Diminution of secreted frizzled-related protein 5 confers development of vascular calcification in chronic kidney disease

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Objectives: Vascular calcification (VC) is frequently accompanied with bone loss in patients with chronic kidney disease (CKD). WNT regulates osteoblast activation through canonical (β-catenin dependent) and non-canonical (β-catenin independent) signaling pathways, but a common pathophysiology between the pathways during VC and bone loss still remained a conundrum. Therefore, we hypothesized that VC results from phenotypic conversion of vascular smooth muscle cell (VSMC) into an osteoblast-like cell involves induction of an osteoblast transcriptional program via a non-canonical WNT pathway, while bone loss is mainly regulated by canonical WNT pathway.

Methods: Adenine-induced CKD animal model with VC was induced in male Sprague Dawley rats fed 0.75% adenine (2.5% protein, 0.92% phosphate) and intraperitoneal calcitriol (0.08 µl/kg/day) injection for 4 weeks. In an angiotensin II (3µM)-induced VC in high phosphate milieu (3mM) through its effect on VSMC, the effect of WNT signaling on VC was determined by expression of osteoblastic transcriptional factor (RUNX2), Von Kossa stain and WNT downstream signaling factors.

Results: In mRNA profiler PCR assay of WNT signaling pathway from animal model, secreted frizzled-related protein 4 (sFRP4) were increased, while sFRP5 was decreased than those of control group fed with normal rat chow (0.62% phosphate). From the in vitro study, the protective effect of sFRP5 on VSMC differentiation was mediated through the inhibition of Rho/ROCK and JNK pathways. Moreover, the effect of Rho/ROCK and JNK pathways on sFRP5 repression through VSMC differentiation were aggravated by anisomycin (JNK activator), whereas recovered with SP600125 (JNK inhibitor). Those expressions of RUNX2 and WNT signaling factors in adenine-induced CKD animal model with VC showed in the similar patterns.

Conclusions: Our study suggests that repression of sFRP5 was associated with VC in CKD environment by activating non-canonical WNT pathway, which indicate that sFRP5 may be a new therapeutic target in VC in CKD environment.