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INSIDE JEB

How poison dart frogs export potent poisons to their skins

A pair of little devil frogs (*Oophaga sylvatica*). Photo credit: Elicio Tapia.

Dining on toxic ants and mites in their tropical rainforest homes, poison dart frogs are literally what they eat. The minute amphibians lace their skins with neurotoxins ingested as part of their diet, warning off predators with their gaudy colours. However, when deprived of their natural diet in captivity, the toxins fade, transforming some of the animals into popular pets. 'The ability to sequester toxic chemicals from prey and use those chemicals as a defence mechanism against predators is a marvellous example of evolution', says Stephanie Caty, from Stanford University, USA. Yet it was unclear how the fearless amphibians transport these potent poisons from their intestines to glands in the skin. Intrigued by the puzzle, Caty and PI Lauren O'Connell travelled to Ecuador to collect wild little devil frogs (*Oophaga sylvatica*) with Elicio Tapia to find out how the amphibians export toxins to their skins.

'Elicio grew up in the Ecuadorian rainforest and he can find frogs even when we can't see them', explains Caty, adding that travelling to the amphibians' home was the most difficult part of the study. However, once located, the elusive creatures were content to hop inside the bottom halves of plastic bottles placed beside them, posing no risk to the researchers. After collecting the skin, intestines and liver from a small number of frogs, Tapia returned to the Centro Jambatu de Investigación y Conservación de Anfibios, in Quito, Ecuador, where he fed the remaining animals on non-toxic fruit flies and crickets for 6 months before collecting the detoxed animals' organs.

Back in the USA, Gary Byrd analysed the amphibians' skin toxins, identifying 10 neurotoxins, including lehmizidines and indolizines, which inactivate ion channels in nerve and muscle cells. And when Caty compared the gene expression patterns of the wild and detoxified frogs, she noticed that the toxic wild frogs were producing less of the mRNA required to generate sodium transporting ion channels, possibly to help the frogs retain the neurotoxins from their diet.

Then she analysed the proteins carried in the frogs' blood and noticed several that might contribute to neurotoxin transport, including a bile acid transporter protein (known as solute carrier protein 51a), which usually transports oily molecules in the blood. The team was also surprised when they noticed that the levels of a protein known as saxiphilin – which removes saxitoxin neurotoxin from the blood of bullfrogs – increased dramatically in the detoxed frogs. 'We were expecting to see greater expression in the toxic frogs', says Caty, who had thought that the little devils might use the toxin-transporting protein to make themselves more toxic. However, O'Connell suspects that there are several possible explanations for the unexpected discovery, including the protein vanishing from the blood of the wild frogs because it is bound up with toxins in the skin glands or, alternately, the non-toxic frogs might elevate levels of the protein in readiness for toxins reappearing in their diet. And when Aurora Alvarez-Buylla added a sample neurotoxin to the wild frogs' blood in search of molecules that may be involved in transporting toxins to the frogs' skin, a heat shock protein – Hsp90, which protects proteins from damage when the frogs overheat – and saxiphilin both popped up as potential carriers.

Caty admits that she is excited that saxiphilin, which is involved in bullfrog detoxification, has turned up in the poison dart frogs. 'There are likely many more pathways involved in this accumulation than we had originally anticipated', she says. And O'Connell is keen to learn more about the effects of the frogs' diets on their toxic alkaloid cocktails.

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