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ARTICLE

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The lncRNA *Snhg11*, a new candidate contributing to neurogenesis, plasticity, and memory deficits in Down syndrome

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Down syndrome (DS) stands as the prevalent genetic cause of intellectual disability, yet comprehensive understanding of its cellular and molecular underpinnings remains limited. In this study, we explore the cellular landscape of the hippocampus in a DS mouse model, the Ts65Dn, through single-nuclei transcriptional profiling. Our findings demonstrate that trisomy manifests as a highly specific modification of the transcriptome within distinct cell types. Remarkably, we observed a significant shift in the transcriptomic profile of granule cells in the dentate gyrus (DG) associated with trisomy. We identified the downregulation of a specific small nucleolar RNA host gene, *Snhg11*, as the primary driver behind this observed shift in the trisomic DG. Notably, reduced levels of *Snhg11* in this region were also observed in a distinct DS mouse model, the Dp(16)1Yey, as well as in human postmortem brain tissue, indicating its relevance in Down syndrome. To elucidate the function of this long non-coding RNA (lncRNA), we knocked down *Snhg11* in the DG of wild-type mice. Intriguingly, this intervention alone was sufficient to impair synaptic plasticity and adult neurogenesis, resembling the cognitive phenotypes associated with trisomy in the hippocampus. Our study uncovers the functional role of *Snhg11* in the DG and underscores the significance of this lncRNA in intellectual disability. Furthermore, our findings highlight the importance of DG in the memory deficits observed in Down syndrome.

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INTRODUCTION

Down syndrome (DS) is caused by trisomy of Homo sapiens chromosome 21 (HSA21) and is the most common cause of genetic intellectual disability, affecting more than 5 million people globally. DS alters central nervous system development and function, impairing cognition, and adaptive behavior. Deficits in hippocampal-mediated learning and memory processes are hallmarks of DS [1, 2], and molecular and cellular defects have been detected in post-mortem fetal DS hippocampus [3, 4]. DS is a disorder of gene expression deregulation, as the triplication of HSA21 results in a broad disturbance of the transcriptome that is proposed to contribute to the phenotypic manifestations of DS [5]. This broad gene expression deregulation is likely caused by alterations intrinsic to the extra copy of HSA21, such as the overexpression of genes involved in epigenetic regulation. In fact, several studies have suggested chromatin dysfunction in DS [6–11]. However, other possible mechanisms associated with the regulation of chromatin function are still unexplored. Despite HSA21 being the smallest autosome, it is highly enriched in long-non-coding RNAs (lncRNAs) [12], which are transcripts with a length of more than 200 nucleotides that are not reported to be translated into functional proteins. Moreover, a high number of lncRNAs are abnormally expressed in DS [13–15]. Interestingly, a growing body of evidence from recent studies emphasize the role of lncRNAs in brain function, including learning and memory [16–18] and adult neurogenesis [19, 20], but little is known about their direct function.

The expression of lncRNAS is highly cell-type specific, thereby providing a layer of regulation for precise transcriptional control in each cell type. Therefore, their deregulation is expected to have a differential impact on the transcriptome of each cellular subtype. In fact, although bulk RNA-sequencing studies have provided evidence of broad disturbance of the transcriptome in the trisomic brain [5, 12, 21], the high cell heterogeneity of the brain tissue greatly hampers the capacity of these studies to elucidate the full complexity of gene expression deregulation in the trisomic brain and to identify specific genes responsible for specific clinical phenotypes.

Here, we used single nucleus RNA sequencing to dissect transcriptional dysregulation associated with specific cell types in the DS mouse model Ts65Dn. Of the DS mouse models generated to date only Ts65Dn, Tc1, Ts66Yah, and TcMAC21 are true aneuploid models with a freely segregating supernumerary chromosome, which may be important for some of the DS features not found in other DS mouse models with an intrachromosomal segmental duplication. We selected for our study the Ts65Dn, as it recapitulates many of the features found in DS. However, Ts65Dn mice also carry a triplication of 43 coding

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