INTERPLAY BETWEEN GLIAL-IMMUNE CELLS IN MULTIPLE SCLEROSIS

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In Multiple Sclerosis (MS), an autoimmune and chronic demyelinating disease of the CNS, there is a crucial interplay between the immune cells that target myelin components and the resident glial cells that exacerbate the neuroinflammatory milieu but are also necessary for recovery. Within the inflammatory repertoire we found that S100B, a small inflammatory molecule, is increased in the CSF and serum of MS patients, and using an ex vivo demyelination model we further correlated increased levels of S100B with demyelination and inflammatory processes. Most attractively we showed that blockade of S100B using several approaches could reduce demyelination, improve oligodendrogenesis and myelin repair and shift microglia from a pro-inflammatory phenotype into a more neuroprotective one. Next, we used the experimental autoimmune encephalomyelitis (EAE) animal model, that mimics MS pathogenesis since it is based on CD4+/CD8+ T-cell mediated self-reaction against myelin MOG protein, eliciting focal demyelination, immune cell infiltration and gliosis in parallel with neurological affections. Interestingly, we observed that clinical disease onset was delayed in EAE animals following S100B blockade using a small molecule, reaching a lower clinical score and having a faster recovery, which was corroborated by less motor disability as assessed by rotarod and pole tests. Further, brain/spinal cord histopathology revealed a decreased level of demyelination and immune cell infiltration in EAE-induced animals when S100B was neutralized. These results were corroborated by a reduction of astrocytes and microglia reactivity, prevention of the exacerbated expression of inflammatory factors (TNF-α/IL-1β) and increasing that anti-inflammatory ones (IL-10). Additionally, discrimination of the brain infiltrating immune cell populations of EAE-induced animals demonstrated that S100B blockade decrease the percentage of Th1 and Th17 cells alongside with decreased Th17/Treg ratio. Overall, our results indicate that S100B is involved in MS pathology both with an effect at CNS resident cells as well as at the immune cells, suggesting that its inhibition may be a new therapeutic strategy acting in the interplay of glia-immune cells during MS pathogenesis.
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