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Review article

MicroRNA: Small RNA mediators of the brains genomic response to environmental stress

Sharon L. Hollins[a], Murray J. Cairns[a,b,*]

[a] School of Biomedical Sciences and Pharmacy and the Hunter Medical Research Institute, the University of Newcastle, Callaghan, NSW 2308, Australia
[b] Schizophrenia Research Institute, Sydney, NSW, Australia

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ABSTRACT

The developmental processes that establish the synaptic architecture of the brain while retaining capacity for activity-dependent remodeling, are complex and involve a combination of genetic and epigenetic influences. Dysregulation of these processes can lead to problems with neural circuitry which manifest in humans as a range of neurodevelopmental syndromes, such as schizophrenia, bipolar disorder and fragile X mental retardation. Recent studies suggest that prenatal, postnatal and intergenerational environmental factors play an important role in the aetiology of stress-related psychopathology. A number of these disorders have been shown to display epigenetic changes in the postmortem brain that reflect early life experience. These changes affect the regulation of gene expression though chromatin remodeling (transcriptional) and post-transcriptional influences, especially small noncoding microRNA (miRNA). These dynamic and influential molecules appear to play an important function in both brain development and its adaption to stress. In this review, we examine the role of miRNA in mediating the brain's response to both prenatal and postnatal environmental perturbations and explore how stress- induced alterations in miRNA expression can regulate the stress response *via* modulation of the immune system. Given the close relationship between environmental stress, miRNA, and brain development/function, we assert that miRNA hold a significant position at the molecular crossroads between neural development and adaptations to environmental stress. A greater understanding of the dynamics that mediate an individual's predisposition to stress-induced neuropathology has major human health benefits and is an important area of research.

Contents

Abbreviations: miRNA, microRNA; DGCR8, DiGeorge syndrome critical region gene 8; Ago, Argonaut; RISC, RNA- Induced Silencing Complex; MRE, miRNA recognition element; poly I:C, polyinosinic-polycytidylic acid; INF-α, Interferon alpha; PFC, prefrontal cortex; THC, Δ^9tetrahydrocannabinol; CB_1, cannabinoid receptor; DA, dopamine; endocannabinoid, endogenous cannabinoid; eCB, endocannabinoid; AEA, anandamide; $GABA_A$, gamma-aminobutyric acid A; MIA, maternal immune activation; EC, entorhinal cortex; GD, gestational day; GCs, glucocorticoids; FAS, Fetal Alcohol Syndrome; HPA, hypothalamic-pituitary-adrenal; NMDA, N-methyl-D-aspartate; PND, post-natal day; MEF2, Myocte Enhancer Factor 2; MHCI, Major histocompatibility complex class I; IL-6, interleukin-6; MAPK, mitogen-activated protein kinase; TLR, toll-like receptor; LPS, lipopolysaccharide; IFN-γ, interferon-gamma; TNF- α, tumour-necrosis factor-alpha; nAChRs, nicotinic acetylcholine receptors; CHRNA7, α7 nAChR subunit; ACh, acetylcholine; AChE, acetylcholinesterase; mPFC, medial prefrontal cortex; PVN, paraventricular hypothalamus; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; GR, glucocorticoid receptor; BDNF, brain-derived neurotrophic factor; IPA, Ingenuity Pathway Analysis; GATHER, Gene Annotation Tool to Help Explain Relationships; WNT, Wingless/int.

* Corresponding author at: School of Biomedical Sciences and Pharmacy MSB, University of Newcastle, Callaghan, NSW 2308, Australia.
E-mail address: Murray.Cairns@newcastle.edu.au (M.J. Cairns).

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1. Introduction

The adult brain is an incredibly complex organ comprising many different cells types with an astonishing capability for intercellular connectivity. This is utilized to generate even more complicated networks with the capacity to integrate neural input through synapses and synaptic plasticity to form, maintain and modify circuits. These circuits provide the neural basis for sensation, cognition, memory and motivation. The organisation of this assembly at the molecular level is no less complex and involves many layers of gene regulation. At the transcriptional level there is a myriad of epigenetic influences on chromatin structure including DNA methylation and histone modifications that modify the synthesis of RNA. This however, is just the beginning of mRNA's journey that will take it from the nucleus out into the cytoplasm to a discrete site of translation or interaction point. The intracellular traffic and fate of RNA is highly organized by ribonucleoprotein complexes and small non-coding RNAs. As relative newcomers on this scene, miRNAs are small non-coding RNAs (~22 nucleotides) that post- transcriptionally modulate gene expression by either repressing translation or inducing degradation of mRNA. MiRNAs are abundant in the human brain and display a diverse range of regulatory functions in the central nervous system (CNS). One role emerging for miRNAs is in the cellular response to stress. These molecules and their extensive gene networks provide a mechanism to both drive important developmental initiatives and maintain system homeostasis. This later feature, in particular, comes to the fore at times of environmental adversity and may be modifying the system dynamics to provide the most appropriate conditions to buffer against cellular crisis.

The activation of the stress response by the CNS is necessary to maintain health and homeostasis, however, there are also consequences as these mechanisms can induce significant changes in neural structure and function that lead to the development of a broad range of psychopathology. One of the manifestations of this response is stress-induced neuronal atrophy (dendritic retraction) in key brain regions implicated in "depressive illness" (Christian et al., 2011; Cook and Wellman, 2004). Environmental stressors may be physiological, such as through exposure to toxins, pathogens, or nutrient deprivation; or psychological, occurring when we face a situation deemed to exceed our potential for coping. Both types of stress produce physiological and psychological responses, such as elevated blood pressure, elevated corticosteroids and deficits in sustained attention (reviewed by Evans and Cohen, 1987).

In particular, exposure to environmental stressors can bring about changes in expression of genes involved in the modulation of miRNA expression, as well as changes in expression of miRNA involved in the development and function of the CNS (Conaco et al., 2006; Uchida et al., 2010; Wiesen and Tomasi, 2009). This may be reflected in changes to the brain observed following stress exposure such as region-specific increases in microglia (Tynan et al., 2010); microglial and glutamatergic pyramidal neuron activation (Hinwood et al., 2011a,b; Tynan et al., 2010); dendritic retraction (Brown et al., 2005; Christian et al., 2011; Cook and Wellman, 2004; Martin and Wellman, 2011) and cognitive deficits (Hinwood et al., 2011a,b; Wei et al., 2007). Indeed, changes in miRNA expression levels are linked to neurodegeneration (reviewed by Nelson et al. (2008)), with recent evidence supporting a role for the dysregulation of miRNA expression in psychiatric and neurological disorders (Beveridge and Cairns, 2012; Geaghan and Cairns, 2014; Miller and Wahlestedt, 2010).

2. MiRNA biogenesis and function

MiRNA biogenesis is a two-compartment process (Fig. 1) beginning in the nucleus, with the transcription of primary (pri-) miRNAs by RNA polymerase II (pol II). The pri-miRNAs are 5′ capped and poly-adenylated, can be several kilobases long and may comprise of one (monocistronic) or several (polycistronic) miRNA precursors (Lee et al., 2002). The stem- loop (hairpin) structure is recognized by DGCR8 (DiGeorge syndrome critical region gene 8), which then docks with the RNase-III enzyme Drosha to form what is known as the Microprocessor complex (Gregory et al., 2006). Upon guidance by DGCR8, Drosha cleaves the stems to release the precursor (pre-) miRNA, hairpins of ~70 nucleotides with a two-nucleotide overhang at the 3′ end and 3′ hydroxyl and 5′ phosphate groups (Han et al., 2004; Lee et al., 2003, 2002). Pre-miRNAs are transferred to the cytoplasm by exportin-5 where they are further cleaved by Dicer, another RNase-III family member, to yield the mature, double-stranded duplex (~18-25 nucleotides), consisting of the antisense, or guide strand (miRNA) and a sense, or passenger strand (Lee et al., 2002; Yi et al., 2003). The guide strand becomes integrated with proteins from the Argonaut (Ago) family to form the RNA-Induced Silencing Complex, or RISC (Gregory et al., 2005; Preall et al., 2006; Siomi and Siomi, 2009). As either strand can be incorporated into the RISC, miRNA derived from the 5′ arm or 3′ arm of the precursor are denoted by a -5p or -3p postscript respectively (Alexiou et al., 2010). The miRNA 'activated' RISC then