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Contribution of bioinformatics prediction in microRNA-based cancer therapeutics ☆

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ABSTRACT

Despite enormous efforts, cancer remains one of the most lethal diseases in the world. With the advancement of high throughput technologies massive amounts of cancer data can be accessed and analyzed. Bioinformatics provides a platform to assist biologists in developing minimally invasive biomarkers to detect cancer, and in designing effective personalized therapies to treat cancer patients. Still, the early diagnosis, prognosis, and treatment of cancer are an open challenge for the research community. MicroRNAs (miRNAs) are small non-coding RNAs that serve to regulate gene expression. The discovery of deregulated miRNAs in cancer cells and tissues has led many to investigate the use of miRNAs as potential biomarkers for early detection, and as a therapeutic agent to treat cancer. Here we describe advancements in computational approaches to predict miRNAs and their targets, and discuss the role of bioinformatics in studying miRNAs in the context of human cancer.

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1. Introduction

Cancer is one of the deadliest diseases with very low survival rate in the world. It is characterized by an uncontrolled growth of damaged cells. Scientists have been trying to decipher the molecular mechanism of cancer cell formation and the role of onco (cancer promoting) and tumor suppressor (cancer preventing) genes in cancer development [1]. Despite numerous efforts, the cancer cell formation mechanism is yet to be discovered. The discovery of various oncogenes and tumor suppressor genes has provided insight into the biology of cancer and the development of drugs to combat these potential targets [2]. The small non-coding RNAs including miRNAs have shown the potential to act as biomarkers for cancer diagnosis as well as therapeutic agents to cure cancer [3].

miRNAs are tiny non-coding RNAs that post-transcriptionally regulate the expression of target genes by translational repression or mRNA cleavage. Recently, researchers have observed the role of miRNAs in apoptosis and cell proliferation that are key biological processes in cancer progression and metastasis [4]. The potential role of miRNAs in human cancer diagnosis, progression and metastasis has been studied using various molecular techniques like northern blots, microarray analysis and RNAseq. These miRNAs are expected to provide new insight in cancer research. Recently, the potential role of miRNAs as therapeutic agents has been explored in various cancer types. The oncogenic or tumor suppressor behavior of miRNAs is being exploited to treat cancer. miRNAs can be used as therapeutic agents by either reducing or increasing their expression level or interfering with the miRNA–mRNA regulatory interaction.

Bioinformatics provides a new avenue of understanding cancer biology through intelligent systems. The National Institutes of Health (NIH) working definition of Bioinformatics is "Research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, organize, archive, analyze, or visualize such data" (http://www.nih.gov/).

Bioinformatics approaches have shown considerable potential in biomedical research. Computational approaches reduce the search space and provide probabilistic and biologically meaningful outcomes. We consider the systems biology view to be the best path for diagnosing and developing therapies against cancer [5]. Integrating the existing cancer biology knowledge with powerful computational and statistical methods has shown the potential to identify miRNAs as novel biomarkers to diagnose cancer and its various sub-types [6]. Integrating gene and miRNA expression data with computational analysis tools has helped to identify the role of miRNAs in cancer progression and metastasis and their potential role in acting as therapeutic agents in the treatment and cure for cancer [7].

Our goal here is to summarize various existing computational approaches and potential use of bioinformatics in the field of cancer biology. In Section 2, we describe miRNA biogenesis and the mechanism of miRNA mediated post-transcriptional regulation. In section 3, we summarize the role of miRNAs in human cancer. Here, we briefly described the experimental efforts that have been taken to establish the role of miRNA in cancer. In Section 4, we summarize the role of miRNAs as oncogenes and tumor suppressors in various human cancers by providing specific examples from experimental studies. Section 5, we focus on the role of bioinformatics to identify novel miRNAs, their targets and involvement in cellular pathways. In Section 6, we summarize the computational studies done to establish the role of miRNA as therapeutic agent with pancreatic cancer as a case study. Finally, we conclude with the potential of miRNAs as therapeutic agents in human cancers.

2. miRNA biogenesis

Eukaryotic gene regulation is a complex process involving multiple factors such as transcription machinery, activators, repressors and chromatin. Chromatin maintains inactive genes by guarding them against access by RNA polymerase and other factors. The study of eukaryotic gene regulation has repeatedly shown the regulatory role of the 5′-end of the gene during transcription. Both enhancer and repressor transcription factors can enhance or decrease gene expression through their interaction at the 5′-end of the gene. Beyond chromatin and transcription factors, the discovery of RNA interference (RNAi) has added a layer to our understanding of gene regulation and the role of non-coding RNA sequences in gene regulation [8,9].

miRNAs are short ~21–22 nucleotide long non-coding RNAs that have been widely studied as regulators of gene expression [10–12]. In 1993, the first miRNA, lin-4, was identified in *Caenorhabditis elegans* [13,14]. miRNAs have been found in both protein coding, intronic and intergenic regions. While the miRNAs located in intronic and protein-coding regions are expressed along with their host mRNAs, those found in intergenic regions use their own promoter elements for expression [15]. Interestingly, prior to the discovery of miRNAs, Mizuno et al. (1984) showed that translation could be repressed by small RNA (~100 nucleotides) in *Escherichia coli* [16]. Later, these and other studies helped catalyze the discovery of the RNAi process for which Andrew Z. Fire and Craig C. Mello received the Nobel Prize in Physiology in 2006 [17].

The miRNA genes are known to be transcribed in the nucleus by RNA polymerase II or RNA polymerase III into primary miRNA transcripts called pri-miRNAs [18,19]. As shown in Fig. 1, the pri-miRNA is subsequently processed into mature miRNA through cleavage of pri-miRNA by the endonuclease RNA III enzymes — Drosha and Dicer. Cleavage of pri-miRNA in the nucleus by Drosha produces an approximately seventy nucleotide long pre-miRNA [20]. This pre-miRNA is then exported to the cytoplasm where Dicer cleaves pre-miRNA into a 22 nucleotide long duplex containing the mature miRNA (the guide strand) and its antisense compliment (the passenger strand). Gene silencing is achieved through the RNA-induced silencing complex (RISC), an effector ribonucleo-protein complex. RISC is a powerful gene silencing machine

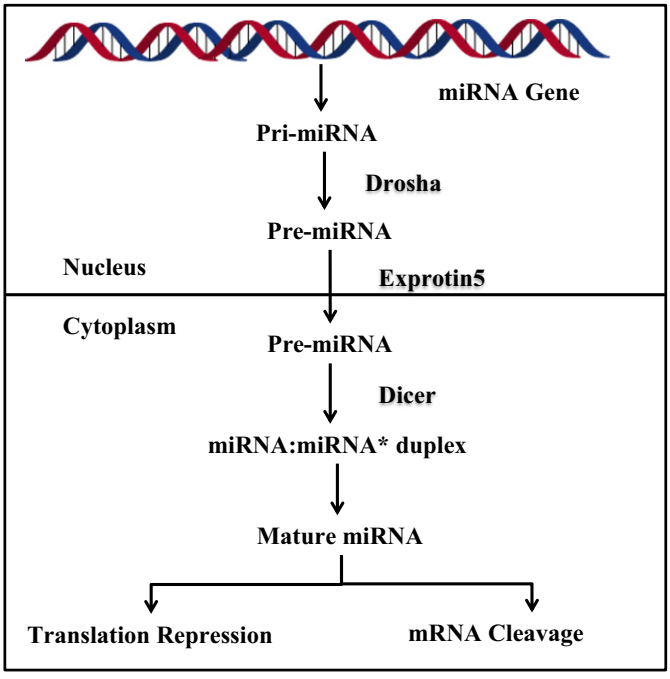

Fig. 1. miRNA biogenesis: miRNA genes are transcribed in the nucleus, and undergo subsequent processing by the endonucleases Drosha and Dicer to produce a duplex comprised of mature miRNA and its antisense strand (miRNA*). The mature miRNA strand is incorporated into the ribonucleoprotein complex (RISC), which mediates interaction with the target mRNA and mRNA silencing, either through mRNA (messenger RNA) cleavage or translational repression.
Adopted from [27].