Rosuvastatin elicits KDR-dependent vasculogenic response of human placental stem cells through PI3K/AKT pathway.


Abstract

The growth and plasticity of engrafted human mesenchymal stem cells is regulated by external stimuli. Rosuvastatin (RSV) promotes myocardial neovascularization and limits myocardial remodeling in patients with chronic heart failure (CHF). While these non-lipid benefits may in part depend on the activation of stem cells, experimental evidence that RSV directly elicits vasculogenic differentiation of human mesenchymal stem cells is still lacking. We assessed whether RSV may drive a gene program of vascular commitment and the secretion of trophic mediators with antiapoptotic, angiogenic and antifibrotic activities in human mesenchymal stem cells from full-term placentas (FMhMSCs). With real-time RT-PCR, immunofluorescence, chemiluminescence, Western blot analysis, and in vitro vasculogenesis assays, we show that RSV enhanced expression of vascular endothelial growth factor (VEGF), kinase insert domain receptor (KDR), encoding a major VEGF receptor, hepatocyte growth factor (HGF), and platelet-derived growth factor-BB (PDGF-BB) in a time- and dose-dependent manner. GATA-4 and Nkx-2.5 transcription was not affected. RSV enhanced capillary-like formation in vitro, but capillary-embedded FMhMSCs lacked endothelial marker expression, suggesting a role of pericyte-like elements in tube formation. In HUVEC/FMhMSC cocultures, RSV increases PDGFRβ expression in FMhMSCs, and enhanced capillary density and organizational efficiency, promoting a long-lasting survival of tubular networks. RSV also activated PI3K-Akt pathway; the vasculogenic effects of the statin were abrogated following PI3K inhibition by LY294002. In conclusion, RSV-induced increase in capillary formation was dependent on VEGF and KDR. RSV promotes the activation of paracrine signals for vascular commitment of FMhMSCs through PI3K-Akt pathway. This observation may pave the way to the use of RSV as a pharmacological enhancer of stem cell potential for cardiovascular cell therapy.