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Editorial

The Three Assassin Proteins; Alpha-Synuclein, Beta-Amyloid and Tau, and their Potential Neurodegenerative Pathways

Jeswinder Sian-Hulsmann*

Department of Medical Physiology, University of Nairobi, Kenya

***Corresponding Author**: Jeswinder Sian-Hulsmann, Department of Medical Physiology, University of Nairobi, Kenya.

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Neuropathological findings furnish the compelling evidence for the involvement of accumulated misconformed proteins; alpha-synuclein, beta-amyloid (β-amyloid) and tau in pathogenesis of prevalent disease process(es). Their precise role as either a cause or consequence has still not been clearly defined. Nevertheless, their aggregation in the brain can evoke catastrophic effects on healthy neurons and certainly contributes to cell death in chronic progressive neurodegenerative illnesses.

Misfolded alpha-synuclein (β sheet synuclein) aggregates [1], are observed in Parkinson's disease dementia (PDD), dementia with Lewy Body (LB) disease (DLB), and other alpha-synucleinopathies. This deadly form of the protein is notorious and rapidly infects the normal cells and propagates in a prion-like fashion, thus marking destruction in its wake.

In contrast, the normal form of alpha-nuclein, appears to exert a protective role in the gut by deploying immune cells in the event of an intestinal infection [2]. It activates microgliosis and thus precipitates inflammatory cascade [3]. Similarly, the misfolded form of the protein can also attract white blood cells and precipitate inflammation. However, in event of chronic intestinal infections, there is an overproduction of alpha-synuclein by the gut nerves and their subsequent migration to the brain perhaps via the vagus nerve. The protein overload in the brain may overwhelm the protein clearance mechanisms and thus resulting in the accumulation of alpha-synuclein.

Nevertheless, the question that arises from this hypothesis are, what factor(s) triggers its incorrect folding and thus a dramatic change in its role from protective to a rogue? Both *in vitro* and *in vivo* studies have suggested that the protein can easily assemble into oligomers under an array of conditions. Additionally, environmental agents can also promote the aggregation of the protein. More importantly, the trigger factor(s) may operate on a genetic level, since about 90% of the alpha synuclein is phosphorylated at serine 129, in contrast to only 4% in the normal state [4]. The phosphorylated form of alpha-synuclein has a propensity to assemble in a disordered manner. There are two potential candidates that may lead to the genetic pathway for generating LB production include; firstly the involvement of a defective gene in protein breakdown system and/or secondly mutations on the alpha synuclein genes itself.

Kinase dependent pathways have been linked to PD pathology. Indeed, protein kinases such as, casein kinase 2 and polo-like kinase are able to mediate serine 129 phosphorylation [5] and thus provoking alpha synuclein aggregation LB formation and other related LB pathology. Furthermore, mutations of the alpha-synuclein gene as reported in families with autosomal dominant PD may induce generation of LB [6]. Similarly, studies in familial AD have found mutations in amyloid precursor protein, presenilin 1 and presenilin 2 may be associated with LB generation [7].

Interestingly, alpha-synuclein was first described in association with Alzheimer's disease (AD) β-amyloid plaques (or amyloid plaques), this was before the elucidation of its critical role in LB formation. A significant population of the AD (circa 50%) exhibit LB pathology in addition to the characteristic amyloid plaques. The presence of amyloid plaques in the neurons, are a characteristic feature of AD. It is a protein fragment that has been sliced from the amyloid precursor protein. Under normal conditions these proteins fragments are disposed, however in the diseased state they accumulate (plaques) in the brain and spinal cord [8].

DLB and PDD share many neuropathological and biochemical changes, additionally they can exhibit both Lewy bodies and β-amyloid plaques. This lends support to the notion that perhaps there is a common neurodegenerative pathway, which may also be employed by AD [9]. This common pathway appears to be exclusive for Parkinson's disease related disorders and is not observed in other synucleinopathies such as multiple systems atrophy.

In the normal state, alpha synuclein and β amyloid do not co-exist, thereby limiting the possibility of interaction between these two corrupt proteins [10]. However, a disruption of the protein clearance and lysosome system may furnish the opportunity for the interaction of the two proteins. Indeed, vital pathways for protein clearance, autophagy-lysosome pathway, serine proteases and the ubiquitin pro-

tease system have been found to be dysregulated in PD and AD. This may suggest that the disordered proteins may overwhelm the failing protein clearance system. The toxic and aggregate prone form β-amyloid 42 has been reported to provoke lysosomal leakage.

In the ailing state, mutation of the presenile 1 results in the elevation in concentrations of the β-amyloid 42 form. It has been suggested that alpha-synuclein favors to bind with the β-amyloid 42 form [11]. Alpha-synuclein and β-amyloid can form complexes or aggregates which can have catastrophic cellular effects including: influx of cellular calcium ions, aggregates such hybrid pore like oligomers that can hinder protein clearance via β-amyloid induced malfunction of proteasome. β-amyloid has been found to be an active member of these dysregulated proteins. Indeed, it induces a host of deleterious effects including, inflammation, alpha-synuclein phosphorylation and then aggregation (leading to LB production) and tau pathology. Nevertheless, LB pathology can also occur in the absence of β-amyloid, as observed in idiopathic PD and incidental Lewy body disease. In AD, β-amyloid is a key neuropathological observation. Indeed, risk of β-amyloid positive patients developing dementia is approximately two fold, thereby reflecting its integral role in the illness. However, for reason(s) unclear, this direct interaction of these two proteins only occurs in some patients and certain regions of the brain.

In vitro studies have shown that alpha-synuclein can serve as a cofactor in the polymerization of tau [12]. Tau protein [13], is another member of the disordered proteins. Its phosphorylation and subsequent aggregation results in the formation of neurofibrillary tangles, which represent another hallmark of AD.

In contrast alpha-synuclein, is independent and can self polymerize. Furthermore, it can operate synergistically with tau protein to evoke processes that lead to neuronal death. Tau pathology is associated to cognitive deficits in PD without dementia [14]. Analogous to the other two defective proteins, over expression of tau may instigate inflammatory processes [15].

Both β-amyloid and alpha-nuclein can independently modulate tau phosphorylation. Furthermore, aggregated alpha-synuclein and oligomers of β-amyloid can blight the normal operation of ubiquitin-proteasome pathway. This pathway is vital for the degradation of tau proteins [16]. Thus, the involvement of debilitated protein clearance mechanism is implicated again.

Interestingly, a marked number of patients exhibit different combinations of alpha-synuclein, β-amyloid and tau protein pathologies, thereby making it difficult to make a definite diagnosis of the patients. The occurrence of a cocktail of these culprit proteins prophesizes a poor prognosis. This is high-lighted by accelerated neuronal death, rapid cognitive decline, aggressive dementia and shorter survival rate [17].

The labyrinth reflected by the presence and accumulation of alpha-synuclein, β-amyloid and/or tau protein is complicating. The appearance of overlaps or mixed pathologies, may suggest some common pathway for either their formation or mode of neuronal degeneration occurring in AD, dementia and the spectrum of PD. However, the differences observed in anatomical distribution and the different of protein aggregates (and inclusions) may be related to the characteristic type of neuropathology manifested by the disorder.

Therefore suboptimal functioning of the protein system mechanisms appears to play an integral role in orchestrating accumulation of the disordered proteins that subsequently provoke deleterious effects on vulnerable neurons. Nevertheless, evidence furnished by various studies suggests the participation of the other processes/factors in the generation and cytotoxic effects of these corrupt proteins; inflammation, synergistic interactions between the disconfirmed proteins, genetic link and finally age. Perhaps the ageing brain cells lack the plasticity to cope with an excess protein production/accumulation and thus compensatory mechanisms fail to be initiated and thus disease ensues.

Finally, to effectively halt or delay the progression of these proteinopathies, it is imperative to elucidate the trajectory of these rogue proteins to effectively target them, so that selective therapeutic agents can salvage the wretched neurons from the rogue proteins' savage wrath.

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