INVITED RESEARCH HIGHLIGHT

Speckle-type POZ protein mutations interrupt tumor suppressor function of speckle-type POZ protein in prostate cancer by affecting androgen receptor degradation

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Regulation of AR degradation by ubiquitination was first discovered a decade ago with MDM2 being the first E3 ubiquitin ligase identified to be involved in AR degradation. More recently, other E3 ligases, including RNF6 and SIAH2 have been identified to have differential expression in prostate cancer and have been implicated in AR regulation. The downstream consequences of protein ubiquitination depend on the type of modification, varying from protein degradation by the proteasome, detection of DNA damage and repair receptor internalization, vesicular transport and signal transduction. Nevertheless, the ubiquitin-mediated regulatory pathway is an essential component of prostate cancer cells that determines AR protein turnover. In a recent study, An et al.4 systematically and comprehensively determined that an additional E3 ubiquitin ligase SPOP (a member of bric-a-brac/Tramtrack/Broad complex [BTB] domain proteins) polyubiquinates the AR. Their in-depth analysis indicated that a consensus ASSTT SPOP binding motif in the hinge domain of the AR is critical for AR binding to the BTB domain of SPOP, and that this interaction is dependent on SPOP complexing with CUL3 and RBX1, which are E3 ligases. The AR-SPOP-CUL3-RBX1 complex results in degradation of the AR but importantly, also loss of gene expression of genes such as kallikrein-3 prostate-specific antigen and TMPRSS2 that are regulated by the AR. However, the greatest impact of this study stems from the potential correlation of these findings with previous observations in the prostate cancer field. For example, there are many AR variants that are expressed in the prostate, but only the full-length AR and AR variant v567es harbor the critical hinge region which contains the ASSTT SPOP binding motif. Not surprisingly, An et al.4 found that four AR variants that lack the hinge region were not affected by SPOP-mediated proteasomal degradation. Importantly, it has been reported that AR variants that lack the hinge region (Figure 4a) can activate transcription independent of androgen, thus possibly potentiating the CRPC phenotype. Thus, AR escape of SPOP-mediated proteasomal degradation coupled with androgen-independent transcriptional activity may represent a compounding effect through which these prostate cancers develop castrate resistance.

The paper further highlighted the clinical relevance of SPOP-mediated AR degradation by assessing the functional effects of somatic mutations (Y87C, Y87N, F102C, S119N, F125V, W131G, F133L, F133V) that are frequently detected in prostate tumors from exome sequencing projects. Interestingly, these mutations are located within the MATH domain (which is a substrate-binding motif, Figure 5a) and none are found in the BTB domain (which is a substrate-binding motif, Figure 5a) and none are found in the BTB domain.

Nevertheless, An et al.4 demonstrate that these SPOP variants cannot bind to the AR to mediate ubiquitin-mediated proteasomal degradation. Thus, these somatic mutations can serve as an alternative or complimentary mechanism that allows the AR to escape SPOP-mediated proteasomal degradation in CRPCs. An et al.4
further investigated other factors that could disrupt AR-SPOP interactions that ultimately deregulate SPOP-mediated degradation of the AR. To this end, the authors conducted a series of western blot experiments for AR expression as a function of SPOP-mediated degradation in C4-2 and 22Rv1 prostate cancer cells that were treated with mibolerone (synthetic androgen) or enzalutamide (anti-androgen that is currently used in the clinic). They discovered that AR that is bound to enzalutamide enhanced (Figure 7) SPOP-mediated AR degradation, whereas mibolerone protects against AR degradation. Similar to their earlier observations, the ligand-specific degradation of AR by SPOP is dependent on the allelic status of SPOP, whereby the previously described F133V variant is unable to mediate AR degradation.4

The AR signaling pathway is an important pathway in prostate cancer progression, which is why it is targeted therapeutically in the clinic using hormone therapy. Recent large scale exome sequencing studies indicate that SPOP is another important gene that might contribute to the CRPC phenotype. Interestingly, the authors reveal a functional relationship between these two important prostate cancer genes, specifically through ubiquitin-mediated proteasomal degradation. Importantly, they report how the functional interaction between the AR and SPOP may be altered by factors such as somatic mutations within the SPOP gene, AR variants, and anti-androgen therapy. An et al.’s4 study highlights the complexities of biomolecular interactions within a cell, and how many different factors can deregulate a critical pathway that can promote cancers such as those of the prostate. Understanding the mechanisms behind many of the observations from recent exome sequencing studies poses the greatest challenge in translating these data into practical results that can be used in the clinic. To this end, the study by An et al.4 is one of the first to have started this process, and many more are likely to follow, opening new avenues for targeted drug therapies.

COMPETING INTERESTS

The authors declare no competing interests.

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