THE GRADUATE COLLEGE OF THE

UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Shayna Medley

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE

Department of Cell Biology

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Biomedical Research Center, Room 109

The role of STAT1 in the myofibroblast transition: a parallel assessment in fibroblasts and vascular smooth muscle cells

COMMITTEE IN CHARGE: Lorin E. Olson, PhD; James J. Tomasek, PhD; Eric W. Howard, PhD; Courtney T. Griffin, PhD; Florea Lupu, PhD; Jonathan D. Wren, PhD

ABSTRACT: The myofibroblast is a transient cell identity induced during times of stress (i.e. inflammation, physical injury), and they exhibit several functions integral to injury repair including contractility, proliferation, migration, and the production of extracellular matrix (ECM). Fibroblasts and vascular smooth muscle cells (VSMCs) are the most common myofibroblast origins, but regulation of the transition process likely differs between these two cell types because while fibroblasts must acquire a nascent contractile apparatus, VSMCs must weaken their existing dominant contractile infrastructure.

Signal Transducer and Activator of Transcription (STAT1) is the primary downstream effector of interferon signaling, but whether it plays a role in myofibroblast transitioning has not been well characterized. We have previously shown that STAT1 is constitutively activated in both fibroblasts and VSMCs when the same cells are also experiencing hyperactive PDGFRβ signaling. STAT1 deletion under these conditions leads to an increase in the fibroblast-to-myofibroblast transition (FMT) but has no significant effect on the VSMC-to-myofibroblast transition (VMT), suggesting that STAT1 functions differently in FMT versus VMT. Here, I have characterized the regulatory role of STAT1 during FMT and VMT in parallel *in vitro* and *in vivo* under physiological PDGFRβ signaling conditions. I have shown that STAT1 inhibits collagen and αSMA expression during FMT *in vitro* and during *in vivo* dermal wound healing. *In vitro* proliferation and migration were unaffected by STAT1 deletion in both cell types suggesting that STAT1 is negligible for these functions. In addition, RNA sequencing demonstrated that STAT1 does not transcriptionally regulate the majority of genes known to drive FMT/VMT. However, *in vivo* STAT1 deletion exacerbated myofibroblast-driven bleomycin-induced lung fibrosis and carotid artery ligation-induced adventitial remodeling while VSMC-driven phenotypes were not STAT1-dependent, suggesting that STAT1 may regulate FMT post-transcriptionally. Comparable STAT1 transcript levels between fibroblasts and VSMCs as demonstrated by RNA sequencing suggests that differential STAT1 function during FMT and VMT is not attributable to overall STAT1 expression levels. In conclusion, I find that the mechanisms driving FMT and VMT differ, and STAT1 regulates collagen and αSMA production during FMT but is negligible during VMT.