Exploring *Streptomyces ambofaciens* secondary metabolism

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The growing prevalence of pathogenic bacteria resistant to multiple antibiotics is increasingly considered as a serious threat to public health[1]. Yet, the rate of new antibiotics (especially new classes of antibiotics) introduced into the market has sharply declined during the last thirty years[2]. This is due, in part, to a marked decline of antibacterial research and development by major pharmaceutical companies. However, as the majority of antibiotics derive from natural products (about 80%)[3], it is also often considered that finding new natural products antibiotics is getting more difficult as the most abundant antibacterial molecules, both in terms of quantity produced by a microorganism and of distribution amongst producers, have already been discovered. One of the strategies for the discovery of new antimicrobial molecules is the genome exploration of species well known for their capacity to produce antibiotics, such as *Streptomyces* species. Indeed, two thirds of the marketed antibiotics are, or derive from, molecules produced by *Streptomyces*. Moreover, genome sequencing of *Streptomyces* species known to produce two to five natural products has revealed an untapped reservoir of potentially bioactive molecules, with up to thirty gene clusters likely directing natural product biosynthesis[4,5].

Streptomyces ambofaciens has been known for the last fifty years to produce two antibiotics: spiramycin, a macrolide antibiotic used in human medicine and congocidine, a pyrrolamide antibiotic. Spiramycin biosynthetic gene cluster has already been characterized in our laboratory[6]. Together with the laboratory of P. Leblond (Nancy, France), we have undertaken the exploration of *S. ambofaciens* secondary metabolism, based on approaches combining genome mining and decryptification of silent gene clusters. Genome sequence analysis has already revealed about 25 gene clusters putatively directing the biosynthesis of secondary metabolites. Among them, one was shown by our collaborators to direct the biosynthesis of kinamycin, an antibiotic whose production by *S. ambofaciens* was not previously known[7]. Moreover, we have identified and characterized the gene cluster directing the biosynthesis of congocidine[8]. Finally, using a strain in which known antibiotics production has been abolished, we were able to new antibacterial activities by modifying growth conditions. Thus it appears that *S. ambofaciens* is able to produce, in addition to spiramycin and congocidine, at least four other molecules with antibacterial activity.

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