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Short Communication

Polyketide Synthases

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Introduction

Antibiotics are substances produced by microorganisms, which inhibit the growth of or kill other microorganisms at very low concentrations [1]. Amongst these substances, polyketides are a large class of secondary metabolites, in bacteria, fungi, plants, and a few animal lineages. They are used in medicine mainly as immunosuppressants, antibiotics and cholesterol-lowering, antitumour or anti-parasitic agents, and they are primarily derived from acetic acid, one of the simplest building blocks available in nature. Their biosynthesis shares with fatty acids, not only the chemical mechanisms involved in chain extension but also the pool of precursors used as acetyl coenzyme A and malonyl-CoA [2].

Macrolides are a group of drugs that belong to the polyketide class of natural products and whose activity results from the presence of a macrolide ring, a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose or desosamine, may be attached. The lactone rings are usually 14, 15, or 16-membered.

Macrolide antibiotics, produced by Streptomyces species, are used primarily against gram-positive bacteria. The use of macrolide antibiotics includes a range of challenges such as the increase in the resistance of gram-positive and gram negative strains, slow bactericidal action, associated gastrointestinal disturbances, allergic reactions, and hepatotoxic effects [3, 4]. Therefore, the number of novel 14-, 15-, and 16-membered macrolides has been increasing over the past few years [5]. The most commonly used macrolide antibiotics consist of a macrocyclic lactone ring containing 14, 15, or 16 atoms with sugars linked via glycosidic bonds [6].

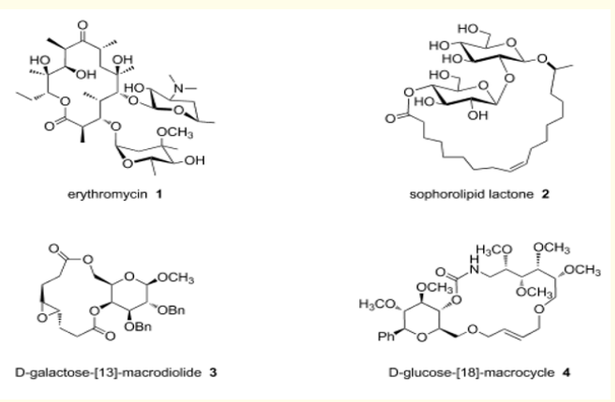

Figure 1: Some examples of macrolides.

Polyketide Biosynthesis

The biosynthesis of polyketides is modular at many levels and closely resembles fatty acid biosynthesis. First, the genes responsible for polyketide biosynthesis are typically clustered in the genome, forming a biosynthetic gene cluster (BGC). Each BGC encodes the Polyketide Synthases (PKS) responsible for the formation of the carbon backbone, together with the tailoring enzymes required for primary tailoring events, for example cyclization and dimerization of the β-keto-acyl carbon chain, subsequent tailoring events to form the final polyketide structure as well as genes encoding the regulation of the BGC and resistance to the end product if applicable, for example in the case of antibiotic end products. Once transcribed and translated, the PKS enzymes themselves are also modular in nature [7].

Diversification of polyketides can occur at four steps throughout biosynthesis resulting from: (1) the choice of building blocks and chain length, (2) the extent of reduction and stereochemistry of β-keto intermediates, primary cyclization, alkylation and branching, (3) rearrangements and secondary cyclization and (4) post polyketide tailoring: glycosylation, oxygenation, etc [7].

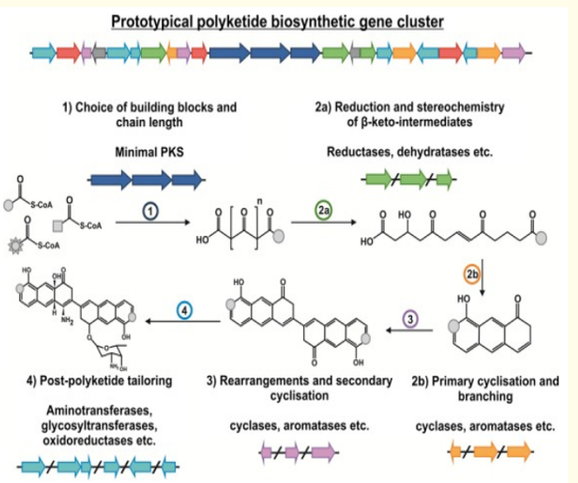

Figure 2: Polyketide biosynthetic gene cluster.

Tacrolimus is a 23-member lactone secondary metabolite belonging to the group of macrolide lactones, produced by Streptomyces tsukubaensis. The biosynthesis of tacrolimus is mediated by a hybrid polyketide synthase (PKS)–Non-ribosomal peptide

synthase (NRPS) system. The synthesis of this complex polyketide involves large polyfunctional PKS comprising multi-fatty acid synthase-like domains arranged in sets of modules. Each module normally consists of ketoacyl synthase (KS), acyltransferase (AT) and acyl carrier protein (ACP) for chain elongation, and it optionally contains dehydratase (DH), enoylreductase (ER) and ketoreductase (KR). Thus, the PKSs are responsible for the assembly of specific carboxylic acid-derived extender units into polyketide chains as well as the subsequent reductive reactions. In addition, NRPSs incorporate various amino acids derivatives (like pipecolate from lysine) or amino acid into non-ribosomal synthesised peptides [2].

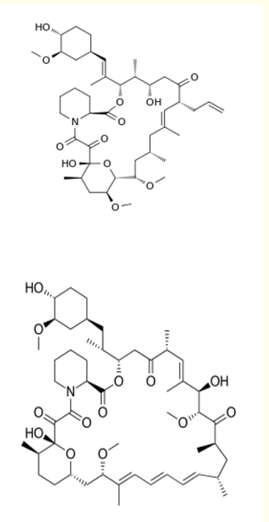

Figure 3: (a)Tacrolimus. (b)Sirolimus.

31 membered sirolimus and it's analogues are clinically important macrolide compounds produced by Streptomyces hygroscopicus. They exhibit antifungal, immunosuppressive, antitumor, neuroprotective and antiaging activities. The core macro lactone ring of sirolimus is biosynthesized by hybrid type I modular polyketide synthase (PKS)/Non-ribosomal peptide synthase systems primed with 4,5-dihydrocyclohex-1-ene-carboxylic acid. The linear polyketide chain is condensed with pipecolate (derived from lysine) by peptide synthetase, followed by cyclization to form the macrolide ring and modified by a series of post-PKS tailoring steps [8].

While both tacrolimus and sirolimus contain lysine derived pipecolate in their structures, presence of pure lysine as a precursor in the fermentation broth is not a prerequiste for the synthesis of both these macrolides, i.e., other complex nitrogen sources in the broth can provide this precursor in an optimal manner.

Presence of acyltransferase (AT)-less hybrid PKS–NRPS

Virginiamycin M (VM) of Streptomyces virginiae is a hybrid polyketide-peptide antibiotic with peptide antibiotic virginiamycin S (VS) as its synergistic counterpart. VM and VS belong to the Streptogramin family, which is characterized by strong synergistic antibacterial activity [9].

The starter unit of VM biosynthesis is isobutyryl-CoA, generated by the specific biosynthetic pathway comprised of two sequential enzymatic steps (a deamination step and decarboxylation step) on branched-chain amino acids. VS is a cyclic hexadepsipeptide containing a nonproteinogenic amino acid, Lphenylglycine (L-pheGly), in its core structure.

Sequence analysis of the VM biosynthetic gene cluster from S. virginiae has revealed that the region consists of 19 complete open reading frames (ORFs) and one C-terminally truncated ORF, encoding hybrid polyketide synthase (PKS)-nonribosomal peptide synthetase (NRPS), typical PKS, enzymes synthesizing precursors for VM, transporters for resistance, regulatory proteins, and auxiliary enzymes. The involvement of the cloned gene cluster in VM biosynthesis was confirmed by gene disruption of virA encoding a hybrid PKS–NRPS megasynthetase, which resulted in complete loss of VM production without any effect on VS production. To assemble the VM core structure, VirA, VirF, VirG, and VirH consisting, as a whole, of 24 domains in 8 PKS modules and 7 domains in 2 NRPS modules were predicted to act as an acyltransferase (AT)-less hybrid PKS–NRPS, whereas VirB, VirC, VirD, and VirE are likely to be essential for the incorporation of the methyl group into the VM framework by a HMG-CoA synthase-based reaction. [9]

Among several uncommon features of gene organization in the VM gene cluster, the lack of AT domain in every PKS module and the presence of a discrete AT encoded by virI are notable. The finding led the way to enhance VM production via over expression of the discrete AT [9].

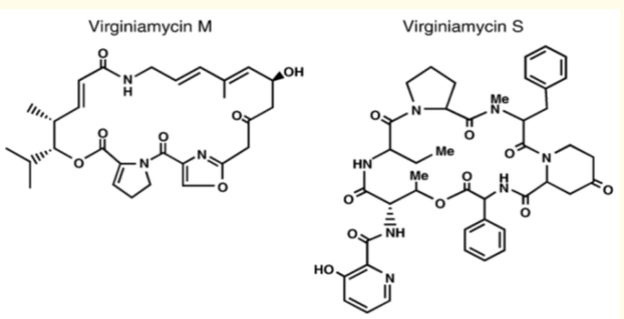

Figure 4: Chemical structure of virginiamycin M and virginiamycin S from S. virginiae.

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