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Drug design benefits from Gila monster venom evolution

Scientists have identified the evolution of venom proteins in lizards such as the Gila Monster, a discovery which could help provide clues to future drug development. The new study reveals extraordinary genetic rearrangements which have produced novel toxins in the Gila Monster and Beaded Lizard venoms.

The discovery coincides with the 150th anniversary of the publication of Charles' Darwin's 'On the Origin of Species' and the study's lead author, Dr Bryan Fry from Department of Biochemistry and Molecular Biology, Bio21 Institute, University of Melbourne, says the work is a prime example of the impact of evolution.

"These results highlight the importance of using evolutionary-based search strategies for the virtually unexplored potential of lizard venoms in drug design and discovery. A lot is known about snake venom, but lizard venom is also clinically complex and remains an untapped resource," says Dr Fry.

"These critters are the master chemists, far more clever than we are. Evolution has been tinkering with their genetics for millions of years. The work has already been done for us, we just need to be smart enough to understand what they have already accomplished."

The work was conducted by a team from Melbourne, Brussels, Monash and Belfast universities and Museum Victoria and will be published in the journal 'Biology & Evolution' this month.

The study has important implications for the type 2 diabetes treatment known as Byetta, which is a protein found in Gila Monsters, called exendin-4. The team discovered that exendins 3 and 4 are actually precursors to the more recently evolved and more toxic exendins 1 and 2. Dr Fry hopes that by understanding which parts of molecules have been changed by evolution, we can better understand which parts are essential for particular activities, thereby zeroing in on those with therapeutic potential.

The researchers found that the Gila Monster and Beaded Lizard venom evolution occurred via the duplication and shuffling of genes from a common ancestor. The process is similar to the doubling and shuffling of a pack of cards, with evolution selecting an Ace for important functions such as more powerful venom. They showed that unique rearrangement of parts of the genes in three of the toxin families produced entirely new toxin types.

To undertake the study the team extracted venom from a gland at the base of the Gila Monster's grooved teeth to create a library of venom genes. They compared these to the function of known genes and investigated new venom proteins for their function in animal studies.

Gila monsters can grow to up to 60cm in length and are brightly patterned. They are the only venomous lizards in North America, and are native to Mexico, as are their close relatives the Beaded Lizard. Dr Fry emphasizes that these species belong to an ever-growing group of threatened species that may affect biodiversity and cause an important loss of genetic information. He hopes this study will not only stimulate further research and provide a new understanding and realisation of conservation efforts, but will also encourage the utilisation of these precious natural resources in a sustainable and ethical manner.

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