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PRESS RELEASE

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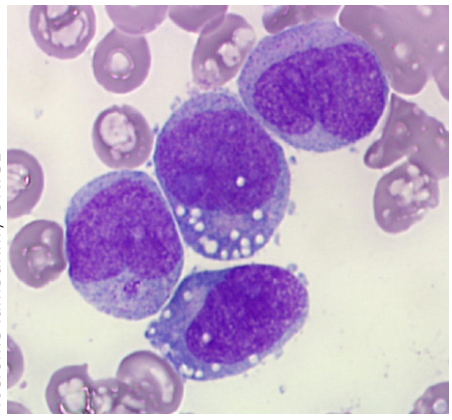
Defeating leukaemia cells by depriving them of energy

A Swiss-French team that includes UNIGE scientists has discovered how to trigger apoptosis in leukaemia cells by disrupting their energy maintenance mechanism.



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Selective activation of the AMPK enzyme would lead to the death of leukaemia cells (in purple in this image).

High resolution pictures

Acute myeloid leukaemia, which affects blood and bone marrow cells, is a particularly dangerous form of cancer. More than half of patients under the age of 60 die. This proportion rises to 85% for patients over 60. A team from the University of Geneva (UNIGE), Switzerland, and from Inserm[1], in France, have identified a previously unknown mechanism that could lead to the development of new therapies. The selective activation of AMPK, a key enzyme in the energy balance of tumour cells, would indeed lead to their death by triggering the cells stress response. Moreover, the scientists have successfully exploited this energy gap in an animal model of the disease: a combination of two drugs — one of which is already on the market — has indeed shown promise. However, their effectiveness has yet to be confirmed on leukaemia stem cells, which have the ability to escape many treatments to restart tumour growth. These results can be found in the journal *Cell Reports*.

Jérôme Tamburini, an associate professor in the Department of Medicine and in the Translational Research Centre in Onco-Haematology (CRTOH) of UNIGE Faculty of Medicine and at the Swiss Cancer Center Léman (SCCL) and a professor at Université de Paris, is working on the energetic mechanisms of tumour cells in acute myeloid leukaemia. A cell signalling pathway called AMPK is of particular interest to him. "AMPK is the main detector of the cells energy level", explains Jérôme Tamburini. "This pathway is activated when energy is lacking and initiates the degradation of certain nutrients to produce the necessary energy – a process called catabolism. As without energy, no cell can survive, could it be possible to selectively manipulate this mechanism in tumour cells to cause their destruction, while preserving healthy cells?"

In 2015, Jérôme Tamburini and his colleagues at Inserm in Paris participated in the development with the GlaxoSmithKline (GSK) laboratory of a pharmacological component — GSK621 — which proved to be an excellent activator of AMPK in vitro. "After this initial proof of principle, we had to decipher the biochemical mechanisms at work in order to understand them in detail, and in particular which cellular pathways did GSK621 activate in leukaemia cells, the first step in hoping to exploit this phenomenon for therapeutic purposes," explains Jérôme Tamburini.

1. Several laboratories were involved, including Institut Cochin (Inserm/CNRS/University of Paris), the Cancer Research Center of Lyon (Inserm/CNRS/Claude Bernard Lyon 1 University/ Léon Bérard Centre) and the Toulouse Cancer Research Center (Inserm/CNRS/Toulouse III - Paul Sabatier University)

An effective combination of two drugs

The first step was to perform a gene expression analysis of human tumour cells, which identified an enzyme, PERK, particularly activated in response to the presence of GSK621. This is a key element in the stress response of the endoplasmic reticulum, an intracellular structure specialised in the metabolism of proteins and lipids. “The activation of AMPK thus triggers the activation of PERK, followed by a chain of reactions leading to apoptosis, the programmed death of the cell,” explains Jérôme Tamburini. “In addition, the activation of AMPK by GSK621 sensitises the cells to the effects of another pharmacological drug, the venetoclax, which is now widely used to treat acute myeloid leukaemia, although with limited effectiveness when used alone.”

The scientists then combined the two drugs in mice carrying human tumour cells, and found that this combination controlled tumour development much more effectively than in monotherapy. While GSK621 was not designed to be a drug, other products are currently in clinical trials to combat metabolic diseases, which activate the AMPK pathway. “Understanding the mechanism involved has brought to light potential therapeutic targets that were previously unknown,” explains Jérôme Tamburini. “We will now be able to review all the drugs known to have an effect on these pathways and determine which combinations would be the most effective.”

What about leukaemic stem cells?

Leukaemic stem cells consists in a small population of cells within the tumour that can only be detected by their ability to spread again the tumour after an initially successful treatment. The main cause of relapse, these cells are sensitive to very few of the therapies usually used in leukaemia. Furthermore, evidence is still lacking to determine the effect that massive activation of AMPK would have on them. “Before testing drug combinations targeting this AMPK/PERK mechanism in human beings, we need to determine their effect on leukaemic stem cells,” the authors conclude.

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About the University of Geneva
The University of Geneva (UNIGE) enjoys worlwide recognition and ranks amongst the top 100 best universities in the world. Founded in 1559 by Jean Calvin and Theodore de Beze, it welcomes nearly 19 000 students in its nine faculties and thirteen interdisciplinary centres and constantly strengthens its links with the International and Non-Governmental Organisations based in Geneva, one of the world's capitals for multilateralism. A member of the League of European Research-intensive Universities, the UNIGE fullfills three missions: education, research and knowledge-sharing. **www.unige.ch**

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Université de Paris is one of the leading research-intensive universities in France (4th in the ARWU ranking, 1st in the Leiden ranking for the 1% of the most cited publications). Across a broad range of disciplines that include health sciences, formal and experimental sciences and the humanities and social sciences, Université de Paris builds on the highest quality disciplinary research to cultivate multi and interdisciplinary collaborations in research and education. Université de Paris is composed of three Faculties (Health, Sciences and Humanities and Social sciences), a component institution, the Paris Institute of Earth Physics, (IPGP) and now a partner research organisation, the Institut Pasteur. Université de Paris has 63,000 students, 7,500 teacher-researchers and researchers, 21 doctoral schools and 119 research units. **www.u-paris.fr**

About Inserm
Founded in 1964, Inserm is a public scientific and technological institute which operates under the joint authority of the French Ministries of Health and Research. The institute is dedicated to biomedical research and human health, and is involved in the entire range of activities from the laboratory to the patient's bedside. It also partners with the most prestigious research institutions in the world that are committed to scientific challenges and progress in these fields. **www.inserm.fr**

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