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Letter to Editor Open Access

mTOR Silencing in Parkinson's Disease both *in vitro* and *in vivo*

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Letter to Editor

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that regulates processes including mRNA translation, proliferation, and survival [1]. As a central element signaling cell growth and enhancing protein translation, (mTOR), when inhibited, induces autophagy. Moreover, as a critical feedback mechanism, reactivation of mTOR terminates autophagy and initiates lysosome reformation [2]. The phosphatidylinositiol 3-kinase (PI3K), AKT, mammalian target of rapamycin signaling pathway (PI3K/AKT/mTOR) is frequently dysregulated in disorders of cell growth and survival, including a number of malignancies [3]. It seems that autophagy dysregulation, is not involved only in cancer as growing evidences support its possible role in aging diseases [4] especially neurodegenration. Recently, many researches showed the important role of such pathway in Parkinson's disease pathogenesis. UCH-L1 is the first deubiquitinating enzyme discovered. Mutations of UCH-L1 have been identified that impact the pathogenesis of Parkinson's disease [5,6]. Hussain and colleagues found that UCH-L1 impairs mTORC1 activity toward S6 kinase and 4EBP1 while increasing mTORC2 activity toward Akt. These effects are directly attributable to a dramatic rearrangement in mTOR complex assembly. UCH-L1 disrupts a complex between the DDB1-CUL4 ubiquitin ligase complex and raptor and counteracts DDB1-CUL4-mediated raptor ubiquitination. These events lead to mTORC1 dissolution and a secondary increase in mTORC2. The net result of such cascade of events is dysregulated autophagy. This can be linked to the recent findings of UCH-L1 capacity to modulate alpha-Synuclein in PD-like models [7]. Moreover, paraquat and maneb (herbicides known to induce PD) were found to inhibit autophagy through increasing the level of mTOR [8]. We believe these data offer an evidence that mTOR can play critical role in the pathogenesis of PD. Since the mammalian target of rapamycin has emerged as an attractive therapeutic target. Many agents have been designed to target the mTOR pathway, such as temsirolimus and everolimus. These have been used recently as anti-cancer therapy for different purposes [9,10]. However, we believe these mTOR inhibitors may serve alternatively as successful anti-Parkinsonian drug through enhancing autophagy.

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