

Toxic mushroom-based drug may help battle colorectal cancer

April 22 2015



Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

For some time, cancer scientists have considered the toxin, alpha-amanatin derived from "death cap" mushrooms, as a possible cancer treatment. However, due to its penchant for causing liver toxicity, its potential as an effective therapy has been limited.

Researchers at The University of Texas MD Anderson Cancer Center looked at antibody drug conjugates (ADCs) based on alpha-amanatin as one solution. They found that ADCs, when aimed at a gene called POLR2A, are highly effective in mouse studies in treating [colorectal cancer](#). The drug caused complete tumor regression and greatly reduced toxicity. ADCs allow for improved targeting of [cancer cells](#), resulting in less impact on healthy cells.

Xiongbin Lu, Ph.D., associate professor of Cancer Biology, observed that when the common [tumor suppressor gene](#), TP53 is deleted resulting in [cancer](#) growth, another nearby gene, POLR2A is also deleted. Normal cells have two copies of POLR2A and TP53 genes. Lu's study targeted cancers that had a single copy of both genes, representing 53 percent of colorectal cancers, 62 percent of breast cancers and 75 percent of [ovarian cancers](#).

"POLR2A is an essential gene for cell survival, including cancer cells," said Lu. "Because there is only one copy, the cancer cells are more susceptible to suppression of this gene."

Lu's study was published in the April 22, 2015 issue of *Nature*.

Discovering that POLR2A is deleted at the same time as TP53 means that therapies can more narrowly target the genetic processes allowing cancer cells to thrive. Understanding that one copy of POLR2A can allow cancer to grow gives researchers a new target to hit. As it turns out, it can be suppressed by an ADC based on the mushroom toxin. Lu's team tested the drug, alpha-amanatin as it was believed that it specifically inhibited POLR2A.

"A tremendous effort has been made to restore TP53 activity in cancer therapies," said Lu. "However, no TP53-based therapy has been successfully translated into clinical [cancer treatment](#) due to the

complexity of TP53 signaling. POLR2A encodes an enzyme that is inhibited by alpha-amanatin. We found that suppression of POLR2A with low-dose alpha-amanatin stopped [cancer cell growth](#) and reduced toxicity."

"We anticipate that inhibiting POLR2A will be a novel therapeutic approach for human cancers harboring such common genomic alterations," said Lu.

More information: TP53 loss creates therapeutic vulnerability in colorectal cancer, *Nature*, [DOI: 10.1038/nature14418](https://doi.org/10.1038/nature14418)

Provided by University of Texas M. D. Anderson Cancer Center

Citation: Toxic mushroom-based drug may help battle colorectal cancer (2015, April 22)
retrieved 19 November 2023 from
<https://medicalxpress.com/news/2015-04-toxic-mushroom-based-drug-colorectal-cancer.html>

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