ORGANOIDS

Venomous organoids

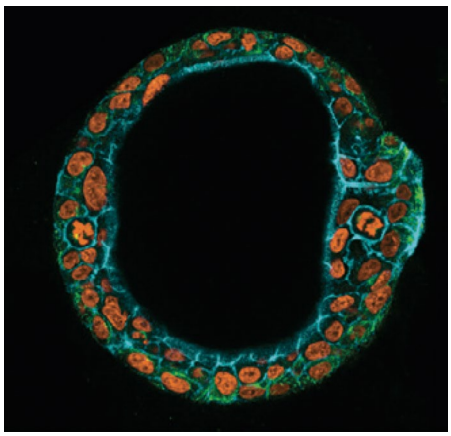
Snake venom gland organoids provide a glimpse into the cell biology of the respective organ and serve as a platform for producing snake toxins.

A variety of organoid culture systems have been established and proven their utility as models for development and disease. "As almost any human/murine organ could be grown as an organoid, we were wondering to what extent these principles could be applied to other animal species," says Jens Puschhof, a graduate student in Hans Clevers's lab at the Hubrecht Institute in the Netherlands. The snake venom gland was appealing because "it has a very clear function — the production of toxins — which is easy to be assessed in vitro says Puschhof.

Puschhof teamed up with fellow graduate students Joep Beumer and Yorick Post, who came up with the idea of trying to establish organoids from snake venom glands. The trio were able to obtain venom gland organoids from nine different snake species. While they sourced some live species from local breeders, other species were less readily available. Puschhof says that "on rare occasions, we received a call from the collaborating reptile zoo when a snake had passed away. On these days, we rushed into the car and drove to the zoo to obtain tissue." Puschhof found it a lot of fun to research the obtained species and to discuss its characteristics with other lab members after returning in the 'snake tissue taxi'.

To generate venom gland organoids, the researchers dissociated the cells of snake venom glands and embedded the material into basement membrane extract. "It took some optimization to arrive at the final media recipe," says Puschhof, but organoids could be grown and expanded using essentially the same cocktail used for expanding mammalian epithelial organoids, with the difference that snake organoids need to be kept at 32 °C.

While the expansion medium supports propagation of the organoids, their differentiation into venom-producing organoids requires a change in media composition. Withdrawal of most of the growth factors leads to less proliferation, and the organoids are then composed of polarized cells that secrete functional toxins. To characterize toxin expression, the researchers assembled the transcriptome of one snake species de novo. Toxins dominated the gene expression profile of the venom gland organoids. In follow-up experiments, the researchers identified known as well as previously uncharacterized toxins with species-specific differences.



Section through a snake venom gland organoid. Reproduced with permission from Post, Y. et al. *Cell* **180**, 233–247 (2020), Elsevier.

Having access to venom gland organoids allows the assessment of cell heterogeneity in the underlying tissue, using single-cell RNA-seq. "We find that different populations of venom gland cells produce specific sets of toxins, rather than one cell type making all venom factors," says Puschhof.

As their organoids produce functional toxins, Puschhof says that "this may help both in venom-based drug development and the generation of next-generation antivenoms." He says that they plan to set up a "living biobank" by growing organoids from 50 venomous animal species to better understand venom production and that "we are exploring the possibilities to grow organoids from various other species, to learn both about their biology and the boundaries of adult stem cells."

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