Molecular dynamics and atomic resolution crystallography of human SOD1 shed light on structural features relevant to its role in familial ALS.

Richard W. Strange, Chin Yong, Svetlana V. Antonyuk, William Smith & S. Samar Hasnain

CCLRC Daresbury Laboratory, Warrington, Cheshire WA4 4AD, England U.K.

Dominant inheritance of point mutations in Cu-Zn superoxide dismutase (SOD1) has been implicated in about 20 % of familial cases of the neurodegenerative disease amyotrophic lateral sclerosis (ALS) [1]. Current research strongly suggests that the gain of a toxic property, rather than decreased SOD1 function, is responsible for ALS pathogenicity [2]. The nature of mutant SOD1 toxicity in familial ALS may be related to altered metal ion binding, non-specific chemical reactivity or to abnormal interactions of mutant SOD1 with itself and/or with other cellular constituents [3]. Using atomic resolution protein crystallography and molecular dynamics, we have investigated structural features of SOD1 that are relevant to these potential disease causing factors.

The crystal structure of fully metallated wild-type human SOD1 was determined to 1.15 Å resolution, the highest resolution for this enzyme. Molecular dynamics trajectories for the SOD1 dimer were calculated using the atomic resolution coordinates, over a time domain currently up to 2.5 nanoseconds duration. This time-length permits us to examine intermolecular interactions, domain and loop movements, the presence of symmetric or asymmetric motions within the dimer, and to reveal dynamical communication between the two subunits of the functional dimer.

All calculations were done using the HPCx system, currently No. 27 on the Top 500 List (www.top500.org). The HPCx, which is located at Daresbury Laboratory U.K., comprises 50 IBM POWER4+ Regatta nodes, i.e. 1600 processors, delivering 10.8 TeraFlop/s peak, or up to at least 6 TeraFlops/s sustained (upgraded to 12 TeraFlops from 2006). The system is equipped with 1.6 TByte of memory and 36 TByte of disk space. Additional technical details are available at the web site www.hpcx.ac.uk.

[1] Rosen, D. R., Siddique, T. et al. (1993) *Nature* 362, 59-62.

[2] Cleveland, D.W. and J. D. Rothstein (2001), *Nature Reviews Neuroscience* **2,** 806-819.

[3] Valentine, J. S. and P. J. Hart (2003) *PNAS* 100, 3617-3622.