

IDENTIFICATION OF AR -INDEPENDENT MECHANISMS OF ACTION OF BETI IN A NOVEL MURINE MODEL OF PROSTATE CANCER

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Background: The development of non-androgen receptor (AR) based therapies for metastatic castration resistant prostate cancer (mCRPC) is an unmet clinical need. Recently, chromatin modifying enzymes have emerged as important oncology drug targets and those targeting the so-called “reader” proteins that contain bromodomains (referred to as BET [bromodomain and Extra-Terminal proteins]) are particularly intriguing. Bromodomains are a conserved protein module that recognize and bind to acetylated lysines. Two main mechanisms have been put forth regarding how BET inhibitors (BETi) suppress tumor cells. First, these inhibitors can result in down regulation of MYC in cells that overexpress MYC, and second, they have been shown to inhibit activity of the androgen receptor. At Johns Hopkins, we observed a patient with heavily pretreated mCRPC achieve a complete metabolic response, in the absence of a PSA response, following BETi administration suggesting a non-AR based mechanism of action.

Methods: We have established a new trigenic mouse model (referred to as BMPC) that features forced overexpression of MYC and deletion of Pten in the mouse prostate using the Hoxb13 transcriptional control elements. Upon developing invasive prostate cancer, this model losses expression of AR. We have generated two AR negative murine prostate cancer cell lines, BMPC-1 and BMPC-2, derived from metastatic deposits in these animals.

Results: We observed a significant effect of BETi on in vitro cell growth in both cell lines. Moreover, MYC expression, which is under the control of an exogenous promoter, was not reduced following BETi treatment. Similar growth suppressive effects were observed in human AR-negative prostate cancer cell lines.

Conclusions: The finding of efficacy in an AR negative model of prostate cancer would suggest that AR negative prostate cancers (i.e. neuroendocrine, AR-negative adenocarcinoma) may derive clinical benefit from therapy. Also, suppression of growth in the BMPC cell lines appears independent of MYC inhibition. Thus, we obtained significant cell growth suppression without affect two of the main pathways assumed to mediate BETi effects. These studies may lead, therefore, to the identification of additional mechanisms of BETi action and, additionally, identifying both synergistic partners and/or mechanisms of resistance may enhance the use of BETi in the clinic.

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