ELSEVIER

Mechanisms of exercise-induced cardiac growth

Carolin Lerchenmüller[1,2] and Anthony Rosenzweig[1,2]

[1] Cardiovascular Division, Beth Israel Deaconess Medical Center, Boston, MA, USA
[2] Harvard Medical School, Boston, MA, USA

Exercise is a well-established intervention for the prevention and treatment of cardiovascular disease. Increase in cardiomyocyte size is likely to be the central mechanism of exercise-induced cardiac growth, but recent research also supports a role for the generation of new cardiomyocytes as a contributor to physiological cardiac growth. Other cardiac cell types also respond to exercise. For example, endothelial cells are important for the regulation of large vessels and expansion of microvasculature in meeting demands of the growing heart. Cardiac fibroblasts are known to generate and respond to important signals from their environment, but their role in exercise is less well defined. Therefore, cardiac growth relies on complex, finely regulated and interdependent signaling pathways as well as cross-talk among cardiac cell types.

Clinically, it is well established that exercise is helpful in preventing and treating cardiovascular disease [1–3]. Cardiac hypertrophy is one major feature of endurance exercise leading to physiological heart growth. However, the heart also grows in response to pathological stimuli, and the initially similar clinical characteristics of both growth patterns can be challenging diagnostically. Yet, the molecular mechanisms and profiles, as well as the outcomes of physiological versus pathological growth, are distinct. Understanding the root causes of these differences and how endurance exercise leads to a physiological rather than pathological adaptation of the heart could provide a foundation for future efforts to realize the therapeutic potential of endogenous beneficial pathways activated in exercise. In addition to the local cardiac effects, systemic (muscular, vascular, metabolic, among others) effects also have crucial roles in the benefits of endurance exercise. In this review, we focus on local effects within the myocardium itself, but the interested reader is referred to other papers that include discussion of the systemic effects [4–7].

Whereas growth in cell size or hypertrophy of cardiomyocytes is likely to be the central mechanism of adult cardiac growth, particularly over the short-term, recent research also supports a role for the generation of new cardiomyocytes (cardiomyogenesis), resulting in an increase in cardiomyocyte number (hyperplasia), as potential contributors in both physiological and pathological remodeling [8–10]. The origin of these new cardiomyocytes and their contribution to favorable ventricular remodeling are focal points for ongoing research and remain somewhat controversial. Other cell types also respond to physiological stimuli. Although the role of vascular cells, particularly the endothelium, in meeting the demands of the growing heart has been extensively researched [4–6], the role of cardiac fibroblasts remains less explored and relatively unclear. Therefore, here we review recent and emerging data regarding the mechanisms of exercise-induced cardiac growth, including cardiomyocyte hypertrophy and renewal, vascular remodeling and the role of cardiac fibroblasts.

Physiological versus pathological cardiac growth

The heart responds to acute and transient increases in demand, by raising its stroke volume and/or rate to increase cardiac output [11]. For these acute responses, the heart does not immediately change its structure but dynamically regulates existing molecules governing excitation–contraction coupling. By contrast, in response to repetitive or chronic increases in demand, the heart will change in size, shape, structure and physiology, as seen in response to endurance exercise, or hypertension and aortic stenosis, for example [11]. Impressively, ventricular mass can even

Corresponding author:. Rosenzweig, A. (arosenzw@bidmc.harvard.edu)

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.03.010

double in response to pathological stimuli [12]. A similarly impressive hypertrophy can also be seen in response to endurance exercise, which can induce up to a 60% increase in left ventricular mass [12,13]. These two kinds of growth look grossly similar and can be a challenge to distinguish clinically but lead to different outcomes [14,15]. Correspondingly, at a molecular level, they also have distinct patterns on expression profiling. For example, recent genome-wide profiling of transcriptional regulators revealed a different profile for either pathological or physiological cardiac growth [16,17].

One theory for why these patterns might be distinct is that physiological overloads are usually intermittent, whereas pathological overloads are often constant. Animal studies of intermittent pressure overload that applied a pathological stress for periods identical to a swimming exercise protocol revealed that, not surprisingly, the intermittent pathological pressure overload resulted in a milder hypertrophic response and a favorable fetal gene expression profile compared with constant pressure overload. However, the hearts still displayed pathological features, such as the activation of the β-adrenergic signaling pathway and vascular rarefaction, which are not seen with endurance exercise [18]. These data support the model that distinct pathogenic signaling pathways rather than the duration of stress or the hypertrophic growth per se, underlie the differences between the pathological and physiological cardiac hypertrophic response and could be the molecular trigger of cardiac dysfunction.

Although cardiomyocyte hypertrophy is likely to be the dominant contributor to exercise-induced heart growth, with increases in cardiomyocyte size up to 17–32% after exercise training [19], recent data from animal models and human studies suggest that the heart also has some capacity for cardiomyogenesis [10,20,21]. Endurance exercise might enhance this endogenous regenerative capacity. In animal models, exercise induces both an increase in markers of cell cycle progression in cardiomyocytes and the number of potential cardiac stem cells [16].

An increase in left ventricular mass is generally also observed with aging, although the heart has a reduced compensatory capacity and is more susceptible to myocardial dysfunction and failure. In fact, studies suggest that cardiomyocyte number declines by approximately 30% because of cardiomyocyte death by apoptosis or necrosis and potentially the impairment of endogenous cardiomyogenesis [22,23]. However, exercise training could protect against cardiomyocyte death during aging. Regular physical activity favorably modulates proapoptotic and antiapoptotic genes [9,24].

Cardiomyocytes: growth response to exercise

Hypertrophy

Extensive research over the past decades has elucidated signaling pathways involved in cardiac growth. Pathological hypertrophy is associated with the activation of G protein-coupled receptors by secreted factors such as angiotensin II (ATII) and endothelin (ET1) and subsequent signal transduction via the mitogen-activated protein kinase (MAPK) pathway and others that ultimately lead to increases in protein synthesis, activation of the fetal gene expression pattern and cellular growth [12,25,26]. Another feature that distinguishes pathological from physiological growth is the cardiomyocyte length:width ratio. A proportionate increase in myocyte length and width is typically seen with endurance exercise, whereas a disproportionate increase in length over width is a hallmark of heart failure.

Proportionate cardiomyocyte growth can be induced via increased cardiac insulin-like growth factor-1 (IGF-1) expression and subsequent activation of the phosphoinositide-3 kinase (PI3K) axis (Fig. 1) [27]. After IGF-1 binds its tyrosine kinase receptor IGF1-R, the p110α subunit of PI3K is activated via the adaptor proteins insulin receptor substrate (IRS)-1 and -2. Mice with constitutively active PI3K(p110α) display a significantly increased heart weight and, importantly, are protected against heart failure after pathological stress, such as transverse aortic constriction (TAC) and myocardial infarction (MI) [28]. Mice expressing a dominant negative form of PI3K(p110α) manifest a normal response to TAC but a blunted growth response to exercise [29]. Downstream of PI3K, the serine-threonine protein kinase v-akt murine thymoma viral oncogene homolog 1 (AKT1) is phosphorylated in response to endurance exercise [30,31]. Mice deficient in AKT1 show almost no hypertrophy in response to exercise but an exaggerated response to TAC [31]. As one of its downstream signaling targets, AKT1 downregulates the transcription factor CCAAT/enhancer binding protein β (C/EBPβ). C/EBPβ interacts with serum response factor (SRF) and contributes to regulating the so-called 'physiological gene set', genes with known roles in cardiomyocyte hypertrophy and differentiation and altered levels after endurance exercise that include GATA binding protein 4 (*GATA4*), T-box 5 (*Tbx5*) and NK2 homeobox 5 (*Nkx2.5*) [16]. Mice with reduced cardiac C/EBPβ levels displayed substantial resistance to cardiac failure upon pathological pressure overload and recapitulate the physiological hypertrophic phenotype [16].

The role of miRNA in regulating the physiological changes of exercise in the heart has also sparked interest. Studies in exercised rats first suggested the importance of regulating miRNAs in the context of cardiac hypertrophy. For example, downregulation of miR-133 and miR-1 is involved in both physiological and pathological cardiac hypertrophy [32]. Also, miR-1 has been shown to be downregulated by IGF-1 through inhibition of the transcription factor forkhead box O3 (Foxo3a) in an AKT1-dependent pathway, pointing towards a role in the exercise response [33]. In another study, miR-29c was found upregulated in response to exercise [34]. Although miR-29c has also been shown to suppress the PI3K–AKT1 pathway, which is crucial in the physiological growth response to exercise, it might be possible that it has an important role in fine-tuning the activity of this pathway [35]. This is especially important because the effects of AKT1 are particularly dependent on the timing and chronicity of AKT1 activity, and chronic AKT1 overexpression has been linked to maladaptive remodeling and heart failure [36]. The interactions of these pathways are illustrated in Fig. 1.

Cardiomyogenesis

It was long thought that mature cardiomyocytes irreversibly withdraw from the cell cycle shortly after birth, remain silent in G_0 phase throughout their lifetime [37] and thus that the adult heart has no capacity for cardiomyogenesis. However, recent studies suggest that, in addition to hypertrophy, the heart is capable of mounting a slow hyperplastic response, enabling it to cope with the continuous loss of cardiomyocytes over time [8,38,39]. Independent