# ALS/MND의 병리에 대한 최신지견

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## Recent Update in Pathogenesis of ALS/MND

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Recent genetic screenings have identified novel mutations and genetic etiology related to the ALS, and some of which consistently suggest the specific biochemical pathways underlying the pathology of ALS. One of the important pathways newly identified is related to the RNA processing. For example, mutations in TARDBP, FUS, TDP43, and HnRNPA1 which are involved in the RNA processing have been identified as ALS-causing mutations. Dysfunction in RNA processing is also linked with protein homeostasis, and protein and RNA homeostasis system appear to form a positive feedback loop so that ALS-related, RNA-processing proteins generate prion-like aggregation, and the impairment of RNA processing further develops the progression of ALS-like pathology. One additional emerging issue on ALS pathology is the malfunction of mitochondrial dynamics and cellular metabolism. Mitochondria are highly dynamic oraganelles, and spontaneously remodel their shapes by fusion and fission in many cells. In neurons, this process is known to be implicated in the nervous system development. Furthermore, reduction in the mitochondrial length is one of the early symptoms found in the G93A ALS model mice, suggesting that disturbance of mitochondrial dynamics might be an early driving-force of motoneuron (MN) degeneration. Recently, we found that the length of mitochondria is progressively reduced during the MN development in chick embryo. Mitochondrial shortening is partly controlled by a fission-promoting protein, dynamin-related protein-1 (Drp1). Interestingly, suppression of Drp1 activity markedly increased the mitochondrial length, and promoted programmed cell death. Drp1 suppression also depolarized mitochondrial membrane potential and impaired axonal growth, suggesting that deficits in the ATP production and axonal growth may cause MN death. In this lecture, I will further discuss the possible involvements of Drp1 and its upstream regulatory machineries are critical for the pathogenesis of ALS.

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