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Ion mobility separation coupled with MS reveals alternative structural forms of Alzheimer's disease A β peptide

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The application of mass spectrometry for protein studies extends far beyond classic proteomic analyses in which proteins and their post-translational modifications are identified and/or quantified. Recent developments of new approaches, like ion mobility separation – IM (providing access to collisional cross section values) or technical improvements in the methods already known (like measurements of the hydrogen-deuterium exchange kinetics) enable efficient application of MS for protein structure studies. These methods allow structural insight into a large group of targets difficult in structure analysis. Among them are oligomerising peptides, including A β peptide, main neurotoxic agent in Alzheimer's disease, responsible for synaptic dysfunction and neuronal injury. The mechanism of the A β peptide self-assembly is still under debate. Using Ion Mobility separation coupled with MS we have measured collisional cross-section values of different oligomeric forms of A β , from dimers to hexadecamers. For several oligomers, at least two different forms of different Ω values were detected, indicating the presence of at least two families of conformers: compact and extended. We have also characterized numerous factors shaping the compact/extended species equilibria, like metal binding or point mutations. IM-MS thus detected oligomeric species being both on-pathway in the process of fibril formation, but also alternative structures which may represent potentially most neurotoxic, off-pathway oligomers and allowed their basic structural characterization in the context of complex mixture of interconverting species.

Biography

Michał Dadlez has completed his PhD in 1992 from the Institute of Biochemistry and Biophysics, Pol. Acad. Sci. and Postdoctoral studies from Whitehead Institute, MIT, Cambridge, MA, supervised by Prof. Peter S. Kim. He organized Mass Spectrometry Lab, IBB PAS in 2001, being its head since then. In 2006 he became a Professor of Biophysics. He has published more than 90 papers in peer-reviewed journals. His major fields of interests are protein structure studies with use of MS-based methods (HDex, X-linking, Ion Mobility separation, etc.)

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