Finding long strands of RNA in skin development and disease

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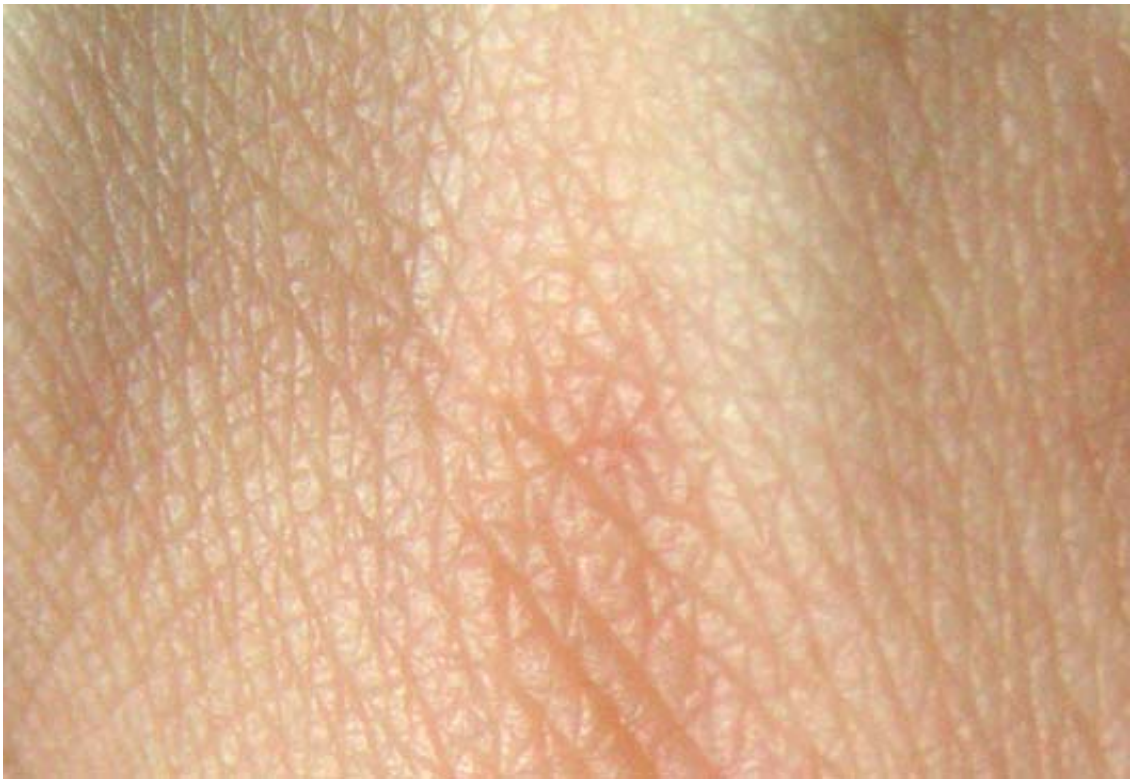

Human skin structure. Credit: Wikipedia

Researchers from Case Western Reserve University School of Medicine have discovered how unusually long pieces of RNA work in skin cells. The RNA pieces, called "long non-coding RNAs" or "lncRNAs," help skin cells modulate connective tissue proteins, like collagen, and could represent novel therapeutic targets to promote skin repair.

In a recent *Frontiers Genetics* study, researchers identified specific lncRNAs that control genes and behavior of mouse skin cells. The team found 111 lncRNAs that work with a highly conserved protein network called the Wnt/β-catenin pathway. The Wnt/β-catenin pathway serves as a signaling hub that helps cells across species adjust gene expression in response to their environment. The new study connects this important pathway to a new form of genetic control—lncRNAs.

"LncRNAs are a newly discovered class of genes, and we've been working to elucidate their functions and mechanisms as they appear to be critical for human health," said Ahmad Khalil, PhD, assistant professor of genetics and genome sciences and member of the Case Comprehensive Cancer Center at Case Western Reserve University School of Medicine. "Our findings show that the Wnt/β-catenin pathway activates certain lncRNAs to directly control gene expression in skin fibroblast cells." Khalil served as co-senior author on the study with Radhika Atit, PhD, professor of biology at Case Western Reserve University School of Medicine. Two Case Western Reserve undergraduates, Nathaniel Mullin and Nikhil Mallipeddi, served as co-first authors.

The team studied skin cells, called dermal fibroblasts, that help hair follicles develop, wounds heal, and generally maintain the structural integrity of skin. Fibroblasts orchestrate these important functions with the help of the Wnt/β-catenin pathway, among others. Sustained activation of the Wnt/β-catenin pathway can cause fibroblasts to overproduce connective tissue proteins, like collagen, causing harmful skin fibrosis. According to the new study, lncRNAs serve as an intermediary between Wnt/β-catenin and fibroblast genes.

The researchers showed fibroblasts genetically modified to overproduce β-catenin had 8-14 times higher levels of two specific lncRNAs when compared to control fibroblasts. The researchers named the lncRNAs

Wincr1 and Wincr2—Wnt signaling induced non-coding RNA." The lncRNA levels correlated with significantly higher levels of proteins that help fibroblasts move and contract. The findings suggest disrupting lncRNA levels could change how fibroblasts function in skin.

The study adds to a growing body of evidence that lncRNAs could represent a new arena for drug developers. LncRNAs are intriguing therapeutic targets—recent studies by Khalil and others have implicated lncRNAs defects in all kinds of diseases, including infertility and cancer.

Said Atit, "Specific lncRNAs that operate downstream of the Wnt/β-catenin pathway could serve as drug targets for chronic and acute skin fibrosis conditions." The researchers are now working to understand how lncRNAs work in various animal models, and how their dysfunction may promote disease.

More information: Nathaniel K. Mullin et al, Wnt/β-catenin Signaling Pathway Regulates Specific lncRNAs That Impact Dermal Fibroblasts and Skin Fibrosis, *Frontiers in Genetics* (2017). DOI: 10.3389/fgene.2017.00183

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