Key player found for a cancer typical in Down syndrome

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Between 5 and 10 percent of babies with Down syndrome develop a transient form of leukemia that usually resolves on its own. However, for reasons that haven't been clear, 20 to 30 percent of these babies progress to a more serious leukemia known as Down syndrome acute megakaryoblastic leukemia (DS-AMKL), which affects the blood progenitor cells that form red blood cells and platelets. Now, researchers at Children's Hospital Boston have found a gene regulator they believe to be a key player in DS-AMKL, advancing understanding of how the disease develops and how to treat it.

The study findings, published in the March 1 issue of *Genes and Development*, may also help in understanding other forms of leukemia, the researchers say.

The gene regulator, miR-125b-2, belongs to a class of molecules known as microRNAs, which silence gene expression by halting the manufacturing of different proteins. While microRNAs are important to normal cell function, unusual amounts of them can lead to disease. "DS-AMKL has a very strong genetic basis," says senior investigator Stuart Orkin, MD, of the Division of Hematology/Oncology at Children's. "However, there aren't that many cancers in which a particular microRNA can be pointed to as contributing."

Because children with Down syndrome have three copies of chromosome 21 rather than the usual two copies, the researchers focused on the five microRNAs produced by this chromosome, and zeroed in on

miR-125b-2.

"In human primary DS-AMKL cells, this microRNA is quite dramatically over-expressed," says Zhe Li, PhD, of Children's Division of Hematology/Oncology and first author of the paper. "We then went back and studied how over-expression or downregulation of this microRNA affects the phenotype of leukemia cells."

DS-AMKL is always associated with mutations in the gene GATA1, which helps make and regulate red blood cells and megakaryocytes (the cells that produce platelets). The increased incidence of this leukemia in children with Down syndrome convinced the researchers that a GATA1 mutation may be joining forces with some genetic factor on chromosome 21 - specifically, miR-125b-2.

"GATA1 is always mutated, while miR-125b-2 is always over-expressed in leukemic cells," Li says. "Do they cooperate?"

The researchers experimented on genetically engineered mice that specifically expressed the mutant version of GATA1. Cells were taken from the fetal livers of these mice and induced into becoming blood progenitor cells that either made both red blood cells and megakaryocytes (MEP) or only made megakaryocytes (MP). The researchers then used a virus to over-express miR-125b-2 in these cells and compared them to MEP and MP cells without a GATA1 mutation.

Although over-expression of miR-125b-2 caused increased growth and replication of MEP and MP cells with or without the GATA1 mutation, the growth was further enhanced in the presence of the GATA1 mutation. But once the researchers down-regulated this microRNA in DS-AMKL leukemic cells, which have both GATA1 mutation and miR-125b-2 over-expression, the aberrant growth stopped. These observations support the notion that GATA1 mutation and over-

expression of miR-125b-2 are both needed for DS-AMKL to develop.

Further tests on these cells suggested that over-expression of miR-125b-2 spurs the leukemia by silencing two genes: one for tumor-suppression, and another for producing other regulatory microRNAs.

Genetic analyses of leukemia cells taken from DS-AMKL patients confirmed the results seen in the mouse models. The next step is for researchers to model DS-AMKL in vivo, using animal cells and, eventually, fetal cells.

Studying leukemia in Down syndrome patients may help scientists understand and treat other forms of the cancer, says Orkin. Past research has shown that other genes on chromosome 21 may be involved in other types of leukemia. "Learning more about the genetics of leukemia will then lead to some thoughts about other ways to interfere with the growth of the cells," Orkin says.

More information: Jan-Henning Klusmann, Zhe Li, Katarina Böhmer, Aliaksandra Maroz, Mia Lee Koch, Stephan Emmrich, Frank J. Godinho, Stuart H. Orkin, Dirk Reinhardt. miR-125b-2 is a potential oncomiR on human chromosome 21 in megakaryoblastic leukemia. *Genes and Development* March 1, 2010.

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