Disrupted interferon-related molecular networks and the over-expressed Ifnar1 in the brain of adult Ts1Cje mouse model of Down syndrome

ABSTRACT

Down syndrome (DS) is a chromosomal disorder resulting from trisomy of human chromosome 21 (HSA21) and all DS individual exhibit cognitive impairment. Ts1Cje mouse model of DS has a triplicated region of mouse chromosome 16 (MMU16) which is homologous to HSA21. Three interferon receptor genes (Ifnar1, Ifnar2 and Ifngr2) are located at the triplicated region in MMU16 and also in HSA21. In this study, we aimed to determine the disrupted molecular networks and the role of the candidate gene in the neurogenic-to-gliogenic shift of Ts1Cje mouse brain. A functional transcriptome analysis was performed on the cerebral cortex, cerebellum and hippocampus of Ts1Cje mice at 4 time-points: postnatal day (P)1, P15, P30 and P84. Functional clustering analysis of the identified 317 differentially expressed genes reported interferon-related signalling networks as the most significantly dysregulated pathway in Ts1Cje postnatal brain. Both Ifnar1 and Stat1 were found over-expressed in P84 Ts1Cje cerebral cortex and cerebellum when compared to wild type littermates through qRT-PCR and western blotting analysis. Subsequently, the role of triplicated Ifnar1 was determined by treating Ifnar1 antagonist on differentiating neural stem cells derived from the SVZ of adult Ts1Cje. The assessment on the antagonistic effect of Ifnar1 antagonist reported successful attenuation on the aberrant Stat1 expression in the Ts1Cje group to an expression level which was similar to the wild type group.

Keyword: Down syndrome; Chromosomal disorder; Ifnar1; Adult brain