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Combinatorial Biocatalysis of Bioactive Molecules: Another Challenge of Microbial Genomics for the Discovery of Bioactive Molecules

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Biocatalytic reactions have powerful advantages over synthetic chemical reactions, when they are applied to the modification and optimization of existing lead structures. The biocatalysis is applied to wide range of reactions such as high regioselective and stereoselective site-directed modification, one-step reactions that avoid the need for protection and deprotection steps, mild reaction conditions that are suitable for complex fragile molecules, and prochiral transformations to synthesize potent libraries without undesirable racemates. A variety of enzymes and microbial catalysts have been utilized to generate libraries through a wide range of biocatalytic reactions of lead compounds, including acylation, glycosylation, halogenation, oxidation, and reduction. Accordingly, combinatorial biocatalysis has been highlighted as a powerful tool, especially useful for creating focused libraries having the same pharmacophore of bioactive natural products or synthetic compounds.

Recent advances in microbial genomics, metagenome, and bioinformatics have enabled us to fish out useful genes of biocatalytic enzymes from microorganisms. Especially, the genetic information from the microorganisms that produce novel bioactive compounds or live at extreme conditions such as high or low temperature, high metal ions or solvents would be valuable sources for such biocatalytic enzymes. Based on this idea, we have isolated several biosynthetic enzymes for terpestacin, a new angiogenesis inhibitor from *Embellisia chlamydospore,* and new thermostable enzymes from *Thermus caldophilus* using homology based PCR cloning. Terpestacin is a unique bicycle sesterterpene having 5 isoprenoid and 3 hydroxyl groups in the ring structure, suggesting that the producing fungus has monooxygenase, oxidoreductase, and cyclase to synthesize the compound. From the sequence information of cDNA of the fungus, we successfully isolated several genes including 3 genes of biocatalytic enzymes described above. These genes will be utilized for biocatalytic modification of the ring structure compounds that are frequently found in bioactive compounds such as radicicol and rapamycin. We also expand this idea to isolate some thermostable enzymes since these have been known as good tools for biocatalysis because of their stability. Thermostable lipase, monooxygenase, and histone deacetylase (HDAC) have been isolated from Thermophilic bacteria. Interestingly, thermostable lipase L1 showed the activity to catalyze benzyl alcohol to benzyl octanoate by esterification of octanoic acid to benzyl alcohol. Moreover, newly cloned thermostable HDAC deacetylates the acetyl protected lysine at more mild conditions than those of chemical deprotection, providing a possible biocatalytic process of amino acid synthesis for lysine.

Together, our combined approach with microbial genomics, organic chemistry, biochemistry, molecular biology, and bioinformatics will help to develop potential drug candidates from biocatalytic modification of known lead compounds and useful biocatalytic processes that have advantage over conventional synthetic chemistry.