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Phospholipase A_2 substrate and inhibitor specificity revealed at the molecular level

The phospholipase A_2 (PLA_2) superfamily exhibits a large array of functions, but of special interest is the inflammatory cascade which is initiated by the release of free arachidonic acid by some types of phospholipase A_2, all of which interact with membrane phospholipids. However, different PLA_2 types have unique three-dimensional structures and unique catalytic residues as well as specific tissue localization, distinct biological functions, and with which membrane phospholipids have unique allosteric interactions. Understanding how the different PLA_2s associate with phospholipid membranes, specific phospholipid substrate molecules, and inhibitors on a structural and molecular basis has advanced in recent years due to the introduction of hydrogen/deuterium exchange mass spectrometry approaches. We will emphasize recent results utilyzing hydrogen/deuterium exchange approaches and molecular dynamics on the major types of PLA_2, including secretory s-PLA_2, cytosolic c-PLA_2, lipoprotein-associated LpPLA_2, and calcium-independent iPLA_2 with inhibitors and substrates. We will also discuss new results on the precise nature and molecular dynamics of the interaction of these enzymes with specific substrate phospholipids pulled into the catalytic site from membranes and how new potent specific inhibitors block substrate phospholipid binding. Phospholipase A_2 is the initiator of eicosanoid formation in inflammatory processes, so it is a critical enzyme and inhibitors could provide new approaches to disease treatment.

Biography

Edward A Dennis is a distinguished Professor of Chemistry and Biochemistry and of Pharmacology in the School of Medicine at the University of California at San Diego (UCSD). He received his BA from Yale and a PhD from Harvard and was a Post-doctoral fellow at Harvard Medical School. He has served as Chair of the Department of Chemistry and Biochemistry. His research focus has been on the mechanism of the enzyme phospholipase A_2, signal transduction, inflammation, lipid metabolism, eicosanoid action, and lipidomics. He authored over 380 publications, is Editor-in-Chief of the *Journal of Lipid Research* and Director of the LIPID MAPS Consortium.

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