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PROSTATE CANCER

TRIM24 acts as a transcriptional activator

Transcription intermediary factor 1-α (TRIM24) promotes prostate cancer cell proliferation in low-androgen conditions and augments androgen receptor (AR) signalling according to new research published in *Cancer Cell*. These results provide a rationale for therapeutic targeting of TRIM24.

Groner and colleagues showed that levels of TRIM24 were changed in the presence of a number of different speckle-type POZ protein (SPOP) mutations in LNCaP cells; however, no effect was observed on *TRIM24* mRNA suggesting SPOP mutations regulate TRIM24 at the protein level. Experiments using haemagglutinin-tagged TRIM24 indicated that this protein decayed more rapidly in the presence of wild-type (wt)SPOP than the SPOP-F133L mutant.

In androgen-depleted conditions, SPOP-mutant cells had a growth advantage over those with wtSPOP, which was abrogated when *TRIM24* expression was silenced. Furthermore, overexpression of TRIM24 induced increased cell proliferation in low androgen conditions. When TRIM24 expression was reduced in the castration-resistant prostate cancer (CRPC) cell line LNCaP-abl, cell proliferation was impaired.

TRIM24-dependent gene expression was identified using micro-array analysis. Silencing of *TRIM24* caused more genes to be downregulated than upregulated, and many TRIM24-activated genes are involved in cell-cycle processes. In androgen-depleted conditions, androgen-responsive genes were more frequently activated by TRIM24 in LNCaP and LNCaP-abl cells than when androgen was readily available.

Significant overlap between the TRIM24 and AR cistromes was discovered and TRIM24 binding at shared sites in LNCaP cells showed an androgen-dependent increase. Also, weak interaction between the AR and TRIM24 was observed in LNCaP cell nuclei, indicating direct cooperation of these proteins in gene activation in prostate cancer.

In vivo, LNCaP-derived prostate tumours overexpressing TRIM24 showed increased proliferation, and increased expression of TRIM24 also promoted tumour growth in a castration-resistant setting.

The team then created an AR–TRIM24-regulated gene signature of 21 genes derived from cistrome and gene expression data from LNCaP-abl cells. Stratification of gene expression data from publicly available databases using this signature identified two prominent clusters, one with relatively high gene expression and the other with relatively low expression. Patients stratified into the high cluster had an increased risk of disease recurrence and metastatic tumour samples had enriched expression of genes in the high cluster, indicating this signature has predictive power.

In samples from patients, TRIM24 showed increasing expression from BPH through primary prostate cancer to CRPC, and TRIM24 levels significantly positively correlated with Gleason score, tumour size and Ki67-positive nuclei. These results indicate that TRIM24 has an oncogenic role as a transcriptional activator in a castration-resistant setting, and protein expression of TRIM24 is stabilized by mutations in SPOP. TRIM24 promotes cell proliferation and acts cooperatively with the AR and shows increased expression in CRPC, which provides a rationale for therapeutic targeting of TRIM24 in SPOP-mutant and castration-resistant disease.

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ORIGINAL ARTICLE Groner, A. C. *et al.* TRIM24 is an oncogenic transcriptional activator in prostate cancer. *Cancer Cell* http://dx.doi.org/10.1016/j.ccell.2016.04.012 (2016)