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Review Article

Toll-like receptors in the pathogenesis of neuroinflammation

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ABSTRACT

Toll-like receptors (TLRs) are discovered as crucial pattern recognition receptors (PRRs) involved in the recognition of pathogen-associated molecular patterns (PAMPs). Later studies showed their involvement in the recognition of various damage/danger-associated molecular patterns (DAMPs) generated by host itself. Thus, TLRs are capable of recognizing wide-array of patterns/molecules derived from pathogens and host as well and initiating a proinflammatory immune response through the activation of NF-κB and other transcription factors causing synthesis of proinflammatory molecules. The process of neuroinflammation is seen under both sterile and infectious inflammatory diseases of the central nervous system (CNS) and may lead to the development of neurodegeneration. The present article is designed to highlight the importance of TLRs in the pathogenesis of neuroinflammation under diverse conditions. TLRs are expressed by various immune cells present in CNS along with neurons. However out of thirteen TLRs described in mammals, some are present and active in these cells, while some are absent and are described in detail in main text. The role of various immune cells present in the brain and their role in the pathogenesis of neuroinflammation depending on the type of TLR expressed is described. Thereafter the role of TLRs in bacterial meningitis, viral encephalitis, stroke, Alzheimer's disease (AD), Parkinson's disease (PD), and autoimmune disease including multiple sclerosis (MS) is described. The article is designed for both neuroscientists needing information regarding TLRs in neuroinflammation and TLR biologists or immunologists interested in neuroinflammation.

1. Introduction

Neuroinflammation plays a very important role in the pathogenesis of various infectious including bacterial/viral meningitis and non-infectious disease brain diseases including neurodegenerative diseases that include Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) etc., motor neuron diseases (MNDs) including amyotrophic lateral sclerosis (ALS), traumatic brain injury (TBI), stroke, and autoimmune diseases of nervous system including multiple sclerosis (MS) (Amor et al., 2010; Chen et al., 2016; Amor et al., 2014; Stephenson et al., 2018). Both the components of the immune system (innate and adaptive immunity) play a crucial role in the generation of neuroinflammation in diverse neurological diseases. (Amor and Woodroofe, 2014; Fakhoury, 2015). The astrocytes, microglia, oligodendrocytes, and glial cells serve as the brain's local sentinel innate immune cells, and the activation of these cells under diverse conditions leads to the development of neuroinflammation. The process involves the migration of other potent immune cells including monocytes/macrophages, neutrophils, and T cells ($CD4^+$, $CD8^+$, and regulatory T cells (Tregs) due to the disruption of blood-brain-barrier (BBB) in response to the generation of pro-inflammatory molecules including cytokines (IL-1α, IL-1β, IL-6, and TNF-α etc.) and reactive oxygen species (ROS) etc. (McGavern et al., 2002; Korn and Kallies, 2017; Obermeier et al., 2013; Patel and Frey, 2015; Ransohoff and Brown, 2012; Walsh et al., 2014; Wraith and Nicholson, 2012). PRRs play a crucial role in the recognition of various PAMPs and DAMPs generated by the host during sterile and infectious inflammatory conditions. If the inflammatory process is not controlled or subsided, it may cause persistent inflammation inducing inflammatory tissue damage or neuroinflammation, in the case of the brain.

Toll-like receptors (TLRs) are one of the several PRRs including intracellular PRRs (Nod-like receptors (NLRs), NOD1 and NOD2), C-type lectin receptors (CLRs) [Dectin 1 or CLEC7A (C-type lectin domain family 7 member A), dectin 2 or CLEC6A (C-type lectin domain family 6 member A), DC-specific ICAM3-grabbing non-integrin (DC-SIGN)], complement receptor 3 (CR3), Triggering receptors expressed on

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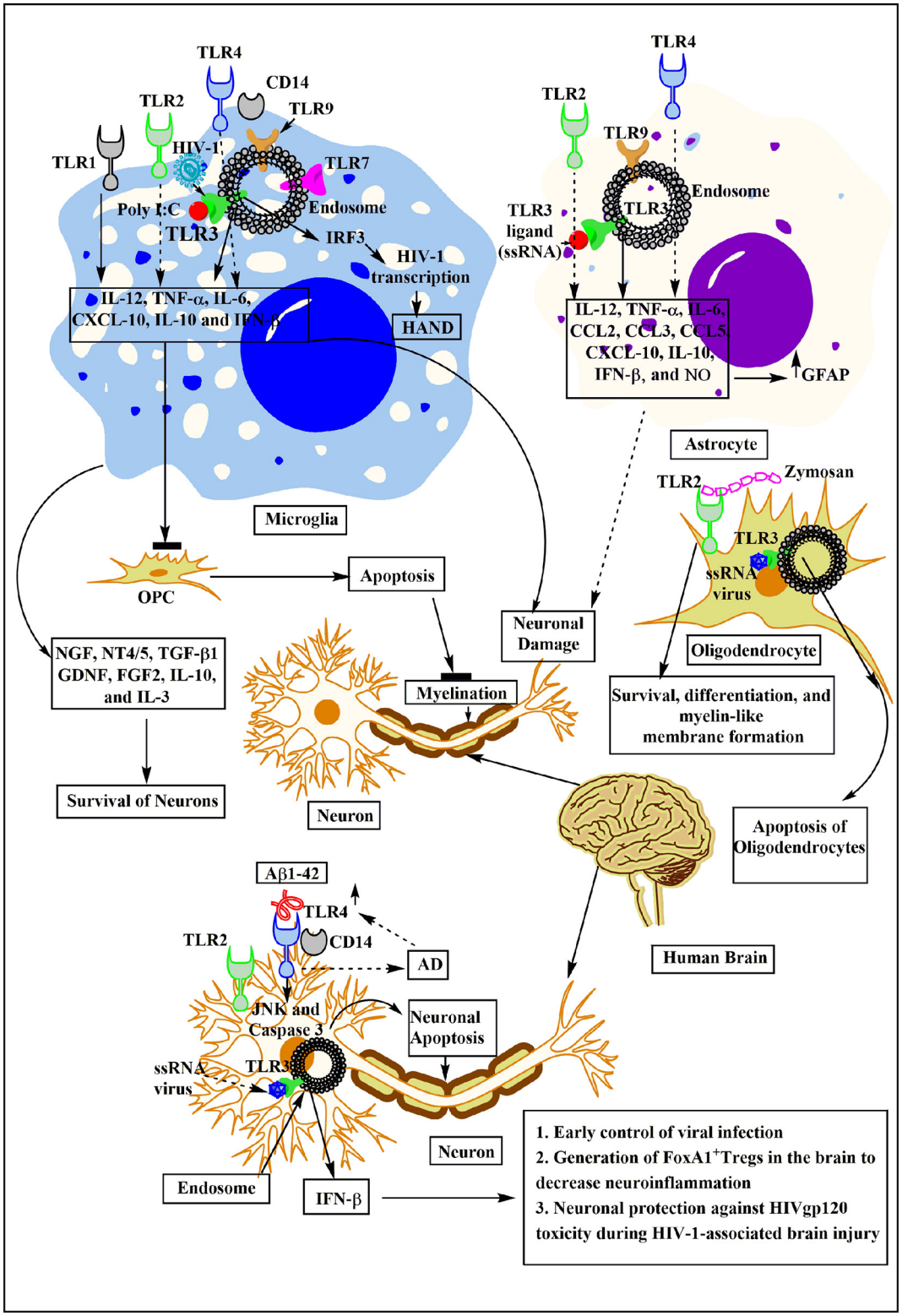

Fig. 1. Expression of various TLRs on different cells of brain including microglia, neurons, and astrocytes. The TLR1, TLR2, and TLR4 are expressed on the cell surface of microglia, while TLR3, TLR7, and TLR8 are expressed intracellularly (i.e. in endosomes) in microglia. The activation of TLR3 in the presence of viral antigens and the activation of other cell surface TLRs generate various proinflammatory cytokines, chemokines, and IFNs. The extracellular release of these proinflammatory molecules proves lethal to neuron due to their damaging action on neurons and oligodendrocytes involved in the synthesis of myelin sheath of the neurons. Whereas various growth factors and anti-inflammatory molecules (i.e. IL-10) released by microglia promote the survival of the neurons. The TLR3 activation in microglia during HIV-1 infection causes the activation of IRF3 that further increases the transcription of HIV-1 and induces the HIV-1-associated neurocognitive disorder (HAND). While, the activation of TLR3 in neurons by viral antigens proves beneficial to neurons due to neuroprotective action via different mechanisms described. While the activation of TLR4 by amyloid β (Aβ1-42) causes neuronal apoptosis due to the activation of JNK kinases and caspase 3 (CASP3) causing AD. The activation of various TLRs including TLR3 and TLR4 on astrocytes stimulates the synthesis and release of various proinflammatory molecules causing neuroinflammation and neuronal death. The detail is described in the text.

myeloid cells (TREM-1) and myeloid DAP-12 associated lectin (MDL-1) responsible for the recognition of several PAMPs and DAMPs and are regulated via the mechanism of post-translational modification (Kumar and Sharma, 2008; Romani, 2011; Areschoug and Gordon, 2008; Kumagai and Akira, 2010; Takeuchi and Akira, 2010; Takeuchi and Akira, n.d.; Liu et al., 2016; Liu and Cao, 2016). TLRs are highly conserved PRRs that are present in animals as low as nematodes [i.e. *Caenorhabditis elegans* (*C. elegans*)] and in ascidians [i.e. *Ciona intestinalis* (*C. intestinalis*)] *(Azumi* et al., *2003; Tenor and Aballay,* 2008*; Irazoqui* et al., *2010; Brandt and Ringstad,* 2015*)*. They were first discovered in 1988 in *Drosophila melanogaster or D. melanogaster* (Hashimoto et al., 1988) and thereafter in 1997 its one homolog known as TLR4 was discovered in humans (Medzhitov et al., 1997). This discovery of TLR4 in humans or mammals revolutionized research in the field of innate immunity, infection and inflammation. Researchers have identified ten functional TLRs (TLR1-TLR10) in humans and 13 active TLRs in laboratory mice to date (Kawai and Akira, 2011). The primary aim of the article is to describe the role of different TLRs in the pathogenesis of neuroinflammation that plays a crucial role in various inflammatory diseases of the CNS.

2. Immunopathogenesis of neuroinflammation

Neuroinflammation can be originated due to various causes including infections, accumulation of toxic metabolites, peptides or proteins as observed during various neurodegenerative disorders (AD, PD, HD etc.). The brain was considered for a long time as an immune-privileged organ, but the presence of microglial cells (a kind of brain macrophages), astrocytes, oligodendrocytes, and glial cells serving as brain's innate immune cells has omitted this concept of immune privilege. In addition during brain infection or inflammation, the disruption of BBB further promotes the infiltration of the brain by various immune cells including monocytes, neutrophils, dendritic cells (DCs), T cells, and B cells interacting with local immune environment to mount an effective immune response to clear the infection or remove the protein complexes. However, the uncontrolled activation of these local immune cells causes a profound invasion of peripheral immune cells into the brain that proves detrimental to the host leading to different neuroinflammatory diseases.

2.1. Microglial cells in neuroinflammation and TLR expression

Microglia are considered brain's macrophages and more specifically parenchymal tissue macrophages with delicate ramified or treelike branching processes that act as sentinel innate immune cells comprising 10 % of cells of adult CNS (Aguzzi et al., 2013). In comparison to CNS macrophages located in brain meninges, choroid plexus, and perivascular spaces microglia are derived from macrophages produced via primitive hematopoiesis in the yolk sac (Alliot et al., 1999). This is because they can be detected in the brain rudiment from eighth embryonic day after their appearance in the yolk sac and thereafter their number keeps on increasing until late gestation (Alliot et al., 1999). These highly motile treelike or ramified branching processes of resting microglia constantly keep a vigil on local microenvironment and frequently respond to the injury or infectious agent or particle with their directed process/protrusions or via migration to the corresponding site (Nimmerjahn et al., 2005; Wake et al., 2009). Furthermore, the disruption of BBB during infection or neurodegeneration is reported that also leads to the immediate and focal activation of microglia, reprogramming their behaviour form patrolling to protective to injured tissue (Nimmerjahn et al., 2005). The microglia are also involved in the clearance of apoptotic cells and functional synapse formation via contributing to increased turnover of synaptic connections (Wake et al., 2009; Tremblay, 2011). Besides expressing various immune receptors, microglia express various TLRs including TLR1, TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, TLR9 and co-receptor CD14 (Fig. 2) (Bsibsi et al., 2002; Olson and Miller, 2004). The expression of these TLRs on microglia increases with the presence of pathogens or other pro-inflammatory stimuli (Olson and Miller, 2004). Of note, these microglia with various TLR expression are present at different areas of brain with their high preference to the areas contiguous to blood circulation including meninges and circumventricular organs (Chakravarty and Herkenham, 2005). Thus the presence of TLRs on microglia in brain may play a crucial role in the generation of neuroinflammation in response to circulating endotoxin or lipopolysaccharide (LPS) along with other TLR ligands. It should be noted that microglia do not express TLR10 (Bsibsi et al., 2002; Jack et al., 2005). Human microglia upon stimulation with TLR3 ligands (Poly I:C (Polyinosinic-polycytidylic acid) and dsRNA) synthesize and release IL-12, TNF-α, IL-6, chemokine (C-X-C motif) ligand 10 (CXCL-10), IL-10 and IFN-β (Fig. 2) (Jack et al., 2005; Alexopoulou et al., 2001). Furthermore, the activation of human microglial TLR3 is involved in the induction of reactivation of HIV-1 transcription in infected microglia via activation of IRF3 and may contribute to HIV-associated neurocognitive disorder (HAND) (Fig. 1) (Alvarez-Carbonell et al., 2017). On the other hand the activation of microglial TLR3 promotes the survival of neurons after cerebral ischemia (Jeong et al., 2016). While the stimulation of microglia with TLR agonist including LPS blocks the proliferation of oligodendrocyte progenitor cells (OPCs) and stimulates their apoptotic death in the presence of astrocytes due to the release of a high amount of TNF-α, thus blocks the process of myelination or remyelination required after neuronal damage under certain conditions including ischemic stroke (Fig. 1) (Li et al., 2008).

The activated microglia release neurotrophic factors including nerve growth factor (NGF), neurotrophin (NT)-4/5, transforming growth factor β1 (TGF-β1), glial-derived neurotrophic factor (GDNF), fibroblast growth factor 2 (FGF2), IL-10 and IL-3 affecting survival of neurons (Nakajima et al., 2007). Microglia-derived factors also include proinflammatory mediators such as TNF-α, IL-6, or nitric oxide (NO), which confer neuronal damage. However, the proinflammatory secretory function of microglia depends on severity of the infection or strength of other inflammatory signals (chemokines, ATP etc.) as shown during the pathogenesis of several neurodegenerative diseases (Hanisch and Kettenmann, 2007; Kettenmann et al., 2013). Accordingly, two kinds of signals are mainly responsible for controlling microglial behaviour/function during injury: “find-me” signals attract microglial cells to the site of inflammation, and “eat-me” signals provide an opportunity to microglia to recognize the target for initiating the process of phagocytosis (Kettenmann et al., 2013). Another classification distinguishes between “on signaling” that includes newly synthesized or highly upregulated factors (i.e. purines, chemokines, and glutamate etc.) during the process of pathogenesis of neuroinflammation and “off signaling” including factors getting downregulated or disappeared in the process of induction of neuroinflammatory changes (Biber et al., 2007). However, the theme of the article is to highlight the importance of TLRs in the pathogenesis of neuroinflammation so TLRs are described in context to microglial functional regulators here. The updated information regarding role of microglia in neuroinflammation and neurodegeneration is described somewhere else (Song and Colonna, 2018; Butovsky and Weiner, 2018).

2.2. Astrocytes in neuroinflammation and TLR expression

Astrocytes are crucial regulators of innate and adaptive immune response in the injured CNS and their activity may exacerbate the inflammatory response and tissue damage or may promote immunosuppression or tissue repair depending on the duration and situation of the context to that they are activated by producing several cytokines and chemokines (Colombo and Farina, 2016; Chiara and Cinthia, 2010). In addition they also play a crucial role in integrating signals and maintaining homeostasis between its, nervous, vascular, and immune components including neurons, oligodendrocytes, and

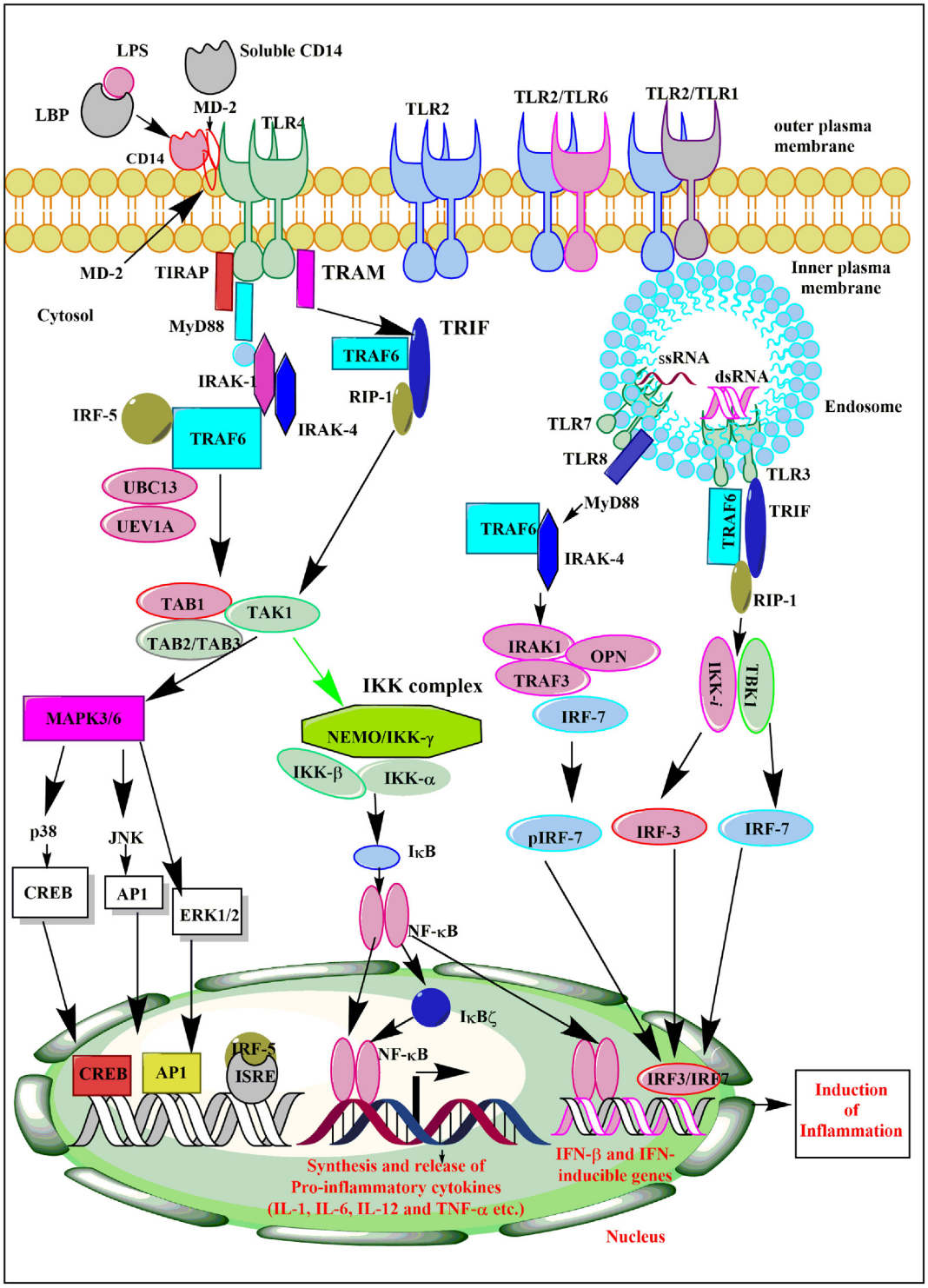

Fig. 2. TLR signaling responsible activation of inflammatory pathways involved in the induction of neuroinflammation.
TLRs signaling occurs either MyD88-dependent or MyD88-independent or TRIF-dependent manner. MyD88 signaling initiates after binding of the different ligands to the TLRs expressed on the cell surface (TLR2/1, TLR2/6, TLR4/MD-2 and TLR5) or intracellularly (i.e. on endosomal membranes (TLR7, TLR8, TLR9). The TIR domain of the TLR recruits the adaptor molecule MyD88 directly or via TIRAP forming the myddosome; a complex containing MyD88, IRAKs and TRAF6 to the plasma membrane. Phosphorylated IRAK1 and TRAF6 then dissociate from the myddosome, phosphorylates and activate TAK1 and TAB1 in the TAK1/TAB1//TAB2-3 complex. TRAF6 ubiquitination activates TAK1 to activating the IκB kinase (IKK) complex comprising of two kinase subunits (IKKα and IKKβ) and a regulatory subunit called IKKγ or NEMO. It phosphorylates and degrades IκB releasing NF-κB that moves into the nucleus. As shown in the Figure, activated TAK1 also activates MAPK (p38 and JNK) that phosphorylates AP-1 and CREB. Phosphorylated AP-1 and CREB homodimerize and translocate to the nucleus. In parallel, the myddosome also phosphorylates IRF5. The phosphorylated IRF5 homodimerizes and translocates to the nucleus. The TRIF signaling pathway is activated upon TLR4 and TLR2 stimulation in both compartments including plasma membrane and/or endosome. The TIR domain of the TLRs recruits TRIF forming a triffosome, a complex comprising TRIF, TRAF3, TBK1 and IKKi (also known as IKKε). Activated TBK1 phosphorylates IRF3, which then homodimerizes and translocates to the nucleus. The detailed signaling pathway is describe in the text.

microglia (Cekanaviciute and Buckwalter, 2016). For example, astrocytes provide trophic and functional support to neurons by transporting glucose, neurotrophic factors, and neurotransmitters including glutamate along with keeping the brain immune system at controlled/quiescent or at baseline through regulating BBB permeability and activation of microglia (Cekanaviciute and Buckwalter, 2016; Anderson and Swanson, 2000). They play role in the activation and trafficking of immune cells. TLR2, TLR3, TLR4, and TLR9 are expressed on astrocytes (Fig. 1) (El-Hage et al., 2011). However, TLR3 is a major TLR expressed on rodent and human astrocytes and its level of expression increases upon inflammatory stimuli including viral infections (Jack et al., 2005; Farina et al., 2007; Park et al., 2006; Farina et al., 2005; Scumpia et al., 2005). For example, TLR3 exerts a protective action against West Nile Virus (WNV) that causes a neurotropic infection (i.e. WNV encephalitis), by restricting their replication in neurons (Daffis et al., 2008; Lim et al., 2011). The engagement of TLR3 expressed on astrocytes with their potent ligands activates TLR3 downstream signaling causing the induction and release of proinflammatory molecules including cytokines, chemokines (i.e. CCL2, CCL3 and CCL5 etc.), and nitric oxide (NO) (Fig. 1) (Scumpia et al., 2005; Brahmachari et al., 2006; Okun et al., 2009a). For example, cytoskeletal glial fibrillary acidic protein (GFAP) is widely used for the identification of astroglia *in vivo* and *in vitro*, and upregulation of this marker in astrocytes is a typical hallmark for CNS pathologies (Sofroniew, 2009). And this GFAP is increased in astrocytes stimulated with TLR3 ligands due to the production of NO (Fig. 1) (Brahmachari et al., 2006). A parallel activation of astrocytes with dsRNA (a TLR3 agonist) and LPS (a TLR4 agonist) causes the secretion of IL-1α, IL-1β, IL-6, TNF-α, GM-CSF, LTβ and TGF-β3 cytokines with an inhibition of macrophages migration inhibitor factor (MIF) (Okun et al., 2009a; Krasowska-Zoladek et al., 2007). However, this condition does not affect the secretion of IL-2, IL-3, IL-4, IL-5, IL-10, TGF-β1, TGF-β2, TNFβ and IFN-γ (Krasowska-Zoladek et al., 2007).

2.3. Oligodendrocytes in neuroinflammation and TLR expression

Oligodendrocytes are the myelinating glial cells of the CNS that in spinal cord are mostly derived from specialized domain of the ventral ventricular zone that first causes the development of motor neuron precursors, and thereafter the neurogenic/gliogenic switch, to oligodendrocyte precursor cells/progenitors (OPCs) (Lu et al., 2002; Bradl and Lassmann, 2010). Thereafter, OPCs, migrate across whole spinal cord and differentiate into oligodendrocytes (Bradl and Lassmann, 2010). TLR2 and TLR4 signaling in intraspinal macrophages influences the generation of oligodendrocytes (Schonberg et al., 2007). For example, activation of TLR4 signaling promotes the generation of oligodendrocytes by upregulating ciliary neurotrophic factor, while TLR2 activation through zymosan inhibits their generation (Schonberg et al., 2007). Thus, the activation of different TLRs during neuroinflammatory conditions [i.e. multiple sclerosis (MS)] may impact the process of oligodendrocyte generation and thus the process of myelination. Rat oligodendrocytes are found to express TLR2 and TLR3 (Bsibsi et al., 2012). However, they exert different effects on these cells, for example, an activation of TLR2 with zymosan promotes their survival, differentiation, and myelin-like membrane formation but TLR3 activation with Poly I:C induces their apoptosis (Fig. 1) (Bsibsi et al., 2012). Thus, TLR2 activation on oligodendrocytes exerts a protective action and increases their myelination capacity required for myelination of neurons in CNS. Furthermore, TLR2 or TLR4 KO mice show a defective process of myelination of neurons after spinal cord injury (Kigerl et al., 2007). However further studies are required in this field.

2.4. Neurons in neuroinflammation and TLR expression

Neurons are direct target of inflammatory damage observed during neuroinflammation generated by the overactivation of innate immune cells of CNS (i.e. microglia and astrocytes), endothelial cells or immune cells migrated during the process of generation of neuroinflammation. However, neurons themselves also express various TLRs (mRNAs of TLR1-TLR9 and proteins of TLR2, TLR3, TLR4, and TLR6) (Fig. 1) (Prehaud et al., 2005; Cameron et al., 2007). The sensing of viruses by TLR3 and its activation on neurons produces IFN-β even in the absence of microglia (Fig. 2) (Prehaud et al., 2005; Delhaye et al., 2006). The production of IFN-β by neurons exerts a protective action via different mechanisms including the early control of infection, reprogramming the encephalitogenic T cells (T_{enc}) into anti-inflammatory $FoxA1^+$Tregs and induction of secretion of the β-chemokine CCL4 from astrocytes during HIV-1 infection (Fig. 2) (Cavanaugh et al., 2015; Liu et al., 2014; Thaney et al., 2017; Rosato and Leib, 2015). The $FoxA1^+$ T_{regs} develop mainly in the CNS during autoimmune inflammatory conditions and have a distinct transcriptional profile and are $CD4^+FoxA1^+CD47^+CD69^+PD\text{-}L1^{hi}FoxP3^-$ (Liu et al., 2014). The IFN-β stimulates neuronal PI3K/Akt signalling. Consequently, Akt binds to transcription factor FoxA1 that translocates to the nucleus and induces PDL1 expression on neurons inducing the generation of $FoxA1^+$Tregs (Liu et al., 2017). The TLR4 expressed on neurons sense $A\beta_{1\text{-}42}$ and their number increases during the pathogenesis of AD (Fig. 1) (Tang et al., 2008). The activation of neuronal TLR4 by Aβ activates c-Jun amino terminal kinase (JNK) and caspse-3 inducing their apoptotic death (Tang et al., 2008). While, TLR6, TLR7, TLR8, TLR11, TLR12, and TLR13 are found to express on murine neurons during parasitic infection causing neurocysticercosis (Mishra et al., 2006; Mishra et al., 2008). The co-expression of CD14 with TLR4 on neurons indicates the ability of bacterial LPS to activate TLR4 signaling in neurons during bacterial infections (Wadachi and Hargreaves, 2006).

3. TLRs controlling neuroinflammation

3.1. TLR signaling responsible for the induction of pro-inflammatory immune response responsible for pathogenesis of neuroinflammation

The recognition of PAMPs associated with bacterial pathogens including LPS, lipoteichoic acid (LTA), peptidoglycan (PGN), porins, flagellin, CpG-DNA by their corresponding TLRs (TLR4, TLR2, TLR5, and TLR9) (Feuillet et al., 2006) induces the events causing NF-κB activation leading to the transcription of genes responsible for the synthesis and release of different pro-inflammatory molecules including cytokines, chemokines, ROS and reactive nitrogen species (RNS) etc. (Fig. 2).

TLRs expressed by various brain innate immune cells i.e. microglia, astrocytes, and even by neurons of the brain that recognize their potential PAMPs that is LPS, PGN, LTA etc. along with peptides and protein are involved in the pathogenesis of neuroinflammation and neurodegeneration. For example, fibrillary amyloid beta (Aβ) binds to TLRs to stimulate brain's innate immune response inducing the pro-inflammatory activation of microglia and clearance of $A\beta_{1\text{-}42}$ that delays the cognitive decline in the experimental model of AD (Landreth and Reed-Geaghan, 2009; Richard et al., 2008; Chen et al., 2006). Furthermore the mutation causing an alteration in TLR4 expression in mice called TLR4 mutant AD model (TLR4M Tg) decreases the microglial activation, increases the deposition of Aβ and soluble $A\beta_{42}$ in the brain, and a rapid decline in cognition and memory due to the diminished production of IL-1β, CCL3, and CCL4 (Song et al., 2011; Tahara et al., 2006). The inhibition of TLR2 and TLR4 in microglia by means of pharmacological or antibody-based blocking agents cause a reduced production of nitrite, TNF-α, and IL-6 upon treatment with aggregated, fibrillar $A\beta_{42}$ exposure (Walter et al., 2007). However, the nonfibrillar $A\beta_{42}$ is unable to stimulate TLR signalling (Walter et al., 2007). Additionally, microglia lacking the expression of TLR2, TLR4 and CD14 are unable to mount a pro-inflammatory immune response (i.e. increased expression of TNF-α, IL-1β, IL-6, integrin markers (i.e. CD11b, CD11c, and CD68), ROS, and NO synthase), and phagocytosis upon

exposure to fibrillar $A\beta_{42}$ (Jana et al., 2008; Reed-Geaghan et al., 2009a). TLR2 is shown to be a primary receptor for $A\beta_{42}$ peptide to initiate the neuroinflammation during AD as its deficiency increases the phagocytosis of $A\beta_{42}$ peptide but inhibits the proinflammatory action of microglia under *in vitro* conditions (Liu et al., 2012). Furthermore TLR2-mediated recognition of Aβ42 peptide and trigger of inflammatory pathway is enhanced by TLR1 and suppressed by TLR6 (Liu et al., 2012). However the receptor complex comprising $\alpha_6\beta_1$ integrin, CD47 (integrin-associated protein), and CD36 (B-class scavenger receptor) are also involved in the recognition of fibrillar Aβ and is required for the production of cytokines, ROS, and their phagocytosis (Bamberger et al., 2003; Koenigsknecht and Landreth, 2004).

3.2. General mechanism of activation of TLR signaling to initiate a proinflammatory immune response

The recognition of LPS by TLR4 involves the binding of circulating LPS to LBP (lipid binding protein) and transfers LPS to CD14 (point of note, CD14 is a glycophosphatidylinositol-anchored membrane protein that also exists in the soluble form and binds to LPS-LBP complex and is responsible for recognition of smooth LPS but not for rough LPS) (Jiang et al., 2005). Membrane bound CD14 does not have its intracellular domain and it combines with TLR4 to develop a functional LPS receptor complex. The binding of LPS to TLR4 also requires MD-2 molecule that associates itself with extracellular domain of TLR4 (Park et al., 2009). Thus, the active LPS receptor complex is comprised of TLR4, CD14 and MD-2, where CD14 and LBP are responsible for enhancing the TLR4 dependent LPS signaling and cell stimulation (Lizundia et al., 2008). Once the extracellular binding of LPS to TLR4 is complete, it leads to the downstream signaling involving various adaptor molecules, kinases, phosphatases and causing an activation of NF-κB, leading to the release of proinflammatory cytokines (TNF-α, IL-1α, IL-6, IL-8 etc.) and other molecules responsible for induction of inflammatory pathways responsible for neuroinflammation. This rapid LPS detection by TLR4 induces the formation of Supramolecular Organizing Center (SMOC) called myddosomes (Bonham et al., 2014; Motshwene et al., 2009; Lin et al., 2010; Kagan et al., 2014). This myddosome at its minimum composition comprises of MyD88 and TIRAP (adaptor molecules) with several serine threonine kinases of IRAK family (Rosadini and Kagan, 2017). Myddoomes act as the organizing center of subcellular site for the signals from TLR4 to promote NF-κB and AP-1 activation leading to gene expression of pro-inflammatory genes (Rosadini and Kagan, 2017). These all different downstream signaling pathways will be described here, however, TLR signaling pathways have been described in detail by many researchers previously and are recommended for further reading (Akira and Takeda, 2004; Kawai and Akira, 2010; Tartey and Takeuchi, 2017).

3.3. MyD88-dependent and MyD88-independent signaling pathways in TLR4 signaling

The formation of LPS, CD14, MD-2 and TLR4 complex causes conformational changes in TLR4 molecule due to the homodimerization of TLR4 receptors via interaction between their intracellular TIR-domains (Vaure and Liu, 2014). This causes recruitment of TIR-domain containing adaptor molecules that is My-D88 towards the cytoplasmic domain of the TLR4 homodimer through homophilic interactions between TIR-domains (Vaure and Liu, 2014) (Fig. 2). At least 5 TIR-domain-containing adaptor molecules from two different pathways are known to play a direct important role in TLR4 signaling. These include, 1) Myeloid differentiation factor-88 or MyD88, 2) MyD88-adaptor-like (MAL) protein also called TIR-domain containing adaptor protein (TIRAP), 3) TIR-domain containing adaptor inducing interferon-β (TRIF) or TIR-domain containing adaptor molecule-1 (TICAM-1), 4) TRIF-related adapter molecule (TRAM) or TIR-containing protein (TIRP) or TIR-containing adaptor molecule-2 (TICAM-2) and 5) sterile α-and armadillo-motif-containing protein (SARM) (Vaure and Liu, 2014; O'Neill and Bowie, 2007). All these four adaptor proteins are essentially required by TLR4 to mount a comprehensive immune response against inflammogens able to cause neuroinflammation. TIRAP and TRAM, the TLR regulatory proteins also called as sorting adaptors interact with phosphoinositides (PIs) for promoting LPS induced proinflammatory signaling (Kagan, 2012). These sorting adaptors are specific regulatory factors for TLR4 signaling in terms that these proteins are present at the site of their requirement (for example, TIRAP and dMyD88 located in phosphatidylinositol 4,5 bisphosphate (PIP2)-rich regions of the cell surface (i.e. inner leaflet of plasma membrane) and TRAM is located on plasma membrane and endosomes) before the initiation of signaling event and they define the type of signaling pathway initiated from that location (Rosadini and Kagan, 2017). This is because they bind to PIs found on cellular organelles that is inner surface of plasma membrane of cell or endosomes the eventual site of TLR4 signal transduction (Rosadini and Kagan, 2017). These sorting adaptors recognize the dimerized TLR4 at the cell surface or on endosomes and form the myddosomes or TRIF signaling to promote inflammatory signaling (Rosadini and Kagan, 2017). Thus, PI(4,5)P2 plays an important role in the initiation of TLR4 signaling at the plasma membrane and its modulation has potential to modulate TLR4 pathway (Rosadini and Kagan, 2017).

The intracellular signaling pathway of TLR4 signaling is mainly controlled by two main pathways:

a) MyD88-TIRAP dependent pathway is mainly involved in early regulation of NF-κB activation and related pro-inflammatory cytokine production that is IL-12. MyD88 was first named in 1990s as a protein that was induced during the terminal differentiation of $M1D^+$ myeloid precursors in response to IL-6 – the 'MyD' part of the name stands for myeloid differentiation and '88' depicts the gene number in the list of induced genes (Lord et al., 1990). The MyD88-dependent pathway mainly involves its recruitment and attachment with cytoplasmic portion of TLR4, which further recruits IL-1R-associated kinase-4 (IRAK-4) and IRAK-1 via death domains. After binding of IRAK-1 with MyD88, earlier gets phosphorylated via activated IRAK-4 and gets attached to the RING-domain E3 ubiquitin ligase or TNFR- associated factor 6 (TRAF-6). TRAF-6 acts as an ubiquitin ligase (E3) (Li et al., 2002). Further TRAF-6 in association with ubiquitination E2 enzyme complex comprising UBC13 and UEV1A, catalyzes the formation of a K63-linked polyubiquitin chain on TRAF6 itself and on IKK-γ/NF-κB essential modulatory (NEMO) (Deng et al., 2000). Additionally, Bcl-2 family protein BH3-interacting domain death agonist (Bid) potentiates the TLR4-NF-κB pro-inflammatory response in glia via promoting the K63-linked polyubiquitination of TRAF6 (Kinsella et al., 2016). Furthermore, Bid promotes E3 ubiquitin ligase-mediated signaling downstream of TLR3 and TLR4 signaling required for the induction of neuroinflammation (Kinsella et al., 2018). Thus, attenuation of Bid via an increased A20-E3 ubiquitin ligase interaction inhibits TLR3 and TLR4 signaling in microglia and thus the neuroinflammation (Kinsella et al., 2018). MAP kinase kinase (MAP3K) TGF-β-activated kinase 1 (MAP3K7 or TAK1) and the TAK1 binding proteins, TAB1, TAB2 and TAB3 complex gets recruited to TRAF6 (Wang et al., 2001; Arthur and Ley, 2013). TAK1 then phosphorylates IKK-β and MAP kinase kinase 6 (MKK6) and modulates the activation of NF-κB and MAP kinases, causing induction of genes responsible for inflammation and associated tissue/organ damage. Additionally, TAK1 or MAP3K7 can directly stimulate MAP kinase (MAP2K) for p38 and JNK and acts as crucial MAP3K for ERK1/2, p38 and JNK activation downstream to TLR signaling causing the activation of AP-1 family transcription factors or stabilization of mRNA regulating pro-inflammatory immune response (Kawai and Akira, 2010; Wang et al., 2001; Sakurai, 2012; Akira et al., 2006) (Fig. 2). Thus, TAK1 plays an important role in TLR signaling along with TNF and

IL-1 signaling pathway (Sato et al., 2005). However, along with NF-κB gene activation the transcription factor IRF-5 also regulates the expression and release of IL-6, IL-12 and TNF-α cytokines (Takaoka et al., 2005) (Fig. 2). The Irf5$^{-/-}$ mice seem to be resistant to lethal endotoxic shock induced by LPS, and exhibit very low serum levels of pro-inflammatory cytokines (Takaoka et al., 2005). Upon stimulation of innate immune cells with TLR4 ligands, IRF-5 translocates into the nucleus and binds to potential IFN-stimulated response element (ISRE) motifs present in the promoter regions cytokine genes. Additionally, I kappa B zeta or IκBζ [also known as Molecule possessing ankyrin repeats induced by lipopolysaccharide (MAIL) and IL-1 inducible nuclear ankyrin-repeat protein (INAP)] is an ankyrin-repeat-containing nuclear protein that is highly homologous to the IκB family member Bcl-3 and is hard to detect in resting cells gets also upregulated during LPS mediated stimulation of TLR4 or by activation of IL-1βR by IL-1β (Yamamoto et al., 2004; Muta et al., 2003). IκBζ stimulates the synthesis and release of IL-6, IL-12 and other pro-inflammatory genes (Yamamoto et al., 2004). Unlike, IκB-α and IκB-β, the IκBζ is located inside nucleus and binds to the p50 subunit of NF-κB and is recruited to the NF-κB binding site of the IL-6 promoter on stimulation and regulates the transcriptional activity of NF-κB in both pro-inflammatory as well as anti-inflammatory manner depending on the activation or suppression of genes involved in the process of inflammation (Yamamoto et al., 2004; Muta et al., 2003; Muta, 2006; Motoyama et al., 2005). Thus, this IκBζ activation occurs downstream of MyD88 and TRAF6 signalling pathway dependent on activation of TLR4 signalling or other TLR signalling occurring via MyD88 that is TLR2 [peptidoglycan (PGN)] or TLR9 (CpG DNA) activation (Eto et al., 2003). The activation of IκBζ occurs rapidly upon TLR4 ligand mediated stimulation that is LPS or other TLR4 ligands regulates the function of NF-κB mediated regulation of genes regulating the function of innate immune response during infection.

b) MyD88-independent or TRIF-TRAM dependent pathway, TRIF-TRAM dependent pathway gets activated in macrophages and dendritic cells upon stimulation of TLR4 with its ligands (i.e. LPS). In addition to TLR4 this pathway also gets activated following the stimulation of TLR3, TLR7 and TLR9 upon the binding of their corresponding ligands that is dsDNA of viruses, ssRNA of viruses and bacterial and mycobacterial CpG DNA and viral DNA) (Fig. 2). However, this pathway is not activated by TLR2 stimulation. TRIF-TRAM pathway leads to the activation of interferon regulatory factor-3 (IRF-3) transcription factor, NF-κB and MAP kinases, responsible for the subsequent up-regulation of genes responsible for type 1 interferons (IFNs) and co-stimulatory molecules and pro-inflammatory cytokines that is TNF-α, IL-6, IL-8 and IL-12 etc. (Fig. 2). This TLR4 and LPS mediated activation of MyD88 independent pathway involves the association of TRAM with TLR4 and TRIM by acting as a bridge between TLR4 and TRIF (Akira et al., 2006). Further, TRIF interacts with TRAF6 and receptor interacting protein 1 (RIP1), which is involved in TLR3-mediated stimulation of NF-κB (Meylan et al., 2004). This interaction of TRAF6 with N-terminal TRAF-binding domain of TRIF activates transforming growth factor beta-activated kinase 1 (TAK1) through similar mechanisms involved in the MyD88-dependent signalling pathway. However, the interaction of TRIF with RIP1 causes K63-linked polyubiquitination. Furthermore, RIP1 also interacts with TNF receptor type 1-associated DEATH domain protein (TRADD), and this multiprotein complex is actively involved in NF-κB activation. On the other hand, TRIF causes the activation of TRAF-family-member-associated NF-κB activator (TANK) binding kinase 1 [TBK1 or TRAF2-associated kinase (T2K) or NF-κB activating kinase (NAK)] through TRAF3, which is important for the induction of type 1 interferons (IFNs) and anti-inflammatory cytokine IL-10 (Hacker et al., 2006; Oganesyan et al., 2006). The family of TBK1 comprises of inducible IκB kinases [IKK-I or IκB kinase-epsilon (IKK-ε)] and are involved in phosphorylation of IRF-3 and IRF-7 (Fitzgerald et al., 2003; Sharma et al., 2003). TBKI along with IKK-*i* is involved in TRIF-mediated IFN response (Hemmi et al., 2004; McWhirter et al., 2004; Perry et al., 2004). Thus, these kinases phosphorylate IRF-3 and IRF-7, which form homodimers and translocate into the nucleus, binds to ISREs, causing the expression of certain set of genes required for IFN-inducible genes (Akira et al., 2006).

Additionally, the Pellino family of E3 ubiquitin ligases are involved in effective TLR signalling via promoting the degradation of TRAF3, a potent inhibitor of MAPK activation and gene induction (Jiang and Chen, 2011; Medvedev et al., 2015). The deficiency of Pellino-1 causes defective TRIF-dependent NF-κB activation and pro-inflammatory cytokine production (Chang et al., 2009). Post-mortem brain samples of multiple sclerosis (MS) patients exhibited a significantly high levels of Pellino-1 as compared to their counterpart healthy controls and Pellino-1$^{-/-}$ mice showed a drastic reduction in the severity of experimental autoimmune encephalomyelitis (EAE), an experimental model of MS (Xiao et al., 2013; Song and Qian, 2013). Microglia express higher levels of Pellino-1 playing an important role in eliciting expression of pro-inflammatory cytokines and chemokines during TLR signalling (Medvedev et al., 2015; Song and Qian, 2013). Now it is cleared that TBK1/IKKi phosphorylate Pellino-1, which in turn leads to ubiquitinilation of RIP-1 and impacts TRIF-dependent NF-κB activation by recruiting RIP-1 (Kawasaki and Kawai, 2014). Furthermore, Pellino-1 also regulates IRF3 activity through DEAF-1 (a transcription factor facilitating binding of IRF3 to IFN-β promoter site) binding (Jiang and Chen, 2011). In addition to Pellino-1, IRF3 activation is also regulated by inositol lipid called, phosphatidylinositol 5 phosphate (PtdIns5P) (Kawasaki and Kawai, 2014). PtdIns5P ligates with both IRF3 and TBK1 to facilitate the TBK1 and IRF3 complex formation, which phosphorylates IRF3 (Kawasaki and Kawai, 2014). Thus, these signals are required not only for the effective innate immune response to clear the pathogens as well as extracellular protein or peptides (i.e. Aβ) or cell debris via inducing the expression of genes required for pro-inflammatory immune response (For example, the extracellular release of TNF-α leads to its direct cytotoxic effects as well as receptor mediated activation of NF-κB, causing further activation of pro-inflammatory genes) but also provide future instruction for adaptive immune response thorough the release of cytokines as well as the expression of co-stimulatory molecules on cell surface of antigen presenting cells (i.e. macrophages, neutrophils, DCs and B cells etc.) (Tahara et al., 2006; Tartey and Takeuchi, 2017; Yu et al., 2010). Thus, TRIF-TRAM pathway or MYD88 independent downstream signaling pathway of TLR4 signaling acts as late activator of NF-κB via IRF3 and TNF-α secretion and majority of LPS responsiveness of innate immune cells via TLR4 activation is operated via MyD88-independent manner.

4. TLRs in infection-induced neuroinflammation

4.1. TLRs during bacterial meningitis

The bacteria responsible for causing meningitis may vary from gram negative bacteria to gram positive ones including *Neisseria meningitides (N. meningitides)*, *Streptococcus pneumoniae (S. pneumoniae)*, *S. agalactiae*, *Escherichia coli (E. coli)*, *Listeria monocytogenes (L. monocytogenes)* and *Mycobacterium tuberculosis (M. tuberculosis)* etc. (*Hanke and Kielian,* 2011*; Koedel, 2009*). All the PAMPs expressed by these pathogens are recognized by TLRs expressed by the cells of CNS including neurons, microglia, astrocytes, and oligodendrocytes that play a crucial role in the pathogenesis of neuroinflammation during bacterial infections. However, here I am not concerned about the complete pathogenesis of bacterial meningitis but the importance of TLRs. For example, LTA, PGN, and other lipoproteins of the gram positive bacteria (*S. pneumoniae, S. agalactiae,* and *L. monocytogenes*) are recognized by the TLR2 expressed in CNS (Klein et al., 2008). The *N. meningitides*

stimulates TLR2 via its porin B or PorB protein (the major outer membrane protein of the bacteria) that via forming TLR2/TLR2 heterodimer initiates downstream proinflammatory signaling involved in the activation of NF-κB transcription factor and the proinflammatory cytokines causing meningitis (Massari et al., 2006). In addition of PorB, another protein of *N. spp.* called Lip protein containing a conserved epitope known as H.8 is also capable of stimulating TLR2 and forming TLR2/TLR1 heterodimer responsible for NF-κB activation (Fisette et al., 2003). While, LPS of the gram-negative bacteria is recognized by TLR4. The bacterial DNA is recognized by TLR9 expressed by microglia and astrocytes. While, the bacterial flagellin of *L. monocytogenes* is recognized by TLR5 of microglia and astrocytes. And the selective deletion of TLRs causes a decreased production of pro-inflammatory cytokines and molecules required to induce neuroinflammation during bacterial infections of the brain (Klein et al., 2008).

Human studies have shown that the genetic polymorphism of TLR2 and TLR9 affects the severity and prognosis of bacterial meningitis in Chinese children (Zhang et al., 2017). However the single nucleotide polymorphism (SNP) of TLR2, TLR4, and TLR9 does not affect the incidence of bacterial meningitis in children as they are equally frequent among patients and their family members (Gowin et al., 2017). But TLR2, TLR4, and TLR9 are associated with hearing loss in patients recovered from bacterial meningitis (van Well et al., 2012). For example, persons carrying either *TLR4* + 896, *TLR9*-1237 or both the mutant alleles exhibit a higher risk for hearing loss (van Well et al., 2012). Thus, TLRs expressed on the cells of CNS play important role in the generation of neuroinflammation in both laboratory mice and humans.

4.2. TLRs in virus induced neuroinflammation

TLR3, TLR7, TLR8, and TLR9 are involved in the recognition of viral PAMPs including dsRNA, ssRNA, and non-methylated CpG motifs of oligdeoxyonucleotides (CpG-ODNs). In addition to recognizing dsRNA, TLR3 also recognizes dsRNA intermediates that are formed during the replication cycle of ssRNA and DNA viruses (Kawai and Akira, 2010). TLR3 and TLR7 also recognize host-derived self RNA that moves to cytosolic environment form the nucleus during cellular stress or injury and are involved in autoimmune diseases (Hoffman et al., 2004; Fairhurst et al., 2008). The downstream signaling pathway during TLR3 activation involves TRIF-dependent pathway required for the induction of proinflammatory type 1 interferon (IFN) important for antiviral defence, while TLR7 signaling occurs via MyD88-dependent pathway (Akira, 2006; Kawai and Akira, 2007).

Different viral infections are involved in CNS inflammation (Furr and Marriott, 2012). For example, Japanese encephalitis (JE) is one of the several emerging viral diseases causing neurological dysfunction and neuroinflammation caused by JE virus, an arbovirus belonging to Flavivirus genus of the *Flaviviridae* transferred to human by mosquito (i.e. *Culex* type) bite. TLR3 is shown to play an important role in the induction of neuroinflammation via generating the proinflammatory immune response causing neuroinflammation (Han et al., 2014). $TLR3^{-/-}$ mice are more susceptible to develop JE, while $TLR4^{-/-}$ mice exhibit resistance to JE due the generation of potent type 1 IFN response. The depletion of TLR3 causes severe neuroinflammation as indicated by an early infiltration of inflammatory monocytes $CD11b^{+}Ly\text{-}6C^{++}$ monocytes, overburden of JE virus, overwhelming production of proinflammatory cytokines and chemokines and the disruption of BBB permeability (Han et al., 2014). JE virus interacts with TLR2 of neurons and TLR3 and TLR7 of the microglia (Nazmi et al., 2014; Jiang et al., 2014; Fadnis et al., 2013). TLR7 exerts a protective action against JEV infection via releasing type 1 IFNs. Microglia deficient in TLR3 upon exposure to JEV secrete less amount of TNF-α, IL-6, and CCL-2, thus microglial TLR3 is required for effective immune response to clear the virus (Jiang et al., 2014). The small hairpin RNA-mediated loss of TLR3 in microglia increases the virus titre in the infected microglia (Jiang et al., 2014). Also the brain-specific TLR7 knockdown (KD) does not influence the mortality among JEV infected animals, while the systemic KD of TLR7 leads to the increased mortality among these animals upon infection with JEV in comparison to wild-type (WT) controls (Lannes et al., 2017). Furthermore, mice with systemic TLR7-KD exhibit an increased load of virus in brain as compared to the brain-specific TLR7-KD (Lannes et al., 2017). Thus, peripheral virus detection plays a crucial role in controlling the JEV neuroinvasion. In addition, a higher level of brain IL-6 is reported in systemic TLR7-KD mice than brain TLR7-KD in mice (Lannes et al., 2017). However, the JEV infection in mice increases the TLR7 expression (Awais et al., 2017). No difference in survival rate and body weight was observed among $TLR7^{-/-}$ and WT mice that can be explained as the induction of an upregulated expression of TLR8 in $TLR7^{-/-}$ mice (Awais et al., 2017). The decreased expression of TNF-α by $TLR7^{-/-}$ microglia upon JEV exposure can be explained as result of inhibition of NF-κB that further inhibits the NOTCH signaling (Mukherjee et al., 2018).

Another arborvirus in the category of neurotropic flavivirus called West Nile virus (WNV) also causes encephalitis or meningitis or neuroinflammation via their recognition by TLR3 and disruption of BBB barrier permeability (Wang et al., 2004). The $TLR3^{-/-}$ mice show resistant towards lethal WNV infection and reduced neuroinflammation (Wang et al., 2004). Thus, TLR3 plays a crucial role in the induction of neuroinflammation during WNV infection. While, another study showed that intracranial inoculation of the WNV virus in $TLR3^{-/-}$ mice showed increases the viral load in the brain due to the increased replication of virus in neurons (Daffis et al., 2008). SARM is TIR-containing adaptor protein involved in TLR3 and TLR4 negative regulation via modulating MyD88-dependent TLR signaling through BB-loop dependent TIR-TIR interactions via a glycine residue G601 located in the BB-loop of the SARM TIR domain (Carlsson et al., 2016). SARM comprises of two sterile-alpha motif (SAM) domains flanked by an N-terminal Armadillo motif (ARM) and a C-terminal TIR domain (Jenkins and Mansell, 2010). SARM is found to be expressed in brain-resident cells including neurons and may suppress TLR signaling in brain (Yuan et al., 2010; Belinda et al., 2008; Rodet et al., 2015). SARM plays a crucial role in viral infections (Panneerselvam and Ding, 2015). The SARM KO mice exhibit an increased replication of WNV in the brain stem causing an increased mortality, a decreased production of TNF-α, a decreased activation of microglia, and the increased death of neurons in the brain stem (Szretter et al., 2009). Furthermore, MyD88-deficient mice exhibit a severe form of WNV infection with higher viral load in the brain, increased virus replication in neurons, and increased mortality (Szretter et al., 2010). However, TLR3 signaling is important for providing protection against herpes simplex virus type-1 (HSV-1) induced encephalitis via inducing the mTORC2 signaling (Sato et al., 2018). Thus, further studies are required in the direction identify the different roles of TLRs in different viral infections capable of inducing neuroinflammation.

5. TLRs in neuroinflammation-associated with sterile inflammatory conditions

5.1. TLRs in stroke and associated neuroinflammation

Stroke is a most common ischemic brain injury occurring due to the loss of blood flow to the particular region of the brain most frequently occurring due to development of emboli in the arteries supplying blood to the brain (Bejot et al., 2009). Thus, this blockage in the blood supply to the specific region of the brain may cause the death of brain cells including neurons via apoptosis or necrosis or both (Love et al., 2000; Sairanen et al., 2009; Guan et al., 2006). Ischemia in the local tissue induces the inflammatory reaction that is immediately coordinated by microglia and are activated within minutes of the infarct (Giulian and Vaca, 1993; Banati et al., 1993; Zhang et al., 2011; Kreutzberg, 1996). The death of the brain cells during ischemia-induced stroke causes the activation of TLRs expressed by microglia, astrocytes, and

oligodendrocytes via the recognition of different DAMPs including hyaluronic acid, HMGB1 (High-mobility group box 1), mRNA, and different heat shock proteins (HSPs) acting as ligands for different TLRs expressed (Singh et al., 2016; Tian et al., 2017; Richard et al., 2017; Lee et al., 2017; Ebid et al., 2014; Campo et al., 2012; Kim and Yenari, 2013a). For example, HSP70 via activating TLR2 and TLR4 signaling pathway in microglia can aggravate the neuroinflammation during stroke when gets outside of the cells due to their death but can also inhibit NF-κB signaling via binding to IKK complex or by binding IkB, p65, p50 and c-Rel, and preventing TRAF activation of IKK (Giffard et al., 2008; Ran et al., 2004; Kim et al., 2012; Kim and Yenari, 2013b). The TLR-dependent activation of microglia during stroke stimulates the release of various proinflammatory cytokines including TNF-α, IL-1α, IL-1β, IL-6, IFNs and the upregulates the expression of TNF-α receptor (TNFR) (Minami et al., 1992; Block et al., 2000; Chen et al., 2007; Luheshi et al., 2011; Sobowale et al., 2016; Lakhan et al., 2009; Lambertsen et al., 2007). The TLR activation on microglia also causes the upregulation of certain chemokines that include CCL2 or monocyte chemoattractant protein-1 (MCP-1) and CCL3 or macrophage inflammatory protein-1 alpha (MIP1-α), acting as chemoattractant for macrophages and monocytes (Cowell et al., 2002; Schilling et al., 2009). These proinflammatory cytokines lead to the development of neuroinflammation causing synthesis and release of various other proinflammatory molecules including prostaglandin (PG)-E_2, IL-6, nitric oxide (NO), IL-10 and neurotrophins (Pinteaux et al., 2002; Murray et al., 2015). These neurotrophins or neurotrophic factors exert a protective action during stroke at least in animal models but failed in their clinical application due to very small time window to execute their protective action in stroke patients (Cai et al., 2014; Wu, 2005). Thus all the clinical trials of neurotrophic factors failed till date including in stroke and other neuroinflammatory or neurodegenerative conditions (Cai et al., 2014).

5.2. TLRs in neuroinflammation associated with Alzheimer's disease (AD)

AD is a progressive neurodegenerative disorder that is characterized by the gradual onset and advancement of memory loss and other cognitive impairments in the affected patients due to the loss of progressive loss of pyramidal neurons primarily within the cerebral cortex and hippocampus (Minter et al., 2016; Okun et al., 2009b). The histopathological analysis of the brain of the affected patients shows the accumulation of extracellular amyloid β plaques comprising of amyloid β peptide (Aβ) generated from β-amyloid precursor protein (APP) and intracellular neurofibrillary tangles (NFT) containing hyper-phosphorylated microtubule-associated protein tau exerting toxic effects to neurons if not cleared by the brain macrophages called microglia (Selkoe, 2001; De-Paula et al., 2012; Mattson, 2004). Despite various mechanism involved in the pathogenesis of AD and associated memory loss, TLRs are also shown to play a crucial role in the pathogenesis of the disease and associated neuroinflammation (Walter et al., 2007). The neuroinflammation is observed at the site of Aβ plaques accumulation as indicated by the presence of increased proinflammatory cytokines along with other proinflammatory components of innate immunity due to the recognition of Aβ plaques by microglia and astrocytes expressing various innate immune receptors including TLRs (McGeer et al., 2006; Tuppo and Arias, 2005). An upregulation of TLR2, CD14, and TLR7 in mouse models of AD is observed, while in human cases of AD upregulated TLR2 and TLR4 are observed in their brain (Walter et al., 2007; Letiembre et al., 2009). However, a decreased expression of TLR9 in the brain of AD patients is observed (Chakrabarty et al., 2018). More specifically in the temporal cortex (TCX) region that is directly affected by AD, a significant upregulation of six TLR genes (1, 2, 4, 5, 6, and 8) is observed (Chakrabarty et al., 2018). While in cerebellum only TLR1, TLR4, and TLR6 are upregulated in AD patients (Chakrabarty et al., 2018).

Humans with TLR4 gene having Asp(299)Gly (D299G) missense polymorphism, where aspartic acid is replaced by glycine at amino acid 299 exhibit a decreased risk of a late-onset of AD in Italian population (Minoretti et al., 2006). This missense polymorphism in TLR4 gene attenuates the TLR4 receptor signalling and blunts the process of inflammation (impaired activation of p38 and TANK-binding kinase 1 (TBK1), activation of NF-κB, and IFN regulatory factor 3 (IRF3), and the induction of IL-8 and IFN-β mRNA) involved in the process of neuroinflammation leading to the AD-associated neurodegeneration (Figueroa et al., 2012). The D299G missense polymorphism interferes with TLR4 dimerization and assembly of intracellular docking platforms for adapter recruitment required for TLR4 signaling and its proinflammatory action (Figueroa et al., 2012; Long et al., 2014). The activation of TLR4 signaling in neurons by Aβ plaques leads to the reactive oxygen species (ROS) production and lipid peroxidation (LPO)-mediated neuronal damage (Tang et al., 2008). Along with direct neuronal damage via LPO, the apoptosis of neurons also occurs due to the activation of JNKs and p38MAPK signaling pathway downstream to TLR4 signaling (Tang et al., 2008; Tamagno et al., 2003). In addition to TLR4, the activation of TLR2 and TLR9 expressed on microglia by their corresponding ligands that are PGN and CpG-ODN also promotes the clearance of Aβ (Chen et al., 2006; Tahara et al., 2006; Iribarren et al., 2005). Whereas the phagocytic uptake of fibrillar Aβ by microglia involves both TLR2 and TLR4 and requires CD14. The mice deficient in TLR4 are defective in clearing the Aβ (Tahara et al., 2006; Reed-Geaghan et al., 2009b; Liu et al., 2005). While, APPswe/PSEN1dE9 double transgenic mice with TLR2 deficiency exhibit a delayed Aβ deposition (Richard et al., 2008). Whereas anti-TLR2 antibody treatment of microglia stimulated with LPS and Aβ increases the phagocytic uptake of Aβ via attenuation of LPS and Aβ induced activation of inflammasome (Rubio-Araiz et al., 2018). Furthermore, treatment with anti TLR2 antibody decreases the expression of 6-phosphofructo-2-kinase/fructose-2,6 biphosphatase (PFKFB)3 and thus decreases the increased glycolysis in microglia treated with LPS and Aβ. However, an increase in oxidative phosphorylation (OXPHOS) in microglia was observed upon treatment with anti-TLR2 antibody (Rubio-Araiz et al., 2018). Thus, the inhibition of TLR2 activity in microglia during AD may enhance the phagocytosis of Aβ due to the inhibition of inflammasome activity, glycolysis and an upregulation of OXPHOS. The most recent study has shown that the adeno-associated virus (AAV)-mediated expression of human TLR5 ectodomain called soluble TLR5 (sTLR5) alone or fused to human IgG4 Fc (sTLR5Fc) leads to the efficient attenuation of Aβ accumulation in a mouse model of AD (Chakrabarty et al., 2018). The sTLR5Fc binds to the oligomeric and fibrillar Aβ with high affinity to form a complex that blocks the Aβ toxicity in neurons. The oligomeric and fibrillar Aβ do not activate TLR5 signaling by themselves but only modulate the TLR5 signaling activated by bacterial flagellin.

5.3. TLRs in Parkinson's disease (PD) and associated neuroinflammation

PD is another neurodegenerative disorder characterized by the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SN) region of the brain leading to the development of both motor (i.e. tremor, rigidity, bradykinesia and gait imbalance) and non-motor (i.e. executive dysfunction deficits, sleep disturbances and depression) symptoms (Fahn, 2003). The loss of DA neurons during PD is accompanied by the accumulation of cytoplasmic eosinophilic inclusions (Lewy bodies) comprising of alpha (α) synuclein in these neurons that are also known as neuromelanin-containing monoamine neurons (Fahn, 2003; Spillantini et al., 1997). Neuroinflammation also comprises an important role in the pathogenesis of PD (Gelders et al., 2018). For example, a higher expression of certain chemokines and their cognate receptors (i.e. CXCL12 and its receptor CXCR4) along with different proinflammatory and anti-inflammatory cytokines including IL-1β, IL-6, IL-2, TNF-α, and TGF-β, interferons (IFNs) and ROS are increased in SN of the PD patients (Shimoji et al., 2009; Mogi et al., 1996; Sawada et al., 2006; Hwang, 2013; Puspita et al., 2017). However, the detailed

mechanism of neuroinflammation involved in the pathogenesis of PD is beyond the scope of this article and is described somewhere else (Gelders et al., 2018; Hirsch and Hunot, 2009; Hirsch et al., 2012).

Studies have shown an upregulation of TLR 1, 2, 3, 4, and 8 in SN of the brains of PD patients regulates the function of microglia during the induction of neuroinflammation (Watson et al., 2012; McCabe et al., 2017; Beraud and Maguire-Zeiss, 2012). Further studies have indicated the upregulation of TLR4 and TLR2 in both blood and brain of patients suffering with PD and mice subjected to PD as well (Drouin-Ouellet et al., 2014). However, TLR4 and TLR2 responses are affected differently during PD pathogenesis depending on the age of the patients (Sobrinho et al., 2018). For example, the upregulation and activation of TLR4 in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of the PD is shown to be associated with the increased death of neurons due to the activation of microglia in SN (Noelker et al., 2013). TLR2 is found to be overexpressed in microglia and neurons, but its level of expression is higher in neurons comparing to microglia (Dzamko et al., 2017). However, the expression of TLR2 in neurons is highly correlated with the α-synuclein levels in the Lewy bodies. Under *in vitro* conditions simulating PD pathogenesis the stimulation of TLR2 of neurons generates inflammatory response via releasing various cytokines, chemokines and ROS (Dzamko et al., 2017). Furthermore, an activation of neuronal TLR2 also increases the accumulation of endogenous α-synuclein that is associated with autophagy/lysosomal pathway marker p62. Thus TLR2 plays a very important role in the generation of neuroinflammation involved in the pathogenesis of PD. However, TLR2 expression in microglia controls the neuroinflammation during PD via recognizing α-synuclein during the early stage of the pathogenesis of PD called incidental Lewy Body disease (iLBD) (Doorn et al., 2014). However studies have also indicated a correlation between TLR2 (TLR2 -196 to -174 del polymorphism) and TLR9 (rs352140) gene polymorphism with the susceptibility to PD in Greek and Chinese Han population (Female) (Kalinderi et al., 2013; Zhu et al., 2016). Thus studying TLRs during PD may provide novel immunomodulatory or immunotherapeutic approach to target neuroinflammation during PD.

6. TLRs during neuroinflammation associated with multiple sclerosis (MS), an immune-mediated disease of CNS

MS is an autoimmune disease of the CNS which involves the infiltration of immune cells into the perivascular spaces causing demyelination of neurons, diffuse activation of microglia, and damaging oligodendrocytes at focal areas of brain and spinal cord (SC) (Miranda-Hernandez and Baxter, 2013). The clinical symptoms involve weakness, numbness, decreased muscle coordination, problem in speech, vision, and bladder control that create a substantial health-care problem at all levels including individual, family and community levels (Miranda-Hernandez and Baxter, 2013; Ontaneda et al., 2017). The classical pathological hallmark of MS involves the presence of focal white matter demyelinating lesions but pathological changes can also be seen in otherwise normal appearing white matter along with the grey matter of the CNS as indicated by the presence of focal grey matter lesion and grey matter atrophy (Filippi et al., 2012; Di Filippo et al., 2018).

TLRs also play a crucial role in the pathogenesis of MS. For example, TLR1 expression downregulates in peripheral blood monocytes (PBMCs) of MS patients. However, the level TLR2 on PBMCs, cerebrospinal fluid (CSF) mononuclear cells and in demyelinating lesions of MS patients upregulates (Sloane et al., 2010). Several TLR2 ligands including PGNs, and HMGB1 have been seen in the brain and CSF of MS patients that can activate TLR2 signaling in neurons and microglia to increase the levels of IL-1α, IL-6, IL-12, TNF-α, and INF-γ (Schrijver et al., 2001; Andersson et al., 2008). The accumulation of hyaluronan in MS lesion is also reported that via activating TLR2 signaling prevents the process of remyelination via blocking the maturation of oligodendrocyte precursor or progenitor cells (OPCs) maturation into myelin producing oligodendrocytes (Sloane et al., 2010; Back et al., 2005). While, TLR3 signaling through its endogenous ligand stathmin (a microtubule regulatory protein) in brain is shown to be protective via inducing the production of neuroprotective factors (Bsibsi et al., 2010). TLR4 is also shown to be upregulated in the lesions of MS patients (Andersson et al., 2008; Gooshe et al., 2014). The increased levels of plasmacytoid dendritic cells (pDCs) expressing higher levels of TLR9 are present in leptomeninges and in the demyelinating lesions of patients with MS (Miranda-Hernandez and Baxter, 2013). The stimulation of TLR9 signaling during MS causes an enhanced secretion of type 1 IFNs and IFN-α, while the treatment with IFN-β inhibits the TLR9 processing and decreases the levels of IFN-α, IL-6, and TNF-α (Balashov et al., 2010; Hundeshagen et al., 2012). The treatment with IFN-β also upregulates the expression of TLR3, TLR7, and MyD88 in PBMCs and pDCs isolated from MS patients (Derkow et al., 2013).

Similar to human studies the experimental model of MS called experimental allergic/autoimmune encephalomyelitis (EAE) also shows the upregulation of TLR1, TLR2, TLR4, TLR6, TLR7, TLR8, and TLR9 in the early stages (Gooshe et al., 2014; Prinz et al., 2006). The TLR8 is shown to be involved in axonal damage in mouse model of MS called EAE via increasing the neutrophil and leukocyte infiltration and this signaling pathway remains active even after the disappearance of focal inflammatory infiltrates (Gooshe et al., 2014; Soulika et al., 2009). However another study has shown the decreased expression of TLR8 in PBMCs of MS patients and showed the decreased production of IL-12B transcripts and protein (Johnson et al., 2013). Studies have also indicated that the activation of My-D88-independent or TRIF-dependent TLR signaling suppresses the EAE and My-D88$^{-/-}$ mice resistant to develop active EAE (Prinz et al., 2006; Racke and Drew, 2009). Thus, TLRs are important in the regulation of immunopathogenesis of neuroinflammation of observed during MS.

7. Conclusion

TLRs are very important PRRs expressed by immune cells involved in the recognition of exogenous and endogenous molecules capable of eliciting a potent immune response. CNS is also not immune privileged due to presence of immune cells including microglia and other immune cell. These immune cells play a crucial role in the generation of neuroinflammation involved in the immunopathogenesis of different CNS diseases varying from infectious brain diseases (i.e. meningitis) to sterile inflammatory damage to the brain including stroke, neurodegenerative diseases, and autoimmune diseases of the brain. Thus TLRs should be studied in detail in context with neuroinflammation to targeting these PRRs specifically for various immunomodulatory and immunotherapeutic approaches. This is because TLR-based adjuvants are used in immunotherapeutics against different cancers and infectious diseases. For example, the selective disruption of TLR2-MyD88 interaction by a peptide corresponding to the TLR2-interacting domain of MyD88 (TIDM) that binds specifically to the BB loop of TLR2 has inhibited the inflammation and AD pathology along with inhibiting the neuroinflammation observed during EAE (Rangasamy et al., 2018). However targeting of TLRs during neuroinflammation developed due to different causes including different pathogens (viruses and bacteria), neurodegeneration, or sterile neuroinflammation should be cautioned. Future studies in the direction will help us to design other novel molecules targeting different TLR-signaling pathways to limit the neuroinflammation observed during both sterile and infectious neuroinflammatory conditions including neurodegeneration.

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