HHS Public Access

Author manuscript

Mult Scler. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Mult Scler. 2019 January ; 25(1): 19–20. doi:10.1177/1352458518796693.

Astrocytes play a crucial role in the formation and evolution of multiple sclerosis lesions - commentary

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Astrocytes perform varied functions in the context of inflammation, neurodegeneration and in general, during the response of the CNS to a broad range of challenges[1,2]. In multiple contexts, these functions have been shown to both promote and limit CNS pathology. In this issue of the Multiple Sclerosis Journal, Kerlero de Rosbo, Pitt and Ponath discuss the role of astrocytes in the formation and evolution of MS lesions.

At least three of their functions are relevant for the role of astrocytes in MS lesions. *First*, astrocytes can limit the recruitment of inflammatory cells to the CNS by modulating BBB integrity and stability[3], and also by forming an inducible barrier with their foot processes at the glia limitans[4,5]. *Second*, astrocytes control lesion-promoting functions in other cells. For example, astrocytes produce molecules that modulate T-cell function such as IL-27, which limits effector T cell responses directly and indirectly[6–8]. Astrocyte products can also promote neurotoxic activities in microglia, and recruit pro-inflammatory monocytes which contribute to disease pathology and lesion formation[2,9–11]. *Third*, astrocytes themselves can display neurotoxic activity, the factors controlling it and the specific neurotoxic astrocyte populations involved are just starting to be identified[12,13]. Based on these and other functions, astrocytes are likely to participate in the formation and evolution of MS lesions. Indeed, as suggested by Pitt and Ponath, some efficacious disease modifying therapies (DMTs) are known to act on astrocytes[14]. However, as mentioned by Kerlero de Rosbo, it has to be kept in mind that other DMTs whose mechanisms of action do not involve the direct modulation of astrocyte function are also highly efficacious, highlighting the crucial role of other cell types such as T cells, microglia and monocytes in lesion pathology.

While considering the contribution of astrocytes to MS pathology it should be kept in mind that multiple astrocyte populations have been identified based on phenotype and function. However, their specific roles in MS pathology are still unknown. Thus, it is possible that specific astrocyte populations may promote or limit lesion development; these populations have yet to be clearly identified to establish whether they represent different lineages or activation/polarization states of astrocytes, and also to determine whether they may be differentially targeted with specific therapeutics. In addition, astrocytes also play an

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important role in the neurodegeneration associated to MS progression[15–17]. Thus, it is important to identify specific astrocyte populations and mechanisms relevant to different aspects of MS pathogenesis (e.g. lesion formation versus brain atrophy), to define mechanisms of disease pathogenesis and develop new therapies targeting astrocytes and other CNS-resident cells.

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