Int J Biochem Mol Biol 2012;3(2):152-164
www.ijbmb.org /ISSN:2152-4114/IJBMB1203004

Review Article

14-3-3 proteins in neurological disorders

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Received March 14, 2012; accepted April 28, 2012; Epub May 18, 2012; Published June 15, 2012

Abstract: 14-3-3 proteins were originally discovered as a family of proteins that are highly expressed in the brain. Through interactions with a multitude of binding partners, 14-3-3 proteins impact many aspects of brain function including neural signaling, neuronal development and neuroprotection. Although much remains to be learned and understood, 14-3-3 proteins have been implicated in a variety of neurological disorders based on evidence from both clinical and laboratory studies. Here we will review previous and more recent research that has helped us understand the roles of 14-3-3 proteins in both neurodegenerative and neuropsychiatric diseases.

Keywords: 14-3-3, neurodegenerative diseases, neurodevelopment, neuropsychiatric diseases

Introduction

The 14-3-3 proteins are a family of homologous proteins that consist of seven isoforms (β, γ, ε, η, ζ, σ, and τ/θ) in mammals [1, 2]. Structurally, 14-3-3 proteins exist as homo- and heterodimers, with each monomer comprising of nine α-helices that are organized in an antiparallel array. Among them, helices αA, αC and αD are involved in dimerization, and helices αC, αE, αG and αI form a concave amphipathic groove as the site of ligand binding [3-5]. To date, 14-3-3 proteins are known to interact with over 200 proteins that contain specific pSer/pThr motifs [6, 7]. Through binding to their target proteins, 14-3-3 proteins participate in the regulation of a wide range of biological processes including signal transduction, cell cycle, transcription, apoptosis and neuronal development [8-14].

14-3-3 proteins are ubiquitously expressed in various types of tissues, but their highest expression is in the brain, where they make up approximately 1% of its total soluble proteins [15, 16]. In neurons, 14-3-3 proteins are present in the cytoplasmic compartment, intracellular organelles and plasma membrane. Some of the 14-3-3 isoforms are particularly enriched in the synapses, to regulate transmission and plasticity [15, 17-20]. In addition, 14-3-3 is thought to play a functional role in other cellular processes such as neuronal differentiation, migration and survival, neurite outgrowth and ion channel regulation [21].

While their precise neurophysiological function is not fully understood, 14-3-3 proteins have been implicated in a number of neurological disorders [21, 22]. In this review paper, we will discuss the potential role of 14-3-3 in the pathogenesis and neurobiology of these diseases.

Neurodegenerative disease

Parkinson's disease

Parkinson's disease (PD) is an age-related neurodegenerative disease characterized by the presence of Lewy bodies and the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) [23]. 14-3-3 proteins have been associated with PD based on their localization, binding partners, and neuroprotective function.

Lewy body colocalization

Lewy bodies are abnormal protein aggregates developed inside nerve cells in cortical and subcortical regions of PD brains. The main component of Lewy bodies is α-synuclein, a regulator of the MAPK pathway that is involved in dopamine synthesis [24-26]. Several immunohistochemical studies have identified that four of the

seven 14-3-3 isoforms (ε, γ, σ, and ζ) are also present in Lewy bodies [21, 27, 28]. Interestingly, α-synuclein and 14-3-3 proteins share a substantial sequence homology and may interact with each other [29, 30]. In transgenic mice overexpressing human wildtype α-synuclein, several 14-3-3 isoforms (γ, τ, ε, and σ) were found to have reduced gene expression [31]. The level of 14-3-3 proteins is also dysregulated in an isoform-specific manner in the α- and β-synuclein double knockout mice [32]. In addition, binding of 14-3-3η to α-synuclein is disrupted by PD-causing mutations of α-synuclein (30P and A53T), suggesting a potential role for this interaction in PD [33]. However, it is not known whether the presence of 14-3-3 proteins in Lewy bodies is mediated by their interactions with α-synuclein.

Binding partners

In addition to α-synuclein, 14-3-3 proteins are reported to interact with several other proteins implicated in the pathogenesis of PD (**Table 1**). Firstly, 14-3-3ζ was determined as an endogenous binding partner and activator of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine synthesis [34]. Interestingly, α-synuclein not only interacts with 14-3-3, but also binds to TH and reduces its activity [26]. Thus, a complex interaction of these three proteins may be important in the regulation of dopamine biosynthesis in PD. Secondly, it was reported that 14-3-3η binds to and negatively regulates parkin, an E3 ubiquitin ligase that is important for protein degradation. This 14-3-3η-parkin interaction is disrupted when the parkin gene (*PARK2*) has mutations that cause autosomal recessive juvenile parkinsonism (ARJP) [33, 35], indicating a functional significance of this interaction in PD pathogenesis. Thirdly, 14-3-3 proteins have also been shown to interact and regulate phosphorylated FOXO3a, a transcription factor that is involved in cell-fate decisions and linked to PD based on its localization in Lewy bodies [36, 37]. Lastly, two recent studies have identified 14-3-3 as a binding partner of LRRK2 (leucine-rich repeat kinase 2), whose mutations are a common cause of familial and sporadic PD [38]. 14-3-3 binding regulates LRRK2-mediated cellular functions by preventing its dephosphorylation [39]. As 14-3-3 binding to LRRK2 is disrupted by common PD-related mutations in the LRRK2 gene, this protein-protein interaction may play a role in the pathological processes of LRRK2-related PD [40-42].

Neuroprotective effect

14-3-3 proteins are known to promote cell survival by inhibiting apoptotic processes via multiple mechanisms [43-45]. In cellular models of PD, a subset of 14-3-3 isoforms (θ, γ, ε) decreases toxicity induced by rotenone or MPTP, two neurotoxins that cause cell death in dopaminergic cells and induce parkinsonian syndromes [46]. In an α-synuclein transgenic *C. elegans* model, overexpression of 14-3-3θ protects against dopaminergic cell loss [31]. Collectively, these studies provide evidence for a positive role of 14-3-3 in abating PD-related dopaminergic neuron death. Additionally, 14-3-3 proteins may exert their neuroprotective effect by promoting the formation of aggresomes, and thereby facilitating the sequestration and degradation of misfolded toxic proteins [47]. This was first demonstrated by a study conducted in budding yeast, in which one of the two yeast 14-3-3 proteins (Bmh1) is found to be essential for aggresome formation induced by the expression of proteins with an expanded polyglutamine domain [48]. We have recently discovered that 14-3-3 proteins are indispensable for directing several different misfolded proteins into aggresomes in mammalian cells (Xu et al., in preparation). Given that accumulation of toxic proteins is one of the leading causes of neurodegeneration, elucidation of molecular mechanisms underlying 14-3-3-dependent aggresome formation may provide novel insights into pathogenesis of PD and other neurodegenerative diseases.

Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease with progressive dementia characterized by two pathological hallmarks: amyloid plaques and neurofibrillary tangles (NFTs) [49]. Amyloid plaques are the extracellular deposits of amyloid-beta fibrils which are considered to be neurotoxic and result in neuronal dysfunction [50]. NFTs are mostly composed of paired helical filaments formed by aggregation of the abnormally hyper-phosphorylated tau proteins [51]. Several studies have implicated a role of 14-3-3 proteins in the neuropathology of AD based on their colocalization with NFTs, interactions with AD-associated proteins, and their po-

Table 1. Potential 14-3-3 binding partners for neurodegenerative diseases.

Binding Partner	Protein Function	Disease Association		Evidence of 14-3-3 Interaction	Reported By
α-synuclein	MAPK pathway regulator and plays a role in the regulation of dopamine biosynthesis	PD	The main structural component of Lewy bodies	14-3-3 proteins and a-synuclein share over 40% homology	Ostrerova et al., 1999
				Positive staining of 14-3-3 proteins in Lewy bodies	Kawamoto et al., 2002; Ubl et al., 2002; Berg et al., 2003 (1)
				14-3-3 protein colocalize with α-synuclein in Lewy bodies	Shirakashi et al., 2006
				α-synuclein binds to 14-3-3η and abolishes its suppression of parkin activity	Sato et al., 2006
δ-catenin	Presenilin-1 interacts with δ-catenin to modulate Wnt signaling	AD	Binds to presenilin-1, the gene most commonly mutated in familial AD	14-3-3ζ is a binding partner of δ-catenin	Mackie and Aitken, 2005
FOXO3a	Transcription factor important in cell-fate decisions including apoptosis, proliferation, and cell metabolism.	PD	Localizes in Lewy bodies	Phosphorylated *FOXO3* binds to 14-3-3 proteins	Brunet et al., 1999
				Both colocalize to Lewy Bodies	Su et al., 2009
GSK3β	Regulator enzyme that phosphorylates several substrates	AD	Activated in pretangle neurons, accumulates in NFTs, and phosphorylates tau	14-3-3ζ binds to and links GSK3β and tau in the multiprotein microtubule-associated complex, promoting GSK3β phosphorylation of tau	Agarwal-Mawal et al., 2003; Yuan et al., 2004;
LRRK2	A member of the Roco protein family with kinase and GTPase activity	PD	Autosomal dominant missense mutations of the *LRRK2* gene are associated with PD	14-3-3 interacts with phosphorylated *LRRK2*, where disruption of this interaction, via dephosphorylation or mutation, leads to the accumulation of *LRRK2* in inclusion bodies	Dzamko et al., 2010; Nicohols et al., 2010; Li et al., 2011
parkin	Ubiquitin ligase protein important for degradation pathway	PD	Mutation of parkin gene (*PARK2*) is the main cause of ARJP	14-3-3η functionally links parkin and α-synuclein 14-3-3η negatively regulates parkin's activity	Sato et al., 2006
tau	Microtubule-associated protein that promotes the assembly and stability of microtubules	AD	Hyperphosphorylated form of tau is the main component of paired helical filaments of NFTs	14-3-3 localized to neurofibrillary tangles	Layfield et al., 1996
				14-3-3ζ binds to and promotes the phosphorylation of tau	Hashiguchi et al., 2000; Sadik et al., 2009
Tyrosine Hydroxylase (TH)	Rate-limiting factor of DA synthesis	PD	A hallmark of PD is loss of dopaminergic neurons	14-3-3ζ is an endogenous activator of TH in dopaminergic neurons	Wang et al., 2009

Abbreviations: AD, Alzheimer's disease; ARJP, Autosomal Recessive Juvenile Parkinsonism; PD, Parkinson's disease.

tential utility as an AD biomarker.

NFT colocalization

A postmortem study first identified the presence of 14-3-3 proteins in NFTs of hippocampal brain sections from AD patients [52, 53]. Further analyses of 14-3-3 immunolocalization in AD brains revealed that 14-3-3 proteins are present both intra- and extracellularly in the NFTs. In particular, 14-3-3ζ was shown to have the highest immunoreactivity to NFTs compared to other isoforms (β, γ, σ, and ε), suggesting an isoform-specific involvement of 14-3-3 proteins in the pathological processes of AD [54].

Binding partners

14-3-3 proteins interact with several AD-associated proteins (**Table 1**). One of the notable 14-3-3 binding partners is the microtubule-associated protein tau, whose hyperphosphorylation results in the formation of NFTs in AD and other tauopathies [49, 51]. 14-3-3ζ stimulates tau phosphorylation by several protein kinases including glycogen synthase kinase-3 beta (GSK3β) [53, 55]. In fact, it has been suggested that 14-3-3ζ acts as an adaptor protein bridging the interaction of GSK3ζ with tau and thereby facilitating GSK3β-mediated phosphorylation of tau [56]. Even though it was disputed by one study [57], the presence of the 14-3-3ζ, tau and GSK3β protein complex was confirmed by a follow-up study, in which they further determined that the phosphorylation of GSK3β on residue Ser9 is required for 14-3-3ζ-facilitated tau phosphorylation [58]. Another binding partner of 14-3-3ζ is δ-catenin, a brain-specific member of the adherens junction complex that is required for the maintenance of neural structure and implicated in the regulation of cognitive function [59]. The 14-3-3 and δ-catenin interaction was first identified by a yeast two-hybrid screen and subsequently confirmed in a follow-up study [60, 61]. Interestingly, δ-catenin also interacts with presenilin-1, which is an important modulator of Wnt signaling during neuronal development and the gene most commonly mutated in early onset familial AD [62]. Thus, its interaction with δ-catenin may provide evidence for a potential link between 14-3-3 and AD.

Biomarker

In order to provide accurate diagnosis of AD, several attempts have been made to identify possible biomarkers for this neurodegenerative disease. Postmortem studies have revealed increased expression of several 14-3-3 isoforms in different brain regions of AD patients [63]. In addition, 14-3-3 proteins have been detected in the cerebrospinal fluid (CSF) of some cases of AD [64-66]. However, in a study conducted to analyze 14-3-3 isoform specificity in the CSF of patients with Creutzfeldt-Jakob disease and other dementia cases, including patients with AD, 14-3-3η was detected in the CSF of all dementia patients [67], suggesting that 14-3-3 may be a general biomarker for neurodegenerative diseases with dementia but not a suitable marker for the differential diagnosis of AD [64, 65].

Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease (CJD) is a rare, fatal neurodegenerative disease belonging to a family of human transmissible spongiform encephalopathies or prion diseases. These diseases are caused by the aberrant metabolism and resulting accumulation of prion proteins in the brain [68]. Clinically, patients with CJD display signs of rapidly progressive dementia, neurological symptoms, ataxia, and impaired vision [69]. The World Health Organization (WHO) diagnostic criteria for CJD includes the detection of periodic sharp wave complexes on electroencephalographic (EEG) records, spongiform changes in brain biopsy, and positive detection of CJD biomarkers in the CSF [70]. However, these diagnostic tests have proven to be somewhat inconsistent and not always practical. Thus, much effort has been placed into developing premortem assays for prompt and accurate CJD diagnosis, such as biochemical analyses of the CSF contents from CJD patients [71]. These analyses have led to the identification of several potential CJD biomarkers, including tau protein, neuron-specific enolase, amyloid beta, and 14-3-3 proteins [70-73].

Biomarker

The presence of elevated 14-3-3 proteins in CSF of CJD patients was identified by a number of groups using two-dimensional electrophoresis and immunoblot analyses [72, 74, 75]. It was further determined that only certain 14-3-3 isoforms (β, γ, ε, and η) are present in the CSF of these CJD patients [67, 76], suggesting that 14-3-3 proteins may participate in the pathological

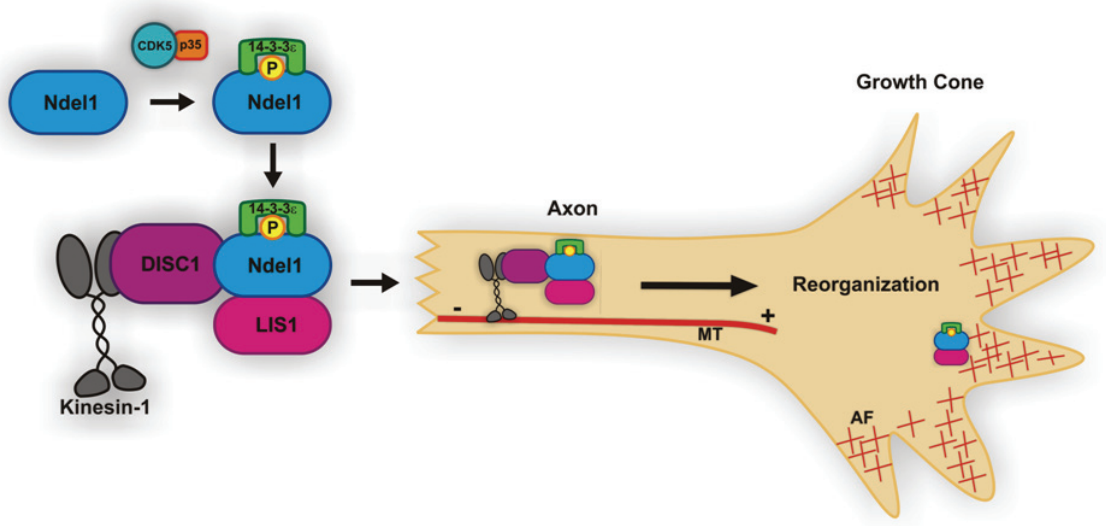

Figure 1. The Ndel1/Lis1/14-3-3ε Protein Complex for Neurite Outgrowth. 14-3-3ε binds to phosphorylated Ndel1 to promote the formation of the Ndel1/Lis1 protein complex. This protein complex binds to DISC1 and is then translocated to the axonal growth cone for cytoskeletal reorganization. Abbreviations: AF, actin filaments; MT, mircotubules; P, phosphorylation.

process of this disease. Among different subtypes of CJD, classical and frequently occurring cases have the most elevated levels of 14-3-3, whereas CJD subtypes with long disease duration and atypical clinical presentation have significantly lower levels [77, 78]. In general, the detection of CSF 14-3-3 in CJD patients has proven to be a reliable and stable biomarker for CJD and is included in the WHO diagnostic criteria [79].

Neurodevelopmental disorder

Lissencephaly

Lissencephaly, or 'smooth brain', is a neuronal migration disorder that is characterized by abnormal cortical thickness and the absence of the characteristic cerebral cortex gyri [80]. During embryogenesis, post-mitotic neurons from the ventricular zone migrate to the cortical plate. When this process is compromised, it leads to severe brain malformations such as those associated with lissencephaly [81]. Genetic factors play a large role in the pathology of lissencephaly. Specifically, the genes associated with classical lissencephaly include *LIS1*, *DCX*, *TUBA1A*, *VLDLR*, *RELN*, *ARX*, and *YWHAE* (encoding 14-3-3ε) [82]. There are different classifications of lissencephalies based on the severity of malformations and their underlying genetic cause. Among them, Miller-Dieker syndrome (MDS), a more severe form of classical lissencephaly, is associated with craniofacial defects and results from a deletion in 17p13.3 that includes genes encoding LIS1 and 14-3-3ε proteins [83, 84].

The Ndel1/Lis1/14-3-3ε complex

14-3-3 proteins, particularly the ε isoform, are functionally important in neuronal development [13]. One potential underlying mechanism involves the Ndel1/LIS1/14-3-3ε protein complex that is critical for proper neuronal migration by promoting the recruitment, organization, and movement of microtubules (**Figure 1**). In this pathway, 14-3-3ε interacts with phosphorylated Ndel1, protecting it from dephosphorylation, which in turn allows for the recruitment of LIS1 to this protein complex [81, 83, 85]. DISC1 is thought to regulate the translocation of this Ndel1/LIS1/14-3-3ε complex to axonal growth cones by linking it to the Kinesin-1 motor. Disruptions in the axonal transport of this protein complex result in improper neuronal migration and development, which is implicated in neurodevelopmental diseases such as lissencephaly and schizophrenia [83, 86].

Evidence

14-3-3ε's pivotal role in neuronal migration and development has been further validated by ro-

dent studies and clinical reports. Mice deficient in 14-3-3ε display changes in their brain structures, which include hippocampal defects, cortical thinning, decreased migrational distances and increased neuronal cell death. Moreover, mice with 14-3-3ε and *LIS1* mutations exhibit more severe neuronal migration defects compared to mice with a single mutation [83]. In humans, small deletions encompassing the 14-3-3ε gene lead to dramatic neurodevelopmental defects including malformations of the cortex, corpus callosum, and other brain regions. These patients also display significant postnatal growth retardation, mild to moderate mental retardation and facial dysmorphic manifestations [87, 88]. Moreover, 14-3-3ε gene microduplications result in autistic manifestations, subtle facial dysmophic features, and a tendency for postnatal overgrowth in patients [89].

Neuropsychiatric disorders

Schizophrenia

Schizophrenia is a life-long neuropsychiatric disorder that is among the leading causes of disease-related disabilities in the world. Schizophrenia is characterized by a combination of positive, negative and cognitive symptoms which vary in severity [90]. Diagnosis is based on the presence of hallucinations, delusions and disorganized thoughts and behavior. In particular, reality distortion is thought to mark the actual onset of schizophrenia [91]. Although the precise cause of schizophrenia is not fully understood, evidence from family, twin and adoption studies has indicated that this neurological disorder has a high degree of heritability [92].

Genetic association

Genetic analyses have suggested a linkage between schizophrenia and the chromosomal region 22q12-13, in which 14-3-3η gene *YWHAH* is located [93]. Indeed, a significant association between single nucleotide polymorphisms (SNP) of the 14-3-3η gene and schizophrenia has been established in a majority of studies using human samples from different ethnic groups [94-96]. In addition, genetic and post-mortem mRNA analyses have identified other 14-3-3 isoforms as potential susceptibility genes for schizophrenia, including the genes encoding 14-3-3ε and ζ (**Table 2**) [97-99].

Expression changes

A number of studies have identified down-regulations of 14-3-3 mRNAs in the brain samples of schizophrenia patients (**Table 2**). In particular, 14-3-3η was found to have a significantly decreased mRNA level in the cerebellum of schizophrenics [100]. Another study also revealed significant reductions in mRNA expression levels of six 14-3-3 isoforms (β, η, ε, σ, θ, and ζ) in the prefrontal cortex of schizophrenia patients [101]. In addition, proteomic analyses have determined a reduction of 14-3-3 proteins in schizophrenic brains, with 14-3-3ζ decreased expression having been consistently reported in multiple studies [102].

Animal models

In light of its high degree of heritability, various animal models have been created to examine the potential genetic causes of schizophrenia (**Table 2**). Among them, the 14-3-3ε heterozygous knockout mice were initially proposed to be a schizophrenia-related animal model based on the presence of hippocampal and cortical structure alterations and behavioral endophenotypes such as deficits in working memory [99]. Recently, it was reported that deletion of the 14-3-3ζ isoform in mice results in neurodevelopmental abnormalities of the hippocampus. The 14-3-3ζ knockout mice also exhibit behavioral changes that are characteristic of schizophrenic animal models including hyperactivity, impaired learning and memory, and reduced prepulse inhibition [103]. Moreover, we have generated several lines of 14-3-3 functional knockout mice by transgenically expressing the 14-3-3 binding antagonist (R18 peptide), which competitively inhibits all 14-3-3 isoforms in specific regions of the mouse brain [104]. Thus far, our analyses revealed that some 14-3-3 functional knockout lines exhibited a variety of behavioral endophenotypes consistent with current schizophrenic animal models. Interestingly, these behavioral deficits were correlated with a high level of 14-3-3 binding antagonist expression in hippocampus and prefrontal cortex, which are the two key brain regions affected in schizophrenia (Foote et al, in preparation). Collectively, these findings provide strong support for the involvement of 14-3-3 proteins in this complex mental disease. Future studies utilizing these and other 14-3-3 animal models may help identify the altered cellular processes in schizophrenia and aid the

Table 2. Genetic Evidence of 14-3-3 proteins in neurological disorders.

14-3-3	Gene	Chromosome	Neurological Disorder/Genetic Evidence		Reported By
β	YWHAB	20q13.1	SZ	↓ Cortex Expression	Middleton et al., 2005
γ	YWHAG	7q11.23	SZ	↓ Cortex Expression	Wong et al., 2003
ε	YWHAE	17p13.3	BP	SNP association	Higgs et al., 2006; Liu et al., 2010
			MDS	14-3-3ε-deficient mice	Toyo-oka et al., 2003
			SZ	↓ Cortex Expression	Middleton et al., 2005
				DISC1 interacting protein	Ikeda et al., 2008
				14-3-3ε-deficient mice exhibit SZ behaviors	Toyo-oka et al., 2003
ζ	YWHAZ	8q23.1	BP	↓ DLPFC Expression	Wong et al., 2005 ; Elashoff et al., 2007
			SZ	↓ Cortex Expression	Middleton et al., 2005
				SNP association	Wong et al., 2005
				14-3-3ζ-KO mice exhibit SZ behaviors	Cheah etal., 2011
η	YWHAH	22q12.3	BP	Chromosomal location	Muratake et al., 1996; Potash et al., 2003
				SNPs association	Fallin et al., 2005; Grover et al., 2009; Pers et al., 2011
			SZ	Chromosomal region location	Muratake et al., 1996; Toyooka et al., 1999
				↓ Cerebellum Expression	Vawter et al., 2001
				↓ Cortex Expression	Middleton et al., 2005
				SNP association	Toyooka et al., 1999; Wong et al., 2003
σ	SFN	1p35.3	SZ	↓ Cortex Expression	Middleton et al., 2005
θ	YWHAQ	2p25.1	BP	↓ DLPFC Expression	Elashoff et al., 2007
			SZ	↓ Cortex Expression	Middleton et al., 2005

Abbreviations: BP, Bipolar disorder; DLPFC, dorsolateral prefrontal cortex; MDS, Miller-Dieker syndrome; SNP, single nucleotide polymorphism; SZ, schizophrenia; KO, knockout

development of new drug therapies.

Bipolar disorder

Bipolar disorder is a severe psychiatric illness described as alternations between mania and depression, with periods of normal mood [105]. Several lines of evidence suggest an overlapping of schizophrenia and biopolar disorder, both in their clinical presentation and candidate risk genes [106, 107]. Along these lines, 14-3-3 proteins have also been linked to BP.

Genetic association

Linkage studies have identified specific chromosomal regions that share candidate risk genes for both bipolar disorder and schizophrenia (**Table 2**). One such associated region is 22q12-13, which contains the gene for 14-3-3η (YWHAH) [93, 106, 107]. In fact, a genetic analysis study has identified 5 SNPs of YWHAH in a sample set that consists of 1,211 subjects from 213 nuclear families including 554 bipolar -positive offspring [108]. Moreover, YWHAH was found to have a statistically significant association with bipolar disorder based on findings from a recent meta-analysis that prioritized genes by combing information from genome-wide associations, candidate gene interaction, linkage intervals, phenotype similarity and differential gene expression studies [109].

Other genetic evidence

In addition to 14-3-3η, other 14-3-3 isoforms have been implicated in bipolar disorder (**Table 2**). Several microarray studies have identified decreased mRNA expression levels of 14-3-3ε, -σ and -ζ in brain samples from bipolar patients [98, 110, 111]. Furthermore, genetic analyses have begun to reveal additional associations of

other 14-3-3 isoforms with this neurological disorder. Recently, one of these studies was conducted using samples from a Han Chinese population, in which three SNPs of *YWHAE* (14-3-3ε) were considered to have a marginal association with bipolar disorder [112].

Conclusion

Supported by data from *in vitro* studies, animal models, post mortem analyses and genetic associations, 14-3-3 proteins have become an interesting target for the investigation of their role in various neurodegenerative and neuropsychiatric diseases. Given their multitude of binding partners and critical roles in various physiological processes, 14-3-3 proteins should be considered a pathfinder into further exploration of the neurobiological and pathological basis underlying these neurological disorders.

Acknowledgements

This work was supported by NIH grant NS50355 (to Y.Z.). We thank people in the Zhou lab for permitting us to discuss their unpublished results. We would also like to thank Kourtney Graham for her help in editing this manuscript.

Abbreviations: PD, Parkinson's disease; ARJP, Autosomal Recessive Juvenile Parkinsonism; LRRK2, leucine-rich repeat kinase 2; AD, Alzheimer's disease; NFTs, neurofibrillary tangles; GSK3β, glycogen synthase kinase-3 beta; CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; BP, Bipolar disorder; DLPFC, dorsolateral prefrontal cortex; MDS, Miller-Dieker syndrome; SNP, single nucleotide polymorphism; SZ, schizophrenia

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