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Recent advances in the mechanisms of neuroinflammation and their roles in neurodegeneration

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ABSTRACT

Neuroinflammation is associated with the pathogenesis of many neurological disorders including Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis and Huntington disease. Current studies in this area have advanced the mechanism of neuroinflammation and its role in neurodegeneration. Studies from epidemiologic, clinical and animal models also contributed in the various new mechanisms of neuroinflammation. In this line, activation of monocytes is an important emerging mechanism that has a, profound role in neuroinflammation and neurodegeneration. Ion channels, matrix metalloproteases and microRNAs are also found to be the key players in the pathogenesis of neuroinflammation. In particular, microRNA-32 regulates microglia-mediated neuroinflammation and thus neurodegeneration. Notably, some important studies describe the role of Th17 cells in neuroinflammation, but, very little knowledge is available about their mechanism of action. Particularly, the role of autophagy gets emphasized, which plays a very critical role in protein aggregation and neurodegeneration. In this review, we highlight and discuss the mechanisms of these mediators of inflammation by which they contribute to the disease progression. In conclusion, we focus on the various newer molecular mechanisms that are associated with the basic understanding of neuroinflammation in neurodegeneration.

1. Introduction

It is widely accepted that, neuroinflammation (the inflammatory process in the brain) plays a key role in the pathogenesis of the various neurological disorders including Parkinson's disease (PD) and Alzheimer's disease (AD) (Aid and Bosetti, 2011; Aktas et al., 2007). Neuroinflammation can be triggered by various biological mechanisms including oxidative stress and glial reactions (Agostinho et al., 2010; Alcendor et al., 2012; Allaman et al., 2011; Niranjan, 2014). The mediators of neuroinflammation such as cytokines and prostaglandins play an important role in the development of neurodegenerative diseases (Agrawal and Yong, 2011; Sekeljic et al., 2012). Despite a large amount of research about the mechanism of neuroinflammation, some facts still remain unexplored (Abdul Muneer et al., 2012; Aktas et al., 2007; Drake et al., 2011). Neuroinflammation was previously understood as a local tissue response without any or with very limited involvement of the peripheral immune system, but now recent data support that, it gets influenced by a number of peripheral and other factors (Adalid-Peralta et al., 2012; Adzemovic et al., 2012; Machado et al., 2011a, 2011b). Nowadays, tremendous new findings have further advanced the mechanism of neuroinflammation associated with neurodegenerative disorders. Notably, some new important concepts get explored in this area and need detailed descriptions (Alcendor et al., 2012; Alexander and Popovich, 2009). Therefore, the recent advancements in the mechanisms of neuroinflammation need to be extensively reviewed in more detail to understand the pathogenesis of neurodegenerative disorders.

The role of monocytes in the development of neuroinflammation is an entirely new concept that demands the attention of scientists working in this area (Harms and Standaert, 2014; Williams et al., 2012). Similarly, it is vital to understand the role of matrix metalloproteinases (MMPs) in neuroinflammation (Nuttall et al., 2007; Vos et al., 2000). Other emerging mechanisms in the process of neuroinflammation include, ion channels in autoimmune neuroinflammation and micro-RNAs, as novel regulators of neuroinflammation (Fernandez-Ruiz et al., 2013; Omran et al., 2012). Similarly, epigenetics is also an

Abbreviations: ASIC, acid-sensing ion channels; ALS, amyotrophic lateral sclerosis; MMPs, matrix metalloproteases; PD, Parkinson's disease; AD, Alzheimer's Disease; ROS, reactive oxygen species; RNS, reactive nitrogen species; TNF-α, tumor necrosis factor-α; NF-kB, nuclear factor kappa -B; COX-2, cyclooxygenase-2; GFAP, glial fibrillary acidic protein; iNOS, inducible nitric oxide synthase; IL-1α, interleukin-1α; IL-1β, interleukin-1β; IL-6, interleukin-6; P-p38 MAPK, phosphorylated p38 mitogen activated protein kinase; NO, nitrite; CNS, central nervous system; LPS, lipopolysaccharide; Th, T helper cells; NLRP3, NLR family pyrin domain containing-3; mTOR, mammalian target of rapamycin; Tregs, T regulatory cells; TNFR-AF3, tumor necrosis factor receptor-associated factor −3

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important area that needs to be explored extensively (Fujimoto et al., 2011; Kiguchi et al., 2012). The role of T cells was speculated in the pathogenesis of neuroinflammation, which has now been more strongly confirmed by recent evidences (Sajic et al., 2012). Specifically, the Th-17 cells get involved in the various inflammatory processes in the brain leading to neurodegeneration (Saresella et al., 2011; Segal, 2010; Yao et al., 2010). The T-regulatory cells are also now gaining much attention for their role in regulating other immune cells and thus the neuroinflammatory process. This review focuses on the above mentioned areas and their possible relation to neurodegenerative events in different neurological disorders including Parkinson's disease and Alzheimer's disease (Downes and Crack, 2010).

2. The role of monocytes in neuroinflammation

Latest research described the involvement of monocytes in the initiation of brain inflammation, suggesting their pivotal role in the mechanisms of neuroinflammation (Harms and Standaert, 2014; Jones et al., 2018; Saresella et al.,). It is now known that, degenerative events inside the brain trigger initial peripheral immune cells recruitment in the forebrain of mice (Scheld et al., 2016). Study, on the *in vivo* model of PD revealed that, peripheral blood monocytes enter the brain and mediate neurodegeneration (Harms et al., 2018; Hui et al., 2016). The infiltration of peripheral blood monocytes into the brain was also shown in the pathology of stroke (Williams et al., 2012). Monocytes also secrete some anti-neurodegenerative mediators in patients with multiple sclerosis (Molnarfi et al., 2012). This fact was further supported by a study showing that, depletion of monocytes enhances neurodegeneration in a model of PD (Cote et al., 2015). It was shown that, CXCL12 induces monocytes to stimulate endothelial cells, thus facilitating lymphocyte transmigration across an in vitro blood-brain barrier, showing the role of monocytes in the deployment of immune cells to brain (Man et al., 2012). Another study also demonstrated that brain leucocytes infiltration is initiated by peripheral inflammation (Schmitt et al., 2012). The circulating Ly-6C + myeloid precursors migrate to the central nervous system (CNS) and play a pathogenic role in patients with autoimmune demyelinating disease (King et al., 2009; Vojdani and Lambert, 2011). Monocytes contribute in the process of phagocytic activity of the brain and engulf some unwanted proteins (Hendriks et al., 2005; Kadiu et al., 2005). They also participate in amyloid beta clearance, which is further potentiated by the herbal drug curcumin (Cashman et al., 2012). In a mice model of stroke, it was shown that, monocytes derived macrophages are responsible for neuroprotection (Wattananit et al., 2016). A similar study also showed that, monocytes in facts are protective and provide bioactive substances to the brain cells (Bottger et al., 2010). Some mediators of inflammation such as saturated fatty acid induces human monocytes cells to become toxic towards neuronal cells (Little et al.,). In evidence, infiltrating monocytes trigger experimental autoimmune encephalitis progression, but they do not contribute to the resident microglia pool (Ajami et al., 2011). Constitutive activity of NF-kappa B derived pathogenesis of monocytes and macrophages during autoimmune neuroinflammation (Ellrichmann et al., ; Karlmark et al., 2012). Interestingly, microRNAs-7 activated monocytes in a model of PD (Zhou et al., 2016). These above mentioned mechanisms show a clear involvement of monocytes in the process of neuroinflammation which subsequently cause neurodegeneration.

3. The role of matrix metalloproteinases in neuroinflammation

The matrix metalloproteinase (MMPs) are widely known to play a critical role in the initiation and progression of neuroinflammation and related disorders (Abdul Muneer et al., 2012; Liu et al., 2013; Vafadari et al., 2016). The activation of MMPs may cause blood-brain barrier injury which is a novel mechanism of neurodegeneration (Haorah et al., 2008; Niranjan and Thakur, 2017). MMPs are also associated with increased blood-brain barrier opening in vascular cognitive impairment (Candelario-Jalil et al., 2011). Thus MMPs, which are released by microglia cells might control the extra cellular matrix proteins (Liu et al., 2013). The inhibition of MMP-3 and MMP-9 suppressed the expression of proinflammatory cytokines and inducible nitric oxide synthase (iNOS) in LPS-induced microglia, supporting the role of MMPs in the neuroinflammation (Woo et al., 2008). In fact, MMPs are involved in the second step of neuroinflammation (Brkic et al., 2015; Florczak-Rzepka et al., 2012; Liu et al., 2013). Notably, matrix metalloprotease-9 released by the monocytes increases as a function of differentiation and is involved in neuroinflammation mediated neurodegeneration (Vos et al., 2000). MMPs are also reported to cause spontaneous intra-cerebral hemorrhage in humans (Florczak-Rzepka et al., 2012). They play a role in the activation of peripheral immune cells and mediate neuroinflammation (Schiffmann et al., 2014). SB-3CT, an inhibitor of MMP-9, ameliorates impairments in behavior and improves hippocampus loss in a rat model of traumatic brain injury (Jia et al., 2014). Another important study described that MMP-9 is required for the migration of astrocytes in patients with neuroinflammatory disorder (Yang et al., 2015). In this study functionally active IL-1β induced MMP-9 expression, which in turn promoted migration of astrocytes (Yang et al., 2015). The over expression pattern of MMP-14 correlates with the neurodegenerative process in familial amyloidotic polyneuropathy (Martins et al., 2017). MMP-3 (also known as an endogenous neuronal activator of microglia) up regulated cytokine release from microglia (Connolly et al., 2016). Similarly the role of matrix metalloproteinase-2 in the streptozotocin-induced model of dementia was described (Ali et al., 2014). DP-b99, another inhibitor of matrix metalloproteinase has shown its role in the regulation of neuronal plasticity (Yeghiazaryan et al., 2014). Over expression of MAP-2 also plays an important role in the formation of microtubules in a rat model of epilepsy (Tang et al., 2014). Thus, it can be said, that matrix metalloproteases are extensively involved in the pathogenesis of neuroinflammation.

4. Role of ion channels in the process of neuroinflammation

Ion channels are a very important aspect in the process of neuroinflammation and they regulate a variety of functions associated with neuronal damage (Kozela et al., 2011; Kumar et al., 2016). Owing to ubiquitous expression of ion channels across all tissues and their essential role for cellular functions, targeting of ion channels largely opens up the possibility of modulation of immunological and neuroinflammatory mechanisms (Hajieva et al., 2018; Volpi et al., 2012). The new advancement in the ion channel research paved the way of their involvement in the process of neuroinflammation (Niranjan, 2013; Skaper, 2011). Recently, the role of pannexin and connexin membrane channel proteins in the process of neuroinflammation has been emphasized (Giaume et al., 2017). Similarly, acid-sensing ion channels (ASICs) also play an important role in the process of neuroinflammation associated neurodegeneration (Ortega-Ramirez et al., 2017; Quintana et al., 2015). In a study it was shown that, acid-sensing ion channels modify α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic-acid receptors functions in ischemic conditions (Quintana et al., 2015).

The voltage gated ion channels are now known to be responsible for the activation of microglial cells (Hossain et al., 2017). Cannabinoids ion channels are most important and widely studied for neurodegenerative disorders (Fernandez-Ruiz et al., 2013). Cannabinoids also attenuate the effects of aging during neuroinflammation and neurogenesis (Marchalant et al., 2009). The alpha7 nicotinic acetylcholine receptors channel on microglial cells are involved in the C/IP3 pathway and modulate the cell activation in the process of neuroinflammation (Suzuki et al., 2006). Interestingly, the chemokine interleukin-8 (IL-8) acutely reduces $Ca^{(2+)}$ currents in identified cholinergic septal neurons expressing CXCR1 and CXCR2 receptor mRNAs (Puma et al., 2001). It was found that, ion levels are associated with increased expression of MMPs (Mairuae et al., 2011). Chronic intra-cerebroventricluar