RELAZIONE ORALE

MODELING NON-CELL AUTONOMOUS MECHANISMS IN THE ALS PERIPHERAL NERVOUS SYSTEM

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Amyotrophic lateral sclerosis (ALS) has long been viewed as a motor neuron disease, with research focusing on the intrinsic vulnerability of these neurons. While this approach has advanced understanding of disease mechanisms, it has also led to the underappreciation of non-cell-autonomous processes. Recent evidence challenges this perspective by showing that other cells contribute to pathogenic mechanisms. This is particularly true for the peripheral nervous system (PNS), which is affected early in the ALS pathogenic process, with axonal degeneration, peripheral axon loss, and nerve terminal destruction occurring before motor neuron loss and the onset of clinical symptoms.

Increasing evidence suggests that Schwann cells (SCs), the principal glial cells of the PNS, are also involved in ALS pathogenesis. Nevertheless, current experimental models are limited in their capacity to replicate the dynamic, bidirectional interactions between motor neurons (MNs) and SCs in human nerves under both physiological and pathological conditions.

This talk will describe how integrating complementary experimental models can help overcome these limitations and define the role of SCs in physiology and ALS pathology. In vivo approaches using TDP-43-based mouse models of ALS demonstrate that targeting SCs affects MN integrity and disease progression, highlighting the role of peripheral glial cells in modulating neurodegeneration. To complement the in vivo approach, human-induced pluripotent stem cell (hiPSC)-based microfluidic organ-on-a-chip (OoC) systems enable precise modeling of MN-SC interactions in a human-relevant context. The OoC approach reveals that SCs facilitate axonal growth under normal conditions, while SCs derived from patient hiPSCs impair axon outgrowth in both healthy control and patient-derived MNs. Interestingly, the employment of hiPSC-based microfluidic systems allows the identification of early, disease-relevant pathogenic mechanisms that are undetected in standard models.

Overall, these advances demonstrate that a model-driven approach can reshape ALS biology by identifying non-cell-autonomous interactions as key factors of ALS onset and progression. Additionally, they open up to new therapeutic targets that focus on peripheral components of neurodegenerative processes.