

Project title: “Circulating sortilin level as a potential biomarker for endothelial dysfunction and hypertension”.

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Summary

Sortilin has been positively correlated with vascular disorders in humans. Previous studies showed that sortilin promotes activation of acid sphingomyelinase (ASMase) and subsequently induces an increase of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in coronary endothelial cells. Although preclinical and clinical investigations have highlighted the critical role of sortilin in the pathogenesis of vascular disorders, no studies have yet evaluated the direct effect of sortilin in the modulation of vascular function. Thus, using pharmacological and genetic approaches, coupled with murine and human samples, we aim to unravel the mechanisms recruited by sortilin in the vascular system. We showed that sortilin induced endothelial dysfunction of mesenteric arteries through the activation of the NADPH oxidase 2 (NOX2) isoform, dysfunction prevented by knockdown of acid sphingomyelinase (ASMase) or sphingosine kinase 1. In vivo, recombinant sortilin administration induced arterial hypertension in wild-type mice. In contrast, genetic deletion of sphingosine-1-phosphate (S1P) receptor 3 and gp91phox/NOX2 resulted in preservation of endothelial function and blood pressure homeostasis after 14 days of systemic sortilin administration. Translating these research findings into the clinical setting, we detected elevated sortilin levels in hypertensive patients with endothelial dysfunction. Furthermore, in a population-based cohort of 270

subjects, plasma levels of sortilin, ASMase activity, and S1P and sNOX2-dp levels were found increased in hypertensive subjects as compared to normotensive controls, being more pronounced in hypertensives with uncontrolled blood pressure.

In conclusion, this study uncovers a previously unknown mechanism underpinning the role of sortilin in the dysregulation of sphingolipid metabolic pathway and NOX2-derived oxidative stress to impair vascular function and blood pressure homeostasis. Furthermore, we suggest the potential of sortilin and its mediators as novel biomarkers for the prediction of vascular dysfunction and high blood pressure (Di Pietro et al. 2022).