ENZYME'S DUAL NATURE REVEALED

ENZYMOLOGY: Structure shows taxadiene synthase contains domains from two enzyme classes

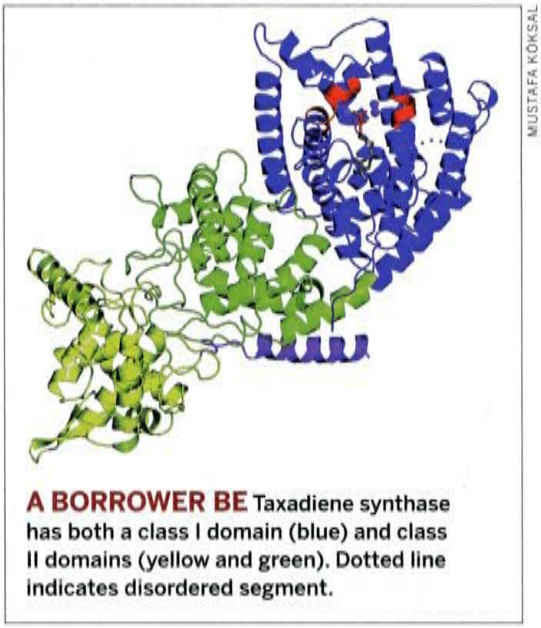
A CRYSTAL STRUCTURE of the enzyme taxadiene synthase confirms a theoretically predicted link between two enzyme classes in the evolution of some biomolecules that biosynthesize terpenes (*Nature*, DOI: 10.1038/nature09628). Terpenes are complex organic compounds that play key biological roles in a wide range of living organisms.

The structure—determined by postdoc Mustafa Köksal and chemistry professor David W. Christianson of the University of Pennsylvania, in collaboration with Robert M. Coates's group at the University of Illinois, Urbana-Champaign (UIUC), and Rodney B. Croteau at Washington State University, Pullman—could aid in the engineering of novel enzymes. Scientists could use such enzymes in drug discovery—for example, to produce designer biomolecules in microorganisms.

Taxadiene synthase catalyzes the first committed step in biosynthesis of the anticancer agent paclitaxel (Taxol). Terpenoid synthases, the family to which the agent belongs, come in two varieties: Class I terpenoid synthases catalyze couplings and cyclizations leading to carotenoids, steroids, and phytohormones by the metal-ion-dependent ionization of diphosphate groups, and class II terpenoid synthases catalyze cyclizations that lead to steroids and hopanoids by protonation of C=C bonds or epoxides.

Taxadiene synthase's structure shows that it borrows domains from both classes, although only its class I domain is catalytically active. "In a remarkable piece of bioinformatics-based work," Christianson says, UIUC chemistry professor Eric Oldfield and colleagues recently predicted that enzymes like taxadiene synthase would contain both class I and class II folds, and they now turn out to be right.

"This is a beautiful confirmation of Oldfield's prediction," says C. Dale Poulter, an isoprene biosynthesis expert at the University of Utah. "It looks like a fusion event put class I and class II enzymes together into a single enzyme so they could make structures more complex by combining the elements of both reactions. But the Christianson group can now see how this fusion is put together and why this particular enzyme uses a class I process—because the class II process has been disabled by crucial mutations."



MUSTAFA KÖKSAL

A BORROWER BE Taxadiene synthase has both a class I domain (blue) and class II domains (yellow and green). Dotted line indicates disordered segment.

Protein-evolution specialist Joseph P. Noel of the Salk Institute for Biological Studies, in La Jolla, Calif., says: "There have been rumors for many years that Christianson's group had crystals of taxadiene synthase, and the field has been waiting to see the structures. So it is quite nice and, indeed, a breakthrough for the field."

The structure "sets the foundation for structure-based protein engineering experiments," Christianson says. "We anticipate that we will be able to simplify terpenoid synthase structures to generate new biological catalysts that, for example, can be incorporated into engineered metabolic pathways in host organisms."—STU BORMAN