Ageing Research Reviews 12 (2013) 1–7

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Statins and stem cell modulation

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ARTICLE INFO

Article history:
Received 12 April 2011
Received in revised form 21 March 2012
Accepted 30 March 2012
Available online 6 April 2012

Keywords:
Statins
Stem cells
Tissue regeneration

ABSTRACT

Stem cell-based therapy is a promising option for the treatment of ischemic heart diseases. As to a successful stem cell-based therapy, one of the most important issues is that the stable engraftment and survival of implanted stem cells in cardiac microenvironment. There are evidences suggest that pharmacological treatment devoted to regulate stem cell function might represent a potential new therapeutic strategy and are drawing nearer to becoming a part of treatment in clinical settings. Statins could exert cholesterol-independent or pleiotropic effects to cardiovascular system. Recent studies have shown that statins could modulate the biological characteristics and function of various stem cells, thus could be an effective method to facilitate stem cell therapy. This review will focus on statins and their modulation effects on various stem cells.

1. Introduction

Stem cell-based therapy is a promising option for the treatment of ischemic heart diseases. Infusion or injection of different types of stem or progenitor cells have been shown to improve heart function after acute myocardial infarction (AMI) in various experimental models and in clinical trials (Orlic et al., 2001; Schachinger et al., 2004; Strauer et al., 2002). One potential limitation for the use of autologous stem cells, however, is the decline in the number and function of stem cells, particularly in patients with coronary artery disease (CAD), diabetes and heart failure (Heeschen et al., 2004; Tepper et al., 2002; Vasa et al., 2001b). Moreover, most of the engrafted cells cannot survive in the local milieu of infarcted myocardium that releases cytotoxic factors (Muller-Ehmsen et al., 2002; Zhang et al., 2001), thus limiting the efficacy of stem cell transplantation. Therefore, as to a successful stem cell-based therapy, one of the most important issues is that the stable engraftment and survival of implanted stem cells in the post-infarct microenvironment.

Up to date, there have been three major points which are focusing on the transplantation effects of stem cells: (i) to modulate their self-renewal and differentiation potential and obtain sufficient numbers of stem cells for transplantation; (ii) to enhance their mobilization and homing properties towards injured tissues; (iii) to protect implanted stem cells against the adverse microenvironment in the post-infarct myocardium.

Statins, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are a class of drugs that inhibit the rate-limiting step in cholesterol biosynthetic pathway. By inhibiting cholesterol biosynthesis, statins emerge as a principal agent in lowering the incidence of cardiovascular disease (Shiota et al., 2008). However, statins also exert cholesterol-independent or pleiotropic effects, including improving endothelial function, increasing bioavailability of nitric oxide (NO), immunomodulatory and antiinflammatory properties, stabilization of atherosclerotic plaques, antioxidant activity, as well as anti-cancer and stem cell-regulating capacities (Blum and Shamburek, 2009; Palaniswamy et al., 2010; Walter et al., 2001; Wassmann et al., 2002). These properties, together with a high safety profile, have made statins widely prescribed in clinical practice.

In this review, we have summarized the effects of statins on stem cell modulation related to the above three major points (Table 1). Furthermore, we have raised several potential questions that should be resolved in the future before stem cell transplantation could be considered a routine therapeutic approach in the clinic.

2. Statins and self-renewal and differentiation of stem cells

Stem cells are undifferentiated cells with special ability to self-renew, differentiate into multiple cell lineages and reconstitute a given tissue (Wagers and Weissman, 2004). The self-renewal/differentiation decisions of stem cells must be carefully controlled during organogenesis, tissue homeostasis, and tissue regeneration. Functional disorder of self-renewal of stem cells can lead to progressive tissue degeneration, while excessive self-renewal can induce tumorigenesis (Liu et al., 2010). Besides,

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http://dx.doi.org/10.1016/j.arr.2012.03.006

Table 1
The effect of statins on different types of stem cells.

Type of stem cells	Type of statins	Modulation effects	Underlying mechanisms
EPCs	Atorvastatin/Mevastatin	Inhibit senescence/promote proliferation	GGPP/FPP, ROS, TRF-2
	Atorvastatin	Augment differentiation of MNCs and HSCs to EPCs	PI3K/Akt
		Promote neovascularization from EPCs	VEGF
	Pravastatin	Promote differentiation of EPCs to cardiocytes	eNOS/NO, PI3K/Akt
	Simvastatin	Promote mobilization and recruitment into the vascular lesions	eNOS, PI3K/Akt, VEGF
	Simvastatin/Rosuvastatin	Enhance mobilization in stable CAD and post-infarction patients (dosage-dependent)	
MSCs	Simvastatin	Increase differentiation into ECs	Notch
		Induce osteoblastic differentiation and bone formation, inhibit adipocyte differentiation	BMP-2, ER-alpha
	Simvastatin/Atorvastatin	Promote mobilization into peripheral circulation	eNOS, Akt
		Improve survival and differentiation in the post-infarct myocardium	
	Rosuvastatin		JAK2/STAT3
	Fluvastatin/lovastatin	Induce neuroglial-like differentiation	GGPP
	Lovastatin	Reduce Hypoxia/SD induced apoptosis	PI3K/Akt, ERK1/2
	Atorvastatin		AMPK/eNOS
BMSCs	Simvastatin	Mobilize into peripheral circulation	eNOS, Akt
$CD133^+$/c-Kit^+ cells	Pravastatin	Mobilize into peripheral circulation	
mESCs	Simvastatin	Reduce expression of specific ESCs markers	GGPP/RhoA/ROCK
		Induced morphological changes	
		Downregulate proliferation and self-renewal	
hESCs	Simvastatin/lovastatin/mevastatin	Inhibit proliferation and self-renewal capacity	FPP, GGPP
CSCs	Simvastatin/mevastatin/lovastatin	Inhibit proliferation and self-renewal capacity	FPP, GGPP
CPCs/cardiac myoblast	Simvastatin	Attenuate cytokine-stimulated iNOS expression and NO synthesis, and improve survival	L-mevalonate/GGPP, Rho, IkappaB/NF-kappaB

EPCs, endothelial progenitor cells. MNCs, mononuclear cells. HSCs, hematopoietic stem cells. MSCs, mesenchymal stem cells. BMSCs, bone marrow-derived stem cells. mESCs, mouse embryonic stem cells. hESCs, human embryonic stem cells. CSCs, cancer stem cells. CPCs, cardiac progenitor cells.

ex vivo expansion of stem cells is extensively utilized for in vitro study and stem cell-based therapy. However, cultivation of primary stem cells lead to premature replicative senescence, thereby limiting the proliferative capacity of stem cells (Assmus et al., 2003). Both experimental and clinical studies have revealed that statins could increase the numbers and enhance the lineage-differentiation ability of stem cells. Moreover, the effects of statins could be various as concerned to different kind of stem cells (Assmus et al., 2003; Li et al., 2008; Suzuki et al., 2009; Xu et al., 2009).

2.1. Endothelial progenitor cells

Bone marrow derived-circulating endothelial progenitor cells (EPCs) contribute to reendothelialization of injured vessels as well as ischemia-induced neo-vascularization (Umemura and Higashi, 2008). Therefore, circulating EPCs represent important endogenous repair mechanism by which the body maintains the integrity of the endothelium (Kong et al., 2004; Werner et al., 2003). Several clinical studies have shown that the number and function of EPCs are impaired in several pathological conditions. In patients with CAD and metabolic syndrome, the number of circulation EPCs is significantly reduced (Jialal et al., 2010; Vasa et al., 2001b). Moreover, several risk factors associated with cardiovascular diseases, such as diabetes, smoking and age, inversely correlate with the number of circulating EPCs (Jung et al., 2010; Umemura and Higashi, 2008; Yue et al., 2010). These findings suggested that it could be very important to increase the number of EPCs and to augment their biological activity. Statins have been demonstrated to inhibit EPCs senescence and promote their proliferation, thus seem to be an effective therapeutic method for reversing the pathophysiological process of EPCs loss (Assmus et al., 2003; Spyridopoulos et al., 2004).

Assmus et al. elucidated that statins inhibit senescence and promoted proliferation and colony formation of EPCs in vitro dose-dependently, thus increased the number of circulating EPCs (Assmus et al., 2003). The inhibition effects of statins were mediated by modulation of various cell cycle proteins, including upregulation of cyclins and downregulation of the cell cycle inhibitor p27Kip1. The process was dependent on the isoprenoid intermediates of mevalonate, geranylgeranylpyrophosphate (GGPP) or farnesylpyrophosphate (FPP) pathway, but independent of NO synthase, reactive oxygen species (ROS) and Rho kinase. Therefore, it seems that a reset of the mitotic clock of EPCs occur after statin treatment (Assmus et al., 2003). In another study, treatment of statins prevented the functional impairment of EPCs during culture as well as the loss of an essential telomere capping protein: telomere repeat-binding factor 2 (TRF2, which could prevent from apoptosis or senescence and capable of protecting against fusion of the chromosome ends), thus elucidating a beneficial effect of statins on telomere biology of EPCs (Spyridopoulos et al., 2004). Besides, statins also reduced age-induced ROS formation and subsequently delayed stem cells senescence (Haendeler et al., 2004).

Dimmeler et al. demonstrated that statins potently augment EPCs differentiation from peripheral human mononuclear cells (MNCs) and CD34-positive haematopoietic stem cells (HSCs) in vitro. Treatment of statins also increased the number of HSCs in mice bone marrow and further elevated differentiated EPCs. Furthermore, the statins mediated-induction of HSCs differentiation was inhibited by pharmacological PI3K blockers or by overexpression of a dominant negative Akt, thus indicating a PI3-kinase/Akt (PI3K/Akt) pathway conducted effect (Dimmeler et al., 2001). It is reported that circulating vascular progenitor cells can be divided into EPCs and smooth muscle progenitor cells (SMPCs) (Kusuyama et al., 2006). EPCs participate in angiogenesis and reendothelialization after vascular injury, while SMPCs have important roles