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WHAT'S NEW

Breaking ground in skin research: biology enabled by mechanics and materials

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The collaborative work was performed by Lorenza Garau Paganella and colleagues, including SKINTEGRITY.CH Principal Investigators Profs. Edoardo Mazza, Mark Tibbitt, and Sabine Werner.

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Lorenza Garau Paganella. In the body, cells are embedded in the 3D extracellular matrix (ECM), consisting of a solid polymeric network and a fluid interstitial phase, providing mechanical support and guiding biological function. Upon mechanical deformation of tissues, such as stretching, mechanical stresses are transmitted through both the solid and fluid phases. This not only results in deformations of the matrix polymers but also drives fluid and ion flow, leading to variations in osmotic pressure, hydrostatic pressure, and electric field. These variations can impact cell behavior, particularly in the dermis. While much attention has been given to characterizing fibroblast response to mechanical changes in the solid ECM, the effects of osmotic pressure and hydrostatic pressure on fibroblast homeostasis remain poorly understood.

Addressing such open questions requires a multidisciplinary approach. Historically, scientists like Leonardo da Vinci mastered fields as diverse as mathematics, biology, and the arts. Today, while specialization is often favored, collaborative teams, where specialized scientists merge their expertise toward a shared goal, are critical to address such multidisciplinary challenges. For example, understanding the effects of mechanical and biochemical changes on fibroblast biology requires insights from biology, mechanics, and bioengineering to advance skin health and therapeutic modalities. However, studying these effects in vivo is challenging due to limited control over individual mechanical cues. Advanced 3D hydrogel culture models offer a solution, replicating the native ECM and enabling precise investigations of fibroblast responses to selected stimuli.

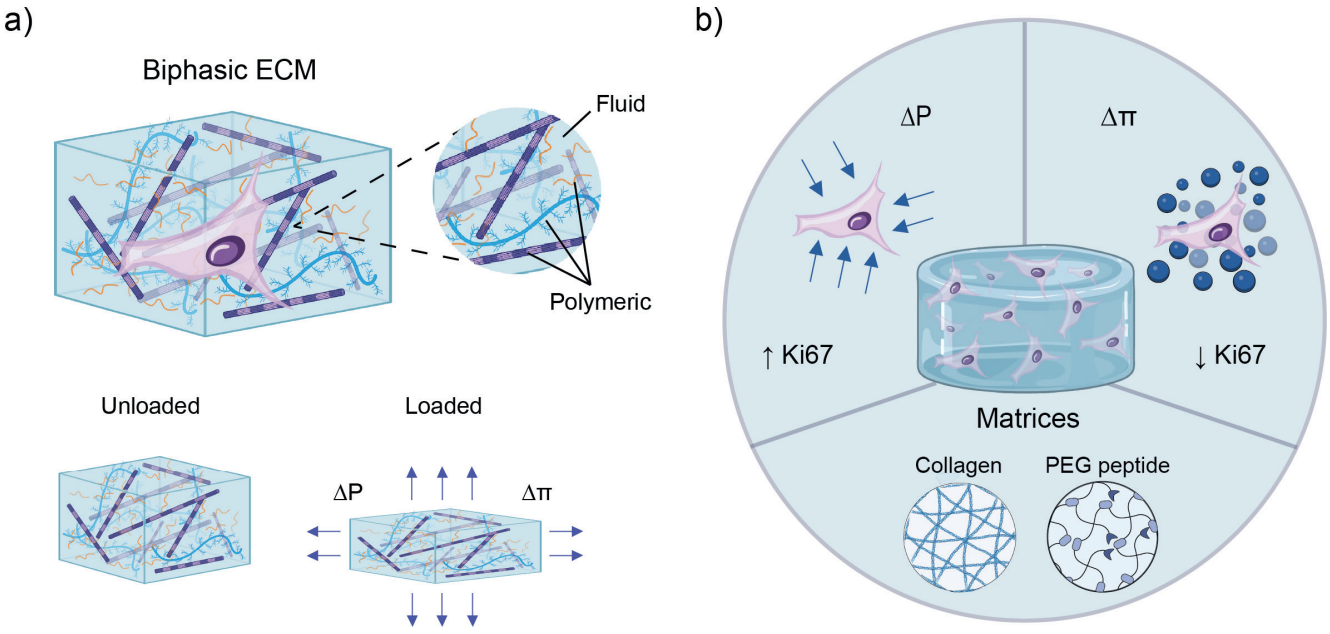

Figure 1: Influence of mechanical forces on dermal fibroblasts.
a) The ECM is multiphasic and composed of a solid component (polymer phase) and a fluid phase. The fluid phase can be displaced upon mechanical loading, leading to variations in hydrostatic pressure (ΔP) and osmotic pressure (Δπ). b) Collagen or PEG hydrogels were used as tissue-like matrices for dermal fibroblasts. The application of hydrostatic pressure induced increase in proliferation (Ki67 ↑) while osmotic pressure induced decrease in proliferation (Ki67 ↓).

In our work, we combined expertise in skin mechanics, polymer networks, and dermal fibroblast biology to assemble an interdisciplinary and collaborative team within the SKINTEGRITY.CH consortium. We have developed suitable 3D in vitro platforms to culture dermal skin fibroblasts, apply mechanical or biochemical stimulation, and characterize the cell response. Building on our shared passion for skin research, we have integrated diverse expertise toward a common goal of understanding dermal fibroblast response to tissue stretch. This includes a focus on fibroblast mechanobiology and mouse models (Werner lab), characterization and modeling of soft tissue biophysics, and bioreactor design (Mazza lab), and defined 3D biomaterials for fibroblast culture (Tibbitt lab). Regular team-wide meetings that give a chance to present our work to a diverse audience, exchange ideas, and seek feedback are essential ingredients for success. **With this approach that integrates mechanics, materials, and biology, we are breaking new ground in skin research.**
In a recent publication, we used biomimetic 3D collagen and 3D poly(ethylene glycol) (PEG)–peptide hydrogels to study the response of fibroblasts to hydrostatic and osmotic pressure. In collagen gels, hydrostatic pressure increased the number of Ki67+ cells, indicating increased proliferation. On the contrary, hyperosmotic stress decreased Ki67 levels. These responses were conserved in PEG-peptide hydrogels with mixed ECM-mimicking epitopes. This suggests dermal fibroblasts can sense hydrostatic and osmotic pressure independently of the 3D hydrogel matrix and the epitopes. In addition, hyperosmotic stress induced expression of the *PRSS35* gene, a recently identified osmoresponsive gene by the Werner lab. In our work, the expression of *PRSS35* differed between cells cultured in 3D hydrogel or on 2D, stressing the importance of 3D-tissue like culture models. Overall, both hydrostatic and osmotic pressure affect dermal fibroblast mechanobiology, which is crucial to better understand skin mechanobiology in health and disease.
This was one of the many examples of successful collaboration of our multidisciplinary team. In the future we aim at exploring other aspects of skin research, ranging from fundamental investigations to clinically relevant studies, while fostering in-depth communication between team members with very different backgrounds so to develop skills that will be essential for the next generation of skin scientists.

Author

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