50

Endothelium-selective activation of AMP-activated protein kinase alleviates diabetes-induced endothelial dysfunction by enhancing reendothelialisation and endothelial progenitor cell mobilisation in mice

FYL Li, YQ Wang, KSL Lam, A Xu
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Vascular dysfunction is commonly observed in diabetic patients. Endothelial injury can be repaired in part by endothelial progenitor cells (EPCs). In diabetes, impaired functionality and reduced number of EPCs are reported. AMP-activated kinase (AMPK) is a well-known target of several anti-diabetic and cardiovascular drugs. The objective of this study was to examine whether the activation of AMPK in endothelium alone is sufficient to prevent diabetes-induced impairment in vascular function, possibly by improving EPC function and endothelial repair using a tissue-specific transgenic mouse model.

Methods: Transgenic mice with endothelium-selective expression of a constitutively-active AMPK (AMPK-Tg) were generated using the T-cadherin gene promoter. Type 1 diabetes was induced by i.p. injection with streptozotocin. Wire-mediated injury was introduced to the right common carotid artery of both WT and AMPK-Tg mice. Vascular relaxation to the α2-adrenergic receptor agonist UK14304 was assessed using a wire myograph. Vascular repair, or reendothelialisation, was examined using Evans blue staining. Circulating EPC numbers were quantified by flow cytometry analysis. Bone marrow-derived EPCs (BM-EPCs) were subjected to high glucose (25 mM) stimulation and expression of the antioxidant protein heme oxygenase (HO)-1 and mobilisation regulator stromal cell derived factor (SDF)-1, together with generation of reactive oxygen species (ROS), were studied.

Results: (1) Dose-dependent relaxation to UK14304 in injured carotid arteries was augmented in AMPK-Tg mice compared to WT mice in both healthy (pEC50 = 5.3 ± 0.1 vs 4.4 ± 0.6) and diabetic (pEC50 = 5.9 ± 0.1 vs 3.9 ± 0.1) conditions. (2) Reendothelialisation of carotid injury was improved in diabetic AMPK-Tg vs diabetic WT mice (147.2 ± 7.9% vs 95.6 ± 3.5%). (3) concomitant with elevated levels of circulating EPCs (AMPK-Tg vs WT mice = 0.15 ± 0.02% vs 0.06 ± 0.02%), indicating enhanced EPC mobilisation. (4) Mechanistic studies revealed an elevated level of SDF-1 in cultured BM-EPCs from AMPK-Tg compared to WT mice, in addition to a higher level of expression of HO-1 (the upstream regulator of SDF-1). (5) Further studies demonstrated a diminished production of ROS in AMPK-Tg BM-EPCs, showing a relationship between suppressed oxidative stress and the increased antioxidant protein expression, and higher SDF-1 levels in AMPK-Tg mice.

Conclusion: The improvement in vascular reactivity in diabetic AMPK-Tg mice could be attributed to the accelerated vascular repair and improved EPC mobilisation upon endothelial activation of AMPK. Concurrently, a lower level of oxidative stress and increased expression of HO-1 and SDF-1 may provide mechanistic explanation for the improvement in EPC function. Activation of AMPK may represent an attractive therapeutic strategy for cardiovascular disease in diabetes.

Acknowledgement: This study is supported by RGC GRF (HKU 779608M).