A high-throughput innervated co-culture device to model peripheral nerve-mediated fibroblast activation

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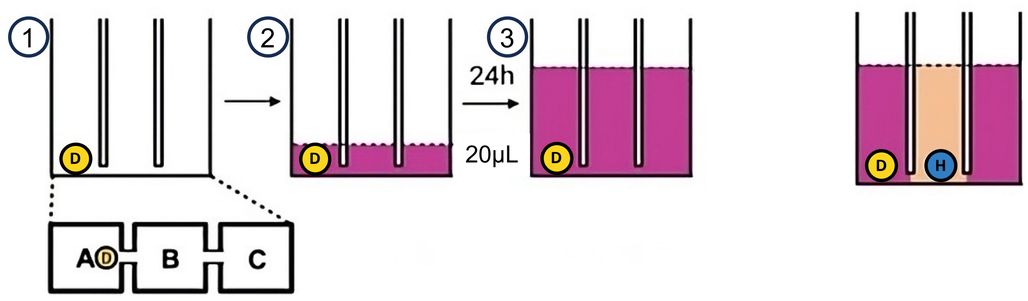
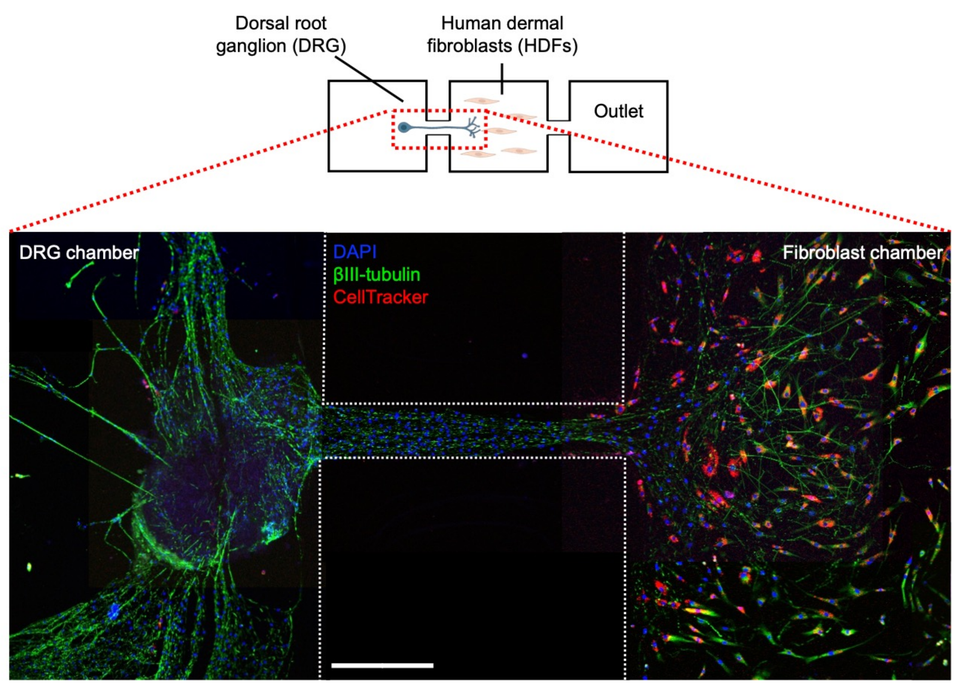
Introduction

Understanding the role of nerves in biological systems such as wound healing, regeneration, and cancer is an important research goal[1], but these processes are difficult to model *in vitro*. Our system provides a new platform for which to create customizable, innervated models of various tissues and systems using the ***IFlowPlate^{TM}384.*** We developed a co-culture model to study the interaction between peripheral nerves and dermal fibroblasts using the IFlowPlate, the first time this device has been used to culture nerves[2]. Using the IFlowPlate, we demonstrate that co-culture of sensory nerves with dermal fibroblasts increases fibroblast activation, suggesting that nerves can promote wound healing by directly modulating fibroblast function. We also provide an example of high throughput use for our system, demonstrating that nerves co-culture increases secretion of trophic factors by fibroblasts that are important for wound healing.

IFlowPlate^{TM}384 for innervated model

The engineered chambers of the IFlowPlate support long-term viability and facilitate extension of primary dorsal root ganglion (DRG) neurites through the channel to study the effects of direct peripheral innervation on human dermal fibroblast (HDF) activity. Direct contact of peripheral nerves with HDFs mimics *in vivo* conditions and the configuration of the chambers supports the use of different culture media.

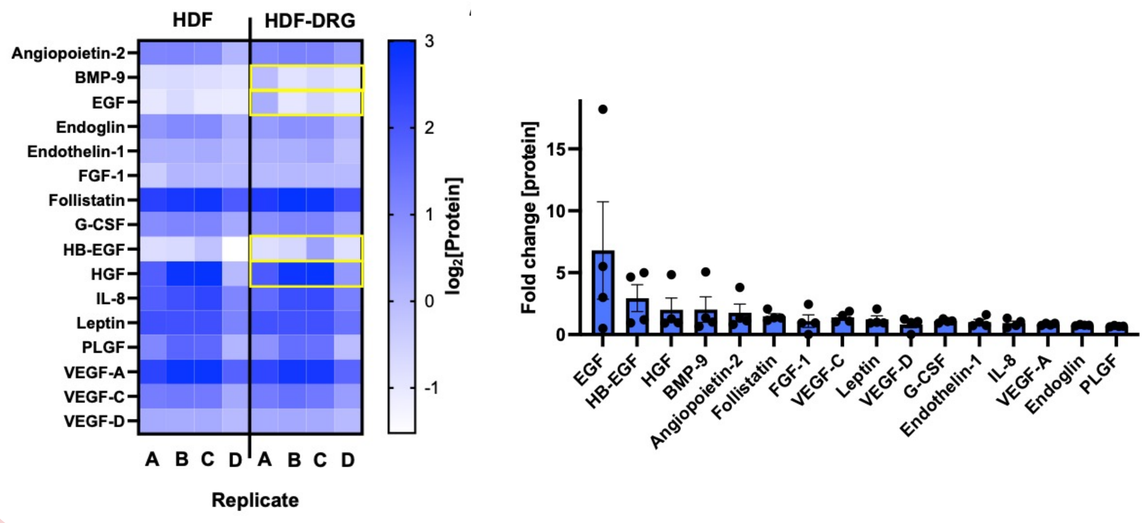




The IFlowPlate supported DRG viability, neurite growth and co-culture with HDFs for at least 21 days. In addition, we demonstrated that one device can support at least 4 biological replicates of harvested DRG in a high-throughput manner, as many experimental groups and biological replicates can be assessed on one device.

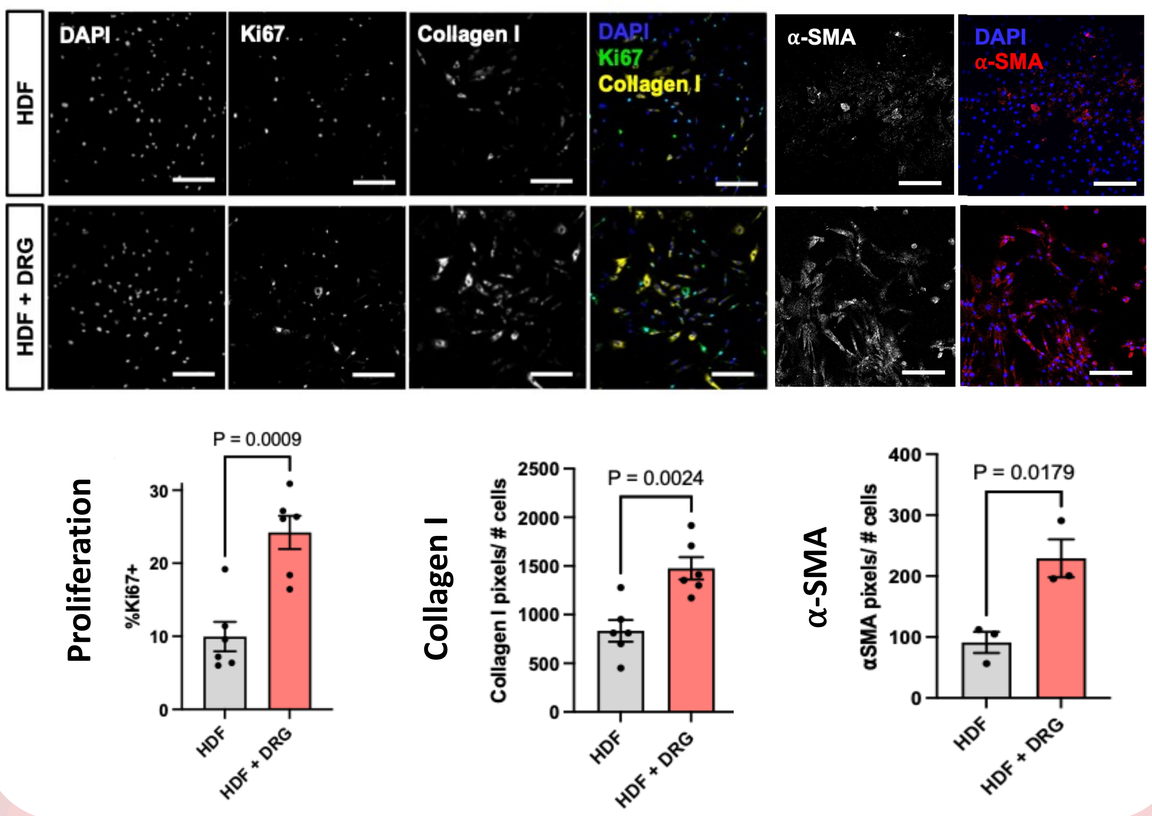
Expression of pro-healing factors in HDFs

Dermal fibroblasts play a pivotal role in wound healing, releasing cytokines, chemokines and growth factors to promote wound closure and angiogenesis[3]. We collected HDF-conditioned media and performed a cytokine analysis to determine if co-culture with DRG produces changes in the fibroblast secretome. We identified several proteins with elevated concentration levels with DRG-coculture, suggesting that nerves can directly modulate trophic factors from HDFs.



Direct contact promotes HDF activation

The effect of peripheral nerves on HDF activation was assayed using immunocytochemistry to quantify proliferation, collagen I expression, and α-smooth muscle actin (α-SMA) expression. After 14 days of co-culture, we found that co-culture with DRG increased fibroblast proliferation, collagen I, and aSMA compared to fibroblasts alone. These data demonstrate that nerves can directly modulate fibroblast activation in the IFlowPlate device.



Conclusion

The IFlowPlate^{TM}384 platform provides a simple and versatile model with high throughput capability to investigate the effects of peripheral nerve activity on HDF activation. This device is able to support DRG viability as well as simultaneous culture and testing of a large quantity of innervated samples and experimental conditions, for further downstream analyses.

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References

[1]Boilly et al., *Cancer Cell* 2017
[2]Cariba, Srivastava et al., Submitted.
[3]Shaabani et al., *Mol Therapy* 2022

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