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RESEARCH ARTICLE

Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase-1A (DYRK1A), A Master Regulatory Protein Involved in Down Syndrome Brain Alterations and Mental Disability, A Key Contributor to Neurodegenerative Disorders of Alzheimer's Disease and A Potential Therapeutic Target

Mohammed Rachidi*

Molecular Genetics of Human Diseases, French Polynesia and University Paris Denis Diderot, France

***Corresponding author:** *Dr. Mohammed Rachidi, Molecular Genetics of Human Diseases, French Polynesia and University Paris Denis Diderot, Paris, France*

Abstract

Down syndrome (DS) is the most frequent genetic disease characterized by several neuropathological features including alteration in neurogenesis, mental disability, cognitive impairments, learning-memory deficits and early onset of Alzheimer's disease (AD). Over expression of chromosome 21 genes, localized in Down Syndrome Critical Region (DSCR), is the main cause of DS neuropathological features. We studied herein one of DSCR genes, DYRK1A (Dual-Specificity Tyrosine-Phosphorylation-Regulated Kinase 1A), well-known Drosophila Mini-Brain gene, as a master regulator involved in DS neuropathological features and associated AD. DYRK1A is a central member of phosphorylation pathways regulating cell cycle and belongs to a family of Dual-Specificity Protein Kinases (DYRK kinases) playing key roles in central nervous system. DYRK1A regulates several transcriptional factors, such as CREB (cyclic-AMP response element-binding protein), NFAT (nuclear factor of activated T cells) and signaling pathways playing critical roles in brain functions. Significant associations were found between DYRK1A and regulation of cytoskeletal dynamics of actin, tubulin or microtubule-linked protein Tau, regulation of Tau phosphorylation, Amyloid Precursor Protein (APP) or Presenilin 1 (PS1), regulation of neurogenesis, synaptogenesis, and AD-like neurofibrillary tangles formation. Interestingly, normalization of DYRK1A overexpression by DYRK1A inhibitor, epigalloctechin-3-gallate (EGCG), rescues brain defects, restores cognitive impairments in DS trisomic and DYRK1A transgenic mouse models and DS patients,modulates Amyloid Precursor Protein (APP) cleavage and reduces cerebral amyloidosis in AD transgenic mouse models. DYRK1A inhibitors such as Harmine, LeucettineL41, SM07883 successfully reduces Tau phosphorylation at multiple AD-related sites, rescues AD phenotypes in APP/PS1 mice and correct cognitive and memory deficits in AD animal models. These results indicates DYRK1A inhibitors as effective treatments and identifies DYRK1A as a master regulatory protein involved in DS and AD neuropathological features suggestingDYRK1A as promising potential drug target for therapeutics and treatments of DS and AD.

Keywords

Down syndrome, Alzheimer's disease, Mouse genetic models, Brain abnormalities, Cognitive deficits, Mental disability, DYRK1A inhibitors, DYRK1A therapeutic target

Introduction

Trisomy of human chromosome 21 or Down syndrome is the most common genetic disease, with an incidence of 1/700 live births, characterized by various developmental defects including congenital heart disease, cranio-facial abnormalities, learning and memory deficits, cognitive impairments, mental retardation and the early onset of Alzheimer's disease. The neurological features and particularly the mental disability remains the invariable hallmark of Down syndrome and its more invalidating pathological

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aspect with a hard impact in the public health. This neurocognitive and genetic disorder is mainly a consequence of functional and developmental brain alterations, in neurogenesis, neuronal differentiation, myelination, dendritogenesis and synaptogenesis [1-3].

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

Gene expression profiling provides two kinds of research to understand the molecular basis of brain alterations and mental disability pathogenesis in Down syndrome [8,9]. On one hand, these investigations allowed the identification of genes specifically expressed in the brain and, on the other hand, the genes restricted to the key brain regions involved in the cognitive functions that we have selected and studied as critical candidate genes for neuronal abnormalities and mental disability [10-14]. The majority of trisomic or triplicated genes showed transcript levels increase of about 1.5 fold in human trisomic tissues [15,16] and in trisomic mouse models [17-19]. Particularly, in trisomic tissues, although most of the trisomic genes show transcriptional variations on average 1.5 fold the normal level, only a subset of candidate genes show a significant difference of expression level between trisomic and diploid individuals [19,20].

Two types of murine models of Down syndrome have been developed for investigating the molecular genetics of Down syndrome, the trisomic and the transgenic mouse models that represent powerful tools to study the kinetics of developmental phenotypes and the molecular 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 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 over expression of a unique critical gene and associated molecular pathway [22,23]. Among the critical genes, localized in the critical region DSCR, that we have determined specific and restricted 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, we have identified and studied herein DYRK1A as a master regulatory protein involved in developmental and functional brain alterations, cognitive impairments, learning-memory deficits, mental disability, as a key contributor to neurodegenerative disorders of Alzheimer's disease and as a promising potential drug target for multiple Down syndrome and Alzheimer's disease neuropathology opening news directions for developing new preventive and therapeutic treatments of Down syndrome and Alzheimer's disease [22,23].

Results and Discussion

Dual-Specificity Tyrosine-Phosphorylation-Regulated Kinase 1A (DYRK1A), well-known as Drosophila Mini-Brain gene (MNB), maps to 21q22.2 in Down Syndrome Critical Region (DSCR) and encodes a proline-directed Serine/Threonine kinase [24-26] 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 disability seen in Down syndrome [22,23].

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 [27,28]. DYRK1A phosphorylates numerous important transcriptional factors, such as endocytic proteins, cyclic AMP response element-binding protein (CREB), fork head in rhabdomyosarcoma (FKHR), or nuclear factor of activated T cells (NFATc) [29-34]. DYRK1A over expression was associated with an increase in the phosphorylation of fork head transcription factor FKHR and with high levels of cyclin B1, suggesting a significant association between DYRK1A over expression and cell cycle protein alteration [32].

Interestingly, DYRK1A is expressed in the key neuronal regions altered in Down syndrome brain patients [24,35] 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 over expression in the neuronal abnormalities seen in DS and indicates that this 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 over expression contribute to neurogenesis alteration in the brain of Down syndrome patients [23].

In addition, DYRK1A phosphorylates also several endocytic proteins, such as dynamin 1 and amphiphysin 1 and consequently regulates the assembly of endocytic complexes, endophilin 1 and Grb2, suggesting that DYRK1A is strongly associated with the endocytic pathway [33,34]. Furthermore, the expression of DYRK1A associates cell cycle exit and differentiation of neuronal precursors by inducing p27KIP1 expression and suppressing NOTCH signaling [37]. The up regulation of DYRK1A contribute also to altered neuronal proliferation in the brain of Down syndrome patients through the specific phosphorylation of p53 and inhibition of proliferation of embryonic neuronal cells [38].

The DYRK1A over expression combined with the over expression of DSCR1,dysregulates the nuclear factor of activated T cells NFAT pathway that play a critical role in the central nervous system anddemonstrates a functional interaction between two critical genes in Down Syndrome Critical Region (DSCR) explaining a molecular 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 view of a molecular mechanism in accordance with our previous proposed molecular and cellular mechanisms [8,22,23] elucidating a functional association between dysregulation in critical chromosome 21 genes and related molecular pathways, brain alterations and related mental disability, and suggesting also a critical 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 [8,22,23]. Overall, and in addition to its key role as a member of DYRK kinases, all these results suggest that DYRK1A is widely 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 over expressing DYRK1A showed neurodevelopment 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]. The 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].

Interestingly, the 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 trisomicmouse models of Down syndrome, indicates DYRK1Aas a potential therapeutic target [44,45]. In addition, 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 over expression 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].

Remarkably, one of the major neuro-pathological features of Down syndrome is a sign of early onset of Alzheimer's disease-like symptoms, characterized by the formation of amyloid senile plaques (insoluble deposits of β-Amyloid) and of neurofibrillary tangles (hyperphosphorylated Tau aggregates) [49,50]. Interestingly, DYRK1A phosphorylates key substrates implicated in Alzheimer's disease such as Tau, Amyloid Precursor Protein (APP) andPresenilin 1 (PS1) and indicates an important role of DYRK1A in the onset of Alzheimer's disease [51-53].

DYRK1A phosphorylates several serine and threonine residues of Tau and the Tau hyperphosphorylation mediated by DYRK1A results both in the brain of Ts65Dn trisomic mouse models of Down syndrome as well as in the brain of Down syndrome patients. More interestingly, DYRK1A immunoreactivity in Tau positive neurofibrillary tangles in Down syndrome brains supports a significant association between DYRK1A and Tau and the contribution of DYRK1A over expression to neurofibrillary degeneration indicates a key role of over expressed DYRK1A protein in the early onset of neurofibrillary degeneration seen in the brain of Down syndrome patients [54,55]. The over expression of DYRK1A increases Tau expression and cognitive deficits in Ts65Dn trisomic mouse models of Down syndrome [56] and the hyperphosphorylation of Tau mediated by DYRK1A showed a functional association between Down syndrome and Alzheimer's disease [51].

Moreover, DYRK1A is significantly associated with the regulation of cytoskeletal protein such as actin, tubulin and microtubule-linked protein Tau through DYRK1A phosphorylation of many substrates that consequently contributes to the regulation of neuritogenesis, synaptogenesis, and Alzheimer's disease-like neurofibrillary tangles formation [57-60]. Remarkably, DYRK1A plays a role in β-amyloid production and senile plaques formation and phosphorylate the intracellular domain of Amyloid Precursor Protein (APP), for which the encoded gene APP is also mapped to human chromosome 21. Furthermore, the DYRK1A gene encoded in the chromosome 21 Down Syndrome Critical Region bridges between β-Amyloid production and Tau phosphorylation in Alzheimer's disease [61]. In addition, the phosphorylation of Amyloid Precursor Protein (APP) mediated by DYRK1A evidenced also a functional association between Down syndrome and Alzheimer's disease [52].

The normalization of DYRK1A dosage, by DYRK1A inhibitors, in mouse models of Down syndrome rescues also several Alzheimer's disease phenotypes indicating DYRK1A as a potent therapeutic target. In addition, DYRK1A inhibition improves Alzheimer's disease-like pathology and the effect of DYRK1A inhibitors on Tau and amyloid pathologies confirmed well the DYRK1A inhibition as a potential and an effective treatment for Alzheimer's disease [62-65].

Interestingly, the treatment with an inhibitory DYRK1A, the epigallocatechin-3-gallate (EGCG), modulates also the amyloid precursor protein (APP) cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice [66]. The treatment by the inhibitor of DYRK1A, the Harmine, specifically and successfully inhibits the protein kinase DYRK1A activity and reduced Tau phosphorylation in neuroglioma cell line at multiple Alzheimer's disease-related sites [67]. The treatment by another inhibitor of DYRK1A, the Leucettine L41, effectively inhibits DYRK1A activity, rescues Alzheimer's disease phenotypes in APP/PS1 mice and corrects the cognition deficits and memory impairments in Alzheimer's disease animal models [68,69]. In addition, the treatment by an oral DYRK1A inhibitor, the SM07883, significantly inhibits Tau hyperphosphorylation, aggregation, neurofibrillary tangles formation, and associated Alzheimer's disease phenotypes in mouse models suggesting also this novel DYRK1A inhibitor as a potential treatment for Alzheimer's disease [70].

Conclusion

DYRK1A (Dual-specificity tyrosine phosphorylation-Regulated Kinase 1A) is one influential and key member of the phosphorylation pathways that regulate the cell cycle and belongs to a family of dual-specificity protein kinases (DYRK kinases) that play a critical role in central nervous system and in several crucial signaling pathways that control various cellular processes. In addition, DYRK1A regulates and phosphorylates also several important transcriptional factors, such as fork head (FKHR), cyclic AMP response element binding protein (CREB), endocytic proteins and nuclear factor of activated T cells (NFAT) and associated pathways that play critical roles in the central nervous system indicating a central role of DYRK1A in the brain development and function of trisomic and transgenic mouse models of Down syndrome and in the brain of Down syndrome patients.

The significant associations between DYRK1A and regulation of cytoskeletal dynamics of actin, tubulin or microtubule linked protein Tau, regulation of phosphorylation of Tau, Amyloid Precursor Protein (APP) or Presenilin 1 (PS1), regulation of neurogenesis, neuritogenesis, synaptogenesis, and Alzheimer's disease-like neurofibrillary tangles formation is of the most interest indicating DYRK1A as a potent candidate and a master regulatory protein involved in Down syndrome brain alterations, cognitive impairments, learning-memory deficits, mental disability, and a key contributor to neurodegenerative disorders of Alzheimer's disease.

Interestingly, the normalization of the gene dosage of DYRK1A in mouse models of Down syndrome rescues also several Alzheimer's disease phenotypes indicating DYRK1A as potent therapeutic target and the effect of DYRK1A inhibitors on Tau and amyloid pathologies confirmed well the DYRK1A inhibition as a potential and an effective treatment for Down syndrome and Alzheimer's disease.

The DYRK1A inhibitors such as the epigalloctechin-3-gallate (EGCG)specifically inhibits the protein kinase DYRK1A activity, rescues the brain defects and restores the cognitive impairments in DYRK1A transgenic mouse models and in trisomic mouse models of Down syndrome and in Down syndrome patients. Moreover, the epigallocatechin-3-gallate (EGCG) modulates also the Amyloid Precursor Protein (APP) cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice.The DYRK1A inhibitors such as the Harmine, LeucettineL41 and SM07883 successfully reduces Tau phosphorylation at multiple Alzheimer's disease-related sites and rescues Alzheimer phenotypes in APP/PS1 mice and correct the cognition deficits and memory impairments in Alzheimer's disease animal models indicating these DYRK1A inhibitors as active inhibitors and potential therapeutics for Down syndrome and Alzheimer's disease.

Overall, these results indicate DYRK1A as a promising potential drug target for multiple Down syndrome and Alzheimer's disease neuropathology opening news directions for developing new preventive and therapeutic treatments of Down syndrome and Alzheimer's disease.

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