MicroRNA Pathways: An Emerging Role in Identification of Therapeutic Strategies

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Abstract: For years researchers have exerted every effort to improve the influential roles of microRNA (miRNA) in regulating genes that direct mammalian cell development and function. In spite of numerous advancements, many facets of miRNA generation remain unresolved due to the perplexing regulatory networks. The biogenesis of miRNA, eminently endures as a mystery as no universal pathway defines or explicates the variegation in the rise of miRNAs. Early evidence in biogenesis ignited specific steps of being omitted or replaced that eventuate in the individual miRNAs of different mechanisms. Understanding the basic foundation concerning how miRNAs are generated and function will help with diagnostic tools and therapeutic strategies. This review encompasses the canonical and the non-canonical pathways involved in miRNA biogenesis, while elucidating how miRNAs regulate genes at the nuclear level and also the mechanism that lies behind circulating miRNAs.

Keywords: miRNA biogenesis, canonical pathways, non-canonical pathways, circulating miRNAs.

1. INTRODUCTION

Science is in fact abounding with mysterious cellular functions. Through the discovery of genes, retrospectively, countless attempts have been made to determine how and what governs the expression of genes and proteins in cells. In disentangling these mysteries only a small portion of the whole gene regulation has been observed, for instance, the discovery of governing regulatory proteins and the transcription of DNA. Similarly, RNAs, such as non-coding small RNAs, were discovered to be vital in gene silencing.

The central dogma of molecular biology comprises replication, transcription, and translation, which presides over the flow of genetic information within the biological system. During the flow, a diverse collection of miRNAs are transcribed. MicroRNAs (miRNAs) have emerged recently as a new class of small evolutionarily conserved non-coding RNAs that negatively regulate gene expression [1-3]. miRNAs are a class of noncoding RNAs 18 to 25 nucleotides long that inhibit the expression of target genes by affecting the translation and/or stability of mRNA by binding to their target sites in the 3′UTR and 5′UTR of the mRNA [4]. According to the miRNA database miRBase, 2578 human mature miRNA sequences have been published (http://www.mirbase.org) [5]. These minuscule miRNAs (~21-23 nt) perpetrate heterochrony, cell differentiation, cell proliferation, cell death, metabolic control, transposon silencing and antiviral defence in cells [6]. MicroRNAs regulating cell function both at transcriptional and posttranscriptional levels which open up a new area of research and plays an emerging role in the identification of new therapeutic strategies. Endogenous miRNA endures across diverse array of plants, animals and fungi by expressing through transcriptional machinery hijack [7]. Evolutionary duplication generates clustered miRNAs which are co-transcribed to primary transcripts and cleaved into multiple miRNAs. Ordinarily, miRNAs are found in three genomic locations such as introns of protein-coding genes, introns of non-coding genes and exons of non-coding genes. As an exception, others have reported that miRNA genes possess their very own independent transcription units [8-10]. Analysis of miRNA genes indicates large numbers of miRNAs decoded within introns of protein-coding genes while 30% were reported within exons of long non-protein coding transcripts [11]. Presence of RNA Polymerase II (Pol II) in miRNA transcription instigated the exploration of miRNA gene structure as promoters and terminators [12, 13]. Many miRNAs regardless intergenic or intronic, possess their very own transcription initiation regions, adding more layers to complexity. Nevertheless, de novo research has led to the consensus that intragenic miRNAs on the same strand as the host are co-transcribed by Pol II while intergenic miRNAs are transcribed from their own Pol II or RNA Polymerase III (Pol III) promoter [7]. The Pol III promoters while permitting transcription of miRNAs with the Alu sequences, mammalian wide inter-