Journal of Molecular and Cellular Cardiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

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

Original article

The role of heat shock protein 90 in migration and proliferation of vascular smooth muscle cells in the development of atherosclerosis

Jeonghan Kim [a], Sung-Wuk Jang [b], Eunsoo Park [a], Minseok Oh [a], Sodam Park [a], Jesang Ko [a,*]

[a] Division of Life Sciences, Korea University, Seoul 136-701, South Korea
[b] Department of Medicine, Graduate School, University of Ulsan, Seoul 138-736, South Korea

ARTICLE INFO

Article history:
Received 13 September 2013
Received in revised form 7 March 2014
Accepted 10 March 2014
Available online xxxx

Keywords:
Atherosclerosis
Smooth muscle cell
Heat shock protein 90
Restenosis

ABSTRACT

The molecular chaperone heat shock protein 90 (HSP90) is overexpressed in plaques of atherosclerosis patients, and is associated with plaque instability. However, the role of HSP90 in atherosclerosis remains unclear. The present study investigated the effects of HSP90 inhibition on migration and proliferation of vascular smooth muscle cells (VSMCs) and involvement in atherosclerosis. To examine the role of HSP90 in VSMC migration, VSMCs were treated with the specific HSP90 inhibitors, 17-N-allylamino-17-demethoxygeldanamycin (17-AAG) and STA-9090. Results of a chemotaxis assay showed that the HSP90 inhibitors suppress migration of VSMCs. HSP90 inhibition also prevented invasion and sprout formation of VSMCs *via* inhibition of matrix metalloproteinase-2 proteolytic activity. Results of a flow cytometric analysis showed that HSP90 inhibition induces cell cycle arrest *via* regulation of cyclin D3, PCNA and pRb. To investigate the role of HSP90 in the development of atherosclerosis, low-density lipoprotein receptor (LDLR) deficient mice were fed with a high cholesterol diet for 4 weeks and treated with 17-AAG for 8 weeks. HSP90 inhibition suppressed migration of VSMCs into atherosclerotic plaque lesions in high cholesterol diet-stimulated $LDLR^{-/-}$ mice. Inhibition of HSP90 attenuates formation of atherosclerotic plaques *via* suppression of VSMC migration and proliferation, indicating that HSP90 inhibitors can be used as therapeutic agents for atherosclerosis and in stent restenosis.

1. Introduction

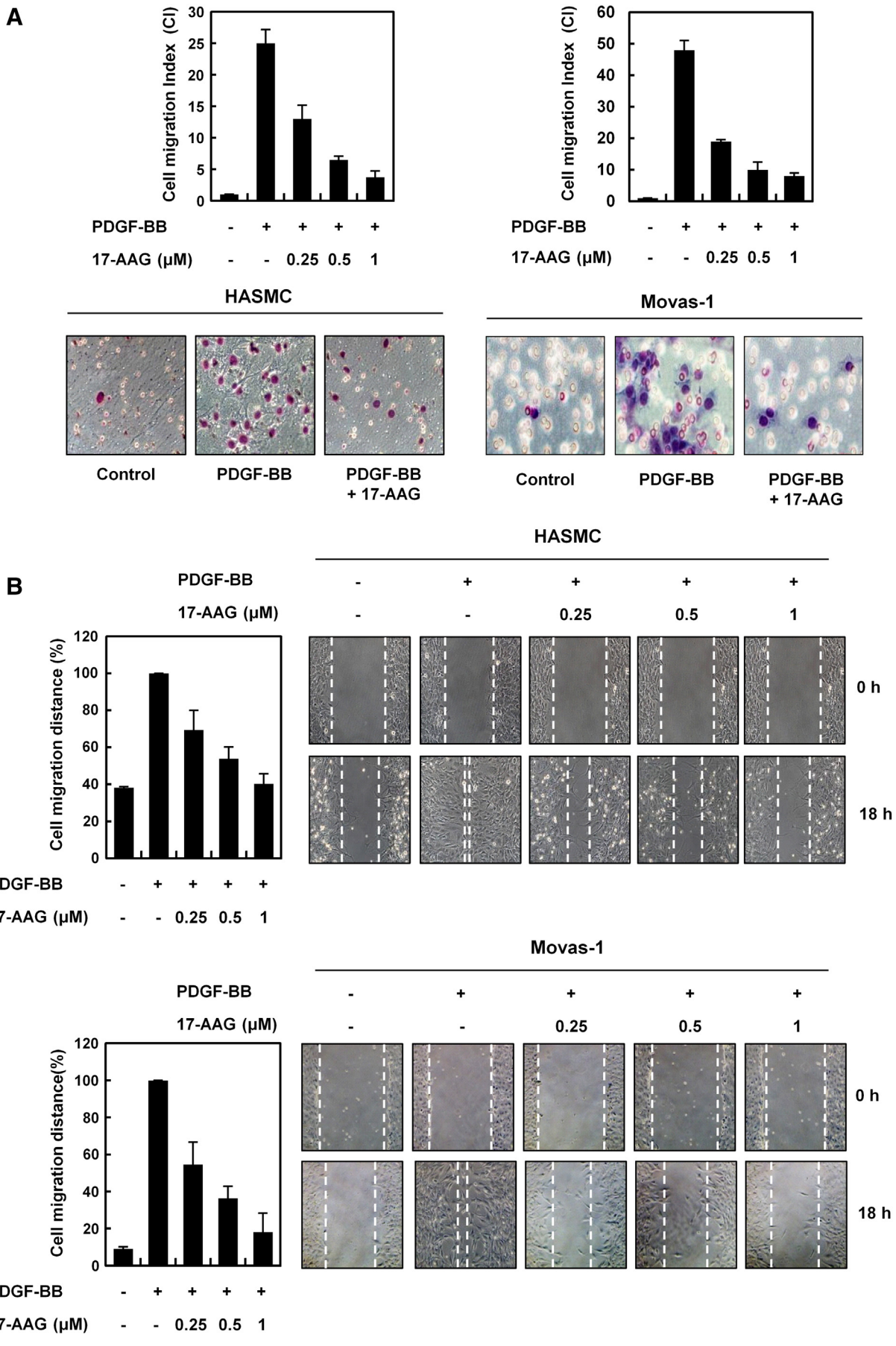
Atherosclerosis is a chronic progressive disease in which arteries thicken as a result of accumulation of cholesterol, lipids, vascular smooth muscle cells (VSMCs), and immune cells [1,2]. VSMC migration is an important process that occurs during progression of atherosclerosis and tissue repair in response to vascular injury [3,4]. VSMCs are mostly found in the media layer of normal arteries; however, VSMCs migrate from the media towards the intima during the development of atherosclerosis or vascular damage [3,4]. Many factors, including matrix metalloproteinases (MMPs), growth factors, cytokines, and chemokines, affect migration of VSMCs in the microenvironment of atherosclerotic lesions [5,6].

MMPs are a family of zinc-dependent endopeptidases that are produced by various types of cells, including foam cells, endothelial cells, and VSMCs in atherosclerotic lesions [5]. MMPs play a major role in degradation of extracellular matrix (ECM) components, as well as release and activation of ECM-bound latent factors, such as cytokines and growth factors, which result in significant changes in atherosclerotic lesions [5]. MMP-2 and -9 typically contribute to degradation and turnover of ECM, thus allowing migration of VSMCs [7]. Expressions of MMP-2 and -9 are up-regulated during VSMC migration in pathological conditions, such as development of restenosis and atherosclerosis [8]. MMP-2 and ApoE double-knockout mice exhibit reduced VSMC migration and attenuated intimal thickening in atherosclerosis [7]. MMP activity is tightly regulated by transcription, post-translational activation, and tissue inhibitors of metalloproteinases (TIMPs) [6,9]. Inflammatory cytokines, growth factors, and chaperones, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-β), IL-6, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), heat shock protein 60 (HSP60), and HSP90, regulate transcriptional expression and post-translational activation of MMPs, while glucocorticoids and TIMP exert inhibitory effects [5,6,9,10].

HSPs are highly conserved molecular chaperones that assemble various types of client proteins and regulate protein folding, signal transduction, translocation and transcription [11,12]. Many types of HSPs, including HSP27, HSP60, HSP72, and HSP90, are associated with atherosclerosis [12–15]. A recent study revealed that HSP90 is highly expressed in human atherosclerotic plaques with increased VSMCs and collagens, suggesting that HSP90 contributes to instability of advanced human atherosclerotic plaques by regulating VSMC migration and collagen contents [14,16]. Geldanamycin, a natural product

* Corresponding author at: Division of Life Sciences, Korea University, 5-1 Anam-dong, Seongbuk-gu, Seoul 136-701, South Korea. Tel.: +82 2 3290 3445; fax: +82 2 927 9028.
E-mail address: jesangko@korea.ac.kr (J. Ko).

http://dx.doi.org/10.1016/j.yjmcc.2014.03.008
0022-2828/



Please cite this article as: Kim J, et al, The role of heat shock protein 90 in migration and proliferation of vascular smooth muscle cells in the development of atherosclerosis, J Mol Cell Cardiol (2014), http://dx.doi.org/10.1016/j.yjmcc.2014.03.008