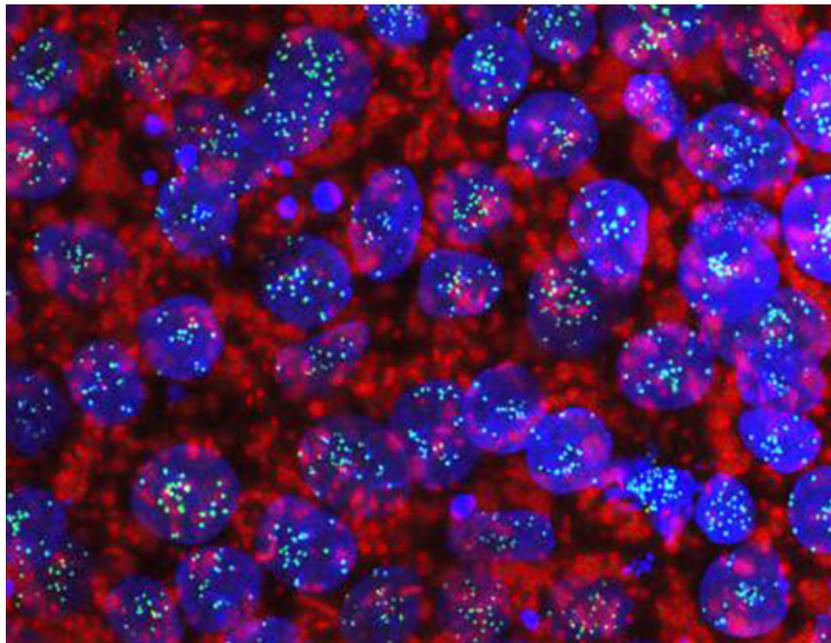


CRISPR SCREENS STEM CELL GENOME, CHARTS ESSENTIALOME

Health



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Scientists at the Hebrew University of Jerusalem have generated an atlas of genes, the essential one, that are essential for the normal growth and maintenance of human pluripotent stem cells (hPSC). The team, led by Nissim Benvenisty, MD, Ph.D., director of the Azrieli Center for Stem Cells and Genetic Research and the Herbert Cohn Chair in Cancer Research, conducted a CRISPR-Cas9 function loss screen throughout the genome in haploid human embryonic stem cells (hESCs) to highlight which of more than 18,000 genes are needed for the growth and survival of pluripotent cells and which genes restrict cell growth.

"Our screen revealed the essential genes specific for hPSC, and highlighted the major pathways that regulate the growth of these cells," the researchers write in their paper published in *Nature Cell Biology*. The findings also uncovered opposing roles for the tumor suppressor and oncogenes, evaluated the role of genes for hereditary disorders in early human growth and development and demonstrated how cancer-causing genes could affect the growth of the human embryo.

"This study creates a new framework for understanding what it means to be an embryonic stem cell at the genetic level," says co-principal Atilgan Yilmaz, Ph.D. "The more complete the image we have of the nature of these cells, the better we have of having successful therapies in the clinic." The researchers report their findings in a document entitled "Definition of essential genes for human pluripotent stem cells by CRISPR-Cas9 screening in haploid cells".

Scientists at the Hebrew University recently identified a haploid hESC type that retains characteristics of human pluripotent stem cells signatures of gene expression and epigenetic profiles; it can be differentiated into haploid somatic cells both *in vitro* and *in vivo*; and a normal haploid karyotype can be cultured and retained in culture. These characteristics make the cells "an efficient screening platform to address issues related to pluripotency at the entire genome level," the researchers write.



רק לזכויות האינטרנט של בוק
נהנים מ-Be במחיר שאסור לפספס

Carried out a loss-of-function screen based on the CRISPR-Cas9 genome on all haploid cells, using a library of single-leader RNAs (sgRNAs) targeting more than 180,000 mutations in approximately 18,000 coding genes. The aim was to "identify mutations in essential genes that affect the survival or normal growth of hESCs based on their depletion in the hESC population, as well as mutations in growth restriction genes that provide a growth advantage to hESCs".

Results from the screen suggested that, while 9% of all genes are essential for the growth and survival of these human pluripotent stem cells (hPSC), 5% acts to limit cell growth. The loss of function of these genes gives hPSCs a growth advantage. "We found that 66% of the essential genes in the cell encode proteins that are located in the nucleus, 12% encode mitochondrial proteins and 8.5% encode cytosolic proteins, while the rest encode proteins that are distributed between the endoplasmic reticulum, the plasma membrane and the extracellular space, the cytoskeleton and the Golgi apparatus," the researchers write.

Many of the essential genes identified are also mutated in human autosomal recessive (RA) genetic disorders. "Of the 2099 human genes related to RA reported in the Mendelian Heredity in Man online database (OMIM) that were also represented in our library, 226 (10.8%) were essential for the growth of hESC," the authors note. The genes responsible for RA disorders that have a growth retardation phenotype were highly represented in the set of essential genes. "Our analysis suggests that the phenotype of growth retardation associated with RA disorders can begin, in a fifth of the disorders, in very early stages of embryogenesis," the researchers continue. These findings open an exciting future direction towards modeling the growth retardation phenotype already in hPSCs for a broad group of AR disorders.

Nearly all oncogenes whose mutations affect the growth of hESCs were also classified as essential for normal growth, with the exception of one, *JUN* which was growth restrictive. In contrast, tumor suppressors were classified into essential and growth restricting fields, with analyzes indicating an enrichment of genes related to apoptosis among tumor suppressors of growth restriction, while essential tumor suppressor genes were more likely to participate in processes such as genomic instability and DNA repair "This analysis therefore points to different roles for tumor suppressor genes in hPSCs," the researchers say. In particular, a role for the p53-mTOR pathway (mechanical target of rapamycin) in the regulation of hESC growth was identified. "Our screen also led to the identification of growth restriction genes whose loss of function provides a growth advantage to hPSCs, highlighting the role of the P53-mTOR pathway in this context."

Additional analyzes of detection results also uncovered a set of genes that are essential for the survival of hPSC, but not of other cell types, and are believed to play a role in maintaining ESC identity, by slowing down cell differentiation and preventing stem cells from becoming cancerous. "Essential genes enriched with hPSC encode mainly transcription factors [TFs] and proteins related to the cell cycle and DNA repair, revealing that a quarter of the nuclear factors are essential for normal growth," they write. "Our characterization of hESC essentialome extends the definition of pluripotency beyond TF-centric vision and suggests that the genes that regulate cell cycle and DNA repair, enriched in hESCs, are also essential for normal growth and play a role vital in pluripotent cellular identity. "

The team suggests that their findings could lay the groundwork for future studies investigating the essential genes of human pluripotency, the regulation of hPSC growth, and the modeling of diseases using hPSCs. "This atlas gene allows a new functional vision on how we study the human genome and provides a tool that will change the fashion with which we analyze and treat cancer and genetic disorders," Dr. Benvenisty concludes.

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