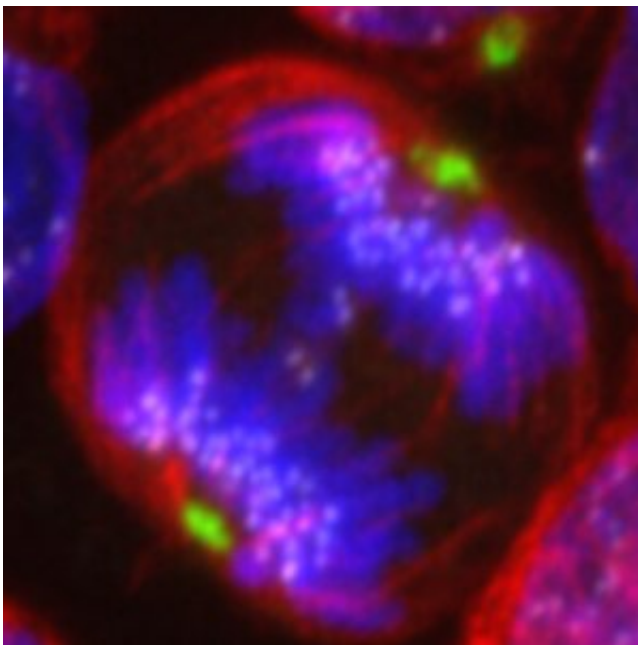


The physiopathological mechanisms underlying the most common pediatric leukemia

April 23 2020, by Oscar Molina



Hyperdiploid B-ALL blast in mitosis with lagging chromosomes. Confocal microscope image of a hyperdiploid B-ALL sample stained with tubulin (red), pericentrin (green), centromeres (purple) and DNA (blue). Credit: Oscar Molina

B-cell acute lymphoblastic leukemia (B-ALL) is characterized by the accumulation of abnormal immature B-cell precursors (BCP) in the bone marrow (BM), and is the most common pediatric cancer. Among the different subtypes known in B-ALL, the most common one is

characterized by the presence of a higher number of chromosomes than in healthy cells and is called high hyperdiploid B-ALL (HyperD-ALL). This genetic abnormality is an initiating oncogenic event affiliated to childhood B-ALL, and it remains poorly characterized.

HyperD-ALL comprises 30% of pediatric B-ALL and usually has a favorable clinical outcome, with 90% of survival in patients with this hematologic cancer. Despite this, until now, there was very little knowledge on how hyperdiploidy occurs in HyperD-ALL, as an initiating oncogenic event in B-ALL and which secondary alterations are necessary for leukemic B-ALL [cells](#) accumulation in the [bone marrow](#), impeding the growth of [healthy cells](#) and leading to clinical leukemia complications.

A precise knowledge of the physiopathological mechanisms underlying HyperD-ALL was necessary because the morbidity/mortality associated with HyperD-ALL still represents a clinical challenge due to the high number of patients suffering from this type of B-ALL. For this reason, Oscar Molina, researcher of the Group of Stem Cells, Developmental Biology, and Immunotherapy of the Josep Carreras Leukaemia Research Institute, has led research on the mechanisms underlying HyperD-ALL, unveiling how and why it happens, published in *Blood*.

Molina and the co-authors of the study hypothesized that the origin of the pathogenic mechanisms associated with hyperdiploidy in B-ALL could be at the moment of the cell's division, known as mitosis, which is a highly orchestrated [cellular process](#) that controls the equal distribution of genetic material, already duplicated and compacted in [chromosomes](#), in two "newborn" cells.

"We knew already that HyperD-ALL arises in a BCP in utero. However, the causal molecular mechanisms of hyperdiploidy in BCPs remained elusive. As faithful chromosome segregation is essential for maintaining

the genomic integrity of cells, and deficient chromosome segregation leads to aneuploidy and cancer, we wanted to observe and deepen our knowledge on what is happening in chromosomes' segregation in HyperD-ALL, because we suspected that by studying cell division in these cells we would find an explanation to this oncogenic process."

Molina was right. Researchers used a large cohort of primary pediatric B-ALL samples, 54. What Molina and his colleagues discovered was that three key processes and actors for correct mitosis or cell division and chromosome segregation were malfunctioning in hyperdiploid cells; that artificial disruption of these processes in [blood cells](#) with normal chromosome numbers generated hyperdiploid cells resembling those in B-ALL samples. Therefore, shedding light on the cellular and molecular mechanisms involved in HyperD-ALL origin and progression.

The main proteins and processes leading to fatal error were a malfunctioning of the Condensin complex, a multiprotein complex responsible for helping condense the genetic material correctly into chromosomes; the protein Aurora B kinase, that is responsible for a correct chromosome attachment to the spindle poles, thus ensuring proper chromosome segregation; and the mitotic checkpoint, or Spindle Assembly Checkpoint (SAC), the cell machinery involved in controlling that chromosomes are correctly separated to each pole of the cell that is dividing.

With these findings, Molina et al. have unveiled the molecular mechanisms that are altered in this frequent type of pediatric blood cancer.

"Next steps would be to study whether other subtypes of B-ALL with abnormal chromosome numbers, such as hypodiploid B-ALL, a very aggressive subtype of pediatric blood cancer characterized by lower numbers of chromosomes, share a common molecular [mechanism](#).

These studies will allow generating the first in vivo models of leukemias with abnormal chromosome numbers in mice that will be crucial to understand its origin and development, thus facilitating the development of more targeted and less toxic therapies for these pediatric blood cancers," stated Oscar Molina.

More information: Oscar Molina et al. Impaired Condensin Complex and Aurora B kinase underlie mitotic and chromosomal defects in hyperdiploid B-cell ALL, *Blood* (2020). [DOI: 10.1182/blood.2019002538](https://doi.org/10.1182/blood.2019002538)

Provided by Josep Carreras Leukaemia Research Institute

Citation: The physiopathological mechanisms underlying the most common pediatric leukemia (2020, April 23) retrieved 4 May 2024 from <https://medicalxpress.com/news/2020-04-physiopathological-mechanisms-underlying-common-pediatric.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.