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ABOUT COVER

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Too hard to die: Exercise training mediates specific and immediate SARS-CoV-2 protection

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Abstract

Several mechanisms may explain how exercise training mechanistically confers protection against coronavirus disease 2019 (COVID-19). Here we propose two new perspectives through which cardiorespiratory fitness may protect against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Physical exercise-activated adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling induces endothelial nitric oxide (NO) synthase (eNOS), increases NO bio-availability, and inhibits palmitoylation, leading to specific and immediate SARS-CoV-2 protection. AMPK signaling also induces angiotensin 1-7 release and enhances eNOS activation thus further mediating cardio- and reno-protection. Irisin, a myokine released from skeletal muscles during aerobic exercise, also participates in the AMPK/Akt-eNOS/NO pathway, protects mitochondrial functions in endothelial cells, and antagonizes renin angiotensin system proinflammatory action leading to reductions in genes associated with severe COVID-19 outcomes. Collectively, all the above findings point to the fact that increased AMPK and irisin activity through exercise training greatly benefits molecular processes that mediate specific, immediate, and delayed SARS-CoV-2 protection. Maintaining regular physical activity levels is a safe and affordable lifestyle strategy against the current and future pandemics and may also mitigate against obesity and cardiometabolic disease syndemics. Move more because a moving target is harder to kill.

Key Words: Adenosine monophosphate-activated protein kinase; Irisin; Physical exercise; Nitric oxide; Endothelial nitric oxide synthase; Severe acute respiratory syndrome coronavirus-2

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Core Tip: Increased nitric oxide bio-availability through exercise training-induced activation of the master regulator of metabolism, the energy-sensing cellular enzyme adenosine monophosphate-activated protein kinase and irisin, the fat browning exercise hormone, released from skeletal muscles during aerobic exercise may mediate specific, immediate, and delayed severe acute respiratory syndrome coronavirus-2 protection. Move more because a moving target is harder to kill.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of the coronavirus disease 2019 (COVID-19), has to date (December 2021) infected over 270 million people worldwide and the death tally approaches 5.5 million[1]. Evolutionary evidence supports the survival of the fittest through natural selection for pathogen resistance, with effects mediated through younger age, lifestyle choices and importantly, genetics[2]. Epidemiological data support a lower COVID-19 incidence and severity in children and adolescents[3], individuals with high cardiorespiratory fitness (CRF) and muscle strength[4] as well as certain protective erythropoietin (EPO) augmenting genetic variants[3]. At the other end of the spectrum, inactivity, obesity, insulin resistance, diabetes, and hypertension, are associated with worse SARS-CoV-2 infection course and disproportionate COVID-19 mortality risk[5,6]. Public policies should promote increased physical activity and endeavor to increase the overall physical fitness in society by all available means. This is especially imperative for the population groups associated with worse SARS-CoV-2 prognosis[7]. The scope of this minireview is to focus on the mechanistical perspectives of two novel pathways, namely adenosine monophosphate (AMP)-activated protein kinase (AMPK) and irisin, through which exercise training may mitigate against SARS-CoV-2 infection and improve COVID-19 prognosis.

We conducted a PubMed literature search for publications in the English language since the start of the pandemic until September 2021, using the keywords: “AMPK”; “Irisin”; “physical exercise”; “renin angiotensin system (RAS)”; “angiotensin-converting enzyme 2 (ACE2)”; “nitric oxide (NO)”; “endothelial nitric oxide (NO) synthase (eNOS)”; “beta common receptor (βCR)”; “SARS-CoV-2”; and “COVID-19”. We noticed a veritable dearth of publications, especially when the keywords “eNOS”, “Irisin”, “AMPK” were used in different combinations together with “physical exercise” and “SARS-CoV-2 or COVID-19” which prompted us to focus on AMPK/eNOS and Irisin. Those pathways are known for their cardiometabolic, and vascular protective properties and suggest concrete mechanisms that offer immediate and delayed SARS-CoV-2 protection[8].

HOW DOES EXERCISE IMPROVE IMMUNITY?

Several reviews have described numerous immune mechanisms which may explain how exercise training mechanistically confers protection against COVID-19. First, exercise downregulates the expression/activation of proinflammatory Toll-like receptors (TLR)[5]. Second, exercise training demonstrates an anti-inflammatory cytokine profile with increased levels of anti-inflammatory interleukin (IL)-10, IL-1 receptor antagonist (IL-1ra), and IL-37, which in turn inhibits the TLR-inflammation pathway and counteracts the inflammatory response induced by the inflammasomes[5]. In general, exercise promotes the recirculation of key immune cells and mediates an anti-inflammatory and antioxidant state through multiple mechanisms[5]. Effective rehabilitation programs for sarcopenia, could reduce inflammation and the need for IL-37 to exert its negative feedback to control the release of inflammatory cytokines[9].

NEWER PERSPECTIVES ON EXERCISE PROTECTION IN COVID-19

AMPK

A more specific mechanism with immediate antiviral effects involves AMPK. We propose two new perspectives through which high CRF may protect from SARS-CoV-2. AMPK is an energy-sensing heterotrimeric enzyme, able to detect minute changes in cellular ADP and AMP as well as glucose availability[10]. Located in various cells and organs, AMPK modulates numerous downstream targets through switching phosphorylation on-off, including targets in the RAS[11]. AMPK is activated through several physiological and pathological conditions, such as hypoxia, caloric restriction, and physiological exercise but also *via* certain well known pharmacological agents as metformin, aspirin, canagliflozin, telmisartan, and herbal substances such as resveratrol, berberine, and quercetin[11,12]. Since activating AMPK has been shown to suppresses the Angiotensin II-induced vascular smooth muscle proliferative pathway and improve cardiometabolic disease, we believe that physical exercise-induced AMPK regulation of diverse cellular pathways is a reasonable mechanism in mediating both immediate and delayed SARS-CoV-2 protection (Figure 1)[11,13,14]. Physiological exercise induces AMPK activation as an important molecular mechanism of adaptation after physical activity. AMPK-eNOS phosphorylation-activated formation of NO appears to be a signal that impacts metabolic activity[15]. Mice with an eNOS mutation that prevents AMPK-dependent phosphorylation and impedes NO-biosynthesis develop hyperinsulinemia and insulin resistance with high fasting blood sugar, increased adiposity, elevated inflammatory markers and weight gain when fed a high-fat diet[16]. eNOS phosphorylation through AMPK will lead to increased NO generation and NO bio-availability in the lung and blood vessels[17]. Host endothelium is where the critical COVID-19 battle between SARS-CoV-2 and the host is fought with NO as one of the main contenders (Figure 1)[18]. SARS-CoV-2 spike (S) protein induces endotheliitis *via* downregulation of angiotensin-converting enzyme 2 (ACE2) and NO impairment[18]. At the same time, increased generation and bio-availability of NO inhibits SARS-CoV-1/2[19] replication through two clearly different mechanisms: (1) Decline in the production of viral RNA in the very first stages of viral replication; and (2) decrease in the palmitoylation of nascently-expressed S protein that impacts the fusion of the S protein with ACE2[20]. Similar NO effects are presumed for SARS-CoV-2, given both SARS-CoV-1/2 engage ACE2 in the same manner[21]. Palmitoylation of SARS-CoV-2 S protein is critical in controlling membrane fusion and virion infectivity[22]. Inhibition of acetyl-CoA carboxylase by AMPK will directly inhibit palmitate synthesis thus engendering additional SARS-CoV-2 protection[23]. In addition, orlistat, a pharmaceutical substance used in weight loss treatment also inhibits fatty acid synthase[23]. Through both mechanisms of increased NO bio-availability and directly reducing palmitate synthesis, physical exercise engenders specific and immediate SARS-CoV-2 protection[20,22,23].

Chronic exercise induces EPO elevation, a well-known neuroprotective hormone, which mediates COVID-19 protection[3]. EPO's protective effects are mediated through AMPK-dependent signaling, leading to enhanced phosphorylation of the beta common receptor (β cR) and eNOS, increased β cR-AMPK-eNOS complex formation, NO production, increased NO bio-availability, and ultimately tissue protection (Figure 1)[24]. Elevated, protective EPO mRNA levels were recently reported to be 2.6 times higher in nasopharyngeal swab samples of adult SARS-CoV-2 patients that were asymptomatic or showing mild COVID-19 symptoms, as compared to a control group[25]. Patients with acute respiratory distress syndrome (ARDS) in a moderate-sized COVID-19 cohort showed lower soluble eNOS levels, implying that greater eNOS activity and the presumed increased NO synthesis probably prevent patients from serious lung complications[26]. Fluvoxamine, intensely investigated as a SARS-CoV-2 protective agent, also mediates its action through sigma-1 receptor (S1R) agonism that induces eNOS, albeit *via* phosphatidylinositol-3-kinase and protein kinase B signaling[27].

Moreover, AMPK signaling exerts beneficial effects through RAS by elevating the protective arm of ACE2 and angiotensin (Ang) 1-7 through the Mas receptor (MasR) (Figure 1)[11]. Phosphorylation of ACE2 by AMPK enhances the stability of ACE2 and increases Ang 1-7 and eNOS-derived NO bio-availability further sustaining increased, protective NO levels[28]. Reduced inflammatory responses in lung emphysema, mitigation of pulmonary hypertension and protection against lipopolysaccharide-induced acute lung injury and ARDS have been reported with increased AMPK signaling[28-30]. Later in the course of SARS-CoV-2 infection, AMPK/ACE2/Ang 1-7/MasR-induced NO-increase may be cardio-, and renoprotective through lower oxidative stress, apoptosis, and systemic inflammatory responses[11,31].

Irisin perspectives in COVID-19

Irisin is a myokine, cleaved as a peptide hormone of 112 amino acids from fibronectin type III domain containing 5 in skeletal muscle and secreted during aerobic exercise[32]. Irisin is positively correlated with an active lifestyle and vigorous intensity physical activity[32]. Both aerobic and resistance exercise are associated with high irisin levels, especially in older age groups[32]. Irisin is involved in muscle hyper-trophy and controls energy levels in muscle, participates in glucose homeostasis and browning of white adipose tissue, and has been implicated in exercise-induced neuroprotection as it is highly expressed in the brain[33,34]. Furthermore, exercise-derived irisin reduces arterial stiffness and lowers

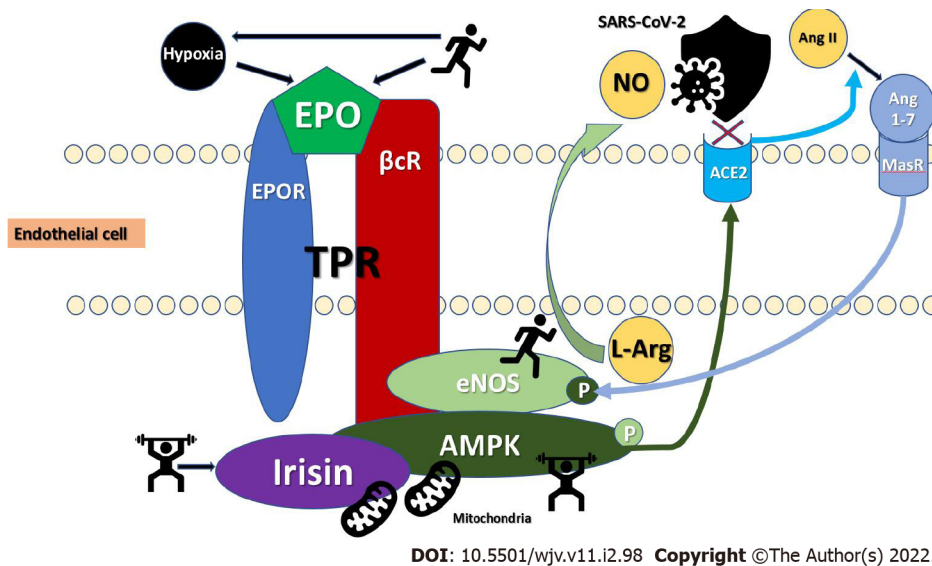


Figure 1 Molecular mechanisms of exercise. Chronic exercise induces transient hypoxia and elevates erythropoietin (EPO) that induces endothelial nitric oxide synthase (eNOS) via the tissue protective receptor (EPOR/ β cR). Exercise activates adenosine monophosphate-activated protein kinase (AMPK) and releases Irisin, resulting in eNOS activation and subsequent nitric oxide production inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication and mitigating cell entry (X). AMPK stabilizes angiotensin-converting enzyme (ACE) 2 and increases protective angiotensin (Ang) 1-7 conversion which in turn activates eNOS via the MasR. Irisin also exerts protective functions on mitochondria. AMPK: Adenosine monophosphate-activated protein kinase; EPO: Erythropoietin; EPOR: EPO receptor; β cR: β -common receptor; TPR: Tissue protective receptor; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; L-Arg: Arginine; ACE2: Angiotensin-converting enzyme 2; Ang II: Angiotensin II; Ang1-7: Angiotensin 1-7; MasR: Mas receptor; P: Phosphorylation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

blood pressure through activation of the AMPK/Akt-eNOS/NO pathway and has thus the potential to impact cardiovascular health (Figure 1)[8,35]. Irisin also protects mitochondrial function in endothelial cells and benefits endothelial barrier integrity through the integrin α V β 5 receptor and activated AMPK signaling[36]. Moreover, irisin can directly antagonize Ang II-induced cardiac profibrotic response *in vitro* as well as *in vivo*[37]. In addition, serum irisin levels were decreased and negatively correlated with disease severity and mortality in ARDS patients[36]. Recently, irisin modulation of genes associated with severe COVID-19 outcomes was reported in human subcutaneous adipocyte cell culture[38].

Collectively, all the above findings point to the fact that increased AMPK and irisin activity with exercise training greatly benefits molecular processes that mediate specific, immediate, and delayed SARS-CoV-2 protection.

CONCLUSION

Evolution arms us with ingenious and adaptive defense structures - our immune system, musculature, and cardiovascular system. Increased CRF through regular aerobic exertion and resistance exercise, greatly benefits all the above systems promoting survival and longevity[5]. Regular physical exercise enhances vaccination response and immunoprotection[5]. Maintaining regular physical activity levels along with prudent and balanced nutrition are safe and affordable lifestyle strategies against the current and future pandemics. Physical exercise may also reverse insulin resistance, alleviate hypertension, and mitigate against obesity and cardiometabolic disease syndemics[39]. While observing social distancing, exercise is still possible in public indoor spaces or outdoors. Exercise prescription for vulnerable groups and free or subsidized use of digital technology with online platforms delivering exercise classes could be employed to achieve the recommended exercise guidelines. For greater health benefits, 300 min of aerobic activity is recommended along with strength training exercises for all major muscle groups at least two times a week[40]. "Work from home" directives along with time savings from daily commuting have potentially freed up time for exercise that can be achievable in the home environment. The beneficial effects of exercise training in communicable and non-communicable disease prevention must remain central when deciding appropriate public health policies and subsidies. Government bodies should heed the Damoclean warning in this pandemic of the excess mortality threatening over 500 million people affected with obesity and diabetes worldwide or risk new hecatombs. We may have to learn to live with the virus for many years to come. It is thus imperative, on an individual level, to devise personal strategies for exercise training that do not depend on access to public gymnasiums. The takeaway message is once again to move more because a moving target is harder to kill.

FOOTNOTES

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