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Bioactive Metabolites of Actinomycetes – Screening from Genomic and Metabolomic Approach

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Abstract

The urgency for new and novel therapeutic agent has increased since last few decades by the serious advent of resistant pathogens and our lifestyle. The situation is becoming scary due to very less arrival of new antibiotics or other bioactive agents. Since past few years the concept of drug discovery has changed dramatically. Several modern strategies have adopted and by using different revolutionary tools and techniques and software based program it has now become easier to screen the potential strain as well as purify those highly demanding molecules. Few significant approaches that are being taken recent days to face the challenge, have discussed in this editorial.

Keywords: Therapeutics; Drug discovery; Genome based screening; Actinomycetes

Introduction

Screening for bioactive natural molecules is a continuous and ever demanding task. Arising of new diseases, widespread of drug resistance superbugs, emergence of newer version of pathogens and harmful side effect of chemotherapeutics embolden us in finding of novel natural bioactive compounds. Historically, our nature provides enormous source of active medicinal compounds from plant and microbial sources for millennia but the microorganisms contribute majority active compounds that are clinically used present days. Lots of efforts were put forward for screening of potent microbes from different niches. As scrutinized by Newman and Cragg [1], near about 28% of the new chemical entities and 42% of the anticancer drugs acquainted into the market worldwide from 1981 to 2006 were natural products and their derivatives. More than 22,000 biologically active compounds have been achieved from microbes by the end of 2002 among which, 45% were formed by different actinomycetes, exclusively the excellent producers were in the genus *Streptomyces* [2]. This group of microbes has shown an exceptional contribution with greater potential to the health and well-being of people throughout the world [3]. Aerobic actinomycetes of spore forming types (*Streptomyces*) are not impeded in their growth by other organisms, but, on the contrary, are competent in spite of their slow development, to annihilate the growth of almost all bacteria and fungi. Secondary metabolites are by products of some complex metabolic pathways that exploit primary metabolites as precursors. In an attempt to screen the potent resource of bioactive natural compounds it is observed that actinomycetes produces most of so far useful secondary metabolites which includes toxins, antibiotics, pigments, effectors of ecological competition and symbiosis, enzyme inhibitors, pheromones, immunomodulating agents, receptor antagonists and agonists, pesticides, antitumor agents and growth promoters of plants and animals [4]. They have considerable repercussions to the health, nutrition and economics of our society.

Traditional Screening of Potential Microorganisms

Microorganisms are ubiquitous in nature. They can be isolate from any ecological site like soil, any aquatic system, air, decomposed materials, animal gut microflora or of endophytic origin. In microbial drug discovery, compound isolation from large number of isolates is often labour-intensive and time-consuming. They are isolated by conventional plating on solid or nutrient media after serial dilution and the selection of candidate strains depended on bioactivity screening. Each of isolates individually has to screen for desired bioactivity. For this purpose each strain has to culture individually in general media under unoptimized conditions that might not be favourable for the specific expression of the desired set of genes and it is too laborious and equally time consuming to find the potential strain after optimizing the production from every isolates [5]. To reduce the repeated isolation of known compounds, dereplication of the source strain prior to further processing is a useful task. However, bioactivity analyses alone do not support any chemical or structural information on the underlying compounds

Genome Base Screening of Bioactive Actinomycetes

Gram positive actinomycetes grow in combination of steady hyphal growth and addition of new hyphal tips via branching of the mycelium. Such prokaryotes are considered the factory of quality compounds as they occupy clusters of genes of secondary metabolites. Polyketides represent a high structurally diverse class of compounds with significant bioactivities. The diverse spectrum of polyketides makes them clinically, economically and industrially the most demanding. Many microbes, especially actinomycetes are well known to produce such compounds as secondary metabolites through polyketide biosynthetic [6]. At least three architecturally different types of PKSs have been discovered in the microbial world. Each PKS module encodes various domains encoding several enzymes involved in programmed synthesis of newly polyketide compound. Nonribosomal Peptides (NRP) are a class of peptide secondary metabolites synthesized by nonribosomal peptide synthetases, which, unlike

the ribosomes, are independent of messenger RNA [7]. Often have cyclic and/or branched structures, can contain non-proteinogenic amino acids including D-amino acids, carry modifications like N-methyl and N-formyl groups, or are glycosylated, acylated, halogenated, or hydroxylated. They are very diverse family of natural products with an extremely broad range of biological activities and pharmacological properties. Previously, natural products screening was emphasized to the strenuous determination of huge number of isolates for their bioactivity. Whereas, discoveries in genetic engineering have opened an earlier and easiest method for screening of potential actinomycetes strains by primer based targeting of their specific biosynthetic genes. We have now several useful primers to check presence of some novel microbial secondary metabolite synthetic genes (PKS-I, PKS-II, NRPS) by which we can easily detect if any strain have potentiality to produce such novel gene products [8]. Genome mining approaches such as searching for biosynthetic genes, resistance genes, regulatory genes, genetic activation of silent gene clusters can eliminate the rediscovery of known natural products from Actinomycetes isolates. These new approaches can lead us to successful novel compounds from different unexplored ecosystem.

Metabolites Study for Easy and Fast Screening

Secondary metabolites are low molecular weight organic compounds considered as far non-essential to producer strains. Most of such metabolites have been found of great importance in mankind. They have wide application as therapeutic agents; e.g. antibiotics, antitumor agents, antiviral, anti-diabetic and immunosuppressives. Advances in genome based study help us enormous in modern drug invention. It revealed the secret mines of secondary metabolites gene cluster encode the potential to produce many more secondary metabolites than was originally expected. Applying metabolomics it has become very easy task for isolating and characterizing secondary metabolites in their metabolic perspective in wild type or engineered biosystems, by concurrently computing low molecular weight compounds in crude. Chemical screening of effective metabolite is the key concept for easy and fast determining the bioactive potential of a strain. Sophisticated analytical instruments are currently in use to determine the metabolic profile and elucidate the structural properties of metabolites [9]. The high-performance liquid chromatography, mass spectrometry or their coupled form like LCMS, infrared spectroscopy and nuclear magnetic resonance are frequently employed to screen the bioactive potential of isolated strains. Various metabolomics tools such as Cycloquest, GNPS-Genome to Natural Product Platform, NRPquest (Nonribosomal Peptide), PEP2 path are currently available to characterize the bioactive gene clusters to better understand actinomycetes metabolic profile whereas databases for bioactive compounds like Novel antibiotics, Antibiticome, CHEBI-Chemical Entities of Biological Interest, PubChem, Chemspider are extensively used for metabolite profiling of isolated actinomycetes however MODEL-SEED is only known high throughput modelling tool which has been set up to renovate multiple actinomycetes species for large scale metabolic studies.

Considerations

Considering the natural products as best source and the global demand of therapeutics we cannot avoid the modern target based drug research. The directed screening is very practical and sensible in identifying bioactive compounds that hit an identified and authenticated molecular target. High-throughput metabolic modelling tools let us linking between genotype, metabolic phenotype and biosynthetic gene cluster of secondary metabolite producing microbes. The combinatorial approach (genomic and metabolomic) thus is very useful in predicting intracellular molecular profile of actinomycetes for production novel molecule for mankind.

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