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GEMMs shine a light on resistance to androgen deprivation therapy for prostate cancer

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Summary

Androgen deprivation therapy (ADT) for advanced prostate cancer inexorably leads to resistance, and clinically useful biomarkers are lacking. The value of genetically engineered mice for co-clinical studies is clearly demonstrated in a recent publication that reveals XAF1, XIAP, and SRD5A1 as novel predictive biomarkers and therapeutic targets for ADT resistance.

The mainstay of therapy for metastatic prostate cancer for more than 70 years has been systemic androgen ablation, aimed at suppressing androgen receptor (AR)-mediated signaling as a growth and survival pathway for prostate cancer cells (Huggins and Hodges, 1941). The discovery that AR signaling remains active in castration-resistant prostate cancers (CRPCs) (Chen, et al., 2004) led to the introduction of novel anti-androgen therapies, namely abiraterone and enzalutamide. The sustained ADT leads to a variable initial response, due to genetic heterogeneity of this disease. Sadly, this initial response is almost invariably followed by disease progression. Unfortunately, there are no reliable biomarkers to predict response to ADT. The discovery of novel targets and biomarkers for personalized therapy for CRPC remains a critical need.

Current concepts and models have focused largely on persistent AR signaling as the driving event in the development of ADT resistance. Specific mechanisms that override AR signaling and that de-repress gene activities inhibited by AR signaling have been defined (Cai, et al., 2011). However, important fundamental genetic and biologic pathways including genetic predisposition, apoptotic signaling, and proliferative signaling remain fertile ground for understanding and improving upon ADT. The use of genetically engineered mouse models (GEMMs) provides unique opportunities in this regard.

In a recent report, Lunardi et al. evaluated the course and androgen dependence of prostate cancers that developed in GEMMs with prostate-specific deletion of *Pten* alone (*Pbsn-cre4;Pten*$^{fl/fl}$) and in combination with deletion of *Zbtb7a (Pbsn-cre4; Pten*$^{fl/fl}$*; Zbtb7a*$^{fl/fl}$) or *Trp53 (Pbsn-cre4; Pten*$^{fl/fl}$*; Trp53*$^{fl/fl}$) (Lundardi, et al, 2013). They showed that loss of either *Zbtb7a* or *Trp53* confers an initial resistance to ADT manifested as increased proliferation, decreased apoptosis, and sustained growth upon castration. AR was localized

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mainly in the cytoplasm one month after castration in all genotypes. However, tumors with inactivation of either of the two tumor suppressor genes demonstrated significantly increased nuclear AR localization, suggesting that the deletion of these two genes leads to earlier reactivation of AR signaling than in tumors with functional alleles.

According to data generated by immunohistochemical staining analysis of tissue micro arrays that included prostatectomy samples from patients who had been treated with ADT, and from genomic hybridization analysis of metastatic prostate cancer that included CRPC (Taylor, et al. 2010), the loss of *ZBTB7A* was associated with poor response to ADT, and the loss of both *ZBTB7A* and *TP53* was frequent in metastatic CRPC. Interestingly, loss of *ZBTB7A* was significantly associated with *PTEN* loss in metastatic CRPC, suggesting that the concomitant loss of these genes may be a better predictor of progression upon androgen deprivation than *PTEN* deletion alone.

Comparative analysis of gene expression profiles of mouse prostate specimens from *Pbsn-cre4;Pten*$^{fl/fl}$ with those from *Pbsn-cre4;Pten*$^{fl/fl}$*; Zbtb7a*$^{fl/fl}$ mice revealed down regulation of the pro-apoptotic gene *Xaf1*, a p53 target gene that antagonizes the anti-caspase activity of XIAP (Liston, et al., 2001), and upregulation of *Srd5a1*, which catalyzes the production of dihydrotestosterone by passing testosterone (Chang, et al., 2011) in mouse prostates with *Pten* and *Zbtb7a* deletion compared with *Pten* deletion alone (Wang, et al., 2013). Notably, Xaf1 and the *Srd5a1* were found to be down- and upregulated, respectively, in prostate cancers with double gene inactivation compared to tumors with *Pten* deletion alone one month after castration. In addition, when *Pten*-null tumors presented evidence of resistance to ADT, expression of *Xaf1* was reduced and *Srd5a1* expression increased, further indicating that this gene expression signature reflects CRPC. Mechanistically, the reduced expression of *Xaf1* may explain the lack of apoptotic induction and proliferation arrest in CRPCs; and upregulation of *Srd5a1* and the subsequent increase in dihydrotestosterone levels may explain early reactivation of AR signaling in these tumors. Consistent with these data, *XAF1* downregulation and *XIAP* and *SRD5A1* upregulation were found to be associated with a high Gleason score, recurrence, and metastasis in human samples.

These p53- and ZBTB7A-regulated biologic and genetic activities led Lunardi et al. to hypothesize that inhibition of XIAP and SRD5A1 sensitizes prostate cancer cells to AR inhibition. Indeed, embelin, a XIAP inhibitor, significantly increased the apoptotic effects of ADT and radiation therapy on AR-positive and AR-negative human prostate cancer cells in vitro, respectively. Moreover, treatment of *Pbsn-cre4;Pten*$^{fl/fl}$*; Zbtb7a*$^{fl/fl}$ or *Pbsn-cre4;Pten*$^{fl/fl}$*; Trp53*$^{fl/fl}$ mice with bicalutamide together with embelin significantly enhanced the therapeutic effects. Further, the addition of dutasteride, a SRD5A1 inhibitor, to the above-mentioned combination therapy inhibited growth more effectively than with bicalutamide and embelinin human prostate cancer cell lines and GEMMs.

On the basis of these results, the investigators suggested that inactivation of *ZBTB7A* and *TP53*, potentially through XAF1-mediated inhibition of apoptosis and SRD5A1-mediated dihydrotestosterone production may provide survival benefit to prostate cancer cells following ADT and promote the CRPC phenotype. Knowledge of these genetic pathways may translate into reliable markers for the detection of this type of disease, and also beneficial therapeutic targets. These new findings show that directly addressing the biologic pathways that are affected by ADT— i.e., apoptosis and proliferation within the context of genetic predisposition by using GEMMs—can result in clear, clinically relevant advances in this important area of prostate cancer research.

The development of resistance to anti-cancer therapies, through selection of cancer cells harboring genetic alterations including deletions, is a fundamental challenge in medical

oncology. Sustained targeting of AR signaling by ADT activates and de-represses multiple signaling networks such as PI3K/Akt (Carver, et al., 2011), promoting dedifferentiation and enhancing tumor aggressiveness and resistance to hormonal manipulation. Identification of specific genetic alterations that contribute to the development of resistance to ADT may enable the prediction of initial resistance and direct disease management that is focused on novel therapeutic targets. By using GEMMs, Lunardi et al. showed that downregulation of XAF1 and upregulation of *XIAP* and *SRD5A1* predicted poor response to ADT and suggested that the addition of embelin and dutasteride will improve response. It would be interesting to evaluate whether genetic alterations other than the *TP53* and *ZBTB7A* deletions can generate this expression profile and whether tumors with initial or acquired resistance related to this signature will respond to these novel agents (Figure 1).

The *Pten* prostate-specific knockout model has been described in multiple reports because PTEN inactivation has been discovered in 15% of primary prostate tumors and in up to 60% of metastatic disease, while genetic alterations of the PI3K signaling occur in 100% of metastatic prostate cancers (Taylor, et al., 2010). The well-established responsiveness of the *Pten*-deleted tumors to castration (Wang, et al., 2003) along with the results of early clinical trials evaluating the combination therapies targeting AR signaling and PI3K/Akt suggest that the *PTEN* deletion is a frequent event during prostate cancer progression but is not sufficient to create the phenotype of CRPC. Thus, co-clinical GEMMs based on prostate-specific *Pten* deletion that mimic the course of prostate adenocarcinoma provide a very efficient and flexible platform for evaluating additional oncogenic events and alterations contributing to the development of lethal CRPC. These results can be translated to the clinical setting and validated by pre-existing expression profile datasets. This approach can set the stage for the identification of reliable predictive markers to guide clinical decisions and the discovery of effective combination therapies that will hopefully result in substantially increased survival for patients with the currently incurable metastatic CRPC.

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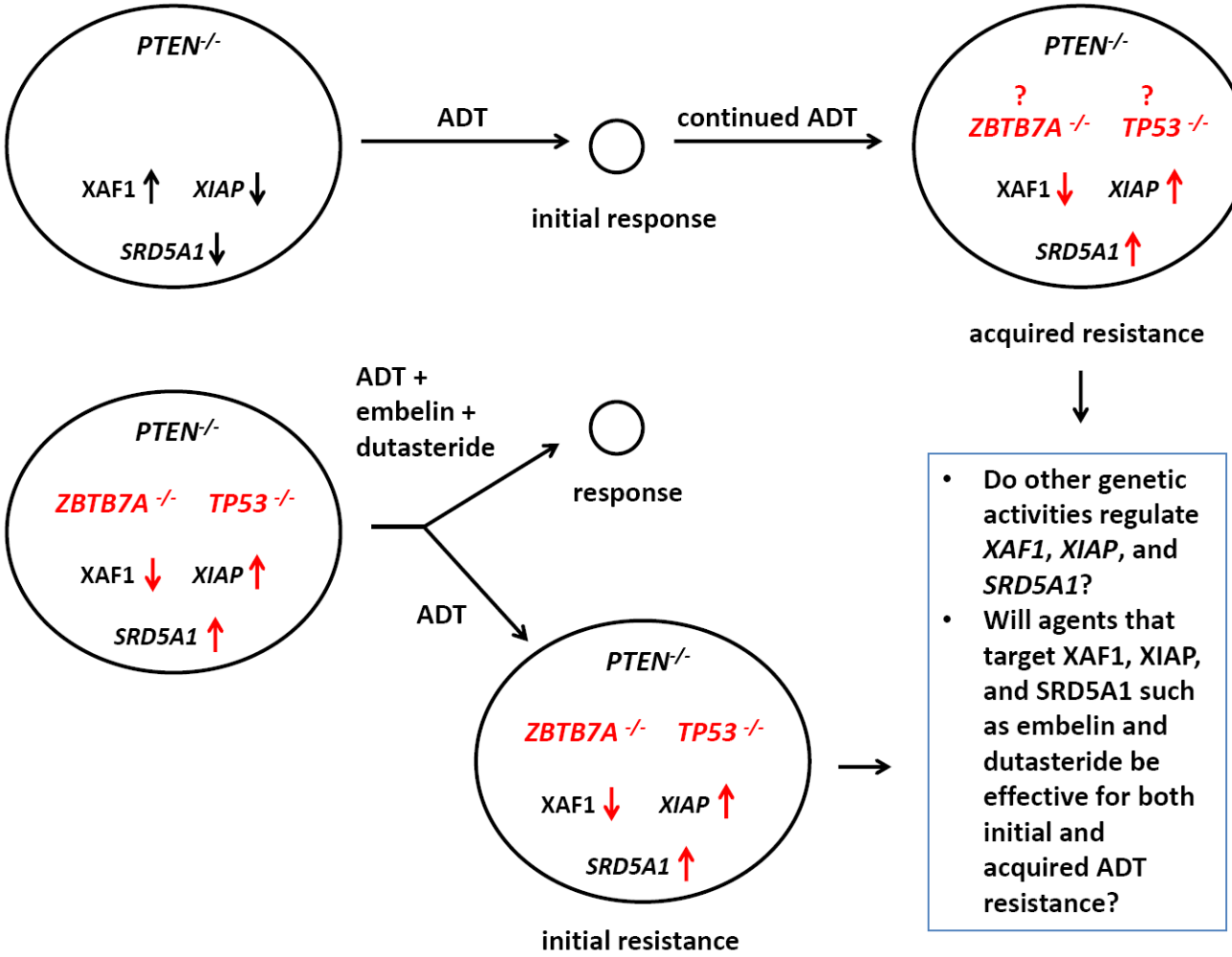

Figure 1. The genetic profile of prostate cancers predicts response to ADT and guides therapeutic decisions

Prostate cancers with genetic alterations resulting from *PTEN* deletion will present initial sensitivity to ADT translated to an early tumor regression, but the acquisition of oncogenic events and alterations will lead to an acquired resistance to ADT and cancer relapse. These tumors demonstrate XAF1 downregulation and *XIAP* and *SRD5A1* upregulation. Prostate cancers with *TP53* and *ZBTB7A* deletions will present initial resistance to ADT while the addition of embelin and dutasteride will increase their sensitivity to ADT and eventually lead to tumor regression. The potential sensitivity of tumors with initial resistance related to this *XAF1*, *XIAP*, and *SRD5A1* genetic profile to embelin and dutasteride may provide a second-line therapy for cancers with poor response to ADT.