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NEURODEGENERATIVE DISEASES

# Ropin' in ALS

Amyotrophic lateral sclerosis (ALS) is a genetically heterogeneous, progressive neurodegenerative disease with few treatment options. Using patient-derived induced pluripotent stem cells (iPSCs) from individuals with familial or sporadic ALS, Fujimori et al. generated multiple in vitro cellular models of the disease. From phenotypic screening of these models, they found that ropinirole — an approved drug for Parkinson disease and restless leg syndrome — could prevent the progression of neurodegenerative phenotypes in their in vitro ALS models.

Numerous efforts to understand ALS, particularly in mouse models, have focused on *SOD1*, mutations in which cause some forms of familial ALS. However, >90% of ALS cases are sporadic, and there are substantial clinical differences between *SOD1*-mutant ALS and other forms of this disease, including sporadic ALS. Mutations in *FUS* or *TDP-43* are also found in familial ALS, and, unlike *SOD1*, the proteins encoded by these genes are often misfolded in sporadic ALS, suggesting that mutations in *FUS* or *TDP-43* could have mechanistic similarities to sporadic forms of the disease.

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Fujimori et al. began by establishing novel culture conditions to derive motor neurons, the key cell type affected in ALS, from iPSCs of patients with familial ALS and mutations in *TDP-43* or *FUS*. A library of 1,232 approved drugs was screened to find compounds that slowed motor neuron degradation, and ropinirole, a dopamine D2 receptor (D2R) agonist, was identified as the top candidate. Using other D2R agonists and derivatives of ropinirole, the authors established that some, but not all, of the effects of ropinirole could be attributed to D2R activation. Indeed, ropinirole also prevented mitochondrial dysfunction, which contributed to its cell-protective effects.

In vitro iPSC-derived motor neuron models were also established from 32 patients with sporadic ALS. These samples could be stratified according to in vitro phenotypes, which correlated with clinical parameters.

Twenty-four of these cultures, which spanned the observed in vitro and clinical heterogeneity, were selected to evaluate drug candidates. The top nine drug candidates from their phenotypic screen in non-*SOD1*-mutant familial ALS cultures were tested in the sporadic ALS cultures. Of these compounds, ropinirole was the most effective as it prevented apoptosis and other ALS-related phenotypes (neurite regression, abnormal protein aggregates and cytotoxicity).

Transcriptional profiling of sporadic and familial ALS cultures demonstrated that dopamine signalling and inflammation are altered in sporadic ALS and non-*SOD1*-mutant familial ALS relative to healthy donors, and fatty acid metabolism is also altered in sporadic ALS. Lipid peroxidation was increased in the sporadic ALS cultures and ropinirole treatment reduced this lipid peroxidation; oxidized lipids could be the pathogenic species that results from mitochondrial dysfunction. Interestingly, the transcriptional profile of a sporadic ALS culture that did not respond to ropinirole was most similar to the transcriptional profile of *SOD1*-mutant familial ALS, which further suggests that this subcategory of ALS is mechanistically distinct from most cases of sporadic ALS.

These results highlight dopamine receptor signalling as well as mitochondrial dysfunction and the resulting lipid peroxidation as potential therapeutic target pathways in a range of ALS subtypes. They further identify ropinirole as a compound that could potentially be repurposed for the treatment of ALS.

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**ORIGINAL ARTICLE** Fujimori, K. et al. Modeling sporadic ALS in iPSC-derived motor neurons identifies a potential therapeutic target. *Nat.Med.* https://doi.org/10.1038/s41591-018-0140-5 (2018)