Scientists develop new method to distinguish newly made gene transcripts from old ones

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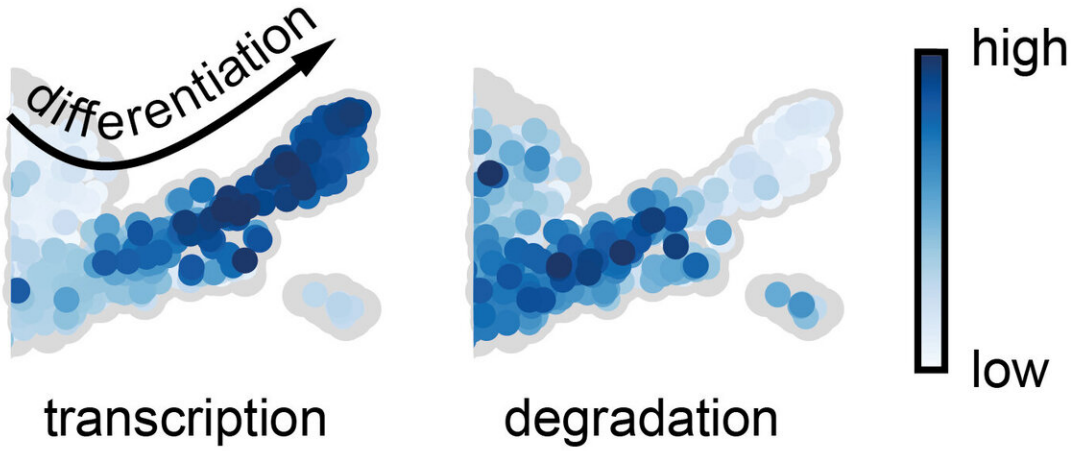


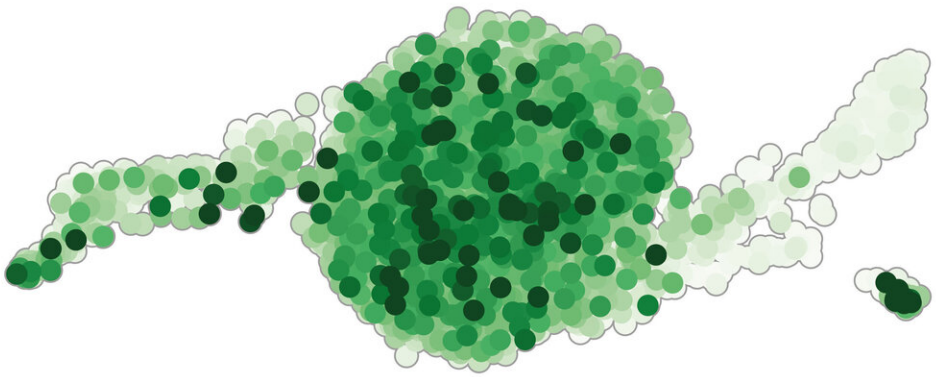
As cells specialize, or differentiate, the levels of transcription and degradation of gen transcripts changes. Transcription rates become higher, while degradation seems to go down. Credit: Nicolas Battich, ©Hubrecht Institute

Researchers from the Hubrecht Institute (KNAW) have developed a new method to assess how production and degradation of gene transcripts are regulated. In this study, published in *Science* on the 6th of March, they found that cells use distinct strategies to control the number of transcript copies, which is required for the cell to function properly.

Our bodies consist of trillions of cells that all contain the same DNA. Even though the DNA in each cell is the same, organisms consist of many distinct cell types, each with different functions. In different cell types, different sets of genes on the DNA are active—different recipes are being used to build the components of the cell. This in turn determines what kind of cell it is, for instance, a skin cell or a muscle cell. To do this, the cell makes copies of the genes, so-called transcripts, that can be used to produce proteins.

Balancing creation and destruction

The number of transcripts of each gene in a cell is a measure of the activity of these genes. This number can be influenced by making new copies, a process called transcription, and by destroying already existing copies, a process called degradation. In individual cells, the number of transcript copies is typically measured by breaking up the cell and thus cannot be followed over time in the same cell. Until now it was therefore unclear how a combination of transcription and degradation in a single cell regulates the number of copies of a particular transcript.



When cells specialize (on both sides of the center), transcript levels a gene that marks stem cells, Lgr5, go down. Darker green means higher transcript levels. Credit: Nicolas Battich, ©Hubrecht Institute

Labeling new copies

Researchers from the groups of Alexander van Oudenaarden, Hans Clevers and Marvin Tanenbaum at the Hubrecht Institute set out to solve this problem by developing a new single-cell sequencing technique to distinguish freshly made transcripts from pre-existing transcripts.

Distinct strategies

By combining these data with computer models, the researchers determined that both transcription and degradation are heavily involved in regulating the number of copies of a transcript. Battich says, "Cells seem to use distinct strategies to regulate the activity of their genes—or the number of copies of these transcripts. For some genes, the cell has to be able to very quickly change the number of copies. Those genes were both being transcribed and degraded at high levels. By involving both processes, cells were able to change the number of copies very quickly, for instance, by decreasing transcription and increasing degradation simultaneously."

The new method, called scEU-seq, can be used to study many processes, such as the specialization of cells during development, the regulation of cell division in healthy and cancer systems.

More information: Sequencing metabolically labeled transcripts in

single cells reveals mRNA turnover strategies. Nico Battich, Joep Beumer, Buys de Barbanson, Lenno Krenning, Chloé S. Baron, Marvin E. Tanenbaum, Hans Clevers, Alexander van Oudenaarden. *Science* 2020. science.sciencemag.org/cgi/doi … 1126/science.aax3072

Provided by Hubrecht Institute