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VASCULAR CALCIFICATION IN CARDIOVASCULAR PATHOLOGIES: ROLE OF O-GLCNAC MODIFICATION

Chang Hyun Byon[1,2*], Yong Sun[2], Chen Yabing[2], and Soo Wan Kim[1]

[1] *Nephrology, Chonnam National University Hospital, Korea*
[2] *Pathology, University of Alabama at Birmingham, USA*

changhyunbyon@gmail.com

Abstract

Vascular calcification is prevalent in patients with atherosclerosis, diabetes mellitus and chronic kidney disease, which increases the risk of cardiovascular events and mortality. Recent studies have further demonstrated that increased vascular calcification in diabetes is associated with elevated protein O-linked GlcNAc modification (O-GlcNAcylation). As O-GlcNAc transferase (OGT) is the key enzyme that control O-GlcNAcylation by adding O-GlcNAc onto proteins, we determined the effects of inhibition of OGT on diabetic vascular calcification and the underlying molecular mechanisms. By using new inducible smooth muscle-specific OGT deletion mice, we demonstrated that smooth muscle-specific OGT deletion did not affect blood glucose, but significantly inhibited protein O-GlcNAcylation exclusively in smooth muscle layer and inhibited vascular calcification in diabetic mice. Inhibition of vascular calcification by OGT ablation was associated with inhibition of Runx2, the key osteogenic transcription factor that is essential for vascular smooth muscle cell calcification. Further analysis showed that inhibition of Runx2 O-GlcNAcylation by site-directed mutagenesis was found to decrease Runx2 transactivity and alter intracellular localization of Runx2. Our studies have provided novel molecular insights into Runx2 regulation by OGT-dependent O-GlcNAcylation in diabetic vascular calcification, which may shed lights on novel targets that are amenable to drug discovery for diabetic vascular calcification.

Keywords

Vascular calcification, O-GlcNAcylation, Smooth muscle cells, Runx2, atherosclerosis, diabetes, chronic kidney disease