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Local expression of SOD1G93A mutant protein triggers neuromuscular junction dismantlement

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The alteration of Reactive Oxygen Species (ROS) homeostasis plays a causal role in several chronic pathology such as aging and neurodegenerative diseases like Amyotrophic Lateral Sclerosis (ALS). Although it is recognized that axon and synapses are first cellular sites of degeneration in ALS disease, controversy exists on whether pathological events initially begin at the NMJs and then, in a dying back phenomena, contribute to motor neuron degeneration. Moreover, the precise molecular mechanisms of pathology-associated deterioration in neuromuscular system have remained elusive (1). Here we provide evidences that muscle specific accumulation of SOD1G93A in the transgenic mice model MLC/SOD1G93A (2) induces mitochondria dysfunction and triggers NMJ dismantlement. Further, we demonstrate that treatment of MLC/SOD1G93A mice with Trolox, a potent antioxidant, is sufficient to rescue mitochondria and NMJ defects in the MLC/SOD1G93A mice, stabilizing muscle-nerve connection. The analysis of potential molecular mechanisms that mediate the toxic activity of SOD1 revealed the activation of specific Protein Kinase as a downstream player of NMJ dismantlement. Overall our data demonstrate that muscle specific expression of SOD1G93A mutation causes mitochondrial impairment and NMJ dismantlement, suggesting that muscle defects and NMJs alteration precede motor neuron degeneration rather than resulting from it.

References

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