ANTICANCER DRUGS

Blocking RAS effects

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Owing to their driver status in many cancers, members of the RAS family of oncoproteins have been strongly pursued as drug targets. However, inhibitors of proteins that farnesylate RAS proteins have shown limited clinical efficacy, hence alternative routes to RAS inhibition are required. A recent study has identified new RAS-binding inhibitors that can block RAS effector functions and that show antitumour effects in RAS-mutant tumours.

In previous structural studies, Tohru Kataoka, Fumi Shima and colleagues identified a surface pocket on RAS proteins that might be amenable to drug targeting to block effector protein binding. In their current study they used computational screening of a virtual library of >40,000 compounds to search for small molecules that might bind this pocket. Promising leads were functionally tested for their ability to disrupt the interaction between $HRAS^{G12V}$ and the CRAF effector protein, and two structurally similar compounds (Kobe0065 and Kobe2602) were found to be the most potent.

The authors found that the proliferation of $HRAS^{G12V}$-transformed NIH3T3 cells was inhibited by low micromolar doses of the compounds. Treatment inhibited various pathways downstream of RAS, including the MAPK, AKT and RALA pathways, indicating that the compounds inhibit the interaction of RAS with multiple effector proteins. Additionally, human cancer cell lines with hyperactivated mutant forms of KRAS, HRAS or NRAS were more sensitive to the growth-inhibitory effects of the compounds compared with cells that were wild-type for RAS isoforms. Thus, these compounds seem to have selectivity for RAS-mutant cells. Furthermore, when used in mice, these compounds resulted in modest growth inhibition and apoptosis of KRAS-mutant SW480 human colon carcinoma cell xenografts.

Finally, to characterize in detail the binding interactions of these compounds, the authors used NMR to solve the atomic structure of a trimeric complex of HRAS bound to a water-soluble derivative of Kobe0065 and a GTP analogue. They indeed found that inhibitor binding occurred in the identified pocket and that this resulted in steric hindrance of effector binding. Moreover, the mode of inhibitor binding was distinct from other recently identified RAS-binding compounds that do not disrupt interactions with RAS effector proteins. Such interaction data could aid the development of future inhibitors with improved RAS-binding potency.

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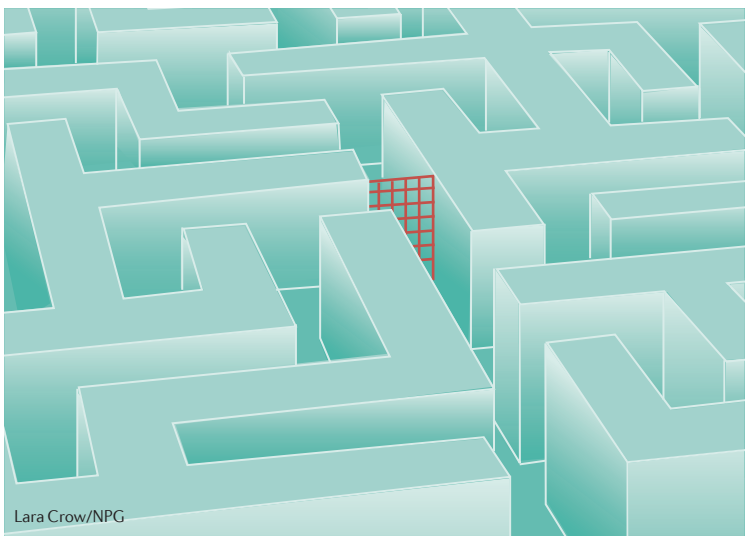
ORIGINAL RESEARCH PAPER Shima, F. *et al.* *In silico* discovery of small-molecule Ras inhibitors that display antitumor activity by blocking the Ras–effector interaction. *Proc. Natl Acad. Sci. USA* 29 Apr 2013 (doi:10.1073/pnas.1217730110)



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