UCSD researchers pinpoint the genetic mechanisms associated with leukemia in children

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UCSD RESEARCHERS PINPOINT THE GENETIC MECHANISMS ASSOCIATED WITH LEUKEMIA IN CHILDREN

Scientists at the University of California, San Diego (UCSD) have uncovered a genetic underpinning associated with a deadly strain of leukemia, a breakthrough that could lead to more potent ways of fighting the disease.

In the Sept. 28 issue of the Proceedings of the National Academy of Sciences (PNAS), Kees Murre and John McWhirter of UCSD's Department of Biology describe the inappropriate expression of a novel gene in patients with pediatric leukemia that may contribute to a process in which cells divide uncontrollably. Leukemia, the most common form of cancer in children, causes more deaths in the U.S. than any other disease in children under age 15.

As the name impliespediatric leukemiaone subset of the many varied leukemias (disorders of the blood cells), targets children.

In healthy children, bone marrow will produce cells, called "pre-B" cells, that will develop into mature B cells that travel to the spleen and ultimately become involved in immune response. In pediatric leukemia patients, however, pre-B cells never mature. Rather, they continually divide uncontrollably.

Researchers had traced the causes of pediatric leukemia to two genes, E2A and PBX. In healthy children, E2A is responsible for developing blood cells. PBX's role is believed to be in morphogenesis, the development of organs such as the brain.

In pediatric leukemia patients, E2A and PBX fuse together in the cell nucleus. Scientists had known that this mutation was characteristic of pediatric leukemia, but the effects of the fusion were unclear.

Murre's and McWhirter's research experiments traced the problem to a third gene, called WNT-16, which encodes a "growth factor" that is known to belong to a family of proteins that is involved in cell growth, cell survival and the development of breast cancer in mice. Murre's and McWhirter's findings demonstrate that the E2A-PBX mutation in pediatric leukemia induces the permanent expression of WNT-16. Since the E2A-PBX mutation is a genetic defect, WNT-16 never stops. It may continue to signal for increased cell division, ultimately causing leukemia.

"WNT-16 is present in normal cells, but it is quietly expressed at very low levels," said Murre. "In other parts of a normal body, such as the brain, WNT is regulated by PBX and cells do not divide more than they are supposed to. The E2A-PBX mutant gene turns on the wrong gene at the wrong time, and it continually does so."

In Murre's and McWhirter's experiments, when E2A-PBX was halted from being able to express, there was a significant decrease in WNT-16 levels. This suggested that WNT-16 is a "downstream" target triggered by the E2A-PBX mutant gene.

These findings may turn out to be a key step in the development of the disease process. If so, Murre believes they open the door to new treatments for pediatric leukemia. Stop the WNT16 growth factor and you may be able to stop the disease.

"In the future, we will have to prove that WNT-16 is not just associated with this type of leukemia, but that it causes it, or contributes to it." said Murre. "We also will need to test the natural inhibitors of WNT. It would be a new, better way to deliver therapy in this disease."

Co-authors of the paper include Saskia T.C. Neuteboom of UCSD, Edward V. Wancewicz and Brett P. Monia of Isis Pharmaceuticals and James R. Downing of St. Jude Children's Research Hospital.

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Note: Copies of the paper may be obtained by calling the National Academy of Sciences Office of News and Public Information at (202) 334-2138.

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