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Disturbances in blood cell gene transcription may lead to leukemia

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Researchers have succeeded in shedding light on the pathogenesis of DNA breakpoints that are associated with leukemia. A mechanism discovered in a recent study can explain up to 90% of DNA damages present in the most common type of leukemia in children. The study was carried out by the University of Eastern Finland and the University of Tampere, and the findings were published in *eLife*.

Leukemia is the most common form of cancer in children. Thanks to several genome-wide studies carried out over the past years, our understanding of the biology of leukemia has increased rapidly. The fact that gene deletions in leukemic blood cells are often associated with specific genes or DNA regions has caught the eye of researchers, but the underlying reason has remained in the dark.

Led by Academy Research Fellow Merja Heinäniemi at the University of Eastern Finland and involving the research group of Chief of Department, Docent Olli Lohi at the University of Tampere, a new study finally sheds light on the pathogenesis of DNA lesions present in leukemia. For the first time, researchers were able to show that DNA damage associated with leukemia occurs in regions in which the DNA is being transcribed particularly actively. The explanatory power of the observed mechanism is different in different types of leukemia; however, in the most common type of leukemia in children, the mechanism explains up to 90 per cent of damages occurring in the gene regions. In addition, the study identified a new, high-risk subtype of leukemia, which is characterised by abnormal expression of enzymes

that cause DNA damage.

"When we studied the characteristics of a signal that describes gene transcription, we discovered that in regions that are susceptible to damage, gene transcription slows down and temporarily exposes the DNA to enzymes that cause DNA damage," Heinäniemi says.

"It's kind of like a "car crash" taking place within blood cells:

the transcriptional machineries that are going in different directions within gene regions collide, possibly causing irreversible damage. Luckily, most of these "accidents" are just close calls and they only become dangerous in children whose blood cell progenitors have other predisposing gene damages," Lohi explains.

A similar mechanism has previously been discovered in lymphomas, which are cancers of the lymphatic tissue. At the moment, mechanisms relating to the pathogenesis and repair of DNA damage are a hot topic of research. This study increases our understanding of the diversity of gene damage and leukemia, as well as of mechanisms by which cancer can become resistant to treatment.

The mechanism was discovered by using several deep sequencing methods such as GRO sequencing, which was used to analyse the DNA regions actively read by RNA polymerases. The measurements were carried out at the University of Eastern Finland from samples collected at the Tampere Center for Child Health Research at the University of Tampere. The modelling and integration of various measurement results relied on expertise in computer science, while the interpretation of the results was a joint effort by experts of medicine, bioinformatics and genomics.

More information: Merja Heinäniemi et al. Transcription-coupled

genetic instability marks acute lymphoblastic leukemia structural variation hotspots, *eLife* (2016). DOI: 10.7554/eLife.13087