Crystal structure of the peptidyl-cysteine decarboxylase EpiD

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Epidermin from *Staphylococcus epidermidis* Tü3298 is an antimicrobial peptide of the lantibiotic family which contains the amino acids lantionine and meso-lantionine, which are characteristic for this family, and the unusual amino-acid *S*-[(*Z*)-2-aminovinyl]-*D*-cysteine. This residue is introduced by post-translational modification of the ribosomally synthesised precursor EpiA. Modification starts with the oxidative decarboxylation of its C-terminal cysteine by the flavoprotein EpiD, generating a reactive (*Z*)-enethiol intermediate. We have determined the crystal structures of EpiD and a substrate complex of EpiD H67N with the pentapeptide DSYTC at 2.5 Å resolution [1]. This analysis has demonstrated a 23 symmetric dodecamer for EpiD, with trimers disposed at the vertices of a tetrahedron. The monomers bear a topological similarity to the Rossmann-type fold also found in flavodoxins and AtHal3. However the latter forms only trimers [2]. A central parallel β-sheet of six strands (S1-S6) arranged in the topology 3-2-1-4-5-6 is surrounded by nine α or 3_{10} helices generating a three layer αβα protein. In the trimer the plane of the β-sheet of each monomer runs parallel to the threefold axis, with the strands running perpendicular to this axis. Oligomer formation is essential for binding of FMN and substrate. The substrate is buried by an substrate recognition clamp, which is formed by the strands S7, S8 and is disordered in the free enzyme. A pocket for the tyrosine residue of the substrate peptide is formed by an induced fit mechanism. The substrate contacts FMN only via Cys-Sγ suggesting its oxidation as initial reaction step. The unusual substrate recognition mode and the type of chemical reaction performed provide insight into a novel family of flavoproteins, the **h**omooligomeric **f**lavin-containing **C**ys **d**ecarboxylases (HFCD-proteins). There are two characteristic sequence motifs: PA/LS/TANT/IL/I and PXMNXXMW, which are involved in FMN as well as in substrate binding. Further members of this family are MrsD, MutD, Dfp and HAL3/SIS2. MrsD and MutD are very homologous and perform the same reaction than EpiD in the biosynthesis of mersacidin and mutacin III, respectively. The sequence homology of the N-terminal domain of Dfp-proteins and the conserved residues, which are critical for binding of Cys in the vicinity of the active site have allowed to identify the substrate of *E. coli* Dfp, which decarboxylates (*R*)-4´-phospho-N-pantothenoyl-cysteine to 4[1]-phosphopantetheine *in vitro.* This reaction is one step of coenzyme A biosynthesis [3]. AtHal3 and SIS2-proteins are involved in processes with quite diverse effects on cell cycle regulation, salt and osmotic tolerance and plant growth, however the molecular substrates are not known so far.

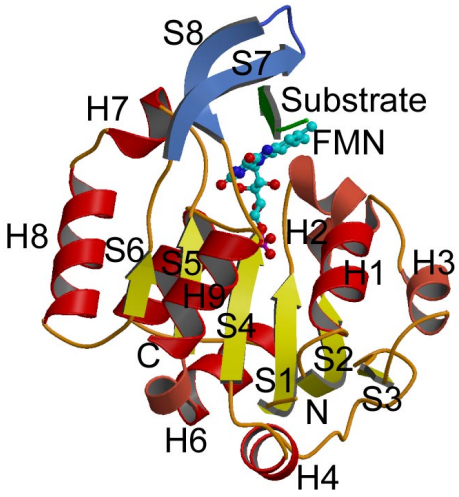

Figure 1: Secundary structure of a EpiD monomer
Strands S7 and S8 form the substrate recognition clamp

References

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