MedicalXpress

Researchers follow a path to a potential therapy for NF2, a rare tumor disorder

April 15 2011

The proteins that provide cells with a sense of personal space could lead to a therapeutic target for Neurofibromatosis Type 2 (NF2), an inherited cancer disorder, according to researchers at The Wistar Institute. Their findings, which appear in the April 12 issue of the journal *Cancer Cell*, could have profound implications for NF2 and related cancers, such as mesothelioma.

The researchers describe, for the first time, that Merlin, the protein encoded within the NF2 gene interacts with a protein called angiomotin. This connection between Merlin and angiomotin also brings together two important information networks in cells, both of which have been implicated in numerous forms of cancer. It is a connection, the researchers say, between the sensors that detect interactions between cells and the signaling networks that drive cell division.

"Angiomotin is required for movement of cells that form new blood vessels, so it is fascinating to see it so closely linked to merlin, the product of the NF2 gene, loss of which leads to tumor formation," said Joseph Kissil, Ph.D., senior author of the study and associate professor in the Molecular and Cellular Oncogenesis Program of The Wistar Institute Cancer Center. "The discovery opens up a potential new method to treat NF2 by attacking the tumor cells directly and by starvation, a strategy already employed in certain cancer therapies."

"Drugs like Avastin, for example, target the growing blood vessels," Kissil said, "but what makes angiomotin a tempting target is that it is

used by both blood vessels and the growing tumor cells that need the nutrients these blood vessels provide."

NF2 is a genetic disorder caused by a mutation in both copies of a person's NF2 gene. It occurs in about one in every 30,000 people, and it is mostly hereditary. NF2 generally appears as benign tumors in the nervous system of young adults, often causing deafness as tumors affect the auditory nerves. While the tumors are mostly benign, more malignant tumors may eventually arise. Moreover, even the benign tumors often cause debilitating pain as they spread throughout the nervous system. There is currently no treatment for NF2 other than surgery to remove tumors as they appear.

Mutations in the NF2 gene disrupt the function of the gene's protein product, Merlin, which is part of an elaborate molecular signaling pathway that regulates how cells grow and divide. These pathways are akin to information channels, and disrupting one protein can alter the function of other proteins both upstream and downstream along the channel. Merlin is particularly interesting to cancer biologists, as the mutations have been found in about half of all cases of the deadly lung cancer mesothelioma, and in some instances of thyroid, bladder and other cancers.

According to Kissil, Merlin normally stops cells from growing once they come into contact with adjacent cells. That is, Merlin binds to the angiomotin at "junctions," areas where cells come into contact with each other. When bound together, the interacting proteins relate a signal to the cell that, essentially, orders it to cease further growth and movement. It is a way for cells to coordinate their growth within a tissue. Cancerous cells, for example, often lack that sense of inhibition, and they will continue growing unchecked.

The Kissil laboratory plans to continue their exploration of angiomotin

as a potential therapeutic target for treating NF2, as well as look into the role of angiomotin in other cancers known to be affected by NF2 mutations.

Provided by The Wistar Institute