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Recent advances in signal amplification strategy based on oligonucleotide and nanomaterials for microRNA detection-a review

Ying-Xu Chen[a,b], Ke-Jing Huang[a,b,*], Ke-Xin Niu[a,b]

[a] College of Chemistry and Chemical Engineering, Xinyang Normal University, Xinyang 464000, China
[b] Henan Province Key Laboratory of Utilization of Non-metallic Mineral in the South of Henan, Xinyang Normal University, Xinyang 464000, China

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ABSTRACT

MicroRNAs (MiRNAs) play multiple crucial regulating roles in cell which can regulate one third of protein-coding genes. MiRNAs participate in the developmental and physiological processes of human body, while their aberrant adjustment will be more likely to trigger diseases such as cancers, kidney disease, central nervous system diseases, cardiovascular diseases, diabetes, viral infections and so on. What's worse, for the detection of miRNAs, their small size, high sequence similarity, low abundance and difficult extraction from cells impose great challenges in the analysis. Hence, it's necessary to fabricate accurate and sensitive biosensing platform for miRNAs detection. Up to now, researchers have developed many signal-amplification strategies for miRNAs detection, including hybridization chain reaction, nuclease amplification, rolling circle amplification, catalyzed hairpin assembly amplification and nanomaterials based amplification. These methods are typical, feasible and frequently used. In this review, we retrospect recent advances in signal amplification strategies for detecting miRNAs and point out the pros and cons of them. Furthermore, further prospects and promising developments of the signal-amplification strategies for detecting miRNAs are proposed.

1. Introduction

Mature microRNAs (miRNAs), a sort of endogenous noncoding RNAs consisted of approximately 19–23 nucleotides (nt), play an essential role in every biological process such as cell proliferation, differentiation, apoptosis and other physiological or pathological processes (Richard et al., 2016). MiRNA was first discovered in Elegans by Lee and his colleagues in 1993 (Wightman et al., 1993). However, they have been kept out of the spotlight for decades due to its' small size and lack of poly-A tails. At present, nearly 2800 human miRNAs are expounded in public repositories. Nevertheless, Londin et al. (2015) revealed the existence of 3707 new human miRNAs expressed throughout the genome which may play pivotal roles in disease etiology. These discoveries suggest that the repertoire of human miRNAs is larger and more varying than may be suggested by the publicly available repositories. The production of mature miRNA encompasses a great deal of RNA processing steps according to the biogenesis of miRNA. The basic process and expression of mature miRNA is outlined in Fig. 1. Firstly, miRNA coding genes are generally transcribed by RNA polymerase II within the nucleus producing large capped and polyadenylated pri-miRNA transcripts. These pri-miRNA transcripts are processed by the RNase III enzyme and Drosha-DGCR8 to generate an imperfect stem-loop hairpin structure precursor miRNA (pre-miRNA). Those pre-miRNAs have approximately 70–90 nucleotides which are transported from the nucleus into the cytoplasm by the exportin-5. After Dicer processing, the pre-miRNA is transformed into a transient 22 nt mature double stranded (ds) miRNA: miRNA*. The Dicer also processed the unwinding of these miRNA duplexes to the mature sequence. One strand of the functional mature miRNA then associates with other proteins and enzymes to form the miRNA-induced silencing complex (RISC). The RISC complex functions perfectly or imperfectly match with its complementary target messenger RNA (mRNA), and induces target mRNA degradation, translational inhibition or mRNA cleave (João et al., 2015). Hence miRNA acts as regulators of gene expression via this mechanism (Alan et al., 2014). MiRNA imperfects complementary with 3′-untranslated regions of mRNA to produce RNA interference pathway, in which mRNA transcripts can be cleaved by RISC. It goes the further step to interfere the translation of the mRNA and impair the production of protein (Asahiro et al., 2015). The mechanism eventually results in reducing protein level and deep-seated influences on cellular homeostasis. Therefore, miRNA analysis seems important exceedingly.

To date, extensive methods for detecting miRNAs have been developed such as northern blot analysis (Válóczi et al., 2004),

* Corresponding author at: College of Chemistry and Chemical Engineering, Xinyang Normal University, Xinyang 464000, China.
E-mail address: kejinghuang@163.com (K.-J. Huang).

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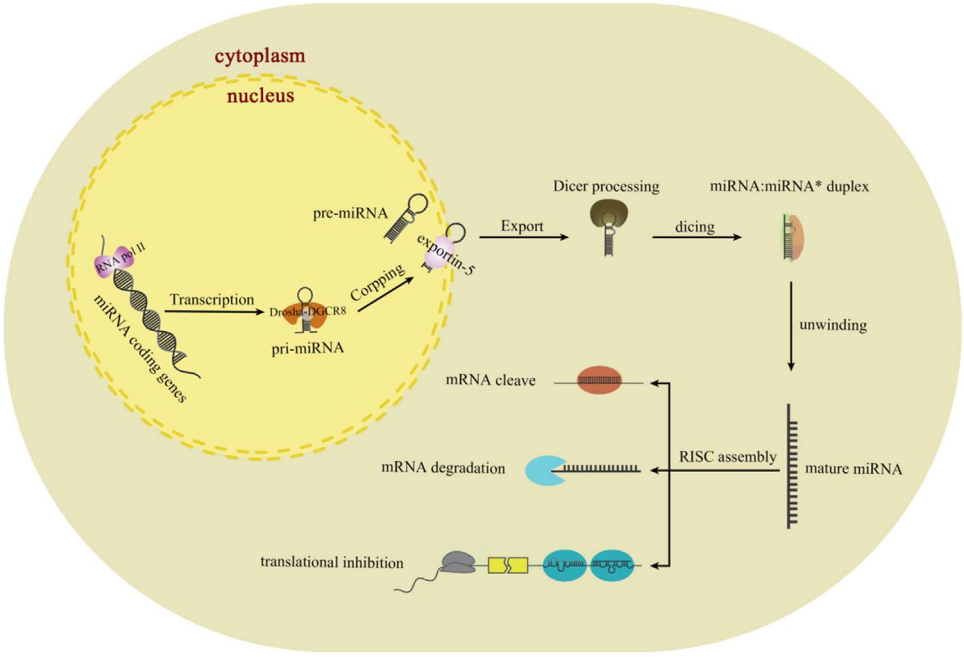

Fig. 1. Schematic illustration of miRNA biogenesis and functions.

polymerase chain reaction (PCR) (Zhang et al., 2013), microarray assay (Clancy et al., 2017), fluorescence (Chi et al., 2017), electrochemiluminescence (ECL) (Peng et al., 2017), photoelectrochemical (Li et al., 2015), surface plasmon resonance (SPR) (Liu et al., 2017a), capillary electrophoresis (Khan et al., 2011), colorimetric measurement (Li et al., 2016b) and electrochemical biosensor (Shuai et al., 2016a). Among them, northern blotting, microarrays and quantitative reverse transcription polymerase chain reaction (qRT-PCR) are the traditional methods for miRNA detection. Many reports have been conducted to evaluate the advantages and disadvantages of these methods. The northern blotting method is considered as the “gold standard” for miRNA, but it encounters the issues of time and sample consuming with low sensitivity and throughput, therefore it is still not very suitable for practical clinic tests. Although microarray technology make multiple miRNA analysis feasible due to high through put screening ability, the requirements of complicated probe, sophisticated instrumentation and trained person limits the application in point-of-care settings. QRT-PCR offers high sensitivity and covers broad dynamic range for miRNA expression profiling. However, the susceptible to contamination and only performance in centralized laboratories limit its application. To overcome these shortcomings, great efforts have been made to develop new techniques by using different signal readout assays including fluorescence, colorimetry, SPR and electrochemistry. Among them, colorimetric assays, without the aid of advanced instrumentation, offer a cost-effective, rapid and convenient option for miRNA detection. SPR, as a biorecognition transducer, transforms the concentration of biomolecule into optical signal attracts researcher's interest owing to its label-free, real-time, and in-situ detection of nucleic acids, proteins, and small analytes (Yang et al., 2016). However, SPR sensors suffer from nonspecific adsorption on the surface of chips. This drawback limits its practical application (Homola et al., 2008). The application of electrochemical sensors for miRNA detection exhibits many advantages such as high sensitivity and selectivity, reliable reproducibility, simple use for continuous on-site analysis, minimal sample preparation, relatively low cost and short time of response (Wu et al., 2014b).

However, miRNA is traced in cells and having its own intrinsic characteristics, such as short sequence, vulnerable degradability, low abundance in total RNA samples, relatively low expression levels in cells and high sequence similarity among family members (Zhao et al., 2015). Without the elaborate separation and enrichment processes, it is extremely challenged to detect low abundance of miRNAs in real samples (Shen et al., 2015). In an attempt to surmount these difficulties, a number of signal amplification strategies such as hybridization chain reaction (HCR) (Hong et al., 2013), nuclease amplification (Miao et al., 2015a), rolling circle amplification (RCA) (Jiang et al., 2016), catalyzed hairpin assembly (CHA) (Cai et al., 2017) and nanomaterials based techniques (Shuai et al., 2017a) have been developed. Moreover, the integration of two or more signal amplification strategies has been used for the lower detection limit and higher sensitivity (Wei et al., 2016).

This article provides an overview on the recent development of research in the field of signal-amplification techniques for miRNA detection. It starts by introducing the basic mechanism of five classical amplification methods and seriatim discuses their advantages and disadvantages. Some basic and novel methods are presented. Finally, the possible challenges and potential opportunities of signal-amplification techniques for miRNA detection are proposed.

2. The development and applications of miRNA

The major clinical challenge of some malignant diseases is that it conceals onset and the difficult to diagnose in early stage diagnostics (Leni et al., 2014). A biomarker can be generally defined as a measurable indicator of a particular disease state or some other physiological state of an organism (Yang et al., 2014). Therefore, specific and sensitive non-invasive biomarkers for the detection of human multifarious serious illnesses are urgently required to reduce the worldwide morbidity and mortality. After years of effort, scientists find that the expression of miRNA can be changed in the blood because of cellular damage and tissue injury, such as in acute myocardial infarction (Gupta et al., 2016), osteoarthritis (Kung et al., 2017), skin fibrosis (Harmanci et al., 2017) and atherosclerosis (Baldán et al., 2016). Unlike intracellular miRNAs, circulating miRNAs release from cells based on their targeted functions. They may shuttle in and out of circulation (Singh et al., 2016). Their discovery has ushered in new approaches for clinical fields and led to a quest for targeted biomarkers. Facts prove that the expression profiles of these circulating miRNAs in