Poster Presentation

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Structural basis for a novel model for myotoxic activity on phospholipases A2

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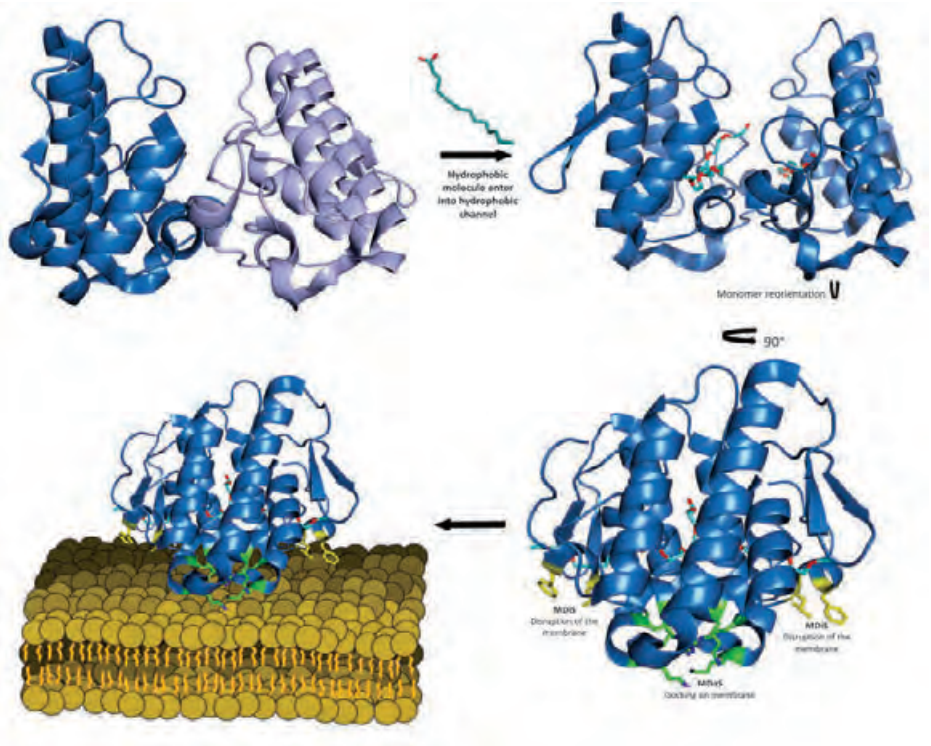
Envenoming due to snakebites is an important public health problem in many tropical and subtropical countries which, in addition to mortality, may result in permanent sequelae as a consequence of local tissue damage, i.e. necrosis and hemorrhage. Toxins that play a leading role in the complex pathogenesis of these feared venom actions have been identified as members of the phospholipase A2 (PLA2) and metalloproteinase protein families. Phospholipases A2 are enzymes responsible for cellular membrane disruption through Ca2+-dependent hydrolysis of phospholipids. A class of these proteins (Lys49-PLA2s) does not show catalytic activity but can exert a pronounced local myotoxic effect that is not neutralized by serum therapy. After more than 20 years of structural, biochemical and biological studies with this class of proteins, its biological mechanism still remain not totally understood. Here, based in a comprehensive study including over than 30 crystallographic structures, Small Angle X-ray Scattering, Dynamic Light Scattering, Isothermal Titration Calorimetry, Biochemical, Bioinformatics, Phylogenic and Myografic experiments, we proposed a complete myotoxic mechanism. This work confirms the biological dimer indicated by recent studies in which both C-termini are in the dimeric interface. In this configuration, we propose that the myotoxic site of these toxins is composed by the Lys 20, Lys115 and Arg118 residues. The extensive structural analysis also include: (i) the function of hydrophobic long-chain molecules as Lys49-PLA2s inhibitors, (ii) the role of Lys122, previously indicated as being responsible for Lys49-PLA2s catalytic inactivity, (iii) a structural comparison of the Ca2+-binding loop region between Lys49 and Asp49-PLA2s, (iv) the importance of Tyr119 residue, (v) the role of different classes of inhibitors and (vi) the role of hydrophobic knuckle. Taking into account all these issues we were able to propose a complete mechanism of action of these proteins and also proposed the different ways to inhibit them. These results may be useful to guide new experiments that can definitively clarify the action mechanism of snake venom PLA2s and lead to the design of structure-based inhibitors to complement the serum therapy.



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