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PROSTATE CANCER

Epigenetic AR regulation

A new study in *Cancer Cell* describes an epigenetic mechanism that increases androgen receptor (*AR*) transcription in castration-resistant prostate cancer (CRPC) via the nonreceptor tyrosine kinase ACK-1, WD repeat-containing protein 5 (WDR5), and histone-lysine N-methyltransferase 2D (KMT2D, also known as MLL2). An ACK-1-specific inhibitor suppressed both AR and AR-V7 levels and reduced *in vivo* CRPC tumour growth.

ACK-1 expression had previously been shown to correlate with prostate cancer progression to castration resistance and poor prognosis. Mahajan *et al.* investigated epigenetic mechanisms in CRPC pathogenesis and found phosphorylation of tyrosine 88 in histone H4 (pY88-H4) in three of five tested CRPC samples and predominantly in ACK-1-positive cells. Suppression of ACK-1 through knockdown or the inhibitor (*R*)-9bMS abrogated pY88-H4. pY88-H4 marks were found in distinct regions upstream of *AR* that seemed to act as enhancers of *AR*.

Further studies in prostate cancer cell lines showed that ACK-1 activity was required for AR expression in an androgen-deprived setting. In addition, ACK-1 inhibition suppressed both AR and AR-V7 expression and had effects on DNA repair, transcription factor E2F, and MYC target gene signatures. Evaluation of the epigenetic mechanism revealed that a complex of WDR5–MLL2 recognizes pY88-H4 marks and creates transcriptionally activating H3K4me3 marks that promote *AR* transcription.

Analyses of clinical samples suggested that pY88-H4, H3K4me3, and AR expression increase during prostate cancer progression. In mouse xenograft models of CRPC, (*R*)-9bMS treatment halted tumour growth. The authors suggest that an epigenetic circuit of ACK1–pY88-H4–WDR5–MLL2–AR drives CRPC and is required to maintain the malignant state.

Clemens Thoma

> “ACK-1 activity was required for AR expression in an androgen-deprived setting”

ORIGINAL ARTICLE Mahajan, K. *et al.* ACK1/TNK2 regulates histone H4 Tyr88-phosphorylation and AR gene expression in castration-resistant prostate cancer. *Cancer Cell* http://dx.doi.org/10.1016/j.ccell.2017.05.003 (2017)