Promoting oligodendrocyte progenitor cell maturation and remyelination as a novel therapeutical approach for multiple system atrophy

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Received: November 03, 2014
Published online: November 17, 2014

Alpha-synuclein (aSyn) aggregation within mature oligodendrocytes is the characteristic neuropathological feature of multiple system atrophy (MSA). In fact, dysfunction of oligodendrocytes is considered as a primary event in MSA pathogenesis leading to myelin loss and, ultimately, reduced axonal integrity and neuronal cell loss. Oligodendrocyte progenitor cells (OPCs) are widely distributed in the adult central nervous system and represent a potential endogenous source for replacement of such dysfunctional oligodendrocytes. The extent to which OPCs are affected in MSA or even contribute to MSA pathogenesis remains undefined. Thus, we analyzed OPCs post-mortem in MSA brains and in a pre-clinical MSA mouse model expressing aSyn under the myelin basic protein (MBP) promoter. Importantly, we detected elevated numbers of striatal OPCs in MSA and its model [1]. Observing aSyn-positive OPCs in MSA patients, we additionally established two independent in vitro models in order to explore the effect of intracellular aSyn on OPC maturation. Both stable aSyn expressing OPC-like central glia-4 (CG4) cells [1] and transiently aSyn expressing primary OPCs derived from neonatal rats [2] robustly showed a severely reduced maturation. Similarly, primary OPCs exhibit a delayed maturation upon uptake of recombinant aSyn [2]. Taken together, our findings indicate that OPC dysfunction is a pathological feature of MSA. In addition, promoting OPC differentiation may represent a novel and promising interventional strategy for therapeutic approaches in MSA.

To cite this article: Benjamin Ettle, et al. Promoting oligodendrocyte progenitor cell maturation and remyelination as a novel therapeutical approach for multiple system atrophy. Ther Targets Neurol Dis 2014; 1: e409. doi: 10.14800/ttnd.409.

The neurodegenerative disorder multiple system atrophy (MSA) is clinically characterized by rapid disease progression with predominantly either parkinsonism (MSA-P) or cerebellar features (MSA-C). Both clinical phenotypes show varying degrees of autonomic failure. Unfortunately, symptoms of MSA are only very limited responsive to dopaminimetics. In fact, a disease-modifying therapy slowing MSA progression is currently not available [3].

Although featuring widespread neuronal cell loss accompanied by astro- and microgliosis, the leading neuropathological hallmark of MSA is the presence of glial cytoplasmic inclusions (GCIs) within oligodendroglial cells [4]. Immunocytochemical characterization revealed alpha-synuclein (aSyn) as the major proteinaceous constituent of GCIs classifying MSA as synucleinopathy [5,6]. The presence of GCIs within oligodendroglial cells, the detection of an oligodendroglial dysfunction preceding aSyn accumulation and GCI formation, as well as the recapitulation of MSA symptoms in transgenic mouse models expressing aSyn under the control of oligodendroglia specific promoters suggest a pivotal, if not a causal, role of oligodendroglial cells in MSA pathogenesis [7-10].
Oligodendrocytes (OLGs) are the myelinating cells of the central nervous system (CNS) insulating axons and representing the cellular correlate for the saltatory action potential conduction along axons. In addition to their essential contribution to the rapid nerve impulse propagation, OLGs regulate ionic homeostasis and provide trophic and metabolic support to axons thereby ensuring axonal maintenance and overall CNS connectivity [11-13]. Although OLG generation and myelin formation peak during early infancy, oligodendrocyte progenitor cells (OPCs) persist in the adult CNS distributed within both the gray and white matter [14]. Besides remodeling myelin and contributing to the plasticity of the adult CNS, OPCs are the endogenous mediators of myelin repair in response to demyelination [15-17]. However, as OLG dysfunction and myelin loss are major pathological features of MSA, comprehensive analyses on the role and functionality of OPCs in regard to replacement of dysfunctional OLGs in MSA are crucial, but have not yet been conducted.

We recently addressed the role of OPCs in MSA by investigating human post-mortem tissue as well as pre-clinical animal and cell culture models for MSA [1,2]. Intriguingly, we observed increased numbers of striatal platelet-derived growth factor receptor-alpha (PDGFRα)-positive OPCs in MSA patients suggesting a proliferative reaction of OPCs in response to demyelination in MSA [1]. Similar results have been obtained by Ahmed and colleagues analyzing cerebellar white matter of MSA patients [16]. In line with these observations, we detected increased numbers of proliferative OPCs in transgenic mice expressing aSyn under the control of the OLG specific myelin basic protein (MBP)-promoter (MBP::aSyn) [1]. This transgenic mouse line represents a pre-clinical MSA model showing a profound myelination deficit accompanied by a severe motor phenotype [8]. Applying a bromodeoxyuridine (BrdU) based fate mapping, increased numbers of newborn striatal OPCs were detected in MBP::aSyn mice compared to non-transgenic littermates while numbers of glutathione-s-transferase-pi (GST-pi)-positive OLGs were unaffected. Further analyzing MSA post-mortem tissue and in contrast to previous reports, we detected a small fraction (5-8%) of aSyn-positive striatal OPCs indicating that aSyn accumulation is not restricted to mature OLGs but also affects OPCs [1,18].

The observation of i) increased OPC numbers in MSA patients and MBP::aSyn mice and ii) aSyn within OPCs of MSA patients prompted us to further investigate the effect of aSyn on OPC functionality, particularly the impact of elevated intracellular aSyn levels on OPC maturation. For this purpose, we used OPC-like central glia-4 (CG4) cells and generated a stable aSyn expressing CG4 line. To achieve a stable aSyn expression, CG4 cells were transfected using the Sleeping Beauty transposon system. In comparison to venus expressing control cells, aSyn expressing CG4s showed a severely reduced upregulation of myelin protein expression, namely 2’, 3’-cyclic-nucleotide-phosphodiesterase (CNPase) and MBP, when cultured under differentiation promoting conditions. These in vitro results indicate a detrimental effect of aSyn on OPC maturation [1].

Using a complementary in vitro model to study oligodendroglial maturation, we transduced primary OPCs derived from neonatal rats with lentiviral vectors enabling aSyn expression driven by the elongation factor 1-alpha (EF1a) promoter [2]. Analyzing OPC maturation during a 6 day differentiation paradigm, aSyn expressing OPCs (SYN-OPCs) robustly showed a delayed onset of maturation evident by increased levels of PDGFRα and decreased levels of myelin proteins, i.e. CNPase and MBP. Moreover, SYN-OPCs exhibited an altered morphological phenotype as fewer and shorter primary processes were detected in SYN-OPCs compared to control OPCs. Remarkably, there were no differences in terms of transduction efficiency and toxicity between SYN-OPCs and control OPCs during maturation. After ceasing aSyn expression due to reduced activity of the lentiviral EF1a promoter, the maturation potential of SYN-OPCs was restored to control levels indicating that the intracellular level of aSyn is a crucial determinant of OPC maturation. Matching these results, primary OPC differentiation was impaired after uptake of recombinant aSyn and restored upon reduction of intracellular aSyn levels [2].

In summary, our studies using human post-mortem MSA tissue as well as pre-clinical in vitro and in vivo models reveal an additional pathological feature of MSA [1,2]. Besides the accumulation of insoluble aSyn within GCIs in mature OLGs, the presence of aSyn within OPCs severely inhibits their maturation and ultimately prevents replacement of dysfunctional OLGs and remyelination in MSA. Similarly, an affection of OPC differentiation has been proposed for multiple sclerosis (MS), an autoimmune disease directed against myelin components with severe focal demyelination [19,20]. Cell- and drug-based therapies to promote remyelination are currently explored for MS treatment [21]. In addition to the investigation of experimental strategies in pre-clinical MSA models including immunotherapeutic reduction of aSyn aggregates [22] and autologous cell replacement by mesenchymal stem cells [23], enhancing OPC maturation and remyelination represents a novel interventional target not only for MS, but also for MSA [24].
therapeutic approach for MSA.

Acknowledgements

This research was supported by the Interdisciplinary Center for Clinical Research (IZKF; E18: “Assessing developmental potential and differentiation capabilities of NG2-positive cells in the healthy and diseased central nervous system”). The authors would like to thank Simone Reiprich and Michael Wegner (Institute of Biochemistry, Friedrich-Alexander-University Erlangen-Nürnberg) for enriching discussions.

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