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O-GlcNAcylation of Runx2 is critical for diabetic vascular calcification

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Objectives: Vascular calcification is prevalent in patients with diabetes mellitus that increases the risk of cardiovascular events and mortality. Our recent studies have demonstrated that elevated protein O-GlcNAcylation was associated with increased vascular calcification in diabetic mice. The present studies determined a causative function of O-GlcNAcylation in regulating diabetic vascular calcification and the underlying molecular mechanisms.

Methods: The definitive role of O-GlcNAcylation in regulating vascular calcification was determined, using a new mouse model with smooth muscle cell (SMC)-specific deletion of O-GlcNAc transferase (OGT), the enzyme that adds O-GlcNAc onto proteins.

Results: We found that SMC-specific OGT deletion markedly inhibited vascular calcification and stiffness in low-dose streptozotocin-induced diabetic mice. Inhibition of vascular calcification by OGT deletion was associated with the inhibition of O-GlcNAcylation and Runx2 expression in mouse arteries as well as vascular smooth muscle cells (VSMC). Immunoprecipitation analysis identified a direct O-GlcNAcylation of Runx2, which was inhibited in the OGT deficient VSMC. By generating a serial of Runx2 point mutants, we further determined point mutations on Runx2 O-GlcNAcylation sites (threonine 404, 406, 412 and serine 413) inhibited Runx2 O-GlcNAcylation, Runx2 transactivity, and Runx2-induced VSMC calcification. Those mutations also inhibited Runx2 binding to the BMP-regulated Smad 1/5/8 signals, but not the TGF-β-regulated Smad 2/3 signals.

Conclusions: In summary, our studies have provided the first genetic proof demonstrating a causative role of SMC-specific OGT in regulating vascular calcification in diabetes. Furthermore, we have uncovered a mechanism underlying posttranslational modification of Runx2 by O-GlcNAcylation in regulating Runx2 interaction with Smads 1/5/8 that is essential for Runx2 osteogenic activity and VSMC calcification. The novel molecular insights into Runx2 regulation by O-GlcNAcylation in diabetic vascular calcification may shed lights on new targets that are amenable to drug discovery for the patients with diabetes.