Genetic source of rare childhood cancer found; gene is implicated in other cancers

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The search for the cause of an inherited form of a rare, aggressive childhood lung cancer has uncovered important information about how the cancer develops and potentially sheds light on the development of other cancers.

The finding by researchers at Washington University School of Medicine in St. Louis, Children's National Medical Center in Washington, D.C., the International Pleuropulmonary Blastoma Registry at Children's Hospitals and Clinics of Minnesota, and other collaborating institutions adds the final link to the chain connecting the gene DICER1 to cancer development — something that had been suspected but until now not definitively demonstrated.

The results were presented April 19, 2009, at the 100th Annual Meeting of the American Association of Cancer Research in Denver. The study shows that some children with the rare cancer pleuropulmonary blastoma (PPB) are born with a deleterious mutation in DICER1, a master controller gene that helps regulate the expression of other genes. The children studied came from families with a history of PPB or related disorders.

"PPB is the first malignancy found to be directly associated with inherited DICER1 mutations, making the cancer an important model for understanding how mutations and loss of DICER1 function lead to cancer," says lead author D. Ashley Hill, M.D., chief of pathology at Children's National Medical Center. "Additionally, we now believe that

PPB tumors arise from an unusual mechanism in which cells carrying mutations induce nearby cells to become cancerous without becoming cancerous themselves."

Hill was principal investigator of the study, which began while she was on the Washington University faculty.

Only 50 to 60 cases of PPB are diagnosed each year around the world. Most children with PPB are under five years old. The cancer progresses from air-filled lung cysts in the early stage to solid lung tumors in later stages. If detected in the earliest stage, 90 percent of patients can be cured when treated with surgery and sometimes chemotherapy. Overall survival drops to about 40 percent if the cancer is diagnosed in the latest stage.

The researchers found that all the children studied with PPB carried damaging mutations in one of their DICER1 genes, giving them one functional and one nonfunctional DICER1 gene in all their body's cells. The researchers indicate that PPB lung tumors probably originate when one or more cells in the lung acquire a harmful mutation in their functional copy of the DICER1 gene.

The researchers also found that PPB lung tumors appear to result from a novel cancer induction mechanism not previously demonstrated. They discovered that loss of DICER1 protein specifically in lung airway cells appears to deregulate signals to nearby cells and somehow causes those cells to transform into malignant cells. However, the cells with the loss of DICER1 do not progress to malignancy.

DICER1 is so-named because its job is to chop up large molecules into smaller control molecules that help regulate the output of many of the 30,000 human genes. The short bits of genetic material it produces during its dicing activities are termed microRNAs.

"Prior research showed that the microRNA profiles of cancer cells are different from those of normal tissue, which pointed toward a possible role for DICER1 in cancer," says senior author Paul Goodfellow, Ph.D., co-director of the Hereditary Cancer Core at the Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis. "Very recently, other research found that reduced DICER1 gene expression in tumor cells is associated with worse outcomes in patients with ovarian, lung, breast and prostate cancers. Now we've shown that mutations in the DICER1 gene are directly linked to the development of PPB."

"For years, our large collection of cases of PPB and families has revealed the strong genetic component of this disease," says Jack Priest, M.D., research director of the International PPB Registry in Minnesota. "We are thrilled that our colleagues Dr. Hill and Dr. Goodfellow uncovered an important mutation and have begun to understand the cellular mix-up that results in malignancy."

Current studies show that about 40 percent of PPB cases occur in families with a history of the disease or certain other childhood cancers. Most pediatric cancers occur sporadically, without any familial patterns. This led scientists and doctors to suspect that PPB was caused by an inherited genetic abnormality. To uncover the role of DICER1, the research team studied the genetic makeup of 11 extended families with two or more members having PPB or related childhood cancers.

The scientists say that finding this variant form of a gene in some PPB families is a first step to understanding why PPB and other conditions may occur in some families. But, because only a small number of families were studied it isn't known whether DICER1 mutations explain all PPB cases, and much more needs to be learned before this information can be directly helpful to PPB families.

In collaboration with Hill and Goodfellow, and with Louis P. Dehner, M.D., professor of pathology and immunology at Washington University School of Medicine, who first described PPB in 1988, the International PPB Registry in Minnesota has collected and analyzed PPB cases from around the world for more than 20 years. More than 260 confirmed cases are being followed. The registry is funded by Minneapolis/St. Paul-area foundations and is the only organization in the world focused exclusively on PPB.

Source: Washington University School of Medicine (news : web)