CELL BIOLOGY

Prostate cancer in 3D

Researchers grow genetically stable organoids from mouse and human prostate cells in the lab and establish patient-derived lines that model prostate cancer.

It had been known for many years that embryonic stem cells can form organoids, cell-derived three-dimensional (3D) structures that self-assemble *in vitro* and resemble their tissue of origin. Then, several years ago, Hans Clevers's group showed that adult tissue stem cells can also form organoids. Since then, work from the Clevers laboratory at the Hubrecht Institute in the Netherlands and by others has shown that, under the right conditions, organoids derived from colon, liver, pancreas and other tissues can be maintained in culture for years.

Now, a team from the Clevers laboratory, in collaboration with Charles Sawyers and Yu Chen and their colleagues at Memorial Sloan Kettering Cancer Center in New York, have shown that mouse and human prostate cells can be maintained in 3D culture (Karthaus *et al.*, 2014). Further, they have generated multiple organoid lines from prostate cancer patients (Gao *et al.*, 2014).

"There is only a handful of prostate cell lines, so the resources to study the prostate and prostate cancer are very limited," says Clevers. Drawing on knowledge of factors important for the growth and maintenance of other types of organoids and of prostate cells, the researchers first defined a combination of factors that enable growth of mouse prostate organoids. They were able to manipulate the cells with retroviral gene expression and use cells from tumor-prone animals to model disease (Karthaus *et al.*, 2014).

For these 3D cultures to model their tissue of origin, a critical factor is whether the cells acquire new mutations while in culture. But after months of passaging the cells, the researchers found that they did not acquire mutations and remained strikingly similar to the first organoid generations, which "makes them more like a primary cell than like a cell line," says Clevers.

The genetic stability of the cells raises the exciting possibility that organoid culture could be used for gene therapy purposes. "We could take cells from a patient, manipulate them, for example, using CRISPR-Cas9 technology, show that we altered only the genes we wanted to alter, and give them back to the patient," says Clevers. Another potential avenue of application for this technology is regenerative medicine and tissue transplantation, as cells can be expanded *in vitro* but retain their genetic identity and stem cell qualities.

The team then successfully modified the culture conditions to sustain the growth of human-derived prostate organoids, which is "harder to do than with mouse cells," Clevers says (Karthaus *et al.*, 2014). In both mouse and human prostate lines, they showed that both basal and luminal cells of the prostate epithelium behave like stem cells, confirming earlier reports based on lineage-tracing experiments.

Clevers recalls that it was a chance meeting at a workshop that sparked the collaboration with Sawyers and Chen. The groups from Memorial Sloan Kettering had access to an exceptional set of samples from patients with advanced prostate cancer. They joined forces to generate seven prostate organoid lines from these—six from metastatic tissue and one from circulating tumor cells—which essentially double the number of prostate cell lines available to the community (Gao *et al.*, 2014).

Examining copy number and single-nucleotide variations, the scientists found that the patient-derived organoids are highly representative of prostate cancer and also genetically stable in the laboratory. Each of the organoid lines has a different set of mutations, some of which were known to be associated with tumor development. Because every tumor is genetically distinct and responds differently to therapeutic drugs, the ability to generate cells lines that model disease is an opportunity for a personalized approach to medicine.

Clevers and his colleagues are working to create an easily accessible bank of organoid cell lines derived from different tissues. He hopes that this resource, which would be available to both the academic research community and the pharmaceutical industry, will lead to exciting discoveries in biology and therapeutics.

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RESEARCH PAPERS

Gao, D. *et al.* Organoid cultures derived from patients with advanced prostate cancer. *Cell* **159**, 176–187 (2014).

Karthaus, W.R. *et al.* Identification of multipotent luminal progenitor cells in human prostate organoid cultures. *Cell* **159**, 163–175 (2014).