Inhibition of Wntless expression suppresses growth of neuroendocrine tumors

Leandro S D'Abronzo, Alan Lombard, Shu Ning, Cameron M Armstrong, Chengfei Liu, Wei Lou, Jinge Zhao, Allen C Gao
Department of Urology · University of California Davis

BACKGROUND: The current mainstream treatment for advanced prostate cancer (PCa) is AR-targeted therapies such as enzalutamide and abiraterone. Unfortunately, prostate tumors may develop mechanisms by which they can circumvent therapeutics. Neuroendocrine differentiation, which can occur *de novo* or in response to AR-targeted therapy, is one such means by which tumor cells can resist treatment. Neuroendocrine prostate cancer (NEPC) cells often do not respond to AR-targeted therapy and respond only transiently to chemotherapy. Therefore, there is an urgent need to understand the mechanism of NEPC development and develop therapeutic strategies that are independent of the androgen/AR axis. In this study we investigate the role and potential targeting of Wntless (WLS) in the development and treatment of NEPC.

METHODS: To examine the expression of WLS in NEPC, we utilized western blotting and qPCR to compare protein and mRNA levels of WLS in prostate cancer cells with neuroendocrine features as well as the established neuroendocrine cell line NCI-H660. Cell proliferation was assessed by CCK8. In vivo studies were carried out by treating H660 tumor bearing mice with a novel WLS inhibitor, NicS, via gavage administration.

RESULTS: We found that WLS is overexpressed in models of NEPC including NCI-H660, PC3 and CWR22rv1 cells. Downregulation of WLS by siRNA inhibits the markers of NEPC differentiation including chromogranin A (CHGA), neuron-specific enolase (NSE) and synaptophysin (SYP). WLS inhibition also reduces cellular viability. We synthesized a library of drug derivatives from niclosamide, and found one of the derivatives, NicS, can inhibit WLS expression and cellular viability and decrease neuroendocrine markers. To examine if NicS can inhibit tumor growth in vivo, we treated H660 tumor bearing mice with NicS and found that it significantly reduced tumor growth of H660 cells.

CONCLUSIONS: Our results show that WLS is overexpressed in NEPC cells and targeting WLS by either siRNA or NicS suppresses tumor cell growth, suggesting that NicS could be potentially developed to treat NEPC.