Experiments could lead to new treatments for neuroblastoma

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Neuroblastoma is one of the most devastating diagnoses a child can receive. The cancer's victims average 2 years old when the disease is detected, most often by a parent feeling a lump in a child's abdomen. By then, the disease has often reached an advanced stage, and advanced neuroblastoma kills more than 50 percent of the children in whom it develops, despite aggressive treatment with surgery, chemotherapy and radiation.

Now, though, University of Texas Medical Branch at Galveston researchers believe they've found a critical weakness in the deadly cancer — one that could lead to the development of a lifesaving therapy. In a paper published this week in the "*Proceedings of the National Academy of Sciences*," a team led by associate professor of surgery Dr. Dai H. Chung describes cell-culture and animal experiments that demonstrate how shutting down a single biochemical signaling connection dramatically suppresses neuroblastoma tumor formation and slows the cancer's spread.

Their investigation centered on an intercellular signaling molecule known as gastrin-releasing peptide, or GRP, and the receptor molecule with which it docks on the cell's surface. GRP activates the production of gastrin, a hormone that among other things controls the release of gastric acid in the stomach; GRP is also produced by neuroblastoma cells and acts to accelerate their proliferation, a discovery made earlier by the UTMB group.

"We had previously demonstrated that GRP stimulates the growth of this particular cancer," said Chung. "This time we wanted to demonstrate the opposite effects by targeting GRP receptors in neuroblastoma, to see if we could make the cancer regress."

To "target" GRP, the researchers took a line of aggressive human neuroblastoma cells and added short-hairpin RNAs, tiny bits of genetic material specifically designed to keep cells from making particular proteins — in this case GRP receptor molecules. Experiments with the GRP-receptor-silenced human neuroblastoma cells revealed that they grew much less quickly than unaltered neuroblastoma cells, and showed less activity on a biochemical signaling pathway that is associated with abnormal cell proliferation.

The scientists then cultured the customized cells in soft agar, a gelatin-like material that gave them no surface to which they could attach themselves. Most cells need be solidly anchored to multiply and form colonies, but neuroblastoma cells (like other cancer cells) thrive in soft agar suspension

"In order for cells in a soft agar colony to proliferate and grow without adhering to a surface, they have to possess malignant properties, as in the original neuroblastoma cells," Chung said. "However, our GRP receptor-silenced neuroblastoma cells behaved like nonmalignant cells — their growth was significantly inhibited, and they formed fewer new colonies."

To further test what effect blocking GRP/GRP receptor binding would have on neuroblastoma in experimental animals, the researchers injected their GRP receptor-silenced neuroblastoma cells into immune-deficient mice. "We wanted to see how these neuroblastoma cells would behave, whether they would grow and/or metastasize to the liver," Chung said. "But instead, tumor growth was significantly attenuated." In control

group mice, by contrast, "the cancer cells that expressed the GRP receptors behaved as we expected with rapid growth as well as aggressive liver metastases. The implication is that the metastatic behavior of this cancer is driven by GRP and its receptor."

Although researchers are discussing the use of short-hairpin RNA and other RNA interference techniques as potential therapies for patients with neuroblastoma and other cancers, Chung said, a compound that blocks the GRP receptor has already been approved by the FDA for adult use.

"With the publication of our data, we would like to propose an application involving a number of institutions to move forward with a phase 1 clinical trial using this FDA-approved GRP receptor antagonist for neuroblastoma," Chung said. "We hope to demonstrate the safety of targeting GRP receptors for effective inhibition of neuroblastoma growth and metastasis. This is just such a tragic disease, and with all the advances we're making, we ought to be able to make a dent in it."

Source: University of Texas Medical Branch at Galveston

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