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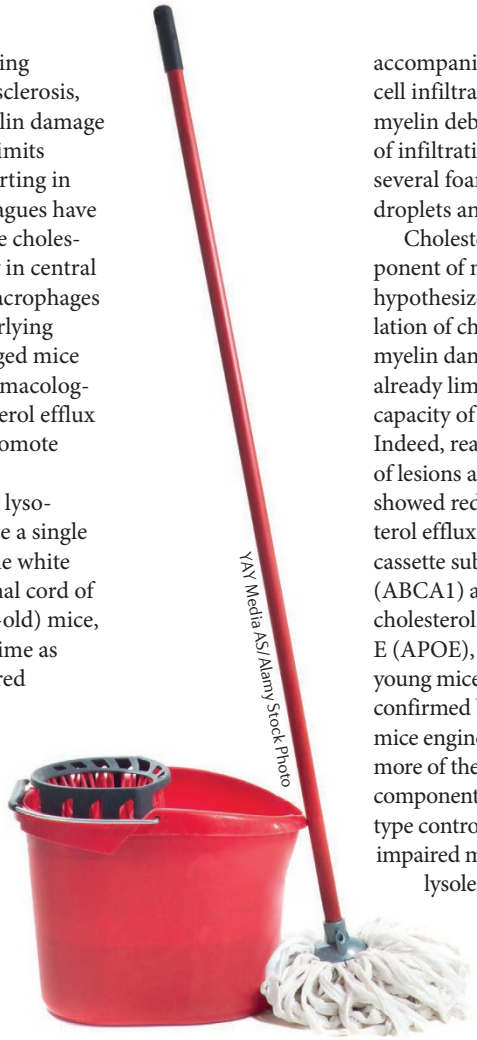
REGENERATIVE MEDICINE

Cholesterol clearance restores remyelination



In progressive demyelinating diseases such as multiple sclerosis, the capacity to repair myelin damage declines with age, which limits functional recovery. Reporting in *Science*, Simons and colleagues have pinpointed overload of the cholesterol clearance machinery in central nervous system (CNS) macrophages as a key mechanism underlying remyelination failure in aged mice and have shown that pharmacological stimulation of cholesterol efflux from macrophages can promote myelin repair.

The researchers used a lysolecithin injection to induce a single demyelinating lesion in the white matter of the brain or spinal cord of mice. In young (3-month-old) mice, lesion size declined over time as damaged myelin was cleared followed by remyelination. By contrast, lesion repair was hampered in aged (12-month-old) mice, as evidenced by significantly larger lesions than in young mice. Lesion persistence in old mice was accompanied by sustained immune cell infiltration and accumulation of myelin debris within the lysosomes of infiltrating phagocytes, as well as several foam cells containing lipid droplets and cholesterol crystals.

Cholesterol is the main component of myelin. The authors hypothesized that rapid accumulation of cholesterol following myelin damage might overwhelm the already limited cholesterol-handling capacity of phagocytes in aged mice. Indeed, real-time quantitative PCR of lesions at 4 days post-injection showed reduced levels of the cholesterol efflux transporters ATP-binding cassette subfamily A member 1 (ABCA1) and ABCG1, and of the cholesterol carrier apolipoprotein E (APOE), in aged compared with young mice. The findings were confirmed by studies in knockout mice engineered to lack one or more of these cholesterol-handling components: compared with wild-type controls, mutant mice showed impaired myelin restitution following lysolecithin-induced CNS lesion.

Next, Simons and co-workers tested the effect of GW3965, an agonist of the liver X receptor — a nuclear receptor that controls the expression of *Abca1*, *Abcg1* and *Apoe*. Oral treatment of aged mice with GW3965 significantly improved lesion recovery, reducing lesion size, infiltration of immune cells and accumulation of foam cells and cholesterol crystals.

Last, studies in mouse bone marrow-derived macrophages suggested that accumulation of myelin debris triggers an inflammasome-mediated pyroptotic death pathway involving lysosomal permeabilization and activation of caspase 1. Moreover, mice and macrophages with impaired cholesterol handling owing to lack of APOE showed increased activation of caspase 1 compared with wild-type counterparts in response to myelin debris.

These studies suggest that interventions to improve cholesterol handling could promote regenerative processes following demyelination.

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ORIGINAL ARTICLE Cantuti-Castelvetri, L. *et al.* Defective cholesterol clearance limits remyelination in the aged central nervous system. *Science* http://dx.doi.org/10.1126/science.aan4183 (2018)