The rapid evolution of cobra venom

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King cobra. Credit: Khao Khieo

A new study has provided the first comprehensive insight into how snake venom evolved into the sophisticated cocktail of different proteins it is today.

It turns out that snakes' venom glands have co-opted many proteins that originally played more mundane roles elsewhere in their bodies. This constant innovation was needed to help them stay ahead of the animals they eat, which tend to develop resistance to particular venoms over time.

Researchers at Bangor University, the Liverpool School of Tropical Medicine and the universities of Leiden in Holland and Texas, Arlington in the USA sequenced genomes of the deadly venomous King Cobra and the non-venomous Burmese Python, and compared the two to shed light on how each evolved. They also looked at the only other venomous

vertebrate genome that's been sequenced so far - that of the platypus.

In particular, lead author Dr Nick Casewell and his colleagues were interested in how the cobra's venom evolved. It contains dozens of highly specialised toxins, and exactly how this complex brew could have come about has long been a puzzle.

Analysing the newly-sequenced cobra genome confirmed the hypothesis that the individual toxins that make up the venom developed from proteins that originally evolved for unglamorous day-to-day tasks elsewhere in the body.

The genes responsible for these proteins have been duplicated many times, allowing the original version to keep doing its job while the copy mutates further and takes on new functions. This allows the proteins taken up by the venom system to multiply and diversify away from their original purposes and contribute to the increasingly complex venomous cocktail, forming lethal suites of chemicals that interact with each other to do more harm to prey.

'There are four main gene families that create venom proteins in the King Cobra, and they have all expanded hugely compared to other parts of the genome,' Casewell explains. 'Many of these genes have been duplicated many times. It could be that this just lets the snake deliver more of the same toxins, but it's also highly likely that these duplications led to the evolution of new functions. We think it's probably a combination of these two factors.'

This drive to greater complexity arose because snakes are locked in an evolutionary arms-race with their prey; if their venom stays the same for too long, there's a risk their prey will become immune to it. For instance, there are ground squirrels in the USA that are so resistant to rattlesnake venom that their blood plasma could theoretically be used to treat

rattlesnake bite in humans. Venomous snakes rely almost totally on their venom to kill prey, so prey immunity would be a disaster; to avoid that risk, the venom has to keep developing new tricks.

The results, which probably apply to other venomous snakes beyond the King Cobra, will help researchers develop better antivenoms that can protect against the bites of many species of snake. At present, antivenom manufacture is a relatively primitive business in which horses or sheep are injected with tiny amounts of venom, and the antibodies they produce collected and concentrated.

Because each snake possesses its own venom with a distinctive mix of chemicals, antivenom developed for one snake often doesn't work against the venom of another. Snakebite is a major killer in many tropical nations, and if we can learn how to artificially produce antivenom that's effective against a wider range of species by focusing on the most important proteins that are shared between the venoms of different snakes, many thousands of lives could be saved each year.

Casewell says the next step is to do similar research on other snake species. Cobras belong to the elapids, one of the two major families of venomous snake alongside the vipers. He now hopes to look at the evolution of venom in a member of the latter family, such as a rattlesnake or adder.

He says how complex a particular snake's venom gets may depend on how specialised its diet it is; the more it depends on a small number of prey, the more it risks those prey developing immunity to its venom. 'It's almost certainly a balance of factors around the snake's diet and the resistance of its prey that determines the complexity of its venom and the speed with which it evolves,' adds Casewell.

The paper appears in *Proceedings of the National Academy of Sciences*.

At the same time another paper, this one led by Dr Todd Castoe of the University of Texas at Arlington and with Casewell as a contributing author, has been published in the same journal. This approaches the cobra-python comparison from the other direction, looking at the Burmese Python's genome to unravel the genetic basis of incredible physiological changes that happen when the snake has eaten a big meal.

Once it's managed to swallow a piglet or other outsized prey, the python's metabolism greatly accelerates and its heart, liver, small intestine and kidneys all swell by as much 150 per cent over just a day or two. These changes let the snake digest its prey in a reasonable amount of time, after which its physiology returns to normal.

This kind of sudden adaptation is believed to happen in many snakes, particularly those that ambush prey rather than actively hunting, though the Burmese Python may be the most extreme case. Examining its genome in comparison to the King Cobra's revealed that a similar process of co-option and adaptation of genes from other parts of the body is behind the snake's extraordinary capacity to change its whole body to deal with the situation.

More information: "The king cobra genome reveals dynamic gene evolution and adaptation in the snake venom system," by Freek J. Vonk et al.*PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1314702110

https://phys.org/news/2013-12-rapid-evolution-cobra-venom.html