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Genes & Nutrition

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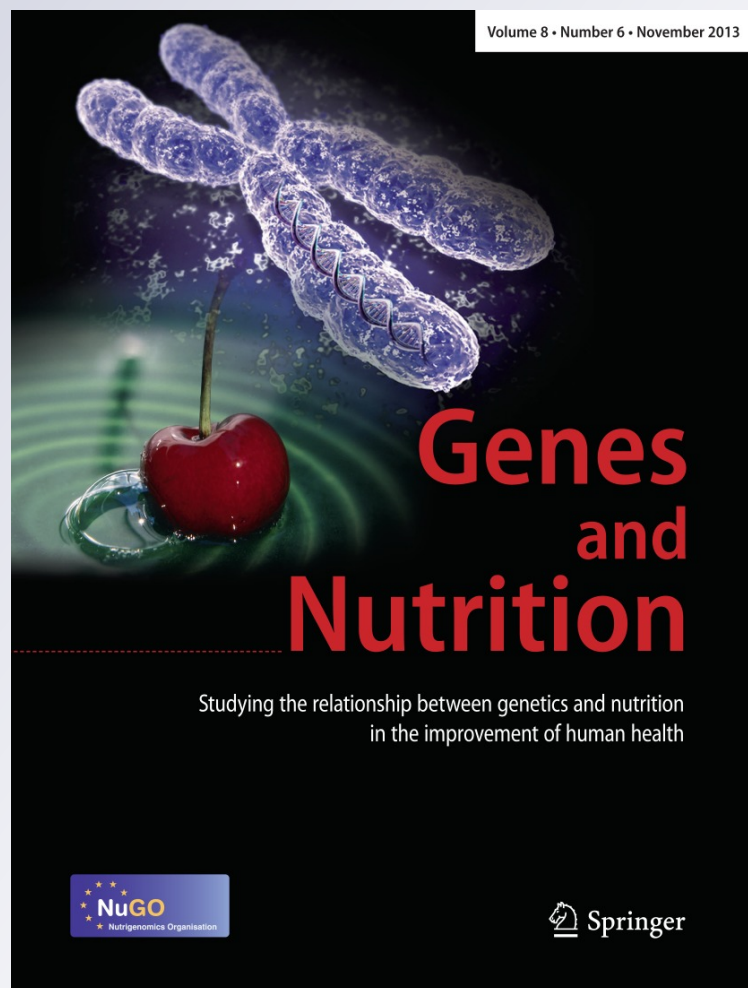
ISSN 1555-8932

Volume 9

Number 1

Genes Nutr (2014) 9:1-9

DOI 10.1007/s12263-013-0360-8



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Nutritional factors and aging in demyelinating diseases

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Received: 24 July 2013 / Accepted: 7 November 2013
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Abstract Demyelination is a pathological process characterized by the loss of myelin around axons. In the central nervous system, oligodendroglial damage and demyelination are common pathological features characterizing white matter and neurodegenerative disorders. Remyelination is a regenerative process by which myelin sheaths are restored to demyelinated axons, resolving functional deficits. This process is often deficient in demyelinating diseases such as multiple sclerosis (MS), and the reasons for the failure of repair mechanisms remain unclear. The characterization of these mechanisms and the factors involved in the proliferation, recruitment, and differentiation of oligodendroglial progenitor cells is key in designing strategies to improve remyelination in demyelinating disorders. First, a very dynamic combination of different molecules such as growth factors, cytokines, chemokines, and different signaling pathways is tightly regulated during the remyelination process. Second, factors unrelated to this pathology, i.e., age and genetic background, may impact disease progression either positively or negatively, and in particular, age-related remyelination failure has been proven to involve oligodendroglial cells aging and their intrinsic capacities among other factors. Third, nutrients may either help or hinder disease progression. Experimental evidence supports the anti-inflammatory role of omega-6 and omega-3 polyunsaturated fatty acids through the

competitive inhibition of arachidonic acid, whose metabolites participate in inflammation, and the reduction in T cell proliferation. In turn, vitamin D intake and synthesis have been associated with lower MS incidence levels, while vitamin D–gene interactions might be involved in the pathogenesis of MS. Finally, dietary polyphenols have been reported to mitigate demyelination by modulating the immune response.

Keywords Demyelination · Remyelination · Nutritional Factors

Abbreviations

OLs	Oligodendroglial cells
CNS	Central nervous system
MS	Multiple sclerosis
EAE	Experimental autoimmune encephalomyelitis
CPZ	Cuprizone
OPCs	Oligodendroglial progenitor cells
PDGFR α	Platelet-derived growth factor receptor α
GFAP	Glial fibrillary acidic protein
SVZ	Subventricular zone
PLP	Proteolipid protein
MBP	Myelin basic protein
CNPase	2',3'-Cyclic nucleotide 3'-phosphodiesterase
TNF α	Tumor necrosis factor- α
IL	Interleukin
NPCs	Neural precursor cells
EGFR	Epidermal growth factor receptor
LINGO-1	Leucine-rich repeat- and Ig domain-containing NOGO receptor-interacting protein 1
Shh	Sonic hedgehog
Hes	Hairy/enhancer of split
aTf	Apotransferrin
IGF-1	Insulin growth factor-1

This paper is part of Genes and Nutrition's "Topical Collection on Ageing."

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PUFAs	Polyunsaturated fatty acids
TGF- β	Tumor growth factor- β
PPAR	Peroxisome proliferator-activated receptors
25(OH)D	25-Hydroxyvitamin D

Introduction

Myelin biology dates back to 1,717, when Leeuwenhoek established the existence of *nervules surrounded by fatty parts* (Rosenbluth 1999). Two and a half centuries later, such fatty parts were shown to belong to a highly specialized membrane, i.e., myelin, generated by mature oligodendroglial cells (OLs) in the central nervous system (CNS) and by Schwann cells in the peripheral nervous system. Myelin is a very special membrane, with unique molecular composition and architecture. One of its main functions is to isolate axons and cluster sodium channels at Ranvier nodes, thus allowing for saltatory transmission of action potential between nodes (Waxman 2006). Myelin development and saltatory nerve conduction constitute the basis for fast information processing in a relatively small space.

Demyelination is a pathological process consisting in the loss of myelin sheaths around axons. In the CNS, demyelination is usually a consequence of OL damage and is referred to as *primary demyelination*, as opposed to that occurring as a consequence of primary axonal loss, regarded as *secondary demyelination* or *Wallerian degeneration* (Franklin and Ffrench-Constant 2008).

Demyelinating diseases

From a clinical standpoint, white matter disorders involving myelin affect approximately a million people around the world and include a wide range of pathologies. Two key causes of primary demyelination are the following: (1) genetic abnormalities affecting OLs (leukodystrophies) and (2) inflammatory damage affecting myelin and OLs.

Genetic abnormalities affecting glia comprise inherited lysosomal storage diseases, including metachromatic leukodystrophy and Krabbe disease; peroxisomal disorders, including X-linked adrenoleukodystrophy; and deficiency or misfolding of select myelin proteins, including Pelizaeus–Merzbacher disease, among others. Multiple sclerosis (MS) is the most prominent among inflammatory demyelinating diseases and, unlike leukodystrophies, is characterized by the presence of focal neurological lesions. It is, however, a complex disease whose clinical features vary among patients.

Multiple sclerosis clinical progression is variable, generally beginning with reversible episodes of neurological disability between the third and fourth decades of life and progressing to continuous and irreversible neurological disability between the sixth and seventh decades (Trapp and Nave 2008). MS symptoms are the result of myelinated tract interruption in the CNS. Several lines of mice carrying myelin protein null mutations provided the proof that axonal degeneration is a consequence of chronic demyelination (Trapp and Nave 2008). In this context, remyelination is defined as the process through which myelin sheaths are restored to demyelinated axons, which is associated with functional recovery (Franklin 2002). Remyelination is the response to demyelination and is necessary for axon survival. Thus, it should be considered as a regenerative process, similar to other regenerative processes taking place in other tissues. In toxic-based models of demyelination, as opposed to experimental autoimmune encephalomyelitis (EAE) or virus-induced demyelination, full remyelination takes place spontaneously, which allows for a thorough study of the mechanisms involved in demyelination/remyelination processes.

Demyelination is undoubtedly part of MS pathology; however, in recent years, neuronal loss and axonal loss have been proven to be a consequence of chronic demyelination and the main driving force for neurodegeneration (Trapp and Nave 2008) in demyelinating disorders.

Underlying mechanisms in demyelination/remyelination processes

Animal models widely used to study demyelination processes include (1) EAE, (2) virus-induced models such as Theiler's murine encephalomyelitis virus, and (3) toxin-induced models, such as cuprizone (CPZ) administration and focal demyelination through lysolecithin injection. These experimental models have provided a vast amount of information on remyelination. Findings in this field have established that (1) the number of oligodendrocytes present in a remyelinated area is larger than the number of these cells present in the area previous to demyelination, which indicates that new oligodendrocytes are generated (Prayoonwiwat and Rodriguez 1993), and (2) post-mitotic oligodendrocytes that survive the lesion produced by the demyelinating agent do not contribute to remyelination (Keirstead and Blakemore 1997). The question raised from these findings refers to the origin of these new oligodendrocytes. There is a consensus in the hypothesis that most of them, probably all of them, derive from oligodendroglial progenitor cells (OPCs) widely spread throughout the CNS (Wood and Bunge 1991; Blakemore and Keirstead 1999), which are usually identified through the expression of

proteoglycan NG2 or platelet-derived growth factor receptor- α mRNA (Wilson et al. 2006). In addition, remyelination can be mediated by periventricular cells, such as progenitors derived from the rostral migratory stream or from glial fibrillary acidic protein-positive B-type stem cells present in the adult subventricular zone (SVZ) (Menn et al. 2006). It is worth pointing out that these alternative sources of OPCs only contribute to remyelinating areas that are anatomically close to the SVZ, and, even in these cases, their relative contribution is uncertain. For remyelination to actually take place, it is necessary to populate the demyelinated area with enough OPCs, either those resident in the area or those that can be recruited from neighboring white matter (Carroll and Jennings 1994). Recruitment involves both the proliferation and migration of OPCs, which, once in the area, have to differentiate to mature OLs with myelinating capacity in order to complete remyelination.

The toxin-induced models mentioned above have proven NG2-positive cell recruitment from the SVZ to the demyelinated area. These cells differentiate and become mature OLs sequentially expressing myelin proteins such as proteolipid protein (PLP), myelin basic protein (MBP), and 2',3'-cyclic nucleotide 3'-phosphodiesterase. These findings prove that remyelination mechanisms are tightly regulated and involve a wide range of molecules, including cytokines (Mason et al. 2001) and chemokines (Patel et al. 2010), transcription factors (Qi et al. 2001), growth factors (Aguirre et al. 2007; Murtie et al. 2005), micro-RNA (Junker et al. 2009), and different signaling pathways (John et al. 2002).

Cytokines mediate the inflammatory response that promotes pathogen removal and thus prevents excessive tissue damage. However, excessive cytokine production may lead to exacerbated inflammation and consequent cell death. In the CNS, in particular, certain cytokines play a key role in regenerative processes. Tumor necrosis factor- α (TNF α), through TNF α receptors R1 and R2, activates cell death, on the one hand, and NF κ B-mediated survival, on the other. MS patients tend to have higher levels of TNF α , both in cerebrospinal fluid and in serum, than control patients. In turn, these values correlate with disease severity (Beck et al. 1988; Maimone et al. 1991). Interleukin (IL)-1 β is another pro-inflammatory cytokine related to the pathology of demyelinating diseases such as MS and, similarly to TNF α , is associated with the worsening of CNS pathology (de Jong et al. 2002).

Chemokines induce chemotaxis, which is necessary to attract cells to take part in the immune response at the infected or injured site. Certain chemokines, such as CXCL12 and CXCL1, are induced during CNS development and coordinate the proliferation, migration, and differentiation of neural precursor cells (NPCs) (Stumm et al. 2007; Tsai et al. 2002), which suggests they might also

participate in CNS regenerative processes. In this way, Patel et al. (2010) demonstrated that CXCR4 (the receptor of CXCL12) activation is important for the remyelination of the CPZ-demyelinated mouse by induction of OPC differentiation.

Growth factors are biologically active polypeptides controlling target cell growth and differentiation and are important during the remyelination process. Thus, it was demonstrated that epidermal growth factor receptor signaling is involved in both the repopulation by OPCs and the remyelination of lysolecithin-induced corpus callosum demyelination (Aguirre et al. 2007).

Signaling pathways possibly involved in the remyelination process include those mediated by leucine-rich repeat- and Ig domain-containing NOGO receptor-interacting protein 1 (LINGO-1), Wnt, Sonic hedgehog (Shh), and Notch1. LINGO-1 has been identified as a negative regulator of OL differentiation (Mi et al. 2005). The treatment of OPC cultures with anti-LINGO-1shRNA has been reported to generate an increase in cell morphological differentiation. On the other hand, LINGO-1-deficient mice or mice treated with an anti-LINGO-1 antibody exhibited greater remyelination and functional recovery when submitted to EAE (Mi et al. 2007). The same observations were made when animals were submitted to toxin-induced demyelination (Mi et al. 2009). As for the Wnt signaling pathway, Fancy et al. (2009) identified pathway-associated genes that are induced during remyelination in mice submitted to experimental demyelination. During remyelination, Tcf4-mediated activation of Wnt negatively regulates OPC differentiation (Fancy et al. 2009; Ye et al. 2009).

During CNS development, the secretion protein Shh is necessary for the commitment of the first wave of OPCs arising from the ventral region of the spinal cord and forebrain (Fuccillo et al. 2006). In the adult brain, Shh delivery induces an increase in the population of OPCs in the cerebral cortex and corpus callosum (Loulier et al. 2006). Recent studies using lysolecithin-induced corpus callosum demyelination showed that the Shh signaling is activated during remyelination and that adenovirus-mediated Shh delivery stimulates OPC proliferation and maturation (Ferent et al. 2013).

The Notch signaling pathway has been implicated in the selection process of neural progenitors present in the neural tube of vertebrates (Lewis 1996). Notch is a type I transmembrane receptor which responds to the binding of specific ligands and consequently undergoes a sequence of two proteolytic cleavages. The γ -secretase complex releases the Notch intracellular domain (NICD), which translocates to the nucleus and activates the transcription of Notch target genes (Kopan and Ilagan 2009), such as the bHLH-type transcriptional repressors known as hairy/enhancer of split (Hes) genes. Upon binding to canonical Delta, Serrate/

Jagged, and Lag-2 ligands, Notch activation maintains the pool of NPCs in their undifferentiated state and allows for the generation of OPCs (Artavanis-Tsakonas et al. 1999), thus blocking OL maturation through these ligands (Wang et al. 1998). In addition, NB-3 and F3/contactin, two neural cell adhesion molecules, act as non-canonical Notch ligands participating in OL generation (Cui et al. 2004; Hu et al. 2003). NB-3 triggers NICD nuclear translocation, promoting oligodendrogenesis from progenitor cells and OPC maturation via Deltex1 (Cui et al. 2004). We found that the treatment of demyelinated rats with a single apotransferrin (aTf) (350 ng) injection at the time of CPZ withdrawal induces a marked increase in myelin deposition as compared to the spontaneous remyelination observed in control animals (Adamo et al. 2006). Accordingly, different authors have reported the relevant role of aTf during myelination increasing brain myelin content, including proteins and their mRNAs (Escobar Cabrera et al. 1997, 1994, 2000), regulating MBP gene transcription (Espinosa de los Monteros et al. 1989, 1999), synergizing with insulin growth factor-1 (IGF-1), and enhancing myelination in myelin-deficient rats (Espinosa-Jeffrey et al. 2002). We recently observed that both canonical and non-canonical Notch signaling pathways are involved in demyelination/remyelination. Notch activation was observed to trigger Hes5 expression as a consequence of lyssolecithin-induced focal demyelination of corpus callosum, which might promote OPC proliferation. During aTf-induced remyelination, the expression of F3/contactin appeared to mediate Notch activation and thus induce aTf-mediated OL maturation (Aparicio et al. 2013).

In summary, remyelination occurring after demyelinating injuries is a very complex process involving different cellular populations, regulated by several molecules (e.g., growth factors, cytokines) and involving multiple signaling cascades (e.g., Notch signaling, Shh signaling). Knowledge of these events has significantly advanced in the last decades. However, many aspects remain unknown, and remyelinating therapeutic approaches remain limited and constitute a challenging field of research.

Remyelination and aging

Remyelination occurs efficiently in some situations and fails in others. This irregularity in remyelination has been studied using toxin-induced demyelination models. In this context, *age* was demonstrated to be one of the most important factors influencing CNS remyelination after a demyelinating event. In particular, the rate of remyelination is what changes in the aging CNS rather than its extent (Shields et al. 1999). The decrease in CNS remyelination rates occurring as a consequence of aging is a major

complication for remyelinating therapies, in particular for long-lasting demyelinating disorders such as MS. It is also important to consider the age-related modifications of the innate immune and growth factor responses to the demyelination process which interfere with myelin repair (Hinks and Franklin 2000; Zhao et al. 2006). Studies of OPC response during remyelination of toxin-induced demyelination in the caudal cerebellar peduncle from young and old adult rats indicate that the inefficiency of remyelination associated with aging is due to the impairment of OPC recruitment and the subsequent failure of OPCs in differentiating into myelinating OL (Sim et al. 2002). In this regard, it was demonstrated that the epigenetic control of gene expression related to aging regulates remyelination. Therefore, in young animals, remyelination occurs as a consequence of the downregulation of inhibitors of OPC differentiation, concomitantly with the recruitment of histone deacetylases to promoter regions. In old animals, this recruitment is inefficient and thus hinders efficient remyelination due to a decrease in the ability of OPCs to differentiate into mature OLs with myelinating capacity (Shen et al. 2008). Using heterochronic parabiosis (Villeda et al. 2011) in a toxin-induced focal demyelination model of mouse spinal cord, Ruckh et al. demonstrated improvements in the remyelination of aged brains mediated by endogenous OPCs whose differentiation capacity was restored by exposing them to a youthful systemic environment. Considering previous hypotheses about the role of the innate immune system in remyelination (Kotter et al. 2006), these results support the idea that young macrophages recruited during remyelination facilitate OPC differentiation by removing inhibitory myelin debris (Ruckh et al. 2012).

Taken together, the above findings give rise to the notion that age-related remyelination failure may implicate not only factors associated with aging OLs and their intrinsic capacities, but also a number of external factors, even outside the CNS, that affect OPC differentiation capacity and ultimately impact myelin repair (Redmond and Chan 2012).

Demyelination/remyelination and nutrients

MS is the most common CNS-specific demyelinating disorder affecting young adults, and it is a multifactorial disease with unclear etiology. In addition to a genetic predisposition (Ebers and Sadovnick 1994), epidemiological studies suggest a strong association between increased MS prevalence and particular diets (Antonovsky et al. 1965; Cendrowski et al. 1969; Berr et al. 1989; Tola et al. 1994). Studies conducted on dietary factors associated with MS have included fat consumption, particularly saturated

animal fat (Payne 2001); breastfeeding duration (Isaacs et al. 2010); and the intake of sweets (Antonovsky et al. 1965), alcohol (Berr et al. 1989; Sepcic et al. 1993), smoked meat products (Sepcic et al. 1993), coffee, and tea (Tola et al. 1994). However, Agranoff and Goldberg (1974) implicate foods rich in both omega-6 and omega-3 polyunsaturated fatty acids (PUFAs) in negative correlations with MS—omega-3 PUFAs are derived from fish oils, whereas omega-6 PUFAs are obtained from plants such as sunflower, corn, wheat germ, and soybean oils. In particular, it was observed that linoleic (18:2n-6) and arachidonic acids (20:4n-6) are decreased in plasma, platelets, erythrocytes, leukocytes, and cerebrospinal fluid in patients with MS (Baker et al. 1964; Sanders et al. 1968; Gul et al. 1970; Neu 1983). The use of linoleic acid alone or oil containing linoleic acid and γ -linolenic acid (ratio 7:1) in the treatment for EAE—an induced animal model of CD4 T cell-mediated demyelination characterized by inflammation—produced a partial suppression of the incidence and severity of the pathology (Meade et al. 1978). It was further demonstrated that the γ -linolenic acid had a protective, dose-dependent effect on EAE because of the increase in T cell tumor growth factor- β (TGF- β) transcription and prostaglandin E₂ production (Harbige et al. 2000).

Even though the relationship between the dietary intake of fat and the risk of MS is not clear, the anti-inflammatory effects of omega-6 and omega-3 PUFAs are well known. Both omega-6 and omega-3 PUFAs are competitive inhibitors of arachidonic acid, whose metabolites are involved in the inflammation process (Callegari and Zurier 1991; Gil 2002), and were demonstrated to decrease T cell proliferation (Rossetti et al. 1997). On the other hand, molecules derived from PUFAs could have positive effects on the treatment of MS: Lipoxins might reduce inflammation by decreasing neutrophil activity (Yacoubian and Serhan 2007), while resolvins and protectins, derived from omega-3 PUFAs, seem to control inflammation in the nervous system (Serhan et al. 2002). An important role assigned to PUFAs is that of ligands for peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-activated nuclear transcription factors whose PPAR γ isoform is present in human T lymphocytes, and omega-3 PUFAs, acting as PPAR γ agonists, ameliorate inflammation in EAE rats (Niino et al. 2001). Furthermore, omega-3 PUFAs were demonstrated to promote, *in vivo*, the expression of myelin-related proteins such as the PLP and MBP (Salvati et al. 2008).

Considering the relevance of blood–brain barrier integrity in MS physiopathology, Liuzzi et al. (2007) demonstrated that the *in vitro* treatment of microglia with omega-3 PUFAs decreases the LPS-induced production of matrix metalloproteinase-9, which is involved in the mechanism of blood–brain barrier disruption, the penetration of

inflammatory cells into the CNS, and, consequently, demyelination.

Finally and most importantly, clinical trials have been conducted over the last few years in MS patients, with results supporting the positive role of dietary PUFAs in disease progression.

The fact that MS has low prevalence in equatorial regions and increasing prevalence toward the north and south poles and that sun exposure is inversely related to the risk for MS development (Munger et al. 2006) suggest that vitamin D3 (cholecalciferol) could have a significant influence on MS progression (Smolders et al. 2008a). Vitamin D can be obtained directly from dietary sources or through skin synthesis, in which case sunlight is essential to the conversion of pre-vitamin D3 to active vitamin D3 through the cleavage of the B-ring. Vitamin D is hydroxylated in the liver to render 25-hydroxyvitamin D (25(OH)D). A high percentage of MS patients have low plasma levels of 25(OH)D (Mahon et al. 2003; Nieves et al. 1994; Ozgocmen et al. 2005). In this regard, studies in USA populations have proven that a 50-nmol increase in 25(OH)D correlates with a 40 % decrease in MS incidence. Also, while low levels of vitamin D are associated with relapse and disability in MS patients (Smolders et al. 2008b), high serum 25(OH)D levels reduce the hazard ratio for new relapses in a dose-dependent manner (Simpson et al. 2010). It has been proposed that the protective effects of vitamin D on MS are mostly related to the critical functions of this vitamin in the immune system. However, in the cuprizone model of demyelination in rats, which is independent of lymphocyte infiltration, vitamin D3 supplementation decreases the magnitude of white matter demyelination and mitigates the activation of microglia (Wergeland et al. 2011). In a more recent study, involving 141 participants with relapsing–remitting MS, Lin et al. studied 276 single nucleotide polymorphisms in 21 genes related to vitamin D metabolism and vitamin D receptor factor complex formation. They hypothesized that the interaction between genes and vitamin D may affect the clinical course of MS and, in particular, that the PKC family genes may be involved in the pathogenesis of relapsing–remitting MS modulating the association between 25(OH)D and relapse (Lin et al. 2013).

On the other hand, vitamin B12 cyanocobalamin can also have a positive influence on remyelination. B12 administered concomitantly with interferon- β favors OL maturation both *in vivo*, in non-autoimmune primary demyelinating ND4 (DM20) transgenics, and *in vitro*, in the human MO3-13 cell line and in rat spinal cord oligodendrocytes. These actions involve a decrease in Notch1 signaling and an increase in the expression of Sonic hedgehog and its receptor, Patched, which induces OL maturation and helps improve remyelination (Mastrorardi et al. 2004).

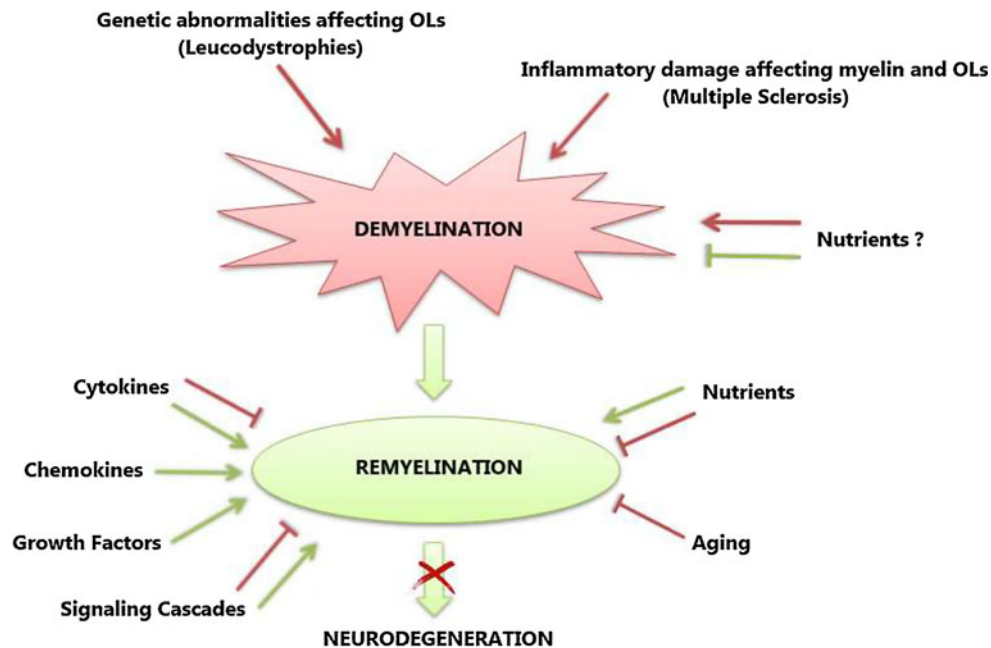


Fig. 1 Primary demyelination may be caused either by genetic abnormalities affecting OLs or by inflammatory damage affecting myelin and OLs, as is the case in MS. While some nutrients may play a protective role against demyelination (green line), others may play a negative role (red arrow). Remyelination is the physiological response to demyelination. During remyelination, some molecules act positively (green arrows) on the process, such as chemokines and

growth factors, while others may play a dual role (green arrows for positive, red lines for negative), such as certain signaling cascades and cytokines. Among environmental factors, nutrients may also play a dual role, and finally, aging has an unequivocally negative impact on the process. The interplay of these factors determines the fate of the remyelination process, whose failure leads to neurodegeneration

Dietary polyphenols could also mitigate demyelination by modulating the immune response. In this regard, epigallocatechin-3-gallate, a flavan-3-ol abundant in green tea, reduces the autoimmune response in the EAE through the inhibition of immune cell infiltration and the regulation of pro- and anti-autoimmune CD4(+) T cells (Wang et al. 2012).

In summary, recent experimental evidence suggests that nutrition could influence the development of demyelinating/remyelinating processes by mitigating demyelination and favoring remyelination. Given the nutritional imbalances associated with aging, further advances in the knowledge of how nutrients impact myelination could be of major relevance in the treatment of demyelinating conditions.

Conclusions

In demyelinating disorders in general and MS in particular, the failure of prompt remyelination is associated with axonal injury and degeneration, which is accepted as the major cause of neurological disability in the disease. Remyelination process recapitulates myelination during development, but in a pathological environment. Different molecules and signaling pathways are involved in the

remyelination process, inducing or inhibiting the proliferation and maturation of OPCs engaged in the generation of new myelin sheaths around axons. In the same way, non-disease-related factors, such as age and genetic background, and environmental factors, such as dietary components, could act as predisposition factors or exert a protective or even therapeutic effect during certain disease stages, rendering either negative or positive outcomes (Fig. 1).

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