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Metabolism, Model Systems and Therapies for ALS

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ABSTRACT

Modelling amyotrophic lateral sclerosis in the era of precision medicine

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Amyotrophic lateral sclerosis (ALS) is a disease in which the neurological system responsible for voluntary movement (the corticomotorneuronal network) undergoes degeneration due to complex and varied causes. Even genetic mutations, an apparently unitary cause of ALS in up to 10% of cases, are tolerated from conception and must also act in combination with multiple age-related secondary events to cause neurodegeneration. This suggests that, like cancer, ALS arises through a multistep process. Genuine therapeutic advances will therefore require a precise understanding of the sequence of events leading to motor neuron degeneration. In the majority of patients without an identifiable single gene disorder, therapies are likely to be multimodal, reflecting this biological diversity.

In vitro and *in vivo* models based on specific genetic mutations have typically used overexpression of mutant gene products to provoke a strong phenotype. However, this favours the recruitment of pathways downstream of disease initiation which may reflect secondary consequences of neurodegeneration and be less therapeutically tractable. We have therefore tried to focus on models of disease in which the earliest changes in motor neuron dysfunction can be explored.

Mice expressing TDP-43 M337V at low level from a BAC construct stably integrated in a single genomic copy exhibit defects in axonal transport prior to neuromuscular failure. Primary motor neurons from these mice show alterations in stress granule dynamics, also present in iPSC-derived motor neurons from patients with the same TDP-43 mutation, which can be used as a tool for high throughput compound screening. In this model we have demonstrated that loss of neuromuscular integrity occurs without protein aggregation or neuroinflammation.

C9orf72 hexanucleotide expansion mutations are the commonest single cause of neurodegeneration. We have shown that iPSC-derived spinal motor and cortical neurons in culture display subtle but

reproducible alterations in cellular homeostasis before cell death. We are using FAC sorting and single cell RNA sequencing, as well as bulk cell RNA sequencing to identify the transcriptional signature of this cellular perturbation, both as a read-out of response to potential therapies and also to identify the earliest pathways associated with disease.

Collectively these models provide the basis for a thorough exploration of disease pathogenesis and for drug screening, aimed at identifying early disease targets for therapy.