New Dimensions of Research on Actinomycetes: Quest for Next Generation Antibiotics

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Starting with the discovery of streptomycin, the promise of natural products research on actinomycetes has been captivating researchers and offered an array of life-saving antibiotics. However, most of the actinomycetes have received a little attention of researchers beyond isolation and activity screening. Noticeable gaps in genomic information and associated biosynthetic potential of actinomycetes are mainly the reasons for this situation, which has led to a decline in the discovery rate of novel antibiotics. Recent insights gained from genome mining have revealed a massive existence of previously unrecognized biosynthetic potential in actinomycetes. Successive developments in next-generation sequencing, genome editing, analytical separation and high-resolution spectroscopic methods have reinvigorated interest on such actinomycetes and opened new avenues for the discovery of natural and natural-inspired antibiotics. This article describes the new dimensions that have driven the ongoing resurgence of research on actinomycetes with historical background since the commencement in 1940, for the attention of worldwide researchers. Coupled with increasing advancement in molecular and analytical tools and techniques, the discovery of next-generation antibiotics could be possible by revisiting the untapped potential of actinomycetes from different natural sources.

Keywords: actinomycetes, natural products, antibiotics, drug discovery, genomics, metabolomics

INTRODUCTION

Actinomycetes are ubiquitous Gram-positive bacteria that constitute one of the largest bacterial phyla with characteristic filamentous morphology and high G+C DNA. The actinomycetes have been recognized as premier source and inspiration for a substantial fraction of antibiotics that play an important role in human health. The most striking fact is that these filamentous bacteria have
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FIGURE 1 | Graphical summary of research and developments focused on antibiotic discovery from actinomycetes over 76 years. Hunting of antibiotics from actinomycetes has emanated with the discovery of actinomycin in 1940 (a) and lined up with several commercially important antibiotics and their derivatives: streptomycin (b), cephalosporins (c), Chloramphenicol (d), neomycin (e), tetracycline (f), nystatin (g), virginiamycin (h), erythromycin (i), lincomycin (j), vancomycin (k), novobiocin (l), rifamycin (m), kanamycin (n), nalidixic acid (o), fusidic acid (p), gentamicin (q), trimethoprim (r), fomotycin (s), ribostamycin (t), mupirocin (u), linezolid (v), daptomycin (w), and platensimycin (x). Classic actinomycetes research was driven by isolation and activity screening approach. Whereas, modern actinomycetes research is driven by array of breakthroughs in genetics, genomics, metagenomics, genome mining and editing and high-resolution metabolomics, in association with classical approach.

evolved with the wealth of biosynthetic gene clusters and thereby show an unprecedented potential in production biologically active natural product scaffolds. However, last two decades has seen a move by pharmaceutical giants away from microbial natural product discovery efforts, and such efforts continue to flourish in research institutes with promising results. The continued research efforts of academic research institutes, with post-genomic technological innovations, rejuvenate natural product research and compose a clarion call to worldwide researchers for tuning into microbial natural products research.

THE CLASSIC ACTINOMYCETES RESEARCH

If we look back to about 76 years of actinomycetes research that focused on hunting bioactive metabolites of public welfare, over 5000 compounds have been reported and contributed to the development of 90% of commercial antibiotics being used for either clinical or research needs. In this long course, actinomycetes research evolved several aspects from isolation and activity screening to modern post-genomic secondary metabolites research (Figure 1). The first report of streptomycin by Selman Waksman and associates in the 1940s and subsequent development as drug encouraged pharmaceutical companies and researchers to put their large scale efforts on microbial natural products research (Demain and Sanchez, 2009). The efforts were largely depending on the recovery of microorganisms from diverse environmental samples, and screening for the desired bioactivity. The approach brought the golden era (1950–1970) of antibiotic discovery evidenced by the commercialization of several life-saving antibiotics including streptomycin, vancomycin, rifamycin, and so on (Mahajan and Balachandran, 2012). In subsequent decades, the rediscovery of known compounds and technical challenges associated with purification and structure elucidation of new compounds largely declined the classic efforts (Bérdy, 2012). Despite the evidence of a decline in microbial natural products research, continued innovations in sampling and acquisition of potential actinomycetes from previously unexplored sources are being continued by several academic research groups and mitigate risks of the rediscovery of known compounds and augmented availability of diverse actinomycetes that are fundamental matters to the long term actinomycetes research.

IN PROGRESS

Progress is crucial in several aspects of actinomycetes research that includes (1) isolation and dereplication of actinomycete isolates, (2) prediction and identification novel compounds, (3) enhancing production titers of potential compounds, (4) uncovering genome information and associated biosynthetic potential, (5) collection and processing of genomic data, (6) mining, editing and heterologous expression of cryptic gene clusters, and (7) comprehensive metabolic profiling, under a broad spectrum of main areas such as genetics, genomics and metabolomics.

Establishing actinomycete resources is one of the basic requirements for culture-dependent natural products research.
Salinispora has been established as a robust model organism for uncharacterized gene clusters, metabolic enzymes, particularly and with the advent of molecular genetics and next-generation actinomycetes genome have been reported as on March 2016 actinomycetes is being promptly updated. Over 1304 which only four had been linked to their respective products. biosynthetic capacities with 17 diverse biosynthetic pathways of natural product research (Jensen et al., 2015). It has remarkable S. coelicolor of and and the whole genome was announced with versatile genetically been recognized as a model for the actinomycetes, group. As a noteworthy foundation, endurance of natural product search in this admirable bacterial Streptomyces secondary metabolites biosynthesis in actinomycetes, especially increase in understanding the genetics and enzymology of actinomycetes through genetics has provided a foremost share to our current knowledge. Dramatic and sustained increase in understanding the genetics and enzymology of secondary metabolites biosynthesis in actinomycetes, especially Streptomyces throughout the 1990s have also facilitated endurance of natural product search in this admirable bacterial group. As a noteworthy foundation, S. coelicolor A3(2) has genetically been recognized as a model for the actinomycetes, and the whole genome was announced with versatile in vivo and in vitro genetics (Bentley et al., 2002). The genome analysis of S. coelicolor A3(2) has revealed the abundance of previously uncharacterized gene clusters, metabolic enzymes, particularly those likely to be involved in the production of natural products. As a latest accomplishment, the marine actinomycete genus Salinispora has been established as a robust model organism for natural product research (Jensen et al., 2015). It has remarkable biosynthetic capacities with 17 diverse biosynthetic pathways of which only four had been linked to their respective products. The genome information of cultured and uncultured actinomycetes is being promptly updated. Over 1304 actinomycetes genome have been reported as on March 2016 and with the advent of molecular genetics and next-generation genome analysis rapid submissions are expected in near future. Analyses of genomes of actinomycetes have revealed that numerous ‘cryptic’ or ‘orphan’ biosynthetic gene clusters with the potential to direct the production of an ample number of novel, structurally diverse natural products (Challis, 2014; Gomez-Escrubano et al., 2016). Subsequently, mining of actinomycetes genome has sketched new directions into the ongoing drug discovery efforts. One such approach has been to mine a collection of 10,000 actinomycetes for novel phosphonic acids, and have laid an intriguing foundation for rapid, large-scale discovery of other classes of natural products (Ju et al., 2015).

Improvements made in bioinformatics methods, particularly specific for natural product gene cluster identification and functional prediction aids in the processing of bulk genomic data of actinomycetes (Alam et al., 2011; Doroghazi et al., 2014; Abdelmohsen et al., 2015). However, sufficient insights into the biology and ecology of antibiotic production are needed to understand the precise triggers and cues required to activate silent gene clusters (Abdelmohsen et al., 2015; Kolter and van Wezel, 2016).

As a great breakthrough, the advent of RNA-guided DNA editing technology Clustered Regularly Interspaced Short Palindromic Repeats (CRISPRs)/Cas9 substantially promises for application to genome modification in biosynthetic gene clusters of actinomycetes (Huang et al., 2015). Obviously, this molecular tool can be used in the engineering of non-model native hosts to heterologous production hosts for the biosynthesis of desired natural products. Continued technological and conceptual advances in engineering microbial hosts will open up opportunities to fully explore and harness Nature’s immensely diverse chemical repertoire (Zhang et al., 2016).

FUTURE PERSPECTIVES

Actinomycetes have been recognized as a premier source of biopharmaceuticals especially antibiotics over several decades. Our universe is rich of diverse unexplored and underexplored environments that could be considered for isolation of novel members of actinomycetes. This could amend our actinomycetes repository with a continuous supply of novel biosynthetic gene clusters and natural product scaffolds on which current research reorient on. Continued advances in genomics and metabolomics reserve a next-generation natural products research and unwrap the wider opportunities on the exploitation of actinomycetes that represent an important asset for the discovery of pharmaceutically valuable compounds. The technological and conceptual advances will drive a transition of “searching for desired natural products” to “designing for desired products” from actinomycetes. Through this article, it is evinced that despite an interim decline in actinomycetes research, new avenues are open now and seek the active attention of researchers throughout the world. Those countries well endowed with the natural resources may deem to fund microbial natural products research especially actinomycetes research for extending the inventions of novel antibiotics of industrial
significance to triumph the escalating microbial resistance and infectious diseases.

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All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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