Functional Roles of Nurr1 in AD Related Pathophysiology

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USA

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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD), the most common neurodegenerative disease, affects more than 35 million patients worldwide (>5 million in US). With an aging population, the number of people suffering from AD and the burden on our society will escalate; a recent report by the US Congress estimates that federal spending on AD

will increase to over $1 trillion (in today's dollars) per year by 2050 (A National Alzheimer's Strategic Plan: The report of the Alzheimer's study group, 2009; ://www.alz.org/documents/national/report_asg_alzplan.pdf). Since there is no therapy that can slow down or halt the disease process, it is of paramount significance to identify novel pathways and mediators that critically regulate the pathophysiology of AD. The orphan nuclear receptor Nurr1 play a critical role for development and maintenance of midbrain dopamine neurons as well as their protection from inflammation-induced cell death. However, its role in Alzheimer's disease (AD)-related pathogenesis is completely unknown. Although Nurr1 is considered to be a ligand-independent and constitutively active transcription factor, we recently identified small molecules (e.g., amodiaquine (AQ) and chloroquine (CQ)) that prominently modulate Nurr1's transcriptional function via direct interaction with its ligand-binding domain (LBD), suggesting that Nurr1's activity can be modulated by agonists/synthetic ligands. Furthermore, using our Nurr1-specific antibodies, we found that Nurr1 is prominently expressed in the hippocampal formation and frontal cortex and that the number of Nurr1-expressing cells significantly declines in the 5XFAD mouse, a valid animal model of AD, in an age-dependent manner, accompanied with increased plaque deposition. In addition, we found that Nurr1 expression is significantly reduced in the hippocampus of AD postmortem brain, compared with age-matched healthy control brain, suggesting that Nurr1 may have functional roles related to AD pathophysiology. Based on these findings, this proposal will address our hypothesis that Nurr1 plays critical roles in AD-related pathophysiology and that Nurr1 activation by its agonist(s) provides a novel therapeutic approach for AD. If goals of this project are successfully achieved, it will spark a new direction of AD research by demonstrating that Nurr1 is a key mediator and a valid target for therapeutic development.

Further information available at:

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