Genotype-Property Patient-Phenotype Relations Suggest that Proteome Exhaustion Can Cause Amyotrophic Lateral Sclerosis

Late-onset neurodegenerative diseases remain poorly understood as search continues for the perceived pathogenic protein species. Previously, variants in Superoxide Dismutase 1 (SOD1) causing Amyotrophic Lateral Sclerosis (ALS) were found to destabilize and reduce net charge, suggesting a pathogenic aggregation mechanism. This paper reports analysis of compiled patient data and experimental and computed protein properties for variants of human SOD1, a major risk factor of ALS. Both stability and reduced net charge correlate significantly with disease, with larger significance than previously observed. Using two independent methods and two data sets, a probability <3% (t-statistical test) is found that ALS-causing mutations share average stability with all possible 2907 SOD1 mutations. Most importantly, un-weighted patient survival times correlate strongly with the misfolded/unfolded protein copy number, expressed as an exponential function of the experimental stabilities (R-2 = 0.31, p = 0.002), and this phenotype is further aggravated by charge (R-2 = 0.51, p = 1.8 x 10-5). This finding suggests that disease relates to the copy number of misfolded proteins. Exhaustion of motor neurons due to expensive protein turnover of misfolded protein copies is consistent with the data but can further explain e. g. the expression-dependence of SOD1 pathogenicity, the lack of identification of a molecular toxic mode, elevated SOD1 mRNA levels in sporadic ALS, bioenergetic effects and increased resting energy expenditure in ALS patients, genetic risk factors affecting RNA metabolism, and recent findings that a SOD1 mutant becomes toxic when proteasome activity is recovered after washout of a proteasome inhibitor. Proteome exhaustion is also consistent with energy-producing mitochondria accumulating at the neuromuscular junctions where ALS often initiates. If true, this exhaustion mechanism implies a complete change of focus in treatment of ALS towards actively nursing the energy state and protein turnover of the motor neurons.