A NEW NEUROPROTECTIVE ROLE FOR DIMETHYL FUMARATE IN EXPERIMENTAL MULTIPLE SCLEROSIS: INHIBITION OF MIR-142-3P TO PREVENT INFLAMMATION-DRIVEN SYNAPTIC TOXICITY

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Excitotoxic synaptopathy is emerging as an early pathophysiological hallmark of multiple sclerosis (MS) and of its mouse model, experimental autoimmune encephalomyelitis (EAE). It includes increased glutamategic transmission induced by inflammation that, in the long-term, can cause disabling neuronal damages, leading to motor and cognitive dysfunctions. Recently, by investigating the molecular mechanisms underlying EAE synaptopathy, we revealed IL-1beta- miR142-3p-GLAST/EAAT1 as a new regulatory axis in EAE cerebellum. Since EAE/MS synaptopathy is precocious and potentially reversible, it represents an attractive therapeutic target. Thus, we asked whether EAE synaptopathy could be directly targeted by disease-modifying treatments, like the oral drug dimethyl fumarate (DMF), which metabolizes to active metabolite monomethyl fumarate (MMF). Both peripheral and intracerebroventricular therapeutic treatments revealed that, respectively, DMF and MMF ameliorate cerebellar glutamatergic transmission in EAE mice, exerting a neuroprotective effect. Additionally, ex vivo electrophysiological experiments in EAE cerebellar slices showed that acute MMF incubations are able to correct glutamategic current abnormalities. Mechanistically, we observed that MMF reduces the expression of miR-142-3p, the crucial effector of the Il-1beta excitotoxic signal, with consequent increase of its target the glial glutamate transporter GLAST/EAAT1.
The observation that DMF and MMF led to inhibition of miR-142-3p pathway both in vivo and ex vitro prompted us to determine the effects of DMF treatment in EAE miR-142 defective mice. Notably, we earlier observed that miR-142 knock-out mice were fully resistant to EAE induction, highlighting an important role for miR-142-3p also in the immune system. Here, we characterized EAE miR-142 heterozygous (HE) mice and we noticed that their susceptibility to EAE induction was similar to the wild type (WT) littermates but, most importantly, that cerebellar glutamatergic synaptopathy was already rescued in EAE-miR-142 HE mice. Moreover, a preventive and peripheral DMF treatment was more effective in improving motor disability in EAE-miR-142 HE mice than in WT mice.
Altogether these results reveal for the first time that DMF or MMF exert neuroprotective and therapeutic effects by the inhibition of miR-142-3p in EAE and highlight miR-142-3p as promising molecular target in both the nervous and immune systems with relevant therapeutic implication for MS.