Astrocyte TrkB may regulate copper transport and foster demyelination

Emanuela Colombo[1], Daniela Triolo[1], Bassani Claudia[1], Francesco Bedogni[2], Marco Di Dario[1], Giorgia Dina[1], Evelien Fredrickx[1], Isabella Fermo[3], Vittorio Martinelli[1], Jia Newcombe[4], Carla Taveggia[1], Angelo Quattrini[1], Giancarlo Comi[1] and Cinthia Farina[1]

[1]Institute of Experimental Neurology (INSpe), Division of Neuroscience, IRCCS San Raffaele Hospital, Milan, Italy. [2]San Raffaele Rett Research Centre, IRCCS San Raffaele Hospital, Milan, Italy. [3]Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Hospital, Milan, Italy. [4]NeuroResource, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, London, UK.

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS) characterized by demyelination, inflammation and neuronal damage. Astrocytes are the largest population of glial cells in the CNS and participate to both repair and inflammatory reactions occurring during neuroinflammation. In fact, the activation of specific intracellular signalling pathways may drive glial response from beneficial to detrimental, depending on the stimuli offered by the local inflamed milieu.

Here we investigated the contribution of the neurotrophin receptor TrkB in astrocytes to demyelination. Histological studies in MS lesions showed that astrocyte TrkB finely demarcated chronic demyelinated areas and was paralleled by neurotrophin loss, suggesting that a role for astrocyte TrkB in demyelination in response to stimuli other than neurotrophins. In vitro approaches highlighted that TrkB supported glia migration and proliferation even in absence of neurotrophins, indicating transactivation of TrkB signalling in response to inflammatory or toxic mediators. In vivo modeling of MS showed that mice with astrocyte-specific TrkB deletion were resistant to demyelination induced by autoimmune or toxic insults. Neuropathological investigations in MS and model lesions revealed upregulation of copper transporters in glia cells, and evidenced TrkB-dependent expression of the copper transporter CTR1 on glia cells during neuroinflammation. In vitro experiments confirmed that astrocyte TrkB supported expression of CTR1 via modulation of glial calcium flux in response to stimuli distinct from neurotrophins, thus leading to copper uptake and release which in turn caused oligodendrocyte and myelin loss.

Collectively, these data demonstrate a novel demyelination mechanism supported by astrocyte copper and dependent on astrocyte TrkB, and open to the possibility of restoring proper copper homeostasis as therapeutic target in MS.

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