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BIOMIMETIC HYDROGELS RESTORE FIBROBLAST QUIESCENCE AND ENHANCE THE PREDICTIVE VALUE OF *IN VITRO* MODELS

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1. CONTEXT

Skin is a soft tissue (with stiffness in the kPa range, depending on its physiological state).

Biomechanical properties of the skin, which are determined by tissue stiffness, strongly regulate dermal fibroblast phenotype & function.

Conventional plastic culture dishes are up to one million times stiffer than skin and therefore represent an irrelevant substrate for skin cells.

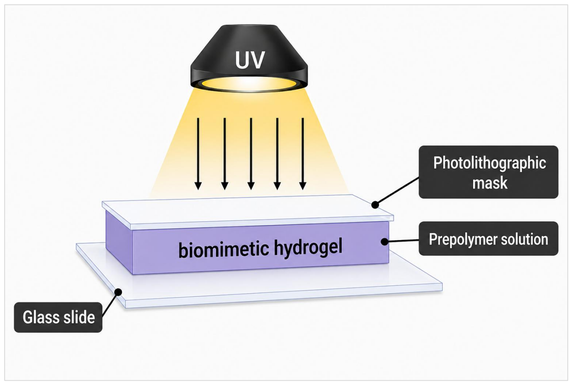
Biomimetic hydrogels matching the stiffness of skin tissue are emerging as a promising strategy to enhance the physiological relevance of *in vitro* skin models.

OBJECTIVE

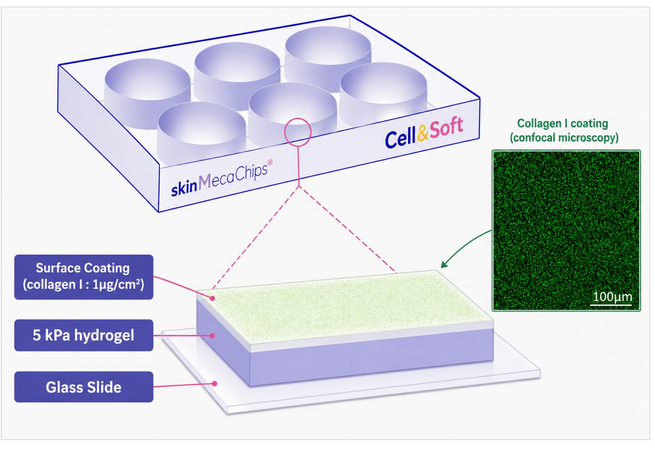
To demonstrate the added value of **5 kPa-biomimetic hydrogels** over conventional plastic substrates for preserving a **physiologically relevant dermal fibroblast phenotype and function**.

2. TECHNOLOGY

skinMecaChips® **Cell&Soft** has developed a pioneering method to produce **synthetic polymerized hydrogels matching skin stiffness**, with robust and reproducible functionalization ensuring efficient cell adhesion.



Patented photolithography technology enables spatial control of hydrogel stiffness via UV exposure. AFM validation confirms homogeneous and reproducible stiffness (5.4 ± 0.7 kPa).

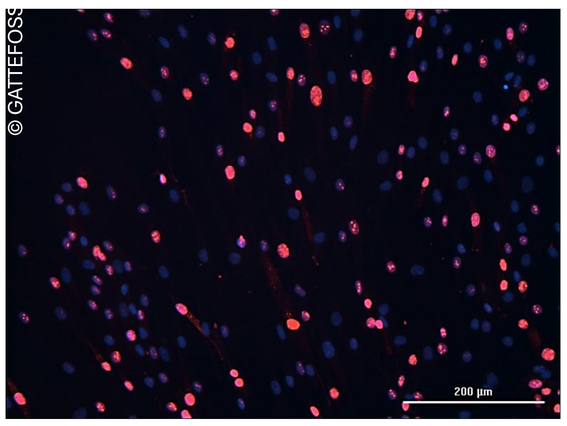


Biomimetic hydrogels compatible with standard bottomless culture plates. Confocal imaging demonstrates homogeneous and uniform collagen I coating over the entire hydrogel surface.

3. RESULTS

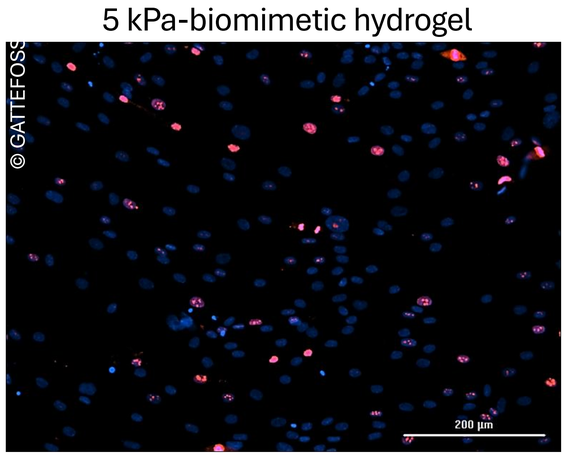
Hydrogels restore fibroblast quiescence

Plastic substrate

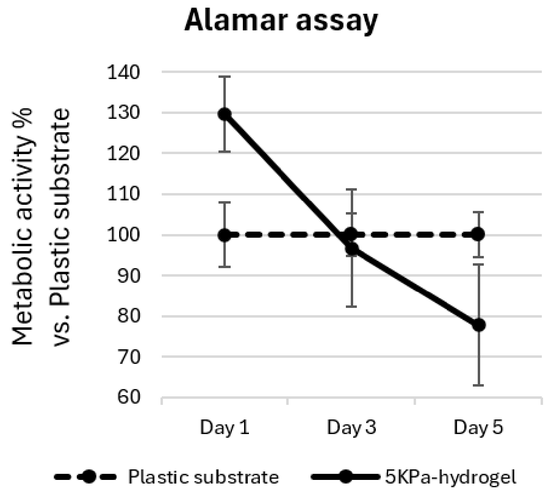


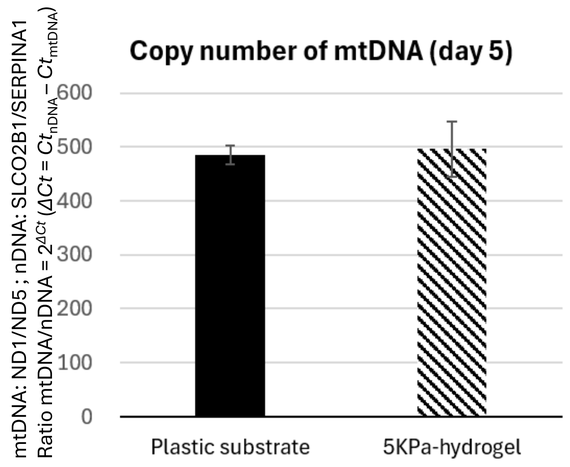
KI67
DAPI

5 kPa-biomimetic hydrogel



54.7% — KI67-positive nuclei % at day 5 — **13.4%**

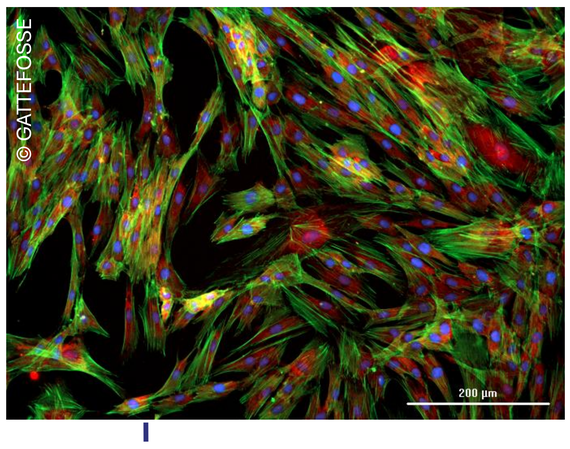




- Plastic-cultured fibroblasts exhibited a highly proliferative and metabolically active phenotype throughout the culture period.
- Conversely, **hydrogel-grown cells** showed **minimal Ki67 expression** and **lower metabolic activity** over time, **without alteration of the mtDNA/nDNA ratio.**

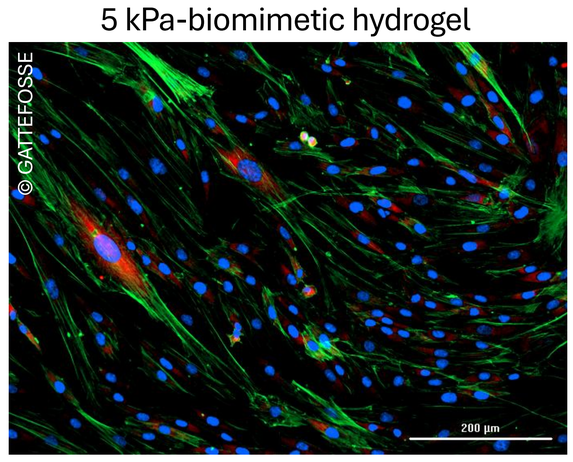
Hydrogels prevent myo-fibroblastic activation and preserve a non-contractile actin cytoskeleton architecture

Plastic substrate



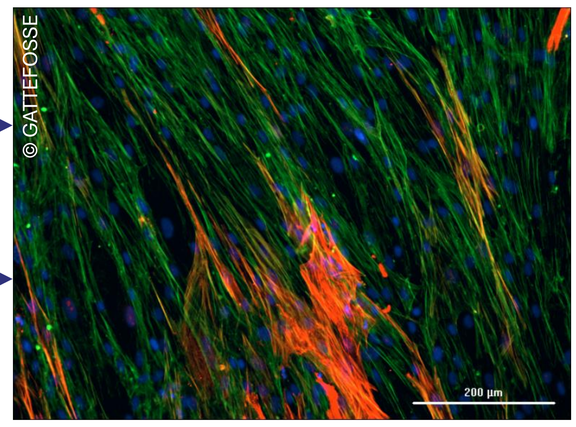
α-SMA
F-actin
DAPI

5 kPa-biomimetic hydrogel



1.37-fold decrease in α-SMA expression

1.13-fold decrease in F-actin expression



Cell re-seeding onto plastic substrate

- **Hydrogel-cultured fibroblasts lacked α-SMA expression** and exhibited a **poorly organized actin cytoskeleton** compared with plastic-cultured cells.
- Re-seeding hydrogel-cultured cells onto plastic **induced α-SMA expression** (1.37fold lower than plastic controls) and promoted the formation of a **dense contractile actin network.**
- This finding highlights the **reversibility of the hydrogel-induced phenotype** upon transfer to a stiffer substrate.

4. CONCLUSIONS

- Plastic substrates induce baseline biomechanical activation of dermal fibroblasts, promoting a proliferative and metabolically active phenotype.
- **Biomimetic hydrogels** preserve fibroblasts in a **quiescent, skin-like state**, providing a more **physiologically relevant and predictive *in vitro* model**.
- This platform enables mechanistic investigations of **mechanobiology, skin aging and cellular senescence**, and supports the evaluation of strategies aimed at **preventing or reversing age-associated dermal alterations**.