Heads and tails

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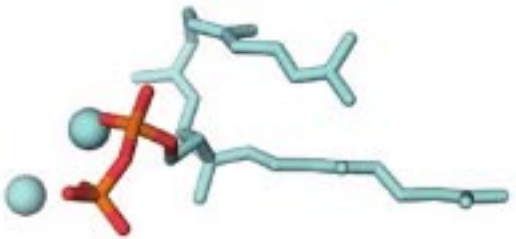

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The head-to-head condensation of two isoprenoids represents the first committed step in sterol and carotenoid biosynthesis. The dehydrosqualene synthase CrtM catalyzes both formation of the isoprenoid dimer, presqualene diphosphate (PSPP), and its subsequent ring-opening to dehydrosqualene. A previous structure of CrtM identified binding sites for two isoprenoid substrates, but the mechanism of the two-step process was unclear. Now, Lin *et al.* report a series of structures and biochemical results that shed light on the reaction. In particular, the comparison of a CrtM-PSPP cocrystal structure with previously reported structures, in combination with studies of inhibitors, identified the substrate in site S1 as the prenyl donor and that in S2 as the prenyl acceptor. This analysis also suggested a reaction mechanism in which one substrate is ionized to form a carbocation, which then dips down into the protein to form the cyclopropane ring. The second half-reaction—ring opening—was probed by a series of alanine mutations that indicated the newly formed PSPP must move back into a conserved Mg^{2+}-binding domain to complete the reaction. The authors also explored inhibitor binding, which suggested that docking to both S1 and S2 by a branched hydrophobic tail significantly enhances inhibitor affinity. The results provide new insights into terpene biosynthesis and set the stage for further development of prenyl synthase inhibitors as anti-infectives. *CG*