Microglial cells are non-neuronal cells which serve as the first line of defence against various injuries and insults in the central nervous system (CNS). They act as sentinels that constantly patrol the surrounding parenchyma through their ramified processes in the CNS. In response to any pathological insult, microglia become activated, undergo proliferation, migrate to the site of injury or infection, and release chemokines and cytokines followed by the phagocytosis of dead cells and debris.

In the last few decades, microglia have been extensively studied and associated with brain infections and inflammation, though the entirety of their roles in a normal healthy brain still remains elusive. Intriguingly, several studies have suggested that microglial cells also aid in shaping brain development and maintaining homeostasis in a healthy brain. Through in vivo time-lapse imaging studies, microglia were ascertained to be highly dynamic even in their resting state in a healthy brain, frequently interacting with synapses in the brain parenchyma (Nimmerjahn et al., 2005; Wake et al., 2009). Visual sensory experience and/or neuronal activity appeared to majorly alter these dynamics between microglial processes and neuronal synapses, attributing to their vital roles in regulating experience-dependent synaptic plasticity.

Normal brain development involves neurogenesis, neuronal differentiation and pathfinding, and synaptogenesis which is characterized by overproduction of synapses followed by a phase of synaptic pruning. The electron microscopic imaging studies in the hippocampus and the dorsal lateral geniculate nucleus during early postnatal development have established that microglia function as the key regulator of synaptic pruning (Paolicelli et al., 2011) which is an essential mechanism for eliminating weaker synapses to ensure stronger synaptic transmission and proper neuronal network. Several microglial immune-related pathways such as fractalkine chemokine (CX3CL1/CX3CR1) signaling and complement related but distinct genes which are CAMK2A, CAMK2B, Camk2c, and Camk2d have been implicated in targeted engulfment of weaker synapses through phagocytosis.

Intriguingly, microglia have been also found to be capable of regulating synaptic plasticity in the adult brain. Acute application of CX3CL1 over hippocampal slices has been shown to induce long-term depression in synaptic transmission through its microglial counterpart, CX3CR1. Further, CX3CR1 regulates synaptic plasticity by modulating the inflammatory mediators released by microglia. Deletion or reduction of CX3CR1 in mice was reported to show impair cognitive functions and long-term potentiation (LTP) via increasing the levels of inflammatory cytokine interleukin, interleukin-1β. An increased level of tumor necrosis factor α (TNFα) in response to CNS inflammation has also been associated with reduced LTP.

In addition to pruning and regulating the synaptic plasticity, microglial TNFα also modulate the synaptic strength through synaptic scaling, a mechanism to maintain homeostatic activity. Overall, such emerging pieces of evidence affirm that microglial-mediated immune signaling is critical for shaping neural networks and modulating synaptic plasticity, essential for normal brain growth and development, paving the path for a new subfield of microglial research. Interestingly, apart from immune molecules, recent study has demonstrated the role of microglial brain-derived neurotrophic factor (BDNF) on synaptic plasticity. The young and adult mice deficient in microglial BDNF also displayed impaired motor-learning based synapse formation and behavioral performance, suggesting a vital role of microglial BDNF in modulating synaptic plasticity. This study establishes the key role of microglia in learning-dependent synaptic remodeling in a healthy mature brain. However, the study opened up the avenue for further research into investigating the signaling pathways regulating BDNF release from microglia for synaptic plasticity (Parkhurst et al., 2013).

Recent studies by our group demonstrated the crucial role of microglial phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)-BDNF pathway in LTP, a process that forms the cellular basis for learning and memory (Saw et al., 2019). Though the neuronal PI3K/AKT pathway has been implicated in synaptic plasticity via BDNF, the microglial PI3K/AKT pathway has been primarily shown to be essential for the inflammatory response of microglia. Our studies confirmed that the microglial PI3K/AKT-BDNF pathway is also essential for LTP since, 1) selective ablation of microglia in hippocampal slices failed to evoke neuronal LTP; and 2) addition of PI3K or BDNF was able to rescue the neuronal LTP, indicating that microglia play a unique role which is independent but crucial in synaptic plasticity. This study further explored the epigenetic mechanisms such as histone modification and sumoylation, a posttranslational modification regulating the microglial PI3K/AKT pathway which modulates LTP via BDNF. Altogether, this study confirmed that microglial PI3K/AKT-BDNF pathway regulates LTP in the healthy brain.

More recently, a miRNA microarray study performed on activated primary rat microglial cells revealed that the miRNA-142 family which putatively target the 3’UTR of calcium/calmodulin-dependent protein kinase 2a (Camk2a) gene, was significantly upregulated in activated microglia (Gupta et al., 2020). CAMK2A is a subunit of CAMK2, a ubiquitous calcium-activated serine/threonine protein kinase, which is abundantly present in the brain. Over the years, several lines of evidence have demonstrated CAMK2 as a key protein, contributing to LTP and synaptic plasticity. CAMK2 acts as a holoenzyme, composed of 12 subunit proteins encoded by four very closely related but distinct genes which are Camk2a, Camk2b, Camk2c, and Camk2d, encoding CAMK2A, CAMK2B, CAMK2C, and CAMK2D respectively. Among the four, CAMK2A and CAMK2B are expressed predominantly in the nervous system with CAMK2A being expressed 3–4 times more than CAMK2B. Several studies using Camk2a transgenic/mutant mice have shown that CAMK2A plays an important role in spatial and contextual learning and memory consolidation (Achterberg et al., 2014). It has been previously demonstrated that CAMK2A is involved in learning and memory by activating phosphorylation of cAMP-response element binding protein (CREB), a transcription factor that regulates its target protein, BDNF. A similar CAMK2A-CREB-BDNF signaling pathway in microglia was found to be functional in microglia and has shown to be regulated by miRNAs. Among the many miRNAs tested in activated microglia using microarray, miR-142-3p, which was predicted to target Camk2a gene was found to be significantly upregulated in activated microglia. The inverse relationship between the miR-142-3p and Camk2a mRNA expression was confirmed by loss-of-function and gain-of-function studies. Further, the shRNA-mediated Camk2a knockdown resulted in a significant decrease in the expression of the CAMK2A-CREB-BDNF signaling pathway, confirming the miRNA-mediated regulation of the pathway in microglia. Overall, this study revealed that upregulation of miR-142-3p in activated microglia in response to pathological conditions perturbs the CAMK2A-CREB-BDNF pathway involved in learning and memory. This suggests that microglia known to be involved in phagocytosis may also aid in neuronal functions such as synaptic plasticity during neurodegenerative disease conditions.

The past few decades have observed substantial progress in the understanding of functions of microglia which have been shown to be key players in neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease (Streit et al., 2009; Katsumoto et al., 2018), Huntington’s disease and amyotrophic lateral sclerosis (Sapp et al., 2001; Franciosi et al., 2012; Simmons et al., 2007). In uncovering therapeutic approaches for neurodegenerative disease and memory decline, the main focus of research tends to be in the modulation of neuronal pathways and signaling, while glial cells, recently shown to be vastly important and influential, seem to be side-lined.

The findings from our recent studies indicate that exposure to inflammatory challenges, microglia exhibit impaired signaling pathways (PI3K/CAMK2A-BDNF) dedicated towards synaptic plasticity, learning and memory functions, suggesting their roles in neuroinflammation associated cognitive impairment. Since microglia have been shown to undergo cellular senescence and dystrophy in the aging brain, it can be further speculated that given the importance of microglia in maintaining synaptic plasticity, dystrophic A paradigm shift: emerging roles of microglia, a non-neuronal cell, in learning and memory

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modifying the microglial functions can be strategies focused towards manipulating or holding clinical relevance. Devising treatment of microglial cells towards cognitive functions further insight into the significant contribution with neurodegenerative disorders like future investigation will be to observe the contribution of microglial CAMK2A and by generating a microglial specific CRISPR/Cas9 based functional miRNA knockout mice by which we may be able to modulate synaptic transmission and plasticity via microglial secretion of BDNF, which has been shown to influence neuronal synaptic plasticity. In this regard, an in vivo validation of the crucial role of micro RNA-mediated regulation of PI3K/CAMK2A-BDNF pathway by which we may be able to modulate synaptic transmission and plasticity via microglial secretion of BDNF, which has been shown to influence neuronal synaptic plasticity. In order to comply with the limited space, we apologize for not citing most of the work presented here done by our colleagues in the field. The right-panel of the image represents upregulation of microglial BDNF eventually culminates in the increased neuronal LTP, suggesting an upregulation of microglial BDNF eventually culminates in the increased neuronal LTP, thereby compromising the cognitive functions in response to neurological insults/injuries. Red arrow indicates upregulation and green arrow indicates downregulation. AKT: Protein kinase B; BDNF: brain-derived neurotrophic factor; Camk2a: calcium/calmodulin-dependent protein kinase 2a; CREB: CAMP-response element binding protein; LPS: lipopolysaccharide; LTP: long-term potentiation; PI3K: phosphatidylinositol 3-kinase. Adapted from Saw et al. (2019) and Gupta et al. (2020).

microglia may contribute to age related cognitive impairment which could be mainly caused by neurodegeneration. Our study has also elucidated the epigenetic and post-translational mechanisms that regulate PI3K/ CAMK2A-BDNF pathway in microglia. By being able to regulate microglial PI3K/CAMK2A-BDNF pathway both epigenetically and posttranslationally, this opens an avenue into ways by which we may be able to modulate synaptic transmission and plasticity via microglial secretion of BDNF, which has been shown to influence neuronal synaptic plasticity. In order to comply with the limited space, we apologize for not citing most of the work presented here done by our colleagues in the field.

In conclusion, studying microglia-mediated chronic neuroinflammation in neurodegenerative diseases which could cause impaired synaptic plasticity and memory deficits hold clinical relevance. Devising treatment strategies focused towards manipulating or modifying the microglial functions can be a promising approach in mitigating cognitive decline. Overall, these studies discussed above appear to shift the researchers’ several decades of cognitive paradigm that microglia function only as the resident immune cells and respond to pathological insults in the CNS and unveiled the indispensable role of microglia in neuronal LTP and synaptic plasticity. The results of this study further suggest that targeting microglial signaling pathways may be an effective alternate or complementary approach in neurodegenerative disease therapies with the potential of modulating synaptic transmission and plasticity. However, further in vivo studies possibly with neurodegenerative disease animal models should be carried out to determine the full extent of microglial contributions to LTP and synaptic plasticity in neurodegenerative diseases.

In conclusion, studying microglia-mediated chronic neuroinflammation in neurodegenerative diseases which could cause impaired synaptic plasticity and memory deficits hold clinical relevance. Devising treatment strategies focused towards manipulating or modifying the microglial functions can be a promising approach in mitigating cognitive decline. Overall, these studies discussed above appear to shift the researchers’ several decades of cognitive paradigm that microglia function only as the resident immune cells and respond to pathological insults in the CNS and unveiled the indispensable role of microglia in neuronal LTP and synaptic plasticity. The results of this study further suggest that targeting microglial signaling pathways may be an effective alternate or complementary approach in neurodegenerative disease therapies with the potential of modulating synaptic transmission and plasticity. However, further in vivo studies possibly with neurodegenerative disease animal models should be carried out to determine the full extent of microglial contributions to LTP and synaptic plasticity in neurodegenerative diseases.