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Cardiomyocyte Proliferation, Stem Cells and Aerobic Training

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Abstract

While research to date has shown that cell-based therapy can improve LV function in myocardial infarction (MI), low progenitor cell engraftment rates have limited treatment success. Interventions improving the environment of the heart to facilitate stem cell retention and activity are needed. One promising candidate is aerobic exercise, which may potentially "precondition" the heart and coronary vasculature to improve the efficacy of stem cell therapeutics. In this brief review, a summary of how aerobic exercise impacts endogenous cardiomyocyte renewal and exogenous stem cell therapy will be presented.

Keywords: Heart; Exercise; Remodeling

Introduction

While mature cardiomyocytes have been historically been thought to not undergo mitotic cell division, over the last two decades, a paradigm shift toward the plausibility of cardiomyogenesis has gained momentum. It is now recognized that some degree of cardiomyocyte renewal does occur, albeit at very low rates [1]. Thus, while most cardiomyocytes in the adult heart are terminally differentiated, some new cardiomyocytes, smooth muscle, and endothelial cells can be formed from endogenous progenitor sources [1]. These findings have also stimulated interest in designing therapeutic approaches utilizing exogenous stem cells to drive cardiomyogenesis after myocardial injury, a field that started with the utilization of skeletal myoblasts to repopulate the damaged heart [2].

One major problem that has limited the success of cell-based therapy is the ability to have a high percentage of progenitors engraft and differentiate within the heart, particularly in the face of accelerated apoptosis associated with various types of cardiovascular disease. Thus interventions that favorably alter the metabolic milieu of the heart and provide a more hospitable environment for transplanted stem cells to flourish are needed. One likely candidate is aerobic exercise, which may potentially "precondition" the heart and coronary vasculature to improve the efficacy of stem cell therapeutics. In this brief review, a summary of how aerobic exercise impacts endogenous cardiomyocyte renewal and exogenous stem cell therapy will be presented.

Cardiomyocyte Renewal

Isotope dating studies have provided powerful evidence of cardiomyocyte renewal in the human heart. Given shifts in atmospheric carbon-14 levels secondary to nuclear bomb testing, Bergmann et al. utilized carbon-14 DNA integration to establish the rate of cardiomyocyte renewal in humans. They found a renewal rate of 1% per year in young individuals (25 yrs. of age), which declined to 0.45% per year in older subjects (75 yrs. of age) [3]. Similarly, using an imaged-based assay in donor hearts acquired for transplantation, Mollova et al. more recently reported a cardiomyocyte renewal rate of 1.9% in young individuals (20 yrs. of age) [4]. These human data are in accord with studies in mice which have shown an annual cardiomyocyte renewal rate of approximately 1% per year [5-7], which interestingly increases following myocardial infarction [1].

While the mechanisms of cardiomyogenesis require further elaboration, some have hypothesized that progenitor cells directly differentiate and give rise to new cardiomyocytes [2]; while others have postulated that mature cardiomyocytes reenter the cell cycle, hence stimulating cardiomyogenesis [2]. A genetic lineage tracing study by van Berlo et al. in 2014 specifically examined the role of c-Kit$^+$ progenitor cells to make new myocytes in normal and injured hearts [1]. The results of those studies showed that a very small number of fibroblasts, smooth muscle cells, and cardiomyocytes [0.05%

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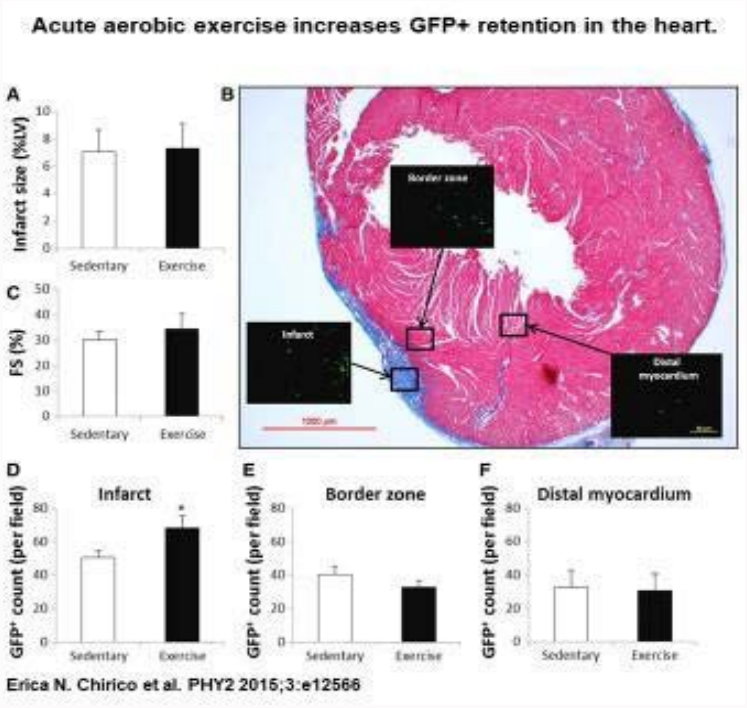

Figure 1: Acute aerobic exercise increases GFP+ retention in the heart. Cryoinjury induced small nontransmural MIs [A] that were nearly identical between sedentary and exercise hearts. Panel B shows a representative Massons trichrome stained cross section. Fractional shortening was similar between sedentary and exercise hearts [C]. GFP+ BMC's were measured in the infarct, border zone, and distal myocardium [1000μm from infarct] [Panel B]. GFP+ BMC retention was greatest in the infarct region and was increased with exercise [D]. Less GFP+ BMC retention was seen in the border zone and distal myocardium, and was not significantly different between sedentary and exercise hearts [E and F]. *indicates P < 0.05 versus sedentary. Reproduced from Chirico et al.

annual rate] were formed from endogenous c-Kit+ progenitors, likely not providing a significant cardiomyocyte number toward influencing cardiac function [1]. It should be noted though, that van Berlo et al. did show a significant number of endothelial cells were derived from c-Kit+ progenitors in the heart. These findings have more recently been supported by an independent lineage tracing study by Sultana et al., who targeted the c-Kit locus with multiple reporter genes in mice [8]. Their results showed that c-Kit expression rarely co-localized with Nkx2.5 or cardiac troponin T, but instead with endothelial cells [8]. Thus taken in sum total, the results of these and many other studies support the plausibility of cardiomyocyte renewal in human and animal hearts, which occurs at very low rates from a pool of c-Kit+ progenitors. These studies also suggest that c-Kit+ progenitors are a significant source for endothelial cells in the heart.

Aerobic Exercise Training and Cardiomyocyte Renewal

The literature is replete with studies showing that aerobic exercise training initiates a program of cardiovascular adaptations that are consistent with improved overall health [9]. Enhanced myocardial function, training-induced bradycardia, and physiologic cardiomyocyte hypertrophy concomitant with whole heart remodeling are all phenotypical features of the trained heart [9,10]. Training has also been shown to upregulate endogenous progenitor cell formation in bone marrow [11] and may increase local progenitor number in peripheral tissues [12,13]. Moreover, exercise training has been shown to attenuate cardiomyocyte apoptosis [14], offset cellular senescence [15] and protect the heart from necrosis associated with ischemia-reperfusion injury [16]. These adaptations collectively lead to greater cardiomyocyte size [length] [17] and preserve cardiomyocyte number, particularly in response to metabolic stressors [18].

While multiple intracellular signaling pathways are involved in training-induced cardiac remodeling; the protective phenotype appears largely reliant on insulin growth factor-1 (IGF)/ phosphatidylinositol-3-kinase (PI-3 kinase) -protein kinase B (Akt) – mammalian target of rapamycin [mTOR] signaling [17]. The mTOR pathway is uniquely suited to regulate cardiomyocyte growth, survival, and proliferation by integrating energy status via AMPK, with growth factor signaling at mTOR complex 1 (mTORC1) [17]. Given the feedforward signaling of this system toward potential cardiomyocyte proliferation, the question of whether exercise can stimulate cardiomyocyte renewal arises.

Several independent groups have shown evidence of enhanced cardiomyocyte cell cycle entry with training [18-23]. In the earliest study, Kolwicz et al. showed that treadmill running tended to increase the proliferative potential [Ki67+ cells] of hypertensive hearts [SHR] relative to sedentary, SHR animals. In this study, trained SHR hearts also tended to have an increased myocardial abundance of endogenous stem cells [c-Kit+ cells]. As expected, training attenuated apoptosis in hypertension -thereby preserving cardiomyocyte number [18]. Next, in a very elegant study, Boström et al. showed that swim training stimulated cardiomyocyte proliferation. Using an RT- PCR transcriptional screen technique, Boström et al. observed a downregulation in the transcription factor C/EBPβ and an increased expression of ED-rich carboxy-terminal domain 4 (CITED4) with training. Interestingly, by reducing C/EBPβ *in vitro* and *in vivo*, Boström et al. were able to recapitulate the effects of training on the heart, i.e. increased cardiomyocyte hypertrophy and proliferation [19], an effect also shown to be regulated by several microRNA's

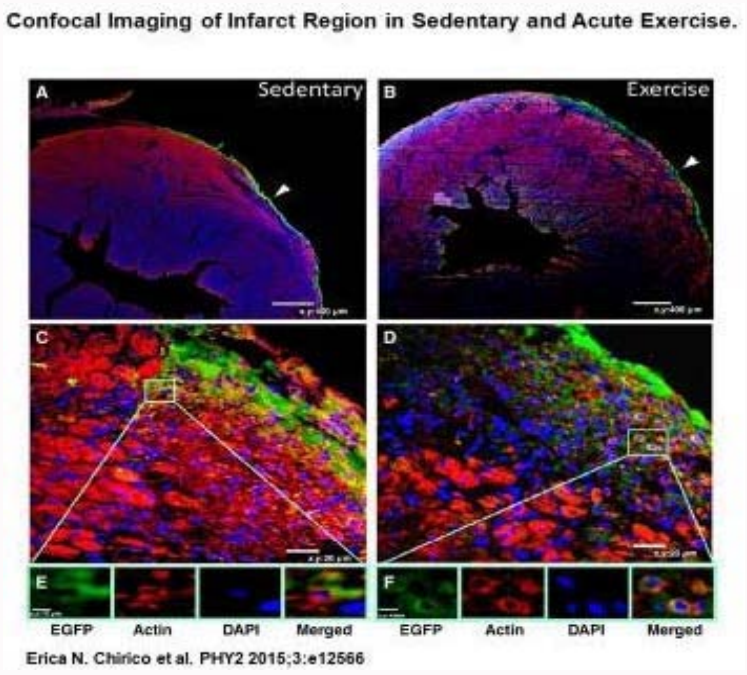

Figure 2: Confocal imaging of infarct region in sedentary and acute exercise. Representative samples of heart sections were immunostained and imaged with confocal microscopy. Injected BMC's are labeled with green [EGFP], nuclei are labeled with DAPI [blue], and sarcomeric actin [red]. Top row: Low magnification view of myocardial infarct [MI] area in sedentary [A] and exercised [B] mice. Middle row: Higher magnification of infarct area in corresponding mice. Bottom row: squared area at higher magnification showing individual and merged staining. Exercised hearts showed more actin-containing nucleated GFP+ cells compared to sedentary hearts. Reproduced from Chirico et al.

[22,23]. Waring and colleagues then followed up on these studies by exposing male, Wistar rats to two intensities of treadmill running; low (55-60% VO_{2peak}) or high intensity (85-90% VO_{2peak}) for 30 minutes, 4 days/week, for 4 weeks. They quantified cardiac stem cells with immonhistochemistry and newly formed cardiomyocytes with both BrdU and Ki67 staining [21]. They found an increased number and enhanced activation of c-Kit$^+$ cells in the trained heart, with increased expression of Nkx2.5 or Ets-1, indicative of progenitor commitment to either cardiomyocyte or capillary lineages. They also reported increased cardiomyocyte proliferation following training; with both low and high intensity training eliciting a significant effect relative to sedentary animals [approximately 1% and 2.5% for low and high intensity training respectively, measured by Ki67$^+$ cardiomyocyte nuclei: approximately 3.5% and 7.5% for low and high intensity training respectively, measured by BrdU$^+$ cardiomyocyte nuclei]. Several growth factors [IGF-1, transforming growth factor-β1, neuregulin-1, bone morphogenetic protein-10, periostin] were upregulated with training, and stimulated c-Kit$^+$ cardiac stem cell proliferation and commitment *in vitro* [21]. This study was then followed by Xiao et al., who used swim training to compare the regional number of c-Kit$^+$ and Sca-1$^+$ cardiac progenitors in the heart along with endogenous growth factor appearance [23]. They found swimming increased mRNA for hepatocyte growth factor and IGF-1 and upregulated c-kit$^+$ in both the left and right ventricles after 3 weeks of training. Sca-1$^+$ progenitor cells were also increased in the left ventricle and outflow tract after 3 weeks of training [23]. Most recently, Vugic et al, showed that 8 weeks of voluntary wheel running increased the generation of new cardiomyocytes by 4.6 fold. This effect was inhibited by inhibition of miR-222, which has been shown to increase with training [22].

Collectively, these studies (Table 1) suggest that both treadmill and swim training can stimulate cardiomyocyte entry into the cell cycle and regional growth factor signaling in the heart, an effect that appears to be dependent on exercise intensity. These studies also suggest that exercise activates c-Kit and Sca-1 progenitors in the heart, which may further differentiate towards cardiomyocyte or vascular lineages, and/or augment paracrine growth factor signaling toward neighboring cells. However, despite enhanced stem cell activation and cardiomyocyte cell cycle entry with aerobic exercise training, the heart has shown a limited ability to favorably remodel with exercise after myocardial infarction [1], calling into question the physiologic ramifications of these findings.

Aerobic Exercise Training and Stem Cell Therapy

Cell-based therapies for the treatment of heart disease, particularly myocardial infarction, hold great promise in regenerating myocardium and reducing the development of heart failure [2]. In both humans and animals, injection or infusion of different types of cardiac and noncardiac- derived progenitor cells have been shown to stimulate new cardiomyocyte formation and improve cardiac function [2]. However, while the effectiveness of cell therapy has been remarkable in animal models, its clinical translation has been less impressive [2]. More work is needed to define the optimal conditions for stem cell therapy; including progenitor type, optimal transplanted cell number, vectors of transplantation, and mechanisms of benefit. Given the inability to explain the putative actions of transplanted stem cells purely on their differentiation into new cardiomyocytes; paracrine signaling mechanisms through cytokines, chemokines, growth factors, and exosomes/micro-particles have gained considerable attention [2]. Paracrine secretions from exogenous stem cells activate endogenous cardiac stem cells,

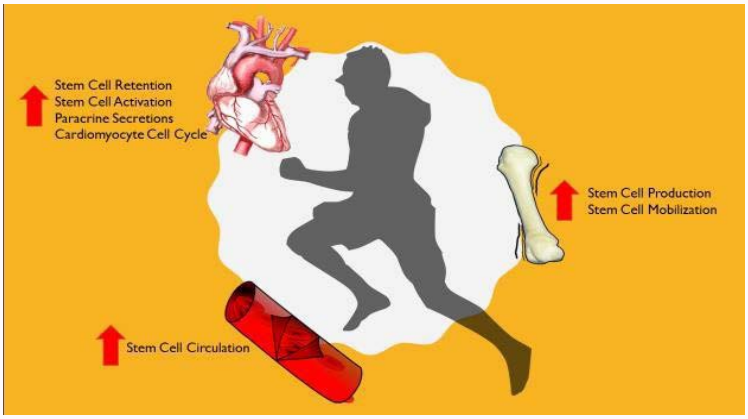

Figure 3: Influence of aerobic exercise on stem cells in the heart and circulation. Aerobic exercise has been shown to increase stem cell retention and activate c-Kit$^+$ and Sca-1$^+$ in the heart. Exercise promotes myocardial growth factor secretion and stimulates cardiomyocyte entry into cell cycle. In the periphery, aerobic exercise increases stem cell production, mobilization, and circulation, particularly in endothelial progenitors.

Table 1: Exercise, Endogenous Progenitors, & Cardiomyocyte Cell Cycle.

References	Models	Exercise Outcomes
Kolwicz SC et al, 2009	Rat; Treadmill, Moderate Intensity [12 weeks]	Increased Ki67$^+$ and c-Kit$^+$ in trained hearts
Boström P et al, 2010	Mouse; Swimming Ramp Protocol [14 days]	Increased cardiomyocyte proliferation; Downregulation of C/EBPβ and increased expression CITED4
Waring CD et al, 2014	Rat; Treadmill, Low & High Intensity [4 weeks]	Increased number and activation of c-Kit$^+$ cells; Increased Ki67$^+$ and BrdU$^+$ cardiomyocytes
Xiao J et al, 2014	Mouse; Swimming Ramp Protocol [3 weeks]	Increased growth factors and upregulated c-Kit$^+$ and Sca-1$^+$ in the heart
Vujic et al, 2018	Mouse; Wheel Running [8 weeks]	Increased cardiomyogenesis [4.6 fold]

Table 2: Exercise and Exogenous Stem Cell Therapy.

References	Models	Exercise Outcomes
Cosmo S et al, 2012	Rat, Swimming [30 days]	Increased LV ejection fraction and improved adverse ventricular remodeling following cell transplantation $^+$ training
Chirico EN et al, 2015	Mouse, Treadmill, Moderate Intensity, 1 Bout Acute Exercise & Chronic Training [5 weeks]	Increased BMC retention with acute exercise; Increased Ki67$^+$ in border zone with training
Lavorato VN et al, 2016	Rat, Treadmill, Moderate Intensity [12 weeks]	No observed summative effects with training and MSC cell therapy
Arisi MF et al, 2017	Rat serum in vitro, 1 Bout Acute Exercise	Exercise serum prompts an MSC inflammatory response, with no changes in paracrine-mediated survival toward cardiomyocytes

promote neovascularization, induce alterations in the extracellular matrix, and inhibit apoptosis and hypertrophy, leading to improved whole heart remodeling and function following myocardial infarction [24]. However, despite these promising effects, a consistent problem with cell-based therapy is the low rate of progenitor engraftment and survival in the heart, particularly within the harsh metabolic micro-environment following myocardial infarction [2]. Thus identifying interventions that positively impact the myocardial retention and survival of exogenous progenitors is of great importance. Given the effects of aerobic exercise on endogenous c-Kit activation and cardiomyocyte renewal, it is reasonable to hypothesize that exercise may serve as an efficacious therapeutic adjuvant for stem cell therapy [25-38]. Moreover, understanding how exercise alters stem cell therapy has clinical translation, as patients that receive cell therapy will likely be advised to assume a physically active lifestyle. In this regard, both acute and chronic aerobic exercise may be useful approaches in enhancing the efficacy of stem cell therapy.

Acute aerobic exercise

The metabolic, neurohumoral, paracrine and mechanical milieu of the heart in response to acute aerobic exercise may stimulate exogenous progenitors to be retained after cell therapy [30]. Acute exercise increases substrate flux and potentiates inflammation, oxidative, and catecholaminergic stress. These exercise-induced stressors have been shown to damage the heart in both humans [39] and animals [31], a response which may stimulate progenitor activation, recruitment, and retention [31]. Acute aerobic exercise also increases heart rate, stroke volume, blood pressure, cardiac output, and coronary flow via enhanced sympathetic drive, which may enhance the exposure of circulating progenitor cells to the heart.

Beyond stimulating exogenous cell retention of the heart, acute aerobic exercise potentiates mobilization and circulation of endogenous progenitors from the bone marrow pool [25,26,37,38]. Bone marrow serves as a host for a variety of stem cell populations including mesenchymal, hematopoietic, and endothelial progenitors. The bone marrow mobilizes these cells into the systemic circulation, and subsets of these cells home to tissues, including the heart, in response to injury. Recognizing that bone marrow retention of hematopoietic stem cells is critically regulated by stromal cell-derived factor 1α (SDF-1) and its receptor CXCR4, the up-regulation of the SDF-1/CXCR4 axis may likewise increase endogenous bone marrow cell (BMC) mobilization with exercise [39,40]. This hypothesis is supported by studies reporting increased serum SDF-1/CXCR4 with acute and chronic exercise in healthy volunteers, heart failure patients, and post- MI patients [25,26,37,38]. Thus, acute exercise invokes a

wide array of potential mediators, including alterations in cytokines and cell adhesion molecules, that may promote endogenous and exogenous progenitor cell homing and retention in the heart [40].

To test if acute exercise could potentiate exogenously-infused stem cell retention in the heart, Chirico et al. tracked GFP$^+$ BMC's intravenously-infused immediately after acute treadmill exercise or sedentary conditions in a mouse model of epicardial myocardial infarction [30]. Acute treadmill exercise increased myocardial BMC retention in the infarct zone of the heart, but not the border or distant MI zones (Figure 1). Some of the retained BMC's showed co-expression with alpha sarcomeric actin twenty-four hours after cell injections, suggesting differentiation toward cardiomyocytes (Figure 2). The transcription of cell adhesion molecules such as P-selectin, MMP-1a, MMP-2, MMP3, CXCR-4, and integrin-2 were not changed with exercise. Pharmacologic administration of dobutamine did not recapitulate the improved BMC retention with exercise, suggesting that factors other than increased flow mediated the effect [30].

A follow-up study by Arisi et al. tested if serum factors from exercised animals altered mesenchymal stem cell (MSC) homing and paracrine signaling toward cardiomyocytes *in vitro*. Serum drawn from exercised animals (1 bout of moderate treadmill running) did not affect the survival, proliferation, or chemotaxis of MSC's toward cardiomyocytes, despite markedly increasing their production of IL-6, TNF-α, IL-1β, and IFN-γ compared to MSC's cultured in sedentary serum [31]. Cardiomyocyte survival was increased nearly 500% when co-cultured with MSCs, but this effect was not altered under exercise plasma conditions. These data suggest the serum milieu of acute aerobic exercise prompts an MSC inflammatory response, but does not alter paracrine-mediated survival cues from MSC's toward cardiomyocytes. While data on the effects of acute aerobic exercise are sparse, the potential of acute exercise to improve exogenous stem cell retention appears to hold promise. Much greater study is required, including the identification of the optimal levels of acute exercise to provide benefit [31].

Chronic aerobic exercise training

Chronic exercise training is associated with an array of beneficial cardiac adaptations [9,10]. Hence given the many putative benefits of aerobic exercise training on the heart, it is important to consider whether it can improve the efficacy of cell therapy. The first study to broach this topic was performed by Cosmo et al. who looked at the impact of chronic exercise training combined with mononuclear cell transplantation therapy after myocardial infarction induced through ligation of the left anterior descending artery [29]. In this small study, it was reported that 30 days of swimming exercise plus cell therapy tended to increase LV ejection fraction and improve adverse ventricular remodeling compared to sedentary conditions. While these data were encouraging, the mechanisms of improvement with exercise were not elucidated in this report, as the authors did not measure markers of stem cell activation or cardiomyogenesis.

Chirico et al. tested if treadmill exercise training (10–13 m/min; 45min/day; 4 days/week; 5 weeks) altered the efficacy of stem cell therapy following myocardial infarction. Trained and sedentary mice were followed up with graded exercise tests, echocardiography, and histology after cell transplantation. Exercise capacity was enhanced following training, and training increased the number of Ki67$^+$ nuclei in the border zone, but not the infarcted zone of the heart. Animals treated with chronic exercise training showed increased exercise capacity and cardiac mass without any change in LV ejection fraction, infarct size, or regional wall thickness relative to sedentary controls. These studies suggest that that chronic training in conjunction with cell therapy can increase the proliferative activity of cells in the border zone of the infarcted heart, an effect which may prove beneficial in long term compensatory remodeling [30].

Lavorato et al. then tested how chronic exercise training impacted MSC therapy administered via the caudal vein infusions [concentration: 1×106 cells]. In this study male, Wistar rats were trained by treadmill running [5 days/week; 60 min/day; 60% of maximal running velocity] for 12 weeks. Cardiac structure and function were measured with echocardiography, and intracellular calcium transients [Ca^{2+}]i and contractility were both determined in isolated left ventricular cardiomyocytes. Lavorato et al. reported that adverse remodeling was improved with MSC therapy. MSC therapy also restored cardiomyocyte amplitude and time to half decay of the [Ca^{2+}]i transient. Independent from MSC therapy, treadmill training alone also improved markers of adverse remodeling and LV ejection fraction, while shifting cardiomyocyte [Ca^{2+}]i transients and increasing the expression of SERCA2a and PLB_{ser16}. Despite the success of MSC therapy and exercise training individually, there were no summative benefits when exercise was combined with MSC therapy [32].

Thus, these preclinical results (Table 2) using both acute and chronic exercise suggest exercise may be an efficacious adjunct to optimize stem cell therapy. Further work is required to test the long term impact of exercise training on stem cells and its subsequent functional consequences, particularly on cardiomyogenesis in large, transmural infarcts. Also more work is required to establish the most beneficial training paradigm to induce benefit [33].

Summary

As exercise is being used more and more as a clinical tool in cardiovascular medicine, understanding how it impacts progenitor cell biology is a critical next step. We are in the infant stages of such inquiry, and there are very sparse data on this important topic. As summarized in Figure 3, aerobic exercise has been shown to activate endogenous stem cells in the heart and increase cardiomyocyte entry into the cell cycle. Aerobic exercise also has been shown to enhance the production, migration, and circulation of stem cells-particularly endothelial progenitors. While these observations hold biological significance, their translation to exercising patients remains unknown. While the data are few, acute and chronic exercise, may likewise improve the efficacy of exogenous stem cell therapy via increased stem cell retention and enhanced border zone remodeling after myocardial infarction. Much more research is required to understand these potential putative mechanisms of exercise.

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