

Towards the Identification of Genetic Targets for Therapeutics of Intellectual Disability in Down syndrome

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Abstract

Down syndrome, or Trisomy 21, is the most frequent genetic cause of the intellectual disability, a cognitive disorder with hard impact on public health. The expression of this feature is due to the overexpression of the human chromosome 21 genes. The genetic dissection of the Down syndrome neurological phenotypes in trisomic mouse models greatly enhanced our understanding of cellular and molecular mechanisms of gene dosage effects and the associated signalling pathways involved in the morphological and functional brain alterations, and in the pathogenesis of intellectual disability towards the identification of molecular targets for clinical therapeutics.

Introduction

Trisomy of human chromosome 21 (HSA21) is the most frequent genetic cause of mental retardation or intellectual disability and other variable phenotypic expression, including developmental defects, dysmorphic features, cognitive impairments and similar neurologic disorders seen in Alzheimer's disease, collectively known as Down Syndrome (DS) affecting 1 in 700 live births [1].

In the most cases, DS results from an extra copy of chromosome 21 in all cells of the afflicted individuals. In some rare cases, DS results from a partial trisomy 21 showing variable phenotypes depending of triplicated region. Clinical, cytogenetic and molecular analysis of such patients allowed the identification of the minimal region or Down Syndrome Chromosomal Region (DSCR), at 21q22.2 sub-band, responsible for many features of DS, including intellectual disability [2,3].

Therefore, intellectual disability is the most prominent and invariable feature of DS and the most invalidating neuropathological aspect, with hard impact on public health, caused by the overdosage of HSA21 genes. Consequently, the transcriptional map of the DSCR [4], the complete sequenc-

ing of human chromosome 21 [5], the analysis of the transcriptional activity of HSA21 [6], the gene expression map of human chromosome 21 genes orthologues in the mouse [7], and the transcriptome analysis in DS patients and trisomic mouse models [8,9] facilitated the identification of DS candidate genes involved in functional brain alterations and intellectual disability [10].

Remarkably, the development and characterization of DS mouse models, showing similar DS neurological phenotypes, has considerably contributed to the discovery of altered molecular pathways, and has highlighted the possible relevance of particular HSA21 genes for the DS cognitive phenotype [10]. Thus, these important advances have paved the way for searching possible drug targets.

The first altered genetic pathway involved in some DS phenotypes, including neurological and cognitive disorders, has been identified in which two critical HSA21 genes are involved MNB/DYRK1A (Minibrain/dual specificity tyrosine phosphorylation-regulated kinase 1A) and DSCR1 or RCAN1 (Regulator of the Calcineurin 1 protein). Both these critical genes, located in the Down Syndrome Critical Region (DSCR), act synergistically to control the phosphorylation levels of Nuclear Factor of Activated T cells (NFATc) and NFATc-regu-

lated gene expression [11]. It has been demonstrated that the overexpression of DYRK1A and RCAN1 dysregulates the NFATc pathway which play an essential role in the central nervous system and that the NFATc mice show neurological dysfunctions similar to those seen in DS patients and trisomic mouse models Ts65Dn [11].

DYRK1A has been the most extensively studied chromosome 21 gene due to the remarkable correlation of its functions in the brain with important DS neuropathologies, such as neuronal deficits, dendrite atrophy, spine dysgenesis, and cognitive deficits.

Treatment of DYRK1A transgenic mice with injection into striatum of inhibitory Dyrk1A shRNA restores motor coordination, attenuates hyperactivity and improve sensorimotor gating [12]. Moreover, treatment of DYRK1A transgenic mice with epigallocatechin-3-gallate, a major polyphenolic constituent of green tea, rescues brain defects and ameliorate cognitive impairments induced by the overexpression of DYRK1A gene [13]. These findings indicate DYRK1A as a therapeutic target in the mouse models of DS.

Interestingly, it has been demonstrated that administering the GABAA antagonists picrotoxin, bilobalide or Pentylenetetrazol (PTZ) restored cognition and long-term potentiation LTP in the Ts65Dn mouse model [14]. These studies were confirmed using the non-competitive GABAA antagonist pentylenetetrazole (PTZ) that rescued learning and memory performance of Ts65Dn mice in the Morris water maze [15]. These findings illustrate that GABAergic inhibition of specific brain circuits is a potential cause of intellectual disability in DS, and that GABAA antagonists may be useful therapeutic tools to facilitate functional changes that can ameliorate the cognitive impairment.

Furthermore, it has been demonstrated that acute injections of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine rescue the performance deficits in the Ts65Dn mouse model of DS on a conditioning fear test, and that one target of memantine is the NMDA receptor, whose function is predicted to be perturbed by the integrated effects of increased expression of critical HSA21 genes RCAN1 and DYRK1A localized in the critical region DSCR [16,17].

Remarkably, these treatments with NMDA receptor or GABAA antagonists allowed post-drug rescue of cognitive deficits in DS mouse models indicating a promising post-drug rescue of cognitive deficits in DS children and young adults.

Other pharmacological approaches have been developed to treat mouse models of DS in utero and demonstrated therapeutic effects that persisted to adulthood. In Ts65Dn trisomic mice, fluoxetine treatment restored the expression of serotonin 5-HT1A receptors and Brain-Derived Neurotrophic Factor (BDNF) and also the cognitive performance [18].

The early treatment of Ts65Dn trisomic mice with fluoxetine fully restored all the defects of the dendritic pathology (hypotrophic dendritic arbor, fewer spines and reduced innervations) in the dentate gyrus [19]. In adulthood, it has been demonstrated also that fluoxetine normalizes GABA release and rescues hippocampal synaptic plasticity and spatial memory in Ts65Dn trisomic mice [20].

An important progress in the genetic dissection of the DS phenotypes in trisomic mouse models greatly enhanced our understanding of cellular and molecular mechanisms of gene dosage effects and the associated signalling pathways involved in the brain alterations and intellectual disability towards the identification of molecular targets for clinical therapeutics.

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