PERSPECTIVE

A radical scavenger edaravone and oligodendrocyte protection/ regeneration

Cerebral white matter is vulnerable to oxidative stress: Oxidative stress is one of the major harmful conditions for the central nervous system (CNS). Oxidative stress is a state from an imbalance between free radical production and their removal by antioxidants, resulting in an excessive amount of reactive oxygen species (ROS) in cells and tissues. ROS causes cell damage due to oxidation of cellular components, including DNAs, proteins, and lipids. During physiological conditions, small amounts of ROS are generated in the process of normal biological activity, and ROS at physiological levels play important roles in maintaining cellular homeostasis (Chen et al., 2018). However, during pathological conditions, ROS levels are increased and excessive ROS can lead to deleterious effects on many kinds of cells.

The brain is vulnerable to oxidative stress because of its high iron content, which results in an increased generation of ROS and because of low levels of endogenous molecular antioxidants, which leads to increased accumulation of ROS (Friedman, 2011). Within the brain, cerebral white matter, which is mainly made up of myelinated axons, is highly vulnerable to oxidative stress. In fact, white matter damage is a characteristic of many neurodegenerative diseases, including stroke and vascular dementia. Because of the critical role of myelinated axons in the salutatory conduction of action potentials, damage to white matter causes severe cognitive and/or behavioral deficits.

The myelin sheath is formed by the oligodendrocyte, a sub-type of glial cell that wraps neuronal axons with multilamellar lipid structures, characteristic of the myelin sheath. Oligodendrocytes derive from oligodendrocyte precursor cells (OPCs). OPCs are most active during the developmental stage as new myelin is being formed in the growing brain. But some populations of OPCs are still reserved in adult brains and these residual OPCs contribute to oligodendrocyte renewal and regeneration when needed. Oligodendrocytes are sensitive to oxidative stress because (i) oligodendrocytes contain a large amount of iron, which generates ROS, and of polyunsaturated fatty acids, which are sensitive to injury by ROS, (ii) high mitochondrial activity, which is related to ROS generation, is required for oligodendrocytes to maintain myelin integrity, and (iii) oligodendrocytes have relatively low stores of glutathione, an important anti-oxidant (Roth and Nunez, 2016). Therefore, protection of oligodendrocytes against oxidative stress and accelerating oligodendrocyte regeneration after white matter injury are potential approaches for treating white matter-related CNS diseases. Thus far, anti-oxidant drugs that focus on oligodendrocyte protection are not yet available, but work from our and other groups have demonstrated that the radical scavenger edaravone may be useful for this purpose.

Edaravone is protective for oligodendrocyte lineage cells: Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, MCI-186, Radicut) is a small molecule compound, which counteracts some of the damaging effects of hydroxyl radicals and lipid-peroxidation. Edaravone is now in clinical use in Japan, China, South Korea, and US for stroke and/or amyotrophic lateral sclerosis (ALS) (Readers are encouraged to see a recent review manuscript by Watanabe et al. (2018), which thoroughly summarized how edaravone is effective for stroke and ALS). Although both clinical and basic studies have demonstrated that edaravone is effective in protecting several types of brain cells against oxidative stress, its efficacy in preserving oligodendrocyte function is still relatively understudied, with only a small number of reports focusing on this subject. Nonetheless, Ueno et al. (2009) reported that edaravone protected oligodendrocytes in a rat chronic hypoperfusion model. In the study, rats were subjected to ligation of bilateral common carotid artery to induce chronic cerebral hypoperfusion. Rats with cerebral hypoperfusion exhibited oligodendrocyte damage along with white matter lesions and cognitive deficits in the Morris water maze test. Edaravone treatment significantly reduced the loss of oligodendrocytes, and importantly, the hypoperfused rats that received edaravone showed better cognitive function than the vehicle-treated hypoperfused rats. Our group also confirmed the oligodendrocyte-protective effects of edaravone using a mouse model of prolonged cerebral hypoperfusion induced by bilateral common carotid artery stenosis. Similar to the findings from Ueno et al. (2009), edaravone was effective in protecting oligodendrocytes against hypoperfusion stress in mice (Miyamoto et al., 2013).

In addition to oligodendrocytes, edaravone may also be protective for OPCs during oxidative stress. OPCs play an essential role in oligodendrocyte regeneration after white matter injury because mature oligodendrocyte cannot proliferate. In general, residual OPCs in adult brain are quiescent, but in response to oligodendrocyte damage, OPCs rapidly proliferate and differentiate as a compensative response for oligodendrocyte restoration. Recently, our group demonstrated that edaravone treatment reduced OPC damage using the same model of prolonged cerebral hypoperfusion in mice (Takase et al., 2018). In addition to the *in-vivo* experiment, we also used an *in-vitro* model to confirm that edaravone directly protected OPCs against ROS-induced stress. An important observation from these experiments is that edaravone may increase oligodendrogenesis after white matter damage by enhancing OPC differentiation. In our cerebral hypoperfusion model, mice with cerebral hypoperfusion showed a transient increase in OPC proliferation, but the proliferated OPCs often failed to differentiate into mature oligodendrocytes. In this setting, edaravone treatment was effective in promoting both OPC proliferation and differentiation - two essential steps in white matter repair/remodeling (Miyamoto et al., 2013). Edaravone supports OPC survival, proliferation, and differentiation activities, which are beneficial for white matter function; however interestingly, edaravone also suppresses one of the OPC activities, which can be deleterious for white matter function. Data from our cerebral hypoperfusion model shows that during the early phase of cerebral hypoperfusion, OPCs release matrix metalloprotein-9 (MMP-9), which may damage the blood-brain barrier and may cause white matter dysfunction at later time points (Seo et al., 2013). However, edaravone treatment successfully suppressed MMP-9 secretion from OPCs and protected blood-brain barrier integrity in white matter (Miyamoto et al., 2014). Because cerebral hypoperfusion is closely related to vascular cognitive impairment (Ihara et al., 2014), these studies provide a proof-of-concept that edaravone may be effective for white matter protection and repair in the pathology related to vascular dementia

After oligodendrocyte death and myelin loss, remyelination through OPC proliferation/differentiation is a critical step for white matter repair. Because multiple deleterious cascades that damage white matter are activated under the diseased conditions, therapies to boost endogenous remyelination process may have therapeutic value in white matter-related diseases. Interestingly, a drug screening study by Eleuteri et al. independently suggested that edaravone is a candidate drug for promoting OPC proliferation and differentiation (Eleuteri et al., 2017). Within a library of 2000 compounds which were mainly composed of U.S. Food and Drug Administration (FDA)-approved drugs and natural products, edaravone was identified as the top 42nd molecule with significant stimulating effects on OPC metabolic activity. In a second screening test using the top 42 molecules, edaravone was one of only three compounds which were confirmed to have positive effects on OPC proliferation and differentiation. Taken together with the findings from rodent hypoperfusion models, edaravone appears to be an attractive candidate drug for the purpose of restoring oligodendrocyte/myelin after white matter damage.

Future perspective of antioxidant therapy for white matter damage: Edaravone is now widely used in the clinical treatment of stroke and ALS, and holds promise for the treatment of white matter damage due to its oligodendrocyte protecting effect from its anti-oxidant property (**Figure 1**). However, caution should be taken

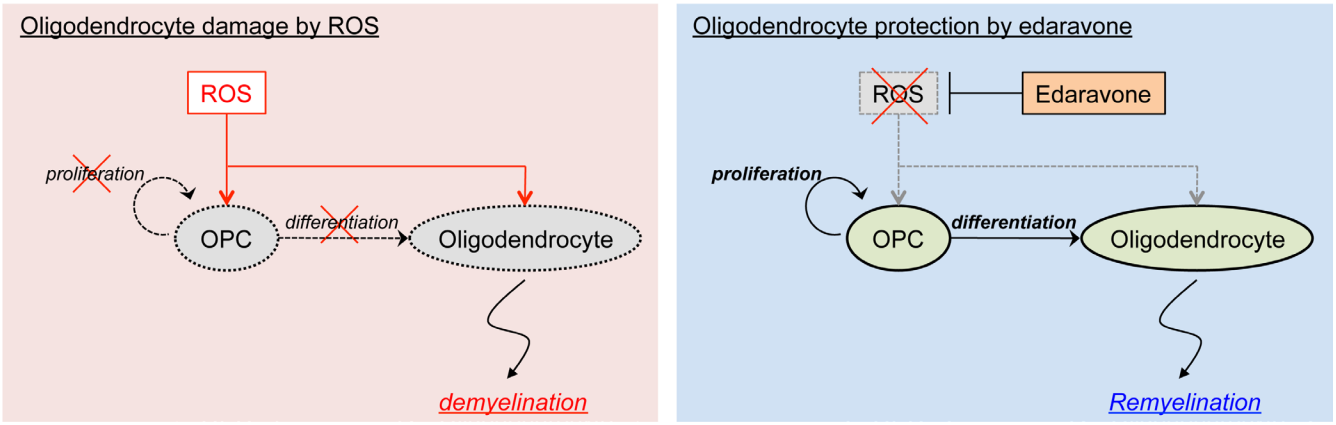

Figure 1 Summary for edaravone's effects on oligodendrocyte lineage cells.
Oligodendrocytes are instrumental in forming myelin sheaths in the white matter. Mature oligodendrocytes do not proliferate, but when needed, residual oligodendrocyte precursor cells (OPCs) proliferate and differentiate into oligodendrocytes. After white matter damage, however, accumulated reactive oxygen species (ROS) attack both OPCs and oligodendrocytes, which eventually cause oligodendrocyte loss and demyelination. Edaravone, a radical scavenger, protects oligodendrocyte lineage cells under diseased conditions, suggesting that the use of anti-oxidants may constitute an effective approach to the treatment of white matter-related diseases, such as vascular dementia and stroke.

in translating the positive effects of edaravone on oligodendrocyte lineage cells in the laboratory to meaningful success in the clinical setting. Over the past 30 years, several free radical scavengers have been developed and evaluated for stroke therapy, but despite promising pre-clinical data, all of the anti-oxidant compounds, except for edaravone, have failed in clinical trials to provide neuroprotection in stroke. For example, Ebselen, a free radical scavenger which showed positive effects in neuroprotection and oligodendrocyte-protection in basic studies, did not show positive effects in stroke patients. Another free radical scavenger, Tirilazad, showed positive effects in animal models of stroke but had no beneficial effects for stroke patients in phase III clinical trials. NXY-059 (Cerovive, AstraZeneca), a free radical scavenger which was effective/tolerated in animal models and in Phase II clinical trials, failed in the large randomized controlled trials Stroke-Acute Ischemic NXY Treatment (SAINT)1 and 2. It is possible that problems in blood-brain barrier (BBB) penetration or patient recruitment, rather than lack of drug efficacy, may be involved in the failure of those clinical trials (Ford, 2008); however, these disappointing results is a reminder of the difficult hurdle from basic research to clinical translation. Nevertheless, there is little question that oxidative stress is involved in the pathology of white matter-related diseases, and that oligodendrocyte lineage cells play important roles in white matter function and recovery. Therefore, developing strategies for oligodendrocyte protection and regeneration continue to be imperative in efforts to treat patients with white matter diseases. Edaravone has been demonstrated to be effective for this purpose in both basic and clinical studies; careful (re)assessment of its potential role in supporting oligodendrocyte function may lead to successful anti-oxidant therapies that protect and repair white matter in CNS diseases.

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