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> *SPOP* mutations influence BET degradation and sensitivity to BET inhibitors in prostate cancer

PROSTATE CANCER

# BET inhibitors — *SPOP* right there!


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Speckle-type POZ protein (SPOP), the substrate-binding subunit of a cullin-3 (CUL3)-based E3 ubiquitin ligase complex, mediates the ubiquitylation and degradation of target proteins. Despite being the most frequently mutated gene in primary prostate cancer, the therapeutic implications of *SPOP* mutations are incompletely understood. Now, three studies in *Nature Medicine* identify bromodomain and extraterminal (BET) proteins — oncogenic transcriptional co-activators that are promising targets for epigenetic therapy — as SPOP substrates, and offer mechanistic insights into how *SPOP* mutations influence BET degradation and sensitivity to BET inhibitors in prostate cancer.

The three groups unanimously reported that wild-type SPOP promotes the ubiquitylation and proteasomal degradation of BET proteins, including bromodomain-containing protein 2 (BRD2), BRD3 and BRD4. Zhang *et al.* and Dai *et al.* identified an evolutionarily conserved SPOP-binding motif situated between two BET bromodomains, which was required for SPOP-dependent BET degradation. As prostate cancer-associated *SPOP* mutations map to the substrate-recognition domain, the groups hypothesized that they might impair BET degradation. Indeed, Zhang *et al.* and Dai *et al.* found that SPOP mutants failed to interact with and degrade BET proteins in cell line models, leading to accumulation of BET proteins. Elevated BRD4 levels had pro-tumorigenic effects *in vitro* and *in vivo*, and immunohistochemistry analysis demonstrated that BRD4 levels were elevated in *SPOP*-mutated primary prostate cancer specimens, which was associated with poor survival outcomes and progression.

Next, the groups explored whether aberrant BET degradation, conferred by *SPOP* mutations, could alter sensitivity to BET inhibitors. Zhang *et al.* reported that expression of the SPOP mutants in cell lines and xenograft mouse models conferred resistance to the anti-growth effects of BET inhibitors JQ1 and I-BET. Similarly, Dai *et al.* found that *SPOP*-mutated prostate cancer cell lines and patient-derived organoids were intrinsically resistant to BET inhibitor-induced apoptosis and growth arrest. Importantly, both studies noted that depletion of BET proteins — notably BRD4 — in the *SPOP*-mutated models resensitized prostate cancer cells to JQ1, demonstrating that stabilization of BET protein levels confers resistance to BET inhibitors. Using transcriptome and BRD4 chromatin immunoprecipitation–sequencing (ChIP–seq) analyses in *SPOP*-mutated prostate cancer cells, Zhang *et al.* demonstrated that BRD4 accumulation induced upregulation of the GTPase *RAC1* and cholesterol biosynthesis pathway genes, which elicit BET inhibitor resistance by activation of AKT–mTOR complex 1 (mTORC1) signalling. Accordingly, coadministration of AKT inhibitor ipatasertib abrogated BET inhibitor resistance.

Intriguingly, Janouskova *et al.* uncovered a paradox whereby cancer-type specific *SPOP* mutations that map to the same substrate-recognition domain confer differential sensitivity to BET inhibitors. Consistent with the other studies, prostate cancer-associated *SPOP* mutations impaired BET degradation and conferred resistance to JQ1. However, endometrial cancer-associated *SPOP* mutations enhanced BET degradation and sensitized endometrial cancer cells to JQ1, providing a preclinical rationale for BET inhibitor monotherapy in *SPOP*-mutant endometrial cancer.

Collectively, the findings provide a rationale for the evaluation of *SPOP* mutations or BET protein levels as predictive biomarkers to guide BET inhibitor therapy in prostate cancer. Furthermore, detection of cancer-type specific *SPOP* mutations could be used to select patients who might benefit from BET inhibitor therapy.

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**ORIGINAL ARTICLES**
Janouskova, H. *et al.* Opposing effects of cancer-type-specific SPOP mutants on BET protein degradation and sensitivity to BET inhibitors. *Nat. Med.* http://dx.doi.org/10.1038/nm.4372 (2017) | Dai, X. *et al.* Prostate cancer–associated SPOP mutations confer resistance to BET inhibitors through stabilization of BRD4. *Nat. Med.* http://dx.doi.org/10.1038/nm.4378 (2017) | Zhang, P. *et al.* Intrinsic BET inhibitor resistance in SPOP-mutated prostate cancer is mediated by BET protein stabilization and AKT–mTORC1 activation. *Nat. Med.* http://dx.doi.org/10.1038/nm.4379 (2017)