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Proprotein Convertase Subtilisin/Kexin Type 9 Enhances Arterial Medial Calcification in a Uremic Rat Model of Chronic Kidney Disease

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Abstract : A complex interplay among chronic kidney disease, lipid metabolism and aortic calcification has been recognized starting from results of many clinical and experimental studies. Here we investigated the influence of kidney function on PCSK9 levels, both in uremic rats and in clinical observation study, and its potential direct action on cultured smooth muscle cells (SMCs) calcification. In a cohort of 594 subjects enrolled in a single centre, observational, cross-sectional and longitudinal study, a negative association between GFR and plasma PCSK9 was found. Atherosclerotic cardiovascular disease (ASCVD), as co-morbidity, further increased PCSK9 plasma levels. Diet-induced uremic condition in rats, induced aortic calcification and increased total cholesterol and PCSK9 levels in plasma, livers and kidneys. Immunohistochemical analysis confirmed PCSK9 expression in aortic SMCs. SMCs overexpressing PCSK9 (SMCsPCSK9), cultured for 7-days in a pro-calcification environment (2.0mM or 2.4mM inorganic phosphate, Pi) showed a significantly higher extracellular calcium (Ca2+) deposition compared to mocked SMCs. Under the same experimental conditions, the addition of exogenous recombinant PCSK9 did not increase the extracellular calcification of SMCs. By flow cytometry analysis we showed that SMCsPCSK9, in response to 2.4mM Pi, released higher number of extracellular vesicles (EVs) positive for three tetraspanin molecules, such as CD63, CD9, and CD81. EVs derived from SMCsPCSK9 tended to be more enriched in calcium and alkaline phosphatase (ALPL), compared to EVs from mocks SMCs. In conclusion, our study reveals a direct role of PCSK9 on vascular calcification induced by higher inorganic phosphate levels associated to CKD condition. This effect appears to be mediated by a positive effect of endogenous PCSK9 on the release of EVs containing Ca2+ and ALP, which facilitate the deposition inorganic calcium phosphate crystals.

Keywords : PCSK9, calcification, extracellular vesicles, chronic kidney disease
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