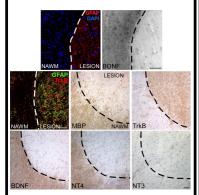
Astrocyte TrkB may regulate copper transport and foster demyelination

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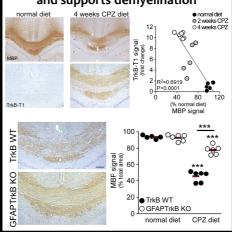
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Background Astrocytes are the largest population of glial cells in the CNS and participate to both repair and inflammatory reactions occurring during neuroinflammation. In fact, the activation of specific intracellular signalling pathways may drive glial response from beneficial to detrimental, depending on the stimuli offered by the local inflamed milieu. We have previously shown that upregulation of the neurotrophin receptor TrkB on astrocytes promotes neurodegeneration via glial production of nitric oxide. Here we demonstrated the contribution of astrocyte TrkB to demyelination, a key pathogenic feature of multiple sclerosis.

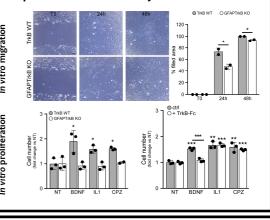
Chronic demyelinated MS lesions are finely demarcated by TrkB but lose neurotrophin expression



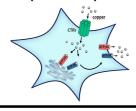
TrkB is upregulated on astrocytes in mice during cuprizone diet and supports demyelination

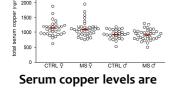


Astrocyte TrkB promotes migration and proliferation independently of specific ligand binding, indicating TrkB transactivation in response to inflammatory or toxic mediators



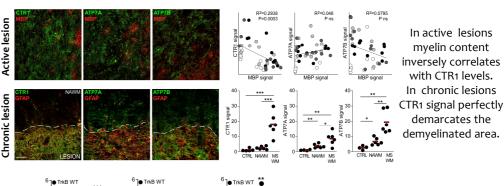
Copper trafficking is regulated by specific transporters





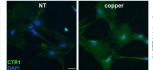
higher in women than in men but are comparable in healthy and MS subjects

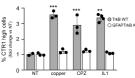
Astrocytes upregulate copper transporters in human and experimental MS



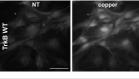
In animals under CPZ diet astrocytes upregulate copper transporters. CTR1 expression is mostly dependent on TrkB.

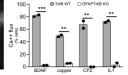
Inflammatory and toxic mediators upregulate astrocyte CTR1 in vitro via TrkB-dependent calcium flux

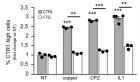




CPZ model







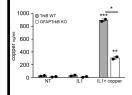
In active lesions myelin content

with CTR1 levels.

demarcates the

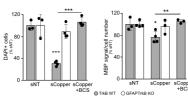
Under inflammatory conditions astrocytes release copper in a TrkB-dependent manner

Astrocyte-derived copper may promote oligodendrocyte death and myelin loss









CONCLUSIONS: We describe of dysregulation astrocyte MS mav demyelination. These observations open to the possibility of restoring copper homeostasis in the white matter as new therapeutic target in MS. Colombo et al. PNAS 2021

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