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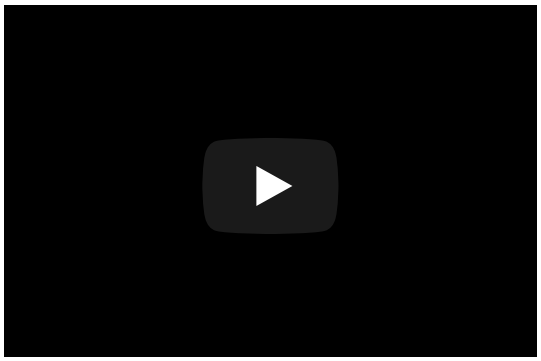
3D Enzyme Model Provides New Tool for Anti-Inflammatory Drug Development

Researchers develop first computer models of phospholipase A2 enzymes extracting their substrates out of the cell membrane, an early step in inflammation

Phospholipase A_2 (PLA_2) enzymes are known to play a role in many inflammatory diseases, including asthma, arthritis and atherosclerosis. It then stands to reason that PLA_2 inhibitors could represent a new class of anti-inflammatory medication. To better understand PLA_2 enzymes and help drive therapeutic drug development, researchers at University of California, San Diego School of Medicine developed 3D computer models that show exactly how two PLA2 enzymes extract their substrates from cellular membranes. The new tool is described in a paper published online the week of Jan. 26 by the *Proceedings of the National Academy of Sciences*.

“This is the first time experimental data and supercomputing technology have been used to visualize an enzyme interacting with a membrane,” said Edward A. Dennis, PhD, Distinguished Professor of Pharmacology, chemistry and biochemistry and senior author of the study. “In doing so, we discovered that binding the membrane triggers a conformational change in PLA_2 enzymes and activates them. We also saw several important differences between the two PLA_2 enzymes we studied — findings that could influence the design and development of specific PLA2 inhibitor drugs for each enzyme.”

The computer simulations of PLA_2 enzymes developed by Dennis and his team, including first author Varnavas D. Mouchlis, PhD, show the specific molecular interactions between PLA_2 enzymes and their substrate, arachidonic acid, as the enzymes suck it up from cellular membranes.



Make no mistake, though — the animations of PLA_2 in action are not mere cartoons. They are sophisticated molecular dynamics simulations based upon previously published deuterium exchange mass spectrometry (DXMS) data on PLA_2. DXMS is an experimental laboratory technique that provides molecular information about the interactions of these enzymes with membranes.

“The combination of rigorous experimental data and in silico [computer] models is a very powerful tool — the experimental data guided the development of accurate 3D models, demonstrating that these two scientific fields can inform one another,” Mouchlis said.

The liberation of arachidonic acid by PLA_2 enzymes, as shown in these simulations, sets off a cascade of molecular events that result in inflammation. Aspirin and many other anti-inflammatory drugs work by inhibiting enzymes in this cascade that rely on PLA_2 enzymes to provide them with arachidonic acid. That means PLA_2 enzymes could potentially also be targeted to dampen inflammation at an earlier point in the process.

Co-authors include Denis Bucher, UC San Diego, and J. Andrew McCammon, UC San Diego and Howard Hughes Medical Institute.

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