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APE1/Ref-1 Inhibits Vascular Calcification And Loss Of The Smooth Muscle Phenotype In Vascular Smooth Muscle Cells

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Objectives: Vascular calcification plays a role in the pathogenesis of therosclerosis, diabetes, and chronic kidney disease; however, the role of apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) in inorganic phosphate (Pi)-induced vascular smooth muscle cell (VSMC) calcification remains unknown. In this study, we investigated the possible role of APE1/Ref-1 in Pi-induced VSMC calcification.

Methods: To determine the possible role of APE1/Ref-1 in Pi-induced VSMC calcification. We observed that Pi decreased endogenous APE1/Ref-1 expression and promoter activity in VSMCs, and that adenoviral overexpression of APE1/Ref-1 inhibited Pi-induced calcification in VSMCs and in an ex vivo organ culture of a rat aorta.

Results: We investigated a redox mutant of APE1/Ref-1(C65A/C93A) did not reduce Pi-induced calcification in VSMCs, suggesting APE1/Ref-1-mediated redox function against vascular calcification. Additionally, APE1/Ref-1 overexpression inhibited Pi-induced intracellular and mitochondrial reactive oxygen species production, and APE1/Ref-1 overexpression resulted in decreased Pi-induced lactate dehydrogenase activity, pro-apoptotic Bax levels, and increased anti-apoptotic Bcl-2 protein levels. Furthermore, APE1/Ref-1 inhibited Pi-induced osteoblastic differentiation associated with alkaline phosphatase activity and inhibited Pi-exposure-induced loss of the smooth muscle phenotype.

Conclusions: Our study demonstrated a novel role for APE1/Ref-1 in Pi-induced vascular calcification and phenotype changes in VSMCs. APE1/Ref-1 inhibited Pi-induced vascular calcification, and the redox function of APE1/Ref-1 played an inhibitory role against Pi-induced vascular calcification by inhibiting osteoblastic differentiation and reducing oxidative stress. Uncovering the pathogenesis associated with vascular calcification will be helpful in the design of new target molecules or treatments targeting vascular calcification in chronic kidney diseases.