ASH1L methyltransferase: a therapeutic target in prostate cancer?

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Background

The histone 3 lysine 36 (H3K36) when methylated is crucial for transcriptional regulation, splicing, DNA repair and genome stability [1]. The tri-methylation status of H3K36 has been shown to guide RNA methylation co-transcriptionally [2]. Both methyltransferases and demethylases that target H3K36me have been shown to play a role in cancer. ASH1L, trithorax histone methyltransferase, that di-methylates H3K36, has shown to function through binding of MRG15 at the chromatin [3] and is involved in global nuclear excision repair [4]. Recent study has shown, that compared to the other H3K36 di-methylators NSD1 and NSD2, ASH1L methylation is restricted to active regulatory elements of developmental genes [5]. ASH1L is not well studied in prostate cancer, with a recent study showing its role in castrate resistant AR-negative prostate cancer (CRPC) [6]. With the development of ASH1L inhibitor [7], this study aims to identify whether ASH1L is a potential therapeutic target in AR-positive CRPC.

Methods

Immunohistochemistry staining performed in a UK cohort of 100 tumour and 45 non-malignant samples and H-scored. AR-positive CRPC cell lines were utilised to measure mRNA (QPCR) and protein levels of ASH1L (western blotting). AS-99, ASH1L inhibitor was used to look at cell proliferation (measuring DNA content), invasion (transwell assay) and transcriptome (RNA-Seq). Combination therapies of AS-99 and enzalutamide were tested.

Results

ASH1L nuclear levels did not vary significantly in primary adenocarcinomas compared to non-malignant samples. ASH1L levels varied in AR-positive CRPC cell lines and was no longer androgen-regulated. ASH1L methyltransferase inhibition resulted in, differential gene expression, splicing, loss of proliferation and invasion. Inhibition of ASH1L lead to sensitisation of 22RV1 cells to enzalutamide.

Conclusions: ASH1L could be a potential target for inhibition in AR-positive CRPC to resensitise to current AR-targeted therapies. Ongoing investigation is underway on pinpointing ASH1L target genes and ASH1L regulation in CRPC.

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Conflicts of Interest Disclosure: No conflicts of interest to disclose.

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