

# Unique adaptive evolution in snake proteins -- insight into vertebrate physiology

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Prior to the advent of large sequence datasets, it was assumed that innovation and divergence at the morphological and physiological level would be easily explained at the molecular level. Molecular explanations for physiological adaptations have, however, been rare.

In a study published in *PLoS ONE* on Wednesday, May 21, Pollock and colleagues provide evidence that major macroevolutionary changes in snakes (e.g., physiological and metabolic adaptations and venom evolution) have been accompanied by massive functional redesign of core metabolic proteins.

“The molecular evolutionary results are remarkable, and set a new precedence for extreme protein evolutionary adaptive redesign. This represents the most dramatic burst of protein evolution in an otherwise highly conserved protein that I know of,” said Dr. David Pollock, a professor of Biochemistry & Molecular Genetics at the University of Colorado Denver School of Medicine.

Over the last ten years, scientists have shown that snakes have remarkable abilities to regulate heart and digestive system development. They endure among the most extreme shifts in aerobic metabolism known in vertebrates. This has made snakes an excellent model for studying organ development, as well as physiological and metabolic regulation. The reasons that snakes are so unique had not previously been identified at the molecular level. In this recent study by Pollock and colleagues, the researchers show that mitochondrially-encoded oxidative phosphorylation proteins in snakes have endured a remarkable process of evolutionary redesign that may explain why snakes have such unique metabolism and physiology.

Amino acids that are normally highly conserved in these proteins have been altered, affecting key molecular functions such as proton transfer (which

establishes a proton concentration gradient that drives energy production in the cell). In addition to the accelerated burst of amino acid replacements, evidence for adaptation comes from the remarkable levels of molecular coevolution and convergence that were observed.

The function of core oxidative metabolic proteins in vertebrates remains extremely controversial, mostly because of the difficulty of experimentally manipulating these membrane-embedded proteins. By integrating analyses of molecular evolution with protein structural data, the authors show that critical functions of mitochondrial proteins, such as the channeling of oxygen, electrons, and protons through cytochrome C oxidase, have been fundamentally altered during the evolution of snakes. Snakes have been previously proposed as an ideal metabolic, physiological, and ecological model system to study evolution, and the current results support that idea, showing that their utility as a model system can extend to the molecular level.

“Snakes are an invaluable resource for structural biologists and biochemists, who can use comparative genomics to generate hypotheses on how COI and oxidative phosphorylation function, and how these functions may be altered and redesigned,” said Dr. Todd Castoe, a lead author on the paper.

“We believe that our results will provide a textbook case as the most clear and dramatic example of adaptive evolution in a core metabolic protein to date, as well as providing the implication that strong molecular and physiological adaptation can be linked,” said Pollock.

“The manuscript represents an important milestone in molecular evolution and vertebrate adaptation, and opens up clear and well-justified directions for further research. Snake metabolic proteins may significantly clarify understanding about the

operation of these critical yet functionally elusive metabolic proteins”.

Citation: Castoe TA, Jiang ZJ, Gu W, Wang ZO, Pollock DD (2008) Adaptive Evolution and Functional Redesign of Core Metabolic Proteins in Snakes. *PLoS ONE* 3(5): e2201.  
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