Developing IMS-SID/MAD-MS Instrumentation for Characterizing Intrinsically Disordered Protein Structure

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Country

USA

Title of project or programme

Developing IMS-SID/MAD-MS Instrumentation for Characterizing Intrinsically Disordered Protein Structure

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,263,074.31

Start date of award

01/06/2015

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

ion mobility, Spectrometry, protein structure, Dissociation, instrumentation

Research Abstract

? DESCRIPTION (provided by applicant): The long-term objective of our research is to develop powerful mass spectrometry (MS)-based instrumentation and methods for characterizing the structures of biomolecules. Of particular interest are molecules for which structure determination is intractable by conventional techniques such as intrinsically disordered proteins (IDP) and large protein complexes. Technological advances such as those proposed here hold great promise for determining molecular mechanisms associated with disease onset and progression for a diverse array of health conditions ranging from cardiovascular disease to cancer. During the proposal time period we will design and construct a prototype instrument that couples new gas-phase separation capabilities with novel ion fragmentation techniques for the characterization of protein ion structures. Specifically, a compartmentalized drift tube will be coupled to a time-of-flight (TOF) mass spectrometer. The new instrument will be outfitted with surface-induced dissociation (SID) and metastable atom activated dissociation (MAD) capabilities. The new instrument will enable gas-phase hydrogen deuterium exchange (HDX) experiments with top-down protein ion structure characterization for specific conformers. The dual fragmentation process will enable the determination of accessible exchange sites for specific protein complexes according to select ion conformations. Finally, the modified drift tube will allow the determination of such sites for structures arising from ion activation within the drft tube device. The optimized instrument will be used to study a number of peptide sequences associated with the Huntington (htt) protein. These initiatory studies will test the role of the poy-proline region of htt on the aggregation process. Specifically, IMS-HDX-SID/MAD-MS will be used to examine structures of the 17-residue N-terminal region (Nt17), the N-terminal region with poly-glutamine (50 residues), and the full exon 1 model (Nt17Q50P10KK). Here, we will investigate poly-proline binding sites on Nt17 as well as its influence on the types and structures of toxic oligomeric species formed in solution for the different peptides. The successful demonstration of the instrument will not only provide valuable knowledge regarding molecular mechanisms associated with the progression of HD but also will lay the foundation for studies of a wide variety of disease processes.

Lay Summary

PUBLIC HEALTH RELEVANCE: A prototype instrument combining novel ion mobility spectrometry (IMS) separation techniques with a dual ion fragmentation device and time-of-flight mass spectrometry (TOFMS) will be developed to study protein ion structures. The completed device will be used to characterize protein sequences related to Huntington’s Disease (HD). The powerful new instrumentation will lay the foundation for the characterization of intrinsically disordered proteins (IDP) and protein complexes associated with disease processes.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

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N/A

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