Medical Xpress

Can leukemia in children with Down syndrome be prevented?

July 8 2021

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For the first time, Princess Margaret researchers have mapped out where and how leukemia begins and develops in infants with Down syndrome in preclinical models, paving the way to potentially prevent this cancer in

the future.

Children with Down syndrome have a 150-fold increased risk of developing myeloid leukemia within the first five years of their life. Yet the mechanism by which the extra copy of chromosome 21 predisposes to leukemia remains unclear.

Down syndrome is a genetic disorder caused by a random occurrence in cell division in early human development that results in an extra copy of chromosome 21. This extra copy is what causes the developmental changes and physical traits associated with the syndrome, including the predisposition to leukemia.

However, the exact blood cell type in which leukemia begins in fetal development, along with the genetic alterations that cause this cell to become preleukemic, has eluded researchers until now. Furthermore, the additional mutations that must accumulate during childhood to transform preleukemia into acute leukemia were unknown.

The study and results of the early evolution of leukemia in Down syndrome from the laboratory of Princess Margaret Senior Scientist Dr. John Dick are published in *Science*, July 9, 2021. Post-doctoral fellow Dr. Elvin Wagenblast is first author, and Affiliate Scientist Dr. Eric Lechman is co-senior author, along with Dr. Dick.

"A whole sequence of cellular events have already happened before a person is diagnosed with the disease," explains Dr. Dick. "You can't tell at that point which sequence of events happened first, you just know that it has already happened.

"For the first time, our model is giving us insight into the human leukemia process. Ultimately, we may be able to prevent the acute illness by treating it in its earliest phase, when it is preleukemic, to prevent its

progression to full blown leukemia."

Using a preclinical model that includes human Down syndrome cells from a human tissue biobank, along with an enhanced CRISPR/Cas9 method for gene alteration in human blood stem cells that was developed by Drs. Wagenblast and Lechman at Princess Margaret, the team set out to chart the steps involved in this specific leukemia evolution.

Transient preleukemia is a unique condition frequently occurring in newborns with Down syndrome, which can either spontaneously disappear within days to months of birth, or transform into acute myeloid leukemia within four years by acquiring additional mutations in some individuals.

What Drs. Wagenblast, Lechman and Dick revealed in this work was the distinct cellular and genetic events related to transient preleukemia, from their beginnings in the fetus, to further progression to leukemia in childhood.

Specifically, the team was able to test a variety of blood cell types and pinpoint that transient preleukemia originates only from long-term hematopoietic stem cells (HSCs), with the GATA1 mutation, as early as the second trimester of a fetus with Down syndrome. Preleukemia does not begin in HSCs from non-Down syndrome samples.

Only HSCs are able to regenerate the entire blood system and maintain long-term output due to their unique continuous capacity for self-renewal. In a broader picture, the fact that the cellular origin of pediatric leukemia is limited to only long-term HSCs might have implications for other kinds of childhood leukemias beyond Down syndrome.

Acute leukemia happens only after the first two mutations—the extra copy of chromosome 21 and the GATA1 mutation—are in place and

have "primed" the progeny or descendants downstream of the altered long-term HSCs to acquire further mutations that lead to fully transformed acute leukemia, explains Dr. Lechman.

"We actually created a human disease in a preclinical model by showing how the genetically edited, as well as the normal human blood stem cells, behave in it, and we succeeded in recreating the precise, progressive steps of how leukemia develops," says Dr. Dick. "We now have a lot of clues as to the genetic abnormalities these mutations are driving when they cause leukemia."

The team also identified CD117/KIT as a unique protein cell surface marker on the altered disease-driving stem cells that causes the cells to proliferate. In the preclinical model and setting, the researchers were able to target and eliminate preleukemic stem cells using small molecule CD117/KIT inhibitors to prevent their progression to acute leukemia.

The researchers note that this preventative strategy could potentially be used in Down syndrome newborns and even expanded to other childhood leukemias that are known to be initiated during fetal development.

"The clinical significance of being able to target pre-cancerous lesions and preventing progression to cancer is profound," says Dr. Dick, "It would transform the pediatric cancer field."

More information: "Mapping the cellular origin and early evolution of leukemia in Down syndrome" *Science* (2021). science.sciencemag.org/cgi/doi … 1126/science.abf6202

Provided by University Health Network