Repair of DNA by Brca2 gene prevents medulloblastoma

21 May 2007

Investigators at St. Jude Children's Research Hospital have gained some of the first major insights into how certain genes known to prevent cancer also guide the normal development of the nervous system before birth and during infancy by repairing DNA damage.

The St. Jude researchers demonstrated that the Brca2 gene plays a dual role in the developing nervous system, eliminating errors in the DNA of newly made copies of chromosomes and suppressing the onset of the brain cancer medulloblastoma. Medulloblastoma is a cancer of the cerebellum—the lower back part of the brain that controls complex motor functions and communicates with other parts of the brain. This cancer accounts for about 20 percent of childhood brain tumors, about half of which occur in children younger than six years.

The role of Brca2 is important because as the cerebellum grows in size and complexity before and shortly after birth, it rapidly produces many new nerve cells.

"Our study showed that the Brca2 gene acts as a surveillance mechanism that triggers repair of DNA that is damaged when the cell makes a duplicate set of its chromosomes each time it divides," said Peter McKinnon, Ph.D., associate member of the Genetics and Tumor Cell Biology department at St. Jude. "The enormous rate of cell divisions during growth of the cerebellum greatly increases the risk of DNA damage. So the cell must have a way to ensure that the damage is quickly repaired to prevent the accumulation of abnormal cells that can cause abnormalities, such as medulloblastoma." McKinnon is senior author of a report on this work in the advanced online version of "The EMBO Journal" (doi: 10.1038/sj.emboj.7601703).

When researchers eliminated Brca2 from the developing nervous system in mice, the loss of this gene led to widespread apoptosis, or cell suicide, triggered by the cell's inability to repair DNA damage. This reduced the size of the cerebellum, led to malformation in the shape of the brain and disrupted the movement of certain nerves cells that normally migrate through the cerebellum during development. When the team blocked cell suicide by eliminating both copies of p53, a gene needed to trigger apoptosis, the brain developed its normal size, but most of the mice developed medulloblastoma.

The study also gave the St. Jude researchers insights into a childhood disease called Fanconi anemia, which is caused by a mutation in the human version Brca2. Children with Fanconi anemia are at increased risk for tumors and small brain size, among other problems. In the current study, the St. Jude team showed that mice lacking Brca2 had neurologic defects similar to those of humans with Fanconi anemia who carry the mutated gene. Specifically, the loss of Brca2 led to defective DNA repair and the accumulation of mutations in the so-called progenitor cells that give rise to many regions of the nervous system. This resulted in small brain size due to apoptosis of the abnormal cells.

These findings showed that the mouse model closely copied the human characteristics of Fanconi anemia and could become a valuable tool for studying the cause and treatment of this disease.

Researchers also discovered that another gene, ATM, plays a secondary but important role in protecting the developing nervous system by triggering apoptosis in cells that have stopped dividing but still contain DNA damage. ATM prevents these abnormal cells, called granule precursors, from becoming incorporated into the developing cerebellum. In this way, ATM plays a backup role in further ensuring normal gene function after the period of rapid growth is complete.

The St. Jude team demonstrated the role of Brca2 in the developing mouse nervous system using a laboratory technique called conditional gene inactivation. This process eliminated the gene from the nervous system, but left it intact in the rest of the body. The use of this technique was important because previous studies showed that mouse embryos cannot develop when the gene is absent from all the cells of the body. The team observed how the specific loss of Brca2 activity from the nervous system affected its embryonic and postnatal development. The finding helps explain how rapidly dividing cells in the developing cerebellum identify and repair errors in the DNA that occur during the duplication of chromosomes before cell division occurs.

"Our work is a significant step in understanding the interplay of genes linked to DNA repair and their role in preventing disease," said Pierre-Olivier Frappart, Ph.D., a postdoctoral researcher in McKinnon’s laboratory, who did much of the work on this project. "As more mouse models lacking specific genes in certain tissues become available, we’ll be able to further determine the relationships among various DNA repair pathways during the development of the nervous system."

Source: St. Jude Children's Research Hospital