The Dark Side of Alzheimer's Disease and Amyloid Formation by Signal Peptide of Amyloid Precursor Protein

A Thesis

Submitted

by

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Affectionately Dedicated to my Family, Friends, Teachers, Indian Farmers and Soldiers

Declaration by the Research Scholar

I hereby declare that the entire work embodied in this Thesis entitled "**The Dark Side of Alzheimer's Disease and Amyloid Formation by Signal Peptide of Amyloid Precursor Protein**" is the result of investigations carried out by me in the ***School of Basic Sciences***, Indian Institute of Technology Mandi, under the supervision of ***Dr. Rajanish Giri***, and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgments have been made wherever the work described is based on finding of other investigators.

IIT Mandi (H.P.) Signature:

Date: **Kundlik Bhagwan Gadhave**

Declaration by the Research Advisor

I hereby certify that the entire work in this Thesis has been carried out by ***Kundlik Bhagwan Gadhave,*** under my supervision in the ***School of Basic Sciences,*** Indian Institute of Technology Mandi, and that no part of it has been submitted elsewhere for any Degree or Diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on finding of other investigators.

IIT Mandi (H.P.)

Date:

Signature:

Dr. Rajanish Giri

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Abstract

Alzheimer's disease (AD) is a leading cause of age-related dementia worldwide. Despite more than a century of intensive research, the structural and unstructural biology of its signalling proteins are not understood completely. It is known that two major proteins related to AD pathology, Aβ peptide, and microtubule-associated protein tau, belong to the category of intrinsically disordered proteins (IDPs), which are the functionally important proteins characterized by a lack of fixed, ordered three-dimensional structure. IDPs and intrinsically disordered protein regions (IDPRs) play numerous vital roles in numerous cellular processes, for example signaling, regulation of cell cycle, macromolecular recognition, and promiscuous binding. Knowing the intrinsic disorder status and disorder-based functionality of proteins associated with AD signaling pathways may help to untangle the mechanisms of AD pathogenesis and help identify therapeutic targets.

As an essential step in that direction, we have studied the intrinsic disorder profile of proteins from two different important signaling pathways such as amyloid cascade signaling and the ubiquitin-proteasome system (UPS) which are strongly associated with AD pathogenesis. We found an abundance of intrinsic disorder, short linear motifs (SLiMs), and molecular recognition features (MoRFs) in signalling proteins of these pathways. These regions have important roles in protein-protein interaction and may have a link with AD pathogenesis.

Further, we experimentally studied the MoRF region of amyloid precursor protein (APP) and ultimately focused on its signal peptide (APP_{1-17} SP) and found that it is intrinsically disordered. Evidently, AD is the protein aggregation disease and aggregation behavior of the domains of APP other than Aβ has also been studied extensively. Nonetheless, APP_{1-17} SP has not been studied for its conformation, aggregation and cytotoxic behavior. Therefore, we studied the amyloid formation of disordered APP_{1-17} SP at the physiological condition. Overall, our study provides significant information on the intrinsic disorder profile of proteins from the amyloid cascade signaling and the UPS and reports that APP_{1-17} SP can self-assemble into β-sheet rich cytotoxic amyloid-like aggregates. These findings represent an important foundation and provide new insights to untangle the molecular mechanisms that underlie the pathophysiology of AD.

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