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New Aspects of Neurodegeneration in Multiple Sclerosis: The Other Side of the Coin

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Abstract

Multiple sclerosis (MS) is a classical model of human autoimmune disease. Recently, in addition to the still not completely understood mechanisms that trigger autoimmune attack, a new component of the disease is coming to our attention: early neural degeneration and cell death, that are a more and more appreciated and important causal component of this pathology.

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Multiple sclerosis (MS) is the most common chronic neuro-inflammatory disease affecting young adults. The clinical signs of MS are variable but include motor dysfunction, sensory and visual deterioration, and neuropsychological problems. Following the first attack the disease history typically comprises periods of relapse and remission. 50%–60% of patients then go on to develop secondary progressive disease, with progressive neurological deficits without definite remission between the acute relapses. Ten to twenty percent of patients have primary progressive MS and show no remission after the first attack, instead displaying progressive decline from the onset of symptoms. Regardless of the exact MS subtype, neurological decline is inevitable and, within 25 years after diagnosis, about half of patients require the permanent use of a wheelchair [1].

The precise pathophysiological mechanisms that cause MS remain to be fully elucidated. However, the disease is considered to be an autoimmune condition initiated by auto-reactive immune cells that cross the blood-brain barrier and target the central nervous system (CNS). The inflammatory infiltrate leads to the formation of lesions that are a key disease feature and are characterized by the presence of immune cells, demyelinated axons, lower oligodendrocyte numbers, transected axons, and glial hypertrophy. The infiltration eventually promotes continued activation of macrophages that home to the CNS and of resident microglia, thereby further disseminating the inflammation and ensuing demyelination and axonal damage. From time to time, the neurodegenerative process becomes self-perpetuating, resulting in irreversible disability [1-3].

The appreciation of immune dysfunction as a driver of MS development has had a catalytic effect clinically: today there are some ten different immune-modulatory drugs (IMDs) available [8]. However, despite this progress, these IMDs have varying efficacy and are associated with a number of unwanted side effects ranging from flu-like symptoms to cancers and even deadly opportunistic infections [1,9]. Furthermore, even if they reduce relapses, none of the IMDs ultimately prevent or halt neurodegeneration. The implications of this clinical outcome can be considered as two sides of the same coin. First, it is now apparent that there is an unmet need for novel therapeutic strategies that can specifically target neurodegeneration, changing the balance toward reduced axonal damage and increased neuroprotection and/or regeneration. Second, although CNS damage in MS may be initiated by the inflammatory infiltrate, neurodegeneration should not be considered as the second phase of the disease but as an early process that is already ongoing by the time of clinical diagnosis [3].

Axonal injury is a critical event in the history of the disease: following the initial description by Trapp and al. [10] it has been established that axonal damage can be detected even in MS lesion axons that are still myelinated [11] and axonal loss perhaps provides the best correlate of the neurological disability seen in the disease [12-14]. Although the more traditional methodologies, such as CNS tissue immunohistochemistry, have provided some information regarding the pathogenic features of axonal injury, the studies of the dynamics of axonal dysfunction has necessitated technological advances such as the use of in vivo two-photon imaging [15].

Axonal transport is the process by which cargo shuttles long distances between the neuronal cell body and synapses along the axon; it is essential to neuronal function and permits axons to be loaded with lipids, proteins, and organelles from the soma (through anterograde transport), while components that require degradation or recycling are moved back to the cell body (through retrograde transport). Axonal transport impairment has been described in the more classical neurodegenerative diseases, but it has been demonstrated very recently [16] that it is also a prominent feature of neuro-inflammatory lesions in MS-like disease. Using mice in which the transport of single, fluorescently-labeled organelles (mitochondria in Thy1-MitoCFP mice and peroxisomes in Thy1-PeroxiYFP animals) can be tracked along the spinal axons in vivo, transport in the healthy as opposed to inflamed spinal cord was compoared [16]. Of note, it was found that transport was not only reduced in the degenerating axons but also in the majority of normal-appearing axons found in the lesions, indicating that transport disturbances may promote and demarcate the more pervasive axonal dysfunction that precedes progressive degeneration.

Notably, the localized transport deficits were detected acutely but also persisted for a number of weeks in a chronic EAE model [16]. A net deficiency of organelle delivery from the cell body to the synapses was observed as anterograde rather than retrograde transport was more significantly affected. This also coincided with organelle arrest in areas of neuro-inflammation such that mitochondrial accumulation, for example, was observed within the lesions. To better comprehend the mechanism originating this impaired mitochondrial transport,

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it was thus determined whether or not damage to mitochondria, which has been previously described in lesions [11], might contribute to the observed deficit-especially as axonal transport itself is highly energy demanding. However, there was no correlation between altered mitochondrial morphology and impaired transport rates [16]. Microtubule stability was also assessed, given the role of this cytoskeletal component as a dynamic platform for trafficking along axons, using quantitative immunohistochemistry for stabilization status markers, and electron microscopy and in vivo two-photon imaging with Thy1- EB3-YFP mice to assay microtubule orientation. The transport deficits were observed prior to the marked microtubule destabilization detectable in the swollen axons found in lesions [16]. This is consistent with transport impairment occurring in normal-appearing as well as degenerating axons running through lesions and perhaps also suggests that microtubule destabilization marks more permanent structural axon damage. Importantly, the establishment of axonal transport deficiency as an early phenomenon in the development of progressive axonal dystrophy could pave the way to a reversal of damage in axons not structurally ruined. While transport deficits are thus locally induced, they likely also affect organelle flux in axons both proximal and distal to the lesion area, which could further affect the transport rates measured in those axons that pass through several lesions. Still, when short-lasting, such transport deficits probably have no immediate detrimental consequences for affected axons and even structurally affected axons can recover during remission [11]. However, in situations in which inflammation persists, even at low levels, as in progressive MS and its models, transport deficits are perpetuated. As anterograde transport is predominantly affected, this limits the provision of vital organelles and ultimately results in "starvation" of distal axonal arbors. Ensuing axonal dystrophy would probably first manifest most distally at the synapse [17]. Indeed, recent histopathological studies provide evidence for prominent synaptic pathology in progressive MS patients [18,19] Preventing persistent transport deficits, e.g., by prolonged redox scavenging, might thus help to reverse transport-based axon dysfunction and help to counteract the emerging axonal suffering and death. How closely the characteristics of axonal transport deficits observed in models of MS correspond to the human disease? This is a pivotal point, since it would relevant to ascertain the temporal sequelae triggered by CNS inflammation and also to rationally design new more specific and effectives therapies. Furthermore, more stringent models of EAE are sorely needed [20,21] and this will be undoubtedly an area of robust investigation in the near future.

Considering the complexity and chronicity of neurodegeneration in MS, a combinatorial treatment approach may very well be required to keep inflammation at bay, dampen down and contain axonal damage and death, boost defensive mechanisms, and promote re-myelinaton and repair. These new insights in the role and nature of neuro-degeneration in MS will pave the way to a new era of deeper understanding of the disease and ultimately will lead to new multi-faceted and more effective therapies.

Competing Interests

The author declare that he has no competing interests.

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