Androgen deprivation promotes neuroendocrine differentiation and angiogenesis through CREB-EZH2-TSP1 pathway in prostate cancers

Yan Zhang[1], Dayong Zheng[1], Ting Zhou[1], Haiping Song[1], Mohit Hulsurkar[1], Zheng Wang[1], Shao Long[2], Ladan Fazli[3], Michael Ittmann[2], Martin Gleave[3], **Wenliang Li[1,4,5]**

1. The Brown Foundation Institute of Molecular Medicine, McGovern Medical School, University of Texas Health Science Center at Houston (UTHealth), Houston, TX. 2. Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX. 3. Department of Urologic Sciences and Vancouver Prostate Centre; University of British Columbia, Vancouver, BC, Canada. 4. Division of Oncology, Department of Internal Medicine, and Memorial Herman Cancer Center, UTHealth, Houston, TX. 5. University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX.

Background: The incidence of aggressive neuroendocrine prostate cancers (NEPC) related to androgen-deprivation therapy (ADT) is rising. NEPC is still poorly understood with no effective treatment. Elevated levels of neuroendocrine differentiation (NED) and angiogenesis are two prominent phenotypes of NEPC, whose direct molecular links have been largely unknown.

Methods: In this study, we employed a number of genetic manipulations (gene overexpression and silencing) and pharmacological perturbations (chemical activators and inhibitors) for genes under investigation to study their connections to each other and their implications in NED and angiogenesis. Several prostate cancer cell and xenograft models in culture and in mice were utilized. ADT was achieved by treating androgen-responsive cells in culture with MDV3100 or by growing the cells in hormone-deprived media, as well as by surgical castration for xenograft tumor growth. Gene expression data from TCGA and other public sources, as well as tissue microarrays of prostate normal and tumor tissues from patients were used to evaluate the clinical relevance of this work.

Results: NED and angiogenesis are molecularly connected through EZH2 (enhancer of zeste homolog 2). NED and angiogenesis are both regulated by ADT-activated CREB (cAMP response element-binding protein) that in turn enhances EZH2 activity. We also uncover anti-angiogenic factor TSP1 (thrombospondin-1, THBS1) as a direct target of EZH2 epigenetic repression. TSP1 is downregulated in advanced prostate cancer patient samples and negatively correlates with NE markers and EZH2. Furthermore, castration activates the CREB-EZH2 axis, concordantly affecting TSP1, angiogenesis and NE phenotypes in tumor xenografts. Notably, repressing CREB inhibits the CREB-EZH2 axis, tumor growth, NED and angiogenesis in vivo.

Conclusions: We have elucidated a new critical pathway, consisting of CREB-EZH2-TSP1, underlying ADT-enhanced NED and angiogenesis during prostate cancer progression. The investigation of molecular mechanisms underlying EZH2 activation by CREB signaling and the induction of NED by EZH2 is underway.

Conflict of Interest: No conflict of interest to declare.

Funding Acknowledgements: This work was supported by awards from the Cancer Prevention and Research Institute of Texas and American Cancer Society to W Li.