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Editorial

Bioinformatics approach: A powerful tool for microRNA research

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Bioinformatics is an important approach for the management of biological data on a larger scale. It is basically an emerging interdisciplinary field of modern biotechnology that develops methods and softwares for an understanding of biological data. For data analysis or interpretations, bioinformatics utilizes *in-silico* approach to answering the biomedical questions using mathematical and statistical methods.[1] The basic objective of bioinformatics approach is storage of extensive molecular biology data in database forms. These data must be assigned in a ways to give suitable meaningful information in different grades.[1,2] As for example, GenBank nucleotide sequence information, etc. Another objective of bioinformatics approach is data analysis. As of *BLAST* to analyze a nucleotide sequence of the same type to design primers or probes for polymerase chain reaction technique, etc. However, the central objective of bioinformatics approach is to interpret extensive biomedical data, resulting to give meaningful biological information.[1,2] So far, bioinformatics approach has got super success for the determination of nucleotide sequence alignment, gene expression prediction, prediction of protein structure, alignment of protein structure and also in studies of genome-wide association, assembly of the genome and also for modeling of evolution.[1-3]

MicroRNAs (miRNAs) are key regulators of genes at the post-transcriptional level, they are basically single-stranded non-protein coding RNAs of just 20-25 nucleotides, and now it is well-documented that miRNAs are involved in almost all physiological and pathological mechanisms.[2,4-8] According to the latest updates, 2588 mature miRNAs have been processed from 1881 precursor miRNAs in human genome (miRBase: http://www.mirbase.org/index.shtml, release #21, June 2014). Now it is well reported that miRNAs expression levels are widely distributed in humans; some are universally expressed while others are expressed in tissues and/or cells and now miRNAs network seems to be a complex regulatory network.[2,4-10] As for example, individual miRNA can act on numerous target mRNAs, and every mRNA can be targeted by multiple miRNAs that promote numerous regulatory mechanisms.[2,8] Altered miRNAs expression have been reported in almost all disorders and studies concluded that deregulation of miRNAs expression effects on the development and progression of many human disorders and now many investigators pointed out that miRNAs could serve as potential molecular biomarkers not only for disease detection but also for therapeutic application.[4-10]

To develop the bioinformatics programs for the management of miRNA research data and to identify miRNA targets, the following prime features are often used: (1) Base pairing pattern between miRNA and 3'untranslated region (3'UTR) of target mRNA sequence, (2) miRNA-mRNA duplex thermodynamic stability, and (3) evolutionary conservation of target sites of miRNAs in different species, investigation of multiple target/binding sites.[2,8] Recently, many bioinformatics algorithms have been introduced for the management of miRNA research data. Most of these are utilizing different features for the identification or validation of individual miRNA, prediction of miRNAs target sequences, identification of miRNA expression, miRNAs signaling pathways determination, determination of miRNA metabolic pathways, analysis of regulatory networks of miRNAs, identification of miRNA-transcription factor interplay and investigation of miRNA link to human disorders.[2,8-10] Although all online available bioinformatics approaches have been well studied and revised by many investigators,[2,8-10] but here a briefly description of the most

user-friendly approaches are given, which are widely used in miRNA research. (1) TargetScan and TargetScanS algorithms: TargetScan and TargetScanS are two different algorithms of online available TargetScan program. TargetScan is one of the most common user-friendly programs based on the two classic features for miRNA target prediction. First is the seed match sequence between miRNA and 3'UTR of a target gene using base pairing rule and other feature of this algorithm is free energy. Whereas TargetScanS is an updated version of TargetScan, in contrast to TargetScan, TargetScanS does not use free energy feature for miRNA targets prediction. Recent data showed that the false positive rate by TargetScanS is reduced from 30% to 22%.[2,8] (2) DIANA-microT-CDs algorithm: It is an excellent algorithm with a user-friendly interface for miRNA target prediction. It is basically an updated version of DIANA-microT algorithm, which predicts miRNA target by the combination computational and experimental algorithms. This bioinformatics approach considers the following features such as binding group mass, closest distance of the end of the coding sequences or closest distance of 3'UTR to an adjacent binding site, AU content and conservation and also it utilizes the free energy of miRNA and target hybrid. This web-based algorithm utilizes an extensive connectivity to numerous web-based biological servers, which provide us collective information of the predicted miRNA-target hybrid interaction.[2,8] (3) PicTar algorithm: This algorithm requires the feature of binding sites which are co-regulated by multiple miRNA across species. It basically investigates the binding alignments of 3'UTRs of target genes to miRNAs, and it also filters the binding alignments via thermodynamic stability of miRNA-target hybrid.[2,8] (4) MiRanda algorithm: This algorithm also utilizes two features for miRNA target prediction, which is nucleotides complementarity and binding energy of the duplex. In the first step, miRanda algorithm utilizes Watson-Crick and G-U matching rule between aligned miRNA and 3'UTR of the target gene, and in the second step it calculates the binding energy of miRNA-sites duplex by Vienna package.[8] (5) RNA hybrid algorithm: This algorithm predicts multiple miRNA targets in large 3'UTRs of target genes. It basically uses three features such as seed matching, free energy feature and an additional feature of free energy of P value.[2,8] There are many others bioinformatics algorithms for miRNA target predictions such as PITA, Tarbase, rna22, MiRDB, STarMir, microInspector, Mirpath, MaMi, MiRecords, mirDIP, miRGator, Magia, miRTar, and miR Trail all utilize different modes for the detection of miRNA target genes in humans, which are extensively reviewed.[2,8-10] All of this above information of bioinformatics approaches clearly indicated that all current approaches are based on different operational modes and models for target predictions, therefore it is important for the researcher to check the underlying strengths and weakness of bioinformatics tools before use. So far, TargetScan, DIANA-microT-CDs, and miRanda are highly adopted with the most common user-friendly interface, whereas PicTar, RNA hybrid are also accepted by the miRNA researchers. However, it is also suggested that combining results from multiple approaches are always encouraged to minimize the chances of errors and to reduce the negative outputs.

As miRNAs are involved in almost all human biological mechanisms and their deregulation has been reported in the pathogenesis of numerous human disorders such as cancer and arthritis and now it seems that miRNAs research has a valuable impact on human health.[2,4-10] In spite of these important implications of miRNA research in the pathogenesis of human disorders, but still, huge scale of deregulatory mechanisms of miRNA remains unknown. Introduction of bioinformatics approaches in miRNA research is making possible to address a variety of aspects of ongoing miRNA researches. Investigators from all over the world have reviewed almost all major and minor resources of bioinformatics tools, which are now applicable in miRNA research, that cover all aspects of miRNA target predictions to their functional implications. In contrast, these approaches are still having limitations, which are needed to be addressed. The most common and vital flaw of these approaches is the generation of false-positive data on a large scale.[2,8] Therefore, there is an urgent requirement to refine these machine-learning-based algorithms which will minimize these flaws. As dysfunctioning of miRNAs are frequently reported in almost all human disorders and now it is well-established that miRNA are considered to be the most suitable therapeutic targets for the management of human disorders, bioinformatics tools in the next generation biomedical research will greatly benefit to handle the massive flow of miRNA data and to provide us an accurate miRNA target prediction algorithm which will solve the secrets of miRNAs association with human disorders.

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