



Clinical and Neurobiological Aspects of TAO Kinase Family in Neurodevelopmental Disorders

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Despite the complexity of neurodevelopmental disorders (NDDs), from their genotype to phenotype, in the last few decades substantial progress has been made in understanding their pathophysiology. Recent accumulating evidence shows the relevance of genetic variants in thousand and one (TAO) kinases as major contributors to several NDDs. Although it is well-known that TAO kinases are a highly conserved family of STE20 kinase and play important roles in multiple biological processes, the emerging roles of TAO kinases in neurodevelopment and NDDs have yet to be intensively discussed. In this review article, we summarize the potential roles of the TAO kinases based on structural and biochemical analyses, present the genetic data from clinical investigations, and assess the mechanistic link between the mutations of TAO kinases, neuropathology, and behavioral impairment in NDDs. We then offer potential perspectives from basic research to clinical therapies, which may contribute to fully understanding how TAO kinases are involved in NDDs.

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INTRODUCTION

Neurodevelopmental disorders (NDDs) are a group of heterogeneous conditions that fail to acquire multiple proper developmental milestones involved in cognitive, emotional, and psychomotor skills caused by abnormal changes in early brain development. NDDs include mainly autism spectrum disorder (ASD), intellectual disability (ID), developmental delay (DD), attention deficit hyperactivity disorder (ADHD), schizophrenia, and epilepsy and affect around 3–5% of children worldwide (Fitzgerald et al., 2015; Wilfert et al., 2017; Parenti et al., 2020; Hanly et al., 2021). In general, any possible factor that could disrupt tightly programmed and coordinated events will eventually result in NDDs (Parenti et al., 2020). Although NDDs have been intensively investigated for many years, from the bench to the clinic, little is known about their causal risk factors and/or genes and fundamental neurobiology due to their complexities from their genotypes to phenotypes (Sullivan and Geschwind, 2019; Moyses-Oliveira et al., 2020; Parenti et al., 2020). One of the most productive areas of NDDs research, however, lies in human genetics. The combined genome-wide association study (GWAS; Visscher et al., 2017) and next generation techniques based on whole genome and exome sequencing (WGS and WES; Sanders et al., 2018; Coe et al., 2019; Satterstrom et al., 2020), have identified quite a few of susceptible genes for developing NDDs, which provides further opportunities to study the underlying mechanisms of how genetic mutations contribute to specific NDDs. Thus, to identify reproducible high risk

genes and to reveal their underlying neurobiological mechanisms in molecular, cellular, and circuit-levels is critical for developing personalized treatments for NDDs (Krystal and State, 2014).

TAO (Thousand and one) kinase family belongs to the STE20 group kinases and consists of three genes in vertebrates including *TAOK1*, *TAOK2*, and *TAOK3* that encode TAO1, TAO2, and TAO3, respectively (Dan et al., 2001; Miller et al., 2019). They have relatively close homologs in several invertebrate species like *C. elegans* and *Drosophila*, which structurally contain three conserved domains including the kinase domain, central domain and regulatory domain (Figure 1A). TAO kinases were reported to play multifunctional roles in many molecular and cellular events by interacting with MAPK cascade, MST family kinases, the cytoskeleton, and apoptosis-associated proteins (Duan et al., 2020). Therefore, it is not surprisingly that TAO kinases could regulate neuronal survival (Wakabayashi et al., 2005; Wu and Wang, 2008; Li et al., 2019) and development (Yasuda et al., 2007; de Anda et al., 2012; Ultanir et al., 2014; Yadav et al., 2017; Richter et al., 2018; Dulovic-Mahlow et al., 2019) in the nervous system. Although there is plenty of evidence suggesting that TAO kinases likely contribute to NDDs, the direct association between TAO kinases and NDDs has not been fully discovered until recently.

The original discovery of two genomic deletions in *TAOK1* is from patients with developmental delay (nsv1062993; Cooper et al., 2011), microcephaly, and seizures (Decipher 250045; Decipher database; Xie et al., 2016). In addition, Xie et al. (2016) also identified a 17q11.2 microdeletion that covers *TAOK1* in a patient with developmental delay and postnatal microcephaly, implying the copy number variants (CNVs) of *TAOK1* is likely involved in NDDs. Following the exome sequencing of over 4,200 individuals with developmental disorders, researchers found four missense *de novo* mutations in *TAOK1* that likely contribute to those developmental disorders (Deciphering Developmental Disorders Study, 2017). Subsequently, a WES based analysis further identified eight *de novo* mutations in *TAOK1* from eight patients with different NDDs including speech and language development and/or motor development delay, muscular hypotonia, macrocephaly, seizures, and intellectual disability (Dulovic-Mahlow et al., 2019). In addition, a total 23 patients with NDDs who carry different monogenic *TAOK1* variants (20 individuals) or a microdeletion covering *TAOK1* (three individuals) were discovered in a recent study (Woerden et al., 2021). These studies provide solid evidence that both pathogenic CNVs and single point mutations that disrupt *TAOK1* could have a deleterious effect that contributes to NDDs.

TAOK2 is supposed to be a susceptible gene of NDDs and is based on the findings that 16p11.2 microdeletion or microduplication contributes to multiple NDDs (Weiss et al., 2008; McCarthy et al., 2009; Steinman et al., 2016). Human *TAOK2* is one of the 30 genes located in the microdeletion or microduplication region of 16p11.2. By performing whole-genome sequencing (WGS) of families with ASD, one frame shift deletion of *TAOK2* was identified (Yuen et al., 2017). This was further confirmed in a following study (Richter et al., 2018),

in which two other more *de novo* mutations of *TAOK2* was identified in ASD patients (Richter et al., 2018).

Compared to those repeatedly identified *TAOK1* and *TAOK2* *de novo* mutations in NDDs, less attention was paid to the *TAOK3* gene. A previous analysis of *de novo* CNVs by WGS in individuals suffering from bipolar disorder and schizophrenia showed that a microdeletion that affects *TAOK3* (and *PEBP1*) is present in schizophrenia patient (Malhotra et al., 2011) and *TAOK3* (but not *PEBP1*) was further confirmed in a GWAS analysis (Gilman et al., 2012), suggesting that *TAOK3* alone may contribute to NDDs, at least in schizophrenia. The direct evidence for monogenic *TAOK3* mutations contributing to NDDs is from a comprehensive study with WES, which systematically analyzed over 2,500 autistic children and 1,900 unaffected siblings and the parents of each family and eventually identified two validated *de novo* mutations of *TAOK3* in ASD patients (Iossifov et al., 2014). It would be beneficial to identify more monogenic mutations of *TAOK3* in ASD or other NDDs in future studies.

Because each individual TAO kinase was reported to be associated with NDDs, it is important to investigate and obtain new insights into their biological mechanisms in neurodevelopment to confirm their potential roles in NDDs. Thus, despite the progress made in both basic and clinical research of TAO kinases related NDDs in the last few years, the systematic summary of these findings are lacking. In this review, we will introduce TAO kinases functions in general, summarize the *de novo* mutations that contribute to multiple NDDs, and discuss the possible underlying molecular and cellular mechanisms. Lastly, we propose future directions of an intensive understanding of TAO kinases in neurodevelopment and NDDs, which might be critical in the development of potential and precise treatment of specific NDDs.

TAO KINASES IN GENERAL

TAO Kinase Structure and Expression Patterns in the Central Nervous System (CNS)

The TAO (Thousand and one) kinase subfamily is part of the larger STE20 (sterile 20) kinase family, a diverse group of serine-threonine kinases that participate in a variety of signaling pathways (Dan et al., 2001). The TAO kinase family is highly conserved, and has three members in mammals including *TAOK1/PSK2/MARKK* (Hutchison et al., 1998), *TAOK2/PSK1* (Moore et al., 2000), and *TAOK3/JIK* (Tassi et al., 1999), but just a single representative TAO kinase in *C. elegans* (*Kin-18*; Berman et al., 2001; Spiga et al., 2013; Yin et al., 2016) and *Drosophila melanogaster* (*Tao*); (Liu et al., 2010). Structurally, all members of TAO kinases contain three domains including the N-terminal catalytic domain, the central domain, and the C-terminal regulatory domain which regulates catalytic activity (Figure 1A). Among these domains, the catalytic domains of all TAO kinase members are extremely conserved, but the regulatory domains may determine their distinct functions. In addition, each member of

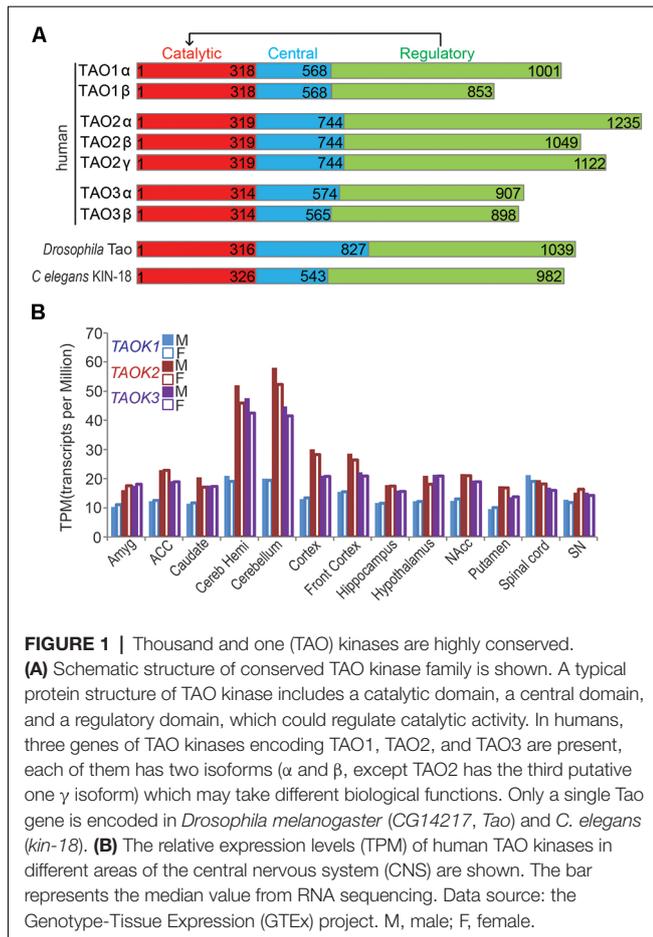


FIGURE 1 | Thousand and one (TAO) kinases are highly conserved. **(A)** Schematic structure of conserved TAO kinase family is shown. A typical protein structure of TAO kinase includes a catalytic domain, a central domain, and a regulatory domain, which could regulate catalytic activity. In humans, three genes of TAO kinases encoding TAO1, TAO2, and TAO3 are present, each of them has two isoforms (α and β , except TAO2 has the third putative one γ isoform) which may take different biological functions. Only a single TAO gene is encoded in *Drosophila melanogaster* (CG14217, *Tao*) and *C. elegans* (*kin-18*). **(B)** The relative expression levels (TPM) of human TAO kinases in different areas of the central nervous system (CNS) are shown. The bar represents the median value from RNA sequencing. Data source: the Genotype-Tissue Expression (GTEx) project. M, male; F, female.

mammalian TAO kinases has two isoforms (α and β) except for TAO2, which has a putative third one (TAO2 γ) which is mainly distinguished by the regulatory domain (Figure 1A), suggesting a distinct biological function of the different isoforms. Thus, it was reported that the two isoforms (α and β) of TAO2 play different roles in dendritic and dendritic spine development (Yasuda et al., 2007; Richter et al., 2018), the possible isoform-dependent functions in other members should be further explored.

TAO kinases are ubiquitously expressed without obvious tissue specificity based on mRNA transcription and protein translational levels (Duan et al., 2020), although it was reported that *TAOK1* and *TAOK2* are highly enriched in the brain by Northern blot detection (Hutchison et al., 1998). In the CNS, TAO kinases are widely distributed in all brain regions and the spinal cord without gender differences¹ (Figure 1B). In addition, TAO kinases are modestly expressed but *TAOK2* and *TAOK3* showed strong expression in the cerebellum (including cerebellar hemisphere) and cortex (including front cortex), implying that the importance of these brain regions are critical for TAO kinase related NDDs.

¹<https://www.gtexportal.org/>

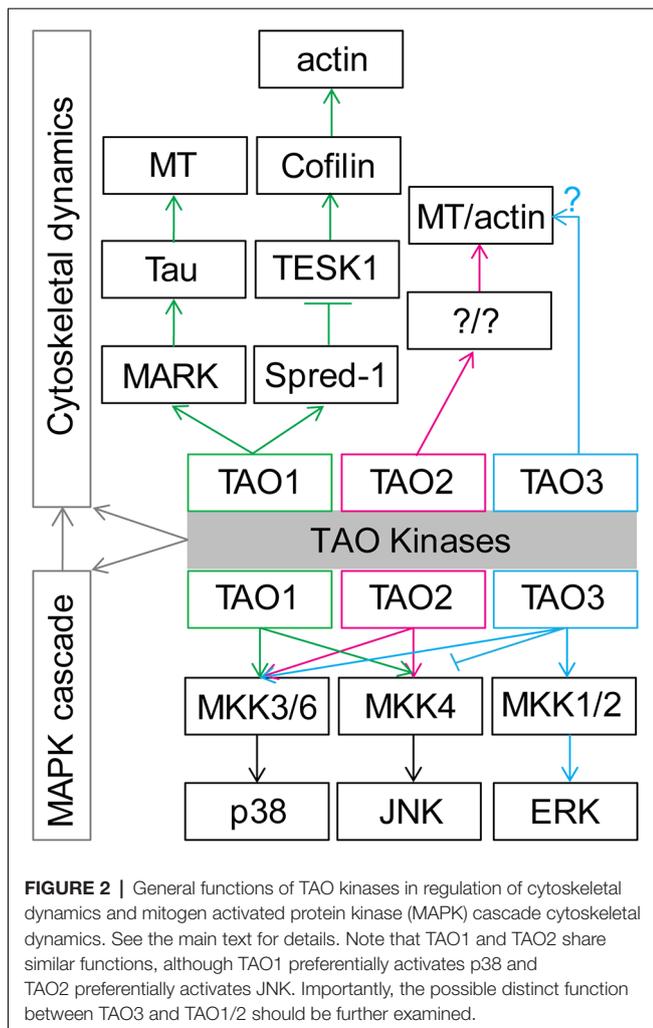
The General Functions of TAO Kinases

As TAO kinases belong to the STE20 kinase family, the original functions of TAO kinase are supposed to act as upstream regulators of mitogen activated protein kinases (MAPKs). Upon extracellular stimulations, conventional MAPK cascades including the ERK1/2, p38 MAPK α , β , δ , and γ , and JNK1/2/3 pathways are selectively activated to integrate, amplify, and regulate signal transduction and eventually affect multiple biological processes including cell proliferation, differentiation, migration, and apoptosis (Johnson and Lapadat, 2002; Kyosseva, 2004; Cargnello and Roux, 2011). TAO1 and TAO2 have a lot in common regarding activating p38 MAPK (Hutchison et al., 1998; Chen et al., 1999) and the JNK cascade (Moore et al., 2000; Zihni et al., 2006). TAO3 shows a relatively distinct function that activates ERKs (Zhang et al., 2000) and p38 MAPK but inhibits the JNK cascade (Tassi et al., 1999). It should be noted that TAO3 may inhibit p38 kinases in certain conditions (Tassi et al., 1999). Thus, the TAO kinases family is a central regulator in controlling MAPKs cascades and may be involved in multiple biological processes (Figure 2).

In addition, TAO1 is also known as MARKK (microtubule affinity regulating kinase) due to its ability to phosphorylate MARK, which can further affect microtubule (MT) arrangement by modulating tau (Giacomini et al., 2018) and other related microtubule-associated proteins (MAPs; Drewes et al., 1997), indicating the functional role of TAO1 in regulating MT dynamics. Further research found that TAO1 could interact with Spred-1 to inhibit TESK1, which could modulate actin dynamics by activating Cofilin (Moore et al., 2000). At the same time, TAO2 was also reported to modulate actin filament and MT rearrangement in cultured 3T3 cells (Moore et al., 2000; Mitsopoulos et al., 2003). Although direct evidence remains is scarce, TAO3 might also play a role in the regulation of cytoskeletal dynamics due to the fact that it has been reported that this kinase modulates the JNK signaling (Kapfhamer et al., 2012; Zeke et al., 2016). It is therefore not surprising that *Drosophila* *Tao*, the only homolog of mammalian TAO kinases, affects actin and MT dynamics in cultured *Drosophila* S2 cells (Liu et al., 2010; Pflanz et al., 2015) and primordial germ cells from developing embryos (Pflanz et al., 2015). It should be noted that the MAPK cascade signaling pathway has a tight connection with cytoskeletal dynamics (Šamaj et al., 2004; Komis et al., 2011). Therefore, TAO kinases' functions may be tightly involved in cytoskeletal dynamics regulation (Figure 2).

CLINICAL ASSOCIATION BETWEEN TAO KINASES AND NDDs

Because TAO kinases is intensively involved in regulating cytoskeletal dynamics, which is required for nearly all processes of normal neuronal and glia development involving cellular survival, migration, polarity, differentiation and plasticity (Conde and Cáceres, 2009; Hoogenraad and Bradke, 2009; Kapitein and Hoogenraad, 2015; Konietzny et al., 2017; Weigel et al., 2020), they are always speculated to be risk genes for NDDs. However, this reasonable speculation has not, until



recently, been proven to be correct, benefiting from powerful next-generation sequencing techniques and the establishment of well-organized cohorts [e.g., Simons Simplex Collection (SSC) cohort; Fischbach and Lord, 2010] and networks [e.g., the Deciphering Developmental Disorders (DDD) network; Firth and Wright, 2011] of investigators.

TAOK1

A rare *de novo* microdeletion at 17q11.2, which covers *TAOK1*, was identified in a patient with a developmental delay and postnatal microcephaly (Xie et al., 2016), suggesting a possible role of *TAOK1* to contribute to NDDs. Two genomic microdeletions in the *TAOK1* genome (without affecting other genes) in patients with developmental delay (nsv1062993; Cooper et al., 2011), microcephaly, and seizures (Decipher #250045, Decipher database) was reported. Importantly, the deletion nsv1062993 completely overlaps the CNV of #250045, and the two partially overlap the *TAOK1* gene. It is assumed that the *TAOK1* gene plays a pivotal role in the phenotype of patients (Xie et al., 2016). In addition, *TAOK1* was predicted to have a haploinsufficiency score less than 10, suggesting one copy deletion of *TAOK1* could cause clinical consequences (Xie et al.,

2016). Followed by an integrated meta-analysis that combines *de novo* mutations from exome sequencing data and CNV morbidity data, *TAOK1* with a missense mutation was identified as a candidate for NDDs (Coe et al., 2019). Furthermore, in a large scale whole exome screening (WES) of patients with autism, *TAOK1* was identified as one of over 100 putative autism spectrum disorder (ASD) associated genes (Satterstrom et al., 2020). In addition, *TAOK1 de novo* mutations were identified from eight children with associated NDDs including delayed speech and language development (5/8), autism (2/8), intellectual deficiency (4/8), macrocephaly (3/8), and motor development delay (6/8; Dulovic-Mahlow et al., 2019). Interestingly, half of these *de novo* mutations locate in the catalytic domain, one truncated mutation is present in the central domain, and the other three are truncated or frameshifted mutations in the regulatory domain. Although the precise functional analysis of these mutations is still lacking, the blood and fibroblast line derived from a patient carrying a variant (c.2366_2367insC) was analyzed. It was found that this variant could decrease cDNA (Sanger sequencing), mRNA (quantitative real time PCR), and protein (western blot) levels of *TAOK1*. In addition, the mutated mRNA could be stabilized by cycloheximide treatment indicating that nonsense-mediated mRNA decay could explain the reduced abundance of the mutant allele (Dulovic-Mahlow et al., 2019). Interestingly, a recent study collected a cohort of 23 individuals with NDDs from a collaboration facilitated by GeneMatcher (Sobreira et al., 2015) with multiple *de novo* variants in *TAOK1*, among which 20 individuals had an intragenic *TAOK1* variant and three patients had a chromosomal deletion including *TAOK1* (Woerden et al., 2021). Importantly, this study tested several variants with functional assays in a mouse model showing that two variants (c.500T>G and c.943C>T) may act with dominant negative (DN) functions and one variant (c.1643T>C) may have a loss of function (LOF) effect. Thus, these studies provide clear evidence that dysfunction of *TAOK1* with either CNVs or mutations with DN or LOF effect will result in NDDs.

TAOK2

TAOK2 is highlighted as a candidate risk gene for NDDs because previous reports showing that microdeletion and microduplication of the 16p11.2 genetic locus are associated with ASDs or schizophrenia (Weiss et al., 2008; McCarthy et al., 2009; Zheng et al., 2013). *TAOK2* is one of the 30 genes that are located in the 16p11.2 region. Recently, more psychiatric features like speech/language impairments, intellectual disability, motor/developmental delay, microcephaly and macrocephaly have been identified in patients with 16p11.2 microdeletion and microduplication (Steinman et al., 2016; Rein and Yan, 2020). Although it has been long been proposed that disruption of monogenic *TAOK2* function might result in NDDs, the clear clinical evidence has only been presented recently. By performing whole-genome sequencing (WGS) of families with ASD, one frame shift deletion of *TAOK2* was identified (Yuen et al., 2017). This was further confirmed in a following study (Richter et al., 2018). Richter et al. (2018) combined WGS and WES to examine over 2,600 families with ASDs and identified 24 different variants in *TAOK2*, including the frame shift deletion identified

by Yuen et al. (2017). They further characterized that three of these variants are known to be *de novo* including a missense mutation in the catalytic domain (A135P), a frameshift deletion resulting in truncation (P1022*) in the regulatory domain, and a *de novo* splice site variant (c.563 + 12_563 + 15del) predicted to cause intron seven retention. Among these three *de novo* mutations, A135P mutation results in lower levels of both phosphorylated and total TAO2 but the P1022* mutation does not affect TAO2 levels in patients with derived lymphoblastoid cells. Combined with more biochemical analysis, A135P and P1022* were confirmed to abolish (LOF) and enhance (GOF) kinase activity, respectively. The impact of the *de novo* splice site variant (c.563 + 12_563 + 15del), however, is still unknown and requires further characterization (Richter et al., 2018). It should be noted that, patients carrying these *de novo* mutations showed typical ASDs symptoms and also have a certain degree of disability or delay in language and speech development, implying the broad function of TAO2 in neurodevelopment.

Although TAO2 contribution to 16p11.2 CNVs pathophysiology is quite convincing, it should be noted that it is TAO2 and other genes (e.g., MAPK3, SEZ6L2 and KCTD13) that act collectively to develop much complex and diverse 16p11.2 CNVs phenotypes (Krishnan et al., 2016), compared to individual gene mutations (Richter et al., 2018; Rein and Yan, 2020). In this review, we focus on TAO2 function only since 16p11.2 CNVs related NDDs have recently been reviewed (Rein and Yan, 2020) and is also out of scope of the current study.

TAOK3

Unlike TAO1 and TAO2, studies on the association of TAO3 with NDDs is relatively scarce. Several GWAS based studies indicate that TAO3 is likely involved in NDDs. A study with a rare CNVs analysis by WGS suggested that a *de novo* deletion that affects TAO3 (and PEBP1) may contribute to schizophrenia (Malhotra et al., 2011) and TAO3 (but not PEBP1) was further confirmed in a GWAS analysis (Gilman et al., 2012), suggesting LOF of monogenic TAO3 may contribute to NDDs, at least in schizophrenia. In another GWAS study, TAO3 was identified as a genetic predisposition to loneliness (Abdellaoui et al., 2019), a status that accompanies NDDs (Kwan et al., 2020; Papagavrieli et al., 2020). In addition, two independent GWAS analyses showed that TAO3 is related to high opioid requirement for patients with advanced cancer pain (Gutteridge et al., 2018) and morphine requirement for postoperative pain in a retrospective pediatric day surgery population (Cook-Sather et al., 2014), suggesting a functional role of TAO3 in controlling pain under certain conditions. Since the impairment of sensory perception/processing is highly associated with NDDs, like autism (Robertson and Baron-Cohen, 2017), the possible function of TAO3 in NDDs is further implied. Except for GWAS studies, in a genome-wide-association meta-analysis (GWAMA), TAO3 was also identified as a susceptible gene for depression (Baselmans et al., 2019). Overall, those studies suggest a possible role of TAO3 in NDDs.

The direct evidence for monogenic TAO3 links to NDDs is based on a large scale WES that compared and analyzed over 2,500 affected ASD children and 1,900 unaffected siblings

and the parents of each family (Iossifov et al., 2014). In this systematical study, two novel missense *de novo* mutations TAO3 (c.1495A>G and c.1894C>T) were identified and validated (Iossifov et al., 2014; Table 1). These two missense mutations encode protein TAO3 with pT199A and pR632W, which are located in the central and regulatory domain, respectively. Although they are likely deleterious mutations as predicted in the gnomAD database, it should be noted that to determine whether these two mutations in TAO3 are pathogenic or not requires a detailed functional analysis and more clinical samples. Thus, it would be better elucidated if more deleterious mutations of TAO3 in ASD or other NDDs patients are identified and validated in future studies.

NEURONAL MECHANISMS OF TAO KINASES IN NEURODEVELOPMENT AND NDDs

TAO kinases mutations that caused multiple NDDs could be a result of neurological and/or non-neurological impairments. So far, however, the non-neurological roles of TAO kinases in neurodevelopment and NDDs has not been reported. We will focus on the neurological aspect and summarize the accumulated data that implies an essential role of TAO kinases in regulating neuronal development (Figure 3), survival, and maturation.

TAO Kinases Regulate Dendrite Development

Although TAO kinases at the mRNA level are widely expressed in adult human brains (Figure 1B), TAO2 is preferentially highly expressed in the intermediate zone and the cortical plate of the developing cortex (E18) in mice (de Anda et al., 2012). Interestingly, TAO2 α is expressed from early embryonic stages (E10) to adults but TAO2 β is only detectable at late stage (from E19) in the mouse brain cortex. Immunostaining with mouse cortical neurons (E17) and cultured 2 days *in vitro*, TAO2 is found to locate in the growth cone where actin is enriched and its active form pTAO2 was found to localize at the neurite shaft where MT is accumulated (de Anda et al., 2012), suggesting a possible role of TAO2 in regulating neuronal cytoskeletal dynamics. Knockdown of *Taok2* decreases basal dendrite arborization and callosal axon projection in the developing cortex (de Anda et al., 2012). Moreover, TAO2 could act downstream of the secreted guidance cue Semaphorin 3A (Sema3A) by interacting with its receptor Neuropilin 1 (Nrp1) to activate the JNK signaling pathway (de Anda et al., 2012).

To further characterize the neurodevelopmental functions of *Taok2* in mice, Richter et al. (2018) systematically analyze the neurological phenotypes in *Taok2* knockout (KO) mice, which were previously found to control behavioral response to ethanol in mice (Kapfhamer et al., 2013). Magnetic resonance imaging (MRI) of fixed 8- to 10-week-old mouse brains of *Taok2* KO and HET (KO/+) brains found that their absolute brain volumes were significantly enlarged compared with wild type (WT) mice but have a relative decrease in the somatosensory cortex and corpus callosum in a gene dose dependent way. Behavioral

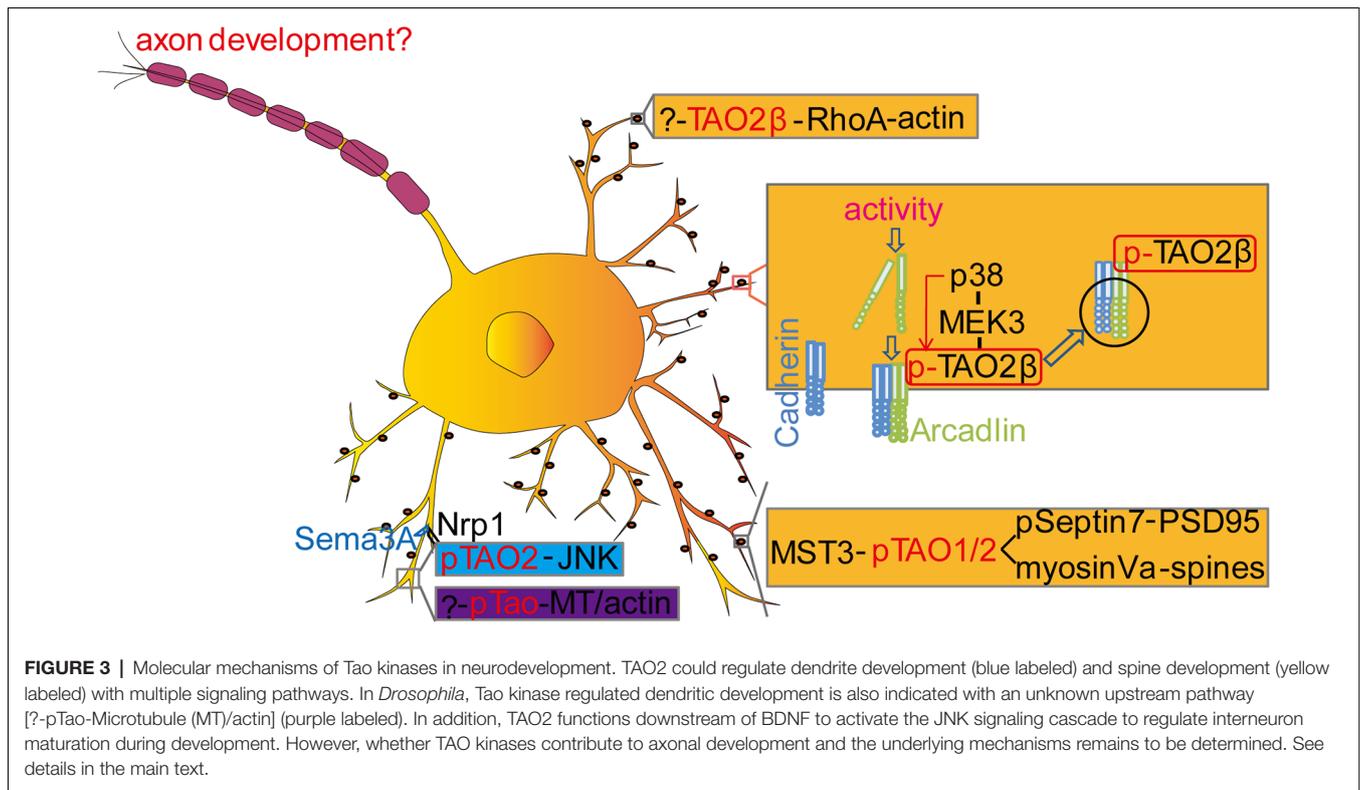
TABLE 1 | A selected list of *de novo* mutations between thousand and one (TAO) kinases and neurodevelopmental disorders (NDDs).

	Variants	Amino acid change	Monogenic	Data type	Diagnosis	Reference/source
<i>TAOK1</i> (NM_020791.2)	c.50A>G	E17G	Yes	WES	Delayed speech and language; ID; ADHD	Dulovic-Mahlow et al. (2019)
(NM_020791.2)	c.332C>T	S111F	Yes	WES	Delayed speech and language; ID; ASD	Dulovic-Mahlow et al. (2019)
(NM_020791.2)	c.892A>G	K298E	Yes	WES	Delayed speech and language; Macrocephaly; ASD	Dulovic-Mahlow et al. (2019)
(NM_020791.2)	c.914A>C	D305A	Yes	WES	ID	Dulovic-Mahlow et al. (2019)
(NM_020791.2)	c.1630C>T	Q554*	Yes	WES	ADHD	Dulovic-Mahlow et al. (2019)
(NM_020791.2)	c.2341G>T	E781*	Yes	WES	ID; Macrocephaly	Dulovic-Mahlow et al. (2019)
(NM_020791.2)	c.2366_2367insC	L790Ffs*3	Yes	WES	Delayed speech and language; ID; ASD	Dulovic-Mahlow et al. (2019)
(NM_020791.2)	c.2488G>T	E830*	Yes	WES	Delayed speech and language	Dulovic-Mahlow et al. (2019)
(NM_020791.2)	c.656C>T	A219V	Yes	WES	Developmental disorders	Deciphering Developmental Disorders Study (2017)
(NM_020791.2)	c.500T>G	L167R	Yes	WES	Developmental disorders	Deciphering Developmental Disorders Study (2017) and Woerden et al. (2021)
(NM_020791.2)	c.70C>A	P24T	Yes	WES	Developmental disorders	Deciphering Developmental Disorders Study (2017)
(NM_020791.2)	c.865G>A	V289M	Yes	WES	Developmental disorders	Deciphering Developmental Disorders Study (2017)
(NM_020791.2)	c.943C>T	L315F	Yes	WES	NDDs	Woerden et al. (2021)
(NM_020791.2)	c.1643T>C	L548P	Yes	WES	NDDs	Woerden et al. (2021)
(NM_020791.2)	Partial deletion chr17:277713 42-27809321	P?	Yes	WGS	Microcephaly and seizures	Decipher database (Xie et al., 2016)
(NM_020791.2)	Partial deletion chr17:277305 73-27802767	P?	Yes	WGS	Developmental delay	Cooper et al. (2011) and Xie et al. (2016)
17q11.2 (covers <i>TAOK1</i>)	Deletion		No	WGS	Developmental delay and postnatal microcephaly	Xie et al. (2016)
17q11.2 (covers <i>TAOK1</i>)	Deletion		No	WES	NDD	Woerden et al. (2021)
<i>TAOK2</i> (NM_016151)	c.403G>C	A135P	Yes	WES, WGS	ASD	Richter et al. (2018)
(NM_004783)	c.3057_3081del	P1022*	Yes	WES, WGS	ASD; Delayed language	Yuen et al. (2017) and Richter et al. (2018)
(NC_000016.9)	c.563 + 12_563 + 15	P?	Yes	WES, WGS	ASD	Richter et al. (2018)
16p11.2 (covers <i>TaoK2</i>)	Deletion		No	WGS	ASD	Weiss et al. (2008)
16p11.2 (covers <i>TaoK2</i>)	Duplication		No	WGS	ASD, Schizophrenia	Weiss et al. (2008) and McCarthy et al. (2009)
<i>TAOK3</i>	Deletion		No	WGS, GWAS	Schizophrenia	Malhotra et al. (2011) and Gilman et al. (2012)
(NM_016281.3)	c.1495A>G	T499A	Yes	WES	ASD	Iossifov et al. (2014)
(NM_016281.3)	c.1894C>T	A632T	Yes	WES	ASD	Iossifov et al. (2014)

CNVs of 17q11.2 and 16p11.2 locus are shown in the list because they cover *TAOK1* and *TAOK2*, respectively. In total, 20 point mutations of *TAOK1* were identified (Woerden et al., 2021) and three of the *de novo* mutations showing functional changes were selected. Note: the gene with the affected mRNA accession no. is indicated if available in the original studies/database. The individual variant is labeled; deletion or duplication means the whole gene is deleted or duplicated in the genomic fragment while partial deletion means the deletion fragment is located in the affected gene, without affecting other genes. Amino acid change: * indicates the stop codon. WGS, whole genome sequencing; WES, whole exome sequencing; GWAS, genome-wide associated study.

analysis indicated that the impairments on cognition, anxiety, and social interaction in *TaoK2* KO mice were consistent with previous clinical studies of ASD patients (Hazlett et al., 2005;

Freitag et al., 2009; Hardan et al., 2009; Vaccarino and Smith, 2009; Lai et al., 2014; Sacco et al., 2015). By examining the dendritic morphology in the prefrontal cortex, they found that



Taok2 KO and HET mice showed a decrease in basal dendritic complexity, which is comparable to the previous *in vitro* study (de Anda et al., 2012).

A recent study also clearly showed that overexpression (OE) of human TAO1 and its several NDDs linked variants in cultured primary hippocampal neurons from mice, could significantly reduce dendritic arborization and length (Woerden et al., 2021) although the detailed mechanisms remain to be further explored. Thus, to obtain more physiological evidence, further exploration of its function in neuronal/dendrite development, by generating *Taok1* KO mice, is required.

We recently also found that *Drosophila* *Tao* could significantly affect peripheral dendritic development of dendritic arborization (da) neurons at whole larval developmental stages and in adults (Hu et al., 2020). da sensory neurons are a well-characterized model system to study neuronal development and functions (Grueber et al., 2002; Williams and Truman, 2004; Shimono et al., 2009; Jan and Jan, 2010; Im and Galiko, 2012; Copf, 2015). Using this model, many of the NDDs related genes and their molecular mechanisms have been confirmed and identified (Gatto and Broadie, 2011; Coll-Tane et al., 2019). We found that *Drosophila* *Tao* is expressed in all da sensory neurons and its active form pTao is discretely distributed along dendrites, suggesting a local function of *Drosophila* *Tao* in regulation of MT and/or actin to affect dendritic development. Loss of *Drosophila* *Tao* increases dendritic complexity and MTs dynamic of all da sensory neurons *in vivo* in a developmental stage dependent way (Hu et al., 2020), which is the opposite to the phenotype of neocortex neurons from an *in vitro* culture

system (de Anda et al., 2012) or *TAOK2* KO mice (Richter et al., 2018). Interestingly, this increased dendritic complexity phenotype could be fully rescued by wild type human TAO2 but not by the ASD linked LOF mutation (A135P), suggesting a conserved function of *Drosophila* *Tao* and TAO2; but its readout varies in different model systems (King and Heberlein, 2011). Moreover, we also found that disruption of *Drosophila* *Tao* in adult sensory neurons caused dendritic over-branching and resulted in impairment of social behaviors, which further confirmed the previous observations that sensory perception is critical for developing ASDs in a mouse model (Orefice et al., 2016, 2019).

Altogether, these different *in vitro* and *in vivo* models clearly showed a critical and complex role of TAO kinases in regulating dendrite development which then affects normal brain functions.

TAO Kinases Regulate Spine/Synapse Development

Both dendrite arborization and synapse formation are critical for wiring the neural circuitry and establishing normal neural functions (Benson et al., 2001; Jan and Jan, 2001; McAllister, 2007; Colón-Ramos, 2009; Batool et al., 2019). Yadav et al. found that TAO2 localizes to dendritic spines and is required for synaptic maturation in a kinase activity dependent way (Yadav et al., 2017). Combined with an elegant chemical-genetic method and mass spectrometry, the authors identified several candidate substrates of TAO2 including Septin6, Septin7, HADC6, Bai1, Caskin1, CEP170, and MST3, and only Septin7 was further confirmed in a subsequent functional analysis. Septin7 is a

GTP-binding protein (Neubauer and Zieger, 2017) that regulates actin (Hu et al., 2012; Mavrikakis et al., 2014) and MT remodeling (Bowen et al., 2011; Hu et al., 2012) to control axon/dendrite branching and spine morphology (Xie et al., 2007; Hu et al., 2012). It was found that TAO2 could directly phosphorylate Septin7 and lead to its trafficking to the dendritic spine where it could associate with and immobilize the synapse scaffolding protein PSD95 to promote spine synapse maturation (Yadav et al., 2017). In addition, a peptide pull-down method to identify binding proteins in neuronal lysates labeled by stable isotope labeling by amino acids in culture (SILAC; Zhang et al., 2011; Deng et al., 2019) was employed to identify possible binding components of TAO1/2, showing that Myosin Va could interact with TAO1/2 in a phosphorylation dependent manner. Moreover, endogenous Myosin Va could bind endogenous TAO1 and be phosphorylated by TAO1/2 in neurons (Ultanir et al., 2014). Myosin Va is a motor protein in charge of the intracellular transport of vesicles, organelles, and protein complexes along the actin filaments (Harrington and Rodgers, 1984; Masters et al., 2016; Guhathakurta et al., 2018; Lombardo et al., 2019) and affects microtubule based transport when recruited on the same cargo with the microtubule motor kinesin (Kapitein et al., 2013), suggesting a role of Myosin Va in promoting synaptic formation/maturation when localized in the spine (Ultanir et al., 2014). In addition, the authors found that TAO1/2 could be phosphorylated by mammalian sterile 20 (Ste20)-like kinase 3 (MST3), a homolog to *Drosophila Hippo* (Harvey et al., 2003). Interestingly, in contrast to the downstream of mammalian Tao Kinase to MST3, it seems *Drosophila Tao* is an upstream signaling component activating Hippo to regulate tissue growth (Boggiano et al., 2011; Poon et al., 2011, 2018; Huang et al., 2014; Chung et al., 2016). However, whether *Drosophila Tao* could phosphorylate Hippo to regulate synaptic growth needs to be further explored.

In another study, it was shown that TAO2 β instead of TAO2 α is essential for activity-induced dendritic spine formation (Yasuda et al., 2007), which rises a possibility that TAO kinases function in an isoform-dependent way. Electroconvulsive or other excitatory stimuli in cultured hippocampal neurons triggers a protocadherin arcadlin that stimulates TAO2 β specifically, which in turn activates p38 MAPK through MEK3, resulting in the endocytosis of N-cadherin and the decrease in spine numbers (Yasuda et al., 2007; Sun and Xie, 2012), suggesting an isoform specific function of TAO kinases in spine development. This finding was further confirmed in the *Taok2* KO mouse model (Richter et al., 2018). It was shown that dendritic spines in hippocampal neurons from *Taok2* KO mice were dramatically decreased compared to WT, possibly by directly affecting the RhoA activity, a kinase which is also preferentially combined to TAO2 β and is highly involved in the regulation of spine mobility. Those data indicate that the C-terminal of distinct TAO kinases is critical for their unique physiological functions.

Using *Drosophila* (neuron-muscle junction) NMJ as a classic system for studying synaptic development (Broadie and Bate, 1995; Menon et al., 2013; Frank, 2014) assists neurobiologist in identifying multiple psychiatric disorder related genes and

their underlying molecular mechanisms (Sun and Xie, 2012; Tian et al., 2017). Knockdown or deactivation (hypomorphic allele) of *Drosophila Tao* increases the number of NMJ (buttons, the single NMJ structure; Politano et al., 2019). However, it seems *Drosophila Tao* that regulates NMJ development is not dependent on the Hippo/MST pathway as it is in hippocampal neurons (Ultanir et al., 2014) but it could negatively regulate BMP signaling as reduction of *Drosophila Tao* leads to an increase in both nucleic pMad levels and BMP target gene expression in motor neuron (Politano et al., 2019). However, another study recently showed that knockdown of *Tao* could decrease the NMJ number (Dulovic-Mahlow et al., 2019). Thus, both studies indicated the important role of *Drosophila Tao* in synaptic development, while the underlying mechanisms for the opposite phenotypes observed independently remains to be illustrated.

We recently developed a novel model for studying synaptic development in *Drosophila larvae* (Tenedini et al., 2019) to compensate for the NMJ model. At larvae stage, peripheral Class IV da (C4da) sensory neurons directly come into contact with a pair of interneurons A08n that can form a functional synaptic structure (Town et al., 2014; Hu et al., 2017; Kaneko et al., 2017), which is closer to mammalian synapses when compared with the classic NMJ synaptic system. By using the Syp-GRASP technique (Macpherson et al., 2015) to label C4da-A08n synapses, we found that loss of *Tao* results in exuberant postsynaptic (comparable to spine structure) specializations and aberrant connectivity during larval growth. Using functional imaging and a behavioral analysis we showed that loss of *Drosophila Tao* could induce ectopic functional synapses formation of the A08n neuron with other types (C3da) of neurons and resulted in altered behavioral responses in a connection-specific manner (Tenedini et al., 2019), indicating that TAO kinase mutations, like other NDDs susceptible genes, can induce abnormal behaviors partially from improper establishment of neural circuits (Kida and Kato, 2015; Kaiser et al., 2017; Südhof, 2017).

TAO Kinases Control Neuronal Apoptosis and Maturation via the JNK Signaling Cascade

The association between neuronal apoptosis and NDDs is not well documented. A previous study showed that overexpression (OE) of the full length or kinase domain of human TAO1 in human neuroblastoma SH-SY5Y cells resulted in cellular apoptosis which was indicated by elevated caspase-3 activity. However, OE of the regulatory domain of TAO1 in SH-SY5Y did not appear to have an obvious change (Wu and Wang, 2008). Importantly, OE of TAO1 induced elevated caspase-3-like activity and apoptosis of neuroblastoma could be reduced by JNK inhibitor SP600125 to some extent. In addition, OE of rat TAO3 in PC12 (a widely used cell line with the properties of intersecting neurons) resulted in elevation of the expression level of BimEL (Wakabayashi et al., 2005), a protein with apoptotic activity. Recently, it was also reported that TAO1 protected MCAO-induced cerebral ischemic stroke by decreasing the pro-inflammatory factors and apoptosis via PI3K/AKT and

MAPK signaling pathways (Li et al., 2019), which further indicates the critical roles of TAO kinases in neuronal apoptosis. Those preliminary studies suggest an underestimated function of TAO kinases in neuronal apoptosis.

Furthermore, TAO2 may play roles in the regulation of neuronal maturation. A recent study showed that BDNF could regulate cortical GABAergic interneuron maturation in a TAO2-JNK signaling pathway in a 16p11.2 duplication mouse model (Willis et al., 2020). Cultured neurons from 16p11.2 duplication mice exhibit an abnormal interneuron developmental phenotype that may be involved in a premature closure of the critical period which is likely to be driven by OE of TAO2 and the subsequent over-activity of JNK, since pharmacological inhibition of TAO kinase could alleviate the 16p11.2 duplication phenotype. Given the importance of parvalbumin (PBV+) interneurons in the regulation of excitatory/inhibitory balance within cortical regions, accelerated GABAergic development by TAO2 over-activity may lead to dysregulated network activity and synaptic connectivity (Willis et al., 2020). In addition, it was reported that OE of human TAO1 could also prevent maturation of cultured primary hippocampal neurons from mice (Woerden et al., 2021), while the role of JNKs involvement is yet to be determined.

TAO Kinases Regulate Neuronal Migration

A recent study investigated a possible function of *TAOK1* in neuronal migration, a process that is critical for normal brain development (Woerden et al., 2021). By employing the *in utero* electroporation in mice at embryonic day 14.5 (a well-established time window when immature neurons generated from progenitor cells start to migrate to their final destination within the cortical plate, which will eventually form the cerebral cortex layer 2/3), the authors found that knockdown of *Taok1* resulted in a clear migration deficit of the neurons when compared to control neurons from postnatal day 1 (p1) to P7, when only 75% of the *Taok1* knockdown neurons were present in cerebral cortex layer 2/3, compared to 95% in control conditions (Woerden et al., 2021). Similar migration deficits were observed when transfection of several NDDs, linked human *TAOK1* variants in developing mouse brains including c.500T>G and c.943C>T (see **Table 1**), suggesting a possible role of *TAOK1* in neuronal migration during early human brain development.

CONCLUSION AND PERSPECTIVE

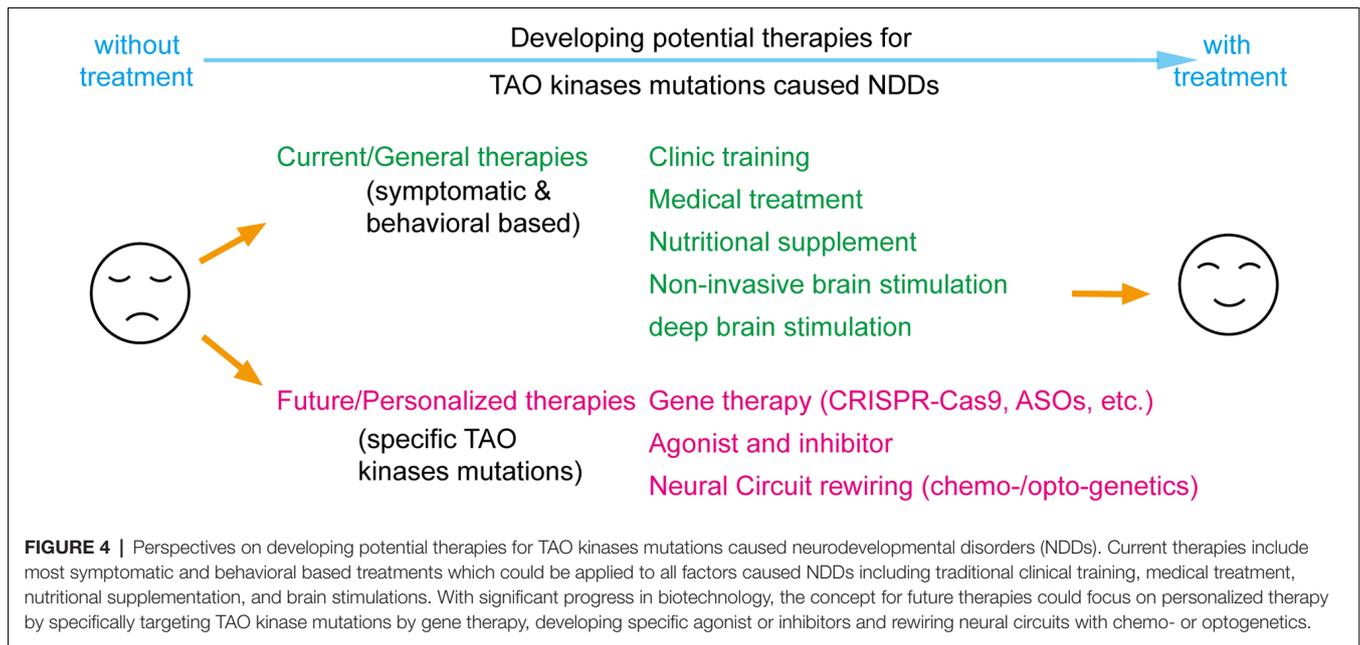
There is solid evidence showing that all TAO kinase members are involved in NDDs including ASD, schizophrenia, and language/speech development delays, implying an indispensable function of the TAO kinase family in neurodevelopment. Although several animal models from *Drosophila* to knockout mice provides us with a preliminary role of TAO kinases in neuronal development, survival and maturation, the detailed mechanisms of how TAO kinases contribute to NDDs still need to be investigated.

First, the neurobiological functions of TAO kinases should be further investigated. At the molecular level, identification of specific up- and down-stream substrates for TAO kinases in

different model systems, especially by combining human induced pluripotent stem cell (iPSC) from patients, is crucial for a better understanding of the mechanisms leading to the onset of a disease-phenotype (Parenti et al., 2020; Zhang et al., 2020). At cellular level, previous reports focus on the cell-autonomous role of TAO kinases in regulating the development of dendrites and dendritic spines. Whether cell-non-autonomous (e.g., different types of glia cells) roles of TAO kinases in neuronal development and functions are present is not reported. In addition, TAO2 was identified to affect axonal development (de Anda et al., 2012). Whether the mechanisms of TAO kinases controlling dendrite/spine development is distinct from axonal development remains unknown. To confirm and further characterize the TAO kinases functions in neurodevelopment or NDDs, non-human primate models are a promising direction.

Second, an obvious question on how Tao kinases contribute to establish and/or modulate disease-related circuits remains unanswered. In *Taok2* knockout mice, the oscillatory events were similar in the PFC and slightly decreased in the HC compared to WT littermates. However, the duration, amplitude, and power in theta (4–7, 12 Hz), beta (12–30 Hz), gamma (30–100 Hz) frequency ranges and coherence within the beta band were significantly increased, suggesting alterations in HC and PFC connectivity (Richter et al., 2018). The limitation of this study is that the animals are studied in an anesthetized status, which may affect the actual physiological responses (Chini et al., 2019). In addition, whether restoring the oscillation pattern by optogenetic stimulation could rescue related phenotypes is also an interesting question that is worth further investigation. A recent study showed a disruption of hippocampal-orbitofrontal-amygdala connectivity in 16p11.2 duplication mice. Whether and how much *Taok2* contributes to this defect needs to be investigated (Bristow et al., 2020).

In addition, the possible non-neurological functions of TAO kinases in developing NDDs should also be highlighted. Increasing evidence suggests a non-neurological role in NDDs including immunity, gut, and microbiota (Cryan and Dinan, 2012; Sharon et al., 2016; Dinan and Cryan, 2017; Stefano et al., 2018; Fattorusso et al., 2019; Pape et al., 2019). Studies investigating the brain-gut axis demonstrate a critical role for the gut microbiota in orchestrating brain development and behavior, and the immune system is emerging as an important regulator of these interactions. Accordingly, both the gut microbiota and immune system are implicated in the etiopathogenesis or manifestation of NDDs (Fung et al., 2017). TAO kinases were reported to regulate immunity (Ormonde et al., 2018, 2019; Zhang et al., 2018), gut development (Huang et al., 2014) and likely in maintenance of microbiota integration since MAPKs are involved (Thomas and Versalovic, 2010). Thus, the possible non-neurological role of TAO kinases in NDDs should be seriously considered. TAO kinases are ubiquitously expressed in all tissues including in the immune and gastrointestinal system (Duan et al., 2020). However, it is still unknown whether TAO kinases play any role in the regulation of the immune system and the coordination of brain-gut axis functions that affects neurodevelopment and contributes to NDDs.



The eventual goal of investigating the roles and functions of TAO kinases in NDDs is to develop potential therapeutic approaches (Figure 4). Although several above-mentioned basic research discoveries may provide directions for developing potential therapies, clinical trials or even pre-clinical studies on treatment of TAO kinases related NDDs are still lacking. Current clinical training intervention and medical treatments offered for NDDs are symptomatic and behavioral based therapy (Levy and Barak, 2021), which could be applied to any possible factors caused by NDDs. In addition, nutritional supplements (Chang and Su, 2020), non-invasive brain stimulation [including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS)] (Khaleghi et al., 2020), and deep brain stimulation in certain cases (Beszej et al., 2019; Lin et al., 2019) are being or will be applied in clinical treatments of NDDs.

Although those general treatments could rescue certain symptoms and behaviors, developing precision medicine that directly and specifically targets disease-causing mutations would be more beneficial (Javed et al., 2020). To functionally rescue TAO kinases mutations caused NDDs, the principle of a long-term rebalancing of their kinase activity should always be followed. One possible strategy is to develop agonists and inhibitors with high specificity and potency for TAO kinases (Fang et al., 2020; Ye et al., 2020). Similar to all standardized drug development processes, the efficacy and toxicity in animal models should be cautiously evaluated before these candidates are applied in human clinical trials. In addition, with the significant progress of gene editing and manipulation in the last decade, gene therapy techniques are a promising direction for personalized medical treatment including CRISPR-Cas9 gene-editing for mutation replacement and antisense oligonucleotides (ASOs) for modifying protein levels (Levy and Barak, 2021). It should be noted that most of those gene therapies are still in preclinical testing stages and the

number of successful clinical trials is quite limited because it is faced with critical issues when implemented *in vivo*, such as limited efficiency, off-target effects, time window and delivery methods, all suggesting that much more effort is required to improve the bench-to-bedside success rate (Levy and Barak, 2021). Theoretically, all those strategies could also be applied to the specific down-stream targets (like Septin7, myosin Va, JNK and RhoA) of TAO kinases which requires further exploration of the signaling network of TAO kinases.

Alternatively, another option is bypassing molecular deficits and directly treating the neural circuit level deficits (Javed et al., 2020). It is widely accepted that NDDs arise from the alteration of normal brain developmental trajectories disrupting the function of specific neural circuits caused by genetic mutations (del Pino et al., 2018). To rewire the neural circuits by chemo- and optogenetic manipulations is a promising strategy to treat NDDs (Ferguson and Gao, 2018). The successful application of optogenetic tools to rebuild the functional neural circuit from dorsal raphe to nucleus accumbens that rescues the social defects in 16p11.2 del mice (Walsh et al., 2018) may prove therapeutically beneficial. Thus, the specific neural circuit defects in TAO kinases related NDDs requires further exploration.

In short, human genetic studies and animal models have linked all TAO kinase members to NDDs such as ASD and schizophrenia. The underlying mechanisms of how TAO kinases regulate neurodevelopment, and how their mutations contribute to NDDs are only just emerging. To dissect more detailed and precise mechanisms is a prerequisite in developing personalized therapies for TAO kinases mutations caused NDDs.

AUTHOR CONTRIBUTIONS

CH wrote the manuscript, prepared the figures, and finalized the manuscript. LX contributed to writing and commenting. PF

and QY contributed to figure and table preparation. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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