frontiers in
NEUROLOGY

OPINION ARTICLE
published: 29 September 2014
doi: 10.3389/fneur.2014.00181

Up-regulation of miRNA-146a in progressive, age-related inflammatory neurodegenerative disorders of the human CNS

Peter N. Alexandrov*[1], *Prerna Dua*[2] *and Walter J. Lukiw*[3,4]

[1] *Russian Academy of Medical Sciences, Moscow, Russia*
[2] *Department of Health Information Management, Louisiana State University, Ruston, LA, USA*
[3] *Department of Neurology, Louisiana State University Health Science Center, New Orleans, LA, USA*
[4] *LSU Neuroscience Center and Department of Ophthalmology, Louisiana State University Health Science Center, New Orleans, LA, USA*
**Correspondence: wlukiw@lsuhsc.edu*

Edited by:
Owen Murray Rennert, National Institutes of Health, USA

Reviewed by:
Travis Dunckley, Translational Genomics Research Institute, USA

Keywords: prion disease, Alzheimer's disease, age-related macular degeneration, miRNA-146a, neuroinflammation, innate-immune response

OVERVIEW

The human brain- and retinal-resident microRNA-146a (miRNA-146a) is an inducible, NF-kB-regulated small non-coding RNA (sncRNA) whose increased expression is associated with pro-inflammatory neurodegeneration in Alzheimer's disease (AD), age-related macular degeneration (AMD), and prion disease (PrD). In AD, AMD, and PrD miRNA-146a modulates the innate-immune response, inflammation, and the microglial activation state. This short paper will review and comment on the role of miRNA-146a signaling and how it underlies common molecular-pathogenetic mechanisms in each of these progressive, age-related neurological disorders for which there are currently no effective treatment or cure.

microRNA-146a

The 22 nucleotide miRNA-146a (miR-146a; hsa-miR-146a-5p; 5′-UGAGAACUGAAUUCCAUGGGUU-3′; 59% A + U; NR_029701; http://atlasgeneticsoncology.org/Genes/GC_MIR146B.html), is one of the most intensively studied small non-coding RNAs (sncRNAs) in all of human neurobiology. Encoded from a single locus at chromosome 5q33.3 in humans and at chromosome 11q in mice, miRNA-146a is a rapidly induced, pro-inflammatory miRNA with a relatively short half-life of about 1.5–2 h in human brain cells and tissues (1–4). This unique member of the miRNA-146 gene family was initially described as being significantly up-regulated after microbial endotoxin, lipopolysaccharide (LPS), or cytokine stimulation of THP1 cells (monocytes; originally derived from an acute monocytic leukemia patient) and under transcriptional control by NF-κB; shortly thereafter this inducible miRNA-146a was found to be up-regulated by metal sulfate-generated reactive oxygen species (ROS), by pro-inflammatory cytokines (such as IL-1β and TNFα) and amyloid peptides (such as Aβ42 peptides) in human primary neuronal-glial (HNG) co-cultures and microglial (HMG) cells (4–7). Each of these independent studies showed the targeting of miRNA-146a to the mRNAs encoding signaling proteins involved in the innate immune and inflammatory response, including complement factor H (CFH) and the interleukin-1 receptor-associated kinase 1 (IRAK-1; the gene partially responsible for IL-1-induced up-regulation of the transcription factor NF-kB; (1–4); see below).

Sequencing and promoter analysis of the human miRNA-146a gene subsequently identified three functional and conserved NF-κB binding sites upstream of the miRNA-146a gene, and combined with functionality and NF-kB-inhibition assays was the first NF-κB-regulated miRNA gene identified in the human brain and central nervous system [CNS; (2–4)]. Interestingly, while miRNA-146a is detectable in mouse and human brain and CNS tissues and primary HNG co-cultures, the most significant miRNA-146a abundances have been found to be in human astroglial (HAG) and microglial (HMG) cells, the later representing the "resident scavenging macrophages" of the brain, and key participants in the brain's innate-immune and inflammatory response (3–9). While expressed modestly in the brain and retina, miRNA-146a can be induced 2- to 10-fold or more in cultured brain cells where miRNA-146a is basally expressed, after the application of several different classes of physiological stressors including treatments with herpes simplex virus (HSV-1), neurotoxic metal sulfates (such as aluminum sulfate at nanomolar concentrations), microbial endotoxins including LPS, pro-inflammatory cytokines or amyloid beta (Aβ) peptides (1–5, 10).

Interestingly, human miRNA-146a has a related miRNA-146b isotype (miR-146b; hsa-miR-146b-5p; 5′-UGAGAACUGAAUUCCAUAGGCU-3′; 59% A + U; NR_030169) encoded at chromosome 10q24.32 (in mice on chromosome 19q); these two miRNAs have an identical seed (primary recognition) region and differ by only two ribonucleotides in the primary sequence of their stem-loop secondary structures (1–3, 10–12). Notably, it is a change in just two nucleotides in the 3′ end, from miRNA-146b (5′-UAGGCU-3′) to miRNA-146a (5′-UGGGUU-3′), which may confer enhanced specificity of miRNA-146a for mRNA targets involved in the innate-immune response of the CNS, and/or the ability to be induced and/or processed by different pro-inflammatory

cytokines [(8, 9, 13); unpublished observations].

ALZHEIMER'S DISEASE

According to the World Health Organization, the total number of people with dementia worldwide is currently estimated to be about 36 million, and this number is expected to almost double by 2030, reaching 66 million, and triple by 2050, reaching 100 million (14). Alzheimer's disease (AD), the leading cause of this dementia, is a progressive, age-related, and ultimately fatal neurological disorder associated with dysfunctional gene expression in the limbic system and entorhinal cortex of the brain that drives amyloidogenesis, pro-inflammatory signaling, and related AD-type neuropathology (15–18). Of all AD cases approximately 5% may be attributed to familial gene mutations while 95% occur sporadically, i.e., are of idiopathic or unknown origin (7, 14).

Amyloidogenesis involves the progressive generation and aggregation of 42 amino acid amyloid beta (Aβ42) peptides and other amyloidogenic peptides into dense, insoluble senile plaques whose recognition by brain cell microglia instigates a pro-inflammatory microglial response and the release of reactive oxygen species (ROS) and pro-inflammatory cytokines (3, 4, 7, 19). The first evidence of sncRNA involvement in sporadic AD reported mis-regulated levels of a polyadenylated brain cytoplasmic ~200 nucleotide (BC200) sncRNA in cases of AD, non-AD dementia, and controls (20). BC200 was found to be down-regulated and reflective of deficits in the abundance of neuron-specific transcripts, consistent with the idea that sporadic AD was characterized by a deficit in the generation of primary brain gene transcription products (20–25). The next reports of specific miRNA up-regulation in AD brain and blood serum did not appear until about 15 years later wherein a brain abundant miRNA-146a was one of the first miRNAs found (i) to be elevated in anatomical regions of the brain affected by the AD process but not in control regions (such as the thalamus and brain stem) of the same brain, or (ii) to be induced by AD-relevant stressors, such as the pro-inflammatory cytokines interleukin 1-beta (IL-1β) or tissue necrosis factor alpha (TNFα) and Aβ42 peptides, or combinations of these noxious factors which are pathologically abundant in the AD brain (6, 7, 21–25).

To date confirmed targets of miRNA-146a include key AD-relevant members of the innate-immune system including the 155 kDa sialic-acid containing glycoprotein immune repressor complement factor H (CFH), the membrane spanning beta-amyloid precursor protein (βAPP)-associated TSPAN12, and the inflammation mediator interleukin receptor-associated kinase IRAK-1 (1). Interestingly, pathologically up-regulated miRNA-146a, as seen in AD brain or pathologically stressed primary HNG co-cultures results in (i) CFH down-regulation and a stimulation of innate immune and inflammatory pathways (10, 25); (ii) down-regulation of TSPAN12 that drives a propensity for the massive production of Aβ42 peptides from βAPP (26); and (iii) down-regulation of IRAK-1 with a compensatory up-regulation of IRAK-2 (1, 4, 10). It is important to point out (i) that multiple NF-kB-regulated miRNAs such as miRNA-9, miRNA-34a, miRNA-125b, and miRNA-155 may have additional or ancillary roles in the pathological regulation of CFH, TSPAN12, and IRAK-1 in the AD brain and (ii) that miRNA abundance and complexity varies among both human cell types and tissues, and there are also obvious variations in pathogenic miRNA expression among various human populations (26–29).

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is an advancing, proliferative degeneration of retinal pigment epithelial, ganglion, and other related cells of the human macula, a highly specialized centralized region of the retina, resulting in the progressive loss of vision near the center of the visual field (8, 30–34). AD and AMD share many common pathological pathways including the appearance of dense, insoluble, Aβ42 peptide-enriched lesions (called drusen in AMD and called senile plaques in AD), a disruption in complement signaling including CFH loss-of-function or down-regulation, and the up-regulation of pro-inflammatory sncRNAs that include, prominently, miRNA-146a (32–35). Importantly, the common neuroectodermal origins of the limbic system, neocortex, and retina may predispose each of these highly integrated, multi-neuronal layered structures to progressive age-related functional impairment, including the involvement of shared pathogenic pathways that drive the development and "spreading" of amyloidogenesis and pro-inflammatory neurodegeneration.

As fore-mentioned, CFH plays an integral role in the regulation of the complement-mediated immune system that is involved in the first line of microbial defense against many pathogens, innate-immune complex processing, and programed cell death. CFH is emerging as an unexpected key player in both AD and AMD (10, 25, 30, 31, 36, 37). Activation of the complement system results in a proteolytic cascade eventually forming the membrane attack complex (MAC) leading to cell membrane perforation, lysis, and the dissolution of cellular contents, and a soluble brain- and retinal-abundant CFH normally protects host cells from unrestrained complement activation (31–34, 36).

Interestingly, the Y402H CFH loss-of-function mutation linked to AMD in many human populations may produce sufficient amounts of a non-functioning CFH, and this may be pathologically equivalent to insufficient amounts of a functional CFH protein, as is observed in sporadic AD, and perhaps other inflammatory degenerative and dementing diseases including Down's syndrome [Trisomy 21; (10, 25, 37)]. Indeed common CFH deficits in AMD and AD underscore the important role of innate-immune system regulation and complement signaling in these age-related progressive, inflammatory neurodegenerative diseases of the CNS. It is further noteworthy that human prion protein (PrP), an endogenous glycosylphosphatidylinositol (GPI)-anchored or transmembrane protein expressed in neurons strongly interacts with CFH, and the CFH-PrP complex pathologically super-activates complement via the classical and alternative pathways, leading to MAC formation and progressive cell dysfunction and ultimately, cell death (38).

PRION DISEASE

Prion diseases encompass a family of self-replicating prion protein (PrP) amyloid and related aggregates – driving pathophysiological conditions that are the primary causative factor of a number of progressive neurological diseases in mammals including humans (39–42). The first report of up-regulated miRNA-146a in prion disease was published in 2008 in a murine model of scrapie, and miRNA-146a was subsequently reported to be significantly up-regulated in the two rare human prion diseases sporadic Creutzfeldt-Jakob disease (sCJD) and Gerstmann–Straussler–Scheinker (GSS) syndrome (40–42). In prion disease miRNA-146a and other NF-kB-up-regulated, inducible miRNAs have been found to target the expression of genes involved in intracellular protein-degradation pathways and signaling pathways related to cell death, synapse function and neurogenesis as well as brain genes modulating microglial function by regulating their activation state during PrP-induced neurodegeneration (39–42). Interestingly, human prion diseases such as sCJD and GSS are highly similar to neurological diseases such as AD involving a significant pro-inflammatory and amyloidogenic component linked to progressive memory, cognitive, and behavioral deficits in the affected patient (39, 41).

CONCLUDING REMARKS

Our perceptions on the relevance and gene expression mechanisms of up-regulated miRNA-146a signaling in progressive, pathologically similar, human neurological diseases continue to evolve. It is now generally accepted that the primary mode of pathological miRNA action in the brain is to recognize and bind to complementary ribonucleotide sequences in the 3′-prime un-translated region (3′-UTR) of their target messenger RNAs and in doing so, down-regulate their expression (1–3, 10–13, 40, 43). Increased expression of miRNA-146a and down-regulation in the expression of miRNA-146a target genes are strongly associated with AD, AMD, and PrD disease phenotype and symptomology, both in cultured cell or animal models for that disease and in the human disease itself (31, 37, 44). miRNA-146a or families of other miRNA-146a-related miRNAs may orchestrate multiple deficits in multiple mRNA targets to coordinately affect the expression of families of brain-relevant innate-immune and inflammatory genes that are related in function in disease initiation, development, and propagation. It is noteworthy that the speciation and complexity of miRNA-146a-related families may differ slightly among different types of CNS cells and tissues, and even among the same cells and tissues of different human populations (25–29). The conclusion of this paper is that *common neurodegenerative diseases of the human CNS and retina including AD, AMD, and PrD, each appear to utilize an overexpressed miRNA-146a in their disease mechanism, and that this anomaly commonly disrupts homeostatic innate-immune signaling to promote an inflammatory phenotype.*

While pro-inflammatory miRNAs such as miRNA-146a are generally considered to be important epigenetic, post-transcriptional regulators of gene expression in both health and disease, it is not often appreciated that these sncRNAs: (i) are very highly selected in their ribonucleotide sequence in mouse and human and exhibit remarkable brain cell and CNS tissue specificity; (ii) are the smallest yet identified ribonucleic acid carriers of highly specific, genetic regulatory information in the human brain and CNS; (iii) are the most abundant extracellular, highly soluble nucleic acids contained in human circulatory fluids including the extracellular fluid (ECF), the cerebrospinal fluid (CSF), and blood serum; and (iv) as such may be capable of spreading genetic signaling information, both homeostatic and pathogenic, among neighboring CNS cells and tissues (20, 44–47). Anti-miRNA-146a (AM-146a) strategies aimed at quenching pathogenic miRNA effects have worked surprisingly well in cell cultures *in vitro*, but their efficacy in progressive neurological disease awaits additional animal experimentation and human clinical trials. Investigations are further warranted for the potential utility of circulating miRNA-146a and its related family members as potential diagnostic biomarkers for AD, AMD, PrD, and perhaps other age-related human neurological diseases with an innate-immune and pro-inflammatory component (31, 48–50).

ACKNOWLEDGMENTS

This research was presented at the Society for Neuroscience (SFN) Annual Meeting, San Diego, CA, USA, 9–13 November 2013. Thanks are extended to Aileen I. Pogue and Darlene Guillot for expert technical and administrative assistance. Research in the Lukiw laboratory on neurotoxic metals, microRNA, small non-coding RNA, the innate-immune response, amyloidogenesis, and neuroinflammation in AD, retinal, and prion disease, was supported through a COBRE III Pilot Award, an unrestricted grant from Research to Prevent Blindness (RPB), the Louisiana Biotechnology Research Network (LBRN), and NIH grants NEI EY006311 and NIA AG038834.

REFERENCES

1. Cui JG, Li YY, Zhao Y, Bhattacharjee S, Lukiw WJ. Differential regulation of interleukin-1 receptor-associated kinase-1 (IRAK-1) and IRAK-2 by miRNA-146a and NF-kB in stressed human astroglial cells and in Alzheimer disease. *J Biol Chem* (2010) **285**:38951–60. doi:10.1074/jbc.M110.178848
2. Lukiw WJ. NF-kB-regulated micro RNAs (miRNAs) in primary human brain cells. *Exp Neurol* (2012) **235**:484–90. doi:10.1016/j.expneurol.2011.11.022
3. Li YY, Cui JG, Dua P, Pogue AI, Bhattacharjee S, Lukiw WJ. Differential expression of miRNA-146a-regulated inflammatory genes in human primary neural, astroglial and microglial cells. *Neurosci Lett* (2011) **499**:109–13. doi:10.1016/j.neulet.2011.05.044
4. Pogue AI, Li YY, Cui JG, Zhao Y, Kruck TP, Percy ME, et al. Characterization of an NF-kB-regulated, miRNA-146a-mediated down-regulation of complement factor H in metal-sulfate-stressed human brain cells. *J Inorg Biochem* (2009) **103**:1591–5. doi:10.1016/j.jinorgbio.2009.05.012
5. Hill JM, Zhao Y, Clement C, Neumann DM, Lukiw WJ. HSV-1 infection of human brain cells induces miRNA-146a and Alzheimer-type inflammatory signaling. *Neuroreport* (2009) **20**:1500–5. doi:10.1097/WNR.0b013e3283329c05
6. Mrak RE, Griffin ST, Graham DI. Aging-associated changes in human brain. *J Neuropathol Exp Neurol* (1997) **56**:1269–75. doi:10.1097/00005072-199712000-00001
7. Butterfield DA, Griffin S, Munch G, Pasinetti GM. Amyloid beta-peptide and amyloid pathology are central to the oxidative stress and inflammatory cascades under which Alzheimer's disease brain exists. *J Alzheimers Dis* (2002) **4**:193–201.
8. Kroesen BJ, Teteloshvili N, Smigielska-Czepiel K, Brouwer E, Boots AM, van den Berg A, et al.

Immuno-miRs: critical regulators of T-cell development, function and ageing. *Immunology* (2014). doi:10.1111/imm.12367

9. Zhao JL, Starczynowski DT. Role of microRNA-146a in normal and malignant hematopoietic stem cell function. *Front Genet* (2014) **5**:219. doi:10.3389/fgene.2014.00219
10. Lukiw WJ, Zhao Y, Cui JG. An NF-kB-sensitive miRNA-146a-mediated inflammatory circuit in Alzheimer disease and in stressed human brain cells. *J Biol Chem* (2008) **283**:31315–22. doi:10.1074/jbc.M805371200
11. Sethi P, Lukiw WJ. Micro-RNA abundance and stability in human brain: specific alterations in Alzheimer's disease temporal lobe neocortex. *Neurosci Lett* (2009) **459**:100–4. doi:10.1016/j.neulet.2009.04.052
12. Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-kB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc Natl Acad Sci U S A* (2006) **103**:12481–6. doi:10.1073/pnas.0605298103
13. Kutty RK, Nagineni CN, Samuel W, Vijayasarathy C, Jaworski C, Duncan T, et al. Differential regulation of microRNA-146a and microRNA-146b-5p in human retinal pigment epithelial cells by interleukin-1β, tumor necrosis factor-α, and interferon-γ. *Mol Vis* (2013) **19**:737–50.
14. World Health Organization (WHO). Dementia: a public health priority. *Alzheimer's Disease Population and Country Statistical Analysis.* (2014). Available from: http://www.who.intmental_health/neurology/dementia/en/
15. Colangelo V, Schurr J, Ball MJ, Pelaez RP, Bazan NG, Lukiw WJ. Gene expression profiling of 12633 genes in Alzheimer hippocampal CA1: transcription and neurotrophic factor down-regulation and up-regulation of apoptotic and pro-inflammatory signaling. *J Neurosci Res* (2002) **70**:462–73. doi:10.1002/jnr.10351
16. Lukiw WJ. Gene expression profiling in fetal, aged, and Alzheimer hippocampus: a continuum of stress-related signaling. *Neurochem Res* (2004) **29**:1287–97. doi:10.1023/B:NERE.0000023615.89699.63
17. Ginsberg SD, Alldred MJ, Che S. Gene expression levels assessed by CA1 pyramidal neuron and regional hippocampal dissections in Alzheimer's disease. *Neurobiol Dis* (2012) **45**:99–107. doi:10.1016/j.nbd.2011.07.013
18. Kikuchi M, Ogishima S, Miyamoto T, Miyashita A, Kuwano R, Nakaya J, et al. Identification of unstable network modules reveals disease modules associated with the progression of Alzheimer's disease. *PLoS One* (2013) **8**(11):e76162. doi:10.1371/journal.pone.0076162
19. Fu R, Shen Q, Xu P, Luo JJ, Tang Y. Phagocytosis of microglia in the central nervous system diseases. *Mol Neurobiol* (2014) **49**:1422–34. doi:10.1007/s12035-013-8620-6
20. Lukiw WJ, Handley P, Wong L, McLachlan DRC. BC200 RNA in normal human neocortex, non-Alzheimer dementia (NAD), and senile dementia of the Alzheimer type (AD). *Neurochem Res* (1992) **17**:591–7. doi:10.1007/BF00968788
21. Lukiw WJ. Micro-RNA speciation in fetal, adult and Alzheimer's disease hippocampus. *Neuroreport* (2007) **18**:297–300. doi:10.1097/WNR.0b013e3280148e8b
22. Schipper HM, Maes OC, Chertkow HM, Wang E. MicroRNA expression in Alzheimer blood mononuclear cells. *Gene Regul Syst Bio* (2007) **1**:263–74.
23. Cogswell JP, Ward J, Taylor IA, Waters M, Shi Y, Cannon B, et al. Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways. *J Alzheimers Dis* (2008) **14**:27–41.
24. Jiang W, Zhang Y, Meng F, Lian B, Chen X, Yu X, et al. Identification of active transcription factor and miRNA regulatory pathways in Alzheimer's disease. *Bioinformatics* (2013) **29**:2596–602. doi:10.1093/bioinformatics/btt423
25. Lukiw WJ, Alexandrov PN. Regulation of complement factor H (CFH) by multiple miRNAs in Alzheimer's disease (AD) brain. *Mol Neurobiol* (2012) **46**:11–9. doi:10.1007/s12035-012-8234-4
26. Zhao Y, Bhattacharjee S, Jones BM, Hill J, Dua P, Lukiw WJ. Regulation of neurotropic signaling by the inducible, NF-kB-sensitive miRNA-125b in Alzheimer's disease (AD) and in primary human neuronal-glial (HNG) cells. *Mol Neurobiol* (2013). doi:10.1007/s12035-013-8595-3
27. Li J, Liu Y, Kim T, Min R, Zhang Z. Gene expression variability within and between human populations and implications toward disease susceptibility. *PLoS Comput Biol* (2010) **6**:e1000910. doi:10.1371/journal.pcbi.1000910
28. Olson MV. Human genetic individuality. *Annu Rev Genomics Hum Genet* (2012) **13**:1–27. doi:10.1146/annurev-genom-090711-163825
29. Lukiw WJ. Variability in micro RNA (miRNA) abundance, speciation and complexity amongst different human populations and potential relevance to Alzheimer's disease (AD). *Front Cell Neurosci* (2013) **7**:133. doi:10.3389/fncel.2013.00133
30. Khan M, Agarwal K, Loutfi M, Kamal A. Present and possible therapies for age-related macular degeneration. *ISRN Ophthalmol* (2014) **2014**:608390. doi:10.1155/2014/608390
31. Lukiw WJ, Surjyadipta B, Dua P, Alexandrov PN. Common micro RNAs (miRNAs) target complement factor H (CFH) regulation in Alzheimer's disease (AD) and in age-related macular degeneration (AMD). *Int J Biochem Mol Biol* (2012) **3**:105–16.
32. Sivak JM. The aging eye: common degenerative mechanisms between the Alzheimer's brain and retinal disease. *Invest Ophthalmol Vis Sci* (2013) **54**:871–80. doi:10.1167/iovs.12-10827
33. Ohno-Matsui K. Parallel findings in age-related macular degeneration and Alzheimer's disease. *Prog Retin Eye Res* (2011) **30**:217–38. doi:10.1016/j.preteyeres.2011.02.004
34. Kaarniranta K, Salminen A, Haapasalo A, Soininen H, Hiltunen M. Age-related macular degeneration (AMD): Alzheimer's disease in the eye? *J Alzheimers Dis* (2011) **4**:615–31. doi:10.3233/JAD-2011-101908
35. Lukiw WJ, Andreeva TV, Grigorenko AP, Rogaev EI. Studying microRNA function and dysfunction in Alzheimer's disease. *Front Genet* (2013) **3**:327. doi:10.3389/fgene.2012.00327
36. Donoso LA, Vrabec T, Kuivaniemi H. The role of complement factor H (CFH) in age-related macular degeneration: a review. *Surv Ophthalmol* (2010) **55**:227–46. doi:10.1016/j.survophthal.2009.11.001
37. Li YY, Alexandrov PN, Pogue AI, Zhao Y, Bhattacharjee S, Lukiw WJ. miRNA-155 upregulation and complement factor H deficits in Down's syndrome. *Neuroreport* (2012) **23**:168–73. doi:10.1097/WNR.0b013e32834f4eb4
38. Sjöberg AP, Nyström S, Hammarström P, Blom AM. Native, amyloid fibrils and beta-oligomers of the C-terminal domain of human prion protein display differential activation of complement and bind C1q, factor H and C4b-binding protein directly. *Mol Immunol* (2008) **45**:3213–21. doi:10.1016/j.molimm.2008.02.023
39. Fraser PE. Prions and prion-like proteins. *J Biol Chem* (2014) **289**:19839–40. doi:10.1074/jbc.R114.583492
40. Saba R, Goodman CD, Huzarewich RL, Robertson C, Booth SA. A miRNA signature of prion induced neurodegeneration. *PLoS One* (2008) **3**(11):e3652. doi:10.1371/journal.pone.0003652
41. Lukiw WJ, Dua P, Pogue AI, Eicken C, Hill JM. Upregulation of micro RNA-146a (miRNA-146a), a marker for inflammatory neurodegeneration, in sporadic Creutzfeldt-Jakob disease (sCJD) and Gerstmann-Straussler-Scheinker (GSS) syndrome. *J Toxicol Environ Health A* (2011) **74**:1460–8. doi:10.1080/15287394.2011.618973
42. Saba R, Gushue S, Huzarewich RL, Manguiat K, Medina S, Robertson C, et al. MicroRNA 146a (miR-146a) is over-expressed during prion disease and modulates the innate immune response and the microglial activation state. *PLoS One* (2012) **7**:e30832. doi:10.1371/journal.pone.0030832
43. Guo H, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. *Nature* (2010) **466**:835–40. doi:10.1038/nature09267
44. Wang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protective protein by mammalian cells. *Nucleic Acids Res* (2010) **38**:7248–59. doi:10.1093/nar/gkq601
45. Hill JM, Zhao Y, Bhattacharjee S, Lukiw WJ. miRNAs and viroids utilize common strategies in genetic signal transfer. *Front Mol Neurosci* (2014) **7**:10. doi:10.3389/fnmol.2014.00010
46. Lukiw WJ, Alexandrov PN, Zhao Y, Hill JM, Bhattacharjee S. Spreading of Alzheimer's disease inflammatory signaling through soluble micro-RNA. *Neuroreport* (2012) **23**:621–6. doi:10.1097/WNR.0b013e32835542b0
47. Zhao Y, Cui JG, Lukiw WJ. Natural secretory products of human neural and microvessel endothelial cells: implications in pathogenic "spreading" and Alzheimer's disease. *Mol Neurobiol* (2006) **34**:181–92. doi:10.1385/MN:34:3:181
48. Alexandrov PN, Pogue AI, Bhattacharjee S, Lukiw WJ. Retinal amyloid peptides and complement factor H in transgenic models of Alzheimer's disease. *Neuroreport* (2011) **22**:623–7. doi:10.1097/WNR.0b013e3283497334
49. Kumar P, Dezso Z, MacKenzie C, Oestreicher J, Agoulnik S, Byrne M, et al. Circulating miRNA biomarkers for Alzheimer's disease. *PLoS*

One (2013) **8**:e69807. doi:10.1371/journal.pone.0069807
50. Alexandrov PN, Dua P, Hill JM, Bhattacharjee S, Zhao Y, Lukiw WJ. microRNA (miRNA) speciation in Alzheimer's disease (AD) cerebrospinal fluid (CSF) and extracellular fluid (ECF). *Int J Biochem Mol Biol* (2012) **3**:365–73.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 14 August 2014; paper pending published: 27 August 2014; accepted: 05 September 2014; published online: 29 September 2014.
*Citation: Alexandrov PN, Dua P and Lukiw WJ (2014) Up-regulation of miRNA-146a in progressive, age-related inflammatory neurodegenerative disorders of the human CNS. Front. Neurol. **5**:181. doi: 10.3389/fneur.2014.00181*

This article was submitted to Neurogenomics, a section of the journal Frontiers in Neurology.