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RAPID VENOM EVOLUTION IN PITVIPERS MAY BE DEFENSIVE

MARSUPIALS THAT PREY ON VENOMOUS SNAKES ALSO EVOLVE RAPIDLY

Research published recently in *PLoS One* delivers new insight about rapid toxin evolution in venomous snakes: pitvipers such as rattlesnakes may be engaged in an arms race with opossums, a group of snake-eating American marsupials. Although some mammals have long been known to eat venomous snakes, this fact has not been factored into previous explanations for the rapid evolution of snake venom. Instead, snake venom is usually seen as a feeding, or trophic, adaptation. But new molecular research on snake-eating opossums by researchers affiliated with the American Museum of Natural History suggests that predators factor into the rapid evolution of snake venom.

“Snake venom toxins evolve incredibly rapidly,” says Robert Voss, curator in the Department of Mammalogy at the American Museum of Natural History. “Most herpetologists interpret this as evidence that venom in snakes evolves because of interactions with their prey, but if that were true you would see equally rapid evolution in toxin-targeted molecules of prey species, which has not yet been seen. What we’ve found is that a venom-targeted protein is evolving rapidly in mammals that eat snakes. That suggests that venom has a defensive as well as a trophic role.”

Several groups of mammals are known for their ability to eat venomous snakes, including hedgehogs, mongooses, and some opossums. Opossums, which belong to the marsupial family Didelphidae, consist of about one hundred known and several dozen undescribed species. Most of these opossums live in Central and South America, although there is one representative in the north that is familiar to those who spend time outside at night: the Virginia opossum.

Some didelphids, including the Virginia opossum, are known to eat rattlesnakes, copperheads, and some species of tropical pitvipers known as lanceheads. All of these pitvipers have venom containing dozens of highly toxic compounds, including many that attack blood proteins, causing massive internal hemorrhaging in nonresistant warm-blooded prey species, mainly rodents and birds.

The new research came out of a previous phylogenetic study of marsupials, published as a *Bulletin of the American Museum of Natural History*, that suggested unusually rapid evolution in one gene among a group of snake-eating opossums. The rapidly evolving gene codes for von Willebrand's factor, an important blood-clotting protein that is known to be the target of several snake-venom toxins. The association of rapid evolution in a venom-targeted gene among just those opossums known to eat pitvipers was the essential clue that prompted further study.

"This finding took us by surprise," says Sharon Jansa, associate professor in the Department of Ecology, Evolution and Behavior at the University of Minnesota and a Museum research associate. "We sequenced several genes – including the one that codes for von Willebrand Factor (vWF) – to use in a study of opossum phylogeny. Once we started to analyze the data, vWF was a real outlier. It was evolving much more rapidly than expected in a group of opossums that also, as it turns out, are resistant to pitviper venom."

The recently published research demonstrates that the rate of replacement substitutions (nucleotide changes that result in amino-acid changes) is much higher than the rate of silent substitutions (nucleotide changes that have no effect on the protein) in the von Willebrand Factor gene among pitviper-eating opossums. Typically, high rates of replacement substitutions means that the gene is under strong, sustained natural selection. That only happens in a few evolutionary circumstances.

"Most nucleotide substitutions have little or no effect on protein function, but that doesn't seem to be the case with vWF in these venom-resistant opossums," says Jansa. "The specific amino acids in vWF that interact with toxin proteins show unexpectedly high rates of replacement substitutions. These substitutions undoubtedly affect protein function, suggesting that the vWF protein can no longer be attacked by these snake toxins."

"It is so uncommon to find genes under strong positive selection, that the exceptions are really interesting and often conform to one evolutionary circumstance when two organisms are coevolving with each other," says Voss. "We've known for years that venom genes evolve rapidly in snakes, but the partner in this arms race was unknown until now. Opossums eat snakes because they can."

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