P67 TCEAL1 loss sensitises prostate cancer cells to docetaxel treatment

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Introduction & Objectives: The standard of care chemotherapy for advanced metastatic prostate cancer is docetaxel, however this drug offers only a modest survival benefit. Thus there is an unmet clinical need to improve the efficacy of chemotherapy. The principal aim of this study was to identify potential gene targets as therapeutic targets to sensitise resistant tumours to docetaxel treatment.

Materials & Methods: We applied a novel murine prostate cancer cell line from a *PbCre Pten*$^{fl/fl}$ *Spry2*$^{fl/+}$ tumour (hereafter referred to as SP1 cells) which contains alterations commonly found in prostate cancer and thus represents a clinically relevant model to carry out *in vivo* genomic screens. We performed a whole-genome CRISPR screen (using the GeCKOv2 library, Addgene) in mice harbouring prostate cancer orthografts, which were then treated with docetaxel or vehicle control. Resulting tumours were harvested, and DNA was extracted and sent for deep sequencing. Data was analysed using the Model-based Analysis of Genome-wide CRISPR/Cas9 Robust Rank Aggregation programme (Mageck RRA) to identify negatively selected genes, which signify potential targets for therapy.

Results: We identified nine negatively enriched genes, with Transcription Elongation Factor A-like 1 (Tceal1) as the top candidate. *TCEAL1* is part of a family of nine transcription elongation factor A-like genes found clustered on the X chromosome. Little is known about the function of TCEAL1, however it is hypothesised to modulate transcription in a promoter context-dependent fashion. We successfully validated our screen findings in SP1 cells, where combining siRNA-mediated knockdown of TCEAL1 with docetaxel treatment was confirmed to have significant additional cell kill compared to treatment alone. We further validated that loss of TCEAL1 also sensitises several human prostate cancer cell lines to docetaxel treatment. Given the fact that the role of TCEAL1 may be to modulate transcription, we performed RNAseq transcriptomic analysis. Gene set enrichment analysis found that G2M checkpoint genes were enriched only with combined TCEAL1 siRNA and docetaxel treatment suggesting the combination is having an important effect on the cell cycle. Using flow cytometry we confirmed that loss of TCEAL1 in combination with docetaxel leads to an altered cell cycle profile compared to docetaxel alone, with increased subG1 cell death and increased polyploidy.

Conclusions: To our knowledge, this is the first *in vivo* whole genome CRISPR screen to study treatment resistance in prostate cancer. We identified and validated TCEAL1 as our top candidate to sensitise prostate cancer cells to docetaxel by altering their cell cycle, and further study is warranted to study the molecular basis of TCEAL1 mediated carcinogenesis, focusing on tumour response to treatment.