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MicroRNAs: Meta-controllers of gene expression in synaptic activity emerge as genetic and diagnostic markers of human disease

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ABSTRACT

MicroRNAs are members of the non-protein-coding family of RNAs. They serve as regulators of gene expression by modulating the translation and/or stability of messenger RNA targets. The discovery of microRNAs has revolutionized the field of cell biology, and has permanently altered the prevailing view of a linear relationship between gene and protein expression. The increased complexity of gene regulation is both exciting and daunting, as emerging evidence supports a pervasive role for microRNAs in virtually every cellular process. This review briefly describes microRNA processing and formation of RNA-induced silencing complexes, with a focus on the role of RNA binding proteins in this process. We also discuss mechanisms for microRNA-mediated regulation of translation, particularly in dendritic spine formation and function, and the role of microRNAs in synaptic plasticity. We then discuss the evidence for altered microRNA function in cognitive brain disorders, and the effect of gene mutations revealed by single nucleotide polymorphism analysis on altered microRNA function and human disease. Further, we present evidence that altered microRNA expression in circulating fluids such as plasma/serum can correlate with, and serve as, novel diagnostic biomarkers of human disease.

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Abbreviations: APT1, Acyl protein thioesterase 1; AD, Alzheimer's disease; Ago, Argonaute; ASD, Autism spectrum disorder; BD, Bipolar disorder; CSF, Cerebrospinal fluid; eIF, Eukaryotic initiation factor; FMRP, Fragile X mental retardation protein; FXR1P/FXR2P, Fragile X-related proteins 1 or 2; Hsa21, Human chromosome 21; HCC, Human hepatocellular carcinoma; LIMK1, LIM Kinase 1; LPS, Lipopolysaccharide; LTP, Long term potentiation; LTD, Long term depression; mRNA, Messenger RNA; mGluR, Metabotropic glutamate receptor; MS, Multiple sclerosis; PUM, Pumilio proteins; PUF, Pumilio-Fem3 binding factor; qRT-PCR, Quantitative real-time PCR; RMS, Rhabdomyosarcoma; RNase, Ribonuclease; RISC, RNA-induced silencing complex; SNP, Single nucleotide polymorphism; TBI, Traumatic brain injury; 5′UTR/3′UTR, 5′ or 3′ untranslated region.

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1. Introduction

The discovery of microRNAs at the turn of the 21st century marked the beginning of a new era in cell biology, and permanently changed our view of the relationship between gene expression and protein expression. Analysis of the correlation between genes encoding messenger RNAs (mRNAs) and human disease has expanded to include those sequences in the remaining ~90% of eukaryotic genomes that generate non-coding RNAs. The microRNAs serve as meta-controllers of gene expression and are crucial for the cellular changes that are necessary for development. In the brain, microRNAs serve essential roles in dendritic spine formation and function, and in synaptic plasticity are required for normal cognitive function. A complete understanding of the mechanisms that regulate microRNA expression is critical, especially given the correlation between dysregulated microRNAs and several neurological disorders (Saugstad, 2010). Although not discussed herein, recent reviews discuss two very important levels of microRNA regulation including new transcription of microRNA-encoding genes by activity-regulated transcription factors like CREB and Mef (Flavell and Greenberg, 2008), and regulation of RNA processing events that lead to mature microRNAs (Newman and Hammond, 2010).

There is intense interest in microRNA gene mutations as the underlying cause for human diseases, and for their potential as novel therapeutics for the treatment of such disorders. The probability that mutations in genes that encode microRNAs, components of the biosynthesis machinery, and/or their mRNA targets, drives new genetic studies to identify links to human diseases. The analysis of single nucleotide polymorphisms provides a powerful tool to link altered microRNA expression with human diseases. MicroRNAs are also found in circulating fluids such as plasma/serum and cerebro-spinal fluid (CSF), and studies show evidence for altered expression of microRNAs correlating with human diseases. Thus, the microRNAs have evolved from their role as metacontrollers of gene expression to serve as genetic markers and non-invasive biomarkers for the diagnosis, treatment and progression of human disease.

2. MicroRNA processing, RISC formation and RNA binding proteins

MicroRNAs are small, ~20–24 nucleotide, genomically encoded RNAs that regulate mRNA expression by base-pairing to sequences in the mRNA, usually in the 3′ untranslated region (3′UTR) (Bartel, 2009). Primary precursor microRNAs are transcribed by RNA polymerase II in the nucleus and are then processed into 70–80 nucleotide precursor microRNAs by the microprocessor complex, minimally composed of the ribonuclease (RNase) III endonuclease Drosha and its binding partner DGCR8/Pasha (Lee et al., 2003; Newman and Hammond, 2010). Precursor microRNAs are exported to the cytoplasm by exportin 5 (Yi et al., 2003) where they are processed again into short ~22 nucleotide duplexes by the RNase III Dicer, which is part of a pre-microRNA processing complex (Lee et al., 2003; Bartel, 2004). The pre-microRNA, Dicer and another RNase III endonuclease, Argonaute 2 (Ago2), form the RNA-induced silencing complex (RISC) (Landthaler et al., 2008). One strand of the short RNA duplex is loaded into the Ago2-containing, RISC (Newman and Hammond, 2010) to form a microRNA silencing complex, while its complementary (passenger) strand is subsequently degraded (Filipowicz et al., 2005). In mammals, Ago2 is the only Argonaute family member with endonuclease activity (Filipowicz et al., 2005; Hock and Meister, 2008). Analysis of the mRNAs that co-immunoprecipitate with Dicer suggests that Dicer and its associated proteins are not part of the microRNA effector complexes, since the Dicer-enriched transcripts share no significant similarity to the microRNA targets immunoprecipitated with Ago (Landthaler et al., 2008). Thus, the Ago proteins disengage from the RISC loading complex before targeting mRNAs (MacRae et al., 2008). Nucleotides in the mature microRNA form base-pairs with complementary sequences in the mRNA which forms a short helix. Complete complementarity between the 20–22 nt length of the small RNA and the mRNA leads to degradation, hence 'silencing' of the transcript. In contrast, partial base pairing, specifically between nucleotides 2–8 of the microRNA (its seed sequence) and the mRNA leads primarily to translation suppression and some degradation (Baek et al., 2008).

A major unresolved question in microRNA-mediated translation regulation is how do the microRNAs physically find their target mRNAs in the cell, and how do protein–protein interactions facilitate targeting (Nelson et al., 2004)? The free energy of base pairing drives association of the complementary microRNA with its target mRNA (Hofacker, 2007); however, it is not known how these two nucleic acid strands are brought into close enough proximity to achieve helix formation. As described above, mature microRNAs are associated with Ago2. A number of proteins have been co-purified with Ago2 that could potentially participate in this interaction, including family member Ago1, several RNA binding proteins such as the Fragile X mental retardation protein (FMRP), and putative RNA binding proteins like Vasa intronic gene (VIG), and an RNA recognition motif-containing protein, Trinucleotide repeat-containing 6B, (TNRC6B) (Caudy et al., 2002; Ishizuka et al., 2002; Meister et al., 2005). Both FMRP and TNCR family members will be discussed in more detail below, along with other proteins that associate with Ago2 or that effect microRNA-mediated regulation, including the Pumilio proteins and the putative helicase MOV10.

FMRP is an RNA binding protein that is absent in the most common form of inherited mental retardation, Fragile X Syndrome (Bassell and Warren, 2008). In addition to associating with approximately 4% of brain mRNAs (Ashley et al., 1993; Brown et al., 2001), FMRP has also been implicated in translation regulation—both activating and suppressing translation of its bound RNAs (Brown et al., 2001). Two separate studies in *Drosophila* showed that FMRP associated with Ago2 (Caudy et al., 2002; Ishizuka et al., 2002). A subsequent study showed that mammalian FMRP and its autosomal paralogs, fragile X-related proteins 1 and 2 (FXR1P and FXR2P) associated with Dicer and other components of RISC including Ago (Jin et al., 2004). Phosphorylation of FMRP eliminates association with Dicer and may function as a switch for association with the microRNA pathway (Cheever and Ceman, 2009). FMRP has been demonstrated to directly associate with microRNAs in vitro and to specifically anneal microRNAs to RNAs containing the correct seed sequence (Plante and Provost, 2006). The *Drosophila* ortholog of FMRP has also been shown to regulate levels of miR-124, a microRNA that regulates dendritic branching (Xu et al., 2008). Importantly, FMRP isolated from brain specifically associates with a collection of microRNAs including miR-134 and miR-125b, the latter regulating NR2A receptor expression in an FMRP-dependent manner (Edbauer et al., 2010) (Fig. 1). Thus, FMRP is an RNA binding protein that directly or indirectly associates with microRNAs to regulate protein expression of FMRP-bound mRNAs.

TNRC6B is one member of a family of proteins that are vertebrate paralogs of the scaffolding protein, GW182. GW182 is present in the core microRNA silencing complex and is important for localization to processing bodies (P-bodies), as well as for translation silencing and mRNA degradation (Behm-Ansmant et al., 2006; Eulalio et al., 2008). All family members contain an abnormally high content of GW/WG repeats and a C-terminal RNA recognition motif domain (Baillat and Shiekhattar, 2009). TNRC6A, -B and -C associate with all four human Ago proteins complexed with microRNAs, and the TNRC6 proteins contain a P-body localization domain (Baillat and Shiekhattar, 2009). GW182 is required for microRNA-mediated silencing, although it is unclear how these proteins perform that function. Recent evidence suggests that GW182 interferes with mRNA circularization and also recruits the deadenylase complex through interaction with poly(A) binding protein C1 (Zekri et al., 2009).

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