Leukemia vulnerability discovered causing drug sensitivity

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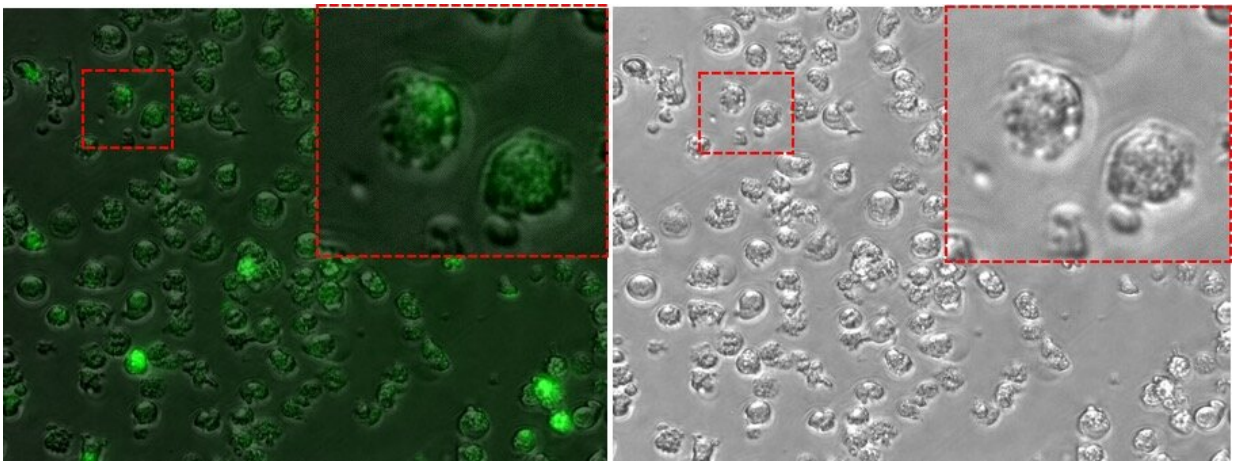

Cells from acute lymphoblastic leukemia, a disease against which treatment with glutathione inhibitors has demonstrated preclinical efficacy, dying by the effect of the pharmacological compound. Credit: Josep Carreras Leukaemia Research Institute

All human tumors originating from various tissues share a series of properties that define them, including the ability to prevent cell death. Instead, healthy organs induce programmed cell death or apoptosis to balance their size and eliminate damaged cells. There is a specific and physiological cell death called ferroptosis that occurs induced by the oxidation of fat mediated by iron content.

Today, an article published in the journal *Redox Biology*, the journal of reference in the field of free radicals and cancer, by the group of Dr. Manel Esteller, Director of the Josep Carreras Leukaemia Research Institute (IJC), ICREA Research Professor and Chairman of Genetics at the University of Barcelona, and headed by Dr. Lucas Pontel, shows that epigenetic changes prevent iron-associated programmed cell death in leukemia and show a new target for treatment with experimental drugs.

"Leukemia cells avoid dying because they have two floats, the metabolism of the biomolecule called glutathione and the FSP1 gene that acts as a shield against this death induced by iron and oxidation," comments Dr. Esteller. "Studying all these metabolic pathways we realized that in acute lymphoblastic leukemia (ALL) the activity of the FSP1 gene was epigenetically lost, so these cells were on the edge of the precipice of their programmed death. We only needed to give them a boost and that is what we did by administering them inhibitors of the glutathione pathway, such as L-BSO and RSL3, which rapidly induced the death of these malignant lymphocytes. In other words, this type of leukemia lives on the edge in terms of its tolerance towards ferroptosis and when you eliminate their last lifeline with a drug, these transformed cells die. This weak spot of acute lymphoblastic leukemia can therefore be explored in precision and personalized treatments for this disease, but it could also occur in other cancers. There are few clinical trials in oncology with glutathione inhibitors, but perhaps this type of work will arouse interest in the study and development of these promising experimental agents," says the researcher.

Dr. Pontel says that "by exploring data from T-ALL and B-ALL patients, we detected that FSP1 is under epigenetic control. Thus, by determining the FSP1 epigenetic status in patients, we might be able to anticipate the success of a therapy based on drugs that induced ferroptosis."

More information: Lucas B. Pontel et al, Acute lymphoblastic leukemia necessitates GSH-dependent ferroptosis defenses to overcome FSP1-epigenetic silencing, *Redox Biology* (2022). DOI: 10.1016/j.redox.2022.102408