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Biosynthetic Gene Cluster for Lovastatin, an Antihypercholesterolemic Agent, in *Aspergillus terreus*

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Abstract

Polyketides, ubiquitous products of secondary metabolism in microorganisms, are made by a process resembling fatty acid biosynthesis that allows the suppression of reduction or dehydration reactions at specific biosynthetic steps, giving rise to a wide range of often medically useful products. Formation of highly reduced fungal polyketides like lovastatin (*syn.* mevinolin, monacolin K), a potent hydroxymethylglutaryl-coenzyme A reductase inhibitor and important serum cholesterol lowering drug, by type I polyketide synthases (PKSs) represents a unique challenge because, unlike bacterial modular PKSs, the postulated iterative nature of such fungal enzymes cannot easily account for the differential processing of biosynthetic intermediates. Cloning of the gene cluster for lovastatin production by *Aspergillus terreus* followed by sequence and mutational analysis has revealed that it contains two type I PKS genes responsible, in part, for the biosynthesis of the 19 carbon polyketide backbone and 2-methylbutyryl side chain. Synthesis of the main nonaketide-derived skeleton requires the previously known iterative LNKS, plus at least one additional protein that interacts with the LNKS enzyme and helps determine the complex reduction and cyclization pattern implicit in the formation of dihydromonacolin L, a lovastatin precursor. The apparently non-iterative LDKS enzyme specifies formation of 2-methylbutyrate and interacts closely with an additional transesterase responsible for assembling lovastatin from this polyketide and monacolin J, itself made from dihydromonacolin L.

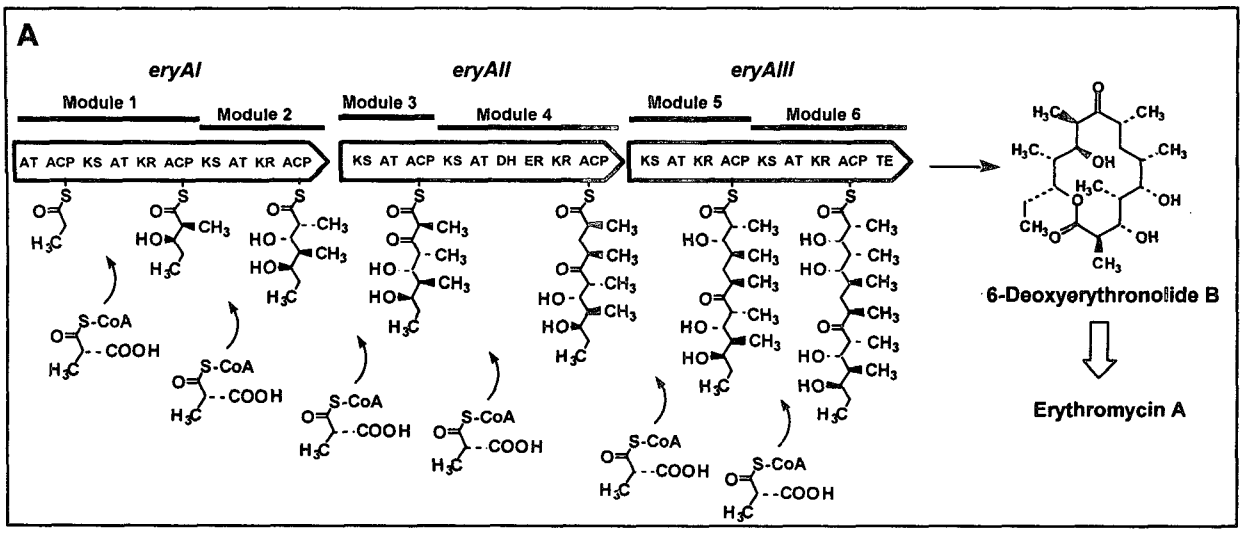

Figure 1. Erythromycin Biosynthesis

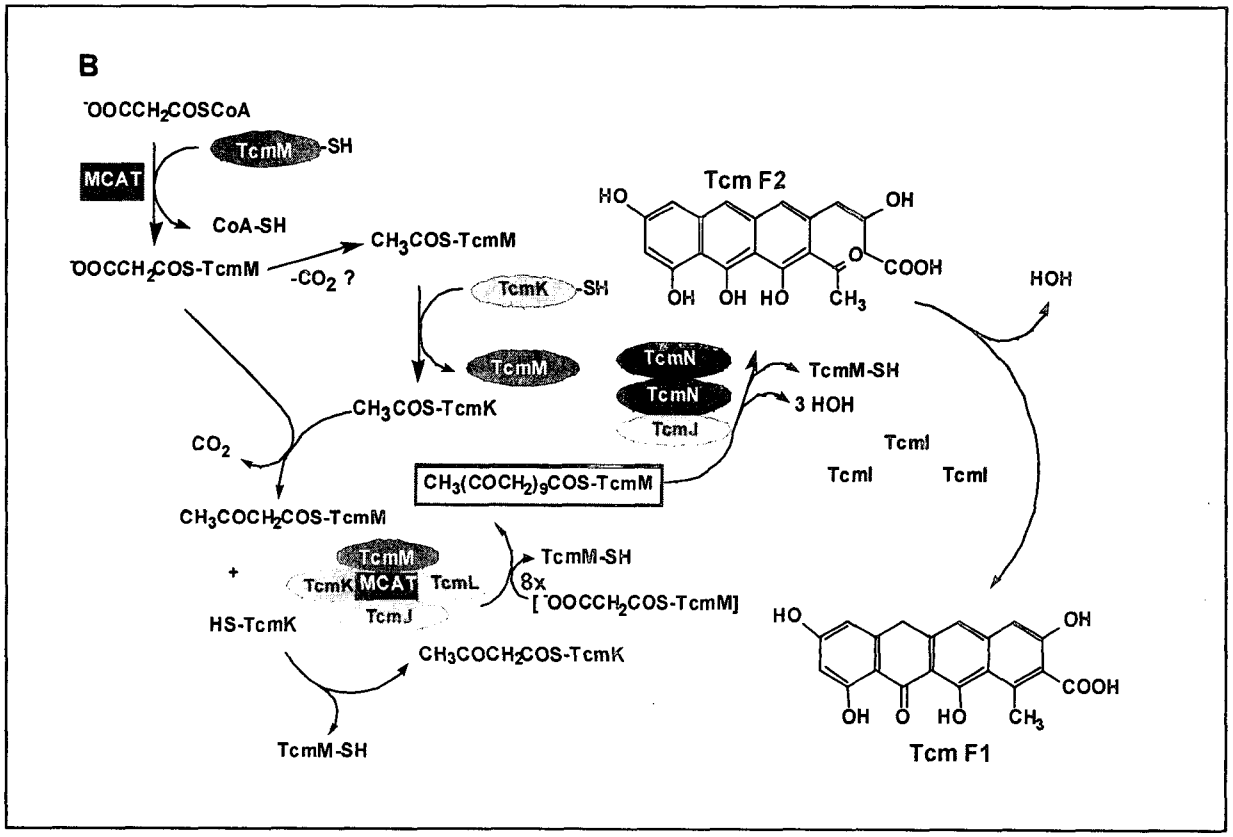

Figure 2. Tetracenomycin Biosynthesis

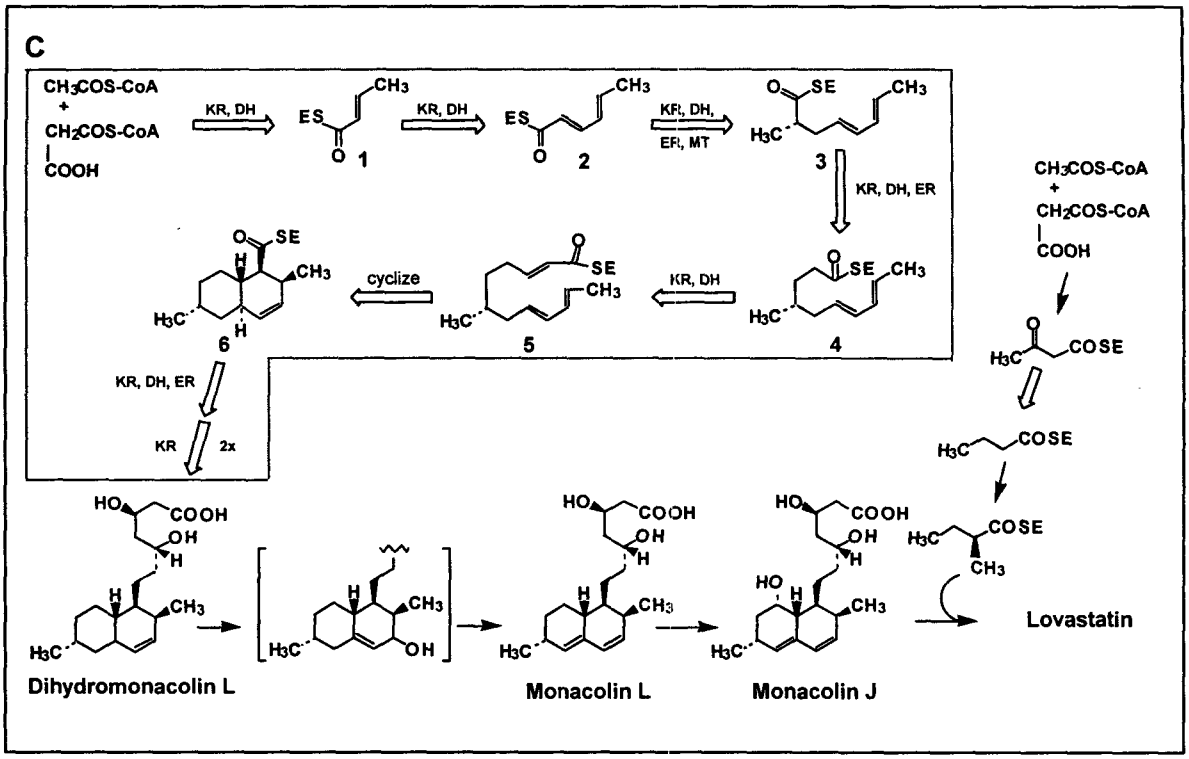

Figure 3. Lovastatin Biosynthesis