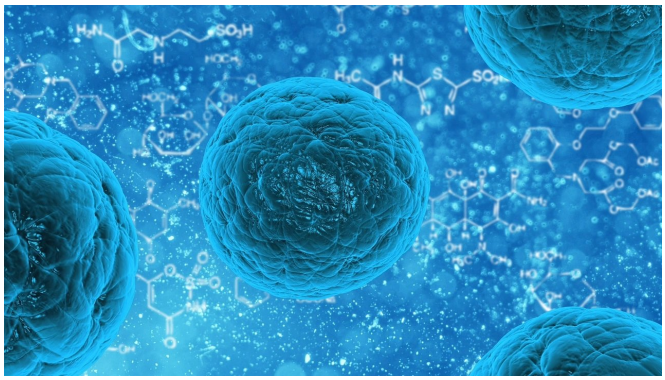
Metoclopramide inhibits proliferation of leukemia stem cells

27 January 2021



Credit: CC0 Public Domain

A research team at Inselspital, Bern University Hospital and the University of Bern has identified and tested the use of an agent that can effectively inhibit the proliferation of leukemia stem cells. Metoclopramide (MPR), used as an anti-emetic medication, interrupts the unique CD93 signaling pathway that only leukemia stem cells use to proliferate. This opens up a therapeutic approach using MPR to selectively eliminate leukemia stem cells.

Chronic myeloid leukemia (CML) results from a degeneration of the hematopoietic stem cells (leukemia stem cells), thereby leading to the uncontrolled formation of specific white blood cells, the so-called granulocytes. Research work at the Department of Medical Oncology at the Inselspital, Bern University Hospital and the University of Bern focused therefore on identifying the signaling pathways and control mechanisms of the leukemia stem cell. A promising approach is provided by working with MPR, an anti-emetic medication commonly used to treat nausea and vomiting.

Specific blocking of leukemia stem cell proliferation with metoclopramide

The exact role of the surface molecule CD93 (cluster of differentiation 93) in controlling the proliferation of leukemia stem cells was analyzed and documented, initially in animal experiments and subsequently in experiments with leukemia stem cells from patients. This revealed a distinct regulatory function of CD93 in leukemia stem cells. To begin with, the effect was demonstrated in vivo in animal experiments. It was further shown that the control function only applies to leukemia stem cells, not to normal hematopoietic stem cells. Furthermore, it was demonstrated that the anti-emetic MPR interrupts the signaling pathway that stimulates cell proliferation of leukemia stem cells in vitro and also, in animal experiments, visibly improves survival with CML by blocking the proliferation of leukemia stem cells. This provides strong evidence that MPR may also show positive results in treating CML in humans.

Extensive research

The study presented in this publication involved exceptionally extensive research. This is also true with regard to the interdisciplinary teams participating from the Department of Medical Oncology, the Department for Biomedical Research, the Institute of Cell Biology and the Department of Orthopedic Surgery and Hematology at the Bern University Hospital and the University of Bern. Prof. Dr. sc. nat. Carsten Riether explains: "In order to develop a new, promising approach to combat CML, contributions from numerous disciplines were necessary and different research approaches had to be pursued. In a screening procedure, we elicited the candidate Metoclopramide and were subsequently able to demonstrate its effect on the CD93 signaling pathway in both in-vitro and in-vivo experiments." The research infrastructure in Bern is optimally designed for such major projects. The expertise in fundamental research at the Department for Biomedical Research (DBMR) and in clinical research at the University Hospital are closely

linked and can rapidly produce sound results.

What are the next research activities?

The results have pinpointed CD93 as a specific regulator responsible for leukemia stem cell proliferation. This identifies a promising pathway to targeting leukemia stem cells. Further studies must now prove the clinical effect and relevance. Prof. Adrian Ochsenbein says "Thanks to this pool of expertise, we were able to identify Metoclopramide as a promising candidate for CML therapy. And with the broad-based research infrastructure and our excellent national and international network, we are hopefully in a position to present clinical results within a reasonable timescale."

More information: Carsten Riether et al, Metoclopramide treatment blocks CD93-signaling-mediated self-renewal of chronic myeloid leukemia stem cells, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2020.108663

Provided by Inselspital, Bern University Hospital