

A system biology approach revealed the nature and the cause of the different metabolic features of weak and strong antibiotic producers of the *Streptomyces* genus.

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ABSTRACT

Introduction: Streptomycetes are efficient producers of chemically diverse bio-active molecules useful to human health including life-saving antibiotics. The biosynthesis of these so called “secondary metabolites” usually occurs in the period of slow or no growth. It is thought to be triggered by nutritional limitations, especially in phosphate, that are correlating with energy shortage. Despite numerous important scientific contributions over the past 40 years, a systemic understanding of the regulation of the biosynthesis and of the function of these bio-active metabolites for the producing bacteria remain incomplete.

Methods: The model strains, *Streptomyces lividans* and *Streptomyces coelicolor*, are extensively studied in the field to address these questions. These closely related species possess identical biosynthetic pathways directing the synthesis of three well characterized secondary metabolites (CDA, RED and ACT) but only *S. coelicolor* expresses them at a high level. A comparative analysis of the proteomes of these strains, grown on phosphate limited R2YE medium, with glucose as main carbon source, was carried out in order to establish the **specific metabolic features linked to weak and strong antibiotic production and revealed a possible direct cause of such differences.**

Results: This study revealed the nature and cause of the distinct metabolic features underpinning the different “biosynthetic abilities” of these strains. It also indicated that the produced antibiotics play a role in the regulation of the energetic metabolism of the producing bacteria in conditions where phosphate is scarce.

Conclusions: A better understanding of the regulation of antibiotic biosynthesis and of the role of the antibiotics in the physiology of their producers is important to conceive clever strategies to access the great metabolic diversity encoded in the numerous silent biosynthetic pathways present in the *Streptomyces* genomes. Indeed, the discovery of novel antibiotics has now become an urgent need to combat the spreading of pathogenic bacteria resistant to most antibiotics in current use.

Keywords: Antibiotics, Streptomyces, glycolytic metabolism, oxidative metabolism, respiration, oxidative stress, triacylglycerol