Lewy Body Pathology: From Amyloidosis to Vesicle Trafficking

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For many decades there have been dilemmas regarding the nature of Lewy bodies (LBs) and Lewy neurites (LNs) found in neurodegenerative disorder Parkinson’s disease (PD) [1]. Most of the scientists in their studies have marked the presence of a small soluble protein called α-synuclein expressed at a pre-synaptic junction that undergoes aggregation and forms LBs and LNs [2]. Under specific conditions, the protein can form stable tetramers and amyloid fibrils, the presence of which was identified by various techniques.

Recently a group of Japanese scientists at Osaka University, led by Suita, confirmed the amyloid nature of LBs using microbeam X-ray diffraction analysis of LBs in thin sections of autopsy brains of patients with PD and using senile plaques of Alzheimer’s disease (from mouse model) as a key reference for β-Sheet characteristic identification [3]. They found the common features in these samples and confirmed the amyloid nature of LBs and LNs in PD, as the samples from the brain of PD patients contained amyloid fibrils with a characteristic cross-β structure.

Now the question that arises is what is the root cause of the release of α-synuclein and its transfer across the neuron. A potential mechanism was discussed by Reyes et al. [4] in their study that was designed to unravel the cellular mechanism implicated in α-synuclein transfer. They found a gap junction protein called connexin-32 (Cx32) acting as a signature lesion for α-synuclein uptake [4]. In another recent study, it has been shown that ROS-mediated oxidative stress in vagal neurons subverts the transmission of α-synuclein across the neuronal cells [5].

The resolution in microscopy has revealed structural polymorphism of α-synuclein fibril, albeit the difference in atomic structure has still been elusive. As an example, a recent study on α-synuclein, supported the conundrum of α-synuclein fibril polymorphism using the cryo-electron microscopic helical reconstruction method [6, 7].

Many scientists have targeted α-synuclein as the prime source of developing PD and neuronal death, and hence many attempts have been made to design a potential drug inhibitor against aggregation of this protein [8]. Most of the people have targeted the non-amyloid-β component (NAC) region of α-synuclein as it has been most susceptible to cause changes in the protein [9]. In their study, Pujols et al. used a high throughput screening method to develop a novel drug candidate against α-synuclein fibrils and found a small molecule that not only inhibits α-synuclein aggregation but also disaggregates pre-formed amyloid fibrils and ultimately inhibiting degeneration of dopaminergic neurons [10].

All these studies supported the amyloid nature of PD until the turning point brought by Shahmoradian et al. who almost waved off the entire amyloid theory of PD. Their study published in Nature Communication revealed the other side of the disease and illuminated using “state of the art” technique that LBs and LNs are mainly composed of membranes, vesicular compartments and dysmorphic organelles [11]. These authors showed using Correlative Light Electron Microscopy (CLEM) that LBs and LNs are a result of distorted vesicle trafficking rather than the previously assumed direct amyloid fibril formation. In fact, they did not mention any significant role of amyloid fibrils in PD. This work brought to the light a contrary theory and generated some turbulence among the scientific groups all over the world. This recent surge of discoveries and breakthroughs in PD brings forth the divergence between the two sides of PD. The Shahmoradian research has acted as a game-changer and questioned the previous concept of α-synuclein amyloid fibril formation as the only and sine qua non for PD development.

However, until now, early events that drive all these processes still remain unclear, as α-synuclein aggregation can affect vesicle trafficking. To some extent, Ray et al. tried to resolve this enigma. Their in vitro and animal model study on α-synuclein suggest a phase transformation from liquid to solid under conditions such as molecular crowding, low pH and familial mutations [12]. This could be somewhat linked to the Shahmoradian study as both involve membrane crowding. This increases the necessity to take now a fresh look at the PD etiology. More therapeutic approaches could be evolved with this.
CONFLICT OF INTEREST

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REFERENCES


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