Special issue on the molecular genetics of streptomyces

David Hopwood’s retirement in September 1998 was the catalyst for this special issue on Streptomyces, a genus of prokaryotes with a developmental life cycle and a propensity for producing clinically important antibiotics. Both these aspects of Streptomyces biology are well represented in 20 peer-reviewed papers that celebrate the molecular biological approach to unravelling the complexity of streptomycese morphogenesis, physiology and biochemistry. The molecular techniques applied in these studies have their origins in Streptomyces genetics, founded by David Hopwood and reviewed by him in the comprehensive opening article – a survey of 40 years that commenced with the meticulous analysis of crosses between S. coelicolor mutants to produce a detailed linkage map, and that will soon culminate in the complete genome sequence for this model species. Streptomyceses have a large genome (approx. 8 Mb) that is now known to be linear (1), and the latest model that rationalizes the circular map and linear chromosome is the subject of one of the reports presented here.

S. coelicolor also contains a large linear plasmid, SCP1 (350 kb), which carries genes for production of the antibiotic methyl- enomycin, but this remains the only authenticated case of plasmid-determined antibiotic biosynthesis. Of the antibiotics whose synthesis is encoded on the S. coelicolor chromosome, actinorhodin has been the most intensely studied, and that activity ultimately led to the marriage of genetic and chemical engineering to design and produce new polyketide antibiotics (2). Not surprisingly, a number of the reports published here focus on the polyketides, or have implications for their synthesis. These include the development of an innovative cloning system to produce modified rifamyccins, an exploration of the relationship between the biosynthesis of fatty acids and polyketide precursors, and identification of a gene involved in the regulation of both morphogenesis and polyketide synthesis in S. coelicolor. Even the report on regulation of branched-chain amino acid biosynthesis in S. coelicolor impacts on polyketide synthesis, as these amino acids are precursors of the acyl group substrates from which the antibiotics are produced.

Of course the spectrum of antibiotic structures synthesized by streptomyceses reaches far beyond the polyketides, and the regulation of their production is intimately associated with morphogenesis. One report extends the application of the reporter gene for green fluorescent protein to study spatial and temporal gene expression in S. coelicolor, and in another molecular biology joins forces with microscopy to analyse phenotypes of developmental mutants generated by the latest gene disruption techniques. Regulation of differentiation and secondary metabolism by a two-component protein signalling system (AbsA) is the subject of another paper. There is a long history of studies on low-molecular-mass effector molecules in streptomyceses, with more recent parallels in the homoserine lactones produced by unicellular bacteria and implicated as extracellular signals involved in quorum sensing. A-factor is the best known of the streptomycese ‘hormones’ that bind to receptor proteins to derepress sporation and initiate streptomycin biosynthesis in S. griseus. In contrast, factor C has been less well studied and is unusually both large and extracellular. It has been identified as a 324 aa protein, and the discovery of the structural gene in several streptomyceses in addition to S. griseus is reported. In another paper, a eukaryotic-type serine/threonine kinase is described which, via phosphorylation of regulatory proteins, regulates antibiotic synthesis in S. coelicolor but morphogenesis in S. griseus. Finally on this topic, there is the report of a promoter and related upstream sequences with a role in regulation of carbon-source-dependent differentiation in S. griseus, identified by an alternative approach to that based on the complementation of developmental mutants.

The large GC-rich genome of streptomyceses is notoriously unstable, exhibiting rearrangements characterized by deletion and amplification events. Investigation of this phenomenon led to the discovery of transposable elements and the addition of transposon mutagenesis to the battery of tools available to streptomycese molecular biologists. More on genetic instability in the archetypal Streptomycese cloning host, S. lividans, is presented in a paper that utilizes transposon mutagenesis to identify rearrangements at just one of the chromosomal ends. S. lividans is also the focus of a paper in which gene disruption by random transposon insertion led to the identification of a gene (sblA) for a putative phosphatase that appears to have a role in glucose

**GUIDELINES**

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repression. So often in *Streptomyces* molecular genetics, research that sets out with a specific objective in mind identifies new features that feed in to our generic understanding of gene regulation. A good example of that is represented here by the search for an extracellular lipase gene in *S. coelicolor*, which was not only successful but also identified a transcriptional activator (lipR) that proved to be a member of a new family of regulatory genes with representatives in other actinomycetes and beyond.

The lifestyle of streptomycetes in the terrestrial environment demands that they produce extracellular enzymes to generate utilizable carbon, and they are indeed good sources of polysaccharide hydrolases and proteases amongst others. It is appropriate therefore that the mechanisms of enzyme secretion are determined, and this is addressed in a paper which describes a unique clustered organization of signal peptidase genes that may be a reflection of the importance of extracellular enzyme activity in the competitive existence of streptomycetes. More information on the molecular biology of protein synthesis in streptomycetes is provided in a paper on the transcriptional analysis of genes for ribosomal proteins associated with guanosine phosphate exchange in *S. coelicolor* and *S. ramocissimus*.

It is tempting to identify rather obvious themes in *Streptomyces* biology in this special issue, and to categorize other reports as miscellany. In fact, links to these themes and microbiological research topics in general can readily be observed right across this collection of papers. The importance of antibiotic resistance genes in pathogenic bacteria and their origins in antibiotic producers is topical, but these genes in streptomycetes have often proved invaluable as entry points for the cloning of antibiotic biosynthesis clusters. There are many reasons therefore for studying antibiotic resistance in streptomycetes, and a detailed analysis of one of the genes encoding spiramycin resistance in *S. ambofaciens* identifies the site of rRNA methylation and demonstrates that the methyltransferase is dispensable. Progress in our understanding of nitrogen metabolism in streptomycetes has lagged behind that in *Escherichia coli*, but one of the studies reported in this issue helps to redress this by cloning a number of the genes involved in regulation of glutamine synthetase and proceeding, via gene disruption, to produce specific *S. coelicolor* mutants. Away from *S. coelicolor* and returning again to the metabolic capacity required by actinomycetes in their natural environment, there is a report on a gene cluster that encodes vanillic acid decarboxylation, an activity involved in the exploitation of lignin-derived carbon sources and one that has commercial applications, if not here then in related catabolic systems that could be identified by gene probing. Finally, homage is paid to the rapidly expanding field of stress responses in micro-organisms, in a paper which identifies a repressor of the heat-shock protein gene *hsp18* in *S. albus*.

We hope you find this special issue on the molecular genetics of streptomycetes as stimulating to read as it was to assemble and review.

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