Commentary

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Genes Link Pluripotency and Self-Destructiveness in Embryonic Stem Cells

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Introduction

Human embryonic stem cells (hESCs) have been discovered to have gene networks that serve two functions at the same time. They keep pluripotency and apoptosis, or programmed cell death, under tight control. This finding, which comes from a study done by Brigham and Women's Hospital and Harvard Medical School (HMS), reveals that defective embryonic stem cells have a built-in mechanism to ensure that they are eliminated before they may harm future cells and tissues.

The researchers utilised genome-wide genetic screening to overexpress and knock off tens of thousands of genes that control embryonic stem cell growth and differentiation into the three germ layers.

The authors of the study noted, "We observed that the chromatin-modifying complex SAGA and, in particular, its member *TADA2B* are important regulators of pluripotency, survival, growth, and lineage specification." "A combined analysis of all screens demonstrated that genetic changes that extensively block differentiation across many germ layers drive proliferation and survival under pluripotency-maintaining circumstances and correlate with established cancer drivers," according to the researchers [1,2].

hESCs are of particular interest to developmental and regenerative biologists because they are pluripotent cells, meaning they can become any type of cell in the body. Many genes that control hESC function have been identified previously, but sophisticated methods that shed insight on the interconnected actions of these genes have only lately been available.

The researchers at Stephen Elledge's Brigham laboratory employed an integrated genome-scale loss- and gain-of-function screening technique in this study. “Our methods allowed us to create a ‘atlas' of nearly every gene in the human genome and determine what overexpression or loss of that gene does to the most fundamental first steps of human development,” said Kamila Naxerova, PhD, a former postdoctoral fellow in the Elledge lab and lead author of the Genes and Development article. “Rather than looking at genes one by one, we looked at thousands of genetic changes at once to see how they affect embryonic stem cell proliferation and, as a result, the formation of the three germ layers that serve as the raw material for human tissues.”

Approximately 18,000 genes were knocked out and 12,000 genes were overexpressed in the screening experiment. When genes known to control pluripotency—genes like OCT4 and SOX2—were removed, the hESCs surprisingly enhanced their resistance to death, demonstrating that pluripotency regulators contribute to apoptotic pathways in normal settings.

These interconnected behaviours were particularly noticeable in the SAGA complex, a pluripotency regulator. For the first time, the researchers showed that in the absence of the SAGA complex, hESCs died less quickly. Furthermore, the loss of the SAGA complex impeded the development of all three germ layers (endoderm, mesoderm, and ectoderm), demonstrating the SAGA complex's importance in a variety of hESC functions. Finally, the researchers discovered that many of the genes that control the creation of the three germ layers are also known to contribute to the genesis of malignancies in somatic cells whether they are over- or underexpressed [3,4].

The study's high-throughput genetic screening approach may inform future work in regenerative biology, in addition to providing a new viewpoint on the genetic underpinnings of malignancies.

"Understanding how genetics controls hESC activity is critical for our understanding of developmental biology and regenerative medicine," said Stephen Elledge, PhD, co-corresponding author and Gregor Mendel professor of genetics and medicine at the Brigham and HMS. "To date, our study is the most comprehensive evaluation of gene functioning in hESCs."

"Genetic screens provide a fantastic opportunity to investigate how genetic networks contribute to interconnected cellular activities including growth, differentiation, and survival," said Naxerova, who is currently an assistant professor at Massachusetts General Hospital's Center for Systems Biology. “This method can aid regenerative and developmental biologists in comprehensively mapping out genetic networks involved in the production of certain tissues and manipulating those genes

to more efficiently generate various types of human tissues from stem cells" [5].

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