Super-resolution imaging can map critical cell changes several days sooner than current method

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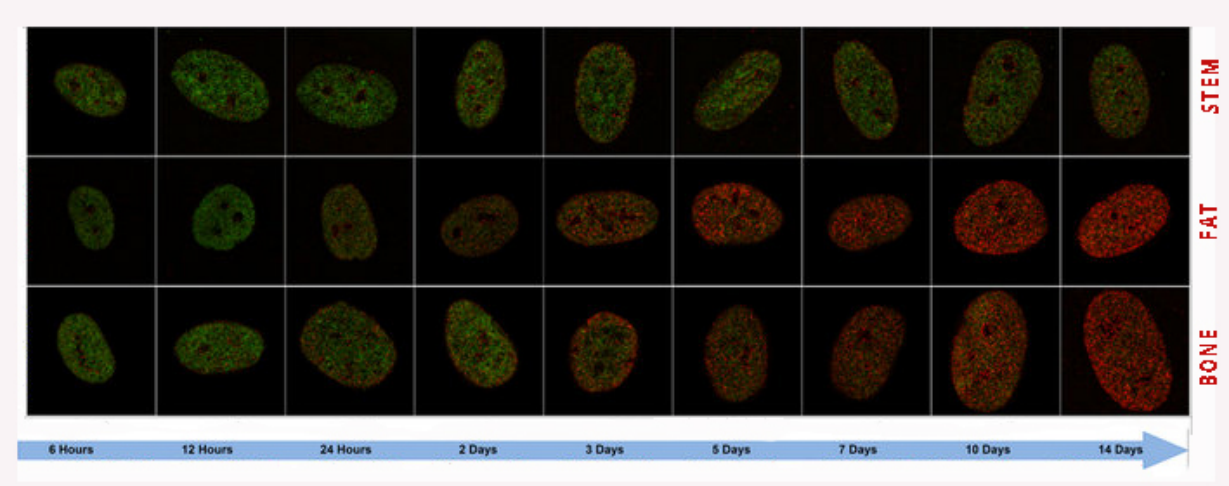

In a time series of super-resolution microscopic images of the epigenetic marks in the nuclei of stem cells, stem cells differentiate into distinct cell types—bone and fat. Using texture analysis, researchers can discern the conversion of stem cells as early as 24 hours and the divergence of lineages at 72 hours with the EDICTS method. Credit: Joseph Kim, PhD., Moghe lab, Rutgers University

Scientists funded by the National Institutes of Health have developed a new way to identify the state and fate of individual stem cells earlier than previously possible. Stem cells are undifferentiated, serving as building blocks for the various tissues and organs of the body.

Understanding a stem cell's fate—the type of cell it will eventually become—and how far along it is in that process can help scientists better manipulate cells for therapies.

To identify these signals of a stem cell's fate, an interdisciplinary team from multiple universities collaborated to use super-resolution microscopy to analyze epigenetic modifications. Epigenetic modifications change how DNA is wrapped up within the nucleus, allowing different genes to become accessible to the gene expression machinery within the cell. While the complete process remains somewhat mysterious, scientists have identified some epigenetic markings for pending gene expression. Using the new method, described in the Jan. 4, 2017, *Scientific Reports*, the team was able to determine a cell's fate days before other techniques.

"This group honed and combined several techniques to deliver a powerful new tool for assessing stem cell fate." says Rosemarie Hunziker, Ph.D., director of the program in Tissue Engineering and Regenerative Medicine at the National Institute of Biomedical Imaging and Bioengineering (NIBIB), part of NIH. "Early predictions of gene expression within individual stem cells will ultimately help us sort them and use them."

Existing approaches to assess the states of stem cells look at the overall population of cells but aren't specific enough to identify the fates of individual cells. Also, current tools can only identify these fate decisions relatively late in the game. To develop therapies with maximum control and flexibility, researchers must have a good idea of how a cell will further develop once it is transplanted into a patient. An ideal solution would be a technology to predict the imminent activation of a particular gene or gene family, that in turn causes the cell serve a particular function.

In the new approach, called EDICTS (Epi-mark Descriptor Imaging of Cell Transitional States), the researchers labeled epigenetic modifications and then imaged the cells with super resolution to see the precise location of the marks.

"We're able to demarcate and catch changes in these cells that are actually not distinguished by established techniques," says Prabhas Moghe, Ph.D., distinguished professor of biomedical engineering at Rutgers University and senior author of the paper. He describes the method as "fingerprinting the guts of the cell;" the results are quantifiable descriptors of each cell's organization, even revealing how particular modifications are distributed throughout the nuclei.

The team demonstrated the method's capabilities by measuring two types of epigenetic modifications in the nuclei of human stem cells cultured in the laboratory. They added chemicals that coaxed some of the cells to become fat cells and others to become bone, while another set served as control. Within three days, cells destined for different fates showed modifications at various locations within the cells. These changes gave researchers the opportunity to distinguish the cell types days before traditional methods could make such distinctions.

The technique had the specificity to look at regional changes within individual cells, while existing techniques can only measure total levels of modifications among the entire population of cells. "The levels are not significantly different, but how they're organized is different and that seems to correlate with the fact that these cells are actually exhibiting different fates," says Moghe. "It allows us to take out a single cell from a population of dissimilar cells," which can help researchers select particular cells for different stem cell applications.

The beauty of the method is its simplicity and versatility, says Moghe; it's as easy as labeling, staining and imaging cells, techniques already

familiar to many researchers. As microscopes capable of super-resolution imaging become more widely available, scientists can use it to sort and screen different types of cells, understand how a particular drug may disrupt epigenetic signaling, or ensure that stem cells to be implanted are not at risk of transforming into the wrong cell type. "It will usher in the next wave of studies and findings," says Moghe.

More information: Joseph J. Kim et al. Optical High Content Nanoscopy of Epigenetic Marks Decodes Phenotypic Divergence in Stem Cells, *Scientific Reports* (2017). DOI: 10.1038/srep39406

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