How Developing Organs Do the Splits

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Cells growing in custom-shaped tubules are revealing how some of the body's most important organs take shape--and how this development goes wrong in cancerous tumors.

One of the common patterns in animal organs is a tube that branches into smaller and smaller tubules. Lungs, kidneys, salivary glands, and breast tissue all grow from such patterning. But piecing together how and where growing tubes branch has proved complicated--not least because such organs are difficult to observe while they are growing.

An experiment that grows artificial tubules in 3-dimensional culture has provided some new clues. Mina Bissell, Celeste Nelson, and their colleagues at the Lawrence Berkeley National Laboratory in California used custom-made microscopic wells to grow tiny tubes of mammary cells. They found that the shape of the well determined where the branches would form. In rectangular wells, the tubules branched only near the short ends of the rectangular depressions, but not near the long sides. In crescent-moon shaped wells, new tubules sprouted only toward the convex side of the well, and in Y-shaped wells, tubules branched at the tips of the Y, but not along the sides or in the middle. Such a glimpse of the dynamic growth of tubules would be very difficult in experimental animals, Bissell says: "You'd have to kill hundreds of mice."

So why do branches form at only particular parts of geometric shapes? Mathematical models employed by the researchers suggest that the key is a molecule that inhibits branching, namely, a protein called transforming growth factor-β (TGF-β), which is produced by mammary cells and which is known to stop branching in developing tissues. When the researchers blocked the molecule, the experimental tubules sprouted branches from all sides, regardless of the shape of the well. Responding to the TGF-β produced by its own cells, the developing tubule can apparently sense where it has the most room to grow away from itself--for example, at the narrow ends of a rectangle or the tips of a Y-shaped well. The system can help scientists determine more about how a cell reacts to its immediate environment, Bissell says, and how that process goes wrong in growing or spreading tumors, in which cells lose their ability to read signals from their environment that would prevent them from dividing. Restoring that ability could be one way to slow or stop their growth. The team reports its findings in tomorrow's Science.

Most work on branching has focused on the molecules that prompt it, rather than those that block it. Since the new experiment shows that the blocking molecules come from the cells themselves, Bissell says it is a new direction for research in the field of branching.

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that inhibit it, says developmental biologist Helen Skaer of the University of Cambridge. The new work is helpful for understanding where branches form, she says, but she cautions that the system is highly artificial and reveals only a small part of the story.

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