

SNAKE VENOMICS AND ANTIVENOMICS OF MIDDLE AND SOUTH AMERICAN RATTLESNAKES. IDENTIFICATION OF NEUROTOXIN CROTOXIN AS AN ADAPTIVE TRAIT DURING *CROTALUS DURISSUS* INVASION OF SOUTH AMERICA

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Venoms of subspecies of neotropical rattlesnakes represent an example of adaptive phenotypic variation. Venom of adult Central American *C. simus*, formerly *C. d. durissus*, cause local tissue damage, hemorrhage, coagulopathy and cardiovascular shock, but is devoid of neurotoxicity and systemic myotoxicity. However, newborn *C. simus* venom resembles that of South American *C.d. terrificus* being both neuro- and myotoxic and devoid of hemorrhagic activity. The pathophysiology of *C.d. terrificus* envenomation is due to the neurotoxic and myotoxic effects of crotoxin, a heterodimeric PLA₂ causing progressive paralysis and myonecrosis. Venoms of the subspecies *C. d. cumanensis* and *C. d. ruruima*, inhabiting northern regions of South America, exhibit a mixed pattern, inducing neurotoxicity and hemorrhage. The phylogeographical pattern of *Crotalus* dispersal is consistent with a stepwise colonization from Mexico along the Central American Isthmus (1.85 Mya), followed by rapid dispersal into and across South America (1.5-1.1 Mya). Our venomomic analyses indicate that the gain of neurotoxicity associated with increasing crotoxin expression represents the key axis along which overall venom toxicity has evolved during *Crotalus durissus* invasion of South America. Assuming a link between venom toxicity and increased crotoxin concentration, the identification of evolutionary trends may have an impact in defining the mixture of venoms for immunization to produce effective antivenoms. A Costa Rican antivenom against *C. simus simus*, is ineffective neutralizing both the venom of South American *Crotalus durissus* subspecies and of newborn *C. simus simus*. Similarly, South American antivenoms against *C.d. terrificus* neutralize lethality of Central American venoms but are ineffective at neutralizing the hemorrhagic activity of venoms from genus *Crotalus*. Such neutralizing profile is fully explained by the proteomic characterization of *Crotalus (simus and durissus)* venoms showing increasing amounts of crotoxin in the venoms of *C. durissus* subspecies along the north to south colonization pattern of this group of snakes.