What Makes ALS-Mutant Copper-Zinc Superoxide Dismutase Toxic?

Joan Selverstone Valentine

Department of Chemistry and Biochemistry, UCLA

Amyotrophic lateral sclerosis (ALS) is a devastating, fatal disease that targets primarily the motor neurons of patients and which can be either sporadic (SALS) or inherited (familial ALS or FALS). Its cause or causes are almost entirely unknown. The most promising clues we have come from the small fraction of cases of FALS in which the affected families have a mutation in the gene for copper-zinc superoxide dismutase (CuZnSOD). Close to 100 different mutations in the gene for CuZnSOD have been identified in the different families suffering from FALS (most are listed at http://alsod.org/). Each one of these mutations is known to confer toxic properties on the protein, but it is not known what those toxic properties are.

It has recently been hypothesized that instability of the apoproteins of ALS-mutant SOD1 proteins is a universal property among the ALS-linked SOD1 mutations and that the destabilized mutant apoproteins are even more destabilized upon reduction of the intra-subunit disulfide bond. We have carried out a study of a group of ALS-mutant SOD1 apoproteins that represents a representative set of the range of ALS mutations using differential scanning calorimetry (DSC) and global hydrogen-deuterium exchange measured by electrospray ionization mass spectrometry. We found that the ALS-mutant apoproteins that are severely destabilized relative to the WT apoprotein represent only a subset of the mutations and that many of the ALS mutant apoproteins in either their disulfide-oxidized or disulfide-reduced states are not destabilized at all but instead exhibit equal or greater stability compared to WT apo-SOD1.

Our results indicate that the causes of SOD1-linked ALS are complex and are not simply related to apoprotein stability and that alternative answers must be sought for what is perhaps the most perplexing question in CuZnSOD-associated FALS, how such a diverse set of mutations could result in the same gain of toxic function that causes motor neurons to die.