A computational surface optimization of lipase A from *Bacillus subtilis* to improve the stability in water-miscible organic solvent

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Deformation of enzyme surface by solvent penetration is known to be one of the most deleterious factors of enzyme destabilization in a water-miscible solvent. Despite this important clue, enzyme stabilization in organic solvents was achieved mainly by random mutagenesis but no significant results by molecular modeling were reported yet. In this study, we attempted to improve the stability of Bacillus subtilis lipase A (lipA) in a water-ethanol cosolvent by a computational optimization of surface residues. Preferred contact sites of ethanol molecules on the lipA surface were investigated to remove unfavorable solvent-enzyme interactions. Target sites were identified by solvent mapping and molecular dynamics simulation. In silico saturated mutation of target sites were performed and mutants with fewer ethanol-contacts were selected for experimental validation. Of single mutants predicted by computational modeling, four mutants showed improved stability in 50 % (v/v) ethanol solvent with comparable thermal stability and specific activity to the wild-type. Our computational modeling strategy can be useful to design organic solvent-stable mutants of industrial enzymes.