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Pediatric cancers: Why some forms of leukemia only affect children

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Acute myeloid leukemia (AML) mainly affects children, with often poor prognosis despite several decades of research into more effective treatments. A new study explains why some forms of leukemia develop in very young children and identifies therapeutic targets.

Each year, 2,500 pediatric cancers are diagnosed in France, with one third of cases concerning leukemia, commonly known as blood cancer. Over recent decades, research into pediatric cancer has intensified and treatments have improved, but the prognosis remains particularly unfavorable for these young patients.

Acute myeloid leukemia (AML) accounts for 15 percent of cases of leukemia diagnosed in children and adolescents. Overall survival at 5 years is around 60 percent, with relapse being the most common cause of mortality.

Abnormal protein fusion

There are several subtypes of AML. One of the most aggressive, which is linked to treatment resistance and a particularly unfavorable prognosis, is acute megakaryoblastic leukemia (AML-M7). In their new study published in *Cancer Discovery*, the team focused their efforts specifically on this type of acute myeloid leukemia."

The scientists obtained samples from young patients with AML-M7. In 2012, their analysis of these samples had already revealed AML-M7 to

frequently present genetic alterations that lead to the expression of an abnormal protein resulting from the fusion of the two proteins normally independent in the cell. At that time, although this fusion—known as ETO2-GLIS2—had been identified in 30 percent of AML-M7 cases, the researchers could not explain its mechanism of action.

They also wanted to understand why AML-M7 is diagnosed in children who are on average a lot younger (under two years of age) than those diagnosed with the other pediatric AML subtypes (on average toward the age of six).

"One of the objectives of our new study was to look at the mechanism of action of the ETO2-GLIS2 fusion, and to better elucidate its consequences. We wanted to answer two major questions, with the first being why this disease is specific to children—since the fusion is not found in adults, and then what the potential therapeutic avenues could be," explains Thomas Mercher.

This involved the researchers analyzing the characteristics of human leukemia cells and developing a mouse model to study the consequences of the ETO2-GLIS2 fusion.

Toward new therapeutic avenues

In this model, the researchers showed that this fusion is sufficient in order to rapidly induce aggressive leukemia, if it is activated in fetal hematopoietic cells. However, there is little to link its activation in adult cells with the development of leukemia. Moreover, blocking the ETO2-GLIS2 fusion in the in vivo model brings tumor proliferation to a halt, with the abnormal blood cells once again able to differentiate into normal blood cells.

These findings suggest that some forms of leukemia develop specifically

in children because the properties of the fetal cells differ from those of adult cells.

Findings which also make it possible to propose new target mechanisms in fetal cells and pediatric leukemia in order to improve treatments for these patients. "We now want to understand exactly how this fusion works. Targeting it in order to directly inhibit it with molecules that could be used in patients is not something we are able to do at present, so instead we will identify and try to target the surrounding proteins that are important for it to function," concludes Thomas Mercher.

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