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Physical activity and maintaining of the proteome in the aging process - are these footsteps on the way to longevity?

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Abstract

Accumulation of dysfunctional and damaged cellular proteins and organelles occurs during aging, resulting in a perturbation of cell homeostasis and inexorable degeneration up to cellular death. Therefore, moderating these components may be a key in the promotion of longevity. Exercise is known to promote healthy aging and mitigate age-related pathologies, and recent studies suggest that exercise modulates the proteome. Autophagy is an evolutionary conserved recycling pathway managing degradation, and it declines during aging. The target of rapamycin complex 1 (TORC1), a central kinase involved in protein translation, is a negative regulator of autophagy, and inhibition of TORC1 enhances lifespan. As a consequence, the longevity effects of exercise may stem from the maintenance of the proteome by balancing the synthesis and recycling of intracellular proteins, and thus may promote longevity.

Participation in vigorous physical activity at a specific time point is an indicator of good fitness and health and is associated with a reduced risk of death. However, randomized controlled trials (RCTs) and translational models have not provided strong evidence to show that physical activity started during adulthood extends lifespan and promotes longevity. Physical activity improves fitness and physical function, and confers other health-related effects.

Keywords: harmful binomial distress - aging, movement and physical activity, mTOR, stress, muscular contraction, autophagy, longevity.

Introduction

Aging is a biological process characterized at the cellular level by a progressive accumulation of dysfunctional proteins and damaged cell compartments. Accumulation and aggregation of these impaired components disrupt cellular homeostasis, progressive degeneration may appear, and the risk of cell death is increased (López-Otín et al., 2013).

Intracellular protein quality concurrently depends upon protein synthesis (Salminen & Kaarniranta, 2009). As such, the degradation of unnecessary and dysfunctional cytosolic elements, occurring through the autophagy process, represents only one aspect of intracellular protein deposits, which is counterbalanced by the regulatory components managing the synthesis of new cellular proteins.

The target of rapamycin complex 1 (TORC1; known as mTORC1 in mammalian species) is a central regulatory kinase that regulates cellular growth and protein synthesis. This complex is stimulated by nutrient availability (i.e. amino acids, ions), mechanical stress, and growth factors (i.e. insulin-like growth factor 1 – IGF-1) and is inhibited by nutrient starvation, energetic stress, and the macrocyclic polyketide *rapamycin* (Jung et al., 2010).

Recently, TORC1 activity has been linked to lifespan and the aging process in a variety of model organisms, whereby inhibition of the TORC1 pathway is consistently observed to enhance longevity in animal and cellular models (Lamming et al, 2013). TORC1 also serves as an inhibitor of autophagy, thus suggesting that autophagy represents a key link between TORC1 activity and the aging process (Xu et al., 2013).

Neither randomized controlled trials (RCTs) nor experimental animal studies have provided good evidence that *physical activity* initiated during adulthood prolongs lifespan, but on the other hand it was demonstrated that physical activity improves fitness and physical function and helps in the prevention of disability (Pasanen et al., 2017). The risk of death during exercise is low and the risk of sudden cardiac death is increased during episodic physical

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activity (Dahabreh & Paulus, 2017). People who usually exercised fewer times per week (once instead of four or five times) had higher relative health risks (Dahabreh & Paulus, 2017). Therefore, increasing levels of habitual physical activity were associated with progressively lower relative risks of myocardial infarction during episodic heavy physical activity (Mittleman et al., 1993). Plaque rupture represents one of the most unpredictable mechanistic causes for sudden death during or after physical exercise among individuals with coronary artery disease, as well as in apparently healthy individuals (Ciampricotti et al., 1990; Burke et al., 1993).

The correlation between the TOR pathway and the aging process

A less researched aspect in recent years has been the role of aging (Meijer et al., 2015). It is not due to the chance that chronic diseases occur simultaneously in most species when individuals reach two thirds of their lifespan, for example at about 60 years in humans. In conclusion, it is not time itself that becomes a variable, but the aging process and *the quality of the components* that are part of it. Thus, the causality of the disease is not given as in the previous century by pathogens or precarious environmental factors. Researchers have identified molecular and cellular mechanisms / pathways that inexorably lead to aging (Bjedov et al., 2010; Vellai et al., 2003). Thus, new pharmacological therapeutic options and dietary supplements such as rapamycin (Wu et al., 2013) and senolytics have been made available (Harrison et al., 2016).

It was predicted in 2003 that the irreversible transformation from cell maturation arrest to senescence (geroconversion) is determined by growth-promoting mediators, such as mTOR, when the cell cycle is blocked (Bitto et al., 2016). Figuratively, geroconversion is "tangled" growth, which occurs only when maturation is complete (Lee et al., 2010; Vincze & Vincze-Tiszay, 2020). In cell cultures, mTOR is activated to the maximum and geroconversion lasts 3-6 days, while in the human body it can take up to a few decades. MTOR drives geroconversion, making cells hypertrophic and hyperfunctional (e.g., secretory phenotype associated with senescence), leading to the development of age-related pathologies. Human fibroblasts, either presenescent (PRE) or senescent (SEN), have been immunostained for inflammatory cytokines such as IL-6 and IL-8 and the senescence marker p16 (Colhero et al., 2016). Various natural compounds have been reported, including epigallocatechin gallate (EGCG), caffeine, curcumin and resveratrol or berberine which inhibit mTOR when applied on cells isolated in cultures, or even diets have been proposed with modest results (Vaupel, 2010) (Fig. 1).

It is known that meclofenoxate (also known as centrophenoxine) is a cholinergic nootropic used as a dietary supplement. Chemically, it is an ester of dimethylethanolamine (DMAE) and 4-chlorophenoxyacetic acid (pCPA). In elderly patients, meclofenoxate has been shown to improve performance on certain memory tests. Meclofenoxate also increases cell membrane phospholipids (Stringhini et al., 2017). Meclofenoxate, as well as DMAE, has been shown to increase the lifespan of mice by 30–50% (Karvinen et al., 2015).

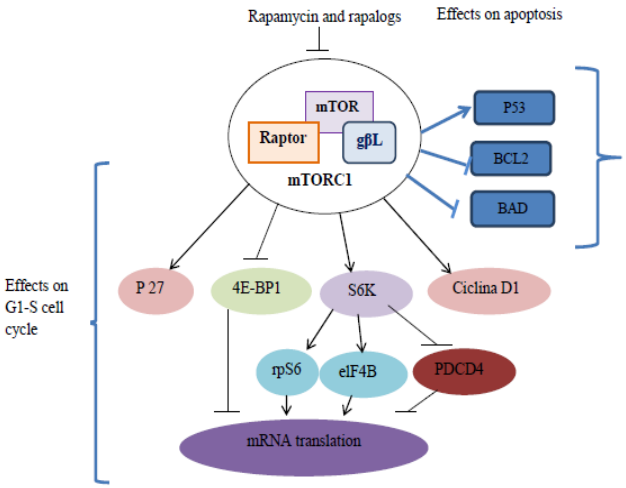

Fig. 1 – Effects of rapamycin and rapalogs on neoplastic cells.

Target of mTORC1 is one of two functionally distinct multi-protein TOR complexes, the second being TOR complex 2 (TORC2). Both complexes are highly conserved in all known eukaryotic cells. TORC1 is a primary mediator of protein synthesis and cell growth, whereas TORC2 remains less understood. TORC2 has been suggested to regulate spatial coordination of the cytoskeleton (Xu et al., 2013), while also being involved in TORC1 activation via the Akt pathway (Jung et al., 2010). Acute rapamycin treatment strongly inhibits TORC1 activity, but the effects of TORC2 are not fully characterized; as rapamycin cannot bind to the fully assembled TORC2, complex chronic rapamycin treatment can also disrupt TORC2 activity. Knowing that inhibition of TORC1 pathway extends lifespan and promotes healthy aging in multiple model species (Laplante & Sabatini, 2012) and that TORC1 also acts as an *inhibitor of autophagy*, we could presume that the lifespan-extending effects of TORC1 inhibition will directly and partially increase autophagic activity, reduce the synthesis of new intracellular proteins, or may be some combination of the two (Xu et al., 2013; Meijer et al., 2015).

It is a plausible hypothesis that increasing protein synthetic activity via TORC1 in post-mitotic cells (i.e. mature cells which have entered cell cycle arrest and no longer split) leads to less autophagy, and consequently the accumulation of superfluous organelles (Xu et al., 2013). What is interesting is that knockdown of *Atg genes* is critical to autophagic function, because it reverses the life-extending effects of rapamycin, allowing to conclude that autophagy does play a key role in TORC1-mediated life extension (Bjedov et al., 2010).

The first observation of extended lifespan due to TORC1 inhibition was made in *Caenorhabditis elegans*, where reducing TORC1 increased lifespan more than twofold (Vellai et al, 2003). In mice, the direct genetic knockdown of mTORC1 resulted in a 20% lifespan extension and a prominent reduction in age-associated pathologies (Wu et al., 2013). Administration of rapamycin at 600 days in mice (equivalent to 50 years in homo sapiens) extended

lifespan up to 14% in female and only 9% in male animals (Harrison et al., 2009). Additionally, 3 months of rapamycin treatment increased life expectancy by up to 60% in middle-aged mice (Bitto et al., 2016). In contrast, silencing expression of *Sestrin*, a TORC1 inhibitor, has been shown to instigate numerous age-related pathologies (Lee et al., 2010).

Movement and physical activity – anti-aging factors

Distress, vulnerability and adaptation are studied comparatively in human ontogenesis during young, adult and old stages of life. The analysis of the negative temporal interrelationships between distress, the exhaustion phase of General Adaptation Syndrome (GAS) originally described by Selye and aging leads to the concept of harmful binomial distress ↔ aging (Riga & Riga, 2009).

This binomial manifests its adverse consequences through muscle hypokinesia or lack of movement of the individual. In addition to well known risk factors such as obesity, lack of physical activity and the inflammatory effect of oxidative stress, it will add exponentially decreased muscle mass and physiological malfunction (sarcopenia), osteoporosis and an increased risk of fractures.

a) Emergence of longevity

Some individuals can survive to old age, even in populations with a relatively low mean life expectancy. In human and animal populations, a low mean life expectancy is associated with low lifespan *equality* (Colhero et al., 2016).

Progress made in lengthening the human lifespan reflects contemporary medical practice and good public health systems, combined with rising standards of living, superior education and healthier nutrition and lifestyle (Vaupel, 2010). Interestingly, the association between socioeconomic status and mortality is comparable in strength and consistency to that of tobacco use, alcohol misuse, sedentariness, hypertension, obesity and diabetes, with smoking having the highest risk estimate (Stringhini, 2017).

b) Bias in interpretation of observational data and risk of death

Unfortunately, a causal relationship between adulthood physical activity and mortality/lifespan has neither been confirmed in randomized controlled intervention studies with initially healthy individuals (Karvinen et al., 2015) nor in animal experiments (Garcia-Valles et al., 2013).

In the first place, selection bias in the population is an alternative explanation. Aged individuals who are healthy enough to exercise (without any chronic disease) will manifest a reduced risk of death irrelevant of their physical activity level. Secondly, studies comparing the predictive role of physical activity at younger versus older age show that older age physical activity is a stronger predictor of death (Bijnen et al., 1999). High cardiorespiratory fitness, as an integrated measure of body function, together with neuromuscular and metabolic function, is a strong predictor of reduced mortality in humans (Kodama et al., 2015) and in rats (Koch et al., 2011). Low cardiorespiratory fitness is associated with an increased risk of multiple chronic diseases and death (Ross et al., 2016).

To increase our understanding of the associations between genes, physical activity and mortality, a study was carried out on separated human dizygotic (DZ) and monozygotic (MZ) twin pairs who were long-term discordant for vigorous physical activity. High heritability of physical activity reduced the number of MZ pairs discordant for physical activity and thus contributed to the only moderate statistical power in analyzing pairwise risk differences among MZ pairs (Karvinen et al., 2015). Therefore, genetic pleiotropy may partly explain the associations observed between high physical activity and mortality in epidemiological studies, and secondly, the inherited aerobic capacity is a predictor of longevity (Kujala et al., 2003). In rodents, physical activity initiated during adulthood (in twins after moving from the childhood home environment or in full-grown animals) did not improve longevity.

Physical activity mismatches in results among DZ pairs may occur due to genetic differences and only findings from MZ pairs control for genes at sequence level. Mendelian randomization analyses (Kennedy et al., 2014) and studies on genetic pleiotropy (Mannick et al., 2014) could also help in clarifying the role of genetic factors. Researchers have tried to develop useful biomarkers of aging to investigate which factors play a role in accelerating or decelerating the inexorable aging process. Biomarkers such as measuring telomere length (Justice et al., 2019) or DNA methylation age (epigenetic clock) could be the answers (Demidenko & Blagosklonny, 2008). Shortening of telomeres that induces cell senescence or apoptosis is associated with shortened life expectancy. Unfortunately, based on a recent meta-analysis, no consistent association has been found between physical activity and telomere length (Justice et al, 2019).

c) Evidence from randomized controlled trials

So far, RCTs have failed to provide conclusive evidence that exercise can extend lifespan/reduce premature deaths when individuals apparently healthy at baseline are randomized to physical activity/exercise versus control groups.

In the LIFE Study, a number of 1635 sedentary individuals aged 70-89 years were assessed (Newman et al., 2016). The intervention was aerobically-based, with a moderately intensive physical activity program, but the results showed no reduction of cardiovascular events although the intervention was effective in preventing mobility disability. Similarly, the Look AHEAD Study of 5145 overweight or obese patients with type 2 diabetes (Wing et al., 2013), including a combination of increased physical activity and improved diet intervention, demonstrated a difference in fitness between the intervention and control groups, but no difference in cardiovascular events.

d) Exercise may maintain the proteome

Exercise may increase autophagic activity in exercised muscle due to cellular mechanisms, including widespread protein or mitochondrial damage, increased mitochondrial respiration, high concentrations of reactive oxygen species (ROS), the presence of certain cytokines or other elements of the immune cascade (Vainshtein & Hood, 2016).

During physical exercise, autophagy mediates the clearance of proteins and organelles damaged by heat, pH changes or mechanical stress, which in fact acts against

the accumulation of cytosolic components and maintains a good myocyte function (Schwalm et al., 2015). Moreover, alterations in calcium, NAD+, and ROS levels are also strong instigators of autophagic activity (Vainshtein & Hood, 2016). Unlike other tissues such as the liver and pancreas, upregulation of autophagy in skeletal muscle persists for days, rather than hours (pancreas or liver), following a period of energy insufficiency, indicating a greater importance of autophagic function in skeletal muscle proteostasis (Sandri, 2010).

Exercise seems to start autophagy in skeletal muscle through AMPK and SIRT1which are sensitive to alterations in AMP and NAD+, respectively. AMPK and SIRT1 actions are to upregulate expression of Atgs by increasing PGC1-α activity, activating FOXO1 and FOXO3 and inhibiting mTORC1 (Vainshtein & Hood, 2016). On the other hand, AMPK initiates autophagosome formation via ULK1 (Mooren & Kruger, 2015).

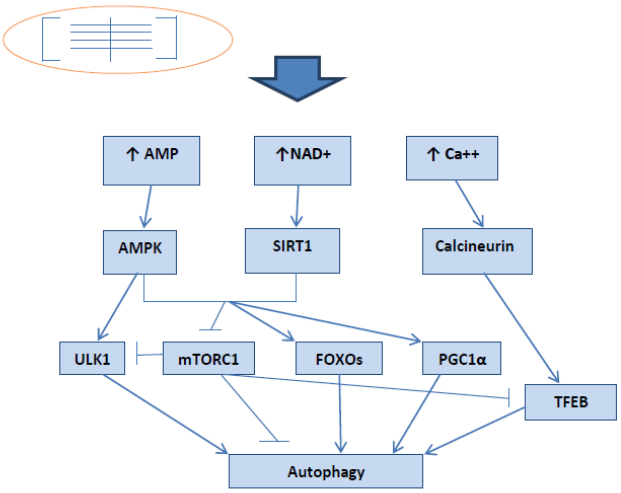

Fig. 2 – Skeletal muscle contraction.

AMPK is also sensitive to changes in the cellular AMP /ATP ratio and so it may be quite increased during exercise (Mooren & Kruger, 2015). The influence of exercise on mTORC1 activation also depends *on the type* of exercise performed, as mTORC1 *integrates* stimuli from growth factors, existing nutrients, and mechanical loading (i.e. resistance exercise type) (Watson & Baar, 2014). While energy demands induce a downregulation of mTORC1-mediated anabolism during exercise that is likely affected via AMPK activation, mTORC1 activity is upregulated in the adaptive post-exercise period, as opposed to a continuing high activity of AMPK (Rowlands et al., 2011) (Fig. 2).

Autophagy possesses a role in conferring the benefits of exercise, including enhanced endurance, mitochondrial biogenesis and angiogenesis (Lira et al., 2013). Chaperone-mediated selective autophagy has also been shown to be involved in skeletal muscle cytoskeleton maintenance and adaptation in response to resistance training (Ulbricht et al., 2015).

Also, exercise increased autophagic flux in the *anterior cerebral cortex* (He et al., 2012). The authors defined physical exercise as a newly created inducer of autophagy *in vivo* and they generated mice with a knock-in non-phosphorylatable mutation in BCL2 (BCL2 AAA), which are defective in exercise- and starvation-induced autophagy but not in basal autophagy (Yang et al., 2014). The results were that BCL2 AAA mice could not run on a treadmill as long as wild-type mice, and did not undergo exercise-mediated increases in skeletal muscle glucose uptake. Unlike wild-type mice, BCL2 AAA mice failed to reverse high-fat diet-induced glucose intolerance after 8 weeks of exercise training, possibly due to defects in signaling pathways that regulate myocyte glucose uptake and metabolism during exercise (He et al., 2012). Secondly, treadmill exercise also induces autophagy in the cerebral cortex of adult animals. Therefore, autophagy may mediate the beneficial effects of exercise in neurodegeneration, neurogenesis, and improve overall cognitive function (Ulbricht et al., 2015).

These mechanisms suggest that exercise has a role in modulating some of the age-related pathologies in which autophagy has been reported to be implicated, which include neurodegeneration (Yang et al., 2014), type 2 diabetes (Quan et al., 2013), neoplasm (Cecoconi & Levine, 2008) or cardiomyopathy (Nair & Ren, 2012), while improving muscle quality and overall function (Fan et al., 2016). Autophagy and mTORC1 represent a key in proteostatic pathways and are involved in aging phenotype (Rubinsztein et al., 2011; Wei et al., 2013). On the one hand, autophagic function declines during aging (Mejias-Pena et al., 2016) and on the other hand, there is empirical support for the important influence of autophagy on organismal lifespan (Martinez-Lopez et al., 2015; Jung et al., 2010).

MTORC1 inhibition is known to upregulate autophagic activity; therefore, there is good evidence of a potent role for autophagy in the aging process, and consequently, reductions in mTORC1 activity may also attenuate aging in an autophagy-independent manner (Xu et al., 2013).

In humans and rodents, acute exercise has been proved to promote autophagic activity in multiple tissues (He et al., 2012; Mooren et al., 2015; Schwalm et al., 2015), and chronic exercise may also induce upregulation of basal autophagy levels (Lira et al., 2015; Feng et al., 2011).

Conclusions

1. Based on observational population studies, high physical activity is associated with a reduced risk of premature death, but the causal relationship remains unproven. Participation in physical activity at a *specific time point* is an indicator of good fitness and health, and is associated with a reduced risk of death. Lifelong physical activity may extend lifespan, but evidence from interventional studies is limited and the potential effects of early adulthood physical activity versus inactivity on later health require more research. The possible life-shortening effects of vigorous physical activity are not completely demonstrated or understood.

2. Physical activity improves fitness and physical function, and confers other health-related benefits. These outcomes have a greater basis in terms of evidence-based data than any claims of a reduced risk of death, especially when recommending physical activity for previously

physically inactive middle-aged and elderly adults.

3. It seems that maintenance of the proteome and organelle population is an important key to the augmentation of lifespan and/or attenuation of many pathologies associated with the aging process. Given that there is quite good evidence that regular exercise promotes healthy aging and mitigates age-related pathologies, it is possible to speculate that there is a common pathway in health and longevity which may be due to proteostatic maintenance. Currently, our understanding of the molecular mechanisms underlying cellular and biological aging and the interplay between physical activity and aging phenotype development requires further trials, especially in humans.

4. Movement, physical activity and sport are key sanogenetic factors in the bio-psycho-social activation context of the elderly. Therefore, physical activity as a goal for health is recommended to be implemented in the elderly population. At individual level, regular physical activity increases muscle mass and strength, improves the functioning of the cardiovascular system, and enhances cognition.

Conflict of interests

None declared.

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