STEM CELLS

Move over, Matrigel

A synthetic hydrogel matrix gives researchers greater control over intestinal organoid culture.

Matthias Lütolf has great respect for Matrigel, an animal-derived extracellular matrix for culturing cells *in vitro*. "Matrigel works for so many different cell types and scenarios; it has been incredibly difficult to find a replacement," he says. But natural matrices have drawbacks for translational work, where safety is paramount, and it isn't straightforward to fine-tune their properties to optimize cell growth. Based at the Ecole Polytechnique Fédérale de Lausanne (EPFL) in Switzerland, Lütolf and his team, with collaborators in the Netherlands, have developed a synthetic hydrogel system for intestinal organoid culture.

Despite some notable inroads, efforts to design fully defined organoid systems have not delivered magic formulations. Nikolce Gjorevski from Lütolf's team took a very systematic approach by carefully monitoring stem cell behavior in response to changes in individual matrix aspects. The work revealed that "different stages in the organoid formation process seem to require different matrix properties," says Lütolf.

The researchers discovered that intestinal stem cells prefer to adhere—through integrin receptors—to a relatively stiff polyethylene glycol (PEG) matrix supplemented with extracellular matrix components such as fibronectin. Once the cells have formed colonies, a softer environment is more conducive to forming organoids. The researchers used a simple trick of mixing hydrolytically degradable PEG into the stable hydrogel network to generate a mechanically dynamic matrix.

Lütolf is excited about the insights that a defined 3D culture system enables. For example, the team showed that the Hippo mechanotransduction pathway is active during stem cell expansion. The discovery of a role for matrix stiffness also emphasized the need for *in vitro* manipulation.

The researchers cultured mouse and human small intestine and human colorectal cancer organoids. Some aspects of the system will generalize, but "there is no one-size-fits-all hydrogel," says Lütolf. Polarized epithelia may not require matrix degradation, and matrix formulations for each organ type will require optimization. Success with the PEG-based matrix has focused Lütolf on new ambitions: producing tissue-scale intestinal surfaces rather than small balloon-like cysts, adding bacterial interactions and trying to understand 'symmetry breaking' (how uniform tissue forms crypts) in order to make the process more deterministic.

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RESEARCH PAPERS

Gjorevski, N. *et al.* Designer matrices for intestinal stem cell and organoid culture. *Nature* **539**, 560–564 (2016).