Model system provides insight into the growth of pancreatic tumors

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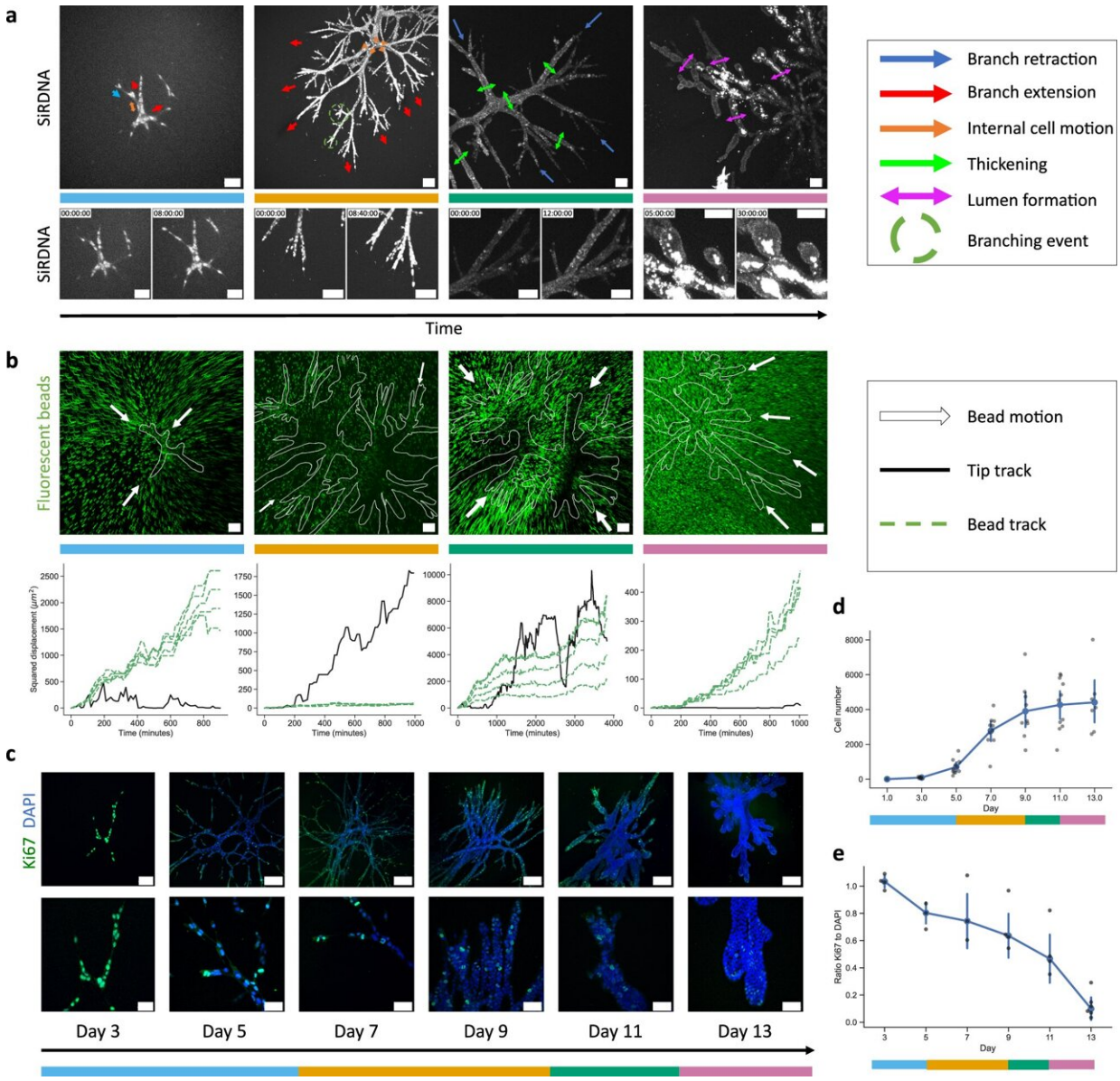

Collagen-grown organoids go through different phases of development. Development phases are denoted by color bars which follow the color code presented in Fig. 1. Blue: onset, orange: extension, green: thickening, pink: lumen formation. Organoids shown here are grown in collagen. a Cellular motion patterns observed with live confocal imaging for each development phase (n = 66 organoids). Cell nuclei are stained with SiRDNA (white). Scale bars: 100 µm. From left to right: Day 4 SUM projection, and Day 7, Day 10, Day 13 maximum projections. b Top, time-projections of fluorescent beads (green, maximum projections) trajectories at different time points, indicating the deformation field around the organoids. Organoids are outlined in white and white arrows denote the direction of bead motion. From left to right: Day 4–5, Day 7–8, Day 8–9, Day 13–14. Scale bars: 100 µm. Bottom, corresponding representative squared displacement of a branch tip (solid black) and the motion of beads (dashed green) in front of it, for each development phase. c Immunostainings of Ki67 (green) and DAPI staining (blue) in organoids at different time points. Top scale bars, from left to right: 80 µm first picture, 200 µm second picture, 200 µm for the rest. Bottom (zoom-in of the top row images) scale bars: 50 µm. Confocal slices. d Cell number evolution in organoids, estimated based on maximum projections of DAPI stainings (n = 56 organoids). Blue line indicates the mean tendency. Error bars: 95% confidence interval (CI). e Ratio of Ki67- over DAPI-positive cells (n = 24 organoids). Blue line indicates the median. Error bars: standard deviation. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-32806-y

Researchers at the Technical University of Munich (TUM) have developed a novel model system that can be used to precisely track the growth steps and three-dimensional arrangement of pancreatic cancer cells. It also provides the basis for testing and developing therapeutic approaches.

Pancreatic cancer accounts for about 3% of all cancer cases in Germany. Although this type of cancer is relatively rare, it is highly aggressive and therefore lethal in most cases. "There is probably no other tumor type

where research is so urgently needed," says Maximilian Reichert, professor for translational pancreatic carcinoma research at TUM Klinikum rechts der Isar. "In contrast to other tumor types such as breast or colorectal cancer, we neither have meaningful early detection programs nor effective treatments."

An interdisciplinary research team led by Maximilian Reichert and Andreas Bausch, professor for cellular biophysics at TUM, has therefore developed a tumor organoid derived from the pancreas. "An organoid is a three-dimensional cell culture that recapitulates key features of the tissue of origin—in this case pancreatic cancer," explains Reichert. Until now, organoid models have always been spherical aggregates of cells. They reflect the molecular characteristics of the tissue, however so far, failed to mirror tissue architecture, which can ultimately be crucial for the function. "We have succeeded for the first time in modeling the morphology of the tumor, consisting of complex tubular structures that are so characteristic of pancreatic cancer," says Reichert.

Collagen facilitates the formation of complex structures

For cells to grow as this multi-branched structure outside the body, they not only need the nutrients in which they can thrive. They also must be embedded in a matrix where they can form a structure through cellular division and migration. The TUM researchers used a matrix primarily composed of collagen. "By doing that we changed the mechanical conditions of the matrix in which the cells grow to permit the formation of complex structures," says Bausch. "It is not only the biochemical conditions, but also the mechanical properties of the matrix that decisively impact growth."

For the formation of the organoid, the mechanical plasticity of the

collagen—in other words, its ability to be reshaped—is an important factor. The forces exerted on the material through cell growth cause permanent deformation—unlike a purely elastic deformation, which would be reversible.

Basis for developing treatments

"This organoid system enables us to track individual growth stages of the pancreatic cancer over time, such as cell divisions and movements, as well as gene expression patterns," says Bausch. "Until now this was simply not possible because an accessible system was lacking."

As a next step the researchers are already working on a tumor organoid grown from human pancreatic cancer cells. "On that basis, new treatments specifically designed for the various tumor progression phases can be identified and tested," says Reichert. The goal is to identify treatments that fight specific subtypes of the pancreatic carcinoma and are thus more effective.

More information: S. Randriamanantsoa et al, Spatiotemporal dynamics of self-organized branching in pancreas-derived organoids, *Nature Communications* (2022). DOI: 10.1038/s41467-022-32806-y

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