# Skin-on-a-chip: Modeling an innervated epidermal-like layer on a microfluidic chip

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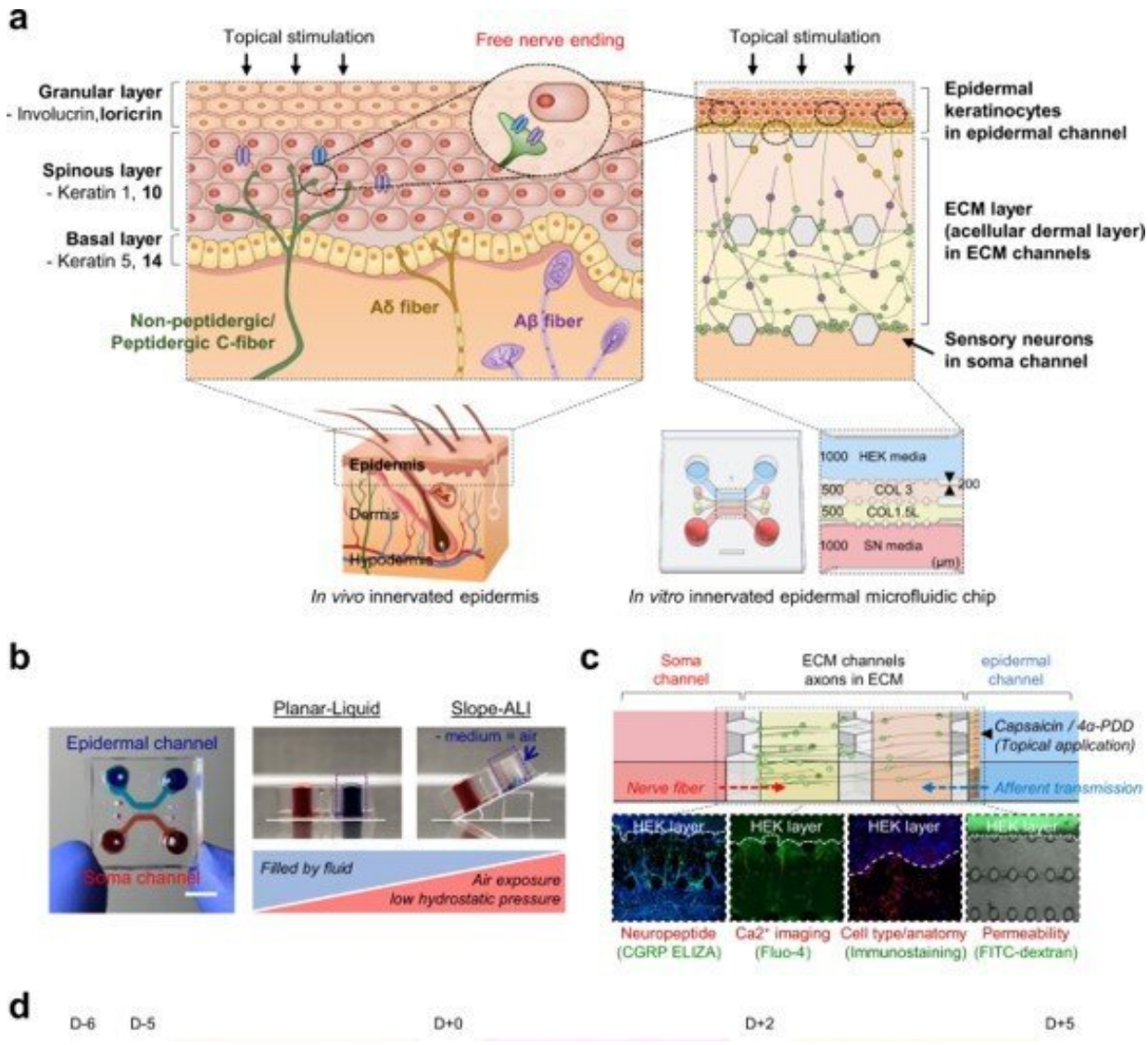



Microfluidic platform and culture system for sensory neurons-keratinocytes co-culture. (a) Schematic illustration and design of human skin anatomy (left) and

the innervated epidermal chip to coculture sensory neurons and keratinocytes (right). Schematic design of the innervated epidermal chip compartments (right lower). HEK; human keratinocyte, SN; sensory neuron, COL 3; collagen I at 3 mg/ml concentration, COL 1.5 L; collagen I at 1.5 mg/mL with 10% laminin, Scale unit; μm. (b) Top view of the microfluidic chip (left) and experimental concept of slope-based air-liquid interface (ALI) method for epidermal development (right, longitudinal vertical section view). Each cell channel was marked with a different color dye. (c) Cell-type-specific assays for the innervated epidermal chip. (d) Experimental workflow of cell seeding and culture for generating the innervated epidermal chip. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-37187-4

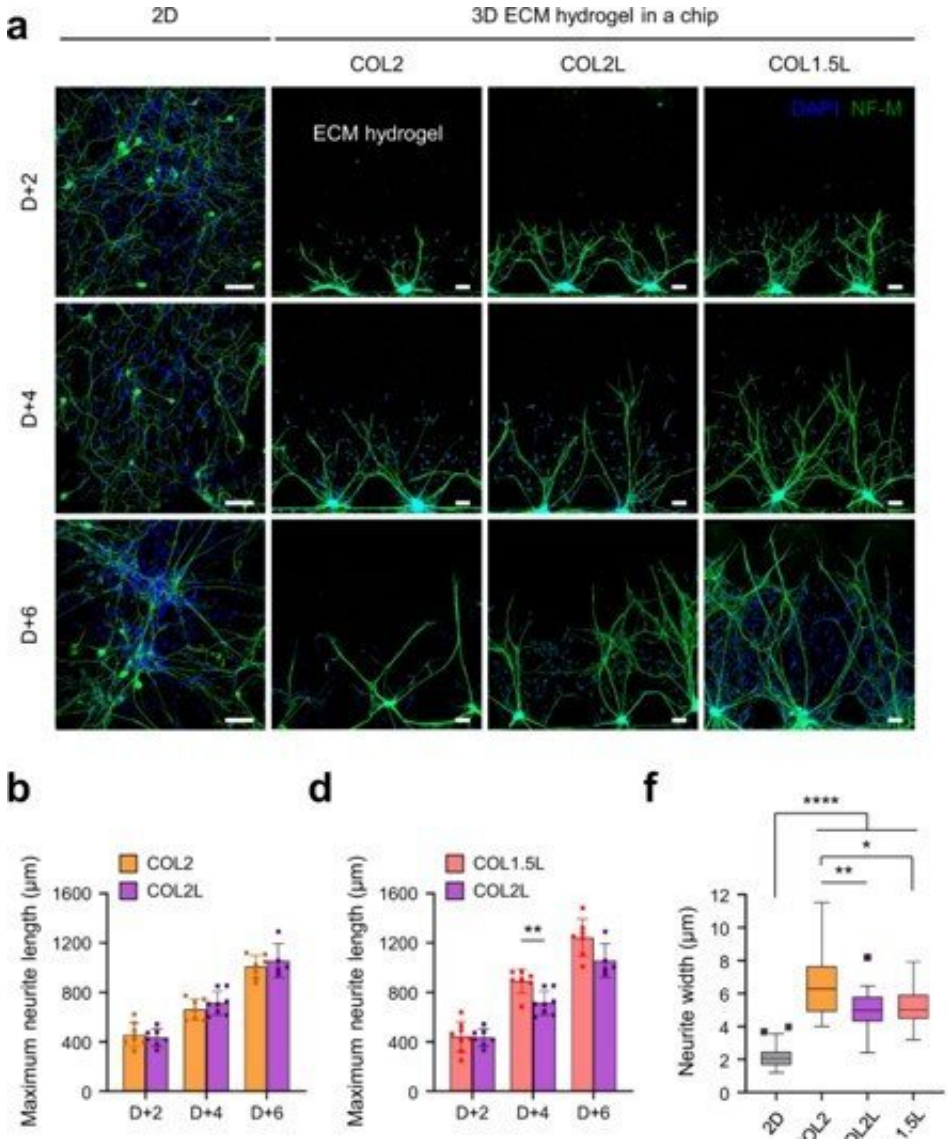
Bioengineers and tissue engineers intend to reconstruct skin equivalents with physiologically relevant cellular and matrix architectures for basic research and industrial applications. Skin pathophysiology depends on skin-nerve crosstalk and researchers must therefore develop reliable models of skin in the lab to assess selective communications between epidermal keratinocytes and sensory neurons.

In a new report now published in *Nature Communications*, Jinchul Ahn and a research team in mechanical engineering, bio-convergence engineering, and therapeutics and biotechnology in South Korea presented a three-dimensional, innervated epidermal keratinocyte layer on a microfluidic chip to create a sensory neuron-epidermal keratinocyte co-culture model. The biological model maintained well-organized basal-suprabasal stratification and enhanced barrier function for physiologically relevant anatomical representation to show the feasibility of imaging in the lab, alongside functional analyses to improve the existing co-culture models. The platform is well-suited for biomedical and pharmaceutical research.

## Skin: The largest sensory organ of the human body

Skin is composed of a complex network of sensory nerve fibers to form a highly sensitive organ with mechanoreceptors, thermoreceptors and nociceptors. These neuronal subtypes reside in the dorsal root ganglia and are densely and distinctly innervated into the cutaneous layers. Sensory nerve fibers in the skin also express and release nerve mediators including neuropeptides to signal the skin. The biological significance of nerves to sensations and other biological skin functions have formed physical and pathological correlations with several skin diseases, making these instruments apt in vivo models to emulate skin-nerve interactions.

To recapitulate the microphysiological architectures, Ahn and colleagues used a microfluidic model to co-culture and analyze 3D interactions of keratinocytes and sensory neurons in the lab. They applied a slope-air liquid interface to provide air contact to successfully differentiate epidermal cells for keratinocyte development and used a multichannel hydrogel system to mimic cellular/subcellular arrangements and cell-cell-matrix interactions to form physiologically-relevant epidermal surfaces. The researchers modeled epidermal keratinocyte sensory neuron crosstalk on the microfluidic chip and induced conditions of hyperglycemia to mimic acute diabetes to investigate the mechanisms underlying pathological conditions in the human skin.




Optimization of 3D extracellular matrix (ECM) hydrogels for axon patterning of sensory neurons in a microfluidic chip. (a) Representative fluorescence images of elongated nerve fibers of sensory neurons in microchannels for each ECM condition. NF-M; neurofilament M, green, DAPI; nuclei, blue. COL 2; collagen I at 2 mg/ml concentration, COL 2 L; collagen I at 2 mg/mL with 10% laminin, COL 1.5 L; collagen I at 1.5 mg/mL with 10% laminin. 2D; conventional monolayer culture method. Scale bars; 100 μm. (b–g) Quantitative analysis of axonal changes according to ECM conditions of the chip. Maximum (b, d) and total neurite length (c, e) of sensory neurons at each time point after culture (n = 5–8 ROIs, at least 10 neurites were measured in each ROI, COL1.5 L(d4) vs COL2L(d4) **p = 0.0014, COL1.5 L(d6) vs COL2L(d6) p = 0.1211 for maximum neurite length, COL1.5 L(d4) vs COL2L(d4) *p = 0.0126, COL1.5

L(d6) vs COL2L(d6) ***p = 0.0006 for total neurite length, 2 independent replicates). Box plot of the neurite width (f) of a sensory neuron 6 days after culture (n = 19 ROIs, 2D vs COL2, COL2L, COL1.5 L ****p