Linkage-specific ubiquitylation patterns as highly sensitive markers for neurodegenerative disease

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Research Abstract

Linkage?specific ubiquitylation patterns as highly sensitive markers for neurodegenerative

disease Abstract: Despite an intensive effort by the government, pharmaceutical companies and academic groups, the diagnosis and treatment of Alzheimer’s disease remains elusive. The incidence of Alzheimer’s disease is predicted to increase, reaching more than 10 million cases in USA by 2025. Thus, the development of quantitative, simple and reproducible diagnostic markers is extremely important. Current methods for diagnosis of Alzheimer’s disease are dependent on clinical and neuropsychological assessment, cerebrospinal fluid (CSF) analysis, and brain- imaging procedures, all of which have significant cost- and access-to-care barriers. Thus the need for simple blood-based biomarkers has never been greater. We hypothesize that dysfunction in the ubiquitin proteasome pathway occurs decades before the clinical manifestation of Alzheimer’s disease symptoms. Neurons generally do not divide, and their survival depends heavily on the removal of misfolded proteins. The first step in neurodegenerative disease begins with a diminished response to unfolded protein removal, and proteasomal dysfunction. Therefore, neuronal diseases are marked by the appearance or change in pattern of ubiquitylated proteins — the main hypothesis of this proposal, which describes a unique combination of affinity purification of ubiquitylated proteins and mass spectroscopy approaches to detect ubiquitylated proteins and also determine the nature of the poly-ubiquitin chain linkage. Although the roles of the ubiquitin pathway in cell physiology and pathology have been recognized for the last three decades, surprisingly there are no reliable and sensitive methods available to monitor patterns of ubiquitylation. The development of this technology will enable clinicians to make early diagnoses of Alzheimer’s disease, facilitate the discovery of disease modifying drugs, and open doors for cell biologists to rapidly identify patterns of poly-ubiquitylated proteins in tissues, cells or body fluids.

Further information available at:

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