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Review Article

Impact of Triplicated *DYRK1A* on Neurogenesis and Intellectual Disability in Down Syndrome and Therapeutic Potential

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Abstract

Full or partial trisomy of human chromosome 21 results in dysregulation of gene expression, leading to the manifestation of specific phenotypes described in individuals with Down syndrome (DS). Defects in brain development, coupled with impairment in neurogenesis, are ultimately expressed as cognitive deficiency, Alzheimer disease (AD), and dementia. Amid the triplication of all human chromosome 21 (HSA21) genes, dual-specificity tyrosine phosphorylation-regulated kinase 1A (*DYRK1A*)-mediated neurogenesis and dendritic development have been attributed to the learning and memory deficits and cognitive impairment in the DS population. Upregulated *DYRK1A* perturbs the development and function of the brain, collectively affecting neurogenesis, synaptogenesis, synaptic transmission, and cell signaling pathways, which might disproportionately produce inhibitory neurotransmission and contribute to the cognitive phenotype. However, the lack of distinct gene-phenotype associations acts as a potential barrier to therapeutic improvement of cognitive performance and amelioration of AD-related neurodegeneration. The present review aims to summarize the neurogenetic consequences of triplicated *DYRK1A* in the DS population in relation to sexual dimorphism and expression of the Apolipoprotein Eε4 (*APOE ε4)* genotype. Notably, normalization of trisomic *DYRK1A* demonstrated improved synaptic plasticity, glutamatergic/GABAergic (excitatory/inhibitory) balance, and learning and memory in DS mouse models. Therapeutic approaches using inhibitors of *DYRK1A*, including catechins present in green tea extract and several other natural and synthetic agents, produced variable outcomes in cognitive improvement, depending on age and dose of administration. Mitigation of impairment in neurogenetic differentiation and cognitive performance might help control AD-related dementia and enhance quality of life. This review highlights the consequences of upregulated *DYRK1A* kinase on impairment of neurogenesis and cognitive deficits, and the therapeutic challenges associated with *DYRK1A* inhibitors for ameliorating dysregulated gene expression in DS models and human DS.

Introduction

A full or partial trisomy (T21) of human autosome 21 (HSA21) causes Down syndrome (DS) and depicts the complex spectrum of characteristic features of the syndrome. As many as 81 features have been described in individuals with DS, which vary greatly in the degree of expression among the affected individuals, though all of them possess T21. Congenital defects, such as characteristic craniofacial and cognitive impairment, are common, and congenital heart defects (~50%) and higher risk of leukemia (~10–50 fold) are prevalent.[1–3] Molecular characterization of T21 revealed overexpression of ~364 protein-coding transcripts, and five HSA21-located microRNAs (miRNAs) and non-coding long RNAs.[4] The HSA21 genes act as transcription factors, regulators, and modulators; as adhesion molecules; and are involved in RNA processing, energy metabolism, and ubiquitin pathways. Altogether, trisomic gene dosage results in genome-wide imbalance and dysregulation of expression in the DS population, which collectively confers the DS-specific features. To understand the gene-phenotype association as to which genes are linked to which specific DS phenotypes, several approaches have been adopted, both at transcriptomic and proteomic levels. To name a few: dissection of genes of the partial T21, creation of trisomic animal models with different HSA21 orthologs (partial T21), study of computational models, and ex-

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Table 1. DYRK1A-mediated hyperphosphorylation of key amino acid substrates[17]

Substrates	Amino acid residue: Serine	Substrates	Amino acid residue: Threonine
Cryptochrome 2	Ser557	Caspase-9	Thr125
p27Kip1	Ser10	Presenilin 1	Thr354
Polo-like kinase 2 (PLK2)	Ser358	Amyloid; precursor protein (APP)	Thr668
Amphiphysin	Ser293	Cyclin D1	Thr286
Septin 4	Ser107	Cyclin D2	Thr280
Nuclear factor of activated T cells (NFATc4)	Ser215	Cyclin D3	Thr283
Dynamin 1	Ser857	Munc18-1	Thr479
N-methyl-D-aspartate glutamate receptor 2A (GluN2A)	Ser1048	Tau (DYRK1A produces 3R-Tau (in DSAD/taupathy) splice isoform by alternative splicing of exon 10; modulates normal 4R-Tau isoform)	Thr212
Myocyte enhancer factor 2D (MEF2D)	Ser251	Glycogen synthase kinase 3	Thr356
Forkhead box protein O1 (FOXO1)	Ser329	DYRK1A	Ser97, Tyr321
Synapsin	Ser551	Regulator of Calcineurin 1 (RCAN1)	Ser112, Thr192
Signal transducer and activator of transcription 3 (STAT3)	Ser727	Neprilysin	(unidentified site)
Synaptojanin 1	Ser1029		
Insulin receptor substrate 1 (IRS1)	Ser312, Ser616		
α-Synuclein (through PLK2)	Ser87, Ser129		

DYRK1A, dual-specificity tyrosine phosphorylation-regulated kinase 1A.

pression analysis in trisomic cells and organs at different developmental stages in human DS and DS models. Also, cell lines (induced pluripotent stem cells (iPSCs) and embryonic stem cells) developed from individuals with DS or trisomic mice are being considered in DS research.[5–8] Mouse chromosomes (MMU) 10, MMU16, and MMU17 have syntenic segments to HSA21; however, differences exist between human and mouse gene content and its expression. Nevertheless, expression studies largely remain inconclusive in associating specific genes of small HSA21 segments with specific DS phenotypes.

Individuals with partial trisomy or chromosomal rearrangements involving segments of HSA21 are rare. Mapping of these segmental T21 cases led to the hypothesis of a small critical region of HSA21 (Down syndrome critical region (DSCR) at 21q21–21q22) responsible for most of the DS phenotypes.[9] However, the DSCR notion has been challenged by findings from segmental trisomies in human DS and DS models, which suggest that DSCR alone is not sufficient for DS features, though it may be necessary.[3,10] Moreover, the impact of dosage compensation, epigenetic expression, and environmental factors might explain the differences between the dosage imbalance and their expression at the genomic level.[9–13] Indeed, understanding whether the dysregulated non-trisomic gene expression is stochastic or the result of influence from trisomic HSA21 genes on specific non-trisomic genes appears to be one of the pertinent questions in DS research. The HSA21 genes are triplicated in people with DS, and thus, an obvious 1.5-fold overexpression is apparent compared to the normal diploid genome. However, gene expression analysis in trisomic lymphoblastoid cells revealed differential expression of HSA21 genes when compared with euploid controls. Classification of expression was demonstrated as follows: 1.5-fold expression level in Class I; >1.64 expression ratio in Class II (e.g., an expression range of 1.64–2.27); a compensated expression level of <1.4 in Class III; and variable expression between 1 to <1.5 in Class IV (e.g., *CBR1, PRDM15, ADARB1* in both DS and control subjects).[14,15]

Among the triplicated HSA21 genes, dual-specificity tyrosine phosphorylation-regulated kinase 1A (*DYRK1A,* a gene at 21q22.13 that encodes a kinase) autophosphorylates tyrosine and serine/threonine residues. *DYRK1A* is expressed as a gene in humans (capitalized and italicized), while it is expressed as *Dyrk1A* for animals (mixed capital and lowercase letters, italicized) and DYRK1A as protein (capitalized, normal font) throughout the manuscript. This gene has gained special attention owing to its involvement in brain development and contribution to cognitive deficits observed in DS, sporadic Alzheimer disease (AD), and DS with AD (DSAD) (Table 1).[16,17] *DYRK1A* is expressed throughout embryonic developmental stages and controls major prenatal consequences of differentiation in the brain and nervous system. Overexpression of *DYRK1A* has been shown to alter developmental trajectories, affecting cognitive, skeletal, and other DS-related behavioral phenotypes.[18] Triplicated Dyrk1A in trisomic tissues of DS models displayed defects in the structure and function of neuronal cells in the brain, leading to cognitive

Table 2. Impacts of hyper- and hypo-expression of DYRK1A on DS and non-DS phenotypes

	Overexpression in DS	Haploinsufficiency in non-DS
Neuronal impairment	Impairs neuronal cell proliferation and differentiation; defects in neurogenesis and brain development; perturbs synaptic plasticity and deregulate the excitatory and inhibitory balance leading to disturbance in neurotransmission, and ultimately cognitive performance and intellectual disability; early onset of Alzheimer disease (EOAD)	Autism spectrum disorder; Epilectic seizures; Neurodegeneration: Parkinsonism; AD; Dementia
Other abnormalities	Congenital heart disease; Leukemia; Craniofacial abnormalities; Otitis media; Diabetes; Skeletal defects	Speech impairment; Microcephaly; Short stature; Skeletal defects; Diabetes

AD, Alzheimer disease; DS, Down syndrome; DYRK1A, dual-specificity tyrosine phosphorylation-regulated kinase 1A.

and behavioral defects that recapitulate the phenotypes observed in individuals with DS, suggesting regulatory control of *DYRK1A* on neurogenesis. Overexpression of *DYRK1A* leads to a premature exit from the divisional cycle of neuronal progenitor cells; however, its underexpression generates an excess of immature neuronal progenitor cells and impairment in differentiation, leading to neuronal death. Notably, its haploinsufficiency due to heterozygous loss-of-function mutations exhibits skeletal defects, microcephaly, developmental delays, motor deficits, and autism-like behavior in mouse and Drosophila.[19] In addition, involvement of this kinase in enhancement of cell proliferation and reduced cell death results in resistance to pro-apoptotic stimuli targeted by chemo- and/or radiotherapy in different types of cancer.[20] In reality, *DYRK1A* kinase stands at the crossroads of several important molecular mechanisms and pathways, and its unbalanced dosage exerts devastating effects in individuals with DS or *DYRK1A* deficiency. Altogether, imbalanced *DYRK1A* plays a pivotal role in neurodegeneration in people with autism, epileptic seizures, intellectual disability, microcephaly, AD, and Parkinson's disease (Table 2). Thus, its hypo- and hyper-expression-mediated neurodevelopmental consequences have drawn attention for understanding and amelioration of its implications. Notably, normalization of *DYRK1A* copy number in trisomic DS models demonstrated rescue of some degree of cognitive performance, early cortical developmental phenotypes, and skeletal health parameters.[21–24]

In DS, 1.5-fold higher expression of the triplicated *DYRK1A* causes various characteristic systemic abnormalities, including heart disease, cancer, neurodegeneration, otitis media, and progeria, by perturbing several mechanisms such as cell proliferation, DNA damage, apoptosis, angiogenesis, signaling and transcription pathways, and stress response.[25–27] This review highlights the impact of triplicated *DYRK1A* on neurogenesis and the pathomechanism of brain development in individuals with DS and DS models. The insights into the pathogenetic cascade of cognitive impairment in this population are addressed with the current understanding of synergism and/or interaction of *DYRK1A* with other trisomic and/or disomic partner genes. Notably, trisomic gene expression is exacerbated by small allelic variation, modifier genes, and epigenetic alterations.[3] This knowledge may help understand the implications of *DYRK1A* on DS brain and cognitive development and may direct therapeutic development for amelioration of its dysregulated expression and improvement of cognitive performance in people with DS. Thus, this review also describes *DYRK1A* inhibitors or activators that have been assessed *in vivo* and *in vitro* and outlines further challenges for future research in this direction.

Genetic consequences of cognitive impairment

Impairment in learning and memory is an obligatory feature of every child born with DS, but with a variable extent of expression of cognitive, speech, and language skills, which directs the need for their mainstreaming (special) education.[28] These children may not develop fine and gross motor skills, as well as emotional, social, and intellectual features, at a pace comparable to non-DS children, which can collectively contribute to cognitive impairment. The cognitive defects in the DS population are different from cognitive issues observed in other syndromes, such as Fragile X syndrome or William syndrome. The intelligence quotient declines with increasing chronological age in people with DS, and the expression of their compromised neural development jeopardizes the quality of life. Learning and memory deficits result from gross abnormalities in the structure and function of the brain, which is 13.3% smaller in individuals with DS.[29] Neurological complications, such as significant reduction in frontal and temporal lobe volumes, microstructural and functional disturbances in the hippocampus and cerebellum, and enlargement of the para-hippocampal gyrus, result in deficits in morphosyntax, short-term memory, and explicit long-term memory.[30] In line with this, mitochondrial dysfunction and oxidative stress-induced elevation of reactive oxygen and nitrogen species production may dysregulate dopamine homeostasis and perturb neurogenesis in individuals with DS.[31]

DS mouse models have demonstrated that impaired neurogenesis, synaptogenesis, synaptic transmission, and cell signaling pathways might produce a disproportionate level of inhibitory neurotransmission, potentially contributing to the cognitive phenotype.[32] Multi-omics studies of brain autopsies highlighted transcriptomic signatures at both the gene and transcript levels, as well as proteomic dysregulation in the hippocampus and cortex.[33] Cognitive ability is subserved by brain morphology, especially the prefrontal cortex, hippocampus, and cerebellum, resulting in delays in developmental milestones. Indeed, decreased spine density and anomalous dendritic spine development, including dendritic functional abnormalities, have been demonstrated in DS mouse models at 18 months postnatal age, which exhibited profoundly impaired hippocampal functions, context learning, and spatial cognition.[34,35]

Collectively, significant cortical atrophy (owing to loss of neuronal cells), attributable to neuronal cell death and impairment in neurodevelopment, underlies cognitive deficits in DS models.[16] Interestingly, seven-month-old Ts65Dn mice, the most studied model, did not exhibit alterations in hippocampal volume; however, neuronal density declined significantly at 16–17 months in the cornu ammonis (CA) 1 region of the hippocampus, along with decreased synapse density in the CA1, CA3, and dentate gyrus, leading to atrophy.[36] *Dyrk1A* was involved in plasticity-related processes, including long-term potentiation (LTP; a form of synaptic plasticity suggested to be the physiological basis of learning and memory) between CA3 and CA1 neurons in the Ts65Dn mouse model.[37] Abnormalities in synaptic plasticity, including an increase in spine size and a decrease in hippocampal spine density,

appeared consistent with the memory impairment observed in human DS. Nevertheless, in parallel with increasing age, impairment in neurogenesis—with reductions in new neurons, neurotransmitter counts, and synaptic proteins, as well as dendritic abnormalities in the hippocampus and dentate gyrus—results in age-related neurodegeneration and dementia.[38] Moreover, cognitive defects in the DS population become more prominent with early-onset Alzheimer disease (EOAD)-related dementia by early middle age (40–60 years).[17,28]

Defects in molecular mechanisms of neurogenesis have been hypothesized to potentially underlie cognitive impairment in the DS population. However, how defects in synaptic development contribute to the cognitive phenotype in DS, or whether this is a secondary consequence of other factors, remains unresolved. In the human fetus, gross alterations in circuit activity before synaptogenesis have been postulated to initiate synaptic irregularities, such as reductions in neuron numbers (of cerebellar granule cells and cortical interneurons). Anomalies in the timing of neuronal cell proliferation in the cortex and thalamo-cortical axon development indicate altered consequences of brain development in DS mouse models. Abnormalities in individual synaptic transmission are presumed to perturb neuroanatomical and neurophysiological systems, leading to cognitive defects in trisomic individuals. Impaired hippocampal LTP has been observed in Ts65Dn mice.[29] Further elucidation of synaptic abnormalities may provide insights into the behavioral phenotypes of these mice. The DS population shows significant LTP impairment, which is proposed to be associated with their memory formation. Nevertheless, systematic assays of other major brain areas in improved DS models and/or cell lines may provide a more comprehensive picture of synaptic anomalies in the trisomic brain. The triplicated gene dosage might confer synaptic defects in trafficking and transmission in trisomic individuals, since many HSA21 genes are involved in synaptic vesicle trafficking processes. Further study on synaptic trafficking may identify deregulated proteins associated with vesicle trafficking mechanisms in trisomic cells and organs.

Trisomy of the 37.94–38.64 Mb region, or most of the distal 4.6 Mb segment in HSA21, contributes to the cognitive deficit in DS; however, mouse cross-breeds containing orthologous MMU10 and MMU17 genes challenged its connection with learning and memory deficits.[18,39] Indeed, Ts1Yah mice, which have 12 trisomic HSA21-orthologs on MMU17, indicated improved performance in the Morris water maze test (assessing spatial learning) compared to euploid mice. Both Ts1Yah and Dp(17)1Yey mouse strains showed improved LTP in the hippocampal region. Studies of DS models with or without trisomic DSCR suggest DSCR is necessary for cognitive development but insufficient to reflect spatial learning.[40]

Overexpression of HSA21 genes has highlighted molecular pathways linked to abnormalities in DS brain development.[41] Dysregulation leads to perturbations of primary functional clusters, such as overexpression of the *APP* hub gene, upregulation of transcription factors *OLIG1/2* and *RUNX1*, and abnormalities in the structure and function of impaired neurogenesis and differentiation of neuronal cells. Partial T21 did not link intellectual disability with DSCR in human DS; however, novel-object-recognition (NOR) tests for assessment of learning and memory demonstrated the contribution of trisomic DSCR to cognitive impairment.[3] More studies are recommended to determine the contribution of the trisomic DSCR to learning disability in people with DS. Of the *DYRK1A, DSCR3, DSCR4, TTC3, PIGP, RIPPLY3, KCNJ6,* and *KCNJ*15 coding genes on 21q22.13, *DYRK1A* has a prevalence score of 91% due to its prominent association with neurodevelopment (neural function, processing, and development) and its consistent overexpression in human DS and DS models.[6,7] Upregulation of *Dyrk1A* specifically impairs a presynaptic form of LTP in 152F7 mice.[37] Studies on neurons obtained from trisomic iPSCs and/or AD, and organoids developed from the human brain, showed *DYRK1A*'s involvement in axonal transport of *APP*, and its overexpression caused a progeroid status from accumulation of unrepaired DNA damage.[17,27,42,43]

Influence of sex on pathogenesis of AD and DSAD

There are divergent reports on sex-related incidences of sporadic AD and DSAD population, such as AD development in women being earlier, later, or no different compared with men, amid limited information available even after adjusting for age and the severity of intellectual disability. The hallmarks or trajectories of AD, including Aβ and phosphorylated tau (p-tau) deposition and neurodegeneration, are subtle for genetically determined AD populations. There is increasing evidence that Aβ deposition and development of AD occur by 12 years and 30 years, respectively, in people with DS, following similar trajectories as late-onset AD (LOAD). Approximately two-thirds of people with AD are women, with a higher pathologic p-tau burden observed on positron emission tomography (PET) imaging, suggesting preclinical onset of p-tau accumulation well before the expression of dementia and a greater vulnerability of women to AD. However, the influence of biological sex on brain function and AD pathogenesis is yet to be fully understood. Nevertheless, such understanding may lead to the development of targeted therapeutics to improve the quality of life of the DSAD population. Collectively, women showed more neurodegeneration, faster cognitive decline, and a higher risk of AD and associated dementia, with increased levels of p-tau181 compared with men.[44,45]

There are conflicting and inconsistent reports on the effects of age, sex, and Apoliprotein E (APOE: *APOE* gene/ApoE protein) levels on AD onset and associated dementia. Some evidence showed a significant influence of sex on AD and associated dementia, with women at higher risk compared with men, though women displayed longer life expectancy but had a higher death rate from dementia. In contrast, most studies did not demonstrate any sex-related difference in AD risk, with similar levels of Aβ, although women showed a higher load of neurofibrillary tangles (NFT). However, under-diagnosis of men with AD is evidenced in the State of Florida brain bank study, which displayed an atypical presentation of AD compared with women.[46] Population-based studies showed earlier onset and a many-fold higher risk of sporadic AD in men, which contrasted with greater risk of AD in women.[47] However, women aged 65–75 years are more prone to AD than men.[48] In contrast, a few studies reported a higher risk of AD in men. Recently, studies in the Down Alzheimer Barcelona Neuroimaging Initiative cohort and in adults with DS participating in Medicaid or Medicare in the U.S. reported no sex-related dimorphism in prevalence, penetrance, and incidence of AD by age.[49,50] The overall inconsistencies have been attributed to variations in study design, age ranges (20 to 70 years), and sample sizes (21 to >100,000).

Notably, Aβ pathology occurs in the frontal cortex approximately five years before its development in the occipital cortex (OC).[51] The study showed that aggregation of p-tau is more pronounced in the OC in women with DSAD compared with DSAD men, which is corroborated by a greater extent of neocortical NFT at autopsy in women. In consistency, sexual dimorphism was noticed in

brain structure. Magnetic resonance imaging screening displayed greater white matter hyperintensity in women with AD, indicating a higher posterior distribution of cerebrovascular disease markers than in men. Overall brain size is larger in men, with greater absolute gray and white matter sizes, higher cortical thickness, and larger unadjusted hippocampal volumes,[52] while women showed relatively larger hippocampal areas (sensitive for memory and AD pathology). Men displayed larger volumes of the amygdala and putamen.[53] However, such results are inconsistent.[49] Nevertheless, the findings suggest that cerebrovascular pathology could implicate the higher p-tau accumulation in the OC in women.[51] Importantly, divergent reports exist on the effects of sexual dimorphism on Aβ biomarkers, including Aβ42 levels, Aβ42/Aβ40 ratios in cerebrospinal fluid (CSF), and PET-amyloid imaging.[54] PET imaging displayed sex-specific differences in the deposition of Aβ or p-tau in AD of autosomal dominant transmission (ADAD). Similar scanning revealed higher p-tau accumulation in key brain regions in females than in men, irrespective of disease severity.[55,56] The study of Martá-Ariza *et al*.[57] demonstrated consistent inflammatory upregulation in women, but no sex-specific differences in tau deposition patterns. Plasma and CSF p-tau181 levels appeared sex-specific in several studies. Men showed earlier reduction in CSF Aβ42 levels.[58] Increased neurofilament light chain in CSF of men indicated axonal damage; however, similar differences were not apparent in plasma p-tau181 levels.[59]

AD onset and dementia might be related to several confounding conditions such as individual genetic makeup, comorbidities, hormonal levels, age, vascular system, social determinants (such as level of education, domestic responsibilities, etc.), and environmental exposure.[60,61] Previously, we showed a significantly higher prevalence of cardiovascular and cerebrovascular diseases among men, while a higher incidence of orthopedic problems occurred among females.[62] In general, sexual dimorphism in cognitive skills exists. Women may be more prone to AD pathology but may outperform men on memory tests (episodic memory, verbal abilities, executive functioning, and attention) or have better cognitive reserve compared with men. A significantly differential cognitive reserve has been reported with elevated neurodegeneration in later stages of the disease.[63] Men perform better in visuospatial tasks, mathematical reasoning, and reaction times. Zou *et al*.[58] did not find any significant association of sex-specific differences in global cognition, episodic memory, or executive function with APOE ε4. Lai *et al*.[47] observed no effect of sex or interaction between sex and APOE on the risk of AD in adults with DS during a 17-year study period. However, by 65 years of age, men with DS showed a three-fold higher risk of AD than DS women, though the authors did not observe any association of sex and age of AD onset. Mhatre *et al*.[46] showed a six-fold higher risk of AD in men over 60 years compared with age-matched women, which was independent of *APOE ε4* level, ethnicity, and depth of intellectual disability. Women showed an age-related faster and steeper decline in memory scores and cognitive performance, with a higher prevalence of AD than men.[64] The Cognitive Function and Ageing Study from the UK demonstrated that dementia was prevalent in men compared to age-matched women in the beginning, but that dementia incidence decreased in men over time.

The general consensus suggests that LOAD is prevalent in women, indicating a possible role of hormones in AD pathogenesis and heightened vulnerability in women, such as age-related loss of estrogen and its bioavailability. Higher AD risk in women could be explained by sex-specific biological factors, particularly the menopausal event. A causal relationship may exist between Aβ and p-tau levels and menopause, with cognitive effects in the general female population. Females with DS showing early onset of menopause are linked to early onset of clinical dementia.[65] Increased levels of follicle-stimulating hormone and luteinizing hormone at puberty indicate primary gonadal dysfunction in both men and women with DS, which progresses more prevalently with age in men than women, making DS men more vulnerable to AD. The group observed that the duration of dementia was significantly longer among deceased DS women compared to men, particularly with LOAD. In line, women with AD live longer compared to their male counterparts.[56] However, clinical trials with hormone replacement therapy remain inconclusive in delaying the onset of dementia and may be associated with negative effects.[56] Estrogen may act as a protective factor against the development of AD. It has antioxidant activities and enhances cholinergic activity in the brain by promoting the growth and survival of cholinergic neurons, which in turn maintains cognitive functions. Estrogen is also involved in the regulation of APP metabolism and the protection of brain regions from the formation of Aß plaques.[46] Low estrogen levels lead to early onset of menopause in DS women compared with non-DS women.

In summary, DS women display greater verbal scores and smaller hippocampal areas, suggesting sexual dimorphism in AD outcomes. Contradictory reports from prospective studies demonstrated no significant sex-specific differences in disease onset, penetrance, clinical progression, or biomarker levels. Interestingly, earlier diagnosis with reduced CSF Aβ42/Aβ40 ratios and lower hippocampal volumes in women with DS carrying the *APOE ε4* allele exhibits a significant interaction between sex and *APOE ε4* in the DS population. Additionally, sex-specific differences appear more pronounced in transcriptomic and multi-omics studies, presenting consistent upregulation of inflammatory and glial genes in females with DSAD compared to sporadic AD, particularly in the late stages of the disease.

Implications of APOE status to DS and AD pathogenesis

The *Apolipoprotein E (APOE* gene/ApoE protein) gene has been demonstrated as the strongest genetic risk factor for AD and acts as a potential modifier of the influence of biological sex on AD development. A genetic interaction of age with the level of *APOE ε4* genotype has been demonstrated to increase the risk of AD at an early age and a higher rate of cognitive decline.[63,66] ApoE protein is involved in the metabolism of plasma lipoprotein and the transport of lipids within cells and tissues and has been associated with neurodegeneration. It plays a key role in clearing the Aβ peptide from the brain. The *APOE ε4* allele increases the risk of cardiovascular disease and diabetes by being associated with elevated levels of total and low-density lipoprotein; however, it demonstrates an inverse association with AD risk.

The potential effects of *APOE ε4* dosage, including its heterozygosity, homozygosity, and absence in non-carriers, appear sex-specific in terms of penetrance, clinical progression, and biomarker trajectories of AD.[67] Of the three polymorphisms in the *APOE* gene *(ε2, ε3,* and *ε4*), the *ε4* genotype acts as a significant risk factor for the EOAD and dementia, although this has been contradicted by other studies.[46] *APOE ε4* in neuronal cells not only influences the risk for AD but is also proposed to confer a higher AD risk for women than men,[68] though several contradictory and inconsistent reports demonstrate *APOE ε4* as a risk factor for DSAD.

The age of AD diagnosis occurs earlier in females with DS carrying *APOE ε4* alleles relative to men.[49] The study showed lower

CSF Aβ42/40 ratios and lower hippocampal volumes in *APOE ε4*-carrier women compared with non-*APOE ε4*-carrier women. Metabolomic and transcriptomic studies display sex dimorphism among *APOE ε4* carriers. *APOE ε4* confers alterations in the volumes of the amygdala and hippocampus in both men and women, leading to cognitive disability, which is more pronounced in women. One copy of *APOE ε4* exerts identical odds of developing AD in both men and women aged 55–85 years; however, between 65 and 75 years, even a single copy of the allele increases AD risk in women, suggesting an interaction between sex and *APOE ε4*.[49] Female *APOE ε4* carriers exhibit higher tau-related susceptibility, earlier onset of AD symptoms, and smaller adjusted hippocampal volumes than male counterparts[49,69,70]; however, men require two copies of *APOE ε4* for tau aggregation similar to that observed in females carrying one copy.[71] Altogether, disease penetrance, age of symptom onset, cognitive progression, and biomarker trajectories (Aβ, p-tau, and neurodegeneration) appear similar in both genders with homozygous *APOE ε4* alleles.[58,69,72] Healthy non-DS, *APOE ε4*-positive women were at a two-fold higher risk of developing AD compared with their *APOE ε4*-negative counterparts, whereas the risk was almost similar among *APOE ε4*-negative and positive men. Individual age might exacerbate the interaction between *APOE ε4* haplotype and AD risk in adults with DS. Notably, the interaction between sex and *APOE ε4* on AD risk is less understood in the DS population.

APOE ε4 accounts for 2% of the global population with homozygous *APOE ε4* and 15–20% of AD cases. Sexual dimorphism in homozygous *APOE ε4* carriers demonstrates poorer episodic memory, global cognition, and executive and visuospatial function in asymptomatic males than females, whereas expressive language and attentional cognition are similar in both genders.[58] Women with two copies of the *APOE ε4* allele experience significant effects on intellectual disability and global cognition, along with worse neuropsychiatric symptoms and reduced cortical thickness, compared to men with a similar *APOE ε4* level.[73,74] Females with homozygous *APOE ε4* alleles display significantly smaller hippocampal volumes across all ages and disease stages compared to their male counterparts.[63,69] However, such reduction does not cause significant cognitive decline over time. Notably, both ADAD and DSAD show a strikingly similar sequence of age-related biomarker changes in *APOE ε4* homozygotes with no sexual dimorphism. An earlier decrease in Aβ42 levels is apparent in males.[69] However, amyloid PET imaging scans do not display any sex-specific differences in Aβ42 and amyloid pathology, though symptomatic female *APOE ε4* homozygotes reveal worse neuropsychiatric symptoms and reduced cortical thickness, especially in the medial-lateral temporal regions, compared to *APOE ε4* homozygous male counterparts.[74] These characteristics observed in symptomatic patients limit the ability to interpret the quantity of decrease or increase in cortical thickness as true gray matter changes in brains affected by AD pathology. Interestingly, *APOE ε4* homozygotes have been classified as another form of genetically determined AD, besides ADAD and DSAD. This form of the disease displays near-full penetrance of biologically defined AD, predictability of symptom onset and clinical changes, and striking similarities in the sequence of biomarker and pathological alterations.[63]

Several multi-omics and transcriptomic studies have demonstrated insights into the molecular mechanisms of AD progression, which are linked to downregulated neuronal gene expression in women and activated transcriptional events in oligodendrocytes in men.[75] Significant sex dimorphism is observed in single-nucleus and spatial transcriptomic analyses in DSAD and sporadic AD.[76] Women with DSAD show consistent upregulation of inflammatory and glial genes across brain regions and stronger signature transcripts involved in neuroinflammation, neurodegeneration, and oxidative stress. Unique transcriptional changes in excitatory neurons and astrocytes demonstrate a discrete neutrophil morphology, characterized by IL-17/IL-1 gene expression in *APOE ε4* carriers with cognitive impairment.[77] The expression is more pronounced in later stages of the disease. Immune-related gene expression is prominent in females, whereas men display sex-specific differences in autophagy and synaptic signalling.[78] However, contradictory reports show more sex-specific differences in region- and stage-specific transcript expression. In females, enhanced modulation in immune and neuronal pathways is significantly associated with Aβ and tau pathologies[79]; however, Martá-Ariza *et al*.[57] did not find significant sex effects on proteomic profiles. Emerging hypotheses highlight the impact of mitochondrial-related impairments on *APOE ε4* expression and its association with AD pathogenesis. Notably, interaction of the *APOE ε4* allele with mitochondria leads to mitochondrial dysfunction and alterations in mitochondrial dynamics, such as fusion, fission, and mitophagy. Such changes ultimately result in neurotoxicity through enhancement of mitochondrial Ca^{2-} and reactive oxygen species levels, leading to oxidative stress.[13,21,80,81] Moreover, trafficking of ApoE ε4 to the nucleus facilitates its involvement in regulating genes associated with aging, Aβ production, inflammation, and apoptosis, potentially contributing to AD pathogenesis.

Metabolomic studies reveal associations of dysregulated lipid and energy metabolism pathways with distinct methylation and RNA profiles in female *APOE ε4* carriers.[82] Females show lower glucose uptake in the brain, indicating metabolic vulnerabilities, which is supported by enhanced CSF p-tau and increased proline levels associated with elevated levels of sphingomyelins and long-chain acylcarnitines.[83] However, plasma metabolomic profiling neither displays any significant effect of age or sex on metabolite patterns or concentrations, nor any sexual dimorphism within age groups in individuals with DS.[84] Notably, *APOE ε4*-related AD risk varies by race and ethnicity,[85] hypothesizing inconsistencies in sex-specific differences in AD risk might be interacted by genetic, racial, and sex-specific factors in *APOE ε4*-carriers. Elevation of acute-phase response proteins in CSF confers a higher risk for AD in non-ε4 carriers compared to ε4 carriers. This is further supported by the lower threshold for inflammatory damage in ε4 carriers compared to non-carriers.[86]

In summary, the *APOE* dosage effect on AD risk may differ between genders, though *APOE ε4* homozygotes do not reveal sex dimorphism in AD outcomes. This discrepancy could be explained by a possible interaction between *APOE ε4* and other genes, which may activate sex-specific differences in biological mechanisms in heterozygotes. However, the homozygous state of *APOE ε4* alleles could overshadow similar expression. The differences between heterozygotes and homozygotes of *APOE ε4* alleles may be described by sex-specific genetic resilience and compensatory mechanisms. Thus, *APOE* is intricately associated with neurodegeneration and AD, though the underlying molecular pathomechanisms of ApoE ε4 neurotoxicity are not completely elucidated. Moreover, ApoE ε4 may be envisaged as a target for the identification of novel therapeutics to counteract AD factors in the brain.

Implication of triplicated *DYRK1A* on neurogenesis and brain development in DS

DYRK1A plays a pivotal role in controlling cellular growth in the

brain, neurogenesis, and neuronal maturation, implicating *DYRK1A* as a significant candidate for developmental cognitive impairment in individuals with DS. Overexpression of *DYRK1A* leads to arrest of neuronal proliferation at the G1 phase through rapid degradation of Cyclin D1. Phosphorylation by triplicated *DYRK1A* is a key mechanism in the regulation of Cyclin D1 (CCND1) and p27Kip1 (CDKN1B) by governing protein turnover during the G1 phase of the cell cycle. Subsequently, *DYRK1A*-dependent stabilization of p27Kip1 and further depletion of Cyclin D1 jointly influence cell cycle exit into G0 and neuronal differentiation. *DYRK1A* can promote degradation of protein Cyclin D1 and reduce its expression through direct phosphorylation at the Thr286 residue via the *GSK3β* mechanism. Such proteasomal degradation of Cyclin D1 during the G1 phase is critical in regulating cell cycle progression and neuro-cellular differentiation. Degradation of Cyclin D1 is influenced by DYRK1A-mediated stabilization of p27Kip1 via its phosphorylation at Ser10. This modulation primarily increases during the G1-G0 phase to enhance the stability of p27Kip1. Several kinases, including CDK5, ERK2, KIS, and HIPK2, may target this Ser10 residue. Triplicated *DYRK1A* presumably perturbs brain development in DS by deregulating the G1 phase of proliferating neuronal precursors and inducing premature differentiation. This reduces the neural progenitor pool, resulting in a decrease in the number of neurons, which eventually impairs brain development in individuals with DS.

Triplicated *DYRK1A* promotes assembly of the DREAM complex via phosphorylation of LIN52 at Ser28, leading to cell cycle exit and quiescence, which is further supported by depletion of nuclear Cyclin D1. *DYRK1A* can exert a long-term effect on stabilization of the DREAM complex to sustain the quiescence period instead of a direct effect on cell cycle exit at G1 by inhibiting the transcription of cell cycle genes in the G0/G1 phase. *DYRK1A* induces a decrease in Cyclin D/CDK4-dependent phosphorylation of p130/RBL2 in the process of DREAM complex formation. In line with this, phosphorylation of the NOTCH transcription factor by *DYRK1A* represses NOTCH signaling in neuronal cells, which promotes differentiation of neuronal cells and neuronal stem cells via a lateral inhibition process. Active NOTCH signaling influences expression of *HES* genes, which maintain neuronal stem cells in a progenitor state.

DYRK1A, as a multipotent protein, enhances neurogenic factor-induced differentiation of neuronal cells in the central nervous system (CNS) in developing normal embryos, indicating its involvement in neurogenesis and brain development.[87] The study on the Drosophila mini brain (hereinafter referred to as *Mnb*) gene, an orthologous gene to *DYRK1A*, reflected its involvement in perturbation of neural proliferation leading to decreased brain size. The adult nervous system has demonstrated expression of *DYRK1A* and its involvement in inhibition of cell proliferation and promotion of premature differentiation of neuronal cells. *DYRK1A* controls important signaling pathways (e.g., AKT, MAPK/ERK, STAT3) and contributes to brain development and neuronal differentiation, either via regulation of NOTCH signaling or NFAT pathways of synaptic function.[41,88,89] *DYRK1A* and *RCAN1* synergistically act to inhibit nuclear translocation of the NFAT-family of transcription factors. A significant association of NFAT-pathway inhibition was demonstrated with both neuronal and cardiac defects in the DS population.[17,90] Alteration in the calcineurin-NFAT signaling pathway displayed critical involvement in differentiation of trisomic neuronal cells and their degeneration (Fig. 1). The conserved N-terminal motif and two protein isoforms of DYRK1A stabilize its kinase domain function, exhibiting its contribution to key functions of the brain in the triplicated state.[16,91,92] Upregulated *Dyrk1A* interacts with *Riply3* overdosage, leading to downregulation of *Tbx1* in brain development in the DS model.[42]

DYRK1A and brain development

DYRK1A plays a multifaceted role in the development of the human brain. Triplication of *DYRK1A* and its 1.5-fold overexpression in individuals with DS jeopardize cellular proliferation and signaling, splicing and chromatin transcription, exo- and endocytosis, and apoptosis, profoundly affecting neuronal cells (Fig. 1).[87] Overexpression of *DYRK1A* significantly reduces neuronal cells and collectively affects neurogenesis, synaptogenesis, dendritogenesis, neurotransmission, and neuronal functions across various DS models.[16,29] Perturbation of *DYRK1A*-mediated neurogenesis and dendritic development has been attributed to learning and spatial memory impairment and intellectual disability in the DS population and DS models. Dendritic abnormalities with fewer thin spines were observed in Ts1Rhr and Tc1 mice at three weeks and three months of age, respectively.[93] Notably, a decrease in mushroom spines and significant growth in stubby spines indicated an association of dendritic spine abnormalities with cognitive disability in DS mice. Overall elevation in spine size and reduction in spine density were featured in the trisomic brain. Posterior cortical atrophy was observed in an individual with DSAD.[94] Nevertheless, triplicated *DYRK1A* did not cause severe impairment in intelligence quotient levels, as revealed through small segmental duplications in HSA21.[95]

Dyrk1A expression has been demonstrated in fetal neuronal progenitor cells and adult brains. Young individuals with DS exhibited a decreased number of dendritic spines in hippocampal pyramidal neurons, while cortical pyramidal neurons showed shortened basilar dendrites in DS individuals aged above four months. However, dendritic differentiation was unaltered in layer IIIC pyramidal cells of the prefrontal cortex in infants aged 2.5 months compared to non-DS infants, suggesting the onset of pathomechanisms in layer III pyramidal neurons after this age in DS infants. Layer III cells appear normal at birth, but a sharp age-related decline in dendritic spines and enhanced degenerative changes occur in hippocampal pyramidal neurons, especially in the dendritic arbors of CA1, CA2, and CA3 regions. The basal dendritic arbors of layer III pyramidal cells appeared smaller and less spinous with fewer branches in the frontal cortex of Ts65Dn mice, which was unaffected by environmental enrichment.[36] In rats, *DYRK1A* expression markedly influenced differentiation of immortalized hippocampal progenitor (H19-7) cells generated from embryonic hippocampal neurons. *DYRK1A* attenuates neurite outgrowth in immortalized hippocampal cells.[96] Thus, several studies in humans and DS models established dysregulation of *DYRK1A* as a primary factor of neuronal abnormalities, which has been targeted for amelioration.

DYRK1A-expression is observed in forebrain neurons, cortical layers, and ventricular cells at different embryonic stages in non-trisomic Institute of Cancer Research mice. Ts65Dn mice showed *DYRK1A* overexpression, implicating structural deficits in cortical, hippocampal, and cerebellar regions at perinatal or early postnatal ages, presumed to be largely caused by dysregulated cell cycle.[97] However, the contribution of these deficits to age-related behavioral impairment is yet to be discerned. Triplicated *DYRK1A* dysregulates the crucial G1/S transition (when cells may either exit the cell cycle to differentiate or proceed through the G1 checkpoint for further division) (Fig. 1). Negative regulation of *DYRK1A* promotes the G0 state of the cell cycle. *Mnb/Dyrk1A* or *Dyrk1A* regulates neuronal differentiation *in vitro*, but differ-

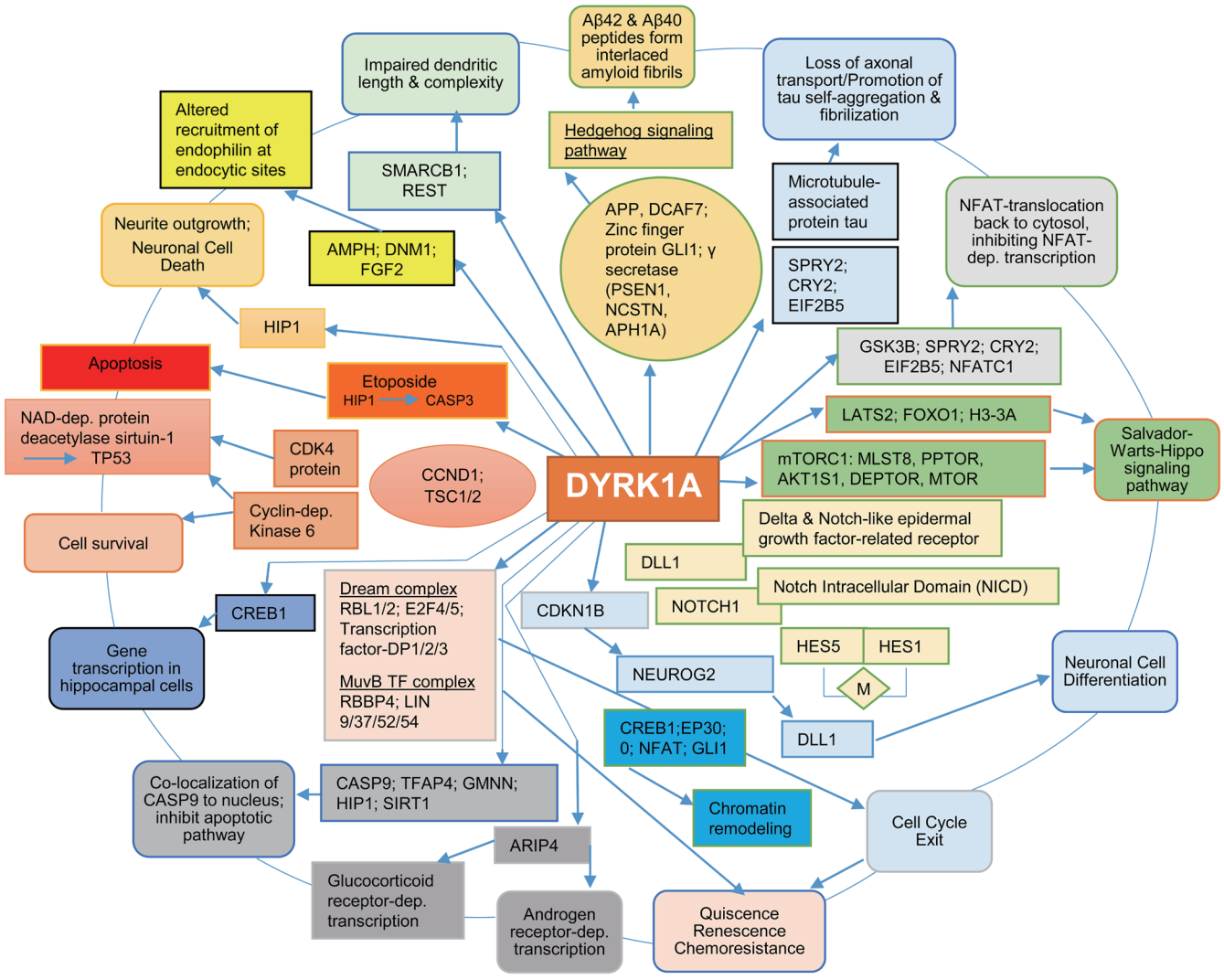

Fig. 1. Interaction of DYRK1A with other genes in different signaling pathways and phosphorylation mechanisms. *DYRK1A* leads to the aggregation of NFTs through hyperphosphorylation of tau and *APP*. Triplicated *DYRK1A* acts as a negative regulator of the calcineurin/NFAT pathway. *DYRK1A* and *RCAN1* synergistically inhibit calcineurin activity. DYRK1A phosphorylates *Dynamin1* and affects its function during dendrite differentiation, neurotransmission, and synaptic development. *DYRK1A*'*s* role as a transcription regulator perturbs the expression of *STAT3, GLI1*, *CREB*, and many other genes. Disruption of the *REST*/*NRSF* results in deregulated gene expression during neuronal cell development and maturation. *DYRK1A* enhances receptor tyrosine kinase signaling through phosphorylation of *SPRY2*. *DYRK1A* interacts with *SIRT1* to control cellular stress-response pathways. *SIRT1* deactivates stress response proteins (NF-κB, HIC1, p53) and DNA damage response factors and maintains cell survival and genomic stability. *DYRK1A* activates p53, and *p53* in turn downregulates *DYRK1A* in a negative feedback loop by activating its ubiquitination and inhibiting its transcription through miR-1246. Under DNA damage, phosphorylation of *p53* by *ATM* activates DNA repair through cell cycle arrest by attenuation of the G1–S phase transition, or apoptosis in case of repair failure. *DYRK1A* regulates the cell cycle and neuronal differentiation by influencing G0/G1 arrest via regulation of cyclin D1 and $p27^{Kip1}$ during the G1 phase, and the *GSK3β* mechanism. DYRK1A promotes assembly of the DREAM complex, leading to cell cycle exit and quiescence. Phosphorylation of the NOTCH transcription factor by DYRK1A represses NOTCH signaling in neuronal cells. APP, amyloid precursor protein; *ATM*, *Ataxia-telangiectasia mutated*; CREB, cAMP-responsive element binding protein; DNA, Deoxyribonucleic acid; DYRK1A, dual specificity tyrosine-phosphorylation-regulated kinase 1A; GLI1, glioma-associated oncogene or Zinc finger protein; *GSK3β*, Glycogen synthase kinase-3 beta; HIC1, hypermethylated in cancer 1 protein; miR-1246, microRNA-1246; NFAT, nuclear factor of activated T cells; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFTs, neurofibrillary tangles; NOTCH, Neurogenic locus notch homolog protein; NRSF, neuron-restrictive silencer factor; $p27^{Kip1}$, cyclin-dependent kinase inhibitor 1B; p53, tumor protein p53; RCAN1, regulator of calcineurin 1; REST, RE1-silencing transcription factor; *SIRT1*, *sirtuin (silent mating type information regulation 2 homolog) 1*; SPRY2, Sprouty RTK signaling antagonist 2; STAT3, signal transducer and activator of transcription 3.

entiation is perturbed by constitutive upregulation of *DYRK1A*.[96] Neurodegeneration appears as a result of diverse dysfunctions in multiple brain cells, including selective impairment and progressive degeneration of neurons, glial cells, and their networks within the brain and spinal cord, leading to gradual cognitive decline and/or motor dysfunction. However, triplication of HSA21 genes may not alter development and function uniformly in every cell. *Dyrk1A*-encoded messenger RNA (mRNA) and protein were reported in the transition phase of neuroepithelial cells from proliferating to neurogenic divisions during early embryonic age. Hence, recogni-

tion of spatial and temporal expression of the trisomic gene and its divergence from normal development is critical in conjunction with specific brain phenotypes.[98] Interestingly, hypo-expression of *Dyrk1A* was demonstrated in reduced brain size in mice, with no apparent alteration in cerebral cortex structure.[99] Haploinsufficiency or hyperexpression of *Dyrk1A* causes cognitive defects with specific DS-like impairment in hippocampal development, leading to learning and memory deficits in transgenic mice.[100] Summarily, *DYRK1A* significantly contributes to neuronal development, proliferation, and differentiation (Fig. 1).

DYRK1A and neurotransmission

The glutamatergic (excitatory, E) and GABAergic (inhibitory, I) neurotransmitters significantly regulate neuronal cortical and subcortical circuits. Overexpression of *DYRK1A* perturbs development of glutamatergic synapses and brain function.[101] Disruption of the E/I balance is hypothesized as an etiological mechanism for several neurodevelopmental disorders. Alteration in E/I balance and enhancement of LTD and LTP in the extracellular hippocampal region display upregulated Dyrk1A-mediated perturbation of learning and memory, along with synapse weakening in transgenic mice. However, such LTD/LTP alterations occurred in the opposite direction compared to Ts65Dn and Ts1Cje mice.[102] The E/I balance is crucial for processing and transmitting information, and is primarily regulated by intrinsic neuronal plasticity, excitability, synaptic transmission, and by glutamatergic and GABAergic neurons. In individuals with DS, abnormal neurotransmitter levels lead to neuronal dysfunction from the embryonic stage. GABA acts as an excitatory neurotransmitter in immature neurons in developing brains due to higher intracellular Cl^- concentration (caused by early expression of Na^+-K^+-$2Cl^-$ cotransporters, which import Cl^- intracellularly, and late expression of K^+-Cl^- cotransporters, which export Cl^- extracellularly).[36] In rodents, increased expression of the neuronal K-Cl channel lowers intracellular Cl^-, causing hyperpolarization and a transition of GABA function from excitatory to inhibitory in mature neurons.[103] The frontal cortex of 61% of trisomic male fetuses showed reduced GABA in the developing brain. Fetal DS brains displayed reduced dopamine and serotonin levels in the frontal cortex, suggesting similar serotonergic and dopaminergic alterations in individuals with DS. Autopsy of the caudate nucleus and temporal cortex revealed age-dependent serotonin reductions of 60% and 40%, respectively, in individuals with DS.[104]

Abnormalities in synaptic plasticity observed in mouse models are relevant to memory deficits in human DS. The prefrontal cortex of Ts65Dn mice showed glutamatergic synaptic loss.[105] Decrease in GABA concentration was noticed in trisomic fetal brains, indicating GABA deficiency-induced over-inhibition due to loss of excitatory synaptic transmission in developing DS brains. GABA regulates dendritic maturation, and its deficiency can impair maturation of the developing brain. Additionally, neurotransmitter deficiency and alterations in neuronal balance may perturb trisomic brain development. GABA deficiency was attributed to the reduction of GABAergic neuron numbers in temporal lobes of children with DS, leading to structural and functional perturbations. High incidence of apoptosis and free radicals is apparent in DS brains.[104]

Glutamatergic and GABAergic neurotransmitter dysfunction, including enhanced GABAergic input and reduced activation of N-methyl-d-aspartate (NMDA) receptors and LTP, was evident in hippocampal CA1 neurons and the dentate gyrus in Ts65Dn mice. Enhancement of hippocampal LTD was attributed to activation of excitatory synapses and NMDA signaling. Subtraction of trisomic *Dyrk1A* improved synaptic plasticity, E/I balance, and learning and memory function in this model.[23] Low dendritic arborization and spine density were noticed in glutamatergic pyramidal neurons of the cerebral cortex in heterozygous *Dyrk1A*-knockout and BAC-transgenic mice, along with altered synaptic proteins in glutamatergic and GABAergic neurons, suggested to be influenced by upregulated *DYRK1A*. Upregulation of *Dyrk1A* potentially inhibits the NMDA-independent form of LTP in 152F7 mice, suggesting that this inhibition is associated with chromatin changes that deregulate genes coding for proteins involved in glutamatergic synapse release.[42] Thus, *DYRK1A* dosage imbalance is critical for alterations in glutamatergic neurons in trisomic brains.

The impact of *Dyrk1A* dosage was not apparent on working memory, social behavior, locomotor activity, or epileptic susceptibility in glutamatergic neurons postnatally in animal models. Molecular analysis indicated its impact on exploratory behavior, long-term explicit memory, and contextual fear memory. *Dyrk1A* dose-response effects on glutamatergic neurons displayed deregulated transcriptional activity on postsynaptic proteins, resulting in long-term enhancement of synaptic plasticity in the transgenic Tg(Camk2a-Cre) line and trisomic Dp(16Lipi-Zbtb21)1Yey mouse model. Transcriptomic analysis of $Dyrk1A^{C/C}$ showed downregulation of genes involved in the presynaptic vesicle cycle, indicating *DYRK1A*'s role in neurotransmitter release.[88] Dp1Yey mice displayed impaired working memory, long-term episodic memory, and associated learning disability. Genetic modification in homo- and heterozygotes and segmental trisomies showed association of *DYRK1A* with memory and learning in the trisomic Dp(16Lipi-Zbtb21)1Yey mouse model. In summary, *DYRK1A* acts as a key factor at glutamatergic synapses and is targeted for treatment of DYRK1A hypo-/hyper-expression-related diseases, including AD. GABA antagonists could potentially rescue cognitive ability in trisomic mice by reducing inhibitory neuronal action.[104]

DYRK1A and AD

Cognitive decline is the hallmark of EOAD in the DS population.[106] The pathomechanism of AD is associated with the buildup of insoluble Aβ-protein aggregates, hyperphosphorylation of tau, development of NFTs, and collective contributions of neuroinflammation, apoptosis, necrosis, and excitotoxicity to neuronal damage and cognitive decline, culminating in AD and dementia.[38,107] *DYRK1A* phosphorylates microtubule-associated "tau" protein at serine and threonine residues (Ser202 and Thr212), priming it as a substrate for further phosphorylation by GSK3β, leading to tau hyperphosphorylation at multiple sites. Hyperphosphorylation of tau reduces its ability to maintain normal microtubule assembly and stability, eventually leading to its aggregation into NFTs in the brain, contributing to AD-like pathology.[17,29,36] Higher risk of EOAD and associated dementia in individuals with DS is a concerted dysfunctional impact of multiple HSA21 genes,[108] especially *APP* (overexpression activates glial cells by increasing *S100B* overproduction), *S100β* (increases intracellular calcium in astrocytes, perturbs neuronal processes, upregulates IL-1β prompting overproduction of pro-inflammatory cytokines and neurodegeneration), *BACE2* (cleaves APP, favors amyloid plaque and NFT formation, contributing to dementia), *RCAN1* (enhances tau hyperphosphorylation by regulating *SOD1* in hippocampus and cortex), *DSCAM* (disrupts neuronal projections and axonal myelination, delays neuronal circuit formation, perturbs axonogenesis and synaptogenesis, promotes senile plaque formation), *SOD1/CAT/GPX* (contribute to H_2O_2 accumulation and mitochondrial dysfunction affecting APP processing and increasing Aβ production),

and *DYRK1A* (hyperphosphorylates tau at multiple sites, triggering NFT formation, synaptic dysfunction, and neuronal loss to enhance cognitive decline and dementia). A self-propagating cycle of IL-1 and *S100B* leads to their own overexpression along with overexpression of neuronal *APP*, exacerbating neurodegenerative effects.[30] *DYRK1A* phosphorylates *APP* at threonine 668 residue, influencing the amyloidogenic pathway and production of toxic Aβ peptides. Proteolysis of the dosage-sensitive *APP* gene generates the main constituent of Aβ plaques. Aβ peptides accumulate as non-soluble Aβ isomers and plaques in the brain, contributing to neurological phenotypes and dementia features in both DS and EOAD.[4,109] Triplication and mutations of *APP* sow the seeds of AD. Transgenic mice showed elevated phosphorylation of *APP* and Aβ, influenced by triplicated *Dyrk1A*. Autopsy of aged brains showed reduced *ACE2* and *TMPRSS2* but increased *STAT2* protein levels in individuals with DSAD compared to normal euploid and sporadic AD groups.

DYRK1A acts as a common factor for both DSAD- and DS-specific cognitive defects. Triplicated *DYRK1A*-mediated increases in mRNA and protein levels were observed in autopsy brains of human AD. DYRK1A-mediated phosphorylation of AD biomarkers, such as *APP*, Tau (also known as microtubule-associated protein tau (hereinafter referred to as MAPT)), presenilin 1, septin, and neprilysin (NEP), designates *DYRK1A* as a regulator of Tau mRNA splicing. In transgenic mice, triplicated *DYRK1A* influenced downregulation of NEP activity (a major Aβ-degrading enzyme) and phosphorylation at the NEP cytoplasmic domain. Trisomic fibroblasts derived from DS individuals revealed significant reduction in NEP activity compared to healthy controls. Brains of people with AD revealed Calpain 1-induced proteolytic cleavage of the C-terminal domain of DYRK1A, producing a low-molecular-weight form with increased kinase activity.[110] The free C-terminal domain may act as a kinase-independent transcription factor.[111]

Overexpression of *DYRK1A* perturbs synaptic plasticity and memory consolidation due to neurofibrillary degeneration and hippocampal cell loss.[39] Partial T21 did not show *DYRK1A* involvement in DS-EOAD but showed increased *APP* dosage, suggesting its pivotal role. Segmental trisomies of animal models could not establish a direct connection between *APP* and learning and memory impairment observed in human DS.[95] Normalization of *DYRK1A* or *DSCAM* copy number failed to rescue submucosal neuron defects in the Ts65Dn model, suggesting contribution of multiple overexpressed genes to bowel problems and Hirschsprung disease in children with DS.[112]

Interaction of genes and proteins on *DYRK1A* expression

Mechanism of DYRK1A action

Triplication of HSA21 results in global transcriptional deregulation in DS individuals, affecting multiple genes that may directly or indirectly contribute to brain development. *DYRK1A* acts as a multi-edged sword: it not only exerts its own trisomic impact on DS characteristics, particularly impaired brain development and EOAD, but it takes into account other triplicated genes to dysregulate genome-wide expression, perturbing the overall life quality of individuals with DS (Fig. 1). DYRK kinases hold dual phosphorylation capacity: they auto-phosphorylate their own tyrosine residue motif (YxY) in the activation loop while still being attached to the ribosome during translation, and they catalyze phosphorylation of serine and threonine residues in protein substrates. Phosphorylation affects protein functions due to conformational changes or addition of a phosphate group and alters stability, cellular localization, and interaction with other proteins and DNA.

Triplication of *DSCAM, KCNJ6, SIM2,* and *DYRK1A* has been identified as dosage-sensitive candidate genes for defects in brain phenotypes in people with DS. Upregulated *DYRK1A* activates transcription of kinases associated with MAPT/TAU phosphorylation through binding of p53 and p44 to its promoter region and demonstrates its association with cognitive decline, premature aging, and synaptic defects. *DYRK1A*'s involvement in phosphorylation of p53 was hypothesized to affect proliferation of neuronal cell lines in rats.[88] Interestingly, *DYRK1A* may self-regulate its auto-phosphorylation, leading to enhancement of self-kinase activity and reduction of self-degradation.[91] Notably, alongside *DYRK1A,* upregulation of several other HSA21-encoded genes, such as *APP, CBS, OLIG2*, and others, collectively contributes to the cognitive impairment phenotype in the DS population.[18,113] Triplicated *CXADR, SOD1,* and *TIAM1* activate the MAPK-p38 pathway, leading to tau phosphorylation and NFT formation, contributing to neuropathological development.[114] *DYRK1A* appears essential in axon guidance and synaptogenesis in developing axons, as measured in MENA (Mammalian enabled protein, encoded by the gene *ENAH*)-dependent translation of DYRK1A mRNA.[88,91] In the Human Trisome Project, a whole-blood RNA-seq dataset generated by single-cell sequencing assessed the impact of overexpression of inflammatory cytokine genes.[115] Individuals with DS showed elevated cytokines, chemokines, and macrophage inflammatory protein-beta levels.[116] In line with this, DS is described as an interferonopathy,[3] in addition to impairment in cognitive functions, associative learning, and spatial memory.[117,118] Chronic hyperactivity of the interferon system was hypothesized to exacerbate neuroinflammation in trisomic CNS cells and may lead to more severe neurological outcomes, as observed in COVID-19–infected DS individuals.[116]

DYRK1A plays key roles in cellular stress-response pathways through involvement of *Sirtuin 1* (*SIRT1* at 10q21.3). *SIRT1*, a NAD-dependent class 3 histone deacetylase, deactivates stress response proteins, such as NF-kB, HIC1, p53, and DNA damage response factors, and maintains cell survival and genomic stability by activating intricate signaling cascades. *DYRK1A*, as a kinase, deacetylates *p53* and deactivates its transcriptional capacity via phosphorylation of *SIRT1*. In line with this, *p53* acts in a negative feedback loop to cross-talk with *DYRK1A* during DNA damage, degrading DYRK1A mRNA expression by activating transcription of miR-1246 (2q31.1). *p53* downregulates DYRK1A protein via indirect activation of MDM2 transcription to ubiquitinate *DYRK1A* and degrade its protein. Summarily, *DYRK1A* activates p53, and *p53* in turn downregulates *DYRK1A* in a negative feedback by activating its ubiquitination and inhibiting its transcription through miR-1246. Although *DYRK1A* phosphorylates *SIRT1* and attenuates *p53* activity, it can directly phosphorylate p53 at the Ser15 residue and enhance its transcription capacity in embryonic neuronal cells. Increased p53 activity lowers neuronal cell proliferation, thus perturbing brain development at the embryonic stage. In cancer cells, *DYRK1A*-activated *SIRT1* influences inhibition of *p53* through its deacetylation at Lys383 residue to sustain cell survival under genotoxic stress and reduce senescence. Activated p53 induces cellular senescence through downregulation of *DYRK1A* and *EGFR* (at 7p11.2). Under DNA damage, phosphorylation of *p53* by ataxia telangiectasia mutated at Ser15 activates DNA repair through cell cycle arrest by attenuation of the G1-S phase transition or apoptosis in case of repair failure. *DYRK1A* activates apoptosis signal-regulating kinase 1 through its phosphorylation, which

in turn activates MAP kinases (*JNK* and *p38α)* under cellular stress and induces apoptosis. *DYRK1A* activates phosphorylation of procaspase 9 at Thr125 residue in the nucleus, preventing its movement to the cytoplasm and auto-processing, leading to resistance to apoptosis.

DYRK1A participates in several signaling pathways, such as NFAT, Tau, cell cycle protein (Cyclin D1), splicing factor (Cyclin L2), tumor suppressor p53, and others. DYRK1A phosphorylates NFAT, leading to inhibition of calcium signaling and inactivation of NFAT (Fig. 1). Triplicated *DYRK1A* acts as a negative regulator of the calcineurin/NFAT pathway. Phosphorylation of NFATc proteins mediated by *DYRK1A* and GSK3β induces nuclear export of NFATc. Dephosphorylation of NFATs is controlled by activation of calcineurin, leading to their nuclear translocation. Inhibition of calcineurin lowers NFAT dephosphorylation and reduces the activity of NFAT transcription factors such as NFATc2, NFATc3, and NFATc4 in the nucleus in association with *RCAN1*. *DYRK1A* and *RCAN1* play synergistic roles in inhibiting calcineurin activity. Suppressed NFAT-dependent transcription leads to alterations in signaling pathways and gene expression associated with many DS features, including impairment in neurogenesis, neuronal proliferation and differentiation, and overall brain development.

DYRK1A can act as a transcription regulator for a wide spectrum of substrates and modulator of gene expression in many cellular pathways through phosphorylation and activation of various other transcription factors such as *STAT3, GLI1*, and CREB. *DYRK1A* influences survival of malignant cells by inhibiting pro-apoptotic signaling and decreases pancreatic β-cell proliferation in humans.[119,120] *DYRK1A* directly phosphorylates transcription factor CREB, stimulating subsequent CRE-mediated transcription during neuronal differentiation. It regulates development of dendritic trees of neurons via modulation of CREB action. *CREB* is involved in signal transduction pathways and controls synaptic plasticity and neuronal characterization.[42] Addition of basic fibroblast growth factor (a neurogenic factor) to H19-7 cells showed enhanced binding of *DYRK1A* specifically to active *CREB*. Perturbation of *DYRK1A* activation significantly inhibited neurite outgrowth and CREB phosphorylation.[96] Thus, activation of *DYRK1A* and subsequent phosphorylation of CREB is crucial for differentiation of hippocampal cells in the CNS. *CREB* contributes to formation of several types of synaptic plasticity, including long-term memory and learning. Trisomic *DYRK1A* can disrupt the transcriptional regulator neuron-restrictive silencer factor (*REST*/*NRSF*), leading to deregulated gene expression during neuronal development and maturation. *DYRK1A* localizes from cytoplasm to the nucleus during dendritic tree formation. *DYRK1A* enhances receptor tyrosine kinase signaling through phosphorylation of Sprouty homolog 2 at Thr75. Sprouty homolog 2 is a negative feedback regulator of multiple receptor tyrosines.

DYRK1A kinases are involved in modulation of dendritic development via regulation of Dynamin 1 (*DYN1*)-dependent vesicle trafficking. *DYN1* acts as a GTPase and a putative substrate of *DYRK1A* and is involved in recycling synaptic vesicles, clathrin-mediated endocytosis, trafficking of intracellular membranes, and neurite outgrowth.[8] *DYRK1A*-mediated phosphorylation of *DYN1* affects its function during dendrite differentiation, neurotransmission, and synaptic development. Notably, co-localization of *DYN1* with *DYRK1A* enhances DYRK1A transport through the growing dendritic tree.[37] *DYRK1A* contributes to regulation of the complex circuitry in the mature cerebral cortex, where 70% of the cells are pyramidal neurons.[4,121] Nevertheless, the contribution of the disrupted pyramidal phenotype to intellectual deficits could be exacerbated by various other dosage-sensitive genes of HSA21 and also non-trisomic genes of non-HSA21 origin.

Protein-protein interactions

DYRK1A protein interacts with 35 protein partners, with strong conservation of interactions across different tissues. Many of these interactors are associated with cell cycle regulation and contribute to neurodevelopmental disorders. In human neuronal stem cells, *DYRK1A* knockdown led to dysregulation of genes for proteins associated with calcium-binding proteins and extracellular matrix, such as COL3A1 and THBS2, which are involved in cellular adhesion and structure. These proteins mediate neural cell interactions and maintain the balance between proliferation and differentiation during brain development.[87] Upregulated *DYRK1A* interacts with synapsin (*SYN*) 1, resulting in *DYRK1A*-mediated phosphorylation of *SYN1* (at S551 residue; both *in vitr*o and *in vivo*) and contributes to *SYN1*-dependent presynaptic vesicle trafficking. *SYN1* is associated with tethering presynaptic vesicles and the actin cytoskeleton. *DYRK1A* activates calcium/calmodulin-dependent protein kinase II (*CAMK2*) to phosphorylate *SYN1* and release the vesicle pool. Proteomic analysis indicates that deregulated *CAMK2* leads to LTP via a glutamatergic postsynapse cascade. Interaction of DYRK1A protein, CAMK2, and other critical proteins of the postsynaptic density complex (PSD), such as SYNGAP, NR2B (a subunit of the glutamatergic postsynaptic NMDA receptor), and PSD95, demonstrates the presence of CAMK2A, NR2B, and PSD95 in the immunoprecipitates of DYRK1A. TgDyrk1A mice with upregulated *Dyrk1A* exhibited deregulated Amphiphysin (a protein known to inhibit *DYRK1A*) and hyperphosphorylation of *SYN2* (a paralog of *SYN1*). In addition, *DYRK1A*-mediated phosphorylation of MUNC18-1 resulted in dysregulation of a major sub-network of biological cascades in mouse models. Interaction of MUNC18-1 with the SNARE complex protein (Syntaxin 1A) reduces its hippocampal transcripts in Dyrk1A$^{C/C}$ mice. Altogether, triplication of HSA21-gene dosage might result in up- or downregulation of synaptic proteins crucial for normal spine development in individuals with DS.

DYRK1A may phosphorylate and regulate expression of Cyclin D1 (for G1/S phase transition and cell proliferation) and p27 (for neuronal differentiation and cell cycle exit) (Fig. 1). The level of Cyclin D1 protein is decreased at various developmental stages in TgDyrk1A mice (e.g., E11.5 and E14.5) due to nuclear export of Cyclin D1 mediated by 1.5-times higher DYRK1A protein levels. Furthermore, arrest of more neuronal cells at G1/G0 phase versus S or G2/M phase caused by overexpression of *DYRK1A/Dyrk1A* results in perturbation of cell proliferation and differentiation due to premature cell cycle exit and nuclear export of Cyclin D1.[122] Recovery of neuronal progenitors, enhancement of neuronal proliferation, and Cyclin D1 levels were achieved by normalization of *Dyrk1A* copy number at different developmental stages. Inappropriate hippocampal neurogenesis mediated by hyperphosphorylation of Cyclin D1 resulted in significant elevation of DYRK1A mRNA and protein levels at P6, with a prevalence in females.[98] In general, sex-specific differences in DYRK1A expression (both mRNA and protein) may be caused by genome-wide transcription dysregulation due to HSA21 dosage imbalance, which may be further exacerbated by sex chromosome complement.[123] Although both the nucleus and cytosolic environment host substrates for DYRK1A phosphorylation (specific for different tissues at different developmental time points), the location of intracellular DYRK1A phosphorylation and involvement of specific cell types (pyramidal cells, neurons, or Purkinje cells) remain less understood.

Variable DYRK1A mRNA and protein levels in different tissues at different developmental stages could be explained by translation lag or posttranscriptional regulation.

Interaction of DYRK1A with APOE

Although APOE is the strongest genetic modifier of LOAD, its interaction with *DYRK1A* or other HSA21 genes leading to increased AD risk seems less pronounced in DSAD compared to sporadic AD. Besides lipid transport as its primary function, ApoE has been reported to influence multiple biological mechanisms. *APOE ε4* predominantly increases the risk of DSAD via Aβ aggregation, p-tau pathogenesis, and neuroinflammation, alongside its influence on cerebrovascular integrity and protection from lipid peroxidation, autophagy, and ferroptotic cell death.[86,124] Interestingly, significantly lower levels of *DYRK1A* were observed in individuals with sporadic AD carrying the *APOE ε4* genotype compared to carriers of *APOE ε2* or *APOE ε3*. Notably, *APOE ε2* is associated with a protective effect on AD: it reduces the risk of AD and delays dementia onset. This effect was observed in DS- and non-DS populations carrying APP gene mutations.[125]

Overall, the interaction of *APOE ε4* appears highly complex in DSAD in the presence of triplicated *DYRK1A*; however, the mechanism itself is less understood and under investigation. Therefore, further study of *DYRK1A*'s role in DSAD pathogenesis, particularly its relationship with APOE and the underlying pathomechanism, may reveal novel therapeutic targets.

Therapeutic targets for DYRK1A inhibition

The link between hypo- and hyper-expression of DYRK1A with various diseases, including neurodegeneration, cancers, and diabetes, has drawn great attention to *DYRK1A* as a potential therapeutic target for ameliorating *DYRK1A* effects (Table 1).[126] Over the past decades, the identification of *DYRK1A* inhibitors has become a major focus for mitigating cognitive deficits in individuals with DS, AD, and DSAD. A number of *DYRK1A* inhibitors have been identified from different sources (Table 3). These inhibitors act by competing with adenosine triphosphate (ATP) at its catalytic site.[100] Notably, targeted inhibitors of *DYRK1A* gene and protein have controlled the upregulated *DYRK1A* expression and improved neurogenesis and cognitive performance in mouse models, DS adults, or in *in utero* treatment.[127] Intervention with selective *DYRK1A* inhibitors reduced the level of APP metabolites in Ts65Dn mice and improved learning and memory in this strain. Inhibition of *DYRK1A* expression rescued the altered NEP activity, suggesting *DYRK1A* inhibitors as potent therapeutic targets for both adults with DSAD and sporadic AD cases. Three mouse models of AD (3xTG-AD, APP/PS1, and Aβ25-35) showed improved cognitive skills via inhibition of *DYRK1A* expression.[23,128] Thus, the identification of potent *DYRK1A* inhibitors for therapeutic intervention was targeted to ameliorate the cognitive deficits manifested in several clinical disorders, especially DS and AD. Notably, the majority of DYRK1A inhibitors are ATP-competitive and have limited specificity for a single kinase.

Natural products

Several natural products, including epigallocatechin gallate (EGCG) and other flavonols, harmine and its analogues (β-carbolines), indolocarbazoles (staurosporine, rebeccamycin, and their analogues), leucettines, benzocoumarins, quinalizarine, and the peltogynoids acanilol A and B, have been recognized as potent inhibitors of *DYRK1A*.[29,126] Flavones act as DYRK1A inhibitors, with hydroxyl moieties contributing to a systematic and rational modification of their interaction with *DYRK1A* at its ATP-binding pockets.[129]

EGCG

The polyphenols were proposed to regulate the expression of the T21 genes and their effects on DS pathogenesis, including *DYRK1A*. Clinical studies with EGCG (since 2010), a flavonoid class of polyphenol present in the extract of green tea (*Camellia sinensis;* IC50 = 330 nM), protect against brain defects induced by overexpression of *DYRK1A* and demonstrated its therapeutic potency as a potent *DYRK1A* inhibitor with safety in human DS.[99] EGCG exhibits low specificity as it also inhibits p38-regulated/activated kinases, which hinders its claim as a strong inhibitor of *DYRK1A*. Simultaneous modulation of multiple systems was achieved in prenatal EGCG treatment in Ts65Dn mice. Oral EGCG (2–3 mg/day) administration to Ts65Dn mice improved cognitive performance and structural development, suggesting normalization of DYRK1A action.[127,130] A double-blind, randomized, placebo-controlled phase II trial displayed improvement in general cognition and adaptive behavior with a 9 mg/kg/day oral dose over one year in DS adults.[131] Similarly, improvement in neuropsychological and behavioral aspects was observed in a child with DS with dietary supplementation of 10 mg/kg/day of EGCG combined with omega-3 fish oil (8 mg/kg/day) over six months, without any adverse effects.[38] However, EGCG treatment failed to correct many DS phenotypes, and the age of EGCG treatment resulted in variable outcomes in Ts65Dn mice. Prenatal treatment altered the expression of trisomic neural crest cells at embryonic age and normalized some craniofacial features and the cranial vault in adult mice of the Ts65Dn strain.[132] Another prenatal exposure reversed neurogenesis and reduced cognitive defects[23]; however, these effects did not persist following discontinuation of treatment for a month after birth.[97] Additionally, relatively high doses of EGCG (10–50 mg/kg/day) appeared harmful, and treatment at the early postnatal stage failed to improve cognition. On the contrary, the treatment induced skeletal and facial abnormalities in Ts65Dn mice.[133,134] Thus, EGCG treatment aggravated many trisomic phenotypes, such as neuro-impairment and adult cognition, which did not support chronic prenatal therapy with EGCG.[24] Nevertheless, EGCG-like non-competitive inhibitors appeared effective for prenatal treatment of DYRK1A-related developmental pathologies in DS models such as Dp(16)1Yey.[135–137]

The non-specific nature of EGCG action has been hypothesized to depend on age at treatment, dosage, and duration of treatment, which could improve cognitive ability and avoid untoward adverse effects. Notably, treatment with pure EGCG in Ts65Dn mice did not significantly improve behavioral performance. Evaluation of various testing modalities revealed decreased swimming speed, cortical bone structure, and strength.[136] The co-existence of other catechins in the green tea extract, such as epigallocatechin, epicatechin (EC), and epicatechin-3-gallate, highlighted the better bioactive potential of EGCG, as observed in elevated plasma levels.[137] Treatment with pure EGCG without these catechins failed to produce its therapeutic potential, particularly for growth and skeletal features of Ts65Dn mice, suggesting empirical support for prenatal EGCG intervention to target specific neural circuitries.[23]

Chronic prenatal administration of EGCG extract enriched with major catechins lowered inhibitory biomarkers and restored VGAT1/VGLUT1 balance in transgenic mice (mBACtgDyrk1A) containing triplicated *Dyrk1A*.[23] The treatment recovered the density of GAD67 interneurons in the cortex of adult Ts65Dn mice. This result was comparable to the interneuron density and GABA-/glutamatergic markers observed in the Dp(16)1Yey strain. EGCG

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Table 3. Inhibition of *DYRK1A* expression for therapeutic targets (reconstructed from ref.# 35, 38)

***DYRK1A* inhibitors (conc., mode of administration)**	**Test models**	**Behavioral tests**	**Alteration in *DYRK1A* expression**	**Outcome**
Genetic correction				
Thymidine Kinase and Neomycin Resistance (TKNEO) fusion transgene (via an altered adenovirus)	Trisomic induced pluripotent stem cells (iPSCs)	Incorporation of fusion transgene (TKNEO) at 21q21.3 of APP in one of the 3 HSA21	Complete loss of one the HSA21 in 20/30 clones; one DYRK1A is lost spontaneously	Other clones showed TAKENO deletion/ point mutation/epigenetic silencing; disomic chromosomes unaffected; faster proliferation in disomic cells
Insertion of XIST gene in at 21q22 obtained from male DS	Trisomic iPSCs	Incorporation of XIST at DYRK1A locus in one of the 3 HSA21	~85% of the cells showed inactivation of one HSA21	One heterochromatinized HSA21 like Barr body; no effect on other chromosomes; female DS spontaneously doesn't inactivate the extra HSA21
ZSCAN4 (zinc finger and scan domain) encoded in Sendai virus	Trisomic iPSCs	Genetic manipulation of the trisomic cells	~24–40% cells showed normal karyotype within few weeks	Embryonic stem cell-specific transcription factor ZSCAN4 necessary for maintaining pluripotency and genomic stability in embryonic stem cells; regulates telomere elongation
Long-term maintenance of independent iPSC lines developed from trisomic fetus	Trisomic iPSCs	Spontaneous development of diploid cells with disomic karyotype	~70 week-old cultures showed downregulation of DYRK1A, SOD1, ETS2, APP, and DSCR1 in 2/3rd of the cells diploid cells	Spontaneous reversion of trisomy to disomy could be resulted from mitotic nondisjunction occurred in long-term (70-week) culture of iPSCs
Normalization of *Dyrk1A;* ^{m1}- disruption of kinase domain	Dp1Tyb$^{+/+}$/Dyrk1A KO vs Dp1Tyb$^{+/+/+}$ vs WT; Dp(16)1/Dyrk1A^{m1} vs Dp(16)1/$^{+}$; cross breeding of Ts65Dn with Dyrk1A$^{+/-}$ vs Ts65Dn	Object in place test; T-maze, fear conditioning; MWM/ contextual and fear conditioning	-	Corrects discrimination ratio; performance and LTP improved but lower than WT; enhanced spatial working, contextual fear conditioning and reference memory/decreased thigmotaxis/partial recovery of contextual conditioning/LTP recovery/ fear conditioning unchanged
AAV2/1-shDyrk1A (stereotaxic injection of AAV2/1 virus – ShDyrk1A in the hippocampus)	Ts65Dn	Morris water maze (MWM)	DYRK1A expression normalized	Enhanced hippocampal LTP/partial recovery of search strategy/decreased thigmotaxis/upgraded synaptic plasticity
AAV-shDyrk1A (stereotaxic injection of AAV virus – ShDyrk1A in the hippocampus)	Tg(*Dyrk1A*)	Locomotor activity/treadmill performance/ startle reflex	DYRK1A expression reduced	Motor alterations reduced
Natural/synthetic products and derivatives				
EGCG (~3 mg in water/day × 5 months)	Ts65Dn	MWM	3R/4R-Tau elevated	Recovery of anxiety & attenuated memory deficits

(continued)

Table 3. *(continued)*

***DYRK1A* inhibitors (conc., mode of administration)**	**Test models**	**Behavioral tests**	**Alteration in *DYRK1A* expression**	**Outcome**
EGCG (ad libitum ~1 mg/day), caffeine, catechins (polyphenon, 0.8 g/L or 1.2 mg EGCG/day), p.o.	YAC152F7 (with extra copies of 5 genes, incl. DYRK1A)	MWM, Y-Maze, NOR		Reduced cognitive deficits
EGCG/Mega green tea extract (2–3 mg/day in drinking water × 1 month)	Tg(Dyrk1A); Ts65Dn	MWM, NOR	Normalized DYRK1A expression	Rescued thigmotaxia, learning deficits and memory impairments
Decaffeinated EGCG (enriched) (50 mg/kg in food pellets × prenatal administration)	Tg(Dyrk1A)	NOR		Improved recognition memory
Environmental enrichment (EE); EGCG (2–3 mg/day; 90mg/mL in drinking water × 1 month)	Tg(Dyrk1A)	MWM	EE/EGCG normalized hippocampal DYRK1A expression	EE/EGCG improved spatial learning; EE rescued neurogenesis in adults
EGCG±Ferulic acid (β-secretase modulator) (30 mg/kg, p.o. × 3 months, single or mixed)	APP/PS1	RAWM, Y-Maze, NOR	Lowered β-amyloid deposits; reduced neuroinflammation, oxidative stress * synaptotoxicity; Shift towards non-amyloidogenic APP processing	Corrected episodic memory impairment, Rescued anxiety-like behavior; Improved spatial working memory; Remediated spatial reference memory and learning
EGCG (25 mg/kg)±Urolithin A (2.5 mg/kg) i.p., 3 days/week × 4 months	Humanized Aβ knock-in mouse	Rotarod, OF, Y-maze, MWM	Lowered mitochondrial dysfunction; reduced Aβ40 & Aβ42; EGCG+Urolithin A showed better outcome than Urolithin A alone	Improved motor coordination & locomotion/exploratory function, spatial learning and working memory
7cc, an EGCG derivative (40 mg/kg for 5 days/week × 2 months)	Dp1Yey	Y-maze	–	Deficit in spatial working memory corrected
Harmine (IC50 = 80 nM) and β-Carboline analogues (10 µM × 1 week)	*Drosophila melanogaster*	Overexpressed minibrain	Orally bioavailable; Inhibit serine/threonine phosphorylation of DYRK1A by competing its ATP binding; strong inhibitor of monoamine oxidase A (MAO-A); inhibit DYRK1A-mediated phosphorylation of *tau* protein	Decreased wing defect; hallucinogenic properties acting as a CNS stimulant; cancer therapy: induce human *β*-cell proliferation; inhibit topoisomerase I, CDKs, induce cell apoptosis and DNA intercalation
PST-001 (334 µM)/DYR219 (304 µM)/DYR533 (284 µM)	*Drosophila melanogaster*	Overexpressed hTau 4R, human amyloid Aβ42 or minibrain; T-maze	Reduced Tau-phosphorylation	Decreased eye degeneration; Increased lifespan; Corrected motor deficits & sleep loss; Rescued memory
Aristolactam BIII (10 µM × 2 weeks)	*Drosophila melanogaster*	Overexpressed *minibrain*	–	Rescued wing defect, impaired neurogenesis &*MNB*+Tau-induced eye defect

(continued)

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Table 3. *(continued)*

***DYRK1A* inhibitors (conc., mode of administration)**	**Test models**	**Behavioral tests**	**Alteration in *DYRK1A* expression**	**Outcome**
CX-945 (10–100 nM × 2 weeks)	*Drosophila melanogaster*	Overexpressed *minibrain* ± Tau	–	Corrected wing and eye defects
ProINDY (2.5 µM) 4 days)/ Leucettine L41 (2 µM × 4 days)/ KuFall194 (10 µM × 4 days)	Zebra fish (*Danio rerio*)	Upregulation of Dyrk1A in cerebellar Purkinje neurons	–	Reversed neuronal phenotypes
ProINDY (2.5 µM & mRNA injection in embryonic blastomeres)	*Xenopus levis*	xDyrk1A or normal xDyrk1A-K180 R mRNA injection	–	Corrected eye and brain deformities
Aristolactam BIII (1, 10, 30 mg/kg, p.o)	Tg(*Dyrk1A*)	OF	–	Decreased Tau phosphorylation, & locomotive and exploratory behavior improved
Leucettines (L41-20 mg/kg, i.p., 5/12/19 days; L92-0.3 mg/kg, p.o. × 10 days; L10-3 mg/kg, p.o., 10/19 days)	Tg(*Dyrk1A*)	NOR; OF, NOR	–	12/19 days treatment recovered NOR fully; repaired spatial and recognition memory defects
Leucettines (L21-0.3/3/6/20 mg/kg, p.o., × 11 days; L92-0.3 mg/kg, p.o., × 11 days)	Dp(16)1Yey	NOR	–	Repaired recognition memory defects
Leucettines (L99–20 mg/kg, i.p., 5/12/19 days; L21-0.4 mg/kg, p.o., × 10 days)	Ts65Dn	NOR	L-99 normalized DYRK1A activity	12/19 days treatment recovered NOR fully; repaired recognition memory defects
Leucettines (L41-1.3/3.9/13 nmols; L10-0.6/3/15 mg/kg, p.o., × 18 days; L92/L21-0.03/0.3/3 mg/kg, p.o., × 18 days; L41-20 mg/kg, i.p., × 18 days	Aβ25-35 injected ICV	PAT/MWM; Y-maze/ NOR; Y-maze	L41 arrested Aβ25-35-induced GSK3β activation and Tau phosphorylation (Ser202/ Thr205), and reduced oxidative stress in hippocampus	L41: Stopped memory impairments (spatial/non-spatial, short-/long-term) and interrupted synaptic integrity; L41-i.p.: recognition memory deficits repaired; L10/L92/L21: Spatial working memory improved

Minibran is the human DYRK1A homolog in Drosophila. AAV 2/1, Adeno-associated virus serotype 2/1; APP, amyloid precursor protein; ATP, adenosine triphosphate; CDK, cyclin-dependent kinase; CNS, central nervous system;

treatment (IC50 = 0.3 μM) recovered LTP defects in CA1-CA3 pyramidal neurons in the Ts65Dn strain and in the neocortex of transgenic mice, suggesting EGCG as a non-competitive inhibitor of *DYRK1A* kinase.[135] Notably, treatment from gestation to adulthood in a transgenic mouse model for human *DYRK1A* resulted in recovery of cognitive deficits measured in the NOR test and molecular levels of brain-derived neurotrophic factor. Expression of *Dyrk1A* in the telencephalon at E11.5 and in the brain at E15.5 in trisomic mice justifies EGCG treatment at prenatal age.[98] The stability of these changes can be measured in adulthood following prenatal administration. Prenatal age appears crucial for GABAergic interneurons. Acute EGCG treatment positively modulated GABA-A-mediated transmission.[23] In this line, the TESDAD clinical trial (NCT01699711) with dietary EGCG supplementation showed some behavioral improvements and partial rescue of cognitive defects in young adults with DS, though the clinical relevance remained below threshold levels. EGCG cannot effectively cross the blood-brain barrier (BBB), and its antioxidant properties or interactions with other proteins may contribute to the beneficial effects of EGCG therapy.[97] Altogether, EGCG treatment showed variable results in different models.

Harmine

Harmine, a natural β-carboline alkaloid isolated from the plants *Banisteriopsis caapi* and *Peganum harmala* L. (a South American vine; Family: Zygophyllaceae), is most widely used in preclinical research studies as a *DYRK1A* inhibitor (IC50 = 80 nM); however, its lack of kinase selectivity does not justify clinical consideration. Harmine and its derivatives inhibit serine/threonine phosphorylation of DYRK1A by competing with its ATP binding. It is used as a scaffold for identifying *DYRK1A* inhibitors with higher potential for kinase selectivity. Harmine also acts as a strong inhibitor of monoamine oxidase A and other DYRK family members (*DYRK2*, IC50 = 0.9 μM, and *DYRK3*, IC50 = 0.8 μM); thus, many derivatives have been targeted to enhance its selectivity for *DYRK1A* in different cell types.[138,139] Its higher doses can produce Parkinsonian-like and hallucinogenic effects. Harmine induced apoptosis in neuroblastoma cell lines.[140,141]

Breitfussin C

Inhibition of *DYRK1A* with Breitfussin C (a family of halogenated compounds with a novel indole-oxazole-pyrrole molecular scaffold; isolated from the Arctic marine hydrozoan invertebrate *Thuiaria breitfussi)* reduced phosphorylation of p27. Breitfussin C plays a pivotal role in the regulation of cell cycles and proliferation by arresting the G0/G1 phase and post-translational modifications. *DYRK1A* stabilizes p27 activity, which subsequently delays cell cycle progression.[120]

Extra virgin olive oil

Chronic consumption of extra virgin olive oil controlled neuroinflammation, memory dysfunction, and synapse function deficiencies in the Ts65Dn mouse model.[142,143] Extra virgin olive oil is enriched with phenolic compounds, such as oleuropein, tyrosol, and hydroxytyrosol, which contribute to its anti-inflammatory and antioxidant properties. Olive oil possesses no direct effect as a DYRK1A inhibitor; however, further studies might investigate whether any of its phenolic compounds have indirect effects on DYRK1A activity or whether they could serve as scaffolds for developing DYRK1A inhibitors.

Aristolactam BIII

Aristolactams, a group of aporphinoid natural alkaloids, are generally present in herbs, including Annonaceae, Aristolochiaceae, Menispermaceae, Monimimaceae, and Piperaceae. These alkaloids contain a phenanthrene chromophore; however, limited information is available about their biological activities. Aristolactam BIII, one such natural extract, acts as a novel *DYRK1A* inhibitor, inhibiting the kinase activity of *DYRK1A in vitro* (IC50 = 9.67 nM) and effectively suppressing DYRK1A-mediated tau hyperphosphorylation in neuronal cells of transgenic mice. It could normalize proliferative defects in transgenic-mouse-derived fibroblasts via cyclin D1 regulation, as well as neurological and phenotypic abnormalities in DS-like Drosophila models.[144] In addition, Aristolactam BIII significantly enhanced exploratory behavior in transgenic mice in the open field test. Altogether, Aristolactam BIII was observed as a potent *DYRK1A* inhibitor and a novel therapeutic candidate for ameliorating DS characteristics and other *DYRK1A*-related diseases, including cancer.

Other natural compounds

Leucettines, obtained from the marine calcareous sponge *Leucetta microraphis*, are potent in recovering cognitive deficiency in DS models; however, they may react with biological nucleophiles and produce adverse effects.[101] Acrifoline, extracted from the stem bark of *Glycosmis chlorosperma,* acts as a potent inhibitor of *DYRK1A in vitro*. However, it has yet to be validated in higher organisms of DS models.[145] Indole alkaloids (meridianins A–E) obtained from the marine tunicate *Aplidium meridianum* of the South Atlantic region have been demonstrated to confer significant inhibitory activity against *DYRK1A* (IC50 ≈ 80 nM); however, they are sparingly soluble in water.[146] Several synthetic derivatives of these natural products are considered useful for *DYRK1A*-targeted therapeutics, such as leucettines.

Synthetic compounds as DYRK1A inhibitors

Several synthetic compounds have been identified as DYRK1A inhibitors.[147] Dyrk1A-IN-5 (compound 5j) exhibited inhibition of phosphorylation at Thr212 (IC50 = 2.1 μM) in HEK293 cells, and Thr434 (IC50 = 0.5 μM) in Tau and SF3B1 in human HeLa cells, respectively, suggesting Dyrk1A-IN-5 as a selective DYRK1A inhibitor for DS research.[148] Bioinformatics-based computational drug discovery has identified small molecule inhibitors of DYRK1A, such as INDY derivatives, leucettine derivative L41, analogues of naturally occurring (aza) indolic compounds (meriolins, lamellarin), GNF4877, F-DANDY, FINDY, amino-quinazolines, pyrazolidine-diones, pyridine and pyrazines, chromenoindoles, 11H-indolo(3,2-c)quinoline-6-carboxylic acids, CC-401, 5-iodotubercidin, thiazolo[5,4-f]quinazolines (EHT 5372), indole-3-carbonitriles, thiadiazines, and others (Table 3). INDY, developed by Ogawa *et al*.,[149] was the first DYRK1A inhibitor tested in animal models to control overexpression-induced deformities. Prenatal stress-mediated cognitive impairment was improved by an antagonist of glucocorticoid receptors, RU486,[129] indicating a possibility of similar outcomes in people with DS. ZINC08300244 and ZINC08964763, identified from the ZINC database through virtual screening of natural bioactive compounds, displayed high *DYRK1A*-specific binding affinity and suitable pharmacokinetic properties.[150] Their complex binding with *DYRK1A* was proposed to prevent tau hyperphosphorylation and neuroinflammation, suggesting their potential as small-molecule inhibitors of *DYRK1A*.

Leucettine L41

Treatment with leucettine L41 (a natural alkaloid available in *Leucetta microraphis*) normalized *DYRK1A* expression and rescued

NOR impairment in three transgenic mouse models (Tg(Dyrk1A), Ts65Dn, and Dp1Yey).[101] Leucettine L41 efficiently stopped memory impairment in DS mice induced by the β-amyloid peptide $A\beta_{25-35}$.[151] The outcome suggested a likelihood of pharmacological recovery of cognitive defects in the DS population with this *DYRK1A* inhibitor; however, similar results have yet to be achieved in human DS. L41 could inhibit proteolysis of DYRK1A in APP/PS1 mice. In addition, L41 could rescue synaptic and memory deficits in APP/PS1 mice by reducing STAT3α-phosphorylation and improving microglia recruitment to Aβ plaques.[152]

GSK3β

GSK3β shows low ATP-binding site similarity with DYRK1A, indicating the non-existence of direct competitive inhibitors between the two, which can be explained by the higher intensity of water molecules in the C region of GSK3β's binding site compared to DYRK1A. However, they share similar signaling pathways, such as Wnt and Tau phosphorylation, suggesting them as potential targets for diseases associated with dysregulated Wnt and Tau phosphorylation. In addition, similar inhibitory potency of Staurosporine (a non-selective kinase inhibitor) for both GSK3β and DYRK1A further indicates the inhibitory potential of a single molecule for both kinases. Altogether, similar signaling and inhibition profiles potentially offer the design of dual-target (GSK3β and DYRK1A) inhibitors as a more prospective therapeutic approach for diseases involving both kinases, such as AD and DSAD. The GSK3β inhibitors, such as AZD 1080 and SB-415286, showed potential for *DYRK1A* inhibition, which was better achieved by SB-415286.[121]

KuFal194

A selective *DYRK1A* inhibitor, KuFal194, rescued the structural misorganization of the Purkinje cell layer in larval and adult brains of a zebrafish model of DS. The result was comparable to ProINDY and leucettine L41, though at two- to four-fold higher concentrations (5 and 10 μM).[153] However, its efficacy is questioned specifically for lowering *DYRK1A* hyperactivity *in vivo* due to reduced solubility in aqueous solutions and average cellular uptake, which is predicted to be overcome by its use as a food additive. KuFal194 appeared efficient as a starting-point treatment to mitigate neurological deficits in DS-like diseases.

7cc

An EGCG analogue, 7cc, was demonstrated to be effective for the treatment of AD at stages when triplicated DYRK1A induces phosphorylation of Tau protein.[17,136] Free hydroxyl groups were demonstrated as necessary for *DYRK1A* inhibition, while methoxy analogues appeared 100 times less active *in vitro*. Effectiveness of a two-week treatment with F-DANDY as a *DYRK1A* inhibitor was reported in a DS mouse model.

Other synthetic DYRK1A inhibitors

DYR291, a synthetic DYRK1A inhibitor, had a hybrid structure of several natural and synthetic compounds, such as harmine, the benzothiazole-derivative INDY, and the imidazole-derivative D15. DYR291 was effective for improvement of memory and learning impairments in 3xTg-AD mice. Its chronic administration at the early stage of AD could prevent AD trajectories such as tau pathogenesis, Aβ accumulation, and NFTs, suggesting its preventive capacity against AD pathology. Another ATP-competitive inhibitor of DYRK1A, Silmitasertib (CX-4945), exhibited higher inhibitory potency on tau hyperphosphorylation in the hippocampus of DS mice compared to harmine and INDY. In addition, its potency to rescue the neurological defects in *mnb*-overexpressing *D. melanogaster* indicated Silmitasertib as a targeted *DYRK1A* therapeutic.[154] PST-001, a benzothiazole molecule, acts as a very selective inhibitor of DYRK1A. Notably, its powerful characteristics include being non-toxic, orally available, having high bioavailability, and good pharmacokinetics. Its BBB-penetration capacity enabled high-end *in vivo* studies in Ts65Dn mice, including enhancement of learning and memory in the contextual discrimination task. A continuous intake of 100 mg PST-001/kg through the animal food revealed 1.25 μmol/g of tissue. Furthermore, PST-001 showed no synergistic or antagonistic effects with the anti-AD drug memantine. However, the lack of preclinical evaluation does not confirm that the improvement in contextual fear conditioning in Ts65Dn mice was certainly due to its DYRK1A-inhibition potency.[148] SM07883, an oral *DYRK1A* inhibitor (IC_{50} = 1.6 nM), has been tested in mouse models for inhibition of tau hyperphosphorylation (at the threonine 212 site), Aβ aggregation, NFT formation, neuroinflammatory effects, and development of associated phenotypes. It also acts as an inhibitor of GSK-3β (IC_{50} = 10.8 nM) kinase activity. SM07883 appeared as a potent brain-penetrant DYRK1A inhibitor with good oral bioavailability, significantly reducing tau pathology and neuroinflammation.[155] This small-molecule DYRK1A-mediated AD inhibitor has been considered for clinical trials.

Targets of folding and proteolysis of DYRK1A

DYRK1A has auto-phosphorylation capacity during its translational process and maturation. FINDY, a rhodamine derivative compound, is capable of inhibiting DYRK1A auto-phosphorylation at the Ser27 residue and interfering with ATP incorporation through the folding of intermediates. Such folding errors subsequently result in degradation of DYRK1A protein. Thus, FINDY actually inhibits DYRK1A during its synthesis, not after maturity. It could rescue the developmental defects in embryos of *Xenopus laevis*. In this direction, the hippocampus of AD patients showed a reduction in full-length DYRK1A with an increase in truncated DYRK1A, suggesting another way of DYRK1A inhibition by targeting its proteolysis. Truncation of DYRK1A increases its affinity to STAT3α *in vitro*. STAT3α is associated with transcription of pro-inflammatory cytokines. These studies showed that identification of targets of DYRK1A folding and/or proteolysis might be challenging to reduce *DYRK1A*-mediated AD risk and neuronal impairments.[29,154]

miRNA as DYRK1A inhibitor

miRNAs, the short non-coding RNAs, regulate gene expression by targeting mRNAs of specific genes and inducing degradation of such mRNAs. Many miRNAs have been implicated in several human diseases. Thus, miRNAs have increasingly been considered in phase 1 and 2 clinical trials to identify novel therapeutic approaches, and also as targets of *DYRK1A* mRNA. The chromosome 2q31.1-encoded miR-1246 is a miRNA that targets DYRK1A mRNA through the p53 transcription factor. Thus, enhancement of miR-1246 expression was hypothesized to be a possible mechanism to treat overexpressed *DYRK1A*-mediated p53-null tumors. In line, miR-199b (9q34.11) acts as a potential candidate to downregulate *DYRK1A* mRNA; thus, its enhancement could inhibit DYRK1A in neurodegeneration and other *DYRK1A*-overexpressed diseases. In addition, upregulation of the 9q21-encoded miR-204-5p was observed in patients with Parkinson disease, indicating its association with AD risk. miR-204-5p may also be involved in the enhancement of apoptosis and hyperphosphorylation of tau and

α-synuclein through activation of the JNK pathway and upregulation of *DYRK1A*, leading to the loss of dopaminergic neurons.[151] Thus, inhibition of miR-204-5p could benefit DYRK1A-mediated neurodegeneration in AD and DSAD.

Synthetic preimplantation factor (sPIF)

Prenatal treatment with a sPIF from gestation until weaning restored *DYRK1A* levels and early postnatal hippocampal neurogenesis in the Dp(16)1Yey mouse model, while perinatal sPIF treatment improved working memory in the adults of this strain.[131] The pups displayed impairments in behavior, neurogenetic mechanisms, and dysregulation of genes linked to regulation of the cell cycle and neuroinflammation. Alongside, the treatment restored cyclin D1, brain-derived neurotrophic factor, S100β, and GLI2 levels, lowered GSK3 activity, and enhanced c-myc level and mTOR activity in this strain. The epistatic interactions with several trisomic and disomic genes, including S100β, GLI2, cyclin D1, and the GSK3/mTOR pathway, resulted in deregulation of genes linked to neuroinflammation and cell cycle regulation.

Antagonists of glutamatergic and GABAergic receptors

Antagonists of glutamatergic and GABAergic receptors have demonstrated cognitive improvement in individuals with DS.[38] GABA antagonists rescued hippocampal LTP in Ts65Dn mice following acute or chronic treatment.[156] Different strategies of treatment—viz., acute application of the GluN2B-selective antagonist Ro25–6981; chronic treatment with EGCG; monoacylglycerol lipase inhibitor JZL184; the neurohormone melatonin; the Sonic Hedgehog agonist SAG1.1; antidepressant antagonist of serotonin Fluoxetine; and exposure to enriched environment—rescued CA3–CA1 LTP and behavioral attributes in Ts65Dn mice.[157] Many of these tests exhibited modulation of the GABAergic mechanism as a direct or indirect effect. In contrast, treatment with Ro25–6981 did not decrease activation of GABAergic interneurons in the hippocampal stratum radiatum. Fluoxetine was proposed to improve cognitive ability in individuals affected by Vascular Cognitive Impairment No Dementia.[158] Perinatal administration of Fluoxetine increased cell proliferation and the number of neuronal cells in Ts65Dn mice. JZL184 lowered GABAergic transmission through alteration of presynaptic cannabinoid receptors.[159] Nevertheless, glutamatergic receptors may be targeted for correction of hippocampal glutamatergic dysfunction and behavioral impairments. A similar approach was proposed to suppress GABA's inhibitory role with inverse agonists or antagonists of GABAergic receptors, which can improve cognitive features in human DS and DS models.[104]

Inhibitors of neuroinflammation

Several other compounds indirectly contribute to ameliorating *DYRK1A* overexpression and DSAD pathogenesis. Four-week treatment with Resolvin E1 inhibited neuroinflammation and lowered pro-inflammatory cytokines in serum, along with a significant reduction in memory loss and hippocampal microglial activation in Ts65Dn mice.[160] A reciprocal link between the inflammatory and noradrenergic systems demonstrated the disease-modifying capacity of norepinephrine and β-adrenergic receptor agonists in DSAD.[161] Several preclinical studies with norepinephrine have described it as a partial agonist of the β1-adrenergic receptor associated with DS pathogenesis, suggesting the enhanced noradrenergic system as a meaningful therapeutic target for DSAD.[162] Norepinephrine activates clearance of Aβ peptide by microglia through involvement of upregulated formyl peptide receptor 2 and β2-adrenergic receptors in the mouse brain. In this direction, treatment with L-threo-3,4-dihydroxyphenylserine (a norepinephrine precursor with BBB penetration capacity) improved contextual learning, fear conditioning, and nest building; whereas treatment with Formoterol (a long-acting β2-adrenergic agonist) corrected cognitive deficits and reduced dendritic complexity in Ts65Dn mice.[104] Treatment with a β2-adrenergic receptor agonist revealed recovery of behavioral symptoms in the DS mouse model, which encountered norepinephrine loss. Trisomic dopaminergic and serotonergic neurons lead to a decrease in secretion of dopamine and serotonin with concomitant upregulation of their transporters. Thus, improvement in behavioral and cognitive impairments was proposed by blocking reuptake of dopamine and serotonin in individuals with DS.

Antisense oligonucleotides (ASOs)

Modulation of upregulated *DYRK1A* transcripts is proposed to be achieved by disruption of the reading frame by ASOs via induction of exon skipping, which will create nonsense-mediated decay of the transcript and diminish (~33%) the function of the overexpressed DYRK1A protein. The short (~12–30 nucleotides) ASOs are synthetic nucleic acid analogues and are used to alter gene expression by Watson-Crick base-pairing hybridization at complementary sites with high sensitivity and specificity.[163] Alteration of *DYRK1A* overexpression at the RNA level by ASO may achieve a highly effective treatment outcome for correction of intellectual disability and cognitive defects, which in turn may improve the overall quality of life of the DS population.[29] Many ASOs approved by the U.S. Food and Drug Administration displayed high specificity for treatment of several neurological disorders such as AD, Huntington's disease, myotonic dystrophies, and amyotrophic lateral sclerosis.

Genetic inactivation of DYRK1A

Further increases in efficacy and safety profile are expected with recent technologies involving peptide-conjugated phosphorodiamidate morpholino oligomers, compared to other targeted *DYRK1A* inhibitors.[29] Consistent with this line, iPSCs extracted from trisomic individuals were genetically modified to create a *DYRK1A*-knockout cerebral organoid model (scDYRK1AKO-COs) with a view to testing the dose response of several *DYRK1A* inhibitors during neurodevelopment for correcting neurodevelopmental phenotypes of DS.[164] Additionally, *in vitro* silencing of the extra HSA21 was successfully achieved through the introduction of the non-coding X-inactivation *XIST* gene into one locus of the triplicated *DYRK1A* on T21 in trisomic iPSCs. Most of the protein-coding genes on the *XIST*-containing chromosome 21 could be inactivated without affecting the expression of other genes located elsewhere in the genome.[165] The outcome of this audacious goal of inactivating protein-coding genes indicated the likelihood of technical success for *in utero* correction of trisomy 21 and/or other aneuploidies at the embryonic stage. Triplicated *DYRK1A* demonstrated a link with impairments in gonadotropin-releasing hormone function, which is involved in cognitive processes and reproductive functions in DS.[166] In the Ts65Dn mouse model, restoration of gonadotropin-releasing hormone rescued the hippocampal transcriptome and connectivity, and improved cognitive performance.[167]

Gene editing by clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 (CRISPR-associated protein 9) systems may destabilize triplicated *DYRK1A* expression and revolutionize therapeutics for diseases linked to hypo- and hyperexpression of DYRK1A, including DS and DSAD.[168] Differential

expression of *DYRK1A* at different developmental stages may result in tissue- and sex-specific phenotypes, and such developmental timelines of *DYRK*1A expression may necessitate differential gene- and expression-specific pharmacological targets. In reality, *DYRK1A* expression in trisomic cells may not necessarily follow the "1.5-fold upregulation rule"; compensatory mechanisms, their different classes, and their variable expression levels may differentially contribute to the development of DS characteristics.[15,98]

Overall outcome and future challenges

In total, *DYRK1A*-related neuro-impairment is a highly complex mechanism. Most small-molecule *DYRK1A* inhibitors have not gone beyond the *in vitro* stage of investigation and are thus yet to be considered for clinical trials testing cognitive improvements in human DS. Notably, three potential druggable DYRK inhibitors were included in clinical trials for various indications. These include: Leucettinib-21 for AD and DSAD Phase I (NCT06206824); SM07883 for AD Phase I (ACTRN 12619000327189); and FRTX-02 (VRN024219; BBI-02) for type 1 diabetes and atopic dermatitis Phase I (NCT05382819); however, only the Leucettinib-21 trial is being continued by Perha Pharmaceuticals.[17] In summary, EGCG has been demonstrated to be a potent allosteric inhibitor of *DYRK1A*, leading to improved cognitive performance in DS models.

Use of artificial intelligence and machine learning with computational biomarkers may identify more effective small-molecule inhibitors and develop promising therapeutics for neurodegenerative diseases, as evidenced in the differentiation of Parkinson's disease from normal individuals.[169–171] Advanced technologies have generated vast amounts of high-dimensional and complex data on gene expression, which are challenging and impractical for traditional approaches to understanding gene-phenotype associations. Application of artificial intelligence for deep learning and computational analysis may offer promising solutions to overcome these challenges. Therefore, implications of triplicated *DYRK1A* on specific brain cell-related phenotypic expression across a wider horizon may be attractive in future research. In addition, investigation of ApoE-based therapeutic strategies is necessary for the prevention or mitigation of AD in genetically at-risk populations, such as the DS population. Moreover, sexual dimorphism, in conjunction with comorbidities, demographics, and severity of neuropsychiatric symptoms, warrants extensive investigation to explore the potential underlying reasons for DSAD manifestation,[45] which will ultimately guide the identification of specific small molecules for inhibition of overexpressed DYRK1A.

Limitations of the study

This article reviews the therapeutic aspects of *DYRK1A* inhibitors in DS and DSAD. However, signaling systems of neurotransmitter, inflammatory, and oxidative stress pathways, as well as the influence of other genetic and epigenetic factors relevant to DS cognition, need to be explored and integrated into such reports. Therefore, future studies should focus on highlighting the gene–neurogenic association on a broader scale, with a view to identifying expression-specific inhibitors of genes in the translational therapeutics of DS research.

Conclusions

Of the 81 phenotypes characterized in the DS population, cognitive deficit and AD are common, with a variable extent of expression. However, molecular dissection of the HSA21 genes has yet to identify the specific gene(s) responsible for specific feature(s) of DS. Mechanistically, defects in neuro-differentiation during prenatal brain development have been demonstrated as the hallmark trajectories of cognitive defects and AD-related dementia in the DS population. Dysregulated *DYRK1A* due to triplication has been attributed to a significant degree of impairment in neurodevelopment and neurotransmission, and the subsequent expression of cognitive deficiency and AD-related features in the DS population. In addition, interaction of the triplicated genes with other trisomic and disomic genes leads to dysregulation of signaling pathways, culminating in disease onset, especially DSAD at an early age. Moreover, genetically determined AD often involves several co-pathologies, which complicate the disease mechanism and expand the overall disease landscape. AD autopsies frequently show several other neurodegenerative conditions (e.g., vascular dementia, Lewy body dementia), for which the biomarkers are less understood. Such complexity makes understanding the disease more challenging and complicates the analysis of factors involved in cognitive deficits, DSAD, and early-onset dementia. In this context, *DYRK1A* inhibitors are being increasingly considered as therapeutic targets to ameliorate DS-specific cognitive phenotypes in DS models developed *in vivo* and *in vitro* with HSA21 orthologs. In addition, understanding sexual dimorphism and the association of *APOE* in AD risk further complicates the basis of DS pathology and the treatment of DSAD. Identification of small-molecule inhibitors of *DYRK1A* overexpression has become a major challenge in therapeutic development for improving the quality of life of the DS population. Nevertheless, *DYRK1*A inhibitors, in relation to hypo- or hyper-expression of DYRK1A, may further delineate context-dependent therapeutic outcomes.

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Conflict of interest

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Author contributions

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