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IDENTIFICATION OF A NOVEL PHOSPHONATE BIOSYNTHETIC GENE CLUSTER IN STREPTOMYCES BY EVOLUTIONARY-DRIVEN GENOME MINING STRATEGY

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Evolution, Metabolism, Phylogenomics

Introduction.

"Functional redundancy" has a primordial role in the arising of new enzymatic functions (1). However, the evolutionary implications of the presence of more than one gene encoding for enzymes capable of performing the same chemical conversions, has been largely neglected in *Streptomyces,* the bacterial genus that produces most of the antibiotics that we use. We defined this apparent functional redundancy as Enzymatic Expansions (EE), which were analyzed trough comparative genomics.

We assume that the *Streptomyces* genome should encode for traits involved on the production of their overwhelming metabolic diversity, and thus, the evolutionary history of the enzymes involved on the biosynthesis of natural products should be tractable.

Methods.

With the release of several genome sequences from *Streptomyces* species, it was possible to perform a comprehensive survey of the distinctive metabolic features of this genus. A particular emphasis was put on enzymes taking part on precursor supply central pathways (PSCP). They were hypothesized to be recruited by natural product biosynthetic pathways to perform new functions. A novel bioinformatic pipeline was developed after such premises, and it was used to identify EEs and recruitment events.

Results.

Our analysis suggests that the chemical repertoire (enzyme superfamilies) in natural product biosynthesis is limited and the metabolic diversity is due to the combination of the functions instead of the evolution of novel chemistry. Our analysis also implicates a particular group of central metabolic enzymes with the radiation of the *Streptomyces* genus (type I), while another group of EEs seems to be related to the diversification of natural product biosynthesis (type II).

Using this evolution-driven approach a phosphonate compound biosynthetic gene cluster (2) was identified on a low quality region of a S*treptomyces* genome draft. The gaps in this region were closed by PCR and the cluster was analyzed. The analysis of the sequence suggests that this gene cluster encodes the biosynthetic pathway of a novel class of phosphonate compound (C-P compound).

The hypothesis derived from this analysis are currently explored experimentally by PCR targeted mutagenesis and phenotypical characterization.

Conclusions.

As genome sequences are becoming more abundant, better genome mining tools are needed to identify the novel natural products (i. e. antibiotics) that we will need in the future. We demonstrated that by using an evolution-driven approach we can identify such novel compounds.

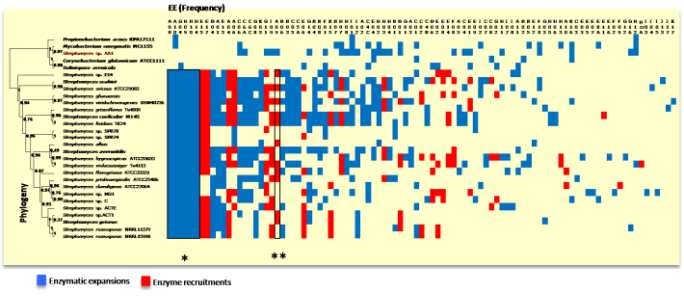

Figure 1. Enzymatic expansion and recruitment survey in *Streptomyces.*

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Bibliografía.

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