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Researchers Identify Core Genetic Networks Driving Human Embryonic Stem Cell Behavior

A genome-wide screening technique reveals mechanisms that may help remove damaged stem cells before they can compromise human development

At the earliest stages of human embryonic development, a small collection of cells known as human embryonic stem cells (hESCs) orchestrates growth and differentiation, eventually giving rise to highly specialized human tissues. As pluripotent cells — progenitors of every type of cell type in the body — hESCs are of central interest to developmental and regenerative biologists. Many genes driving hESC functioning have previously been identified, but powerful tools that shed light on the interrelated activities of these genes have only emerged more recently. Researchers from **Brigham and Women's Hospital** and Harvard Medical School used genome-wide genetic screening to both over-express and inactivate ("knock out") tens of thousands of genes in hESCs. They uncovered key networks that simultaneously control pluripotency and readiness for cell death (apoptosis), helping to ensure optimal conditions for embryonic development. The study's findings, published in ***Genes and Development***, offer new insights into cancer genetics and a novel approach for regenerative medicine research.

"Our methods allowed us to create an 'atlas' of nearly every gene in the human genome and determine what its over-expression or loss does to the most fundamental first steps of human development," said lead author **Kamila Naxerova, PhD,** a former postdoctoral fellow in the Elledge lab in the Brigham's **Division of Genetics**. "Instead of looking at genes one by one, we looked at thousands of genetic alterations at the same time to determine how they affect the proliferation of embryonic stem cells, and, subsequently, the development of the three germ layers that serve as the raw material for human tissues."

"Elucidating how human embryonic stem cell function is controlled by genetics is essential for our understanding of developmental biology and regenerative medicine," said co-corresponding author Stephen Elledge, PhD, the Gregor Mendel Professor of Genetics and of Medicine at the Brigham and HMS. "Our study provides the most extensive examination of gene functionality in hESCs to date."

In conducting their experiment — which involved knocking out roughly 18,000 genes and overexpressing 12,000 genes — the researchers noticed a unique role played by hESC genes that control pluripotency, or differentiation capacities. When the researchers deleted these well-known genes, among them *OCT4* and *SOX2*, the stem cells surprisingly increased their resistance to death, indicating that under normal circumstances pluripotency regulators also contribute to apoptosis pathways. The researchers hypothesized that the genetic link between pluripotency and tightly regimented cell death helps ensure that if a stem cell is damaged, it is destroyed early on in embryonic development before it can compromise the functioning of future cells and tissues.

These interrelated behaviors were especially evident in a pluripotency regulator known as the SAGA complex. The researchers demonstrated for the first time that hESCs died less readily in the absence of the SAGA complex. In addition, its absence inhibited the development of all three germ layers (the endoderm, mesoderm, and ectoderm), testifying to the SAGA complex's central role in a range of hESC activities. Finally, the researchers observed that many of the genes that regulate the formation of the three germ layers also are known contributors to the growth of cancers when they are over- or under-expressed in somatic cells.

Beyond offering a new perspective on the genetic basis of cancers, the study's high-throughput genetic screening approach may inform future work in regenerative biology.

"Genetic screens present a wonderful opportunity to probe how genetic networks contribute to interrelated cellular behaviors like growth, differentiation and survival," said Naxerova who is now an assistant professor in the Center for Systems Biology at Massachusetts General Hospital. "This approach can help regenerative and developmental biologists systematically map out genetic networks that are involved in the formation of particular tissues and manipulate those genes to more efficiently grow different kinds of human tissues from stem cells."

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