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BRAIN RESEARCH

Review

MicroRNAs as a molecular basis for mental retardation, Alzheimer's and prion diseases

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ABSTRACT

MicroRNAs (miRNAs) are small, ~21- to 23-nucleotide (nt) non-coding RNA species that act as key regulators of gene expression along a central and well-defined cellular process known as RNA silencing, and involving the recognition and translational control of specific messenger RNA (mRNAs). Generated through the well-orchestrated and sequential processing of miRNA precursor molecules, mature miRNAs are subsequently incorporated into miRNA-containing ribonucleoprotein effector complexes to regulate mRNA translation through the recognition of specific binding sites of imperfect complementarity located mainly in the 3′ untranslated region. Predicted to regulate up to 90% of the genes in humans, miRNAs may thus control cellular processes in all cells and tissues of the human body. Likely to play a central role in health and disease, a dysfunctional miRNA-based regulation of gene expression may represent the main etiologic factor underlying diseases affecting major organs, such as the brain. In this review article, the molecular mechanisms underlying the role and function of miRNAs in the regulation of genes involved in neurological and neurodegenerative diseases will be discussed, with a focus on the fragile X syndrome, Alzheimer's disease (AD) and prion disease.

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Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; APP, β-amyloid precursor protein; BACE, APP-converting enzyme; FMRP, fragile X mental retardation protein; miRNA, microRNA; miRNP, miRNA-containing RNP; mRNA, messenger RNA; PCR, polymerase chain reaction; qRT-PCR, quantitative real-time PCR; RNP, ribonucleoprotein; RT, reverse transcription; siRNA, small interfering RNA; UTR, untranslated region

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1. Biogenesis and function of microRNAs

The microRNA (miRNA)-guided RNA silencing pathway is a recently discovered gene regulatory process present in eukaryotic cells and based on small, ~21- to 23-nucleotide (nt) non-coding RNAs, known as miRNAs. Our current knowledge on the biogenesis and action of miRNAs in humans has been reviewed recently (Bartel, 2009).

Encoded by the genome of nucleated cells, miRNA genes are transcribed, either by RNA polymerase II (Lee et al., 2004) or III (Borchert et al., 2006), into long RNA transcripts that fold on themselves to form primary miRNAs (pri-miRNAs). These RNA species are recognized and trimmed into miRNA precursors (pre-miRNAs) by the nuclear ribonuclease III (RNase III) Drosha (Lee et al., 2003), acting in concert with the DiGeorge syndrome Critical Region gene 8 (DGCR8) protein within the microprocessor complex (Denli et al., 2004; Gregory et al., 2004; Han et al., 2004). After being exported to the cytoplasm via Exportin-5 (Lund et al., 2004; Yi et al., 2003), pre-miRNAs are processed by the pre-miRNA processing complex, composed of the RNase III Dicer (Provost et al., 2002; Zhang et al., 2002) and its cofactor TAR RNA binding protein (Chendrimada et al., 2005; Haase et al., 2005), into a miRNA:miRNA* duplex. The forming ribonucleoprotein (RNP) complex is then joined by the Argonaute 2 protein, and the miRNA guide strand is selected, based on the relative stability of the duplex extremities, to form a miRNA-containing RNP (miRNP) complex (Chendrimada et al., 2005). The associated miRNAs confer to the miRNP complexes the ability to recognize cellular messenger RNAs (mRNAs) through specific binding sites generally located in the 3′ untranslated region (UTR), guiding the miRNPs for the regulation of specific mRNAs, as reviewed previously (Kim, 2005; Zamore and Haley, 2005). The targeted mRNAs will be cleaved and degraded if the complementarity between the miRNAs and their binding site is perfect, or its translation regulated if the complementarity is imperfect (Bartel, 2004). In this latter case, the repressed mRNAs are translocated to the P-bodies, after which they are either degraded or returned to the translational machinery for expression upon a specific cellular signal (Bhattacharyya et al., 2006; Liu et al., 2005). Although miRNAs are known mainly as repressors of gene expression, they have also been shown to enhance mRNA translation under specific cellular conditions (Vasudevan et al., 2007).

2. MicroRNAs in health and disease

Involving relatively few protein components, this complex and well-integrated regulatory circuit plays a key role in modulating a plethora of mRNA targets (Perron and Provost, 2008). Predicted to regulate up to 90% of the genes in humans (Miranda et al., 2006), miRNAs may control every cellular processes in all cells and tissues of the human body! Involved in the fine tuning of gene expression, a normal miRNA function is required for a tightly regulated expression of the cellular proteins (see Fig. 1A), which is critical for the maintenance of health and prevention of disease, as discussed in Perron et al. (2007). In contrast, deregulated protein expression induced by a dysfunctional miRNA-based regulatory system may represent the main etiologic factor underlying diseases affecting major systems, including the central nervous system (CNS).

For instance, a deregulated miRNA control of mRNA translation may occur when the function of a core protein component of the miRNA pathway is compromised, i.e., is the subject of a deletion, mutation or misexpression. In this situation, a global negative impact on miRNA biogenesis and/or function is observed, as in the case of the fragile X mental retardation protein (FMRP) in the fragile X syndrome (see Section 4) (Plante and Provost, 2006) and of the behavioral and neuronal deficits associated with haploinsufficiency of the *Dgcr8* gene (Stark et al., 2008).

A loss of miRNA control may also result from the deletion, mutation or misexpression of a miRNA, or that of its corresponding binding site, in a sequence of events leading to miRNA:miRNA binding site pairs becoming dysfunctional or to new miRNA:miRNA binding site functional combinations emerging. The ensuing deregulation of mRNA translation may then lead to misexpression, i.e., either downregulated or upregulated expression, of a specific protein and provoke the development of a disease (Perron et al., 2007), which may be the case of the β-amyloid precursor protein (APP)-converting enzyme (BACE) in Alzheimer's disease (AD) (see Section 5) (Boissonneault et al., 2009). Hence the relevance of using miRNAs as biomarkers and therapeutic targets/drugs in human diseases affecting major organs, such as the brain.

3. MicroRNAs in neurological and neurodegenerative diseases

Compelling evidences now link miRNAs to the control of neuronal development and differentiation, as recently reported by Decembrini et al. (2009). In that study, a set of 4 miRNAs (miR-129, miR-155, miR-214 and miR-222) was found to repress translation of mRNAs encoding for Xotx2 and Xvsx1, which directs the differentiation of late retinal progenitor cells into bipolar neurons in *Xenopus*. The interest in the functions of miRNAs in the CNS has also expanded to include their roles in neurodegeneration, of which little is known. Investigations have begun to reveal the influence of miRNAs on both neuronal survival and the accumulation of toxic proteins that are associated with neurodegeneration (Eacker et al., 2009). For instance, conditional Purkinje cell-specific ablation

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