Insight into snake venom evolution could aid drug discovery

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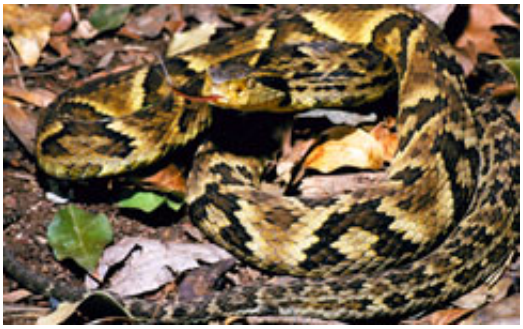

The Jararaca (Bothrops jararaca), a pit viper from Brazil.

UK-led scientists have made a discovery about snake venom that could lead to the development of new drugs to treat a range of life-threatening conditions like cancer, diabetes and high blood pressure.

Most venom contains a huge variety of lethal molecules called toxins, which evolve from harmless compounds that used to do different jobs elsewhere in the body.

These toxins target normal biological processes in snakes' prey, such as blood clotting or nerve-cell signalling, and stop them from working properly.

Now researchers have discovered that the toxins that make snake and lizard venom deadly can evolve back into completely harmless

molecules, raising the possibility that they could be developed into drugs.

'Our results demonstrate that the evolution of venoms is a really complex process. The venom gland of snakes appears to be a melting pot for evolving new functions for molecules, some of which are retained in venom for killing prey, while others go on to serve new functions in other tissues in the body,' says Dr Nicholas Casewell who did the research at Liverpool School of Tropical Medicine, and is now at Bangor University.

Scientists have long recognised that the way toxins work makes them useful targets for drug development. But the fact that they're harmful poses a problem. This means that drug developers have had to modify toxins to retain their potency and make them safe for drug use.

One such drug called Captopril, which treats high blood pressure, was developed from a compound in lancehead viper venom which catastrophically lowers blood pressure in its prey. But its chemical structure had to be modified to make it safe to use as a drug.

But the researchers' discovery that there may be many harmless versions of venom toxins throughout a snake's body opens the door to a whole new era of drug discovery.

Western terrestrial garter snake.

Ex-venom proteins could be valuable because they're made up of what scientists call bioactive proteins. They already target metabolic processes, which is precisely what you need drugs to do.

'So rather than developing synthetic compounds into drugs, our finding suggests you could screen these harmless proteins against whatever target you're interested in. This means using natural products,' says Casewell.

Snake researchers were aware that venom toxins evolve from harmless molecules that do fairly mundane jobs elsewhere in the body. But until now they had assumed that this was a one-way process.

Venom has evolved independently many different times in different creatures. Its role is largely seen as a means by which its owner can feed, or protect itself against predators.

But snakes' and reptiles' prey tends to evolve resistance to venom, which means that venoms have to continually evolve to remain effective.

'Snake venom toxins are the most rapidly-evolving proteins ever identified,' says Casewell.

Casewell and colleagues from Bangor University and the Australian National University used recently published gene sequences from the Garter snake and the Burmese python in their study. They compared these sequences with those from venom glands in a wide range of snakes and lizards, constructing an evolutionary tree to work out the

relationships between the various sequences.

They found that rather than staying stuck in the venom gland, some proteins evolve back into harmless molecules to do different roles in the body.

'Everyone had assumed that these recruitments from ordinary proteins to venomous proteins were rare. But now we know the process might not be that rare, and it goes backwards,' explains Casewell.

Dr Wolfgang Wüster from Bangor University, a co-author of the study says:

'Many snake venom toxins target the same physiological pathways that doctors would like to target to treat a variety of medical conditions. Understanding how toxins can be tamed into harmless physiological proteins may aid development of cures from venom.'

The researchers' findings are published in *Nature Communications* today.

More information: Nicholas R. Casewell, Gavin A. Huttley and Wolfgang Wüster, Dynamic evolution of venom proteins in squamate reptiles, *Nature Communications*, published 18 September 2012

https://phys.org/news/2012-09-insight-snake-venom-evolution-aid.html