**Exploration of YAP/TAZ Signaling in Protecting Endothelial Function in Diabetes and Obesity**

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**Background and aims.** Yes-associated protein (YAP) and transcription activator with PDZ binding motif (TAZ) have been identical as mechanosensors and mechanotransducers, and also found to modulate atherosclerosis. However, its involvement in diabetes-associated endothelial dysfunction is poorly understood. We aim to characterize the role of YAP/TAZ in diabetic vasculopathy and cross talk with endoplasmic reticulum (ER) stress.

**Methods.** Male C57BL/6 mice were fed a high-fat diet for 15 weeks to induce obesity and diabetes, and treated with 4-phenylbutyric acid (PBA; 100 mg/kg/day) and jatrorrhizine (50 mg/kg/day) by oral gavage for 5 weeks. Vascular reactivity was determined by wire myography. Western blot and fluorescence imaging were performed.

**Results.** Treatment with PBA and jatrorrhizine ameliorated endothelium-dependent relaxations as well as inhibited ER stress, YAP/TAZ signaling and oxidative stress in mouse aortas. Of note, phosphorylation of YAP/TAZ were highly expressed in thoracic aorta but low in aortic arch. Phosphorylation of SMAD1/5 were upregulated in inner curvature of aortic arch but downregulated in thoracic aorta. HUVECs were cultured with risk factors (high glucose or ER stress inducer tunicamycin) and co-treated with ER stress alleviators. In HUVECs, ER stress alleviators significantly inhibited YAP/TAZ signaling and increased NO bioavailability, but YAP inhibitor did not suppress ER stress. In HUVECs, YAP/TAZ regulated SMAD1/5 signaling under high glucose stimulation, followed by Akt/eNOS pathway. A natural compound jatrorrhizine was identified to inhibit YAP/TAZ-SMAD1/5 signaling and ER stress, protecting vascular function in diabetes.

**Conclusion/Discussion.** ER stress activates YAP/TAZ and SMAD1/5 signaling, resulting in endothelial dysfunction in diabetes. Inhibition of YAP/TAZ-SMAD1/5, such as by ER stress alleviators and natural product jatrorrhizine ameliorate endothelial dysfunction associated with diabetes. These findings support the cross talk between ER stress and YAP/TAZ-SMAD1/5 as well as their potentials as therapeutic targets.

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