

Organoid engineering for new biomimetic tools to study the intestinal tissue

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The field of intestinal biology is thirstily searching for different long-term culture methods that complement the limitations of organoids. While being recognized as an important milestone for basic and translational biological studies, culture of primary intestinal epithelia besides organoids has been relied on empirical trails using hydrogels of various stiffness, whose mechanical impact on epithelial organization remains vague until now. Here, we report the development of Matrigel and polyacrylamide scaffolds with a range of elasticities and their influence on intestinal epithelium expansion, differentiation and organization. On flat stiff substrates (>5kPa), primary intestinal epithelia cells adapt a flat cell shape and detach in short-term. In contrast, on soft substrates (80 –1000 Pa), they sustain for a long-term, pack into high density, develop columnar shape with improved apical-basal polarity, a phenotype reminiscent of features in organoids. We then developed a novel soft gel molding process to produce 3D Matrigel scaffolds of close-to-nature stiffness, which support and maintain long-term culture of primary intestinal epithelial cells into crypt-villus architecture. Thus, the present work is up-to-date informative for the design of novel biomaterials for *ex vivo* intestinal models, offering new tools to study the intestinal tissue *in vitro*.

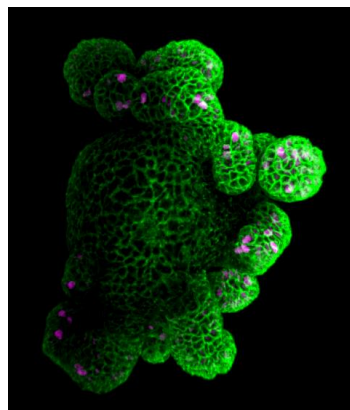


Figure 1: Intestinal organoids cultured in 3D Matrigel matrix

References

- [1] Xi W, Saleh J, Yamada A, Mercier B, Dang T, Janel S, Soleilhac M, Wu H, Tomba C, Romagnolo B, Lafont F, Mège RM, Chen Y, **Delacour D**. *Modulation of designer biomimetic matrices for optimized intestinal epithelial cultures*. *Biomaterials* **282**,121380 (2022).
- [2] Saleh J, Fardin MA, Frenoy O, Soleilhac M, Gaston C, Ciu H, Dang T, Gaudin N, Vincent A, Minc N*, **Delacour D***. *Length-limitation of astral microtubules orients cell divisions in intestinal crypts*. *BioRxiv* doi: <https://doi.org/10.1101/2022.09.02.506333> (2022).
- [3] Steinway SN, Saleh J, Kim DH*, **Delacour D***. *Microphysical models of the human intestine and gut microbiome in health and diseases*. *Frontiers in Bioengineering and Biotechnology* **8**,1-17 (2020).