Key gene in leukemia discovered

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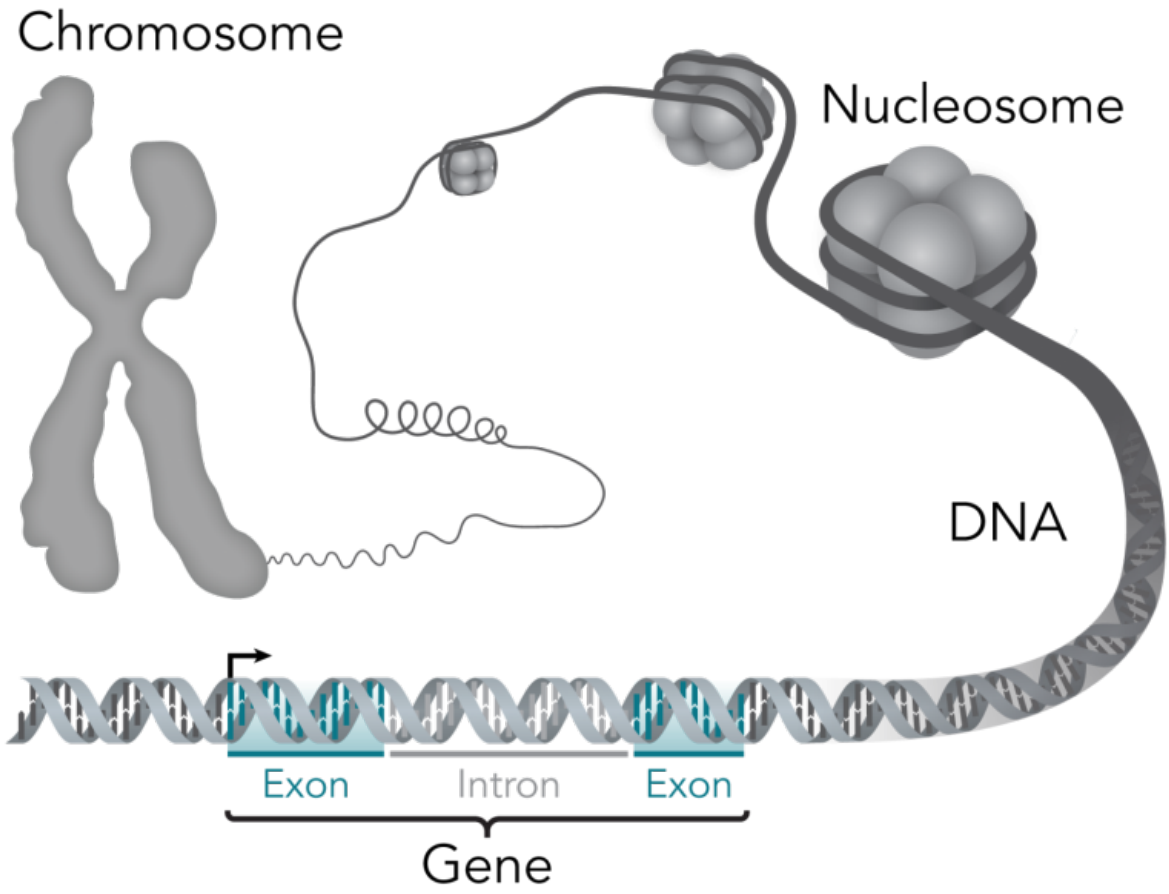

This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas Splettstoesser/Wikipedia/CC BY-SA 4.0

Acute myeloid leukemia (AML) is one of the most common forms of blood cancer among adults and is associated with a low survival rate, and leads to the inhibition of normal blood formation. Now, a research team at Lund University in Sweden has identified one of the genes that is the basis for leukemia stem cells' survival and multiplication. The study is published in *Cell Reports*.

AML is the result of acquired genetic changes in the blood-forming stem cells and among other things affects genes that control the cells' maturation and growth. Although the disease occurs at all ages from childhood onwards, it is more common among the elderly.

"It is the leukemia stem cells in the bone marrow that drive the disease forwards and that is why we want to investigate which genes control these stem cells. By employing special gene scissors, CRISPR, we have been able, using an animal model, to study around 100 genes at the same time. It is the first time we have conducted such a large-scale study", says Marcus Järås, research team manager at Lund University.

The new method using gene scissors means that the researchers can effectively control which gene is turned off, making it possible to study the gene's function and thus better understand how diseases arise. The Lund researchers found that the gene CXCR4 is essential for the leukemia stem cells' survival. When they cut off this gene, the leukemia stem cells could not survive, as they are totally dependent on the protein that the gene produces.

"When we turned off CXCR4 this created oxidative stress and the leukemia stem cells matured into cells with a limited lifetime. Oxidative stress arises due to the waste products formed when oxygen is converted into energy. It is a process that is well regulated in the cell, but when

there is an increase in waste products this results in toxicity which leads to the death of the cell", says Ramprasad Ramakrishnan, first author of the study.

In normal blood formation, the interaction between the proteins CXCL12 and CXCR4 is important for the blood stem cells. In contrast, the research team discovered that CXCL12 is not necessary for the leukemia stem cells, which shows a fundamental difference in how leukemia stem cells and normal blood stem cells are regulated.

"It was surprising that CXCL12 is not significant for the leukemia stem cells. This is somthing that in the long term can be utilised in the design of new drugs against AML", concludes Ramprasad Ramakrishnan.

More information: Ramprasad Ramakrishnan et al. CXCR4 Signaling Has a CXCL12-Independent Essential Role in Murine MLL-AF9-Driven Acute Myeloid Leukemia, *Cell Reports* (2020). DOI: 10.1016/j.celrep.2020.107684

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