Neurogenetic Disorders of Down Syndrome and Potential Pharmacotherapies for Mental Retardation

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Abstract

Background: Trisomy of human chromosome 21 is the most frequent genetic cause of mental retardation or intellectual disability and others phenotypes, including developmental defects, dysmorphic features and cognitive impairments collectively known as Down syndrome. Mainly a consequence of developmental and functional brain alterations, the mental retardation is the most invariable and invalidating neuropathological characteristic caused by the overdosage of genes triplicated in the chromosome 21. Methods and Results: The cytogenetic and molecular analysis facilitate the identification of the minimal region or Down Syndrome Chromosomal Region responsible for many phenotypes including mental retardation as the major constant phenotype caused by the overexpression of chromosome 21 genes. The complete sequence of human chromosome 21 and the transcriptome analysis in Down syndrome patients and in trisomic mouse models facilitate the genetic dissection of neurological and cognitive phenotypes. As a result of high degree of conservation of genomes and of molecular mechanisms between mouse and human, the mouse models of Down syndrome showed similar neuropathological features seen in Down syndrome persons and facilitate the identification of associated genetic targets. Conclusion: The genetic dissection of neurological phenotypes in trisomic mouse models highly developed our understanding of cellular and molecular mechanisms of gene overexpression caused by trisomy 21 and contributed significantly to the identification of specific genetic targets for pharmacological therapeutics. These pharmacological treatments in mouse models of Down syndrome allowed successfully post-drug rescue of neurological alterations and associated cognitive deficits and could be useful therapeutic tools of neurocognitive deficits and mental retardation seen in Down syndrome persons.

Keywords

Down Syndrome and Trisomy 21, Mental Retardation, Trisomic Mouse Models, Neurological Phenotypes, Learning and Memory, Molecular Targets, Genetic Pathways, Pharmacotherapies.

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1. Introduction

Trisomy of human chromosome 21 (HSA21) or Down syndrome (DS), affecting 1 in 700 newborns, produces a variety of developmental anomalies in different organs involving dysmorphic features, hypotonia, immunological, haematological and endocrinical defects, neurological and neurotransmitter alterations, and increased occurrence of Alzheimer’s disease [1-3]. DS is also a risk factor for a number of diseases, such as cardiac malformations, childhood onset leukemia and Hirschsprung disease [4-7]. Down syndrome is the most frequent genetic cause of mental retardation or intellectual disability that is mainly a consequence of functional and developmental brain alterations. DS individuals are characterized by several neurological defects in cortex lamination, in the shape and
volume of several cerebral and cerebellar regions, cognitive impairments and low Intelligence Quotient (IQ). The brain morphological alterations have been found at cellular level determined by alteration in neurogenesis, neuronal differentiation, myelination, dendritogenesis and synaptogenesis [8-12].

The genetic discovery of DS genetic and neurocognitive phenotypes in trisomic mouse models highly developed our understanding of cellular and molecular mechanisms of gene overexpression caused by trisomy of human chromosome 21 and contributed to the discovery of associated genetic pathways and molecular targets for potential pharmacotherapies.

2. Genetic and Neurocognitive Disorders

Generally, DS results from an extra copy of chromosome 21 in all cells of the afflicted individuals and in some rare cases DS results from a partial trisomy 21 showing variable phenotypes depending of the triplicated region. The cytogenetic and molecular analysis of such patients allowed the discovery of the minimal region or Down Syndrome Chromosomal Region (DSCR), at 21q22.2 sub-band, responsible for many traits of DS, including mental retardation as the major constant phenotype caused by the overdosage of genes triplicated in the chromosome 21 [13, 14]. The complete sequence of human chromosome 21 [15], the sequence of the human genome [16], and the transcriptome investigations in DS patients and in trisomic mouse models [17-20] facilitate the genetic dissection of DS neurological and cognitive phenotypes.

The Ts(17;16)65Dn, named Ts65Dn, produced by reciprocal translocation T(16C3-4; 17A2)65Dn, is the first segmental trisomic mice created and is the most commonly used and the best-characterized DS mouse models [21]. Ts65Dn mice are trisomic for the most of HSA21 orthologous genes conserved in the distal end of mouse chromosome 16 and exhibit many neurological features that are reminiscent of those seen in people with DS. The Ts65Dn mouse models showed neurotransmitter alterations [22], reduced hippocampal volume and dentate gyrus density [23], decreased Long-Term Potentiation (LTP) and increased Long-Term Depression (LTD) in the brain [24, 25], reduced cerebellum and granular cell layers [26], degeneration of Basal Forebrain Cholinergic Neurons (BFCN) [27, 28], decreased synaptic density in the cortex [29], decreased neuronal density and decreased synaptic density in the dentate gyrus [30], enlarged synapses in the cortex [31]. The abnormal cognitive behaviors, analogous to DS cognitive defects, have been demonstrated using different behavioral tests for spatial learning and memory such as T-maze, Y-maze, radial maze and Morris water maze. The Ts65Dn mouse models of DS showed motor dysfunction [32], reduced responsiveness to painful stimuli [33], decreased fear conditioning [34], decreased spatial learning and memory in the Morris water maze, the radial-arm maze, the water T-maze and the water radial-arm maze [35-39].

Furthermore, the mouse models of DS are powerful tools that greatly enhanced our understanding of the molecular and cellular mechanisms involved in DS pathogenesis because of the possibility to genetically manipulate their genome, the tissue accessibility and the high degree of conservation of genomes and molecular mechanisms between mouse and human. Interestingly, these mouse models demonstrate similar DS neurological and cognitive phenotypes and have significantly contributed to the discovery of altered genetic pathways associated to DS neurological and cognitive features [40]. Remarkably, an altered genetic pathway implicated in some neurological and cognitive DS phenotypes has been identified in which two critical HSA21 genes are involved and located in the Down syndrome critical region (DSCR). MNB / DYRK1A (Minibrain / Dual specificity tyrosine phosphorylation-Regulated Kinase 1A) and DSCR1 or RCAN1 (Regulator of the Calcineurin 1 protein) operate synergistically to control the phosphorylation levels of Nuclear Factor of Activated T cells (NFATc) and NFATc-regulated gene expression [41]. It has been demonstrated that the overexpression of DYRK1A and RCAN1 genes 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 also in the Ts65Dn mice, the famous and the most extensively studied trisomic mouse models of DS [41].

3. Genetic Targets and Pharmacotherapies

The mouse models overexpressing DYRK1A gene show a significant impairment in spatial learning and memory in the behavioral tests, indicating hippocampal and prefrontal cortex function alterations, particularly concerning a cognitive dysfunction of the reference memory. Moreover, these transgenic mice show abnormal long-term potentiation (LTP) and abnormal long-term depression (LTD), suggesting also a synaptic plasticity alteration [42-44]. These functional brain alterations are comparable with those found in trisomic mouse models of DS and suggest a causative role of DYRK1A in mental retardation in DS persons.

Interestingly, the treatment of DYRK1A transgenic mice with injection into striatum of inhibitory Dyrk1A shRNA restores the motor coordination, attenuates the hyperactivity and improves the sensorimotor gating [45]. In addition, the treatment of DYRK1A transgenic mice with epigallocatechin-
Some pharmacotherapies for cognitive impairments in trisomic mouse models of Down syndrome have been developed. It has been demonstrated that administering the GABA<sub>A</sub> antagonist picrotoxin, bilobalide or Pentylenetetrazol (PTZ) restored cognition and long-term potentiation LTP in the Ts65Dn mouse models of DS [47]. These studies were confirmed using the non-competitive GABA<sub>A</sub> antagonist Pentylenetetrazole (PTZ) that rescued learning and memory performances of Ts65Dn trisomic mice in the Morris water maze tests [48]. These findings illustrate that GABAergic inhibition of specific brain circuits is a potential cause of intellectual disability in DS, and that GABA<sub>A</sub> antagonists may be useful therapeutic tools to facilitate the functional changes that can improve the cognitive deficits (TABLE 1).

In other similar experiments, it has also been established that acute injections of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine rescue the performance deficits in the Ts65Dn mouse models of DS on a conditioning fear test, and that one target of memantine is the NMDA receptor, whose function is predicted to be disturbed by the integrated effects of increased expression of critical HSA21 genes RCAN1 and DYRK1A [49, 50]. Remarkably, these advances contributed significantly to the identification of specific genetic targets for pharmacological therapeutics of neurocognitive impairments in Down syndrome, particularly the mental retardation associated with DS [53].

These early treatments in mouse models of DS are of the most interest because they allowed successfully and completely post-drug rescue of neurological alterations and associated cognitive deficits and could be useful therapeutic tools of neurocognitive deficits and mental retardation seen in DS persons.

4. Conclusion

In parallel to development of genome whole technologies and the promising experimental results obtained in mouse models of DS, considerable progresses have been made in the last years in the cellular biology and molecular genetics of DS. The genetic investigations of DS neurological phenotypes in trisomic mouse models highly developed our understanding of cellular and molecular mechanisms of gene overexpression caused by trisomy 21 and the related molecular pathways involved in the functional neurogenetic and associated cognitive disorders seen in DS persons. Remarkably, these advances contributed significantly to the identification of specific genetic targets for pharmacological therapeutics of neurocognitive impairments in Down syndrome, particularly the mental retardation.

References


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**Table 1. Treatments and pharmacotherapeutic effects in mouse models of Down syndrome.**

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<tr>
<th>Treatments</th>
<th>Pharmacotherapeutic Effects</th>
<th>References</th>
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<tbody>
<tr>
<td>Picrotoxin PTZ</td>
<td>Learning improved in the novel object recognition, in the T-maze, Rescue Long Term Potentiation (LTP).</td>
<td>Fernandez et al., 2007</td>
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<tr>
<td>PTZ Pentylenetetrazol</td>
<td>Learning improved in the Morris water maze. Learning improved in the conditioning fear test, Rescue Morris water maze, water radial arm maze.</td>
<td>Rueda et al., 2008; Costa et al., 2008; Rueda et al., 2010; Ortiz-Abalia et al., 2008</td>
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<tr>
<td>Memantine</td>
<td>Learning improved in the conditioning fear test, Rescue Morris water maze, water radial arm maze. and improve the sensori-motor gating.</td>
<td></td>
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<tr>
<td>Dyrrk1A-sh RNA</td>
<td>Rescue of motor coordination, Hyperactivity, and improve the sensori-motor gating.</td>
<td>Guedj et al., 2009; Bianchi et al., 2010; Guidi et al., 2014; Begensic et al. 2014</td>
</tr>
<tr>
<td>Epigallocatechin-3-gallate</td>
<td>Rescue brain defects and improve cognitive deficits. Rescue: Neurogenesis, Brain development, LTP, Brain-Derived Neurotropic Factor, Serotonin 5-HT1A, Dendritic pathology, Synaptic plasticity, Cognitive deficits, Spatial memory.</td>
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<td>Fluoxetine</td>
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