Nature Reviews Urology | Published online 23 May 2017; doi:10.1038/nrurol.2017.78

Jennie Lewis/Alamy Stock Photo

PROSTATE CANCER

New AR co-regulator with dichotomous functions

A new study shows that Grainyhead-like protein 2 (GRHL2) is a co-regulator of the androgen receptor (AR) in prostate cancer and has dichotomous functions, acting both as an oncogene by enhancing AR signalling and as a suppressor of metastasis-related phenotypes.

"Alterations to the expression and activity of AR co-regulators is an important mechanism driving prostate cancer progression and therapy resistance," explains Luke Selth from the University of Adelaide, Australia, senior author of the study. "However, the identity and precise mode of action of the AR co-regulators that are essential in lethal prostate cancer are poorly characterized."

First, the team used a new proteomic technique called rapid immunoprecipitation mass spectrometry of endogenous proteins (RIME) that enables characterization of chromatin-associated transcription factor complexes. In a cell line pair that express either full-length AR or the constitutively active ARv567es, they identified GRHL2 and confirmed its interaction with AR and ARv567es by co-immunoprecipitation. Analyses of prostate cancer genomic data showed increased *GRHL2* copy number in primary prostate tumours and metastases, and elevated mRNA levels in malignant compared with nonmalignant tissues. Immunofluorescence staining demonstrated cellular AR and GRHL2 co-localization.

Next, in prostate cancer cell lines, the team found that the GRHL2 expression pattern was similar to that of the AR, but nondetectable in AR^- cells. Testosterone treatment induced *GRHL2* mRNA expression, and siRNA knockdown of the AR resulted in GRHL2 loss, indicating that GRHL2 is an AR-regulated factor. Further experiments showed that the AR binds to sites near the *GRHL2* transcription start site, indicating direct transcriptional regulation. Functional evaluation demonstrated that siRNA knockdown of GRHL2 inhibited proliferation of cell lines and suppressed the expression of AR and AR variants and their target genes.

A set of experiments to evaluate the interplay between AR and GRHL2 transcriptional activities suggested that these two factors co-occupy genomic loci that are relevant in prostate cancer. Analysis of the GRHL2-regulated transcriptome by RNA sequencing demonstrated a strong association with the AR pathway. However, following the finding that GRHL2 binds DNA independently of AR, the team found that GRHL2 also regulated the transcription of growth factors, epithelial markers and signatures of epithelial-to-mesenchymal transition (EMT). EMT has a postulated role in metastasis and the team observed that GRHL2 knockdown resulted in increased motility and invasiveness in different experimental models.

"GRHL2 had not been implicated in AR function previously," highlights Selth. "Interestingly, GRHL2 is itself an AR-regulated factor. Thus, there exists a positive feed-forward loop between AR and GRHL2 that might be amplified further in castration-resistant disease in which both factors are commonly amplified and/or upregulated." The dichotomous function of this protein might make its use as a treatment target difficult. Although its inhibition might blunt AR signalling, it could also increase the metastatic potential of tumour cells.

Clemens Thoma

ORIGINAL ARTICLE Paltoglou, S. *et al.* Novel androgen receptor co-regulator GRHL2 exerts both oncogenic and anti-metastatic functions in prostate cancer. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-16-1616 (2017)