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Omics and multi-omics approaches to study the biosynthesis of secondary metabolites in microorganisms

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Natural products produced by microorganisms represent the main source of bioactive molecules. The development of high-throughput (omics) techniques have importantly contributed to the renaissance of new antibiotic discovery increasing our understanding of complex mechanisms controlling the expression of biosynthetic gene clusters (BGCs) encoding secondary metabolites. In this context this review highlights recent progress in the use and integration of 'omics' approaches with focuses on genomics, transcriptomics, proteomics metabolomics meta-omics and combined omics as powerful strategy to discover new antibiotics.

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Introduction

Bacteria, and in particular actinomycetes (Phylum: Actinobacteria), represent one of the most prolific source of bioactive natural products with a wide range of biological activities. Many well-known bioactive molecules, widely used in medicine for treatment of infection diseases, such as tetracyclines, β-lactams, aminoglycosides, macrolides, and glycopeptides have been isolated from the most dominant actinomycetes genus, *Streptomyces*, as products of the secondary metabolism [1].

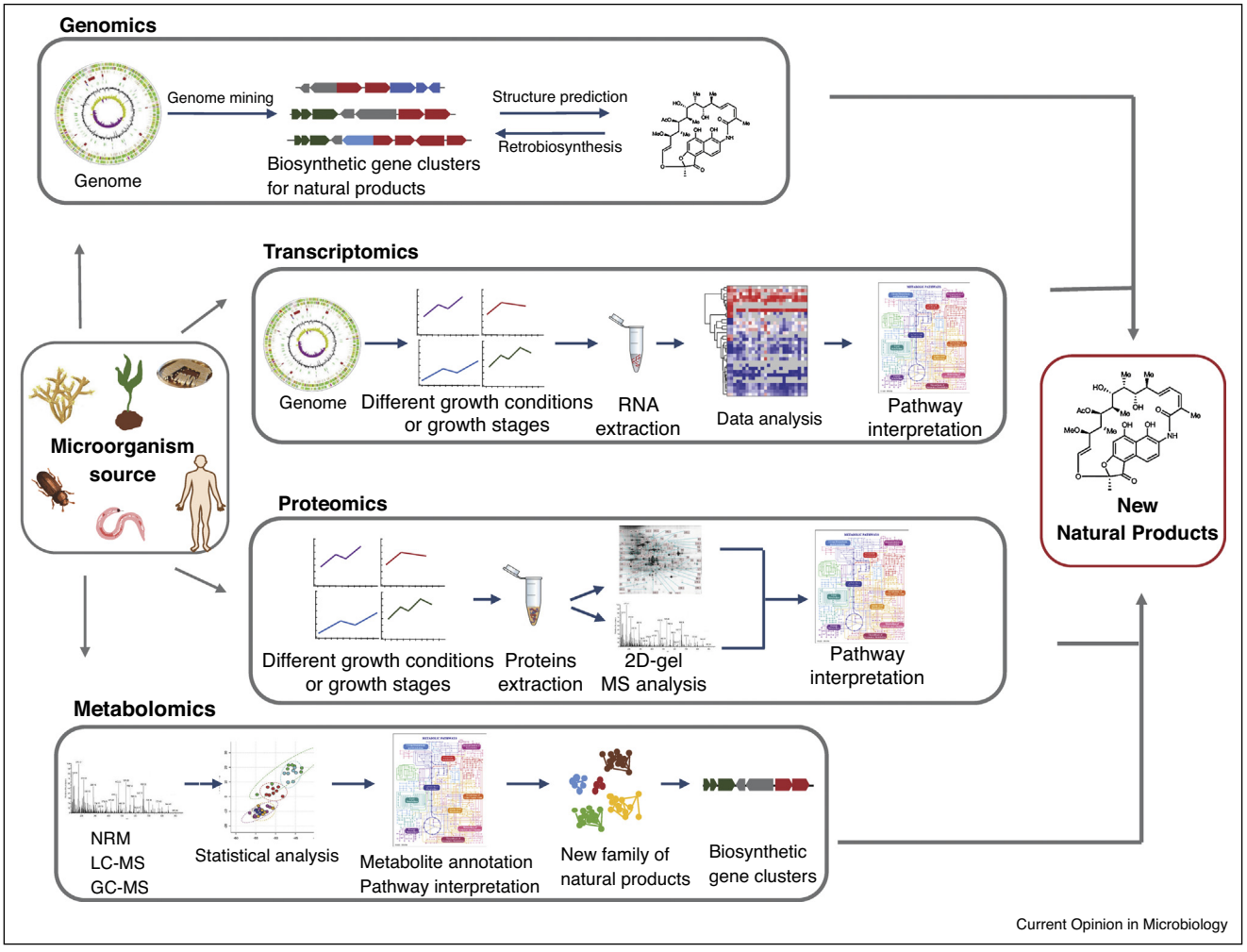
With the advent of next-generation sequencing (NGS) technologies and the possibility to routinely obtain good-quality whole genome sequences, actinomycetes revealed their potential metabolic landscape and thus the far greater potential to produce specialized metabolites than has been discovered by classic screening-based methods in the previous 50 years. In fact, the genome sequences revealed that a typical actinomycete contains on average about 30 secondary metabolite gene clusters and thus theoretically has the genetic potential to produce approximately a 10-times higher number of secondary metabolites than have been detected during screening and chemical analytics [2,3]. These observations strongly contributed to renew the interest for natural product discovery and these prolific microorganisms in the recent years. In addition, the development of high-throughput (omics) techniques, genomics, transcriptomics, proteomics, metabolomics and computational resources have importantly increased our understanding of complex cellular physiology and key pathways affecting secondary metabolites production.

In this context, this review highlights recent progress in the use and integration of 'omics' approaches with focuses on genomics, transcriptomics, proteomics, metabolomics, meta-omics (metagenomics, metatranscriptomics and metaproteomics) and combined omics as powerful strategy to discover new antibiotics in actinomycetes and other microorganisms (Figure 1).

Genomics

The massive development of sequencing technologies over the past decade coupled with efficient bioinformatics tools showed the untapped metabolic potential of actinomycetes triggering a revolution in the drug discovery research. In fact, genomic analyses revealed that silent gene clusters are present even within the genomes of extensively studied species like the model streptomycetes *S. coelicolor* A3(2) or *S. avermitilis* [2,4]. Genome mining has been established as powerful tool to estimate the genetic potential of a strain by scanning the genome of interest and identifying secondary metabolite BGCs [5]. In particular, the antibiotics and Secondary Metabolites Analysis SHell (anti-SMASH) [6••,7] and the connected antiSMASH database [8], Prediction Informatics for Secondary Metabolomes (PRISM) [9,10], Global Alignment for natuRaL-products chemInformatiCs (GARLIC), Generalized Retrobiosynthetic Assembly Prediction Engine (GRAPE) platform [11••] and IMG/ABC [12•] the most well established tools, have been improved with more features to predict and assign functions to enzymes involved in the biosynthesis of secondary metabolites and facilitate the connection of biosynthetic gene clusters to their corresponding natural products [13].

Figure 1



Schematic representation of omics workflow for natural products discovery. The workflow depicted includes the experimental procedures used within genomics, transcriptomics, proteomics and metabolomics approaches.

The availability of these user-friendly genome mining tools has led to the discovery of many novel natural products. Some selected examples published within the last two years are outlined below.

One noteworthy example of new natural product accessed by genomic approach is hexaricins, a new family of polyketides which gene clusters were predicted in the rare marine actinomycete *Streptosporangium* sp. CGMCC 4.7309 [14]. Genome mining analysis was used to explore secondary metabolite diversity of this rare actinomycete revealing 20 cryptic secondary metabolite biosynthetic clusters and among those the unusual type II PKS BGC.

Another example is the identification of the BGC encoding lobosamides A–C in the marine actinobacterium *Micromonospora* sp. These macrolactams, which cluster organization is conserved, displayed growth inhibitory activity against *Trypanosoma brucei* the causative agent of human African trypanosomiasis [15].

In 2017, a study on actinobacteria genome mining lead to discovery of 49 potential producers of Leinamycin-type natural products, a potent antitumor drug [16]. After the first isolation from *Streptomyces atroolivaceus* S-140 in 1989, yet no analogues have been isolated. By mining bacterial genomes novel anticancer drugs producers were identified.

Genome mining and comparative genomic analysis have opened up the prospect of prioritizing gifted strains for metabolic engineering. In *Streptomyces lydicus* 103, producer strain of streptolydigin, the genomics-based bottom up approach have unveiled a biosynthetic potential undetected in standard fermentation condition [17]. The complete genome sequencing and comparative analysis