NEWS RELEASE 23-JAN-2020

Snake stem cells used to create venom-producing organoids

CELL PRESS

Organoids have become an important tool for studying many disease processes and testing potential drugs. Now, they are being used in a surprising and unexpected way: for the production of snake venom. On January 23 in the journal *Cell*, researchers are reporting that they have created organoids of the venom glands of the Cape coral snake (*Aspidelaps lubricus cowlesi*) and that these glands are capable of producing venom.

"More than 100,000 people die from snake bites every year, mostly in developing countries. Yet the methods for manufacturing antivenom haven't changed since the 19th century," says senior author Hans Clevers of the Hubrecht Institute for Developmental Biology and Stem Cell Research at Utrecht University in the Netherlands. "It's clear there is a huge unmet medical need for new treatments."

He adds: "Every snake has dozens of different components in their venom. These are extremely potent molecules that are designed to stop prey from running away. They affect systems as varied as the brain, neuromuscular junctions, blood coagulation, and more. Many of them have potential bioprospecting applications for new drugs."

Clevers' lab traditionally focuses on organoids made from human and mouse cells. But some of his students decided to study stem cells and develop organoids from reptiles. "This is a field that does not exist, so they thought it was interesting to study the most iconic reptilian organ, the snake venom gland," he says. "Once we grew the venom glands as organoids, we realized that they make a lot of venom."

The investigators started with the Cape coral snake because they knew a breeder who was able to supply some fertilized eggs. The snakes were removed from the eggs before hatching, and small pieces of tissue were removed from various organs and placed into gels, along with growth factors. In addition to the venom glands, the researchers also made organoids of the snake liver, pancreas, and gut.

"It would have been difficult to isolate stem cells from these snakes because we don't know what they look like," Clevers explains. "But it turned out we didn't need to. The cells soon began dividing and forming structures." In fact, he says, the venom gland organoids grew so fast that in just one week, they were able to break them apart and re-plate them, generating hundreds of plates within two months. He notes that if it could be commercialized, this method would be much more efficient than the way venom is currently produced--by raising snakes on farms and milking their glands.

The researchers were able to identify at least four distinct types of cells within the venom gland organoids. They confirmed that the venom peptides produced were biologically active and resembled the components of venom from live snakes.

A challenge of the work was determining gene-expression levels in the venom gland organoids. "The genomes of most snakes have not been annotated," Clevers says. The investigators were able to identify certain genes that were active under expansion conditions, suggesting that these pathways--including most importantly the Wnt pathway--may play a role in reptilian stem cell growth.

One of the collaborators on the study was Freek Vonk, a herpetologist and well-known Dutch television host who Clevers calls "the Steve Irwin of Holland." Vonk is affiliated with Leiden University and the Naturalis Biodiversity Center.

###

This study was funded by ALS foundation Netherlands, a Sir Henry Dale Fellowship, the Wellcome Trust, and the Royal Society. Clevers is inventor on several patents related to organoid technology; his full disclosure is given at https://www.uu.nl/staff/JCClevers/. Two of the study's authors are employees of MIMETAS BV, the Netherlands, which is marketing the OrganoPlate. OrganoPlate is a registered trademark of MIMETAS.

Cell, Post et al.: "Snake Venom Gland Organoids"
https://www.cell.com/cell/fulltext/S0092-8674(19)31323-6

Cell (@CellCellPress), the flagship journal of Cell Press, is a bimonthly journal that publishes findings of unusual significance in any area of experimental biology, including but not limited to cell biology, molecular biology, neuroscience, immunology, virology and microbiology, cancer, human genetics, systems biology, signaling, and disease mechanisms and therapeutics. Visit: http://www.cell.com/cell. To receive Cell Press media alerts, contact press@cell.com.

Media Contact

Carly Britton
press@cell.com
617-417-7053

@CellPressNews

http://www.cellpress.com