Convergent evolution of PLA2s: implications for the classification of the PLA2 "superfamily".

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Phospholipase A2 (PLA2) catalyzes the specific hydrolysis of the sn-2 acyl bond of various glycerophospholipids, producing free fatty acids and lysophospholipids. PLA2s are widely distributed in nature and constitute a large »superfamily« of enzymes whose products are important for a multitude of signal transduction processes, lipid mediator release, lipid metabolism, and host defense. According to the localization and the properties of its members, the PLA2 superfamily was divided into 15 distinct groups of PLA2s, and these are divided into 5 main clades within the superfamily: secreted sPLA2s, cytosolic cPLA2s, calcium-independent iPLA2s, platelet-activating factor acetylhydrolases, and the lysosomal PLA2s. PLA2s have been the subject of many studies, however little is known about their evolution and functional diversification. Numerous proteins containing PLA2 domains have been discovered that cannot be easily incorporated into the existing classification scheme, resulting in a growing problem of classifying the PLA2 »superfamily«. A large amount of protein sequence data for this superfamily therefore awaits comprehensive evolutionary classification. My aim has been to obtain a comprehensive insight into their evolution and structural classification.

Although all PLA2 enzymes perform the same function and posses the same EC number (EC 3.1.1.4) they are clearly not evolutionarily related. As this study shows PLA2s exhibit seven different folds and belongs to seven different superfamilies. The PLA2s fold repertoire also includes representatives of four major classes of protein structures, demonstrating that nature has found ways to utilize all varieties of secondary structure combinations to carry out the PLA2 reaction. PLA2s now represent a new example of functional convergence since they have different structural folds, but have the same Ser–His–Asp catalytic triad (or diad) and function as PLA2s via the same catalytic mechanism. Since the enzyme catalytic activity depends upon the precise spatial orientation of only a few amino acids, it is not surprising that the same active site architecture can recur in the contexts of different structural scaffolds.

A comprehensive structural annotation of PLA2s shows that they are a large functional class of proteins. This study challenges the current view on the classification and evolution of the PLA2s, therefore the widely accepted classification scheme of the PLA2 »superfamily« needs to be revised.