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Review

The potential of miR-183 family expression in inner ear for regeneration, treatment, diagnosis and prognosis of hearing loss

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Abstract

miRNA-183 family, in normal biology, is expressed in a harmonious and stable manner in the neurosensory organs and cells. Studies have also shown that miRNA-183 family, in different pathways, affects the neurosensory development, maintenance, survival and function. In addition, it has potential neuroprotective effects in response to neurosensory destructive stimulations. miRNA-96 mutation causes hereditary deafness in humans and mice, and therefore affects the inner ear activity and its maintenance. Certain roles have been identified for miR-96 in the maintenance and function of the inner ear. The comparison of the target genes of family-183 in transcriptomes of newborn and adult hair cells shows that hundreds of target genes in this family may affect development and maintenance of the ears. Identifying the genes that are regulated by miRNA-183 family provides researchers with important information about the complex development and environmental regulation of the inner ear, and can offer new approaches to the maintenance and regeneration of hair cells and auditory nerve.

Keywords: miRNA-183 family; Hearing loss; miRNA; Inner ear; Hair cell

Contents

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1. Introduction

1.1. miRNAs

miRNAs are a group of noncoding small RNAs with 21–23 nucleotides in length, which have specific interactions with their special mRNAs. They degrade the mRNA and inhibit the translation. miRNA genes comprise about 1% of the genome of different species, and each of them has hundreds of target genes. Over 2500 miRNAs have been identified in the human genome that regulate 30% of the proteins' coding genes. These small regulatory molecules were first identified in 1993, are found mainly in the chromosomal fragile sites, and in various diseases, are prone to deletion, addition, chromosomal translocation, and epigenetic changes (Bartel, 2004; Bushati and Cohen, 2007).

1.2. miRNA biogenesis

miRNA in the nucleus transcripts the gene and produces pri-miRNA and subsequently a precursor named pre-miRNA under the nuclear RNaseIII (endonuclease) enzyme called Drosha. Afterwards, pre-miRNA is transported to the cytoplasm by the protein Exportin 5. The molecule is cleaved by another enzyme called Dicer in the cytoplasm and develops a 21- to 23-nucleotide, double-stranded sequence. One of the strands is decomposed and the other strand is localized in the silencer complex (RNA-RISC) (Fig. 1). This activates the complex targets of the intended mRNA, binds to the mRNA 3′UTR end, and exerts its inhibitory effect. Through inhibiting protein translation or decomposing the target mRNA, miRNA exerts its effects in regulating gene expression (Bartel, 2004; Bushati and Cohen, 2007; Brennecke et al., 2005).

2. miRNA-183 family

The family miRNA-183 consists of three miRs: 183, 96 and 182. These miRNAs are concurrently expressed during development and are required for proper development of the sensory organs (Dambal et al., 2015). miR-96 was the first identified human miRNA of the cluster (Mourelatos et al., 2002), and miR-182 and miR-183 were identified one year later (Lim et al., 2003; Lagos-Quintana et al., 2003; Aravin et al., 2003). The three miRNAs are located adjacent to each other, with about 4 kb-span between miR-96 and miR-182, and transcribed as a long primary transcript. Then, they are processed into three individual precursor miRNAs (Jalvy-Delvaille et al., 2012). The sequence homology of miRs-183, - 96 and -182 and the conservation of their genomic organization as a cluster in bilaterian organisms represent an evolutionary benefit. In humans, the cluster is located on chromosome 7, with a 4.2 kb intergenic region between miRs-96 and -182. However, the murine miR-183 cluster is located on chromosome 6 with 3.6 kb between miRs-96 and -182 (Dambal et al., 2015). Mutation in miRNA-96 causes deafness in the locus of DFNA50. However, miRNA-96 is one of the members of miRNA-183 family, and miRNA-183, 182, 96 are all derived from a common primary transcript (Weston et al., 2006; Xu et al., 2007; Saini et al., 2008). In addition, miRNA-183 family members have a highly similar sequence (Mahmoodian sani et al., 2016) (Fig. 2). Interestingly, evolutionary variance from U to A in miRNA-183 causes miRNA-

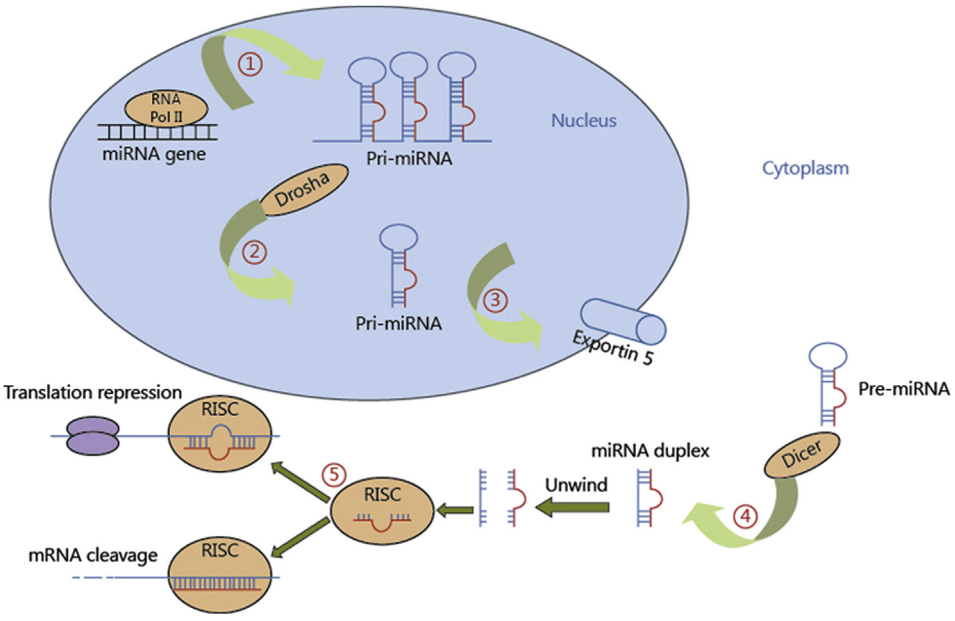

Fig. 1. miRNA biogenesis is a multistep process 1- miRNA genes are transcribed by RNA polymerase II in the nucleus 2- the resulting primary transcript is cleaved by Drosha to produce pre-miRNA 3- exportin-5 mediated transport pre-miRNA to the cytoplasm 4- pre-miRNA undergoes its final processing step, which consists of Dicer-dependent cleavage just below the stem loop to produce a miRNA duplex 5- The mature miRNA strand is subsequently incorporated into the RNA-induced silencing complex (RISC) where it directly binds to a member of the AGO protein family (Bushati and Cohen, 2007; Mahmoudian-sani et al., 2017).

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