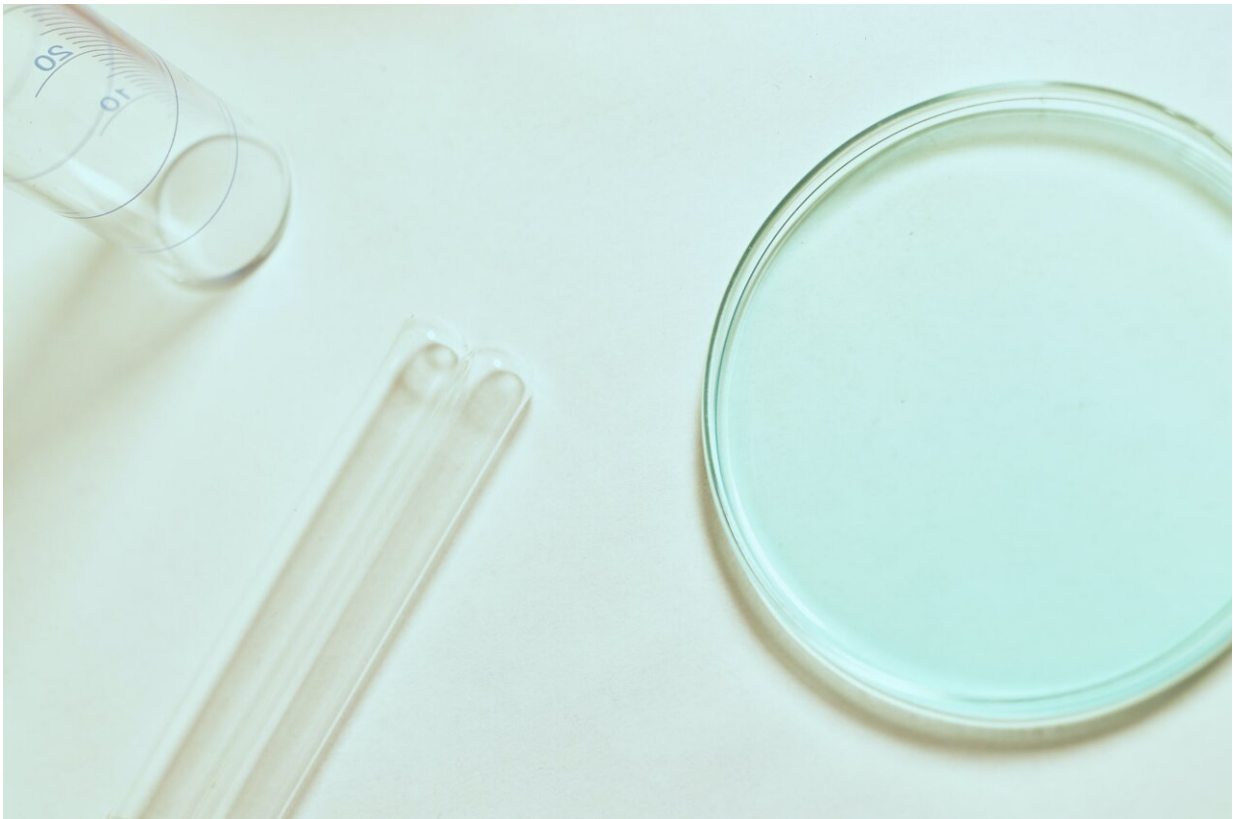


Scientists develop synthetic extracellular matrix that supports endometrial organoids

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Scientists have developed a synthetic extracellular matrix (ECM) that can support the growth of a mini endometrium in a dish for at least two weeks. The endometrium—the mucosal lining of the uterus—has been

historically hard to model in the lab, which has limited scientists' ability to study its role in healthy and diseased states like endometriosis.

The [matrix](#), described in the journal *Med*, allows cells to interact in an environment that recapitulates [human physiology](#) which could help researchers better simulate the healthy and pathological response to [menstrual cycles](#).

"With this matrix, we can begin to extrapolate and utilize samples from patients that have been diagnosed with certain reproductive diseases," says first author Juan Gnecco of Tufts University. "We can begin to explore how organoids grown from patients' cells are behaving differently than those of healthy individuals."

Until now, scientists have been growing organoids—mini organs in a petri dish—with a type of naturally derived hydrogel called Matrigel. Despite allowing a certain degree of support to organoid growth, Matrigel also contains proteins that can interfere with cell-cell communication. This is particularly important when modeling the endometrium, as it is composed mainly of epithelial glands and stromal cells, and their crosstalk affects how the endometrial tissue changes throughout the menstrual cycle under the influence of sex hormones.

"If the stromal cells try to 'talk' to the epithelial cell, it's like trying to talk to your friend if you're standing on the runway at the airport at rush hour," says senior author Linda Griffith of the Massachusetts Institute of Technology about endometrium organoids co-cultured with stroma in Matrigel.

Griffith, Gnecco, and their team designed a synthetic ECM using hydrogel and a minimal set of biological signals. Then they cultured endometrial stromal and epithelial organoids from human donors together in the synthetic matrix, and the co-culture remained intact over

the experiment period of at least 15 days. In contrast, Matrigel did not support stromal cultures and had partly disintegrated and shrunk by day 15.

The design of the synthetic ECM also allows cells to sequester their own matrix as they grow. "One of the things that can be different between a disease and a normal cell is that they may make slightly different sets of matrix molecules," says Griffith. "With this ECM, we can create a microenvironment similar to what the cells are experiencing in vivo. That's something we're very excited about."

To test if the matrix could support the growth and functioning of endometrial epithelial and stromal cells, researchers treated the co-cultures with a synthetic progesterone, a sex hormone that plays a key role in the menstrual cycle, to mimic the conditions of part of the menstrual cycle. The hormone caused the epithelial layer of the organoids to become thicker, increased the secretion of a pro-gestational protein, and induced stromal differentiation, the same changes also observed in humans.

The team then exposed the cultures with a type of pro-inflammatory cytokines linked to endometrial diseases in humans including endometriosis, a condition characterized by endometrial tissues growing outside of the uterus. They saw that in co-cultures that contained both epithelial and [stromal cells](#), the cytokine greatly increased [epithelial cell](#) proliferation, a characteristic observed in people with endometriosis. The abnormal growth was not observed in mono-culture that contained only [epithelial cells](#).

"It really highlights that cell communication is important, not only for sex hormone signaling but even inflammatory communication between [cells](#)," says Gnecco. "There's still more about the mechanism that we need to delve into, and now there is a platform that can be used to

investigate that in more detail. There's going to be a huge benefit for other studies downstream from this."

More information: Organoid co-culture model of the cycling human endometrium in a fully synthetic extracellular matrix enables the study of epithelial-stromal crosstalk, *Med* (2023). [DOI: 10.1016/j.medj.2023.07.004](https://doi.org/10.1016/j.medj.2023.07.004)

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