



NF- κ B (p50/p65)-Mediated Pro-Inflammatory microRNA (miRNA) Signaling in Alzheimer's Disease (AD)

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INTRODUCTION

A small family of NF- κ B (p50/p65)-regulated microRNAs (miRNAs) has been identified and partially characterized in Alzheimer's disease (AD) brain in the hippocampal CA1 and temporal lobe neocortical regions, and in reactive oxygen species (ROS)-, cytokine interleukin 1-beta (IL-1 β)-, amyloid beta 42 (A β 42) peptide- and/or lipopolysaccharide (LPS)-stressed human neuronal-glia (HNG) cells in primary co-culture. This microRNA family currently includes miRNA-9, miRNA-30b, miRNA-34a, miRNA-125b, miRNA-146a and miRNA-155. Other brain-enriched miRNA species may be involved. Experimental evidence suggests that in neurological diseases, the upregulation of this small pro-inflammatory miRNA family orchestrates a pathogenic gene expression program that can explain many aspects of AD onset, and propagation and severity of the disease including failure of microglial-mediated clearance of amyloid-beta (A β) and other end-stage peptides from brain cells, amyloidogenesis, astrogliosis, deficits in neurotrophism, neuronal cell atrophy, and downregulation in the production of essential cytoskeletal components and synaptic signaling elements. This opinion article will contribute to the interpretation of the most recent findings in the current research area involving NF- κ B-regulated miRNA-mediated signaling pathways, and how this information may aid in the advancement of therapeutic strategies for more effective clinical management of AD and other progressive age-related and lethal neurodegenerative disorders.

ALZHEIMER'S DISEASE (AD): EPIDEMIOLOGY AND BASIC FEATURES

AD is a slowly developing, irreversible, progressive, and inflammatory neurodegeneration of the human brain, central nervous system (CNS), and neural vasculature (Alzheimer et al., 1995; Lane et al., 2018; Trejo-Lopez et al., 2021). Due in part to the aging population and demographics, the global incidence and prevalence of AD are sharply increasing, and AD currently represents the largest single cause of age-related memory impairment and behavioral and cognitive decline in Westernized societies. Current estimates put the global incidence of AD at about ~55 million, and this number is expected to reach epidemic proportions and rise to about ~150 million cases by the

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year 2050 (Tahami Monfared et al., 2022; <https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12638>; <https://www.alz.org/media/documents/Alzheimers-facts-and-figures.pdf>; <https://www.Alzint.org/about/dementia-facts-figures/dementia-statistics/last> accessed 13 June 2022). AD places a tremendous socioeconomic burden on caregivers and on the healthcare system as a whole. Despite ~115 years of intense and directed research, no effective treatment or cure for AD exists, although many insights into the molecular-genetic nature of this age-related disease have been established (Alzheimer et al., 1995; Kaur et al., 2015; Lane et al., 2018; Dong et al., 2021; Hermans et al., 2021; Trejo-Lopez et al., 2021; Liu et al., 2022; Olufunmilayo and Holsinger, 2022; Pogue et al., 2022; Rastegar-Moghaddam et al., 2022; Singh et al., 2022; Tahami Monfared et al., 2022; Yoon et al., 2022). As a devastating, inflammatory, and terminal neurodegenerative disorder, one molecular genetic component that has emerged at the forefront of current AD research is the DNA-binding element NF- κ B, probably the single most important transcription factor yet identified in the complex neuropathology of AD. This opinion article will address some recently described effects of NF- κ B on a small family of regulatory miRNAs observed to be significantly altered in abundance, complexity and speciation in AD-affected brain.

NF- κ B-SENSITIVE microRNAS AND INFLAMMATORY SIGNALING IN ALZHEIMER'S DISEASE (AD)

Discovered about ~36 years ago, the heterodimeric transcription factor NF- κ B (p50/p65) was first described as a rapidly inducible nuclear factor κ -light-chain transcription enhancer of activated B cell lymphocytes in part responsible for the humoral immunity component of the immune system (Sen and Baltimore, 1986; Kaltschmidt et al., 1993; Taganov et al., 2006). Since then, recognition sites for this redox-controlled transcriptional activator and DNA-binding protein have been found to occur in multiple gene promoters, and it is now known to drive a broad range of gene expression patterns in diverse cellular types involved in host innate- and adaptive-immune functions with important roles in the clearance of waste molecules from the cytoplasm, inflammatory signaling, differentiation, cell growth, tumorigenesis and neurodegeneration (Taganov et al., 2006; Zhang et al., 2017; Baltimore, 2019). In resting cells the pre-formed NF- κ B (p50/p65; 115 kDa) heterodimer is bound to a hydrophobic inhibitory kappa B protein (I κ B, 36 kDa) that prevents free NF- κ B from promoter-DNA-binding and gene transactivation. However NF- κ B can be rapidly induced in all cell types by treating them with pro-inflammatory mediators that include interleukin-1 β (IL-1 β), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF α), and endotoxins such as lipopolysaccharides (LPS), an intensely inflammatory lipoprotein produced exclusively by Gram-negative bacteria, A β peptides, viral gene products, ultraviolet and other ionizing irradiation, and reactive oxygen species (ROS)-generating and/or oxidizing compounds. Exposure to these factors induces I κ B

decomposition triggered through a site-specific phosphorylation of an I κ B kinase (IKK) complex, followed by degradation via the ubiquitin-proteasome system, and then rapid NF- κ B-activated transcription by multiple pro-inflammatory NF- κ B-sensitive gene promoters. The human brain and CNS contain a very active, pleiotropic NF- κ B-signaling system that has a function in both neurological health and disease (Kaltschmidt and Kaltschmidt, 2009; Christian et al., 2016; Liu et al., 2022; Yoon et al., 2022). While the NF- κ B (p50/p65; also known as p50/RelA) heterodimer is especially abundant in nervous tissues, other homo- or hetero-dimeric NF- κ B transcription factor complexes containing at least 5 other molecular components that include RelA, RelB, c-Rel, p50, p52, and NFKB1 (p105) form at least 12 different identified NF- κ B complexes. All share the conserved Rel homology domain (RHD) responsible for DNA binding, dimerization, and association with the repressor protein I κ B (Zhang et al., 2017; Pires et al., 2018; Baltimore, 2019; <https://www.genecards.org/cgi-bin/carddisp.pl?gene=RELA>; last accessed 25 May 2022). It has been repeatedly demonstrated: (i) that activated NF- κ B subsequently upregulates a select sub-group of disease-associated miRNAs comprising a well-characterized NF- κ B-sensitive *Homo sapiens*-enriched family of potentially pathogenic miRNAs that include miRNA-9, miRNA-30b, miRNA-34a, miRNA-146a, and miRNA-155 normally involved in immunity, inflammation, and brain cell genetic function in the CNS (Lukiw, 2012, 2020; Brennan et al., 2019; Juźwik et al., 2019; Barnabei et al., 2021; Song et al., 2021; Yoon et al., 2022); (ii) that the same miRNAs are upregulated in AD brain; (iii) that this group of significantly over-expressed miRNAs are abundant in progressive and often lethal viral and prion-mediated and/or related neurological syndromes associated with progressive inflammatory neurodegeneration; and (iv) that all of these NF- κ B-sensitive endotoxin-responsive miRNA genes have as many as three tandem, functional NF- κ B binding sites stacked in their immediate 5'-promoter region, making this miRNA gene family exceptionally sensitive to NF- κ B activation and NF- κ B-mediated transcriptional upregulation (Taganov et al., 2006; Lukiw et al., 2008; Alexandrov et al., 2019; Jauhari et al., 2020; **Table 1**). Interestingly, there is also abundant recent evidence (i) that endotoxins such as LPS and other biophysical-barrier-penetrating glycolipids and lipoproteins specifically induce neurodegeneration by promoting neuro-inflammatory signaling by stimulation of Toll-like receptors (TLRs) present on the outer membranes of glial cells of the CNS (Kumar, 2019; Singh et al., 2022); (ii) that extremely potent pro-inflammatory species of LPSs have been found by many independent groups to be localized in human brain neurons in AD brain (Zhan et al., 2018, 2021; Alexandrov et al., 2019; Zhao et al., 2019a; Singh et al., 2022); and (iii) that a life-long supply of microbiome-abundant Gram-negative bacteria-derived LPS would be available over the long-term to chronically upregulate NF- κ B in the brain and CNS, as is observed in LPS-treated human neurons in primary culture and in AD temporal lobe neocortex, the latter an anatomical area targeted by the AD process (Lukiw and Bazan, 1998; Zhang et al., 2017; Zhan et al., 2018, 2021; Zhao and Lukiw, 2018; Alexandrov et al., 2019; Zhao et al., 2019a; Singh et al., 2022).

TABLE 1 | NF- κ B-induced microRNAs (miRNAs), their mRNA targets, functions, and pathways in Alzheimer's disease (AD)-affected brain; all miRNAs listed show: (i) significant upregulation following NF- κ B (p50/p65) activation; (ii) are potentially pathogenic and are upregulated in AD brain, AD cell culture, and transgenic murine models of AD (TgAD); and (iii) have been shown to interactively contribute to the AD process; some closely related work on the functions these miRNAs in neuronal cell culture, TgAD models, and other human neurodegenerative diseases have also been included in the References.

Human miRNA	mRNA target(s)	mRNA function	Result of mRNA and gene expression deficit	Reference
miRNA-9	CFH	complement factor H; repressor of activation of the innate immune response in brain and retina at the C3 to C3b transition	CFH deficits in disease are pro-inflammatory; excessive activation of the innate-immune response, altered immune-signaling, neuroinflammation	Clement et al. (2016), Recabarren and Alarcón (2017), Chen et al. (2018), Natoli and Fernando (2018)
	TREM2	triggering receptor expressed in myeloid and microglial cells; surface receptor essential in removing cellular debris; viral infection	deficits in phagocytosis and clearance of end-stage metabolic products from cells including amyloid beta (A β) peptides	Lukiw et al. (2008), Zhao and Lukiw (2013, 2018), Bhattacharjee et al. (2016), Chen et al. (2021)
	TSPAN-7	transmembrane spanning superfamily member 7; regulator of surface receptor signal transduction; activates ADAM10-dependent cleavage activity of β APP; tau seeding activity; viral infection	amyloidogenesis; impairment of autophagic activity and promotion of amyloid plaque formation; inhibition of autophagy; supports the formation of neurofibrillary tangles (NFT)	Jaber et al. (2019), Perot and Ménager (2020), Chen et al. (2021), Turk et al. (2021)
miRNA-30b	NF-L (NEFL)	neurofilament light chain protein; neuron-specific; supports neuronal cytoarchitecture, radial diameter of axons and synaptic signaling	loss of neuronal cytoarchitecture and signaling capacity; neuronal atrophy; synaptic structural deficits; general biomarker for neurodegeneration	McLachlan et al. (1990), Kittur et al. (1994), Brennan et al. (2019), Xu et al. (2021), Zhao et al. (2021)
miRNA-34a	SHANK3	SH3 proline-rich and multiple-ankyrin-repeat domain (SHANK3) cytoskeletal anchoring protein; gene directional gene expression effects; associated with viral infection	Disruption of the cytoskeleton and post-synaptic structure and scaffolding network; deficits in synaptic organization, dendritic spine maturation and synaptic vesicle release	Lu et al. (2010), Choi et al. (2015), Jaber et al. (2017), Lee et al. (2017), Jin et al. (2018), Zhao et al. (2019b)
	TREM2	triggering receptor expressed in myeloid and microglial cells; surface receptor essential in removing cellular debris; associated with viral (SARS-CoV-2) infection	deficits in phagocytosis and clearance of end-stage metabolic products from cells including amyloid beta (A β) peptides- deficits in AD and AMD	Zhao and Lukiw (2013), Zhao et al. (2013), Hermans et al. (2021), Wu et al. (2021), Olufunmilayo and Holsinger (2022)
miRNA-125b	CDKN2A	cyclin-dependent kinase inhibitor 2A cell cycle inhibitor; induces cell cycle arrest; viral (SARS-CoV-2) infection	downregulation of cell cycle control: astrogliosis and glial cell proliferation	Pogue et al. (2010), Czapski et al. (2021), Valeri et al. (2021)
	SYN-2	synapsin-2: neuron-specific; neuronal synaptic phosphoprotein; coats synaptic vesicles; functions in the regulation of neurotransmitter release	impairment of neurotransmitter release and trans-synaptic signaling; synaptic signaling deficits observed in AD brain and in TgAD murine models	Ferreira and Rapoport (2002), Mirza and Zahid (2018), Zhao et al. (2019a, 2021), Ješko et al. (2021)
	15-LOX-1	ALOX15; arachidonate 15-lipoxygenase; essential in the conversion of docosahexaenoic acid to neuro-protectin D1 (NPD1)	lack of NPD1; lack of neurotrophic support; deficiency of neurotrophic omega-3 fatty acid derivatives in the human brain neocortex	Lukiw et al. (2005), Zhao et al. (2014), Sun et al. (2018), Al-Fadly et al. (2019)
miRNA-146a	CFH	complement factor H; complement control glycoprotein; deficits in disease are pro-inflammatory to the host; viral (SARS-CoV-2) infection; see above	defective control and stimulation of the innate- immune response; and pro-inflammatory signaling; role in neuro-pathological signaling in AD and prion disease	Alexandrov et al. (2019), Slota and Booth (2019), Fan et al. (2020), Yu et al. (2020), Aslani et al. (2021), Pogue and Lukiw (2021), Wu et al. (2021)
	IRAK-1	interleukin-1 receptor-associated kinase 1; initiation and sustenance of the innate immune response and NF- κ B signaling	compensatory surge in IRAK-2 and chronic stimulation of NF- κ B signaling in the brain; neuroinflammation	Cui et al. (2010), Arena et al. (2017), Aslani et al. (2021)
	TSPAN12	transmembrane superfamily member 12; cell surface receptor involved in signal transduction; activates ADAM10-dependent cleavage of β APP and tau seeding activity	pathological shift from neurotrophic (sAPP α) to amyloidogenic (beta- and gamma-secretase cleavage); processing of β APP into neurotoxic A β 42 peptides	Li et al. (2011), Jaber et al. (2017), Aslani et al. (2021), Miyoshi et al. (2021)
miRNA-155	CFH	complement factor H; see above	defective regulation of the innate-immune response (see above)	Chen et al. (2018), Zingale et al. (2021), Rastegar-Moghaddam et al. (2022)

THERAPEUTIC STRATEGIES DIRECTED AGAINST NF- κ B AND/OR PRO-INFLAMMATORY miRNA SIGNALING

Because NF- κ B signaling pathways appear to be centrally involved in a great many immune- and inflammation-linked human diseases from carcinogenesis to neurodegeneration, a large number of natural and synthetic NF- κ B inhibitors have been designed and tested, and are under very active investigation to limit the extent of NF- κ B activation in the cellular environment. The evolution of one single high-potency gene-activating transcription factor in overlapping signaling pathways has made it challenging to find biologically active inhibitory molecules that can interfere with and/or block specific signaling pathways that lead to NF- κ B activation without multiple off-target effects or other complicating factors. Even so, a number of NF- κ B modulator and blocking strategies have been adopted or are undergoing rigorous evaluation in both research laboratories and in clinical settings. In general, therapeutic NF- κ B inhibition can occur *via* four basic mechanistic strategies: (i) by blockage of the original physiological stimulating signals that drive NF- κ B activation; (ii) by targeting phosphorylation pathways associated with NF- κ B activation because NF- κ B phosphorylation controls transcription in a gene-specific manner; (iii) by modulation or activation of the I κ B complex or other NF- κ B subunits; and/or (iv) by blockage of NF- κ B translocation, DNA sequence recognition, and binding and/or modification of NF- κ B that affects its activity or target specificity. These approaches include but are not limited to the following strategies, most of which are under very active research and therapeutic development: (i) antioxidant approaches that neutralize the primary NF- κ B activation signals such as quenching of reactive oxygen species (ROS) and other oxidizing and/or redox compounds (Kaur et al., 2015; Barnabei et al., 2021; Jover-Mengual et al., 2021; Pogue and Lukiw, 2021); (ii) alteration of multiple phosphorylation events that disrupt the activation of the multi-subunit NF- κ B transcription complex and alter the interaction of these phosphorylation sites that ultimately determines the selectivity of NF- κ B effects on transcriptional activity (by advanced investigation of these highly interactive phosphorylation sites and mechanisms it should be possible to modulate or block many aspects of phosphorylation-mediated NF- κ B activation; Christian et al., 2016; <https://360researchreports.com/global-nf-kb-inhibitors-market-20149725>); (iii) as previously pointed out, because active NF- κ B complexes are assembled from various combinations of RelA, RelB, c-Rel, p50, p52, NFKB1 (p105) etc., it may be possible to specifically block the generation and/or assembly of a single monomeric species of NF- κ B by limiting the abundance of one of the subunits of NF- κ B by genome editing, including knock-out technologies and/or the Cas9/CRISPR editing system (Wang et al., 2018; Dai et al., 2020; Katti et al., 2022); (iv) NF- κ B is directed to bind to its genomic targets by topological features located in certain promoter DNA sequences; therefore, these highly specific promoter DNA

binding sites can be masked, blocked, or modulated using genome blocking technologies involving small non-coding RNA (sncRNA), NF- κ B decoy sequence, and/or Cas9/CRISPR editing strategies (Taganov et al., 2006; Christian et al., 2016; Zhang et al., 2017; Baltimore, 2019; Dai et al., 2020; Katti et al., 2022; Yoon et al., 2022); (v) specific upregulated miRNA abundance and speciation may be blocked or modulated using chemically stabilized anti-miRNA strategies or by targeting miRNA processing enzymes, thus preventing the creation of a fully active and/or biologically available miRNA species; (vi) directed delivery systems to the brain and/or CNS or other tissue and/or organ systems to minimize unwarranted off-target effects; (vii) long-term systemic ingestion of low-dose NF- κ B inhibitors including dietary-administered flavonoids, lignans, diterpenes and sesquiterpenes, saponins, polysaccharides, polyphenols, biological fiber, and other natural products that may have general beneficial effects on reducing pro-inflammatory signaling, carcinogenesis, and neurodegeneration by chronic dampening of NF- κ B activities. These have been used for millennia in the pharmacopeia associated with ethnic biomedical-treatment approaches (Gilmore and Herscovitch, 2006; Li et al., 2020a,b; Olajide and Sarker, 2020; Uddin et al., 2021; Al-Khayri et al., 2022; Das et al., 2022); and/or (viii) any combination of these therapeutic strategies. Regarding the creation and testing of synthetic NF- κ B modulatory or blocking compounds, about ~80 pharmaceutical companies are currently in the pursuit of more effective, directed and specifically targeted NF- κ B inhibitors for clinical application in human diseases involving excessive NF- κ B activation and signaling (<https://www.futuremarketinsights.com/reports/nf-kb-inhibitors-market>; <https://www.Globenewswire.com/news-release/2020/12/08/2141093/0/en/NF-kappa-B-Inhibitors-Therapeutics-pipeline-analysis-of-80-Companies.html>; <https://360researchreports.com/global-nf-kb-inhibitors-market-20149725>; last accessed 25 May 2022).

DISCUSSION

The pleiotropic homo- or hetero-dimeric transcription factor NF- κ B is a master regulator of the innate immune system, inflammatory responses, and neurotropic, cytoskeletal, synaptic, phagocytic, and synaptic deficit characteristics of the AD-affected brain and related neurodegenerative disorders. One critically important regulatory action of the NF- κ B complex is to upregulate a small family of pathogenic miRNAs in the brain and CNS, which in turn targets and downregulates a group of mRNAs whose downregulation is decisive in driving the neuropathology of AD (Table 1). It is our opinion that these NF- κ B-regulated miRNA-mRNA linked pathological interactions will provide a wealth of targets for therapeutics and disease intervention. The merging of experimental and human clinical trials will be decisive in the strategic design and application of NF- κ B and NF- κ B-miRNA-induced modulatory agents and drugs useful in the more efficacious treatment of the current AD epidemic.

AUTHOR CONTRIBUTIONS

WL researched, compiled data, and wrote the paper. WL approved and submitted the final version.

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