

Tapeworm drug targets common vulnerability in tumor cells

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A drug used to treat tapeworm infections could also be used to fight a wide range of cancers, an A*STAR study suggests.

More than half of human cancers carry a mutation in the tumor suppressor gene p53, making it an attractive target for <u>cancer</u> therapy. Many research efforts have focused on directly or indirectly restoring p53 function in mutated <u>cells</u>, but the team, led by Chit Fang Cheok of A*STAR's Institute of Molecular and Cell Biology, took a different approach. Instead of trying to fix p53, which mutates in hundreds of ways in cancers, they exploited the differences between wild-type and p53-deficient cells to develop a treatment based on the vulnerabilities of p53," Cheok says.

The team tested the effect of 1,600 FDA-approved compounds on cultured colon cancer cells with normal and mutated versions of p53. The compound that was best at killing p53-deficient cells, rather than cells with p53, was niclosamide, a drug used to treat tapeworm infections. Subsequent tests showed that niclosamide was also effective against other p53-deficient cancer cell lines.

Niclosamide is known to affect cells by interfering with energy production in mitochondria (an effect known as 'mitochondrial uncoupling') and causing changes in <u>fatty acid metabolism</u>. Experiments showed that mitochondrial uncoupling is integral to niclosamide's ability to selectively kill p53-deficient cells, but isn't enough to explain it, since a similar amount of uncoupling was also seen in p53-positive cells. In other words, it was still unclear why the drug was more effective against p53-deficient cells. "We went on a long 'Sherlock Holmes'-like journey



to understand what was happening," says Cheok.

They examined the metabolic profile of niclosamide-treated cells and found that the p53-deficient cells had significantly more of a fatty acid known as <u>arachidonic acid</u>. Their investigation revealed that the mitochondrial uncoupling caused by niclosamide increases the calcium concentration in a cell, which boosts the production of arachidonic acid.

The team showed that this increase is normally counteracted by p53, which switches on two genes that break down arachidonic acid, ALOX5 and ALOX12B. These genes were not activated in p53-deficient cells, allowing arachidonic acid to accumulate, and causing mitochondria to release a molecule known as cytochrome c, leading to programmed cell death. Future work may identify other drugs that activate the same pathway and could also be used to treat p53-deficient cancers. "We were able to join all these dots in a very surprising manner, which was very exciting," says Cheok.

To confirm their model, the researchers knocked out ALOX5 and ALOX12B in cells with a working copy of p53. They found that the engineered cells were more sensitive to niclosamide treatment even though they had a functioning p53 gene. Likewise, knocking out ALOX5 and ALOX12B in p53-deficient cells did not increase their niclosamide sensitivity.

Finally, the team confirmed that niclosamide is effective against p53-deficient cancers in animals, and not only in cultured cells. They injected mice with cells from the colon cancer cultures and measured tumor progress following niclosamide treatment. Niclosamide reduced tumor growth by 50 per cent in mice which had received p53-deficient cells but had no effect on tumors in mice injected with p53-positive cells.



Based on their findings, the researchers have filed a patent for the use of niclosamide to treat p53-deficient cancers. Since this approach targets deficiency rather than a specific mutation, Cheok expects it to be effective against a broad spectrum of cancers. Niclosamide has been used to treat humans for decades and is listed by the WHO as an effective, safe, and cheap medicine, raising hope for its use a potent, safe therapy against a broad spectrum of cancers with non-functional p53.

More information: R. Kumar et al. Mitochondrial uncoupling reveals a novel therapeutic opportunity for p53-defective cancers, *Nature Communications* (2018). DOI: 10.1038/s41467-018-05805-1

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