UTJMS 2025 October 9, **14**(S2):e1-e1 doi:10.46570/utjms-2025-1554

A Novel Link between YAP1 and AMPK/mTORC1 Signaling in Vascular Smooth Muscle Cells

Sanjana Kumariya[1], Joanna Stuck, Arturo Grano de Oro, Islam Osman[2*]

[1]College of Medicine and Life Sciences, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

[2]Assistant Professor, Department of Physiology and Pharmacology, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

Email: islam.osman@utoledo.edu

Received: 1/3/2025

Accepted: 2/7/2025

Published: 10/9/2025

Introduction: Cardiovascular disease remains the leading cause of preventable mortality in the US and worldwide. Vascular smooth muscle cell (VSMC) phenotypic modulation from a contractile to a synthetic state is central to the etiologies of multiple vascular wall diseases. We have previously demonstrated that Yes-associated protein 1 (YAP1), a transcriptional co-activator, induces VSMC phenotypic switching and neointima formation. However, the underlying mechanisms remain largely unknown.

Methods: *In vitro* loss- and gain-of-function studies utilizing human coronary artery SMCs. *Cell proliferation:* WST-1, EdU incorporation, and CyQUANT assays. *Cell migration:* Scratch wound-healing assays. *Cell signaling:* Immunoblotting and qRT-PCR. *Arterial injury:* Left femoral artery wire injury in mice.

Results: Loss- and gain-of-function studies demonstrate, for the first time, that YAP1 is required and is sufficient to activate mTORC1 in VSMCs, a key regulator of VSMC phenotypic switching. Consistently, we found that YAP1 is induced following arterial injury and correlated with mTORC1 activation and VSMC phenotypic switching *in vivo*. Importantly, mTORC1 inhibition with rapamycin markedly abolished YAP1-induced VSMC proliferation and migration. Next, we examined the potential upstream regulatory mechanisms by which YAP1 may activate mTORC1. We found that YAP1 inhibits AMPK signaling, a key negative upstream regulator of mTORC1, suggesting an intermediary role of AMPK in mediating the effects of YAP1 on mTORC1, which was validated by co-transfection studies. Next, we examined the potential upstream regulatory mechanism(s) by which YAP1 may regulate AMPK. ChIPseq data analysis identified the catalytic subunit (PPP2CB) and the regulatory subunit (PPP2R1B) of the protein phosphatase PP2A as potential YAP1 transcriptional targets that may mediate the effects of YAP1 on AMPK signaling. Consistently, we found that YAP1 induces PPP2CB and PPP2R1B at both the mRNA and protein levels.

Conclusion: This study identifies a novel signaling pathway linking YAP1 to AMPK/mTORC1 signaling, which plays a key role in VSMC phenotypic switching.

Keywords: AMPK,YAP1,VSMC - Vascular Smooth Muscle Cells

