Venomous bite: Harmless digestive enzyme evolved into venom in two species

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A harmless digestive enzyme can be turned into a toxin in two unrelated species — a shrew (pictured) and a lizard — thereby giving each a venomous bite. Courtesy of the University of Michigan Museum of Zoology

(PhysOrg.com) -- Biologists have shown that independent but similar molecular changes turned a harmless digestive enzyme into a toxin in two unrelated species -- a shrew and a lizard -- giving each a venomous bite.

The work, described this week in the journal Current Biology by researchers at Harvard University, suggests that protein adaptation may be a highly predictable process, one that could eventually help discover other toxins across a wide array of species.

"Similar changes have occurred independently in a shrew and a lizard,

causing both to be toxic," says senior author Hopi E. Hoekstra, John L. Loeb Associate Professor of the Natural Sciences in Harvard's Department of Organismic and Evolutionary Biology. "It's remarkable that the same types of changes have independently promoted the same toxic end product."

Lead author Yael T. Aminetzach, a postdoctoral researcher in the same department, suggests that the work has important implications for our understanding of how novel protein function evolves by studying the relationship between an ancestral and harmless protein and its new toxic activity.

"The venom is essentially an overactivation of the original digestive enzyme, amplifying its effects," she says. "What had been a mild anticoagulant in the salivary glands of both species has become a much more extreme compound that causes paralysis and death in prey that is bitten."

In the first part of the study, Aminetzach and her colleagues compared a toxin found in the salivary glands of the insectivorous North American shrew *Blarina brevicauda* to its closely related digestive enzyme kallikrein. Enzymes are proteins that catalyze, or increase the rates of, chemical reactions; this rate enhancement occurs at a specific region on an enzyme called the active site.

Aminetzach found that the specific molecular differences between kallikrein and its toxic descendent are highly localized around the enzyme's active site.

"Catalysis is fostered by three specific changes that increase enzyme activity," Aminetzach says. "The active site is physically opened up, and the loops surrounding it become more flexible. The area around the active site also becomes positively charged, serving to better guide the

substrate directly into the active site."

To further demonstrate that these molecular changes to kallikrein are related to the evolution of toxicity, Aminetzach explored the evolution of another kallikrein-like toxin in the Mexican beaded lizard (*Helodermata horridum*). She found that this toxin, while distinct from the analogous toxin in the shrew, nonetheless exhibits the same catalytic enhancement relative to the original kallikrein enzyme.

Equally important, she found that this functional change in the lizard toxin is accomplished through similar molecular modifications of kallikrein, and through identical mechanisms of structural alteration of the active site, as in the shrew toxin.

This insight -- namely, that toxins could arise by increasing the catalytic activity of enzymes through a conserved and predictable mechanism -- could be used both to identify other kallikrein-derived toxic proteins and as a method to evolve new protein function in general.

Source: Harvard University (news : web)