Differences in PLP-dependent cysteinyl processing lead to diverse S-functionalization of lincosamide antibiotics

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With the support of the National Natural Science Foundation of China and the Chinese Academy of Sciences, the research team led by Prof. Liu Wen (刘文) at the State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, uncovered the final biosynthetic pathway toward the distinct S-functionalization in lincosamide antibiotics lincomycin A and celesticetin, which was published in *Journal of the American Chemical Society* (2016, 138: 6348—6351).

Lincosamide antibiotics, characterized by an eight-carbon aminosugar central to an amino acid residue and a sulfur appendage, include the therapeutic anti-infective agent lincomycin A and its naturally occurring analogs celesticetin and Bu-2545. Last year, Liu's group uncovered an intriguing constructive role of two low-molecular-weight thiols, ergothioneine (EGT) and mycothiol (MSH), in the biosynthesis of lincomycin A (Zhao Q et al., *Nature*, 2015, 518:115). This work largely expands our knowledge regarding the intrinsic, versatile functions of thiols, which are apparently far beyond cell protection (Wang M et al., *Bioessays*, 2015, 37:1262).

After clarifying the sulfur origin of lincomycin A, they next focused on how the distinct S-functionalization is formed in lincosamides (in contrast to lincomycin, with its methylated sulfur atom, celesticetin bears salicylate attached to sulfur via a two-carbon linker). In this recent *JACS* paper, they reported that the PLP-dependent enzymes LmbF and CcbF, which are highly related in phylogenesis, process cysteine S-conjugated intermediates (compound **1** and **3**) in different ways and associate with individual downstream enzyme(s) toward distinct S-functionalization of the two lincosamide antibiotics. LmbF is responsible for β-elimination of **3** to generate the thiol **4**, which is subsequently S-methylated by LmbG to produce lincomycin with the methylmercapto group. However, CcbF catalyzes an unusual O_2-dependent reaction that involves decarboxylation-coupled oxidative deamination and converts **1** to aldehyde **2**, which further undergoes reduction by Ccb5 and *O*-methylation by Ccb4 to afford desalicetin with the two-carbon alcohol linker for appending salicylate (Figure). The two tailoring routes are variable and exchangeable to each other, allowing for *in vitro* combinatorial biosynthesis of a number of hybrid lincosamide antibiotics, including the natural product Bu-2545. These findings not only established two paradigms for distinct S-functionalization of the lincosamide antibiotics celesticetin and lincomycin A, but also demonstrated the wide diversity of PLP chemistry in enzymatic catalysis and its promising applicability in creation of new molecules.

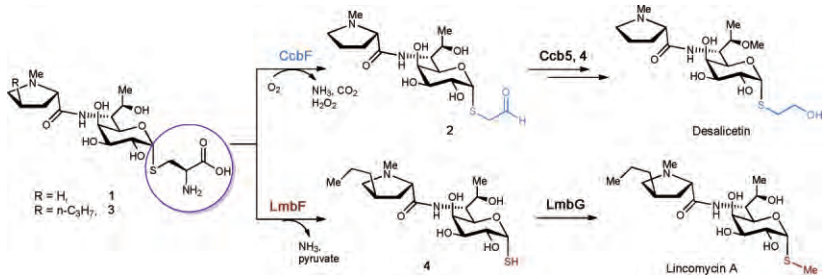

Figure The final biosynthetic pathways toward the distinct S-functionalization of the lincosamide antibiotics celesticetin and lincomycin A.