

The Star Studded Protein and its Chaperone Mediated Pathways: Faulty Lysosomal-Autophagic System, Alpha-Synuclein Aggregates in Parkinson's Disease and its Relevance to Therapeutic Intervention

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Plethora of research findings over recent years have led to the elevation of α -synuclein to star status in the etiology of PD. Rogue pathogenic proteins such as α -synuclein, appear to play a malevolent role in the development of Parkinson's disease (PD) and other α -synucleinopathies. They share a common denominator, which is characterised by aggregates of misfolded α -synuclein, which results in the formation of intra-neuronal inclusions known as Lewy bodies (LB). The presence of LB in substantia nigra is mandatory for the neuropathological diagnosis of PD. Interestingly, the occurrence of these structures appear to mirror areas exhibiting neuronal cell loss such as the substantia nigra pars compacta and other brain areas burdened with the onslaught of the disease, thereby suggesting that they are of focal relevance to the disorder. Furthermore, the presence of LB in the asymptomatic phase of PD (incidental Lewy body disease; [1] endorses their role in the pathogenesis. It is unclear whether they represent a cause or consequence of the illness. Therefore, in order to advocate effective therapeutic intervention it is imperative to elucidate the pathways or mechanism(s) underlying disruption of protein homeostasis, α -synuclein accumulation LB formation.

The presence of α -synuclein inclusions in the substantia nigra can elicit cellular devastating processes by virtue of its ability to function as ferrireductase [2]. The excess α -synuclein/ferrireductase can prompt the conversion of iron (III) to iron (II) resulting in the disruption of iron homeostasis. Although other factors may come into play in the brain iron accumulation exhibited in the illness. The iron overload can generate the production of cytotoxic free radical species, which can in turn trigger oxidative stress resulting in neuronal cell death [3]. Indeed, the occurrence of destructive cellular processes such as oxidative stress can be supported by the marked reduction in levels of nigral antioxidant glutathione in PD [4].

There may be a genetic involvement [5] or some trigger factor(s) that are essential for the improper folding of α -synuclein, and perhaps in the diseased state the lysosomal-autophagal mechanisms may not be functioning at optimum level, resulting in its accumulation. Thus, the failure of the protein degradation pathways may render the dopaminergic neurons more vulnerable to pathological cytotoxic processes in PD. Alternatively it may be a contributor and an active member of the pathogenesis of the illness.

Evidence from recent findings is indicative that the improper folding and accumulation of α -synuclein is likely to be a direct consequence of a malfunction in protein homeostasis. It is imperative to sustain protein homeostasis for normal neuronal functioning. Cells have quality control mechanisms that allow efficiency in the production and destruction of proteins. The endoplasmic reticulum-golgi complex achieves quality control by playing a fundamental role in protein synthesis and secretions. More importantly, this complex also ensures that only correctly folded proteins are allowed to flow through the secretory pathways. Misfolded proteins are directed towards degradative systems such as, lysosomal-autophagal and proteasomes.

Under physiological conditions the lysosomal-autophagal system serves like a hub or signalling centre to maintain protein homeostasis by destruction of improperly folded proteins and clearance of cellular waste. It achieves this by orchestrating an array of functions including, autophagy, regulation of protein translation and chaperone mediated protein folding. This mechanism is also cellular protective effects, since it is boosted by harmful states such as oxidative stress and nutrient loss. Normally, excess α -synuclein is eliminated from cells via macroautophagy and chaperone mediated autophagy (CMA). A breakdown in these protein catabolic mechanisms may allow the unsolicited hoarding of α -synuclein [6].

Macroautophagy plays a pivotal role in maintaining proteostasis. This process of "self-eating" proteins begins at the endoplasmic reticulum and ends with the fusion to lysosomes. Another component involved in protein regulation is CMA; it contributes in maintaining key neuronal homeostasis such as, protein quality control and energy equilibrium.

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Increasing evidence is indicative of a correlation between a defective CMA and the occurrence of PD. This view is supported by the reduced levels of brain CMA markers in PD. There appears to be involvement of a genetic component and this is clearly demonstrated by the diminished or absent CMA activity in some of the familial types of PD (SNCA, DJ-1, UCHL1 and LRRK2). This suggests that α -synuclein aggregation may be induced by defective CMA since, it is one of the major breakdown mechanisms for this protein. In addition, the compromised CMA may also contribute to the carnage of dopaminergic neurons via the inactivation of the transcription factor MEF2D, which plays a crucial part in the neuronal survival.

Molecular protein chaperones such as, ubiquitin proteasome system (UPS) and autophagy-lysosomal pathway (ALP) are also associated protein dyshomeostasis. Cellular stress of a trifling magnitude prompts the intensification of chaperone activity, however, this compensatory response fails in the case of a more persistent stress [7]. Indeed, this notion is endorsed by the reduced UPS and ALP function reported in PD [8]. These mechanisms would be critical for removing abnormally folded α -synuclein protein or to refold it. The net effect is to aim to eliminate such misfolded macromolecules and thereby avoiding occlusion of secretory pathways and thereby assure seamless cellular function. In addition, the disruption of the lysosomal homeostasis may contribute to the mitochondrial impairment and endoplasmic reticulum (ER) stress observed in PD. The ER stress initiates unfolded protein response (UPR), this is an attempt to re-establish cellular protein balance, however in the event of a chronic cellular damage it triggers pathways that result in cellular destruction.

The dysfunctional lysosomal-autophagal system seems to be invoked by a genetic involvement, since mutation gene LRRK2 appears to precipitate ER stress and cell death. The cell death may be a result of the blighted ER- calcium homeostasis as this system is imperative for cell survival. Interestingly, mutations in LRRK2 are also linked to CMA dysfunction. Experiments using mice astrocytes suggest LRRK2 mutation produces an ER calcium ion depletion, which in turn produces an overload of calcium in the mitochondria resulting in its malfunction [9]. Therefore, the gene LRRK2 may mediate neuronal destruction via calcium mediated apoptotic pathways.

However, in the pathological environment such a regimental proteostasis may not be maintained resulting in the aggregation of aberrantly folded α -synuclein proteins. A defective autophagal system has been associated to the manifestation of Lewy body aggregates [10]. More importantly, since CMA pathway is a fundamental regulator of interneuronal α -synuclein, a defective protein catabolic pathway may be a major pathogenic contributor to the disorder [11].

Autophagy collects unwanted proteins and delivers it to the lysosomes. The lysosomes contain a rich supply (over 60) of hydrolases that execute the destruction of macromolecules. The reduced activity of the lysosome hydrolase enzyme, glucocerebrosidase (GCase) has been associated to the build-up of α -synuclein PD. This concept is supported by the reduction in GCase activity corresponding with decrease in protein clearance and thus accumulation of α -synuclein in cultured neurons [12].

Mutations in the GCase gene glucocerebrosidase (GBA1) appear to produce structural changes which results in depletion of the enzyme activity. Indeed, GBA1 mutations confer a genetic risk for the occurrence of PD. Interestingly, an inherited lysosomal disorder called Gaucher's disease, GBA1 mutations coupled with a suboptimal GCase activity is reported. However, only 7 - 12% of patients carrying the GBA1 mutation develop PD. Furthermore, in some cases of idiopathic and sporadic form of PD, a decrease of GCase activity was found in the absence of GBA1 mutation. This suggests that there may be other contributors for the amassing of α -synuclein and formation of LB.

Nevertheless, to employ effective therapeutic intervention, it is important to elucidate the interactions between GCase and this culprit protein and the related surge of events linked to the dysfunctional lysosomal-autophagic pathway.

Targets for therapeutic intervention in PD

The current therapeutic strategies in PD fall short of targeting the underlying pathology, thus the progression of the disease cannot be hindered or halted. In contrast, regulating the autophagal-lysosomal pathways offers an alternative that may be more effective as a disease modifying intervention by maintaining proteostasis.

Experimental models of PD have shown that the benefit of non-specific autophagy stimulation using drugs such as, rapamycin and lithium are largely limited by their unwanted effects. Therefore, a range of more discriminating drugs/compounds that have been developed recently are the drugs of choice. They are more specific and act at various strategic sites in the protein regulatory pathways and other mechanisms underlying the pathogenicity of PD. This includes; CMA regulators, lysosomes enhancers such as GCase, Transcription Factor EB (TFEB), ALP and UPR.

In view of the instrumental role played by the CMA in eradication of the α -synuclein, it would prudent to employ drugs that elevate its diminished activity in PD. Retinoic acid derivatives and imRNAs have been shown to enhance CMA and thus are hopeful candidates [13].

The results obtained from a recent study using the drug ambroxol in PD, are very promising [14]. PD patients both with and without GBA1 mutation treated with ambroxol, exhibited and an increase in GCase levels (probably via the TFEB route) coupled with a reduction of α -synuclein in the cerebrospinal fluid. Its ability to cross the blood brain barrier and perhaps exert a neuroprotective effect in brain areas afflicted by the disease process would be great advantage. Consequently, such an action may halt or delay the progression of the disease, thus it would serve as a neuromodulator. In addition, it was well tolerated with some gastrointestinal disturbances and a modest risk of anaphylaxis. It is has currently completed Phase II of clinical trials. However, these positive findings need to be carefully considered due to some of the limitations of study including; the study engaged only a small number [17]. PD patients, no placebo's was given to the control group, the average age of PD was only 60.2 yrs. (close to the mean age of onset). Nevertheless, the impressive effects of ambroxol should not be shadowed, as it appears to possess genuine potential as the first neuromodulator in PD. Additionally, it would interesting to see its longer term effect particularly on α -synuclein aggregation and motor function. It may somehow blunt the pathological blow, resulting in perhaps a milder form of the disease.

Similarly, ambroxol treatment in Gaucher's disease [15] also resulted in an elevation in GCase activity in lymphocytes, thus endorsing the findings of Mullin and colleagues (2020).

A fascinate finding suggests, lysosomal function can be restored by changing the lysosomal pH [16]. This needs to be carefully considered for the future development of lysosomal enhancers.

TFEB is chiefly directs the functions of lysosomes and mTORC1 dependent and independent macroautophagy. Interestingly, a recent study has shown that both Torin1 (mTORC1 dependent TFEB) and curcumin analog C1 (mTORC1 independent TFEB) are protective to the dopaminergic neurons in oxidative-stress induced by 6-hydroxydopamine PD model [5]. This suggests that TFEB like analogs may have a neuroprotective potential by virtue of rescuing dopaminergic cells from the oxidative stress induced assault exhibited in PD.

ER stress and unfolded protein response (UPR) also aim at restoring proteostasis, however they are overwhelmed by prolonged cellular stress [7]. Therefore, potential therapeutic candidates should target at diminishing ER stress by selectively affecting the UPR, so as to augment the destruction of the misfolded α -synuclein [17].

Therefore, the findings reported strongly support the involvement of dysfunctional proteostasis pathways in the pathogenesis of PD. Novel pharmacological therapies need to target specific stages of lysosomal-autophagal regulation to prove efficacious. This warrants the need to explore and characterise the extent of protein deregulation at various stages of the disease and also in the different PD subtypes.

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