Role of bromodomain-containing androgen receptor cofactors in prostate cancer

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Background:

Castrate Resistant Prostate Cancer (CRPC) is the inevitable outcome of hormone treatment for advanced disease. Although CRPC is no longer dependent on high androgen levels, androgen receptor (AR) remains active and there is evidence that other nuclear receptors (NRs) can drive CRPC progression and/or therapy resistance. NRs share a repertoire of essential coregulators, dysregulation of or alterations in which have been proposed as a potential mechanism for driving lethal disease. We identified distinct alterations of coregulator expression in CRPC and focus on a family of coregulators consistently differentially expressed in CRPC, namely TRIpartite Motif (TRIM) proteins, in particular the bromodomain-containing members TRIM24 and TRIM28.

Methods:

Expression of TRIM genes was analysed across multiple publically available datasets. Physical interactions between TRIM proteins, AR and chromatin was analysed via Co-IP. ChIP assays were performed in both cell lines and patient samples to detect AR, TRIM24, TRIM28 binding sites. siRNAs targeting specific TRIMs, also bromo-domain targeting agents, were used to assess the transcriptomic and physiological importance of TRIMs in androgen signalling, via RT-qPCR, Western blot and proliferation assays. Physiological effects of TRIM targeting with bromo-domain inhibitors were assessed in ex vivo culture of tumour biopsies (explants). Conditioned media (CM) collected from siRNA-treated PCa cells, was applied to HUVEC (endothelial) cells to assess a role for TRIM proteins in mediating angiogenic pathways.

Results:

TRIM24 and TRIM28 were significantly differentially expressed in advanced disease and CRPC datasets. Levels of TRIM24 and TRIM28 also increase in response to enzalutamide treatment, both in cell lines and patient explant tissue. Endogenous TRIM24 and TRIM28 interact with each other and with AR in a ligand-dependent manner. We identified specific DNA regions where TRIM24 and/or TRIM28 bind to AR-enriched chromatin, as detected by ChIP-reChIP. Furthermore, bromo-domain inhibitors reduce TRIM and AR binding to these chromatin regions. Silencing TRIMs can alter androgen regulation of a number of genes, and was also able to reduce cell proliferation and response to androgen; intriguingly, targeting these TRIMs re-sensitized cells to enzalutamide. In explant models, targeting TRIMs with bromo-domain inhibitors induced changes in proliferation and cell markers. TRIM24 and TRIM28 also have a role in the regulation of VEGFA by AR. In tissue microarrays of prostate cancer samples, we found strong correlation between TRIM24, TRIM28 expression and VEGFA levels.

Conclusions:

Our data suggest that TRIM24 and TRIM28 proteins interact, in gene-specific manners, to regulate AR activity and may provide a potential target to increase effectiveness of anti-androgen therapy by regulation of tumour vascularisation.

Conflict of Interest:

No conflict of interest to declare.

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