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Skeletal myotubes and muscles expressing human ALS-causing genes trigger motoneuron neurodegeneration through the release of a toxic factor(s)

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Despite that ALS is considered a central nervous system disease, recent studies show that restricted expression of h*SOD1*^{G93A} in mouse muscles induces motoneuron degeneration and ALS symptomatology. To gain insights into the mechanisms underlying motoneuron neurodegeneration, we established an *in vitro* culture model system using rodent h*SOD1*^{G93A} myotubes and wild-type motoneurons. Muscle conditional media (MCM) was prepared from cultured primary myotubes from neonatal mice expressing human *SOD1*^{G93A} or *C9ORF72* genes. MCM-m*SOD1*^{WT} and non-transgenic *C9ORF72* were used as controls. Wild-type primary rat ventral spinal cord cultures (VSCN) (8-10% motoneurons) at 4 DIV were incubated with MCMs. For each sample we tested motoneuron survival (SMI32/MAP2 immunostaining), ROS production (measured with DCF probe) and c-Abl phosphorylation. MCM-h*SOD1*^{G93A} and *C9ORF72* robustly reduced motoneuron survival (40%) in 7 DIV VSCN cultures. Strong ROS production and c-Abl phosphorylation were observed 30 min after MCM-hSOD1G93A application. Further, we used Drosophila models with muscle-restricted ALS-causing genes to explore whether similar effects could be translated in vivo. Using the fly *GAL4*/UAS system, we expressed ALS-causing genes (h*SOD1*^{G85R}, h*SOD1*^{A4V}, hTDP43 and *C9ORF72*) under muscle *Gal4* promoter MHC. Interestingly, restricted expression of h*SOD1*^{G85R}, h*SOD1*^{A4V}, hTDP43 or *C9ORF72* in muscles of *Drosophila* reduced their climbing ability. Altogether our data provide evidence that skeletal muscle cells expressing ALS-causing genes lead to motoneuron pathology and neurodegeneration through a non autonomous mechanism. We hypothesize the release of unknown toxic factor (s), as a common neurodegeneration pathway.

Biography

Pablo Martinez Contreras is a PhD candidate from Universidad Andrés Bello, with part of his thesis work performed at Massachussets Institute of Technology. In recent years, he has contributed to understanding the non-autonomous cellular mechanisms that trigger motor neuron death in ALS in both *in vitro* and in vivo models. His latest research explores the identification of toxic factors released from skeletal muscle and astrocytes as a possible therapeutic target.

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