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REVIEW

THE ROLE OF AUTOPHAGY IN MODULATION OF NEUROINFLAMMATION IN MICROGLIA

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Abstract—Microglia have multiple functions in regulating homeostasis in the central nervous system (CNS), and microglial inflammation is thought to play a role in the etiology of the neurodegenerative diseases. When endogenous or exogenous stimuli trigger disorders in microenvironmental homeostasis in CNS, microglia critically determine the fate of other neural cells. Recently, it was reported that autophagy might influence inflammation and activation of microglia. Though the interaction between autophagy and macrophages has been reported and reviewed in length, the role of autophagy in microglia has yet to be reviewed. Herein, we will highlight recent advances on the emerging role of autophagy in microglia, focusing on the regulation of autophagy during microglial inflammation, and the possible mechanism involved. **© 2016 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: microglia, inflammation, autophagy.

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INTRODUCTION

With substantial and novel discoveries on the function of microglia in recent years, their role in the central nervous system (CNS) seems much more complex than expected. Microglial cells are the resident immune cells of the brain as classified by Pío del Río Hortega in 1919. They comprise 10–15% of all the CNS cells and present a branched, ramified morphology. Hortega noted that microglia existed in different states, including resting and activated states at least, with a capacity for phagocytosis. However, the function of microglia in the CNS is not limited to phagocytosis. Recent studies utilizing *in vivo* two-photon microscopy have established that microglia are constantly in motion, surveying their microenvironment and communicating with neurons and other glia via motile processes and protrusions (Davalos et al., 2005; Ladeby et al., 2005; Nimmerjahn et al., 2005). Under physical conditions, microglia functions include phagocytosis of synaptic structures, active remodeling of presynaptic environment, and the release of soluble factors in the mature and aging brains (Tremblay et al., 2011). Microglia also act as critical mediators in the modulation of neurogenesis (Cunningham et al., 2013; Gemma and Bachstetter, 2013; Kohman and Rhodes,

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Abbreviations: 3-MA, 3-methyladenine; ACAT1, Acyl-CoA:cholesterol acyltransferase 1; AD, Alzheimer's disease; Atg, autophagy-related protein; AVs, autophagic vesicles; Aβ, amyloid beta; BCAS, bilateral common carotid artery stenosis; CB2R, cannabinoid receptor 2; CMA, chaperone-mediated autophagy; CNS, central nervous system; ERK, extracellular signal-regulated kinase; ES, electric stimulation; HANDs, HIV-1-associated neurocognitive disorders; HIF-1α, hypoxia-inducible factor 1 alpha; ICH, intracerebral hemorrhage; IL-1β, interleukin-1β; LAMP2A, lysosomal-associated membrane protein type 2A; LPS, lipopolysaccharide; LRRK2, Leucine rich repeat kinase 2; M-CSFR, macrophage colony stimulating factor receptor; NF-κB, nuclear factor κB; PD, Parkinson's disease; PGN, peptidoglycan; pMCAO, permanent middle cerebral artery occlusion; PUMA, p53 up-regulated modulator of apoptosis; SCI, spinal cord injury; shRNA, small hairpin RNA; smTN, submedial thalamus nucleus; Tat, HIV-1 *trans* activator of transcription; TBI, traumatic brain injury; TLR2, toll-like receptor 2; TNF-α, tumor necrosis factor-α; UPS, ubiquitin-proteasomal system.

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2013; Su et al., 2014). When pathologically insulted, either via endogenous or exogenous stimulations, microglia can transform to an ‘‘activated” state. Analogous to macrophages, activated microglia modify their shapes to enable their phagocytic functions and induce inflammatory response, releasing multiple cytokines and mediators in response to altered microenvironmental homeostasis. In turn, the actions of microglia critically determine the fate of other neural cells around (Kim and de Vellis, 2005; Garden and Moller, 2006; Fu et al., 2014; Walker et al., 2014).

Microglial activation is a key event in neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) (Ekdahl et al., 2009; Kettenmann et al., 2011; Macchi et al., 2015). The activation state of microglia can be generally divided into two types, namely M1 type and M2 type. M1 type microglial activation, identified as classical activation, leads to proinflammatory effects by producing numerous cyto-mediators, such as proteases, proinflammatory cytokines and reactive oxygen species (ROS), which are cytotoxic to neurons and other glial cells (Moehle and West, 2014). M2 type microglial activation is viewed as an alternative activation, and takes on anti-inflammatory phenotype involved in phagocytosis of cell debris or damaged neurons and the release various neurotrophic factors and cytokines (Cherry et al., 2014; Tang and Le, 2015). The mutual boundaries between M1 and M2 activation are not absolute, and M1 activation may transform to M2 activation under certain condition, and *vice versa*. However, the detailed mechanisms have yet to be fully understood.

Autophagy, as an essential homeostatic process, is a general term for pathways by which cytoplasmic material, including soluble macromolecules and organelles, is delivered to lysosomes for degradation to adaptation to exogenous disruption (Levine et al., 2011). There are three basic types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Jiang and Mizushima, 2014). Autophagy is essential for cell survival and the maintenance of homeostasis. The autophagy system is made up of autophagy-related proteins (Atgs), such as ULK1 (Atg1), Atg3-5, Beclin (Atg6), LC3 (Atg8), Atg12-14, Atg16L1 and FIP200 (Atg17). The coordinated action of Atgs mediates the membrane trafficking required for autophagosome formation (Saitoh and Akira, 2010). Recent advances also reveal a crucial role of autophagic pathway and proteins in immunity and inflammation. Autophagy balances the beneficial and detrimental effects of immunity and inflammation, and thereby may protect against infectious, autoimmune and inflammatory diseases (Saitoh and Akira, 2010; Sumpter and Levine, 2010; Levine et al., 2011). However, the interactions between autophagy proteins and immune signaling molecules are much more complex. The autophagy proteins function as inducers and suppressers of immune and inflammatory responses, and immune and inflammatory signals could also promote or inhibit the process of autophagy.

The pathogenesis of many neurodegenerative diseases, including AD and PD, is closely correlated with autophagy dysfunction (Carroll et al., 2013; Nixon, 2013; Liang and Jia, 2014). As microglia-induced inflammatory response plays an important role in neurodegenerative diseases, the relationship between microglial autophagy and microglial activation has gained increasing attention in recent years. In Drosophila, a special glia cell type, MANF immunoreactive Cells (MiCs), produced an immune response and resembled vertebrate microglia based on their appearance in the brain upon genetically challenged conditions and the expression of molecular markers (Stratoulias and Heino, 2015). This cell type appears in three contexts: (1) after the induction of either immunity, or (2) autophagy, or (3) by silencing of neurotrophic factor DmMANF in glial cells. The study indicated that autophagy is an important component in microglial function.

Though the interaction between autophagy and macrophage has been reported and reviewed in length (Levine et al., 2011; Chuang et al., 2013), the role of autophagy in microglia has yet to be reviewed. Herein, we will highlight recent advances on the emerging role of autophagy in microglia, focusing on the regulation of autophagy during microglial inflammation, and the possible mechanism involved (Fig. 1).

MICROGLIAL AUTOPHAGY IN ACUTE NEUROINFLAMMATION

When the CNS undergoes acute injuries, such as traumatic brain/spinal cord injuries, ischemic reperfusion injuries, acute infection or hypoxia-induced damage, microglia initiate a rapid immune response. Proper activation of microglia can be beneficial to wound repair and microenvironment reconstruction, but excessive activation of microglia may aggravate the damage (Fleming et al., 2006; Heiman et al., 2014). As a result, autophagy may be a critical mechanism in homeostasis, controlling the state of activation in microglia, and autophagy defects in response to nutrient deprivation may increase the degree of microglial activation and inflammation (Table 1).

TRAUMATIC INJURIES AND INTRACEREBRAL HEMORRHAGE (ICH)

Acute spinal cord injury (SCI) is characterized by severe neuronal injury and microglia activation, concomitant with secretion of proinflammatory cytokines, which like a brush fire further aggravate the injuries (Gomes-Leal et al., 2004). Autophagosomes accumulation was observed in activated microglia in the dorsal white matter adjacent to the injury site after SCI. The degree of co-localization of LC3 and CD11b was highest at day 1, but the absolute number of LC3-positive activated microglia in the dorsal white matter peaked at day 7. Notably, no significant co-localization of LC3 with microglia markers was observed in the gray matter at any time points (Liu et al., 2015a,b). In a separate study, levels of tumor necrosis factor-α (TNF-α) in the SCI-treated rats were significantly higher at both 1 and 4 days after injury compared with control, and acute intraperitoneal administration of rapamycin,

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