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Drugging Plk1: An attractive approach to inhibit androgen receptor signaling


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Prostate cancer is the most commonly diagnosed malignancy and is the third leading cause of cancer death among men in developed countries. In the United States alone, an estimated 242,000 men were diagnosed with prostate cancer in 2012 and 28,000 died from their disease. Despite its high incidence and mortality, few risk factors have so far been identified for prostate cancer beyond increasing age, a family history of prostate cancer, certain genetic polymorphisms or mutations, living in a Western nation and African descent. Being of Asian descent is protective for prostate cancer. Prostate cancer treatment is dominated by strategies to control androgen receptor (AR) activity. AR has an impact on prostate cancer development through the regulation of not only transcription networks but also genomic stability and DNA repair, as manifest in the emergence of gene fusions. Therapeutically, the major focus of drug development is therefore to reduce androgen levels, for example, with inhibitors of androgen synthesis, such as abiraterone, or with antagonists that prevent androgen binding to AR, for example, enzalutamide or bicalutamide. These therapies confer survival advantages for patients with metastatic disease, but prostate cancer is nonetheless lethal once progression has occurred.

Personalizing the use of cancer therapeutics is the major focus of current biomedical research. Low molecular weight inhibitors of protein kinases represent a very attractive family of cancer drugs based on multiple observations that cancer cells have elevated kinase activity to enhance proliferation, migration and invasion, but also to maintain apoptosis resistance. Polo-like kinases (Plks) represent a family of very attractive drug targets. In a broad phylogenetic context Plks are master regulators of mitotic progression, involved in the regulation of mitotic entry, the metaphase-to-anaphase transition, and mitotic exit. Plks encompass an N-terminal serine/threonine kinase domain and a conserved C-terminal substrate-binding domain, termed the Polo box domain (PBD). The subcellular localization, the enzymatic activity and the interaction with substrates of Plks is controlled by their PBD.

Considering the clinical importance of prostate cancer, it is of utmost interest to investigate cellular signaling in prostate cancer cells. The study by Zhang and co-workers focuses on the role of Plk1 for the regulation of androgen receptor signaling. Most interestingly, the authors demonstrate diminished AR signaling as measured by reduced levels of SREBP1/2, CYP17A1 and CYP11A1 upon treatment with the small molecule Plk1 inhibitor BI2536. Moreover, Zhang and colleagues provided evidence for a mutual regulation of AR- and Plk1-signaling. Most remarkably, a treatment with the small molecule Plk1 inhibitor led to growth inhibition on tumor cells possessing castration resistance. This observation might have important clinical implications.

A major question relates to the mechanism by which Plk1 regulates AR signaling. Recent investigations revealed that the microtubule-stabilizing drug paclitaxel, which is commonly used for the treatment of prostate cancer, inhibits signaling from the androgen receptor by inhibiting its nuclear accumulation downstream of microtubule stabilization. In this context, Plk1 suppresses kinetochore-microtubule dynamics to stabilize initial attachments in prometaphase. An excellent recent study by the Liu lab relates Plk1 activity directly to the functional regulation of spindle components. Thus, prostate cancer cells are likely to be forced into apoptosis by 2 synergistic mechanisms: the induction of mitotic catastrophe associated with activation of spindle assembly checkpoint, and disturbances of AR signaling as demonstrated convincingly by the Liu lab.

However, additional mechanisms should also be considered: Recent studies by Raab and colleagues have indentified novel targets of BI2536 other than Plk1. Moreover, acetylation of lysine residues is a post-translational modification with broad relevance to cellular signaling and disease biology. Enzymes that ‘write’ (histone acetyltransferases, HATs) and ‘erase’ (histone deacetylases, HDACs) acetylation sites are an area of extensive research in current drug development. The principal readers of e-N-acetyl lysine (Kac) marks are bromodomains (BRDs), which are a diverse family of evolutionary conserved protein-interaction modules. Recently, studies on 2 inhibitors that target BRDs of the BET (bromodomains and extra-terminal) family provided compelling data supporting targeting of these BRDs in inflammation and in an aggressive type of squamous cell carcinoma. Furthermore, it was demonstrated that BI2536 targets the amino-terminal bromodomains of BRD4 and most interestingly BI2536 has the ability to displace BRD4 from chromatin. A new study revealed that AR-signaling-competent human CRPC cell lines are preferentially sensitive to BET inhibition. BRD4 binds with the N-terminal domain of AR and can be disrupted by the BRD4 inhibitor JQ1. Since BI2536 also modulates the function of BRD4, it should be considered that this could be also a mode of action of BI2536 for the downregulation of AR signaling. Taken together, the clinical dual kinase-bromodomain inhibitor BI2536 seems to be a potent and selective drug with polypharmacologies anticipated to add important therapeutic benefit for the treatment of prostate cancer patients.