Histaminergic signalling in amyotrophic lateral sclerosis

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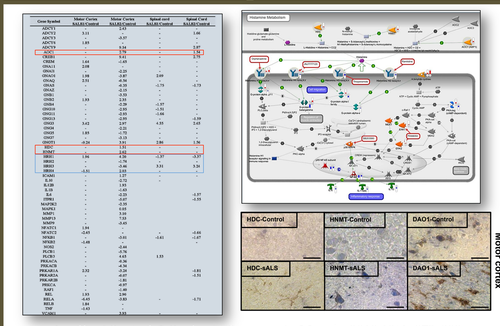
Introduction

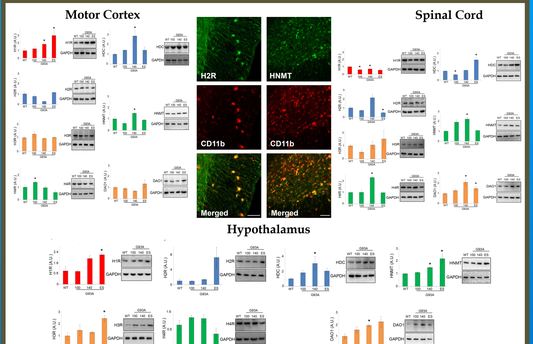
Amyotrophic lateral sclerosis (ALS) is a late-onset neurodegenerative, multifactorial and non-cell autonomous disease where activation of microglia and astrocytes largely contributes to motor neurons death. Histamine is an immune modulator, neuroprotective, and remyelinating agent, beneficially acting on skeletal muscles and promoting anti-inflammatory features in ALS microglia. Drugs potentiating the endogenous release of histamine are in trial for neurological diseases, with a role not fully investigated in ALS. Here, we examine histamine pathway associations in ALS patients and the efficacy of a histamine-mediated therapeutic strategy in ALS mice.

Histamine-related genes are modulated in motor cortex and spinal cord from sporadic ALS patients



- Apolloni S, et al. J Cachexia Sarcopenia Muscle. 2019;10(4):872-893

Histamine receptors and enzymes are dysregulated in the CNS of SOD1-G93A mice during disease progression



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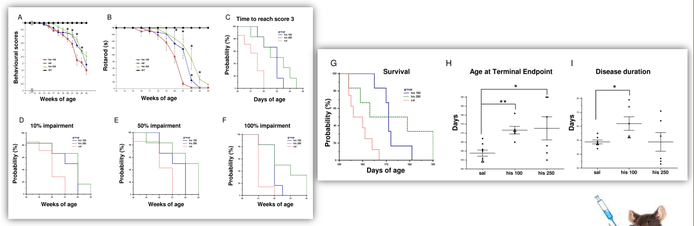
Enhanced histaminergic signalling improves disease progression in SOD1-G93A mice



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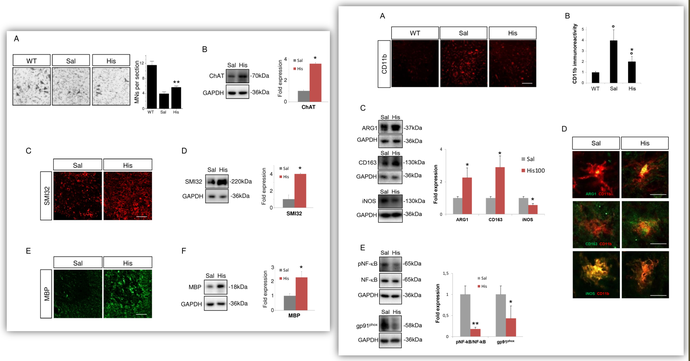
Histaminergic signalling decreases motor neurons loss, axonal degeneration, demyelination, neuroinflammation in the spinal cord of SOD1-G93A mice



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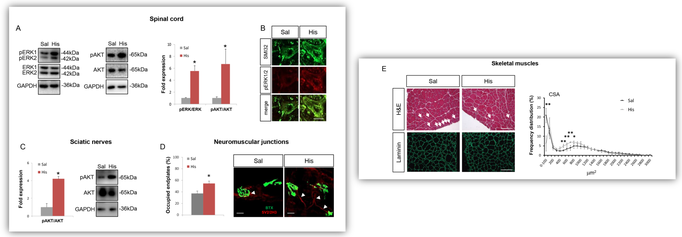
Histidine affects pro-survival pathways in spinal cord and sciatic nerves and decreases denervation atrophy in skeletal muscles of SOD1-G93A mice



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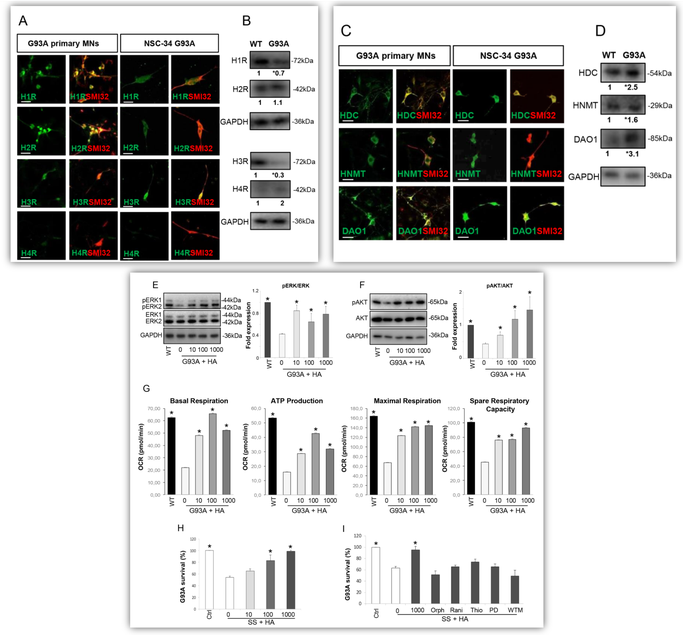
Histamine protects NSC-G93A motor neurons via MAPKs pathways and rescues mitochondrial function



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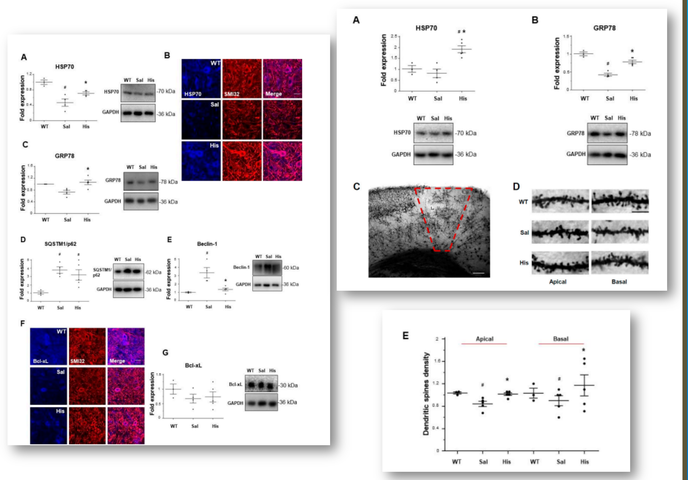
Histaminergic signalling activates the Hsps response and prevents dendritic spine loss in motor cortex from SOD1-G93A symptomatic mice



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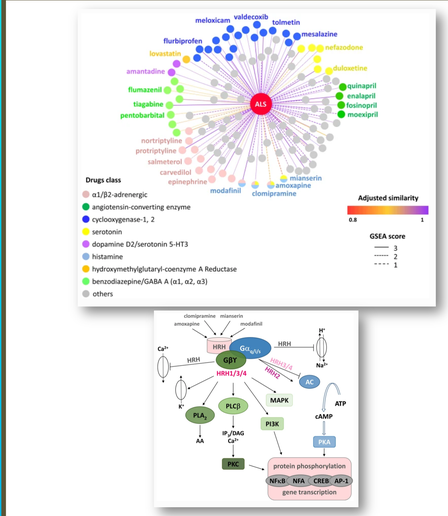
Network-based algorithm for drug repurposing identifies histaminergic drugs as potential innovative solutions for ALS



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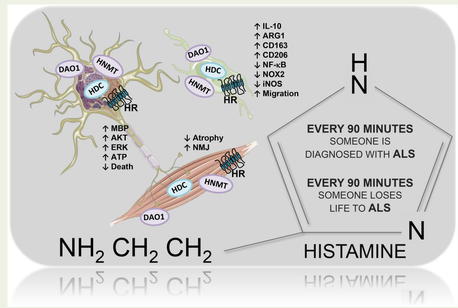
Conclusions



Here we propose that histaminergic modulation might participate to the mechanisms of ALS insurgence, progression, and therapy. Our studies establish that histamine-related genes are modifiers in ALS, supporting their role as candidate biomarkers and therapeutic targets. We disclose a novel important role for histamine in the characterization of the multi-gene network responsible for ALS and in the drug development pipeline.

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