Chapter 4

Microglial Mitophagy and Neurodegenerative Disorders

Eyitayo Adeyemi Oyindamola
Kwame Nkrumah University of Science and Technology, Ghana

Maxwell Kwadwo Agyemang
Kwame Nkrumah University of Science and Technology, Ghana

Joseph Owusu-Sarfo
Kwame Nkrumah University of Science and Technology, Ghana

Oduro Kofi Yeboah
https://orcid.org/0000-0001-7080-0730
Kwame Nkrumah University of Science and Technology, Ghana

Newman Osafo
https://orcid.org/0000-0001-8142-2368
Kwame Nkrumah University of Science and Technology, Ghana

ABSTRACT

Microglia are important in the regulation of the inflammatory response in regulating the release of proinflammatory mediators in the brain. Through their phagocytic actions, microglia are significant in the CNS when it comes to the body’s response to physiological insults by promoting repair of impaired brain function. They do so by engulfing and degrading microbes as well as brain-derived debris and proteins such as myelin and axonal fragments, amyloid-beta, and apoptotic cells. This mitophagic activity of microglia is of importance in neurodegeneration. In most neurodegenerative disorders, mitophagy is impaired with resultant accumulation of dysfunctional mitochondria as well as processes such as lysosomal fusion and autophagosomes. In Parkinson’s and Alzheimer’s for example, impaired mitophagy accounts for the build-up of α-synuclein and amyloid respectively in affected individuals. The chapter discusses extensively the link between microglia mitophagy and neurodegeneration and how dysfunctional mitophagy increases the likelihood of their occurrence.

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INTRODUCTION

The mitochondrion is a membrane-bound organelle with several important roles in cellular function, including the production of adenosine triphosphate (ATP), the main energy currency of the cell, via oxidative phosphorylation, calcium homeostasis, and the metabolism of fatty and amino acids, and steroids (Wager and Russell, 2013). Notwithstanding, the mitochondrion is also the primary source of potentially damaging endogenous reactive oxygen species (ROS), which have been associated with a number of pathological pathways such as neurodegeneration, and the induction of lipid peroxidation, protein carbonyls and DNA damage (Santos et al., 2012; Murphy et al., 2011). It has been shown that the release of the cytochrome c, a hemeprotein relevant in the mitochondrial electron transport system and apoptosis, from mitochondria, triggers apoptosis under the regulation of several regulators, the most prominent being members of the B-cell lymphoma protein-2 (BCL2) family (Ow et al., 2008). ROS can induce mitochondrial permeability transition pore (mPTP) and also increase the release of cytochrome c from mitochondria, both of which results in programmed cell death (Murphy, 2008).

The removal of damaged mitochondria is essential for cell survival. Neurons, being highly specialized cells, are peculiarly liable to defects in autophagic mechanisms. These impairments in mitochondrial function and their dynamics have been identified in many neurodegenerative disorders, and modulators of both mitochondrial physiology and autophagy have presented themselves as promising therapeutic targets (Wager and Russell, 2013). Studies have demonstrated that deletion of certain pivotal autophagic genes such as \(\text{ATG-7}\) and \(\text{ATG-5}\) in successive post-mitotic cells enhances the formation and accumulation of cytoplasmic inclusions and induces neurodegeneration in the absence of any other pathological pathway that can also contribute to neural tissue death (Plaza-Zabala et al., 2017; Hara et al., 2006; Komatsu et al., 2006). This selective degradation of mitochondria by highly specialized autophagic mechanisms is what is termed mitophagy, and represents an important quality control mechanism in protein folding (Wager and Russell, 2013).

Microglia are the brain’s resident macrophages and contribute to a major part of the brain’s innate immune system. By orchestrating an inflammatory response, regulating the release of proinflammatory mediators within the brain and through phagocytosis, microglia respond to physiological insults to the central nervous system (CNS) and promote the correction and repair of the brain function following CNS damage (Plaza-Zabala et al., 2017). In addition to engulfing and degrading microbes, microglia also phagocytose different types of brain-derived cargo such as myelin and axonal fragments, synaptic materials, apoptotic cells, and protein deposits such as amyloid-\(\beta\) (A\(\beta\)), among other things (Sierra, 2013). Autophagy and phagocytosis are strikingly similar in morphology and mechanisms, including the formation of the transient vesicular structures, autophagosomes, and phagosomes, respectively. These vesicular structures aid in the delivery of cargo to lysosomes for digestion and degradation (Martinez et al., 2011). Both processes, as such, play a crucial role in maintaining cellular homeostasis through the degradation of harmful substrates of both intracellular and extracellular origins. However, in contrast to phagocytosis which occurs in a selective population of immune cells including macrophages and microglia, neutrophils and dendritic cells, autophagy occurs in almost all cell types in mammals (Sierra, 2013). It is believed that, the two processes are not mutually exclusive, and that functional cross-talk may exist between them during innate immune response in peripheral macrophages. The potential regulatory action of autophagy over phagocytosis has been suggested to unfold at different steps along the phagocytic cascade, which may affect the engulfment and degradation of the phagocytic cargo (Plaza-Zabala et al., 2017).