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Adding depth to cell culture

The jump from two dimensions to three gives researchers a laboratory model that is just one step removed from working with cells in vivo. Technologies and techniques have recently proliferated—such as matrices, scaffolds, and other geometries—to coax cells to grow in a wide array of 3D structures. By Kendall Powell

As a postdoc studying human brain development and what goes wrong in conditions such as microcephaly, Madeline Lancaster faced the same familiar problems as her fellow lab researchers. For example, mice brains don’t behave or develop like tiny human brains. And the complex layers and involutions of the brain don’t evolve from neural stem cells grown flat on the bottom of a lab dish.

What she really needed was a mini-organ she could grow in the laboratory and manipulate for investigations. In 2013, Lancaster developed a technique to do just that: She grew cerebral organoids from human induced pluripotent stem cells (iPS). The key was selecting neural stem cells and embedding them in a gel made from several proteins typically found in the fortifying and nourishing space surrounding cells. Mimicking this region, called the “extracellular matrix” (ECM), set up the stem cells to grow in three dimensions. The cells spontaneously developed into mini-brains that resembled cooked egg whites, yet shared the proper layering and organizational characteristics of the embryonic human brain.

Providing the cells with the 3D matrix triggers their instincts to self-assemble, says Lancaster, now a group leader at the Medical Research Council Laboratory of Molecular Biology in Cambridge, United Kingdom. Her group has simplified the protocol further so that “it’s possible to generate cerebral organoids in any standard tissue culture room,” she says.

The traditional way of culturing cells in 2D for study in the lab often relied on immortalized cancer cell lines that came with significant problems—accumulated mutations and contaminations with other cell types from years of passaging in the lab. And often, cells grown on flat, hard plastic dishes in the laboratory did strange things, like stretch themselves as thin as possible.

“Many drug candidates have been successes in 2D culture because the cell morphology is flat, and cells can be easily attacked by the drug,” says John Huang, CEO and President of TheWell Bioscience, a biotech company from Newark, New Jersey, that specializes in 3D cell culture reagents. “But once they go into animals, the drugs fail because they don’t work the same way in 3D.” What many cell biologists would like, he says, are cell cultures that can be grown from a variety of patients’ cells, both healthy and diseased, and that act and grow like their counterparts in the body, even forming multilayer and multicell tissues.

Of course, culturing in 3D is not without its challenges. “When you put cells in a 3D environment, it’s harder to image them, to immunostain them to see what proteins are present, and to recapture those cells after you’ve cultured them,” says Kristi Anseth, a bioengineer who leads a research group at the University of Colorado Boulder.

But Anseth’s intuition—and that of the entire field—tells her that 3D culturing is more relevant to biology because the vast majority of cells in our bodies grow that way. Many companies have entered this space, in order to make the practice of 3D cell culturing and the downstream imaging or assaying of cells much more user-friendly.

Mind the scaffolding

The first step for 3D culturing of any kind is to get cells off of that hard plastic and onto something more comfortable. Matrigel is the “grand dame” of 3D matrices, developed nearly 30 years ago by Corning as an animal-derived matrix for tumor-cell invasion studies. It comes from a mouse sarcoma rich in ECM proteins like laminin, collagen, heparan sulfate proteoglycans, and a number of growth factors. That richness can be both a boon to researchers—Lancaster’s neuronal stem cells felt quite at home...
on this scaffold—and a limitation, by introducing unknown biological components into an experiment. Matrigel must also be refrigerated to remain a liquid, and starts to form a gel at just 10°C, requiring cold-room work.

Richard Eglen, vice president and general manager of Corning Life Sciences in Boston, Massachusetts, says many cells thrive in Matrigel with the right growth factors added, for example, hepatocytes that develop into liver organoids. “Matrigel was almost ahead of its time,” says Eglen. “In many cases, you get the proper cell differentiation and the cells start to self-organize as they would in the body.”

The Well Bioscience offers a pared-down, minimalist hydrogel that is easier to use than Matrigel. The animal origin–free polysaccharide VitroGel 3D is room-temperature stable, and only begins to polymerize into a gel when any culture medium containing calcium or sodium ions is added to it. Huang says typical hydrogels take only 10–15 minutes to form with a simple mixing step.

VitroGel 3D can be used as a softer, 2D coating, a 3D matrix for embedding cells, or as an injectable for animal studies. A second product, VitroGel 3D-RGD, includes a cell-surface binding site for most adhesive cells. Huang says it’s a plus for researchers to know that VitroGel 3D has no undesired biologic ingredients. Researchers can tweak the ingredients of their culture media to construct a hydrogel that includes whatever ligands or growth factors they want to be present and influencing the cells there.

Lubna Hussain, senior product manager for primary cells and 3D culture products at Basel-based Lonza Bioscience Solutions, advises researchers to “know what your end goal is and work backwards in 3D culturing.” Lonza’s RAFT (Real Architecture For 3D Tissue) 3D Cell Culture System contains rat collagen, media that supports cells during gelling, and 24- or 96-well absorbers to condense collagen. After mixing cells with the collagen and gelling reagent, the absorbers placed on top of cultures suck up any excess collagen. The end result is a “contact lens–like structure” with embedded cells that takes about an hour to form. Hussain says that the RAFT System creates a high-density environment—up to 80 milligrams of collagen per milliliter—that more closely mimics the ECM surrounding the body’s cells.

The RAFT System allows researchers to set up various types of cultures—with cells embedded in the matrix, layered on top of the gel matrix for invasion assays, or both. Kits with inserts allow researchers to build 3D cultures that include an air–liquid interface, such as that found in skin or respiratory epithelia. Hussain says researchers have become creative in setting up co-cultures to embed cancer cells in a disc, and then layering immune cells on top to investigate how they infiltrate a tumor.

Geometry matters

Sometimes a researcher might want cells growing in 3D, while still having the ease and convenience of culturing cells in solution. Microcarriers enable the best of both worlds. Global Cell Solutions, a company that provides 3D cell-culturing tools and cell-based assays, makes the Global Eukaryotic Microcarrier (GEM) system to grow cells on the surface of 75 µm–150 µm alginate beads for high-density cell culture. These optically clear spheres can be pipetted like water and contain ferromagnetic particles for magnetic levitation or collection in test tubes. The beads come coated in “five flavors of biomimetic coatings,” namely fibronectin, gelatin, collagen, Matrigel, and polylysine, explains Robin A. Felder, co-chairman of the Charlottesville, Virginia–based firm.

A slurry of GEMs offers the “benefits of a suspension culture, but with the cells growing in an orientation on a biomimetic, porous surface,” says Felder. This means GEM-grown cells, unlike cells grown in 2D, express surface features seen in vivo, such as the copious microvilli on human kidney cells. “Cells like to be on squishy, curved surfaces that they can’t tell apart from surfaces in the body,” he says.

In addition, Felder notes that the cells growing on GEMs are easy to image in systems traditionally looking at 2D cultures, including electron microscopy and fluorescence confocal microscopy. The 3D bead offers a rare look at the sides of cells normally hidden in planar 2D cultures. And the increased surface area of the GEMs allows much higher cell counts to be grown in a compact 50-mL tube. Global Cell Solutions is developing a robotic system that could automatically handle the care and feeding of 32 independent GEM cell cultures, adds Felder.

A gel-free existence

Cells grown in matrices, gels, or on gel microcarriers often must be recovered before other assays can be done. This requires partially or fully dissolving the scaffold, or treating the cells enzymatically to dislodge them—all processes that can perturb cells in unexpected or unwanted ways. And many times, researchers want to see how their favorite cells behave in 3D without any interference from a scaffold. Scaffold-free techniques bring the advantage of not introducing anything that...
Life Science Technologies

**cell culture**

might influence cells, either chemically or physically. But until recently, scaffold-free 3D culturing was tricky and inconsistent.

In scaffold-free 3D cell culture, the cells find their neighbors, attach to each other, begin making their own native ECM, and often form a sphere of cells. One popular method uses gravity and a literal “hanging drop” of cell culture media. The other way to coax cells into spheroids is to put them on specially coated “ultra-low attachment” plates. Now, technologies have arrived that make growing spheroids simpler, more consistent, and safer than was possible with previous methods—no more fallen hanging drops of precious cells.

Corning’s Spheroid Microplates offer an ultra-low attachment surface and a U-shaped well bottom in 96- and 384-well plates. The black-sided, clear-bottomed plates ensure reproducibility of the location and size of spheroids for automated imaging.

Timothy Spicer says the Corning plates get his facility that much closer to performing drug discovery high-throughput screening (HTS) on 3D-grown cells. He’s the director of Discovery Biology and HTS for the Lead Identification (ID) division of The Scripps Research Institute in Jupiter, Florida, a core facility for all Scripps researchers as well as outside collaborators.

Spicer has been working with Corning to perfect prototype 1,536-well spheroid microplates, the preferred format for automated HTS for miniaturization and cost savings. In a study using the HT-29 colon cancer cell line, Corning and Scripps researchers performed a direct comparison of the cells grown in 2D with the cells grown as spheroids, and screened both types against a unique collection of more than 3,300 known drugs. The 3D screens returned far fewer hits than the 2D screens, meaning far fewer drugs caused the same level of cytotoxicity in the 3D cultures (2).

“We are not far away from the day when we can take patient-derived tumor cells, put them into these [spheroid] plates, run them against compound libraries, and within a matter of days, find the most effective drugs to kill the cancer cells,” says Spicer.

Also operating in the spheroid market, Zurich-based 3D microtissue company InSphero has a two-plate system that makes going from a hanging-drop culture to a microtissue a snap—and it is automated to boot. Randy Strube, director of global marketing, says the more complex the cellular model, the better suited it is to the hanging-drop system, where gravity and self-assembly drive the formation of microtissues in an oxygen-rich environment.

InSphero’s GravityPLUS plates make hanging drops simple, stable, and transferable in a 96-well format. Featuring a unique hourglass channel within each well, the plates hold drops steady and in a way that allows pipetting in additional media or more cells. Once spheroids or 3D microtissues have formed, they can easily be transferred to matching GravityTRAP 96-well plates. The GravityTRAP plates are spheroid plates with a conical, flat-bottomed well and a specialized ledge for pipetting without disturbing the spheroid. The setup allows researchers to develop scaffold-free, complex microtissues in a reproducible, miniaturized way.

**Additional dimensions**

For scientists who don’t want to spend months developing their own 3D systems, InSphero also supplies prevalidated, assay-ready microtissues directly to researchers in drug discovery and development. InSphero currently produces several varieties of microtissues, focusing on liver models for toxicology, pancreatic islets for diabetes, and tumor–stromal co-culture microtissues for oncology.

Likewise, Lonza’s human primary cells take the guesswork and paperwork out of developing cultures directly from patient samples, saving researchers an average of six months for some cell-type isolations, says Hussain. Researchers who receive cryopreserved or fresh cells from one of 21 cell-type families can simply get their research going, she says.

But the end goal of 3D culturing is not to exactly recapitulate the body’s complexity, says Anseth. To explain, she uses the analogy of flight: “Airplanes don’t fly because they look like birds, but because we understand enough about the mechanics of flight.” Knowing “enough” about a cellular system or process in 3D might be sufficient to intervene when biological processes go awry or to promote healing, she observes.

The next wave in 3D culturing is already underway, with companies designing organ-on-a-chip or body-on-a-chip applications that allow the crosstalk between tissues to be captured, miniaturized, and manipulated in the lab. Studying the growth and modification of 3D structures over time (also known as “4D cell culture”) while adding or subtracting different growth factors will lead to discoveries of how to speed healing or disrupt degeneration.

Hussain says the choices researchers have for growing cells in 3D are like the vast array of cereal boxes in the grocery store, with many options that come in several different flavors. She advises researchers to start with the question they want to answer and work in reverse to figure out the best technology to use: “The question is, what is your specific application and goal for using 3D culture?”

**REFERENCES**


Kendall Powell is a freelance science writer based in Lafayette, Colorado.

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