Transcriptional regulation of alpha-synuclein by the TRIM17-TRIM41-ZSCAN21 pathway

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Résumé

Although accumulating data indicate that increased α-synuclein expression is crucial for Parkinson's disease (PD), mechanisms regulating the transcription of its gene, SNCA, are largely unknown.
To address this question, we used complementary approaches based on SH-SY5Y cells, MPTP-treated mice and genetic data from patients with familial PD. Our results show that the transcription factor ZSCAN21 stimulates α-synuclein expression in SH-SY5Y cells and that TRIM41 is an E3 ubiquitin-ligase for ZSCAN21. In contrast, TRIM17, a partner of TRIM41 from the same family of E3 ubiquitin-ligases, decreases the TRIM41-mediated degradation of ZSCAN21. Silencing of ZSCAN21 and TRIM17 consistently reduces SNCA expression whereas TRIM41 knock-down increases it in SH-SY5Y cells. Moreover, the mRNA levels of TRIM17, ZSCAN21 and SNCA are simultaneously increased in midbrains of mice following MPTP treatment whereas an important down-regulation of TRIM41 precedes the peak of α-synuclein expression in these conditions. In addition, rare genetic variants in ZSCAN21, TRIM17 and TRIM41 genes occur in patients with familial forms of PD, some of them co-segregating with the disease. Expression of these variants in ZSCAN21 and TRIM41 genes results in a stabilization of the ZSCAN21 protein.
Our data thus suggest that a deregulation of the TRIM17/TRIM41/ZSCAN21 pathway may be involved in the pathogenesis of PD. In sporadic cases, TRIM17 which is known to be upregulated in stress conditions, would stabilize ZSCAN21 by inhibiting TRIM41 and would thus favour the expression of α-synuclein. This effect may be reproduced in some familial cases by mutations impairing the interactions between TRIM17, TRIM41 and ZSCAN21 and resulting in an increase in ZSCAN21.

Mots-Clés: alphasynuclein, Parkinson

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