Molecular Aspects of Exercise-induced Cardiac Remodeling

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KEYWORDS

• Exercise • Cardiac remodeling • Molecular mechanisms • Cardiac myocyte • Cardiac hypertrophy • Drug targets

KEY POINTS

- Cardiac enlargement that occurs in response to moderate exercise is typically considered an adaptive physiologic response that is associated with normal or improved cardiac function. This adaptive remodeling is associated with cardiac myocyte hypertrophy and renewal (proliferation and increased endogenous cardiac stem cells), increased cardiac myocyte contractility, sarcomeric remodeling, cell survival, metabolic and mitochondrial adaptations, electrical remodeling, and angiogenesis.
- At the molecular level, adaptive exercise-induced cardiac remodeling has been associated with signaling pathways/modulators activated by growth factors, hormones (growth and thyroid), and mechanical stretch, including the insulin-like growth factor 1 receptor–phosphoinositide 3-kinase–phosphoinositide-dependent protein kinase-1–protein kinase B signaling pathway, β-adrenoreceptors, transcription factors (eg, CCAAT/enhancer-binding protein β, heat shock factor 1), and microRNAs (eg, miR-222).
- By contrast, intense endurance exercise has been associated with some adverse cardiac remodeling, cardiac dysfunction, and arrhythmia. This cardiac remodeling may be more similar at the cellular and molecular levels to disease-induced pathologic remodeling. Molecular mechanisms implicated include β_1-adrenoreceptor desensitization, and prolonged tumor necrosis factor α-nuclear factor kappa B–p38 signaling.
- Novel therapeutic approaches for the treatment of heart failure that target mechanisms responsible for adaptive exercise-induced cardiac remodeling are being developed and tested in preclinical models.

INTRODUCTION

Cardiac remodeling is the result of molecular and cellular changes that manifest clinically as changes in the size, shape, and function of the heart. In response to exercise training, all 4 chambers of the heart can enlarge (left and right atria, and left ventricle [LV], and right ventricle [RV]).[1–3] However, to date, cellular and molecular mechanisms have mainly been studied in the LV. Initiating stimuli/triggers of exercise-induced remodeling include increased hemodynamic load, increased sympathetic activity, and the release of hormones and growth factors, all of which activate multiple molecular pathways. The activation of signaling cascades affects

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multiple processes within different cardiac cell types (eg, cardiac myocytes, fibroblasts, endothelial cells, vascular smooth muscle cells). Cardiac remodeling in response to exercise is generally considered an adaptive response and distinct from the remodeling that occurs in heart disease settings.[4,5] However, it is also recognized that prolonged strenuous exercise can lead to adverse cardiac remodeling and complications such as arrhythmia.[6] To date, the cellular and molecular mechanisms responsible for adaptive heart growth (ie, physiologic hypertrophy) in response to moderate exercise training are better characterized and are the focus of this article (**Table 1**). However, this article also describes what is currently known in relation to the molecular mechanisms that contribute to adverse remodeling in response to prolonged high-intensity exercise (see **Table 1**). In addition, this article discusses novel therapeutic approaches for the treatment of heart failure that target mechanisms responsible for adaptive exercise-induced cardiac remodeling.

MOLECULAR MECHANISMS ASSOCIATED WITH ADAPTIVE EXERCISE-INDUCED CARDIAC REMODELING

Exercise represents a dynamic and intermittent stimulus associated with increased sympathetic activity (release of catecholamines: norepinephrine/noradrenaline, epinephrine/adrenaline), mechanical stress, altered release of hormones (eg, growth hormone [GH] and thyroid hormone [TH]), and the increased production and secretion of several growth factors. Growth factors that have been associated with exercise training or fitness include insulin-like growth factor 1 (IGF1), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and neuregulin-1 (NRG1).[2,7,8] These stimuli subsequently activate numerous signaling cascades within the heart, leading to processes such as cardiac myocyte hypertrophy and renewal/proliferation, cardiac myocyte contractility, sarcomeric remodeling, extracellular matrix (ECM) remodeling, cell survival, angiogenesis, electrical

Table 1
Cellular and molecular features associated with adaptive and maladaptive exercise-induced remodeling

Cellular and Molecular Mechanisms Associated with Adaptive Exercise-induced Remodeling	Cellular and Molecular Mechanisms Associated with Maladaptive Exercise-induced Remodeling
Cellular • Cardiac myocyte hypertrophy and renewal • ↑ eCSCs (proliferation and differentiation) • ↑ myocyte contractility and sarcomere remodeling • ↑ angiogenesis • No fibrosis • No or ↓ apoptosis • ↑ mitochondrial biogenesis	Cellular • Cardiac myocyte hypertrophy • No or ↑ fibrosis • ↑ inflammation
Stimuli and molecular mechanisms • Intermittent release of hormones (eg, GH, TH) and growth factors (eg, IGF1, VEGF, NRG1, HGF) • Intermittent ↑ catecholamines and activation of β-ARs • IGF1R-PI3K-PDK1-Akt (other regulators of pathway: PAK1, PRAS40) • VEGF-PI3K-Akt-eNOS • Akt-C/EBPβ-CITED4 • HSF1 • miR-222	Stimuli and molecular mechanisms • More prolonged release of factors; eg, TNFα • More prolonged ↑ catecholamines and eventual desensitization of β-ARs • ↑ oxidative stress • Activation of NFκB-p38 MAPK • Possible release of ET-1 and TGFβ from cardiac cells (eg, myocytes, immune and vascular) and activation of GPCR signaling cascades

Abbreviations: β-AR, β-adrenergic receptor; Akt1, protein kinase B; C/EBPβ, CCAAT/enhancer-binding protein β; CITED4, CBP/p300-interacting transactivator 4; eCSCs, endogenous cardiac stem/progenitor cells; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; GH, growth hormone; GPCR, G protein–coupled receptor; HGF, hepatocyte growth factor; HSF1, heat shock factor 1; IGF1, insulin-like growth factor 1; IGF1R, insulin-like growth factor 1 receptor; MAPK, mitogen activated protein kinase; miR, microRNA; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NRG1, neuregulin-1; PAK1, p21 protein (Cdc42/Rac)-activated kinase 1; PDK1, phosphoinositide-dependent protein kinase-1; PI3K, phosphoinositide 3-kinase; PRAS40, proline rich Akt substrate; TGFβ, transforming growth factor beta; TH, thyroid hormone; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor.