SNAIL TRANSCRIPTION FACTOR REGULATES REACTIVE OXYGEN SPECIES SIGNALING IN HUMAN PROSTATE CANCER CELLS

Valerie Odero-Marah\textsuperscript{1,2}, Rebecca S. Arnold\textsuperscript{1}, Majd Zayzafoon\textsuperscript{3}, Clayton Yates\textsuperscript{1}, Danielle McKeithen\textsuperscript{2}, Penelope Cipriani\textsuperscript{2}, Tisheeka Graham\textsuperscript{1}, Natalya Klueva\textsuperscript{2}, Haiyen E. Zhau\textsuperscript{1} and Leland W. K. Chung\textsuperscript{1}

\textsuperscript{1}Molecular Urology and Therapeutics Program, Department of Urology and Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322, USA
\textsuperscript{2}Department of Biological Sciences, Clark Atlanta University, Atlanta, GA 30314, USA
\textsuperscript{3}Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama, 35233, USA

Abstract: Snail transcription factor is a zinc finger protein that can induce epithelial-mesenchymal transition (EMT), as evidenced by decrease in cell adhesion-associated molecules like E-cadherin, increase in mesenchymal markers like vimentin, leading to increased motility, invasion and metastasis. We sought to investigate the molecular mechanisms by which Snail promotes tumor aggressiveness utilizing prostate and breast cancer cells. Snail expression was higher in different prostate cancer cells lines as compared to normal prostate epithelial cells and tumor aggressiveness was associated with increased reactive oxygen species (ROS). In addition, treatment of PC-3 prostate cancer cells with Snail siRNA resulted in reduced ROS. Snail over expression increased tumorigenicity in both ARCaP prostate cancer cells and MCF7 breast cancer cells. Additionally, Snail transfection led to increased superoxide and hydrogen peroxide both in vitro and in vivo in ARCaP, but not MCF7 breast cancer cells. The ROS scavenger, N-acetyl cysteine (NAC) partially reversed Snail-mediated EMT after 7 days characterized by increased E-cadherin levels and decreased ERK activity, while treatment with the MEK inhibitor, UO126, resulted in a more marked effect by 3 days, characterized by cells returning back to the epithelial morphology and increased E-cadherin protein. However, vimentin levels remained unchanged by 7 days. In conclusion, this study shows that Snail transcription factor plays a role in prostate cancer progression through ROS-mediated EMT that may be regulated in part by ERK activation. Therefore, therapeutic targeting of Snail may prove beneficial in not only abrogating EMT but also ROS-mediated tumor progression in human prostate cancer.

Keywords: Snail, EMT, ROS, prostate cancer

Acknowledgements: This research was supported by DOD grant PC 040267 (VOM); NIH grants 1P20MD002285 (VOM), G12RR03062 (VOM), CA082739 (HYEZ), and PO1 CA098912 (LWKC)