Review Article:

The role of microRNAs in newborn brain development and Hypoxic Ischaemic Encephalopathy

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Abstract

Newborn babies can develop hypoxic-ischaemic encephalopathy (HIE) due to lack of blood supply or oxygen, resulting in a major cause of death and disability in term newborns. However, the current definitive treatment of therapeutic hypothermia, will only benefit one out of nine babies. Furthermore, the understanding of HIE and mechanisms of therapeutic hypothermia is not fully understood. Recently, microRNAs (miRNAs) have become of interest to many researchers due to its important roles in post-transcriptional control and deep evolutionary history. However, the role of miRNAs in newborns with HIE remains largely unknown due to limited research in this field. Therefore, this review aims to understand the role of miRNAs in normal brain development and HIE pathophysiology with reliance on extrapolated data from other diseases, ages and species due to limited data to date. This will provide us with an overview of how miRNAs in normal brain development changes after HIE. Furthermore, it will indicate how miRNAs are affected specifically or globally by the various pathophysiological events. For those that are interested in studying miRNAs, agents that can manipulate microRNAs are commercially available. In addition, we discuss about how drugs and agents can specifically target certain miRNAs as a mechanism of action and potential safety issue with off target effects. Improving our understanding of the role of miRNAs on the cellular response after HIE would enhance the success of effective diagnosis, prognosis, and treatment of newborns with HIE.

Keywords: Newborns; hypoxic-ischemic encephalopathy; microRNAs; brain development; cellular death; neuroinflammation.

Introduction

MicroRNAs (miRNAs) are evolutionary preserved short non-coding RNA molecules made up of 19 - 22 nucleotides, which are involved in the regulation of gene expression [1]. In central nervous system (CNS), miRNAs have been known to influence varying stages of neurodevelopment, including cell differentiation, proliferation and synaptogenesis [2]. Animal and human studies have shown that majority of miRNAs are expressed in brain tissue, in keeping with the complexity of nervous system and its connections [3]. The unique nature of miRNAs as potential biomarkers for a variety of diseases, including oncology [4], cardiovascular diseases [5], sepsis [6], and neurodegeneration [7], has been recently studied widely in adults and the pediatric population. However, the role of miRNAs in newborns with hypoxic-ischaemic encephalopathy (HIE) remains largely unknown.

MiRNAs are known to be involved in normal brain development. As the newborn brain is still developing, it will be most likely that a number of miRNAs expression that are important in normal brain development are altered in conditions like HIE. Furthermore, animal studies of HIE have demonstrated that miRNAs can induce pathological changes in a variety of organs. Thus, miRNAs can be involved in the mechanism of hypoxic ischaemic injury itself, which could occur before, during and after the hypoxic insult. Furthermore, miRNAs could also be involved in the reparative process that happens after delivery of baby with or without the therapeutic hypothermia treatment.

There are very limited studies on the role of miRNA in newborns under various physiological and pathophysiological conditions. As the miRNAs are evolutionally preserved, and the organs such as brain are still developing, it is likely that the expression of miRNA in newborns may be related to their counterparts in adults, but distinctive based on their regulatory role, . Furthermore, the limitation in the use of human fetal and neonatal tissue in research makes animal studies a useful alternative.

In this article, we set out to review our knowledge on the roles of miRNAs relating to normal newborn brain development and then their roles in brain injury pathophysiology

from exploring published adult and animal studies. Furthermore, we will highlight known drugs and agents that could be used to alter the miRNA expression in future clinical research. This could pave way for future studies on specific miRNAs as a potential biomarker for brain injury in newborns and the development of novel therapeutic targets for perinatal asphyxia.

Literature search

The electronic database of PubMed was used to systematically search for relevant articles published between 1997 to 1st August 2018 by using a variety of search strings. To review the role of miRNAs in normal brain development, the searches involved the keyword miRNA and other keywords: 'neural stem cells', 'neuronal migration', 'axonal and dendritic outgrowth', 'gliogenesis', 'synapse formation', 'biochemical changes', 'myelination', and 'vascular development'. To review the role of miRNAs in brain injury, the keywords: 'miRNA and neuronal cell death', and 'miRNA and neuroinflammation' were chosen. 'MicroRNA and neonatal encephalopathy', 'microRNA and hypoxic-ischaemic encephalopathy', 'miRNA and therapeutic hypothermia/cooling', 'microRNA and neonatal hypoxia', 'microRNA and neonatal brain ischaemia', 'microRNA and neonates / babies', and 'microRNA and neonatal brain' revealed 32 studies. These miRNAs have been discussed in detail later in the HIE pathophysiology section. Due to limited studies in neonates, relevant miRNAs associated with brain injury involving older children, adults, animals or in-vitro cell cultures were also highlighted in the review.

MiRNAs in newborn brain development

Newborn human brain development commences from first few weeks of gestation and continues well beyond the first 2 years of life and into early childhood with ongoing myelination and synaptogenesis. In addition, other major cellular developmental changes in newborn human brain including cell proliferation, neuronal migration, synaptogenesis, synaptic pruning, myelination and connectivity, and immunological changes have been well documented [8]. We aim to detail a complete review of

miRNAs in newborn human brain development using available and extrapolated knowledge on miRNA changes noted in animal in vitro and in-vivo studies.

Neurogenesis and gliogenesis

Neurons and glial cells including astrocytes and oligodendrocytes are formed from the multipotent self-renewing neural stem cells (NSC). Neurogenesis occurs predominantly in early embryonic stage in the ventricular zone and continues until early postnatal life with very little ongoing adult neurogenesis from the quiescent NSCs [9]. A few known miRNAs such as miR-9, miR-25 /106b-25 cluster and miR-134 play a role in enhancing NSC proliferation, but a few others such as Let7b, miR-128 and miR-506 could inhibit NSC proliferation (Figure 1). Several intracellular pathways are involved, including the Notch/Hes signaling with miR-9 to enhance NSC proliferation [10]. Alternatively, overexpression of Let7b reduces NSC proliferation via TLX and cyclin D pathway [11]. Interestingly, perinatal hypoxic-ischaemic injury induces proliferation of NSC in sub-ventricular zone, possibly as a reparative mechanism as progenitor cells are susceptible to this form of injury [12-14].

Distinctively, gliogenesis starts in 2nd trimester and continues until a couple of years of age. In addition to being supportive cells to neurons, glial cells also play a vital role in neurogenesis by influencing neuronal migration, formation of blood-brain barrier and regulation of myelination. In CNS, oligodendrocytes are produced from the oligodendrocyte progenitor cells (OPC) with immature oligodendrocytes peaking around 28 to 40 weeks of gestation. There is a complex network of miRNAs involved in OPC development either alone or in combination through a number of pathways as shown in (Figure 1). For example, increase in OPC miR-219 and miR-338 can promote their differentiation into myelinating oligodendrocytes by repressing their target genes of platelet-derived growth factor receptor α (PDGFRα), Sox6, FoxJ3, and ZFP238 proteins [15, 16]. OPCs are particularly vulnerable to perinatal hypoxic-ischaemic injury, leading to permanent white matter damage [17]. This hypoxic injury also promotes proliferation of sub-populations of NG2 positive neural progenitor cells, which may differentiate into myelinating oligodendrocytes [17, 18]. Since this developmental process is

predominantly ongoing in the 3rd trimester, it is most likely to be interrupted in newborns during hypoxic-ischaemic injury. Moreover, the switch between neurogenesis and gliogenesis has been suggested to be strongly influenced by miRNAs, including miR17/106 based on the timing of the developmental process and complex interaction between various pathways [19, 20].

Neuronal migration, maturation and connectivity

Neuronal migration is an important step following the proliferation and differentiation of precursor neuronal cells, as it helps to bring various types of cells together to their final location. In CNS, this process is supported by radial glial cells. A variety of miRNAs has been shown to be involved in promoting radial migration of neurons and axons through a number of pathways (Figure 1). Inhibition of a brain enriched microRNA such as miR-9 have shown to increase axonal length and reduce axonal branching in culture neurons [21]. Other neuronal processes such as dendritic growth, dendritic spine formation, and development of dendritic complexity as also influenced by miRNAs (Figure 1). As dendrites are the site of most synaptic contacts, adequate growth and branching of dendrites are important for healthy neural circuitry function. Similarly, investigation of miRNAs for their role in synaptic process have been carried out. A few miRNAs including miR-9, miR-124, and miR-132 have been shown to consistently promote synaptogenesis, while miR-125, miR-134 and miR-137 exhibit opposing affects (Figure 1). The structural and functional synaptic plasticity is an important and highly regulated process that is necessary to maintain normal function and repair of nervous system. Numerous miRNAs involved in this process are concentrated in both pre- and post-synaptic junctions, which has been summarised in a few reviews [22-24]. Furthermore, various miRNAs are also altered in the mechanism of long term potentiation which forms the basis for cognition and memory [25]. Thus, miRNAs are not only involved in synaptic protein synthesis, but also in the formation and maturity of the synapses, which are important for learning and memory.

Myelination

Oligodendrocytes in CNS provide the primarily source of myelin sheaths, which is important for axonal insulation to enhance conduction speed of action potentials. Currently, two miRNAs have been implemented with myelination, namely miR23a and miR219 (Figure 1). In particular, miR-23a has been previously shown to suppress laminB1 via the PTEN/PI3K/AKT pathway to enhance oligodendrocyte differentiation [26].

Vascular development

Angiogenesis involving sprouting of new capillaries and neurogenesis are both crucial processes for brain tissue repair and remodeling after brain injury. The blood brain barrier (BBB) is a specialised non-permeable barrier in cerebral microvessels, formed primarily by endothelial cells united through tight junctions with astrocytic end feet surrounding the blood vessels, and pericytes embedded in the vascular basement membranes. In addition, microglia and neurons have essential roles in CNS homeostasis in the form of the neurovascular unit [27]. Several miRNAs are involved in angiogenesis and BBB formation and disruption (Figure 1). For example, miR29b have been hypothesised to regulate BBB dysfunction via the enzymes MMP9 and DNMT3b [28].

Summary of role of miRNA in healthy brain development

There are many organ specific miRNAs, but a significant proportion are expressed in brain [29]. This signifies their importance and complexity of evolution, and their role in neural development. MiRNAs expression can be varied with temporal and spatial differences relating to developmental stages and anatomical areas of the CNS [30]. Therefore, miRNAs can be expressed differently in neuronal precursors and stem cells through the various stages of differentiation to mature neurons [31]. Furthermore, they can have dual action due to its presence in one cell type to suppress expression and to be absent from another cell at another time point to allow for genetic expression. Moreover, miRNAs can not only be present within cells, but can also circulate freely extracellularly within exosomes, and act on other distant cells. For example, miR-21 and miR-29a can act as a ligand on TLR receptors to induce an inflammatory response [32].

With this knowledge of the complex activities of miRNAs, the roles of miRNA in various stages of HIE are further discussed.

Hypoxic-ischaemic encephalopathy

Neonates can be affected by varying degrees of perinatal asphyxia, due to lack of blood supply or oxygen in peripartum period. Those affected by perinatal asphyxia can develop a clinical condition called hypoxic-ischaemic encephalopathy (HIE). It is a major cause of death and disability in term newborns, which affects around 2-3 per 1000 live births in developed countries [33]. HIE is not a specific diagnosis but a constellation of clinical features of encephalopathy related to various aetiologies resulting in perinatal asphyxia. Currently, the standard of treatment is to offer therapeutic hypothermia between 33 – 34^{o}C for a 72 h period to babies with moderate to severe HIE based on a selected clinical criteria [34]. With the current clinical guidelines to select the babies for therapeutic hypothermia, the numbers needed to treat is nine to prevent one additional baby with severe disability or death [35]. This is because of the complex etiologies leading to the clinical presentation and lack of robust biological markers to assist in identification and selection of all babies potentially affected by perinatal asphyxia to initiate therapeutic hypothermia early. Recently, clinical studies have been conducted to identify other neuroprotective or restorative therapies as standalone or adjuncts to therapeutic hypothermia to improve the outcome for HIE babies [36].

MicroRNAs associated with HIE pathophysiology

To date, there are only a couple of published studies studying the expression of miRNA in human neonatal HIE [37, 38]. In a small cohort of babies with HIE, Chen has selectively studied the expression of miRNA-21 and HIF-1α and found them be higher in serum in HIE babies compared to normal controls [37]. In a methodology paper on use of dried blood spots to extract miRNAs, we have previously studied selected miRNAs (Let7b, miR-21, miR-29b, miR-124 and miR-155) and did not find their expression significant in HIE babies [38]. However none of these studies have identified the mechanism of action of relevant miRNAs. Other closely-related studies include those on umbilical cord blood [39-41] and maternal blood [42]. Looney and colleagues have

shown that microRNA miR-374a is downregulated in the umbilical cord blood of infants with HIE and suggested a possible pathway for miR-374a involving activin-A through its receptor AVCR2B [39]. Subsequently, Wang et al has selectively studied miR-210 and miR-374a also in umbilical cord blood and shown its combined potential role as biomarker for severity and prognosis of HIE[41]. A study on maternal blood has shown miR-20b and miR-21 to be related to fetal hypoxia during labour [42]. The remaining published studies vary from in-vivo rat and piglet animal models to cell cultures under various hypoxic-ischaemic conditions. In rat primary hippocampal neuronal cultures. Cai and his colleagues show that miR-27a overexpression attenuates hypoxia- and ischemia-induced neuronal apoptosis by regulating FOXO1 [43]. Similarly, in both in vitro and in-vivo studies, hypoxia induced expression of miR-152 in rats has been shown to suppress cell apoptosis and acts as a protective factor during by repressing PTEN [44]. Other studies on in-vitro cultures has shown upregulation of miR-210 to be neuroprotective through its effects on apoptotic proteins [45] and downregulation of miR-139-5p to be also neuroprotective through activation of Human growth transformation dependent protein [46]. However, a microarray on rat cerebral cortex highlight other miRNA's including mir-429, mir-200b, and mir-182 to be significant in HIE animal model [47], while in another study of microarray of neural tissues a different miR-199a has been shown to be significant [48].

Likewise, studies on piglet model of HIE has shown temporal changes in miRNA expression in mir-23a-5p, mir-27a-5p and mir-31-5p to be useful potential biomarkers to distinguish between hypoxia and infection-sensitised hypoxia [49], and miR-374a and miR-210 to be important regulators in neonatal HIE [50]. Moreover, therapeutic hypothermia, which is now a standard treatment for HIE has also been shown to cause changes in miR-874 and miR-451 in adult rats with traumatic brain injury [51]. Overall, these studies have been varied in methodology and have shown changes in various miRNA in HIE.

None of the above studies have highlighted any specific miRNA to be a reliable and reproducible biomarker or therapeutic target in HIE in neonates. Since we currently

know little about miRNA expression in neonates with HIE, reliance on well-researched diseases such as cancer is necessary. MiRNAs have been successfully shown to influence various pathophysiological changes in these diseases which have much similarities with HIE. As a starting point, this review will extrapolate miRNA expression data from studies that exhibit similar pathological changes as observed in HIE at the cellular level. Although some microRNA targets have been suggested, it is most likely that there are other miRNAs involved in the HIE pathophysiology that are unexplored, due to lack of knowledge and understanding of miRNAs in HIE.

MiRNAs in hypoxic-ischaemic pathophysiology

In simplified terms, two major pathological changes occur in HIE, which include various forms of neuronal cell death involving necrosis, apoptosis, autophagy, excitotoxicity, and axonal degeneration, which is then followed by neuroinflammation triggered through central and peripheral immune cells. This review will explore the role of miRNAs in neuronal death and neuroinflammation obtained from adult human and animal studies, in order to further elucidate the role of miRNAs in newborns with HIE.

Neuronal Cell Death

The initial phase of primary energy failure in HIE results in the first wave of cell death [52]. Although necrosis is the commonest form of neuronal death, other forms of neuronal death such as apoptosis, autophagy and excitotoxicity have been noted in animal models of HIE [53, 54].

Necrosis is initiated due to lack of energy or direct injury to cell membrane. A number of mediators including mitochondrial, lysosomal, nuclear, cytosolic or cell membrane related changes could potentiate the injury. MiRNAs such as miR-19b, miR-21 and miR-23a have found to be involved in necrotic cell death (Figure 2). In a transgenic murine model, miR-23a has been shown to control mitochondrial permeability by targeting peptidylprolyl isomerase F (PPIF), which restricts reactive oxygen species (ROS) flux [55]. In rodent in vitro and in vivo models, miR-21, miR-874 and miR-2861 have been shown to regulate necrosis/necroptosis through complex interaction and disruption of

various protein complexes namely receptor interacting protein 1 and 3 (RIP1/RIP3) [56] or mitochondrial nucleotide transporter, adenine nucleotide translocase 1 (MNTANT-1) [57]. Additionally, many miRNAs involved in necrosis are also involved in inflammatory conditions. Secondary inflammatory response following the release of intracellular contents could be initiated by necrosis [58]. Interestingly, miR-351 has been reported to switch cell death process between necrosis and apoptosis in rodent cell lines [59].

Apoptosis occurs when the cells undergo certain specific changes, including chromatin condensation, nuclear fragmentation and blebbing of intact plasma membrane to form apoptotic bodies [60]. Eventually, these apoptotic bodies are engulfed by phagocytes with no associated inflammatory reaction [61]. A large variety of miRNAs is now known to be involved in apoptotic death across various tissue types [62-65] (Figure 2). Studies on CNS-related miRNAs, come mostly from rodent model or cell lines involving neuroblastoma, glioblastoma, neuronal or retinal ganglion cells. For example, elevated expression of miR-17-5P-92 cluster can inhibit p21 and BIM translation, which leads to activation of apoptosis in neuroblastoma [66]. Another well-studied miRNA is miR-21, which has been shown to exhibit several roles in apoptosis. Although the role of miRNAs and apoptosis is more studied that necrosis, the exact mechanisms of miRNAs in the involvement in apoptosis remain to be determined.

Autophagy is another form of cell death when there is vacuolisation of the cytoplasm within the cell, which causes the cell to degrade their organelles and cytoplasm through the lysosomal system, involving Ras, beclin-1, mammalian target of rapamycin (mTOR), and phosphatidylinositol 3 (PI3)-kinase signaling pathways [67, 68]. A variety of miRNAs is known to be involved in autophagy (Figure 2). For example, the mTOR signaling pathway can be repressed by Let-7 in primary P0 cortical mouse neurons [69] or increased by miR-155 in human cancer cell lines [70]. In an ovarian endometriotic cell line, the beclin-1 signalling pathway have been associated with miR-210 [71]. Overall, the process of autophagy has been shown to be either a pro-survivor of cells or promotor of cell destruction in neonatal HIE models based on injury severity, timing of insult, and brain region involved [54].

Excitotoxic neurodegeneration is a type of neuronal cell death due to activation of glutamate-gated ion channel receptors causing activation of calcium sensitive proteases, protein kinases/phosphatases, phospholipases, and nitric oxide synthase (NOS) [54]. This results in intracellular changes similar to both necrosis and apoptosis especially in immature brain indicating a continuum between the various models of cell death [72]. Some of the miRNAs including miR-19, miR-21 and miR-223 are involved in excitotoxicity (Figure 2). For example, overexpression of miR-223 can lower the levels of GluR2 and NR2B subunits of glutamate receptor, resulting in the inhibition of NMDA-induced influx in hippocampal neurons [73].

Axonal degeneration has been well studied in neurodegenerative and traumatic injury animal models, but relatively unheard of in HIE. Since neuronal cells in grey matter are metabolically more active compared to white matter, the direct injury to axons and glial cells is not often observed in hypoxic-ischaemic injury. However, studies have shown that axonal degeneration induced by hypoxia can been observed in nematode *C. elegans* through induction of HIF-1 [74], and in adult mouse brain through AMPA/kinase receptor activation [75]. It is likely that chronic hypoxia plays a role in axonal degeneration either directly or through triggering inflammatory pathways, but it is not considered a type of cell death, since the neuronal body is often still alive following axonal degeneration. While certain miRNAs, including miR-34, miR-410, miR-431 are found to influence axonal degeneration in spinal cord and peripheral nerves [76], not much is known about role of miRNAs in axonal damage and repair in CNS relating to hypoxia and ischaemia.

Summary of neuronal cell death

Thus, neuronal cell death could follow any of the above modes of neuronal death or injury involving a number of pathways. There is definite cross-linking and signalling between these pathways based on severity and type of injury, which are linked to a number of miRNAs involved in all these processes. Although our understanding of

miRNAs is increasing, we are far from unveiling the mystery of the role of miRNAs in many pathologies of neuronal death in neonatal HIE.

Neuroinflammation

Following initial phase of neuronal cell death by necrosis, the release of inflammatory mediators outside the cells induces further secondary neuronal damage by a number of inflammatory cells from both central and peripheral immune system. Although the role of inflammatory cells is predominantly to remove debris and dying neurons through phagocytosis, they can also cause death of healthy neighbouring neurons through excitotoxicity, microglial activation and apoptosis. This secondary neuronal death process can take a few hours to weeks. As demonstrated in oncology, miRNAs have also been well studied in neuroinflammatory conditions leading to neurodegeneration like multiple sclerosis [77], Alzheimer's disease and Parkinson's disease [78]. Furthermore, miRNAs have been suggested to fine tune inflammation through alterations in immune cell differentiation and function via circulating in extracellular vesicles to communicate between neurons and immune cells [78]. Role of various immune cells in neuroinflammation and their interaction with miRNAs are explored further.

Central inflammatory cell response

Microglia

Microglia are the resident immune cells in the brain, which act as a gate keeper for inflammation through constant surveillance of the CNS microenvironment using their long thin ramified processes. However, once activated they retract their processes to express an amoeboid phenotype and migrate immediately to the area of injury, especially in developing brain. In the activate form, microglia can express a pro- or anti-inflammatory role. The pro-inflammatory pathway is mediated by Th1 type cytokines like IFN-γ or TLR agonists resulting in inflammatory tissue damage through release of pro-inflammatory cytokines including IL-6, TNF-α and NO [79]. Alternatively, microglia can take on an anti-inflammatory phenotype through alternate activation by Th2 type cytokines including IL -4 or IL-13 [79]. The anti-inflammatory role involves the clearing of

debris and ROS, and release neurotrophic factors with an ultimate aim to promote neuronal repair and recovery. Moreover, microglia can switch between the 2 phenotypes based on the timing and type of inflammatory signaling, resulting in a wide spectrum of intermediate phenotypes [80]. Interestingly, microglial activation can also recruit other peripheral immune cells including monocytes, macrophages, neutrophils and T-lymphocytes through chemokine release [81].

The role of miRNAs in development and activation of microglia has been previously reviewed by Ponomarev and colleagues [79]. In summary from various studies on mouse microglial cells, there are a number of miRNAs known so far to promote an anti-inflammatory phenotype via a variety of pathways (Figure 3). For example, Let-7a have been shown to reduce NO and IL-6 [82]. Another example is miR-124, which can act through C/EBP-α–PU.1 pathway [83], or targeting a key mediator of NLRP3 inflammasome, nfkB-regulator ikBzeta and Irf1 [84], or through peroxisome proliferator-activated receptor-gamma pathway [85]. On the other hand, miRNAs including miR-101 via MAPK phosphatase-1 pathway, and miR-155 via anti-inflammatory genes have shown to promote microglia induced an inflammatory response [79]. Interestingly, some miRNAs namely miR-146 and miR-21 control and resolve inflammation through negative feedback signalling [79]. In addition to these miRNAs highlighted in the review by Ponomarev and colleagues, a number of other miRNAs have also been shown to be involved in microglial activation as shown in figure 3. While we understand the extent to which certain miRNAs can activate and regulate microglia induced injury in hypoxic-ischaemic conditions, it is unclear whether additional miRNAs are involved and/or if these expressions hold true in newborns with HIE.

Astrocytes

Astrocytes are the most abundant glial cells in CNS and under normal conditions, contribute to limiting inflammatory responses by formation of glial limitants [86, 87]. However, these glial cells play an important role in brain development, plasticity and homeostasis [88]. In various animal models of HIE, reactive astrogliosis is noted following hypoxic injury, which sets off a cascade of inflammation through release of

inflammatory cytokines (IL-1, IL-6, TNF-α, and IFN-γ) and chemokines [81]. Similarly to microglia, astrocytes can also express an anti-inflammatory role through release of glutathione and superoxide dismutase, and enhancing extra-synaptic glutamate uptake and induction of brain derived neurotrophic factor (BDNF), thus protecting neurons by a number of mechanisms [81]. Ouyang and colleagues have summarised in detail studies on some of the brain enriched miRNAs, namely miR-181 and miR-29 families and miR-146a as they have been found to be highly expressed in astrocytes and noted to have both pro-and anti-inflammatory roles depending on the targets and the cells of expression [88]. The expression of these miRNAs differs greatly based on the brain region and gestation age as demonstrated with human adult and fetal brain tissues [89]. Other miRNAs that involve astrocytes are shown in Figure 3. For example, miR-7 can decrease endoplasmic reticulum (ER) stress protein-HERP2 in primary cultured mouse astrocyte [90]. In primary P1 astrocyte culture model of ischemia-reperfusion injury, miR-29a can target the pro-apoptotic BCL2 family member PUMA [91]. These miRNAs and its associated pathway exhibit a neuroprotective role. Paradoxically, miR-34b can repress Bcl-2 resulting in hippocampal astrocyte apoptosis [92]. In addition, miR-155 have shown to target suppressor of cytokine signaling 1 in cell culture using human fetal tissue [93]. These miRNAs and its associated pathway can worsen the injury through the pro-inflammatory role. Additionally, miR-124a transported as exosomes has also shown to provide an astrocyte-neuron connection [94], thus promising a potential role for astrocytes and its miRNAs in neuroprotection. Therefore, in relation to the pathways the astrocytic miRNAs are involved, it suggests they have a close relationship to neuronal function and structure.

Peripheral inflammatory cell response

Neutrophils

Neutrophils are the most abundant circulating white cells and are the first peripheral inflammatory cell type recruited at both acute and chronic inflammation. Various animal studies have shown infiltration of neutrophils in ischaemic areas of adult brain within hours of insult, while in neonatal models of hypoxic ischaemic injury, the neutrophil response in brain is often diminished, as they seem to stay predominantly intravascular

[81]. Neutrophils help to combat tissue injury by phagocytosis and releasing toxic granulations to destroy the pathogens. However, additional tissue injury can occur through ROS, cascading further inflammation via recruitment of macrophages and its release of cytokines to activate T-helper cells [95]. To date, the role of only few specific miRNAs; namely miR-142, miR-223, miR-451 and miR-446I relating to inflammatory role of neutrophils have been summarised [95](Figure 3). MiR-223 is one neutrophil-related miRNA that has been predominantly studied, which is found to be a negative regulator of granulocyte differentiation and involved in fine tuning neutrophil function [96]. Some of the confirmed targets and modes of action for miR-223 involve targeting C/EBPα and NFI-A [97], NLRP3 [98], suppressing neutrophil infiltration and ROS production [99], or Mef2c, a transcription factor that promotes myeloid progenitor proliferation [100]. However, due to limited studies, the exact role of neutrophils and their expression of miRNAs in HIE of a term human neonate still remains a mystery.

Monocytes/Macrophages

Monocytes/macrophages are also part of innate immunity through their phagocytic actions. However, there is currently no clear study to explain their role in HIE pathogenesis although several miRNAs are associated with monocyte/macrophage (Figure 3). Stimulation of monocytic cells by the bacterial endotoxin lipopolysaccharide (LPS) has shown up-regulation of miR-9 [101], miR-21 [102, 103], and miR-146a [104] all through Nuclear factor-κB pathway. The target of miR-155 has shown to be through enhancing TNF-α translation [105, 106], and JNK pathway [107]. Furthermore, LPS stimulation can cause positive regulation of let-7e and miR-181c, but negative regulation of miR-155 and miR-125b through protein kinase Akt1 [108]. Overall, certain myeloid derived miRNAs mentioned above have been shown to be involved in LPS-induced inflammation via in vitro studies. As HIE could be a triggered by infection, these miRNAs could play a role in the initiation of cellular injury through primary inflammation.

Dendritic cells

Dendritic cells are antigen-presenting cells that play important roles in linking innate and adaptive immune responses. Various types of dendritic cells have been noted in human

and mouse studies including classic or conventional, Langerhans, plasmacytoid and monocyte-derived dendritic cells [109]. Immature dendritic cells produced from haematopoietic stem cells mature on stimulation by toxins. A number of miRNAs involved in other pathophysiological processes in HIE such as Let-7 family, miR-155, miR-223 and miR-29 family, have been shown to be expressed during the process of differentiation and maturation of dendritic cells [109]. Some of the well studied miRNAs involving dendritic cell activation are highlighted in Figure 3.These miRNAs have been noted to either positively or negatively regulate the ability of dendritic cells in processing antigens. Smyth and colleagues describe in detail certain miRNAs are involved in various roles relating to dendritic cells maturation and function [109]. As a vital cell in triggering antigen specific immune response, it is likely that these dendritic cells play a role in inflammation relating to HIE.

T-lymphocytes

T-lymphocytes, which are derived from thymocytes are differentiated from haematopoietic stem cells and have a major role in cell mediated immunity. In vitro and in vivo studies have shown a small number of miRNAs, including miR-142a, miR-146a, miR-155 and miR181a are capable of influencing the function of T-lymphocyte mediated through other inflammatory cells (Figure 3). In particular, miR-155 has been found to be highly related to T-lymphocyte development, as a number of studies have found its role in differentiation of T-helper cell [110], T-regulatory cells [111], T-cell dependent inflammation [110], and for effective function of T- and B-lymphocytes and dendritic cells [112]. MiR-181a expression has been shown to play a key role in maturation of T-lymphocytes through positive selection [113]. The direct role of T-lymphocytes in hypoxia-related inflammatory process is unclear. However, it has been noted that newborns have an equally efficient, although different T-cell immunity response compared to adults [114]. Additionally, unlike adults, neonates have been shown to express CXCL8-producing T-lymphocytes in response to inflammation, very early on even though their immune system is limited in mounting T-helper type 1 cell response to bacteria and virus [115]. These differences between adult and newborns may suggest that adult and neonatal inflammatory process involve different miRNAs.

B-lymphocytes

B-lymphocytes provide humoral immunity through their antibodies and are activated either as T-cell dependent or independent activation depending on the antigen type. A number of miRNAs can regulate B-cell lymphopoiesis and maturation including miR-23a [116], miR-34a [117], and miR-212/132 cluster [118]. Rodent studies have shown that certain well studied miRNAs like miR-155 [119] and miR-181 [120, 121] have also been noted to be involved in the functional aspect of B-lymphocytes influencing their antibody response, in addition to their effect on other inflammatory cells. Figure 3 summarises various other miRNAs involved in B-lymphocytic activation. However, very little is known on B-lymphocytes role and function in hypoxic and ischaemic conditions, even in animal studies to extrapolate to pathogenesis of HIE in neonates.

Summary of neuroinflammation

Some miRNAs such as miR-223, miR-142, miR-146, let-7 family and miR-155 are well known to be involved directly or indirectly in the inflammatory cascade through a number of immune-related cells. While the primary pathology in HIE is cellular death followed by secondary inflammation, the etiology of HIE is often unclear. As described earlier, HIE is currently a diagnosis based on clinical criteria and often causes other than pure hypoxia and ischaemia at birth could mimic as HIE. The most common confounding factor in the etiology of HIE is sepsis and LPS-related injury. These pathological events could thus be a primary cause for hypoxia and ischaemia in perinatal period triggering neuroinflammatory pathways ahead of cellular death.

While there is lack of studies on role of specific cells in HIE in human neonate, understanding the targets and pathways of some of the well-studied miRNAs and their role at cellular level in a variety of inflammatory conditions would be useful to extrapolate for unknown conditions like HIE.

MicroRNA in therapeutic hypothermia

It has been suggested that therapeutic hypothermia being the established treatment modality for HIE works through a number of mechanisms, including reduction in apoptosis, excitotoxicity, and neuroinflammation [122]. Studies on miRNAs in hypothermia have shown that hypothermia can reduce the expression of miR-122 in adult porcine cardiogenic shock model [123], and increase miR-155 expression in primary cultured adult human monocytes exposed to 32 °C [124]. Interestingly, in vitro studies on neuronal cell lines have shown that cold shock protein RBM3 can contribute to therapeutic effects of hypothermia through regulation of protein synthesis [125]. Additionally, another RNA binding protein Lin-28 has also been shown to significantly regulate early embryonic development and differentiation by blocking the biogenesis of let-7 family through their cold shock domain [126]. While therapeutic hypothermia is well studied in preclinical studies, the exact mechanism of how it provides clinical benefit in neonatal HIE remains unclear [127]. The understanding of miRNAs in newborns with HIE could add more information to our current understanding of pathological changes in HIE at the genetic and cellular level.

Modulating microRNA with pharmacological agents

Understanding the role of microRNAs in different pathological events has shown that in addition to being a biomarker, they can also be potential therapeutic targets. Researchers have been able to successfully mimic endogenous miRNA or decrease miRNA expression in vitro and in vivo using commercially available pharmacological agents (Table 1). It should be noted that in RNA interference, miRNA inhibitors should not be mistaken with small interfering RNAs (siRNAs), since miRNA inhibitors can have multiple mRNA targets and siRNAs are specific to one mRNA target [128]. The delivery methods can be used directly in buffer [129], or with transfection reagent such as lipofectamine [130], or plasmid-based [131], or viral vector-based systems [132].

Recently, medications used in clinics have been shown to alter miRNA expression as a mechanism of action (Table 2). For example, nicorandil, an anti-angina drug can upregulate miR-7 to induce an anti-inflammatory effect in primary cultured astrocytes induced by oxygen-glucose deprivation [90]. Pioglitazone, a peroxisome proliferator-

activated receptor (PPAR)-γ agonist used to treat type 2 diabetes can downregulate miR-29 resulting in increased cell survival and decreased caspase 3 activity in a model of ischaemia-reperfusion injury [133]. The anti-cancer drug, bleomycin, acting through inhibition of PDGF-B and TGFβ signaling pathways can reduce miR-29 expression in a model of systemic sclerosis [134]. Furthermore, treatment with an anti-cancer drug, imatinib can restore the levels of miR-29a-c in vitro and in the bleomycin model in vivo [134]. MiR-9 level was decreased by erlotinib, an EGFR inhibitor used to treat non-small cell lung cancer [135]. Valproic acid, an anti-convulsant drug can induce miR-124 to repress guanine nucleotide binding protein alpha inhibitor 1 (GNAI1) [136]. Natalizumab, a humanized monoclonal antibody that is used to treat relapsing-remitting multiple sclerosis has been shown to down-regulate miR-155 and miR-26a in blood of multiple sclerosis patients [137]. Metformin, an anti-diabetic drug used to treat type 2 diabetes can down regulate miR-21 an affecting the PI3K/AKT pathway [138]. Moreover, the anti-fibrosis drug bortezomib restore the miR-21 expression increase in bleomycin-induced skin fibrosis [139]. The pan-deacetylase inhibitor panobinostat used to treat various types of cancer can promote the maturation of let-7b, which inhibit HMGA2 expression [140]. Interestingly, chemical agents present in our diet can also alter miRNA expression (Table 2). Curcumin, which is present in turmeric and curry, has been demonstrated to suppress colon cancer proliferation via the down-regulation of miR-130a by inhibiting Wnt/β-catenin pathways [141]. Epigallocatechin-3-O-gallate, which is present in green tea can up-regulate let-7b causing a down regulation of HMGA2 [142]. Finally, iIsoliquiritigenin, which is present in licorice can inhibit miR-25 and trigger autophagy by increasing ULK1 expression [143].

Potential safety issues in modulating miRNAs during development

Although modulation of miRNAs can be beneficial as previously discussed in the review, it can also give rise to potential safety issues, especially when miRNAs can affect multiple mRNA targets. Since miRNAs can potentially target around 200 genes, any agent aimed to alter a specific miRNA expression could result in off-target effects [144]. For example, miR-155 is involved in autophagy and necrosis, and in neuroinflammation. Furthermore, miR-155 is associated with microglia/macrophages, astrocytes, and

dendritic cells. Therefore, if targeting miR-155 for autophagy and necrosis, it would also affect neuroinflammation, which the process currently remains inconclusive if beneficial or detrimental [145, 146]. Another example is miR-124, which can promote neuronal differentiation via SCP1 or SOX9, inhibit synaptic activity via CREB1, promote neurite outgrowth and neuronal migration via FOXP2, and promote microglia quiescence via C/EBP –alpha-PU.1 pathway [83, 147]. Therefore, it is unknown what will be the overall consequence of altering global brain miR-124 levels has on the unintended pathways for neuronal differentiation, synaptic activity, axonal growth and the innate neuroinflammation. MiRNA can also post-transcriptionally regulate extremely important enzymes, in particularly the cytochrome P450 superfamily, which are involved in the both the catalysing and the activation of agents [148]. In such cases, the off target can be detrimental for the newborn. For example, CYP1B1 has been associated with cancer and is negatively regulated by miR-27b, so an increase in CYP1B1 may lead to carcinogenesis from reducing miR-27b expression [149]. Overall, the use of In Silico programs would minimise any detrimental off target effects. However, since our current knowledge of miRNA and its effects remains limited, further research in miRNA will help us understand better the biology of miRNAs in normal and disease states in newborns.

Conclusion

This review has focused on known changes at cellular level both in the developmental brain physiology and pathophysiology observed in HIE. However, since there are limited data on miRNAs that associate neonates with HIE, this review could only extrapolate from non-neonates and other diseases such as cancer, cardiovascular and neuroinflammatory conditions present in adults. From our understanding of miRNAs, it is likely that the miRNA changes observed in these cellular processes would reflect similar changes in neonates with HIE, since most plants and animal miRNAs are evolutionally conserved as they are vital in gene regulation. As we have discussed in the review, miRNA expression and their regulatory functions are complex mechanisms that requires further studies to fully appreciate role of miRNAs in newborns with HIE. However, the successful could pave way to develop better biomarkers of brain injury and be sought for effective neuroprotective treatments.

Figure legends

Figure 1. MiRNAs involvement in normal neonatal brain development. A variety of processes that occur during brain development are involved with miRNA, including cell division (proliferation, gliogenesis), neuronal changes (differentiation, migration, synaptogenesis, axonal and dendritic outgrowth, and myelination), and vasculature changes (blood brain barrier and angiogenesis). MiRNAs highlighted in blue and red colour indicate an up regulatory and down regulatory role, respectively. References are in italics next to each miRNA in brackets. Superscript letter(s) with reference denotes source of data: [a], rodent cell culture; [b], immature rodent; [c], adult rodent; [d], zebrafish; [e], Drosophila; [f], *C. elegans*; [g], Aplysia; [α], human cell culture; [β], immature human; [γ], adult human.

Figure 2. MiRNAs in cellular death. Cell death can be classified into excitotoxicity, autophagy, necrosis and apoptosis. References are in italics next to the miRNAs in brackets.

Figure 3. MiRNAs in neuroinflammation. Neuroinflammation can be of CNS origin, which involve microglia, astrocytes, and microglia-derived macrophage. Alternatively, neuroinflammation can be of PNS origin, which includes monocytes derived macrophages, neutrophils, dendritic cells, T- and B-lymphocytes. References are provided next to the miRNAs in figure and in the legend below.

Figure 1

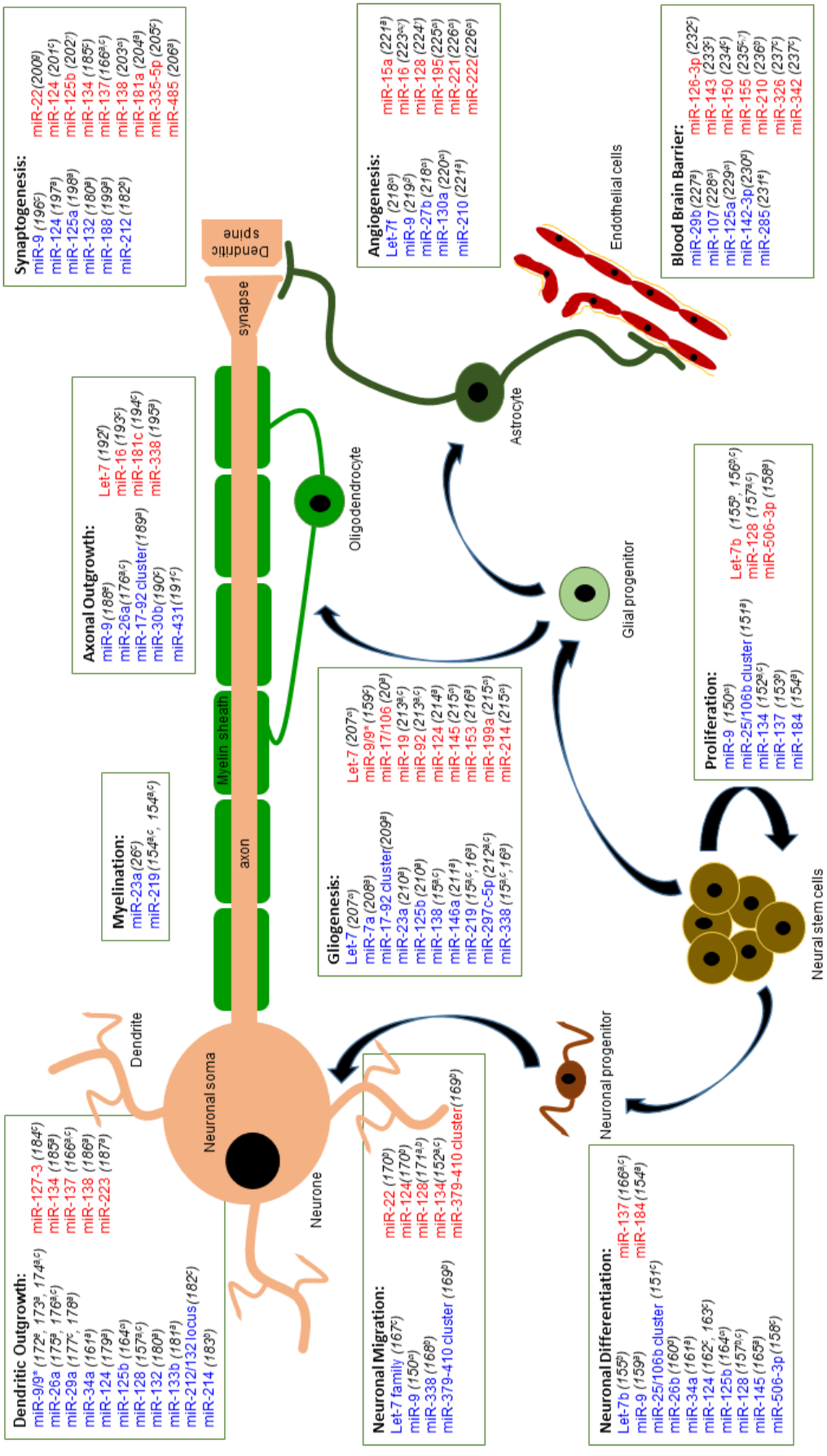
Synaptogenesis:
miR-9 (196c)
miR-124 (197a)
miR-125a (198a)
miR-132 (180a)
miR-188 (199a)
miR-212 (182a)
miR-22(200a)
miR-124 (201c)
miR-125b (202c)
miR-134 (185c)
miR-137 (166a,c)
miR-138 (203a)
miR-181a (204a)
miR-335-5p (205c)
miR-485 (206a)
Dendritic spine
synapse
Axonal Outgrowth:
miR-9 (188a)
miR-26a(176a,c)
miR-17-92 cluster(189a)
miR-30b(190c)
miR-431(191c)
Let-7 (192a)
miR-16 (193c)
miR-181c (194c)
miR-338 (195a)
Angiogenesis:
Let-7f (218a)
miR-9 (219a)
miR-27b (218a)
miR-130a (220a)
miR-210 (221a)
miR-15a (221a)
miR-16 (223a,c)
miR-128 (224c)
miR-195(225a)
miR-221(226a)
miR-222(226a)
Endothelial cells
Blood Brain Barrier:
miR-29b (227a)
miR-107 (228a)
miR-125a(229a)
miR-142-3p(230a)
miR-285 (231a)
miR-126-3p (232a)
miR-143 (233a)
miR-150 (234a)
miR-155 (235a,c)
miR-210 (236a)
miR-326 (237a)
miR-342 (237a)
Myelination:
miR-23a (26c)
miR-219 (154a,c, 154a,c)
Myelin sheath
axon
Dendrite
Neuronal soma
Neurone
Oligodendrocyte
Astrocyte
Gliogenesis:
Let-7 (207a)
Let-7 (207a)
miR-7a (208a)
miR-17-92 cluster(209a)
miR-23a (210a)
miR-125b (210a)
miR-138 (15a,c)
miR-146a (211a)
miR-219 (15a,c, 16a)
miR-297c-5p (212a,c)
miR-338 (15a,c, 16a)
miR-9/9* (159a)
miR-17/106 (20a)
miR-19 (213a,c)
miR-92 (213a,c)
miR-124 (214a)
miR-145 (215a)
miR-153 (216a)
miR-199a (215a)
miR-214 (215a)
Glial progenitor
Proliferation:
miR-9 (150a)
miR-25/106b cluster (151a)
miR-134 (152a,c)
miR-137 (153a)
miR-184 (154a)
Let-7b (155b, 156b,c)
miR-128 (157a,c)
miR-506-3p (158a)
Neural stem cells
Neuronal progenitor
Dendritic Outgrowth:
miR-9/9* (172a, 173a, 174a,c)
miR-26a (175a, 176a,c)
miR-29a (177c, 178a)
miR-34a (161a)
miR-124 (179a)
miR-125b (164a)
miR-128 (157a,c)
miR-132 (180a)
miR-133b (181a)
miR-212/132 locus(182c)
miR-214 (183a)
miR-127-3 (184c)
miR-134 (185a)
miR-137 (166a,c)
miR-138 (186a)
miR-223 (187a)
Neuronal Migration:
Let-7 family (167c)
miR-9 (150a)
miR-338 (168a)
miR-379-410 cluster (169a)
miR-22 (170a)
miR-124(170a)
miR-128(171a,b)
miR-134(152a,c)
miR-379-410 cluster(169a)
Neuronal Differentiation:
Let-7b (155b)
miR-9 (159a)
miR-25/106b cluster (151c)
miR-26b (160a)
miR-34a (161a)
miR-124 (162c, 163c)
miR-125b (164a)
miR-128 (157a,c)
miR-145 (165a)
miR-506-3p (158c)
miR-137 (166a,c)
miR-184 (154a)

Figure 2

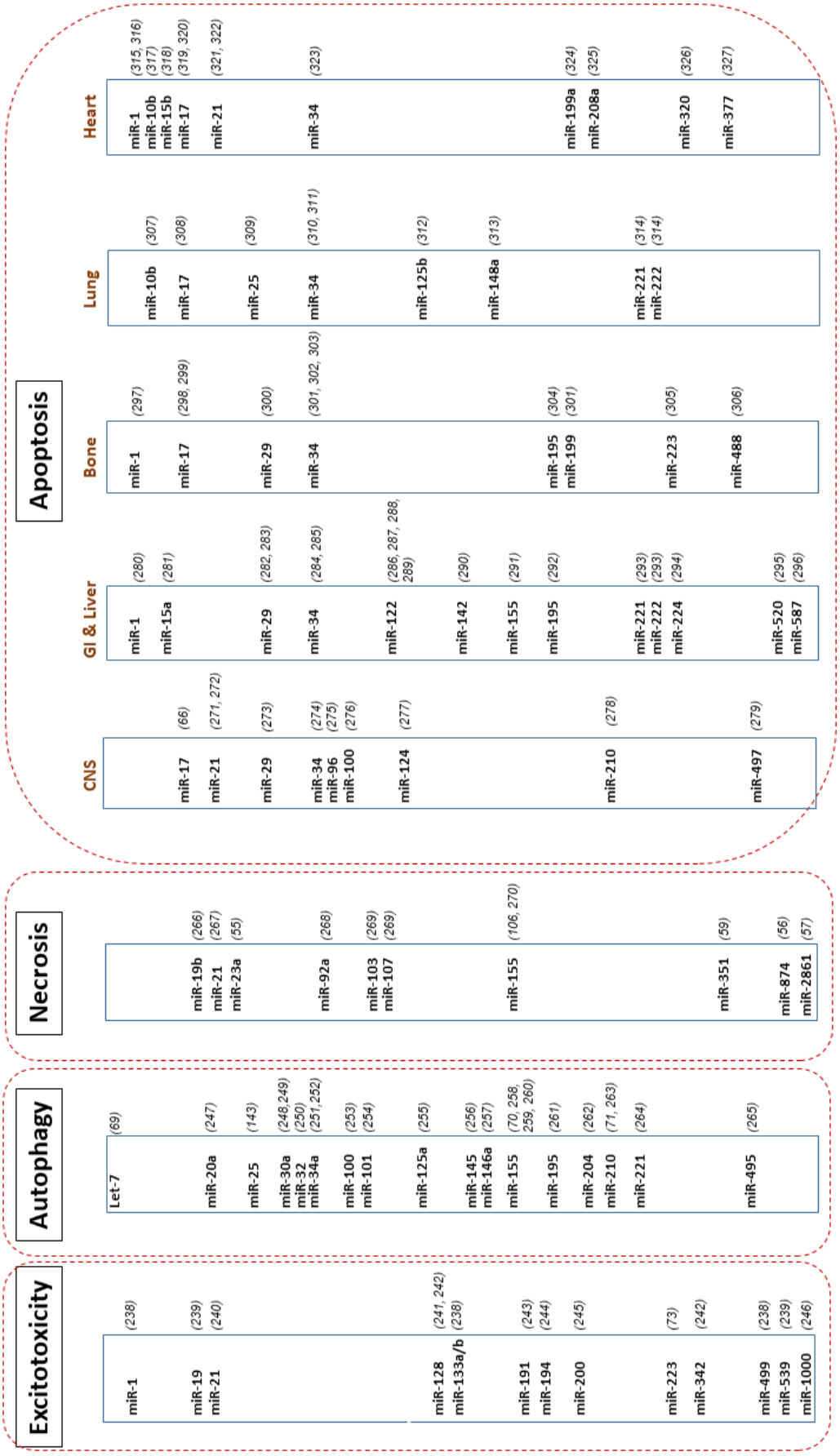
Excitotoxicity
Autophagy
Necrosis
Apoptosis
CNS
GI & Liver
Bone
Lung
Heart
miR-1 (238)
miR-19 (239)
miR-21 (240)
miR-128 (241, 242)
miR-133a/b (238)
miR-191 (243)
miR-194 (244)
miR-200 (245)
miR-223 (73)
miR-342 (242)
miR-499 (238)
miR-539 (239)
miR-1000 (246)
Let-7 (69)
miR-20a (247)
miR-25 (143)
miR-30a (248,249)
miR-32 (250)
miR-34a (251,252)
miR-100 (253)
miR-101 (254)
miR-125a (255)
miR-145 (256)
miR-146a (257)
miR-155 (70, 258, 259, 260)
miR-195 (261)
miR-204 (262)
miR-210 (71, 263)
miR-221 (264)
miR-495 (265)
miR-19b (266)
miR-21 (267)
miR-23a (55)
miR-92a (268)
miR-103 (269)
miR-107 (269)
miR-155 (106, 270)
miR-351 (59)
miR-874 (56)
miR-2861 (57)
miR-17 (66)
miR-21 (271, 272)
miR-29 (273)
miR-34 (274)
miR-96 (275)
miR-100 (276)
miR-124 (277)
miR-210 (278)
miR-497 (279)
miR-1 (280)
miR-15a (281)
miR-29 (282, 283)
miR-34 (284, 285)
miR-122 (286, 287, 288, 289)
miR-142 (290)
miR-155 (291)
miR-195 (292)
miR-221 (293)
miR-222 (293)
miR-224 (294)
miR-520 (295)
miR-587 (296)
miR-1 (297)
miR-17 (298, 299)
miR-29 (300)
miR-34 (301, 302, 303)
miR-195 (304)
miR-199 (301)
miR-223 (305)
miR-488 (306)
miR-10b (307)
miR-17 (308)
miR-25 (309)
miR-34 (310, 311)
miR-125b (312)
miR-148a (313)
miR-221 (314)
miR-222 (314)
miR-1 (315, 316)
miR-10b (317)
miR-15b (318)
miR-17 (319, 320)
miR-21 (321, 322)
miR-34 (323)
miR-199a (324)
miR-208a (325)
miR-320 (326)
miR-377 (327)

Figure 3

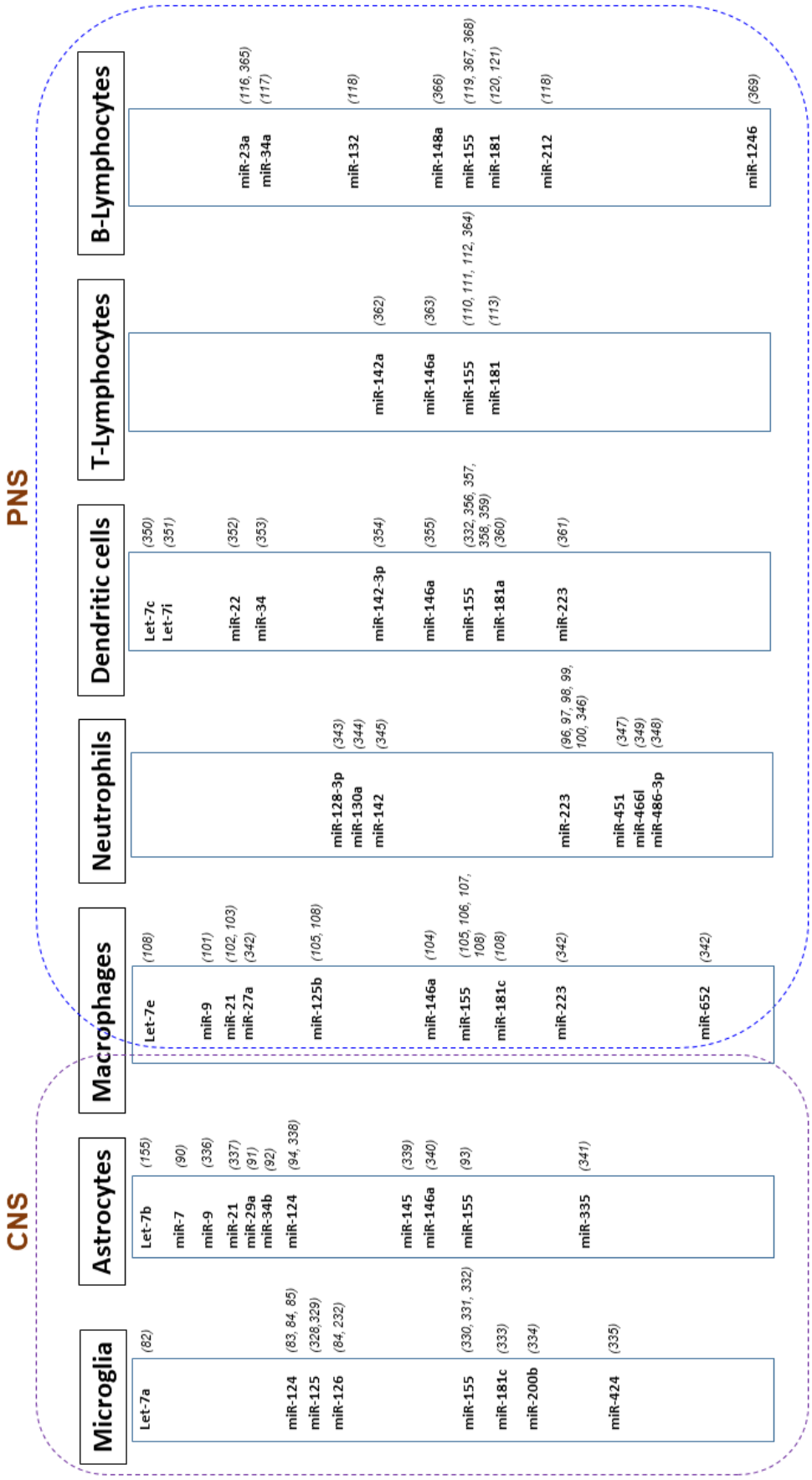
CNS
PNS
Microglia
Astrocytes
Macrophages
Neutrophils
Dendritic cells
T-Lymphocytes
B-Lymphocytes
Let-7a (82)
miR-124 (83, 84, 85)
miR-125 (328,329)
miR-126 (84, 232)
miR-155 (330, 331, 332)
miR-181c (333)
miR-200b (334)
miR-424 (335)
Let-7b (155)
miR-7 (90)
miR-9 (336)
miR-21 (337)
miR-29a (91)
miR-34b (92)
miR-124 (94, 338)
miR-145 (339)
miR-146a (340)
miR-155 (93)
miR-335 (341)
Let-7e (108)
miR-9 (101)
miR-21 (102, 103)
miR-27a (342)
miR-125b (105, 108)
miR-146a (104)
miR-155 (105, 106, 107, 108)
miR-181c (108)
miR-223 (342)
miR-652 (342)
miR-128-3p (343)
miR-130a (344)
miR-142 (345)
miR-223 (96, 97, 98, 99, 100, 346)
miR-451 (347)
miR-466l (349)
miR-486-3p (348)
Let-7c (350)
Let-7i (351)
miR-22 (352)
miR-34 (353)
miR-142-3p (354)
miR-146a (355)
miR-155 (332, 356, 357, 358, 359)
miR-181a (360)
miR-223 (361)
miR-142a (362)
miR-146a (363)
miR-155 (110, 111, 112, 364)
miR-181 (113)
miR-23a (116, 365)
miR-34a (117)
miR-132 (118)
miR-148a (366)
miR-155 (119, 367, 368)
miR-181 (120, 121)
miR-212 (118)
miR-1246 (369)

Table 1. Commercially available pharmacological agents that can mimic or inhibit miRNA response. Depending on the company, the terminology for miRNA mimics and inhibitors can exist in alternative names.

	MiRNA agents	**Company**
Mimic miRNA	microRNA agomirs	Accegen Biotechnology RGBiotech
	micro*UP*™ miRNA agomir	Creative Biogene
	miRIDIAN microRNA mimics	Dharmacon
	MISSION® miRNA mimics	Merck (Previously Sigma-Aldrich)
	miScript miRNA mimics	Qiagen (Previously Exiqon)
	miRNA mimics	RGBiotech
	mirVana mimics	Thermo Fisher Scientific
Inhibit miRNA	microRNA antagomirs	Accegen Biotechnology RGBiotech
	micro*DOWN*™ miRNA	Creative Biogene
	miRIDIAN microRNA Hairpin inhibitors	Dharmacon
	IDT® miRNA inhibitors	Integrated DNA Technologies
	miScript miRNA inhibitors	Qiagen (Previously Exiqon)
	miArrest miRNA inhibitors	Genecopoeia
	miRNA Inhibitors	RGBiotech
	mirVana miRNA inhibitors	Thermo Fisher Scientific
	Ambion® anti-miR™ miRNA inhibitors	Thermo Fisher Scientific
	MISSION® miRNA inhibitors	Merck (Previously Sigma-Aldrich)

miRNA group effect	MicroRNA sponge	Accegen Biotechnology
	MicroRNA sponge	Creative Biogene
	miRIDIAN microRNA mimic and inhibitor libraries	Dharmacon
	miRCURY LNA power inhibitors	Qiagen (Previously Exiqon)
	miRCURY LNA miRNA family power inhibitors	Qiagen (Previously Exiqon)
	miRCURY LNA miRNA inhibitor libraries	Qiagen (Previously Exiqon)
	miRNA expression clone	RGBiotech
	miRNA mimic and inhibitor libraries	Thermo Fisher Scientific

Table 2. Clinical medication and chemical agents present in diet can alter miRNA expression. * includes activated microglia or monocyte-derived macrophages

Pathophysiology		MiRNA target	Drug
Cellular death	Excitotoxicity	miR-21	Metformin, bortezomib
	Autophagy	Let-7	Epigallocatechin-3-O-gallate
			Panobinostat
		miR-25	Isoliquiritigenin
		miR-155	Natalizumab
	Necrosis	miR-21	Metformin, bortezomib
		miR-155	Natalizumab
	Apoptosis	miR-21	Metformin, bortezomib
		miR-25	Isoliquiritigenin
		miR-29	Bleomycin, Imatinib
Neuroinflammation	Microglia	Let-7	Epigallocatechin-3-O-gallate
			Panobinostat
		miR-155	Natalizumab
	Astrocytes	miR-7	Nicorandil
		miR-21	Metformin, bortezomib
		miR-29a, b	Bleomycin, Imatinib
		miR-155	Natalizumab
	Macrophages*	miR-21	Metformin, bortezomib
		miR-155	Natalizumab
	Neutrophils	miR-130a	Curcumin
	Dendritic cells	miR-29b, c	Bleomycin, Imatinib
		miR-155	Natalizumab
	T-lymphocytes	miR-155	Natalizumab
	B-lymphocytes	miR-155	Natalizumab

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Declaration of Interest:

None

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