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Commentary

A new avenue for treating Parkinson's disease targeted at aggrephagy modulation and neuroinflammation: Insights from *in vitro* and animal studies

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Neurodegenerative disorders represent one of the most significant problems in basic and clinical medicine worldwide. Parkinson's disease (PD) is an incurable and widespread neurodegenerative disease, the second most common neurodegenerative disorder after the Alzheimer's disease. According to the European Parkinson's Disease Association, the number of people suffering from PD is approximately 10 million worldwide (https://www.epda.eu.com/). PD causes severe motor impairment and non-motor deficits. The current methods for PD treatment are only symptomatic. Most of them are targeted at supplementation of dopamine to the brain to alleviate motor dysfunction caused by the degeneration of dopaminergic neurons in the nigrostriatal system [1]. Although this approach allows patients to overcome most of the motor and its related symptoms for a considerable period, it does not ameliorate non-motor deficits in PD and does not halt the progression of the disease. Therefore, major efforts are aimed at the discovery of a new effective pathogenesis-relevant therapy for PD that would block the disease course and restore all the compromised functions. The pathogenesis of PD and other synucleinopathies is largely associated with perturbing the cellular proteostasis machinery that leads to the intraneuronal accumulation of so-called Lewy bodies consisting mainly of neurotoxic α-synuclein protein aggregates [2]. Thus, facilitating the neuronal clearance of pathological aggregated protein inclusions via activation of a reparative neuronal autophagy is regarded as a promising therapeutic approach for PD [3]. However, neurodegenerative disorders have a multifactorial etiology and involve various pathological processes that often closely interact and overlap. Neuronal loss induced by the neurotoxic protein aggregates provokes an adverse neuroinflammatory response that further propagates neuronal loss, thus creating a vicious cycle and exacerbating the disease progression [4].

In an article in *EBioMedicine* [5], Suresh and colleagues hypothesized that modulating both neuronal autophagy and neuroinflammation simultaneously could exert neuroprotection *in toto*. They tested a small molecule, PD180970, using several models including non-neuronal, neuronal and microglial cell lines as well as preclinical MPTP-induced mouse PD model. PD180970 is a potent competitive inhibitor of C-Abelson tyrosine kinase (c-Abl TK) enzyme [6]. c-Abl TK is a non-receptor tyrosine kinase that gets activated by oxidative and cellular stress. Recent evidence suggests the involvement of c-Abl TK in the pathogenesis of PD through Parkin inactivation, α-synuclein aggregation, and impaired autophagy of toxic elements [7]. Inhibition of this kinase activity has been suggested as a potential target in the treatment of PD [7,8]. Indeed, Suresh and colleagues [5] found that PD180970 clears toxic protein aggregates and exerts cytoprotection against α-synuclein toxicity in an autophagy-dependent manner through increased autophagy flux and augmented autophagosome numbers *in vitro*. In addition to confirming the promise of PD180970 as a potent autophagy inducer, it also has anti-neuroinflammatory properties. PD180970 curbs inflammatory response *in vitro* through the inhibition of microglial activation and blocking the

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release of proinflammatory cytokines such as MCP-1 and IL-6. Both of these neuroprotective capabilities of PD180970 were further supported using an *in vivo* acute MPTP-based PD mouse model. PD180970 mitigates MPTP-induced neuronal loss and clears toxic α-synuclein oligomers by inducing autophagy in substantia nigra as well as reduces microglial activation. This results in restoration of the behavioral (motor) deficits. Thus, Suresh et al. [5] obtained promising results indicative of an experimental PD therapy. In current clinical practice, one-target monotherapies of neurodegenerative disorders often do not achieve the desired significant improvements in patients. Hence, a combination of therapies and/or the use of multi-target pathogenetically relevant drugs that do not cause adverse side effects are emerging as a novel trend in the field [9]. The combination of toxic protein clearance and anti-neuroinflammatory effect produced by PD180970 seems to be effective in PD-like pathology and has an exciting translational prospect.

However, more basic and preclinical studies need to be provided to meet a number of significant issues prior to clinical trials. From a clinical research perspective, detailed study of PD180970 toxicity and possible side effects would be relevant. Moreover, the present findings should be confirmed in other PD models *in vivo* including those that mimic the advanced stages of PD, *e.g.*, chronic MPTP-induced neurotoxicity or genetic PD models. Pharmacokinetics, optimal dosage and treatment regimen, the effect dynamics and resistance could be addressed as well. Since almost all PD patients suffer from non-motor deficits including cognitive decline [10], it is essential to examine the effects of PD180970 on non-motor symptoms in appropriate animal models. Other challenges concern the mechanisms of the beneficial effects of PD180970. Although the study by Suresh et al. [5] revealed that the mechanism of anti-inflammatory effect was through the inhibition of TLR4-NF-κB and its downstream signaling pathway, the mechanism of autophagy activation is still not clear and requires further molecular research.

Declaration of Competing Interest

I declare no conflict of interests.

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