P66 Androgens and TRIBs pseudokinases in modulating human prostate cells fate

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Introduction & Objectives: Androgens are sex steroid hormones that regulate growth and development of the male reproductive system. Prostate cancer (PCa), similar to normal prostate cells, require androgens for proliferation and survival. Tribbles (TRIBs) proteins are a family of pseudokinases that have been described to have a key role in controlling immunity, metabolism, and cancer. Also, the oncogenic or tumour suppressor actions of distinct TRIBs isoforms (TRIB1, TRIB2, and TRIB3) have been proposed in numerous cancer types. However, their actions in PCa are poorly understood. This study aimed to i) investigate the role of androgens in modulating TRIB1 and TRIB3 expression in prostate cells; ii) analyse human prostate cell fate upon altered TRIBs expression levels.

Materials & Methods: Non-neoplastic PNT1A cells and neoplastic LNCaP and 22RV1 cells were treated with 5α-dihydrotestosterone (DHT, 0-100 nM), in the presence or absence of the androgen receptor (AR) antagonist bicalutamide (10 μM). Overexpression or silencing of TRIB1 protein were performed. Total RNA and protein were extracted for RT-qPCR and Western blot analysis. Cell viability and proliferation were assessed via MTT assay and ki67 staining, respectively.

Results: DHT downregulated TRIB1 and TRIB3 expression in LNCaP and 22Rv1 cells, which was underpinned by the diminished expression of pAKT, AKT, and ERK1/2, downstream signalling targets associated with TRIBs. Also, PCa cell proliferation was enhanced upon DHT-treatment, while no effects on cell death were seen. Bicalutamide blocked the effects of androgens in regulating TRIB1 in PCa cells. The effectiveness of DHT and bicalutamide treatments were confirmed by the expression of the standard AR target, prostate-specific antigen. Additionally, silencing the AR (siRNA) increased TRIB1 expression in 22Rv1 cells confirming the AR involvement. The results obtained upon manipulating TRIBs levels in prostate cells showed that TRIB1 overexpression enhanced the proliferative activity and migration of PNT1A cells. Also, lipid metabolism seems to be affected as increased accumulation of lipid droplets was seen.

Conclusions: These findings demonstrate that androgens and AR have a regulatory role in TRIBs expression in PCa cells. Also, they suggest that increased expression of TRIB1 in non-neoplastic prostate cells has more impact than the knocking-down in neoplastic ones. Future work is underway to study the molecular partners of androgens and TRIBs in the regulation of cell fate and lipid metabolism in prostate cells.