Mechanistic study of the tumor suppressor role of MITF uncovers actionable translation targeting for prostate cancer.

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Background: Prostate cancer (PC) is the most frequently diagnosed non-cutaneous malignancy among men in the US. Currently, the mechanisms of prostate tumor progression to a lethal resistant disease stage are not fully understood. Thus, elucidating novel targetable key molecules that might contribute to PC lethality must be endeavored for improving clinical outcome. We investigated transcription factors (TFs) to understand their role as potential molecular determinants that regulate cells transitioning to a more aggressive phenotype. Our interrogation of publicly-available transcriptomic datasets and experimental models led us to investigate the potential role of Microftalmia transcription factor (MITF) in regulating the aggressiveness of PC cells.

Methods: We used a combination of molecular and cell biology tools (RNASeq, focused loss-of-function genetic screen), comprehensive computational studies using patient datasets and prostate cancer cell models (data analysis), and translational studies in mice.

Results: We observed that MITF mRNA and protein levels were decreased in metastatic lethal PC (LPC) when compared to primary tumors. By performing functional genomic studies using siRNA control and 2 siRNAs targeting MITF in 3 PC cell lines (DU145, 22Rv1 and ARCaPM), we observed that low MITF levels increase the cell proliferation and tumorigenesis of PC cells in vitro and in vivo. Interestingly, the MITF gene signature obtained in our low MITF PC cell models positively correlates with the gene signature of advanced stage PC patients, making our low-MITF cells a good cell model for LPC. Mechanistically, we found that MITF regulates a subset of genes involved in protein synthesis, and particularly, that MITF depletion may lead to increased activity of key prostate cancer drivers, such as MYC and AR. Moreover, preliminary cell-based assays reveal that protein synthesis inhibitors may decrease more efficiently the proliferation and tumorigenicity of MITF-depleted PC cells.

Conclusions: Collectively, this study suggests that MITF has a tumor suppressor role in PC. MITF expression is significantly reduced in LPC and functionally impacts the proliferation and tumorigenicity of PC cells. Furthermore, our data indicate the existence of an interplay between MITF and the protein synthesis machinery that is deregulated in aggressive PC, and may represent an actionable signaling axis to treat lethal PC.

Conflict of Interest: The authors declare no conflict of interest.

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