

# Much, if not all, of the cortical damage in MS can be attributed to the microglial cell – Yes

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For many years, it has been appreciated that multiple sclerosis (MS) pathology is characterized by demyelination of white and gray matter. Whether demyelinating white matter lesions (WMLs) and gray matter lesions (GMLs) represent a distinct type of pathology with a unique origin, or sequential stages in the evolution of a single type of MS, has not yet been resolved. Of interest is that although WMLs and GMLs are characterized by areas of focal demyelination, their histopathological features differ. Besides a lower number of infiltrating leukocytes in GMLs versus WMLs,<sup>1,2</sup> less activated microglia, as seen in WMLs, are present in GMLs. This calls into question the role of microglia in cortical gray matter damage in MS.

Microglia can present with several phenotypes. Under homeostatic conditions, they survey the area for pathogens and show a ramified phenotype. When being challenged, they can adopt multiple morphological (e.g. primed or amoeboid) and functional (e.g. protective or damaging) phenotypes.<sup>3</sup> At first, microglia are considered to have beneficial effects by phagocytosis of pathogens or cell debris. However, when it evolves into a chronic disease state, for example, MS, microglia are supposed to exert detrimental effects. Studies on microglia in MS have focused primarily on WMLs. Using postmortem human or animal-model tissue, microglia in WMLs were visualized using traditional markers like Iba1, MHCII, or CD68. However, in cortical lesions, little expression of MHCII and CD68 markers can be observed.<sup>2</sup> In addition, we previously observed that the chemokine CCL2 and its receptor CCR2 in microglia were highly upregulated in WMLs while being minimally present in GMLs.<sup>4</sup> This can possibly explain the relative paucity of leukocytes in the GMLs.

What we can learn from these studies is that microglia in WMLs and GMLs respond differently during MS pathology. Morphological and functional microglial changes in cortical MS lesions may be more subtle than observed in WMLs. As already shown in normal rat and mouse brain, microglial responsiveness is

influenced by its location.<sup>5,6</sup> Even so, we propose that gray matter-derived microglia can associate with or contribute to cortical damage in MS.

In support of a potential damaging role of microglia in cortical lesions is the observation that if microglia do have an activated phenotype at the rim of subpial cortical lesions, these patients had a significantly shorter disease duration and were younger at the time of death.<sup>7</sup> One of the factors produced by these microglia, possibly contributing to cortical pathology, is reactive oxygen species (ROS), e.g. nitric oxide or NADPH oxidase. Indeed, microarray data showed an increase in NADPH-oxidase subunits in cortical MS lesions compared to cortical control tissue.<sup>8</sup> Moreover, widespread oxidative injury to neurons was present in cortical lesions,<sup>9</sup> and activated microglia in cortical lesions were in close apposition to neurons<sup>2,10,11</sup> all pointing toward a role of microglial-derived ROS in mediating cortical neuronal damage.

Another source of data indicating a role for microglia in cortical damage is positron-emission tomography (PET) imaging studies performed in MS patients using translocator protein (TSPO) ligands binding to microglial cells. It has been shown by the traditional PK11195 ligand, and recently confirmed by the novel PBR28 ligand, that in addition to WMLs, there was clear binding of these ligands to microglia in cortical lesions as well as deeper GMLs.<sup>12,13</sup> Supportive for a role of cortical microglial cells in the disease process was the observation that the level of cortical microglial binding correlated to neurological disability and pathology.

Although not without controversy, meningeal inflammation is considered to facilitate subpial cortical demyelination accompanied by cortical microglial activation. Various immunohistological studies on MS postmortem and biopsy material showed that lymphoid follicles, present in meninges, associated with significant more activation of microglial cells and demyelination in the cortex.<sup>10,11</sup> These findings support, at least, an indirect role of microglia contributing to cortical damage.

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A way to ultimately demonstrate that microglia play a pivotal role in cortical damage during MS is to regionally and selectively ablate microglial function. Thus far, the antibiotic minocycline has been used in animal models of MS to reduce overall microglial activity. As a consequence, less axoglial disruption occurred with subsequent more survival of axons.<sup>14</sup> Also in a combination with hydroxychloroquine treatment of mice suffering from experimental autoimmune encephalomyelitis, minocycline suppressed clinical symptoms.<sup>15</sup> Of clinical interest is the recent observation that minocycline treatment significantly reduced the risk of conversion of clinically isolated syndrome patients to full-blown MS.<sup>16</sup>

Despite all research performed on microglia, there is still a large gap in knowledge of the function of microglia in MS pathology. In particular, the role of microglia in WMLs versus GMLs in MS pathology is largely unexplored. Based on the thus far available evidence, we postulate that microglia have a contributing role to cortical damage in MS. It is a future challenge in microglial research to further specify the role of lesion-specific microglia in MS pathology.

#### Declaration of Conflicting Interests

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