

Evidence for a High Heterogeneity Between the Terminal Regions of the Chromosomes of Two Phylogenetically Close Species, *Streptomyces ambofaciens* and *Streptomyces coelicolor* by Genome Comparison.

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The chromosomal DNA of *Streptomyces ambofaciens* is a 8 Mb linear molecule that ends with large Terminal Inverted Repeats (TIRs) of about 200 kb. The size and the sequence of the TIRs are extremely variable between the different linear replicons of *Streptomyces* (e.g., 21,6 kb in *Streptomyces coelicolor* A3(2), Bentley et al., 2002; 174 bp in *Streptomyces avermitilis*, Omura et al., 2001). Previous works have shown that the terminal regions of the *S. ambofaciens* chromosome are strongly implied in genomic instability. Indeed, large rearrangements can frequently occur in those regions (Leblond et Decaris, 1999). Despite a close phylogenetic relationship between *S. ambofaciens* and the already sequenced species *S. coelicolor* (Bentley et al., 2002), we found out that the terminal regions appear highly variable compared to the central region. A similar situation has been recently described by comparing *S. avermitilis* and *S. coelicolor* A3(2) (Ikeda et al., 2003). However, those two species are phylogenetically distant whereas *S. ambofaciens* is extremely close to *S. coelicolor*. Therefore, comparative genomics between *S. ambofaciens* and *S. coelicolor* will increase our understanding of *Streptomyces* genome evolution.

In the prospect of studying variability and comparative genomics, we have been undertaking the sequence analysis of the terminal regions (about 2.5 Mb) of the *S. ambofaciens* linear chromosome, sequencing being done using a set of ordered cosmids and a BAC library. A PCR approach was also used to sequence the last kilobases at the extremities that were not cloned into the libraries.

The sequence of the TIRs of *S. ambofaciens* ATCC23877 is now nearly completed and the analysis has confirmed that the subtelomeric regions are highly variable compared to *S. coelicolor* for the gene organization and the encoded functions. In the 200 kb already available, we have identified 187 potential genes. About 24% of them are completely absent in the *S. coelicolor* genome and moreover, the other 76% show similarities with genes scattered all along the chromosome of *S. coelicolor*. These results reveal a low level of conservation of gene organization in the terminal regions. Preliminary results suggested a higher conservation of the central region. A library of 8457 sequences of the whole BAC ends, covering approximately 3.5 Mb of chromosomal DNA, has been analysed in order to confirm the conservation of the central chromosomal region. This library was used to carry out a statistical analysis about the conservation and the distribution of DNA homologies in the different regions of the chromosome.

The complete genome sequence of *S. avermitilis* has recently been published and the comparative genomics with this less close species will be presented. Moreover, approximately 1000 kb are now sequenced apart from the TIRs and preliminary analyses revealed the presence of several gene clusters involved in secondary metabolite biosynthesis.

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