Broccoli compound targets key enzyme in late-stage cancer

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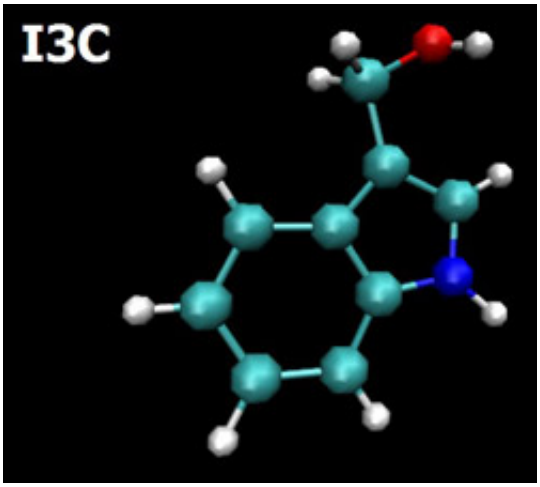

Indole-3-carbinol, or I3C, is a chemical compound found in broccoli and other cruciferous vegetables and which is known to stop the growth of breast cancer cells. UC Berkeley researchers' discovery of how I3C works will help them modify the compound to improve its anti-cancer effects. (Firestone & Bjeldanes labs/UC Berkeley)

(PhysOrg.com) -- An anti-cancer compound found in broccoli and cabbage works by lowering the activity of an enzyme associated with rapidly advancing breast cancer, according to a University of California, Berkeley, study appearing this week in the online early edition of the journal *Proceedings of the National Academy of Sciences*.

The compound, indole-3-carbinol, is already undergoing clinical trials in

humans because it was found to stop the growth of breast and prostate cancer cells in mice.

The new findings are the first to explain how indole-3-carbinol (I3C) stops cell growth, and thus provides the basis for designing improved versions of the chemical that would be more effective as a drug and could work against a broader range of breast as well as prostate tumors.

"I think one of the real uses of this compound and its derivatives is combining it with other kinds of therapies, such as tamoxifen for breast cancer and anti-androgens for prostate cancer," said coauthor Gary Firestone, UC Berkeley professor of molecular and cell biology. "Humans have co-evolved with cruciferous vegetables like broccoli and Brussels sprouts, so this natural source has a lot fewer side effects."

"This is a major breakthrough in trying to understand what the specific targets of these natural products are," said coauthor Leonard Bjeldanes, UC Berkeley professor of toxicology. "The field is awash with different results in various cells, but no real identification of a specific molecular target for these substances. The beauty of identifying the target like this is that it suggests further studies that could augment the activity of this type of molecule and really specify uses for specific cancers."

Firestone, Bjeldanes and their colleagues showed that I3C inhibits the enzyme elastase, which at high levels in breast cancer cells heralds a poor prognosis: decreased response to chemotherapy, reduced response to endocrine treatment and reduced survival rates.

Elastase is an enzyme that shortens a cellular chemical, cyclin E, that is involved in controlling the cell cycle. The shortened version of cyclin E accelerates the cell cycle, making cancer cells proliferate faster. Firestone showed that I3C prevents the elastase shortening of cyclin E, thereby arresting development of breast cancer cells.

For more than 15 years, Firestone, Bjeldanes and their colleagues have studied the anti-cancer benefits of vegetables in the cabbage family that are lumped together in the genus Brassica and, because of their cross-shaped flowers, are often referred to as cruciferous vegetables.

Though the anti-cancer benefits have been recognized since the 1970s, the mechanism is only now being discovered, in part through the work of Firestone, Bjeldanes and their UC Berkeley colleagues.

"We have connected the dots on one extremely important pathway" by which indole-3-carbinol works, Firestone said.

In previous work, they found that indole-3-carbinol interferes with more than cell proliferation. It also disrupts the migration and alters adhesion properties of cancer cells, as well as counteracts the survival ability of cancer cells, all of which are implicated in cancer cell growth. To have such broad downstream effects, I3C must act at the beginning of a major cellular pathway, Firestone said. The newly reported research pins this activity to elastase and its effect on cyclin E.

Bjeldanes noted that I3C is available as a supplement and is a preferred preventative treatment for recurrent respiratory papillomatosis, a condition involving non-malignant tumors of the larynx. Improved versions of the chemical could thus help treat cancers other than those of the breast and prostate.

Graduate student Ida Aronchik and recent Ph.D. recipient Hanh H. Nguyen, along with colleagues in the Firestone and Bjeldanes labs, have already chemically modified I3C and boosted its activity in cell culture by at least a factor of 100. The lab teams currently are probing the elastase structure and how I3C interacts with it to identify the best parts of the I3C molecule to modify.

I3C is only one of many plant-derived chemicals, called phytochemicals, that Firestone is investigating in his laboratory as potential anti-cancer agents. Among them is the anti-malarial drug artemisinin. Last month, the Journal of Biological Chemistry accepted a paper by Firestone and his colleagues showing that artemisinin blocks prostate cancer cell growth by interfering with the same intracellular pathway as does I3C. This pathway involves the transcription factor SP1, which latches onto other genes to boost their activity.

"SP1 could be a generalized target of phytochemicals," Firestone said. "Phytochemicals work because they interact with and inhibit enzymes that control a host of cellular processes, including migration and adhesion."

Provided by University of California - Berkeley