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Genome of antibiotic-producing *Streptomyces*revealed

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Summary

The complete genome sequence of the antibiotic-producing bacterium *Streptomyces coelicolor* should aid the genetic engineering of new anti-bacterial compounds

Significance and context

The actinomycete genus *Streptomyces* is composed of soil bacteria related to the human pathogens *Mycobacterium tuberculosis* (the cause of tuberculosis) and *Corynebacterium diphtheriae* (the cause of diphtheria). But streptomycetes are harmless, and even of great benefit to humans. They produce over two-thirds of the naturally derived antibiotics in current use, as well as anti-tumor agents and immunosuppressants. These compounds are produced within a program of physiological and morphological differentiation unique in the bacterial world. Because of the broad range of metabolic processes and biotransformations they carry out, streptomycetes are also of outstanding ecological importance, particularly in carbon recycling.

The streptomycete chromosome is very large for a bacterium (about 8 mega base pairs, Mbp), with an extremely high G+C content (72-73%) and a large number of genes. It is also one of the very rare examples of a linear bacterial chromosome (although circular forms exist, which can also replicate). It ends in inverted repeats carrying covalently bound proteins involved in the termination of replication. A large (1 Mbp) subtelomeric region is dispensable under laboratory conditions. The genome sequence of the model streptomycete *Streptomyces coelicolor* has now been completed in a collaborative project involving the Wellcome Trust Sanger Institute (Hinxton, UK), the John Innes Institute (Norwich, UK) and the Institute of Genetics of the National Yang-Ming University (Taipei, Taiwan). The project was headed by the pioneer of *Streptomyces* genetics and molecular biology, David Hopwood.

Key results

Outstanding features of the *S. coelicolor* chromosome were confirmed by complete sequencing of a set of ordered cosmids: its large size (at 8,666 kilobases the largest completely sequenced bacterial genome to date), high G+C content (72.12%) and the highest number of genes so far found for a bacterium (7,825). The replication origin is located roughly in the middle of the linear chromosome. Coding density is largely uniform across the chromosome, even in the dispensable subtelomeric regions.

Essential genes for cell division, replication, transcription or amino-acid biosynthesis, for example, are located in a central non-dispensable core region comprising about half the chromosome. Genes coding for functions that are not essential under laboratory conditions, such as secondary metabolites and hydrolytic enzymes, are on the chromosome arms. The core region of the *S. coelicolor* chromosome, but not its arms, shows syntenies with the genomes of *M. tuberculosis* and *C. diphtheriae*. Fourteen regions possibly acquired by horizontal transfer were identified, one of them containing as many as 148 genes.

S. coelicolor has not only more genes (7,825) than other bacteria such as *Escherichia coli* (4,289) and *Bacillus subtilis* (4,099) but also than the eukaryote yeast *Saccharomyces cerevisiae* (6,203). This is due to both horizontal acquisition and internal gene duplication. As many as 12.5% of *S. coelicolor* proteins are predicted to have regulatory functions, for example sigma factors affecting the specificity of RNA polymerase. Two-component regulatory systems translating external stimuli into transcriptional regulation are also well represented, together with other families of transcriptional regulators. The numerous transport proteins and secreted hydrolases reflect the bacterium's interactions with the complex soil environment and the ability to exploit its nutrients. Several duplicated genes encode isoenzymes that are active at different stages of the complex developmental cycle. As many as 21 gene clusters encode enzymes of secondary metabolism, for example, the production of antibiotics. Some clusters seem to be involved in the resistance to physical, chemical and biological stresses. The genome will also provide insights into chromosome replication and partitioning and cell division during the complex morphological cycle of *Streptomyces*.

Links

The%20Sanger%20Institute:%20*Streptomyces%20coelicolor* genome project homepage provides free access to chromosome and clone sequences with annotation and includes a BLAST server. The ScoDB homepage of the *S. coelicolor* genome sequence project gives access to the ScoDB II database, which holds the genome sequence and related material.

Reporter's comments

As expected, the extraordinary bacterial genus *Streptomyces* has an extraordinary chromosome. Genome analysis uncovered numbers of genes and a genetic complexity without precedent in prokaryotes. Streptomycetes are running their own arms race against biotope variations and bacterial competitors. The strategy is to keep essential genes that are not allowed to evolve too drastically within a central chromosomal core region, and to place genes involved in secondary metabolism in a peripheral region more prone to DNA rearrangements and genetic transfer. This might generate new gene combinations and gene regulations better adapted to the physical, chemical and biological challenges streptomycetes meet during their evolution. The genome sequence of *S. coelicolor* will be a milestone in the genetic engineering of new compounds with therapeutic activity. Nevertheless, the diversity of antibiotics and other secondary metabolites produced by streptomycetes indicate that different sets of genes involved in secondary metabolism are probably present in other species, as suggested by

comparisons with the *Streptomyces avermitilis* genome. More chromosomes are needed for us to exploit the formidable evolutionary machinery of streptomycetes in our own arms race against antibiotic resistance in pathogens.

Table of links

Nature

The%20Sanger%20Institute:%20*Streptomyces%20coelicolor*

ScoDB

References

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