

Microbial Natural Products: A Promising Source for Drug Discovery

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Traditionally, microbial natural products (NPs) have been identified as one of the most important source as well as the inspiration for drug discovery. Over the time from 1940s to 2014s, NPs and their derivatives represent a substantial market share in pharmaceutical industries, many of which have already been developed or widely used as frontline treatments for human health, especially for therapies of infectious diseases, cancer, diabetes, etc. [1]. However, it's worth noting that antibiotic resistances in bacteria spread quickly in global. Such a serious situation causes a public health concern, and emphasizes the immediate need to discover new drug candidates with novel action mechanisms.

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Since the discovery of penicillin by Alexander Fleming and streptomycin by Selman Waksman, NPs discovery was initiated through traditional NPs isolation methods and then entered into "the Golden age". Later on, the intriguing NPs structural diversity fascinated synthetic chemists for total chemical synthesis, and attracted biochemists and molecular biologists to explore the enzymology and biosynthesis. For insistence, polyketides (PKs) and non-ribosomal peptides (NRPs) represent abundances of molecules with biological diversity such as daptomycin, erythromycin, and many others. Both NRPs and PKs are biosynthesized through the action of giant multifunctional mega-enzymes, termed non-ribosomal peptide synthetases (NRPSs) and polyketide synthases (PKSs) respectively, which responsible for the incorporation of the selected amino acid or carboxylic acid into the product scaffold utilizing sequential condensation chemistry [2,3]. NRPs and PKs of microbial origin represent a significant proportion of bioactive natural products. The accumulated knowledge of the NRPSs or PKSs constituting biosynthetic pathways or other type of NPs gene clusters provides the potential for predicting and isolating new gene clusters, engineering or production of NPs in heterologous hosts.

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New resources and technologies for drug discovery: In the past, most NPs were isolated from terrestrial bacteria, leading to successful applications in pharmaceutical industries. New sources were expanded beyond soil, which include marine environments (seashores, coastal waters, and bottom sediments), unusual or extreme habitats (high or low temperature or pressure, high level of acidity or alkalinity), etc. These new sources have so far not been exploited to the same extent harbor abundant microorganisms containing novel bioactive natural products. Novel sampling methodologies provide the opportunities to

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isolate microorganisms from these extreme environments [4]. Additionally, endophytic microorganisms are believed to be better sources of diverse secondary metabolites. On the other hand, innovations in modern analytical chemistry, like the high-resolution separation technique and detection systems, enable the scientists to trace compounds and determine the structures at the nanomole scale.

Combinatorial biosynthesis and engineering: NPs are biosynthesized from structurally simple amino acids or carboxylic acids or glucose, catalyzed by a series of enzymes that are encoded by genes. Up to date, biosynthetic gene cluster of hundreds of NPs have been cloned and identified, the biosynthetic pathways have been investigated and the link of among genes, enzymes, reactions and compounds has been elucidated. In addition, the development of recombinant DNA technology and a series of genetic tools facilitate engineering of the natural products producers. On the basis of understanding of the biosynthetic mechanism of NPs, these useful tools can be used to engineer the biosynthetic pathways of the existing NPs to generate multiple derivatives of NPs, leading to the structural diversity of NPs. These tools can also be used to activate or enhance gene transcription, enhance gene expression, and improve the supply

of biosynthetic precursors to achieve the high production of the target compounds for drug development. Besides, biosynthesis based synthetic biology provides great potential and possibilities in pathway refactoring and precisely controlled NP structural diversification and overproduction.

Genome-inspired method: In the last decade, the rapidly increased genome sequencing technology has led to the exponential accumulation of uncharacterized biosynthetic gene clusters of secondary metabolites in public databases [2,5]. Scientists also realized that the potential of NPs from microorganisms had been underestimated, because the genome of actinomycetes usually contains around 20 biosynthetic gene clusters of different secondary metabolites whereas that of fungi in general harbors more than 30 gene clusters of secondary metabolites [6,7]. However, most of the biosynthetic gene clusters are “silent” or “cryptic” in the hosts in laboratory culture condition. Activation of these silent gene clusters spurs much

interest. With the quickly developed bioinformatics methods and genetic technologies, gene clusters that encode the biosynthetic pathways can be easily predicted, characterized and genetically manipulated to produce NPs in native host or heterologous express in chassis cell.

Conclusion

Microorganisms are renowned as a prolific source of natural products, many of which are medically important products. Since scientists still have much to learn from the nature, the rapid development of technologies and tools has made it possible to isolate new and diverse natural products. With the understanding of NPs biosynthesis, the increase of DNA-sequenced big data, advances in bioinformatics and analytical approaches, NPs discovery from microorganism has remained an active field, continuously provide compounds not only reveal unique biochemistry and structure features, but also exhibit novel modes of action to fuel the next generation of drug development.

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