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Presentation Abstract

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Presentation Title: A role for adult neurogenesis in dentate synaptic plasticity deficits and memory impairment in Down syndrome

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Abstract: The hippocampal dentate gyrus (DG) is one of the two sites where neurogenesis continues throughout life in the mammalian brain. Accumulating evidence suggests a unique contribution of adult-generated dentate neurons in hippocampal synaptic plasticity and hippocampal-mediated learning and memory functions. However, the precise involvement of DG adult neurogenesis to disease-related cognitive deficits still remains unclear. Intellectual disabilities are the most striking clinical features of Down syndrome (DS) and are characterized by learning deficits and memory impairment, particularly in hippocampus-related functions. Correspondingly, the Ts65Dn mouse model of DS recapitulate many hippocampal cognitive deficits of the human syndrome, and also show decreased adult neurogenesis and impaired DG synaptic plasticity.
To elucidate the contribution of faulty adult neurogenesis to DG synaptic plasticity deficits and hippocampal-mediated memory impairment in DS we have treated adult Ts65Dn mice with lithium, a widely used mood stabilizer that also promotes adult neurogenesis. Results showed that chronic lithium administration effectively restored adult neurogenesis in the DG of Ts65Dn mice by increasing neural precursor cells (NPCs) proliferation. In vitro experiments on adult dentate NPCs cultures confirmed the reduced proliferation capacity of Ts65Dn cells and also demonstrate that the proliferative action of lithium depended on the stimulation of the Wnt/β-catenin pathway.
As a consequence of increased NPCs proliferation the number of newborn

neurons was fully rescued in the DG of Ts65Dn mice. These newborn neurons were also functionally integrated into the DG circuit because neurogenesis-dependent synaptic plasticity was also totally rescued. Most importantly, restoring adult neurogenesis had a great impact on cognitive impairment in Ts65Dn mice. In fact, we found that deficits of different form of long-term hippocampus-dependent memory, such as contextual learning, spatial memory and object discrimination where totally rescued after reinstatement of the newborn neurons population. Moreover, recovery of neurogenesis-dependent LTP and memory deficits were not rescued in Ts65Dn mice when neurogenesis was concomitantly inhibited.
Therefore, promoting adult neurogenesis may represent a new and promising therapeutic target to alleviate cognitive deficits in DS patients.

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