The Germ Cell Gene TDRD1 as an ERG Target Gene and a Novel Prostate Cancer Biomarker

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Background: TMPRSS2-ERG fusion occurs in about half of prostate cancers and results in over-expression of the oncogenic ERG protein in the prostate. The mechanism by which ERG contributes to prostate cancer initiation and progression remains largely unknown. Because ERG is a transcriptional activator, we reasoned that the target genes regulated by ERG could contribute to prostate cancer development.

Methods: In a search for ERG target genes, we took advantage of published datasets from the MSKCC Prostate Oncogene Project, in which a comprehensive analysis was applied to define transcriptomes in 150 prostate tumors. We retrieved the mRNA expression dataset, split them based on ERG expression, and identified genes whose expression levels are associated with ERG mRNA levels.

Results: mRNA expression levels of 21 genes were found to be significantly increased, while for one gene it was decreased in ERG-positive prostate tumors. Among them, the expression of TDRD1 was the most significantly increased in ERG-positive tumors. Among 131 primary prostate tumors which were primarily from European American patients, TDRD1 is over-expressed in 68% of samples, while ERG is overexpressed in 48% of samples, suggesting an additional ERG-independent mechanism of TDRD1 overexpression. In African American prostate tumors, TDRD1 mRNA is expressed in 44%, while ERG is expressed in 24% of samples. In normal tissues, TDRD1 mRNA is exclusively expressed in germ cells and its protein is also known as cancer/testis antigen 41.1 (CT41.1). We generated a mouse monoclonal antibody that recognizes human TDRD1 protein with high specificity and sensitivity. By Western blot analysis and immunohistochemistry (IHC) staining, we demonstrate that TDRD1 protein is expressed in the majority of human prostate tumors, but not in normal prostate tissue. Finally, TDRD1 is not induced in the prostate of ERG overexpression transgenic mice, suggesting that such model does not fully recapitulate the TMPRSS2/ERG fusion-dependent human prostate cancer development.

Conclusion: Our results suggest TDRD1 as a novel prostate cancer biomarker. As an ERG target gene, TDRD1 might play an important role in human prostate cancer development, and as a cancer/testis antigen, TDRD1 might have long term potential to be a therapeutic target for prostate cancer immunotherapy.

Conflict of interest: None.

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