Sortilin Regulates Arterial Calcification in Atherosclerotic Mice and Associates With Cardiovascular Risk in Humans

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Background: Arterial calcification associates with cardiovascular morbidity and mortality. Human genome-wide association studies linked the SORT1 gene encoding sortilin and coronary artery calcification. We previously demonstrated *in vitro* that calcification requires sortilin phosphorylation by Fam20C. We hypothesized that sortilin mediates arterial calcification *in vivo* and that serum sortilin levels can predict cardiovascular events.

Results: We assessed the effects of genetic deletion of sortilin (*Sort1*) in LDL receptor-deficient mice ($Ldlr^{-/-}$) consuming a high-fat, high-cholesterol diet. $Sort1^{-/-}Ldlr^{-/-}$ mice exhibited 80% lower aortic calcification as compared to control $Ldlr^{-/-}$ mice in intact arteries (fluorescence reflectance imaging of a NIRF calcium tracer, $p<0.01$). $Sort1^{-/-}Ldlr^{-/-}$ mice showed 88% lower extracted aortic calcium ($p<0.05$). Histological analysis revealed less tissue non-specific alkaline phosphatase activity and arterial microcalcification. Transfer of *Sort1*-deficient bone marrow cells to irradiated atherosclerotic mice does not alter aortic calcification, indicating that immune cell-derived sortilin may not contribute to sortilin-mediated arterial calcification. In contrast to arterial calcium, *Sort1*-deficiency did not alter bone mineralization assessed by µCT and histomorphometry. In a community-based cohort of men aged ≥50 ($n=830$), abdominal aortic calcification (AAC) was assessed by dual energy X-ray absorptiometry using Kauppila score. Serum sortilin levels were measured by ELISA. After adjustment for confounders (including cholesterol concentration), sortilin levels correlated positively with severe AAC. The highest sortilin quartile associated with higher odds of severe AAC even in men without ischemic heart disease ($OR=2.0$, $p<0.05$). Among 745 men followed up prospectively for 7.8 years, major adverse cerebrovascular events occurred in 76 men. Elevated serum sortilin associated with higher event risk (adjusted for confounders, $HR=2.8$, $p<0.001$) even in men without diabetes ($HR=3.5$, $p<0.001$).

Conclusions: Sortilin is a novel therapeutic target to modulate the formation of arterial calcification and a biomarker of both aortic calcification and cardiovascular risk.

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