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Editorial

Chronic Neuroinflammatory Cycle: Potential target to halt the Progression of Neurological Disorders

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Neurological and neurodegenerative diseases have become a major social and economic burden worldwide with more individuals predicted to be affected in coming decade. Therefore, understanding the neuropathological mechanism and identifying the promising target for intervention has become an active area of research in neurodegeneration. The chronic neuroinflammation has considered to be fundamental mechanism causing progressive loss of dopaminergic neurons as observed in clinical course of various neurodegenerative diseases. Microglial proliferation and activation are the hallmarks of several neurological disorders. Being the primary immune cells in the brain, microglia rapidly respond to any neuronal insults by proliferation and secretion of pro-inflammatory cytokines. Animal models of several neurodegenerative diseases as well as patients with neurological diseases have shown an increased number of activated microglia in brain along with elevated levels of pro-inflammatory cytokines (Whitton, 2010). Thus, neuroinflammation may be considered to play essential role in the pathogenesis of neurological and neurodegenerative diseases (Zhang et al., 2017). Colony stimulating factor receptor 1 (CSF-1R) signaling plays an instrumental role in regulating the proliferation and activation of microglial cells; as such, CSF-1R is considered a vital target in halting the progression of neurodegenerative conditions (Hume and MacDonald, 2012). The importance of CSF-1R in microglial development can by understood by the fact that mice lacking CSF-1R are devoid of microglia and die before reaching adulthood. CSF-1R exerts its effects on astrocyte functions mainly by regulating targeting astrocyte-microglia communication [1, 3].

CSF-1R signaling leads to an increased production of neuro-inflammatory cytokines in cultured human and mouse microglia (Walker et al., 2017). Recently, regulation of microglial proliferation and microglial ablation has become an active area of research owing to its potential in halting the progression of neurological diseases via reducing the neuro-inflammatory response. However, CSF-1R expression is not just restricted to microglial cells in CNS since CSF-1R has been found to express by other neuronal and non-neuronal cells in human brain. This may limit the applicability of CSF-1R pharmacological inhibitors without a complete understanding of CSF-1R signaling in physiological and pathological conditions.

CSF-1R inhibitors have emerged as promising drug candidates to halt the progression of neurodegenerative diseases in recent years. In 2019, PLX3397 become the first FDA-approved CSF-1R inhibitor as Turalio after undergoing extensive clinical trials for solid tumor and a Phase III trial for tenosynovial giant cell tumors expressing CSF-1 (Lamb, 2019; Tap et al., 2019)

CSF-1R inhibitors have shown potential ability in halting the progression of various neurological and neurodegenerative disease via depleting the microglial population and interrupting the neurotoxic neuroinflammatory cycle. However, the effect of CSF-1R inhibitors on related kinases should be determined to minimize the non-specific side effects. The dose and duration of CSF-1R inhibitor treatment is an important factor that need to be optimized. This could help to understand the variation observed in experimental models of neurodegenerative diseases. Also, it would be essential to investigate whether the optimized treatment paradigm would be applicable

for all neurodegenerative conditions, or it will differ for each neurodegenerative disease. Additionally, the impact of microglia depletion on function of astrocytes and neuronal cells may need to be investigated [4, 6].

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