Stem cell research uncovers importance of cell cycle

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(Medical Xpress)—One of the biggest problems in stem cell research may not be a problem at all. Scientists have worried for years that stem cells grown in their labs were made up of many different kinds of cells, making them useless for stem cell therapies, but new research from the University of Georgia suggests they're not different cells, some are just more mature than others.

Amar Singh, postdoctoral associate in the Franklin College of Arts and Sciences, and Georgia Research Alliance Eminent Scholar of Molecular Cell Biology Stephen Dalton worked together to uncover the mystery about why stem cell populations are thought to be heterogeneous, or made up of a variety of different cells. They discovered the heterogeneity, or difference among the cells, is largely determined by the cell cycle.

Their results were published Dec. 5 in the journal *Stem Cell Reports*.

"Since our study shows that heterogeneity may be a normal part of stem cell growth, this may not be that big of a deal anymore," said Singh, who is a researcher in the Franklin College department of biochemistry and molecular biology. "Also, since the cell cycle controls developmental genes, seeing a certain level of heterogeneity in the cells you want to transplant may also be normal."

The idea that stem cells are heterogeneous, or that the cells making up a population are not all identical, emerged in the mid-2000s, and the

reason has remained a mystery. Stem cells grow as a population of 1 to 2 million cells per culture dish because cells need to be surrounded by neighboring cells to survive. However, cells next to each other may be at different stages of development, which makes them appear like different cell types.

Stem cell transplants are used to assist in the regeneration of vital organs. Patients who suffer heart attacks may need a transplant of cardiomyocytes, a person with diabetes may benefit from a pancreatic cell transplant and liver disease patients can receive hepatic cells. The goal is to provide a transplant of uniform cells, or a homogeneous population. Until now, researchers would discount a heterogeneous cell population as unworthy for transplant.

A cell takes 18-24 hours to progress through the four stages of the cell cycle resulting in mitosis, or the division of the cell resulting in two identical cells. As stem cells turn into lineage cells, they don't shut down stem cell genes and turn on lineage genes. In fact, it is much more dynamic, the gene expression goes up and down as the cell cycle progresses.

"Now that we know that these developmental genes are more dynamic in their expression patterns as it relates to the cell cycle, we should be able to better evaluate cells that will be useful for cell-based therapies," Singh said.

Understanding the importance of the cell cycle in terms of gene development suggests the process should be taken into account in disease modeling and when testing drug effects.

"Since the cell cycle affects the expression of genes, it may be important to consider what phase of the cell cycle a particular cell is in to evaluate drug efficacy," Singh said.

Understanding the cell cycle's effect on the early stages of biological development offers new avenues for future research, including cancer research. Subtle differences in cancer cells may also be explained by the same phenomenon, as tumors are often thought of as heterogeneous.

"It turns out that developmental genes are often switched back on in cancers," Singh said. "Since these genes are controlled by the cell cycle, it may explain the heterogeneity seen here. Understanding how the cell cycle controls the heterogeneity in tumors will be critical for improved cancer treatments."

More information: Cell-Cycle Control of Developmentally Regulated Transcription Factors Accounts for Heterogeneity in Human Pluripotent Cells. "Amar M. Singh, James Chappell, Robert Trost, Li Lin, Tao Wang, Jie Tang, Hao Wu, Shaying Zhao, Peng Jin, Stephen Dalton. *Stem Cell Reports* 05 December 2013. DOI: 10.1016/j.stemcr.2013.10.009

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