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BRAIN RESEARCH

Review

Little but loud: Small RNAs have a resounding affect on ear development

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ABSTRACT

The impact of small RNA function has resonated throughout nearly every aspect of eukaryotic biology and captured the varied interests of researchers, whether they are endeavoring to understand the basis of development and disease or seeking novel therapeutic targets and tools. The genetic regulatory roles of microRNAs (miRNAs) are particularly interesting given that these often highly conserved factors post-transcriptionally silence many complementary target genes by inhibiting messenger RNA translation. In this regard, miRNAs can be considered as counterparts to transcription factors, the ensemble of which establishes the set of expressed genes that define the characteristics of a specific cell type. In this review, evidence supporting a resounding role for small RNAs in development and maturation of sensory epithelia in the mouse inner ear will be considered with an emphasis on the contribution of one hair cell miRNA family (miR-183, miR-96, and miR-182). Although there is much yet to be explored in this fledgling aspect of ear biology, the breadth of miRNA expression and functional requirement for ear development are already sounding off.

Contents

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1. Introduction

Development of the mammalian inner ear requires coordinated transformation of a uniform sheet of cells to form an intricate labyrinthine structure that includes strategic positioning of vestibular and auditory sensory epithelia, and appropriate histological organization of epithelial supporting cells and mechanosensory hair cells. Many studies have revealed the importance of various regulatory proteins including morphogens and transcription factors on patterning, morphogenesis and histogenesis (reviewed in Fritzsch et al., 2007; Kelley, 2007), where coordinated expression and interaction contribute to precision in developmental transitions from precursor cells to differentiated cell types. Nevertheless, recent studies regarding the genetic regulatory roles of small RNAs (reviewed in Amaral et al., 2008) suggest that such developmental transitions in the inner ear are not exclusively orchestrated by the regulatory functions of proteins. Indeed, there is substantial evidence for the widespread importance of microRNAs (miRNAs) in post-transcriptional regulation of target gene expression affecting development, cell differentiation and maintenance, and disease (reviewed in Hobert, 2008; Makeyev and Maniatis, 2008). There are approximately 500 mammalian miRNAs representing about 2% of known genes and estimated to affect the expression of one-third of known protein-coding genes (Griffiths-Jones, 2004; Griffiths-Jones et al., 2006). In this review, consideration will be given to the general function of miRNAs in post-transcriptional regulation of target gene expression and challenges to determining individual miRNA functions. Moreover, evidence for the expression and biological significance of miRNAs in development of the mouse inner ear are presented with a particular focus on specific miRNA families contributing to neurogenesis and innervation, epithelial development, and hair cell differentiation.

2. miRNA biogenesis and function

To best appreciate the role of miRNA-mediate gene regulation and the challenges to determining individual miRNA functions in development and maintenance of the inner ear, a brief review of miRNA biogenesis and function is warranted. The topic has been reviewed in detail from a number of interesting viewpoints including development and disease (Ambros, 2004; He and Hannon, 2004; Wienholds and Plasterk, 2005; Flynt and Lai, 2008; Stefani and Slack, 2008).

2.1. *miRNA biogenesis*

MicroRNA genes are expressed as capped and polyadenylated RNA polymerase II transcripts (Cai et al., 2004). Among human and mouse miRNA genes, approximately half reside within introns and are presumably co-expressed with known protein-coding genes, and approximately one-third reside in tandem with another miRNA gene(s) and exhibit coordinated expression (Saini et al., 2008). The production of functional miRNAs is mediated by the miRNA pathway (Fig. 1A). Unprocessed miRNA transcript, termed primary miRNA (pri-miR), contains the miRNA sequence within either side of a mostly base-paired stem-loop or hairpin structure. In the nucleus, DiGeorge syndrome critical region 8 (Dgcr8) protein is

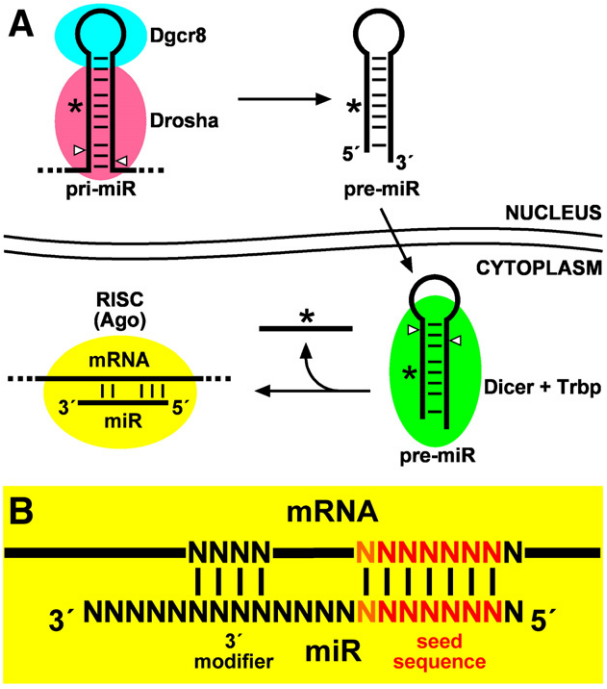

Fig. 1 – miRNA biogenesis and function. (A) The miRNA pathway. Primary miRNA (pri-miR) transcript processing in the nucleus requires Dgcr8 and the ribonuclease III family member, Drosha. The short hairpin precursor miRNA (pre-miR) is exported from the nucleus and subsequently processed by another ribonuclease III family member, Dicer, with Trbp. The mature miRNA strand is separated from the complementary strand (so-called "star" strand denoted by an asterisk) and is associated with an Argonaute (Ago) protein within the RNA induced silencing complex (RISC). RISC utilizes the miRNA as a guide sequence to discriminately bind target mRNAs and primarily affects translational repression. (B) miRNA–target mRNA interaction. Target mRNA is primarily discriminated through Watson–Crick base pairing to the miRNA "seed" sequence comprising nucleotides 2 through 7 (red) or 8 (orange). Other base-pairing interactions near the 3′ end of the miRNA can contribute further specificity and/or affinity.