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New induced stem cells may unmask cancer at earliest stage

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By coaxing healthy and diseased human bone marrow to become embryonic-like stem cells, a team of Wisconsin scientists has laid the groundwork for observing the onset of the blood cancer leukemia in the laboratory dish.

"This is the first successful reprogramming of blood cells obtained from a patient with leukemia," says University of Wisconsin-Madison stem cell researcher Igor Slukvin, who directed a study aimed at generating all-purpose stem cells from bone marrow and umbilical cord blood. "We were able to turn the diseased cells back into pluripotent stem cells. This is important because it provides a new model for the study of cancer cells."

The research was reported today (Feb. 4) in the journal *Blood* by Slukvin and colleagues from the WiCell Research Institute and the Morgridge Institute for Research, private research centers in Madison.

Slukvin's group, using banked healthy and diseased bone marrow and cord blood, employed a technique developed in 2009 by Wisconsin stem cell pioneer James Thomson that sidesteps the problems posed by the genes and viral vectors used to induce mature cells to regress to a stem cell state.

According to the new study, which was funded by the National Institutes of Health and The Charlotte Geyer Foundation, reprogramming blood cells to become induced stem cells is many times more efficient than the

reprogramming of skin cells, which were the first mature cells to be guided back to an embryonic stem cell-like state.

The new work could open to science vast repositories of banked tissue, both healthy and diseased, such as bone marrow, the soft tissue in bones that helps make blood, and umbilical cord blood. The work could underpin insightful models capable of unmasking the cellular events that go awry and cause cancers such as leukemia, and could aid the development of new stem cell-based therapies, according to Slukvin.

Of particular note in the new study, says Slukvin, is the reprogramming of marrow cells from a patient with chronic myeloid leukemia, a cancer of the blood that kills about 1,500 people a year in the United States. The disease, like all leukemias, starts in the cells that produce white blood cells in bone marrow.

According to Slukvin, the induced stem cells generated from the diseased tissue retain the exact same complex of genetic abnormalities found in the mature cancer cells. That means that when the induced cells are turned back into blood, scientists could, in theory, watch cancer develop from scratch as cells bearing cancer mutations become cancer stem cells.

"When we differentiate induced stem cells back to blood, we can identify the stages when the abnormality that leads to cancer manifests itself," Slukvin explains.

The ability to pinpoint the very earliest stages of cancer is a major focus of biomedical science.

"This is very important for developing new leukemia drugs," says Slukvin. "A major focus of leukemia research is to find ways to try and eliminate the most immature leukemia cells - cancer stem cells."

The work by Slukvin and his team may represent the first step in a new understanding of the cascade of events that results in blood diseases such as leukemia.

Employing the reprogramming technique developed by Thomson and his colleagues, Slukvin emphasizes, is important because it eliminates the exotic reprogramming genes, some of which are cancer-related genes, from the induced stem cell equation. In the case of chronic myeloid leukemia and other blood diseases, obtaining stem cells that do not have the genetic reprogramming factors is very important.

"When you use viruses (to ferry genes into a cell) you have chromosomal integration," the Wisconsin researcher notes. "Some of the reprogramming factors are oncogenes and would interfere with a study of chronic myeloid leukemia" whose abnormalities are also encoded on the chromosome.

Provided by University of Wisconsin-Madison