Myelin alters the inflammatory phenotype of macrophages by activating PPARs.

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Research question and background

Foamy macrophages, containing myelin degradation products, are abundantly found in active multiple sclerosis (MS) lesions. Recent studies have described an altered phenotype of macrophages after myelin internalization. However, mechanisms by which myelin affects the phenotype of macrophages and how this phenotype influences lesion progression remain unclear.

Methods and tissues used

By using in vitro assay, we identified the role that PPARs play in the phenotype if myelin-containing macrophages. An animal model for MS was used to define the impact of PPAR ligands on neuroinflammation. MS tissue was used to define PPAR activation in myelin-containing macrophages in MS lesions.

Results and conclusion

We demonstrate that myelin as well as phosphatidylserine (PS), a phospholipid found in myelin, reduce nitric oxide production by macrophages through activation of peroxisome proliferator-activated receptor β/δ (PPARβ/δ). Furthermore, uptake of PS by macrophages, after intravenous injection of PS-containing liposomes (PSLs), suppresses the production of inflammatory mediators and ameliorates experimental autoimmune encephalomyelitis (EAE), an animal model of MS. The protective effect of PSLs in EAE animals is associated with a reduced immune cell infiltration into the central nervous system and decreased splenic cognate antigen specific proliferation. Interestingly, PPARβ/δ is activated in foamy macrophages in active MS lesions, indicating that myelin also activates PPARβ/δ in macrophages in the human brain. Our data show that myelin modulates the phenotype of macrophages by PPAR activation, which may subsequently dampen MS lesion progression. Moreover, our results suggest that myelin-derived PS mediates PPARβ/δ activation in macrophages after myelin uptake. The immunoregulatory impact of naturally-occurring myelin lipids may hold promise for future MS therapeutics.