Synopsis of Original Research Paper

The secretion mechanism of skin cell-protecting protein

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PARK7/DJ-1 is a multifunctional protein which is involved in gene transcription regulation and anti-oxidative defense. DJ-1 plays an important role in protection against UV irradiation and oxidative stress in the skin. Although DJ-1 lacks the secretory signal sequence, it is secreted and plays important physiological and pathophysiological roles. Whereas secretory proteins lacking the endoplasmic reticulum-targeting signal sequence are secreted from cells by the unconventional secretion mechanism, the specific processes responsible for DJ-1 secretion across the plasma membrane have remained unclear. In the present study, we found that DJ-1 secretion was increased by treatment with 6-hydroxydopamine (6-OHDA) via the unconventional secretory pathway in human neuroblastoma SH-SY5Y cells and mouse embryonic fibroblast (MEF) cells. We also found that 6-OHDA-induced DJ-1 secretion was suppressed in *Atg5-, Atg9-,* or *Atg16l1-* deficient MEF cells or ATG16L1 knockdown SH-SY5Y cells, indicating that the autophagy-based unconventional secretory pathway is involved in DJ-1 secretion. We moreover observed that 6-OHDA induced decrease in glutathione levels, which was suppressed by pretreatment with antioxidant N-acetyl-L-cysteine (NAC), and that NAC treatment suppressed autophagy and DJ-1 secretion. We also observed that 6-OHDA-induced autophagy was associated with activation of AMP-activated protein kinase (AMPK) and ULK1 (unc-51 like autophagy activating kinase 1) via a pathway which was independent of mechanistic target of rapamycin kinase (mTOR). Collectively these results suggest that 6-OHDA enhances oxidative stress followed by AMPK-ULK1 pathway activation and induction of secretory autophagy for the unconventional secretion of DJ-1.