Scientists find novel use for old compound in cancer treatment

January 15 2009

The compound, α-difluoromethylornithine or DFMO, targets the activity of a specific enzyme and, even in very limited doses, is effective in protecting against the malignancy in animal models. The study was published in the January 15, 2009 issue of the journal, *Cancer Research* (Volume 69, Issue 2).

"The drug, which was developed as a cancer therapy and later shelved because of toxicity concerns, has been around since the 1970s," said John Cleveland, Ph.D., chair of the Scripps Florida Department of Cancer Biology whose laboratory conducted the study. "But over the past five years, it has undergone a rebirth as a chemoprevention agent, first showing efficacy in animal models of human cancer and more recently in human prostate and colon cancer. Our study shows that it likely works in a large cast of tumors, even those having poor prognosis, like high-risk neuroblastoma."

Neuroblastoma is a childhood malignancy of the sympathetic nervous system (part of the nervous system that serves to accelerate the heart rate, constrict blood vessels, and raise blood pressure) that accounts for nearly eight percent of all childhood cancers and 15 percent of pediatric cancer-related deaths. Its solid tumors arise from developing nerve cells, most commonly in the adrenal gland, but also in the abdomen, neck, and chest. Neuroblastoma usually occurs in infants and young children, appearing twice as frequently during the first year of life than in the second.

Tragically, children with stage IV, high-risk neuroblastoma have a less than a 40 percent chance of long-term survival.

The best-known genetic alteration involved in neuroblastoma is the amplification of the proto-oncogene—a molecule that when overexpressed can cause cancer—called MYCN. Amplification of MYCN occurs in about 20 percent of all neuroblastoma and is associated with the high-risk form of the disease. Targeting this and related genes directly might be therapeutically tempting, the study noted, but highly problematic because the oncoproteins they produce are also required for the growth of most normal cell types.

As a result, Cleveland and colleagues focused on inhibiting ornithine decarboxylase (Odc), a protein that contributes to cancer cell growth and that is a target of the proto-oncogene MYCN. Increased levels of Odc are common in cancer, and forced Odc expression in animal models has been shown to lead to increased tumor incidence. Recent findings have shown that Odc overexpression is also an indication of poor prognosis in neuroblastoma. DFMO, the drug used by the Cleveland team, inhibits the activity of Odc.

To test the effect of DFMO on preventing neuroblastoma, the study used a transgenic mouse that faithfully models many of the hallmarks of MYCN-amplified neuroblastoma in humans.

"We were able to prevent neuroblastoma caused by MYCN, delaying the onset and incidence of this tumor type" said Cleveland. "What's even more compelling, we used low doses of the drug, and DFMO only had to be given for a moderate amount of time to prevent cancer."

While DFMO selectively impaired the proliferation of MYCN-amplified neuroblastoma, it had no appreciable effect on non-MYCN-amplified neuroblastoma cell lines, indicating that the growth of the former is

"addicted" to Odc.

"Our study offers a strong suggestion to the clinical cancer community that they should keep an open mind about the Odc-polyamine pathway, and that this particular pathway might represent a novel therapeutic angle to tackle this malignancy." Cleveland said. "While there are valid safety concerns about giving DFMO to pediatric patients suffering from advanced stage MYCN-amplified neuroblastoma, it may be time to revisit the issue as our study showed that transient treatment with DFMO is sufficient to provide chemoprevention and may show benefit for this otherwise lethal malignancy."

Source: Scripps Research Institute