Review

More Studies of the Deranged Myelinotrophic Factors in Multiple Sclerosis Central Nervous System Are Needed to Clarify Their Pathogenic Meaning

Giuseppe Scalabrino *

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Review

More Studies of the Deranged Myelinotrophic Factors in Multiple Sclerosis Central Nervous System Are Needed to Clarify Their Pathogenic Meaning

Giuseppe Scalabrino

Department of Biomedical Sciences for Health, University of Milan, Milan, Italy; giuseppe.scalabrino@unimi.it

Abstract

Many molecules (mainly growth factors and/or cytokines) are produced by human central nervous system (CNS) cells and may positively or negatively influence oligodendrogenesis, proliferation, and the migration of oligodendrocyte precursor cells (OPCs). Multiple sclerosis (MS) leads to the destruction of CNS myelin sheaths and myelin-producing oligodendrocytes (ODCs). This review considers the few published studies of platelet-derived growth factor (PDGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and ciliary-neurotrophic factor (CNTF) in cerebrospinal fluid and/or *post-mortem* CNS samples which, like previously reviewed studies of epidermal growth factor (EGF), have shown deranged levels in MS, and also considers the abnormal levels of Nuclear Factor kappa-light-chain-enhancer of activated B cells and some microRNAs in MS CNS. The derangements of all of these molecules in MS CNS surely hinder ODC differentiation, proliferation, and migration, and ultimately they contribute to remyelination failure. Despite the differences between MS and experimental autoimmune encephalomyelitis (EAE), it is also worth noting that the individual administration of PDGF, BDNF, CTNF, and EGF prevents the onset and/or "cures" EAE in mice, and so, together with findings concerning other aspects of MS, the results of the reviewed studies seem to support the idea that MS demyelination is a consequence of oligodendrocytopathy followed by an autoimmunity reaction.

Keywords: multiple sclerosis; growth factors; microRNAs; NF-kB; remyelination

1. Introduction

Although none of the different primate experimental models of multiple sclerosis (MS) fully reproduces the histopathological lesions and clinical symptoms of the disease, the main experimental model of active or passive experimental autoimmune encephalomyelitis (EAE) has played an influential role in shaping the widespread dogma that it is a primary autoimmune and inflammatory disease [1,2]. However, although various immunotherapies reduced immune responses and therefore slowed the course of the disease, none have induced the complete remyelination of demyelinated axons and some have actually had adverse effects and, specifically, failed to prevent the accumulation of progressive disability in the chronic phases of the disease [3,4]. Furthermore, target antigen(s) in MS have yet to be identified. It is clear that any treatment is time-limited and doomed to failure without a precise knowledge of the cause(s) of MS.

The ability to reproduce MS-like histopathological lesions and symptoms in primates by immunological means does not necessarily indicate a pathogenesis grounded on immunological aberrations (the epistemological aspects of this have been discussed elsewhere [5]), and so it is worth at least considering the possibility that the abnormal immune response in MS may be secondary to a still unknown pathological cue [6–8]. It is surely plausible that deficiency of a myelinotrophic factor and/or abnormality of its receptor could lead to damage neuronal function and to cause oligodendrocyte (ODC) death, also because healthy central nervous system (CNS) myelin not only promotes salutatory conduction [9] (although the impulse conduction may also be propagated by

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unmyelinated fibers), but also gives axons metabolic support through mechanisms independent of myelination [10–12]. Therefore, these molecules also promote the survival and functions of neurons (NEUs). However, the picture is further complicated by the fact that: i) MS is a heterogeneous disease [13–15]; ii) although MS has long been regarded as a typical white matter disease, demyelination and ODC abnormalities can also be found in CNS gray matter [16–18]; iii) a diffuse injury of the so-called "normal-appearing white matter" can be found in the MS CNS [16]; iv) MS demyelination shows heterogeneous patterns [13]; and v) MS remyelination can be extensive or limited, and therefore highly heterogeneous [19]. Furthermore, the remyelination of MS damaged axons can sometimes be carried out by Schwann cells entering MS CNS [20].

MS is by definition a CNS demyelinating disease [13,21], and so it is logical to look for its primary cause within the CNS, even though the peripheral nervous system may also be affected [22]. The traditional neuropathological view of the MS pathogenesis highlights the role of CNS myelin loss, because it leads to the impaired propagation of action potentials across the areas of demyelinated axons and is the major cause of neurological disability [13,21]. Therefore, the search for mechanisms that primarily cause the demyelination of white matter in MS has always been in the focus of research [6].

Moreover, there are a number of other not-immunology-linked characteristics of the disease. For instance: i) MS remyelination is similar to but distinct from developmental CNS myelination, insofar as it brings about thinner myelin sheaths with a shorter intermodal distance than those of development, despite the fact that the lineage progression and terminal differentiation of ODC precursor cell (OPC)→ODC go through the same stages [9,23–26]; ii) MS remyelination occurs in a developmentally mature CNS but in the presence of unusual amount of immune and inflammatory cells, a dysregulated profile of CNS micro(mi)-RNAs [27,28], and a differently composed extracellular matrix (ECM) [29]; iii) myelin chemical abnormalities have been found in MS [30–32] and citrullinated myelin has been shown to increase microglial tumor necrosis factor(TNF)-α production [33]; iv) some but not all of the growth factors and cytokines involved in MS remyelination and ODC-lineage maturation have different temporal expressions during chemically-induced remyelination [34,35]; v) ODC heterogeneity is altered [36] and MS-specific ODC subsets are present in MS brain [37]; vi) astrocytes (ASTs) represent diverse cell population subsets in healthy CNS, and, when in reactive state, produce molecules capable of promoting or blocking remyelination [38–40]; vii) Jagged1 is expressed by reactive ASTs and Notch1 by ODCs in MS lesions, both of which are negative regulators of OPC→ODC maturation [41]; viii) the connection between ASTs and ODCs in MS is greatly disturbed by the reduction in ODC connexins [42,43]; ix) the MS CNS ECM is inhospitable to remyelination because of the increased presence of AST-derived oligodendrogenesis inhibitors [29,44,45]; x) transcription factor myelin gene regulatory factor is less expressed in MS ODCs [46]; xi) abnormal expression of genes influencing oligodendrogenesis has been found in MS lesions [47]; and xii) epigenetic modifications have been found in MS brain, in particular those dealing with the ODC survival [48–52].

The three molecules, that are dysregulated in MS CNS and will be here discussed, are: i) some CNS-produced molecules that may favour or oppose CNS myelination and/or ODC-lineage maturation effects (i.e., platelet-derived growth factor (PDGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and ciliary-neurotrophic factor (CNTF)); ii) CNS Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-kB) family; and iii) some CNS micro(mi)-RNAs. It is noteworthy that these three families of molecules are strictly connected each other (see below). All of the reviewed studies measured the final active form of the growth factor. The abnormalities of epidermal growth factor (EGF) family (i.e., EGF, neuregulin, and heparin-binding(HB)-EGF, which are a superfamily of related proteins with similar biological effects [53]) in MS CNS have been extensively covered elsewhere [53].

PDGF, BDNF, and CNTF positively modulate the proliferation and/or differentiation of the OPC→ODC lineage in healthy CNS [54,55] (although ODCs are a heterogeneous population [56–58]), whereas NGF is a negative regulator of oligodendrogenesis and CNS myelination [59,60]. Some of these molecules are also produced by extra-CNS tissues and may even pass across blood-brain-

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barrier [61], but it is more likely that the pathogenesis of MS is more directly associated with the derangement of the CNS molecule network, and the abnormal immune response characterizing the disease may be a consequence rather than a cause.

There has been a long-running debate about the role of growth factors in EAE models, also because it is emerging from the literature that some neurotrophic growth factors are locally up-regulated in rodent EAEs [62–69]. However, the expression of the myelinotrophic growth factors during and/or after induced demyelination in EAE models is different from that observed during developmental myelination [34,35]. Moreover, although the effects of the growth factors obviously occur after their high affinity binding to their receptors on the cell membrane, the effects of the receptors themselves on the CNS myelin process will not be discussed here as they are beyond the scope of this article.

CNS myelination is a specialized process that encompasses subsequent steps of OPC differentiation, and myelin sheath formation, and wrapping of axons [70–76]. Furthermore, CNS myelination also requires interactions between ODCs, NEUs, ASTs, and microglia, and each step of the process must be efficiently orchestrated by positive or negative intra- and extra-cellular factors inside and outside OPCs and ODCs [70–77]. CNS myelin is therefore an excellent example of the differentiated product assembled by ODCs [77,78]. Furthermore, CNS myelination and oligodendrogenesis are also regulated by ECM-cell interactions, which involve a variety of cell surface molecules (e.g., integrins, selectins, and adhesion molecules) [79–82].

It is widely known that several molecules are produced and secreted by healthy CNS cells (including ODCs) and these promote OPC differentiation and/or proliferation and affect CNS myelinogenesis in different ways [70–77]. However, despite our extensive knowledge of the steps of CNS myelination [70.72,74,77], the role of some CNS-produced growth factors, cytokines, and miRNAs in the process [26,59,74,76,83,84], no approved anti-MS therapy includes (to the best of my knowledge) any of the CNS-produced growth factors and/or cytokines that induce the differentiation/duplication of the ODC lineage cells and protect CNS myelin morphology and therefore functions.

2. Growth Factors and Cytokines

2.1. PDGF

CNS PDGF modulates the proliferation and differentiation of OPCs, and activates myelin-specific gene expression [85,86]. Although OPCs and ODCs are not a homogeneous population [56–58] and white matter OPCs respond to PDGF differently from grey matter OPCs [87], PDGF is one of the key molecules in maintaining the progression of the OPC→ODC lineage [85,86]. Cerebrospinal fluid (CSF) PDGF levels are significantly lower in primary-progressive(PP)-MS patients [88] than in those with relapsing-remitting(RR)-MS, and higher in patients without a clinical relapse in comparison with those with relapse [89]. CSF PDGF-AA levels are decreased in MS patients, and there is a negative correlation between CSF PDGF-AA level and MS duration [90].

2.2. NGF

CNS NGF inhibits oligodendrogenesis and ODC myelination [59,60,91], also by increasing LINGO-1 (a transmembrane protein containing a leucine-rich repeat and an immunoglobulin domain) [92] and Nogo-A levels [93] in axons and ODCs (which produce both of them). Negative NGF effects on oligodendrogenesis and CNS myelination also include the NGF-induced down-regulation of miRNA-219a-5p levels, a positive regulator of ODC differentiation and CNS myelination [60]. NGF levels are significantly increased in the optic nerve of patients dying with MS, and this is accompanied by myelin loss [94]. CSF NGF levels are increased in MS patients with central neuropathic pain [95] and during acute attacks [96], in patients with secondary progressive(SP)-MS and those with RR-MS not temporally near to relapse episodes [97,98]. Furthermore, cobalamin(Cbl)-CNS-myelinotrophism is also due to the vitamin-induced down-regulation of NGF levels in rat spinal

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cord (SC), and intracerebroventricular microinjections of anti-NGF-antibodies to Cbl-deficient rats normalize SC myelin ultrastructure without modifying their Cbl-deficient status [99].

2.3. BDNF

CNS BDNF has positive effects on the OPC→ODC lineage because it promotes the proliferation and differentiation of OPCs [100,101]. It is also immunomodulatory by inhibiting the microglial activation and release of some pro-inflammatory cytokines [100–102]. CSF BDNF levels are not only higher in RR-MS patients in stable phase than in controls [103], but also in MS patients with cognitive impairment than in those without [104,105]; SP-MS patients have CSF BDNF levels between those of RR-MS patients and controls [103].

2.4. CNTF

CNS CNTF (belonging to the interleukin-6 family) promotes ODC survival, enhances the rate of ODC generation, is involved in OPC recruitment, and favours the maturation of the OPC→ODC cell line [106–109]. It also prevents ODC death and maintains CNS myelin integrity [106–109]. CSF CNTF levels are increased in MS patients recovering from an acute exacerbation [110], and in MS cortical NEUs [108].

2.5. EGF Update

We found a significant decrease in EGF levels of MS CSF and *post-mortem* MS SC samples [53], and other authors have also reported a progressive decrease in CSF EGF levels in patients with repeated relapses and those in the later stages of MS [111]. Conversely, CSF EGF levels are increased in patients with clinically isolated syndrome [111]. Recently, increased EGF expression has been found both in remyelinated and in the active lesions of autoptical MS brain samples [112]. It has been also shown that EGF blocks NF-kB activation in human intestinal epithelial cells [113] and mouse macrophages [114], making it likely that CNS EGF has the same effect on CNS-resident cells. Furthermore, it has been confirmed that EGF promotes the terminal differentiation of OPCs, thus increasing the number of ODCs *in vitro* [115].

3. NF-kB

NF-kB influences many of the gene activities related to innate and adaptive immunity [116–119]. The members of the NF-kB family (considered as latent gene regulatory proteins) are located in the cytoplasm and bound to the inhibitor IkB family [116–119]. Activation of the proper signalling pathway requires inhibitor degradation, thus triggering the release of active transcriptor factor to the nucleus, where it recognizes a specific sequence motif known as the target for DNA interaction and transcriptional activation [116–119]. Most pro-inflammatory mediators are under NF-kB control. In MS, NF-kB is activated in ODCs, hypertrophic ASTs, NEUs, microglia, T lymphocytes, macrophages, and active plaques, but not in healthy white matter [120–122]. Microglia and ASTs induce further neuroinflammation *via* NF-kB in response to an inflammatory reaction [123–125], thus establishing a vicious circle, that worsens neuropathological outcomes of the disease and must be interrupted before any anti-MS therapy can be effective.

AST NF-kB plays a major role in MS pathogenesis because it initiates and maintains CNS inflammation [123–125]; however, it has sometimes been reported that some anti-MS drugs blocking NF-kB activity have detrimental effects [120,126].

SC NF-kB activity is also increased in Cbl-deficient rats as a result of locallly increased NGF and TNF-α (another known NF-kB activator) levels, accompanied by pure myelinolytic lesions in SC white matter without any local ultrastructural signs of inflammatory and immunologic responses and demyelination [99]. Cbl replacement therapy normalises SC NF-kB levels and myelin ultrastructure, thus suggesting that low SC NF-kB levels favour myelin repair [99]. Given that Cbl-

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induced CNS myelinotrophism is mediated locally by increased EGF synthesis [99], it is tempting to speculate that EGF deficiency plays a role in increasing SC NF-kB levels in Cbl-deficient rats [99].

As above reported, it has been shown that EGF blocks NF-kB activation in human intestinal epithelial cells [113] and mouse macrophages [114], although its precise role in immunity and inflammation is still unclear. EGF has been also considered to be an anti-inflammatory molecule [111]. A large reduction in local inflammatory and immunity cells has been found in the SC of EGF-treated EAE mice together with histologically normal-looking myelin [53], as it has also been observed after PDGF [127,128] or CNTF [129] treatment (see below). The administration of EGF to EAE mice "cures" SC myelin morphological lesions, contributes to maturing OPC→ODC lineage and to preventing the immune and inflammatory responses [53,111], and probably contributes to remyelination by moving endogenous neural stem cells from CNS residence zones to lesion sites [53]. It is conceivable that the low SC and CSF EGF levels in MS are insufficient to play a neurotrophic and myelinotrophic role, or to dampen the pro-inflammatory gene transcription triggered by NF-kB activation in MS CNS cells.

4. mi-RNAs

Some CNS mi-RNAs (small endogenous non-coding, single-stranded RNAs regulating gene expression at post-transcriptional level) play a crucial role in controlling the timing of the transition from OPCs to ODCs, which involves arresting OPC proliferation followed by the beginning of OPC differentiation to mature and myelinating ODC [130–132], also because they are strictly connected with NF-kB [133–135] and some CNS-produced growth factors in healthy CNS [131,132]. The interaction between NF-kB signalling and some mi-RNAs is reciprocal insofar as some miRNAs regulate the NF-kB network and *vice versa* [133–135]. Mi-RNAs belong to the so-called "epigenetic triumvirate", active also in ODC development, together with DNA methylation and histone modifications [132]. One mi-RNA may control many genes and one target gene can be regulated by multiple mi-RNAs [133–135].

Several mi-RNAs of different CNS cell types are positive regulators of myelination, whereas others are negative [130,131,136]. Many mi-RNAs are up-regulated and others down-regulated in MS tissues and MS CSF [137–142]. Some mi-RNAs are also involved in MS repair process [83,84,143,144]. For example, mi-RNA-155 drives demyelination by enhancing local NGF expression in MS ASTs and microglia, thus leading to the down-regulation of CD47 protein, which releases macrophages from the inhibition of myelin breakdown and phagocytosis [138,142,145]. Conversely, the inhibition of mi-RNA-155 reduces MS inflammation [143]. The level of mi-RNA-219, which is identified as ODC-specific and represses negative regulators of ODC differentiation [84], is reduced in demyelinated MS lesions [145]. Furthermore, it has been found that the CSF of MS patients lacks mi-RNA-219 [84]. Mi-RNA-219 promotes ODC differentiation by inhibiting the expression of PDGF receptor on the cell [140]. It is conceivable that low MS mi-RNA-219 levels are at least partially connected to increased NGF levels in MS because of the NGF-induced down-regulation of mi-RNA-219 in healthy CNS [146]. Strangely enough, mi-RNA-27 is required for the development and survival of ODCs, but the excess found in MS brain lesions hampers remyelination [10]. The multifaceted roles of mi-RNAs in various cell types of CNS and/or immune system highlight the importance of these molecules in MS pathogenesis, also because mi-RNA dysregulation has also been found in MS brain grey matter [138]. This mi-RNA dysregulation may be relevant to disease pathogenesis, and the readers interested in discovering more details may consult some excellent reviews [28,147–149].

5. Conclusions: The Riddle of the Remyelination Failure in MS

There have been very few investigations of ODC- and/or myelino-trophic factors in MS CSF and even fewer in *post-mortem* MS CNS samples. This is in striking contrast with those considering the immunological aspects of the CSF and peripheral blood cells of MS patients. The CSF levels of a given molecule do not necessarily reflect its levels in different CNS areas, but the lack of EGF in MS CSF mirrors that in MS SC, whereas Cbl levels are increased in MS CSF but decreased in *post mortem* MS

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SC samples. However, it remains to be seen whether this may indicate a decreased entrance of vitamin into MS SC.

MS CNS abnormalities in PDGF, EGF, and Cbl levels seem to be relevant to MS remyelination failure and therefore MS worsening. It is possible that these abnormalities represent one of the starting points of myelin damage and neuroinflammation in the onset of MS. The fact that the individual administration of PDGF [127,128], CNTF [109], BDNF [150], EGF [53], and neuregulin (an EGF-like molecule, also called glial growth factor) [151,152] to EAE mice greatly attenuates SC histopathological, morphological immunological/inflammatory abnormalities, cannot be considered merely incidental, although EAE and MS differ in many respects [153] (see also above). These studies confirm us once again in the belief that these growth factors have impact on all aspects of ODC biology, OPC migration [154], and remyelination. Taken together, all of these findings undermine the classical hypothesis that MS is simply an autoimmune CNS disease [6]. However, this is not to minimize the importance of autoimmune and inflammatory reactions in the development of MS or its ominous prognosis, but to indicate that the pathogenesis of MS may equally be based on factors other than autoimmunity [6]. It is worth noting that many immunomodulatory anti-MS drugs appear to elicit their positive effects, in part, by simultaneously enhancing the production of some CNS growth factors that positively impact remyelination in MS models [155–157]. Therefore, the time is ripe for re-thinking of the pathogenesis of MS in terms of a re-evaluation of the role of the main myelinotrophic molecules (including some CNS growth factors) at the initial phase of the disease.

An accelerated remyelination enhances axonal preservation and neuronal functions in mice with EAE [158,159]. Insufficient MS remyelination is often linked to the ODC loss and/or the failure of OPCs to differentiate into myelinating ODCs [160–165], not only because of the inhospitable environment of ECM [44,45,166–168] (see also above). Myelinotrophic molecules and/or growth factors allow this differentiation under normal CNS conditions [66,154,169]. Some crucial points of the CNS remyelination in MS must be emphasized: i) the activation of gliogenesis of the CNS subventricular zone has been shown in *post-mortem* MS brain and gives rise to OPCs [170]; ii) *Notch-1* signalling is expressed and activated in OPCs from *post-mortem* MS brain [171]; iii) *Notch-1* receptor levels are high in ODCs of MS brain [172]; and iv) the nuclear translocation of *Notch-1*-intracellular domain, required for CNS myelinogenesis, is virtually absent in MS OPCs [171].

The widespread population of multipotent progenitor cells, commonly referred as OPCs, is present in the adult CNS [164,173–175] and in brain and SC of MS [162,173–175] and suggests that a pool of local and/or migrating progenitors is primarily involved in the repopulation and remyelination of demyelinated MS CNS areas. Whether these growth factors and/or miRNAs also modulate ODC immunological activity [176,177], remains a matter of speculation, but we can say that their three-part contribution to CNS neurobiology is highly disorganized in MS patients, and that MS will remain an ominous and incurable disease unless this imbalance is corrected. Nearly twenty years ago, Rasohoff and colleagues cleverly entitled their paper "Growth factor treatment of demyelinating disease: at last, a leap into the light" [178]. However, since then, the research in the field did not go a long way. It is clear that any myelin repair in MS requires the activation of the myelination process, the block of the inhibitors of myelination, and the moving of endogenous neural stem cells towards the lesion areas [179–181]. But, heterogeneity of MS lesions together with the unknown etiology of the disease complicates a possible generalization of an effective therapy in all MS patients [179,181].

Although the production of a wide range of immune-regulatory factors by ODCs and their role in activating microglia to clear myelin debris out are indisputable [176,177], it is probably better to look even more carefully at the growth factors regulating myelinogenic side of the ODC coin and the potential development of the endogenous neural stem cells [160,162,182], because this may help us to resolve the long-running question as to whether ODCs are culprits or victims in the pathogenesis of MS.

Let me conclude by quoting the statements of two authors very distant from each other in time. Friedrich Leopold Freiherr von Hardenberg (called Novalis) wrote in his "Gedichte" (Poetries) (5, B) (1802) that "Hypothesen sind Nietze, nur der wird fangen, der auswirft" (Theories are fishing nets;

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only those who cast them can do the fishing); Paul Feyerabend wrote in his "Against method" (4th part) (1975) that "Knowledge is obtained from a multiplicity of views rather than from the determined application of a preferred ideology".

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Abbreviations

AST	Astrocytes
BDNF	Brain-derived neutrophic factor
Cbl	Cobalamin
CNS	Central nervous system
CNTF	Ciliary-neurotrophic factor
CSF	Cerebrospinal fluid
EAE	Experimental autoimmune encephalomyelitis
ECM	Extracellular matrix
EGF	Epidermal growth factor
HB	Heparin-binding
mi-RNA	Micro-RNA
MS	Multiple sclerosis
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NEU	Neuron
NGF	Nerve growth factor
ODC	Oligodendrocyte
OPC	Precursor of oligodendrocyte
PDGF	Platelet-derived growth factor
PP	Primary progressive
RR	Relapsing remitting
SC	Spinal cord
SP	Secondary progressive
TNF-α	Tumour necrosis factor-α

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