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 phosphatidylinositoil 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 inhibitors may serve alternatively as successful anti-Parkinsonian drug through enhancing autophagy.

References