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BRAINSTORM STUDENT JOURNAL

REVIEW

MicroRNAs in neuronal development and function: focus on Caenorhabditis elegans

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Abstract

MicroRNAs are small non-coding RNAs that post-transcriptionally regulate the expression levels of messenger RNAs, thus controlling local protein expression, a process important for polarized cells like neurons. They were first discovered in Caenorhabditis elegans, a recognized and versatile nematode model organism, as key regulators in developmental timing. Due to the high conservation of genes between the model and mammals, these miRNAs were found in other species as well. In addition, since the milestone discovery of miRNA lin-4 in 1993, more than 250 endogenous microRNAs have been identified, along with a multitude of functions. These small RNAs have been involved in processes at different multi-systemic levels, thus influencing neuronal function in a multitude of ways. However only a specific few have been experimentally proven to be associated with neural function in C. elegans, particularly lin-4, let-7, mir-1, mir-273, mir-84, and mir-29. In this review, we shall explore various miRNAs by presenting and hypothesizing their functions in the nervous system of C. elegans.

Keywords: Caenorhabditis Elegans, Nervous System, Structural and Cellular functions, Gene regulation, MicroRNAs.

Abbreviations

aco-1: aconitase 1

aco-2: aconitase 2

ASEL: ASE Left

ASER: ASE Right

AVM: anterior ventral microtubule

C. elegans: Caenorhabditis elegans

HLH-30: helix-loop-helix 30

IREB2: iron responsive element binding protein 2

miRNA: microRNA

ncRNA: non-coding RNA

shRNA: short hairpin RNA

TFEB: transcription factor EB

TGF: transforming growth factor

UTR: untranslated region

Introduction

Biological compartments can function and adapt with autonomy by localizing biological organelles and machinery. Perhaps the best example of this is the neuron, where local control of protein production and distribution allows for the compartmentalization of synaptic function and plasticity. This compartmentalization and polarization of its structure is possible thanks to the transport and localization of mRNA transcripts in different regions of the neuron. For proper local protein levels in different compartments, aside from local translation, a tight regulation on the level of protein expression is necessary. One such important level of regulation is at the post-transcriptional stage, notably by MicroRNA (miRNA).

MiRNAs are small non-coding RNA (ncRNA) molecules of about 20-25 nucleotides in length. They generally bind to the 3'-UTR (untranslated region) of their target mRNA and repress protein production by destabilizing the mRNA and translational silencing (1). A miRNA can bind many mRNAs and an mRNA can be bound by several miRNAs, resulting in a multi-level regulation on protein levels. Recent evidence suggests that not only mRNAs but also miRNAs are localized and enriched within subcellular outposts, but the mechanism of transport of these ncRNAs remains elusive (2). Some microRNA-encoding genes are expressed only at certain times in neurons, while others are expressed ubiquitously. Thus, they play prominent roles in diverse processes such as cell differentiation, metabolism, and development, highlighting the need to study the function of these ncRNAs in neural functions.

However, to date, few miRNAs have been studied in the global organism due to a lack of mutants in which specific miRNAs can be inactivated. Nevertheless, this can be overcome with the use of Caenorhabditis elegans (C. elegans) (3), a nematode model in which miRNAs were first discovered. The evolutionary conservation of miRNAs across species and the ease of genetic manipulation in this model makes it an ideal tool to study miRNAs (4,5).

With 302 nerve cells out of the 950 somatic cells in this hermaphrodite model, along with the 56 glial cells, the nervous system in C. elegans is its most complex organ by making up 37% of the somatic cells that are classified into at least 118 different neuron classes. This cellular diversity and its extensively mapped neuronal circuit make it a prime candidate for neuronal studies (6). In fact, every neuron in this hermaphrodite system has been labeled for the researcher's convenience.

In this organism, two methods are commonly used to explore miRNA function: (1) Genetic manipulation by silencing miRNA in vivo using short hairpin RNA (shRNA) and, (2) miRNA target prediction via 3'UTR alignment to various mRNA. The former expresses a causative link, while the latter is predictive. Despite the existence of such extensive methods, there are about 110 to 300 miRNAs, many of which are conserved in humans,

left to be explored. Thus, this review aims to study functions explored using one method followed by another, ranging from established to hypothesized, to build a more comprehensive idea of different neural functions of miRNA and how they could be studied.

Methods

This review is a combination of secondary data assimilated from 21 independent studies on specific RNAs and 5 reviews on miRNAs associated with specific functions. Most studies included were done on C. elegans. Articles were acquired through Pubmed and Google scholar searches done for the following terms: C. elegans miRNA function, neuronal miRNA, predictive analysis of miRNA.

An extensive use of abbreviations for different neurons in this model will be used in this review. A neuron's name begins with two or three capital letters which denote the neuronal class, and in some cases are followed by a number that associates its position in that denoted class. The three-lettered title is followed by letters L (left), R (right), D (dorsal) or V (ventral) if the neurons are radially symmetrical. For more information on the complete list of neurons, one could refer to WormAtlas' Individual Neuron Section.

Some functions of certain miRNAs have been established by different genetic knock-out studies, using short hairpin-RNA or deletion models, while others were derived from similarities in homologies by predicting the similarities in the 3'UTR regions of the target of mRNA to other mRNAs. Preliminary analysis was done for certain mRNA using PicTar, a microRNA target-finding algorithm that uses probabilistic models to provide the likelihood of sequences being a target rather than 3'UTR background. This searchable website provides details (3' UTR alignments with predicted sites) regarding microRNA target predictions in vertebrates, seven Drosophila species and three nematode species. Using this, we can identify potential targets of miRNA, and thus extend their pre-existing functions.

Results

Neural Symmetry

Generally, throughout the animal kingdom, one observes symmetry across the nervous system of animals. However, there exist deviations from this, with the size difference between temporal lobes in Humans and habenular nuclei in Zebrafish brain serving as examples (7). The lateralization of the nervous system is thought to increase functionality, which is required for the optimal functioning of complex actions (8). While much interest has been shown in studying the anatomical differences in this lateralization in the past, studies on the molecular mechanisms behind its establishment have picked up momentum. Such molecular factor has been shown to play a role in determining symmetry is the local miRNA population.

Like other members of the animal kingdom, the C. elegans nervous system possesses an overall symmetry in morphology, cell position, and axonal projections, despite the derivation of neurons from different cell lineages. However, the ASE left (ASEL) and ASE right (ASER) neurons, taste neurons located in the nerve ring of the worm, display asymmetries, which are dependent on miRNA lsy-6 and mir-273 (9, 10). The ASER neurons express the putative neuroreceptor gcy-5 and sense chloride ions, while ASEL neurons express the neuroreceptor gcy-7 and sense sodium ions.

The establishment of this left-right asymmetry is done during embryonic programming stages. Six cell divisions before the birth of ASEL neurons, T-box transcription factors TBX-37/38 are transiently expressed, which leads to the priming of lsy-6 locus by chromatin decompaction in the left neurons, but not in the right. This network's core relies on the notion of a bistable feedback loop of two transcription factors, die-1 and cog-1. Lsy-6 represses cog-1 by binding to complementary bases in cog-1 3'UTR. This marks lsy-6 as the first known asymmetrically expressed miRNA in the ASE neurons (11). Simultaneously, since lsy-6 does not effectively repress cog-1 transcription factor in ASER neurons, mir-273 is activated, which displays a complementary base sequence to die-1 3'UTR

region. Silencing of any of these miRNA genes has led to a loss of symmetry, which re-establishes their importance in the process (Fig. 1).

The C. elegans left and right AWC olfactory neurons are another example of asymmetry in this model. They are morphologically similar but take on stochastic asymmetric fates in late embryogenesis, such that the AWCON neuron expresses the chemoreceptor gene str-2 and the contralateral AWCOFF neuron does not. This asymmetry allows for the worm to distinguish between odors and is established by miRNA-71 via calcium mediated UNC-43/TIR-1/NSY-1 kinase signaling pathway in the future AWCON cell. nsy-4, encoding a claudin-like tight junction protein, and nsy-5, encoding an innexin gap junction protein, act in parallel to downregulate this pathway (12). Studies by Hsieh et al., 2012 have placed the function of the miRNA downstream of nsy-4 and nsy-5 junction proteins where it inhibits the expression of tir-1, a calcium signaling adaptor protein gene. Thus, its downregulation would lead to inhibition of Ca+ signaling in AWCON cells.

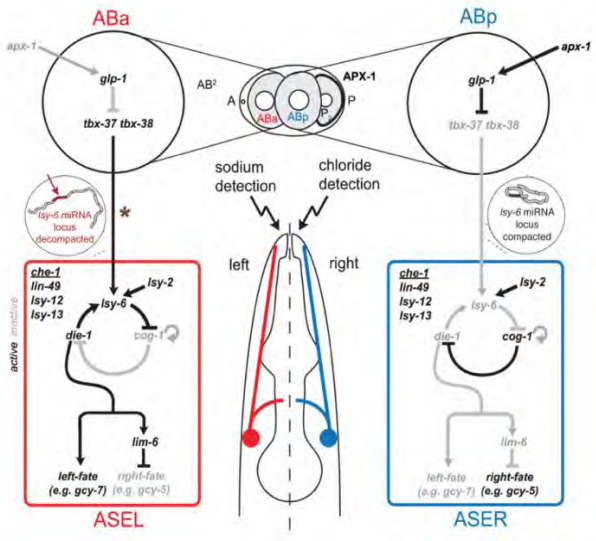

Figure 1. Summary of the previously described bi-stable feedback loop that regulates ASE left-right asymmetry. The bi-stable feedback loop consists of both transcription factors and micro-RNAs thqt controls the expression of downstream terminal differentiation genes. Adapted from Poole et al., (13).

Neural circuit formation and axonal guidance

Aside from systematic functions, miRNAs are also involved in structural functions in C. elegans, such as axon guidance. Lin-4, part of the miR-125 microRNA family, is commonly known to control developmental timings (14). More recent studies point towards a role in netrin-mediated axon attraction, where the abrupt initiation of lin-4 expression coincides with the timing of anterior ventral microtubule (AVM) axon guidance. During development of the nervous system, the AVM is guided to the ventral midline by two cues, one of which is UNC-6 (netrin) attractant. Loss-of-function lin-4 mutations showed increased axon attraction mediated by UNC-6 in AVM neurons, suggesting that the miRNA accumulation is involved in marking the end of axon guidance. This in turn affects neural circuit formation.

Another locale where miRNA have been found regulate circuit formation is in motor neurons. The UNC-129 gene, like the UNC-6 netrin gene, is required to guide pioneer motor axons along the dorsoventral axis of C. elegans (15). It encodes a member of the transforming growth factor-beta (TGF-beta) superfamily of secreted signaling molecules and is expressed in dorsal, but not ventral, rows of body wall muscles. Thus, its expression is required for motor axon guidance and guided cell migration. The gene contains two predicted let-7 sites in its 3'UTR, a miRNA that regulates synaptic remodeling and developmental time in neurons. Temporally, its expression in neurons reduces as it enters late larval stages, which is concordant with an elevation in let-7 levels (16). While this interaction in C. elegans is yet to be established, evidence for this exists in other models (17,18).

Neuronal autophagy

Autophagy, a biological process that involves the enzymatic breakdown of a cell's cytoplasm or cytoplasmic components, is integral to the establishment and maintenance of neuronal structure and function at a cellular level. Transcription factor EB (TFEB), specifically its orthologue helix-loop-helix 30 (HLH-30), is a conserved master transcriptional activator of autophagy and lysosomal genes that modulates C. elegans lifespan regulation and stress resistance (19). Under conditions associated with induction of autophagy, HLH-30 localized to the nucleus, thus

contributing to the transcription of autophagy-related and lysosomal genes.

MiR-1 homologs are muscle-enriched microRNAs that are highly conserved in evolution and important for mammalian heart and muscle development (20). This miRNA has been shown to regulate lysosomal biogenesis and ATP-ase function, through modulations of its subunits, in C. elegans (21). Specifically, the miRNA regulates lysosomal biogenesis through localization of HLH-30/TFEB, and consequently its nuclear localization. Although this experiment solely focuses on miR-1 in muscle function and its response to proteostatic stress, the results could be carried over to neurons as the microRNA and HLH-30 has been shown to be strongly associated with the neuromuscular junctions in C. elegans. Thus, miR-1 might play a role in autophagy at the neuromuscular junction, contributing to neuronal function.

Neuronal iron homeostasis

Balance of biochemical homeostasis is an important factor for neuronal structure integrity. Iron is essential as a cofactor of numerous enzymes, especially for ATP production, myelination and synthesis of DNA, RNA, proteins and neurotransmitters. MicroRNA-29, in mammals, has been linked to compensatory response associated with neuronal iron accumulation during adult life and aging (22). In C. elegans, similar accumulation has been observed, resulting in increased oxidative stress, protein insolubility and aging (23). The mir-29 family, in other models, have been found to target 3'UTR of mRNA off Iron Responsive Element

Binding Protein 2 (IREB2). IREB2 is responsible for the modulation of intracellular iron homeostasis by post-transcriptional regulation of key genes involved in iron uptake, storage, export, and utilization. The miRNA's upregulation with age is thus a mechanism to battle this aging-related increase in iron.

While evidence for miRNA-29 in C. elegans has not been found, miRNA-84 has been found to be homologous to it. Additionally, the C. elegans genome doesn't contain IREB2 homolog. However, looking for regions of local similarity between sequences via Basic Local Alignment Search Tool or BLAST analysis resulted in two genes, aco-1 (Aconitase 1) and aco-2 (Aconitase 2), possessing 57.1% and 26.2% similarity in identity to IREB2. In addition, translated proteins of these genes are capable of binding to mRNA to control the levels of iron inside cells. If the 3' regions of the genes possess the said similarity to IREB2, then the 3'UTR of the miRNA of the genes would be targets of mir-83 in C. elegans, thus may affect neuronal iron homeostasis. The genes themselves have also been shown to work through the tricarboxylic acid cycle, specifically in the mitochondria and the cytoplasm, which is similar to the function of the IREB2 protein output. Thus, this miRNA could be involved in maintaining biochemical balance in the neuron, adding another layer to its range of functions.

Conclusion

In this review, we have seen that microRNAs have various functions in the nervous system of C. elegans, from establishment of neural symmetry to neuronal iron homeostasis, ranging from involvement in more systematic functions to more cellular ones. This model's simple appearance at the gross anatomical level, contrasted with the expression of an incredible number of signaling molecules, makes it an ideal subject for both structural and molecular studies. In addition, given the remarkable conservation of developmental mechanisms across phylogeny, many of the principles of miRNAs discovered in C. elegans are likely to be applicable to higher animals.

A variety of methods, aside from traditional genetic experiments, can be used to understand the function of a miRNA. The ability of predicting the targets of the endogenous miRNAs is then crucial to understand the processes they are involved in. We can use a variety of prediction algorithms to understand and hypothesize their potential function based on the temporal and spatial expression profiles of the miRNA and its potential targets, or vice versa. This is thanks to the recurrent homology of certain miRNAs across species and the intrinsic property of the miRNA to interact with a certain 3'UTR region.

However, there are limitations to this approach. It has been found that miRNA also binds to the mRNA coding region, which is not accounted for in predictive algorithms. This increases the chance of error in our interaction prediction. However, due to the vast number of miRNAs that exist, it is impossible to screen everyone for a particular function, which is where predictive algorithms come into play as powerful screens prior to experimental confirmation.

Post confirmation, recent studies in the field have applied a clinical approach to the miRNA. Aside from miRNA regulation mRNA, they also regulate other miRNA, forming an integrated and tight post-transcriptional regulation network. The proper formation and function of neuronal networks is required for cognition and behavior, and microRNAs have emerged as key players in establishing this. It has also become clear that the miRNAs are often dysregulated in neurodevelopmental diseases, suggesting a role for miRNAs in the etiology and/or maintenance of neurological disease states. Thus, their function as 'master regulators' or 'fine-tuners' of gene expression in the nervous system is a rapidly evolving field (24). Hence, replacement or inhibition of downregulated or overactive miRNAs, respectively, may be clinically beneficial in regulating protein levels in disordered states. Much effort has been directed toward developing modified oligonucleotide mimetics to replace, or antisense oligonucleotides to inhibit, targeted miRNAs (25). Nevertheless, much work remains to be done to understand the precise mechanisms through which miRNAs regulate temporal and spatial dynamics of neuronal function, and to translate this knowledge into novel therapeutics for the treatment of neurological disorders.

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BRAINSTORM STUDENT JOURNAL

LETTER

The temptation of artificial intelligence

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Artificial Intelligence (AI) and neuroscience have a special relationship, with each field contributing to the development of the other. The layers of neurons in the brain were used as the basis for the development of a number of machine learning and deep learning algorithms, particularly the Artificial Neural Networks (ANNs), which have been booming for the last ten years. On the other hand, the usefulness of these ANNs for modelling brain functions in neuroscience is no longer in doubt. From modelling neuronal networks to behavioral responses, these innovative tools have provided means to better address crucial scientific questions in our field. More recently, progress in the field of AI has strongly affected two fundamental aspects of neuroscience –and science in general– namely the production of knowledge and its communication.

The capacity of AI algorithms to analyze and model complex datasets, with a large number of dimensions, makes them a natural ally for neuroscience today. Indeed, when this type of data is produced on a massive scale, it is impossible to analyze them with the scientist's eye only. The use of such algorithms has therefore progressed considerably. AI is able to capture a lot of the complexity of the brain, from the laws of thermodynamics governing signal transmission at the molecular level, to the computations of neural networks. It even allows to a certain extent to make predictions on the decision that a laboratory animal will make, for example, in the context of behavioral experiments. This endeavor is reflected in the Human Brain Project, where the goal is to model the entire brain in order to make predictions at any level (neuronal, circuit, behavioral, etc), thus expanding our knowledge of brain function. With hindsight, we could say that the human brain is not able to understand its own complexity and only powerful algorithms will be able to do so. Therefore, these algorithms could act as mediators between our brain as an object of study and our curious brain which seeks to know the Why and How. The problem, however, is that the AI algorithms that we broadly use are, for the most part, black boxes, impossible to understand from the human point of view. Thus, the knowledge they contain, which allows them to make their predictions and create models, remains inaccessible to us

scientists. A kind of retention of information. Solutions exist to partially solve this problem: AI explainability, a promising field studying how to dissect these deep learning algorithms once trained, to understand their choices. However, these tools have other disadvantages and are not widely used in neuroscience, where our main concern is often to choose a model with a good success rate in its predictions, rather than a model capable of being transparent.

The other field where AI has been frantically developing for the last few years and can significantly affect the field of neuroscience, on the aspect of knowledge communication, is text generation. Text generation algorithms are natural language processing algorithms that allow, for example, with just a few keywords and the choice of a template, to generate a blog post, a newspaper article, a text conversation, tweets, and job advertisements amongst others. Even though it is not yet possible to write scientific articles or grants with just a few clicks, the functions to generate small paragraphs already allow us to move forward more efficiently in bits and pieces in the construction of a scientific text. Scientific writing will become one of the targets of these tools. The functions to rephrase or adjust a text in a certain style can already be a precious help for those who do not master writing in another language than their mother tongue. As you can imagine, like online translators, these tools will soon become indispensable in our writing process. The trap could be that, like online translators, a dependency will be created to the detriment of our learning for scientific writing and its codes by letting the machine do the job for us.

Neuroscience is caught in the middle of these two spectacular advances in AI tools that affect both the generation of knowledge through modelling and the transmission of this knowledge through the generation of texts. The place made to natural intelligences such as our Homo sapiens brains in this science seems little by little eroded and maybe it will need to be redefined in the long term.

These new tools, by entering the field of science, come to push even further the limits of what Jacques Ellul, a thinker from Bordeaux, qualifies as Technician System. A system gathering any entity (information, technological objects, flows, networks...) which has for raison of being the increase of efficiency and which develops in an uncontrolled way with the increase of flows around the world is also alienating Humanity from the world. I strongly invite you to delve into the works of Ellul, which enlighten us on how we progressively arrived at this situation today. Finally, it is just a step to say that such a technician system is in competition with another one: the system of living beings.

Neurojoke

Why is the left cerebral hemisphere always wrong?
Because it is never in the right side.

Maria Fakitsa, 2nd year of NeuroBIM master

Neuromeme

Simon Lecomte, 2nd year of PhD student

Editorial board

Louise Eygret

Born in Gien, France, Louise did her Bachelor's in Life Sciences followed by the NeuroBIM Master's in Neurosciences. Currently, she is pursuing a PhD focused on the neural substrates underlying odor modulation of food intake regulating neuronal circuits. Her research interests are primarily in nutrition, olfaction and hypothalamus.

Juan Garcia-Ruiz

With two Bachelor's degree, in Psychology and Biochemistry, and the NeuroBIM Master's degree in Neurosciences, Juan is now pursuing a PhD at the University of Bordeaux, France. His PhD focuses on the role of lactate in basal synaptic transmission, which allows him to combine his research interests in biochemistry, electrophysiology and neurometabolics. Although he speaks near-perfect French, Juan comes from Huelva, Spain. He is also the co-founder of neuronhub (www.neuronhub.org).

Sara Carracedo

Sara is a PhD student at the Neurodegénératives Diseases Institute (IMN). She comes from Pontevedra, Spain and holds a Veterinary Bachelor's degree from the University of Santiago de Compostela, Spain and she did the International Master of Neuroscience in Bordeaux. Her PhD is focused on understanding the role of P2X4 receptor in ALS pathogenesis and biomarker where she is interested in neuroinflammation and receptor trafficking.

Simon Lecomte

Simon is originally from Lyon, France. He did his Bachelor's of Psychology from Strasbourg, after which he did the International Master of Neuroscience from Bordeaux. He is a PhD student studying how the Fragile X Syndrome impacts the presynaptic mechanisms at the DG-CA3 synapses from which one can guess that his interests lie in memory, synaptic communication and the hippocampus. He also runs a blog "Astrocytes et traumatismes crâniens juvéniles".

Khadija Inam

Khadija is a Pakistani student currently pursuing a training as a Clinical Research Associate at the University of Bordeaux. She graduated with a Bachelor's degree in Applied Biosciences from the National University of Sciences and Technology, and later the NeuroBIM Master's degree in Neurosciences from the University of Bordeaux. Her research interests are in the scope of pharmacology and neurological disorders.

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Are you a MSc or a PhD student in neuroscience? Then you are more than welcome to participate in our journal.

You can write either a short-review on a topic of your choice, or a one-page letter (a reflection, a project or an insight you would like to share with the scientific community), a dissemination article about clinical neuroscience (neurodegeneration, neurodevelopmental disorders, psychiatric disorders…) with the aim to reach a more general public, or a neurojoke.

Don't start to worry, you won't be alone! You will work hand-by-hand with our editors and we will send you guidelines and a template to make your life easier. Perhaps you would like to know that the best review will get a special prize by June 2023.

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