Neurodegenerative Mechanisms of Multiple Sclerosis

Hanpeng Xu*
Department of Neurosurgery, Cedars Sinai Medical Center, USA

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the CNS and the most common cause of neurological disability in young adults, affecting over 2.5 million people worldwide [1].

In 80% of all MS cases, patients suffer from relapsing-remitting (RR) MS, which have clearly defined periods of neurological deficits followed by (partial) recovery [1]. In those RRMS patients, 65% of the disease cases gradually evolves into secondary progressive (SP) MS, with progressive permanent neurological deficits. In 20% of all MS cases, patients have a progressive disease course from onset, which are known as primary progressive (PP) MS.

First symptoms of MS generally appear in early adulthood (20–40 years of age) and approximately half of these patients need help walking within 15 years. During the past three decades, major progress has been made in understanding disease mechanisms in the relapsing-remitting phase of MS, however, the disease mechanisms driving progressive MS remain unresolved.

This lack of MS mechanism understanding has led to the difference in treatment strategies: currently, the most effective treatments are targeted at anti-inflammatory and immunomodulatory, which can reduce the severity and frequency of new demyelinating episodes in RRMS [2,3]. However, once a MS patient has entered the progressive stage, therapeutic options are limited to symptomatic treatments and physiotherapy, current immunomodulatory drugs fail to halt disease progression [4].

Researchers have proposed several hypotheses to explain the mechanism of progressive MS [5]. One opinion postulates that MS might be primarily a neuro-degenerative disease; its progression is modified or amplified by inflammation in the early disease stage. Another opinion postulates that inflammatory processes in progressive MS is similar to those in RRMS, however, that inflammation process is no longer treatable by current therapeutic strategies [6]. The third opinion considers MS as an inflammatory disease, inflammation that contributes to disease progression but neuro-degeneration is a process that occurs independently from the inflammatory response.

DIFFERENT MECHANISMS COEXISTING IN MS PROGRESSION

In patients with RRMS, different demyelination patterns have been observed. The most frequent pattern are pattern II, which is antibody and complement-associated. The second one is pattern III, which is initiated by degeneration of the most distal oligodendrocyte processes and apoptosis of oligodendrocytes. In this pattern, astrocytes also loss their polarity and the glia limits which formed BBB have been disturbed [7]. The third pattern (pattern I) is associated with T cells and activated microglia alone [8].

Contrast to those in RRMS patients, the tissue injuries in either PPMS or SPMS patients are generally homogeneous. All these injuries show demyelination, oligodendrocyte destruction, preferential loss of small-calibre axons, lack of remyelination and astrocystic gliosis [4,9,10].

These different lesions in RRMS might be caused by distinct immune processes, which might contribute to demyelination and neurodegeneration in different patients or different disease subgroups. The homogeneous lesion patterns in the progressive stage of MS might be a result of their slow expansion, which make it difficult to identify the specific immunopathological pathways to different lesion types [11].

Both adaptive and innate immunity components could induce the different types of injuries in MS patients, those immune cells include antigen-specific cytotoxic T cells [12,13] and autoantibodies against neuronal or glial antigens [14,15]. Furthermore, activated macrophages and microglia release cytotoxic cytokines, excitotoxins, reactive oxygen or nitric oxide species also cause myelin sheaths destruction.

Neurodegeneration in progressive MS accumulate over time, axonal injury in focal white matter lesions may play an important role in this process. After the axonal damage in plaques or in the normal-appearing white and grey matter reached certain threshold - the exhaustion of functional compensation, any minor additional axonal injury will lead to slow deterioration of the patient's neurological symptoms [16].

Furthermore, when the lesions in MS patients evolve to the primary and secondary progressive stages, majority of the lesions absence remyelination, even though axons and oligodendrocyte progenitor cells are present in at least a subset of plaques. This remyelination failure might be partly due to a loss of trophic support from microglia or the local hostile environment in demyelinated plaques [17-19].
AXONAL ION CHANNELS CHANGE

Axonal damage in plaques or in the normal-appearing white and grey matter is one of the hallmark in MS lesions. The disturbances of axonal ion homeostasis have an important role in the process of neurodegeneration. These disturbances include aberrant expression of Na+ channels, acid-sensing Na+ channels, glutamate receptors and voltage-gated Ca2+ channels. In dystrophic or demyelinated axons, these changes in ion channels expression and/or activity could lead to intra-axonal Ca2+ accumulation and concomitant axonal degeneration [20-23].

FREE RADICALS AND OXIDATIVE STRESS

In active MS lesions, especially in areas of initial tissue injury, enzymes involved in free radical production are markedly increased [24-28]. Both adoptive and innate immune cells generate oxygen free radicals, which induce mitochondrial DNA damage, inhibit respiratory complex synthesis, modify mitochondrial proteins, interfere enzyme function and speed up their degradation [29,30]. Oxidized DNA, lipids and nitrotyrosine are abundantly present in apoptotic oligodendocytes and dystrophic axons [31-33], axonal tau phosphorylation also increase. The chronic presence of oxidative stress in MS lesions, in both high level inflammatory RRMS lesions and low level inflammatory progressive MS lesions strongly support their important role in demyelination process and neurodegeneration [34-36], though the driven factors of the inflammatory process in RRMS and the progressive MS might be different [33].

MULTIPLE FACETS OF MICROGLIA

Microglial activation is associated with active tissue injury in both RRMS and progressive MS. In the progressive stage of MS, activated microglia and microglial nodules are readily observed in the normal-appearing white matter [37,38]. However, this microglial activation is not specific for MS lesions, it has been recorded in many other neuroinflammatory or neurodegenerative diseases [37,38]. Thus, microglial activation might combine with other additional mechanisms to trigger the specific neurodegeneration lesions in MS. Studies have shown that activated microglia oxidative burst play a major role in demyelination and axonal injury in progressive MS lesions. However, depending on different context of activation, microglia might also secrete neurotrophic molecules, remove damage tissue debris and stimulate remyelination [39].

MITOCHONDRIA - A HUB OF DIFFERENT INJURY MECHANISMS?

The role of mitochondrial injury in demyelination and neurodegeneration [40-42] has recently become a hot spot in MS research community. Mitochondrial injury in MS lesions, such as NADH dehydrogenase and complex IV activity impairments have been first described [43,44]. Subsequent more detailed studies revealed profound mitochondrial injury within MS lesions, which might reflect the increased oxidative damage [45].

In inactive plaques, the disturbed ion homeostasis in demyelinated axons demand increased energy, however, the changes in various Na+ and Ca2+ channels expression and activity [46-48] reduced local energy production. To increase the energy supply, a compensatory increase in mitochondrial content and respiratory function in those axons occurred, which include the increases in mitochondrial numbers and/or individual mitochondria volume as well as the respiratory enzyme activity [49,50]. When damaged mitochondrial could not satisfy the energy need of the axons, those axons might demise. Since thin-calibre axons contain fewer mitochondria and have a relative higher axolemma surface area, they are more sensitive to energy deficiency and usually more severely affected than thick ones [51].

Mitochondrial injury in oligodendrocytes could result in apoptosis and induce demyelination [52]. However, the mitochondrial injuries have different effects on oligodendrocytes and oligodendrocytes progenitor cells. It has been shown that in the absence of astrocytes, oligodendrocyte progenitor cells are more resistant to mitochondria injury than mature oligodendrocytes, but their capacity to differentiate and form myelin sheaths are impaired [53]. This might be an important mechanism of the remyelination failure in chronic MS plaques [54].

Furthermore, the chronicity of MS lesions and mitochondria injury might lead to neurons damage. Cortical neurons with respiration-deficiency have been found in patients with progressive MS, studies on these neurons revealed high levels of deletions of mitochondrial DNA [55]. The accumulation of mitochondrial DNA deletions in neurons might lead to an increased susceptibility of brain tissue to neurodegeneration in patients with PPMS or SPMS, and the mitochondria injury in both oligodendrocytes and neurons might form a vicious interactive cycle in progress of neurodegeneration in MS.

IRON ACCUMULATION – ANOTHER PLAYER

During young adulthood, brain iron loading accumulates and reaches a plateau between 40 and 50 years of age. Most brain iron are stored in oligodendrocytes in a format of binding to ferritin. Under conditions of oxidative stress, such as in MS lesions, the high level of iron in oligodendrocytes put these cells in more susceptible status to degeneration [56]. When oligodendrocyte are destructed, those detoxified accumulated Fe2+ are released into the extracellular space, where it might further amplify oxidative damage in axons and other cells [57-59]. In MS lesions, activated macrophages and microglia take Fe2+ and those Fe2+-containing microglia undergo fragmentation and cellular degeneration [60], leading to a second wave of Fe2+ liberation. These iron releases and absorptions might occur multiple rounds from the early age of MS, since iron accumulation is an age-dependent process, in relapsing–remitting stage of MS, it might just cause mild the injury, however with the progression of the disease, these mild injuries could accumulate and become more pronounced in patients with progressive MS, and finally reached the irreversible, uncompensated stage.

CONCLUSION

An unsolved challenge in MS is how to protect against the late stage neurodegeneration, the major cause of chronic disability in this disease.

Current evidence indicates that in all forms and stages of
the disease, inflammation seems to drive demyelination and neurodegeneration, and in the progressive stage, contrast to early stage with BBB compromise, inflammation are partially trapped within the CNS behind the BBB, this make current anti-inflammatory treatment becomes ineffective.

In the progressive stages of MS, microglial activation and macrophage activity together with oxidative stress and subsequent mitochondrial injury might generate chronic oxidative damage. This chronic injury might lead to oligodendrocytes death, axons and neurons ionic imbalance and finally neurodegeneration. When the functional reserve capacity of the brain have been exhausted, irreversible clinical deterioration will occur.

However, none of the pathogenetic mechanisms described above are able to provide an explanation for all pathological alterations associated with the conversion from RRMS to SPMS. One reason for this hard situation is that our understanding of the molecular and cellular mechanisms underlie MS progression are very poor, we lack ideal experimental animal models which could reproduce the key features of those pathogenesis.

Since we do not have a coherent model of MS pathogenesis, this has also formed a major obstacle for testing new therapies. New experimental models urgently need to be developed that reproduce the neurodegeneration found in the ageing human brain and can be used for systematic screening of potential neuroprotective treatments, which will be a research focus in future.

REFERENCES


