Can Exercise Teach Us How to Treat Heart Disease?

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Exercise is one of the mainstay clinical interventions for the prevention and treatment of cardiovascular disease. Not only does exercise reduce cardiovascular risk factors, such as diabetes mellitus and hypertension, thereby helping to prevent heart disease, it also appears to improve the functional status and outcomes in patients with existing heart disease.1–6 The cardiovascular benefits of exercise are multifactorial, and include important systemic effects (Figure 1) on skeletal muscle, the peripheral vasculature, and metabolism, as well as beneficial alterations within the myocardium itself.7,8

Many current pharmacological treatments for cardiovascular disease are targeted toward inhibiting the adverse remodeling process associated with pathological stress. Specifically, they focus on abrogating the pathological hypertrophy, fibrosis, electric remodeling, and cavity dilatation that accompany disease states such as longstanding hypertension and myocardial infarction (MI).9–11 Interestingly, exercise, like many of these pathological stimuli, can also induce cardiac and cardiomyocyte hypertrophy. However, growing evidence suggests that such physiological remodeling, rather than leading to adverse sequelae, may actually be cardioprotective, and that activating pathways associated with exercise can help to prevent and treat cardiovascular disease.8,12,13

In this review, we discuss recent advances in our understanding of the cellular and molecular mechanisms (Figure 2) that mediate the cardiac response to exercise, including cardiomyocyte hypertrophy and renewal, vascular remodeling, and alterations in calcium handling and metabolism. In addition to classical signaling mechanisms and transcriptional networks, we describe the role of secreted molecules and miRNAs. Finally, an emerging theme is that pathways that are either regulated by exercise or that mediate the response of the heart to exercise often also have the potential to mitigate or even reverse cardiac disease. Thus, we suggest that understanding the effects of exercise more fully may provide useful biological insights and open the door to new therapeutic approaches aimed at restoring cardiovascular health.

**Physiological Cardiac Remodeling**

Exercise is perhaps one of the cheapest—and most effective—interventions for reducing the morbidity and mortality of cardiovascular disease.14 In fact, as little as 45 to 75 minutes of brisk walking each week appears to reduce the relative risk for adverse cardiac events.15,16 Additionally, exercise-based cardiac rehabilitation is recommended by the American Heart Association (AHA) as one of the mainstay interventions after acute MI, with maximal benefit derived from early initiation of exercise (as early as 1 week after MI hospital discharge) and from increased duration of exercise rehabilitation.1–3 Multiple studies have also demonstrated a dose–response relationship between exercise and cardiovascular benefit, but the shape of that curve, and the optimal dosage, intensity, frequency, and duration of exercise, remain incompletely defined.15,17,18

The health benefits of exercise are multifactorial. Studies have demonstrated that physical activity is effective in reducing adipocyte mass and body mass index as well as positively affecting insulin sensitivity, glucose uptake by skeletal muscle, and cholesterol profiles.19 Physical activity—aerobic exercise, in particular—has also been associated with beneficial changes in both the systemic and coronary vasculature, including enhanced endothelial-mediated vasodilation, improved arterial compliance, and reductions in both systolic and diastolic blood pressure.20–22 Although these global effects of exercise are all implicated in improving cardiovascular health, here we will focus primarily on the cardi-specific effects of exercise.

**Cardiac Growth**

The heart has considerable plasticity,9 and its capacity to hypertrophy in response to pathological stimuli, such as hypertension, aortic stenosis, or genetic mutations, is familiar to clinical cardiologists. However, a robust hypertrophic response is also seen with physiological stimuli, including exercise, pregnancy, and postnatal growth. Endurance exercise and pregnancy, for example, can induce up to a 20% increase in left ventricular mass, whereas, even more impressively, the hearts of Burmese pythons can grow by up to 40% after meals.23,24

The cellular response to growth signals is often categorized as either hypertrophic—an increase in cell size—or hyperplastic—an increase in cell number. The adult heart has traditionally been viewed as capable only of hypertrophic growth; however, recent data from animal models and human studies suggest that the heart also has a limited capacity to generate new cardiomyocytes from progenitor cells and existing cardiomyocytes.25–27 In clinical practice, it is impos-
sible, with current imaging modalities, to distinguish between these 2 distinct mechanisms of growth when characterizing cardiac hypertrophy. However, animal studies suggest that an increase in both cardiomyocyte size and number may contribute to heart growth in response to pathological and physiological stimuli.12,28

Figure 1. Overview of the systemic and cardiac-specific effects of exercise. Endurance exercise has multiple systemic effects, ranging from increased skeletal muscle growth to vascular remodeling and improved energetics. Exercise also exerts direct effects on the heart itself, including increased cardiac growth, protection against ischemic damage, and modulation of cardiac function, metabolism, and vascular supply. AMPK indicates AMP-activated kinase; C/EBPβ, CCAAT/enhancer binding protein β; CITED4, cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 4; eNOS, endothelial nitric oxide synthase; IGF-1, insulin-like growth factor-1; MSTN, myostatin; Nrg1, neuregulin1; PGC-1α, peroxisome proliferator activated receptor gamma co-activator 1α; PI3K, phosphoinositide-3 kinase; Pim1, proto-oncogene serine/threonine-protein kinase-1; PLB, phospholamban; SERCA2a, sarco/endo-plasmic reticulum Ca2⁺-ATPase, 2a; and VEGF, vascular endothelial growth factor. (Illustration by A.R.)

Exercise-induced cardiac remodeling is the prototypical example of physiological cardiac growth, and the hypertrophic response to exercise can broadly be described as either concentric or eccentric hypertrophy, or a combination of the 2. Isometric exercises—such as strength training and weight lifting—lead to transient increases in systemic vascular resis-

Figure 2. Key signaling pathways involved in mediating exercise-induced cardiac remodeling. Exercise activates the IGF1–PI3K–Akt cascade. Signals then converge at the level of the nucleus, resulting in inhibition of the transcription factor C/EBPβ. Down-regulation of C/EBPβ, in turn, frees serum response factor to bind target gene promoters, contributing to activation of an exercise gene set, and, ultimately, cardiac growth. Meanwhile, activation of CITED4 may drive cardiomyocyte proliferation, as does signaling through Nrg1 and ErbB4. Akt also mediates angiogenesis and vascular remodeling via eNOS and exerts beneficial metabolic effects through cross-talk with AMPK, Sirt1, and PGC-1α. In mitochondria, Sirt3, which is activated by exercise, works to protect against age-related cardiac dysfunction. Finally, exercise also modulates the secretion of circulating factors, primarily from skeletal muscle and adipocytes, such as adiponectin, myostatin, irisin, and Fstl1. Akt is also known as protein kinase B. AMPK indicates AMP-activated kinase; β3-AR, β3 adrenergic receptor; C/EBPβ, CCAAT/enhancer binding protein β; CITED4, cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 4; eNOS, endothelial nitric oxide synthase; Fstl1, Follistatin-like 1; HIF-1α, hypoxia inducible factor-1α; I/R, ischemia/reperfusion; IGF-1, insulin-like growth factor-1; Met2C, myocyte enhancer factor 2C; MHC, myosin heavy chain; mPTP, mitochondrial permeability transition pore; MSTN, myostatin; NO, nitric oxide; Nrg1, neuregulin1; PGC-1α, peroxisome proliferator activated receptor gamma co-activator 1α; PI3K, phosphoinositide-3 kinase; Sirt1, Sirtuin1; SRF, serum response factor; Tbx5 (T-box transcription factor); TnI, troponin I; and TnT, troponin T.
tance. This increases afterload and results in concentric hypertrophy, in which sarcomere fibers are added in parallel with subsequent thickening of the ventricular wall. Endurance—or isotonic—exercise, such as swimming and running, present a volume challenge to the heart and tend to result in eccentric hypertrophy, with increased preload and end-diastolic volume.29,30 Cardiac MRI studies have suggested that isometric exercises induce minimal changes in right ventricular structure and function, whereas isotonic exercises lead to a balanced biventricular hypertrophy with symmetrical enlargement of both the right and left ventricles.31 Cardiomyocyte hypertrophy is likely the dominant contributor to exercise-induced heart growth, and studies have reported an increase in cardiomyocyte size by up to 17% to 32% after exercise training.32 As noted above, however, recent work suggests that exercise also induces markers of cardiomyocyte proliferation, although the fate and contribution of these newly formed cells remains to be established.12

A recently described model for studying physiological remodeling is the Burmese python, which demonstrates an impressive increase in cardiac size—up to 40%—after meals, which regresses over the subsequent 28 days.24 Emerging data suggest that this increase in heart size is primarily a hypertrophic, rather than hyperplastic, process, and that it is not associated with the characteristic changes seen in pathological cardiac growth such as fibrosis and upregulation of the fetal gene program.33 This lends support to the idea that physiological hypertrophy is primarily an adaptive and beneficial process. Interestingly, new evidence suggests that some of these postprandial cardiac growth effects are mediated by secreted lipids,33 which will be discussed in more detail below. Interestingly, the combination of fatty acids identified in python serum also induced cardiomyocyte hypertrophy in mice.33 It should be acknowledged that the clinical relevance of postprandial changes in the Burmese python remain unclear.

Altered Ca2+ Handling
In contrast to pathological cardiac remodeling, in which hypertrophy is associated with fibrosis, impaired relaxation and contractility, and potential progression to heart failure, both systolic and diastolic cardiac function are preserved, or even enhanced, in exercise-induced hypertrophy.

Exercise has been shown to improve cardiomyocyte Ca2+ sensitivity and contractility.34 In animal models, fractional shortening can increase by as much as 40% to 50% after endurance exercise, with concomitant improvements in contraction and relaxation.35 Increased activity of the sarcoplasmic reticulum Ca2+ ATPase 2a (SERCA2a), which is characteristically decreased in pathological remodeling, appears to contribute to the observed benefits of exercise on Ca2+ handling. This is mediated by direct upregulation of SERCA2a as well as indirectly via increased phosphorylation of phospholamban (PLB), which reduces PLB-mediated inhibition of SERCA2a.36,37 Interestingly, studies in animal models suggest that exercise can improve contractility and normalize SERCA2a function after MI.38–40 Structurally, physiological hypertrophy, unlike pathological hypertrophy, is associated with preservation of t-tubule density and organization, which allows for coordinated myocyte contraction.41

Vascular Remodeling
Exercise significantly increases myocardial oxygen demand and induces changes within the macro- and microvasculature to meet these requirements. Although important vascular changes occur both in the heart and the periphery, here we focus on changes within the heart itself. Specifically, exercise is associated with increased coronary blood flow and oxygen extraction, as well as improved endothelial function.42

Endurance training increases coronary blood flow in a number of different ways. Imaging studies in humans show an increase in the caliber of the large proximal coronary arteries after exercise, in proportion to the increase in left ventricular mass.43,44 In patients with coronary artery disease, endothelium-dependent coronary vasodilation, and subsequently myocardial perfusion, is improved, albeit not to normal levels.45 Exercise also induces angiogenesis in a vascular endothelial growth factor (VEGF)–dependent manner.45 Capillary density increases after the initiation of exercise, but, after sustained activity, normalizes to the extent of cardiac hypertrophy.46 This is in direct contrast to pathological cardiac remodeling: whereas pathological stimuli initially induce angiogenesis, some studies suggest that coordination of hypertrophy and angiogenesis is ultimately disrupted, contributing to the progression to heart failure.47,48 Interestingly, animal studies have shown that exercise can promote angiogenesis after MI, with significant improvements in myocardial perfusion and pump function.49 Thus some of the beneficial effects of exercise are likely related to increased angiogenesis and protective changes in the coronary vasculature. A crucial component of these vascular changes is the upregulation of nitric oxide (NO) production by vascular endothelial cells. The precise cellular and biochemical mechanisms regulating NO production and its downstream effects will be discussed below.

Metabolism
The heart has tremendous energy requirements, both in physiological and pathological states, and a prominent feature of cardiovascular disease is myocardial metabolic dysregulation. Notably, pathological remodeling is associated with a switch from fatty acid metabolism, the primary energy source for the healthy adult human heart, to glucose utilization, which is the main energy source in fetal life.33 In contrast, energy consumption and homeostasis is preserved in physiological cardiac remodeling. An acute bout of physical activity can increase cardiac output as much as 6-fold, and this significant ATP demand is met primarily by mitochondrial oxidative phosphorylation.50 Exercise training promotes efficient glucose and fatty acid handling, as well as mitochondrial biogenesis via upregulation of the glucose sensor AMP-activated kinase (AMPK) and its downstream target, the peroxisome proliferator activated receptor gamma co-activator 1α (PGC-1α).50

Cardiomyocyte Renewal
As noted above, multiple studies have demonstrated that the heart does indeed have some capacity for regeneration and
renewal, with data supporting both the proliferation of pre-existing cardiomyocytes and resident stem cells. Adult zebrafish and neonatal mice (up to 7 days old) are able to fully regenerate cardiac muscle after apical resection, with restoration of contractile function. Independent studies involving carbon-14 dating of genomic DNA from people who were alive during nuclear testing as well as iododeoxyuridine incorporation into the DNA of chemotherapy patients suggest that cardiomyocyte renewal also occurs in humans throughout life. However, the physiological signals that regulate this process remain unclear.

Interestingly, recent collaborative work from our group suggests that the regenerative potential of the heart is dynamically regulated, and that endurance exercise may stimulate cardiomyocyte proliferation in vivo. These studies profiled expression of all known and putative transcriptional components of the mouse genome in hearts from exercised mice, and contrasted differentially regulated genes with those altered in response to pressure overload. Intriguingly, a significant subset of altered transcriptional components had known functions related to cell cycle progression or proliferation in other systems, and confocal immunohistochemistry confirmed a significant increase in all examined markers of cardiomyocyte proliferation in exercised hearts. These results are reminiscent of the hippocampal neurogenesis that is well-documented to occur in response to exercise, which involves the proliferation of precursor cells. Ultimately, cardiomyocyte lineage tracing experiments will be needed to determine the sources and fate of new cardiomyocytes that may form in response to exercise. However, an appealing hypothesis is that exercise may provide a proliferative and potentially regenerative signal affecting multiple tissues.

Molecular Mechanisms

IGF-1–PI3K–AKT Pathway

Genetic interventions in vitro and in vivo have elucidated many of the pathways that regulate cardiac growth. Pathological hypertrophy has previously been reviewed in detail and is associated with activation of G protein–coupled receptors by soluble factors such as angiotensin II and endothelin, signal transduction via, among others, the calcineurin–calmodulin axis and the MAPK pathway, and, ultimately, increases in protein synthesis, cellular growth, and a switch to the fetal gene program.

Physiological hypertrophy, on the other hand, is mediated primarily by the insulin-like growth factor–1, or IGF-1–PI3K–Akt axis. IGF-1 is produced by the liver, and, to a lesser extent, the heart. Exercise induces both hepatic secretion of IGF-1 into the bloodstream, as well as cardiac expression of IGF-1. In the heart, IGF-1 binds its tyrosine kinase receptor, IGF-1R, and activates the PI3K–Akt cascade. Mice with constitutive overexpression of IGF-1 develop an increase in heart size, characterized by both cardiomyocyte hypertrophy and hyperplasia, and are protected against ischemic injury and heart failure. Activation of the IGF-1 receptor also recapitulates the physiological hypertrophic phenotype, with increased cardiomyocyte size and preserved contractile function.

The IGF1-R activates phosphoinositide-3 (PI3K), which consists of a family of heterodimeric kinases composed of regulatory and catalytic subunits. Specifically, activation of the PI3K(110α) isoform has been implicated in the development of physiological cardiac hypertrophy. Mice with constitutively active PI3K(110α) exhibit significantly increased heart weights and are protected from heart failure after pathological stress, such as aortic banding and myocardial infarction. In contrast, mice with cardiac expression of a dominant negative PI3K(110α) isoform, develop hypertrophy normally in response to pressure overload, but have blunted cardiac growth in response to swimming. This observation provides important evidence that distinct intracellular signaling mechanisms mediate physiological and pathological cardiac hypertrophy. Further support for this model is provided by our recent genome-wide profiling of transcriptional regulators, which revealed dramatically different profiles associated with these 2 kinds of growth.

The serine-threonine protein kinase Akt1 is a major downstream effector of IGF1 and becomes phosphorylated (activated) in physiological cardiac hypertrophy. The effects of Akt1 in the heart are diverse, though generally beneficial. These include inhibiting cardiomyocyte death, improving calcium handling, and modulating cardiac growth and metabolism. Interestingly, germline genetic deletion of Akt1 abrogates the cardiac growth response to exercise but results in exacerbated hypertrophy in response to pressure overload. Thus Akt1 is required for physiological hypertrophy, but appears to inhibit pathological hypertrophy in a manner thought to be mediated through cross-talk with MAPK signaling. Most recently, Akt1 has been implicated in promoting proliferation of cardiac stem cells and cardiomyocytes, largely through nuclear activation of a Pim1-dependent pathway.

Endothelial Nitric Oxide Synthase

NO is a ubiquitously expressed molecule that modulates multiple cardiovascular processes, including vascular tone, platelet activation, smooth muscle cell proliferation, and cardiomyocyte contractility. NO is produced by the vascular endothelium as well as the myocardium, where it is generated by the enzyme endothelial NO synthase (eNOS). Multiple
studies have shown that eNOS-mediated production of NO is diminished in patients with heart failure. Interestingly, forced overexpression of eNOS in animal models can reduce the extent of left ventricular dysfunction and remodeling after pathological stress, with overall improvements in mortality.80,81

Exercise training reduces ischemic injury in animal models, and at least part of this benefit appears mediated by upregulation of eNOS. Exercise increases circulating catecholamines, such as epinephrine and norepinephrine, which act on β3-adrenergic receptors to increase eNOS phosphorylation and activity.13 This increases the bioavailability of the NO metabolites, nitrite and nitrosothiol, which can then be used in times of stress to antagonize adverse remodeling processes, such as fibrosis and pathological hypertrophy.13 Of note, the cardioprotective effects of exercise in preventing adverse remodeling are not seen in mice that are deficient in eNOS,83,84 although this is potentially confounded by a reduction in the exercise levels achieved by such mice.83 Interestingly, this pathway also appears essential in promoting the cardioprotective effects of exercise that can persist after exercise training has ceased.13

Sirtuins, AMPK, and PGC-1α
Sirtuins are a family of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases, 7 of which, Sirt1–7, are found in mammals and regulate a variety of cellular functions, including metabolism, cell growth, apoptosis, and aging.84 Sirt1 and Sirt3 are the best studied of the sirtuins in the heart. Sirt1 is upregulated after exercise and has pro- and pro-survival functions in cardiomyocytes.85 Sirt3 is a mitochondrial sirtuin, and, like Sirt1, is upregulated with exercise.86 In the heart, Sirt3 protects against oxidative stress in a Foxo3a-dependent manner, and has also been shown to regulate opening of the mitochondrial permeability transition pore (mPTP) via deacetylation of cyclophilin D.87,88 This latter effect is thought to be protective against age-related cardiac dysfunction, and, in fact, Sirt3 knock-out mice exhibit accelerated pathological hypertrophy, fibrosis, and heart failure.88

Additionally, Sirt3 regulates cardiac metabolism via activation of AMPK and PGC-1α, both of which have been shown to inhibit maladaptive cardiac remodeling.87 AMPK is a serine/threonine kinase that senses energy levels within the cell and, together with its downstream effector, PGC-1α, coordinates metabolic responses to maintain energy homeostasis. Animals deficient in AMPK exhibit increased hypertrophy, accelerated heart failure, and also have increased infarct sizes after coronary artery ligation.89 PGC-1α is a transcriptional coactivator upregulated with exercise and a potent inducer of mitochondrial biogenesis and oxidative phosphorylation. PGC-1α-deficient mice develop early signs of heart failure resulting from an inability of the heart to meet energy demands, thus emphasizing the importance of metabolic and energy homeostasis in cardiac health.50,90 PGC-1α has also been shown to regulate a hypoxia inducible factor-1 (HIF-1)-independent pathway of angiogenesis,91 thereby providing a mechanism for coordinately regulating mitochondrial function and blood supply in exercise.

Myokines, Adipokines, and Other Secreted Molecules
Exercise also exerts a number of indirect benefits on the heart, mediated, in part, by endocrine factors secreted from skeletal muscle and adipocytes, termed myokines and adipokines, respectively. Follistatin-like 1 (Fstl1), for example, is a glycoprotein secreted by both skeletal muscle and cardiac myocytes after exercise. Fstl1 activates the PI3K–Akt pathway in cardiomyocytes and vascular endothelial cells and exerts antiapoptotic and vasodilatory effects.92

A novel hormone and myokine under the regulation of PGC-1α, called irisin, was recently described93 and is implicated in some systemic effects of exercise. After exercise, upregulation of PGC-1α results in increased skeletal muscle secretion of irisin, the proteolytic cleavage product of the type I membrane protein, FNDC5.93 Irisin plays an important role in the browning of white adipose tissue and thermogenesis and may play a role in many of the beneficial systemic effects of muscle PGC-1α expression, such as protection against age-related obesity and diabetes mellitus.93 Whether irisin also contributes to the cardiac benefits of PGC-1α will be of great interest for future studies.

Adiponectin is a hormone secreted by adipocytes, and has anti-inflammatory and antihypertrophic effects on the heart. Plasma adiponectin levels are decreased in patients with obesity and insulin resistance, as well as in associated cardiovascular diseases, such as coronary artery disease and hypertension.94 Interestingly, there is a paradoxical increase in plasma adiponectin levels in heart failure patients, which has been attributed to downregulation of the adiponectin receptor (AdipoR1) and subsequent skeletal muscle adiponectin resistance.95,96 Exercise training normalizes levels of adiponectin in heart failure patients, decreases adiponectin resistance, and also reverses heart failure–associated skeletal muscle wasting, or cardiac cachexia, which is an independent risk factor for mortality.97–99

In addition to adiponectin, an important regulator of cardiac cachexia is myostatin (MSTN), a member of the transforming growth factor β superfamily and a potent negative regulator of skeletal muscle growth.100 Notably, cardiac-specific MSTN knockout mice are protected from pressure overload–induced cardiac cachexia.101 We also found that MSTN directly regulates cardiomyocyte growth in a stimulus–specific way,102 and knockout mice are protected against aging-related cardiac fibrosis and dysfunction.103 There are also data to suggest that MSTN levels are dynamically regulated with exercise. In a rat model of heart failure, elevated skeletal and myocardial MSTN levels associated with heart failure returned to baseline after 4 weeks of endurance exercise.104 In human heart failure patients, exercise also resulted in a significant reduction in skeletal muscle MSTN.105 Thus, it is possible, though speculative, that a reduction in MSTN and related peptides contributes to the cardiac benefits of exercise.

In addition to proteins and peptides, studies in Burmese pythons have also implicated lipids as being potential secreted factors that mediate physiological cardiac hypertrophy. As described above, Burmese pythons exhibit significant cardiac growth after meals. It has recently been shown that an
infusion of 3 lipids—myristic acid, palmitic acid, and palmitoleic acid—found to be elevated in the serum of Burmese pythons postprandially, can induce cardiac growth in the fasting state, thereby recapitulating the hypertrophic phenotype seen after meals. Importantly, these lipids can also induce hypertrophy of cultured mammalian cardiomyocytes. Finally, in a clinical context, the Gerszten laboratory has recently performed plasma metabolite profiling on subjects before and after exercise. In addition to identifying metabolite signatures of potential clinical utility, these studies also revealed a subset of exercise-induced metabolites that regulate muscle expression of Nur77, a nuclear hormone receptor important in regulating glucose and lipid metabolism. These studies add to growing evidence that metabolites and other small molecules regulate diverse physiological processes, likely including the cardiac response to exercise.

**miRNAs**

Since their discovery a little more than a decade ago, miRNAs have become increasingly recognized for their pivotal roles in the regulation of development and disease. Recent studies identified multiple miRNAs that are highly, and almost exclusively, expressed in the heart and skeletal muscle. Among these are miR-208a, miR-208b, and miR-499, which comprise a family of myosin heavy chain-encoded miRNAs, collectively termed MyomiRs. These MyomiRs have been implicated in a wide array of cardiovascular diseases, including cardiac hypertrophy, heart failure, arrhythmias, and congenital heart disease.

In addition, there has also been much interest in examining the role of miRNAs in regulating the physiological processes of exercise. Multiple studies in both animal models and humans suggest that miRNAs are dynamically regulated with physical activity, and, moreover, that acute and chronic bouts of exercise impart differential changes in miRNA expression. Of note, miRNAs are also known to be secreted into the bloodstream, both at rest and after tissue injury.

Recently, changes in levels of such circulating miRNAs, or c-miRNAs, have been described after exercise. Further studies will be needed, however, to identify the cellular sources of these c-miRNAs, and also to better characterize their biological roles. For instance, c-miRNAs secreted as a byproduct of stress and tissue injury, or might they also have important endocrine and paracrine functions?

Although exercise has been shown to regulate miRNA expression, the precise role of miRNAs in regulating physiological hypertrophy and exercise-induced cardiovascular remodeling remains unclear. It has been shown that miR-1 and miR-133, 2 of the most abundant miRNAs in cardiac myocytes, are down-regulated in both pathological and physiological hypertrophy, suggesting that they may mediate a nonspecific cardiomyocyte growth pathway. In a more specific exercise-focused study, female Wistar Rats subjected to swimming training were found to exhibit upregulation of miR-29c. Interestingly, the miR-29 family targets a number of miRNAs that encode proteins essential for fibrosis, and upregulation of these miRNAs has been associated with repression of fibroblast collagen deposition. It is possible, although still speculative, that the miR-29 family might be important in actively suppressing a fibrotic response in exercise-induced cardiac hypertrophy. Of note, miRNA-29c has also been shown to suppress the PI3K–Akt pathway. While activation of the PI3K–Akt axis is crucial to physiological remodeling, it is also known that its effects are dependent on the timing and chronicity of Akt activity. In particular, chronic Akt overexpression has been linked to maladaptive remodeling and heart failure. Thus miR-29 could be important in fine-tuning the activity of the PI3K–Akt axis, thereby maintaining tissue homeostasis and healthy cardiovascular function.

It has become clear that miRNA expression is dynamically, and differentially, regulated by pathological and physiological processes. This provides important implications for the development of both diagnostic and therapeutic tools for the treatment of cardiovascular disease, as will be discussed in more detail below.

**Limitations**

While substantial progress has been made in the understanding of exercise physiology, particularly as it pertains to the heart, certain limitations to these studies deserve mention. One of the most widely accepted animal models of pathological stress is the use of transverse aortic constriction (TAC) to increase afterload, thereby mimicking chronic hypertension or aortic stenosis and resulting in concentric hypertrophy. However, animal models of endurance training most commonly involve the use of isotonic exercises like treadmill running or swimming, which primarily result in cardiac growth via eccentric hypertrophy. These different patterns of growth could potentially confound any direct comparisons made between the two models. Nonetheless, in the absence of more directly comparable animal models, current studies have still provided important insight into mechanisms regulating pathological and physiological cardiac hypertrophy.

Most pathological stimuli are chronic persistent, whereas exercise is intermittent, raising the possibility that the distinct outcomes associated with these stimuli reflect quantitative rather than qualitative differences in exposure. To address this issue, Rockman and colleagues cleverly designed a model of intermittent pressure overload in mice. Interestingly, this induced pathological changes, which—while milder than those seen with persistent pressure overload—emphasizes the importance of qualitative differences independent of exposure duration. Of interest, although most of the cardiac changes associated with endurance exercise are thought to be cardioprotective, with beneficial adaptations to calcium handling, metabolism, and vascular remodeling, recent cardiac MRI data identified a link between lifelong, competitive endurance exercise and an increased prevalence of myocardial fibrosis with subsequent risk for arrhythmias. Such clinical data raise the possibility that too much exercise may have adverse effects. However, observational data on exercise are inherently limited by issues such as self-selection and the possibility of unrecognized confounding. A recent analysis of exercise studies suggests that even moderate exercise may have adverse effects on risk factors such as systolic blood pressure and high-density lipoprotein in some subjects (126 of 1687 analyzed). Why this occurs...
in a subset of subjects and whether these effects result in adverse clinical outcomes despite the other benefits of exercise remain unclear. Further studies are needed to delineate the precise shape of the exercise dose–response curve and characterize the contribution(s) of exercise duration, intensity, and frequency to the cardiovascular effects of exercise.

Finally, as with all experimental animal models, findings in mice may not correlate with human pathophysiology. The molecular mechanisms of exercise-induced cardiac remodeling is particularly difficult to study in human beings, because of the limited availability of tissue samples from healthy subjects. The development of novel technologies to better identify and characterize secreted peptides, circulating miRNAs, and metabolites can help further our understanding of exercise-induced changes in humans in the absence of cardiac tissue. Identification of serum components that are similarly regulated in animals and people, such as the secreted molecule irisin, may help establish parallels between human biology and animal models of exercise.

Clinical Implications

The beneficial effects of exercise in preventing and treating cardiovascular disease have long been appreciated. Data from the Framingham Heart Study, for example, show that exercise, or lack thereof, is an independent risk factor for cardiovascular disease, even after controlling for its effects on other risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus. Additionally, meta-analyses, and, more recently, a large, prospective, randomized, controlled trial, HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), suggest that exercise training has significant benefits for patients with coronary artery disease or heart failure. Of note, in HF-ACTION, the largest randomized exercise trial to date, heart failure patients randomized to exercise had improved quality of life and a trend to reduced mortality, which was significant after adjustment for differences in baseline characteristics. Thus, some might argue that we already have a simple prescription for these benefits: exercise. However, many patients may be unable to exercise, and thus understanding the pathways that mediate these benefits, and learning how to manipulate them in vivo, could yield novel therapeutic approaches.

Genetic interventions in mice provide evidence that manipulation of pathways to mimic the changes that occur with exercise can protect against heart failure after pathological stress. For instance, upregulation of PI3K, Akt1, eNOS, and PGC-1α, as well as repression of the transcription factor C/EBPβ, all result in preserved cardiac contractility and decreased mortality after aortic banding or ischemia–reperfusion. The beneficial effects of these interventions are likely multifactorial, involving a combination of pro-growth and proliferation signals, increased angiogenesis, improved calcium handling and energetics, as well as suppression of fibrosis—a constellation of changes that encompass the physiological hypertrophic phenotype. The molecular regulators of these physiological adaptations may hold promise as potential targets for intervention in the treatment of cardiovascular disease.

These genetic studies provide important proof-of-concept that benefits accrue from recapitulating some of the central molecular changes induced by exercise. However, not all the pathways implicated are ideal candidates for therapeutic targeting. Current attempts at molecular interventions targeting intracellular molecules have been limited, in part, by the difficulty of designing small molecules that activate kinases or inhibit nuclear transcription factors. Moreover, many of these molecules have multisystemic, pleiotropic effects, requiring cardiac-specificity to be engineered elsewhere in the system. On the other hand, secreted factors such as adiponectin, myostatin, or irisin may be more promising drug targets. Inhibitors of myostatin and related peptides, in fact, are already in clinical trials for the treatment of skeletal muscle dystrophies, and could conceivably be extended to use in heart failure patients should additional research support this concept.

miRNAs are also promising targets for clinical intervention because, unlike intracellular enzymes or signaling molecules, they are easily targetable through the use of miRNA mimics and antagonists (antiMirs). Delivery of both miRNA mimics and antiMirs have been efficacious in vitro and in vivo, and could potentially be extended to the clinical setting as well. Some miRNAs also have the advantage of tissue specificity, and most simultaneously modulate multiple signaling cascades via the inhibition of multiple cellular targets. However, many miRNAs are still ubiquitously expressed, and the efficacy of miRNA therapy, like that of peptide or small molecule drugs, may be limited by off-target effects on other organs or pathways.

As a result, there has been much interest in the development of targeted drug delivery tools to enhance delivery of therapies specifically to the heart. For instance, miRNA mimics, antiMirs, or other small molecules could be conjugated to targeting peptides or antibodies for specific uptake by cardiomyocytes. The use of similar nanoparticle drug delivery systems for the targeted drug delivery of chemotherapeutics to prostate cancer is in clinical trials, and it is conceivable that this technology could be extended for the delivery of medications to the heart as well. Additionally, adenoviral delivery systems are currently being investigated as a way to enhance cardiac-specificity as well as for the continuous expression of a particular gene or miRNA of interest, and a number of clinical trials involving adenovectorial viral systems for gene delivery are already under way and have demonstrated a favorable safety profile, and even a suggestion of efficacy. Finally, catheter-based intracardiac delivery is also being explored as a potential drug delivery tool to increase cardiac-specificity. It seems likely that none of these exercise mimetics will fully reproduce all the benefits of exercise. However, the discovery of novel therapeutic targets and the development of improved drug delivery technologies may lead to improved treatments for heart disease, particularly for those patients unable to exercise.

Finally, the exercised heart provides a prototype of the healthy heart that may serve as a useful tool for gauging the response to therapy. Our initial studies of transcriptional coactivators altered in exercised hearts demonstrated a dis-
tinct pattern from those altered in response to pressure overload.12 More extensive profiling of exercised (and dis-
 eased) hearts could ultimately lay a foundation for a systems biology131 approach to cardiac health and disease, allowing interventions to be judged not simply by their effect on one putative target but by their ability to recapitulate the healthy profile (or reverse that of disease). Our studies defined a physiological gene set that was characteristically altered in exercised hearts.12 C/EBPβ appeared to function as a hub in this network, as genetically reproducing the exercise-induced change in C/EBPβ was sufficient to recapitulate the changes seen in slightly more than half of this gene set, and protected against heart failure.12 As noted above, the Gerszten labora-
tory has recently identified plasma metabolite profiles in humans indicative of exercise performance and cardiovascular disease susceptibility.106 These signatures may provide a useful gauge of the response to interventions. Taken together, these studies suggest value in delineating such signatures as a therapeutic road map and aid to evaluating clinical intervention.

Conclusion
Current pharmacological interventions in clinical use for heart failure are focused on preventing the maladaptive changes associated with sympathetic overdrive and activation of the renin–angiotensin–aldosterone system. Emerging technologi-
cal advancements and a better understanding of funda-
mental biological processes have provided us with deepened insight into the cardiovascular effects of exercise. Indeed, physiological cardiac growth appears to encompass not only cardiomyocyte hypertrophy, but also low levels of cardiomyocyte hyperplasia, as well as increased angiogenesis, alterations in calcium handling and metabolism, and secretion of paracrine and endocrine mediators. Overall, these changes are cardioprotective, leading to preserved, possibly even enhanced, cardiac function, and present an enticing avenue both for identifying therapeutic interventions and judging their efficacy.

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None.

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