S06-4 Structure-based engineering of plant type III polyketide synthases

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Pentaketide chromone synthase (PCS) from *Aloe arborescens* is a novel plant-specific type III polyketide synthase that catalyzes formation of 5,7-dihydroxy-2-methyl- chromone from five molecules of malonyl-CoA,.[1)] Interestingly, site-directed mutagenesis revealed that Met207 determines the polyketide chain length and the product specificity; PCS M207G mutant yielded aromatic octaketides SEK4/SEK4b, instead of the pentaketide.[1)] In order to shed light on the molecular basis of the plant polyketide biosynthesis, we carried out crystallography analyses of *A. arborescens* PCS. Here we now present the crystal structures of both the pentaketide-producing wild-type and the octaketide-producing M207G mutant protein complexed with CoA-SH at 1.6 Å resolution. They revealed that PCS and CHS share the same three-dimensional overall fold, including the CoA binding tunnel and the geometry of the Cys-His-Asn catalytic triad. Remarkably, it was clearly demonstrated that the residue 207 lining the active-site cavity indeed occupies a crucial position for the polyketide chain elongation reactions; it is located at the entrance of a novel buried pocket that extends into the "floor" of the active site cavity. The large-to-small M207G substitution widely opens the gate to the buried pocket, thus expanding a putative polyketide chain elongation tunnel, which lead to formation of the longer octaketides SEK4/SEK4b instead of the pentaketide.