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REVIEW ARTICLE

Role of Nuclear Factor Kappa B (NF-κB) Signalling in Neurodegenerative Diseases: An Mechanistic Approach

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Abstract: A transcriptional regulatory nuclear factor kappa B (NF-κB) protein is a modulator of cellular biological activity *via* binding to a promoter region in the nucleus and transcribing various protein genes. The recent research implicated the intensive role of nuclear factor kappa B (NF-κB) in diseases like autoimmune disorder, inflammatory, cardiovascular and neurodegenerative diseases. Therefore, targeting the nuclear factor kappa B (NF-κB) protein offers a new opportunity as a therapeutic approach. Activation of IκB kinase/NF-κB signaling pathway leads to the development of various pathological conditions in human beings, such as neurodegenerative, inflammatory disorders, autoimmune diseases, and cancer. Therefore, the transcriptional activity of IκB kinase/NF-κB is strongly regulated at various cascade pathways. The nuclear factor NF-kB pathway plays a major role in the expression of pro-inflammatory genes, including cytokines, chemokines, and adhesion molecules. In response to the diverse stimuli, the cytosolic sequestered NF-κB in an inactivated form by binding with an inhibitor molecule protein (IkB) gets phosphorylated and translocated into the nucleus further transcribing various genes necessary for modifying various cellular functions. The various researches confirmed the role of different family member proteins of NF-κB implicated in expressing various genes products and mediating various cellular cascades. MicroRNAs, as regulators of NF- κB microRNAs play important roles in the regulation of the inflammatory process. Therefore, the inhibitor of NF-κB and its family members plays a novel therapeutic target in preventing various diseases. Regulation of NF- κB signaling pathway may be a safe and effective treatment strategy for various disorders.

Keywords: Transcriptional, nuclear factor kappa B (NF-κB), MicroRNAs, pro-inflammatory genes, neurodegenerative, inflammatory disorders, autoimmune diseases.

1. INTRODUCTION

A transcriptional factor NF-κB expresses various genes encoding proteins having a vital role in processes of immunity, inflammation, cell growth, cell survival and apoptosis [1, 2]. Therefore, the NF-κB signaling is involved in vital cellular processes as well the negative regulation of NF-κB by suppression or activation of its target genes seem to be elevated under several pathological conditions [3]. The dysregulation of NF-κB is linked with certain mechanisms underlying the involvement of oxidative stress and inflammation in certain pathological conditions such as ischemic stroke, autoimmune and neurodegenerative diseases [3-5]. The activation of NF-κB by various cellular stress stimuli like the release of cytokines (TNF-alpha, Interleukin-1, growth factors), neurotrophic factors or viral infections undergo the transcription of certain genes resulting in increases in the cellular stress responses [6]. In the absence of stimuli, the NF-κB dimers remain in the inactivated state bounded with an inhibitor molecule protein (IkB), inhibiting the NF-κB translocation into the nucleus or altering the transcription [7]. The IkB protein family consists of (IκBα, IκBβ, IκBε, and Bcl-3) proteins; the IκBα appears to be involved in binding to heterodimer (p50/Rel A) protein complex [8]. The NF-κB dimer includes certain proteins c-Rel, Rel B, p65(Rel A), p105/p50 (NF-κB1), p100/52 (NF-κB2) associated with each other forming an homodimeric complex like Rel A/ p65, p50/p50, p52/p52 or heterodimeric complexes *i.e*., RelB/P50, RelB/p52 [9-11]. The Rel homology domain (RHD) region has the N- terminal called the DNA binding site specificities to p50 and p65, dimerization and interaction with intracellular inhibitory protein IkB of NF-κB. The N- terminal NF-κB allows the translocation into the nucleus and binds to the GGGRNNYYCC sequence of NF-κB DNA sites, where R is purine, Y is pyrimidine and N is any bases [9, 10]. Whereas, the C terminal has the remaining DNA contacts and controls the dimerization also known as dimerization domain for the nuclear localization signal or sequence (NLS) as the C terminal has an impact on the transcriptional activation properties or the inhibitory properties. On the basis of C-terminal sequence, the Rel/NF-κB proteins are divided into two

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classes. The class 1 members include NF-κB proteins p105, p100 a precursor for p52 and p50 possessing multiple copies of ankyrin repeat protein found in IkB family member proteins. The second-class members include (Rel proteins) *i.e.* c-Rel, Rel B and Rel A protein region known as NF-κB mediated gene transactivation domain [11, 12]. In response to diverse stimuli like release of cytokines (TNF- alpha, Interleukin-1, growth factors), neurotrophic factors or viral infections, there is an intracellular activation of the IKB kinase (IKK) complex comprising catalytic kinase enzymes including IKK-α; IKK-β; IKK-γ/NEMO; IKK-β), while the IKK-γ /NEMO is a regulator for sensing which further integrates the downstream activating signals by phosphorylation of the inhibitor (IkB) of NF-κB as shown in Figs. **1** & **2** [11]. The IkB gets cleaved converting the NF-κB in active form, resulting in translocation of NF-κB into the nucleus and binding to the enhancer or promoter region of the target gene, initiating the gene transcription [11-14]. The ubiquitination of IkB protein gets regulated and degraded by proteasomes [15, 16]. The re-synthesization of IκB-α & IκB-ε proteins is a time taking process occurring in the cytoplasm inhibiting the nuclear import by mediating the nuclear export of NF-κB/Rel proteins entering the nucleus and exporting the complex back to the cytoplasm [17]. The IκB-β protein only inhibits the import of NF-κB/Rel proteins into the nucleus avoiding the complex protein nucleus exporting into the cytoplasm [14].

The inactivated heterodimer protein complex NF-κB (RelB/P50) is located in the cytosol bounded with an inhibitor molecule protein (IkB). In response to a stimulus, the intercellular activation of certain catalytic kinases (Ikk) getting cleaved by ubiquitination results in activating NF-κB getting translocated into the nucleus further binding to the enhancer or promoter region of the target gene and initiating the gene transcription.

The two signaling pathways, *i.e.* Canonical/classical and the non-canonical/alternative pathway activate the NF-κB [18]. The Canonical/classical pathway gets activated by extracellular stimuli that include TNF-alpha, RANK (receptor activator of nuclear factor kappa B), TCR (T-cell receptor), CD30, CD40, LPS (bacterial lipopolysaccharides) altering IKK trimetric complex comprising of two catalytic subunits of IKKα and IKKβ, and a regulatory subunit IKKγ (also named NF-κB essential modulator or NEMO) leading to phosphorylation of IκB inhibitor (IκB-α) at Ser 32 and Ser 36 by further ubiquitination of IκBα [19, 20]. The free NF-κB dimer comprising g p50/p65 gets activated and translocated into the nucleus, where it binds to the promoter region to activate the transcription of responsive genes [21, 22]. The non- canonical/ alternative pathway is activated by various extracellular stimuli including BAFF-R (B-cell activator receptor), LTBR (lymphotoxin beta receptor), CD40 activating NIK kinase phosphorylating the IKK complex containing IκBα dimerized complex, at Ser 866 and Ser 870 of IκBα further activating the RelB/p100 to RelB/p52, undergoing transcription [20, 23].

The NF-κB overexpresses various genes which tend to be implicated in various diseases like cancer, ischemia and brain trauma, oxidative stress, neurodegenerative diseases (Huntington disease), Alzheimer's and Parkinson's disease, inflammatory diseases, *etc*. [4, 19, 24]. Therefore, the expression of genes is controlled by NF-κB suggesting an attractive therapeutic approach targeting NF-κB by its selective or non-selective inhibitors or agonists [25, 26].

2. DUAL ROLE OF NF-κB IN NEURONAL DEATH AND NEURONAL SURVIVAL IN PATHOLOGICAL CONDITION

NF-κB regulates the expression of many genes involved in cell death and cell survival by expressing the pro-apoptotic and anti-apoptotic genes seem to be involved in various pathological conditions [49-51] Therefore, the NF-κB serves dual function as protective mechanism for cell survival, promoting the cell death by stimulating the intracellular pathways involved in DNA damage [52]. NF-κB signaling in the central nervous system has a vital role by regulating certain functions like neuronal plasticity, neuronal growth and also regulates certain proteins as defense mechanisms acting in response to the certain cellular stress conditions [53, 54]. The subunits p50, p65, IkB-α and MEKK1 are

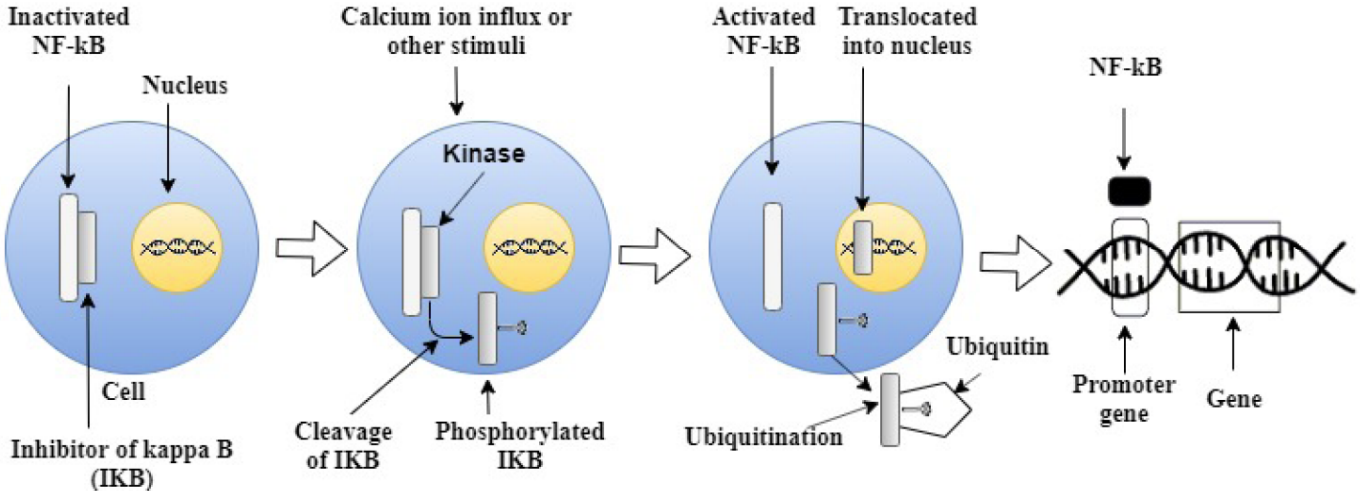

Fig. (1). Mechanisms of activation of NF-κB. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

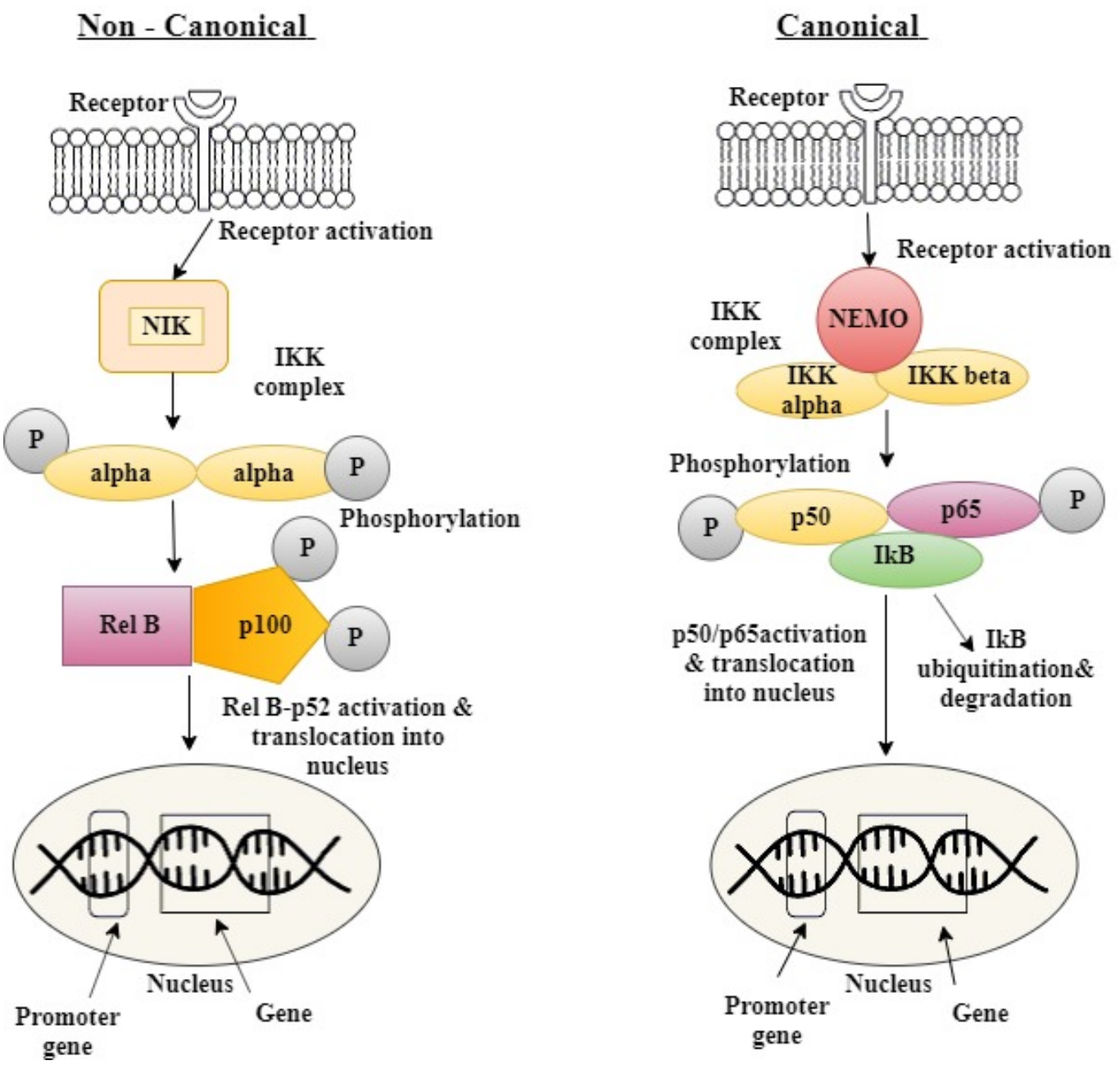

Fig. (2). Canonical/ Classical pathway and the Non- Canonical/ Alternative pathway of NF-κB. In the canonical pathway, the toll-like receptor gets activated by large stimuli and binding of ligand and recruiting the activation of IκB complex (IKK) complex, and then phosphorylates inhibitory enzyme (IKB) getting degraded by ubiquination. Further, the activated NF-κB complex (p50/p65) translocates into the nucleus to transcribe genes. In Non-canonical/alternative pathway, the activation of NF-κB inducing kinase (NIK) in response to very small stimuli (lymphotoxin B, B cell-activating factor) carries the intracellular signaling. The NIK phosphorylates the 2 IKK –alpha subunits phosphorylating p100, further activating heterodimer p52/RelB complex to translocate into the nucleus. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

highly expressed in the neuronal, astrocytes, microglia and oligodenderitic cells. In normal neuronal conditions, the electrical activity and synaptic transmission act as a stimulus to activate the MEKK1, phosphorylating the IkB-α causing the NF-κB translocation into nucleus further transcribing genes for glutamate receptor 2, MnSOD, Bcl2 necessary for the neuronal plasticity and normal physiology [55-57]. Under the normal neuronal development, depolarization of membrane causes the activation of microglial and astrocytes cells producing nerve growth factor (NGF) neurotrophin, IL-6 & nitric oxide; the microglial cells release the cytokines like TNF-α, transforming growth factor (TGF), fibroblast growth factors, nitric oxide, Chemokine (C-C motif) ligand 5 (CCL5) at the site of the cellular stress further acting as an extracellular stimuli for activating NF-κB [56, 57]. Furthermore, the activated NF-κB transcribes genes for certain pro-

Table 1. Describes the NF-κB inducer with variant stimuli activating NF-KB complex by IKK enzyme and transcribing particular genes involved in various pathological conditions.

NF-κB Inducers	Stimuli (Intracellular /Extracellular)	Receptor Activation	Multiple Adaptors	IKK Enzyme Type	NF-κB Complex	Target Gene	Disease	Refs.
Bacteria, Microbes, and viruses.	Pathogen-associated molecular pattern (PAMPs), NOD2 (Nucleotide Binding Oligomerization Domain Containing 2)	Pattern recognition receptors (PRRs), Toll –like receptors. Cytokine receptors (interleukin-1 receptors (IL-1Rs), TNF receptors (TNFRs), NLRs (NOD-like receptors)	TNFR-associated factors (TRAFs), Myeloid differentiation primary response protein 88 (MYD88), TIR domain containing adaptor protein (TIRAP), IL-1 R associated kinases (RIPK3), NIK (NF-κB inducing kinases) or MAP3K14.	IkB α, TBK1, IkB β	p52 RelB, p100 RelB, p50 RelA, p105 RelB	BAFF, BLIMP1, CCL17, CCL19, CCL5, CCL5, IL-1 a, IL-b, IL-2, 6, 8, 9, 10, 11, TNF-α, TNF- β, NOD2	Alzheimer's, Parkinson's, Epilepsy, CNS lymphoma.	[27-38]
Physical stress (UV and gamma radiations), Stress metal	Cell stress	Sensory receptor or non-receptor	P38 /MAPK, CkK II (casein kinase). ASK1, SEK1, MEK2, JNK1, β -TrcP	IκBα	p50 RelA	BAX, Bim, Bcl2	Alzheimer's, Parkinson's, Huntington, Ischemia.	[39-42]
Oxidative stress (Glutathione, H2O2)	TNF-alpha, Reactive oxygen species (ROS), NOD2 (Nucleotide Binding Oligomerization Domain Containing 2)	Toll–like receptors. Cytokine receptors (interleukin-1 receptors (IL-1Rs), TNF receptors (TNFRs), NLRs (NOD-like receptors)	ERKs, JNKs, or p38 MAPKs, tyrosine kinase	MEKK1 (mitogen-activated protein kinase kinase kinase), IκBα, IkB β	p50 RelA)	BAX, Bim, Bcl2, Cu/Zn SOD, SOD1, MAP4K1, CCL17, CCL19, CCL5, CCL5, IL-1 a, IL-b, IL-2, 6, 8, 9, 10, 11, TNF-α, TNF- β, NOD2.	Alzheimer's, Parkinson, Huntington's, Ischemia, Epilepsy.	[43-45]
Apoptotic mediators	TNF-alpha, Reactive oxygen species (ROS), Interleukin (IK)	Toll–like receptors. Cytokine receptors (interleukin-1 receptors (IL-1Rs), TNF receptors (TNFRs),	(Anti-fas/ Apo-1, Ploy(ADP) Ribose polymerase (PARP), TRAIL	IkB α, TBK1, IkB β	p52 RelB, p100 RelB, p50 RelA, p105 RelB	BAX, Bim, Bcl2	Alzheimer's, Parkinson's, Huntington's, Ischemia, Epilepsy.	[31-34, 46-48]

teins IL-6, TNF- α causing the inflammation whereas, the IL-10, TGF countering the inflammation by acting as anti-inflammatory [58-60]. The prolonged neuronal stress, *i.e*. the hyper-activation of the glutaminergic transmission or any other neuronal injury under the chronic pathologies causes the sustained migration of the glial cells which leads to the excitotoxicity stimuli activating the NF-κB to transcribe certain gene of inflammation and regulating the proteins of apoptosis [57, 58, 60]. The pro-apoptotic activity of NF-κB is by transcribing various genes like p53, c-Myc, cyclin D1, Bcl-Xs, BAX, Fas and NOS which seem to be highly elevated by pathological stimuli *i.e*. over-stimulation of NMDA receptor causing neuronal excitotoxicity that directly activates NF-κB and causes apoptosis. Under certain pathological conditions like oxidative stress or any other cell stress stimuli causing the cellular damage, the NF-κB levels seem to be elevated with other proteins like p53, c-Myc, cyclin D1, Bcl-Xs, BAX, Fas and NOS [59]. The various research studies concluded the role of NF-κB with proteins like p53, c-Myc, cyclin D1, Bcl-Xs, BAX, Fas and nitric oxide synthase, *i.e*., by inhibiting the NF-κB, the levels of these elevated proteins causing apoptosis death were decreased in neurodegenerative diseases [1, 59, 61]. On the other side, the NF-κB plays a cell survival role by the activation of a pathway called TNF-alpha/ NF-κB. The Tumor necrosis factor (TNF- α) has a capability to derive apoptosis but also undergoes cell survival pathways in the form of inflammation by cytokine production through NF-κB and avoids the apoptosis process [1]. In apoptosis, the RIP (receptor-interacting protein) and FADDD (Fas-associated protein death domain) molecules are the central regulatory molecules activating the caspase-8 cascade causing the induction of cellular death in the apoptotic pathway [1, 61-63]. In NF-κB pathway, the RIP (receptor-interacting protein) and TRAF2 (TNF receptor-associated factor 2) are the central regulatory molecules regulated by TRADD (TNF receptor-associated receptor-type 1 death domain). Furthermore, the RIP (receptor-interacting protein) and TRAF2 driven NF-κB pathway and apoptosis is inhibited thus, possessing a neuronal survival activity [54, 64]. The cell surface TNFR receptor having a

death domain on its intracellular site is attached to the SODD (silencer of death domain) protein keeping TNFR (Tumor necrosis factor receptor) in an activated state prior to external stimuli [1, 64]. On extracellular TNF- α stimuli, the TNF- α binds to the TNFR receptor causing the conformational changes in TNFR receptor, causing the release of SODD (silencer of death domain) from the death domain. The TRADD (TNF receptor-associated receptor- type 1 death domain) protein binds to the death domain of TNFR, further imitating the downstream signal by recruiting another molecule TRAF2 (TNF receptor-associated factor 2) and thus, avoiding the apoptosis pathway [1, 62, 64, 65]. The NF-κB pathway is initiated by the TRADD & TRAF2 complex recruiting IAP protein to bind to the complex. The TRAF2 also recruits the RIP protein further activating the IKK kinase molecule phosphorylating the IκB- α attached to the NF-κB masks NLS on NF-κB, the phosphorylated IκB- α gets degraded. The NF-κB gets disassociated from IκB-α molecule and translocates into the nucleus, further expressing the pro-inflammatory mediators, cytokine production, anti-apoptotic genes like Bcl-2, Bcl- XL, manganese superoxide dismutase (Mn-SOD) and possessing a neuronal survival activity [1, 55]. Therefore, it has been concluded that in normal physiological conditions, the NF-κB acts as an anti-apoptotic function but in pathological conditions, it is involved in apoptosis depending on the stimulus.

3. INVOLVEMENT OF MICRORNAS IN NEURONAL DEATH AND NEURONAL SURVIVAL

3.1. Role in Neuronal Death

NF-κB promotes the apoptosis by regulating the expression of many pro-apoptotic genes for proteins like p53, c-Myc, cyclin D1, BcL-Xs, BAX and Fas ligand [66-69]. The NF-κB plays a role in neuronal apoptosis by expressing the genes for p53 protein *i.e.*, due to neuronal excitotoxicity and oxidative stress, p53 was found to be elevated in neurodegenerative diseases [66]. The p53 protein is a tumor suppressor causing the neuronal apoptosis by increasing the expression of BAX and PUMA and suppressing the expression of anti-apoptotic genes like Bcl-2 (which acts as cytoprotective and is anti-apoptotic protein) [70-72]. Hence the NF-κB inhibitor-like aspirin, SN50 reduces the high levels of p53, preventing the apoptotic neuronal death in various neurodegenerative disorders [73, 74]. The expression of various miRNAs including miR- 155, miR- 34a, miR- 23b, miR-210, miR- 128a, miR- 25, miR- 145 are involved in production of ROS causing neuronal death [75]. The miR- 155 targets SHIP1 by deregulating its level and increasing ROS; the miR- 25 increases the expression of NOX4 responsible for oxidative stress. In neuronal cell, the miR- 145 increases the calcium influx, miR- 128a for target Bim-1, causing production of ROS further activating NF-κB. The miR- 34a enhances the expression of caspase -3, leading to neuronal death [76].

3.2. Role in Neuronal Survival

NF-κB promotes the anti-apoptotic activity by regulating the genes for superoxide dismutase enzymes and proteins (Bcl-2, Bcl- XL). These proteins are anti-apoptotic proteins regulated by NF-κB [77, 78]. Hence, NF-κB acts as anti-apoptotic having a role in cell protection by upregulating the prosurvival genes. Mn-SOD is an important anti-oxidant enzyme essential for the protection of cellular damage [79]. The various studies have reported the increased level of Mn-SOD and SOD1 in the brain while exposures to the neurotoxins or other conditions like excitotoxicity, ischemia, and amyloid-beta toxicity causing neuronal death [80]. The NF-κB mediates the induction of BCL-Xl and Bcl-2 and the expression of these proteins is upregulated by the NF-κB, further preventing the apoptotic cell death [81]. The up-regulation of various miRNAs like miR-27a, miR-153, miR-27b, miR-181, miR-497, miR-15/16, miR-497, miR-302b, miR-21 are involved in neuronal death by expressing the anti-apoptotic Bcl-2 protein [76, 82-85]. The other miR- 29a decreases the pro-apoptotic PUMA; miR-124 suppresses the neuronal cell apoptosis by decreasing the BAX pro-apoptotic protein and protecting the mitochondrial dysfunction [86].

The dysregulation and alteration in the pattern of expression of microRNAs, *i.e.* either by up-regulation or down-regulation in the expression of miRNAs, further altering the different mechanisms involved in the pathogenesis of neurodegeneration as described in Fig. **3** and Table **3**.

4. NF-κB SIGNALING IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic Lateral Sclerosis (ALS) is a motor neuron degenerative disease of lower motor and upper motor involving the progressive muscular atrophy, clinically characterized by dyspnea and dysphagia [24]. The mutation of various genes, including (C90rf72, SOD1, TARDBP, FUS) has been diagnosed in individuals with ALS and FALS (familial Amyotrophic Lateral Sclerosis) [87]. The mutation in C90rf72 gene causes motor neurodegeneration leading to an increase in the accumulation of toxins in motor neurons, further altering the immune defense and activating the microglial, which increases inflammatory responses by intracellular NF-κB pathway and regulates the transcription of proinflammatory mediator genes enhancing the neurotoxicity [88]. The SOD1 mutation or misfolding of the superoxide dismutase enzyme increase the reactive oxygen species activating the NF-κB transcribing genes involved in neuroinflammation, causing neurotoxicity in motor neurons [89, 90]. The mutations of FUS and TARDBP genes have a similar function of encoding FUS whereas, the *TARDBP* gene encodes TDP-43 protein causing the 60 dominant missense mutation in the nucleus of neuron necessary for the synthesis of other proteins by binding to the DNA and regulating transcription [87]. In ALS, the mutation in TARDBP gene causes the aggregation of neurotoxic TDP-43 fragments protein in nucleus to axon by mutated ubiquitin 2 (UBQLN2) and cleaving of TDP-43 forming an aggregation in nerve cell, which increases the inflammatory responses by activation of NF-κB increasing the neuroinflammation leading to oxidative stress causing excitotoxicity in motor neurons [91]. Furthermore, the NF-κB expression seems to be elevated in the ALS during the damaging of the motor neurons in the spinal cord migrating immune cells *i.e.*, astrocytes and microglial [92]. The various studies have concluded that the mutation in the UBQLN2, SOD1 genes activating NF-κB further causes reactive oxygen species generation aggregat-

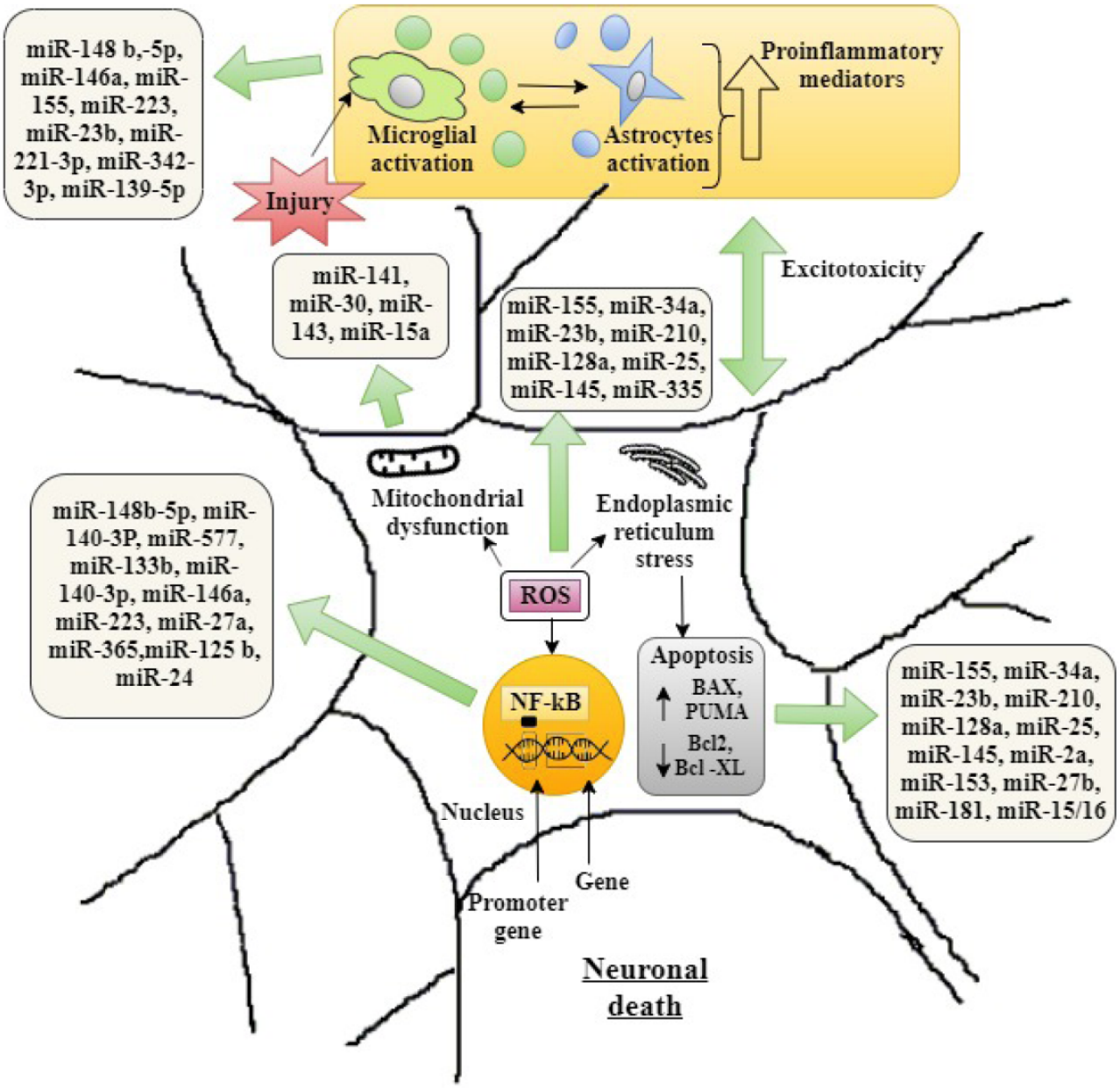

Fig. (3). Involvement of various microRNAs in neuronal death. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ing TDP-43 in nucleus and axon enhancing the cellular dysfunction including endoplasmic stress mediating neuronal death [24, 89, 90, 93]. Therefore, the overexpression of NF-κB in motor neurons contributing to the pathogenesis of ALS and the Withaferin A, maresin 1 (an inhibitor of NF-κB) tends to possess a potential therapeutic activity as neuroprotective by decreasing the ROS produced due to aggregation of TDP-43 protein further improving the ALS symptoms [92, 94-97]. The dysregulation of various miRNAs like miR-206, miR-140-3p, miR-133, miR-149, miR-338-3p, let-7, miR-148b-5p, miR-577, miR-365 and miR-125b seems to be involved in the pathogenesis of ALS by increasing the expression of NF-κB further initiating the activation of microglia causing neuroinflammation and degeneration of motor neurons in ALS [98, 99].

5. NF-κB SIGNALING IN PRION DISEASE

Prion disease is a progressive neurodegenerative disorder or also known as transmissible spongiform encephalopathies (TSE) associated with misfolding of the prion protein (prp) in the brain leading to endoplasmic reticulum stress mediating neuronal death [100]. The abnormality in folding of the prion protein (prp) especially PrP^{Sc} isoform in mitochondria causing the neuronal death by proliferation of the microglia in response to the synaptic damage and up-regulation of the pro-inflammatory mediators in the prion brain with enhanced activity of NF-κB signaling has been reported by many studies underlying chronic inflammation in brain [101-104]. There is an over-expression of miR 16, miR 146a, miR 320, miR 328, miR 128, miR -342-3p and down-regulation of

miR -338-3-p and miR -337-3p causing neurodegeneration in prion disease [105, 106]. The miR 146a seems to initiate the activation of NF-κB signaling mediating inflammatory mediators and migrating microglial cells, causing neurodegeneration [107]. The activation of transcriptional factor (NF-κB) enhances the apoptotic neuronal death by elevating the expression of many pro-apoptotic genes for certain proteins (p53, BcL-Xs, BAX, Fas ligand), thereby releasing cytochrome C undergoing mitochondrial dysfunction and endoplasmic stress further releasing calcium activating Bad (pro-apoptotic protein). The up-regulation of cytokines IL-1 & TNF-alpha at the site of synaptic damage causes reactive oxygen species such as hydrogen peroxide, resulting in excitotoxicity and neurodegeneration [103, 108-110].

6. NF-κB SIGNALING IN HUNTINGTON'S DISEASE (HD)

Huntington disease is an inherited autosomal dominant neurodegenerative disease associated with replication of the mutated CAG trinucleotide in the exon 1 of htt gene translating into abnormal longer polyglutamine (poly Q) stretch (wild- type htt protein) causing neuronal death [111-113]. The wild- type htt protein controls the normal neuronal processes by interacting with the transcriptional factor NF-κB; RE-1 silencing transcriptional factor required for the neuronal development including neuronal transcription, synaptic transmission and intracellular transport [114, 115]. The mutated wild- type htt protein binds to dynein which causes mitochondrial dysfunctioning by increased ROS production and interacting with NF-κB to activate from synapse to nucleus in response to the excitatory synaptic input Huntington disease characterized by motor, cognitive and psychiatric disorders [116-119]. The alteration in various miRNA expressions causing stretching of mutant wild-type htt protein includes: miR- 146a, miR-150, miR- 125b, miR-155 and miR- 9. Out of various miRNA, the down-regulation of miR-146, miR-150 and miR-125b and increased expression of NF-κB contribute to neurodegeneration in the Huntington's disease by aggregation of mutated wild -type htt protein [120, 121].

7. NF-κB SIGNALING IN SPINOCEREBELLAR ATAXIA (SCA)

Spinocerebellar ataxia is an inherited neurodegenerative motor deficit disease associated with a mutation in the Ataxi 1 gene by the repetition of CAG trinucleotide expanding poly Q in ATXN1 protein resulting in cerebellum purkinje neurons atrophy and glutaminergic synaptic loss [122, 123]. The migration of astroglail in response to purkinje neurons atrophy like brain insult resulted, in various studies, in the expression of NF-κB increase and activated the glial cells at the early stage of SCA possessing a neuroprotective effect but at the later stage, the glial cells worsen the disease by dysfunction of purkinje neurons characterized by complete loss of movement control [122, 124, 125]. Therefore, the astroglial NF-κB signaling tends to be neuroprotective at an early stage but at a later stage, progresses the neurodegeneration due to the increased production of pro-inflammatory cytokine TNFα. [124, 126]. The various miRNAs have been analyzed for diagnosis in (spinocerebellar ataxia) SCA involved in the pathogenesis of SCA by targeting DNAJB1, ATXN3, and MIDI proteins. The DNAJ protein is involved in neuroprotection and the microRNA including: hsa-miR-370, hsa-miR-543 which controls the expression of DNAJB1 protein; the down-regulation of hsa-miR-370, hsa-miR-543 expression which causes the reduction of DNAJB1 protein [127-129]. The other microRNAs like hsa-miR 9, hsa-miR -32, hsa-miR -92a, hsa-miR -92b, 363, 367, hsa-miR 383, miR 181, hsa-miR 181b, 181c, 181d are analysed for ATXN3 protein. Out of these microRNAs, the over-expression of hsa-miR 9, hsa-miR-32, hsa-miR 383, hsa-miR 181a, 181c is involved in the reduction of ATXN3 protein causing neuronal toxicity as the ATXN3 protein is involved in the ubiquitin-proteasome system [127, 128]. The other microRNAs miR-19, miR-101, miR-150 and miR-130 are involved in regulating the ATXN1 protein found to be mutated in cerebellar purkinje cells and causing the motor dysfunction [128, 130, 131]. The down-regulation of miR-19, miR 181 increases the expression of NF-κB signaling further increasing the production of pro-inflammatory seem to be elevated and causing degeneration of purkinje cells [127, 132, 133].

8. NF-κB SIGNALING IN ALZHEIMER'S DISEASE

Alzheimer's disease is the most prevalent neurodegenerative disease leading to dementia-like conditions which worsen with time damaging the neurons hippocampus area responsible for memory formation [134]. The hallmark of Alzheimer's disease is due to the formation of abnormal structures of amyloid plaques between the spaces of neurons and neurofibrillary tangles inside the nerve cells made by misfolded proteins in a certain region of the brain initiating the loss in neuronal function causing neuronal death [135]. The abnormal structures of amyloid plaques are caused due to the genetical mutations promoting the production of beta-amyloid peptides *i.e*., the main component of the amyloid plaques [136]. The peptide is the result of the Amyloid precursor protein (APP) that helps neurons to grow and repair by breaking down and recycling . Normally, the enzyme alpha-secretase cleaves the extracellular domain and gamma-secretase cleaves the APP into discrete fragments which are soluble [137]. In Alzheimer pathological condition, the enzyme called beta-secretase (BACE) or beta–site amyloid precursor protein cleaving enzyme 1 (BACE1) initiates the production of the amyloid beta with another protease called gamma-secretase that cleaves the upper part extracellular domain of the APP which is the N- terminus of the amyloid-beta and the gamma–secretase cleaves the C terminal of beta-amyloid [138]. The left-over fragment is insoluble and creates the monomers called Amyloid beta, which is no longer regulated. These monomers tend to be chemically sticky and form clumps by binding together. These clumps are formed outside the neurons and short 42 amino acid peptides are formed called beta-amyloid plaques [134, 139]. The amyloid-beta plaques are secreted potentially between the synapse of the neurons and disrupt the neuronal signaling which leads to impairment of brain function especially the memory by damaging the surrounding neurons and migrating the glial cells, generating neuroinflammation [140]. The down-regulation of miR-29a, miR-2b-1, miR-9 and increase in the level of miR-107 cause abnormality in BACE1 pro-

tein, further increasing the abnormal production of amyloid-beta [141]. The various mRNAs like miR-20a, miR-17-5p and miR-106b have been found to be involved in abnormal APP altering splicing [141, 142]. The studies have concluded the essential role of NF-κB in the regulation of the BACE1 gene expression, which leads to the production of the beta-amyloid and up-regulation of the miR-125b causing neurodegeneration by increasing the levels of pro-inflammatory mediators causing neurodegeneration [143]. The BACE1 expression is mediated by the NF-kB signaling and the inhibition of the NF-κB plays a novel target in Alzheimer's disease therapy.

9. NF-κB SIGNALING IN PARKINSON'S DISEASE

Parkinson's disease is mostly seen among older people as characterized by a degeneration of dopaminergic neurons in substantia nigra affecting movement, cognition, *etc*. [144]. In recent studies, the prominent roles of NF-κB in dopaminergic neurodegeneration have been seen among Parkinson patients [145]. The immune histochemical techniques in the Parkinson patients showed the increased translocation of NF-κB in the nucleus of mesencephalon dopaminergic neurons transcribing the genes of pro-inflammatory mediators (chemokines, cytokines) initiating the production of reactive oxygen species (ROS) by auto-oxidation and enzymatic catabolism of dopamine [146-148]. Furthermore, the excessive production of reactive oxygen species directly damages the neuronal cells by lipid peroxidation and oxidative modification of nucleic acids and proteins or by induction of apoptosis in neurons *i.e*. sphingomyelin or ceramide dependent pathway leading to neurodegenerative process [149]. The various miRNAs found to be expressed in Parkinson's disease for **(**RRK2; DJ-1; *PTEN*-induced kinase *1* (PINK1); Parkin; *α*-synuclein; leucine-rich repeat kinase 2 (LRRK2); Pitx3) genes *i.e*., the down-regulation of precrsor-let7a-1, pre-miR7-2, pre-miR−99a, pre-miR7−130, pre-miR−133b, pre-miR−136, pre-miR−224, and pre-miR−143., pre-miR-133b, pre-miR-218-2, pre-miR-15b, pre-miR −101-1, pre-miR −107, pre-miR −335, pre-miR −345; miR-7 & miR-153; miR-34b and miR-34c [150-153]. The study concluded the down-regulation of miR-34b and miR-34c, stimulating the aggregation of alpha-synuclein in substantia nigra causing neurodegeneration [154]. Furthermore, the miR -124 and miR -146a promote the expression of NF-κB, further enhancing the pro-inflammatory levels causing neurodegeneration in Parkinson's disease [145, 155, 156].

10. NF-κB SIGNALING IN CEREBRAL ISCHEMIA

The cerebral ischemic insult triggers microglia activation; astrocytes cells release inflammatory mediators which further increase cerebral endothelium adhesion causing excitotoxicity with reactive oxygen production [118]. The transcriptional factor NF-κB transcribes various genes for inflammatory mediators like IL-1, IL-6, and TNF- alpha having a prominent role in the activation of intracellular apoptotic pathway causing neuronal death by mitochondrial dysfunction, DNA fragmentation in cerebral ischemic [157]. Therefore, the various medications like Dioscin, Cilostazol as described in Table **2** below for cerebral ischemia act by inhibiting the NF-κB [158]. There are various microRNAs involved in the functioning of the brain; the down-regulation or up-regulation of such microRNAs seem to be implicated in the pathogenesis of cerebral ischemia. The various miRNAs are involved in apoptotic neuronal death which seem to be dysregulated in various pathological conditions like miR-497, miR-181 that unregulate and increase the expression of apoptotic BCL-2, BCL-w genes whereas, the anti-apoptotic miR-320 is down-regulated causing mitochondrial dysfunction. The miR-145, miR -210 expressions are unregulated in cerebral ischemia, further elevating the expression of SOD2 (superoxide dismutase 2) causing oxidative stress [159]. The microRNAs like miR-183, miR-215 and miR-22 regulate the NF-κB expression; the down-regulation of these miRNAs promotes the inflammation, causing excitotoxicity by increasing the tumor necrosis factor-α, interleukin and migrating macrophages and phagocytic neutrophils reactions in

Table 2. List of various NF-κB inhibitors used in neurodegenerative diseases.

NF-κB Inhibitors	Diseases	Refs.
Curcumin, resveratrol, pterostilbene, punicalagin, macranthoin G, salidroside, 4-*O*-methylhonokiol, lycopene, genistein, obovatol and gallic acid. NSAIDs & Polyphenolic; curcuminoids corticosteroids.	Alzheimer's disease	[198-200]
Doxycycline, Sulforaphane, Cannabinoids, δ9-tetrahydrocannabinol and cannabidiol, Isobavachalcone	Parkinson's disease	[201-204]
Genistein, Resveratrol, NSAIDs, Withaferin A, maresin Methylprednisolone.	Amyotrophic Lateral Sclerosis (ALS)	[205-208]
SN50, *Hordeum vulgare*	Prion disease	[209, 210]
Crocin, Pristimerin, Baicalin, PLX3397, SN50	Depression	[211-213]
Dioscin, Cilostazol, Glycyrrhizin, Diosmetin	Cerebral ischemia	[214-217]
Artesunate, Curcumin, Allyl isothiocyanate, Osthole	Traumatic brain injury (TBI)	[218-220]
EVP4593, laquinimod, epigallocatechin gallate; Ethyl-EPA: ethyl-eicosapentaenoic acid, Pridopidine.	Huntington's disease (HD)	[221-225]
Morin	Spinocerebellar ataxia (SCA)	[226]

Table 3. Description of cross-link between NF-κB and altered miRNAs in various pathological conditions.

Disease	Mutated Gene Involved	Atypical Expressed miRNA	NF-κB Role & Pathological Implications	Refs.
Alzheimer disease	BACE1, IRAKI, ERK1, PTBP1, FMR1.	mRNA 3'UTR for (miR-29a/b-1, miR-15a, miR-146 a miR-9, miR-20a, miR-1-5p, miR-106p miR-19b, miR-107). Expansion of CGG in 5'UTR for miR-125 b; miR- 132.	Increased production of Amyloid beta in anterior temporal cortex, Increased inflammation, Overactivation of tau, Abnormal APP mRNA alternating splicing, Altered synaptic plasticity.	[227-229]
Parkinson's disease	RRK2, DJ-1, PTEN-induced kinase 1 *(PINK1),* Parkin, α-synuclein, leucine-rich repeat kinase 2 (LRRK2), Pitx3	Down regulation of precrsor-let7a-1, pre-miR7-2, pre-miR-99a, pre-miR7-130, pre-miR-133b, pre-miR-136, pre-miR-224, and pre-miR-143., pre-miR-133b, pre-miR-218-2, pre-miR-15b, pre-miR pre-miR pre-miR-101-1, pre-miR-107, pre-miR-335, pre-miR -345; miR-7 & miR-153; miR-34b and miR-34c. miR-146a, miR-124.	Loss of dopaminergic neurons in the mid-brain, Pitx3 deficiency results in selective loss of nigrostriatal DA, Increased α-Synuclein undergoes oxidative stress causing dopaminergic degeneration. LRRK2 inhibits let-7 and miR-184 and causes cell death. Depletion of miR-34b and miR-34c causes reduction of Parkin and DJ-1 necessary for mitochondrial homeostasis and cellular redox balance.	[145, 154-156]
Amyotrophic Lateral Sclerosis (ALS)	C90rf72, SOD1, TARDBP, FUS.	Expansion of a GGGGCC hexanucleotide more than 30 repeats upstream of the C9orf72; GLT1mRNA.	frontotemporal lobar degeneration by aggregation of TD43 protein and causing endoplasmic stress mediating neuronal death. Mutated SOD1 targets Glial glutamate transporter GLT1 by decreasing its expression and further impairment of motor dysfunction. Impairment of proteasome-mediated protein degradation.	[230-233]
Prion disease	PrP gene.	PrP mRNA, Increased miR-16, miR-14a, expression causes inflammation signalling.	Missfolding of the prion protein causes endoplasmic stress.	[234, 235]
Depression	BDNF, GPM6A, GPM6B.	BDNF-mRNA, Downregulated GPM6A & GPM6B.	Decreased neuronal plasticity.	[236, 237]
Huntington's disease (HD)	HTT gene.	Mutated CAG trinucleotide in the exon 1 of htt gene.	Abnormal longer polyglutamine (poly Q) stretch (wild- type htt protein) causing neuronal death.	[120, 121]
Spinocerebellar ataxia (SCA)	ATXN1.	Repetition of CAG trinucleotide expanding poly Q in ATXN1 protein. miR-19, miR-101, miR-150, miR-181 and miR-130	Downregulation of miR-19, miR 181 increases the expression of NF-κB causing Cerebellum purkinje neurons atrophy and glutaminergic synaptic loss.	[130-133]
Cerebral ischemia	BCL-2, BCL-w, SOD2.	miR-320, miR-145, miR -210, miR- 497, miR-181, miR-183, miR-215 and miR-22.	Downregulation of miR-183, miR-215, miR-22 and upregulation of miR-181 increase the inflammation-causing excitotoxicity.	[160-162]
Traumatic brain injury	IL-1, TNF- alpha.	miR-144, miR- 153, miR-340-5p, miR-155, miR-223, miR-124-3p.	Up-regulation of miR-155, miR-223 promotes the inflammation and down-regulation of miR-124-3p promotes the apoptotic neuronal death.	[170-172]
Depression	BDNF, NPTX2, TNF-alpha, IL-1 β, IL-6,	let-7e, let-175p, miR -301b, miR -221-3p, miR-21-5p miR-145, miR-223, miR-146a, and miR-155, miR-175p.	up regulating of miR-221-3p, let-7e, miR-223, miR-145, miR-155 and miR-146a increases the inflammation which causes disruption of neurogenesis in depression.	[175-179]
Epilepsy	TNF-alpha, IL-1 β, IL-6, HMGB1,	Upregulation of miR-210, miR-30, miR-27a, miR-183, miR- 134, miR-135a, miR-125b, miR-148a, miR- 146a, miR-124 whereas, the downregulation of miR-128, miR-199a, miR-21a, miR-22.	Dysregulation of miR-181a, miR-129-5p, miR-124, miR- 146a, miR-155 increases the neuroinflammation in epilepsy.	[188-197]

cerebral ischemia [160-162]. Hence, the NF-κB signaling is regulated by various mRNAs which seem to be elevated in cerebral ischemia, causing neurodegeneration.

11. NF-κB SIGNALING IN TRAUMATIC BRAIN INJURY (TBI)

Traumatic brain injury (TBI) is associated with cytotoxic edema due to the complex consequences of immune and inflammatory cascades contributing to the brain injury [163]. The endogenous factors released during the damage in Traumatic brain injury (TBI) are recognized by damage-associated molecular patterns (DAMPs) further initiating the downstream inflammatory signaling and activating the transmembrane toll–like receptors further phosphorylating IKB inhibitor, translocating p65 NF-κB dimer into nucleus and transcribing pro-inflammatory genes leading to oxidative stress [164, 165]. The various studies have concluded that the increased expression of NF-κB in astrocytes and microglial cells migrating at the site of damage neuronal cell generates reactive oxygen species mediating apoptotic neuronal death [166-167]. Therefore, the inhibitor of NF-κB diminishes the Traumatic brain injury by decreasing the levels of IL-1, TNF- alpha and inhibiting the inflammatory cascades causing neurodegeneration [168, 169]. The down-regulation of various miRNA expressions are likely to be involved in TBI including miR-144, miR-153, miR-340-5p which contribute to the cognitive dysfunction by down-regulation of calcium/calmodulin-dependent serine protein kinase (CASK), nuclear factor erythroid 2-related factor 2 (NRF2) and alpha-synuclein (SNCA) target proteins [170]. The other miR-155, miR-223 are upregulated and increase the expression of NF-κB, further promoting the inflammation causing mitochondrial dysfunction which further causes neuronal death and the down-regulation of miR-124-3p promoting apoptotic neuronal death [171, 172].

12. NF-κB SIGNALING IN DEPRESSION

The transcriptional factor NF-κB transcribes Brain-derived neurotrophic factor (BDNF) gene necessary for the regulation of the neuronal plasticity by enhancing the excitatory neurotransmission further modulating the pre and post-synaptic activity [173]. Therefore, suggesting an involvement in the neurobiology of depression depicts a similar function of BDNF and NF-κB in improving the disrupted neuronal circuit [174]. The preclinical studies data of suicidal cases of patients with depression concluded that the decreased expression of the BDNF and the activation of the NF-KB pathway tend to improve the synaptic plasticity by restoring the neurogenesis underlying the therapeutic approach for depression [173]. Whereas, the acute and chronic stress in patients causes the increase in the expression of inflammatory mediators TNF-alpha, IL-1 β & IL-6, causing disruption of neurogenesis in hippocampus cells likely to be increased in stress causing depression [175]. The blockage of the transcriptional factor NF-κB decreases the levels of pro-inflammatory cytokines like TNF-alpha, IL-1 β & IL-6, reversing the depressive behavior in patients [175-177]. The various microRNAs including let-7e, let-175p, miR -301b, miR -221-3p, miR-21-5p miR-145, miR-223, miR-146a, and miR-155, miR-175p tend to be down-regulated or up-regulated in major depressive disorder [178, 179]. The miR -301b targets neuronal pentraxin II (NPTX2) gene involved in depression and increases the expression of NF-κB activating the microglia enhancing the release of inflammatory mediators tumor necrosis factor-α (TNF-α), interleukin-Iβ (IL-Iβ) and cyclooxygenase-2(COX-2), affecting the hippocampus area of brain leading to cognitive dysfunction in depression [179]. The miR-221-3p is up-regulating which increases the expression of IFN-α (Interferon alpha) and activation of NF-κB in mild depressive disorder [179]. The up-regulation of let-7e, miR-223, miR-145, miR-155, and miR-146a regulates the TLR4 expression which further activates NF-κB, causing further disruption of neuronal circuit in depression [178].

13. NF-κB SIGNALLING IN EPILEPSY

Epilepsy is a neurological disease characterized by sudden recurrent long-lasting episodic seizures promoting abnormal brain activity due to the excessive glutaminergic neurotransmission resulting in excitotoxicity causing the brain damage [180]. Therefore, the excessive neuronal excitotoxicity triggers the activation of neuroglial cells releasing the inflammatory mediators and eliciting intracellular cascades of inflammatory events resulting in oxidative stress provoking apoptotic neuronal death in epilepsy [181]. Furthermore, there is an activation of astrocytes, glial cells releasing cytokines and chemokines migrating at the site of brain lesions contributing to neuronal degeneration by mitochondrial dysfunction and activation of the apoptotic caspase -3 protein mediating neuronal death seen in the status epilepticus or prolonged repetitive seizures [182, 183]. The various studies have demonstrated the elevated level of transcriptional factor NF-κB in epileptic brain transcribing genes for pro-inflammatory mediators such as IL-1 beta, IL-6, TNF- alpha; high-mobility-group box 1 (HMGB1) tends to be released from astrocytes and microglia promoting the seizures threshold [184-187]. The dysregulation of various miRNAs is linked with increased epileptic seizures analysed in epileptic models. The up-regulation of miR-210, miR-30, miR-27a, miR-183, miR-134, miR-135a, miR-125b, miR-148a, miR-146a, miR-124 whereas, the down-regulation of miR-128, miR-199a, miR-21a, miR-22 lead to increases in the epileptic seizures [188-192]. The dysregulation of miR-181a, miR-129-5p, miR-124, miR- 146a, miR-155 increases the expression of NF-κB further transcribing genes for pro-inflammatory mediators causing excitotoxicity [193-197].

As mentioned above, the role of NF-κB in different neurodegenerative diseases is related to inflammation and immune responses. In response to various extracellular or intracellular stimuli (Table **1**), the transcriptional factor NF-κB gets activated and transcribes genes for inflammatory mediators seem to be elevated and causing oxidative stress involved in neurodegenerative diseases.

CONCLUSION

The current review categorized the involvement of nuclear transcriptional factor (NF-κB) in neurodegenerative conditions as a prominent modulator, transcribing target genes involved in elevating the stress causing apoptosis in neuronal cells. In addition, the various research studies have

concluded the evidenced-based data depicting the increased expression of NF-κB and dysregulation of various miRNAs either by up-regulation or down-regulation of miRNAs targeting genes further exacerbating apoptotic neuronal death in neurodegenerative diseases. Therefore, targeting NF-κB has provided a successful pharmacotherapy or adjuvant drug therapy for various diseases and also indicates a future direction for the development of new molecules directly targeting miRNAs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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