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Function and regulation of Dyrk1A: towards understanding Down syndrome

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Abstract Down syndrome (DS) is associated with a variety of symptoms, such as incapacitating mental retardation and neurodegeneration (i.e., Alzheimer's disease), that prevent patients from leading fully independent lives. These phenotypes are a direct consequence of the overexpression of chromosome 21 genes, which are present in duplicate due to non-disjunction of chromosome 21. Accumulating data suggest that the chromosome 21 gene product, dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (Dyrk1A), participates in the pathogenic mechanisms underlying the mental and other physical symptoms of DS. In this review, we summarize the evidence supporting a role for Dyrk1A in DS, especially DS pathogenesis. Recently, several natural and synthetic compounds have been identified as Dyrk1A inhibitors. Understanding the function and regulation of Dyrk1A may lead to the development of novel therapeutic agents aimed at treating DS.

Keywords Down syndrome · Dyrk1A · Kinase · Phosphorylation · Inhibitor

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Introduction

Down syndrome (DS) is one of the most common genetic defects, with an incidence of 1 in every ~700 births. This condition arises from a complete or partial duplication of human chromosome 21 (trisomy 21) [1]. The resulting imbalance in gene expression causes more than 20 neural and non-neural symptoms, including a distinct facial appearance, hypotonia, congenital heart defects, mental retardation, early onset Alzheimer's disease (AD), susceptibility to leukemia, gastrointestinal malformations, and immune system defects [2]. To date, more than 530 genes (176 conserved, 355 non-conserved) have been identified on chromosome 21, making identification of the genes responsible for specific DS phenotypes a daunting task [3]. Studies of rare cases of partial trisomy 21 suggest that a defined chromosome 21 region called the Down syndrome critical region (DSCR, 21q22.1-22.3) may cause the typical features of DS [4–6]. Among more than 30 presumed genes located on the DSCR, the dual-specificity tyrosine-(Y)-regulated kinase 1A gene (*Dyrk1A*) is associated with some DS characteristics, mental retardation, and motor defects [7–9], as well as with neurodegenerative diseases such as AD [10–12], Parkinson's disease (PD), and Huntington's disease (HD) [13–15].

Dyrk1A kinase in DS: regulation and function

Drosophila melanogaster minibrain protein kinase, a homolog of Dyrk1A, is essential for normal postembryonic neurogenesis [16]. Mutant flies expressing lower levels of minibrain exhibit a marked size reduction in the optic lobes and central brain, as well as visual, olfactory and motor defects. The human orthologue may have similar functions

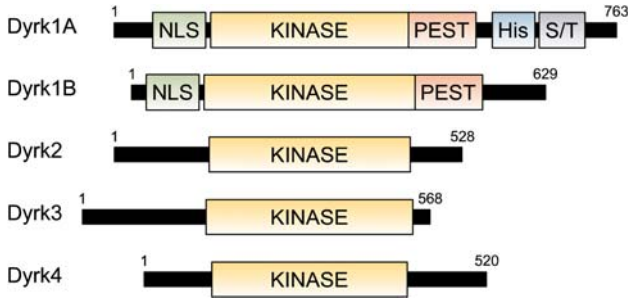

Fig. 1 Domain structure of Dyrk1A and other Dyrk family members. *NLS* Nuclear localization signal, *KINASE* kinase domain, *PEST* (Pro, Glu, Ser, Thr)-rich domain, *His* 13-consecutive-histidine repeat, *S/T* (Ser, Thr)-rich region

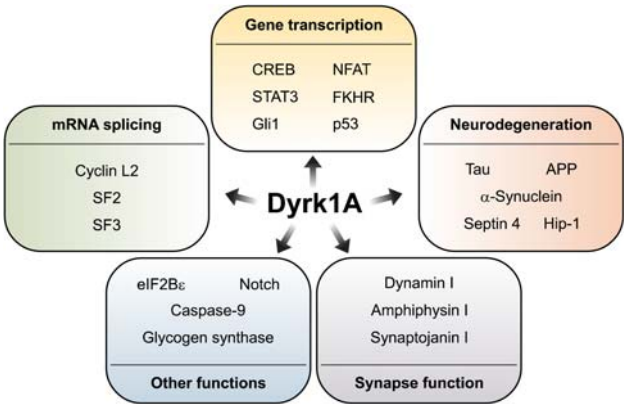

Fig. 2 Substrates and multiple putative roles of Dyrk1A in gene transcription, mRNA splicing, synapse function, and neurodegeneration

that are important to DS phenotypes. This has prompted several research laboratories to isolate mammalian counterparts (i.e., human, rat, and mouse Dyrk1A) that are highly conserved (>99% identity) across all 763 residues [17–19]. The Dyrk family consists of five mammalian members (Dyrk1A, Dyrk1B, Dyrk2, Dyrk3, and Dyrk4). Among them, Dyrk1A is the only member located on chromosome 21 [20]. Dyrk1A is a proline-directed protein kinase that contains multiple domains, including a nuclear localization signal at the N-terminus, a kinase domain, a PEST domain for protein degradation, a 13-consecutive-histidine repeat, and an S/T-rich region that has an unknown function (Fig. 1). Outside the kinase domain, Dyrk1 does not share significant sequence homology with other family members.

As its name implies, Dyrk1A has dual substrate specificities. Dyrk1A undergoes self-activation through autophosphorylation at Tyr 321, which is situated in the kinase domain [18]. Autophosphorylation at Tyr 321 is thought to occur during protein synthesis and through the intramolecular formation of a transitory intermediate, producing a constitutively active form of Dyrk1A [21]. Dyrk1A also phosphorylates target substrates at Ser or Thr residue. Dyrk1A has been shown to phosphorylate or interact with more than two dozen proteins, which are associated with multiple pathways. Even though Dyrk1A has a nuclear localization signal and 13-histidine repeat for nuclear speckle targeting [18, 22], it has also been detected in the soma and dendrites of neurons [23]. Therefore, it is not surprising that Dyrk1A substrates comprise both nuclear and cytosolic proteins, including transcriptional factors (CREB, NFAT, STAT3, FKHR, Gli1), splicing factors (cyclin L2, SF2, SF3), a translation factor (eIF2Bε), synaptic proteins (dynamin I, amphiphysin I, synaptojanin I), and miscellaneous proteins (glycogen synthase, caspase-9, Notch). This substrate diversity points to pleiotropic roles for Dyrk1A [24–28] (Fig. 2). In particular, the involvement of Dyrk1A in the regulation of NFAT pathway plays a role in the cell cycle control and synaptic function [29, 30], and the 1.5-fold increase of *Dyrk1A* gene in mice reduced NFAT transcriptional activity and caused dysregulated vertebrate development, including vascular defects and failed heart valve development [29].

Alterations in Dyrk1A expression are frequently associated with DS phenotypes. *Dyrk1A* mRNA is overexpressed in DS fetal brains and Ts65Dn mice, a well-established murine model for DS [31]. Dyrk1A is elevated approximately 1.5-fold in a gene dosage-dependent manner in DS patients [32]. Clues as to the cellular function of Dyrk1A may be provided by Dyrk1A expression patterns under normal conditions. Dyrk1A is expressed ubiquitously, although not evenly, in fetal and adult tissues as well as in non-neuronal tissues and the central nervous system. Particularly strong expression has been noted in the cerebellum, olfactory bulb, and hippocampus [17, 19]. In the mouse brain, Dyrk1A is present in preneurogenic progenitors as early as embryonic day (E) 8.5, indicating that Dyrk1A participates in early development [23]. The strong Dyrk1A expression seen in mice at embryonic stages and at birth gradually decreases until lower expression levels stabilize at around 3 weeks (Song, unpublished observation). Since over- or underexpression of constitutively active Dyrk1A in transgenic mice produces phenotypes seen in DS, the cellular function of Dyrk1A is presumed to be sensitive to its expression and/or degradation. Dyrk1A expression can be enhanced by treatment with β-amyloid (Aβ) or overexpression of the transcription factor E2F1 [33, 34]. On the other hand, it can be repressed by the AP4-geminin complex [35]. In addition, Dyrk1A activity can be increased by binding of 14-3-3 [36].

Animal models with altered Dyrk1A expression

Several murine models for DS with segmental trisomy of mouse chromosome 16 (MMU16), which corresponds to

human chromosome 21, have been developed by chromosome engineering. There are three representative DS model mice bearing the *Dyrk1A* gene: Ts65Dn, Ts1Cje, and Ts1Rhr. Ts65Dn mice contain an extra segment of a distal ~17 Mb region (~104 genes) of MMU16 [37], while Ts1Cje mice have an extra distal ~8.3 Mb region (~81 genes) [38]. These two models display a number of developmental and neuropathological characteristics similar to DS patients, including learning and behavior abnormalities [37, 38], altered synaptic plasticity [39, 40], and changes in dendritic spines of hippocampus and cortex [41, 42]. Recently, Ts1Rhr mice, which contain an even smaller trisomic segment of MMU16 (~33 genes), were reported to exhibit cognitive and behavior abnormalities and changes in spine density and morphology [43], although they seemed to have normal hippocampal function [44]. Thus, the specific genes on DSCR are suspected of DS pathogenesis. Moreover, the gene dosage effect in DS was further supported by the finding that the pathologic features of DS model mice were restored back to normal when the critical region genes are returned to their normal dosage [44].

Pertaining to *Dyrk1A*, its knock-out mice are embryonic lethal (E14.5), and heterozygous *Dyrk1A* mice (*Dyrk1A* +/−) exhibit decreased neonatal viability, developmental delay, and altered neocortical pyramidal cells. Thus, *Dyrk1A* has vital and sensitive gene dosage effects [45, 46]. Also consistent with a role for Dyrk1A in neurodevelopment, microcephaly has been reported in two unrelated patients with Dyrk1A truncation [47]. Mouse models overexpressing Dyrk1A have also been produced. Mice carry the human Dyrk1A genomic DNA in a bacterial or yeast artificial chromosome, or they carry extra copies of murine Dyrk1A cDNA [7–9]. These transgenic animals exhibit hippocampal-dependent spatial learning and memory deficit in the Morris water maze, developmental delay, and motor deficits, strongly implicating Dyrk1A overexpression in several DS phenotypes.

Role of Dyrk1A in the pathogenesis of other diseases

In addition to participating in DS, Dyrk1A appears to be involved in the pathogenesis of several neurodegenerative diseases such as AD, PD, and HD (Fig. 2). Owing to improvements in living conditions and advances in medical care, DS patients are expected to live up to the end of their sixth decade and in some cases, beyond this age. However, adults with DS typically undergo premature aging and exhibit a rapid decline in memory ability. They are also particularly vulnerable to AD [10–12]. Nearly all DS patients develop AD-like dementia several decades earlier than does the general population. By the age of 40, these patients have the neuropathological lesions seen in AD as well as dementia [48, 49]. The pathogenic DS brains have AD hallmarks including amyloid plaques and neurofibrillary tangles (i.e., insoluble deposits consisting of Aβ and abnormally hyperphosphorylated Tau, respectively). Dyrk1A phosphorylates Thr 668 of amyloid precursor protein. This may increase Aβ production, which in turn enhances Dyrk1A expression [34, 50, 51]. Dyrk1A can also phosphorylate several critical Tau residues in tangles, and it is present in tangles and the sarkosyl insoluble fraction of AD brains [50, 52–54]. Taken together, these findings suggest that the overexpression of Dyrk1A in DS may play a role in accelerating AD pathogenesis. Additional evidence suggests that Dyrk1A participates in not only AD, but also PD. Dyrk1A phosphorylation of α-synuclein, a key Lewy body component, enhances the α-synuclein positive inclusion that leads to neuronal cell death [14]. Involvement of Dyrk1A in AD and PD has been further corroborated by the finding that the GTPase septin 4 present in AD tangles and PD inclusions can be phosphorylated by Dyrk1A [15]. We have previously found that Dyrk1A phosphorylation of huntingtin-interacting protein-1 modulates differentiation and death in hippocampal neuroprogenitor cells, suggesting that Dyrk1A participates in HD pathogenesis [13]. In addition, Dyrk1A affects neuronal proliferation by phosphorylating p53 during embryonic brain development (Park and Chung, submitted).

Therapeutic approaches

Mental retardation affects 1–2% of the general population, and a large percentage of affected individuals suffer from chromosomal abnormalities. Mental retardation caused by DS contributes to about 30% of these cases, making DS the most common cause of mental retardation [55, 56]. For DS patients, mental retardation is the greatest obstacle preventing normal, independent living. Therapeutic agents aimed at treating DS phenotypes by targeting the responsible protein(s) have yet to be developed due to the lack of characterization of the responsible gene(s). Several AD drugs (e.g., acetylcholine esterase inhibitors) have been used to enhance the cognitive function of adult DS patients since DS has neuropathological similarities with AD [57]. However, the results are controversial, ranging from a significant improvement in dementia scores to adverse effects or no improvement at all [58, 59]. A similar controversy exists with regard to efficacy and the treatment of DS children with Piracetam, a nootropic agent known to enhance cognitive performance [60]. Recent attempts to ameliorate the abnormalities of learning and behavior in Ts65Dn mice revealed that non-competitive or competitive

antagonists of $GABA_A$ receptor (picrotoxin, bilobalide, pentylenetetrazole) and NMDA receptor (MK-801, memantine) can rescue them from the defects [61, 62].

Recently, a number of researchers have investigated whether Dyrk1A-associated learning and memory deficits can be alleviated by modulating Dyrk1A expression or activity. Several approaches such as the use of natural products, synthetic inhibitors, or shRNA have been investigated. For example, treatment of Dyrk1A transgenic mice with epigallocatechin-3-gallate, a major polyphenolic constituent of green tea, rescues alterations in brain volume and ameliorates cognitive deficits [63]. In addition, harmine, which is found in the Middle Eastern plant (i.e., *Peganum hamarla*) and the South American vine (i.e., *Banisteriopsis caapi*), inhibits the kinase activity of Dyrk1A at nanomolar range [64]. Injection of adeno-associated virus vector that encodes inhibitory Dyrk1A shRNA into the striata of Dyrk1A transgenic mice restores motor coordination, attenuates hyperactivity, and improves sensorimotor gating [65]. Several synthetic Dyrk1A inhibitors have also been isolated, although their in vivo efficacy has yet to be tested [66, 67].

Closing remarks

Overexpression of genes present on an additional copy of chromosome 21 causes multiple phenotypes seen in DS. Among DS symptoms, mental retardation and early onset AD hinder the normal daily lives of DS patients during early and middle age. The chromosome 21 gene product, Dyrk1A protein kinase, is overexpressed in DS patients and has recently attracted considerable attention due to its association with several DS phenotypes, including mental retardation and AD. The finding that Dyrk1A has more than two dozen substrates in multiple pathways suggests that Dyrk1A participates in multiple DS symptoms as well as neurodegenerative PD and HD. Studies by our laboratory and others show that Dyrk1A functions as a negative regulator of cardiomyocyte hypertrophy [68], and that it participates in bone homeostasis (Lee et al., manuscript in revision) and abnormal immune responses via NFAT phosphorylation (Song et al., unpublished observation). This suggests that Dyrk1A overexpression is responsible for other DS phenotypes such as congenital heart defects, short stature, and immune system defects.

Nonetheless, multiple genes could be involved in the genesis of DS, and there are several examples indicating other genes alone or together in the DSCR could contribute to DS pathogenesis. For example, the 1.5-fold increase of the *DSCR1* gene caused the similar consequences to that observed in *Dyrk1A* transgenic mice by inhibiting calcineurin and eventually increasing NFAT phosphorylation [29]. *DSCR1* transgenic mice also displayed suppression of tumor growth, one of the typical features seen in DS patients, and this suppression was further enhanced by combinatorial overexpression of Dyrk1A [69]. Although trials have been conducted to test the efficacy of AD drugs in treating DS symptoms, novel therapeutic agents are not yet available to DS patients. The development of therapeutic agents that effectively repress Dyrk1A expression or activity is in its infancy. Nevertheless, the results of initial attempts to treat Dyrk1A transgenic mice using this approach are encouraging and suggest that it holds promise for the treatment of DS phenotypes and other neurodegenerative diseases. Knowledge of the mechanisms triggered by Dyrk1A overexpression will bring us closer to understanding DS and developing effective therapies for this condition.

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