Wnt Signaling Targets in ADT Resistant CRPC

Gu ZK [1], Ma F.[1], Ye HH.[2], Yu L.[1], Calagua C.[2], Yuan, A.[2], Russo J.[1], Einstein D.[1], Bhasin M.[1], Balk SP[1], **Yuan X.[1]**

1. Division of hematology/oncology, Department of Medicine. 2. Department of Pathology, 3. Genomics, Proteomics, Bioinformatics and Systems Biology Center, Beth Israel Deaconess Medical Center, Boston, MA, USA.

Background: Genome-wide studies have identified a high prevalence of alternations in the Wnt signaling pathways in CRPC, supporting an important role of Wnt signal in PCa progression and therapy resistance. However, additional non-genomic driving factors for Wnt activity need be defined. In addition, there is a lack of robust tool to measure the Wnt activity in PCa samples.

Methods: Wnt activity gene signatures was identified by the selecting genes that were increased after Wnt activation either by silencing a Wnt inhibitor, APC or by silencing another Wnt inhibitor (RNF43) followed with Wnt3A stimulation. The convergent gene pool was further reduced for their shared presence among the published gene expression datasets of primary and metastatic prostate cancers. In addition, immunohistochemistry of some of the key Wnt pathway components was performed on TMAs derived from a rapid autopsy program.

Results: Molecular interrogation of Wnt targeted genes has defined a set of 49 genes as a signature of Wnt activity. This signature has successfully defined the PCa cases with known genetic alterations that are associated with Wnt activation (such as alternations of APC, β-Catenin and RNF43). The signature also discovered that the Wnt activity in primary and metastatic PCa are of normal and continuous distribution. WLS, a key Wnt secretion factor is expressed among 70% the ADT resistant mCRPC samples. WLS level is also associated with higher Gleason grades. Finally, WLS level increases in VCaP PCa xenograft models during the progression from androgen-dependence to ADT-resistant CRPC.

Conclusions: Wnt activity is increased among a subset of PCa. A dominant presence of WLS in mCRPC strongly supports an important role of Wnt secretion in PCa progression. WLS can be a driver of Wnt activation in mCRPC and may serve as a biomarker for Wnt targeted therapy.

Conflicts of Interest: N/A