Signaling molecule crucial to stem cell reprogramming

November 20 2014

While investigating a rare genetic disorder, researchers at the University of California, San Diego School of Medicine have discovered that a ubiquitous signaling molecule is crucial to cellular reprogramming, a finding with significant implications for stem cell-based regenerative medicine, wound repair therapies and potential cancer treatments.

The findings are published in the Nov. 20 online issue of *Cell Reports*.

Karl Willert, PhD, assistant professor in the Department of Cellular and Molecular Medicine, and colleagues were attempting to use induced pluripotent stem cells (iPSC) to create a "disease-in-a-dish" model for focal dermal hypoplasia (FDH), a rare inherited disorder caused by mutations in a gene called PORCN. Study co-authors V. Reid Sutton and Ignatia Van den Veyver at Baylor College of Medicine had published the observation that PORCN mutations underlie FDH in humans in 2007.

FDH is characterized by skin abnormalities such as streaks of very thin skin or different shades, clusters of visible veins and wartlike growths. Many individuals with FDH also suffer from hand and foot abnormalities and distinct facial features. The condition is also known as Goltz syndrome after Robert Goltz, who first described it in the 1960s. Goltz spent the last portion of his career as a professor at UC San Diego School of Medicine. He retired in 2004 and passed away earlier this year.

To their surprise, Willert and colleagues discovered that attempts to

reprogram FDH fibroblasts or skin cells with the requisite PORCN mutation into iPSCs failed using standard methods, but succeeded when they added WNT proteins - a family of highly conserved signaling molecules that regulate cell-to-cell interactions during embryogenesis.

"WNT signaling is ubiquitous," said Willert. "Every cell expresses one or more WNT genes and every cell is able to receive WNT signals. Individual cells in a dish can grow and divide without WNT, but in an organism, WNT is critical for cell-cell communication so that cells distinguish themselves from neighbors and thus generate distinct tissues, organs and body parts."

WNT signaling is also critical in limb regeneration (in some organisms) and tissue repair.

"We've shown that WNT signaling is required for cellular reprogramming," said Willert. "Some of the processes that occur during cellular reprogramming resemble those that occur during regenerative processes and wound repair. For example, limb regeneration in organisms like axolotl and zebrafish require cells at the injury site to de-differentiate (change their function) and then rebuild the damaged tissue. WNT is essential for these amazing regenerative processes."

Willert cautioned that "it would be a stretch to say that activation of WNT signaling will allow us to regenerate limbs," but said WNT activation is likely valuable in assisting tissue repair.

A variety of efforts are already underway exploring how to leverage WNT signaling to promote wound healing, such as speeding bone fracture repairs, and even hair growth. "That's not really a wound repair process," Willert said, "but WNT is required for hair growth."

The caveat, he noted, is that "there's a fine line between repairing tissue

and promoting cancer growth." Willert said there are efforts underway to create therapeutics that block WNT signaling as a means to block cancer growth. Earlier this year, for example, Willert and colleagues published findings describing the use of an antibody to disrupt WNT signaling in embryonic stem cells. In cancer cells with mutations in the WNT signaling pathway this antibody may inhibit their growth and development.

Provided by University of California - San Diego