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# The Effect of SIAH1 on PINK1 Homeostasis in Parkinson Disease

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**Abstract :** Background: PINK1 is a mitochondrial kinase mutated in some familial cases of Parkinson's disease. Down regulation of PINK1 results in abnormal mitochondrial morphology and altered membrane potential. Although PINK1 has a predicted mitochondrial import sequence, it's cellular, and submitochondrial localization remains unclear, in part because it is rapidly degraded. In this work, we investigated the mechanisms involved in PINK1 degradation and how this may affect PINK1 stability and function, with implications for mitochondrial function in PD. In addition, pharmacological inhibition of proteasome activity was shown to lead to PINK1 accumulation, indicating that PINK1 degradation depends on the ubiquitin-proteasome system (UPS). Methods: Using co-immunoprecipitation assays, we identified E3 ubiquitin ligase SIAH1 as a PINK1-interacting protein in HEK293 cells as well as on rat brain tissues. In addition, we determined the effect of SIAH 1, SIAH2 and Parkin on PINK1 steady-state levels by Western blot analysis, and checked their possibility to ubiquitinate and mediate PINK1 degradation through the proteasome carried out in vivo ubiquitination experiments. Results: We have obtained results showing that SIAH-1 interacts with and ubiquitinates PINK1. The ubiquitination promoted by SIAH-1 leads to the proteasomal degradation of PINK1. We confirmed these findings by knocking down SIAH-1 and observing important accumulation of PINK1 in cells. Besides, we found that SIAH-1 decreases PINK1 steady-state levels but not the E3 ligase Parkin. We also investigated the interaction of SIAH-1 with PINK1 disease mutants and its ability to promote their ubiquitination and degradation. Although, no clear difference in the ability of SIAH-1 to promote the degradation of PINK1 disease mutants was observed. It is possible that dysfunction of proteasomal activity in the disease may lead to the accumulation and aggregation of ubiquitinated PINK1 in patients with PINK1 mutations, with possible implications to the pathogenesis of PD. Conclusions: Here, we demonstrated that SIAH-1 ubiquitinates and promotes the degradation of PINK1. In addition, SIAH-1 represents now a target that may help the improvement of mitophagy in PD. Further investigations needed to understand how mitophagy is regulated by PINK1-SIAH-1 axis to provide targets for future therapeutics.

**Keywords :** PD, Parkinson's disease, PINK1, PTEN-induced kinase1, SIAH, seven in absentia homolog, SN, substantia nigra
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