Sea creature's toxin could lead to promising cancer treatment

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A toxin derived from a reclusive sea creature resembling a translucent doughnut has inspired UT Southwestern Medical Center researchers to develop a related compound that shows promise as a cancer treatment.

In a study appearing online this week in the *Proceedings of the National Academy of Sciences*, the UT Southwestern scientists detail how the toxin blocks uninhibited reproduction of cultured human cancer cells while leaving healthy cells unaffected.

An accompanying study in PNAS shows that, in pre-clinical trials, a synthetic form of the toxin reduced human tumors implanted in mice without the harmful side effects seen using other cancer drugs. "Diazonamide is a special molecule – it's teaching us more than we imagined," said Dr. Patrick Harran, professor of biochemistry and a senior author on both studies.

"This is a truly exciting result," said Dr. John Schwab, a program officer at the National Insti tutes of Health's National Institute of General Medical Sciences, which partly funded the work. "Not only has this UT Southwestern team identified a potent anti-cancer drug, but its unique mode of action avoids the kinds of side effects that make cancer chemotherapy so difficult. It's a great example of how NIH support for fundamental chemical research can benefit the American health-care consumer."

The animal, *Diazona angulata*, is a sea squirt a few inches wide that lives

in colonies anchored to rocks. It was discovered offshore of the Philippines in 1990 as scientists were looking for species that might lead to useful drugs. From a few specimens, scientists extracted a tiny amount of a toxin, diazonamide A, which the animal probably uses to repel predators.

The toxin proved to kill cancer cells in culture, but so little of its natural form was available that a race soon began to synthesize it in the laboratory.

A chemical structure for diazonamide A was published in 1991, but in 2001, Dr. Harran's group showed that initial report to be incorrect, and uncovered the correct structure. In the first of the two new studies, Dr. Harran and his co-workers synthesized several variants of diazonamide A in order to pin down how it prevents cancer cells from dividing.

Normal cell division involves a structure called the mitotic spindle, which pulls apart the chromosomes before the cell splits. The spindle is primarily made out of a substance called tubulin. Some anti-cancer drugs attack tubulin, but they have serious side effects, such as nerve damage and depletion of bone marrow and white blood cells.

The UT Southwestern researchers found that while diazonamide A blocked cell division, it seemed not to bind directly to tubulin. Instead, Dr. Xiaodong Wang, professor of biochemistry, and Dr. Gelin Wang, instructor of biochemistry, found that the toxin interacted with an enzyme called OAT, which was known to be involved in cellular metabolism but had no previously known role in cell division.

Interestingly, diazonamide did not block OAT's enzyme activity, the researchers said. Rather, it uncovered a second function for the protein in cell division.

"The finding that OAT is the cellular target of diazonamide is surprising for two reasons: First, there is no previous report that a mitochondrial enzyme like OAT can play a direct role in mitosis; second, OAT seems dispensable for normal cell division occurring in mice and men but is required for the division of cancer cells. This may explain the cancer specificity of diazonamide," said Dr. Wang, who is also a Howard Hughes Medical Institute investigator.

Dr. Noelle Williams, assistant professor of biochemistry and internal medicine, led the second phase of the research, which tested the effect of a variant of diazonamide A, called AB-5, in mice with tumors.

AB-5 has a structure nearly identical to diazonamide A and is indistinguishable in its biological action, but is easier to synthesize in the lab.

The researchers tested AB-5's effectiveness against cancer by implanting human tumor cells under the skin of m ice and treating them with either paclitaxel (Taxol) or vinblastine – both approved drugs currently used – or AB-5. The trial used tumor cells from human prostate, breast and colon cancers.

While all three drugs reduced tumors in the mice, the known drugs caused significant weight loss and loss of white blood cells while AB-5 caused neither side effect. "That the diazonamide toxin blocks mitosis selectively in cancer cells is almost too desirable an outcome to be true," said Dr. Steven McKnight, chairman of biochemistry and senior author of the second study. "As with any other unanticipated scientific discovery, the validity of these observations will be held to appropriately diligent scrutiny."

Source: UT Southwestern Medical Center