Mini Review
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Natural products remain an important source for drug development in the post–genomic era

Abstract

Natural products or their related derivatives were the most important source of officially–approved drugs owning to the huge chemical structure diversities and their biodiversities. Compared with traditional combinatorial chemistries and high–throughput screening methods, genomics–driven natural product discovery is a rational and an efficient alternative for the discovery of novel structures. In this mini review, process of genomics–driven natural product discovery is highlighted including the main steps, the relevant technologies and bioinformatics tools.

Keywords: natural product, drug discovery, genomics–driven

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Abbreviations: BGCs, biosynthetic gene clusters; antiSMASH, antibiotics and secondary metabolite analysis shell; iChip, isolation chip; PK(S), polyketide (synthase); NRP(S), nonribosomal peptide (synthase)

Introduction

Drug discovery, the first critical step to identify rational lead candidates in the novel drug development, has always been a challenging, time–consuming and laborious scientific task requiring expertise and experience. Historically, natural products or their related derivatives were the main source of officially–approved drugs, with more than 50% of clinical drugs approved between 1981and 2014 were derived from natural products.[1] Even in recent days, natural products have still continued to enter clinical trials or to be approved to market, including Trabectedin (ET–743),[2] Halaven (eribulin mesylate),[3,4] Bryostatin[5] and so on. It is believed that the huge chemical structure diversity and the biodiversity of natural products make the greatest contributions to the success of natural products. However, combinatorial chemistries and high–throughput screening in drug discovery over the past decades have darkened the honorable outlook of natural products to some extent,[6] which lead to the growing studies on the novel drug discovery methods in the post–genomic era.

Drug discovery in the post–genomic era

With the growing development of DNA sequencing and synthetic biology technologies (e.g. proteomics, metabolomics, bioinformatics), great interest has been renewed in natural product discovery.[7] It has been already accepted that natural products are synthesized by specific metabolic pathways encoded by biosynthetic gene clusters (BGCs), based on which virtually all natural products could be identified by DNA sequencing and metagenomic analysis theoretically. In this view, the chemical space could be far more covered and much more novel chemical structures might be discovered such as those encoded by silent biosynthetic gene clusters and uncultured microorganisms.

Genomics–driven natural product discovery usually includes three main steps:

a. Identification of BGCs. Antibiotics from microbes or plants are directly linked to BGCs coding for proteins associated with biosynthesis, resistance, regulation and transport. So how to prioritize and characterize orphan BGCs is the first crucial procedure from the growing genome sequences.[8,9] Genome mining[10,11] is a novel technology developed for the identification and characterization of orphan BGCs, which is designed to analyze the sequenced genome of specific organisms to identify and determine whether the gene clusters involved in the production of new antibiotics. Several bioinformatics approaches have been proposed to satisfy this purpose, such as HMMER, GOLD, NORINE, SBSPKS, SEARCHPKS, NRPSpedictor$_2$, plantiSMASH and so on, among which AntiSMASH (antibiotics and secondary metabolite analysis shell)[12] might be the most widely tools used. It is a comprehensive bioinformatic tool for automated genome mining including the annotation of entire gene clusters.

b. Activation of silent gene clusters. Natural products are usually synthesized through secondary metabolism, which is tightly regulated and considerable BGCs remain silent under laboratory growth conditions. Owning to this, activating these BGCs will make it possible to obtain the potential encoded natural products. Usually, strategies to activate the silent BGCs including physicochemical methods and genomics–driven approaches. It was shown that if the producing host was grown under alternative physicochemical conditions compared with the standard laboratory growth conditions, it will possess the ability to express the originally silent gene clusters.[13–15] Co–cultivation of microorganisms and the application of iChip (isolation chip) have also been proved to be successful in activating the silent gene cluster.[16] Genomics–driven approaches[17] including mainly genome editing and genome engineering technologies by means of genetic manipulation of the target genome is believed to the most efficient but challenging and time–consuming methods to activate the silent or weakly–expressed gene clusters. Researchers have proposed and verified different strategies in this field, such as heterologous expression of BGCs in heterologous hosts functionally,[18] manipulation of global and pathway–specific transcriptional regulators(and/or RNA polymerase or ribosomal proteins),[19] perturbation of epigenetic control(DNA/histone methylation and acetylation).[20]

c. Combinatorial biosynthesis of natural products. With the advance in synthetic biology and genome engineering technologies, it becomes rational and possible to obtain produce key precursors and the core scaffolds exploiting rational engineering of biosynthetic pathways.[21–24] On this basis, increasing attention have been paid to modular PKS/NRPS megaenzymes[25,26] for rational production of complex PK/NRP scaffolds. It was reported firstly by Christian Hertweck et al.[26] that the reprogrammed modular (type I) aur polyketide synthase was successful in generating luteoreticulin through rational genetic recombination and domain exchanges. Combinatorial biosynthesis of target products is a relatively much more sophisticated process including many successive procedures. In brief, it contains 6 main steps:[24] sequencing and bioinformatic analysis, selection of heterologous expression hosts, DNA assembly, refactoring pathways, improved selection of mutants and genome editing.

Conclusion

Natural products (or the semisynthetic/ synthetic derivatives) were widely used in medicine for the past decades. In the genomics era, with the growing development of genomics and metagenomics, natural products has regained the spotlight for drug discovery due to their huge chemical structure diversity and their biodiversity. I believe that more novel bioactive chemical entities will be identified through genomics– driven natural product discovery, and drug development pipelines promise to be revitalized by this method in the long run.

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Conflict of interest

The author declares that there is no conflict of interest.

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