Stem cell study opens door to undiscovered world of biology

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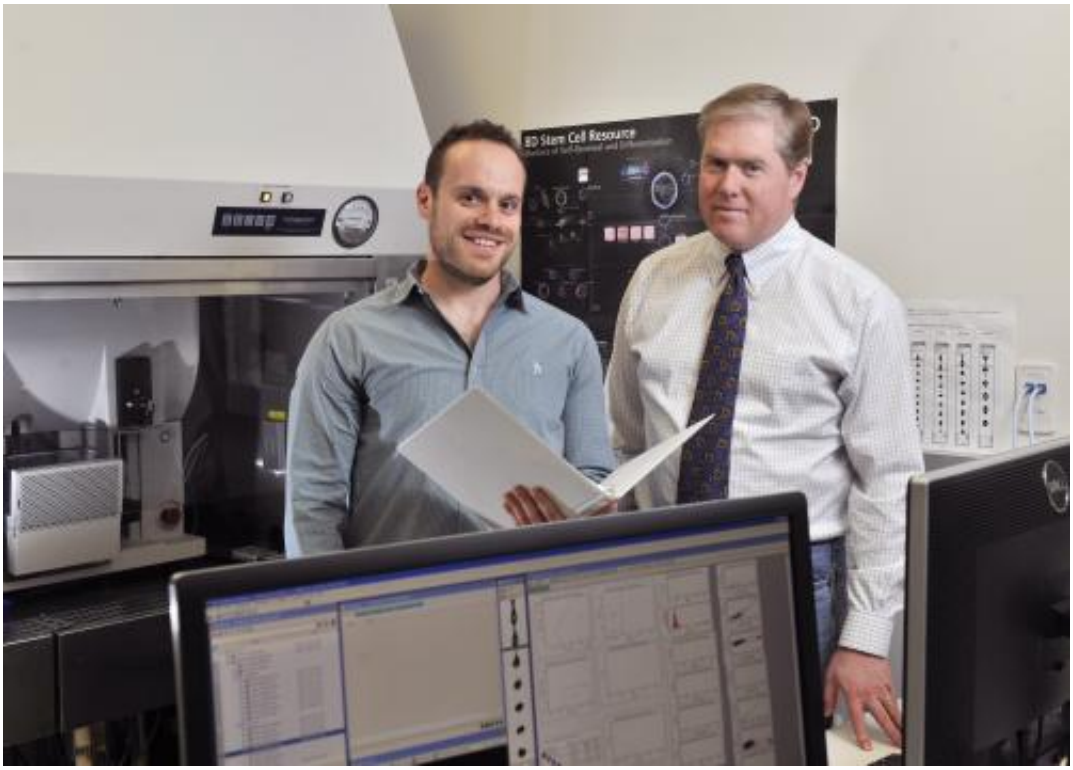

This photo shows Dr. Sean Morrison, Director of the Children's Research Institute and senior author of the study, right, and Dr. Robert A.J. Signer, a postdoctoral research fellow and the study's first author. Credit: University of Texas Southwestern Medical Center

For the first time, researchers have shown that an essential biological process known as protein synthesis can be studied in adult stem cells – something scientists have long struggled to accomplish. The

groundbreaking findings from the Children's Medical Center Research Institute at UT Southwestern (CRI) also demonstrate that the precise amount of protein produced by blood-forming stem cells is crucial to their function.

The discovery, published online today in *Nature,* measures protein production, a process known as translation, and shows that protein synthesis is not only fundamental to how stem cells are regulated, but also is critical to their regenerative potential.

"We unveiled new areas of cellular biology that no one has seen before," said Dr. Sean Morrison, Director of the Children's Research Institute, Professor of Pediatrics, and the Mary McDermott Cook Chair in Pediatric Genetics at UT Southwestern Medical Center. "No one has ever studied protein synthesis in somatic stem cells. This finding not only tells us something new about stem cell regulation, but opens up the ability to study differences in protein synthesis between many kinds of cells in the body. We believe there is an undiscovered world of biology that allows different kinds of cells to synthesize protein at different rates and in different ways, and that those differences are important for cellular survival."

Dr. Adrian Salic's laboratory at Harvard Medical School chemically modified the antibiotic puromycin in a way that made it possible to visualize and quantify the amount of protein synthesized by individual cells within the body. Dr. Robert A.J. Signer, a postdoctoral research fellow in Dr. Morrison's laboratory and first author of the study, realized that this reagent could be adapted to measure new protein synthesis by stem cells and other cells in the blood-forming system.

What they came across was astonishing, Dr. Morrison said. The findings suggested that different types of blood cells produce vastly different amounts of protein per hour, and stem cells in particular synthesize

much less protein than any other blood-forming cells.

"This result suggests that blood-forming stem cells require a lower rate of protein synthesis as compared to other blood-forming cells," said Dr. Morrison, the paper's senior author.

Researchers applied the findings to a mouse model with a genetic mutation in a component of the ribosome – the machinery that makes proteins – and the rate of protein production was reduced in stem cells by 30 percent. The scientists also increased the rate of protein synthesis by deleting the tumor suppressor gene *Pten* in blood-forming stem cells. In both instances, stem cell function was noticeably impaired.

Together, these observations demonstrate that blood-forming stem cells require a highly regulated rate of protein synthesis, such that increases or decreases in that rate impair stem cell function.

"Amazingly, when the ribosomal mutant mice and the *Pten* mutant mice were bred together, stem cell function returned to normal, and we greatly delayed, and in some instances entirely blocked, the development of leukemia," Dr. Morrison said. "All of this happened because protein production in stem cells was returned to normal. It was as if two wrongs made a right."

Many diseases, including degenerative diseases and certain types of cancers, are associated with mutations in the machinery that makes proteins. However, why this is the case has yet to be understood. Discoveries such as this raise the possibility that changes in protein synthesis are necessary for the development of those diseases.

"Many people think of protein synthesis as a housekeeping function, in that it happens behind the scenes in all cells," Dr. Signer said. "The reality is that a lot of housekeeping functions are highly regulated; they

have just not been studied enough to recognize the difference among cells. I think what we are seeing with this study is just the tip of the iceberg, where the process of protein production is probably quite different in distinct cell types."

More information: Haematopoietic stem cells require a highly regulated protein synthesis rate, *Nature*, DOI: 10.1038/nature13035

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