Mini Review

Physical Training and the Putative Benefits of Cell Homing in Cardiovascular Diseases

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Abstract

Physical training clearly brings about physiological benefits in so many ways. It modulates cellular and molecular functions, immune function, homeostasis and oxidative equilibrium. It is recognizably able to prevent diseases, and different modalities of physical training can be useful tools for some treatments. However, there is no cure for many cardiovascular diseases and conventional treatments have no ability to regenerate heart tissue damaged by ischemic injuries such as in acute myocardial infarction. Cell therapy involves local or systemic injection of stem cells that have the potential capacity to proliferate and differentiate and, therefore, replace the lost cells in damaged ischemic tissues. This approach has been singled out as a promising means aiming at the recovery of cardiac function. Apparently, the key mechanism for cell homing effectiveness is the activation of the axis involving stromal-derived factor 1 (SDF-1) and its specific G protein coupled receptor (CXCR4), which can be modulated by physical training and increasing the mobilization of cells with regenerative and angiogenic capacity. We discuss in this review the relevance of physical training for improving the potential of stem cells in tissue repair in cell therapy protocols.

ABBREVIATIONS

SDF-1: Stromal Cell-Derived Factor 1; MSC: Mesenchymal Stem Cell; NO: Nitric Oxide; EPC: Endothelial Progenitor Cells; CHF: Chronic Heart Failure; HIF-1: Hypoxia-Inducible Factor 1; TNF-A: Tumor Necrosis Factor Alpha

INTRODUCTION

Almost all tissues in the human body can be regenerated or repaired through direct action of stem cells. Stem cells have a high potential for multiplication and differentiation. However, the mechanisms that regulate or impair regenerative processes are not well understood yet, particularly the role of external factors such as physical activity. Researchers have sought to further investigate the mechanisms through which adult stem cells promote tissue renewal as well as how these processes are regulated in individuals suffering from injuries or diseases [1]. This process, which involves the recognition of signals emitted from injuries, as well as the activation, migration, proliferation and differentiation of stem cells is named cell homing [2].

Stem cells from different sources such as bone marrow, umbilical cord blood, adipose tissue, among others, have been investigated in clinical and preclinical protocols worldwide. Mesenchymal stem cells (MSC), which derive from the mesoderm and are distributed in adult tissues such as adipose tissue, heart atria, blood vessels, bones and cartilages, among others, have high tissue regenerative capacity [3]. Because of its great therapeutic potential, the use of stem cells in studies and protocols is justified and is commonly called cell therapy. However, most protocols aiming at the recovery of damaged tissue and restoration of cardiac function in cardiac patients achieve only modest results [4]. In the light of that, more studies on the effects of external factors that may stimulate the homing and repair capacity of stem cells are needed. This current scenario calls for improving our understanding of stem cell biology, morphology, and repair mechanisms involving release and uptake of pro-regenerative and modulator factors, especially in the presence of external factors such as physical activity [5]. We discuss in this review aspects related to the efficacy of cell therapy focusing on stem cell ability of homing, and the effects of physical training on these mechanisms.

Essential processes involved in cell therapy effectiveness – stem cell homing

Following an ischemic insult leading to cell loss, adult stem cells from bone marrow or other sources are mobilized in
response to the release of reactive oxygen species, cytokines, mitogenic factors and other signaling molecules. For this reason, the clinical management of stem cells has been proposed therapeutically in patients that require tissue regeneration, as in the case of cardiovascular diseases where there is cellular damage after ischemic events. In this context, several clinical studies have been conducted through the use of adult stem cells, including those derived from the bone marrow, adipose tissue, the isolated from cardiac tissue (cardiac residents) and those with induced pluripotency (iPSCs) [6,7]. However, the protocols are not fully effective in terms of tissue regeneration and return of heart function. Thus, it becomes important to understand the cell homing mechanism and interventions (physical activity, diets, pharmacological treatments, etc.) for proper assistance to these protocols [5].

Cell homing can occur locally originating from resident tissue progenitor cells or through the activation via bloodstream [8]. Stem cell trafficking in the adult human body, which occurs since their embryonic formation, is regulated by the triggering signal of a chemokine released at the injury site, the stromal-derived factor 1 (SDF-1 or CXCL-12) and its specific G protein coupled receptor (CXCR4) [9]. Once the ligand binds to the receptor, intracellular signal transduction leads to chemotaxis and the activated cells move in response to the gradient of chemokines and is further stimulated by paracrine signals activating other processes such as proliferation and differentiation [10]. Accordingly, cell homing is key to cell therapy effectiveness. Once cells are delivered into the body, they must be directed to the injured tissue in order to promote tissue repair. Although cardiac patients also receive other interventions such as special diets and pharmacological treatment, the question is whether physiological adaptations in response to physical training can stimulate cell homing.

Physical training for modulating cell homing

Exercise training is known to be able to chronically modulate tissue metabolism and physiological state. In cardiac tissue, there is evidence in rats showing that exercise training reduces heart dilation and scar development after myocardial infarction [11], mainly due to increased blood perfusion to the heart tissue. Additionally, physical training increases the number and caliber of arterial vessels in both skeletal and heart muscles, particularly in injured heart tissue [12]. Pro-angiogenic adaptations occur through the activation of factors (cytokines, vascular growth factors, and NO) that stimulate mobilization and migration of circulating endothelial progenitor cells (EPC), and induce tissue neovascularization. A study with chronic heart failure (CHF) patients has demonstrated higher mobilization of EPC, higher serum levels of angiotensin-2, and improvement in brachial artery dilation after 3 months of aerobic physical training [13]. In addition, 3 weeks of aerobic training increased the levels of CD34+/CD45+ and CD133+/CD45+, as well as the migratory capacity of EPC in patients at 14 days after acute myocardial infarction [14].

Besides the mobilization of cells with regenerative and angiogenic capacity, physical training influences extracellular environment and cell signaling for appropriate tissue regeneration. After 8 weeks of aerobic training in patients with CHF, Sarto et al. (2007) demonstrated an increase in SDF-1 expression, which in addition to its angiogenic capacity; act as a chemo attractant mediator for progenitor cells in these patients [15]. Besides, it has been demonstrated that physical training can induce the expression of essential proteins for cell homing at the niche. In elderly patients, 12 weeks of physical training on a treadmill increased the expression of the CXCR4 receptor in EPC, which was associated with enhanced reendothelization capacity of these cells [16]. Furthermore, 6 weeks of aerobic training increased the expression of hypoxia-inducible factor 1 (HIF-1), a positive regulator of SDF-1 expression in heart tissue of male Wistar-Kyoto rats [17]. Physical training also creates a less inhospitable environment for mobilized cells through modulation of inflammatory and pro-oxidant state. When Wistar-Kyoto rats with experimental acute myocardial infarction were submitted to 8 weeks of aerobic training, they showed reduced plasmatic levels of interleukin-6, tumor necrosis factor alpha (TNF-α) and higher levels of anti-inflammatory interleukine-10 [11]. Furthermore, 6 weeks of swimming decreased superoxide radical levels and lipid oxidative damage and increased the expression of antioxidant enzyme catalase and the activity of glutathione peroxidase in the left ventricle of male Wistar-Kyoto rats [18]. It demonstrates that, in addition to mobilization of progenitor cells, exercise training also creates a more favorable environment for tissue repair.

CONCLUSIONS

The present data suggest physical training may modulate the metabolic state of damaged tissue, turning it into a more appropriate environment for cell therapy and favoring stem cell homing. Nevertheless, studies have pointed out that regular physical exercise may act as an adjuvant therapeutic modality able to potentiate the effects of other treatments for heart diseases.

REFERENCES


