CANCER

Lipid kinase PIP5K1α as a new target in prostate cancer

Prostate cancer is one of the most common malignancies, and treatment options at an advanced stage of disease are limited. Now, reporting in *Proc. Natl Acad. Sci. USA*, Persson and colleagues present the discovery of a small-molecule inhibitor of the phosphoinositide 3-kinase (PI3K)-related kinase PIP5K1α (phosphatidylinositol 4-phosphate 5-kinase type 1α) and demonstrate its activity in mouse models of advanced prostate cancer.

Members of the PI3K family of enzymes are well characterized and intensively pursued as targets for anticancer drugs. Less is known about the family of PIP5Ks, which act upstream of PI3K — they mediate the synthesis of phosphatidylinositol bisphosphate (PIP_2), a substrate used by PI3K to produce phosphatidylinositol triphosphate (PIP_3). PIP_3, in turn, activates the AKT family of serine/threonine kinases. These are frequently aberrantly activated in cancer cells and act as oncoproteins. In prostate cancer, PI3K–AKT has been reported to cross-activate androgen receptor (AR)-mediated signalling to promote progression to castration-resistant prostate cancer, which is refractory to treatments such as androgen depletion.

> “ISA-2011B was similarly potent at inducing tumour regression as the chemotherapeutic docetaxel”

The small molecule ISA-2011B was discovered in studies of derivatives of 1,2,3,4-tetrahydroisoquinoline heterocyclic compounds, which are commonly used in drug candidate synthesis. ISA-2011B was found to have a strong inhibitory effect on the proliferation of several aggressive cancer cell lines, and high-throughput kinase profiling identified its binding to PIP5K1α. In a mouse xenograft model of invasive human prostate cancer, ISA-2011B was similarly potent at inducing tumour regression as the chemotherapeutic docetaxel, but without the adverse effects of chemotherapy.

Studying the clinical importance of PIP5K1α in prostate cancer, the authors found that it was expressed at a higher level in clinical biopsies from patients with prostate cancer, and that there was a positive correlation between PIP5K1α and AR expression. Furthermore, metastatic lesions were found to contain significantly higher levels of *PIP5K1A* and *AR* mRNA compared with primary tumours. Transfection of non-malignant cells with a vector coding for PIP5K1α led to an increase in PIP_2 levels and AKT activation — and to the induction of key factors upstream and downstream of AKT, including molecules that control proliferation, survival, cell adhesion, invasion, metastasis and angiogenesis. Interestingly, PIP5K1α also appeared to increase the expression of AR — which formed protein–protein complexes in the nucleus with the cell cycle protein CDK1.

Next, the authors showed that treatment of androgen-insensitive prostate cancer cells with ISA-2011B reduced the levels of PIP5K1α. It also inhibited the phosphorylation of AKT, downregulated CDK1 and other cell cycle regulators and increased the expression of P27, a negative regulator of key cell cycle proteins. Together, these effects reduced invasiveness and induced apoptosis. Similar effects were achieved through small interfering RNA (siRNA)-mediated PIP5K1α knockdown — demonstrating that the effects of ISA-2011B are indeed mediated via PIP5K1α. In addition, unlike prostate cancer cells transfected with a control siRNA, prostate cancer cells with a PIP5K1α knockdown rarely gave rise to tumours when injected into mice.

Together, these studies suggest that PIP5K1α could be a promising target for the treatment of advanced prostate cancer.

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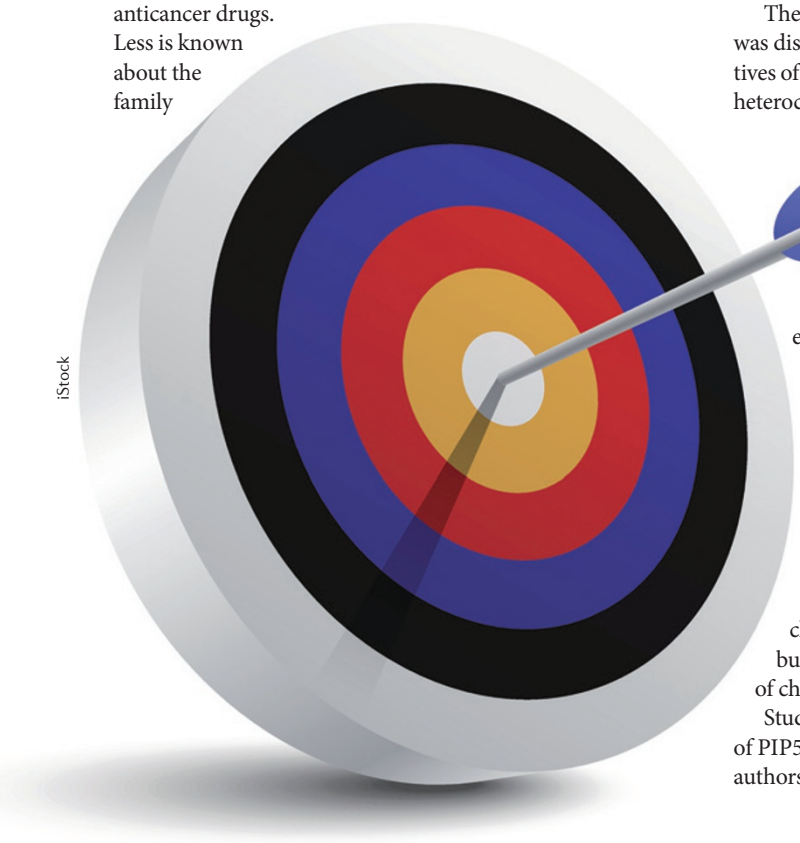

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ORIGINAL RESEARCH PAPER Semenas, J. *et al.* The role of PI3K/AKT-related PIP5K1α and the discovery of its selective inhibitor for treatment of advanced prostate cancer. *Proc. Natl Acad. Sci. USA* **11**, E3689–E3698 (2014)