Convergent Evolution in the Biosynthesis of the Antibacterial Agent Fosfomycin

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The epoxide-containing phosphonate natural product fosfomycin is beneficial for human health as a potent antibiotic in the treatment of urinary tract infections. Two distantly related bacterial genera, the plant pathogen Pseudomonas syringae among other pseudomonads and soil dwelling streptomycetes are known to produce fosfomycin from phosphoenolpyruvate. Evidence from their sequenced genomes suggests that the two biosynthetic gene clusters (BGCs) that encode the enzymes responsible for forming fosfomycin have evolved separately. The P. syringae BGC is composed of an almost entirely different set of genes with only three in common compared to the BGC in the streptomycetes. Both pathways share the first and last steps. The biosynthetic logic for fosfomycin production in streptomycetes has largely been determined, but the P. syringae pathway has yet to be fully elucidated. We demonstrate that the P. syringae pathway has a different penultimate step, which is catalyzed by a NADPH-dependent dehydrogenase (Psf3). The product of the Psf3 reaction functions as the substrate for the conserved epoxide-forming final step. We confirm that this involves the activity of a non-heme iron-dependent peroxidase (Psf4). Comparison of Psf4 activity to other non-heme iron-dependent phosphonate biosynthetic enzymes provides some clues as to why it can function as a peroxidase.