

Disease Propagation in Amyotrophic Lateral Sclerosis: Insights and Hopes

Abbreviations: ALS: Amyotrophic lateral sclerosis; UMN: Upper Motor Neurons; LMN: Lower Motor Neurons; SOD1: Superoxide Dismutase 1

Editorial

Amyotrophic lateral sclerosis (ALS) is a devastating degenerative disorder characterized by a progressive decline of upper (UMN) and lower motor neurons (LMN), leading to muscle wasting and finally death. The cause of the disease is still unknown, with the exception of cases due to ALS-related gene mutations. The phenotypes of ALS are heterogeneous, being different ALS subtypes recognized according to the extent and site of involved UMN and LMN [1]. Although the disease evolves towards a widespread involvement of motor neurons in most patients, survival is significantly influenced by distinct phenotypes [1]. The presence of misfolded protein aggregates, mainly composed of transactive response DNA binding protein of 43 kDa (TDP-43), is the pathological hallmark of the disease regardless the subtype [2].

A feature that is common to all ALS patients is that motor manifestations at clinical onset are focal and they appear randomly in the body [3]. Once the focal onset in ALS occurs, motor impairment appears to spread outward to contiguous body regions. This suggests that the pathological process starting in a discrete region of motor neuron system propagates to adjacent motor neurons. When a diffuse motor neuron involvement is observed at onset, a multifocal onset rather than a noncontiguous pattern of disease propagation may be postulated [4].

To explain the focality and neuroanatomic progression of the disease, a prion-like propagation of altered proteins has been argued. According to this hypothesis, misfolded proteins could induce a self-perpetuating process that leads to amplification, abnormal protein-induced conversion of normally configured proteins to misfolded proteins, and spreading of the pathological proteins from the site of disease onset to the neighboring cells [5]. TDP-43, as well as superoxide dismutase 1 (SOD1), misfolding and aggregating in ALS cases linked to SOD1 mutations, have prion-like properties. The ubiquitinated and phosphorylated C-terminal fragments of TDP-43 within cytoplasmic inclusions of ALS neural cells act as seeds and can template their own self-aggregation [6]. *In vitro* studies have shown that SOD1 misfolding can be transmitted not only from protein to protein but also from cell to cell in a prion-like manner [7]. It is matter of debate whether propagation of neurodegeneration occurs by contiguous spread, i.e., cell-to-cell independent of synaptic connection, or based on neuronal networks, i.e. via synaptic connectivity [8]. Anyway, both types of propagations could be involved in ALS at the same time. Whatever the mechanism, the initial degeneration has been observed to maximally involve UMN and LMN innervating the

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same body region. According to longitudinal and cross-sectional studies, subsequent neurodegeneration spreads medially and laterally at the UMN level and to the contralateral side at the LMN level, in an overall rostral to caudal direction.

There is currently no cure available to treat ALS. Understanding the mechanisms underlying the neuroanatomical spread of ALS pathology could represent an alternative target for developing disease-modifying agents in ALS.

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