P65 Contribution of pseudokinase TRIB1 to prostate cancer biology

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Introduction & Objectives: Prostate cancer (PCa) is the most common cancer among men in Europe and the second worldwide. Whereas some of the key drivers in PCa pathogenesis have been studied, the functional interactions with novel signaling molecules is subject of intense research. Tribbles Homologue 1 (TRIB1), a member of the Tribbles family of pseudokinases, has been shown to play a role in different types of cancers. Yet, the contribution of TRIB1 alterations to PCa pathogenesis and progression remains obscure.
In this study, we evaluated the molecular source and functional consequences of TRIB1 alterations in PCa.

Materials & Methods: We first developed an in silico strategy to ascertain the status and potential upstream regulators of TRIB1 in PCa, taking advantage of publicly available genomics and transcriptomics studies. We next validated the relevance of candidate upstream regulators of the pseudokinase in PCa cell lines and genetic mouse models. To decode the biological consequences of TRIB1 perturbation in tumorigenesis, we generated a new genetic mouse model of prostate cancer based on the concomitant alteration in the tumor suppressor PTEN and TRIB1 in the prostate epithelium.

Results: Our results demonstrate that TRIB1 expression in PCa is the highest among all tumors analyzed. Moreover, we identified genomic amplification of TRIB1 locus in a fraction of PCa patients, which correlated with gene expression changes. Our in vitro and in vivo studies revealed that PTEN/mTOR/c-MYC is a novel upstream signaling regulator of TRIB1 in PCa. Moreover, overexpression of TRIB1 in our PCa mouse model remarkably increased the incidence of PCa.

Conclusions: Our work demonstrates that TRIB1 upregulation is predominant in PCa based on genomic and transcriptomics alterations, and this overexpression contributes to the pathogenesis of the disease.