神經退化性疾病之轉譯醫學研究

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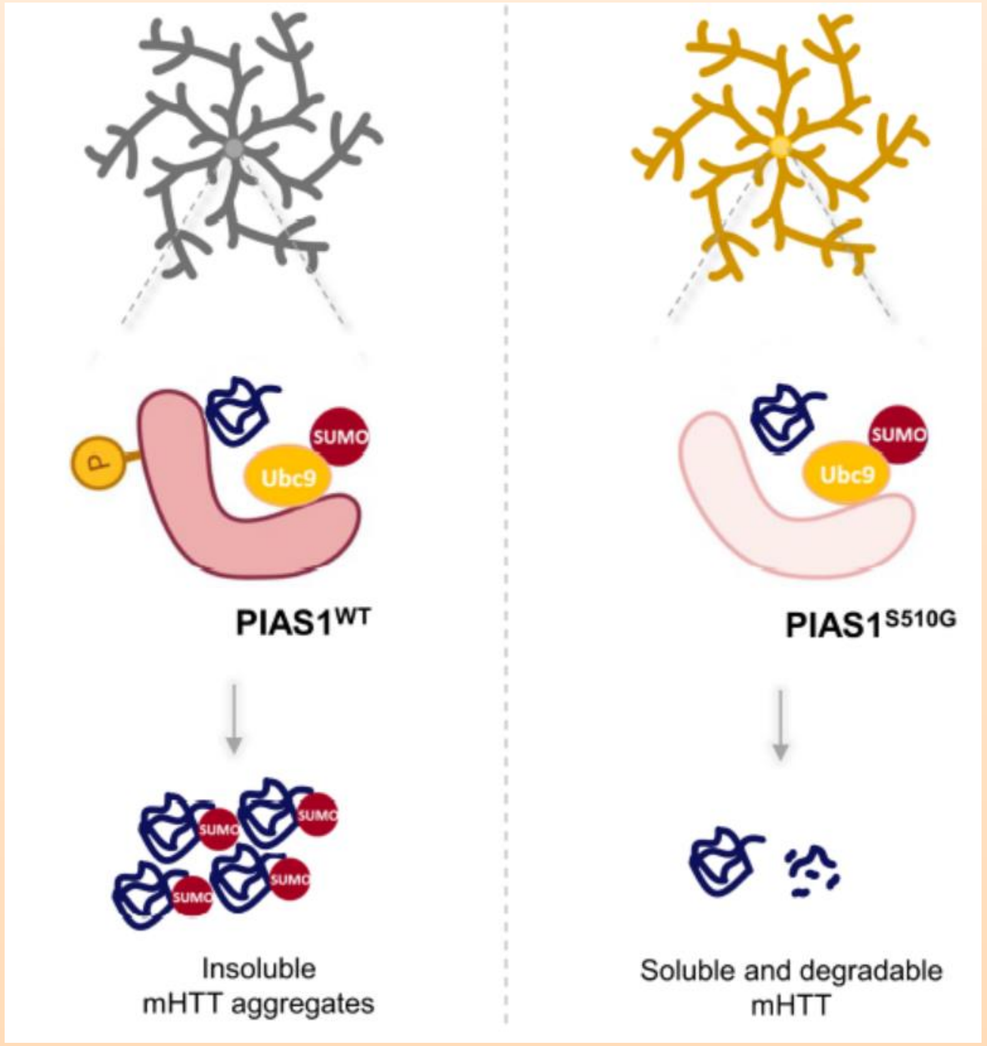
遺傳性腦神經退化性疾病-亨式舞蹈症

- Huntington's Disease (HD) is an inherited neurodegenerative disorder, caused by a monogenic mutation in the coding sequence of the huntingtin (HTT) gene.
- Genetic modifiers are genetic variants that can modify the phenotypic outcome of the primary disease-causing gene.



We identified PIAS1 as a genetic modifier associated with late onset of polyQ diseases. The naturally-occurring PIAS1S^{510G} variant interact with mutant huntingtin (mHTT) poorly, resulting in a lower SUMOylation and accumulation of mHTT. Knock-in of PIAS1S^{510G} ameliorates major symptoms of HD in mice, supporting its protective role.

A PIAS1 protective variant S510G delays polyQ disease onset by modifying protein homeostasis. (Movement Disorders, IF=10.3, in press)

遺傳性腦神經退化性疾病-小腦萎縮症第三型

- Spinocerebellar Ataxia Type 3 (SCA3) is caused by expression of mutant *ATXN3*, encoding a translated product with a long stretch of polyQ that is aggregation-prone and detrimental to neurons.
- Using cellular and biochemical assays, we confirmed that PIAS1 (SUMO E3) enables to enhance ATXN3 protein stability via the mode of sumoylation.

A *PIAS1* gene variant 3, associated with late onset of SCA3, exhibits a decreased interaction with its E2 (UBC9) in the presence of mutant ATXN3, which lead to less amount of SUMO conjugation, protein aggregation and cell death. Our findings provide an insight for the causal role of *PIAS1* gene variant 3 in late disease onset of patients with SCA3.