

Chapter 10

Tau Pathology: A Step Towards Understanding Neurodegenerative Disorders Network Complexity

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ABSTRACT

A number of neurodegenerative disorders (NDs) are usually referred as tauopathies and characterized by the disappearance or disintegration of tau protein from microtubules. Alzheimer's disease (AD), Pick's disease (PiD), Parkinson's disease (PD) are directly or indirectly associated with tauopathy. Tau is a protein which is usually associated with microtubule. Microtubules are the backbone of neurons, and tau provides a support to microtubule stability. Hyperphosphorylation of tau leads to its separation from microtubule, consequently forming neurofibrillary tangles and resulting in a condition of dementia. Therapeutic implication on tauopathy is symptomatic as there is no exact regulation mechanism known till date. This chapter helps in the comprehensive study of biomarkers and pathways involved in tauopathy to decipher the complexity of the system, resulting in candidate drug target for the management of NDs.

INTRODUCTION

NDs like AD and PD are responsible for a notable increase in the proportion of mortality and morbidity in the developed world today (L. E. Hebert, Beckett, Scherr, & Evans, 2001; Liesi E. Hebert, Scherr, Bienias, Bennett, & Evans, 2003). It is due to the result of increase in the life expectancy of individuals and the change in the population demographics like the neurodegenerative movement disorders

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which are more common nowadays, aging of baby boomers as well as the neurodegenerative dementias (Brookmeyer, Gray, & Kawas, 1998; Samii, Nutt, & Ransom, 2004). With the aging of the population will provide an improved perceptive of such diseases and this will provide a vital part in the development of many effective therapies and to combat the shocking costs of such diseases (Ernst, Hay, Fenn, Tinklenberg, & Yesavage, 1997). Unifying pathogenesis theories in ND offers an opportunity for the development of therapeutic strategies with broad range of applications in the prevention of disease and a chance for declining morbidity and mortality due to these disorders in the elderly population (Forman, Trojanowski, & Lee, 2004). The lines of analysis showing convergence have exposed a potential single common pathogenic mechanism that underlies various diverse neurodegenerative disorders (the deposition and aggregation of misfolded proteins). Almost all the major neurodegenerative disease has been characterized pathologically by the insidious buildup of insoluble filamentous aggregates of usually soluble proteins in the central nervous system (CNS) (Irvine, El-Agnaf, Shankar, & Walsh, 2008). Since the filamentous aggregates show the tinctorial and ultrastructural characteristics of amyloid, which are ~10-nm-wide fibrils with crossed β -pleated sheet structures that stain with Congo red, thioflavin-S, etc; these diseases can together be grouped as brain amyloidosis (Rajamohamedsait & Sigurdsson, 2012).

The main question comes in mind, what is actually responsible for the remarkable phenotypic diversity found in the above mentioned diseases? Every associated brain amyloidosis is differentiated by diverse temporal and regional patterns of aggregates deposition, changing cellular hosts or extracellular locales of the aggregates, and various protein constituents of the aggregates (Guo & Lee, 2014). All of these characters, along with the innate and variable reactions of the patients to the aggregates that might vary the cascade of events which guide to a particular temporal and regional pattern of neuronal dysfunction (Morris, Clark, & Vissel, 2014). This can result in death, revealing as a particular clinical syndrome like dementia in AD or a movement disorder in PD. Therefore, looking from a pathological view point, neurodegenerative entity can be well explained by the nature and pattern of the deposition of amyloid in the brain. Unluckily, the category and pattern of the amyloidosis in the brain does not always relate fine with the experimental clinical phenotype which were observed (Allen, Robinson, Snowden, Davidson, & Mann, 2014). The variability in connections has advanced to a perplexing nosology that at times need clinicians to explain phenotypes with respect to the presumed existence of the pathological lesions like dementia along with Lewy bodies. At times there is a necessity for pathologists to illustrate lesions by means of clinical language despite of the patient's actual clinical presentation as in the case of progressive supranuclear palsy (PSP). One of the right ways to get around this turmoil is by achieving chemical analytes of biological fluids and neuroimaging biomarkers. These biological entities will permit the clinicians to differentiate between brain amyloidosis based on the character and level of the brain pathology along with the particular amyloidogenic proteins caught up in disease pathogenesis (Macedo & Cordeiro, 2017). These NDs share common mechanisms which involves accumulation of CNS misfolded proteins which provides an idea that these disorders might be linked to similar targets for the advancement of diagnostic and therapeutic agents.

In this context, AD, tauopathies (PiD, cortical basal degeneration, and PSP), and the synucleinopathies (dementia with Lewy bodies, PD, and multiple system atrophy) are discussed as models of the brain amyloidosis that are found in many ageing-related neurodegenerative disorders (Hassan, Whitwell, & Josephs, 2011; Levin, Kurz, Arzberger, Giese, & Höglinger, 2016; Tsai & Boxer, 2014). It further deals with mechanistic understanding of the deregulation of neurodegenerative pathways through various signaling cascades. In NDs, the disease spread goes behind disease-specific patterns that look like the structural design of brain connectivity networks. The point which still remains unclear is that, what

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