Targeting the druggable interaction between the N-terminal domain of the androgen receptor (AR) and BAG-1L, a key regulator of AR function.

Laura Cato[1], Antje Neeb[2], **Adam Sharp[2]**, Victor Buzon[3], Xavier Salvatella[3], Stephen Plymate[4], Andrew C. B. Cato[5], Johann de Bono[2] and Myles Brown[1].

[1]Dana-Farber Cancer Institute and the Center for Functional Cancer Epigenetics, Boston, MA, USA
[2]The Institute of Cancer Research and The Royal Marsden Hospital, Sutton, UK
[3]Institute for Research in Biomedicine, Barcelona Spain
[4]University of Washington School of Medicine and VAPSHCS-GRECC, Seattle, WA, USA
[5]Karlsruhe Institute of Technology, Eggenstein-Leopoldshafen, Germany

Background:

Progression to lethal castration resistant prostate cancer (CRPC) is associated with ongoing androgen receptor (AR) signaling, due in part to constitutively active AR splice variants (AR-SV) of which AR-V7 is the best studied. Expression of AR-V7 confers resistance to current therapies and correlates with shorter survival from CRPC. Targeting the AR activation function 1 (AF-1) domain, a key regulatory domain of AR, is an attractive therapeutic strategy and may be achieved by disrupting its interaction with key regulatory proteins that bind AR AF-1 (common to nearly all AR-SV), such as the cochaperone BAG-1L. BAG-1L belongs to a family of proteins with four isoforms in humans (BAG-1L, BAG-1M, BAG-1 and BAG-1S). These proteins differ in their N-terminal sequences but have a conserved C-terminal BAG domain. BAG-1L possesses a nuclear localization sequence in its unique N-terminus. BAG-1L, but not the other BAG-1 proteins, enhances the transactivation function of AR. We have shown that BAG-1L may be a promising target to abrogate oncogenic AR signaling in prostate cancer.

Results (and Methods):

We show using immunohistochemistry that AR and AR-V7 expression increases as patients progress from hormone-sensitive prostate cancer (HSPC) to CRPC. Additionally, nuclear AR-V7 increases as patients develop resistance to abiraterone and is associated with poor overall survival. Similarly, nuclear BAG-1L levels increase as patients progress to CRPC and associate with response to abiraterone therapy. Consistent with these findings, overexpression of BAG-1L accelerates progression to CRPC in mouse xenograft models. To investigate the effect of BAG-1L loss in prostate cancer we have developed a Transcription Activator-Like Effector Nuclease (TALEN) BAG-1L specific knockout (KO) model in LNCaP cell line. ChIP-seq experiments demonstrate that BAG-1L regulates the AR cistrome and RNA-seq confirmed that AR target gene expression is dependent on the presence of BAG-1L. These data implicate BAG-1L as a critical coregulator of AR. Using HSQC NMR we have demonstrated that BAG-1L binds the Tau5 region of the AR N-terminus through its highly conserved C-terminal BAG domain. Mutations within the BAG domain disrupt the BAG-1L:AR interaction and inhibit BAG-1L-mediated AR transactivation. Interestingly, the BAG domain of BAG-1L is predicted to be druggable and these mutations lie within this cavity suggesting that the identification of small molecule compounds that bind this cavity may abrupt BAG-1-mediated AR activation.

Conclusions

Here we provide preliminary evidence that targeting the interaction between BAG-1L and AF-1 provides a novel therapeutic strategy to overcome oncogenic AR signaling (through both full length AR and AR-SV) in castration resistant prostate cancer.

Conflict of Interests Statement

The authors declare no conflict of interests

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