Endoplasmic Reticulum Stress-Mediated Apoptosis Contributes to Vascular Calcification via Activating Transcription Factor 4

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Vascular calcification (VC) is a common complication of cardiovascular diseases and contributes to their morbidity and mortality. Our previous work reported that ERS-mediated apoptosis is activated during VC. However, whether ERS-mediated apoptosis affects VC and the mechanism remains unclear. To test whether ERS-mediated apoptosis affects VC and the potential mechanism, in vivo vessel calcification was induced in rat by administrating vitamin D₃ plus nicotine (VDN) and vascular smooth muscle cells (VSMCs) calcification was induced by β-glycerophosphate and CaCl₂. It was showed that ERS markers such as 78-kDa glucose-regulated protein (GRP78), GRP94, cleaved caspase-12 protein levels and the number of TUNEL positive VSMCs, caspase-3 activity in calcifying aorta were decreased when treated with ERS chaperones Taurine (TAU) or phenylbutyric acid (PBA). Calcium content, ALP activity, calcium deposition and VSMCs phenotype transition into osteoblast-like cells in aorta were attenuated by TAU or PBA. ERS chaperones attenuated VSMCs calcification and apoptosis in vitro as well. Most importantly, ATF4 protein levels were increased in human calcified aorta and rat VSMCs. ERS induced VSMCs apoptosis and calcification was reduced when ATF4 was knockdown by siRNA before induced calcification. In addition, ATF4 deficiency restored VSMCs contractile phenotype in calcified VSMCs which suggested that ATF4, at least in part, involved in the process of ERS mediated apoptosis contributing to VC. Our data strongly suggest that ERS is a novel mechanism of VC. ATF4, at least in part, involved in the process of ERS mediated apoptosis and contributed to VC.

Key Words: Endoplasmic reticulum stress ■ apoptosis ■ vascular calcification ■ activating transcription factor 4