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Relationship between Mitochondrial Dysfunction and Multiple Sclerosis: A Review Study

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that inflammation, demyelination, oligodendrocyte loss, gliosis, axonal injury and neurodegeneration are the main histopathological hallmarks of the disease. Although MS was classically thought as a demyelinating disease, but axonal injury occurs commonly in acute inflammatory lesions. In MS microglial activation is not only responsible for inflammatory cascade but also creates degenerative cascade. The evidence has shown mitochondrial dysfunction plays an important role in axonal degeneration in all stages of MS due to neuronal cell loss and activation pro-inflammatory cytokines. Neuronal loss occurs as a result of apoptosis and necrosis and mitochondrial pathway is the main important system for apoptosis and this way was involved in neurodegenerative disorders such as MS. Hence in multiple sclerosis, mitochondrial dysfunction causes energy failure and then increases inflammation and demyelination in neurons.

Keywords: Multiple sclerosis; Mitochondria; Dysfunction; Inflammation; Neurodegeneration

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Introduction

Multiple sclerosis (MS) is a complex chronic inflammatory demyelinating disease of the central nervous system that typically attacks young adults, especially women (1). Onset of MS typically occurs during early adulthood and it is the most common neurological disease affecting people under the age of 30 (2). It is diagnosed based on clinical symptoms, magnetic resonance imaging, evoked potentials and cerebrospinal fluid analysis (3-4). MS has a variety of etiologies, including environmental, immunological, and genetic factors (5). Histopathologically, MS is characterized by inflammation, demyelination, oligodendrocyte loss, gliosis, axonal damage and neurodegeneration (6). Axonal injury occurs frequently in acute inflammatory lesions, which are present in both white and gray matter (7-8). As a whole, there are two main mechanism of pathology including inflammatory and degenerative cascade in MS. The main basis of inflammation is microglial activation, re-activation of antigen-specific cells, recruitment of systemic immune-competent cells and production of cytotoxic mediators (9). Basically mechanism of degenerative is characterized by oxidative stress and excitotoxicity (9). Studies have shown that demyelination is created due to damage to myelin and oligodendrocytes by nitric oxide (NO), reactive oxygen species (ROS), tumor necrosis factor (TNF)-a and myelin specific immunoglobulins (10). ROS are produced by all organisms but there are balance between their generation and the natural antioxidant. However mitochondria are an important source of ROS generation that contains superoxide, the hydroxyl radical and hydroxyl peroxide. Mitochondria ROS (mROS) was regulated by superoxide antioxidants (11). In inflammatory condition production of ROS is elevated and causes mitochondria respiratory chain dysfunction and oxidative stress (9). Studies have showen that mitochondrial defects play a role in axonal degeneration in all stages of MS (12-14). In this study, we aimed to explain the mechanism of mitochondria dysfunction in development of MS.

Multiple sclerosis and Inflammation

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that is characterized by a complex immune response (15). Leukocyte infiltration into the CNS parenchyma is a two-step process: (1) passage across the endothelial cells into the perivascular space and (2) infiltration into the CNS parenchyma across the glia limitans (16). The vast popular inflammatory infiltrates are T lymphocytes with a MHC class 1 CD8+ cells that accumulate in active lesions (17). MHC Class II restricted CD4+ T-cells as well as B-cells or Plasma cells are mainly seen in perivascular spaces and in the meninges (18). CD4 T cells differentiate into Th1 and Th2 cells characterized by the production of different cytokines. Th1 cells produce pro-inflammatory cytokines such as IFN, TNFa interleukin-2 (IL-2) and low levels of interleukin-10 (IL-10), while Th2 cells produce anti-inflammatory cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13) and high levels of interleukin-10 (19-20). In EAE models, after starting inflammation by CD4+ T cells, microglia and macrophage activate into lesion (18). After a few days CD8+ T cells recruit in tissue injury. It is different with MS lesion wherever MHC Class I-restricted CD8+ T cells are prominent into lesion and also on neurons and glia (18, 21). There is close contact between these cells and oligodendrocytes damage (22). As was previously reported active lesions in MS are associated with microglial activation and accumulation of macrophages in initial lesions (23). When microglial cells are activated they can be benign, protective, or contribute to neurodegeneration (24). Microglial activation causes disease initiation before functional deficit and on the other hand, recruitment of monocytes has a major role in progression of disease (25). Activated microglial cells release myelo-peroxidase (MPO) and causes inflammatory cascade and consequently tissue damage (26). Inflammation is appeared at all phases of disease but decays with disease duration (21). Despite extensive and laborious attempts over the years, there is not a single antigen or antibody that could be proven as a candidate for cell-mediated or humoral immune-pathogenesis (27). As a whole, the mechanisms lead to demyelination and degeneration are included infiltration of CD8-positive T cells that identify an antigen expressed in oligodendrocytes, production of demyelinating antibodies and activation of microglia by immunity system (17). In MS patients, after duration times, inflammation will change to axonal degeneration due to production of ROS and nitric oxide from activated microglia and macrophages (25). Therefore inflammation not only provides neuronal and axonal loss but also causes degenerative cascade and neural tissue injury (9).

Multiple sclerosis and Neurodegeneration

Recent documents suggest that acute and chronic inflammation may only be responsible for a part of the disease; therefore there are other mechanisms for tissue damage such as production of oxidative stress and oxygen radicals by inflammation and activated microglia, paly a main role for demyelination and neurodegenaration (28). Therefore, microglial activation is not only responsible for inflammatory cascade but also creates degenerative cascade. Peroxynitrite is the main speices responsible for oxidative stress and oxidative stress is a major factor for destruction of myelin sheaths and oligodendrocytes and also neurodegeneration in MS lesions (9, 23). Formation of peroxynitrite in vivo has been attributed to the reaction of the free radical superoxide with the free radical nitric oxide (29). Nitric oxide (NO) is released by neurons, endothelial cells, mitochondria and microglia and also superoxide is produced by neutrophils and mitochondria (30). Also, the disturbances of axonal ion homeostasis have an important role in the process of neurodegeneration especially, in patients with primary or secondary progressive diseases (31). In these patients remyelination decreases due to loss of trophic support from microglia or the local unreceptive situation in demyelinated plaques (32-33). Patients with progressive course are accompanied with neural and axonal degeneration and brain atrophy more than relapsing-remitting phase (34-35). The main basis for neurodegeneration includes microglial activation, chronic oxidative damage, accumulation of mitochondrial defect in axons, and age-related iron accumulation in the normal appearing white and gray matter (17). Axonal degeneration is now recognized as the main cause of irreversible neurological disability in MS patients and is the hallmarks of MS lesions (36-37).

Mitochondrial dysfunction and inflammatory

Mitochondria are cytoplasmic-located cellular organelles whose the most function is the production of adenosine triphosphate (ATP) in the respiratory chain for survival by oxidative phosphorylation. In addition to energy production, they have roles in cellular activity including, differentiation, signaling, proliferation, cell cycle, apoptosis and also inflammation (38). Mitochondria contain their own genome (mitochondria DNA) that encodes essential subunits of the respiratory chain and outer and inner membranes (39). The process of oxidative phospho rylation on the inner membrane of mitochondria produces mitochondria ROS (40). Respiratory chain complexes in mitochondria contain complex I

(NADH dehydrogenase), complex II (succinate dehydrogenase), complex III (cytochrome C reductase), complex IV (cytochrome C oxidase) and complex V (ATP synthase) (40). As a result of electron's leakage at complex I and complex III free radicals (O2.- and H2O2) are produced that are called mt ROS (41-42). Some studies have shown that mtROS are involved in pro-inflammatory cytokine production and modulate innate immune responses (43). Modulating of innate immunity occur via redox-sensitive inflammatory pathways or direct activation of the inflammasome that can activate inflammatory cytokines (44).

Mitochondrial dysfunction and neurodegeneration

Some studies reported that mitochondrial dysfunction may be involved in neurodegenerative processes and cell death (45). Also, the role of mitochondrial dysfunction has been reported in some neurological diseases, including AD, PD, dementia and multiple sclerosis (46-47). Involvement of CNS is prominent in dysfunction of mitochondria due to some reasons: high metabolic region in brain and vulnerable to energy failure, insufficient antioxidant protection against high ROS production and being post mitotic neuron in brain (48). The main pathology some of neurodegenerative disorders had been injury to the mitochondrial respiratory chain complexes (49) such as decreased complex I activity in the substantia nigra of Parkinson's disease (50) and also decrease in complex IV activity in the cerebral cortex of Alzheimer's disease (46). Mutations within the mitochondrial DNA are other mechanisms that play an important role in certain neurodegenerative disorders such as PD, Huntington's disease (HD), Alzheimer's disease (AD), and Multiple sclerosis (12). As a whole, oxidative stress, inflammation and excitatory process cause neuron degeneration and cell death in patient with neurodegenerative disease (9). Neuronal cell loss occurs as a result of apoptosis and necrosis and mitochondrial pathway is the main important system for apoptosis and this way was involved in neurodegenerative disorders (48).

Multiple sclerosis and mitochondrial dysfunction

MS as a demyelinating disease starts with relapsing remitting course, but after several years it converts to secondary progressive phase (51-52). In addition to demyelination alteration in multiple sclerosis, diffuse neurodegeneration in white matter and gray matter of CNS have also been reported (17). In initial stage of disease inflammatory process is prominent that cause destructs neurons, oligodandrocytes, myelin and axons by activated microglia producing ROS and RNS. With progression of disease oxidative stress may generate mitochondrial damage that increases axonal damage and neural degeneration (23). Therefore in MS, inflammation leads to axonal degeneration after some time (25). A number of studies have shown that mitochondrial dysfunction plays a role in MS disease (10, 53) Mitochondria damage and oxidative stress are two mechanisms that establish neurodegenration in lesions of multiple sclerosis (54). High level of mitochondrial density, mtDNA deletion and loss of complex IV activity was reported in MS lesions (55) also complex I activity is decreased in chronic MS lesions (18). Free radical production in MS disease is dependent on phase of disease. In acute phase, microglia and macrophages produce some amount of free radicals but in progressive phase when inflammation has decreased, mitochondria are more prominent in free radical generation (35). Production of free radicals by mitochondria has the main role in axonal degeneration of MS (56). It is believed that axonal degeneration exists both in acute and chronic phase of disease (57). Horssen et al have reported that mitochondrial deficiency causes neurodegeneration in MS for several reasons: damage of intra-axonal mitochondria by inflammation and producing ROS and RNS in acute lesions, accumulation of mitochondria dysfunction and enhancing energy demand in chronic lesions and high level of mitochondria DNA mutation that all of these cases provide axonal injury and degeneration (35).

Conclusion

MS is considered as an inflammatory mediated demyelinating disease of the CNS and also as a neurodegenerative disease wherein axonal damage, neuronal loss, and atrophy of the CNS are the major causes of irreversible neurological disability in patients. Several studies suggested the mechanisms of neurodegeneration and cell loss may be due to secondary mitochondrial dysfunction (57-58). Mitochondrial deficiency such as mitochondrial DNA deficiency, uncharacteristic mitochondrial gene expression, defective mitochondrial enzyme operations and insufficient mitochondrial DNA repair mechanisms are involved in progression of multiple sclerosis and also mitochondrial structural change (imbalance in mitochondrial fission and fusion) has an important effect on tissues damage in multiple sclerosis (2). In MS mitochondrial dysfunctions according to the explained mechanism, lead to energy failure and then increase inflammation and demyelination in neurons and areas affected.

Authors' contributions

KN and TN collected data. KN wrote the manuscript. TN and AM reviewed and revised the article.

Conflict of interest

There is no conflict of interests.

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