P27 microRNAs regulating Tribbles-1: potential molecular targets in prostate cancer

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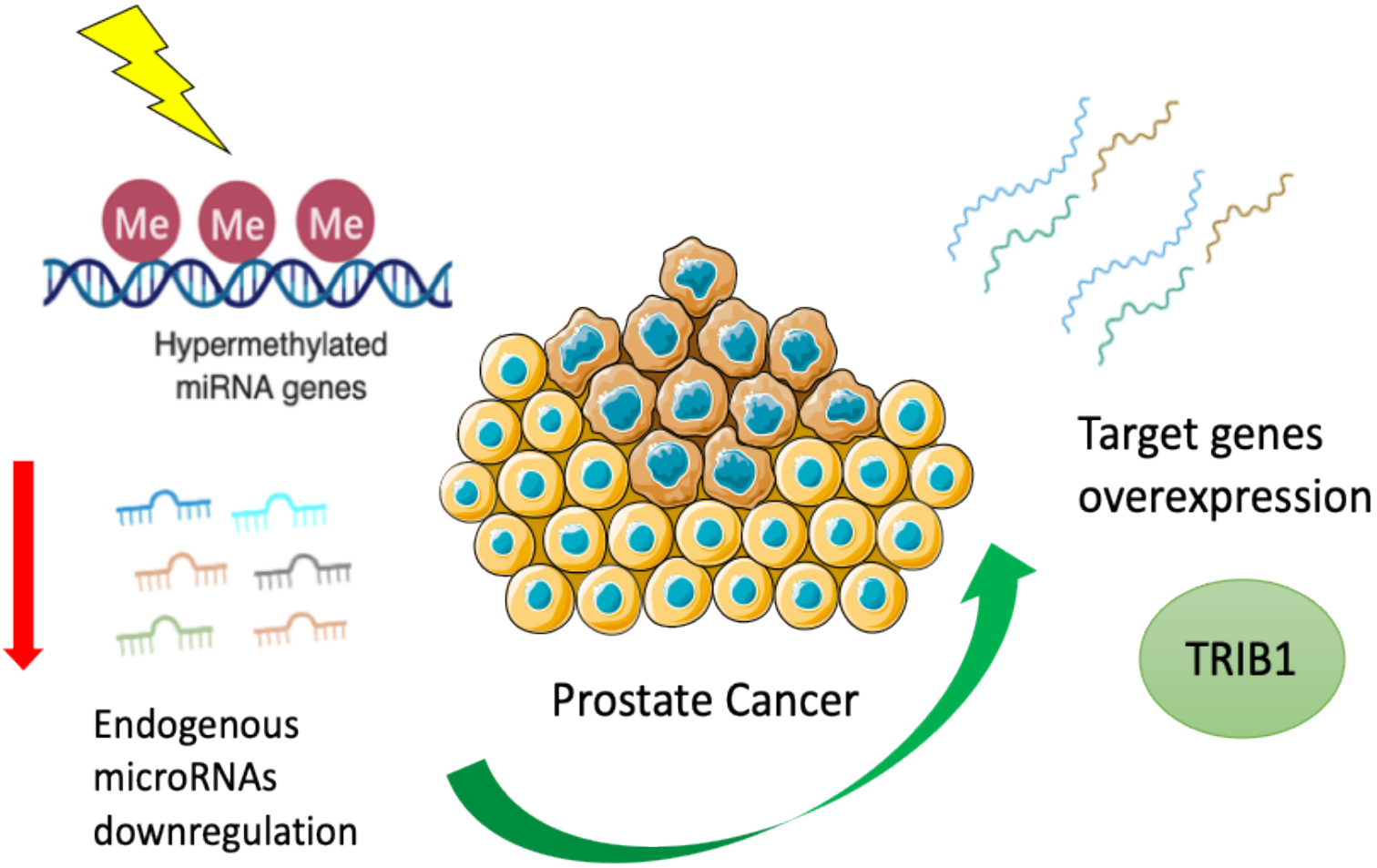
Introduction & Objectives:



Prostate cancer (PCa) is one of the most common male cancers with a poor long-term prognosis, in the Western World. Current treatment for PCa is based on a combination of endocrine therapy, radical prostatectomy, standard cycles of chemotherapy and radiotherapy. However, as the disease progresses the majority of patients experience relapse. Hence, the identification of new molecular targets and the development of new therapeutic strategies is critical. It is well established that microRNAs (miRNAs) have important roles in PCa development and progression, as they are frequently silenced by promoter hypermethylation, thus perturbing the expression of multiple genes. Recent studies have shown that the pseudo-

kinase Tribbles-1 (TRIB1) plays a crucial role in the proliferation and propagation of PCa. TRIB1 RNA is overexpressed in PCa and regulates

the ER chaperone GRP78, essential for prostate tumorigenesis. However, the mechanisms behind TRIB1 upregulation remain unclear. Here we investigate the potential association between TRIB1 overexpression and miRNA silencing in PCa, using both bioinformatics and experimental tools.

Materials & Methods: Publicly available databases and miRNA-target interaction algorithms were used to identify silenced miRNAs in PCa, potentially regulating TRIB1 expression. RT-qPCR was used to assess gene expression in a panel of human prostate cancer cell lines and in wild-type NU/J mice injected with tumour cells; a dual luciferase reporter assay was used to substantiate miRNA-TRIB1 interactions.

Results: Our findings show that TRIB1 is overexpressed in PCa cell lines, compared to cells derived from normal prostatic epithelium, as well as in a murine prostate cancer model. Among the downregulated miRNAs predicted to interact with TRIB1, we have shown that miR-132-3p, an onco-suppressor miRNA, has a functional binding site for the 3'UTR of TRIB1.

Conclusions: The overexpression of TRIB1 in PCa may be explained by the downregulation of endogenous miRNAs, thus offering an interesting, novel therapeutic target. Further work is needed to investigate the role of additional microRNAs and their impact on PCa biology.