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Minireview

Transcriptional regulation of mammalian miRNA genes

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ABSTRACT

MicroRNAs (miRNAs) are members of a growing family of non-coding transcripts, 21–23 nucleotides long, which regulate a diverse collection of biological processes and various diseases by RNA-mediated gene-silencing mechanisms. While currently many studies focus on defining the regulatory functions of miRNAs, few are directed towards how miRNA genes are themselves transcriptionally regulated. Recent studies of miRNA transcription have elucidated RNA polymerase II as the major polymerase of miRNAs, however, little is known of the structural features of miRNA promoters, especially those of mammalian miRNAs. Here, we review the current literature regarding features conserved among miRNA promoters useful for their detection and the current novel methodologies available to enable researchers to advance our understanding of the transcriptional regulation of miRNA genes.

1. Introduction

MicroRNAs (miRNAs), endogenous ~22 nucleotide (nt) single-stranded non-coding RNAs, are members of a growing family of gene regulators found evolutionarily conserved across a diverse array of plants and animals [1]. They are well equipped to regulate the expression of protein-coding genes through a complex network of pathways [2,3]. Recent studies have implicated miRNAs as regulators of diverse vital programs including developmental timing control, hematopoietic cell differentiation, apoptosis, cell proliferation, and organ development [1]. It has been speculated that they regulate more than one-third of all protein-coding genes [4]. Because of their involvement in a wide variety of developmental and physiological processes, it is important to study miRNA functions and their regulation.

Central to studying the regulation of miRNA expression is the clear understanding of their biogenesis, which has been described in several recent reviews [5–8] and summarized in Fig. 1. In mammals, miRNAs are first transcribed as longer primary transcripts called primary miRNA (pri-miRNA). The transcript may contain multiple miRNA stem loops and is capped at the 5′ end through polyadenylation. Drosha, a nuclear RNase III, is recruited to crop the pri-miRNA transcript into a hairpin-shaped structure, about 70nt long, known as precursor-miRNA (pre-miRNA) [9,10]. This cleavage event is critical and site-specific, as it determines the mature miRNA sequence. The pre-miRNA is then exported out of the nucleus [11] for further cleavage into a 22nt duplex [12]. The complementary strand becomes degraded leaving one fully mature miRNA strand [13]. Mature miRNA then associate with several members of the Argonaute protein family to form the RNA-induced-silencing-complex which then binds to specific protein-coding mRNA transcripts, directing mRNA inactivation by translational repression [14], deadenylation [15], or degradation [16].

Advancements in computational and biochemical methods of miRNA identification and expression analysis have predicted and experimentally verified specific mRNA gene targets of many newly identified miRNA, facilitating a necessary step in defining miRNA-induced pathologies thereby allowing for the development of targeted therapies [17,18]. These studies have identified the important functions of miRNAs and have begun to show that we may eventually rescue aberrant miRNA gene expression patterns in diseased organs. However, it is necessary to first identify the factors that regulate miRNA transcription in order to restore aberrantly expressed miRNA to their normal expression pattern.

Paradoxically, transcriptional regulation of miRNAs, the critical step in modulating their expression, remains poorly understood. This is due to previous limitations in methodology available to study primary miRNA transcripts combined with the current deficit in promoter sequence characterization. Recently, description of the RNA polymerases responsible for miRNA transcription have set the foundation to begin detailed exploration, using a few model miRNAs, of miRNA gene structure to determine key features, such as promoters and terminators [1,13,19,20]. Ongoing research in this area has revealed that many miRNAs use their own transcription initiation regions, whether they are located within a stretch of DNA between clusters of genes (intergenic) or embedded within introns of known coding genes (intronic). Intergenic miRNAs have been reported to generally be more evolutionarily conserved than intronic miRNA that use host transcriptional start sites (TSS) [21]. Although these developments provide valuable insight into promoter characterization, they also add new layers of complexity

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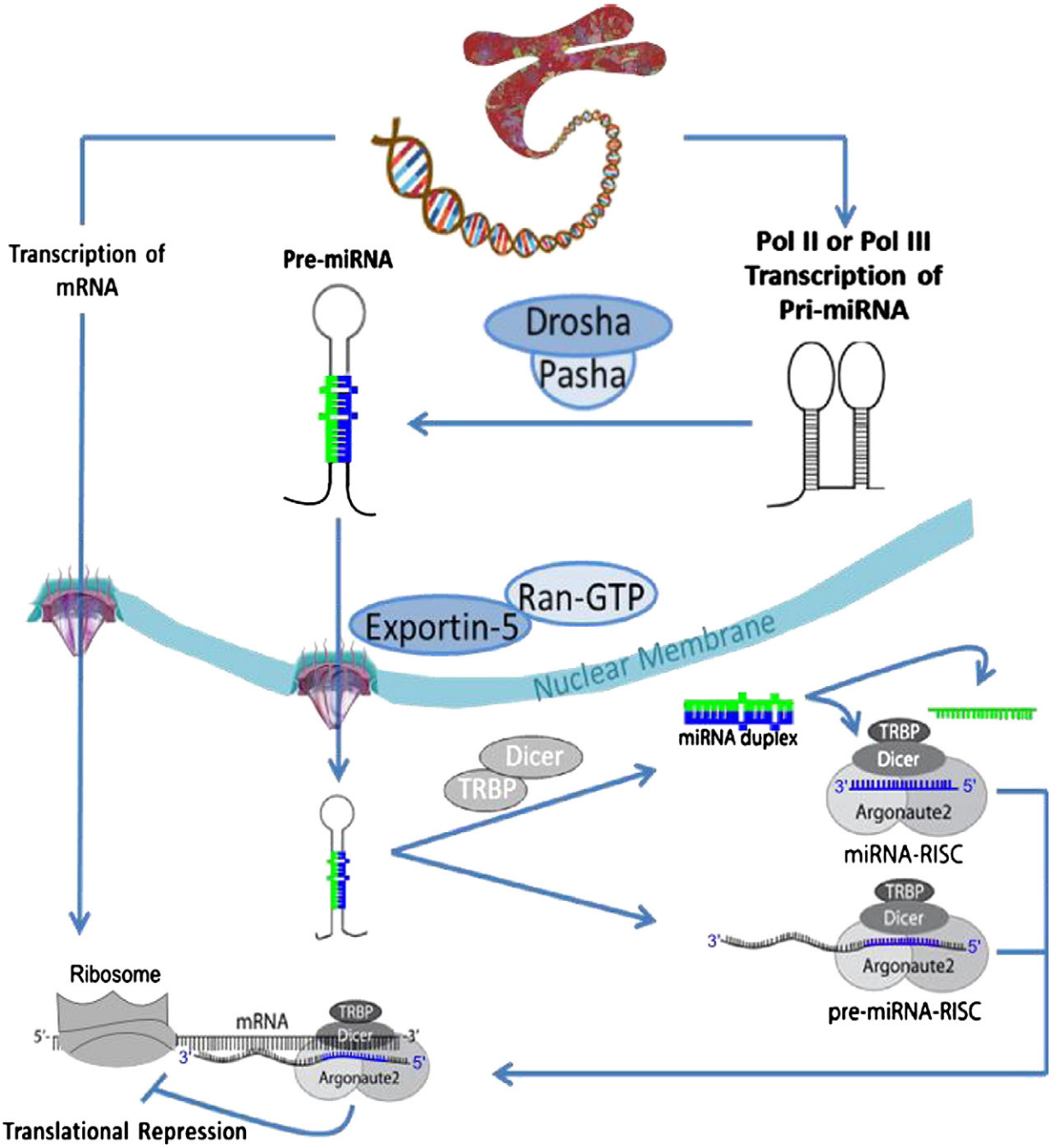

Fig. 1. The biogenesis of miRNA that functions as a translational repressor. Pol II or Pol III transcribes pri-miRNA from non-coding regions of the genome. Pri-miRNAs are usually several hundred bases in length and must be edited down to 70 nucleotide long stem-loop precursors (pre-miRNA) through the action of two RNase III endonucleases (Drosha and Pasha). Pre-miRNAs are then exported to the cytosol by exportin 5 and Ran-GTP through nuclear pores. Pre-miRNAs undergo further processing to isolate the core miRNA duplexes mediated by Dicer1 RNase III and its partner transactivation response RNA-binding protein (NCOA6). The duplex then disassociates through the help of a helicase where the complementary nonfunctional strand (green) is released from the functional strand (blue) which then inserts within the RNA-induced-silencing-complex (RISC) comprised of Dicer1 NCOA6 and the Eif2c2 protein. Alternatively, RISC has also been shown to directly load the pre-miRNA hairpin. The mature miRNA-RISC complex is then able to induce translation repression through binding of the core sequence (blue) to its cognate mRNA.

surrounding the transcriptional regulation of these non-coding RNAs. In this review, we will discuss progress from the past and present, as well as speculate on future developments to expand our current understanding on the transcriptional regulation of miRNA genes.

2. Defining the transcriptional machinery driving miRNA expression

The primary machinery involved in miRNA transcriptional regulation was first investigated by Lee et al. They sought to define the polymerase(s) responsible for miRNA transcription, as few were engaged in this pursuit. It was presumed that transcription of miRNAs was similar to that of small RNAs, namely tRNA, which remains restricted to RNA polymerase III (Pol III) for transcription. However, emerging reports provided evidence to suggest otherwise. Namely, Lee's group published in 2002 that pri-miRNAs are often over several kilobases long and contain enough uracil repeats to terminate transcription by Pol III [22]. Expressed sequence tag analysis further supported this theory with the discovery of chimeric transcripts that