Targeting the co-chaperone Bag-1L as a new strategy to inhibit the N-terminal AF-1 domain of the androgen receptor in castration resistant prostate cancer

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Background: Persistent androgen receptor (AR) signaling is key for the development and progression of metastatic castration-resistant prostate cancer (mCRPC). This is in part due to expression of constitutively active AR splice variants (AR-SV) of which AR-V7 is the best studied. Currently, there are no approved therapies targeting AR-V7, the lack thereof remains a critically important, unmet medical need**.** An attractive strategy for targeting AR-V7 and AR is inhibiting the N-terminal Activation Function (AF)-1 domain. Due to its intrinsically disordered structure, AF-1 is a therapeutically challenging target. Co-activators that exhibit chaperone activity and bind the AF-1, such as the HSP70/HSC70 co-chaperone and AR co-activator Bag-1L, are promising targets for the development of novel prostate cancer therapies.
Methods: Results were achieved using immunohistochemistry (IHC) and modern molecular technologies in prostate cancer cell lines and patient derived organoid models.
Results: IHC studies of patient biopsies demonstrate that nuclear AR-V7 and Bag-1L expression increase as patients develop advanced treatment resistant prostate cancer. We have shown that Bag-1L binds to the AR through its conserved C-terminal Bag domain in prostate cancer cells. Using canSAR (drug discovery knowledgebase) we have identified a druggable cavity within the Bag domain of Bag-1L. Mutations within and around this cavity disrupt the Bag-1L:AR interaction and abrogate Bag-1L mediated AR activity in prostate cancer cells. Moreover, we have shown that the small molecule Thio-2, disrupts the interaction between Bag-1L and AR AF-1 and inhibits BAG-1L mediated AR AF-1 activation and prostate cancer cell growth in a ligand independent way. Furthermore, Thio-2 demonstrates growth inhibitory effects in patient derived organoids and xenografts from metastatic CRPC biopsies resistant to enzalutamide.
Conclusions: We conclude that Bag-1L is essential for AR function and plays a critical role in regulating AR-V7 activity in CRPC. Targeting Bag-1L is therefore a potential novel therapeutic strategy to overcome oncogenic AR signaling in CRPC.

Funding: Prostate Cancer Foundation Challenge Award, Department of Defense, Medical Research Council, Academy of Medical Sciences, Prostate Cancer UK, National Institutes of Health.

The authors declare no conflict of interests.