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REVIEW ARTICLES

An Overview on the Role of Oligodendrocytes and Mitochondria in the Progression of Multiple Sclerosis[1]

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Abstract—Multiple Sclerosis (MS) disease and its related syndromes are initiated by a neurodegenerative process that occurs in the central nervous system with some autoimmunity component. The patients with MS syndrome lose their productivity because of long-term morbidity and need for special assistance in daily activities as well as the need for immunomodulatory treatments and multidisciplinary health care. The remyelination process in the central nervous system due to MS requires proliferation and differentiation of oligodendrocyte precursor cells to generate mature oligodendrocytes that have a capacity for migration and myelin production in the defected area. Remyelination process requires functional mitochondria that can produce sufficient levels of ATP molecules. This method requires high oxygen levels and therefore it generates high levels of destructive reactive oxygen species (ROS) which should be eliminated. A growing body of evidence has shown the crucial role of mitochondrial uncoupling proteins (UCPs) in reducing the production of ROS that leads to a reduction in the harmful effects of oxidative stress and subsequently attenuates neurodegenerative pathology. This review provides an overview of the critical role of oligodendrocyte and mitochondria in the progression of multiple sclerosis.

Keywords: multiple sclerosis, oligodendrocytes, mitochondria, reactive oxygen species, uncoupling proteins
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INTRODUCTION TO THE DISEASE

Multiple sclerosis is a chronic neural disease-causing social and economic consequences, affecting more than 2.1 million people worldwide. In Europe, the highest percentage of MS has been observed in northern countries. The sex ratio was 2 females/male, and the highest rate of MS disease has been observed for the ages between 35 to 64 years [1]. The literature searches and meta-analysis studies have highlighted a global increase in the incidence of this disease over time in Europe and North America [2]. The main symptoms of MS disease that can be noticed in 80% of MS patients are the fatigue, limb weakness, sensory and visual disorder, bladder and bowel symptoms and gait problems [3]. MS disease and its related syndromes are initiated by neurodegeneration in the central nervous system due to autoimmunity. Commonly, patients with MS syndrome lose their productivity because of long-standing morbidity and their need for special assistance in daily living activities as well as the need for immunomodulatory treatments and multidisciplinary health care. The high percentage (about 85%) of MS patients who are suffering from clinical attack showing relapsing-remitting phenotype leading to neurological disorders including transverse myelitis and optic neuritis. Permanent disability has been observed after a transition of about 50% of these patients into a worsening neurological function as a secondary progressive phenotype. Primary progressive MS attacks about 15% of patients that is progressive from the onset of the disease [4].

The unknown aetiology of MS makes this disease a big challenge for the scientific community. MS symptoms are varying from patient to another in addition to an unknown mechanism of disease progression and relapsing patterns. There are several factors involved in disease progressions such as cytotoxic cytokines, activated macrophages or microglia, specific demyelinating antibodies, reactive oxygen species and activated complement components [5]. But, the main feature of this disease is the demyelination process that leads to creating random sclerosis in the central nervous system [5]. It illustrates the development of disease complex syndromes such as primary progressive, secondary progressive and relapsing-remitting courses of multiple sclerosis [6]. Therefore, axonal loss due to

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chronic demyelination and gliosis is the main features of disease progression while inflammatory demyelination is contributing to the disease relapses [7].

CHARACTERISTICS OF NORMAL OLIGODENDROCYTES

Glial cells include oligodendrocytes, microglia, astrocytes, and ependymal cells. These cells are present in the central nervous system (CNS) and provide the optimal environment for neuronal functions and survival [8]. Usually, oligodendrocyte progenitor cells (OPCs) differentiate into mature oligodendrocytes, and some of the OPCs remain in undifferentiated form to serve as a reservoir for providing new oligodendrocytes [9]. Therefore, the OPCs represent the primary source for self-renewable mature oligodendrocytes for CNS remyelination to assist in an efficient conduction of action potential along the axons [10, 11].

Frequently, oligodendrocytes are described as neuronal cells that have rounded nuclei surrounded by a small quantity of cytoplasm and possess short cytoplasmic processes. Oligodendrocytes are located in the central nervous system as satellites around neurons in the grey matter, or it is found in the white matter forming the myelin sheath. The ventral ventricle in the spinal cord represents the central area of oligodendrocytes while the dorsal spinal cord is contributing less than 15%. This area produces motor neuron precursors and then produces OPCs after shifting to gliogenic cells production. From these two positions, the proliferated OPCs separate to all regions of the spinal cord and formed mature myelin-forming oligodendrocytes [12–14]. During nervous system development, the medial ganglionic eminence and anterior entopeduncular area of the ventral forebrain represent the central area of OPCs population. An additional wave of OPCs is derived from the lateral and caudal ganglionic eminences and the postnatal cortex [15].

Oligodendrocytes undergo a programmed process of proliferation, migration, differentiation, and maturation, and finally, the mature oligodendrocytes can produce the myelin sheath [16]. There are two types of myelination in the human nervous system; the first occurs in the central nervous system (brain and spinal cord) by oligodendrocyte that can provide myelin sheath to wrap around 50 axons. The second myelination process occurs in the peripheral nervous system (cranial nerves and peripheral nerves) by Schwann cells that can provide myelin sheath for only one axon segment [16].

OLIGODENDROCYTE DIFFERENTIATION

Through differentiation process, most of the oligodendrocytes express differentiation markers of mature oligodendrocytes, such as Olig2 that has changed expression levels during differentiation, O4 that has a consistent expression through maturation and platelet-derived growth factor (PDGF) receptor. The process of oligodendrocyte differentiation is completed through different stages that include: OPCs expressing A2B5, oligodendrocytes expressing PDGF receptor α, oligodendrocytes expressing O4+ and oligodendrocytes that express myelin essential protein (MBP), myelin-associated glycoprotein (MAG), and myelin oligodendrocyte glycoprotein (MOG) [17]. Besides the significant role of oligodendrocytes in the myelination of axons during development, it also has a crucial role in remyelination of CNS axons in neurodegenerative diseases like multiple sclerosis [18]. Therefore, OPCs represent a potential therapeutic target to replace the apoptotic oligodendrocytes in CNS by mature oligodendrocytes in demyelinating lesions [19].

THE ROLE OF OLIGODENDROCYTE IN MULTIPLE SCLEROSIS

Due to the complicated differentiation process, and their unique metabolism and physiology, oligodendrocytes are among the most vulnerable cells in the CNS. Progression of numerous sclerosis follows the initiation of acute inflammation in the central nervous system, leading to damage of myelin and loss of neuronal axons, which eventually leads to progressive disability. A recent study showed that T lymphocyte population and MOG-specific T cells in lymphoid organs is increased with the progression of MS disease in the CNS. This fact was approved by transferring of T cells derived from oligodendrocyte ablation mouse model (DTA mice) to naive recipients resulting in neurological defects that correlated with CNS white matter inflammation. These data indicate that oligodendrocyte death is sufficient to trigger an adaptive autoimmune response against myelin, suggesting that a similar process can occur in the pathogenesis of multiple sclerosis [20].

Remyelination in the central nervous system requires the proliferation of oligodendrocyte precursor cells and differentiation into mature oligodendrocyte that can migrate and produce myelin in the defected area. It has been known that the myelination process requires functional mitochondria that can provide sufficient levels of ATP molecules that in turn requires high oxygen levels. On the other hand, the high demanding energy cells are always suffering from the production of reactive oxygen species that are considered as toxic by-products and need to be metabolized or deactivated by antioxidant agents [21]. The high activity of oligodendrocytes during myelin synthesis requires eliminating of reactive oxygen species. This process is considered as an Achilles' heels of protein synthesis in oligodendrocyte ability to fold the nascent amino acids chain and prevent accumulation of misfolded protein [22]. Furthermore, some studies showed that the oligodendrocyte progenitor cells and adult oligodendrocytes are able to store iron in the cytoplasm to be used as a co-factor for optimal activity

of enzymes involved in myelination process. Therefore, this high content iron renders the oligodendrocyte to be more susceptible to reactive oxygen species and lipid peroxidation leading to mitochondrial dysfunction [23]. In addition to the above function of oligodendrocytes, these cells have the ability to provide the required metabolites for mitochondria in the axons in order to maintain the optimum levels of energy metabolism because myelin sheath hampers axonal access to extracellular metabolites [24].

MITOCHONDRIAL FUNCTIONS AND OXIDATIVE STRESS

There is a growing body of evidence stating that the oxidative stress is normally linked to mitochondrial dysfunction which has a potential role in inducing neurodegeneration [25]. Interestingly, it has been shown that neurons with demyelinated axons need to produce more energy to sustain neural impulses [26]. Although neurons in MS lesions contain more mitochondria, the majority of these mitochondria are dysfunctional due to the low oxidative phosphorylation (OxPhos) activity and high numbers of mtDNA deletions [27].

Cells undergoing oxidative stress have been found to develop mtDNA deletions that are thought to be irreversible in neurons. Such phenomenon has been described within neurons in motor neuron diseases like Alzheimer's disease, Parkinson's disease and ageing brain [28]. It has been found that demyelination may directly or indirectly lead to increase in mtDNA deletions that may occur independently of inflammation within single neurons [27]. Another source of mitochondrial dysfunction is the elevated levels of cytotoxic cytokines. For example, it has been found that the high levels of tumour necrosis factor alpha (TNFα) have unfavourable effects on mitochondrial function and biogenesis [29].

THE ROLE OF UNCOUPLING PROTEINS IN MITOCHONDRIAL FUNCTIONS

The uncoupling proteins (UCPs) are members of the larger family of mitochondrial anion- carrier proteins located on the inner mitochondrial membrane. UCPs facilitate the transfer of anions from the inner to the outer mitochondrial membrane and the return transfer of protons from the outer to the inner mitochondrial membrane. Therefore, UCPs separate oxidative phosphorylation from ATP synthesis with energy dissipated as heat also referred to as the mitochondrial proton leak. UCP1 represents the typical uncoupling protein and UCP2 and UCP3 are closely related to UCP1 that are considered to be homologues of UCP1, whereas UCP4 and BMCP1 (Brain Mitochondrial Carrier Protein 1) is slightly different [30].

It has been shown that UCP2, UCP4 and BMCP1 are mainly expressed in the central nervous system, but UCP4 and BMCP1 are more widespread in the brain than UCP2. Studies that were designed to investigate the expression levels of UCP2 mRNA in mouse CNS showed that UCP2 mRNA is mainly expressed in the cerebellum, hypothalamus, limbic system, brainstem and choroid plexus and similar distribution had been observed in rats and non-human primates [31, 32]. Further studies are required to explore the function and distribution of UCP4 and BMCP1 in central nervous system.

The neuropathological studies have reported key effects of UCP2 in attenuating neurodegenerative diseases. For example, UCP2 showed protection effect when over-expressed in rat models of focal cerebral ischemia [33], Parkinson's disease [34], seizures [35], encephalomyelitis and traumatic brain injury [33]. Furthermore, experiments on the ischemic preconditioning (IPC) showed that UCP2 has an endogenous neuroprotective effect [33].

A growing body of evidence has shown that UCPs are neuroprotective regulatory proteins. It has been shown that the expression levels of UCPs are closely related to the mitochondrial injury which is related to the physiological status of the body [36, 37]. Previous studies have reported the crucial role of UCPs in reducing the production levels of ROS, leading to a reduction in the harmful effects of oxidative stress and subsequently attenuating neurodegenerative pathology. The purpose of UCPs in decreasing mitochondrial membrane potential is essential to reduce the production levels of ROS [35, 38, 39]. It is further supported by the ability of UCP2 to regulate the mitochondrial production of hydrogen peroxide [40]. Furthermore, UCP2 has been proven to reduce in vivo ROS production using mice that lack UCP2 [34]. Other studies have shown that the induction of UCP4 expression in cultured neurons have led to a decrease in the mitochondrial levels of ROS production and restricted ROS production after treatment with neurotoxins [33]. A similar effect has been observed after overexpression of BMCP1 in cell culture, suppressing mitochondrial ROS production and enhancing uncoupling activity [41]. Overexpression of UCP4 in neural cells stabilized Ca2+ homeostasis in response to thapsigargin-induced endoplasmic reticulum Ca2+ store depletion, preserved mitochondrial function, reduced mitochondrial ROS generation, and increased cell survival against oxidative stress [42]. While the overexpression of UCP4 and UCP5 induced cell proliferation and viability of neural cells, the cells also showed higher ATP levels and lower ROS after exposure to cytotoxic agents [43, 44]. Genetic variants of these genes are believed to influence the mitochondrial energy production in different distress states of the glial cells where myelin protein synthesis takes place [45]. The protective role of UCP2 in neurodegenerative diseases suggests that UCP2 expression could be a potential therapeutic target [46].

MITOCHONDRIAL DYSFUNCTION AND MULTIPLE SCLEROSIS PROGRESSION

Mitochondria have been implicated in some potential factors contributing to MS progression. There are different patterns of mitochondrial dysfunction linked with the progress of MS disease, such as inhibition of mitochondrial respiration, reduction in N-acetylaspartate levels and down-regulation of genes encoding electron transport chain in mitochondria [47, 48]. In addition, mutation of mitochondrial DNA has been linked with this disease, especially mitochondrial DNA deletion that has been shown to be a causative factor in specific cases [49]. A high level of mtDNA deletions has been considered as the main cause of significant lack of the activity of mitochondrial respiratory chain enzymes in the neuronal cell body, in addition to the low expression levels of mitochondrial respiratory chain enzyme [50].

Interestingly, mitochondria in MS neuronal cells have depolarized membrane that leads to cell damage through mechanisms that involve releasing apoptotic factors and increasing ROS production [51]. The systemic pathogenic environment of MS may have a direct or indirect impact on the non-neuronal tissues and cells in patient's body. It has been shown that many categories of neurodegenerative diseases result in muscle degeneration or lead to similar phenotypes [52]. This may have an impact on intracellular organelles of these tissues like mitochondria concerning function, morphology, distribution and proliferation. Therefore, mitochondrial dysfunction may be extended to non-neuronal cells that in turn has a potential contribution to MS progression.

Moreover, it has been shown that the enzymes involved in mitochondrial respiratory chain reactions have the most crucial role in mitochondrial abnormalities that induce MS progressions such as complex I, complex III and complex IV. In the stage of MS progression, studies have shown a significant deficiency in the expression levels of complex I and complex II in the upper cortical layers whereas a substantial deficiency has been observed in complex IV in deep cortical layers. This fact has been approved by some studies that specific mitochondrial abnormalities in neurons by measuring the expression levels of mitochondrial respiratory chain enzymes using post-mortem nerve tissue [27, 47, 48, 53].

Further studies are required to explore mitochondrial dysfunction in the progression of multiple sclerosis. In particular, studies on the neuroprotective role of UCP2, UCP4 and BMCP1. Such studies are important to explore the role of these proteins at different stages of multiple sclerosis progression in vivo using Experimental Autoimmune Encephalomyelitis animal model.

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