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A Novel Role of HSF1 in Vascular Smooth Muscle Cells

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Introduction: Vascular smooth muscle cells (VSMCs) exhibit plasticity that allows them to dedifferentiate from a quiescent, contractile phenotype into a synthetic, proliferative, and migratory phenotype depending on environmental cues. This ability to switch phenotypes is essential for vascular remodeling and wound healing but has also been implicated in many vascular pathologies such as atherosclerosis and neointimal hyperplasia. Heat shock factor 1 (HSF1) is a transcription factor with well-described effects in the heat shock response and tumorigenesis. However, its role in VSMCs has not been explored.

Methods: Human coronary artery smooth muscle cells (HCASMCs) were transduced with HSF1 loss-of-function or control shRNA lentiviral vectors. Cell signaling was analyzed at the protein level utilizing western blot analysis. Gross changes in cell confluency and morphology were analyzed by live cell imaging. A nuclear and cytoplasmic extraction Kit was used to analyze HSF1 abundance in cytoplasmic and nuclear protein fractions.

Results: Silencing HSF1 in VSMCs led to decreased activation of proliferative signaling including pERK½, pAKT, pS6, and pP90S6K, downregulation of proliferation marker expression (cyclin D1), and inhibition of cell proliferation. Conversely, silencing HSF1 led to upregulation of VSMC differentiation markers (SM a-actin and calponin). Culturing HCASMCs in complete versus serum free media led increased abundance of HSF1 in the nuclear fraction, suggesting activation.

Conclusions: Our findings demonstrate, for the first time, that HSF1 may be a novel master regulator of VSMC phenotypic switching from a differentiated into proliferative and migratory phenotype. Ongoing experiments will further examine the effects of HSF1 loss- and gain-of-function on VSMC phenotypic switching, will identify the potential intermediary transcriptional mechanisms, and will test the effects of HSF1 deficiency in mouse models of vascular remodeling *in vivo*.
In summary, these findings suggest a novel role of HSF1 in VSMC phenotypic switching and may provide future therapeutic targets for vascular wall diseases.

Keywords: HSF1,VSMC - Vascular Smooth Muscle Cells

