Pleiotropic effect of statins in diabetic vascular dysfunction

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Abstract

Background: Endothelial dysfunction is a critical and initiating factor in the pathogenesis of diabetic vascular complication. KLF2 has been reported to play an important role in endothelial function. Here, we evaluated the hypothesis of KLF2 suppression by FOXO1 and investigated the protecting effect of statins in type 2 diabetes animal model.

Methods and results: FOXO1 was activated in high glucose condition, and transcriptionally regulated KLF2 expression, which resulted in decreased eNOS expression in endothelial cells. Atorvastatin inhibited FOXO1 by inducing ubiquitination as well as phosphorylation, thus restoring KLF2 expression. In OLETF rats, animal model of obese type II diabetes, FOXO1 was found activated, whereas KLF2 and its downstream molecule, eNOS were found suppressed, which was significantly reversed by atorvastatin treatment. Atorvastatin treatment as well as KLF2 replenishment by adenoviral significantly recovered endothelium-dependent vasodilation in the OLETF rats.

Conclusion) We found FOXO1 activated in endothelial cells suppressed KLF2, which might be a plausible mechanism of diabetic endothelial dysfunction. High glucose induced, FOXO1-mediated KLF2 suppression was reversed by atorvastatin. The findings of this study suggest implication of intensive statin treatment in preventing diabetic vascular dysfunction.