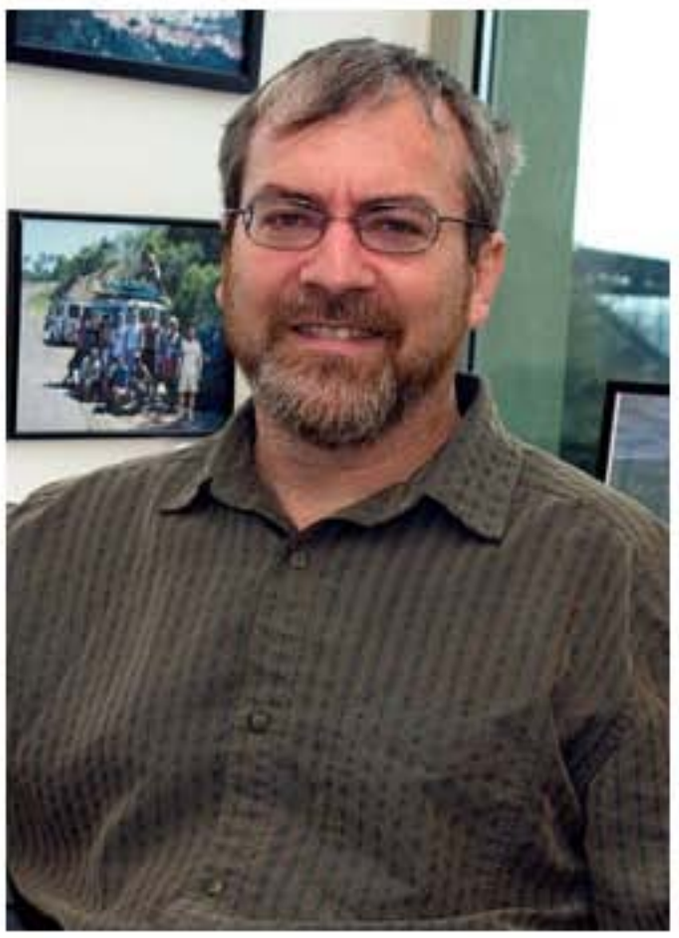
sciencefocus

ASBMB research on venom proteins

Michael H. Gelb
Harry and Catherine Jaynne Boand Endowed Professor of Chemistry
University of Washington, Seattle



Snakes may elicit a lot of fear due to their venomous nature, but in fact, the innocuous-looking honeybee kills more people each year in the U.S.

Of course, the threat of a bee sting is not the toxins themselves but rather the allergic reaction (anaphylaxis) that can occur following injection. This is due in large part to the presence of significant amounts of the allergen phospholipase A2, an enzyme that breaks down phospholipids found on cell membranes.

Over the years, bee venom has been a favorite system for allergy research, and scientists have made strides in adapting bee venom as an immunotherapy agent for insect stings and other immune conditions like arthritis.

However, it was in the 1980s, when researchers had found evidence that mammalian secreted phospholipases A2 might be involved in producing arachidonic acid, the precursor to prostaglandins and other eicosanoids (key inflammatory agents), that even more people took notice, including **Michael H. Gelb**.

Gelb, whose multifaceted interests include medicinal enzymology, drug design and protein prenylation, was interested in the link to inflammation and decided to use bee phospholipase as a model of the mammalian enzymes.

The initial choice was a pragmatic one. "Back then it was quite a challenge to engineer to express these proteins because of their many disulfide bonds," he says. "But we were able to express the bee PLA2 in E. coli and so we went with that, even though the enzyme is more distant to humans than PLA2 found in snakes."

The choice proved to be quite fruitful, and since his first experiments some 20 years ago, Gelb's group has discovered numerous insights into phospholipase biochemistry with the help of the bee model. This work has included structural studies on the enzyme (with renowned structural biologist Paul Sigler of Yale University), which revealed that PLA2 has distinct lipid binding and active sites and that catalysis likely occurs through diffusion of a single phospholipid substrate into the active site slot without a conformational change to the PLA2 upon binding to the membrane surface. His group also has identified mechanisms underlying both membrane binding and antibody binding.

sciencefocus

ASBMB research on venom proteins

With that fundamental knowledge in hand, Gelb now has turned his attention to understanding the function and regulation of human PLA2 enzymes in the eicosanoid pathway. Together with Gerard Lambeau of IPMC-CNRS in Valbonne, France, he has identified and characterized a number of new and unusual PLA2 proteins, including a catalytically inactive variant that may act as a receptor ligand instead of an enzyme. He's also taken an interest in the cytosolic phospholipase enzymes and how they interact with the secreted enzymes in various processes.

Some of these novel proteins could hold therapeutic promise, including one (sPLA2-X) that participates in the synthesis of asthma-inducing leukotrienes and another (sPLA2-IIa) that is involved in rheumatoid arthritis.

"We've got some exciting results, though it hasn't been quite enough yet for pharmaceutical companies to take notice," says Gelb. "I guess they're being a little cautious these days."

It's no big deal, though; with nine different phospholipase A2 groups in humans, along with several variants in each group, Gelb has plenty of work to keep him busy until that day comes along.

JBC highlight: Valentin, E., Ghomashchi, F., Gelb, M. H., Lazdunski, M., and Lambeau, G. (200) ***Novel human secreted phospholipase A2 with homology to the group III bee venom enzyme.*** *J. Biol. Chem. 275, 7492 – 7496.*

***