

New culturing method mimics the natural forces acting on liver cells

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Scientists have greatly improved the usefulness of liver cell cultures by simulating the pressure that the liver undergoes in the body. The scientists, led by Harry Yu of the A*STAR Institute of Bioengineering and Nanotechnology, designed a cell culturing system that directs a perpendicular, pressurized flow of culture nutrients on to a membrane containing liver cells, or 'hepatocytes', which compacts and encourages the cells to adopt a morphology akin to that in the body.

Historically, cultures of hepatocytes quickly lose their function once taken out of their host, an obvious detriment to the validity of experiments using these cultures. "After hepatocytes are dissociated from the [liver](#), they lose their polarity because there is no cell-cell contact," said Liang Zhu, the study's first author, supervised by Yu and Zhenfeng Wang from the A*STAR Singapore Institute of Manufacturing Technology (SIMTech). The cellular activity of the hepatocytes would decline and the [cells](#) would adopt a flatter morphology.

"It's very rare for current systems to allow for the fact that organs in the abdomen undergo pressure," said Zhu. Previously, the collaborators demonstrated the success of this cell culturing technique as a proof-of-concept in a smaller system. In the current study, their first-of-a-kind bioreactor shows the viability of this method in a larger system, with channels for up to 24 independent cultures.

Culturing hepatocytes from rats, the researchers found the compaction

provided by their bioreactor allowed cells to form tighter colonies and maintain their morphology. Hepatic enzymes were expressed at significantly higher levels than those of non-compacted hepatocyte cultures. Importantly, in 12 hours the researchers' colonies formed channels through which hepatocyte waste—or bile—could flow. These 'bile canaliculi', like liver enzyme production, are essential for drug metabolism, which highlights the potential of compaction cultures in drug candidate testing.

"If waste cannot be cleared from the [hepatocytes](#), they lose liver functions rapidly, whereas compaction promotes polarization and therefore maintains the function in long-term [culture](#)," explains Zhu, comparing standard hepatocyte cultures to compaction cultures.

The experiment's success overcame technical challenges in fabricating the bioreactor with the support of the SIMTech Microfluidics Foundry.

The investigators are pleased with the unexpected implications of their culture technique for future research. "The platform was designed for drug testing, but it can actually benefit all in vitro cell culture applications because it highlights an important factor—compaction pressure—for researchers to consider," says Zhu.

"We plan to conduct further studies on the molecular mechanism to determine how the compaction pressure induced the observed cell behaviors. This will allow us to engineer simpler drug testing platforms in 96- or 384-well plates, and provide insights into cell culture systems in gravity-controlled environments, such as in space or deep ocean," adds Yu.

More information: Liang Zhu et al. A vertical-flow bioreactor array compacts hepatocytes for enhanced polarity and functions, *Lab Chip* (2016). [DOI: 10.1039/c6lc00811a](https://doi.org/10.1039/c6lc00811a)

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