Protective Effect of Exercise on Age-Related Oxidant and Inflammatory Events

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1 Exercise and Ageing

There is much evidence indicating that regular exercise counteracts the negative effects of ageing. For example, regular exercise is associated with reduced risks of all-cause and cardiovascular mortality [1–3], and also with increased longevity [4–7]. Furthermore, exercise reduces the risk of cardiovascular diseases [8], type 2 diabetes [9], metabolic syndrome [10], colon cancer [11], obesity [12], osteoporosis (Kelley 1998; Marques et al. 2012), sarcopenia [13], anxiety (Wipfli et al. 2008), and cognitive impairment [14]. Most importantly, exercise improves the quality of life of elderly people [15].

2 Ageing and Oxidative Stress

Ageing is associated with oxidative stress that is mainly due to defective (leaky) mitochondria [16], probably resulting from lower cytochrome C oxidase (complex IV) activity (Navarro et al. 2003) and peroxidative damage of mitochondrial membrane lipids [17]. Hence more electrons escape from the mitochondria, generating a

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long trail of reactive oxygen species (ROS) [18, 19] leading to progressive mitochondrial dysfunction and further exacerbating ROS generation, thus creating a vicious cycle of oxidative damage. Age-associated increases in ROS production occur in skeletal muscles [20] and other organs such as the heart, liver, brain, and kidney [5, 18, 21].

Reduced protein synthesis limits antioxidant defense mechanisms and repair capacity in aged individuals, which further contributes to the state of oxidative stress. The free radicals theory of aging hypothesizes that oxidative stress causes damage to macromolecules, including lipids, proteins and nucleic acids that overwhelms cellular antioxidant defense and repair mechanisms, leading to progressive deleterious changes over time [22, 23].

3 Aging and Inflammation

Age-associated progressive loss of muscle mass and strength, known as sarcopenia [24, 25], increases the incidence of muscle injury [6] and subsequently increases the infiltration of immune cells into the injured muscles. Activated immune cells release ROS, reactive nitrogen species (RNS) and proinflammatory mediators during the respiratory burst [26]. Similarly, the injured muscles generate and release proinflammatory mediators, which bind with membrane receptors and activate specific ROS-generating enzymes such as lipooxygenase, NADPH oxidase, and xanthine oxidase [27–32].

Sarcopenia can also lead to reduced physical activity and increased adiposity. Accumulation of excess adipose tissues induces a state of low-grade but chronic inflammation through the release of a multitude of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1beta (IL-1β) [33–35]. Indeed, ageing is associated with increased levels of circulating pro-inflammatory cytokines such as TNF-α, IL-6, and interleukin-1 receptor agonist (IL-1ra) and systemic inflammatory biomarkers such as C-reactive protein (CRP) as well as higher count of inflammatory cells (neutrophil and monocytes) [36–38]. Hence, aging is associated with a state of oxidative stress and chronic inflammation. The major events related to age-associated oxidative stress and inflammation is shown in Fig. 1.

4 Oxidative Stress and Inflammation Overlapping Signaling Pathways

Oxidative stress and inflammation share common and overlapping signaling pathways. ROS initiate and augment inflammation, and are also products of inflammation. During the inflammatory response, particularly during the respiratory burst, immune cells generate ROS and RNS via NADPH oxidase and nitric oxide synthase

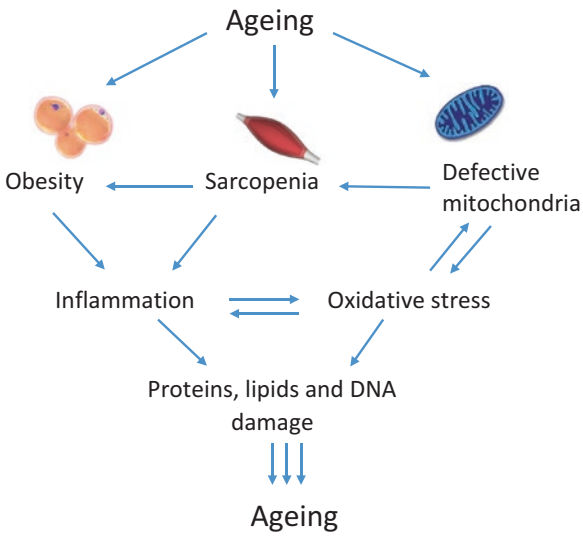

Fig. 1 Some important events related to oxidative stress and inflammation during the ageing process

(NOS), and also release proinflammatory cytokines such as TNF-α, IL-1β and IL-6 [26, 39, 40]. Similarly, the injured tissues release proinflammatory cytokines. These cytokines/proinflammatory mediators bind to membrane receptors and activate specific ROS-generating enzymes, such as lipooxygenase, NADPH oxidase, myeloperoxidase and xanthine oxidase [27–32] and specific RNS generating pathways such as NOS, protein kinase B (Akt) and Sph1P (sphingosine-1-phosphate) [41–43].

ROS overproduction activates redox-sensitive transcription factors, namely nuclear factor kappa B (NF-kB) and activator protein-1 (AP-1) via stress kinases such as extracellular signal regulated kinases (ERKs), c-jun N-terminal kinases (JNKs), mitogen activated protein kinase p38 (MAPK p38), protein kinase C (PKC), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt, Src family kinases (SFKs) leading to increased expression of inflammatory target proteins genes such as matrix metalloproteinase-9 (MMP-9), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), prostaglandin E_2 (PGE_2) and cytosolic phospholipase A2 (cPLA2) (Kim et al. 2008, 2014; Lee et al. 2012) [44–50].

Interestingly, NF-kB has been shown to regulate the transcription of TNF-α gene [51] as well as other proinflammatory mediators such as IL-1, and interleukin 8 (IL-8) [50]. Furthermore, many of NF-kB-induced proteins such as NOS, COX and PGE_2 are prominent sources of ROS and RNS [52] forming an auto-activating loop which feeds the vicious cycle of inflammation and oxidative stress. In short, proinflammatory mediators such as TNF-α, IL-1, IL-6 activate redox-sensitive transcription factors such as NF-kB and AP-1 through redox signaling, resulting in the generation of large amounts of these proinflammatory mediators and ROS (Fig. 2). Indeed, aging is associated with adverse health conditions characterized by elevated levels of both oxidative stress and inflammatory markers such as atherosclerosis,

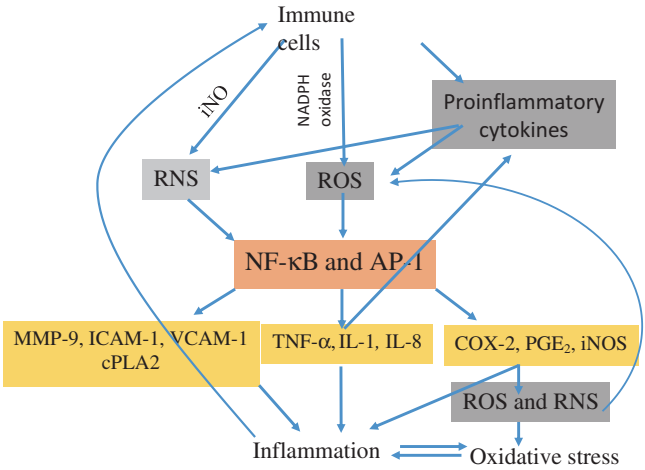

Fig. 2 Overlapping signaling pathways of oxidative stress and inflammation in aging. *AP-1* activator protein-1, *COX-2* cyclooxygenase-2, *cPLA2* cytosolic phospholipase A2, *ICAM-1* intercellular adhesion molecule-1, *IL-1* interleukin-1, *IL-8* interleukin-8, *iNOS* inducible nitric oxide synthase, *MMP-9* matrix metalloproteinase-9, *NF-kB* nuclear factor kappa B, *PGE_2* prostaglandin E_2, *RNS* reactive nitrogen species, *ROS* reactive oxygen species, *TNF-α* tumor necrosis factor-alpha, *VCAM-1* vascular cell adhesion molecule-1

metabolic syndrome, sarcopenia, arthritis, and chronic obstructive pulmonary disease [53].

Not surprisingly, ROS can also induce proteins such as heat-shock proteins (HSPs), HSP70 in particular [54] and heme oxygenate 1 oxygenase (HO-1) (Lee et al. 2012) that can protect cells and tissues from the deleterious effects of inflammation. However, in aging the balance of antioxidant/anti-inflammatory to oxidant/inflammatory proteins is tilted towards the latter

5 Exercise: Anti-inflammatory and Antioxidant Effects

Regular exercise reduces the risk of a wide range of oxidative stress and inflammation associated diseases including cardiovascular diseases [8], type 2 diabetes [9], metabolic syndrome [10], cancer [11], obesity [12], and sarcopenia [13].

5.1 Anti-inflammatory Effects of Exercise

Acute bouts of exercise cause transient damage to the contracting skeletal muscles, so triggering an inflammatory response that increases the levels of pro-inflammatory cytokines and acute-phase reactants in the blood [55, 56]. However, regular exercise is associated with reduced levels of systemic inflammatory markers such as CRP,

IL-6 and TNF-α that occur independently of weight loss in young and middle aged adults [57–62], as well as in the elderly [57, 63–70]. Also, many interventional studies report that exercise reduces inflammatory markers, particularly CRP, TNF-α, monocyte chemoattractant protein-1 (MCP-1) and (IL-8), soluble TNF-α receptor 2 (sTNFR2) and soluble IL-6 receptor (sIL-6R), and increases the anti-inflammatory mediators interleukin-10 (IL-10), interleukin-4 (IL-4), and transforming growth factor beta 1 (TGFβ1) [71–80]. However, only a few randomized controlled trials were conducted to confirm that [81–84]. These benefits of exercise were also evident in the elderly [81, 85–89]. It is likely that exercise causes the most significant anti-inflammatory effects in patients with high baseline inflammatory biomarkers, particularly when exercise is associated with weight loss.

However, it is worth noting that some interventional and randomized controlled trials studies did not detect a significant effect of regular exercise on systemic inflammatory biomarkers in adults [59, 90–92], or in aged adults [93–96]. A meta-analysis conducted in 2006 found only five randomized controlled trials that examined the effects of regular aerobic exercise (at least 4 weeks duration) in adults and concluded that aerobic exercise did not reduce CRP levels [97]. It is likely that these discrepancies may be attributed to the smaller sample size used in the clinical trials examined.

On the other hand, the effects of resistance exercise on inflammatory mediators are mostly negative [98–100], although Brooks et al. [101] reported that 16-week resistance training reduced CRP and increased adiponectin levels in older diabetic patients. Clearly, the effects of exercise depends on the type (aerobic/resistance), intensity (mild/moderate/intense/exhaustive), and frequency (sessions per day/week/month) of exercise, and also on the subject's basic condition and endurance capacity.

5.1.1 Anti-inflammatory Signaling Pathways of Exercise

The signaling pathways underlying the anti-inflammatory effects of exercise are complex and not completely understood but for the sake of convenience, can be divided into three main pathways according to the site of action. The main sites of action are the adipose tissue, the immune system and skeletal muscles.

- ***Anti-inflammatory effects of exercise on adipose tissue***

Obesity is associated with chronic inflammation. Adipose tissue, particularly visceral fat depots, and macrophages trapped in the adipose tissue release pro-inflammatory cytokines such as IL-6 and TNF-α [33–35, 102]. Exercise increases energy expenditure and burns off some of the body fat, which can result in weight loss, particularly visceral fat loss [12, 103, 104]. Subsequently, the production and release of pro-inflammatory adipokines such as IL-6 and TNF-α are reduced [79, 105–107]. Exercise also induces the release of adiponectin from adipose tissues [108, 109]. Adiponectin exerts anti-apoptotic, anti-inflammatory and anti-oxidative activities [110, 111]. Exercise inhibits the infiltration of M1-type macrophages into

adipose tissue and also induces the switch of macrophages from the more inflammatory phenotype M1-type to the less inflammatory phenotype M2-type in obese mice [112].

- ***Anti-inflammatory effects of exercise on the immune system***

Aerobic exercise downregulates the innate immune response and activates the adaptive immune system with consequent suppression of inflammation. Exercise modulates the immune system by reducing the number of inflammatory CD14+CD16+ monocytes [113], increasing the number of CD4CD25 regulatory T cells [114, 115], increasing the dominance of Type 2 helper T cell over Type 1 helper T cell [116–118], and reducing the expression of toll like receptor-4 (TLR4) on monocyte surfaces [119, 120]. TLR4 signaling participates in several innate immunity and inflammatory processes [121]. Exercise also reduces the production of proinflammatory cytokines such as interferon gamma (INFγ), TNFα, IL-1α, IL-8, MCP-1 and the receptors for TNF-α (sTNFR2) and IL-6 (sIL-6R). In addition, exercise releases anti-inflammatory cytokines such as IL-10, IL-4, TGFβ1 and adiponectin [71–76, 78–81, 85–89, 108, 122].

Exercise is a positive stressor to the body; it stimulates the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis. Therefore, exercise increases serum glucocorticoid levels [123] to cause a subsequent inhibition of the immune system [124].

- ***Anti-inflammatory effects of exercise on skeletal muscles***

By improving muscle mass and strength, exercise renders skeletal muscles less vulnerable to acute injury and the associated inflammatory responses [125–129]. Also, by stimulating mitochondrial biogenesis [130] and enhancing mitochondrial oxidative capacity [131], exercise mitigates mitochondrial aging and interrupts the vicious cycle of oxidative damage.

Exercise induces the release of several cytokines (myokines) from skeletal muscle, most notably IL-6 [132, 133]. IL-6 triggers the release of several anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1ra) and IL-10, in addition to cortisol [134, 135]. IL-10 inhibits the synthesis of several pro-inflammatory cytokines such as TNF-α and IL-1β [136]. Exercise also reduces TNF-α and IL-1β production in skeletal muscles [137–141], and upregulates the expression of the anabolic myokine IL-15 [136, 142] and HSPs in skeletal muscles [143–145]. **The mechanisms underlying the anti-inflammatory actions of exercise are summarized in Fig. 3**.

5.2 Anti-oxidant Effects of Exercise

There is little doubt that generation of ROS is increased acutely during exercise. However, the incidence of diseases associated with oxidative stress is reduced by regular exercise. Exercise training attenuates oxidative damage in the brain [5,

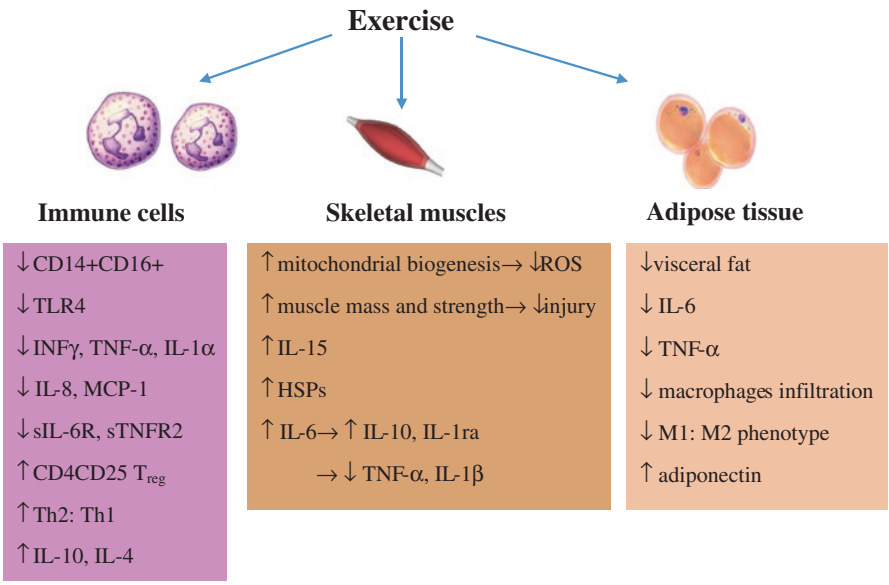

Fig. 3 Signaling pathways underlying the anti-inflammatory actions of exercise. *HSPs* heat shock proteins, *IL-1α* interleukin-1 alpha, *IL-1ra* interleukin-1 receptor antagonist, *IL-1β* interleukin-1 beta, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *IL-15* interleukin-15, *INFγ* interferon gamma, *M1* macrophage phenotype 1, *M2* macrophage phenotype 2, *ROS* reactive oxygen species, *sTNFR2* soluble TNF-α receptor 2, *sIL-6R* soluble IL-6 receptor, *TLR4* toll like receptor-4, *TGFβ1* transforming growth factor beta 1, *TNF-α* tumor necrosis factor-alpha, *Th1* Type 1 helper T cell, *Th2* Type 2 helper T cell

146–149], liver [5, 150–152] (Radak et al. 2004), kidney [5], skeletal muscles [153] and heart [5, 154].

Importantly, regular exercise ameliorates age-associated oxidative stress in the heart [154, 155], liver (Radak et al. 2004), and skeletal muscle [156] (Radak et al. 2002). In the study of Navarro et al. [5], exercise reduced age-associated mitochondrial oxidative damage and upregulated mitochondrial NADH-cytochrome-*c* reductase and cytochrome oxidase activities in brain, heart, liver, and kidney of 52 week old rats. However, exercise caused an increase in oxidative damage in skeletal muscles [157] and hearts [158] of aged rats.

In elderly people, exercise reduced serum levels of myeloperoxidase, a marker of inflammation and oxidative stress [125] and thiobarbituric-reactive acid substances, a marker of lipid peroxidation [159]. However, de Gonzalo-Calvo et al. [160] reported that although regular exercise increased protein carbonyl content and lipid peroxidation levels in the plasma and erythrocytes of long-term trained elderly men, their overall health condition was markedly improved. Another clinical study showed that 8 weeks of walking exercise did not significantly change low density lipoprotein (LDL) oxidation or nitration in the elderly [161].

5.2.1 Anti-oxidant Signaling Pathways of Exercise

By suppressing inflammatory pathways, exercise inhibits prominent sources of ROS and RNS generation and thus exerts beneficial antioxidant effects. Exercise also upregulates the antioxidant defense mechanisms and repair proteins in the body via redox-sensitive transcription factors, mainly NF-kB, AP-1 and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α).

The energy demand of contracting muscles increases during exercise and the body responds by increasing oxygen uptake and delivery to muscles. The increased metabolic rate results in greater ROS production not only in muscles [20, 148, 149], but in other organs as well [21, 162]. Sources other than the mitochondrial electron transport chain enzymes, such as xanthine oxidase [163–165] and NADPH oxidase [20, 166] contribute to ROS generation during exercise.

- **Effects of exercise on NF-kB and AP-1 signaling**

Exercise-induced increase in ROS levels preconditions the body against oxidative damage by evoking an adaptive process that is mediated via mitogen-activated protein kinases (MAPK p38, ERK 1 and ERK 2) [163, 167–169], cAMP-response-element binding (CREB) [170, 171], and synapsin [170, 171]. These effects lead to activation of redox-sensitive transcription factors such as NF-kB [163, 172, 173] and AP-1 [169, 173], resulting in increased expression of antioxidant enzymes [174] such as superoxide dismutase [163, 173] and catalase [173], repair proteins such as heat shock proteins HSP25, HSP60, HSP72, HSP70, heat shock cognate 70 HSC70 [157, 173–176], proteasomes complex and NOS [150, 163]. These signaling cascades were demonstrated in skeletal muscles [163, 172], brain [170, 171], leukocytes [177] and hearts [169] of experimental animals as well as in humans [167, 177] and in aged animals [173, 176, 178] and humans [177]. However, other studies reported that exercise-induced activation of NF-kB and AP-1 [173] and upregulation of HSP70 were attenuated in fast skeletal muscles of old rats [179]. Interestingly, ageing also increased ROS production and NF-KB activity in the livers of aged rats; these effects were attenuated by exercise (Radak et al. 2004) [150].

- **Effects of exercise on PGC-1α signaling**

Exercise stimulates mitochondrial biogenesis [130] and ameliorates the age-associated decline in mitochondrial oxidative capacity in skeletal muscles [131], and other organs [180] (Navarro et al. 2003) via PGC-1α signaling [181, 182]. PGC-1α is a redox-sensitive transcription factor that is activated by 5′-AMP-activated protein kinase (AMPK), [168, 183–185] to trigger the transcription of nuclear respiratory factor 1 (NRF-1) and expression of mitochondrial transcription factor A (mtTFA), a key regulator of mitochondrial DNA replication [186]. PGC-1α also increases the expression of antioxidant proteins such as glutathione peroxidase (GPX) and SOD-2 [187]. Safdar et al. [188] reported that exercise reversed most of the multisystem pathology and premature mortality in mice which were genetically modified to accumulate mitochondrial mutations. The effects of exercise on AMPK, and PGC-1α were preserved in the hippocampus of aging rats. However, results

from Derbré et al. [181] suggest a blunted effect of exercise response in PGC-1α, NRF-1 in skeletal muscles of aged rats.

- **Effects of exercise on antioxidant enzymes expression and activity**

The NF-kB and PGC-1α signaling cascades converge to upregulate antioxidant defense mechanisms in cells to counteract and interrupt the vicious cycle of inflammation and oxidative stress associated with ageing. The most studied antioxidant enzymes systems in laboratory animals and in humans are SOD, catalase, GPX and glutathione reductase.

Regular exercise increases the activities of SOD in the brain [189, 190], erythrocytes [191–193], heart [154, 158, 194–196], tissues from the lung [197], and liver [197]. Exercise increases the protein expression of SOD in blood vessels [195, 198, 199, 200] (Lee et al. 2001), liver [201] and blood [202].

The activity of GPX was increased by exercise in the brain [189, 190], erythrocytes [191, 192, 203], blood (Elosua et al. 2008), liver, heart, lung [18, 197] and skeletal muscles containing a high percentage of type I or type IIa fibers of old rats [156]. Similarly, exercise increases the activities of plasma glutathione reductase (Elosua et al. 2008) and catalase in erythrocytes [193], heart [154, 158, 204] and liver [18]. Some studies reported no changes in the activities of SOD, CAT, or GPX in the brain [205] or skeletal muscle [153].

Several studies investigated the effects of exercise on antioxidant enzymes at old age. For example, exercise enhances the activities of SOD in the heart [154, 158, 195, 197], brain [189], and lung [197] and increases GPX activities in the brain, liver, heart, lung and skeletal muscles of old rats [156, 189, 197, 206] and in erythrocytes of elderly people [203]. Catalase activity is upregulated by exercise in the liver [197] and heart [154, 158] of aged rats. In the study of Navarro et al. [5], exercise reduced the extent of age-associated decline in SOD and catalase activities in brain, heart, liver, and kidney of 52 week old but not older mice (72 week old). Exercise also up-regulated the protein expression of SOD-1 and GPX in the hippocampus of aged rats [147].

Exercise-induced adaptation of antioxidant enzymes is highly isoform, tissue and time course specific. Exercise modulates the three SOD isoforms differently [195, 199, 201, 202, 207, 208] as the promoter region of SOD-2 contains more ROS-sensitive binding sites [209]. Exercise-induced protein expression of SOD is time dependent (Navarro et al. 2003); SOD-1 protein expression was increased in rat skeletal muscles 48 h post exercise, whereas SOD-2 protein content was increased after 10 and 24 h, but not 48 h [208].

- **Effects of exercise on repair mechanisms**

Exercise can also stimulate the proteasome complex, which is responsible for the degradation of oxidatively damaged proteins [150, 210, 211] (Radak et al. 2000), and therefore enhances the cellular repair processes. Exercise also modulates the activity of DNA repair enzymes, particularly oxoguanine DNA glycosylase (OGG1) and uracil DNA glycosylase (UDG), and thus reduces the accumulation of nuclear 8-hydroxydeoxyguanosine (8-OHdG) and mutations in skeletal muscles (Radak

et al. 2002) [212, 213], but not brains of aged rats [214]. Exercise increased thioredoxin reductase 1 (TrxR1), one of the thioredoxin system enzymes with direct and indirect antioxidant effects, in peripheral blood mononuclear cells in humans [125] (Wadley et al. 2015).

Exercise increases the content of the brain-derived neurotrophic factor (BDNF), a critically important neurotrophic factor that is involved in higher cognitive function [170, 171].

Telomeres are considered '*the guardians of the genome*'. Telomere dysfunction activates p53, leading to suppression of PGC-1α and PGC-1β promoters with consequent metabolic and organ failure [215]. The leukocyte telomere was 200 nucleotides longer in people who exercise regularly, which roughly corresponds to a 10-year increase in longevity [216]. Exercise increases the activity of telomerase, and induces the expression of telomere repeat-binding factor 2 and Ku70 in the thoracic aorta and in leukocytes from mice and humans [217]. **The signaling pathways underlying the antioxidant actions of exercise is summarized in Fig. 4**.

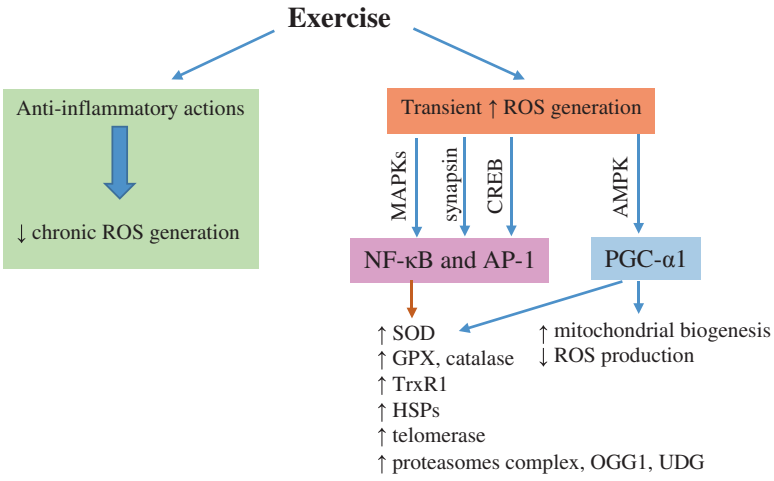

Fig. 4 Signaling pathways underlying the antioxidant actions of exercise. *AMPK* AMP-activated protein kinase, *AP-1* activator protein-1, *CREB* cAMP-response-element binding, *HSPs* heat shock proteins, *GPX* glutathione peroxidase, *MAPKs* mitogen activated protein kinases, *NF-kB* nuclear factor kappa B, *OGG1* oxoguanine DNA glycosylase, *PGC-1α* peroxisome proliferator-activated receptor gamma, coactivator 1-alpha, *SOD* superoxide dismutase, *ROS* reactive oxygen species, *TrxR1* Thioredoxin reductase 1, *UDG* uracil DNA glycosylase

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