Protein may be key to new treatment in a childhood cancer

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After analyzing hundreds of proteins produced by the DNA of tumor cells, researchers have identified one protein that may be central to a new treatment for the often-fatal childhood cancer neuroblastoma. Oncologists hope to translate the finding into pediatric clinical trials of a drug that blocks the protein's activity.

"Our study implicates this protein as a promising treatment target for high-risk neuroblastoma," said pediatric oncologist Kristina A. Cole, M.D., Ph.D., of the Cancer Center at The Children's Hospital of Philadelphia. "The fact that drugs acting on this protein are already being studied in clinical trials for adult cancers may hasten the process of testing this treatment strategy in children."

Cole is the lead author of a study published online Feb. 2 in the Proceedings of the National Academy of Sciences.

Neuroblastoma, a cancer of the peripheral nervous system, usually appears as a solid tumor in the chest or abdomen. It accounts for 7 percent of all childhood cancers, but because it is often aggressive, it causes 15 percent of all childhood cancer deaths. While low-risk forms of neuroblastoma may spontaneously disappear, in high-risk forms, the cancer tends to return after initial treatment, usually with lethal results.

In the current study, the Children's Hospital researchers performed a comprehensive screen of hundreds of protein kinases encoded by the DNA of neuroblastoma cells. As enzymes, kinases stimulate chemical

reactions in the cell, and have been implicated in many cancers as promoting growth and survival of cancer cells. The study team used RNA interference, a powerful research tool that uses small RNA sequences to prevent cells from producing proteins, to interrupt the action of each of the more than 500 kinases made by neuroblastoma tumor cells.

Methodically testing each kinase, one after the other, the researchers identified 30 kinases that, when depleted, caused neuroblastoma cells to die. Among those kinases, cell checkpoint kinase 1 (CHK1) had the strongest effect. "This screen was an unbiased study," said Cole. "We did not know beforehand which kinase would have the most potent effect. In fact, we would not have suspected CHK1, which was thought to be a tumor suppressor. It actually has the opposite effect in neuroblastoma. Its signals appear to drive neuroblastoma growth, likely by allowing them to tolerate stress to DNA caused by the MYC and MCYN oncogenes, which are active in neuroblastoma. Blocking CHK1 activity by RNA interference or by small-molecule inhibitors kills neuroblastoma cells."

When cancer cells are treated with chemotherapy, they can repair themselves though CHK1 signaling, making the chemotherapy less effective. Normal cells have redundant repair pathways and are not affected by CHK1 inhibition. Therefore CHK1 inhibitors are already being tested in adult clinical trials, in combination with chemotherapy, as a possible treatment for lung cancer, pancreatic cancer and other solid tumors. The current study suggests that neuroblastoma cells are particularly sensitive to CHK1 inhibition, without being combined with other agents.

CHK1 is not the first kinase with an important role in neuroblastoma. Some of the collaborators in this study from The Children's Hospital of Philadelphia previously discovered that the anaplastic lymphoma kinase gene (ALK), which carries the code for the ALK kinase, gives rise to

some high-risk forms of neuroblastoma. Children's Hospital is currently testing ALK inhibitors in pediatric clinical trials of neuroblastoma, under the sponsorship of the Children's Oncology Group, a cooperative multicenter research organization.

"While it is compelling that there is single-agent activity in neuroblastoma," said Cole. "we anticipate that CHK1 inhibitors combined with chemotherapy will be significantly more potent." Cole expects pediatric oncologists to begin testing CHK1 inhibitors in pediatric clinical trials for neuroblastoma within the next few years.

More information: "RNAi screen of the protein kinome identifies checkpoint kinase 1 (CHK1) as a therapeutic target in neuroblastoma," *Proceedings of the National Academy of Sciences*, Early Edition published online Feb. 2, 2011. doi: 10.1073/pnas.1012351108

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