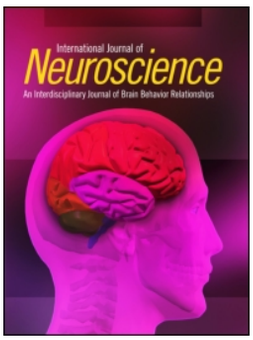

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REVIEW ARTICLE

Neuroinflammation pathways: a general review

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Activated microglial cells play an important role in immune and inflammatory responses in central nervous system and neurodegenerative diseases. Many pro-apoptotic pathways are mediated by signaling molecules that are produced during neuroinflammation. In glial cells, NF-κB, a transcription factor, initiates and regulates the expression of several inflammatory processes during inflammation which are attributed to the pathology of the several neurodegenerative diseases. In this review, we discuss the most important neuroinflammatory mediators with their pathways. Attenuating cytokines production and controlling microglial inflammatory response, which are the result of understanding neuroinflammation pathways, are considered therapeutic strategies for treating neurodegenerative diseases with an inflammatory component.

KEYWORDS: neuroinflammation, NF-κB pathway, microglia, neuroinflammatory diseases

Introduction

Inflammation is a key biological process in response to injury, infection and trauma suffered by cells or tissues. A successful inflammatory response mechanism eliminates invading pathogens, and initiates wound healing and angiogenesis [1]. In relation to the brain, inflammation may be a negative contributing factor towards acute and chronic brain disorders [2,3]. Thus, neurons in the brain carry out neuro-protective efforts in combating the negative side of inflammation by clearing of cellular debris and regulating secretion of neurotrophic factors, cytokines and proteases. While inflammation in the brain can have negative effects on recovery following injury, other actions appear to be beneficial and essential. In this framework, inflammation can be viewed as a complicated series of local immune responses that serve to deal with a threat to the neuronal microenvironment [2]. Understanding the reason that sometimes inflammation is protective and sometimes damaging could be crucial in brain related injuries [4].

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Neuroinflammation is a response that involves all the cells present within the central nervous system (CNS), including the neurons, macroglia and microglia. There are some factors such as initiating insult, genetic background, environmental factors and age or past experiences that combine to activate microglia and the complex neuroinflammatory pathway [5,6]. For instance, lipopolysaccharide (LPS), which is an endotoxin in the outer membrane of Gram-negative bacteria, induces systemic inflammatory response syndrome through toll-like receptor (TLR) signaling [7]. LPS binding to TLR4 on the microglia surface activates several signal transduction pathways, including phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR), which in the end lead to NF-κB activation. Activation of NF-κB then mediates production of pro-inflammatory cytokines, chemokines and inducible enzymes, namely, inducible nitric oxide synthase (iNOS) and COX-2 which all together result in neuroinflammation [8,9]. Therefore, it is important to understand how immune system processes the information and senses pathogens through NF-κB activation [10]. Neuroinflammation is an important feature of many neurodegenerative diseases such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), narcolepsy and autism [1].

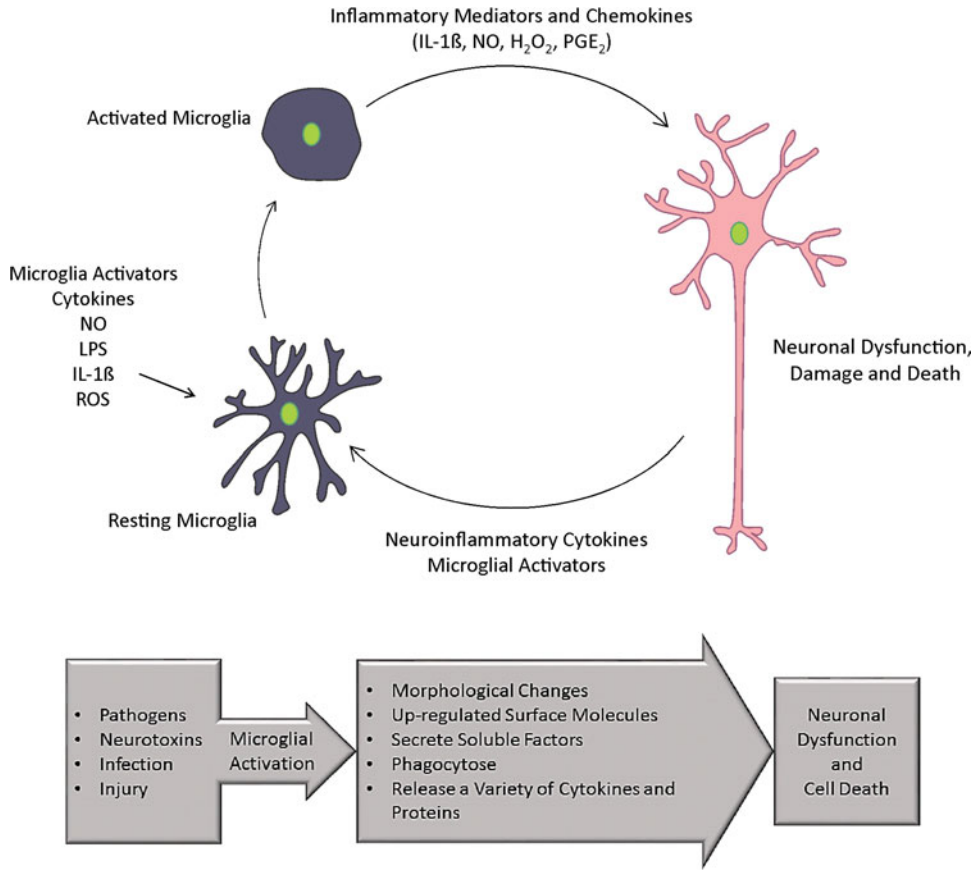

Figure 1. Microglia activation and neuronal cell death. Infection, oxidative stress and neurotoxins activate microglia. Activated microglia secrete inflammatory proteins which lead to neuronal dysfunction and cell death.

Microglia and neuroinflammation

Microglia are the resident brain macrophages which play a critical role in an organism's defense and in tissue repair. They are the key cells in the brain inflammation and inflammatory neurodegenerative diseases [11]. The first indication of neuroinflammation is microglia activation [6]. Microglia becomes activated in the presence of pathogens, tissue damage, abnormal stimulation, neurotoxins, infection or injury. In this case, they can even attack healthy neurons either physically, as by phagocytosis, or via secreted apoptosis factors [9].

After being activated, microglia round up, proliferate, migrate, phagocytes, present antigens to T-cells, release a variety of oxidants and activate various genes and proteins, including iNOS, pro-inflammatory cytokines like Interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), COX-1, COX-2, reactive oxygen species (ROS) and potentially neurotoxic compounds which cause neuronal dysfunction and cell death (Figure 1) [9]. In terms of chronic neuroinflammation, these cells can remain activated for extended periods, releasing cytokines and neurotoxic molecules that contribute to long-term neurodegeneration [7]. Hence, inhibiting pro-inflammatory mediators caused by microglia activation would be an effective therapeutic approach in order to mitigate the progression of neurodegenerative diseases [12].

Activated microglia can kill neurons (neurodegenerative role). However, they may also kill and/or remove pathogens (neuro-protective role) [6]. The release of damaging and/or pro-inflammatory intracellular components is prevented by microglial phagocytosis of dead or dying neurons [13]. An efficient, active process for the phagocytosis and clearance of aberrant or excess proteins is necessary for maintaining homeostatic balance of the protein burden in the brain and preventing development of neurodegeneration. Many pro-apoptotic pathways are mediated by signaling molecules that are produced in excess during neuroinflammation, which suggests that neuroinflammation could directly influence neuronal apoptosis and activate microglia [2].

NF-κB history and structure

David Baltimore (1986) was the first person to discover NF-κB as a B-lymphocyte cell-specific pleiotropic

transcription factor that binds to the κB site in the immunoglobulin kappa-light-chain-enhancer in B cells and regulates it [14]. It was first described as a nuclear factor κB or nuclear factor kappa enhancer binding protein (NF-κB) [15], and now it is recognized that its inducible activity is present in all cell types [16]. NF-κB proteins are part of a cascade which begins outside the cells and ends in the nucleus. When pro-inflammatory cytokines and chemokines are expressed, they move to different tissue sites and cause tissue injury which leads to functional and structural changes [17].

In all eukaryotic cells, majority of extracellular signals, including infections, inflammatory cytokines and multiple stress situations can activate NF-κB. NF-κB controls many processes, including inflammation, apoptosis, immunity, cell survival and cancer, and regulates inducible expression of immune and inflammatory response genes [17,18]. More interestingly, the activation of NF-κB in neurons promotes survival and plasticity. On the other hand, NF-κB activation in glial cells plays a major role in inflammatory processes which is neurodegenerative [19].

The family of NF-κB is composed of structural homologs that in mammals include NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB and c-Rel. All NF-κB proteins contain a DNA-binding and dimerization domain called Rel homology domain which is responsible for DNA-binding, dimerization, nuclear translocation and interaction with the IκB proteins [18]. In immune cells, NF-κB is usually found either as a p65/p65 homodimer or as a heteromeric complex of two components, p65 (RelA) and p50 [20]. The p65 component contains the main trans-activating domain responsible for transcription factor function of NF-κB [21]. The best-known form of NF-κB consists of the DNA-binding subunit p50 and a transcription activator, p65 [17]. NF-κB proteins bind to specific sequences of DNA called κB sites. Individual dimmers show variable affinity towards a collection of related κB sites. p50-RelA is the same in all cells. The activity of different NF-κB dimmers is regulated by interaction with inhibitory proteins that hold these complexes in the cytoplasm in an inactive form [18]. These inhibitors include p105, p100 and IκB α, β, γ and proteins which interact with NF-κB [17].

Nf-κB activation in neuroinflammation pathway

TLRs are important signal transduction membrane proteins in the innate immune system and the inflammatory response. TLRs are the first line of defense against pathogens, and their activations result in the death or disposal of the invading pathogen. TLRs are composed of highly conserved structural domains, containing the binding sites for both their ligands and their co-receptors. They recognize specific ligands to initiate the inflammatory process, activating signaling molecules such as NF-κB to promote microglial phagocytosis, cytokine release and the expression of the co-stimulatory molecules needed for adaptive immune responses. Microglia express a range of TLRs that activate these cells and initiate a neuroinflammatory reaction [7]. TLRs contain an extracellular leucine-rich repeat domain which is involved in specific pathogen recognition, and a Toll/IL-1 receptor (TIR) domain in the cytoplasmic region which is involved in the signaling pathway (Figure 2). Myeloid differentiating factor 88 (MyD88), which is an adaptor protein, binds to TLRs via their TIR domains, which activates several signal transduction pathways and in the end lead to NF-κB activation and inflammation. All TLRs are activated by MyD88 except TLR3; instead MyD88 may be restricting TLR3 signaling. MyD88 pathway plays a role in CNS infection and consequent astrocyte activation. MyD88 might be also involved in optic nerve injuries, PD and AD [22,23]. TLR4/MyD88/NF-κB signaling cascade pathways may be a useful therapeutic target for the pharmacological treatment of neuroinflammatory injuries [24].

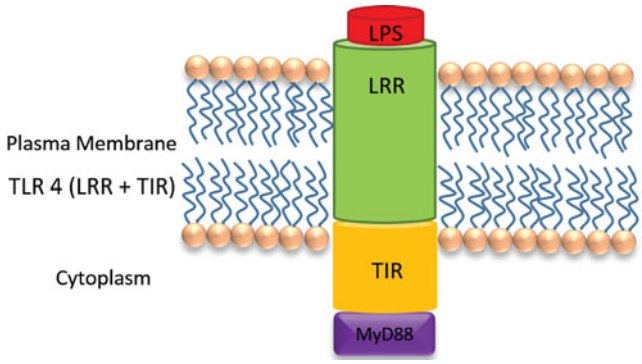

Figure 2. TLR4 activation by MyD88. MyD88 is a critical signaling ligand of TLR4 receptor complex and also is an important adapter protein of NF-κB signaling pathway, contributing to the expression of inflammatory genes.

Regulation of NF-κB activity is dependent on its nuclear translocation in association with an inhibitory molecule, IκBα. Due to their interaction with IκB inhibitory family, NF-κB dimmers are in passive form in the cytoplasm and are activated by removal of the inhibitory IκB protein and translocation of the liberated NF-κB dimmer to the nucleus. The pathway gets activated, when appropriate stimulation, such as necrosis factor TNF-α, IL-1β, is received by the cells. As a consequence of the intracellular kinase signaling cascades, a ternary IκB kinase (IKK) complex (which consists of two catalytic subunits IKKα and IKKβ and a regulatory/structural subunit called inhibitor of κB kinase

gamma (IKKγ) or NF-κB essential modifier (NEMO)) induces IκBα inhibitory protein phosphorylation, to result in its ubiquitination, and also degradation by the proteasome. Hence, the interaction between IκBα and NF-κB is disrupted plus NF-κB is liberated allowing nuclear translocation of p65/RelA from the cytoplasm to the nucleus where it binds to specific promoter elements to activate the expression of specific cellular genes [21,17]. Depending on whether activation of NF-κB involves IκB degradation, IKK stimulates NF-κB in two distinct pathways, the canonical and non-canonical [18]. Ubiquitin is involved in at least three steps in NF-κB pathway which are NF-κB inhibitor IκB degradation, NF-κB precursors processing and IKK activation. Ubiquitination is a reversible covalent modification catalyzed by three enzymatic steps [15].

Pro-inflammatory cytokines and neuroinflammation pathway

A cytokine in the same cell depending on the functional context in which it acts can have paradoxical effects, inducing proliferation, cell death and survival. The net efficacy of many of these actions can lead to an increased invasion of leucocytes into the brain parenchyma which can contribute to injury [25]. Microglia functions related to an innate immune response are associated with TNF-α signaling and its regulation of both inflammation and apoptosis. It is known that the degree of hippocampal neuron apoptosis is related to TNF-α messenger ribonucleic acid (mRNA) levels and there is a possibility that a threshold for TNF-α concentration is required for the initiation of apoptotic pathways [26,7]. Increases in TNF-α and IL-1β have been observed prior to neuronal death. In the beginning, inflammation is usually defined and determined by the release of pro-inflammatory cytokines, such as TNF-α, IL-1β as well as adhesion molecules. IL-1β and TNF-α play an integral role in pathological inflammation and the acceleration of disease [7]. They can cause blood–brain barrier (BBB) breakdown, up-regulate adhesion-molecule expression and stimulate diffusion of toxic substances such as nitric oxide (NO) [27]. IL-1β plays a crucial role in the progression of chronic neurodegenerative diseases such as AD and PD as well as acute neuroinflammatory conditions including stroke, ischemia and brain injury [28]. TNF-α is a multi-potent, inflammatory cytokine that can induce apoptosis via activation of receptors containing a homologous cytoplasmic sequence identifying an intracellular death domain (Figure 3). This includes tumor necrosis factor receptor 1 (TNFR1) (p55) or 2 (p75) and CD95 (APO-1/Fas) with their corresponding death ligands, TNF-α, and the structurally related type II transmembrane protein, FasL. For IL-1β, these

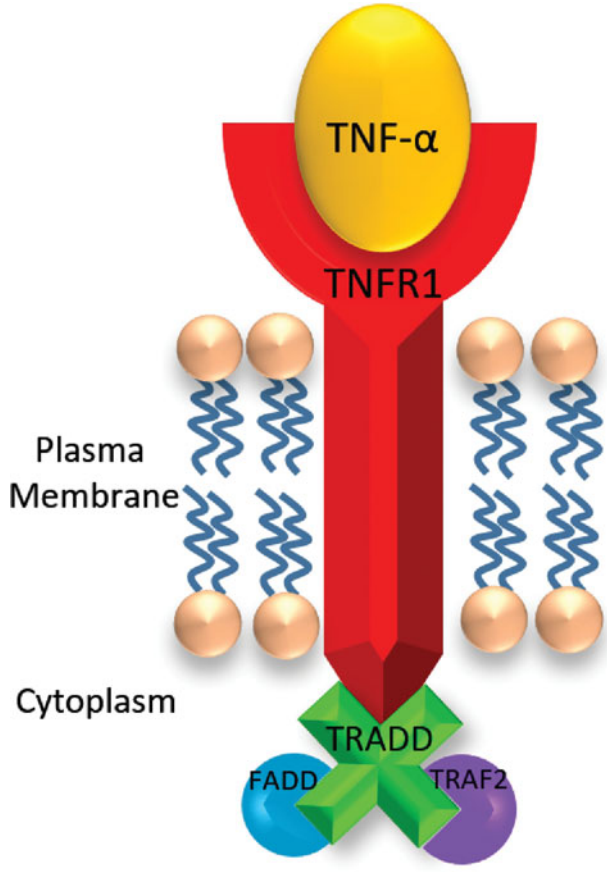

Figure 3. TNFR1 signaling pathway. TNF-α binds to its receptor (TNFR1), and following tumor necrosis factor receptor 1-associated death domain protein (TRADD), binding, neuroinflammation and apoptosis pathways can be initiated.

effects are mediated primarily by interlukin 1 receptor (IL-1R1). TNFR1 activation can cause quick apoptosis of neurons through a caspase 3-mediated pathway by providing a molecular mechanism. Membrane receptor mechanisms of apoptosis which are implicated in neuronal death involve intracellular death-signaling complexes, such as activator protein 1 (AP-1), NF-κB and caspases [29,2].

ROS and neuroinflammation pathway

Inflammation induces oxidative stress and DNA damage, which leads to the overproduction of ROS by macrophages and microglia. Oxidative stress-damaged cells produce larger amounts of inflammatory mediators to promote microglia aging [30]. Throughout life, the brain is exposed to oxidative stress and free radicals, which can be causes or consequences of a number of diseases. ROS are multi-potent, diffusible species of chemicals atom or molecule which possess an unpaired

electron so they are capable of carrying out signal transduction processes in response to extracellular stimuli. In addition to ROS direct toxic impact on biological macromolecules, they can trigger the inflammatory response by stimulating a number of genes which are regulating the inflammatory-signaling cascades. Acute, chronic inflammatory diseases and aging process are some of the main reasons for excess production of ROS. In neuronal tissue, there are sources of oxidative stress, which are unique for neuronal tissue, such as excitatory amino acids and neurotransmitters. The metabolism of these amino acids and neurotransmitters produces ROS [31].

Use of oxygen in mitochondria to supply the energy for the tissue is a source of oxidative stress. Mitochondria are an important source of ROS leaked from the electron transport chain while they are susceptible to oxidative damage, leading to mitochondrial dysfunction and tissue injury. The redox-sensitive factor NF-κB pathway can be activated by mitochondrial dysfunction through oxidative stress. Mitochondrial dysfunction is commonly observed in many types of neurodegenerative diseases such as AD, PD, Huntington's disease (HD), alcohol-related dementia and brain ischemia-reperfusion related injury, although many of these neurological disorders have unique etiological factors. Normalization of mitochondrial function can become a potential target for pharmacological interventions to prevent or treat many metabolic and neurodegenerative diseases. Furthermore, mitochondria-targeted antioxidants reduce systemic inflammation and neuroinflammation [32,33].

Nitric oxide and neuroinflammation pathway

NO, which is a free gaseous signaling molecule, regulates the nervous and immune system. There are three isoforms of nitric oxide synthase (NOS) that account for NO production, namely neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS) and iNOS. iNOS may become important under pathological conditions, otherwise, in the brain under normal physiological conditions, there is no role for that [34]. iNOS-expressing microglia are found in the neuritic plaques of AD patients. Various stimuli such as LPS, interferon gamma (IFN-γ), TNF-α and IL-1β can induce the expression of iNOS [35]. NO is synthesized by inducible isoform of iNOS, which catalyzes the reaction of l-arginine to l-Citrulline and NO which is another way in which neuroinflammation can directly influence neuronal apoptosis [7,36]. Increased NO levels can stimulate nitration of many proteins which is reported in the neuronal tissues of patients with neurodegenerative diseases including AD, PD, HD and amyotrophic lateral sclerosis (ALS). Under pathological conditions and after exposure to neurotoxic agents, increased amounts of superoxide anion and NO can be produced, resulting in nitroxidative stress in the brain. Co-existence of NO and superoxide anion can generate more cytotoxic agents which have been implicated in neuronal cell death [33].

The generation of ROS leading to the induction of iNOS enhances nitric oxide production of glial and endothelial cells. An excessive amount of NO leads to inflammatory diseases such as neurodegenerative diseases [35]. NO and ROS at low concentrations signaling molecules regulate cell proliferation. On the other hand, at high concentrations, they are key cytotoxic molecules.

Cyclooxygenases and neuroinflammation pathway

COX-1 and COX-2 are two forms of cyclooxygenases (COX) or prostaglandin H synthesis which are being encoded by different genes and have inflammatory functions [37,7]. The pathways of COX-1 and COX-2 are associated with neuroinflammation and neurodegeneration. Both these isoforms have different roles both in normal physiology and pathology [7]. These two isoforms catalyze the same reaction of dioxygenation of arachidonic acid to yield prostaglandin G2 (PGG2), and a peroxidase reaction, which converts PGG2 to prostaglandin H2 (PGH2) [38]. PGH2 is then transformed into PGE2 which is a neuroinflammatory mediator [37]. Many aspects of the COX-1 pathway are pro-inflammatory and result in neuroinflammation [7]. COX-1 expression is up-regulated in a group of brain resident macrophages after being induced by LPS, which shows the role of COX-1 in the immune-to-brain signaling. COX-1 inhibition attenuated BBB disruption during TNF-α or LPS-induced neuroinflammation. COX-1 plays an important role in the process of neuroinflammation and neurodegeneration. COX-2 may mediate a neurotoxic or an anti-inflammatory role which depends upon the stimulus and the cell type targeted by the insult [37]. The COX-2 expression is mainly observed in neurons, and it is associated with synaptic functioning and memory formation. COX-2 overexpression may only be exhibited in direct neuronal damage and their pathway has been observed in neurodegenerative diseases. The strong involvement of COX-1 in neuroinflammation compared to COX-2 could be related to its expression in microglia, whereas, COX-2 overexpression may only be exhibited in direct neuronal damage. Cytokine signaling also interacts with these pathways [39,7].

PI3K/AKT/mTOR pathway in neuroinflammation pathway

Microglia activation induces several intracellular signaling pathways, for instance, MAPK family and PI3K/AKT pathways [40]. The PI3K/AKT pathway is known to coordinate inflammatory responses, cellular activation and apoptosis. The activation of PI3K triggers a signaling cascade which leads to NF-κB translocation. PI3K is a family of lipid kinases that consist of three classes of family members. AKT activation initiates a cascade of downstream signaling through a variety of targets and activates the PI3K pathway [41].

The mTOR, as its name suggests, is the target of a molecule named rapamycin. It is an atypical serine/threonine protein kinase belonging to the PI3K-related kinase family. There are two possible cellular complexes for mTOR. These two complexes are mTOR complex 1 (mTORC1) and mTORC2 which can be distinguished due to their compositions and substrates. PI3K activation activates AKT which activates mTOR. Phosphorylation of mTOR pathway is a considerable reason for activation of microglia. mTOR pathway plays important roles in the regulation of NF-κB activity and inflammations. Activated mTOR increases the activity of NF-κB and promotes the expressions of inflammatory molecules including iNOS and COX-2 [42].

MAPK pathway in neuroinflammation

Microglia activation induces MAPK family. MAPKs, including p38 MAPK and Stress-activated protein kinases/Jun amino-terminal kinases (SAPK/JNK), are activated by stress and inflammation, and in turn, activate inflammatory mediator cascades in response to LPS stimulation which is a critical initiator of a number of signal transduction cascades [43,9,44]. p38 MAPK regulates inflammatory processes, such as the production of cytokines and pro-inflammatory mediators and expressing iNOS and COX-2 in LPS-induced microglia [45,46]. SAPK/JNK which are members of the MAPK family can be activated by a variety of environmental stresses and inflammatory cytokines. They are shown to phosphorylate c-Jun and regulate the activity of multiple transcription factors after translocation of activated SAPK/JNK to the nucleus. When SAPK/JNK is activated, it binds to the amino-terminal trans-activation domain of c-Jun and increases AP-1-dependent gene expression. AP-1 controls the expression of inflammatory mediators, including COX-2 and iNOS [41]. In summary, p38 MAPK, AKT, mTOR pathways have been shown to play important roles in LPS-induced microglia activation during neuroinflammation (Figure 4).

Neuroinflammatory diseases

Abnormal microglial activation is attributed to the pathology of the several neurodegenerative diseases including AD, PD, MS, psychiatric disorders such as stress, depression and schizophrenia, and metabolic syndromes such as hypertension, obesity and type 2 diabetes [28] (Figure 5). The cellular and molecular mechanisms of neuroinflammation are likely the same in aging [47]. Microglia aging, which is a brain aging accelerator, is associated with cognitive decline during aging and in AD [30]. Brain inflammation contributes to the pathology of neurodegenerative diseases, meningitis and brain trauma [7]. Chronic systemic inflammation promotes microglia aging even at middle age. Certain nutrients may, therefore, be beneficial for delaying brain aging by preventing or reversing microglia aging [30]. Neuropathological and neuroradiological studies indicate that neuroinflammatory responses may begin prior to significant loss of neuronal populations in the progression of diseases [48].

AD, a neurodegenerative disease that is characterized by a progressive decline in cognitive and functional abilities, is one of the leading causes of disability among the elderly [23,33]. Disease progression is associated with degeneration of cholinergic neurons and buildup of amyloid b (Ab) plaques [49]. Neuronal cells start degenerating, and whole brain size shrinks eventually. Consequently, the brain tissue would have progressively fewer nerve cells with reduced mitochondrial function and lost synaptic connections between each other. Oxidative stress is considered to be the main cause of AD, and mitochondrial dysfunction is considered one of the most prominent features observed in vulnerable neurons of the AD patients' brain [33]. In microglia, mitochondrial dysfunction leads to the excess production of ROS, which promotes the redox imbalance and stimulates pro-inflammatory gene transcription and the release of cytokines, such as IL-1β, IL-6 and TNF-α, thereby, inducing neuroinflammation. The oxidative modification of proteins, DNA/RNA oxidative damage and high levels of DNA breaks are shown in AD patients. Activated microglia-mediated neuroinflammation is closely associated with the pathogenesis of AD, because activated microglia trigger neuroinflammation to promote neuronal damage. Moreover, anti-inflammatory agents improve the cognitive functions of AD patients [30,50]. AD is a complex multifactorial disorder which may require equally complex approaches to treatment. Early disease detection, combination therapies and lifestyle choices are all contributors to the successful eradication of the pathology [51].

MS is an immune-mediated inflammatory disease with a pathophysiology characterized by CNS demyelination and inflammation. Activation of innate immune

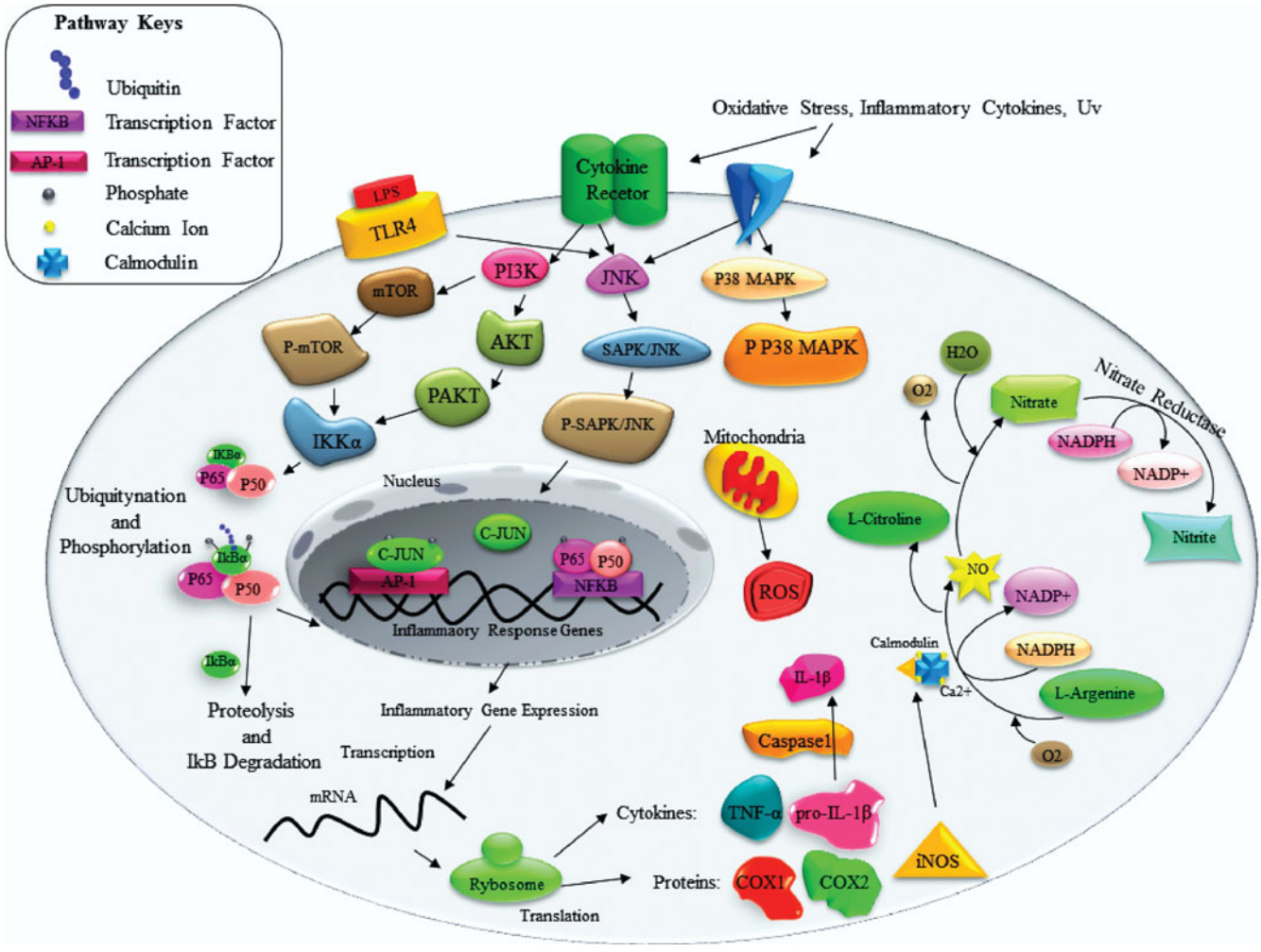

Figure 4. Overview of neuroinflammation pathway. This pathway shows how microglial cells get activated by LPS. During this pathway, as a result of oxidative stress, inflammatory cytokines and UV, some proteins inside the cells (AKT, mTOR, p38 MAPK) get phosphorylated and activated which end up in phosphorylation and ubiquitination of NF-κB. NF-κB is then secreted to the nucleus where it can bind to a specific binding site in order to activate the transcription and translation of inflammatory cytokines and chemokines. Then, these cytokines (TNF-α and IL1-β) and proteins (COX-1, COX-2 and iNOS) are released from the microglia. Apart from that, due to mitochondrial dysfunction, some ROS is also secreted in the microglia which is another cause of neuronal damages. Furthermore, iNOS eventually produce nitrate and nitrite where all together result in neuroinflammation.

responses, in the form of macrophages and microglia, contributes to axonal damage similar to that seen in MS. Systemic inflammation might damage myelinated cells in MS, and this relationship could be the explanation of relapses following infection [7].

PD is characterized by loss of dopaminergic neurons from the substantia nigra pars compacta and reduction of levels of dopamine in the striatum. Symptoms include rigidity, resting tremor and motor function impairment, including freezing and bradykinesia. The presence of inflammatory mediators in the cerebrospinal fluid of patients with PD is confirmed [48,49].

HD is an autosomal dominant neurodegenerative disorder that has been linked to mutations in the huntingtin gene which leads to increased number of glutamine residues in the huntingtin protein and causes degeneration of neurons, causing HD patients to suffer from uncontrolled movements, emotional disturbances and dementia. Inflammation is an important player in HD and appears both peripherally and in the CNS during the progression of HD and HD-like pathology [48].

ALS, also known as Lou Gehrig's disease, involves a progressive degeneration of motor neurons in the brain and spinal cord. The levels of general markers of inflammation in the serum of ALS patients correlate positively with the severity of their disability. ALS can be either sporadic or familial in origin, and a variety of genes are linked to disease development [48,49].

Gene therapy is a powerful tool for treating neurodegenerative diseases such as ALS, PD and AD [49]. Stem

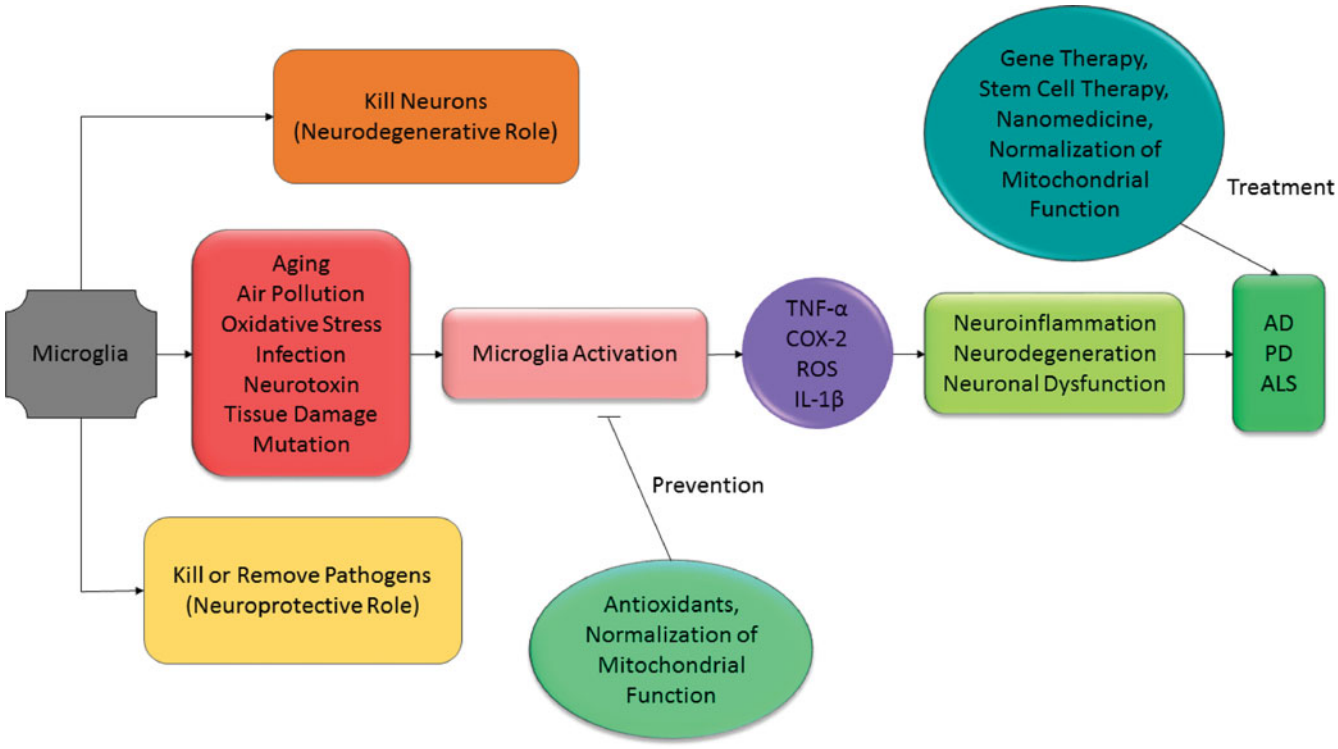

Figure 5. Relation between microglia activation and neuroinflammatory diseases. Microglia get activated due to aging, air pollution, oxidative stress and infection which lead to neuroinflammation and neurodegeneration. Activated microglia produce excessive ROS during aging, resulting in NF-κB activation. Activated microglia trigger neuroinflammation to promote neuronal damage and cell death. Preventing microglia activation and normalization of mitochondrial function are therapeutic strategies.

cell therapy offers new approaches in treating AD and PD [52]. Moreover, antioxidant nutrients inhibit the production of TNF-α, IL-6 and NO by the stimulated microglia in a concentration-dependent manner. Vitamin E provides neuro-protection by attenuating TNF-α and NO production, and it reduces the LPS-induced increase in ROS and IL-6 in microglia [30]. Polyphenolic compounds like flavonoids and vitamin C may prevent age-related neurodegenerative diseases. Flavonoids, that are present in daily dietary fruits and vegetables, protect neuronal cells by reducing oxidation of proteins, inhibiting of JNK and p38 pathways and preventing generation of ROS [53]. Nanomedicine could be a strategy for AD, PD and ALS treatment. A major challenge in the treatment of neurodegenerative diseases is the restricted access of drug molecules across the BBB. Hence, nanotechnology-based drug delivery strategies offer possibilities in the treatment of these diseases [54].

Conclusion

Microglia get activated due to aging, air pollution, oxidative stress and infection which leads to production of pro-inflammatory mediators such as NO, iNOS and COX-2. Excess production of pro-inflammatory components in over-activated microglia could be a risk factor to initiate neurodegeneration via many inflammatory pathways such as MAPK and PI3K/AKT pathways. Furthermore, activated microglia produce excessive ROS, resulting in NF-κB activation which trigger neuroinflammation to promote neuronal damage and cell death. Microglia activation is one of the earliest features that occur in nearly any neuronal physiology changes. Inhibiting pro-inflammatory mediators and cytokines, modulating microglial activation, normalizing mitochondrial function could be effective therapeutic strategies to mitigate the progression of neurodegenerative diseases.

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Declaration of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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