INTRODUCTION

Ompla, a phospholipase located in the bacterial outer membrane of E. coli, degrades a wide variety of phospholipids in cells with a perturbed envelope. It is a 12 stranded β-barrel and exists in monomeric and dimeric forms. Enzymatic activity is regulated by reversible dimerization in conjunction with Ca\(^{2+}\)-binding, leading to 2 active sites at the monomer-monomer interface. Recently, crystal structures of monomeric and dimeric Ompla with and without Ca\(^{2+}\) were solved (Snijder et al., 1999 and 2001) including apo- and inhibitor-bound forms. An improved understanding of the structure-function relationship in terms of dimerization, the role of Ca\(^{2+}\) and structural impact of the cell envelope can be gained from computational approaches.

Molecular Dynamics Simulations of Outer Membrane Phospholipase A

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**MOLECULAR DYNAMICS IN A LIPID BILAYER**

Molecular dynamics simulations in full atomic detail have been initiated in order to study the conformational dynamics of mono- and dimeric Ompla in a membrane-like environment. Three systems were considered for molecular dynamics simulations in a membrane-like environment: the Ca\(^{2+}\)-free monomer, the Ca\(^{2+}\)-bound dimer and the dimer with inhibitor bound to S144.

SIMULATION SETUP

Calcium interactions were implemented using a modified forcefield for Ca\(^{2+}\) itself and the surrounding residues S152, R147 and S106. Partial atomic charges and Lennard-Jones parameters were adapted from Shirotani & Nakagawa, 1991. In addition, distance restraints of 200 kJ mol\(^{-1}\) were placed between calcium and these residues.

The hexadecanesulphonyl inhibitor was modeled by modifying S144, leading to a hexadecanesulphonyl serine (HDS) residue generated via PRODRG (van Aalten, 1996). The system was then inserted in a lipid bilayer consisting of palmitoyl-oleyl-phosphatidylcholine (POPC) and hydrated with an aqueous phase of about 0.1M in NaCl.

**REFERENCES & ACKNOWLEDGEMENTS**

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Many biological nano-devices are based on membranes (e.g. liposomes and nanosomes). To maintain membrane integrity under various conditions one might add specific proteins, like anti-freeze (glyco)proteins. In this context the Ompla enzyme could help to develop a security valve with respect to mechanical stress.

The Ompla enzyme functions as a kind of security valve in the bacterial outer membrane. It’s enzymatic cycle is activated by a mechanical deformation of the membrane, which triggers lysis of phospholipids. The mechanical trigger may be caused by an imbalance in membrane composition or by physical stress. Lysis and hence removal of phospholipids from the membrane helps to restore it’s integrity.

If the activity of Ompla could be controlled and fine-tuned, one might be able to develop self-regulating devices, with a capacity of dealing with a certain amount of environmental stress and membrane distorsion.

A first step is to fully uncover the enzymatic mechanism of Ompla, which is related to the presence of calcium ions, a specific hydration shell, dimerization and membrane distorsion.

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