Poster Presentation

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Structural studies on leukotriene A4 hydrolases reveal their catalytic mechanism

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Vertebrate leukotriene A4 hydrolases are zinc metalloenzymes with an epoxide hydrolase and aminopeptidase activity belonging to the M1 family of aminopeptidases. Bestatin, an amino peptidase inhibitor, can inhibit both the activities. The human enzyme produces LTB4, a powerful mediator of inflammation and is implicated in a wide variety of rheumatoid diseases. The yeast homolog scLTA4H contains only a rudimentary epoxide hydrolase activity. Both the structure of the human enzyme and recently the structure of scLTA4H and have been solved to investigate the molecular architecture of the active site both with and without inhibitor Bestatin. The structure of scLTA4H shows large domain movements creating an open active site. In the human enzyme the LTA4 binding side is a narrow hydrophobic channel. Upon inhibitor a domain shifts occurs and the final binding pocket is formed. The fact that scLTA4H displays this induced fit is an interesting observation. Many members of the M1 family seem to display a certain degree of induced fit, a feature, which however, has never been observed for humLTA4H. Our recent solution SAXS studies show that humLTA4H does not make any conformational changes upon inhibitor binding which is consistent with our previous speculation that it functions by a lock and key mechanism rather than induced fit and is better suited to supply the protective and precise environment for hydrolysis of LTA4 into LTB4. On the other hand Xenopus LTA4H shows conformational change in the higher/wide angular region (>1 nm-1) and decrease in Porod volume of approximately 20 nm3 but no change in Rg or Dmax was observed. It is also observed that like in crystal structure Xenopus LTA4H forms dimer in solution. Similarly scLTA4H forms dimer in solution, which is unlike the crystal structure, and also make conformational changes upon inhibitor binding. Taken together, Xenopus and scLTA4H makes more compact form, with decrease in flexibility, to perform it's catalytic action.

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