.g., stimulated walking, hip marching, standing rear leg extension, <i>etc.</i>) twice a week	Maintained concentrations of peripheral markers for BBB integrity and improved cytokine balance
77	RCT	Patients with moderate-to-severe COPD	30 (C = 15; I = 15)	>40 ^a	30 min of respiratory muscle-stretching exercise (intervention group) or upper and lower limb muscle-stretching (control group), followed by 30 min of aerobic training (treadmill running), twice a week for 12 weeks	Aerobic training combined with respiratory muscle-stretching increases the functional exercise capacity with decreased dyspnea in patients with COPD
89	RCT	Healthy young adults	16	24 \pm 5	A 30-min CE and a 60-min IE (1-min work and 1-min rest) at 70% of their maximum work rate on separate occasions in a random order	The 30-min CE caused mild airway damage, while a time- or work-matched IE did not
97	RCT	Patients with venous leg ulcers	59 (C = 30; I = 29)	71.5 \pm 14.6	12 weeks of home-based progressive resistance exercise	A trend toward healing at a faster rate and better functional outcomes
98	RCT	Healthy adults	28 (C = 15; I = 13)	61.0 \pm 5.5	1 h exercise per day (start with 10 min of warm-up floor exercises and stretching, followed by 30 min cycling, 15 min of brisk walking and/or jogging and arm-strengthening exercise, 5 min of cool-down exercise), 3 days per week for 3 months	Enhance rates of wound healing
132	RCT	Healthy adults	144 (Cardio = 74; Flex = 70)	69.9 \pm 0.4	10-month cardio intervention (began at 45%–55% of VO _{2max} and progressed to 60%–70% of VO _{2max} within 3 months, 3 days/week, the duration of each session increased from 10–15 min to approximately 45–60 min by the 4th month) was compared to Flex intervention (2 days/week for approximately 75 min/session)	Cardio intervention resulted in a longer-lasting seroprotective response to influenza vaccination

^a The data are not mean \pm SD.

Abbreviations: BBB = blood–brain barrier; C = control; Cardio = cardiovascular exercise group; CE = continuous exercise; COPD = chronic obstructive pulmonary disease; Flex = flexibility and balance group; I = intervention; IE = intermittent exercise; RCT = randomized controlled trial; VO_{2max} = maximal oxygen uptake.

show altered nuclear shape.⁴⁵ The selectivity of the transit channel is controlled by the proteins of the nuclear pore complex.⁴⁶ It has been reported that 4 months of running wheel exercise is capable of preventing the decline of Lamin B1 and nuclear pore complex protein in older sedentary mice,⁴⁶ indicating that exercise can help sustain the integrity of the NE.

2.4. Exercise and plasma membrane (PM) integrity

PM integrity is essential for cellular function and survival. Besides serving as a physical barrier between the extra- and intra-cellular environment, the PM bridges intracellular signaling and extracellular signals (e.g., ions, hormones, cytokines, enzymes), thus allowing for cellular communication with the

surrounding environment. Rupture of the PM can have deleterious consequences on a cell's fate. Cells are equipped with repair mechanisms to ensure membrane integrity, including membrane fusion and replacement strategies, means for removal of the damaged membrane, and protein-driven membrane remodeling and wound closure methods.⁴⁷ Exercise can induce changes in the lipid composition of membranes that affect fluidity and cellular function.⁴⁸ For example, a 2-week course of treadmill exercise (13.5 m/min, 10% grade, 50 min/day) administered to high-fat diet (HFD)-fed mice prevents cholesterol accumulation in the PM of skeletal muscle cells.⁴⁹ The excess of PM cholesterol may contribute to insulin resistance in the skeletal muscle of mice who are fed an HFD.⁵⁰ Moreover, acute endurance exercise (120 min) is capable of

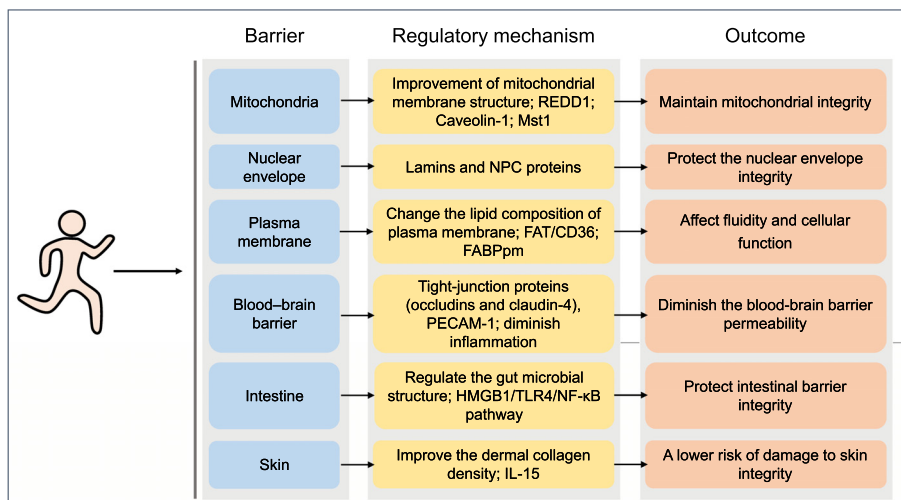


Fig. 2. Effects of exercise on the integrity of barriers and the underlying mechanisms. The biological changes of barriers through which exercise sustains health. FABPpm = plasma membrane fatty acid-binding protein; FAT = fatty acid translocase; HMGB1 = high mobility group box 1; IL-15 = interleukin-15; Mst1 = mammalian sterile 20-like kinase 1; NF-κB = nuclear factor-kappa B; NPC = nuclear pore complex; PECAM-1 = platelet and endothelial cell adhesion molecule 1; REDD1 = regulated in development and DNA damage 1; TLR4 = toll-like receptor 4.

increasing the expression of fatty acid translocase/CD36 and PM fatty acid-binding protein in human and rat muscle, indicating increased fatty acid transport in exercised muscle.⁵¹

2.5. Exercise supports the integrity of the blood–brain barrier (BBB)

The BBB is an active interface that separates systemic circulation from the central nervous system with a dual function: the barrier limits the entry of blood-derived potentially toxic or harmful substances into the brain, and the carrier function is responsible for the transport of molecules and cells into and out of the central nervous system as well as for the removal of metabolites. Every cell type (e.g., endothelial cells, astrocytes, pericytes) and extracellular matrix makes an indispensable contribution to the BBB's integrity.⁵² Specifically, pathways like Wnt/β-catenin, sonic hedgehog, retinoic acid, angiopoietins, and others are involved in the regulation of barrier maintenance.⁵³

Exercise has been shown to maintain BBB selective permeability in health and disease.⁵⁴ For example, a previous study showed that both strength training and endurance training exercises could prevent BBB disruption in a mouse model of multiple sclerosis by increasing the expression of tight-junction proteins (occludins and claudin-4) and decreasing the expression of platelet and endothelial cell adhesion molecule 1.⁵⁵ Moreover, exercise can protect against BBB disruption occurring in the context of substance use disorders.⁵⁶ Of note, in a clinical trial, a 14-week-long combined resistance and aerobic exercise training intervention is capable of maintaining BBB integrity and decreasing chronic inflammation in older women.⁵⁷ Mechanistically, regular exercise may diminish BBB permeability by enhancing antioxidative capacity, reducing oxidative stress, diminishing inflammation, enhancing neurotrophic factors such as brain-derived neurotrophic factor

(BDNF), and improving tight junction.^{54,55,58} On the other hand, the BBB has a selective permeability in order to receive systemic signals. Acute exercise increases phosphoinositide 3-kinase (PI3K)-p110α protein in the hypothalamus, enhancing the regulation of food intake.⁵⁹

2.6. Exercise effects on intestinal barrier integrity

The intestine acts as a barrier to the external environment that defends against the invasion of pathogens and harmful food ingredients. The intestinal epithelial tight junction proteins (e.g., occluding, claudins, zonula occludens) and gut microbiome play a pivotal role in the maintenance of barrier integrity.⁶⁰ Accumulating evidence suggests that exercise affects the integrity of the intestinal barrier. For instance, small intestinal permeability is increased in healthy individuals after 1 h of treadmill running at 80% VO_{2max} .⁶¹ Moreover, a significant increase in intestinal permeability has been observed in participants immediately after completing a standard marathon (42.16 km).⁶² Gut barrier permeability was elevated in runners who completed two 1-h-long bouts of submaximal treadmill exercise (65% VO_{2max} , determined by a graded treadmill test⁶³) under normoxic and hypoxic conditions.⁶⁴ Similarly, endurance exercise (1100 miles in 10 days) is associated with increased intestinal permeability in racing dogs.⁶⁵ Another study reports that mice subjected to acute treadmill running at 80% VO_{2max} (determined by a progressive exercise test on a small rodent treadmill) until exhaustion (running for at least 30 min) exhibit increased permeability in the small intestine.⁶⁶

Intestinal barrier permeability is impaired under heat stress⁶⁷ and with strenuous exercise⁶⁸ due, in part, to visceral hypoperfusion during exercise. Of note, glutamine supplementation appears to attenuate intestinal permeability and maintain intestinal integrity in response to a 60-min treadmill run at

70% of $\text{VO}_{2\text{max}}$ in an environmental chamber set at 30 °C with 40%–45% humidity.⁶⁹ It has also been shown that 5 weeks of combined aerobic and resistance training counteracts HFD-induced rat microbial dysbiosis, thus protecting intestinal barrier integrity.⁷⁰ Furthermore, 6 weeks of aerobic exercise (10 m/min for 30 min/day, 6 days/week) can protect against obstructive jaundice-induced intestinal mucosal barrier damage in mice.⁷¹ Mechanistically, exercise increases the level of endogenous H_2S and inhibits the high mobility group box 1–toll-like receptor 4–nuclear factor-kappa B pathway, thereby protecting the intestinal mucosal barrier.⁷¹ Also, 7 weeks of swimming exercise (1 or 1.5 h/day for 5 days/week) attenuates the effect of dextran sulfate sodium–induced rat intestinal aggression by improving crypt status through regulating inflammation, oxidative stress, and apoptosis.⁷² Moreover, training improves zonula occludens 1, occludin, claudin-2, and the intestinal peptide transporter-1 messenger RNA expression.⁶⁸ Thus, physical exercise has an ambiguous, context-dependent effect on intestinal barrier integrity.

2.7. The effects of exercise on the barrier integrity in the respiratory tract

The respiratory system, roughly divided into the upper (nasal passages, pharynx, and larynx) and the lower (trachea, bronchial tree, and lungs) respiratory tract, provides a physical, secretory, and immunologic barrier to exclude harmful substances such as ozone, particulate matter, pathogens, *etc.*⁷³ As a mucosal organ system in direct contact with the external environment, protection of the respiratory barrier is vital to human health. The mechanisms contributing to increased epithelial permeability involve internal (type 2 cytokines such as interleukin-4 (IL-4) and IL-13), external (environmental molecules such as allergens, pathogens, and pollutants), genetic (e.g., protocadherin-1, cadherin-related family member 3, or somuroid-like 3), and epigenetic (e.g., DNA methylation, histone deacetylases) factors.⁷⁴

Although exercise can trigger bronchial hyperresponsiveness in cold and dry environments,⁷⁵ it also has numerous health benefits, including its positive effects on individuals with chronic respiratory disease.⁷⁶ For example, 12 weeks of aerobic exercise (30 min of treadmill running) combined with respiratory muscle stretching improves the functional exercise capacity and reduced dyspnea in patients with chronic obstructive pulmonary disease.⁷⁷ Even low levels of physical activity in older patients with cardiovascular disease are associated with decreased mortality and hospitalization from pneumonia.⁷⁸ Thus, exercise training has been recommended to support pulmonary rehabilitation in chronic disease management.⁷⁹

Exercise exerts beneficial effects on cardiovascular and respiratory diseases partly via endothelial protection^{80,81} and also by decreasing the Th2 inflammatory response of the airways.⁸² During exercise, fitness level could modulate the concentration and secretion of salivary antimicrobial proteins, which function as the first line of defense against invading microorganisms.⁸³ However, the effects of exercise on the

integrity of the respiratory tract, including epithelial and endothelial barriers, has not been investigated in detail. In fact, it is well-known that athletes have an increased risk of developing upper respiratory tract infections.⁸⁴ It seems that prolonged intensive exercise compromises the barrier function of respiratory epithelium⁸⁵ and increases the incidence of upper respiratory tract infections.^{86,87} However, this topic remains the subject of debate.⁸⁸ Otherwise, compared to continuous exercise, the matched-intensity and volume intermittent exercise leads to lesser respiratory epithelial cell damage,⁸⁹ indicating that intermittent exercise may benefit respiratory tract health.

2.8. Exercise and skin integrity

Skin is the body's primary defense structure and is composed of the epidermis and the dermis. In general, the epidermis consists of epithelial cells that are responsible for the skin barrier and thus protect from the harmful effects of the external environment, while the dermis contains the extracellular matrix that includes collagen, elastin, and glycosaminoglycans.⁹⁰ Skin integrity is restored by a complex multi-step process that includes blood clot formation, inflammation, re-epithelialization, granulation tissue formation, neovascularization, and remodeling. Skin repair requires the activation of a variety of modulators, such as growth factors, cytokines, matrix metalloproteinases, cellular receptors, and extracellular matrix components.⁹¹ Research evidence reveals that regular exercise confers advantageous effects on skin integrity. For example, an epidemiology study reports a clear correlation between skin integrity and exercise in older adults. Individuals that do not practice regular exercise have a higher risk of damage to skin integrity (27.02%) compared to those who exercise regularly (8.77%).⁹² Moreover, endurance running exercise (15 m/min for 45 min, 3 times/week for 5 months) prevents the age-associated thinning of the dermis in mitochondrial DNA mutator mice (PolG; *PolgA*^{D257A/D257A}), a model of progeroid aging.⁹³ In obese mice, 8 weeks of voluntary exercise improves the dermal collagen density and decreases the amount of subcutaneous tissue and adipocyte size.⁹⁴ A later study demonstrates that endurance exercise protects against age-associated structural deterioration of skin that compromises its barrier function in both humans and mice, and it identifies exercise-induced IL-15 as a novel mediator of skin health.⁹⁵ Functional studies indicate that daily IL-15 administration mimics some of the anti-aging effects of exercise on the skin in mice.⁹⁵

3. Exercise benefits the maintenance of local homeostasis

While a single bout of exercise may cause local perturbation, long-term moderate-intensity exercise generally contributes to the maintenance of systemic homeostasis and the improvement of health (Fig. 3).

3.1. Exercise promotes barrier healing

Skin wound healing is a major health concern. Exercise is a relatively cheap and effective strategy that could be adopted

clinically to prevent or treat damage to the skin.^{96,97} Moderate-intensity aerobic exercises have been shown to promote skin wound healing in both humans and mice.^{98,99} In addition, 4 weeks of voluntary wheel exercise decreases skin graft rejection and increases graft survival through CD4⁺ T cell proliferation and interferon- γ production.¹⁰⁰ A recent study reports that exercise-associated microRNA-122-5p (miR-122-5p) is capable of promoting wound healing via increasing capillary density in the perilesional skin tissues of mice.¹⁰¹ However, the molecular and cellular mechanisms through which exercise stimulates healing require further investigation.

Of note, the intensity of exercise could influence the healing process. For example, in a mouse study, compared to high (80% VO_{2max}) and strenuous intensity (90% VO_{2max}), moderate-intensity physical training (70% VO_{2max}) is particularly efficient in improving wound healing.¹⁰² Moreover, in diabetic mice, low-intensity treadmill exercise (12 m/min for 30 min, 5% incline, 5 days/week for 3 weeks) benefits the wound healing process, while high-intensity treadmill exercise (18 m/min for 30 min, 5% incline, 5 days/week for 3 weeks) does not.¹⁰³

3.2. Exercise prevents the invasion of foreign bodies

The invasion of foreign bodies (e.g., pathogens) represents a threat to health. Lifestyle interventions, including exercise, have been identified as an effective approach to controlling certain conditions associated with viral infection. The antiviral role of exercise has received a great amount of attention. Several scientific findings indicate that exercise training contributes to the improvement of physiological and functional parameters in patients with human immunodeficiency virus

(HIV) or acquired immunodeficiency syndrome (AIDS).¹⁰⁴ Exercise could help to prevent viral infection and/or promote viral clearance. For example, regular physical activity is associated with decreased risk of infection.^{105,106} In mice, chronic exercise at moderate intensity may have an attenuating effect on influenza infection by decreasing viral load and illness severity.¹⁰⁷ Indeed, exercise is considered to be supportive of the medical care and treatment of HIV-infected patients.¹⁰⁸

A large body of investigations has highlighted the indispensable role of the immune system in combating viral infection. Exercise is well-known to have a major effect on the functioning of the immune system. In particular, regular moderate exercise is considered to be a safe and cost-effective strategy to enhance the immune system and provide protection against pathogenic viral infection.^{108,109} Recent studies reveal that a regular program of aerobic exercise with an intensity of 55%–80% VO_{2max} is associated with increased immunological biomarkers, such as circulating leukocytes, lymphocytes, monocytes, and neutrophils, and thus helps to reduce the risk of coronavirus disease 2019.^{110,111} Aerobic exercise affects several molecules in various tissues that are involved in severe acute respiratory syndrome coronavirus 2 virus entry angiotensin-converting enzyme 2, FURIN, and transmembrane protease serine 2. However, the overall effect on the disease is not yet known.¹¹²

3.3. Exercise improves systemic inflammation

Exercise training exerts anti-inflammatory effects on the periphery and the brain.¹¹³ For example, in mice, moderate voluntary wheel running (30 days of access to wheels) attenuates colitis symptoms and reduces inflammation in response to oral

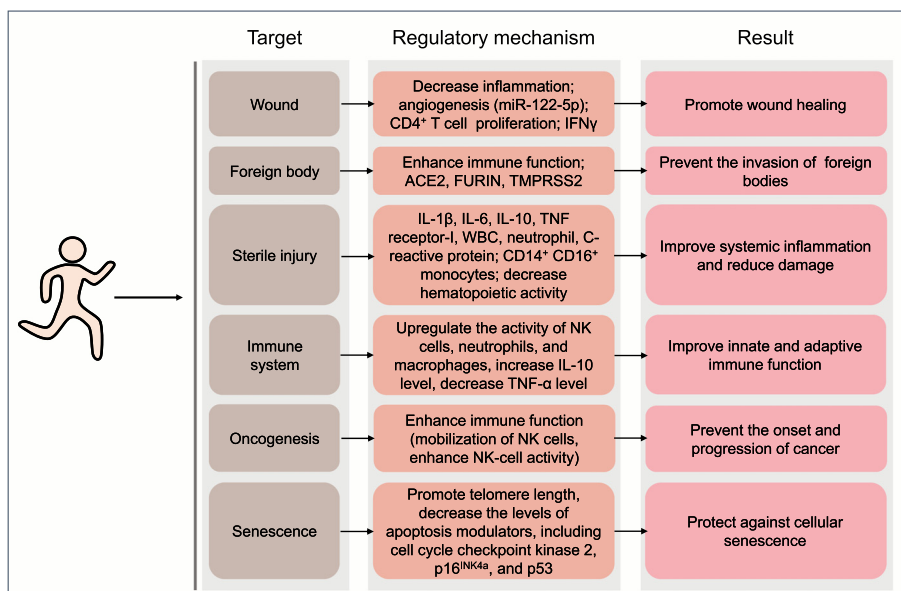


Fig. 3. Benefits of exercise on the maintenance of local homeostasis and the involved mechanisms. Regular exercise at moderate intensity generally contributes to the maintenance of systemic homeostasis. ACE2 = angiotensin-converting enzyme 2; IFN γ = interferon- γ ; IL = interleukin; miR = microRNA; NK = natural killer; TMPRSS2 = transmembrane protease serine 2; TNF- α = tumor necrosis factor- α ; WBC = white blood cell counts.

administration of dextran sulfate sodium.¹¹⁴ In addition, regular training in mice attenuates sepsis-induced lung damage; the effect is mediated by a reduced inflammatory response, modulated by decreased IL-1 β and increased IL-10.¹¹⁵

Moreover, the percentage of inflammatory CD14⁺CD16⁺ monocytes is reduced in older adults (65–80 years old) after completing a 12-week-long (3 days/week) combined endurance (20 min at 70%–80% heart rate reserve) and resistance exercise (8 sets of exercises, 2 sets at 70%–80% of one-repetition maximum) program,¹¹⁶ suggesting reduced systemic inflammation in exercised older individuals. Similarly, studies focusing on healthy adults who are aged 40 years or older show that more frequent physical activity is associated with lower systemic cellular and molecular inflammation, as evidenced by a lower level of white blood cell counts and neutrophil counts, as well as lower levels of C-reactive protein, IL-6, IL-10, IL-1 receptor antagonists, and soluble tumor necrosis factor receptor-1.^{117,118}

Furthermore, mice subjected to regular voluntary running show decreased hematopoietic activity and reduced circulating leukocyte numbers compared to sedentary mice, indicating that regular physical activity confers health benefits partially via decreased systemic inflammation.¹¹⁹ Mechanistic studies indicate that voluntary running exercise regulates hematopoietic activity via lowering leptin production in adipose tissue, augmenting hematopoietic stem and progenitor cell quiescence via modulation of their niche, and reducing the hematopoietic output of inflammatory leukocytes.¹¹⁹

3.4. Exercise and the innate and acquired immune responses

Proper immune function is fundamental for maintaining health in most chronic conditions. In recent years, the role of exercise training in regulating the immune system has received considerable attention.^{120,121} Most of the current published literature suggests that regular moderate exercise exerts a positive effect on the immune system, thus reducing the incidence of disease.¹²² Exercise modulates both innate and adaptive immune responses, particularly upregulating the activity of natural killer (NK) cells at rest¹²³ but also of neutrophils and macrophages following moderate exercise (about 60% of VO_{2max}).^{120,121,124} In addition, regular exercise is associated in healthy individuals with decreased tumor necrosis factor- α expression levels, reduced pro-inflammatory adipokine levels, downregulated Toll-like receptor levels on monocytes and macrophages, and increased circulating levels of anti-inflammatory cytokines.¹²⁵ Moreover, in healthy young men, 1 h of cycling at 70% of VO_{2max} is sufficient to induce the number of circulating peripheral blood mononuclear cells,¹²⁶ which are composed of monocytes and lymphocytes and have a critical role in immune function.^{127–129}

Of note, moderate-to-vigorous intensity endurance exercise bouts may also exert positive immunological effects.⁸⁸ For example, master athletes with lifelong regular exercise exhibit signs of anti-inflammatory regulation, as revealed by higher plasma IL-10 levels compared to the age-matched untrained control group.¹³⁰ Further investigation demonstrates that the

circulating IL-10 levels in lifelong trained athletes are similar to those in young adults.¹³¹ Moreover, clinical trials show that regular moderate exercise (60%–70% of VO_{2max}) significantly improves the immune response to vaccination in adults over age 65,^{132,133} indicating an improved adaptive immune function in older adults.

3.5. Exercise benefits the anti-cancer immunosurveillance

It is well-accepted that the immune system has the ability to suppress certain types of cancer, and immunotherapy is recognized as a promising strategy in the treatment of cancer. A sedentary lifestyle has recently emerged as a potential independent risk factor for cancer. Conversely, exercise is associated with a reduced risk of certain cancers, including colon cancer, endometrial cancer, breast cancer, *etc.*¹³⁴ Moreover, the Mendelian randomization analysis also found that genetically elevated physical activity levels were associated with lower risks of breast and colorectal cancer,^{135,136} highlighting the promotion of physical activity as a critical intervention to reduce the incidence and prevalence of these cancers. Mechanistically, exercise reduces tumor size partly via enhancing immune function. For example, tumor-bearing mice subjected to voluntary exercise (wheel running) shows a more than 60% decrease in tumor volume across different tumor models, an effect that has been attributed to the exercise-associated mobilization of NK cells, which is necessary and sufficient for this anti-tumor effect.¹³⁷ Moreover, evidence indicates acute exercise could induce a preferential redeployment of NK cell subsets with a highly-differentiated phenotype and confer protection against tumor cells.¹³⁸ Thus, exercise could play a role in the prevention and treatment of cancer.

3.6. The protective role of exercise on cellular senescence and its clearance

Cellular senescence has been linked to multiple aging-related illnesses and risk factors. Many stimuli, such as telomere erosion, oxidants, ultraviolet B light, and DNA-damaging chemotherapies that engage the DNA damage response, can induce cellular senescence.¹³⁹ Long-term endurance training upregulates telomerase activity and telomere-stabilizing proteins and decreases the levels of apoptosis modulators (including cell cycle checkpoint kinase 2, p16^{INK4a}, and p53), pointing to the protective role exercise has on cellular senescence.^{140,141}

One biomarker and effector of senescence is p16^{INK4a}. The expression of p16^{INK4a} in peripheral blood T lymphocytes increases with age.¹⁴² The level of p16^{INK4a} is positively associated with circulating IL-6 concentrations, which is a marker of cellular senescence. One recent study reports the 4-week treadmill exercise has a significant effect on attenuating senescence in white adipose tissue, as indicated by decreased p16 level. In old mice, exercise induces changes in the immune-cell distribution (e.g., NK cells, CD8⁺ T cells, eosinophils, neutrophils), which may contribute to the anti-senescence effect of exercise.¹⁴³ Since p16^{INK4a} expression is strongly correlated with reduced exercise,¹⁴² this is further evidence that exercise may prevent cellular senescence by

downregulating p16^{INK4a} expression. In the aging rat model, 12 weeks of swimming training significantly reduces the senescence markers (p53 and p21) and inflammatory cytokine (IL-6) in the liver.¹⁴⁴

However, in some settings, exercise elicits positive impacts on health via promoting senescence. As an example, the pro-senescent effect of exercise on fibro-adipogenic progenitors contributes to muscle regeneration and the improvement of muscle function.¹⁴⁵

4. Benefits of exercise in recycling and turnover

The proper recycling and turnover of different components of the organism (e.g., cell, organelle, protein) enables healthy cell and organismal development. Each of the subcellular, cellular, and supracellular units composing the organism is replaced continually by newly synthesized ones to maintain cellular homeostasis. The health benefits of exercise may be partly due to its remarkable ability to induce cellular remodeling, including cell self-renewal and turnover of dysfunctional organelles (Fig. 4).

4.1. The effects of exercise on cell death, removal, and replacement

It is reported that regular moderate exercise promotes cell survival and reduces cell death. Regular exercise is well-known to promote cardiomyocyte proliferation and growth while

preventing cardiomyocyte apoptosis. Mechanistically, the CCAAT/enhancer-binding protein β -CBP/p300-interacting transactivators with E (glutamic acid)/D (aspartic acid)-rich-carboxyl terminal domain (C/EBP β -CITED4) signaling and the insulin-like growth factor 1 (IGF1) signaling are well-established as essential regulating pathways that mediate exercise-related cardiomyocyte proliferation. Additionally, the C/EBP β and IGF1-PI3k/Akt pathways play vital roles in exercise-induced cardiomyocyte growth. Exercise also prevents cardiomyocyte death through pathways for SIRT1 and peroxisome-proliferator-activated receptor coactivator 1 α (PGC1 α) as well as for apoptosis signal-regulating kinase 1/p38 signaling, *etc.*¹⁴⁶ Moreover, 21 days of voluntary wheel running exercise is capable of enhancing cardiac myocyte survival and preventing cell death in the heart through the regulation of telomerase reverse transcriptase, endothelial nitric oxide synthase, and IGF1.¹⁴¹ Accordingly, treadmill exercise-induced myokine (Myonectin) inhibits hypoxia-induced cardiomyocyte apoptosis via activation of the cyclic adenosine monophosphate/Akt signaling pathway.¹⁴⁷ It has been reported that long-term exercise-derived plasma exosomes are capable of attenuating hypoxia/reoxygenation-induced cardiomyocyte apoptosis via exosomal miR-342-5p.¹⁴⁸ Mechanistically, miR-342-5p prevents cell apoptosis by targeting the mRNAs coding for caspase 9 and mitogen-activated protein kinase 9 (MAPK9, also known as JNK2), and it promotes cardiomyocyte survival by elevating Akt phosphorylation.¹⁴⁸ Furthermore, swimming exercise-induced long non-

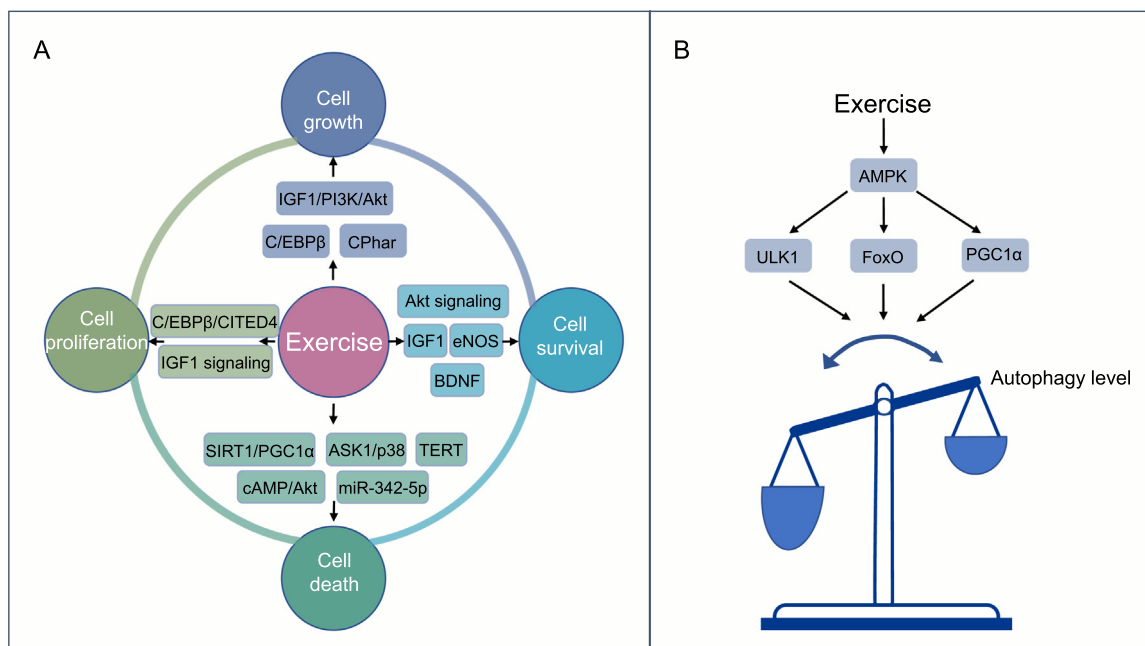


Fig. 4. Benefits of exercise for recycling and turnover. (A) The critical regulators and signaling pathways involved in the positive effects of exercise on cellular remodeling, including cell proliferation, cell growth, cell survival, and cell death; (B) The regulation of autophagy during exercise training. The common regulatory pathways underlying exercise-induced autophagy involve the activation of the AMPK-ULK1 signaling pathway, FoxO, PGC1 α , *etc.* AMPK = adenosine monophosphate-activated protein kinase; ASK1 = apoptosis signal-regulating kinase 1; BDNF = brain-derived neurotrophic factor; cAMP = cyclic adenosine monophosphate; C/EBP β = CCAAT/enhancer-binding protein β ; CITED4 = CBP/p300-interacting transactivators with E (glutamic acid)/D (aspartic acid)-rich-carboxyl terminal domain; CPhar = cardiac physiological hypertrophy-associated regulator; eNOS = endothelial nitric oxide synthase; FoxO = forkhead box O; IGF1 = insulin-like growth factor 1; miR = microRNA; PGC1 α = peroxisome-proliferator-activated receptor coactivator 1 α ; PI3K = phosphoinositide 3-kinase; SIRT1 = sirtuin 1; TERT =telomerase reverse transcriptase; ULK1 = unc-51-like kinase 1.

coding RNA (lncRNA) named cardiac physiological hypertrophy-associated regulator (CPhar), reduces oxygen-glucose deprivation/reperfusion-induced apoptosis in cultured neonatal mouse cardiomyocytes.¹⁴⁹ Finally, in rats subjected to injury of the optic nerve, 4 weeks of treadmill running (5 days per week for 30 min each day at a moderate intensity of 9 m/min) significantly increases the survival rate of retinal ganglion cells, likely due to an increase in the local expression of BDNF.¹⁵⁰

4.2. Exercise and autophagy

Virtually all eukaryotic cells depend on autophagy to maintain cellular homeostasis. Autophagy is a highly conservative recycling mechanism that is responsible for the turnover of cellular proteins and organelles. The mechanism that regulates autophagy is complex, and its upstream signaling pathway mainly includes mammalian target of rapamycin (mTOR)-dependent and mTOR-independent signaling.^{151,152} Mitophagy, a form of vital autophagic response for the turnover of dysfunctional or aged mitochondria, serves to maintain mitochondrial quality control. The regulatory mechanisms of mitophagy mainly involve putative kinase 1–Parkin pathway and receptor-mediated mitophagy.¹⁵³ In (PINK1) mammals, 2 major types of receptors have been implicated in mitophagy. One group includes BCL2 and adenovirus E1B 19-kDa-interacting protein 3 (BNIP3) and NIP3-like protein X (NIX), and the other group contains FYN14 domain-containing protein 1 (FUNDC1).¹⁵⁴

The regulation of autophagy during exercise training is a dynamic and complex process.¹⁵⁵ On the one hand, exercise promotes the level of basal autophagy and enhances cell viability. For instance, endurance exercise training (long-term voluntary running) stimulates autophagy in the skeletal muscle of mice.¹⁵⁶ This exercise-induced increase of basal autophagy is required for muscle adaptation and improvement of physical performance in endurance and resistance.^{157,158} The common regulatory pathways underlying exercise-induced autophagy involve the activation of adenosine monophosphate–activated protein kinase (AMPK)—unc-51-like kinase 1 signaling pathway, forkhead box O (FoxO), and PGC1 α , *etc.*^{159,160} On the other hand, exercise could play a role in adjusting the level of autophagy in disease states. For example, 8 weeks of treadmill exercise improves cardiac autophagic flux in a rat model of post-myocardial infarction (MI)-induced heart failure.¹⁶¹

Importantly, exercise-induced autophagy seems to mediate many of its beneficial effects.¹⁶² Thus, exercise-stimulated autophagy plays an important role in muscle glucose homeostasis. Mice with a BCL2 mutation (Thr69Ala, Ser70Ala, and Ser84Ala) that prevents this exercise-induced increase in autophagy exhibit deficient exercise endurance and deficient glucose metabolism in muscle during acute exercise. Moreover, in such B-cell lymphoma-2 (BCL2)-mutated mice, long-term exercise loses its capacity to prevent type 2 diabetes induced by an HFD.¹⁶³ It has also been found that exercise stimulates autophagy in the brain.¹⁶⁴ As compared to wild-type mice, systemic autophagy-deficient (*Atg4b*^{-/-}) mice exhibit reduced levels of resistance capacity after exercise training, and exercise-induced hippocampal adult neurogenesis is undetectable within them.¹⁵⁸

Altogether, these data highlight the essential role of autophagy in exercise-induced neurogenesis.

Nonetheless, it is worth noting that excessive exercise induces excessive autophagy.¹⁶⁵ Thus, the inhibition of autophagy reportedly alleviates heart injury induced by strenuous exercise.¹⁶⁵ Ultimately, exercise without overtraining helps to prevent the development and progression of Alzheimer's disease via improving mitochondrial fitness, which may be accomplished by mitigating mitochondrial dysfunction with SIRT1–FoxO 1/3–putative kinase 1–Parkin-mediated mitophagy.^{166,167}

5. The effects of exercise on the different circuitries

The maintenance of whole-body health involves successful crosstalk among multiple tissues and organs as well as the body microbiota at the cellular and systemic levels. Exercise evokes the coordinated and integrated adaptation of different circuitries, including the intracellular circuitries, inside–outside communication, interorgan communication, and the dialog between microbiota and the organism (Fig. 5).

5.1. Intracellular circuitries

The health-promoting effects of exercise involve a wide range of metabolic changes, which are mediated by numerous molecules, such as metabolites, proteins, non-coding RNAs, extracellular vesicles, *etc.* Firstly, exercise modifies the energy sensor AMPK.¹⁶⁸ Moreover, ketone bodies are markedly elevated in response to exercise. In addition to serving as a bioenergetic fuel, ketone bodies function as signaling metabolites and confer a variety of benefits for performance and recovery.¹⁶⁹ The transcription of genes is also influenced by exercise. For example, exercise can downregulate cardiac homeodomain interacting protein kinase 2, the suppression of which prevents the apoptosis of cardiomyocytes and protects against MI by reducing the activation of tumor protein p53.¹⁷⁰ Mice subjected to 3 weeks of swimming exercise exhibit elevated adenosine deaminases acting on RNA2, which is an enzyme that deaminates adenosine to inosine nucleotide in double-stranded RNA and functions as a protective factor in MI and doxorubicin-induced cardiac injury.¹⁷¹ Swimming exercise also upregulates the levels of cardiac miR-486 and lncRNA-CPhar, both of which confer protection against cardiac ischemia/reperfusion injury in mice.^{149,172} Furthermore, exercise can induce cytokines that prevent myocardial fibrosis.¹⁷³ Interestingly, circulating miRNAs could be considered biomarkers of the response to exercise.^{174,175}

Exercise-associated health benefits may involve epigenetic changes. For example, exercise directly modulates the epigenetics of cardiac and other tissues, thereby mitigating the risk of developing cardiac disease and conferring cardioprotective effects via exerkinases.¹⁷⁶ Exercise also improves brain health by reducing DNA methylation in the mouse hippocampus.¹⁷⁷

5.2. Inside–outside communication

The endocrine system is strongly affected by exercise. For instance, the expression of fibroblast growth factor-21

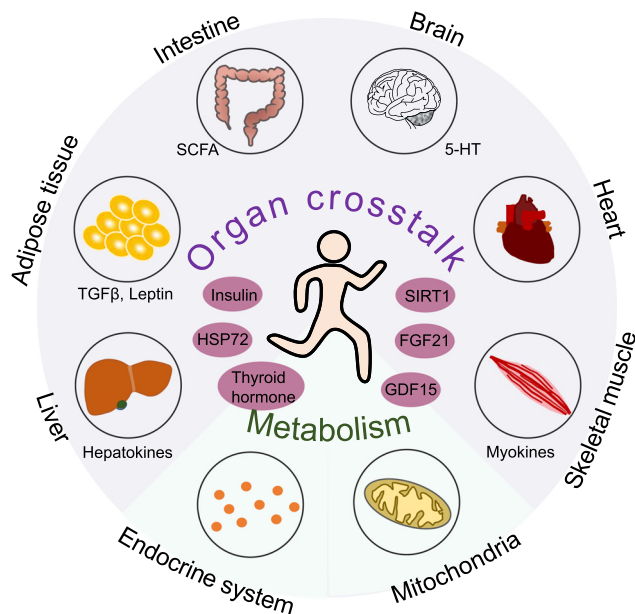


Fig. 5. Exercise has systemic effects. Exercise leads to systemic effects by evoking the coordinated and integrated adaptation of multiple organ systems. Exercise results in the secretion of myokines, adipokines (e.g., TGF β , leptin), and hepatokines as well as by-products of gut microbiota (e.g., SCFA) that have key roles in interorgan communication and, thus, mediate many of the beneficial effects of exercise. 5-HT = serotonin; FGF21 = fibroblast growth factor-21; GDF15 = growth differentiation factor-15; HSP72 = heat shock protein 72; SCFA = short-chain fatty acids; SIRT1 = sirtuin 1; TGF β = transforming growth factor- β .

(FGF21) increases in response to experimental acute exercise.^{178–182} FGF21 is an endocrine member of the FGF superfamily responsible for the modulation of energy homeostasis, glucose and lipid metabolism, and insulin sensitivity. In adipose tissue, exercise training downregulates lipid content and inflammation, promotes browning and thermogenesis, and modulates the production of adipokines.^{183–185} Treadmill exercise reportedly protects mice from HFD-induced metabolic dysfunction, including hyperglycemia, hyperinsulinemia, and hyperlipidemia, by enhancing FGF21 sensitivity in adipose tissue.^{186,187}

In addition, the plasma levels of growth differentiation factor-15 increase immediately in runners following a marathon race.¹⁸⁸ It has also been induced in response to an experimental single bout of exercise¹⁸⁹ and a cycling race.¹⁹⁰ The exercise-induced levels of circulating growth differentiation factor-15 correlate with the duration of endurance exercise.¹⁹¹

5.3. Functional units in organs

Exercise is a complex process that involves the coordinated and integrated adaptation of numerous cells, tissues, and organs. In response to chronic exercise training, organs such as the heart and skeletal muscle undergo physiological remodeling and may grow in size, which is called hypertrophy. The plasticity of the organ allows for adaptation to multiple cell types or functional units. For example, cardiac hypertrophy requires increased cardiomyocyte growth, cardiomyocyte fate

reprogramming, enhanced angiogenesis and lymphangiogenesis, mitochondrial remodeling, enhanced endothelial function, and quiescent cardiac fibroblasts.¹⁴⁶

Exercise protects against pathogenic changes in organs or tissues. For example, a 9-week treadmill exercise program has been shown to reverse the diabetes-induced ultrastructure changes in the heart. Specifically, in diabetic rats, exercise inhibits the reduction of mitochondrial mass, decreases the percentage of dysfunctional mitochondria, and prevents the increase of collagen fiber cross-sectional surface area in the heart.¹⁹² In aging rats, a 3-week treadmill exercise program increases angiogenesis, leading to improved brain function.¹⁹³ High-intensity interval exercise (5 days a week for 7 weeks)-induced increase of vascularization is mediated via the lactate receptor (hydroxycarboxylic acid receptor 1), which upregulates cerebral vascular endothelial growth factor A (VEGFA).¹⁹⁴

5.4. Organs, tracts, and systemic circuitries

Exercise induces adaptive responses throughout the entire body. For example, exercise stimulates the upregulation of heat shock proteins (HSPs),¹⁹⁵ which are a widespread family of molecular chaperones that play a variety of vital roles in maintaining cellular functions via regulation of chaperone activity, protein folding, and remodeling processes.¹⁹⁶ Specifically, HSP72 is upregulated in the circulation system and multiple organs (including the liver, skeletal muscle, heart, brain, *etc.*) in response to various forms and types of exercise.¹⁹⁷ Overexpression of HSP72 (induced by heat shock therapy, transgenesis, or specific drugs) protects against HFD-induced glucose intolerance and skeletal muscle insulin resistance.^{198,199} Moreover, induction of HSP72 in mice increases mitochondrial mass and endurance running capacity.²⁰⁰ Therefore, the upregulation of HSP72 might account for at least some of the beneficial effects of exercise on diabetes, obesity, and ischemic brain injury.^{201,202} However, the precise role of exercise-induced HSP72 expression in treating metabolic diseases warrants further investigation.

Exercise induces numerous adaptive responses in tissues and organ systems as well as with respect to interorgan communication. Many of these adaptations are observed primarily in skeletal muscle, which plays a major role in modulating whole-body functional capacity and health outcomes. In response to exercise, skeletal muscle secretes myokines, extracellular vehicles, and metabolites that facilitate crosstalk with other tissues. This crosstalk is thought to benefit the function of multiple systems and organs, such as the brain, heart, adipose tissue, gut, immune system, *etc.* It is noteworthy that the adaptive responses are not limited to skeletal muscle. Exercise also results in the secretion of adipokines (e.g., transforming growth factor β , leptin) and hepatokines as well as by-products of gut microbiota (e.g., short-chain fatty acids (SCFA)) that play key roles in interorgan communication and, thus, mediate many of the beneficial effects of exercise.²⁰³ Furthermore, exercise has been shown to modulate the composition of the gut microbiome, which may mediate improvements in both the gut and the brain. Exercise could also increase levels of

serotonin, which is a vital neurotransmitter and hormone and is involved in the regulation of intestinal secretion and motility.²⁰⁴ In addition, a recent study reported that the extracellular vesicles secreted by brown adipose tissue contribute to exercise-mediated cardioprotection by delivering cardioprotective miRNAs to the heart.²⁰⁵

5.5. *The meta-organism*

It is well-known that the gut microbiota plays an essential role in many aspects of human biology, affecting metabolism, endocrine, and immune functions. Dysbiosis of the gut microbiome is associated with multiple pathological states, including systemic inflammation, obesity, cancer, mental disorders, and others.²⁰⁶ Beyond its local effects on the barrier function of the intestinal mucosa, the gut microbiota provides several compounds and micronutrients that mediate long-range effects on the immune and neuroendocrine systems.^{207,208}

Endurance and resistance exercise have been shown to have a differential effect on the gut microbiota of mice.²⁰⁹ Moreover, a number of studies have determined that exercise influences the gut by enhancing the number of beneficial microbial species, thereby enriching microbiota diversity and functional metabolism in both humans and mice.^{206,210–212} Thus male elite professional rugby players have lower inflammatory and improved metabolic markers relative to healthy controls with a similar body mass index. As compared to controls, athletes carry a more diverse gut microbiota, and several taxa are significantly higher.²¹³ In mice, antibiotic-mediated depletion of gut microbiota compromises exercise performance.²¹⁴ In addition, monocolonization of germ-free mice with *Bacteroides fragilis*, which is a health-associated gram-negative bacterium, increases endurance exercise time.²¹⁴

In sum, exercise-induced shifts in the microbial composition of the gut may contribute to the beneficial effects of physical activity on obesity, metabolic diseases, and neurological disorders.²¹⁵ Indeed, exercise-induced alteration of the gut microbiome may regulate brain function.²⁰⁴ For example, SCFA, as microbiota-derived products, favor microglia maturation and function in the brain. Supplementation of SCFA is capable of reversing the microglial defects observed in mice lacking a healthy gut microbiota.²¹⁶

6. The effects of exercise on rhythmic oscillations

The circadian rhythms represent a number of daily oscillations in physiology and behavior that take place over a 24-h period and enable the body and brain to adapt to daily changes in the environment. Virtually all cells of the body express a molecular clock that requires extremely precise regulation. Exercise is a nonphotic cue capable of restoring the transiently disturbed clock.²¹⁷ Here we present examples of how exercise modulates the circadian rhythms.

6.1. *Mechanics of the circadian clock*

The circadian rhythms are a common trait among practically all living organisms. Accumulating evidence reveals that

disruption of mammalian circadian rhythms is deleterious to health. For instance, mice with muscle-specific deletion of *Bmal1*, which is the core clock gene, exhibit impaired insulin-stimulated glucose uptake and metabolism, indicating that disruption of the intrinsic muscle clock system leads to muscle insulin resistance.²¹⁸ In addition, night shift work-related disturbance of the circadian clock is associated with a higher risk of type 2 diabetes in humans.^{219,220}

Several reviews have highlighted the positive effects of exercise on circadian disturbances.^{221–223} In particular, exercise acts as a strong zeitgeber (time cue) for the skeletal muscle clock.²²⁴ We know that exercise is capable of readjusting the molecular circadian clock and, thus, reducing the harmful effects of disrupted sleep patterns;^{221,225} however, exercising at different times of the day can lead to markedly different stimulation of signaling pathways and exercise performance.^{226,227} In a recent study, mice exhibited better performance in the maximal running test during the early daytime, and clear differences are observed in the muscle transcriptome, proteome, and phosphoproteome patterns of mice subjected to day-time exercise as compared to those subjected to night-time exercise.²²⁸ However, few studies have focused on how to apply physical exercise to achieve the restoration of circadian rhythms or on the metabolic consequences and associated health outcomes of exercising at different times of the day.

6.2. *Exercise contributes to the maintenance of immune rhythmicity*

The immune system exhibits rhythmicity, and the rhythmic expression of clock genes has been implicated in both innate and adaptive immune cells.^{229,230} Moreover, the impairment of clock gene signaling causes chronic inflammation or aggravates the symptoms in older adults.²³¹ Evidence indicates that lifelong regular exercise (no less than 20 years) decelerates the aging-related decline of immune system function and contributes to the maintenance of circadian rhythms throughout life.^{131,232,233} In addition, clock gene expression patterns following acute exhaustive exercise are different in lifelong athletes compared to those in the sedentary group. Specifically, the acute bout of exercise modulates the clock machinery mainly in effector-memory CD4⁺ T cells.²³⁴

7. Benefits of exercise in homeostatic resilience

Physiological homeostasis is a major requisite for the survival of any organism. However, exposure to stressful life events is common. Hence, the maintenance of positive adaptation by individuals in the face of stress is important. Resistance to environmental risk experience or adaptation to stress/adversity is known as “resilience”,²³⁵ and resilience can be regulated via neural, genetic, metabolic, immunological, and microbiome-based mechanisms. Exercise appears to be a protective strategy for improving homeostatic resilience and preserving human health and a good quality of life. Engaging in exercise that leads to improved cardiorespiratory fitness can reduce the risk of various diseases, and these beneficial effects

involve the widespread adaptations of multiple tissues (Fig. 6). Here we present examples of how exercise modulates homeostatic resilience.

7.1. Neural mechanisms

The brain is the key organ of stress response. Stress and stress hormones cause both adaptive and maladaptive effects on the brain throughout life.²³⁶ Moderate-intensity exercise improves brain function and helps to maintain brain health.^{237,238} Exercise elicits a wide range of biological changes in the nervous system. In addition to alleviating clinical symptoms, the advantageous effects of exercise include improved afferent signals, autonomic balance, mitochondrial function, increased neurogenesis, and synaptic plasticity, as well as improved metabolism and angiogenesis.^{238–242}

Adult hippocampal neurogenesis is a complex and highly dynamic process that can be regulated by exercise.²⁴³ Mice subjected to endurance training (voluntary wheel running and treadmill running) and resistance training (climb the ladder) are associated with a significantly increased rate of proliferation of neural progenitor cells, indicating enhanced neurogenesis.^{158,244} Several receptor signaling cascades have been implicated in the exercise-modulated enhancement of adult hippocampal neurogenesis, including neurotrophic factors, such as BDNF and neurotransmitters.^{245,246} In addition, dexamethasone-induced Ras-related protein 1 (Dexas1), a small GTPase, modulates exercise-induced neurogenesis in the adult hippocampus. Dexas1 deletion leads to a reduced proliferation of neural progenitors, suppressed pro-mitogenic pathways, and an increased number of mature newborn granule neurons in exercised mice. At the molecular level, the deletion of dexamethasone-induced Ras-related protein 1 abolishes exercise-triggered activation of extracellular signal-regulated kinase and cyclic adenosine monophosphate response element binding protein, and it prevents the increase of N-methyl-D-aspartate receptor subunit NR2A, *Bdnf*, *Vegf-a*, and tropomyosin receptor kinase B in the dentate gyrus.²⁴⁷

7.2. Genetic factors

Genetic factors have been found to influence an individual's level of resilience. Results from adult twin studies show that between 31% and 52% of observed individual differences in resilience to stressful life events can be explained by genetic factors.^{248–250} Research suggests that the BDNF and neurotrophic tyrosine kinase receptor type 2 gene polymorphisms are associated with stress tolerance.^{251,252} In addition, the BDNF polymorphism appears to modulate exercise-induced cognitive benefits. For example, exercise-induced cognitive improvement has been observed to be more profound in terms of the mental status and word recall of individuals carrying the *BDNF Val66Met* variant than of individuals with the *BDNF Val66Val* genotype (wild type).²⁵³

Interestingly, genetic factors appear to influence exercise participation. For example, a study based on the exercise participation of 37,051 pairs of twins from 7 countries (Australia, Denmark, Finland, the Netherlands, Norway, Sweden, and the

United Kingdom) shows that the resemblance in exercise participation during leisure time of monozygotic (genetically identical) twins is higher than that for dizygotic twins, who share about half of their segregating genes on average.²⁵⁴ Moreover, genetic factors may confound the observed association between low levels of physical activity and higher disease and mortality risk.^{255–257}

In addition, several genetic polymorphisms related to elite athletes seem to be associated with exercise performance.²⁵⁸ For example, elite-level athletes show higher frequency of the IGF1 promoter T allele polymorphism.²⁵⁹ Notably, the effect of these gene variations seems to be influenced by type of exercise. The prevalence of carrying both *IL-6 G174C* and insulin-like growth factor-binding protein 3 (*IGFBP3*) *A202C* mutations is obviously higher among long-distance swimmers (major event: 400–1500 m) compared to long-distance runners (major event: 5000 m marathon), and among short-distance swimmers (major event: 50–100 m) compared to power athletes (major event 100–200 m sprinters and jumpers). The *IGFBP3 A202C* polymorphism may compensate for the potential genetically non-beneficial effect of the higher *IL-6 G174C*.²⁶⁰ In addition, the *IGF1 C1245T* (*rs35767*) single nucleotide polymorphism with the minor T allele is significantly associated with higher circulating IGF1 concentrations.²⁶¹ In summary, exercise-related genetic polymorphisms at least partly contribute to the maintenance of body health.

Of note, current Mendelian randomization studies have reported findings that conflict with those of traditional observational studies. For example, observational studies show that the level of physical activity is inversely correlated with the risk of several diseases, including type 2 diabetes and cardiovascular disease. However, the two-sample Mendelian randomization study reveals that physical (in)activity is unrelated to the risk of type 2 diabetes²⁶² and cardiovascular disease, including coronary artery disease, MI, and ischemic stroke.²⁶³ Thus, future work should pay more attention to the biological processes influenced by exercise as well as to the underlying mechanisms, which may explain the confusing results.

7.3. Hormones and metabolism

Exercise is a powerful regulator of metabolism. Generally, aerobic and resistance exercise training is associated with improved metabolic health. Organs such as skeletal muscle, the liver, the brain, and adipose tissue are important metabolic communicators, and interorgan communication during exercise contributes to whole-body homeostasis.²⁶⁴ Exercise-induced increase of energy demand is associated with increased mobilization of substrates, including carbohydrate, fat, and glucose, during and after exercise.²⁶⁵ The utilization of extracellular substrates is partly mediated by rapid and coordinated changes in the endocrine system. The hormones associated with the endocrine system exhibit autocrine, paracrine, or endocrine actions on the tissues of the body that regulate a variety of processes, such as growth and

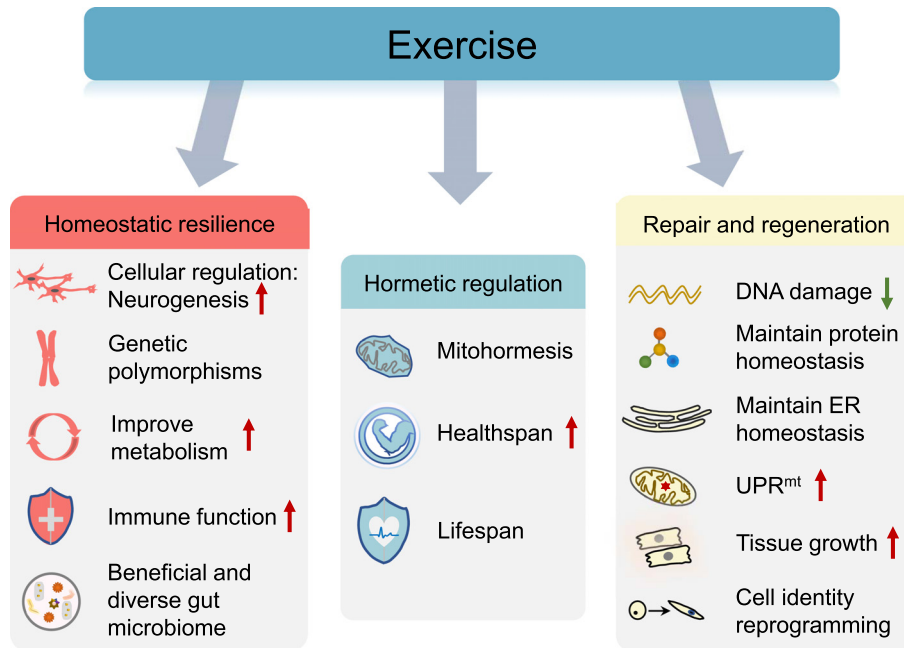


Fig. 6. Exercise-associated beneficial adaptations in response to stress. Exercise confers multiple health benefits via different strategies, including improving resilience, hormetic regulation, and modulating the process of repair and regeneration in response to damage. ER = endoplasmic reticulum; UPR^{mt} = mitochondrial unfolded protein response.

development, metabolism, and immune response.^{266,267} Exercise causes strong effects on the release of these hormone-like substances and thus the processes these substances modulate.⁶ Two major hormones whose functions are influenced by exercise are insulin and thyroid hormone. Exercise increases insulin sensitivity through several molecular pathways, including upregulation of glucose transporter protein 4 in the cell membrane of insulin-dependent cells, improvement of β cell function, modulation of insulin receptor substrate 1 phosphorylation, induction of angiogenesis, reduction in adipokines, improvement of the redox state, and downregulation of ceramide plasma levels.²⁶⁸ Therefore, exercise has been recommended as the management strategy for patients diagnosed with type 2 diabetes.²⁶⁹ Changes in thyroid hormone levels (e.g., T3, T4) are observed following exercise. However, it is hard to draw any conclusions concerning the effects of exercise on thyroid hormone.²⁷⁰ These controversial results could be due to the physical status of subjects, the type, intensity, and duration of exercise, or the differences in age and gender among subjects. In general, the effects of exercise on the endocrine system are of a positive nature and help to improve functional aspects of tissue and organs, resulting in improved health. For instance, exercise prevents the loss of activity of the endocrine system that is associated with aging.²⁷¹

Metabolic adaptation is related to the specific type and mode of exercise. For example, regular endurance exercise enhances muscle capillarity, increases mitochondrial biogenesis, and promotes the fiber-type shift toward the type 1 phenotype, but it has no significant effect on the fiber cross-sectional area. On the contrary, strength training induces muscle

hypertrophy, mainly due to the greater muscle fiber cross-sectional area.²⁶⁵

7.4. Immune system

The immune system responds to any type of insult that challenges cellular homeostasis. While a single bout of exercise may represent a perturbation to homeostasis, long-term moderate-intensity exercise can benefit the immune system by enhancing immunosurveillance and immunocompetence.²⁷² Regular exercise leads to an elevated anti-inflammatory capacity, which is a critical factor in maintaining health, particularly in the context of chronic diseases.²⁷³ For example, the number of inflammatory CD14⁺CD16⁺ monocytes decreases after 12 weeks of combined moderate-strength and endurance training, indicating a reduction of more proinflammatory monocyte subtypes.¹¹⁶ In addition, acute bouts of exercise also elicit beneficial effects on immunological health partly through transiently mobilizing immune cells to peripheral tissues to conduct immune surveillance.²⁷⁴

Long-term exercise can prevent the age-associated degradation of immune system function (known as immunosenescence), which is characterized by considerable shifts in the balance of leukocyte subsets and a decline in various immune cell functions.²⁷⁵ As an example, long-term exercise from adulthood to old age (training time = 49 ± 8 years (mean \pm SD)) induces a healthy profile of inflammatory-related cytokines, as indicated by a decline in inflammatory biomarkers, including decreased levels of white blood cell counts, neutrophil counts, IL-6, IL-10, IL-1 receptor antagonist, and soluble tumor necrosis factor receptor-1.¹¹⁸ Additionally, participation

in long-term (training time = 45.1 ± 11.0 years) easy- to moderate-intensity exercise is associated with a more differentiated adaptive immune response.¹²³ Furthermore, athletes with life-long aerobic training have a lower percentage of senescent T cells when compared to healthy controls,²³² suggesting that exercise has a beneficial effect on immune function.

7.5. Gut microbiota

The human gut microbiota contains numerous microorganisms essential to maintaining homeostasis and normal gut physiology. Gut microbiota composition is highly variable. Each individual is linked to a unique gut microbiota profile that plays an important role in their metabolism and in the maintenance of a healthy host microorganism. Sometimes, the gut microbiota composition may vary within a single individual²⁷⁶ because the gut's ecosystem development and stability can be affected by intrinsic and extrinsic factors, including exercise and diet, which in turn can influence health.²⁷⁷

Exercise-induced alterations in the diversity, composition, and functional profiles of the intestinal microbiome have been widely documented.^{278,279} Moderate endurance exercise has been shown to expand the number of beneficial microbial species, enrich microflora diversity, and promote the development of commensal bacteria.^{215,278} All these effects are beneficial for the host and contribute to the improvement of their health status. Indeed, elite athletes elicit uniquely beneficial and diverse gut microbiome characteristics, including a higher gut microbial diversity and a shift toward bacterial species associated with increased production of the SCFA implicated in the maintenance of intestinal barrier integrity and regulation of host immune function.²⁸⁰ Furthermore, exercise-induced gut microbial changes confer protection against certain diseases. For example, treadmill running exercise ameliorates cardiac dysfunction in MI mice by altering the diversity and community structure of the gut microbiome. Mechanistically, exercise increases the metabolites 3-hydroxyphenylacetic acid (3-HA) and 4-HA, which are thought to protect against cardiac dysfunction by activating nuclear factor E2-related factor 2 (Nrf2).²⁸¹

Interestingly, the composition of the gut microbiota can be differently modulated by distinct types and modes of exercise. For instance, 4 weeks of resistance and endurance exercise training leads to significant differences in the gut microbiota composition in mice.²⁰⁹ Accordingly, mice subjected to endurance training exhibit higher diversity and evenness of gut microbiota. Specifically, endurance training is associated with a greater relative abundance of *Desulfovibrio* and *Desulfovibrio* sp., while *Clostridium* and *C.cocleatum* are enriched in mice that undergo resistance training.²⁰⁹

8. Benefits of exercise in hormetic regulation

There is some evidence that mild stressors inducing hormesis can contribute to the extension of lifespan and healthspan.²⁸² A single bout of exercise represents a challenge to cellular homeostasis. However, regular exercise confers multiple health benefits and better survival (Fig. 7). Therefore, it is

possible that the beneficial outcomes of exercise may be achieved partly by hormetic regulation (Fig. 6).

8.1. Exercise and mitohormesis

Mitohormesis is characterized as hormesis in mitochondria and is associated with the adaptive response processes that maintain cellular homeostasis. In response to a disturbance, mitochondria can generate and transmit a signal to the nucleus that triggers a transcriptional response leading to mitochondrial and non-mitochondrial adaptations. Although direct evidence linking mitohormesis to the exercise response is limited, mounting studies suggest that mitohormesis plays a role in mediating exercise-induced adaptations. Various signals are released from the mitochondria in response to exercise, with ROS being the primary candidate for inducing mitohormetic response.²⁸³ Mitochondrial ROS are vital signaling molecules necessary for health-promoting and lifespan-extending effects.²⁸⁴ The benefits of exercise are at least partly regulated by ROS signaling,²⁸⁵ and Nrf2 is one of the important regulators that mediates redox homeostasis during exercise. Exercise induces the activation of Nrf2, which modulates the gene level of endogenous antioxidant synthesis and ROS-eliminating enzymes.²⁸⁶ However, low-level and high-level mitochondrial stress could lead to opposing metabolic effects. In a recent study, severe mitochondrial stress due to mitoribosomal protein CR6-interacting factor 1 (*Crif1*) homo deficiency in hypothalamic proopiomelanocortin neurons of mice appeared to cause adult-onset obesity while mild mitochondrial stress caused by *Crif1* heterodeficiency in proopiomelanocortin neurons was associated with higher metabolic turnover and resistance to diet-induced obesity in mice. The beneficial metabolic effects induced by mild stress are mediated by enhanced thermogenesis and mitochondrial unfolded protein responses (UPR^{mt}) in distal adipose tissue. Interestingly, regular exercise with moderate intensity resembles the metabolic phenotype of *Crif1* heterodeficiency, indicating the important regulatory role of mitohormesis in moderate-intensity regular exercise.²⁸⁷

8.2. The benefits of exercise on healthspan

Healthspan is characterized as healthy life expectancy or the period of life spent free of illness and disability.²⁸⁸ In addition to a healthy diet and mental well-being, the positive effects of regular moderate exercise on the prevention, treatment, and management of chronic disease affecting healthspan are well-established. For example, in a landmark 21-year longitudinal study, it is reported that participation in long-term running and other vigorous exercises among older adults is associated with less disability and lower mortality in later life.¹⁹ Regular exercise induces systemic adaptations in virtually all organ systems, producing multifaceted benefits for health. In particular, exercise can attenuate multi-system age-related declines and help maintain physical fitness generally, including cardiorespiratory fitness and muscle function as well as flexibility and balance. The mechanisms through which exercise improves cardiorespiratory fitness include nitric oxide-induced vasodilatation,

VEGFA-mediated angiogenesis, and VEGFR3-mediated lymphangiogenesis, *etc.*^{146,289} The main signaling pathways involved in the effects of exercise on muscle include calcium/calmodulin-dependent protein kinase signaling, MAPK signaling, AMPK signaling, SIRT6, PGC1 α , *etc.*^{290,291}

Moreover, exercise benefits brain health via antioxidant defense (e.g., glutathione peroxidase, superoxide dismutase), neurotrophic factors (e.g., BDNF, VEGF, nerve growth factor), neurogenesis (e.g., BDNF, VEGF, IGF1), and protein homeostasis (e.g., proteasomes, neprilysin, tau ubiquitination), *etc.*²⁹¹ Exercise also reduces adipocyte size and lipid content, increases mitochondrial activity, and alters adipokines secretion in white adipose tissue.²⁹² In mice, the exercise-induced adaptations in white adipose tissue improve glucose tolerance and insulin sensitivity, indicating improved whole-body metabolic health.^{293,294} These positive effects of exercise are supposed to be mediated by exercise training-induced adipokines.²⁹⁴ Furthermore, exercise may enhance immune function and prevent immunosenescence, as explained in [Section 7.2](#). Altogether, adaptations in multiple tissues and organ systems contribute to the maintenance of whole-body health. Thus, exercise has been proposed as medicine to delay dependence and prolong healthspan.²⁹⁵

8.3. The effects of exercise on lifespan

A large body of studies suggest that exercise is a promising intervention for extending a healthy lifespan.^{296,297} The positive effects of exercise on lifespan are mainly achieved

through the attenuation of aging phenotypes or by delaying the process of aging. One of the essential regulators of the antiaging effects of exercise is AMPK.²⁹⁸ Activating AMPK is sufficient to promote longevity in multiple organisms.^{299,300} In muscle specifically, AMPK is an important regulator of exercise effects that are activated by increased AMP/ATP and (nicotinamide adenine dinucleotide/ nicotinamide adenine dinucleotide hydride) ratios.³⁰¹

Generally, regular exercise is considered to be fundamental to overall health and longevity. However, some of the commonly ascribed beneficial effects of exercise seem to be unsupported by current randomized control trial studies. For example, current randomized control trial evidence shows that exercise does not prevent premature mortality or cardiovascular disease in older adults or in people with chronic conditions.³⁰² Thus, additional large-scale investigations would be of value, especially high-quality studies with insights on molecular mechanisms.

9. The effects of exercise on repair and regeneration

The prompt repair and regeneration response to damage is a hallmark of health.²⁸ Here we present examples of how exercise modulates the process of repair and regeneration in response to damage ([Fig. 6](#)).

9.1. DNA damage and repair

Oxidative DNA damage is associated with increased risk of chronic diseases, such as cancer, neurodegenerative disease,

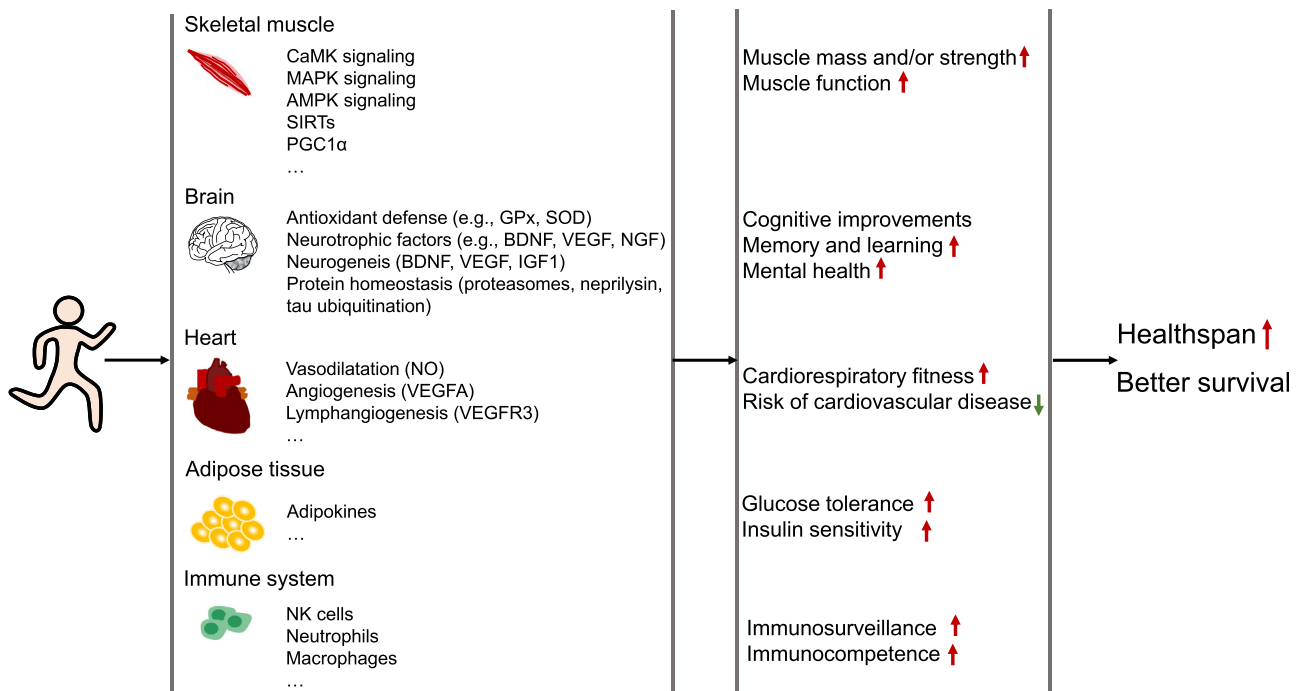


Fig. 7. Regular exercise confers multiple health benefits and better survival. The adaptations in multiple tissues and organ systems contribute to the maintenance of whole-body health. AMPK = adenosine monophosphate-activated protein kinase; BDNF = brain-derived neurotrophic factor; CaMK = calcium/calmodulin-dependent protein kinase; GPx = glutathione peroxidase; IGF1 = insulin-like growth factor 1; MAPK = mitogen-activated protein kinase; NGF = nerve growth factor; NK cells = natural killer cells; NO = nitric oxide; PGC1 α = peroxisome-proliferator-activated receptor coactivator 1 α ; SIRT6 = sirtuins; SOD = superoxide dismutase; VEGF = vascular endothelial growth factor; VEGFA = vascular endothelial growth factor A; VEGFR3 = vascular endothelial growth factor receptor 3.

atherosclerosis, and diabetes.^{303,304} Therefore, interventions aimed at repairing DNA strand breaks or lesions could be useful for inhibiting or delaying the progression of disease. Regular moderate exercise confers substantial health benefits, including a lower risk of the above-mentioned diseases.²⁴

Exercise has been directly implicated in the enhancement of DNA damage repair. As an example, 8 weeks of treadmill running leads to a decreased accumulation of oxidative damage to DNA and proteins in rat skeletal muscle.³⁰⁵ Moreover, exercise may promote the inherent DNA repair abilities of neurons through upregulation of BDNF.³⁰⁶ Several mechanisms have been implicated in the decrease of exercise-associated oxidative damage in the brain, including upregulation of antioxidant capacity, reduced production of oxidants, and consequently reduced nuclear DNA damage.³⁰⁷ However, acute and strenuous exercise could induce oxidative stress via increased accumulation of reactive oxygen and nitrogen species, which may have negative effects on DNA stability.³⁰⁸ Additionally, high-intensity normoxic exercise induces DNA double-strand breaks, as revealed by increased detection of gamma-H2A histone family member X and p53-binding protein 1. Furthermore, levels of these oxidative stress biomarkers are significantly increased following exercise in hypoxia.³⁰⁹

Therefore, a better understanding of the effects of different types of exercise on DNA damage and repair is necessary. Future studies focusing on exercise-induced mechanisms are critical for developing better approaches to improving health.

9.2. Protein damage and proteostasis

Proteostasis refers to the dynamic processes contributing to the maintenance of protein homeostasis, which depends on adjustments to protein synthesis and degradation. Disturbance of proteostasis contributes to the pathogenesis of many degenerative diseases through the aggregation of damaged proteins.^{310,311} Regular exercise induces substantial positive effects on health, with muscle being its predominant effector.³¹² For example, aerobic exercise increases the capacity for maintaining mitochondrial proteostasis in skeletal and heart muscle.³¹³ Regular voluntary wheel running reduces the accumulation of cytotoxic misfolded proteins in the heart of α B-crystallin mutated (CryAB^{R120G}) mice, a model of desmin-related cardiomyopathy, by increasing autophagy.³¹⁴ One week of exercise training could reverse angiotensin II-induced muscle atrophy by activating peroxisome proliferator-activated receptor gamma and inhibiting miR-29b.³¹⁵ Exercise also causes protein degradation followed by a similar scale rebuilding process, thus maintaining protein homeostasis.³¹⁶

Moreover, exercise activates autophagy and re-establishes proteostasis in cardiac diseases. For example, 4 weeks of treadmill running improves skeletal muscle autophagic flux and proteostasis in the rat model of neurogenic myopathy.³¹⁷

9.3. The ER stress response

The ER is a versatile organelle that involves the synthesis and folding of proteins as well as calcium homeostasis and signaling. Perturbation of ER function causes ER stress and subsequently

activates the unfolded protein response (UPR), which is conducive to cellular homeostasis. However, if the ER stress remains unmitigated or is too strong and the UPR fails to restore ER function, the cells may degrade part of the ER via autophagy in order to maintain homeostasis in the ER. Defects in ER homeostasis have been implicated in the pathogenesis of metabolic diseases.^{318,319} Exercise training represents a promising strategy for reestablishing ER homeostasis in cardiovascular diseases and obesity. For instance, 8 weeks of treadmill exercise can reestablish cardiac protein quality control and reduce ER stress, which is associated with improved cardiac function in the failed hearts of rats.³²⁰ Moreover, 8 weeks of swimming exercise is capable of suppressing aging-induced ER stress and ameliorating cardiac dysfunction in aged mice by enhancing cyclic guanosine monophosphate (cGMP)—protein kinase G signaling. Likewise, the inhibition of cGMP-specific phosphodiesterase type 5 leads to reduced ER stress and improved cardiac function in aged mice while activation of ER stress eliminates the protective effect of exercise in the same population.³²¹ Furthermore, in humans, 3 months of moderate exercise alleviates obesity-related ER stress by downregulating glucose-regulated protein 78 signaling.³²² In a mouse model of Alzheimer's disease, exercise improves vascular function and attenuates ER stress.³²³

Additionally, in a recent study, acute exercise is reported to activate ER-phagy, which is a selective ER autophagy regulated by ER-localized receptors, in order to ensure proper cellular homeostasis. Mechanistically, ER-phagy receptor named family with sequence similarity 134, member B anchors and fragments ER and then binds with microtubule-associated protein light-chain-3 to promote ER membrane degradation.³²⁴ This study suggests that acute exercise-induced ER-phagy may serve as an important adaptive stress response to maintain ER homeostasis.

9.4. Mitochondrial stress responses

Mitochondria are essential semi-autonomous cellular organelles that are maintained through complex remodeling processes, including biogenesis, dynamic fission and fusion, and mitophagy. These remodeling processes collectively contribute to mitochondria quality control. Mitochondrial stress induced by aggravated misfolded mitochondria proteins in the mitochondrial matrix, an impaired protein quality control system, mitonuclear imbalance, or inhibition of the electron transport chain can trigger the UPR^{mt}.³²⁵

Regular endurance exercise is a powerful stimulus that promotes mitochondrial remodeling. Activation of the UPR^{mt} may mediate some of the exercise-induced mitochondrial adaptations.³²⁶ For example, the activation of UPR^{mt} is observed in skeletal muscle during the acute phase of the contractile period and chronic contractile activity.³²⁷

Exercise also increases levels of the mitochondrial encoded peptide mitochondrial open-reading-frame of the 12S rRNA-c, which can directly mediate mitonuclear communication by translocating to the nucleus and regulating adaptive nuclear gene expression to promote cellular homeostasis. Treatment of mice with mitochondrial open-reading-frame of the 12S

rRNA-c is associated with metabolic benefits, such as weight loss, enhanced antioxidant capacity, and increased insulin sensitivity.^{328,329}

9.5. Lysosomal damage response

Lysosomes are the main organelles that account for proteolytic degradation and recycling.³³⁰ Exercise influences the release of lysosomal enzymes in several cell types,^{331,332} suggesting that physical activity could modulate lysosomal membrane permeability. Thus, 4 weeks of aerobic exercise could mitigate the HFD-associated lysosomal membrane permeabilization via the reduction of ROS.³³³ However, studies focused on exercise-induced changes in lysosomal adaptations are still limited.

Finally, lysosomal biogenesis is also elevated in response to exercise. The increased lysosomal biogenesis coordinates with mitophagy to enhance the breakdown of dysfunctional mitochondria, thereby contributing to the maintenance of mitochondrial quality.³³⁴

9.6. Tissue-level regeneration

The positive effects of exercise on cardiac regeneration are well-established. Regular endurance exercise is capable of promoting heart growth and inducing cardiac remodeling.^{335,336} An enlarged heart due to regular exercise training is associated with normal or enhanced heart function. Moreover, it is well-known that exercise confers protection against heart failure.³³⁷ Mechanistically, exercise-induced cardiac adaptation mainly includes cardiomyocyte growth, cardiomyocyte fate reprogramming, angiogenesis and lymphangiogenesis, mitochondrial remodeling, epigenetic alteration, enhanced endothelial function, quiescent cardiac fibroblast, and improved cardiac metabolism.^{146,338} For instance, 3 weeks of swimming exercise causes a remarkable increase in cardiac lymphangiogenesis via VEGFR3 activation. By contrast, VEGFR3 inhibition is capable of mitigating exercise-induced cardiac growth, indicating the essential role of cardiac lymphangiogenesis in exercise-associated cardiac growth.³³⁹ In particular, IGF1–PI3K signaling is one of the essential pathways responsible for exercise-related heart enlargement and protection.³⁴⁰

Skeletal muscle exhibits high plasticity and adaptation in response to various demands. Adult skeletal muscle has the remarkable ability to regenerate after injury due to the ability of muscle stem cells, also called satellite cells, to generate both new myofibers and new muscle stem cells.³⁴¹ Exercise training is a strong stimulator of muscle plasticity, as it activates several intracellular signaling pathways that mediate muscle growth and adaptations.³⁴² For example, 4 weeks of treadmill training improves muscle regeneration and induces muscle hypertrophy via the IGFBP7–Akt–mTOR axis in mice.³⁴³ Moderate exercise improves tendon injury healing in aging rats by increasing the number of tendon stem/progenitor cells.³⁴⁴

9.7. Cell identity reprogramming

Research studies demonstrate that exercise training can trigger metabolic reprogramming in multiple cell types and, thus,

alter their functional phenotypes. For example, 16 weeks of treadmill exercise induces macrophage phenotypic switching from M1 to M2 in the adipose tissue of obese mice, indicating improved inflammatory outcomes in exercised obese mice.³⁴⁵ Additionally, 10 weeks of treadmill running could promote the differentiation of mesenchymal stem cells into osteoblasts to increase hematopoiesis.³⁴⁶ Moreover, 4 weeks of exercise training before surgery offers protection against hepatic injury via the metabolic reprogramming of immune cells. Specifically, exercise encourages Kupffer cells toward an anti-inflammatory phenotype with trained immunity.³⁴⁷

10. Integrative effects of exercise on health

Exercise maintains and restores homeostasis at the organismal, tissue, cellular, and molecular levels to stimulate positive physiological adaptations and, subsequently, to protect against various disease conditions.²⁷ The health benefits of regular exercise training involve the acclimatization to repeated metabolic, thermoregulatory, hypoxic, oxidative, and mechanical stress. An individual exercise bout elicits a rapid but transient response while the repetition of the stimulus causes compensatory physiological changes that confer protection against greater subsequent stress.^{348,349}

Exercise elicits systemic impacts. The preventive and therapeutic potential of exercise to combat the development and progression of various diseases lies in the remarkable integrative adaptation that takes place at the whole-organism level. Exercise-related physiological adaptations are characterized by complex interplay among multiple organ systems, including the skeletal muscle, lung, heart, brain, vascular system, liver, adipose tissue, *etc.*^{350,351} Exercise therapy has been proposed as an effective pre-operative therapy providing a series of positive effects on a patient's physical fitness prior to surgery, on their recovery period, and on the length of hospital stay.^{352–354} It has been suggested the protective effects of pre-operative exercise are largely due to an enhanced tolerance to systemic perturbation as well as an improved metabolism. For example, 4 weeks of aerobic pre-operative exercise is capable of significantly ameliorating liver injury and inflammation in mice with hepatic ischemia/reperfusion injury. Mechanistically, exercise promotes the production of high mobility group box 1 and upregulates the itaconate metabolism in Kupffer cells, thereby inducing anti-inflammatory trained immunity.³⁴⁷

11. Conclusion and prospects

The beneficial effects of exercise have been well-documented for a range of improved metabolic and cardiorespiratory fitness-related outcomes.³⁵⁵ Regular exercise is essentially considered a non-pharmacological polypill for patients with certain comorbidities. Therapeutic exercise can be adopted to prevent, manage, and treat diseases such as obesity, type 2 diabetes, cardiovascular disease, aging-related muscle atrophy, and certain cancers. However, caution should be taken when interpreting these discoveries, as exercise protocols may vary across studies.

Exercise is a complex, multidimensional process that is challenging to accurately assess in free-living individuals. The lack of consistency in the methods applied to quantify exercise is a limitation to data analysis and may hinder the translation from experimental findings to clinical practice. Thus, future work involving exercise should be performed based on strictly designed and well-reported trials with good reproducibility.³⁵⁶

In this review, we have attempted to summarize the health benefits of exercise from the view of biological causes. Due to limited space, it is hard to provide a comprehensive review for each individual topic. However, the topics and characteristics that have been discussed may provide a mechanistic view for exercise-related studies. As the biology of exercise is complex, we have listed examples to explain the effects of exercise on each topic and characteristic, which may be helpful for gaining a comprehensive understanding of exercise-induced adaptations.

Regarding the conflicting findings between current Mendelian randomization studies and traditional observational studies in [Section 7.2](#), future researchers should perform more mechanistic studies in order to unravel the biological pathways of exercise. In addition, exercise-stimulated interorgan communication is less well-investigated. Further detailed study of exercise-related interorgan communication and its underlying mechanisms may shed light on the identification of exercise-responsive molecules. Regular exercise is undoubtedly beneficial for overall health. Yet, the mechanisms that underlie the multiple health benefits of exercise are complex, and efforts devoted to exploring the adaptation of organelles (e.g., mitochondria, nuclei, ER) may be helpful for understanding the positive effects of exercise.

Further investigation of the mechanisms underlying the beneficial effects of exercise will help to improve the design and maximize the curative effects of exercise interventions. Therefore, there is a need for prior in-depth knowledge of the scientific basis of exercise in order to better understand the effects of potential subsequent interventions oriented toward the modification of exercise methods for health promotion and to research specific molecules that may improve the health of those who are unable to exercise. We hope that continuing investigation in this field will increase our understanding of the processes involved in the beneficial role of exercise and facilitate the identification of new therapeutics to improve quality of life.

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Authors’ contributions

YQ and BFG drafted the manuscript; GK, CLO, and JX came up with the idea and edited the manuscript; HIL and GL reviewed and edited the manuscript. All authors have read and approved the final version of this manuscript, and agree with the order of presentation of the authors.

Competing interests

GK has held research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sotio, Tollys, Vascage, and Vasculox/Tioma. GK has consulted for Reithera and is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics, and Therafast Bio. GK is the inventor of multiple patents covering the therapeutic targeting of aging, cancer, cystic fibrosis, and metabolic disorders. Among these, patents were licensed to Bayer (WO2014020041-A1 and WO2014020043-A1), Bristol-Myers Squibb (WO2008057863-A1), Osasuna Therapeutics (WO2019057742A1), Pharmamar (WO2022049270A1 and WO2022048775-A1), Raptor Pharmaceuticals (EP2664326-A1), Samsara Therapeutics (GB202017553D0), and Therafast Bio (EP3684471A1). The other authors declare that they have no competing interests.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at [doi:10.1016/j.jshs.2022.10.003](https://doi.org/10.1016/j.jshs.2022.10.003).

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