MedicalXpress

Insights into psoriasis suggest a new treatment target

December 11 2019

Psoriasis is a skin disorder that affects at least 100 million individuals worldwide. Its economic impact is more than $10 billion annually in the U.S. alone. Involved skin becomes thickened, red, and covered with silvery scales, while changes to the nails and deforming inflammation of the joints may also occur in up to one-third of affected individuals. The underlying cause of psoriasis remains a mystery, and effective targeted therapies remain to be developed.

Now, investigators from Brigham and Women's Hospital and the Harvard Stem Cell Institute have uncovered a novel pathway that may explain why skin thickens in psoriasis and suggests new strategies for developing therapies for the condition. The team's results are published in the *Journal of Investigative Dermatology*.

"Psoriasis places social and psychological stress on patients and is associated with risk of diabetes, cardiovascular disease and more. While steroids and biologics can be prescribed, we don't have a cure because we haven't understood the cause," said co-senior author George Murphy, MD, director of the Program in Dermatopathology in the Department of Pathology at the Brigham. "Our initial finding that skin thickening in psoriasis is due to build-up of dysregulated stem cells and their progeny are exciting because it represents a new way of thinking about an old and significant skin disease."

To better understand the basis for the dysregulated skin stem cell behavior, the investigators focused on the epigenome, the methylated

wrapping that covers each DNA strand and orchestrates how individual genes behave.

"Without understanding the mechanism underlying a disease, it's hard to find effective treatments," said co-senior author Christine Lian, MD, a dermatopathologist in the Department of Pathology at the Brigham. "The question we decided to pursue was: Is there an epigenetic abnormality in psoriasis that may explain why stem cells are misbehaving?"

Lian, Murphy and their colleagues found a defect in the epigenetic covering that resulted in the loss of a DNA methylation hydroxymethylation mark. Known as loss of 5-hmC, this defect was found in cells from patients with psoriasis but not other skin conditions that produce a similar skin thickening, such as callous-like areas from chronic irritation. The team replicated the defect in a mouse model of psoriasis and found that it preferentially affected genes that regulated the function of skin cells.

Lian and Murphy have previously shown that 5-hmC loss in the skin epigenome can be reprogrammed using agents as fundamental as ascorbic acid (vitamin C). They reasoned that therapeutic correction of the epigenomic defect in psoriasis might reverse the entire process. Based on experiments using skin stem cell cultures in the lab, the team presents promising preliminary data suggesting that 5-hmC levels can be restored to correct the deficiency seen in psoriasis.

The investigators note that while there is much interest in the role of vitamin C, additional research is needed to develop and test effective treatments since simply taking a vitamin supplement is likely to have little effect. The team has begun work on the next research steps, which will involve three-dimensional bioprinting of skin stem cells in the context of their supportive niches to test other epigenetic reprogramming agents.

"If successful, our epigenetic stem cell explanation for psoriasis hopefully could transform therapy, allowing for more personalized and targeted approaches directed at the very cells that accumulate to form the heartbreak of this all-too-often devastating skin condition," said Murphy.

Provided by Brigham and Women's Hospital