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The concept of a "polypill" is receiving growing attention to prevent cardiovascular disease. Yet similar if not overall higher benefits are achievable with regular exercise, a drug-free intervention for which our genome has been haped over evolution. Compared with drugs, exercise is available at low cost and relatively free of adverse effects. We summarize epidemiological evidence on the preventive/therapeutic benefits of exercise and on the main biological mediators involved.

An Evolutionary Perspective

Despite recent strong selection pressure (495), our genetic makeup is largely shaped to support the physical activity (PA) patterns of hunter-gatherer societies living in the Paleolithic era, for which food/fluid procurement (and thus survival) was obligatorily linked to PA (71, 347). The energy expenditure of hunter-gatherers during PA (~1,000–1,500 kcal/day) can be reached with 3–4 h/day of moderate-to-vigorous PA (MVPA), e.g., brisk/very brisk walking (71, 346). Yet technological improvements over just ~350 generations (agricultural followed by industrial and, most recently, digital revolution) have led to dramatic reductions in human PA levels (26, 475): ~1/3 of adults worldwide are currently inactive, and the endemic inactivity trend starts in early life (166).

Physical inactivity in contemporary obesogenic environments initiates maladaptations that cause chronic disease and is becoming a major public health problem (36). In contrast, regular PA has a profound effect on the expression of a substantial proportion of our genome (474), which has been selected for optimizing aerobic metabolism to conserve energy in an environment of food scarcity (40, 41), resulting in numerous beneficial adaptations and decreased risk of chronic diseases, as discussed below.

Epidemiological Evidence I: Exercise Benefits–How Protective is Exercise per se Against Conventional Cardiovascular Risk Factors Compared With Drugs?

The main outcome of regular PA[1], achieving moderate-to-high peak cardiorespiratory fitness (>8 METs[2]), reduces the risk of cardiovascular events and all-cause mortality (234). There is strong epidemiological evidence indicating that regular PA is associated with reduced rates of all-cause mortality, cardiovascular disease (CVD), hypertension, stroke, metabolic syndrome, Type 2 diabetes, breast and colon cancer, depression, and falling (see Ref. 255 for a review). Especially provocative are recent findings showing a positive and negative association between leisure time spent sitting or doing PA, respectively, and mortality risk among survivors of colorectal cancer (55). Furthermore, the benefits of PA are such that a dose response is usually observed in the general population. Higher MVPA levels [≥450 min/wk, clearly above the minimum international recommendations of 150 min/wk of MVPA (515)] are associated with longer life expectancy (317). And athletes, who are those humans sustaining the highest possible PA levels, live longer than their nonathletic counterparts (415). Most epidemiological research up to date has focused on exercise and CVD risk factors or cardiovascular outcomes. For instance, the benefits of regular exercise on all-cause mortality and CVD are well above those of a nutritional intervention, supplementation with marine-derived omega-3 polyunsaturated fatty acids (PUFAs), which has gained considerable popularity owing to the potential ability of omega-3 PUFAs to lower triglyceride levels, prevent serious arrhythmias, or decrease platelet aggregation and blood pressure (BP) (423). These protective roles of omega-3 PUFAs are, however, controversial since a recent meta-analysis showed that omega-3 PUFAs are not significantly associated with decreased risk of all-cause mortality and major CVD outcomes (405).

Exercise training has a restoring/improving effect on endothelial function (103, 158, 500). This is an important consideration because endothelial dysfunction is a risk factor for CVD, whereas normal or enhanced endothelial function has a protective

[1]The terms "PA" (physical activity) and "exercise" are used interchangeably in this review to make reading more fluent.

[2]1 MET equals an oxygen consumption of 3.5 ml·kg^{-1}·min^{-1}.

effect (158–160). In previously sedentary middle-aged and older healthy men, regular aerobic exercise can prevent the age-associated loss in endothelium-dependent vasodilation (as assessed by vasodilatory response to acetylcholine) and restore this variable to levels similar to those of young adults (103). Exercise also reduces more "traditional" CVD risk factors, albeit probably its effects are modest compared with the impact of medications, with the possible exception of (pre-) diabetes. This is illustrated in the paragraphs below, where we compare the effects of exercise interventions alone to those of common drugs on conventional CVD risk factors. There is scant biomedical literature containing direct comparison of exercise to pharmacological intervention. Therefore, the comparisons presented herein are based on the results of recent meta-analyses (independently searched by two authors, C. Fiuza-Luces and N. Garatachea) of *1*) randomized controlled trials (RCTs) of drugs or drug combinations and *2*) RCTs of exercise training alone.

Exercise vs. Drugs: Glucose Intolerance

A recent meta-analysis has reported that exercise training is associated with an overall 0.67% decline in glycosylated hemoglobin (HbA1c) levels [95% confidence intervals (CI), −0.84 to −0.49] (479). Separate analyses showed that each of aerobic (−0.73%; 95% CI, −1.06 to −0.40), resistance (−0.57%; 95% CI, −1.14 to −0.01), or combined aerobic and resistance training modes were associated with declines in HbA1c levels compared with control participants (−0.51%; 95% CI, −0.79 to −0.23). The overall reduction in HbA1c of −0.67% brought about by exercise compares relatively well with the recently reported reductions achieved by commonly used oral antidiabetic medications such as metformin monotheraphy and dipeptidyl peptidase inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin), which can lower HbA1c levels by 1.12% (95% CI, −0.92 to −1.32) (182) and 0.76% (95% CI, −0.83 to −0.68), respectively (362). On the other hand, a recent meta-analysis has shown that non-drug approaches (diet, exercise) are superior to drug interventions in diabetes prevention [risk ratio of 0.52 (95% CI, 0.46–0.58) vs. 0.70 (95% CI, 0.58–0.85), respectively ($P < 0.05$)] (191).

Exercise vs. Drugs: Blood Lipids

A recent meta-analysis of RTCs (223) has shown a significant decrease in triglycerides after exercise interventions (−6.0 mg/dl; 95% CI, −11.8 to −0.2) but not in total cholesterol (0.9 mg/dl; 95% CI, −3.2 to 5.0), high-density lipoprotein (HDL) cholesterol (1.0 mg/dl; 95% CI, −0.2 to 2.1), or low-density lipoprotein (LDL) cholesterol (2.1 mg/dl; 95% CI, −1.5 to 5.7). Relative to baseline values, changes were equivalent to 0.4%, 2.1%, 1.5%, and −5.7% for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, respectively. Statins, especially simvastatin and atorvastatin, are the most widely prescribed cholesterol-lowering drugs (113). A meta-analysis of 21 trials testing statin regimens reported a weighted mean difference after 1 year of treatment of 1.07 mM (−29%) for LDL cholesterol (18). A more recent meta-analysis of the effects of atorvastatin on blood lipids showed decreases of 36–53% for LDL cholesterol (2).

Exercise vs. Drugs: Blood Pressure

A recent meta-analysis reported BP reductions with aerobic exercise in healthy subjects [−2.4 mmHg (95% CI, −4.2 to −0.6) for systolic BP (SBP) and −1.6 mmHg (95% CI, −2.4 to 0.74) for diastolic BP (DBP)] and in hypertensive people [−6.9 mmHg (95% CI, −9.1 to −4.6) for SBP and −4.9 mmHg (95% CI, −6.5 to −3.3)] for DBP (73). Resistance training, including either dynamic (72, 74, 222) or static exercises (74, 221, 358), also has a BP-lowering effect in people with normal pressure or prehypertension, overall, −3.87 mmHg (95% CI, −6.19 to −1.54) for SBP and −3.6 mmHg (95% CI, −5.0 to −2.1) for DBP. Of note, it is difficult to compare the effects of exercise and drugs since we are not aware of a meta-analysis comparing the effects of BP-lowering drugs vs. no drug administration. Nevertheless, the effects of exercise on BP are probably of higher magnitude than those obtained with any single BP-lowering drug, e.g., aliskiren, a renin inhibitor that induces an overall BP reduction of −0.18 mmHg (95% CI, −1.07 to 0.71) or angiotensin receptor blockers, which induce an overall BP reduction of −0.15 mmHg (95% CI, −1.38 to 1.69) (138). Exercise effects on BP are, however, likely to be similar or slightly lower than those of drug combinations, as suggested by the fact that drug combinations are substantially more efficacious than monotherapy in lowering BP. For instance, aliskiren combined with angiotensin receptor blockers would be superior to aliskiren monotherapy at the maximum recommended dose on SBP (−4.80 mmHg; 95% CI, −6.22 to −3.39) and DBP reduction (−2.96 mmHg; 95% CI, −4.63 to −1.28). Similar results can be found for aliskiren combined with angiotensin receptor blockers vs. angiotensin receptor blockers monotherapy (SBP: −4.43 mmHg, 95% CI: −5.91 to −2.96; DBP: −2.40 mmHg, 95% CI: −3.41 to −1.39) (531).

Exercise vs. Drugs: Thrombosis

Longitudinal studies have shown that increased levels of PA reduce thrombosis-related cardiovascular events, e.g., nonfatal myocardial infarctions, strokes, and mortality, in people with (252, 376,

504) or without a history of CVD (279, 330, 496). A recent meta-analysis has concluded that moderate exercise training after successful coronary stenting, compared with control group, does not significantly change the incidence of stent thrombosis and major adverse cardiovascular events (death, myocardial infarction, stroke) for up to 3 years (1.8% vs. 2.0%, $P = 0.73$; and 14.9% vs. 15.0%, $P = 0.97$, respectively) but is effective in reducing unscheduled hospital visits for worsening angina (20.2% vs. 27.2%, $P < 0.0001$) (451). Comparisons with drugs are also difficult here, but pharmacological interventions would seem to outweigh exercise benefits. For instance, in a meta-analysis with 5,821 patients undergoing coronary stenting, the use of cilostazol-based triple antiplatelet therapy (TAT) was associated with a significant reduction in the risk of major adverse cardiovascular events compared with dual antiplatelet therapy (DAT) (9.2% vs. 13.4%; odds ratio of 0.59; 95% CI, 0.46 to 0.76) (142).

Thus, although regular exercise and cardiorespiratory fitness are associated with a significant reduction in cardiac events (165, 329, 442), it seems that the benefits of regular exercise go beyond reducing traditional CVD risk factors. This is consistent with classic (see Ref. 213 for a review) and recent reports showing that high cardiorespiratory fitness can reduce morbidity and mortality independent of standard CVD risk factors (254, 354, 445). Notably, Mora et al. evaluated 27,055 apparently healthy women and found that ~59% of the risk reduction for all forms of CVD associated with higher levels of PA could be attributed to the effects of exercise on known risk factors, with inflammatory/hemostatic biomarkers (e.g., C-reactive protein, fibrinogen) making the largest contribution to PA reduction of CVD, followed by BP, lipids, and body mass index (319). So, where is the "risk factor gap" explaining the remaining variance (~40%) in CVD risk reduction achieved by regular exercise?

Epidemiological Evidence II: Exercise Attenuates Aging Autonomic Dysfunction

Besides improving endothelial function (see above), regular exercise contributes to attenuate aging autonomic dysfunction; thus autonomic dysfunction could be one of the missing or nonconventional risk factors that is altered by exercise, as elegantly hypothesized by Joyner and Green in a recent review (213) and summarized below.

Aging is associated with marked increases in sympathetic nervous system (SNS) activity to several peripheral tissues, possibly to stimulate thermogenesis to prevent increasing adiposity (436). This tonic activation of the peripheral SNS has, however, deleterious consequences on the structure and function of the cardiovascular system, e.g., chronically reduced leg blood flow, increased arterial BP, impaired baroreflex function, or hypertrophy of large arteries, which in turn can increase CVD risk (436). Chronically augmented SNS-mediated reductions in peripheral blood flow and vascular conductance can also contribute to the etiology of the metabolic syndrome, by increasing glucose intolerance and insulin resistance (23, 270). Heart rate variability (HRV) is a noninvasive measure of the autonomic nervous system function and a surrogate index for clinical outcome in trials of CVD prevention (344), with high values reflecting a survival advantage, whereas reduced HRV is a marker of autonomic dysfunction that may be associated with poorer cardiovascular health and outcomes (412), including also a substantial increase in the incidence of coronary heart disease, myocardial infarction, fatal coronary disease, and total mortality in diabetic individuals (269). A recent study has shown that a simpler marker of SNS, elevated resting heart rate, is a risk factor for mortality (16% risk increase per 10 beats/min) independent of conventional CVD risk factors (208). Furthermore, high levels of sympathetic outflow in conjunction with endothelial dysfunction may have a synergistic and detrimental effect in terms of CVD risk (89). On the other hand, there is evidence that exercise training can keep the autonomic nervous system healthy, including in old people.

Moderate aerobic exercise (brisk walking) for 3 mo attenuates age-related reductions in baroreflex function, and there appears to be an exercise "dose-response" with regard to the exercise benefits, with endurance-trained older individuals showing similar baroreflex function than their moderately active younger peers (316). A recent meta-analysis has shown that HRV increases with exercise training (344), with this effect being reported in middle-aged or old people who are either healthy (106, 134, 374) or have myocardial infarction (51, 65, 108, 245, 262, 288, 289, 295, 359, 421), chronic heart failure (227, 288, 375, 440), transluminal coronary angioplasty, coronary artery bypass grafting (197, 281, 464, 477), or diabetes (123, 277, 535). Although angiotensin II and nitric oxide ($NO^{\cdot}$) may play a mediating role and more research is needed, to date, it seems that exercise may influence HRV in humans via increasing vagal modulation and decreasing sympathetic tone (412).

Autonomic dysfunction can also contribute significantly to the risk for sudden death due to ventricular fibrillation, which is the leading cause of death in most industrially developed countries (33). Alterations in cardiac parasympathetic control are

indeed associated with an increased risk for sudden death (34, 56, 90, 413), and there is a particularly strong association between reductions in HRV or baroreceptor reflex sensitivity and increased incidence of sudden cardiac death in patients recovering from myocardial infarction (14, 31, 112, 187, 244, 246, 466). This provides evidence supporting the probability that myocardial infarction reduces cardiac parasympathetic regulation and enhances β2-adrenoceptor expression sensitivity, leading to intracellular calcium dysregulation and arrhythmias (33). Thus not only β-adrenoceptor antagonists but also aerobic exercise interventions, which favorably improve cardiac autonomic balance by increasing parasympathetic or decreasing sympathetic activity (114, 290, 353, 370, 450), could reduce the incidence of lethal ventricular arrhythmias (32, 33). Evidence from canine models indicates that exercise training improves cardiac parasympathetic regulation (as reflected by increased HRV), restores a more normal β-adrenoceptor balance (i.e., reducing β2-adrenoceptor sensitivity and expression), and protects against ventricular fibrillation induced by acute myocardial ischemia (see Ref. 33 for a review).

Epidemiological Evidence III in the Context of the 21st Century's Medicine: Exercise Has "Polypill-Like" Effects

Paradoxically, the pandemic spread of cardio-metabolic diseases has paralleled the ground-breaking advances in pharmacology, and CVD remains the leading cause of death worldwide (307). Further complicating the problem, therapeutic strategies designed to control several CVD risk factors simultaneously in people without evidence of CVD are expensive and difficult to implement. The development of fixed-dose drug combinations originally designed for the treatment of myocardial infarction such as statins, diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or aspirin in one pill could help to potentially overcome these limitations and is gaining attention as a promising preventive strategy in the 21st century (335, 422).

Wald and Law first described a combination pill for CVD prevention (498), which they called a "polypill" (499). In 2001, a World Health Organization and Wellcome Trust meeting of experts concluded that a fixed-dose polypill containing aspirin, statin, and two BP-lowering agents may improve adherence to treatment as well as substantially reduce the cost of the drugs, particularly for low- and middle-income countries (516). And, in 2003, Wald and Law claimed that CVD could be reduced by 88% and strokes by 80% if all those over 55 years of age were given a polypill containing three low-dose BP-lowering medications: a statin, low-dose aspirin, and folic acid (499). This controversial and provocative approach of "medicalizing" the population has been followed by more targeted approaches. For instance, a large clinical trial is being conducted in five countries to investigate the effects of a polypill (aspirin, an ACE inhibitor, and a statin) on ischemic heart disease recurrence (137). Yet polypill-like benefits are achievable with a drug-free intervention, regular PA.

Elley et al. recently conducted a meta-analysis (the only one we are aware of) on both the efficacy and tolerability of polypills (115). They reviewed data on six RCTs, including a total of 2,218 subjects (1,116 in a polypill group and 1,102 in a comparison group) who were mostly middle-aged adults (men/women, 50–60 yr) with no previous CVD but with ≥1 risk factors. The polypill consisted of one to three antihypertensive drugs (calcium channel blocker, thiazide, ACE inhibitor or angiotensin receptor blocker, or combinations of the above) and one lipid-lowering medication (atorvastatin or simvastatin) with or without aspirin for primary CVD prevention, and treatment lasted 6–56 wk. In FIGURE 1, we compare the results of the above-mentioned meta-analysis on important outcomes related to CVD risk factors (BP, total and LDL cholesterol), with those reported in two recent meta-analyses of the effects of regular exercise in middle-aged adults: a study by Pattyn et al. in 272 middle-aged men/women with the metabolic syndrome but with no other CVD (median age 52 yr, 82 sedentary controls, and 190 individuals exercising during 8–52 wk) (364) and a report by Cornelissen and Smart in 5,223 middle-aged men/women without CVD (1,822 controls and 3,401 people who were exercise training for 4–52 wk) (75). Comparable and in fact slightly higher benefits on total and LDL cholesterol can be obtained with endurance exercise compared with polypills. Whereas isometric exercise and polypills have an overall similar BP-lowering effect, as FIGURE 1 shows, the other exercise modes have a more modest effect. Of note, additional and important health benefits of exercise interventions that are unlikely to be achieved by polypills are significant decreases and increases in adiposity and cardiorespiratory fitness, respectively (364). Rates of tolerability/adherence to the intervention also seem to favor exercise interventions, with an average drop out from the exercise programs of 10% (364), whereas those taking polypills are more likely to discontinue medication compared with placebo or one drug component (20% vs. 14%) (115).

Despite provocative reports in the literature, e.g., orally active drugs such as the AMPK-activator 5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide (AICAR) can increase endurance without exercise

training (331), it would be unrealistic to think that the multi-systemic benefits of regular PA can be replaced by ingesting daily an "exercise-like" polypill (95, 155). Nonetheless, identification of the bioactive molecules and biological mechanisms that are candidates for mediating exercise benefits through biological pathways that are largely different from those targeted by common drugs, is of medical interest, since it might help to improve our knowledge of the pathophysiology of diseases of modern civilization as well as to maximize the efficacy of PA interventions by implementing the best possible exercise dosage, resulting in optimal circulating levels of "beneficial" molecules.

Although describing in detail all the biological mechanisms/mediators (including complex molecular-signaling pathways) that can potentially respond and adapt to exercise stimuli is beyond our scope, the intent of the subsequent part of this review is to summarize the current body of knowledge on the main biological mediators (ingredients) of the preventive/therapeutic effects of regular PA against most prevalent chronic diseases, cardiometabolic disorders, and cancer, and of its anti-aging effects.

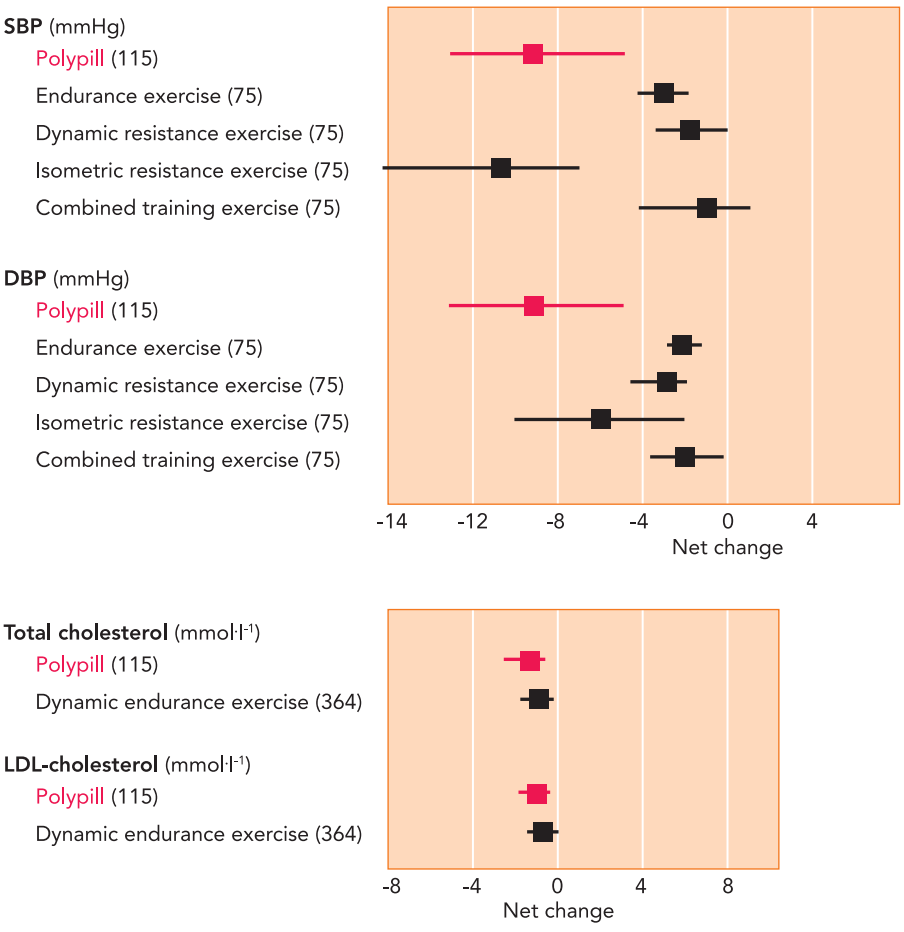

FIGURE 1. **Comparison on the effects of the polypill vs. exercise interventions on outcomes related to CVD risk using data from meta-analyses (see text for more details)**
Data of mean change in the outcomes are expressed in mean and 95% confidence intervals.

Skeletal-Muscle Manufactures the Pill

Skeletal-muscle fibers can produce several hundred secreted factors, including proteins, growth factors, cytokines, and metallopeptidases (42, 178, 345, 407, 527), with such secretory capacity increasing during muscle contractions (13, 94, 163, 190, 286, 357, 367), myogenesis (85, 87, 178), and muscle remodeling (529), or after exercise training (102, 345, 407). Muscle-derived molecules exerting either paracrine or endocrine effects are termed "myokines" (367) and are strong candidates to make up a substantial fraction of the exercise polypill. Here, we focus on the main myokines and their putative protective role against disease phenotypes (see also FIGURE 2 and Table 1).

Myostatin, the first described secreted muscle factor to fulfil the criteria of a myokine, is a potent muscle-growth inhibitor (302) that acts via SMAD signaling (398) or mammalian target-of-rapamycin (mTOR) inhibition (12, 249, 271, 301, 403, 426, 476). Acute endurance (170, 278) or resistance (228, 397) and chronic endurance exercise reduce myostatin expression (170, 184, 236, 237, 292). Although myostatin increases might contribute to insulin resistance (184, 360), obesity (185), muscle wasting (63, 70, 97, 154), or aging-sarcopenia (523), its loss/inhibition decreases adiposity (164, 303, 521, 530), induces browning of the white adipose tissue [through AMPK-peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α)-iriscin pathway] (443), and ameliorates muscle weakness (29, 38, 241, 256, 272, 323, 328, 386, 448, 478, 497, 532).

IL-6 is probably the myokine prototype (366); its release by working muscles explains the consistently reported increase in blood IL-6 with exercise (118, 183, 212, 220, 278, 369, 411, 457, 458). Muscle release of IL-6 increases with exercise intensity (356) and duration (125), with muscle-mass recruitment (368), and when muscle glycogen stores are low (220, 456), but decreases with muscle damage (285, 509) or with carbohydrate ingestion (179, 248, 265–267, 339–341). Endogenous nitric oxide ($NO^{\cdot}$), interaction between Ca^{2+}/nuclear factor of activated T-cell (NFAT), and glycogen/p38 MAPK pathways are putative upstream signals leading to muscle-IL-6 secretion (368). More controversial are the effects of chronic exercise on muscle-derived IL-6 (81, 126), yet a training increase in the sensitivity of its receptor IL-6Rα has been reported (219). This myokine exerts its action locally (within muscles) or peripherally (in a

hormone-like fashion) to mediate, among others, important metabolic and anti-inflammatory/immune modulatory effects. IL-6 has "leptin-like" actions: through AMPK activation in both skeletal-muscle and adipose tissue (6, 61, 145, 224), it increases glucose uptake (126) and intra-muscle (50, 61, 373) or whole-body (486) lipid oxidation (61, 214). Systemic low-level inflammation is a cardinal feature of aging, cardio-metabolic diseases, and some types of cancer that can be attenuated by the cumulative effect of regular exercise bouts, during which the muscle can release myokines such as IL-6; this creates a healthy milieu by inducing the production of the anti-inflammatory cytokines
IL-1Ra, IL-10, or sTNF-R, and inhibiting the pro-inflammatory cytokine TNF-α (122, 294, 312, 355, 356). Other potential roles of IL-6 are stimulation of muscle growth (7, 441) and angiogenesis (172).

Another prototype of contraction-induced myokine is IL-15, with resistance exercise stimulating its secretion (338, 402). In addition to its local anabolic/anti-catabolic effects (59, 60, 135, 338, 390, 391), IL-15 plays an anti-obesogenic effect (337, 388), mainly by inhibiting lipid deposition (8–10, 24, 59, 136, 389). Thus muscle-derived IL-15 is advocated as one of the mediators of the anti-obesity effects of exercise (520). Although leukemia inhibitory factor (LIF) can be released by many tissues and have multiple effects, the functional role of contraction-induced LIF (e.g., after resistance exercise) would be restricted to skeletal muscles, where it stimulates hypertrophy/regeneration, mainly through satellite cell proliferation (47–49, 161, 216, 217, 243, 418, 452, 453, 506). Contraction-induced myokines IL-7 (174) and IL-8 (86, 278, 341) also work mainly at the local level, where they modulate muscle development (174) or promote angiogenesis through

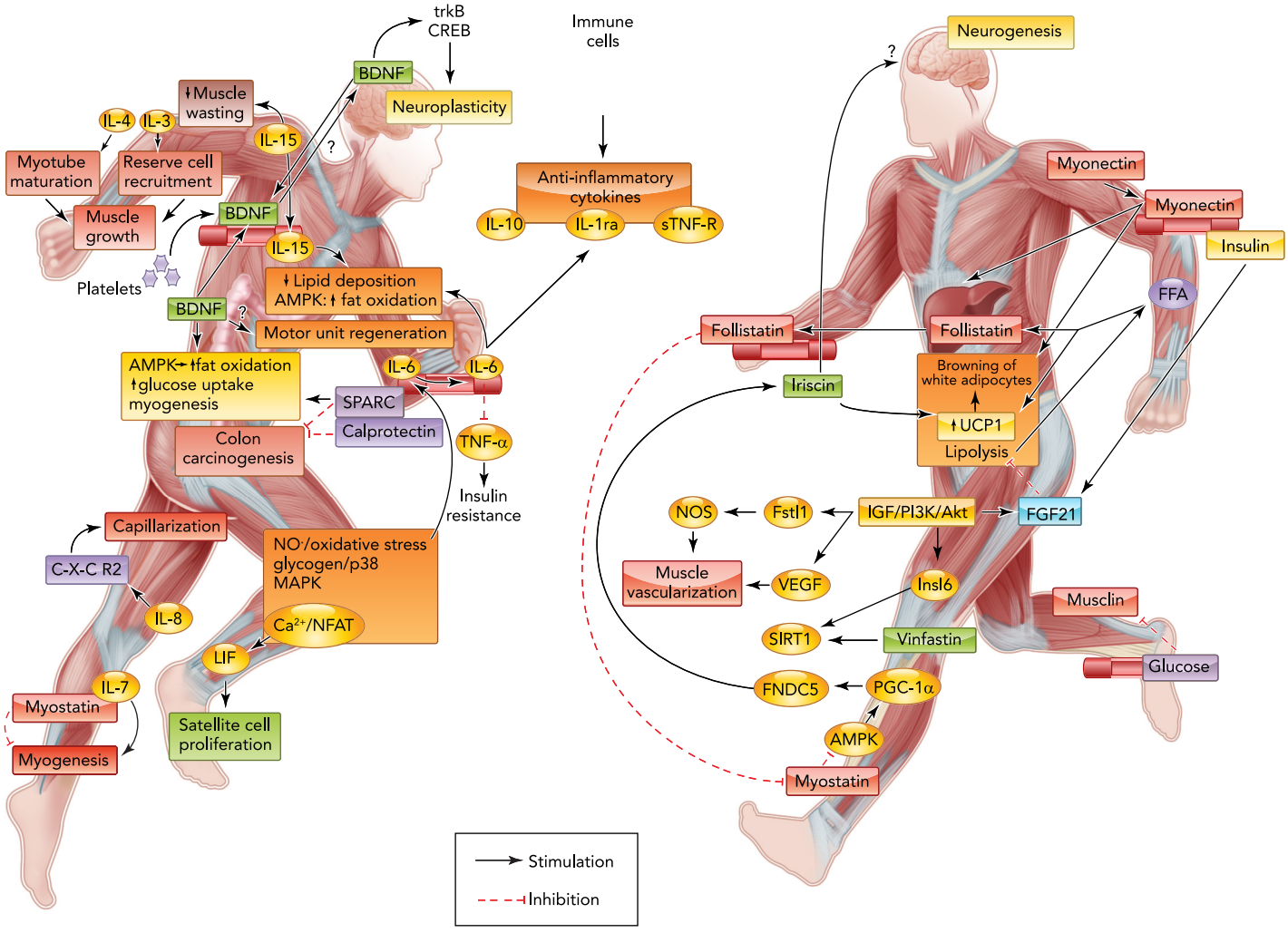

FIGURE 2. **Summary of the main myokines, their putative effects, and the molecular signals/pathways involved**
AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; CREB, cAMP response-element-binding protein; C-X-C R2, C-X-C receptor 2; FFA, free-fatty acid; FGF21, fibroblast growth factor 21; Fndc5, fibronectin type III domain-containing 5 protein; Fstl1, follistatin-like 1; IGF, insulin-like growth factor; IL-1ra, IL-1 receptor antagonist; Insl6, insulin-like 6; LIF, leukemia inhibitory factor; NO·, nitric oxide; NOS, nitric oxide synthase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; PI3K, phosphatidylinositol 3-kinase; SIRT1, sirtuin 1; SPARC, secreted protein acidic and rich in cysteine; sTNF-R, soluble TNF receptors; trkB, tropomyosin receptor kinase; UCP1, uncoupling protein 1.

Table 1. ***The exercise "vademecum": characteristics of the main myokines that are candidates to be ingredients of the exercise polypill (stem cells are also listed)***

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/ Target Diseases	Dietary Considerations
BDNF (brain-derived neurotrophic factor)	Similar to other neurotrophins; is initially synthesized as a precursor (pro-BDNF, of 32 kDa), which is subsequently cleaved to generate the mature BDNF (mBDNF, 14 kDa)	Neuronal tissues: brain (e.g., hippocampus) and rest of central nervous system	Moderate-intensity aerobic exercise	Skeletal muscle	↑ Muscle fat oxidation	↑ Capillarization of ischemic tissues	Enhancing anti-depressant/ anxiolytic treatment; protection against neurodegeneration (including possibly dementia)	Caloric restriction might maximize exercise effects (at least in diabetic murine models)
		Nonneuronal tissues: vascular endothelial cells, platelets, lymphocytes, eosinophils, monocytes, pituitary gland, working skeletal muscle (possibly mainly type II fibers and satellite cells or neurons within muscle beds)		Brain	↑ Neuroplasticity	↑ Brain maintenance/ function and promotes neuroplasticity		
				Motoneurons	↑ Motor unit regeneration	↑ Motor neuron maintenance/repair		
CAC [circulating angiogenic cells including EPCs (endothelial progenitor cells)*]	Any circulating mononuclear cell supporting vascular repair and re-endothelialization	Bone marrow	Vigorous aerobic exercise (e.g., bicycling, running), especially if inducing transient ischemia in cardiac patients	Damaged endothelium (although actual CAC engraftment remains to be clearly shown in humans)	↑ Endothelial repair and vasculogenesis	↓ CVD risk	Use of exercise preconditioning to increase the efficacy of regenerative therapies with stem-cells (by increasing circulating levels of CAC), especially in cardiovascular medicine	
	Bone marrow-derived stem/progenitor cells (i.e., mainly EPCs) Non bone marrow-derived (pro-angiogenic macrophages and T-cells, circulating cells originating from the vessel itself)	Bloodstream and vessels (but to a lower extent)				↓ Disease progression once CVD is already established		
FGF21 (fibroblast growth factor 21)	Member of the fibroblast growth factor (FGF) super family	Mainly liver	Not clearly known yet (increased secretion shown with both aerobic and resistance exercise)	Adipose tissue	↓ Lipolysis	↓ Lipotoxicity of chronically elevated FFA	Use of exercise in obese people as a coadjuvant therapy to decrease insulin resistance and diabetes risk	
		Skeletal muscle				↓ FFA-induced insulin resistance		
		Other tissues (pancreas, adipose tissue, thymus)						
Fst1 [follistatin-like 1, also known as TSC-36 (TGF-beta-stimulated clone 36)]	Extracellular glycoprotein that, despite limited homology, has been grouped into the follistatin family of proteins	Myocardium	Not known yet	Skeletal muscle	↑ Endothelial function and revascularization	Coadjuvant in muscle regeneration	To be determined (yet likely muscle atrophy conditions)	
		Skeletal muscle						

Table 1. (continued)

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/Target Diseases	Dietary Considerations
IL-4 and IL-13	Share substantial structure homology and redundant functions	Lymphocytes (TH2 CD4+ helper cells),mast cells and neutrophils Various origins (brain, cancer cells, liver, fibroblasts, and muscle cells)	Intense strength exercise	Skeletal muscle	↑ Muscle growth	↓ Muscle atrophy ↑ Muscle repair following damage	Muscle atrophy (e.g., IL-4 co-injection with transplanted myoblasts might be an approach to enhance the migration of transplanted cells for the treatment of Duchenne dystrophy)	
IL-6 (also termed interferon, beta 2)	Belongs to the IL-6 cytokine superfamily (LIF, IL-11, CNF, cardiotrophin-1, oncostatin) that share structural similarities and the gp130 receptor subunit Low-weight protein like all cytokines (pro-peptide of 212 amino acids is cleaved into a mature IL-6 peptide (184 amino acids)	Working muscles Working muscles [type I and II fibers, satellite cells (rodents)] Immune cells Adipocytes	Intense aerobic exercise involving large muscle mass but non-damaging (e.g., running in trained athletes or brisk/very brisk walking in general)	Skeletal muscle Adipose tissue Pituitary gland-liver Immune cells	↑ Muscle lipolysis ↑ Muscle growth ↑ Adipocyte lipolysis ↑ Liver-glucose release to blood ↓ Inflammation Immunomodulation	Protection against cardio-metabolic diseases ↓ Inflammation	Cardio-metabolic diseases	Carbohydrate ingestion during exercise (e.g., brisk walking) inhibits the release of muscle-IL-6 and, unless in highly performing athletes, is probably not necessary or justified
IL-7	Predicted molecular mass of 17 kDa and ~25 kDa for non-glycosylated and glycosylated protein, respectively	Lymphoid organs (spleen) Epithelial cells Skeletal muscle	Strength exercise	Skeletal muscle	Regulation of muscle development	?	?	
IL-8	Belongs to the C-X-C chemokine family, low-molecular protein of ~8 kDa, which has an amino acid sequence Glu-Leu-Arg preceding the first conserved cysteine amino acid residue in the primary protein structure	Monocytes and macrophages Endothelial cells Working skeletal muscle	Probably exhaustive endurance exercise (e.g., distance running)	Skeletal muscle	Muscle angiogenesis, i.e., contributes to the exercise training effect on muscle capillarization	?	?	Like for IL-6, low glycogen stores increase muscle secretion of this myokine
IL-15	Belongs to the IL-2 superfamily (14–15 kDa, four-helix configuration)	Working muscles (type I and mainly type II fibers)	Mainly strength exercise	Skeletal muscle	Promotes muscle anabolism/inhibits catabolism	Protection against muscle wasting caused by aging or chronic disease	IL-15 and IL-15Rα are potential pharmacological targets against: muscle wasting and its end-points associated with disease or aging (sarcopenia and cancer-cachexia)	Anti-obesogenic effects are likely independent of diet

Table 1. (continued)

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/Target Diseases	Dietary Considerations
	Two IL-15 isoforms exist: a long signaling secreted peptide (48 amino acids) and a short signaling peptide (21 amino acids)	Various origins (lymphoid tissues, kidney, brain, cardiac muscle, lung, pancreas, testis, liver, placenta, epithelial cells, and activated macrophages, and maybe adipocytes)		Adipose tissue	Anti-obesogenic (↓ mainly visceral fat) effect	Protection against obesity	Obesity	
				(Skeletal muscle-adipose tissue cross talk)	Insulin-sensitizing effect			
Insl6 (insulin-like 6)	Member of the insulin-like/relaxin family	Male germ cells	Unknown	Skeletal muscle	Muscle regenerative factor (↑ activation of satellite cells in injured muscles)	↑ Muscle regeneration	Strategies to enhance Insl6-mediated signalling could be a useful treatment for skeletal muscle myopathies or trauma-induced muscle injuries	
Irisin	112-amino acid glycoprotein that is derived from the cleavage and secretion to circulation of the type I membrane protein Fndc5 (209 amino acids)	Skeletal muscle Working skeletal-muscle (muscle is the main tissue where *FNDC5* gene is expressed) Muscle-related tissues (e.g., pericardium, heart) To a minor extent, kidney, liver, lung, or adipose tissue	To be clearly determined	White adipose tissue	"Browning" of white adipose tissue through ↑ UCP1 and thus ↑ thermogenesis	Protection against diabetes and obesity	Exercise as a coadjuvant for anti-obesogenic/ and anti-diabetic therapies targeting irisin	
LIF (leukemia inhibiting factor)	Belongs to the IL-6 cytokine superfamily Long-chain four α-helix bundle protein, which is highly glycosylated (38–67 kDa, which can be deglycosylated to ~20 kDa)	Working muscles (type I fibers, satellite cells) Central nervous system (hypothalamus, hippocampus, amygdala, cerebellum, cerebral cortex, and basal forebrain nuclei)	Mainly strength exercise	Skeletal muscle	Mainly local (autocrine/ paracrine effect): ↑ Muscle growth (satellite cell proliferation) ↑ Muscle regeneration	Protection against muscle wasting	Muscle wasting	
MSCs (mesenchymal stem cells)	Mononuclear cell population that, when cultured ex vivo, adheres to plastic with a fibroblast-like morphology. In vivo characteristics include adherence to plastic, specific surface antigen expression pattern and differentiation potential	Bone marrow	Eccentric exercise inducing muscle damage	Skeletal muscle	Tissue repair and vasculogenesis in damaged skeletal muscle	↑ Muscle repair (complementing the effects of muscle satellite cells)	Muscle atrophy	

Table 1. (continued)

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/Target Diseases	Dietary Considerations
		Adipose tissue	Vigorous aerobic exercise inducing no muscle damage but transient myocardial ischemia in case of CVD patients	Myocardium?	Same effect in damages in myocardium?	↑ Myocardium repair?	Peripheral arterial disease	
		Others sources: dental pulp, cord blood, and a variety of MSCs (mMSCs) residing in skeletal muscles			Note: tissue engraftment of exercise-released nonresident MSCs remains to be demonstrated in humans		Same as with CAC: use of exercise to increase the efficacy of regenerative therapies with stem cells (by increasing circulating levels of MSCs)	
Myonectin [also termed CTRP5 (C1q/TNF-related protein 5)]	340-amino acid-protein. Tends to form heteromeric complexes with other proteins of the CTRP family, possibly to expand its function	Skeletal muscle (especially in type I fibers, at least in animals)	Remains to be determined in humans	Liver	↑ FFA uptake in liver and adipocytes	Control of whole body metabolism (muscle-liver-adipose tissue cross talk)	?	
Musclin (also termed osteocrin)	20-kDa protein, contains a region homologous to members of the natriuretic peptide family, i.e., it can share related functions or receptors	Skeletal muscle (mainly type II fibers)	Remains to be determined whether exercise actually induces musclin expression in humans	Adipose tissue Skeletal muscle	↓ Glucose uptake in muscle	?	?	Musclin expression increases with obesity and with feeding
		Non-muscle sources (osteocytes, osteoblasts)						
Myostatin [also termed, GDF8 (growth differentiation factor 8)]	378-amino acid protein, belongs to the TGB family	Skeletal muscle	Acute endurance and resistance exercise decrease myostatin expression, but decreased expression has been more consistently shown with aerobic training than with resistance training	Skeletal muscle	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	Use of exercise as a coadjuvant of myostatin-inhibition therapies for muscle wasting	
				Adipose tissue?		Obesity/diabetes prevention		
$NO^{\cdot}$ (nitric oxide)		Contracting muscles (with the main NOS isozyme expressed in muscles being nNOSμ)	Vigorous aerobic exercise (e.g., bicycling)	Skeletal muscles	↑ Glucose uptake	↑ Glucose control in Type 2 diabetes	Therapeutics that mimic the muscle-NO pathway (e.g., Type 2 diabetes)?	
						Duchenne muscular dystrophy? (Disease associated with decreased nNOSμ) ↑ Myogenesis and muscle repair		

Table 1. (continued)

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/Target Diseases	Dietary Considerations
NSCs (neural stem cells, also termed neural progenitor cells)	Stem cells that, at least in embryonic state, can differentiate into neurons, astrocytes, and oligodendrocytes	Central nervous system	Aerobic exercise (only shown in rodent models)	Central nervous system	Increased neurogenesis	↑ Neural plasticity ↑ Brain function (included cognitive capacity)	Using exercise as a co-adjuvant therapy against aging neuro-degeneration	
NT4 (neurotrophin-4, also known as NT4/5)	Member of the nerve growth factor family, which also includes BDNF. The mature peptide has a predicted molecular mass of approximately 14 kDa, and is 130 amino acid in length	Working muscles (type I fibers)	?	Motoneurons	Growth and remodeling of adult motoneuron innervation	↑ Neuromuscular performance	Using exercise to attenuate age loss of neuromuscular performance or as a coadjuvant treatment against neuromuscular disorders?	
S100A8-S100A9 complex (calprotectin)	S100 family proteins MRP-8 (S100A8) and MRP-14 (S100A9) are small (10–14 kDa) calcium-binding proteins that form a heterodimer	Neutrophils, monocytes, acute-phase macrophages Secretory epithelia Working muscles	Exhausting endurance exercise (e.g., marathon running)	Remains to be clearly elucidated	Among other effects (including cytokine-like action), anti-tumor effect	↑ Protection against cancer (e.g., colon)?	Using exercise as a coadjuvant treatment against colon cancer (not only for prevention)	
SPARC [secreted protein acidic and rich in cysteine, also known as basement membrane protein (BM)-40]	Multifunctional nonstructural, matricellular glycoprotein (43 kDa) associated with the extracellular matrix that is expressed abundantly in basal lamina	Skeletal muscles (progenitors cells, fibers, endothelial cells) Tumors (ovarian, colorectal, melanomas) Adipocytes, fibroblasts, endothelial cells, cardiac myocytes (at low levels), α-smooth muscle actin-positive myofibroblasts, CD45-positive leukocytes	Strength exercise?		Regulation of glucose metabolism Inhibits proliferation of colon cancer cells	Prevents tumorigenesis of colon cancer	Same as above	
Visfatin [also known as NAMPT (nicotinamide phosphoribosyltransferase) or PBEF (pre-B cell enhancing factor)]	Multifunctional protein. Polypeptide of 491 amino acids with a molecular mass of 52 kDa	Ubiquitous expression in human tissues, including adipose and skeletal muscle tissue (i.e., it is both an adipokine and a myokine) Liver Bone marrow Lymphocytes Beta-cells and human islets Heart	Endurance exercise	Skeletal muscle and adipose tissue	AMPK activation → ↑ SIRT1 → PGC-1α It provides NAD^+	Might mediate major exercise-induced health/anti-aging effects involving SIRT1-pathways: anti-oxidant defense, macromolecular damage repair, or mitochondriogenesis	Exercise as a major component of anti-aging medicine	

AMPK, adenosine monophosphate-activated protein kinase; CVD, cardiovascular disease; FFA, free-fatty acids; Fndc5, fibronectin type III domain-containing 5 protein; IL-15Rα, interleukin-15 receptor; NOS, nitric oxide synthase; PPAR-α, peroxisome proliferator-activated receptor α; SIRT1, sirtuin 1; TGB, transforming growth factor; UCP1: uncoupling protein 1. *Research is growing fast in the field since the original paper by Asahara et al. (15) where the term endothelial progenitor cell (EPC) was first introduced, and caution is needed with nomenclature. The difficulty of identifying cells with a unique EPC phenotype (based on cell membrane antigens) as originally defined by Asahara et al. and the fact that a variety of hematopoietic cells (including stem and progenitors) participate in initiating and modulating neo-angiogenesis make the issue complicated and the term EPC too restrictive (see Ref. 181 for a review). As such, the broader term circulating angiogenic cells (CAC) is being used in the literature instead of EPC.

C-X-C receptor 2 receptor signaling (131). IL-4 and IL-13, which share a substantial fraction of their sequence structure and biological roles, are upregulated by resistance training (385), with IL-4 mediating NFATc2-induced muscle growth (192) and myotube maturation (247) and IL-3 stimulating additional recruitment of reserve cells during IGF-I-induced hypertrophy (204).

Among all neurotrophins (molecules that stimulate neuronal survival, differentiation, or growth), brain-derived neurotrophic factor (BDNF) is the most affected by exercise (231). Circulating BDNF increases with aerobic exercise (121, 147, 409, 437, 465, 510), especially with high-intensity exercise (121, 431, 510), and rapidly decreases to basal levels shortly after exertion (431), suggesting its clearance is mediated by target-tissue uptake (284). Less clear is its response to acute resistance exercise (76, 146, 429) or resistance exercise training (66, 146, 263, 429, 435, 437, 524, 534). Several tissues, such as contracting muscles (111, 152, 293) or platelets (465), can express BDNF. Yet the main origin of exercise-induced blood BDNF is likely the brain before this molecule crosses the blood-brain barrier (284). Increased BDNF transcripts in exercised rodents' brains are well documented, providing mechanistic support for a beneficial exercise effect in cognitive function (4, 5, 30, 153, 193, 275, 315, 333, 334, 352, 396, 417, 425, 460, 488, 507), e.g., through the downstream signals tropomyosin receptor kinase (trkB), cAMP response-element-binding protein (CREB), or synapsin I (488). Exercise-induced BDNF in rodents is also likely to contribute to the anticancer effect of PA (57). Muscle-produced BDNF could act locally, enhancing muscle lipid oxidation via AMPK-activation (293), whereas exercise-induced BDNF coming from different sources might improve depression (526) or anxiety symptoms through MAPK signaling pathways (110), maintain brain function and promote neuroplasticity (78, 153), or enhance the efficacy of antidepressant treatment (416). BDNF can also help maintain/repair motoneurons (327) like other muscle-derived neurotrophins such as neurotrophin 4 (133, 162) or could regulate satellite-cell function/regeneration (69, 326).

Secreted protein acidic and rich in cysteine (SPARC), is a matricellular protein that regulates cell proliferation/migration and is implicated in numerous biological processes (45). It was recently identified as a myokine (13, 345) whose expression increases with resistance training (345). SPARC, which is in fact a potential target in cancer immunotherapy (198), might mediate the preventive effects of exercise on colon cancer by suppressing the formation of aberrant crypt foci, probably through stimulation of apoptosis via caspase-3 and -8 (13). Circulating (117, 318, 324, 365) and muscle-transcript levels of S100A8-S100A9 complex (calprotectin) increase with acute endurance exercise (324). Potential beneficial effects (yet to be demonstrated) of muscle-derived calprotectin might also be cancer protection for its ability to induce apoptosis in certain tumor lines (528), including colon cancer lines (143), or to inhibit matrix metalloproteinases associated with cancer invasion and metastasis (200).

Although there is controversy (473), recent research has identified a novel PGC-1α-induced myokine called iriscin (43). In white adipocytes, iriscin induces expression of uncoupling protein 1 and other brown adipose tissue-associated genes [partly via increased peroxisome proliferator-activated receptor α (PPAR-α)] and thus increases thermogenesis and switching of these cells toward a brown, fat-like phenotype (43). These provocative findings have led to the postulation that iriscin may be a therapeutic agent against cardiometabolic disorders and a major component of the exercise polypill (420). Iriscin is linked with improved aerobic fitness in cardiac patients (253), muscle mass, and metabolic factors in healthy people (195), and neurogenesis in animal models (171).

IGF-phosphatidylinositol 3-kinase (PI3K)-Akt signaling plays a central role in muscle regeneration (88, 372), inducing myokines with an essentially local action: insulin-like 6, which activates satellite cell activation (529); follistatin-like 1, which promotes endothelial function and revascularization in response to ischemic insult through endothelial $NO^{\cdot}$ synthase (eNOS) signaling (357); and VEGF, which stimulates angiogenesis (463). The Akt pathway also upregulates muscle fibroblast growth factor 21 (FGF21) (201), an insulin-regulated myokine (188) that is released to the blood during exercise (84), although there exists controversy on the effects of regular exercise in its basal levels (83, 287, 522). By inhibiting lipolysis in adipocytes, exercise-released FGF21 could play a protective role against lipotoxicity, i.e., ectopic deposition of lipids in the liver or muscle (84).

Other myokines and their putative roles (awaiting more human research) include myonectin, a metabolic regulator that stimulates uptake of free-fatty acids in liver and adipocytes (439); musclin (343, 525), an inhibitor of muscle-glucose uptake (274); and visfatin (503), a NAD+ biosynthetic enzyme whose expression and circulating levels increase (77) and decrease, respectively, with exercise training (93). By virtue of its activating effect on NAD+-dependent sirtuin 1 (SIRT1), visfatin might mediate major exercise-induced health/anti-aging effects involving SIRT1-pathways (235): anti-oxidant defense, macromolecular damage repair, or mitochondriogenesis. Of note, visfatin is also an adipokine with rather different

functions, i.e., pro-inflammatory (410) and anti-apoptotic effects (91, 268).

Exercise and Regenerative Medicine

Pluripotent stem cells (SCs) able to differentiate into many cell types are proposed as a valuable therapeutic source, notably in ischemic tissues with low self-repair capacity. Because using embryonic SCs has ethical and immune-related limitations (401), researchers have explored other means of obtaining SCs, e.g., isolating them from extracorporeal sources (placenta, umbilical cord) or reprogramming of mature cells. Yet another strategy is stimulating adult SC proliferation and migration from their home tissue (e.g., bone marrow) to target damaged tissue for subsequent engraftment and cell regeneration by applying specific physiological stimuli, of which exercise is a good example (284) (FIGURE 3).

Together with macrophage-mediated reverse cholesterol transport[3] the capacity for vessel wall regeneration and angiogenesis is the main mechanism responsible for maintaining cardiovascular health (321). The lower CVD risk associated with regular exercise is largely mediated by an improvement in such capacity (511). Endothelial regeneration and neovascularization not only depends on cells residing within the vessel wall but also on circulating SCs coming from other sources, notably the bone marrow. A specific SC subset, originally identified as endothelial progenitor cells (15) or now more broadly referred to as circulating angiogenic cells

[3]Although there is some recent controversy (305), regular exercise seems to stimulate macrophage-reverse cholesterol transport RCT in vitro (351) and in vivo (408), with exercise-triggered activation of peroxisome proliferator-activated receptor gamma (abbreviated as PPARγ or NR1C, according to the unified nomenclature system for the nuclear receptor superfamily) within these cells being advocated as a putative involved mechanism (52, 472).

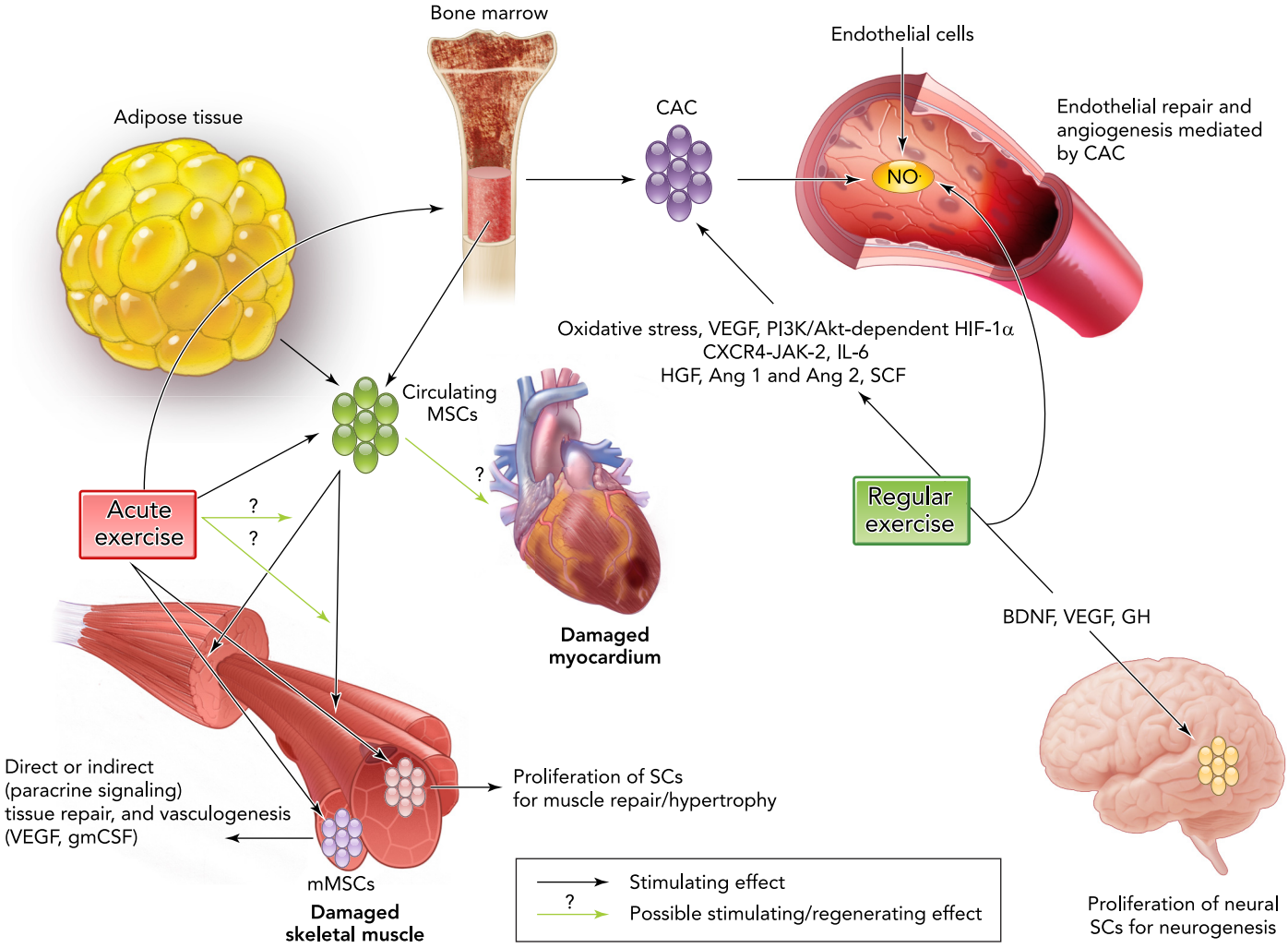

FIGURE 3. **Summary of the main types of stem cells associated with exercise, their main putative effects, and the molecular signals/pathways involved**
Ang, angiopoietin; CAC, circulating angiogenic cells; C-X-C R4, C-X-C motif receptor 4; GH, growth hormone; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor 1-α; JAK-2, janus kinase-2; mMSC, muscle-derived mesenchymal stem cells; SC, stem cell; SCF, stem cell factor.

(CAC), target the vascular endothelium, where they can engraft and promote repair and angiogenesis (82, 505). Low CAC counts/function is correlated with risk of CVD (19) or diabetes complications (308) and decreases with senescence (480, 508), whereas high CAC (see below) represents a link between regular exercise and decreased CVD risk (250), with such exercise benefits starting early in life (501). CAC increases could also provide mechanistic support for the training-induced improvement in myocardial perfusion and lower disease progression in CVD patients (167, 173, 336, 434); they also could complement the exercise benefits in endothelial $NO^{\cdot}$ production and thus in vascular tone regulation, with regular bouts of exercise-increased laminar flow increasing the expression/activation (through phosphorylation via Akt) of eNOS while attenuating $NO^{\cdot}$ degradation into reactive oxygen species (ROS) or reactive nitrogen species (RNS) (144).

Circulating CAC increase with acute exercise in healthy individuals (39, 157, 313, 322, 485), people at risk for CVD (399), and CVD patients (3), although this effect is blunted with age (276, 471). Intense exercise, especially if inducing transient myocardial ischemia, seems the most potent stimulus for CAC release and subsequent vasculogenesis in CVD patients (3). Acute exercise also appears to reverse CAC dysfunction in CVD patients (483, 484). Regular exercise increases CAC number (250, 282, 424) or function in people with CVD (44, 141, 459, 484), metabolic syndrome (120), peripheral artery disease (430), or obesity/overweight (68), and in the elderly (519). However, this effect has not been corroborated in some healthy cohorts (394, 471, 512), and data from animal studies showing actual CAC engraftment in injured tissues (92) remains to be validated in humans. Postulated biological mediators of exercise-induced CAC proliferation and release to the bloodstream are reduced CAC apoptosis (250), oxidative stress (511), thrombin (276), VEGF (3, 250), stimulation of PI3K/Akt-dependent hypoxia-induced factor-1α (92) or C-X-C motif receptor 4-janus kinase-2 signaling pathways (519), IL-6 (39), pro-angiogenic factors (hepatocyte growth factor, angiopoietin 1 and 2 or stem cell factor) (39), endothelial-derived $NO^{\cdot}$ (512) or maybe $NO^{\cdot}$ produced locally in the bone marrow (511), and $NO^{\cdot}$/oxidative stress interaction (314, 511). Increases in $NO^{\cdot}$ produced inside CAC might mediate the improvement in the function of these cells with exercise (206).

Research on another type of SC, mesenchymal stem cells (MSCs) (129), has grown fast in the last decade (139). Regardless of their origin (mainly, but not only, bone marrow and adipose tissue), they represent pluripotent progenitors of mesoderm- or even non-mesoderm-derived tissues with a wide variety of therapeutic potential (graft vs. host or Crohn's disease, wound healing or as vehicles of anticancer genes) (139, 536). Intense exercise, whether inducing (395) or not inducing eccentric muscle damage, is a potent stimulus for MSC release to the bloodstream (280, 432). Vigorous exertion also increases the migratory capacity of MSCs, an effect potentially mediated by the myokine IL-6 (432). Similar to what occurs with CAC, intense exercise-inducing transient ischemia can increase circulating MSCs in CVD patients (280), which is a potentially promising finding because, together with the few cardiac-resident SCs, MSCs have the potential to repair damaged myocardium (518). However, actual engraftment of migratory MSCs in damaged tissue (muscle, myocardium) remains to be demonstrated.

SCs can also reside within the perivascular niche of a variety of tissues, directly repairing injury or indirectly facilitating regeneration by excreting cytokines/growth factors that can stimulate other resident SCs (58, 304). This seems to be the case for skeletal muscles, where not only satellite cells but also a variety of resident MSCs (mMSCs) can repair damage (16, 100, 325, 419, 482). Proliferation of mMSCs is stimulated by the muscle protein α7 integrin or by eccentric exercise (482), and these cells can secrete angiogenic factors (VEGF, granulocyte-macrophage colony-stimulating factor), contributing to vessel remodeling in skeletal muscles following eccentric damage (196).

Proliferation of neural SCs might also contribute to improve brain regenerative capacity and cognitive ability, with some rodent models showing training increases in hippocampal (242, 514) or periventricular progenitors (35). Current candidate neutrophins mediating exercise-induced neurogenesis are above-mentioned BDNF (231, 533), growth hormone (35), or VEGF (79, 116).

The ROS Paradox

As first reported 35 years ago (105), acute exercise generates ROS (see Ref. 384 for a review) and does so in an intensity- (209, 387, 428) and duration-dependent manner (37). Exercise-generated ROS come from many sources (384) and include hydrogen peroxide (H_2O_2) (28, 297, 487, 492), superoxide anion ($O_2^{-}\cdot$) (22, 296, 400), or hydroxyl radicals (OH^{-}) (104, 124, 348, 381) (FIGURE 4). However, strong evidence showing that regular exercise upregulates endogenous antioxidants not only in muscles (1, 27, 80, 148, 149, 156, 169, 177, 180, 189, 207, 211, 225, 251, 259, 260, 264, 296, 297, 299, 309, 349, 377–379, 381, 404, 428, 446, 470, 490, 493, 494), where the effect can be evident after just five consecutive training days (493, 494), but also in liver

(194, 211, 491), blood (17, 21, 46, 53, 62, 64, 96, 98, 107, 127, 128, 140, 151, 215, 229, 232, 238, 239, 258, 264, 291, 306, 311, 342, 350, 404, 406, 433, 438, 444, 449, 461, 467, 469, 470), or other tissues (brain, heart, kidney, stomach, intestine, vessels) (27, 96, 132, 186, 264, 332, 404, 468, 490) has changed the old view of exercise as a potential source of harmful oxidative damage. In fact, muscle-derived ROS occurring during prolonged inactivity contribute to disuse muscle atrophy (382, 383), whereas the same stimulus coming from working fibers is required for training adaptations to occur (149, 150, 168, 404). This apparent paradox could be explained by the hormesis theory (54, 210, 392, 393): chemicals and toxic substances that are deleterious at high doses can have a low-dose beneficial effect. Thus increases in ROS elicited by moderate-intensity exercise could lead to beneficial adaptations, especially increased muscle oxidative capacity (109, 202). Yet, if ROS levels are increased many-fold above basal levels and antioxidant defense capacity, muscle atrophy can occur, e.g., Duchenne muscular dystrophy (383, 393). A second potential factor is differences in the ROS origin between contracting and resting muscle fibers, with mitochondria being the primary source in the latter (218) but not in the former (380).

ROS might play an important signaling role in angiogenesis (67), improved vascular distensibility (261), PGC-1α upregulation (404, 447), PGC-1α/nuclear

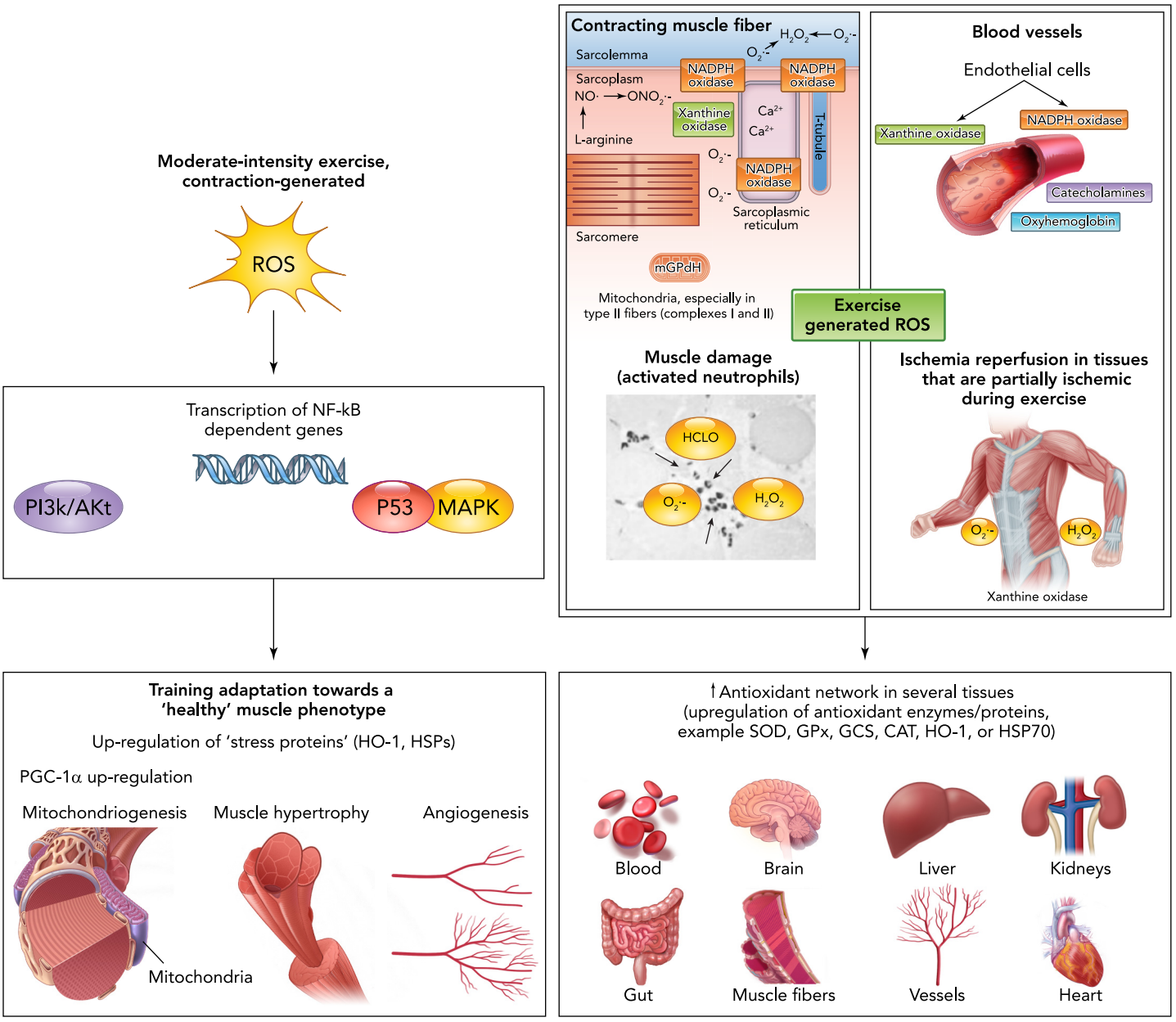

FIGURE 4. **Summary of exercise-generated ROS, their main putative effects, and the molecular signals/pathways involved**
CAT, catalase; GCS, γ-glutamylcysteine synthetase; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; HO-1, heme oxygenase-1; HSP: heat shock proteins; NADPH, nicotinamide adenine dinucleotide phosphate; $O_2^{-}\cdot$, superoxide anion radical; SOD, super oxide dismutase.

respiratory factor 1-stimulated mitochondriogenesis (199, 371, 517), upregulation of cytoprotective "stress proteins" (heme oxygenase 1, heat shock proteins like HSP60 and HSP70) in muscle (25, 101, 119, 273, 298, 363, 454, 455), or skeletal muscle hypertrophy (203, 427). An important signaling link between contraction-induced ROS production and exercise adaptations involves the redox regulation of NF-κB, a family of transcriptional activators controlling the expression of genes involved in inflammation, cell growth, stress responses, or apoptosis (109, 210, 240, 310, 481). Other pathways are MAPK, PI3K/Akt, or p53 activation (11, 203, 361). Interestingly, despite its popularity among westerners for its hypothetical anti-disease/rejuvenating effects, antioxidant supplementation does not mimic, and in fact can reverse, beneficial exercise adaptations (127, 148, 149, 226, 404).

Skeletal muscle also generates RNS including $NO^{\cdot}$ (20, 99, 233, 462, 502) or nitrite ion (NO_2^-) (489), which at high doses may cause nitrosative stress and tissue damage but at low doses has beneficial regulatory effects in vasodilation, glucose uptake, or immune function (300).

Autophagy

Autophagy, a cellular quality control mechanism of degradation and recycling of damaged macromolecules and organelles, is gaining attention for its potential involvement in longevity promotion (414) and defense against chronic diseases (320). It could also mediate some of the exercise benefits (FIGURE 5), as suggested by recent data from rodent models.

In normal mice, acute exercise increases autophagy activity in skeletal/cardiac muscles and tissues involved in glucose/energy homeostasis (pancreas, liver, adipose tissue), whereas transgenic mice deficient in stimulus-induced autophagy show decreased endurance and altered glucose metabolism (175). Exercise also induces autophagy in mouse brain, supporting its potential to promote elimination of damaging proteins causing aging

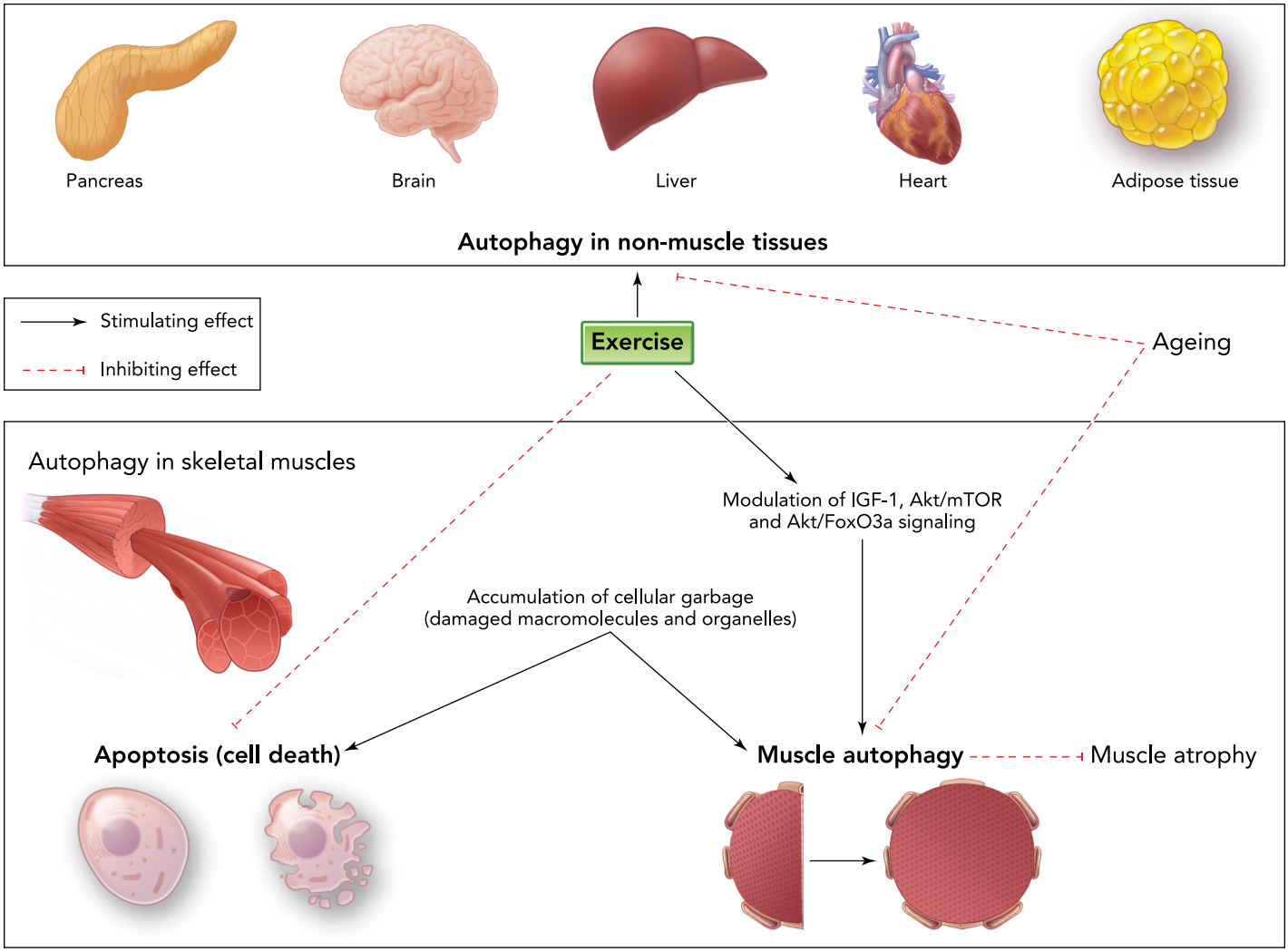

FIGURE 5. **Exercise and autophagy**
FoxO3a, FOXO transcription factor; mTOR, mammalian target-of-rapamycin.

neurodegeneration (176). Chronic exercise increases autophagy activity and reduces apoptosis in aging muscle (230, 283) by modulating IGF-I, Akt/mTOR, and Akt/FoxO3a signaling, thereby preventing loss of muscle mass/strength (283). Others, however, found the protective effect of chronic exercise on diabetes-induced muscle atrophy was probably due to decreased muscle autophagy (257). Taken together, these apparently controversial data would suggest an optimal balance is obtained in the trained muscle between "healthy" autophagy-induced turnover of damaged cellular components (which attenuates/prevents muscle atrophy), and "excessive" autophagy-mediated protein degradation (which eventually leads to muscle atrophy).

Data is still scarce in humans, yet recent preliminary reports suggest upregulation of muscle markers of autophagy after strenuous acute endurance (205) or resistance exercise (130), or after a combined weight loss and moderate-intensity exercise program in old obese women (513).

Summary and Perspective

There is strong epidemiological evidence on the beneficial effects of regular exercise, which are likely to go well beyond reducing CVD risk factors. Furthermore, exercise benefits can overcome those of common drugs when one considers that the exercise polypill combines preventive, multi-systemic effects with little adverse consequences and at lower cost. Exercise, and especially the contracting muscle, is indeed a source of numerous drug-like molecules with beneficial effects across all ages. Furthermore, regular exercise is probably the lifestyle intervention with the most profound upregulating effect on hundreds of genes involved in tissue maintenance and homeostasis, implying a complex cross talk between muscles and other tissues. Progress in proteomics and other techniques is allowing identification of a myriad of novel myokines and also is unraveling the fact that many molecules can have a quite different effect depending on their tissue of origin, as well as on the metabolic state (rest vs. exercise) during which they are secreted to the bloodstream.

Identification of exercise adaptations is helping to improve our understanding of the pathophysiology of chronic diseases and changing old views, which could help investigate new therapeutic targets and approaches. For instance, ROS signals are increasingly viewed as mediators of the health-promoting, lifespan-extending capabilities of exercise, even questioning the classic Harman's Free Radical Theory of Aging. With regard to aging, the "oldest old" are the most rapidly growing population segment among westerners. As opposed to exercise, no drug intervention has proven efficient to maintain muscle fitness, a key factor to ensure independent living throughout all stages of life. ■

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