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Much, if not all, of the cortical damage in MS can be attributed to the microglia cells - NO

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Microglia are the resident immune cells of the central nervous system (CNS). In contrast to the sparsely-distributed innate immune cells in other organs, microglia form a tile-like network that covers the entire brain parenchyma. They play an essential role in removing apoptotic neurons and sculpting synaptic fields during brain development^{1,2}. Microglia, therefore, are essential for establishing and maintaining CNS networks that are critical for maximizing brain function³. While studies implicate microglia in the pathogenesis of neurodegenerative diseases, we argue that there is little evidence to support a destructive role for microglia in CNS disease in general, and no evidence that they play a primary role in cortical damage in multiple sclerosis (MS).

Harmful microglia: guilt by association

The most compelling evidence for microglia performing a destructive role in neurodegenerative disease is their physical association with dying cells, dystrophic neurites, and cellular debris². As the innate immune cell of the CNS, this is what microglia are supposed to do: remove cellular debris and promote wound healing and tissue repair. By removing dead and dysfunctional structures, they are neuroprotective, not destructive. Why is it accepted that microglia have a beneficial role in removing cellular debris during development, but then the same function during disease is presumed to be destructive? We argue that the concept of microglia being destructive in CNS disease has never been convincingly demonstrated. How would one obtain such evidence? One approach is to investigate human disease caused by mutations in innate immune cells. Microglia can promote neurodegeneration in these diseases, but do so by loss of protection, not by a gain of destructive behavior. For example, loss-of-function mutations in the microglial protein, Trem2, lead to increased susceptibility to Alzheimer's disease and frontotemporal dementia⁴. In an AD rodent model, failure to recruit activated microglia to A β deposits increases disease progression and decreases lifespan⁵. Similar attempts to produce gain-of-

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destructive mutations in experimental models of neurodegenerative diseases including ALS⁶, Rett syndrome⁷, and retinitis pigmentosa⁸ support loss (mostly phagocytic) of a protective role for microglia in these models. Consequently, gain-of-function mutations that activate microglia to damage the CNS have not been identified.

Do microglia play a role in cortical damage in multiple sclerosis?

We focus on subpial cortical demyelination for several reasons. Subpial cortical lesions are abundant, they contain few peripheral immune cells, most demyelinate cortical layers I-IV⁹, and they are generally considered to be most prominent in chronic MS brains¹⁰. Microglia are activated in MS cerebral cortex; they change shape and upregulate activation markers, including MHC Class II and CD 68. Neither activation marker is specific for microglia in cortical layers I-IV. In many postmortem MS brains, all cortical microglia, including those in myelinated cortex, have been found to be activated using these criteria. Based upon detection of oxidative enzymes and lipid peroxidation products in microglia¹¹, microglia-mediated oxidative stress has been proposed to cause cortical damage in MS. This is another instance of 'guilt by association' as neither the mechanisms nor the targets of microglia-mediated oxidative stress have been identified. Attempts to identify oxidative injury, mitochondrial damage, and iron-related pathology in rodent models of MS have also been disappointing¹². Oligodendrocyte progenitor cells (OPCs), which express low levels of antioxidant enzymes¹³, have been proposed as primary targets of microglia-mediated oxidative stress. Since OPC densities are increased in subpial lesions¹⁴, it is unlikely that microglial-mediated oxidative stress has a negative effect on cortical OPCs. In fact, microglia-mediated myelin removal during demyelination has been shown to facilitate remyelination¹⁵.

A possible role for B Cells in cortical demyelination

There is significant interest in the possible role of B cell follicles located in cortical meninges in causing subpial demyelination. While the presence of B cell follicles in MS brain meninges is controversial¹⁶, meningeal inflammation consisting of T and B cells has been documented by several studies¹⁷. While the number of these immune cells is low, their detection continues to support the concept that these immune cells secrete molecules that diffuse through the pial surface and cause subpial demyelination. Our studies of MS brains, however, provide several interesting observations that question such a mechanism. First, subpial demyelination does not occur as a continuous wave from the pial surface to cortical layer IV. They often skip layer I and simultaneously demyelinate layers II-IV. These demyelination dynamics do not support a diffusible factor that activates microglia as the cause of subpial demyelination. Secondly, these lesions seldom progress to subcortical white matter. There is no rationale for limiting the effect of such molecules, if they exist, on microglia present only in cortical layers I-IV. Finally, it is presently impossible to distinguish a destructive role of microglia from their phagocytic role in removing myelin debris in cortical lesions.

Whether microglia have a role in cortical damage is extremely important for the MS community. If this concept is accepted, development of therapies to reduce microglial activation could have devastating consequences. Microglia are in the brain to protect it and

they do so through several mechanisms. Phagocytic removal of debris is fundamental to slowing the progression of MS and other neurodegenerative diseases. Many brains in our MS autopsy cohort have lost over 30% of their volume and include significant cortical thinning. Amazingly, little cellular debris can be detected in these brains, which is indicative of the efficiency of microglia in removing cellular debris. Inhibition of microglial activation and suppression of debris removal would accelerate, not ameliorate, disease progression.

In summary, we conclude that there is no convincing evidence supporting the concept that microglia are responsible for the cortical damage in MS. Microglia respond to cortical damage, rather than causing it. Transection of cortical neuronal projections and loss of efferent inputs to the cortex have direct effects on cortical neurons and are responsible for much of the cortical damage. Finally, it is possible that a primary neurodegenerative process independent of the adaptive and innate immune systems plays a significant role in cortical damage in MS.

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