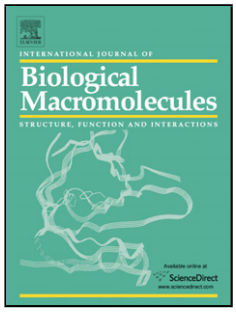

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Alzheimer's disease-associated ubiquitin mutant Ubb^{+1}: properties of the carboxy-terminal domain and its influence on biomolecular interactions

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Abstract

Ubb^{+1}, a ubiquitin (Ub) mutant protein originating from misreading of the Ub B gene, is found accumulated in brain tissues of Alzheimer's disease patients. The mutant attracts strong interest due to its possible participation in the molecular events leading to neurodegeneration. Ubb^{+1} is composed of the globular domain of Ub, linked to a 19-residue C-terminal peptide. Based on NMR relaxation and solvent accessibility measurements we obtained new insight into the molecular properties of Ubb^{+1}. We further determined the thermal stability of Ubb^{+1} in the monomeric form, and in Lys48- and Lys63-linked dimers. Finally, we explored the influence of the C-terminal fragment on the interactions of Ubb^{+1} with an isolated UBA2 domain and with membrane mimics.

Our data indicate that the C-terminal fragment of Ubb^{+1} is overall highly flexible, except for a short stretch which appears less solvent-exposed. While influencing the hydrodynamic properties of the globular domain, the fragment does not establish long-lived interactions with the globular domain. It results that the structure and stability of Ub are minimally perturbed by the peptide extension. However, binding to UBA2 and to membrane mimics are both affected, exemplifying possible changes in biomolecular recognition experienced by the disease-associated Ubb^{+1} compared to the wild-type protein.