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Review

Local cholesterol metabolism orchestrates remyelination

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Cholesterol is an essential component of all cell membranes and particularly enriched in myelin membranes. Myelin membranes are a major target of immune attacks in the chronic neurological disorder multiple sclerosis (MS). During demyelinating insults, cholesterol is released from damaged myelin, increasing local levels of this unique lipid and impeding tissue regeneration. Here, we summarize the current knowledge of cholesterol-dependent processes during demyelination and remyelination, emphasizing cell type-specific responses. We discuss cellular lipid/cholesterol metabolism during early and late disease phases and highlight the concept of lipid-based pharmacological interventions. We propose that knowledge of the interplay between cell type-specific cholesterol handling, inflammation, and blood–brain barrier (BBB) integrity will unravel disease processes and facilitate development of strategies for therapies to promote remyelination.

Highlights

The myelin sheath is a structure of layered cholesterol-rich membranes that extend from the plasma membrane of oligodendrocytes. Myelin membranes wrap around and insulate neuronal axons to facilitate rapid impulse conduction.

Myelination starts during embryogenesis and continues postnatally. Myelin integrity is crucial to maintain CNS function. As cholesterol import into the CNS is very limited, developmental myelination is driven by local synthesis, predominantly in oligodendrocytes.

Perturbation of CNS cholesterol metabolism is often linked to neurological disease, including the most common inflammatory neurological disorder, multiple sclerosis (MS). MS is characterized by focal loss of myelin, referred to as demyelinated lesions.

Repair of lesions is linked to local cholesterol metabolism, involving the cooperation between CNS cell types. Endogenous repair strategies differ between the acute and chronic phases of myelin disease, and their efficacy attenuates with disease chronicity.

Future therapeutic interventions might consider targeting critical steps of CNS cholesterol metabolism to support remyelination.

CNS lipid metabolism

The primary origin of brain cholesterol is *de novo* synthesis, likely involving all cell types of the CNS. The entry of peripheral cholesterol to the brain is prevented by the shielding properties of the BBB. In the adult CNS, the majority (~70–80%) of cholesterol is located in lipid-rich myelin membranes [1,2]. As a multilayered stack of oligodendrocyte membranes that wrap around neuronal processes, myelin insulates axons to effect fast nerve conduction.

During early postnatal development, oligodendrocyte precursor cells (OPCs) differentiate to mature oligodendrocytes. This involves crosstalk between a plethora of stage-specific transcription factors [e.g., Olig1/2, SOX10, Myrf, retinoid X receptors (RXRs)], signaling pathways [e.g., mammalian target of rapamycin (mTOR), Wnt/β-catenin, Sonic hedgehog, fibroblast growth factors (FGFs), peroxisome proliferator-activated receptors (PPARs)], and increased cholesterol synthesis [3–5]. This is followed by enhanced intracellular lipid trafficking to the growing myelin sheath [3,6,7]. In mammals, cholesterol production in the brain accounts for the highest synthesis rates across the body [1]. Cholesterol availability is rate-limiting for myelination, and the majority of the cholesterol required for myelination is synthesized by oligodendrocytes themselves [8]. In addition, astrocyte-derived cholesterol complements oligodendrocyte-synthesized cholesterol by transfer of apolipoprotein E (ApoE)-containing lipoproteins, the transport vehicles for cholesterol and lipids in the CNS [9]. After completion of developmental myelination, oligodendrocytes continue low-rate cholesterol synthesis for myelin maintenance. In adults, steady-state brain cholesterol production is chiefly attributed to astrocytes that supply neighboring neurons and glial cells to meet their cellular demands [10]. CNS cholesterol has a very long half-life (about 1 year in mice and 5 years in humans), compared with peripheral cholesterol (a matter of days) [10–12]. Accordingly, in adult mice, genetically induced loss of cholesterol synthesis in one CNS cell type, that is, astrocytes, oligodendrocytes, neurons, microglia, or endothelial cells, is efficiently compensated by enhanced transport from other cell types [8,9,13,14], highlighting the flexibility of CNS cholesterol metabolism.

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Of note, cholesterol synthesis rates decrease in the aging brain [15–17]. Together with dysregulation of metabolic pathways, increasingly compromised functions of microglia/macrophages, and elevated inflammatory processes collectively called 'inflammaging', perturbed cholesterol homeostasis likely contributes to aging and its risk to develop neurodegenerative disease [18], particularly ones involving impairments of white matter tracts [19,20].

Perturbations in CNS cholesterol homeostasis are not only caused by primary defects in lipid/cholesterol metabolism, but can also result from diverse pathologies unrelated to lipid metabolism [21,22]. Especially, etiologies affecting myelin membranes such as MS are linked to dysregulated cholesterol homeostasis [23–25]. This review article focuses on the current knowledge of the relevance of cell type-specific cholesterol metabolism to demyelinating disease. We propose different disease mechanisms related to cholesterol metabolism during acute and chronic demyelination. While cholesterol recycling processes dominate repair after acute demyelination, newly synthesized cholesterol drives remyelination in chronic disease. Moreover, the analysis of cell type-specific defects in cholesterol metabolism has revealed the importance and the limits of cholesterol transport between the cells in the brain. The understanding of disease mechanisms in models of myelin disease may lead to therapeutic advances.

Cholesterol metabolism during demyelination and remyelination

In demyelinating diseases such as MS (Box 1), damaged myelin is cleared by phagocytes and new myelin sheaths are generated from existing or newly differentiated oligodendrocytes. Demyelination/remyelination events likely occur also during the prodromal disease phase in MS, before manifestation of symptoms, as well as in healthy individuals. In both cases, endogenous repair efficiently restores myelin sheaths [26,27]. However, with disease progression and chronicity, these regenerative processes exhaust and the failure to remyelinate ultimately leads to axonal damage, preventing clinical recovery [27,28].

In MS patients, new lesions can develop regardless of the discrete relapsing and remitting neurological events. Moreover, the development of a new lesion can coincide with the repair of another lesion. Therefore, rodent MS models with induced causality and spatiotemporal predictability of

Box 1. Multiple sclerosis

MS is the most common inflammatory, demyelinating neurodegenerative disease of the CNS worldwide. The pathological hallmark of this chronic disease is demyelinating lesions driven by impaired immune regulation. Concordantly, peripheral immune cells such as B and T lymphocytes as well as microglia, the resident immune cells of the CNS, have been linked to expression of MS risk variant genes that were discovered by genome-wide association studies [119,120]. MS typically manifests in young adults as clinically isolated syndrome, but is likely preceded by subthreshold demyelinating events. Pathophysiological and clinical presentations are highly heterogeneous. In most cases, in early disease, autoinflammatory episodes with neurological symptoms (relapses) alternate with remission phases. However, lesion development and regeneration can occur in parallel in MS patients. Complete repair of demyelinated lesions might be possible in early disease. However, disease chronicity, further aggravated by aging and environmental and/or genetic factors, persistently damages the CNS, leading to progressive neurological disability.

The cause of MS is unknown and likely multifactorial. Disease mechanisms differ in the acute and chronic disease phases, but also share several common features. Autoreactive T lymphocytes and other effector immune cells enter the brain parenchyma by diapedesis across the BBB and attack myelin membranes and/or neurons. Inflammatory mediators contribute to pathogenesis by triggering myelin degeneration. Phagocytes, mainly CNS microglia and macrophages, mediate removal of myelin debris. In addition, inflammatory mediators perturb CNS homeostasis and locally compromise the BBB, allowing the entry of blood-borne factors.

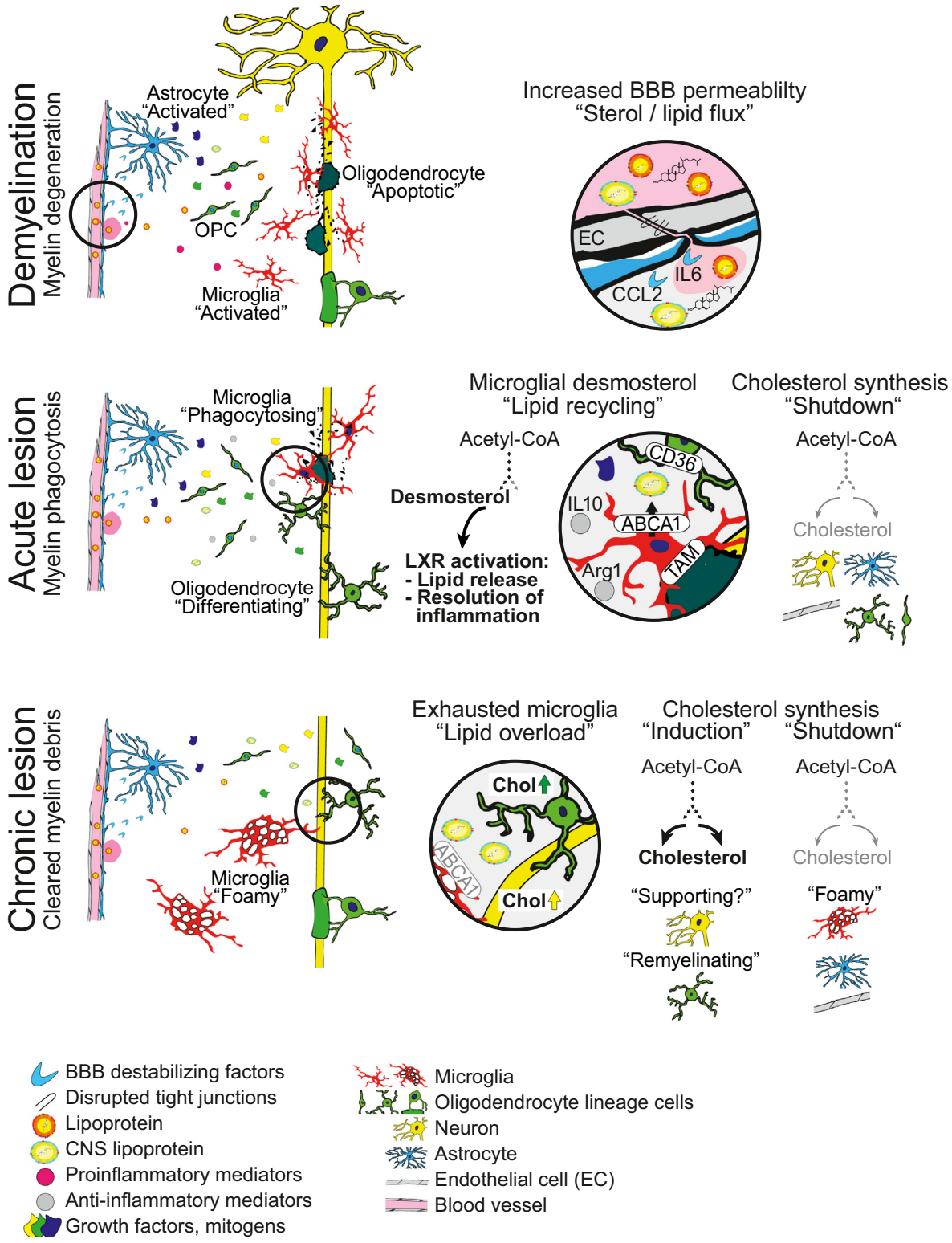
The current MS treatments mainly target neuroinflammation and efficiently alleviate symptoms as well as reduce the rate of demyelinating episodes but do not cure this devastating disease. There is an urgent need for medications that support myelin repair. Several such compounds are currently in development and might in combination with immunomodulators change the landscape of MS therapy in the future.

pathology have been instrumental in exploring distinct phases of demyelination and remyelination [29,30]. In experimental animals, a cycle of inflammatory demyelination and remyelination essentially involves sequential phases of phagocyte activation, myelin clearance, resolution of the inflammation, and establishment of a local proregenerative microenvironment [31]. Activation of phagocytes precedes phagocytosis of myelin debris, involving the TAM receptor tyrosine kinases (Tyro3, Axl, MerTK) and triggering receptor expressed on myeloid cells 2 (TREM2) that are part of the disease-associated microglia (DAM) program [32–37]. Microglia/macrophages show the highest phagocytic activity, but also astrocytes contribute to myelin clearance [38]. The internalization and turnover of myelin lipids and proteins in these cells, which involve autophagic processes [39–42], then contributes to the resolution of neuroinflammation [43,44]. As myelin debris and a proinflammatory environment strongly inhibit oligodendroglial differentiation [45], the lysosomal degradation of myelin lipids and proteins in phagocytes is a prerequisite for repair of demyelinated lesions. Moreover, recycling of internalized lipids and export to oligodendrocytes can support oligodendrocytes to enrich lipids for remyelination.

Cholesterol is a major and essential component of myelin membranes. As mammals cannot degrade it, the cholesterol from degenerating myelin membranes is either locally recycled, as described previously, or exported from the brain. Experimental interference at distinct levels of cholesterol/lipid metabolism has unraveled the intimate interplay between myelin membrane destruction, intracellular cholesterol/lipid trafficking, efflux, and recycling, as well as the inflammatory profile of phagocytes [46–48]. Based on these lines of evidence, we hypothesize that cholesterol metabolism critically influences repair of demyelinated lesions. However, the particular roles of this metabolic pathway in the different disease phases differ. While repair of acute lesions is driven by cholesterol recycling, remyelination after chronic demyelination requires local cholesterol synthesis, as outlined later (Figure 1).

The uptake of cholesterol from degenerating myelin increases cellular cholesterol levels in phagocytes, which in turn inhibits their rate of cholesterol synthesis. Feedback regulation of cholesterol synthesis occurs at transcriptional, translational, and post-translational levels. It involves sterol regulatory element-binding protein 2 (SREBP2), the master transcriptional regulator, as well as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and squalene monooxygenase, the rate-limiting enzymes of this pathway [49]. Excess intracellular cholesterol can also enhance the synthesis of oxysterols [50,51]. By contrast, uptake of cholesterol from myelin debris in the proinflammatory environment of actively demyelinating lesions increases the sterol synthesis pathway, occurring exclusively in phagocytes [13]. During active demyelination at the edge of expanding lesions, phagocytes contain myelin debris including lipids but, in contrast to chronic lesions, only rarely appear lipid-laden and foamy [52]. This is notable given the high amount of released lipids from first-time degenerating myelin in white matter areas and suggests instantaneous recycling and export of internalized cholesterol to facilitate the rapid functional repair of demyelinated lesions in early disease. Likely recycled cholesterol, presumably contained in lipoproteins, is transferred to astrocytes, oligodendrocytes, endothelial cells, and neurons, where it leads to local downregulation of cholesterol synthesis and increased synthesis of several oxysterols [13,53–55].

Remarkably, functional CNS phagocyte sterol synthesis following myelin uptake mediates cholesterol efflux and limits inflammation [13]. Similarly, phagocytosing macrophages in atherosclerosis increase reverse cholesterol transport and suppress inflammatory responses [56]. By limiting enzymatic activity of the terminal cholesterol synthesis enzyme 24-dehydrocholesterol reductase (Dhcr24) by transcriptional downregulation, lipid-internalizing phagocytes synthesize the immediate cholesterol precursor, desmosterol (Figure 1). By its liver X receptor (LXR)-activating function (Box 2), desmosterol induces expression of cholesterol efflux genes such as *Abca1* and



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Box 2. LXR signaling

LXRs are transcription factors of the nuclear receptor family. The NR1H3 and NR1H2 genes encode the two isoforms of LXR, LXRα and LXRβ. LXRs heterodimerize with RXRs and interact with agonists, coactivators, or corepressors to regulate transcription. LXRs were originally identified based on their function as major regulators of cellular lipid/cholesterol transport and metabolism. Only recently, it has become evident that LXRs couple lipid/sterol metabolism to inflammatory responses.

Natural activators of LXR signaling are intermediates of the cholesterol synthesis pathway as well as oxidized derivatives of cholesterol. LXR activation leads to the reduction of cellular cholesterol levels in two ways: it promotes the efflux and attenuates the uptake of cholesterol. Cholesterol efflux is facilitated, for instance, by upregulation of the expression of efflux ATP binding cassette (ABC) transporters and of extracellular lipid acceptors, apolipoproteins such as ApoE in the CNS. Enhanced turnover of members of the low-density lipoprotein receptor (LDLR) family mediates attenuated uptake of cholesterol. In addition, LXR activation increases fatty acid synthesis, especially of long-chain polyunsaturated fatty acids, by activating expression of several genes, including the master regulator of fatty acid synthesis, SREBP1c, and key enzymes such as fatty acid synthase. Increased fatty acid synthesis and transport might contribute to the reduction of cellular levels of free cholesterol by promoting esterification and/or export. The anti-inflammatory activity of LXRs requires agonist binding and SUMOylation to mediate transrepression of nuclear factor kappa B (NF-κB) target genes such as interleukin-1β (IL-1β).

Because of the potential relevance for treating various inflammatory or inflammation-related disorders including atherosclerosis, cancer, and neurodegenerative diseases, several synthetic LXR agonists have been developed with the aim to reduce known side effects such as hepatic steatosis, hypertriglyceridemia, and elevated LDL cholesterol. Despite encouraging preclinical studies, LXR agonists are not in clinical use due to adverse reactions.

facilitates the resolution of the proinflammatory phenotype [13,56], likely by direct and indirect mechanisms [57,58]. Conversely, genetic loss of sterol synthesis in microglia leads to the appearance of proinflammatory, lipid-loaded foamy phagocytes, due to downregulated efflux transporters [13]. In active MS lesions, DHCR24 is downregulated, desmosterol levels are increased, and the LXR signaling pathway is activated [13,59,60]. Together with the observation that mutation in the LXRα [nuclear receptor subfamily 1 group H member 3 (NR1H3)] gene leads to increased disease risk [61], these findings point to a pivotal role for LXR signaling in phagocyte-mediated MS lesion repair. In addition to desmosterol, oxysterols are potent endogenous LXR agonists that contribute to LXR activation. As oxysterols can readily pass the BBB, they might serve as candidate disease biomarkers [62]. It remains debated whether the rate of myelin degradation depends on the presence of a proinflammatory environment during demyelination. It is possible that proinflammatory mediators serve to maintain desmosterol synthesis in phagocytes. In this model, the resulting activation of LXR signaling then prevents intracellular lipid accumulation and facilitates efficient lipid/cholesterol recycling in early MS lesions.

In chronic lesions, however, local cholesterol/lipid metabolism is strikingly different and LXR signaling is less relevant (Figure 1). In particular, the rim of chronic active MS lesions contains numerous foam cells with internalized myelin, suggesting suboptimal lipid recycling. Although the underlying mechanism leading to the formation of foam cells in human disease is still not

Figure 1. Cholesterol-dependent endogenous repair processes in demyelinated lesions. This schematic depicts a proposed model of endogenous, cholesterol-dependent repair processes in both acutely and chronically demyelinated lesions. For simplicity, peripheral effector cells have been omitted. Demyelination: experimental demyelination leads to oligodendrocyte death, oligodendrocyte precursor cell (OPC) proliferation, and gliosis that is accompanied by increased blood–brain barrier (BBB) permeability mediated by astrocyte-derived BBB-destabilizing factors such as CC chemokine ligand 2 (CCL2) and interleukin-6 (IL-6), enabling influx of peripheral factors including lipids. Active lesions: in response to destruction of the lipid-rich myelin sheet, expression of cholesterol synthesis genes is reduced in most glial cells and neurons ('Shutdown'). Myelin clearance by CNS phagocytes, predominantly microglia, is essential for the resolution of inflammation and the establishment of a local proregenerative microenvironment that allows oligodendrocyte differentiation. Following myelin uptake, which involves TAM receptor tyrosine kinases (Tyro3, Axl, MerTK), microglia synthesize the liver X receptor (LXR) ligand desmosterol to enable ATP binding cassette subfamily A member 1 (ABCA1)-mediated cholesterol efflux ('Lipid recycling') and adaption of an anti-inflammatory expression profile [e.g., interleukin-10 (IL-10), arginase 1 (Arg1)]. Thus, in acute experimental lesions, oligodendrocytes rely on lipid import, presumably by upregulating lipid receptors such as scavenger receptor class B, member 3 (CD36), for differentiation and myelination. Chronic lesion: chronic experimental demyelination leads to suboptimal lipid recycling and the appearance of numerous foamy phagocytes, possibly a consequence of ineffective LXR signaling ('Exhausted microglia'). In addition, persistent astrocyte reactivity with downregulated expression of cholesterol synthesis genes contributes to limited remyelination. Partial remyelination in chronic lesions is attributed to endogenous cholesterol synthesis in oligodendrocytes and neurons.

resolved, their signature is compatible with a rather anti-inflammatory, proregenerative phenotype in MS and atherosclerosis [56,63]. The entity of foamy phagocytes possibly encompasses the entire spectrum of myelin-containing anti-inflammatory foamy phagocytes in early disease as well as dysfunctional cholesterol crystal-containing lipid droplet-rich proinflammatory foam cells. While during early disease, cholesterol efflux transporter-deficient (*Abca1/Abcg1* knockout) foamy phagocytes have an anti-inflammatory phenotype, suggesting LXR signaling, sterol synthesis-deficient microglia also downregulate efflux transporters but increase expression of proinflammatory mediators, reflecting compromised LXR activation [13].

Aging is one of the major impediments in adequate remyelination contributing to reduced OPC proliferation and differentiation [28]. In the aging brain, reduced cholesterol synthesis and progressively reduced cholesterol content in aged myelin coincides with low-grade inflammation [16,64]. Reduced expression of cholesterol synthesis genes during aging has been attributed to reactive astrocytes [17,65], likely affecting their supply to oligodendrocytes. The altered astrocyte signatures might also contribute to the increasingly compromised clearance of myelin debris by microglia/macrophages in the aging brain [20,66,67]. Ineffective LXR signaling perturbs lipid recycling and interferes with remyelination, which in preclinical models, can be overcome by rejuvenation of microglia/macrophages as shown in mice by parabiosis experiments [68], or by LXR/RXR agonists [66,69].

Thus, genetic predisposition, environmental and age-related cues, or disease chronicity can affect sterol synthesis or directly interfere with LXR activation and stimulate the development of proinflammatory foam cells [70]. However, several signaling routes beyond LXR that also compromise lipid trafficking and efflux can be involved in the transition of phagocytes to foam cells, for example, PPAR signaling [71,72]. In phagocytes, extensive lipid loading ultimately leads to inflammasome activation and cell-autonomous death [13,66,73]. Despite extensive lipid loading of phagocytes, enhanced OPC proliferation can occur [13,66]. However, oligodendrocyte differentiation and remyelination is limited under these conditions. Together with the downregulation of cholesterol synthesis in oligodendrocytes during early disease [13,55], these findings underscore the importance of an equilibrated microenvironment and horizontal cholesterol transfer to oligodendrocytes to facilitate remyelination.

Under physiological conditions, the BBB prevents the exchange of cholesterol between the circulation and brain. However, in MS as well as in animal models of demyelinating disease, the BBB is locally compromised already early during lesion formation [74–77]. We hypothesize that part of the cholesterol from damaged myelin, either directly or contained in lipoproteins, is lost from the CNS across the impaired BBB (Figure 1). Moreover, during chronic disease, myelin debris is absent, having been cleared, and only residual (exhausted) lipid-laden foamy phagocytes that are incapable of lipid recycling remain. Hence, after chronic demyelination, local cholesterol levels might be very low. Consequently, remyelination requires active cholesterol synthesis in oligodendrocytes [13,54]. Moreover, the efficacy of lesion repair depends not only on the synthesis of myelin membranes but also on the recruitment of OPCs and their differentiation to mature oligodendrocytes. Correspondingly, chronic MS lesions can contain numerous OPCs that fail to differentiate [27]. By contrast, a local environment that supports repair beyond the clearance of myelin debris and resolution of inflammation (see the aforementioned information) facilitates oligodendrocyte differentiation. A study from our group has shown that dietary cholesterol supplementation during remyelination in chronic disease alters the local expression of growth factors and mitogens [23]. More specifically, increased cholesterol availability modulated the expression of factors such as platelet-derived growth factor A, Sonic hedgehog, and members of the FGF family (e.g., *Fgf1* and *Fgf2*), which have been critically linked to lesion repair [78–80].

Thus, increasing cholesterol availability especially during chronic disease, when cholesterol is limited, favors a microenvironment that allows expression of cues that support oligodendrocyte proliferation and differentiation [23] (Figure 2). Furthermore, enhancement of local cholesterol levels can directly facilitate oligodendrocyte differentiation and remyelination. Microglia and astrocytes downregulate cholesterol synthesis in chronic lesions and hence do not supply sufficient amounts of cholesterol. Our group has found that in addition to oligodendroglial synthesis, unexpectedly, neurons increased cholesterol production, which contributed to lesion repair especially in the presence of neuronal activity [55].

Taken together, we hypothesize that repair after acute demyelination is facilitated by cholesterol recycling. In active lesions, the sterol synthesis pathway is active only in microglia and leads to the synthesis of the cholesterol precursor desmosterol, which activates LXR signaling. Moreover, promoting sterol synthesis by adding the pathway intermediate squalene feeds into desmosterol synthesis. By contrast, after chronic demyelination, this recycling pathway is inefficient. Here, local cholesterol availability facilitates repair, which can originate from oligodendroglial or neuronal synthesis as well as from the circulation.

Toward lipid-based therapy and dietary interventions

Therapeutic management of MS has largely focused on targeting inflammation. Current disease-modifying treatments provide a variety of ways to decrease the rate of inflammatory events and delay disease progression. Nonetheless, strategies that combine anti-inflammatory and

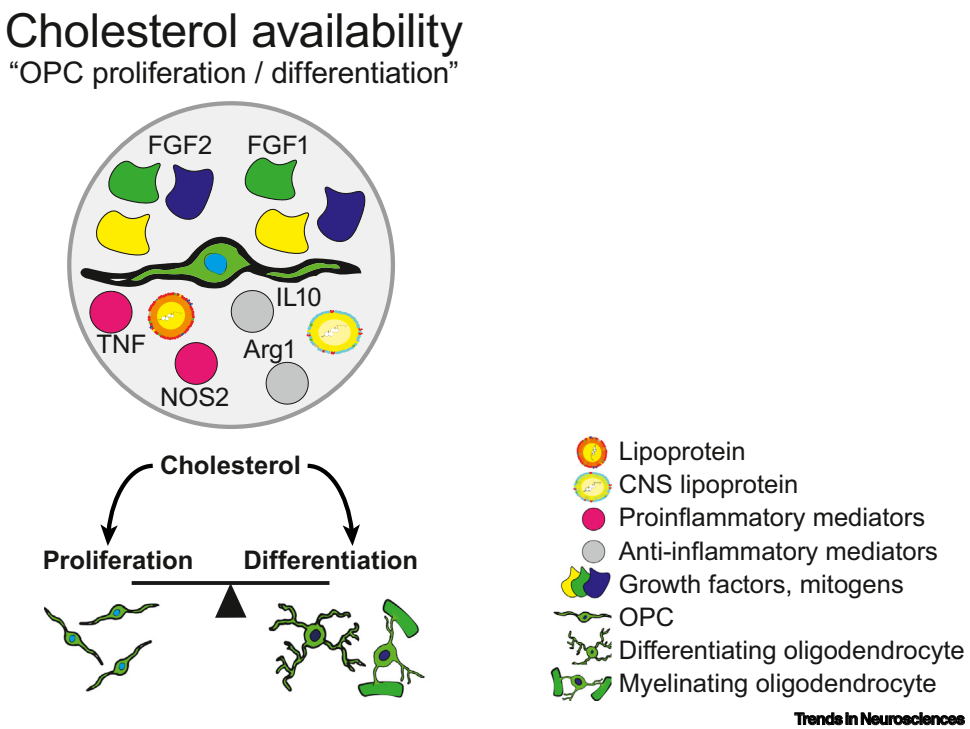

Figure 2. Influence of the local environment of demyelinated lesions on oligodendrocyte precursor cell (OPC) proliferation and oligodendrocyte differentiation. The fate of demyelinated lesions is determined by the local microenvironment involving proinflammatory mediators such as tumor necrosis factor α (TNFα), anti-inflammatory mediators such as interleukin-10 (IL-10), mitogenic factors such as fibroblast growth factor 2 (FGF2), and factors that promote oligodendrocyte differentiation such as FGF1. Cholesterol availability critically balances proliferative and prodifferentiation signals to local OPCs. Abbreviation: NOS2, nitric oxide synthase 2.

proregenerative approaches are likely needed to effectively restore neurological function. Interestingly, compounds that are directly or indirectly linked to lipid metabolism have recently gained attention as potential remyelination therapies (emerging myelin repair agents are reviewed in [81–83]).

In line with the fact that cholesterol is essential for myelin membrane synthesis, the complete block of cholesterol synthesis by simvastatin after cuprizone-mediated demyelination impairs OPC differentiation and remyelination [84]. Clinical trials with statins in patients with MS have yielded mixed results[i–v]. However, several compounds (e.g., tamoxifen, clemastine, benztropine) that inhibit enzymes of the cholesterol synthesis pathway downstream of HMG-CoA reductase and squalene synthase stimulate OPC differentiation and myelination. This dichotomy may be explained by the fact that these compounds do not deplete cellular sterols. Rather, increased OPC differentiation after treatment with these drugs has been attributed to accumulation of either 8,9-unsaturated sterol intermediates or 24,25-epoxycholesterol [85–87]. However, the mechanism(s) by which these sterol compounds induce OPC differentiation remains unsolved. In addition to interfering with sterol metabolism, pleiotropic effects of these inhibitors might support remyelination, such as estrogen receptor targeting of tamoxifen [88] and the antimuscarinic effect of clemastine [89,90]. Interestingly, short-term treatment with simvastatin can also induce OPC differentiation *in vitro* [91], arguing in favor of a mechanism related to altered gene transcription signatures. Following demyelination *in vivo* in mice, and in cell culture experiments, supplementation of cholesterol or the cholesterol synthesis intermediate squalene leads to enhanced OPC differentiation and (*in vivo*) myelination [13,23,24].

In studies in mice, pharmaceutical inhibition or genetic ablation of cholesterol synthesis in the oligodendrocyte lineage strongly limits developmental myelination and remyelination in chronic disease [8,13,84]. Thus, in the lipid-rich environment of an acute demyelinating lesion, recycled cholesterol facilitates remyelination, while in chronic disease, remyelination requires local cholesterol synthesis. Hence, due to potential inhibitory effects on repair processes, therapeutic interventions that inhibit cholesterol synthesis and lack cellular specificity should be administered with caution [92,93]. This becomes even more relevant in light of the chronicity of MS and the gradual decrease of cholesterol availability in the aged brain. Of note, the standard first-line interferon-beta treatment itself reduces total serum cholesterol [94]. By contrast, cholesterol synthesis-stimulating antipsychotic drugs such as quetiapine and clozapine have shown potent proregenerative effect by inducing oligodendrocyte differentiation and limiting inflammation in MS mouse models [95–100]. A Phase I/II human trial[vi] evaluates the safety and tolerability of quetiapine in patients with relapsing and progressive MS. Stimulation of cholesterol synthesis by quetiapine might favor application specifically in the latter patient group.

The concept of enhancing cholesterol trafficking in MS has considerable experimental corroboration. For example, supporting cholesterol trafficking facilitates remyelination in preclinical experiments, for example, by LXR agonists that stimulate cholesterol recycling [13,101], by the disaccharide trehalose that promotes noncanonical autophagy-mediated lipid clearance [42], as well as by ApoE mimetics that enhance CNS delivery of cholesterol/lipids [102]. LXR signaling has the added benefit of simultaneously dampening inflammation and facilitating cholesterol recycling, thus stimulating oligodendrocyte differentiation and supporting remyelination. Interestingly, a synthetic desmosterol mimetic preferentially regulates LXR signaling in the CNS, highlighting the therapeutic potential of this pathway [13,103]. Of note, besides its well-described function as sphingosine-1-phosphate receptor modulator [104], the first oral MS drug fingolimod could potentially support remyelination by influencing intracellular cholesterol trafficking via Niemann–Pick type C proteins [105,106]. Fingolimod and dimethyl fumarate elevate plasma levels of high-density lipoprotein (HDL) cholesterol, pointing to a general modulatory impact on reverse cholesterol transport [107].

The cholesterol derivative olesoxime also supports oligodendrocyte differentiation and myelination in MS mouse models and is currently evaluated in a Phase I clinical trial[vii] in patients with relapsing–remitting MS [108,109]. Olesoxime supports oligodendrocyte differentiation likely by scavenging reactive oxygen species [110], an important anti-inflammatory feature of lipid-based compounds to target the CNS.

Recently, the promising results of therapeutic applications of ketogenic diet (KD), fasting-mimicking diets, or metformin in mouse models of demyelinating disease have highlighted the potential of dietary approaches [111–113]. These three interventions lead to the production of ketone bodies that are known to enter the CNS. In the CNS, ketone bodies promote repair by restoring functionality of axonal mitochondria and as precursors for lipid synthesis [113]. In addition, elevated peripheral ketone bodies reduce inflammatory responses by a variety of mechanisms [114,115]. Several clinical trials aim to assess these lipid-based therapies in MS patients[viii–xii]. First results have confirmed the feasibility of these potentially effective treatments [111,116,117][viii–x]. However, these strict dietary regimens often face patients' compliance challenges. Other lipid-based therapies that have shown promising results in preclinical models, such as CDP-choline or the cholesterol intermediate squalene, should be evaluated in human clinical studies [13,118].

Concluding remarks and future perspectives

Cholesterol/lipid metabolism is intimately linked to myelination and myelin maintenance to ensure brain homeostasis. In demyelinating disease, myelin-bound cholesterol is released and alters brain lipid metabolism, which is accompanied by secretions of inflammatory mediators. CNS cells respond to this pathological insult by adapting their cholesterol metabolism in a cell type-specific manner. Moreover, cellular responses strikingly differ in early and chronic disease phases. Better understanding of cell type-specific cholesterol/lipid handling and LXR signaling in the context of inflammatory disease is important to evaluate changes in lipid/oxysterol composition together with inflammatory signatures as potential diagnostic indicators of disease or even disease phase (see Outstanding questions). However, considerable efforts are still needed to identify reliable biomarkers. In addition, cell type- and disease phase-specific alterations in lipid composition and inflammatory signature could help design novel therapeutic strategies that support remyelination in addition to diminishing inflammation to promote functional recovery.

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Declaration of interests

S.A.B. and G.S. are listed as inventors on pending patent claims (PCT/EP2020/084338) filed by MPG covering the application of squalene in demyelinating disorders.

Resources

[i]https://clinicaltrials.gov/ct2/show/NCT00094172
[ii]https://clinicaltrials.gov/ct2/show/NCT00647348
[iii]https://clinicaltrials.gov/ct2/show/NCT01111656
[iv]https://clinicaltrials.gov/ct2/show/study/NCT00668343
[v]https://clinicaltrials.gov/ct2/show/study/NCT00261326
[vi]https://clinicaltrials.gov/ct2/show/NCT02087631
[vii]https://clinicaltrials.gov/ct2/show/NCT01808885

Outstanding questions

MS therapy by dietary supplementation with lipids including cholesterol might be hampered by the limited access of the supplemented lipids and especially cholesterol to the diseased brain because of the BBB. In addition, cholesterol/lipid treatment of peripheral organs might cause adverse side effects. Are there vehicles that could facilitate efficient and specific transport of the supplemented lipids to the brain?

LXR signaling orchestrates repair in acute myelin disease. The different LXR agonists lead to specific patterns of gene expression. What determines the particular activation pattern and the cell type specificity of LXR signaling?

CNS cells respond to demyelinating disease in a cell type-specific and disease phase-specific manner. Each of these cell types secretes a particular set of inflammatory mediators and, in addition, might also secrete lipids such as oxysterols or extracellular vesicles. These secreted molecules and vesicle cargoes may potentially be released into the peripheral circulation and serve as disease markers. Can such blood sample-based disease biomarkers be identified? Are there patterns of such biomarkers that reflect the different disease phases?

In MS patients, demyelination and remyelination occur simultaneously. However, the different disease phases might require specific treatments that might be contraindicated in another disease phase. What are the features of future therapies that require consideration in view of these issues?

[viii]https://clinicaltrials.gov/ct2/show/NCT03740295

[ix]https://clinicaltrials.gov/ct2/show/NCT01538355

[x]https://clinicaltrials.gov/ct2/show/NCT02647502

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