

Toward constructing a library of prenylated compounds by using prenyltransferases for aromatic substrates

Tomohisa Kuzuyama

(Biotechnology Research Center, The University of Tokyo)

Prenylation is a general term for the chemical or enzymatic addition of a hydrophobic isoprenoid side chain to an accepting molecule (another isoprenoid chemical, small aromatic molecule, protein, etc). Prenylation of aromatic natural products plays a critical role in the biosynthesis of chemically complex and structurally diverse molecules playing important biological functions across a wide phylogenetically diverse group of organisms, from bacteria to mammals (1). Hybrid natural products such as the anti-oxidant naphterpin that contain a polyketide core decorated with 5-carbon (dimethylallyl), 10-carbon (geranyl) or 15-carbon (farnesyl) isoprenoid chains possess biological activities distinct from their non-prenylated aromatic precursors. These hybrid natural products represent new anti-microbial, anti-oxidant, anti-inflammatory, anti-viral and anti-cancer compounds.

Enzymes capable of regiospecific prenylation of bioactive compounds will serve as novel chemoenzymatic tools for natural product diversification and the chemo-enzymatic development of therapeutically novel synthetic compounds. In the presentation, I describe the gene identification, biochemical characterization, and X-ray crystal structure with a novel a protein fold of a prenyltransferase NphB from *Streptomyces* sp. strain CL190, a naphterpin producer. This promiscuous prenyltransferase catalyzes the formation of a C-C bond between a geranyl group and an aromatic acceptor including flavonoids and plant polyketides such as olivetol and resveratrol. It also displays a novel C-O bond forming activity against naringenin, genistein and daidzein (2). Characterization of Sco7190, a NphB homolog from *S. coelicolor* A3(2), will be also presented.

(1) B. Botta *et al.*, *Curr. Med. Chem.* 2005, 12, 717

(2) T. Kuzuyama *et al.*, *Nature* 2005, 435, 983