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COMMENTARY

High-throughput Strategy Accelerates the Progress of Marine Anticancer Peptide Drug Development

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1. INTRODUCTION

With regard to the increasing requirement of novel anti-cancer drug, naturally occurring peptides/venom-based peptides are gaining much more attention. These natural peptides have demonstrated the convincing potential due to their high selectivity and diverse bio-functions in cancer cells. According to the literatures, more than 7000 therapeutic peptides have been successfully identified from different natural sources, including amphibians, snakes, scorpions, insects and marine cultures [1-3]. As of 2017, 484 therapeutic peptides are reported to be actively evaluated in different pre-clinical/clinical trial stages. Among these, 260 peptides have been tested in human clinical trials and more than 60 therapeutic peptides are approved by the FDA [4-6]. Although, the number of peptide therapies in the drug market is relatively small, the development of peptide-based therapies is reported to be steadily accelerating, where approximately 20 therapeutics peptides entered clinical trials per year in the past decade [7].

Marine sources itself have been receiving much more attention as a therapeutic peptide pool for the pharmaceutical industry in the last few years. According to the review article by Zheng and his colleagues [8], more than fifty marine-based anticancer peptide drugs have been well studied and patented since 2011. Several marine-based peptides/peptidomimetics have been clinically used to treat cancer [9]. In 2011, Adcetris (Brentuximab Vedotin), which is a marine peptide-based drug was approved by the FDA for Hodgkin lymphoma and ALCL (a type of T cell non-Hodgkin lymphoma) treatment [10]. On top of that, other marine peptide-based drugs such as Plitidepsin [11, 12], HTI-286 [13], Kahalalide F [14, 15], and Elisidepsin [16] are currently being assessed in different clinical trial phases for the treatment of various cancer types [17]. All these examples revealed that marine derived peptides have been proved to be a prolific source of anticancer drug discovery.

However, there are two major impediments that delay the development of marine source peptide-based drug discovery. The first challenge is that most of the marine source are very difficult to collect due to their small physical size and marine environment. Moreover, the application of 'classical' peptide purification and identification techniques requires quite a large quantity of marine source to begin with. Consequently, only around 8% of marine peptides were identified and further studied [18]. Thus, a high-throughput platform combining transcriptome and proteome will be a more efficient and effective approach to accelerate the process of marine derived peptide discovery [19].

Another challenge is that the current technologies restrict a thorough mechanistic investigation of the anticancer peptide drugs. The traditional mechanism studies are based on certain targets and phenotype changes, which are also known as target-centric or phenotypic mechanism study. These traditional mechanism studies approach has been developed in the last decade, and several targets/pathways for anticancer peptides, such as the extrinsic (death receptor-mediated) pathway and the intrinsic (mitochondrial) pathway which induced apoptosis, p38 MAPK/ JNK pathway, tubulin-microtubule disruption and PI3K/Akt pathway, have been verified and well-studied [8, 20]. However, as reported by Zheng and his colleagues [8], there is still only a small number of marine-derived anticancer peptides that are being intensively studied nowadays. More than 80% of the therapeutic peptide mechanisms still remain unclear even though these peptides are reported to be potential anti-cancer agents [8]. Insufficient mechanistic study always created a further delay in therapeutic development of marine-derived peptide into clinical stage. This predicament highlights the importance of a novel method which could allow a comprehensive and rapid mechanism study of therapeutic peptides, which is definitely essential.

2. HIGH-THROUGHPUT MARINE VENOM-DERIVED PEPTIDE DISCOVERY APPROACH

Traditional biochemistry, peptide identification, and purification processes such as microfiltration, gel filtration, reverse-phase HPLC, and ultracentrifugation are commonly utilized [21]. A large amount of crude venom/ marine source is required to unravel the complex peptide compounds in a single venom. In recent years, the dramatic development of mass spectrometry [22-24] and next-generation sequencing [25, 26] allowed high-throughput identification of venom peptides. The high resolution mass spectrometry approaches allowed the characterization of thousands of different peptides with a very small amount of crude venom/marine source [27]. Liquid Chromatography-Mass Spectrometry

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(LC-MS) is able to separate and analyze the venom mixtures in a single run. Typically, marine venoms were first lysed into peptide fragments. After the desalting process, the sample was injected into the high resolution LC-MS system. Large-scale peptide fragment sequence data were then obtained and analyzed by proteomics assemble software for *de novo* assemble [28-33]. In addition, transcriptome data can be obtained by next-generation sequencing techniques such as RNA-seq [19]. Through matching the proteomics and transcriptome data, a systematic overview of venom peptide library is provided beyond the efficiency of classical venom peptide identification approaches. This approach provides integrated, high resolution and rapid proteomics analysis of venoms. This cutting edge approach can accelerate the development of potential marine-derived therapeutic peptide discovery.

3. PATHWAY-CENTRIC ANTICANCER MECHANISM STUDY APPROACH

Most of the anticancer peptides induced multi-target and complex changes within the cancer cells. It is challenging to systematically identify their mechanism of action with any traditional biochemistry technologies [34]. A systematic and accurate approach using next-generation sequencing technique has been proposed to study the most relevant gene(s) responses, which are able to provide evidence in the whole transcriptome alterations after the therapeutic peptide treatment. Subsequently, bioinformatics method would able to further enrich the dysregulated transcriptome genes into several pathways. This approach retains the advantages of phenotypic and target-centric approaches and allows more comprehensive studies of the mechanism of anticancer peptides. Currently, the development of Next-Generation Sequence (NGS) technique allows the high-throughput and large-scale applications in drug discovery and clinical studies [35]. The broad utility of this approach will utmost enhance the efficiency and accuracy of marine-derived anticancer peptide mechanism study.

4. THE FUTURE OF MARINE ANTICANCER PEPTIDE THERAPY

The rapid development of marine-derived anticancer peptide therapy enriches the anticancer drug pool, however, at the same time, exposes the shortcomings of traditional peptide identification and mechanism study methods. In the past years, the development of next-generation sequence and high-resolution mass-spectrometry techniques provided large-scale and high-throughput marine-derived peptide identification and comprehensive mechanism study. The robustness and broad utility of these novel methods have been proved [19, 36-38], and are capable to accelerate the discovery and development of marine anticancer peptide therapy.

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