

INVITED LECTURE H16

SOD1-associated ALS: a promising system for elucidating the origin of protein-misfolding disease

Mikael Oliveberg

Department of Biochemistry and Biophysics, Arrhenius Laboratories of Natural Sciences, Stockholm University, S-106 91 Stockholm, Sweden.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease linked to misfolding and aggregation of the homodimeric enzyme *superoxide dismutase* (SOD1). In contrast to the precursors of other neurodegenerative diseases, SOD1 is a soluble and simple-to-study protein with immunoglobulin-like structure. Also, there are more than 120 ALS-provoking SOD1 mutations at the disposal for detailed elucidation of the disease-triggering factors at molecular level. In this article, we review recent progress in the characterisation of the folding and assembly pathway of the SOD1 dimer and how this is affected by ALS-provoking mutations. Despite the diverse nature of these mutations, the results offer so far a surprising simplicity. The ALS-provoking mutations decrease either protein stability or net repulsive charge - the classical hallmarks for a disease mechanism triggered by association of non-native protein. In addition, the mutant data identifies immature SOD1 monomers as the species from which the cytotoxic pathway emerges, and point at compromised folding cooperativity as a key disease determinant. The relative ease by which these data can be obtained makes SOD1 a promising model for elucidating also the origin of other neurodegenerative diseases where the precursor proteins are structurally more elusive.