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Myelin induced alterations in cellular lipid metabolism direct the reparative properties of microglia.

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Infiltrated macrophages and resident microglia play a central role in the pathology of demyelinating diseases such as multiple sclerosis (MS). They promote lesion development by stimulating neuroinflammation, demyelination, and neurodegeneration by releasing inflammatory and toxic mediators. However, phagocytes can also adopt a lesion-resolving phenotype that facilitates remyelination through the secretion of anti-inflammatory and neurotrophic factors, and by the clearance of myelin debris. Our findings show that the lipid load of macrophages and microglia is a major determinant of their reparative potential. Phagocytosis of myelin initially reduces the inflammatory activity of phagocytes. However, continuous accumulation of myelin-derived lipids eventually blunts their protective features, and induces an inflammatory transcriptional profile. We show that promoting lipid efflux from foamy phagocytes resolves inflammation and promotes remyelination. Hence, targeting lipid metabolism in macrophages and microglia provides a promising strategy to induce repair in the central nervous system.