ANTICANCER DRUGS

# Blocking phospholipid–protein interactions

Most strategies that target the phosphoinositide 3-kinase (PI3K) pathway — which is frequently dysregulated in tumorigenesis — have focused on inhibitors of downstream targets such as the protein kinase Akt. Now, Miao and colleagues describe a new way of modulating the pathway by blocking a key phospholipid–protein interaction, which suppresses tumour growth in a mouse cancer model.

The signalling molecule phosphatidylinositol-3,4,5-triphosphate ($PtdIns(3,4,5)P_3$; also known as PIP3) — which is the product of PI3K activity — controls cell growth, proliferation and survival through its interaction with proteins which contain pleckstrin homology (PH) domains. To identify inhibitors of this interaction, the authors performed a high-throughput screen of 50,000 small molecules, and found two compounds which disrupted the interaction between $PtdIns(3,4,5)P_3$ and the Akt PH binding domain with micromolar potency. Further characterization of one compound — termed PIT1 — suggested that it directly binds to the Akt PH domain, rather than targeting the lipid, and that the PIT1 binding site overlaps with the $PtdIns(3,4,5)P_3$ binding site.

The inhibitor exhibited selectivity towards a distinct subset of $PtdIns(3,4,5)P_3$-specific PH domains, including those of Akt and 3-phosphoinositide-dependent protein kinase 1 (PDK1), without affecting several $PtdIns(4,5)P_2$-selective PH domains. Comparison of the crystal structures of the PH domains of Akt, PDK1 and general receptor of phosphoinositides 1 (GRP1; a protein tyrosine kinase also known as cytohesin 3) showed that hydrophobic groups in the R2 and R3 positions of PIT1 would be preferred for Akt and disfavoured for PDK1 and GRP1 binding, suggesting that it would be possible to rationally modulate the selectivity of compounds that inhibited the interaction between $PtdIns(3,4,5)P_3$ and Akt PH binding domains.

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In glioblastoma cells — which show elevated basal levels of $PtdIns(3,4,5)P_3$ due to mutations in the phosphatase and tensin homolog (PTEN) — PIT1 suppressed PI3K-PDK1-Akt-dependent phosphorylation. Similar effects were also observed in growth factor-stimulated breast carcinoma cells. Moreover, the differential mechanism of action of PIT1 compared to several previously reported Akt inhibitors suggests that such compounds could be used in combination.

Next, the authors explored the potential anticancer activities of PIT1. The compound reduced the viability of multiple cancer cell lines, and caused preferential death of the cells which contained elevated $PtdIns(3,4,5)P_3$ levels (that is, cells with inactive PTEN) compared to cells expressing wild-type PTEN. PIT1 caused dysregulation of energy homeostasis, induced metabolic stress in cancer cells and led to the induction of autophagy. *In vivo*, a dimethyl analogue of PIT1 (used to improve solubility) attenuated tumour growth in a mouse model of breast cancer.

This study describes new small molecule antagonists of $PtdIns(3,4,5)P_3$–PH domain interactions, which could be used as leads for further optimization. Compounds such as PIT1 could be useful — either alone or in combination with existing Akt kinase inhibitors or PI3K inhibitors — in the therapy of tumours characterized by elevated $PtdIns(3,4,5)P_3$ levels, such as glioblastomas.

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**ORIGINAL RESEARCH PAPER** Miao, B. *et al.* Small molecule inhibition of phosphatidylinositol-3,4,5-triphosphate (PIP3) binding to pleckstrin homology domains. *Proc. Natl Acad. Sci. USA* **107**, 20126–20131 (2010)

**FURTHER READING** Liu, P. *et al.* Targeting the phosphoinositide 3-kinase pathway in cancer. *Nature Rev. Drug Discov.* **8**, 627–644 (2009)