Study finds that cancer-causing gene crucial in stem cell development

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Stem cells might be thought of as trunks in the tree of life. All multi-cellular organisms have them, and they can turn into a dazzling variety other cells—kidney, brain, heart or skin, for example. One class, pluripotent stem cells, has the capacity to turn into virtually any cell type in the body, making them a focal point in the development of cell therapies, the conquering of age-old diseases or even regrowing defective body parts.

Now, a research team at the University of Georgia has shown for the first time that a gene called Myc (pronounced "mick") may be far more important in the development and persistence of stem cells than was known before. Myc is traditionally thought of as a cancer-causing gene, or oncogene, but recent studies from the UGA team have established critical roles for it in stem cell biology. The discovery has important implications for the basic understanding of developmental processes and how stem cells can be used for therapeutic purposes.

"This new research has uncovered a really unexpected role for Myc," said Stephen Dalton, GRA Eminent Scholar of Molecular Cell Biology and Georgia Cancer Coalition Distinguished Scientist at UGA. "Our work here represents the first mechanistic characterization of how Myc controls the pluripotent stem cell state."

The research was published today in the journal *Cell Stem Cell*. Other authors of the paper include Keriayn Smith and Amar Singh of the Dalton lab at UGA. Smith left recently to begin a postdoc at the

University of North Carolina. Dalton also is a member of the department of biochemistry and molecular biology in the Franklin College of Arts and Sciences and is affiliated with the UGA Cancer Center and the Biomedical and Health Sciences Institute.

In previous work, Dalton and his colleagues showed that Myc is critical for stem cell maintenance and that it affects widespread changes in gene expression. This latter function is crucial when stem cells differentiate into more specific cell types. In the new research, Dalton's team showed that Myc sustains the important pluripotency process by repressing a "master regulator" gene called GATA6.

"Pluripotency is the inherent property of a cell to create all cell types, from an embryo to an adult organism," said Dalton. "It's an extremely important biological process, and knowing how it is controlled is crucial not only from a basic developmental perspective but also so that we can harness the potential of stem cells for the development of therapies, including those for diabetes, cardiovascular disease and a range of neurological disorders. Through a detailed understanding of early development, we hope to apply this information so that pluripotent stem cells can be differentiated into therapeutically useful cell types. These cells can then be used in a clinical setting to cure degenerative diseases and treat acute injury."

The finding that Myc inhibits GATA6 came as a big surprise to the Dalton team and points out that researchers have only seen the tip of the "molecular iceberg" in terms of what Myc does in stem cells. It now seems likely that understanding Myc's role in further detail will reshape current ideas about the basic biology of stem cells.

Dalton's new work addressed the uncertainty about how Myc maintains the pluripotency of stem cells by examining what happens when two forms of Myc—c-Myc and N-Myc—are inactivated in pluripotent stem

cells. What he found was that either c- or N-Myc is sufficient to maintain pluripotency, but that the absence of both triggers the differentiation of pluripotent stem cells. Myc is therefore acting as a "brake" to restrain differentiation. When the "differentiation brake" is removed, cells lose their stem cell properties, and, potentially, they can become any one of over a hundred different cell types.

Pluripotent stem cells can now be made from skin fibroblasts and even from blood samples. (Fibroblasts are cells common in connective tissues of animals and play an important role in the healing of wounds, among many functions.) The conversion of mature fibroblast or blood cells back to pluripotent stem cells is called "reprogramming." Myc also has a critical role in this process. The ability to make stem cells from a patient's blood or skin is going to revolutionize medicine as it opens the way for patient-specific stem cells that would circumvent problems associated with immune rejection, said Dalton.

"During the reprogramming of cells, Myc represses genes associated with the differentiated state and primes them for the expression of stem cell genes," he said. "We now speculate that during the early reprogramming stage, Myc serves to change the cell cycle so that stem cells can divide for long periods of time without aging. This is also what Myc does in cancer cells."

Dalton said that there is an intriguing relationship between normal stem cells and cancer cells. Since Myc is crucial for maintenance of stem cells and for the development of cancer, pluripotent stem cells represent a good model for tumor biologists. Cancer is thought to be initiated by rogue stem cells found in different tissues, further highlighting the link between stem cell biology, cancer and Myc.

"This is clearly going to be a major area of research for many years to come," Dalton said.

Provided by University of Georgia