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Exercise Attenuates the Major Hallmarks of Aging

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Abstract

Regular exercise has multi-system anti-aging effects. Here we summarize how exercise impacts the major hallmarks of aging. We propose that, besides searching for novel pharmaceutical targets of the aging process, more research efforts should be devoted to gaining insights into the molecular mediators of the benefits of exercise and to implement effective exercise interventions for elderly people.

Introduction

The number of people aged ≥60 years worldwide is expected to nearly triple by 2050, with the ''oldest old'' group (≥85 years) being the most rapidly expanding segment. A growing challenge is to maintain elderly people independently until end of life. In them, functional independence is directly dependent on physical fitness, *i.e.* ''the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy [leisure] pursuits and to meet unforeseen emergencies.''[1] In turn, physical fitness is determined by several measurable health-related phenotypes, including mainly cardiorespiratory fitness and muscle function.[1] Among the physiological changes associated with aging, those affecting the cardiorespiratory and vascular system and skeletal muscles most affect physical fitness, whereas exercise can attenuate multisystem age declines, as explained below.

Summary of the Impact of Aging on the Main Physical Fitness—Related Phenotypes

Aging and cardiorespiratory fitness

Maximal oxygen uptake (VO_2max; sometimes referred to as maximal aerobic capacity or simply aerobic capacity or aerobic endurance) is a main indicator of cardiorespiratory fitness. There is variability among studies,[2–4] but the average rate of VO_2max decline in old people is ≥4–5 $mL \cdot kg^{-1} \cdot min^{-1}$/decade.[5] Mostly reduced maximal cardiac output[6–10] but also a decline in maximal arteriovenous oxygen difference (a-vO_2 diff) (minus ~3%/decade)[7,11] contribute to age reductions in VO_2max.[12,13] Aging skeletal muscles have a low capacity to use O_2 due to several factors, such as decreased muscle mass (see below),[14,15] increased peripheral resistance,[16] reduced muscle capillary density,[17] endothelial dysfunction,[18] changes in skeletal muscle microcirculation,[19] and reduced muscle oxidative capacity.[20]

Aging and muscle function

Muscle mass usually starts to decline after 25–30 years of age,[21,22] such that on average 40% of muscle mass is lost by 80 years.[22,23] In turn, a quantitative loss in muscle cross-sectional area is a major contributor to the decrease in muscle strength seen with advancing age, *i.e.*, after 60–70 years of age.[24] The term ''sarcopenia'' was originally created to refer to age-related loss of muscle mass with consequent loss of strength.[25] There are now four international definitions of sarcopenia.[26–29] In essence they all agree, requiring a measure of impaired walking capability (either low gait speed or a limited endurance [distance] in a 6-min walk), together with an appendicular lean mass of less than 2 standard deviations of a sex- and ethnically-corrected normal level for individuals 20–30 years old. Sarcopenia (see below for details on signaling pathways involved) occurs due

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to several age-related factors, such as gradual muscle denervation,[23,30] diminished satellite cells,[31] low muscle protein synthesis,[32] low anabolic hormone levels,[33] malnutrition,[34] increased pro-inflammatory cytokines,[35] oxidative stress,[36] mitochondrial dysfunction,[37–40] and physical inactivity.[41] Although there are differences between studies, on average, 5%–13% and 11%–50% of people aged 60–70 years and ≥80 years, respectively, suffer sarcopenia,[42–47] with a higher prevalence (68%) reported in nursing home residents ≥70 years.[48] Sarcopenia needs to be differentiated from ''cachexia,'' a combination of both muscle and fat loss that is usually attributable to an excess of catabolic cytokines associated with a disease process, *e.g.*, cancer.[49–51] Sarcopenia is linked with increased disability, falls, hospitalization, nursing home admission, and mortality.[48,52–54]

Frailty and disability

A consequence of the aforementioned effects of aging on cardiorespiratory and muscle fitness (especially sarcopenia), alone or in combination with co-morbidities such as neurodegeneration, is the ''frailty syndrome.''[55] Although no single operational definition of the frailty syndrome has been agreed upon, two major definitions with proposed assessment tools have predominated over the past decade—the frailty phenotype, also known as Fried's definition,[56] and the frailty index.[57] The most widely cited is the frailty phenotype, which is operationalized as a syndrome meeting three or more of the following five phenotypic criteria: Weakness as measured by low grip strength, slowness (low walking speed), low level of physical activity, low energy or self-reported exhaustion, and unintentional weight loss.[56] A prefrail stage, in which one or two criteria are present, identifies a subset at high risk of progressing to frailty. Older individuals with none of the above five criteria are classified as nonfrail. The frailty index was developed on the basis of a comprehensive geriatric assessment by counting the number of deficits accumulated, including diseases, physical and cognitive impairments, psychosocial risk factors, and common geriatric syndromes other than frailty.[57,58] Whereas the frailty index may have clinical utility in risk assessment and stratification, it is less clear that it adds significant value to comprehensive geriatric assessment.[59]

Frailty is an important and growing problem in aging western populations, because it potentially affects 20%–30% of adults older than 75 years.[60] For instance, the prevalence of prefrail and frail individuals is high in the Spanish population (41.8% and 8.4%, respectively) and increases with age, according to a recent a population-based study conducted on 2488 individuals aged 65 years and older in a central area of the country.[61] On the other hand, frailty could eventually result in disability,[62], *i.e.*, ''difficulty or dependency in carrying out activities necessary for independent living, including roles, tasks needed for self-care and household chores, and other activities important for a person's quality of life.''[63]

For the above-mentioned reasons, it is of paramount medical importance to attenuate age-related declines in physical fitness. Yet no single drug can reverse the age-related loss of physical fitness because none benefits all of the systems involved, whereas regular exercise has multi-system anti-aging effects (see below and Fig. 1, left column for a summary).

Exercise Attenuates Fitness and Multisystem Age-Related Declines

Benefits of exercise (particularly aerobic exercise) in cardiorespiratory fitness/cardiovascular disease

Regular exercise, particularly dynamic exercise of moderate intensity (≤70% of VO_2max or ≤80% of maximum heart rate) involving mostly the aerobic energy pathway and large muscle mass (*e.g.*, brisk walking, bicycling) attenuates age declines in cardiorespiratory fitness (see Chodzko-Zajko et al.[64] for an in-depth review and experts' recommendations). This type of exercise, commonly referred to as ''aerobic exercise'' (or ''endurance exercise''), has a restoring effect on an important risk factor of cardiovascular disease (CVD), *i.e.*, endothelial dysfunction.[65–67] It also increases endothelial nitric oxide (NO•) production and thus vascular tone regulation. Regular bouts of exercise-increased laminar flow activate (through phosphorylation via protein kinase B, Akt) endothelial NO• synthase while attenuating NO• degradation into reactive oxygen species (ROS) and reactive nitrogen species.[68] Together with increased angiogenesis (see further below), an additional benefit of aerobic exercise in endothelial health is stimulation of macrophage-mediated reverse cholesterol transport through activation of peroxisome proliferator-activated receptor gamma (PPARγ).[69,70] Yet aging autonomic dysfunction has a synergistic effect together with endothelial dysfunction in increasing CVD risk[71] and raises the risk of a leading cause of death in most industrialized countries, sudden death due to ventricular fibrillation.[72]

During aging, the sympathetic nervous system (SNS) outflow to several peripheral tissues increases to stimulate thermogenesis and thus to prevent increasing adiposity.[73] Chronically activated SNS has deleterious effects on the cardiovascular system, *i.e.*, reduced leg blood flow, increased arterial blood pressure, impaired baroreflex function and hypertrophy of large arteries; it can also increase insulin resistance, thereby raising the risk of metabolic syndrome.[74,75] Importantly, aerobic exercise training (*e.g.*, brisk walking) has a beneficial, dose–response effect in attenuating aging autonomic system dysfunction, with trained elderly individuals showing similar baroreflex function compared with their moderately active younger peers.[76] Heart rate variability (HRV), a marker of autonomic function and a powerful predictor of CVD outcome (high HRV is associated with a better prognosis), increases with aerobic exercise training in old people.[77] Reduced angiotensin II, increased NO•, and mainly improved vagal modulation and decreased sympathetic tone are implicated in the beneficial exercise effects on HRV.[78]

Benefits of exercise (particularly resistance exercise) in the aging muscle function

Training programs, especially if including resistance (strength) exercises (*i.e.*, movements, such as weightlifting or exercises with resistance bands, performed against a specific external force that is regularly increased during training) are especially useful for improving muscle mass and/or strength in the elderly,[79] including in the oldest old[80] (see Table 1 for a summary of controlled exercise interventions [mostly based on resistance exercises] in the oldest

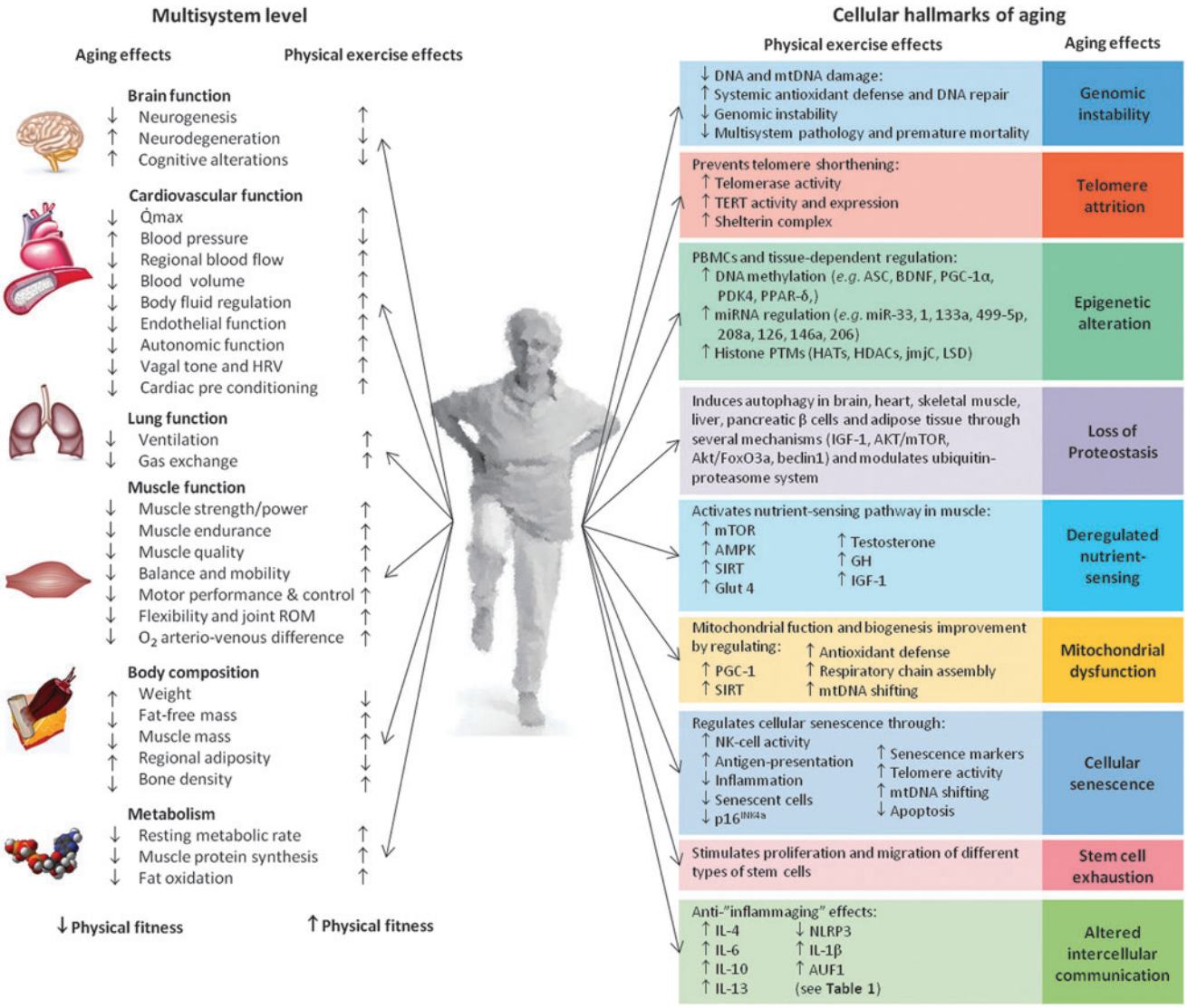

FIG. 1. Summary of the main anti-aging effects of regular exercise vs. aging effects at the multi-systemic (*left*; see Chodzko-Zajko et al.[64] for an in-depth review) and cellular level (*right*; see text). AKT, protein kinase B; AMPK, AMP-activated protein kinase; ASC, apoptosis-associated speck-like protein caspase; AUF1, AU-binding factor 1; BDNF, brain-derived neurotrophic factor; FoxO3a, human protein encoded by the FOXO3 gene; Glut 4, glucose transporter type 4; HATs, histone acetyltransferases; HDACs, histone deacetylases; HRV, heart rate variability; IGF-1, insulin-like growth factor 1; IL, interleukin; jmjC, jumonji C proteins; LSD, lysine-specific histone demethylase; miR, micro-RNA; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; NK cell, natural killer cell; NLRP3, NOD-like receptor protein 3; PBMCs, peripheral blood mononucleated cells; PDK4, pyruvate dehydrogenase kinase isoenzyme 4; PGC-1, peroxisome proliferator-activated receptor gamma coactivator 1; PPAR-δ, peroxisome proliferator-activated receptor δ; PTMs, post-translational modifications; Qmax, maximal cardiac output; ROM, range of motion; SIRT, sirtuin; TERT, human telomerase reverse transcriptase. Color images available online at www.liebertpub.com/rej

old). In general, published resistance exercise interventions in old people had a duration ranging from 4 to 48 weeks and were in agreement with accepted or ''traditional'' exercise recommendations for older people,[81] with the usual weekly schedule including two to three nonconsecutive sessions with one to three sets of 10–15 repetitions of classic weightlifting exercises, such as leg presses.

Other interventions feasible in old people include ''high-velocity resistance training,'' *i.e.*, focusing on speed of movement,[82,83] or even explosive-type heavy-resistance training, *e.g.,* weightlifting exercises with a load equivalent to 75%–80% of one repetition maximum (1RM) and performed with maximal intentional acceleration of the training load during the concentric movement phase.[84] In general, besides being feasible and well tolerated even by the oldest old,[84] this alternative type of intervention would elicit similar[85] or even higher improvements in functional performance and disability compared with more traditional, lower-velocity resistance training.[86] Another approach is the use of a weighted vest, which has proved effective to improve perceived health in old people,[87] as well as lateral stability, lower-body muscular strength, muscular power,

Table 1. Summary of Controlled Exercise Interventions (Mostly Based on Resistance Exercises) in the Oldest Old

				Training						
Reference	*Group*	n *(% women)*	*Mean age (SD or range in years)*	*Length (weeks)*	*Type*	*Frequency (sessions/ week)*	*Sets*	*Exercises/session (repetitions per (×) exercise)*	*Intensity/duration*	*Effects*
356	Exercise	46 (72%)	80 (7)	24	Low intensities +	3		Flexibility, balance, coordination, movement speed and strength of all major muscle groups	5–15 min (0–12 weeks)	↑ Knee extension strength ↑ Fast walking speed ↑ Total free mass
					Strength	3	1–3	6–12× knee extension	65–100% 1RM (12–24 weeks)	
							1–3	6–12× knee flexion	65–100% 1RM (12–24 weeks)	
							1–3	6–12× seated bench press	65–100% 1RM (12–24 weeks)	
							1–3	6–12× seated row	65–100% 1RM (12–24 weeks)	
							1–3	6–12× leg press	65–100% 1RM (12–24 weeks)	
							1–3	6–12× biceps curl	65–100% 1RM (12–24 weeks)	
	Control	44 (77%)	81 (8)	24		3		Flexibility, balance, coordination, movement speed and strength of all major muscle groups		↑ Knee extension strength ↑ Fast walking speed ↑ Total free mass (Significantly less pronounced than in the exercise group)
357	Exercise	11 (91%)	88.6 (86–95)	12	Strength	3	8	8x 90° knee flexion	50–80% 1RM	↑ Extensor and flexor muscle strength
							8	8x 90° knee extension	50–80% 1RM	
	Control	12 (92%)	90.6 (86–95)	12	No PA	2		Social activities, including group gatherings		↑ Extensor and flexor muscle strength (Significantly less pronounced than in the exercise group)
358	Exercise	11 (NA)	93.4 (3.2)	12	Strength +	2		8–10x upper body (1 exercise: seated bench press)	40–60% 1RM High velocity	↑ Quadriceps femoris CSA ↑ Hand grip ↑ Hip flexion strength
					Balance + Gait + Stretching (cold down)			8–10x lower body (bilateral leg extension and bilateral knee extension)	40–60% 1RM High velocity 10 min 5 min	↑ Knee extension strength ↑ Upper-body 1RM ↑ Lower-body 1RM ↑ Maximal power at 30% 1RM ↑ Maximal power at 60% 1 RM ↓ Falls incidence
	Control	13 (NA)	90.1 (1.1)	12	Mobility	4		Active and passive movements	30 min	= Quadriceps femoris CSA ↓ Hand grip strength ↓ Hip flexion strength ↓ Knee extension strength

(*continued*)

TABLE 1. (CONTINUED)

Reference	Group	n (% women)	Mean age (SD or range in years)	Training: Length (weeks)	Training: Type	Training: Frequency (sessions/week)	Training: Sets	Training: Exercises/session (repetitions per (×) exercise)	Training: Intensity/duration	Effects
359	Lifestyle integrated functional exercise	107 (55%)	82.8 (4.48)	48	Functional exercise	Several		Set of exercise		Ankle strength, knee strength and function effects were significantly better than in control group
	Exercise	105 (54%)	84.0 (4.38)	48	Strength + Balance	3		6× lower limb strength 7 exercise	"Hard zone"	Ankle strength, knee strength and function effects were significantly better than in control group
	Control	105 (55%)	83.5 (3.81)	48	Gentle + Flexibility			2 sessions, 1 booster session and 6 follow-up phone calls *e.g.*, hip rotations		Ankle strength, knee strength and function effects were significantly lower than in exercise or functional exercise group
360	Exercise	15 (NA)	86.7 (6.1) (77–98)	10	Warm-up + Strength + Balance + Cool-down	3	1	10–15× muscle group Balls, balance disc, and blocks	10 min Elastic therabands and soft weights 10 min 5 min	↑ Muscle-strength ↑ BMI ↑ Mean lean body mass (no significant)
	Control	15 (NA)	86.9 (5.7) (77–94)	10						No effect ↓ Mean lean body mass (no significant)
361	Exercise	25 (64%)	86.2 (1.0) (72–95)	10	Strength	3	3 3	8× lhip extensor 8× knee extensor	80% 1RM 80% 1RM	↑ Muscle-strength ↑ Thigh-muscle CSA ↑ Stair-climbing power
	Exercise + Nutritional supplement	25 (64%)	87.2 (1.2) (76–98)	10	Strength + 240 mL liquid + CHO (60%) + fat (23%) + soy-based protein (17%) Aerobic or flexibility activities	3	3 3	8× hip extensor 8× knee extensor 3 activities (*e.g.*, walking)	80% 1RM 80% 1RM	Idem exercise group
	Nutritional supplement + Placebo activities	24 (71%)	85.7(1.2) (75–97)	10	240 ml liquid + CHO (60%) + fat (23%) + soy-based protein (17%) Aerobic or flexibility activities	3		3 activities (*e.g.*, walking)		No effect
	Placebo activities + Placebo supplement	26 (54%)	89.2 (0.8) (78–98)	10	Aerobic or flexibility activities Minimally nutritive (4 kcal)	3		3 activities (*e.g.*, walking)		No effect

(*continued*)

TABLE 1. (CONTINUED)

Reference	Group	n (% women)	Mean age (SD or range in years)	Training						Effects
				Length (weeks)	Type	Frequency (sessions/ week)	Sets	Exercises/session (repetitions per (×) exercise)	Intensity/duration	
362	Exercise + Traditional balance training	12 (50%)	81.1 (6.0) (69–95)	12	Strength +	2		Larger over extremity muscles (pulley stations)	10–15 RM	↑ Strength knee extension ↑ Sitting to standing test ↑ Static Balance
								Large under extremity muscles (leg press and pulley stations)	10–15 RM	
								Step machine	100 steps level 2 150 steps level 2 100 steps level 3 150 steps level 3	
					Aerobic + Balance			Static cycle Standing, one-legged balance and walking on different surfaces (open and closed eyes)	> 15 min and > 3km	
	Exercise + Visual computer feedback	15 (80%)	81.5 (7.7) (69–95)	12	Strength +			Larger over extremity muscles (pulley stations)	10–15 RM	↑ Strength knee extension ↑ 6 minute walk test
								Large under extremity muscles (leg press and pulley stations)	10–15 RM	↑ Training-specific performance
								Step machine	100 steps level 2 150 steps level 2 100 steps level 3 150 steps level 3	
					Aerobic + Balance			Static cycle Visual computer feedback	> 15 min and > 3km	
363	Exercise	31 (NA)	82.2 (4.1) (75–90)	12	Strength	3	3	10x knee extensions	70–90% of maximal	↑ Leg extension strength ↑ Knee extension strength
							3	10× hip extension	70–90% of maximal	↑ Knee flexion strength
							2	10× left lifts	70–90% of maximal	↑ Ankle plantar flexion strength
							2	10× right lifts	70–90% of maximal	↑ Handgrip strength
							2	15 lifts of bilateral plantar flexion (2–4 cm support)		↑ Functional motor performance
					Functional-Balance training + Physiotherapy	2		Multifactorial activities *e.g.*, massaging or stretching	45 min per training session 25 min	↑ Balance Improvements persisted during 3-month follow-up with only moderate losses
	Control	26 (NA)	82.1 (4.8) (75–90)	12	Placebo activities + Physiotherapy	3		Motor activities (*e.g.*, flexibility, calisthenics, ball games and memory tasks)	1 hr	No effect during intervention and follow-up
364	Exercise	62 (74%)	82.3 (6.6)	12	Strength	3		Relevant muscle group	70–80% 1RM	↑ Knee extension strength ↑ Knee flexion strength ↑ Ankle flexion strength ↑ Handgrip strength ↑ Functional performance

(*continued*)

TABLE 1. (CONTINUED)

Reference	Group	n (% women)	Mean age (SD or range in years)	Training						Effects
				Length (weeks)	Type	Frequency (sessions/week)	Sets	Exercises/session (repetitions per (×) exercise)	Intensity/duration	
	Control	60 (73%)	82.9 (7.0)	12	Placebo activities	2		Flexibility exercise, calisthenics, low-intensity training with hand-held weights and ball games		No effect or ↓
365	Exercise	15 (80%)	88.5 (1.0) (85–98)	12	Strength	3	1	Upper and lower extremities	5–10 min	↑ 1RM
							3	8x knee flexion + 8x knee extension	50% 1RM (0–2 weeks) 80% 1RM (2–12 weeks)	↑ Isokinetic knee extension ↑ Isometric knee extension
	Control	15 (73%)	90.9 (1.1) (85–98)	12	No PA					= 1RM = Isokinetic knee extension = Isometric knee extension
366	Exercise in long-term care-high mobility	22 (NA)	81.3 (5.3)*	4	Warm-up/stretching +				5 min	↑ Mobility ↑ Balance ↑ Flexibility
					Aerobic + Strength			Walking	10–15 min	↑ Knee strength ↑ Hip strength
					Balance		1–2	2–10× lower body	Soft-weights and Theraband	
					Cool-down/stretching		1–2	2–10× upper body	10 min	
									5 min	
	Exercise in long-term care-low mobility	14 (NA)	81.3 (5.3)*	4	Warm-up/stretching + Aerobic +				5 min	↑ Mobility ↑ Balance
					Strength			Walking	< 1 min – 15 min	↑ Flexibility
					Balance		1–2	2–10× lower body	Soft-weights and	↑ Knee strength
					Cool-down/stretching		1–2	2–10× upper body	Theraband	↑ Hip strength
									10 min	
									5 min	
	Range of motion	32 (94%)	81.3 (5.3)*	4	Introductions				10 min	↑ Shoulder strength
					Vocal exercises				5 min	↓ Hip Strength
					Memory games				5 min	↓ Mobility
					Range of motions			Fingers, hands, arms, knees, ankles		↓ Functional ability
					Relaxation exercises				5 min	
367	Exercise	19 (95%)	91.7 (6.3)	12	Aerobic	5		Walking	↑ 10% weekly (maximum 30 min) (Baseline intensity defined by each participant)	↑ Maximal walk endurance ↑ Maximal walk distance (significant) = Hand-grip strength = BMI
	Control	12 (100%)	89.3 (4.4)	12	Social control	1			30 min	= Maximal walk endurance ↑ Maximal walk distance (no significant) = Hand-grip strength = BMI

(*continued*)

TABLE 1. (CONTINUED)

Reference	Group	n (% women)	Mean age (SD or range in years)	Training						Effects
				Length (weeks)	Type	Frequency (sessions/ week)	Sets	Exercises/session (repetitions per (×) exercise)	Intensity/duration	
368	Exercise	36 (81%)	83.7 (8) (67–98)*	24	Warm-up +	2			10 min	↑ Quadriceps strength
					Strength + Cool-down			Isometric exercises major muscle groups	25 min (Intensity was graduated by the n° of repetitions and the gravity-resistance) 10 min	
	Control	29 (90%)	82 (9.6) (67–98)*	24	Reminiscence	2		Reminiscence therapy	45 min	↓ Quadriceps strength
369	Exercise	21 (90%)	81.4 (3.4) (75–96)*	24	Stretching + Range of movements exercises		1	5–10× each exercise	Support of a chair or work surface	No significant differences between the groups with regard to changes in any of the outcome variables (grip strength, 'up & go' test, 'sit to stands' test, functional reach, spinal mobility, Barthel index, Philadelphia Geriatric Center Morale Scale) Trend toward improvement in comparison with control group ('sit to stand 'tests and 'up & go' tests)
					Strength			5–10× yellow-blue	Therabands	
	Exercise	20 (85%)	82.9 (4.4) (75–96)*	24	Mobility					No significant differences between the groups with regard to changes in any of the outcome variables (grip strength, 'up & go' test, 'sit to stand' test, Functional reach, Spinal mobility, Barthel Index, Philadelphia Geriatric Center Morale Scale) Trend towards improvement in comparison with control group ('sit to stand' and 'up & go' tests)
	Control	28 (89%)	81.9 (4.7) (75–96)*	24	Health education				30 min	No significant differences between the groups with regard to changes in any of the outcome variables (grip strength, 'up & go' test, 'sit to stand' test, functional reach, spinal mobility, Barthel index, Philadelphia Geriatric Center Morale Scale)

(*continued*)

TABLE 1. (CONTINUED)

Reference	Group	n (% women)	Mean age (SD or range in years)	Training						Effects
				Length (weeks)	Type	Frequency (sessions/week)	Sets	Exercises/session (repetitions per (×) exercise)	Intensity/duration	
370	Exercise	39 (67%)	82.2 (1.3)	8	Strength + Balance + Functional mobility	3		Combined progressive exercises	1 hour	↑ 6-min walk test
	WBV	38 (68%)	80 (1.4)	8	Vibration + Strength + Balance + Functional mobility	3	5	Whole body vibration	1 min 15–30 Hz 2–8 mm peak-to-peak	↑ 6-min walk test (greater improvements than exercise group)
371	Exercise	94 (81%)	87 (8)	32	Strength	5		Upper body resistance training (arm curls or arm raises)	Implement every 2 hr for a possible total of 4 care episodes per day	↑ Arm raise ↑ Arm curl ↑ Stands 30 sec
					Aerobic			Walking or wheeling	75–90% of the maximal distance	
	Control	96 (86%)	88 (7)	32	UCG					↓ Meter walked or wheeled
92	Exercise	20 (80%)	92 (2) (90–96)	8	Mobility exercise + Stretching + Aerobic + Strength	2	1	Major muscle groups	40.45 min	↑ 1RM leg press ↑ FAC (in participants with FAC > 3)
								Rest periods		
						3	1	Cycling (cycle ergometer)	10–15 min; RPE:12–13	↓ Falls (1.2 fewer per participant than in the control group)
						3	2-3	Leg press exercise	30–70% 1RM (↑ 5%weekly)	
							1-8	10× biceps curls, arm extension, arm side lifts, shoulder elevations, seated bench presses and calf raises	1–3 kg or low-medium resistance bands	
	Control	20 (80%)	92 (2) (90–97)	8	UCG	5	1	Mobility exercises in major muscle groups	40–45 min	14 of 18 participants showed ↑ RM leg press
372	Exercise	34 (100%)	83.5 (4.1)	10	Warm-up +	2			15 min	= Abilities to carry out instrumental activities of daily living
					Strength +		1-2	8–30× knee extension 8–30× knee flexion 8–30× hip abduction 8–30× hip adduction	Gradually increased	
					Functional exercises +		2	15× exercise (*e.g.*, rising from a chair or elbow flexion using light loads (1–2 kg))	30 min	
					Relaxation				15 min	
	Control	34 (100%)	82.6 (3.7)	10	Home exercise program	2–3	2	15× functional exercises		= Abilities to carry out instrumental activities of daily living

Of note, the mean age of the subjects in all the studies was ≥ 80 years.

*Data provided by the total number of participants.

BMI, Body mass index; CHO, carbohydrate; CSA, cross-sectional area; FAC, functional ambulation classification; NA, not available; PA, physical activity; RPE, rating of perceived exertion (Borg's conventional scale, 6–20 points); 1RM, one repetition maximum; SD, standard deviation; SO, social activities; TG, training group; UCG, usual care group; WBV, whole-body vibration.

and leg lean mass (and thus likely to reduce risk fall) in postmenopausal women aged 50–75 years.[88] Preliminary findings also support the potential effectiveness of including a weighted stair climbing exercise in the training programs of old people.[89] Others, however, found no significant benefits of a home-based intervention using a weighted vest.[90]

Benefits of exercise in the frail elderly

Although numerous studies have shown the benefits of resistance training in old people in general, less research has focused specifically on the frail elderly. This is an important issue because frailty status might influence the potential applicability and effectiveness of the different training programs. For instance, Faber et al. found that fall-preventive, moderate-intensity, group exercise programs (mostly based on walking and balance exercises) had positive effects on fall risk and physical performance in pre-frail but not in frail elderly (mean age 85 years).[91]

Fiatarone et al. reported that physically frail, oldest old men and women improved their leg muscle strength outcomes by 220% after a 10-week strength training program (three sets of eight repetitions at 80% of 1RM, three times a week).[80] Serra-Serra-Rexach et al. found an increment of 17% in the leg press strength of nonagenarians after 8 weeks of progressive strength training with lower loads (two to three sets of eight to 10 repetitions at 30% of 1RM in the initial phase progressing to 70% of 1RM at the end of the intervention).[92] Lustosa et al. found significant improvements in the knee extensor muscle power of pre-frail elderly women after 12 weeks of strength exercises of the lower extremities at 70% of 1RM, three times a week.[93] Although more research is needed, higher-intensity exercises seem to elicit higher gains. Thus, Sullivan et al.[94] found greater increases in the muscle strength of frail elderly after a 12-week resistance training program of progressive intensity (starting at 20% and ending at 80% of 1RM) compared with a continuous, lower intensity protocol (20% of 1RM during the entire 12-week period).

The American College of Sports Medicine recommends a multi-component (strength, endurance, flexibility, and balance) exercise program to maintain physical fitness in old adults.[95] Villareal et al. studied the effect of such a multicomponent exercise program on physical fitness in frail, obese older adults during 3 months, finding beneficial effects on muscle mass and physical function.[96] Lord et al. found significant improvements in choice stepping reaction time test, 6-min walking distance, and simple reaction time requiring a hand press, after training (aerobic exercises, specific strengthening exercises, and activities for balance, hand-eye and foot-eye coordination, and flexibility) during 12 months in frail older people living in retirement villages.[97] Eshani et al.[98] assessed the effect of a 6-month aerobic training program on frail elderly (consisting of walking at 70%–75% of maximal heart rate during 20 min at the initial phase and progressing to 60 min at the end of the program) and found a 14% of increase in VO_2max.

Evidence on the benefits of exercise interventions in elderly with frailty, co-morbidities, and subsequent physical disability comes from a recent meta-analysis by deVries et al.[99] This study included data on 18 randomized controlled trials (2,580 participants in total) of physical training interventions in community-dwelling adults aged 60–85 years who were physically frail and/or had physical disability and/or multi-morbidity. Half of the included studies used multi-component training programs, and intervention duration ranged from 5 weeks to 18 months. There were statistically significant benefits with physical exercise therapy compared to no exercise in mobility and physical functioning. There were no differences in effectiveness with regard to the duration of the program (short vs. longer interventions), whereas high-intensity programs elicited greater gains compared to low-intensity ones. The interventions that showed the largest effect sizes were those using resistance training components.

Benefits of exercise (particularly, resistance exercise) in the aging muscle tissue—main signaling pathways involved in exercise adaptations

The molecular mechanisms involved in the activation of signal transduction cascades regulating the adaptations to exercise are dependent on specific signaling pathways activated or repressed by numerous stimuli such as alterations in metabolites concentrations, adenosine triphosphate (ATP)-to-adenosine diphosphate (ADP) ratio, calcium flux, intracellular pH, redox balance, ROS production, and intracellular oxygen pressure.[100–103] Post-exercise changes in gene transcription involve immediate early genes, myogenic regulators, genes that regulate carbohydrate metabolism and lipid mobilization, transport and oxidation, mitochondrial metabolism, and oxidative phosphorylation, as well as transcriptional regulators of gene expression and mitochondrial biogenesis,[104–107] or alterations in the DNA-binding activity of a variety of transcription factors, such as myocyte enhancer factor 2 (MEF2),[107] histone deacetylases (HDACs),[108] and nuclear respiratory factors (NRFs).[109,110]

The most relevant signaling pathways modulated by exercise include calcium/calmodulin-dependent protein kinase (CaMKs) signaling, mitogen-activated protein kinases (MAPKs) signaling, ATP turnover and adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling, oxidized nicotinamide adenine dinucleotide (NAD^+)/reduced nicotinamide adenine dinucleotide (NADH) ratio and sirtuins (SIRTs), activation of mammalian target of rapamycin (mTOR), oxygen sensing and the hypoxia-inducible factor 1 (HIF-1), mitochondrial biogenesis pathway, and the PPARγ co-activator-1α (PGC-1α) and -1β(PGC-1β).[111] Accordingly, several important adaptations in skeletal muscle, such as mitochondrial biogenesis, anti-oxidant defense, hypertrophy, cytoprotection, and fiber transformation, are regulated primarily by these pathways. Below we summarize the main biological mechanisms and pathways through which exercise may attenuate sarcopenia (see also Fig. 2).

Calcium is implicated in the regulation of numerous intracellular proteins, such as protein kinase C, calcineurin, and CaMKs that mediate cellular signal transduction.[112] Exercise increases CaMKII phosphorylation in an intensity-dependent manner. CaMKs and calcium signaling affect glucose transport,[113] lipid uptake and oxidation,[114] and skeletal muscle plasticity.[115] In addition, the transcription factors cyclic AMP response element-binding protein (CREB), MEF2, and HDACs are CaMK targets involved in the regulation of skeletal muscle gene expression. Exercise

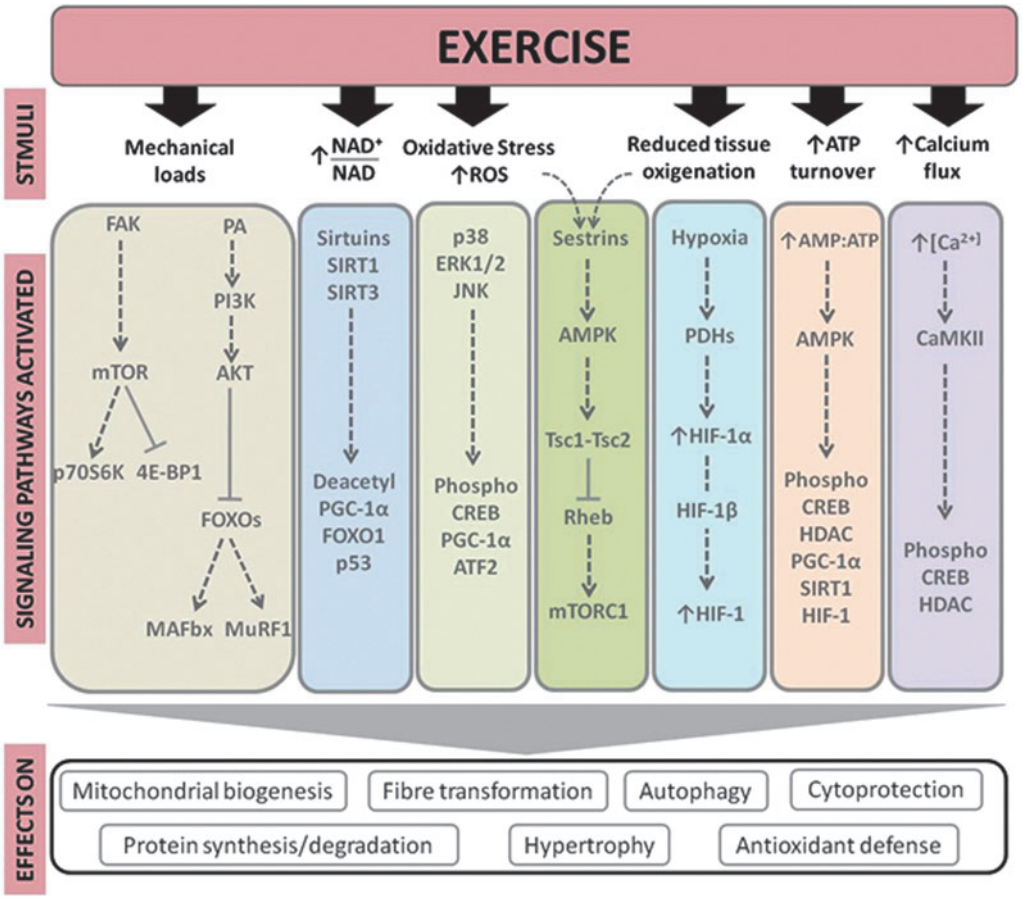

FIG. 2. Main signaling pathways involved in the exercise effects in the skeletal muscle tissue. 4E-BP1, eukaryotic translation initiation factor 4E (eIF4E) binding protein; AKT, protein kinase B; AMP, adenosine monophosphate; AMPK, AMP activated protein kinase; ATF2, activating transcription factor 2; ATP, adenosine triphosphate; CaMKII, calmodulin-dependent protein kinase II; CREB, cAMP response-element-binding protein; ERK1/2, extracellular signal-regulated kinase 1 and 2; FAK, focal adhesion kinase; FoxO1, human protein encoded by the *FOXO* gene; FOXOs, Forkhead box-O transcription factors; HDACs, histone deacetylases; HIF, hypoxia-inducible factor; JNK, c-Jun NH_2-terminal kinase; MAFbx, or Atrogin-1; MuRF-1, muscle RING-finger protein-1; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; NAD, nicotinamide adenine dinucleotide; PA, phosphatidic acid; p70S6K, ribosomal protein S6K; PDH, prolyl hydroxylase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PI13K, phosphatidylinositol 3-kinase; Rheb, Ras homolog enriched in brain gene; ROS, reactive oxygen species; SIRT, sirtuin; Tsc1, tuberous sclerosis complex 1; Tsc2, tuberous sclerosis complex 2. Color images available online at www.liebertpub.com/rej

also stimulates MAPK-related pathways, including extracellular signal-regulated kinase 1 and 2 (ERK1/2),[116] p38,[117] and c-Jun NH_2-terminal kinase (JNK).[116] For instance, p38 MAPK can stimulate upstream transcription factors of the *PGC-1α* gene through skeletal muscle contraction.[118] Moreover, MAPKs regulate a wide range of physiological processes, such as differentiation, hypertrophy, inflammation, and gene expression.[119]

The role of ROS in the exercise-induced adaptations of skeletal muscles has been studied extensively, particularly with regard to aerobic exercise.[120,121] Contracting skeletal muscles produce ROS, activating MAPK signaling and transcription factor nuclear factor-kappa B (NF-κB), thereby linking signal transduction to transcriptional processes.[122] Acute exercise activates JNK signaling in a ROS-dependent manner, as evidenced by attenuated JNK signaling during exercise with infusion of the anti-oxidant *N*-acetylcysteine.[123] Contraction-induced increases in interleukin-6 (IL-6) secretion, an exercise-associated cytokine with potent multi-organ metabolic effects[124] (see further below), is JNK dependent,[125] which attests to the likely importance of JNK signaling in mediating metabolic adaptations to exercise. AMPK is a serine/threonine kinase that modulates cellular metabolism acutely through phosphorylation of metabolic enzymes[126] and, over time, via transcriptional regulation.[127,128] Given the rate of ATP turnover during muscle contraction, AMPK acts as a signal transducer for metabolic adaptations by responding to an altered cellular energy status. Overall, AMPK activation preserves ATP by inhibiting both biosynthetic and anabolic pathways, while simultaneously stimulating catabolic pathways to re-establish cellular energy stores.[129] Chronic AMPK activation modifies metabolic gene expression and stimulates mitochondrial biogenesis,[127] partly via AMPK-induced modulation of the DNA-binding activity of transcription factors, including NRF-1, MEF2, and HDACs.[127,130]

Sestrins are a recently discovered hallmark of aging sarcopenia. Mammalian cells express sestrins in response to stress including DNA damage, oxidative stress, and hypoxia. Sestrins can inhibit the activity of the mTOR complex 1 (mTORC1) through activation of AMPK.[131] Sestrins prevent sarcopenia, insulin resistance, diabetes, and obesity. They also extend life span and health span through activation of AMPK, suppression of mTORC1, and stimulation of autophagic signaling.[131] Recently, we proposed a possible role of the AMPK-modulating functions of sestrins in the benefits produced by exercise in older subjects.[132]

The regulation of the SIRT family of protein deacetylases is NAD^+ dependent.[133] Both deacetylases SIRT1 and SIRT3 respond to elevations in [NAD^+] and the NAD^+/NADH ratio. Increased SIRT activity is associated with positive adaptations in skeletal muscle metabolism, including improved mitochondrial function and exercise performance.[134,135] Likewise, the adaptive muscle growth consequent to mechanical loads induced by resistance exercise is largely determined by the enhanced skeletal muscle protein synthesis due to the activation of mTOR, ribosomal protein S6K (p70S6K), and downstream targets.[136] p70S6K is a major regulator of muscle protein synthesis through pathways of protein translation and ribosome biogenesis involving eukaryotic translation initiation factor 4E (eIF4E), 4E binding protein 1 (4E-BP1), and elongation factor 2 (eEF2). Phosphorylation of 4E-BP1 by mTOR suppresses binding and inhibition of eIF4E by 4E-BP1. Phosphorylation of S6K leads to the phosphorylation of the 40S ribosomal protein S6 (rpS6) and eukaryotic translation initiation factor 4B (eIF4B). Collectively these events lead to the formation of the translation initiation complex and activate protein synthesis inducing cellular hypertrophy.[137] Mechanosensory regulation of muscle protein synthesis also involves other signaling proteins, such as focal adhesion kinases (FAK), a class of transmembrane receptors that act as protein tyrosine kinases. FAK proteins are pivotal points for the transmission of contractile force throughout the skeletal muscle structure and a central component of integrin signaling. The grade of expression and activity of FAK in skeletal muscle is loading dependent,[138,139] and contraction results in conformational modifications and activation of FAK phosphotransferase,[138,140] which can trigger muscle protein synthesis through mTOR-dependent or -independent mechanisms.[141]

Oxygen sensing is also involved in the adaptations of skeletal muscle fibers to exercise, particularly aerobic exercise. Hypoxia-inducible factor (HIF), a heterodimeric transcription factor composed of two subunits (HIF-1α and HIF-1β), regulates the major signal transduction pathway sensitive to the intracellular partial pressure of oxygen. Activation of HIF-1 by many stimuli, including aerobic exercise, induces transcription of target genes involved in erythropoiesis, angiogenesis, glycolysis, and energy metabolism.[105,142,143]

Exercise benefits in neurodegeneration—main signaling pathways involved

Physical exercise produces important benefits in several neurodegenerative diseases.[144,145] Here we focus on the effects of exercise in Alzheimer's disease, which comprises *per se* 50%–56% of all causes of aging dementia (an additional 13%–17% is caused by Alzheimer's disease combined with vascular diseases).[146] Exercise, especially aerobic exercise, is beneficial for patients with Alzheimer's disease,[147] not only because it attenuates patients' physical and psychosocial dependence[148] but it also because it improves several features of the pathophysiology of this disorder,[149,150] including oxidative stress regulation, autophagy systems, neurotrophic signaling, mitochondrial biogenesis, angiogenesis, neurogenesis, and the modulation of specific amyloid-β (Aβ)-degrading enzymes (see Table 2 for a summary of intervention studies in humans and Fig. 3 for a summary of the putative molecular pathways involved).[149,150]

Oxidative stress plays an important role in the etiology of Alzheimer's disease.[151–154] The brain is especially sensitive to oxidative stress compared to other organs owing to its high metabolic rate (*i.e.*, high O_2 consumption) together with its relatively low anti-oxidant defense capacity and its high levels of polyunsaturated fatty acids and metals.[151,155] Elevated levels of brain oxidative stress are found with normal aging,[156,157] and this phenomenon is exacerbated in Alzheimer's disease due to additional sources of ROS such as Aβ accumulation and mitochondrial dysfunction.[151,153,154,158] Although there is some controversy, aerobic exercise enhances anti-oxidant defense and mitigates oxidative damage in the brain of rodent models.[150] Thus, exercise increases glutathione peroxidase (GPx) activity in whole brain,[159] as well as superoxide dismutase (SOD) and GPx activity in the brainstem and corpus striatum.[160] Using a triple transgenic mouse model of Alzheimer's disease, we recently showed that aerobic exercise training can increase hippocampal catalase mRNA levels.[161]

Exercise attenuates aging neurodegeneration partly by upregulating neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF).[162,163] Circulating BDNF levels increase with aerobic exercise, especially when intensity is high.[164–166] Exercise-produced BDNF can help maintain brain function and promote neuroplasticity[167,168] as well as repairing motor neurons.[169] Increased BDNF transcripts in exercised rodents' brains are well documented, which provides a biological explanation for the beneficial effect that exercise has in cognitive function, with tropomyosin receptor kinase (trkB), CREB, or synapsin I signaling been involved.[170] These pathways are involved in synaptogenesis[171] and long-term memory formation.[172] Furthermore, the activation of the transcription factor CREB leads to induction of several genes that regulate neurotrophic effects, including those encoding PGC-1α,[173] dynorphin, and BDNF.[174] In addition, when the exercise induction of the BDNF pathway is blocked, aerobic exercise is unable to activate CREB and stimulate cognition.[170,175] The hippocampal regulation of BDNF induced by exercise is mediated by neurotransmitters,[167,176] neuroendocrine mechanisms,[167] and insulin-like growth factor 1 (IGF-1) modulation.[177,178] Thus, hippocampal IGF-1 levels increase with exercise training[177] and have neurotrophic effects because IGF-1 activates BDNF signaling[177] and increases trkB levels.[179] Aerobic exercise induces other neurotrophic factors, such as vascular endothelial growth factor (VEGF),[180] nerve growth factor (NGF),[181] glial-derived neurotrophic factor (GDNF),[182] neurotrophin (NT)-3,[183] and NT-4/5,[184] all of which act synergistically to induce neurogenesis and neuroplasticity.[167,180]

Table 2. Summary of Controlled Exercise Interventions in Biomarkers of Neurodegeneration

Reference	*Group*	n *(Age, years)*	*Health status*	*Sex*	*Effects*
373	High-intensity ET	Women: 10 (65.3 ± 9.4 years) Men: 9 (70.9 ± 6.7 years)	Amnestic mild cognitive impairment	Both	BDNF increased in men but decreased in women. ET group improved cognitive function compared to controls.
	Control (stretching)	Women: 5 (74.6 ± 11.1 years) Men: 5 (70.6 ± 6.1 years)			
374	High-intensity ET Control (stretching)	29 (74.3 ± 2.8 years)	Glucose tolerance criteria for pre-diabetes or newly diagnosed	Both	Although BDNF did not change, ET group improved cognitive functions compared to controls.
375	ET Control	20 (62 years) 19 (63 years)	Coronary artery disease	Both	No changes were observed in VEGF concentrations for both groups.
376	High-intensity ST Moderate-intensity ST Control (stretch)	62 (65–75 years)	Healthy	Men	IGF-1 increased in both ST groups.
377	ST (non-frail) ST (pre-frail)	24 (70.5 ± 4.6 years) 24 (72.5 ± 4.3 years)	Pre-frail and non- frail	Women	BDNF increased in both groups. No changes in GDNF or NGF.
378	ET Control (stretching)	60 (67.6 ± 5.8 years) 60 (65.5 ± 5.4 years)	Healthy	Both	ET increased the size of the hippocampus and BDNF.
379	ST	21 (85.0 ± 4.5y)	Healthy	Women	No changes on VEGF after ST
380	Combined Control	10 (66.1 ± 3.1 years) 10 (67.7 ± 5.2 years)	Obese	Women	VEGF increased after 12 weeks of combined training.
381	ET ST	181 (70.3 ± 4.5 years) 167 (71.0 ± 4.5 years)	Healthy	Women	Only ST increased BDNF
382	Combined (aerobic and resistance) Control	20 (92.3 ± 2.3 years) 20 (92.1 ± 2.3 years)	Healthy	Both	No changes in BDNF, ACE, APP, EGF, and TNFα
383	Exercise + medical treatment Medical treatment	20 (69 ± 8 years) 20 (70 ± 11 years)	Peripheral artery disease	Both	Exercise increased circulating EPC counts and decreased ADMA levels. No changes in VEGF and SDF-1.
384	Multi-modal (aerobic, strength and motor fitness) Control	25 (69.0 ± 3.1 years) 24 (68.8 ± 3.5 years)	Healthy	Women	Exercise increased BDNF and cognitive performance.
385	ET Control (flexibility, toning and balance)	30 (67.3 ± 5.8 years) 35 (65.4 ± 5.2 years)	Healthy	Both	No changes in BDNF, IGF-1, VEGF
386	Acute exercise ET Control	18 (62 ± 10 yeasrs) 7 (64 ± 6 years) 6 (56 ± 9)	intermittent claudication	Both	No change was observed in VEGF concentrations in response to acute exercise and to the training

ACE, angiotensin-converting enzyme; APP, amyloid precursor protein; DMA, asymmetric dimethylarginine; BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor; EPC, endothelial progenitor cells; ET, endurance training; GDNF, glial-derived neurotrophic factor; IGF-1, insulin like growth factor 1; NGF, nerve growth factor; SDF-1, stromal cell-derived factor-1; ST, strength training; TNFα, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

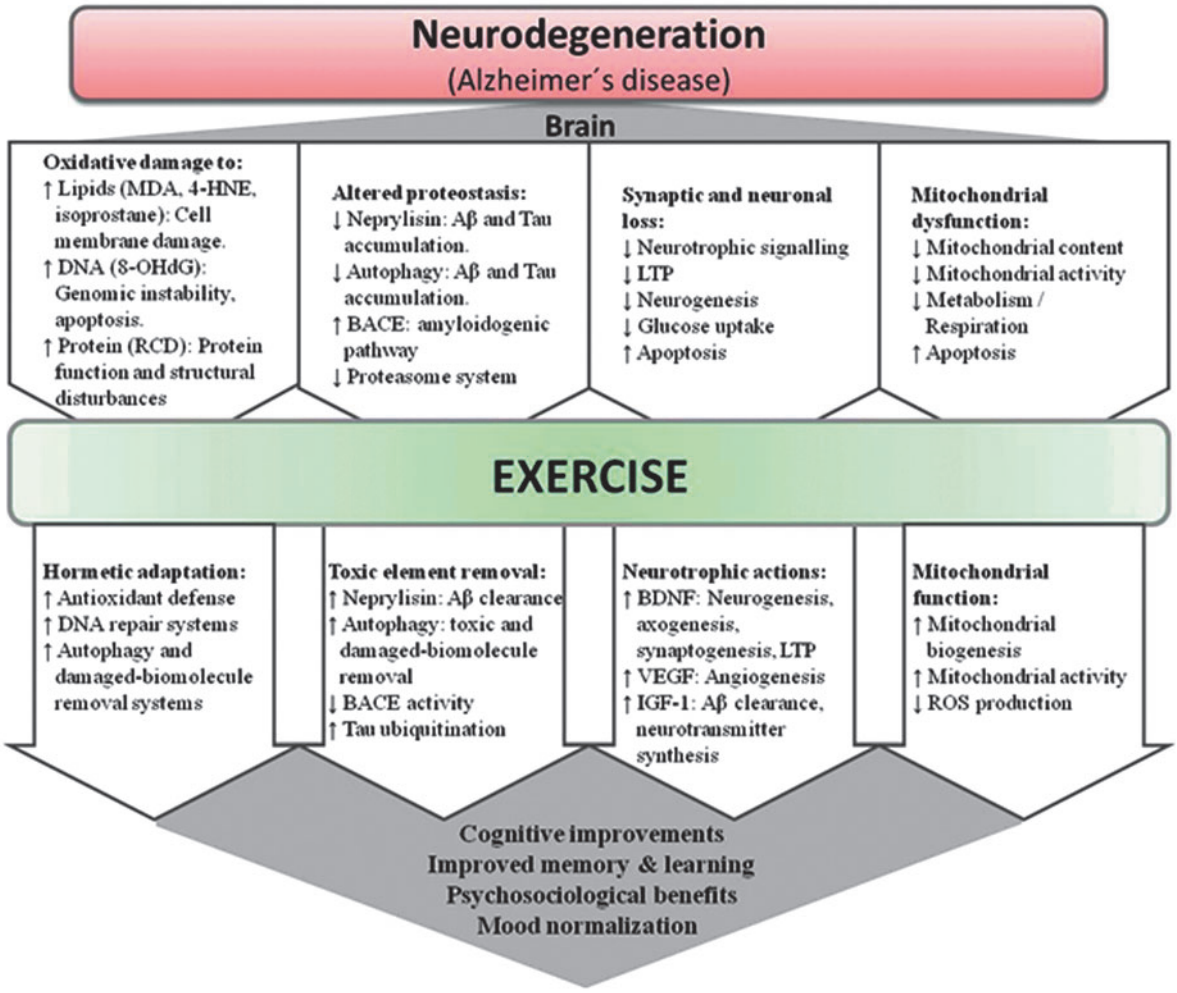

FIG. 3. Main signaling pathways involved in the exercise effects in neurodegeneration, especially with regard to Alzheimer's disease. 4-HNE, 4-hydroxynonenal; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; Aβ, amyloid-pβ; BACE, β-secretase; BDNF, brain-derived-neurotrophic factor; IGF-1, insulin-like growth factor 1; LTP, long-term potentiation; MDA, malondialdehyde; RCD, reactive carbonyl derivative; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor. Color images available online at www.liebertpub.com/rej

Although neurons are post-mitotic cells, neurogenesis can still occur in specific areas of the adult hippocampus[185] with some stimuli such as ischemia/reperfusion, aging, metabolic pathology, or physical exercise being able to change the rate of neurogenesis.[150] Van Praag and collaborators have extensively studied the effects of exercise, particularly of the aerobic type, on adult neurogenesis[186] and have demonstrated that the newly formed neurons are associated with the cognitive and synaptic effects induced by exercise.[187] This phenomenon is especially important in age-related neurodegeneration because attenuation of accelerated neuronal loss can prevent several age-related disorders, including Alzheimer's disease. Several signaling pathways induced by aerobic exercise have been suggested to mediate this process such as BDNF,[188,189] VEGF,[180] and IGF-1.[190]

Both age and disease-induced neurodegeneration are partially produced by a dysregulation of protein homeostasis (see further below on the exercise effects in aging ''proteostasis''). Aerobic exercise increases proteolytic degradation by proteasomes and neprilysin, a specific Aβ-degrading enzyme.[167,191] Activation of the brain proteasome is important in preventing Alzheimer's disease because proteasome inhibition produces Aβ accumulation, a hallmark of this disorder.[192] The neurofibrillary tangles produced by an accumulation of hyperphosphorylated tau proteins is also an important hallmark of Alzheimer's disease. Lysine residues of tau are susceptible to ubiquitination, indicating interaction of tau aggregation by oligomerization and ubiquitination-mediated degradation through the proteasome system.[193] The proteasome might also be involved in the learning process, because its inhibition in the hippocampus blocks long-term memory.[194–195]

Exercise and the Cellular Hallmarks of Aging

In a recent state-of-the-art review, López-Otín et al.[196] nicely postulated nine hallmarks of aging that might be targeted in future pharmacological interventions—genomic instability, telomere attrition, epigenetic alterations, loss of protein homeostasis (proteostasis), deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

Although more research is needed, exercise, which is available at low cost and largely free of adverse effects,[111] can influence, at least partly, most of these hallmarks (see Fig. 1, right column, for a summary).

Genomic instability

A 5-month aerobic exercise program prevented mitochondrial DNA (mtDNA) instability in multiple tissues of mtDNA mutator (progeroid) mice, thereby reducing multisystem pathology and preventing premature mortality.[197] Oxidative damage to DNA occurs during the aging process.[198] Resistance exercise decreases such damage in old people, as indicated by 8-hydroxy-2′-deoxyguanosine (8-OHdG) determination, through stimulation of endogenous anti-oxidant defense,[199] whereas in rodent models aerobic exercise improves DNA repair mechanisms (*e.g.*, proteasome complex),[200] as well as NF-κB and PGC-1α signaling.[121,201]

Telomere attrition and telomerase activity

Accelerated telomere shortening is linked with numerous age-related chronic diseases and risk factors.[202–210] On the other hand, there is increasing evidence supporting an association between habitual physical exercise, particularly aerobic exercise, and longer leukocyte telomere length.[211–217] Leukocyte telomere length is also positively associated with cardiorespiratory fitness (expressed as VO_2max),[213,218,219] which, in turn, is associated with lower CVD and all-cause mortality.[220] Long-term aerobic exercise can modulate leukocyte telomere length as well as the network of proteins that interact with telomeres, through activation and induction of telomerase enzyme activity (mediated by human telomerase reverse transcriptase [TERT]) and the shelterin complex (or telosome).[217] In effect, TERT mRNA expression is upregulated in leukocytes after exercise.[221] Exercise also regulates the microRNAs (miRNAs) that control the downstream expression of genes involved in telomere homeostasis.[221] The association between physical exercise and telomere length could also be due to lower oxidative stress and inflammation, exercise-induced regulation of telomeric genes, or a complex interplay between these processes.[221,222] The effects of exercise on skeletal muscle tissue telomeres have been less studied compared with leukocytes, and the results are less conclusive.[223,224]

Epigenetic adaptations

The relationship between epigenetics regulation (*e.g.*, DNA methylation) and aging is complex and controversial, *i.e.*, hypomethylation or hypermethylation might be either beneficial or detrimental depending on the different cell types; and, whether manipulations of histone-modifying enzymes can influence aging through purely epigenetic mechanisms remains to be clarified.[196] While keeping in mind the above-mentioned controversy, exercise seems to induce epigenetic modifications that can help attenuate age-deregulations,[225] and several mechanisms, such as metabolic adaptations and transient hypoxia conditions, have been proposed recently.[226] Regular aerobic exercise can modify genome-wide DNA methylation in humans.[227] Animal[216,228,229] and human research[216] suggests that aerobic exercise induces, through epigenetic mechanisms, telomerase activity and the transcription of genes encoding telomere-stabilizing proteins. Both resistance and aerobic exercise can increase DNA methylation, cause histone modifications, and induce miRNAs in a wide range of tissues, including among others, muscle, brain, and cardiovascular system.[225,226] Transient DNA hypomethylation of gene-specific promoter regions precedes increases in mRNA expression in response to acute exercise.[230] In turn, these pulses of elevated mRNA during recovery from acute exercise facilitate protein synthesis and induce gradual structural remodeling and long-term functional adjustments.[231] In general, these adaptations are intrinsic to the working skeletal muscle and collectively contribute to maximize substrate delivery, mitochondrial respiratory capacity, and contractile function during exercise. The net effect is promotion of optimal performance during a future exercise challenge, resulting in a robust defense of homeostasis in the face of metabolic perturbation and, consequently, enhanced resistance to fatigue.[232,233] Several epigenetic mechanisms, including histone H4 deacetylation and loss of promoter methylation, have been implicated in the modified gene expression profile that occurs as an adaptation to aerobic exercise.[234]

Epigenetic mechanisms are not restricted to early stages of human development but are broad dynamic controllers of genomic plasticity in response to environmental factors such as exercise.[235] For instance, in young adults, the class II HDACs 4 and 5 (transcriptional repressors) can translocate from the nucleus to the sarcoplasm of muscle fibers in response to aerobic exercise.[108] Over-expression of HDAC5 in transgenic mice blocks the effects of exercise training, further suggesting a contribution of histone modifications in the transcriptomic response to muscle contraction.[236] In human and mouse muscles, methylation of *PGC-1α,* mitochondrial transcription factor (*TFAM*), *MEF2A,* citrate synthase (*CS*), and pyruvate dehydrogenase kinase isozyme 4 (*PDK4*) gene promoters decreases after an acute bout of aerobic exercise.[230] The degree of DNA methylation of a large number of genes changes in response to exercise in both skeletal muscles and adipose tissue.[237,238] In addition, aerobic exercise-induced SIRT-1 regulates the tumor suppressor p53, PGC-1α, NF-κB as well as other transcription factors via its deacetylase activity.[225,239]

Chronic moderate aerobic exercise increases the methylation levels of the pro-inflammatory apoptosis-associated speck-like protein caspase (*ASC*) gene, which modulates IL-1β and IL-18 in the leukocytes of old people, thereby contributing to attenuation of age-related increases in pro-inflammatory cytokines.[240] Aerobic exercise training also alters DNA methylation in a chronic manner.[241] Thus, 48 hr after a bout of aerobic exercise, the DNA methylation profile of genes involved in diverse metabolic pathways, as well as in calcium and insulin signaling, was recently found to be differentially methylated in skeletal muscle.[241] A majority of the detected genes in this study were chronically hypomethylated after exercise training. Both aerobic and resistance exercise also can help combating aging sarcopenia and frailty by modulating, through epigenetic mechanisms, several myogenic regulatory factors, *e.g.*, myogenin, myoblast determination protein 1 (MyoD), or myogenic factors 5 (Myf5) and 6 (Myf6, also known as myogenic regulatory factor 4 [Mrf4] or herculin).[242–244] Exercise also helps to attenuate the aging-related

epigenetic deregulation of growth factors in neurodegenerative diseases, not only by up-regulating BDNF induction as mentioned above, but also by promoting remodeling of the chromatin containing the *BDNF* gene.[245]

Overall, the study of exercise-induced epigenetic modifications is just in its infancy. Yet the studies available have already provided new insights into the potential tissue-specific alterations in DNA methylation induced by exercise and into some of the mechanisms explaining the beneficial effects of regular exercise.

Loss of proteostasis

Proteostasis is defined as the protein homeostasis that is responsible for refolding or degrading altered proteins by several mechanisms, such as autophagy, proteasomal degradation, or chaperone-mediated folding. A loss of function in these processes leads to an aggregation of damaged proteins and thereby proteotoxic effects that have been associated with aging[196,246] and age-related conditions such as Alzheimer's or Parkinson's disease.[247]

The autophagy–lysosomal and the ubiquitin–proteasome systems, two important proteostatic mechanisms, are impaired by aging.[248,249] Exercise has a beneficial effect in autophagy.[250] In aging mouse models, aerobic exercise induces autophagy in: (1) The brain, supporting its potential to promote elimination of damaging proteins causing neurodegeneration[251]; (2) heart[252]; or (3) muscle (besides preventing apoptosis), by modulating IGF-1, Akt/mTOR, and Akt/Forkhead box O3A (FoxO3a) signaling, thereby preventing loss of muscle mass/strength.[253,254] Although data are still scarce in aging humans, autophagy muscle markers are up-regulated after combined exercise training (walking and moderate-intensity leg resistance exercises) in old women.[255]

Aerobic exercise induces autophagy in mice through activation of the BCL-2–beclin-1 complex,[256] whereas beclin-1 disruption in transgenic mice reduces autophagy leading to neurodegeneration.[257] Moreover, the aging human brain shows a down-regulation of beclin-1,[258] whereas healthy centenarians have higher serum levels of beclin-1 compared with young controls, suggesting that elevated basal levels of autophagy may be related to healthy human exceptional longevity.[259] MacKenzie et al. showed that acute high-resistance exercise evoked increased muscle protein synthesis and decreased protein degradation in rats, through activation of the class 3 phosphatidylinositol 3OH-kinase (PI3K) Vps34 mVps34,[260] which is known to regulate autophagy by forming a complex with beclin-1.[261] Using an atrogin-1 (also known as MAFbx) knockout mouse model, Zaglia et al. demonstrated that autophagy dysfunction promotes cardiomyopathy and premature death.[262] Atrogin-1 is a muscle-specific ubiquitin ligase involved in muscle atrophy through FoxO signaling.[263] Similar to skeletal muscle, atrogin-1 up-regulation in the heart leads to atrophy.[264] Interestingly, aged atrogin-1 knockout mice have reduced tolerance to treadmill exercise and shortened life span compared with age-matched controls.[262] In this animal model, muscle age-related increases in oxidative damage and apoptosis are attenuated by regular aerobic exercise, whereas both mechanisms are negatively correlated with autophagy.[261]

Deregulated nutrient sensing

Exercise exerts protective effects against age declines in the glucose-sensing somatotrophic axis,[265] and also activates at the muscle level the three main interconnected nutrient-sensing systems, *i.e.*, the amino acid–sensing mTOR pathway[266,267] and the low energy–sensing AMPK and SIRT pathways,[132,268] thereby promoting a beneficial muscle anabolic state. On the other hand, exercise improves insulin sensitivity through increased production of the glucose transporter type 4 (Glut 4).[269]

In addition, resistance exercise acutely increases the circulating levels of testosterone, growth hormone (GH), and IGF-1, with the magnitude of the effect usually increasing with higher exercise intensity[270] or duration,[271] shorter rest intervals,[272] and higher exercising muscle mass.[273,274] Thus, resistance exercise is a useful approach to prevent sarcopenia by virtue of its ability to increase protein synthesis[275–277] and skeletal muscle mass.[278,279] However, the rate of muscle protein synthesis in response to exercise training is lower in the elderly than in younger people,[280,281] leading to a lower capacity to improve skeletal muscle strength and fiber size.[282] On the other hand, supplementation with essential amino acids together with resistance training increases muscle protein synthesis both in young and old individuals, although such an effect is also attenuated in the latter, owing, at least partly, to lower ERK1/2 and mTOR signaling.[280] (For a more extensive description about nutrient-sensing modulation by exercise, see above.)

Mitochondrial dysfunction

mtDNA mutations (typically deletions) accumulate with age in different tissues,[283,284] including mainly the nervous and skeletal muscle tissue.[37,285] Mutations in muscle mtDNA play a causal role in the physiological mechanisms implicated in sarcopenia,[37–40] particularly in abnormalities of the electron transport system, muscle fiber atrophy, and breakage.[37,39,40] Despite classic studies demonstrating exercise-induced mitochondrial biogenesis in young but not in aged mice,[286] recent findings have shown that aerobic exercise training attenuates mitochondrial dysfunction and loss of mitochondrial content in the aging human skeletal muscle while increasing oxidative capacity and the activity of different electron transport chain protein complexes.[287]

The accumulated damage to the mitochondria due to the ROS generated from the electron transport chain is the base of the mitochondrial theory of aging first proposed by Harman.[288] Oxidative damage to mtDNA increases with aging, affecting mtDNA replication and transcription, which, in turn, alters the functionality of mitochondrial proteins.[289,290] Lanza et al. demonstrated that age-related decline in mitochondrial oxidative capacity was absent in endurance-trained humans, who showed elevated expression of mitochondrial proteins, mtDNA, and mitochondrial transcription factors.[291] In mtDNA mutator mice, aerobic exercise promoted systemic mitochondrial biogenesis, prevented mtDNA depletion and mutations, increased mitochondrial oxidative capacity and respiratory chain assembly, restored mitochondrial morphology, and blunted pathological levels of apoptosis in multiple tissues. Thus, the authors concluded that a systemic ''mitochondrial rejuvenation'' occurred as a result of the training program.[197]

The lower mitochondrial enzyme activity commonly shown in older compared with younger adults[17,292] is associated with a down-regulation of the mRNAs encoding mitochondrial proteins in skeletal muscle.[293–295] Aged subjects have cytochrome *c* oxidase (COX)-deficient muscle fibers,[296] especially in sarcopenic muscles or in those focal regions with higher content of mtDNA mutations.[39,296–299] Yet resistance exercise training can reverse the muscle transcriptional signature of aging back to that of younger levels for most genes involved in mitochondrial function.[299] Gomes et al.[300] recently provided novel insights into the mechanisms responsible for the age decline of mitochondrial homeostasis by elegantly showing a regulatory pathway that is SIRT1-mediated and independent of PGC-1α and -β, with aging declining NAD^+ levels and thereby reducing SIRT1 activity and leading to impaired oxidative phosphorylation (OXPHOS). Short treatment (1 week, or $\sim$8 months, when translated to the human life span) of 22-month-old mice with nicotinamide mononucleotide (NMN) (a precursor to NAD^+ increasing NAD^+ levels *in vivo*) reversed several biochemical indicators of muscle mitochondrial senescence, with increased OXPHOS transcripts in the gastrocnemius muscle. It was proposed that NMN or other compounds able to increase NAD^+ are candidates to be included in the human anti-aging armamentarium. And yet NMN, as opposed to exercise, was unable to reverse other age-dependent whole-organism effects, such as loss of muscle strength.

Besides the above-mentioned benefits of resistance exercise on muscle strength until end of life (which were summarized in Table 1), regular exercise has a profound beneficial effect on human mitochondrial function/biogenesis,[301] with this effect being both PGC-1 and SIRT mediated.[111] An active lifestyle attenuates aging mitochondrial dysfunction, promoting longevity through pathways common to the effects of caloric restriction.[291] In addition, some ''myokines'' (see further below for the definition of myokine) have a mitochondrial rejuvenating effect, *e.g.*, visfatin, a NAD^+ biosynthetic enzyme that stimulates the SIRT-1 pathway.[252]

Cellular senescence

Cellular senescence is defined as a stable arrest of the cell cycle coupled with stereotyped phenotypic changes, and its regulation during aging is a complex process. Indeed, the same phenomenon, *i.e.*, elimination of senescent cells, that is beneficial to delay age-related pathologies and thus to promote longevity, could also stimulate cancer development.[196] Besides inducing secretion of antitumorigenic myokines such as secreted protein acidic and rich in cysteine (SPARC, also known as basement membrane protein [BM]-40), calprotectin, or leukemia inhibitory factor,[302] exercise, mainly aerobic exercise, may decrease cancer incidence and help improve cancer prognosis through several mechanisms, including greater natural killer (NK) cell activity, enhanced antigen presentation, reduced inflammation, and prevention of functional senescent cells' accumulation.[303] Telomere-associated proteins regulate cellular senescence and, as described above, are up-regulated by exercise. Moreover, aerobic exercise increases the aortic expression of telomere repeat-binding factor 2 and Ku70 and reduces the expression of apoptosis regulators, such as cell-cycle-checkpoint kinase 2, $p16^{INK4a}$, and p53 or survival regulators.[216]

Telomere-associated proteins, as well as $p16^{INK4a/Rb}$ and $p19^{ARF}$/p53 signaling, are considered main pathways in the control of human aging and age-associated pathologies.[196] $p16^{INK4a}$ and p21 are cell cycle inhibitors that are up-regulated in senescent cells.[304,305] p21 is a downstream target of p53 and telomere dysfunction, whereas $p16^{INK4a}$ appears to be up-regulated in a p53- and telomere-independent manner.[306] Sousa-Victor et al. recently highlighted the importance of $p16^{INK4a}$ in the modulation of cellular senescence. In a geriatric mouse model, muscle satellite cells lose their quiescent state owing to deregulation of $p16^{INK4a}$, whereas repressing $p16^{INK4a}$ restores muscle regenerative capacity.[307] Thus, we suggested the importance of $p16^{INK4a}$ modulation as a new target for combating aging-related chronic diseases.[308] Lifestyle factors, including smoking and physical aerobic exercise practice, have been associated with $p16^{INK4a}$ mRNA levels in peripheral blood T ymphocytes,[309] a biomarker of human aging.[310] Thus, physical exercise is inversely correlated with $p16^{INK4a}$ mRNA levels, *i.e.*, higher amounts of physical exercise leads to down-regulation of $p16^{INK4a}$ in blood cells, which might promote protective effects against age-dependent alterations.[309]

As exposed above, cellular senescence plays a key role not only in cancer development[311,312] but also in aging.[313] In fact, cell senescence is one of the major paradigms of aging research through the acquisition of the senescence-associated secretory phenotype (SASP) or senescence-messaging secretome.[314] SASP is a DNA damage response, which, through production of inflammatory, growth-promoting, and remodeling factors can potentially explain how senescent cells alter tissue microenvironments.[315] Different animal model investigations have shown that exercise modulates senescence associated to aging. Thus, 12 weeks of aerobic (swimming) exercise training suppressed liver senescence markers and down-regulated inflammatory mediators by reducing gamma glutamyltranspeptidase activity and levels of p53, p21, and IL-6 in a D-galactose–induced senescence rat model.[316] Werner et al.[228] studied the effect of aerobic exercise on telomere-regulating and cellular senescence mechanisms at the cardiac level in wild-type, endothelial NO• synthase (eNOS)-deficient and TERT-deficient mice models. Their results showed that exercise up-regulated cardiac telomere-stabilizing proteins, promoted anti-senescent effects, and provided protection against doxorubicin-induced cardiomyopathy. Werner et al.[216] also studied the effects of aerobic exercise on vascular telomere biology and endothelial apoptosis in mice and the effects of long-term aerobic training on telomere biology in circulating leukocytes in humans. Besides improving telomere biology in the thoracic aorta and in mononuclear cells, exercise reduced the vascular expression of apoptosis regulators. Moreover, endurance athletes had increased telomerase activity and down-regulated cell cycle inhibitors compared with sedentary subjects. These findings are supported by Song et al.,[309] who found that in humans aerobic exercise reduced the expression of DNA damage biomarkers and correlated positively with $p16^{INK4a}$ expression and negatively with telomere length in peripheral blood T lymphocytes.

Stem cell exhaustion

The decline in the regenerative potential of tissues is a main characteristic of aging, whereas exercise is one of the most potent stimuli for the proliferation/migration of the different adult stem cell subsets from their home tissue (*e.g.*, bone marrow) to target damaged tissues for subsequent engraftment and regeneration.[252] Thus, regular exercise attenuates age-associated reduction in the endothelium-reparative capacity of endothelial progenitor cells.[317] Exercise activates mesenchymal stem cells, which are pluripotent progenitors with a wide variety of therapeutic potential (*e.g.*, as vehicles of anti-cancer genes) and promotes proliferation of neural stem cells, thereby contributing to improve brain regenerative capacity and cognitive ability.[252]

Arguably the most affected stem cell type during aging is the myogenic one, known as satellite cells.[318] Although the human skeletal muscle tissue maintains myofiber replacement and repair potential throughout most of life, the efficiency of this process declines with aging, owing to satellite cell alterations. Age-reduced number or functionality of these myogenic cells prevents proper maintenance of muscle mass.[318–321] Specifically, aging atrophy of type II muscle fibers is accompanied by a specific decline in the content of type II muscle fiber satellite cells.[318] Thus, since sarcopenia is associated with atrophy of type II muscle fibers, its pathophysiological mechanisms are closely related with the decline in satellite cell content with aging.[31] Both aging reductions in muscle mass and strength are positively correlated with muscle fiber type specific cross-sectional area, myonuclear content, and satellite cell content.[322]

Animal studies have demonstrated that aerobic exercise increases myofibers that contain higher numbers of satellite cells in both young and old rats,[323] and also promotes expansion of the satellite cell pool in young and old mice.[324] The contribution of these stem cells to skeletal muscle regeneration has been well documented.[325,326] As stated by Hawke and Garry,[326] because adult myofibers are postmitotic cells, the regulation of skeletal muscle is dependent on a small population of resident cells that are the satellite cells. The regulation of satellite cells involves several mechanisms, including immune response, neurotransmitters, neurotrophic and vascular factors (among other growth factors such as IGF-1[327]), cytokines such as IL-6,[328] testosterone, or NO•, most of which are modulated by exercise.[111]

Not only in young adults[329] but also during aging, resistance training is able to induce skeletal muscle satellite cell proliferation and differentiation, thereby resulting in hypertrophy of type II fibers.[330] The latter phenomenon, in turn, attenuates the pro-sarcopenic physiological events related to type II fiber atrophy associated with aging,[31,318, 322] On the other hand, although resistance training in the elderly of both sexes can counteract the loss of muscle mass and strength,[331] a recent study reported that satellite cell induction in response to a single bout of resistance exercise is delayed in old men.[332] McKay et al.[333] also showed that, compared to young adults, muscle levels of myostatin, a protein that inhibits muscle differentiation and growth in the myogenesis process, were two-fold higher in older individuals, who also had 35% fewer basal stem cells and a type II fiber-specific impairment in stem cell content. The authors concluded that the co-localization of myostatin with satellite cells explains the worsened myogenic capacity of the aged skeletal muscle.[333] In fact, an aging-blunted activation of type II muscle fiber satellite cells in response to an acute bout of resistance exercise was recently shown by Snijders et al.[332] In addition, the satellite cell response to resistance exercise is related to the extent of muscular hypertrophy induced by training.[334]

Altered intercellular communication

Aging is associated with altered intercellular communication leading to inflammation or ''inflammaging.''[196] Several mechanisms are responsible for this process, including accumulation of pro-inflammatory tissue damage, immune dysfunction, release of pro-inflammatory cytokines by senescent cells, higher activation of NF-κB, or impaired autophagy regulation.[196,335] These events activate the NOD-like receptor protein 3 (NLRP3) ''inflammasome,'' characterized by elevations in IL-1β, tumor necrosis factor-α (TNF-α), and interferons.[335,336] Interestingly, calorie restriction and exercise-mediated weight loss in obese individuals with type 2 diabetes lead to a reduction in adipose tissue expression of the NLRP3 inflammasome and IL-1β, and thus to reduced inflammation.[337]

The decay factor AUF1 (AU-binding factor 1, also known as heterogeneous nuclear ribonucleoprotein D or hnRNP D) is implicated in the cessation of the inflammatory response (by mediating cytokine mRNA degradation) and also in the maintenance of telomere length by modulating TERT.[338] Down-regulation of AUF1 leads to accelerated cellular senescence and premature aging in mice, which is rescued by normalizing the expression of this factor.[196] Lai et al. found that chronic muscle contractile activity increased different AUF1 isoforms (p37, p40, and p45) in the muscle of healthy rats, resulting in improved muscle plasticity in response to subsequent contractile activity.[339] Senescent cells transmit their condition to other cells through multiple mechanisms, including ROS, growth factors, and interleukins.[340] As mentioned above, chronic physical exercise (mostly of the aerobic type) decreases ROS damage, and it does so by decreasing ROS production at the mitochondrial level while up-regulating endogenous anti-oxidant defense.[121]

Importantly, skeletal muscle fibers produce hundreds of secreted factors or ''myokines'' (including the above-mentioned neurotrophins) with a potential drug-like effect at the local and systemic levels, *i.e.*, proteins, growth factors, cytokines, or metallopeptidases, and this secretory capacity increases during and after exercise training (see Fiuza-Luces[252] for an in-depth review and Table 3 for some illustrative examples). Systemic low-level inflammation and related conditions such as CVD or cancer can be attenuated by the cumulative effect of regular exercise bouts, during which the muscle can release IL-6, arguably the myokine prototype.[341] This, in turn, creates a healthy milieu by inducing the production of the anti-inflammatory cytokines IL-1 receptor antagonist (IL-1Ra), IL-10, or TNF soluble receptors (sTNF-R) while inhibiting the pro-inflammatory cytokine TNF-α.[341] The release of IL-6 from working muscles increases with exercise intensity[342] and duration,[343] and endogenous NO• and the interaction between Ca^{2+}/nuclear factor of activated T cell (NFAT) and glycogen/p38 MAPK are the proposed upstream signals leading to its

Table 3. Examples of Myokines Released During Exercise with a Potential Anti-Aging Effect

Name of molecule	*Main tissue(s) of origin*	*Main type of exercise inducing its release/ secretion*	*Main target tissue(s)*	*Main biological effect(s) associated with exercise-induced release/secretion*	*Main aging hallmark targeted*	*Potential future anti-aging application*	*Illustrative references*
Brain-derived neurotrophic factor (BDNF)	Central nervous system Vascular endothelial cells, platelets, lymphocytes, eosinophils, monocytes, pituitary gland, working skeletal muscle	Moderate-intense "aerobic" exercise (*e.g.*, brisk walking)	Brain Motor neurons	↑ Neuroplasticity ↑ Motor unit regeneration	Cellular senescence in the brain	Protection against neurodegeneration (including possibly dementia)	167–169
Interleukin-4 (IL-4) and IL-13	Lymphocytes, mast cells and neutrophils Various origins (brain, cancer cells, liver, fibroblasts, and muscle cells) Working muscles	Resistance exercise (*e.g.*, weightlifting)	Skeletal muscle	↑ Muscle growth	Loss of muscle proteostasis	Aging muscle atrophy/sarcopenia	387–389
IL-6 (also termed interferon, beta 2)	Working muscles Immune cells Adipocytes	Intense 'aerobic' exercise (*e.g.*, brisk/very brisk walking)	Skeletal muscle Adipose tissue Pituitary gland-liver Immune cells	↑ Muscle lipolysis ↑ Muscle growth ↑ Adipocyte lipolysis ↑ Liver-glucose release to blood ↓ Inflammation ↑ Immunomodulation	Altered inter-cellular communication ('inflammaging')	Age-related cardiometabolic diseases	129, 390–393
IL-15	Working muscles Various origins (lymphoid tissues, kidney, brain, cardiac muscle, lung, pancreas, testis, liver, placenta, epithelial cells, and activated macrophages, and maybe adipocytes)	Mainly resistance exercise	Skeletal muscle Adipose tissue	Promotes muscle anabolism/inhibits catabolism Anti-obesogenic (↓mainly visceral fat) effect Insulin-sensitizing effect	Loss of muscle proteostasis	Aging muscle wasting/ sarcopenia	394–397
Leukemia inhibitory factor (LIF)	Working muscles Central nervous system	Mainly resistance exercise	Skeletal muscle	Mainly local (autocrine/ paracrine effect): ↑ Muscle growth (satellite cell proliferation) ↑ Muscle regeneration	Loss of muscle proteostasis	Aging muscle wasting/ sarcopenia	398–401
Myostatin (also termed, growth differentiation factor 8 [GDF8])	Skeletal muscle	Both "aerobic" and resistance exercise	Skeletal muscle Adipose tissue	Main effects associated to myostatin inhibition which can be partly achieved by exercise are: ↑ Muscle growth ↓ Adiposity ↑ Insulin sensitivity	Attenuation of disease/age muscle wasting Obesity/diabetes prevention	Use of exercise as a coadjuvant of myostatin-inhibition therapies for muscle wasting	402–406
Visfatin (also known as (nicotinamide phosphoribosyltransferase [NAMPT] or pre-B cell enhancing factor [PBEF])	Ubiquitous expression in human tissues, including adipose and skeletal muscle tissue (*i.e.*, it is both an adypokine and a myokine), liver, bone marrow, lymphocytes, β-cells and human islets, heart	"Aerobic" exercise	Skeletal muscle and adipose tissue	AMPK activation → ↑ sirtuin1 (SIRT1) → peroxisome proliferator-activated receptor γ co-activator α (PGC-1α) It provides NAD^+	Mitochondrial dysfunction	Exercise as a major component of anti-aging medicine	407–410

The information provided in the table is based (and adapted from) a previous review paper by the authors.[111]
AMPK AMP-activated protein kinase; NAD^+, oxidized nicotinamide adenine dinucleotide.

secretion.[344] Other anti-inflammatory myokines include IL-4, IL-10, or IL-13.[345,346] Thus, life-long aerobic exercise training is associated with lower inflammation levels.[347–349] Higher levels of aerobic exercise have also been associated with lower levels of C-reactive protein (CRP), IL-6, and TNF-α in people aged 70–79 years.[350] However, although exercise training is known to have beneficial anti-inflammatory effects across a broad spectrum of organs and systems, more research is needed in the elderly, particularly to determine if the molecular mechanisms and pathways involved are similar in old people compared with younger population segments.[351]

Perspective

The benefits of regular exercise are such that a dose–response is usually observed in humans. Higher levels of moderate-to-vigorous exercise ($\geq$450 min/week, clearly above the minimum international recommendations of 150 min/week) are associated with longer life expectancy.[352] Furthermore, elite athletes—those humans sustaining the highest possible exercise levels (*e.g.*, former participants in the Tour de France cycling race or former Olympic marathoners)—usually live considerably longer than the general population.[353]

Physical exercise has a profound effect on the expression of a substantial proportion of our genome, which has evolved to optimize aerobic metabolism in an environment of food scarcity. Thus, physical inactivity is becoming a major public health problem worldwide.[354] Exercise certainly cannot reverse the aging process, but it does attenuate many of its deleterious systemic and cellular effects. Most common age-associated chronic conditions are diseases of physiology and thus physiological interventions, of which physical exercise is arguably the best example, are largely the answer.[355] We propose that more research efforts should be devoted to gain insights into the molecular mediators of the exercise benefits. Besides putting more anti-aging drugs on the market, it would be wise to determine which are the most effective combinations, types, and dosages (frequency, duration, intensity) of exercise for older people and to implement efficient exercise interventions for this and younger population segments. **Note:** For the purposes of simplicity in this review, we have mostly used the common term ''exercise'' instead of ''physical activity.''

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