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DYRK1A (Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A), a Master Regulatory Protein Involved in Down Syndrome Clinical Neurological Abnormalities and Associated Mental Retardation and a Promising Potential Drug Target for Therapeutics and Treatments

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Mini Review

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Abstract

Over-expression of chromosome 21 genes, particularly in Down Syndrome Critical Region (DSCR), is the main cause of Down syndrome (DS) neuropathological features including mental retardation, cognitive impairments and early onset of Alzheimer's disease. One of DSCR genes, that we studied herein, DYRK1A (Dual-Specificity Tyrosine-Phosphorylation-Regulated Kinase 1A), is a master regulatory protein involved in DS neuropathological features and associated mental retardation. Interestingly, normalization of DYRK1A over-expression by DYRK1A inhibitor, epigalloctechin-3-gallate (EGCG), rescues brain defects, restores cognitive impairments in DS trisomic and DYRK1A transgenic mouse models and in DS patients. These results indicates DYRK1A inhibitor epigalloctechin-3-gallate (EGCG) as an effective treatment and DYRK1A as a key regulatory protein involved in DS clinical neuropathological features suggesting DYRK1A as a valuable potential drug target for therapeutics and Treatments of DS and mental retardation opening new directions for developing new medical preventive and therapeutic treatments.

Keywords: Down syndrome, DYRK1A (Dual-Specificity Tyrosine-Phosphorylation-Regulated Kinase 1A), Trisomic Mouse models, Transgenic Mouse models, DYRK1A inhibitor, Epigalloctechin-3-gallate (EGCG), DYRK1A Therapeutic Target

Abbreviations: DSCR: Down Syndrome Critical Region; DS: Down Syndrome; EGCG: Epigalloctechin-3-Gallate; MNB: Mini-Brain; DYRK1A: Dual-Specificity Tyrosine-Phosphorylation-Regulated Kinase 1A; CREB Cyclic Response Element-Binding; NFAT: Nuclear Factor of Activated T.

Introduction

Down syndrome or Trisomy of human chromosome 21 (with an incidence of 1/700 live births) is the most common genetic disease characterized by neuropathological

abnormalities including learning and memory deficits, cognitive impairments, mental retardation and the early onset of Alzheimer's disease. These developmental and functional brain alterations in neurogenesis, dendritogenesis and synaptogenesis remain the invariable hallmarks of Down syndrome and its more invalidating pathological aspects with a hard impact in the public health [1-3].

Cytogenetic, molecular and clinical studies identified a critical triplicated region of human chromosome 21 termed Down Syndrome Chromosomal Region or Down Syndrome Critical Region (DSCR) on the distal part of the long arm, around the D21S55 marker and flanked by D21S17 and ERG. The extra copy of DSCR is also associated with the expression of similar developmental features of Down syndrome including similar clinical neurolpathological features. Consequently, the major phenotypes in Down syndrome patients and in mouse models, particularly the neurological disorders and mental disability, have their origin in the over-dosage of critical genes localized in Down syndrome Critical Region (DSCR) [4-7].

Remarkably, the transcriptome and gene expression profiling studies permitted to understand the molecular basis of brain alterations and mental disability pathogenesis in Down syndrome [8,9]. First, these investigations allowed the identification of genes specifically expressed in the brain and, second, they allowed the identification of genes restricted to key brain regions involved in the cognitive functions that we have selected and studied as critical candidate genes for neuronal abnormalities and mental retardation [10-20].

Interestingly, the trisomic and the transgenic mouse models represent powerful tools to study the dynamic of clinical and developmental phenotypes and the molecular genetics and cellular basis of functional brain alterations seen in Down syndrome. The trisomic mouse models carrying segmental trisomy for mouse chromosome 16 (Ts65Dn and Ts1Cje), contains the orthologous conserved chromosomal regions of the most part of human chromosome 21q, including also the Down Syndrome Critical Region (DSCR), and mimic the same evolutionarily conserved interactions between different homologous genes present at 3 copies. These mouse models have similar clinical phenotypes seen in Down syndrome and facilitate our previous and recent investigations for identification, characterization and comparative analyses of similar critical candidate genes and their similar associated molecular pathways involved in similar clinical neurological alterations including brain aberrations, cognitive impairments, learning and memory deficits seen in Down syndrome patients [21,22]. The transgenic mouse models of Down syndrome are also of the most interest because they have been generated to study the effect of cell-specific and stage-specific overexpression of a unique critical gene and the associated molecular genetic pathway [22-24].

Between the critical genes, localized in the critical region DSCR, we have determined specific and restricted gene expressions in the key brain regions involved in cognitive and learning-memory functions similarly in Down syndrome patients and in related Down syndrome mouse models, and we have identified and studied DYRK1A, or mini-brain (MNB), a master regulatory protein involved in developmental and functional brain alterations, cognitive impairments, learning-memory deficits, mental retardation in Down syndrome, and valuable potential drug target for therapeutics and Treatments of DS [22,23].

We studied DYRK1A (Dual-Specificity Tyrosine-Phosphorylation-Regulated Kinase 1A), that maps to 21q22.2 in Down Syndrome Critical Region (DSCR) and encodes a proline-directed Serine/Threonine kinase [25-26] involved in functional and developmental brain alterations, in neurogenesis, in neuronal differentiation, in neuronal proliferation, in neuritogenesis, in dendritogenesis, in synaptogenesis, in cognitive impairments, in learning and memory deficits and mental retardation seen in Down syndrome patients [22,23].

Remarkably, DYRK1A is one powerful member of phosphorylation pathways that regulate the cell cycle and belongs to a family of Dual-Specificity Protein Kinases (DYRK kinases) with Serine/Threonine phosphorylation activity that contribute in several critical signaling pathways controlling various cellular processes, cell survival, cell proliferation, cell differentiation and have a key role in central nervous system [27-38].

Interestingly, DYRK1A is expressed in the key neuronal regions altered in Down syndrome brain patients [23,35] and is implicated in the neuronal differentiation of hippocampal progenitor cells through the phosphorylation of cyclic AMP response element-binding protein (CREB) [29,31]. In addition, the altered phosphorylation of transcription factor CREB supports an important role of DYRK1A overexpression in the neuronal abnormalities seen in DS and indicates that this human pathology is associated to altered levels of proteins involved in the regulation of cell cycle [36]. Altogether, these results suggest a central role of DYRK1A in the pathways of cell cycle control and the DYRK1A overexpression contribute to neurogenesis alteration in the brain of Down syndrome patients [26].

More interestingly, the DYRK1A overexpression associated with the overexpression of DSCR1, dysregulates the nuclear factor of activated T cells (NFAT) pathway that play a fundamental critical role in the central nervous

system and demonstrates a significant functional interaction between two critical genes in Down Syndrome Critical Region (DSCR) explaining a key functional mechanism involved in DS phenotypes [30]. This molecular mechanism demonstrated by a cooperative and functional interaction between the critical genes DYRK1A and DSCR1 provides an important central view of a molecular mechanism in accordance with our previous proposed molecular and cellular mechanisms [8,22,26] elucidating a functional association between dysregulation in critical chromosome 21 genes and related molecular pathways, brain alterations and associated mental disability, and suggesting also a critical central role of DYRK1A dosage-sensitive gene in the central nervous system and in neurocognitive and functional impairments associated with brain alteations and the pathogenesis of mental disability in Down syndrome [8,22,26]. Overall, in accordance with our and all these significant results, we suggest, in addition to its key role as a member of DYRK kinases, that DYRK1A is commonly involved in various cellular events and contribute significantly in several critical signaling pathways that control important neuronal processes, proliferation and differentiation, cell cycle and neurogenesis in Down syndrome.

The transgenic mouse models overexpressing DYRK1A showed neurodevelopmental delay, motor abnormalities and cognitive deficits with significant impairments in spatial learning and memory, indicating hippocampal and prefrontal cortex function alterations, comparable with those found in trisomic mouse models of Down syndrome, and suggesting a causative role of DYRK1A in neurological and functional brain alterations and mental disability seen in Down syndrome patients [39-41].

Remarkably, the original genetic reductions of DYRK1A copy number in trisomic mouse models of DS revealed important corrections of Down syndrome phenotypes and showed important improvements in cognitive and behavioural phenotypes [42,43].

Elegantly, the innovative treatment of DYRK1A transgenic mouse models of Down syndrome with injection into striatum of inhibitory Dyrk1A shRNA restores the motor coordination, attenuates the hyperactivity and improves the sensorimotor gating, and the normalization of DYRK1A expression by AAV2/1-ShDyrk1A attenuates the hippocampal-dependent defects in Ts65Dn trisomic mouse models of Down syndrome, indicates DYRK1A as a potential therapeutic target [44,45].

Very interestingly, and in addition to these two exceptional advanced genetic and molecular treatments, the treatment of DYRK1A transgenic mouse models of Down syndrome with an inhibitory DYRK1A, the epigalloctechin-3-gallate (EGCG), rescues the brain defects and restores the cognitive impairments induced by the overexpression of DYRK1A and indicates DYRK1A as a therapeutic target in DYRK1A transgenic mouse models and in trisomic mouse models of Down syndrome and in human [46-48].

Conclusion

In conclusion, our results combined to all other studies demonstrate and suggest mutually DYRK1A as a promising potential drug target for therapeutics for multiple clinical Down syndrome neuropathologies opening new directions for developing new medical preventive and therapeutic treatments of Down syndrome and mental retardation.

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