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Commentary

The dark side of HDAC inhibition in ALS

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In this article of *EBioMedicine*, Viviana Moresi and colleagues provide genetic evidence that skeletal muscle HDAC4 exerts a protective role for neuromuscular junction and muscle innervation in amyotrophic lateral sclerosis (ALS) [1].

HDACs are enzymes able to remodel the chromatin through histone deacetylation. The hypothesis that alterations in chromatin remodeling participates in ALS progression comes from studies published 10 years ago showing that ALS disease progression in a mouse model is associated with a loss of the histone acetyl transferase CBP and decreased histone acetylation in motor neurons at disease onset [2]. However, counteracting pharmacologically decreased histone acetylation by broad HDAC inhibition had a moderate effect on whole animal survival [3,4]. More particularly, such treatment efficiently protected motor neuron cell bodies, and slightly delayed the onset of motor decline, but was unable to prevent disruption of neuromuscular junctions [5]. It is therefore likely that HDAC inhibitors might negatively influence other cell types involved in ALS. Pigna and collaborators show here that muscle HDAC4 is a strong candidate for these negative effects of HDAC inhibition.

HDAC4 is a member of the class IIa family that is devoid of deacetylase activity, and likely leads to histone desacetylation through binding of Class I HDACs [6]. In neurons, HDAC4 is predominantly cytoplasmic, particularly concentrated in dendritic spines [7]. Specific neuronal loss of HDAC4 leads to defects in motor coordination, learning and anxiety disorder [8]. HDAC4 is also expressed in muscle, and has a critical developmental role through inhibition of the transcriptional activity of MEF2 [9]. HDAC4 is highly upregulated upon denervation, as occurs in ALS, and is enriched at neuromuscular junctions where it activates the subsynaptic gene expression program [10,11]. Muscle specific deletion of HDAC4 thus leads to defective induction of subsynaptic gene expression but without impacting muscle mass [12,13]. Surprisingly, such manipulation also leads to better muscle reinnervation after nerve injury, in part through relieving the expression of FGF-related retrograde signals to motor neurons [14]. In patients, high muscle HDAC4 expression was correlated to faster disease progression [15]. Given the broad roles of HDAC4 in the different cell-types, it was difficult to predict whether HDAC4 loss would be beneficial or deleterious in ALS.

Pigna and collaborators here used an elegant genetic strategy to dissect the role of HDAC4 in muscle in a mouse model of ALS. Using a conditional allele of *Hdac4*, they ablated HDAC4 in muscle through crossing with transgenic mice expressing CRE under the *Myog* promoter, and introduced a transgene allowing expression of mutant SOD1, a cause of familial ALS. They observed that muscle HDAC4 deletion exacerbates a number of disease parameters in this model: acceleration of weight loss, muscle atrophy and weakness leading to acceleration of disease onset although overall survival remained unaffected. Consistent with a critical role of HDAC4 in neuromuscular junction, muscle HDAC4 ablation led to smaller and more frequently denervated neuromuscular synapses in mutant SOD1 mice, and potently blunted the induction of the so-called denervation response mounted by muscle in response to inactivity. Notably, no effect was observed on motor neuron survival. Muscle proteolytic pathways were also less activated in ALS mice without muscle HDAC4. Interestingly, HDAC4 ablation led to transcriptional dysregulations related to metabolism, ubiquitin-dependent catabolism and skeletal muscle response to denervation, including the upregulation of mitochondrial uncoupling protein 1, whose muscle expression is sufficient to recapitulate most of the observed effects in these animals [16]. As an overall conclusion of the study, Pigna and collaborators demonstrate that the pathways activated by HDAC4 in muscle during ALS are responsible for compensatory reinnervation through the myogenin pathway. Ablation of this key player in the pathway blunts this response and negatively affects NMJ response to denervation, while potentially inducing hypermetabolism.

The study by Pigna and collaborators provides an elegant demonstration why class IIa HDAC inhibition may not be suitable to protect the neuromuscular function in ALS, consistent with a recent study that showed only a transient protection of motor performance after treatment of the same ALS model with the class II specific HDAC inhibitor MC1568 [17]. The current study also nicely confirms 10 years old studies using the pan-HDAC inhibitor valproic acid that potently protected motor neurons, likely via class I HDACs inhibition-dependent effects, but did not prevent NMJ denervation at late stages, possibly because of class IIa HDACs inhibition-dependent effects. In the context of ALS, recent work has shown that HDAC6 inhibitors could provide interesting protection in various mouse models [18] and inhibitors of class I HDACs remain also interesting targets for neuronal protection, especially as HDAC1 appears as a downstream target of both FUS and TDP-43 related ALS. Future work in this area should focus on increasing selectivity of HDAC inhibitors, and ameliorate targeting of the CNS to avoid the deleterious effects of HDAC inhibition in the periphery.

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Author's contribution

ALB, LT and LD performed literature search and wrote the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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