Defining SOD1-toxicity with obligate SOD1-dimers

Call for projects 2009
Grant: 50 000 €
Project Duration: 1 year

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Although the etiology of most of the ALS cases is unknown, it is believed that the identification of the pathomechanisms of mutant SOD1 toxicity will provide the basis for the development of new therapies. SOD1 is a major enzyme of the cellular defense against free radicals. The dismutase active enzyme consists of two SOD1 monomers. Recent evidence suggests that not only mutant SOD1 but also heterodimers of mutant and wild-type SOD1 [SOD1(WT)] contribute to the disease process. We found that heterodimers of mutant and SOD1(WT) had at least a similar, in some cases an elevated toxicity in a cellular model, compared to mutant homodimers, although the aggregation propensity of the heterodimers was reduced. With support from the Foundation Thierry Latran we were able to investigate the structural and biochemical properties of mutant homo- and heterodimers in further detail, and found that the presence of wild-type SOD1 stabilizes the conformation of mutant variants. These data support the view that mutant proteins in the soluble state mediate toxicity.

CHARACTERIZATION OF THE BIOCHEMICAL AND BIOPHYSICAL PROPERTIES OF OBLIGATORY DIMER PROTEINS REPRESENTING THE TWO MAJOR CLASSES OF SOD1 MUTANTS IN THE C. ELEGANS MODEL

C. Behl, A. Clement, Germany
Grant: € 50 000

A subset of familial forms of ALS is caused by mutations in the gene of the Cu/Zn-superoxide dismutase (SOD1). Although the etiology of most of the ALS cases is unknown, it is believed that the identification of the pathomechanisms of mutant SOD1 toxicity will provide the basis for the development of new therapies. SOD1 is a major enzyme of the cellular defense against free radicals. The dismutase active enzyme consists of two SOD1 monomers. Recent evidence suggests that not only mutant SOD1 but also heterodimers of mutant and wild-type SOD1 [SOD1(WT)] contribute to the disease process.

We have generated fusion proteins consisting of two SOD1 monomers linked by a short oligo-peptide in order to study its potential toxic properties of these heterodimers.

Indeed, heterodimers of mutant and SOD1(WT) had at least a similar, in some cases an elevated toxicity in a cellular model, compared to mutant homodimers, although the aggregation propen-sity of the heterodimers was reduced.

These data provide evidence that mutant SOD1 toxicity is largely independent of the formation of aggregates.
In the proposed project we want to characterize the biochemical and biophysical properties of mutant homo- and heterodimers thereby analyzing aberrant enzymatic activities, the structural stability and metal content of purified dimer proteins.

TEAM

These experiments will be performed partially in collaboration with the Institute for Molecular Biophysics headed by Prof. Decker and the Institute for Analytical Chemistry headed by Prof. Bings, both at the Johannes Gutenberg-University of Mainz.