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The membrane bound aromatic *p*-hydroxybenzoic acid oligoprenyltransferase (UbiA) - how iterative improvements lead to a realistic structure that offers new insights into functional aspects of prenyl transferases and terpene synthases

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Prenyltransfering enzymes are at the basis of the vast isoprenoid natural product diversity. 4-Hydroxybenzoate oligoprenyltransferase of *E. coli*, encoded in the gene *ubiA*, is a key enzyme in the biosynthetic pathway to ubiquinone. No X-ray structure exists of this membrane protein. It catalyses the prenylation of 4-hydroxybenzoic acid in the 3-position using an oligoprenyl diphosphate as second substrate.

With homology modeling techniques, a first model indicated two putative active sites [1]. Based on this model, amino acids identified as important for the catalytic mechanism were selectively replaced to obtain five new mutants. All mutants were tested for their ability to form geranylated hydroxybenzoate from geranyl diphosphate, but only the unmodified UbiA-enzyme and to minor extent one mutant showed enzymatic activity. These results indicated the involvement of all mutated amino acids in the catalytic mechanism but at the same time demanded a remodelling of the previously proposed enzyme structure combining two active sites. They have been placed into close proximity in the new model. Based on these experimental results and structural classification of prenyl enzymes, a highly relevant 3D-model could be developed. This model is able to explain a wide range of substrate specificities and is in complete agreement with the results of site directed mutagenesis [2].

Aromatic prenyl transferases, prenyl diphosphate synthases, and terpene synthases, activate an (olig)prenyl diphosphate to form a stabilized prenyl cation reactive intermediate that, after addition to a nucleophile (C=C bond) and deprotonation delivers the product(s). Aromatic amino acids have been suggested to stabilize the cation intermediate. Ab inito LMP2 calculations indicate not only stabilization of a prenyl cation by aromatic amino acid side chains but also by a methionine side chain. This suggestion is supported by site directed mutagenesis, bioinformatics, and modelling studies. In addition, a new catalytic diad composed of Tyr and Asp, represented by a Yx(x)xxD-motif, is identified as important player for deprotonation and proton-relay in intermediates, or for the finalizing deprotonation step of many prenyl transferring and cyclizing enzymes.

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