Cisd2 ameliorates cognitive impairment and attenuates Aβ-mediated neuroinflammation in Alzheimer's mouse model

Cisd2 改善阿茲海默症小鼠 Aβ 誘導的認知缺失與神經性發炎

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder highly associated with aging and characterized by a gradual decline of cognitive and memory functions. Our previous studies revealed that elevated expression of Cisd2, a pro-longevity gene encoding a protein localized on the ER and mitochondrial outer membrane, can alleviate neurodegeneration and cognitive decline in AD mouse model. In this study, we aim to explore Cisd2 as a novel therapeutic target for AD and decipher the underlying mechanisms. We apply both transgenic study and pharmacological approach of using a promising Cisd2 activator, PZ-19b. Several significant findings are pinpointed. Firstly, Cisd2 displayed a reduction of over 65% in the hippocampus of 5xFAD mice compared with that in WT mice. Secondly, upregulation of Cisd2 by transgenic augmentation or treatment with PZ-19b significantly ameliorates cognitive decline and spatial memory impairment in 5xFAD mice. Finally, the transcriptomic profiles are dysregulated in the hippocampus of 5xFAD mice. Notably, the programmed cell death-related pathways are upregulated, and the neuron related pathways are dysregulated. Intriguingly, treatment of Cisd2 activator PZ-19b appears to reverse the dysregulated transcriptome toward a normal pattern in the hippocampus of 5xFAD mice. In summary, these findings reveal a protective role of Cisd2 in the pathogenesis of Aβ-mediated cognitive impairment and neuroinflammation in AD mice, and highlight the potential of Cisd2 as a promising therapeutic strategy for the development of AD medication.

Key Word: Cisd2, Alzheimer's disease, PZ-19b