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WHAT'S NEW

The dermal mechanome: expanding our understanding of skin mechanobiology

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The present work was performed by Dr. Anastasiya Martyts and colleagues, including SKINTEGRITY.CH Principal Investigators Profs. Edoardo Mazza, Sabine Werner, and Mark Tibbitt.

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It is now well established that mechanical forces influence living cells and tissues - a field of study known as mechanobiology. Our skin is no exception, as it can be strongly influenced by the mechanical forces exerted on it. Surgeons have long observed that wounds healing under tension often form more noticeable scars, leading to the development of techniques specifically designed to reduce tension during surgical wound closure. More recently, medical devices have been developed to stress-shield healing wounds to reduce the resulting scars. While these clinical observations confirm the critical role of mechanics in skin biology, the underlying mechanisms are poorly understood. In this interdisciplinary work, we brought together complementary approaches from engineering and biology to elucidate how mechanical stimuli affect dermal fibroblasts. First, we performed experiments to determine the biomechanical response of ex vivo human skin to mechanical loading. Next, we built computational models of the skin to predict various internal mechanical stimuli that occur in the skin during loading but cannot be measured experimentally. Lastly, we subjected human dermal fibroblasts to these stimuli in vitro to evaluate their biological response.

Computational model predicts a variety of secondary mechanical stimuli

Usually, when we think about mechanical loading of the skin, we only consider stretch or compression. Much of the skin mechanobiology literature is focused on studying precisely these stimuli, and the stiffening of the skin extracellular matrix (ECM) induced by skin stretch. As it turns out, this is far from the full picture. Our computational model of the skin includes not only the solid extracellular matrix of the skin but also the ions and fluid inside the tissue. Given that the skin is about 70 % water by weight, water is a crucial component of the ECM but is rarely considered in computational and experimental skin models. With this extension of the more traditional models of the skin, our model predicted that there are indeed many other secondary stimuli triggered by something as simple as physiological skin stretch, namely: changes in osmotic pressure (Δπ), hydrostatic pressure (ΔP), fluid flow (Δv), and electric field (ΔE) inside the skin. We named these «mechanocoupled» stimuli, since they are inevitably coupled to the more general stretch or compression of the skin *(see Figure 1)*. More broadly, we termed the entire collection of mechanical stimuli occurring in the skin the dermal mechanome. We then tested whether dermal fibroblasts could sense or respond to the stimuli predicted by our computational model.

Dermal fibroblasts sense and respond to mechanocoupled stimuli

While we were not the first to study the effects of osmotic pressure, hydrostatic pressure, fluid flow, and electrical potential on cells in vitro, we were the first to do so at physiologically relevant magnitudes. Given that our computational model predicted mechanocoupled stimuli at very low magnitudes,

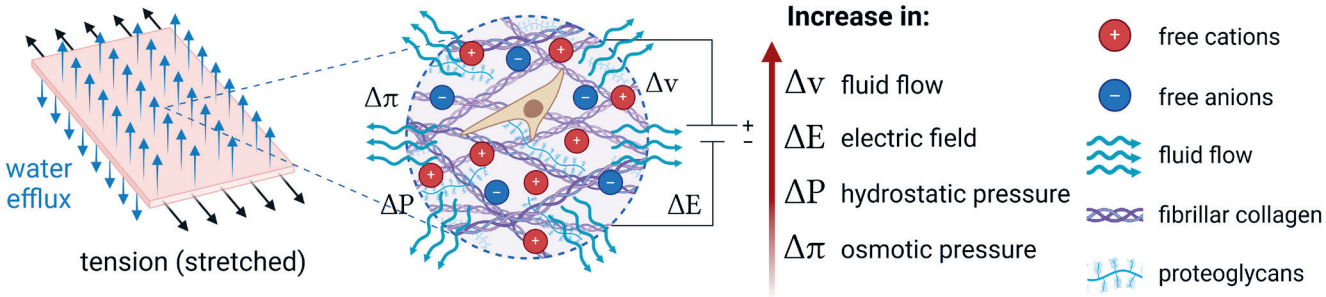

Figure 1: When skin is deformed by mechanical loading, such as stretch, the fibrous components of the extracellular matrix rearrange and align in the direction of the applied force. This leads to an efflux of extracellular fluid from the stretched area, along with the ions in the fluid, leading to concurrent changes in fluid flow, electric field, hydrostatic pressure, and osmotic pressure.

we first set out to study whether dermal fibroblasts could sense these mild stimuli at all.

To test this, we constructed bioreactor systems that could expose cells to these stimuli while we monitored intracellular calcium levels via fluorescent live cell microscopy. This technique visualizes intracellular calcium as a green fluorescent signal. While cells left unstimulated (control condition) showed a relatively constant signal, cells that were subjected to hydrostatic pressure, fluid flow, or electrical potential all showed changes in the intracellular calcium concentration *(Figure 2)*. This was a clear indicator that dermal fibroblasts could sense the model-predicted stimuli.

We also performed Western blots to check for changes in intracellular signaling, and found that fluid flow and electrical potential reduced the phosphorylation of the S109 YAP residue, indicating increased activity of the YAP protein, commonly known as a sensor and transducer of mechanical stimuli. This confirmed that dermal fibroblasts can sense these mechanocoupled stimuli and convert them into biochemical signals.

Dermal fibroblasts respond to changes in the mechanome with altered gene expression

We further assessed gene expression in dermal fibroblasts cultured in 2D and 3D models using RT-qPCR to check whether these stimuli could affect cell biology beyond mechanosensing. We found that fluid flow significantly reduced collagen 1 and collagen 3 expression, and increased MMP-1 expression while electric field increased collagen 1 expression. This suggests that not only did dermal fibroblasts sense the stimuli, but also responded to some of them by regulating key genes that lead to ECM remodeling. This may be one potential mechanism that allows cells to modify their environment and modulate mechanocoupled stimuli.

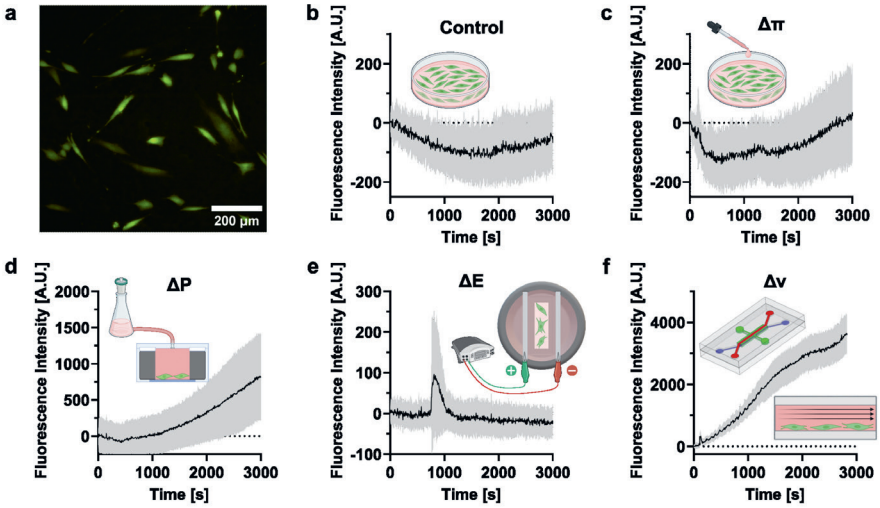

Figure 2: An overview of different intracellular calcium signaling patterns in dermal fibroblasts subjected to different mechanocoupled stimuli, along with the model systems, i.e. bioreactors, that were built to study these stimuli in live cells. (a) A calcium dye allows to visualize intracellular calcium in dermal fibroblasts as a green fluorescent signal. (b) Cells in the unstimulated control condition do not show fluctuations in the intensity of the fluorescent signal, indicating stable low intracellular calcium levels. (c) Dermal fibroblasts stimulated with low osmotic pressure show a low signal similar to that of the untreated cells. (d) Application of 20 kPa of hydrostatic pressure to dermal fibroblasts leads to gradually increasing intracellular calcium. (e) The application of an electric field (20 mV/mm) causes a pulse of intracellular calcium. (f) The application of fluid flow (20 um/s) leads to a strong increase in intracellular calcium - note the scale on the y-axis.

Taken together, our results suggest that the biological response of dermal fibroblasts to skin deformation may be governed by a much richer variety of mechanocoupled stimuli than previously known, and that the dermal mechanome extends well beyond stretch and stiffness of the solid extracellular matrix. It remains to be explored how these individual mechanocoupled stimuli are altered in skin aging and skin disease, and whether some of them can be leveraged for a therapeutic benefit.

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Reference

Martyts, A., Sachs, D., Stracuzzi, D., Kromer, D., Al-Nuaimi, D., Pramotton, F., Robmann, S., Kourouklis, A., Hopf, R., Ehret, E., Tibbitt, M.W., Werner, S., Giampietro, C. & Mazza, E. (2025). Quantification of stretch-induced stimuli altering the mechanome of dermal fibroblasts. J Invest Dermatol, In press.
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