Researchers identify protein crucial for stem cell survival using editing tool CRISPR

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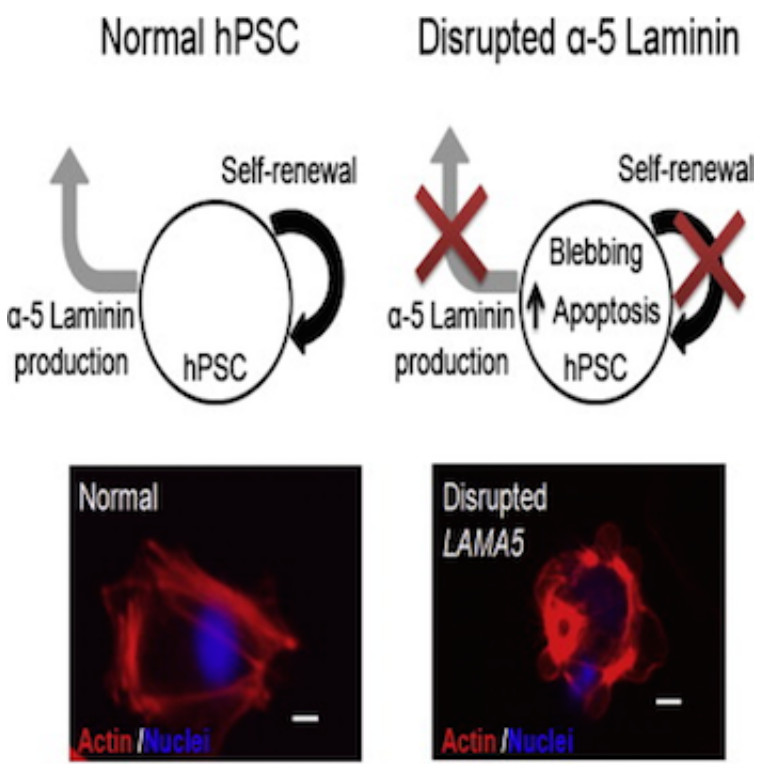

The production of protein α-5 laminin is critical for the self-renewal processes of a human pluripotent stem cell (hPSC)

In a multidisciplinary effort, a team of University of Wisconsin-Madison engineers has identified a protein that is integral to the survival and self-renewal processes of human pluripotent stem cells (hPSC).

The UW-Madison team, which published its findings online in the

journal *Stem Cell Reports* on July 30, 2015, includes Alex Laperle, who earned his PhD in biomedical engineering in 2015; Kristyn Masters, an associate professor of biomedical engineering; Kris Saha, an assistant professor of biomedical engineering; and Sean Palecek, the Milton J. and A. Maude Shoemaker professor of chemical and biological engineering.

Identifying the protein α-5 laminin as a crucial component of a stem cell's extracellular matrix could help inform the development of synthetic environments, or substrates, that support hPSC culture, says Masters.

"If you take an array of substrates that support hPSC growth and maintenance of pluripotency, one of things they all have in common is that they allow the hPSCs to produce α-5 laminin," she says.

The goal for many researchers who work with stem cells is simply to produce an environment that allows the cells to support their own survival. By identifying α-5 laminin as an important key to a cell's survival, the researchers can work to create a synthetic culture environment that encourages the protein's production, says Saha.

Designing new synthetic substrates is about providing a receptive surface that keeps what the cells are producing endogenously in the right place, he says.

Spurred by growing expertise in and demand for genome editing, UW-Madison recently opened a genome-editing facility in its Biotechnology Center that allows researchers to take advantage of a relatively new tool called Cas9-CRISPR gene editing. The innovative technique enables researchers to disrupt a genome sequence with high precision, especially in hPSCs.

The research team used the tool to identify α-5 laminin as a key

ingredient for stem cell survival. This tool can completely "knock out" a gene, not only reducing its expression, but removing it completely. Tailoring the method to a specific DNA sequence is faster and more practical than other well-known gene editing tools, such as zinc finger nucleases or transcription activator-like effector nucleases.

By knocking out the α-5 laminin gene, the team determined that without α-5 laminin, hPSCs can no longer survive, let alone maintain their pluripotency.

The evolution of substrates plays a definitive role in this research. Currently, most stem cell substrates are animal-derived and ill-defined, and researchers are working toward developing a more controlled synthetic environment that is less expensive and takes advantage of the cell's natural processes.

"This work gives us a better idea of how to improve the substrate to make a completely defined and inexpensive culture system that's synthetic," says Palecek.

If stem cell researchers can create a supportive environment, the stem cells themselves can then modify that environment to suit their needs. Identifying α-5 laminin is a small step in the big picture of stem cell research, but it helps scientists and researchers further understand the demand and processes of these cells. Since inserting recombinant α-5 laminin into a cell's environment can be very expensive, presenting an environment where a cell can produce this protein on its own is a practical pathway to developing more effective, less expensive substrates.

In the future, the researchers are looking into how a stem cell modifies its extracellular matrix during differentiation, says Palecek. This not only takes into account a cell's general well-being, but its ability to carry out

processes, and what exactly the cell is doing and producing to promote these processes.

"The implication here is, if we want to drive differentiation, what cues do we need to provide to the cell, and what is the cell going to make for itself?" he says. "If the cell is going to make it for itself, we can simplify the process by not adding it."

Provided by University of Wisconsin-Madison

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