Key stem cell dormancy mechanism discovered

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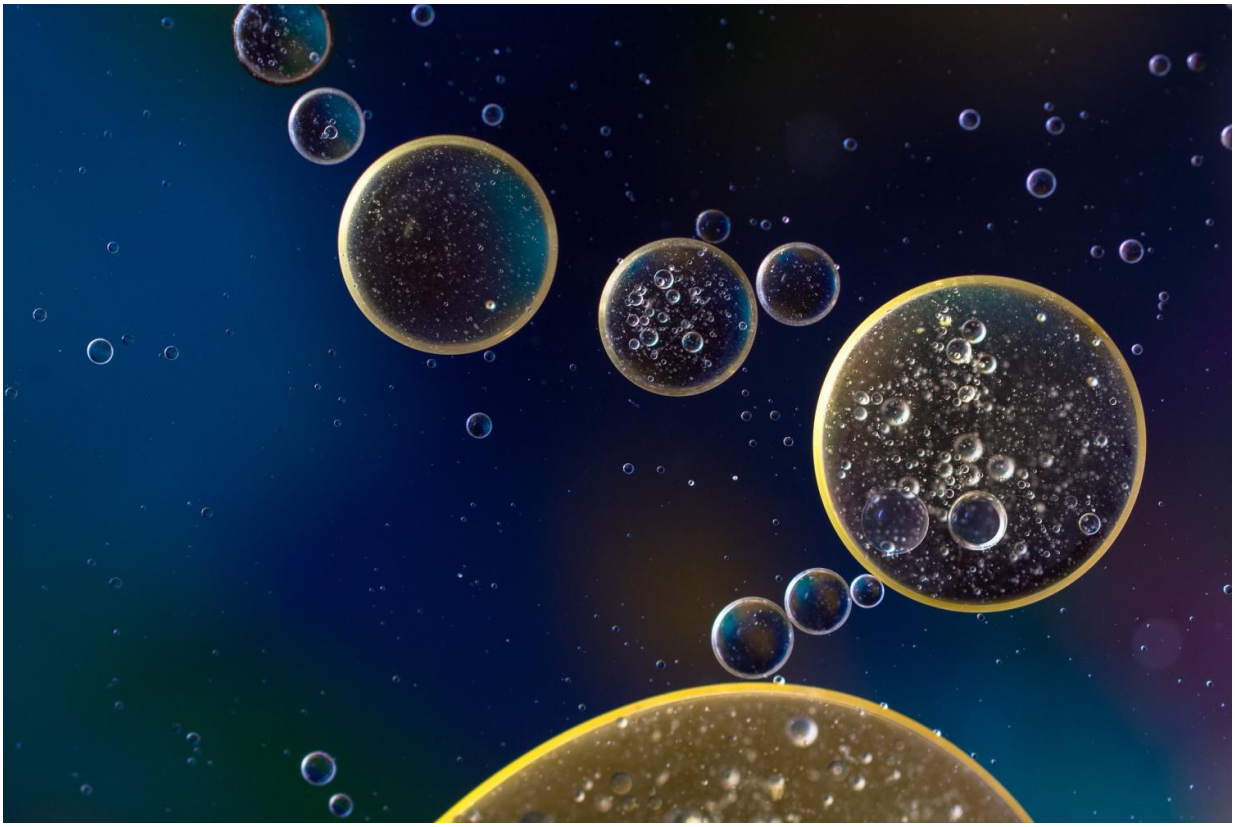

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Princess Margaret Cancer Centre researchers have made new findings which provide a broader understanding of how dormant hematopoietic stem cells are activated and could pave the way towards therapeutic

treatments for a number of cancers.

The team has made the discovery by performing a deep mechanistic study of lysosomes, which are membrane-bound organelles found in all cells. Lysosomes were once believed to merely be the 'garbage bin' of the stem cell, recycling waste material, regulating cellular regeneration and functioning the same in all cell types. But the PM team's research builds on new knowledge about lysosomes which shows they act as key signaling hubs, regulating long-term hematopoietic stem cells.

Work done by the researchers examines why a hematopoietic stem cell can remain dormant for years, and how the lysosome constantly acts as a sensor even in that deeply inactive state. The Princess Margaret team found that in spite of the cell's dormancy, the lysosome inside it is still very active, "clipping and inactivating" receptors involved in growth signaling and nutrient transport within the stem cell membrane, allowing it to remain asleep.

The findings could have implications beyond the study, potentially allowing for control of the balance between cell dormancy and when stem cells are activated to help replenish the blood supply.

The results come from the laboratory of Princess Margaret senior scientist Dr. John Dick and are published in *Cell Stem Cell* on Aug. 2., 2021. Post-doctoral fellow Dr. Laura Garcia-Prat is first author, and affiliate scientist Dr. Stephanie Xie is co-senior author along with Dr. Dick.

"The study has discovered a new mechanism of dormancy, which is to harness an organelle, a lysosome, and keep that cell dormant," says Dr. Garcia-Prat. "This opens a way that lysosomes could potentially be harnessed as a therapeutic target."

Every year, tens of thousands of people around the world receive bone marrow transplants to help fight leukemia. High doses of chemotherapy are used to kill the rapidly dividing cancer cells, but at the same time it also kills stem cells needed to reproduce healthy blood.

Stem cell transplants are used to regenerate a patient's heathy blood supply, but finding a matching donor can be challenging, especially within different ethnic communities where donor lists may not be extensive or exist at all. Stem cells found in cord blood would have considerable value as additional donor sources, but the number of stem cells is often too low for an adult recipient. Understanding how to activate and expand stem cells in a controlled way could make cord blood more widely useful.

Being able to control the activation of stem cells might also be useful for situations where stem cells are inappropriately activated due to disease, inflammation or drug treatment, helping to restore dormancy to conserve these valuable commodities.

"Learning how to conserve, and preserve, blood stem cells is vital," says Dr. Dick. "If that stem cell gets activated in an inappropriate way that can have huge consequences for the blood system because you're now losing your stem cells and you're not going to have that for your lifetime."

"You've got to do everything you can to keep that cell dormant. And one way you do that is by preventing it from sensing any signals from the surface," added Dr. Dick.

The work could also be used to help more fully understand leukemia stem cells which closely mimic regular stem cells and sometimes are able to go dormant and evade treatments.

"Now it will be interesting to look at these leukemia stem cells and see how this mechanism is regulated," says Dr. Stephanie Xie. "We may see differences and utilize them for treatment."

Dr. Garcia-Prat, the lead author, said this is work could have only done at Dr. Dick's lab at the Princess Margaret Cancer Centre at the University Health Network.

"We are one of the few labs in the world working with human hematopoietic stem cells," says Dr. Garcia-Prat. "So that makes a huge difference in terms of translating our research into therapies for humans."

Provided by University Health Network