



Functions of GSK-3 signaling in development of the nervous system

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Glycogen synthase kinase-3 (GSK-3) is central to multiple intracellular pathways including those activated by Wnt/ β -catenin, Sonic Hedgehog, Notch, growth factor/RTK, and G protein-coupled receptor signals. All of these signals importantly contribute to neural development. Early attention on GSK-3 signaling in neural development centered on the regulation of neuronal polarity using *in vitro* paradigms. However, recent creation of appropriate genetic models has demonstrated the importance of GSK-3 to multiple aspects of neural development including neural progenitor self-renewal, neurogenesis, neuronal migration, neural differentiation, and synaptic development.

Keywords: GSK-3, neural progenitor, neuronal migration

INTRODUCTION

Glycogen synthase kinase-3 (GSK-3), a serine–threonine kinase, was originally identified as an important component of the glycogen metabolism pathway. Later, however, it was found to be an important regulator in multiple intracellular contexts. Recent studies using pharmacological and genetic approaches have suggested important functions for GSK-3 in an array of neural developmental activities including neural progenitor homeostasis, neuronal migration, neurite growth/specification, and synapse development. Further, recent data indicate that the Disrupted in Schizophrenia protein, DISC1, acts in part via GSK-3 suggesting that dysregulated GSK-3 activity during development may contribute to the pathogenesis of schizophrenia. Multiple proteins that play important roles during neural development have been identified as either GSK-3 substrates or binding partners (Table 1).

ISOFORMS OF GSK-3 IN THE NERVOUS SYSTEM

In mammals, the GSK-3 family consists of two members, GSK-3 α and GSK-3 β that show 98% sequence identity within their kinase domains and overall share 85% amino acid sequence identity (reviewed in Doble and Woodgett, 2003). Both GSK-3 isoforms are highly expressed in the nervous system including brain and spinal cord. There are two splice variants of the GSK-3 β and one variant GSK-3 β 2 is highly expressed in the developing nervous system (Mukai et al., 2002). It is interesting that GSK-3 β 2 is only expressed in differentiated neurons, not in glial cells while GSK-3 β 1 is expressed in glial cells (Wood-Kaczmar et al., 2009). Further, GSK-3 β 2 is upregulated in PC12 cells when induced by nerve growth factor to differentiate into a neuronal phenotype (Goold and Gordon-Weeks, 2001). These findings suggest that differential regulation of GSK-3 β isoform levels may be important in the initiation of neuronal differentiation and the maintenance of neurons during nervous system development.

Most functional studies of GSK-3 functions in mammalian neural development have relied on pharmacological inhibitors in dissociated preparations. However, since pharmacological GSK-3 inhibitors target ATP-binding pockets of both isoforms, distinctive functional analysis of each isoform using pharmacological inhibitors is not possible. Recently, studies in gene targeted mice have begun to yield decisive information regarding the roles of GSK-3 isoforms in neural development. Gene targeting of GSK-3 β leads to late embryonic lethality via liver apoptosis or heart defects (Hoeflich et al., 2000; Kerkela et al., 2008). Surprisingly, the developing nervous system of GSK-3 β null mice including the brain and spinal cord exhibits grossly normal morphology (Kim et al., 2006). GSK-3 β heterozygous (+/–) mice, however, show multiple neurobehavioral abnormalities including aggressive behaviors, increased anxiety, reduced movement, and poor memory processing (O'Brien et al., 2004; Beaulieu et al., 2008; Kimura et al., 2008). Further, overexpression of GSK-3 β in the brain results in hyperactivity and mania (Prickaerts et al., 2006). Finally GSK-3 β is important in signaling downstream of dopamine receptors (Beaulieu et al., 2004). These results demonstrate that the GSK-3 β isoform has important functions in regulation of behavior, probably via regulation of signaling downstream of neurotransmitter receptors.

GSK-3 α null mice are viable and fertile (MacAulay et al., 2007) and show no abnormalities of gross anatomy in the developing brain (Kim et al., 2009; Yokota et al., 2010). However, young adult GSK-3 α null mice show decreases in the size and number of cerebellar Purkinje cells and changes in social interaction and locomotion (Kaidanovich-Beilin et al., 2009). GSK-3 α deletion also partially rescues the dendritic abnormality in cortical neurons of DISC1-L100P mutant mice that show reduced spine density compared to wild type mice (Lee et al., 2011). Further, GSK-3 α null mice are hypersensitive to insulin (MacAulay et al.,

Table 1 | Glycogen synthase kinase-3-interacting proteins associated with neural development and diseases.

Name	Neural development	Diseases
Amyloid precursor protein	Neurogenesis, neuron migration, synaptic development	Alzheimer
APC	Neurogenesis, neuron migration, neurite growth/polarization	Autism, cancer
Axin	Neurite growth/polarization	Cancer
β -catenin	Progenitor renewal, neurogenesis, neuron migration, neurite growth/polarization, synaptic development	Cancer
CDK5	Neurogenesis, neuron migration, synaptic development	Alzheimer, Parkinson, Huntington, ALS
c-Jun	Progenitor apoptosis, neuron migration, neurite growth/polarization	Cancer, Alzheimer, Parkinson
CLASP1, CLASP2	Neurite growth/polarization	
c-Myb	Progenitor renewal, neuronal apoptosis	Cancer, liver disease
c-Myc	Progenitor renewal, neurite growth/polarization	Cancer, Alzheimer
CREB	Progenitor renewal, neurogenesis, neuron migration, neurite growth/polarization, synaptic development	Alzheimer, Huntington
CRMP2	Neurite growth/polarization	Alzheimer
cyclin D1	Progenitor renewal, neurogenesis	Cancer
δ -catenin	Neurite growth/polarization, synaptic development	Cri-du-Chat Syndrome
DISC1	Progenitor renewal, neuron migration, neurite growth/polarization synaptic development	Schizophrenia, autism
Dvl	Neurite growth/polarization	Cancer
eIF2B	Neurite growth/polarization	Leukoencephalopathy
Kinesin light chain	Progenitor renewal, neuron migration, neurite growth/polarization	Alzheimer, ALS
LRP6	Dopaminergic neuron differentiation	Heart disease
MAP1B	Neurite growth/polarization	Fragile X syndrome, giant axonal neuropathy, Alzheimer, Parkinson
MAP2	Neurite growth/polarization	Alzheimer
Myelin basic protein	Myelination	MS, seizure
NCAM	Neuron migration, neurite growth/polarization	Depression, Alzheimer, Parkinson
NeuroD	Neurogenesis, neurite growth/polarization	
Neurogenin2	Neurogenesis, neurite growth/polarization	
NFAT	Progenitor renewal, neurogenesis, neurite growth/polarization	Cancer, Alzheimer, heart disease, kidney disease
Ninein	Progenitor renewal, neurite growth/polarization	
P53	Neurite growth/polarization, neuronal apoptosis	Cancer
Presenilin 1	Neuron migration, neurite growth/polarization, synaptic development	Alzheimer
PTEN	Progenitor renewal, neurogenesis, neuron migration, neurite growth/polarization, synaptic development	Autism, cancer, Cowden syndrome
SMAD1	Neurite growth/polarization	
Tau	Neurite growth/polarization	Alzheimer
TSC2	Neuron migration, neurite growth/polarization	Tuberous sclerosis, autism

2007), suggesting the potential roles of GSK-3 α in hypothalamic regulation. Using brain lysates of GSK-3 α null, β null, and double knockout mice, a recent study has demonstrated isoform-specific activities on substrate phosphorylation in the brain. Each isoform produces distinct phosphorylation patterns of CRMP2, CRMP4, and Tau (Soutar et al., 2010). Together, these results indicate that GSK-3 α isoform has important specific functions in postnatal neuroanatomy and behavioral regulation.

The lack of gross brain developmental abnormalities in GSK-3 α null and GSK-3 β null mice suggests that either isoform might compensate for the other in the regulation of differentiation, survival, and morphogenesis of neurons and glia. Indeed, axon and dendritic morphogenesis is normal in cultured hippocampal neurons from GSK-3 β null embryonic brains (Kim et al., 2006). However,

genetic elimination of GSK-3 using an shRNA that targeted both GSK-3 isoforms lead to strong changes in axon and dendritic morphogenesis in cultured hippocampal neurons (Kim et al., 2006). Further, the possibility of compensation has now been confirmed *in vivo*. Conditional elimination of both GSK-3 α and β at an early stage (\sim E10) of mouse nervous system development results in dramatic effects on murine brain development (Kim et al., 2009).

REGULATION OF NEURAL PROGENITORS

There are several types of neural progenitors in rodent developing brains (Figure 1). Radial neural progenitors are a major population of neural progenitors and occupy the ventricular zone in the developing brain. They display long radial processes to form a scaffold covering from apical ventricular membrane to pial surface.

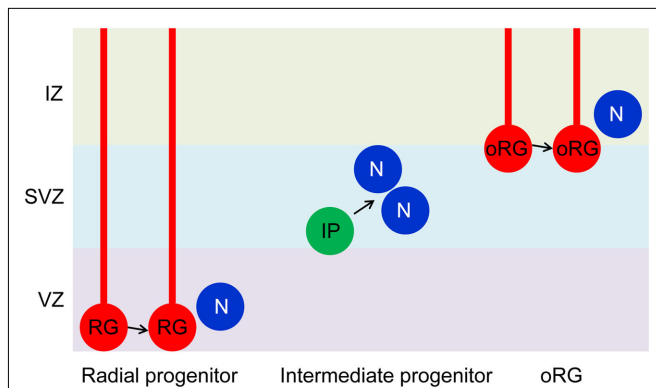


FIGURE 1 | Neural progenitors in the developing brain. Radial glial progenitors (RG) arise early in development from neuroepithelial cells. They are located in the ventricular zone (VZ) and have long radial processes that extend from VZ to the pial surface. A RG divides symmetrically to self-renew and asymmetrically to generate a daughter RG and a post-mitotic neuron or an intermediate progenitor (IP). IPs localize in the subventricular zone (SVZ) and divide symmetrically to produce neurons. There is another type of progenitors (oRG) in the superficial layer of SVZ or in the intermediate zone (IZ). Like RGs, oRGs have glial processes and can self-renew as well as generate neurons. For more information on oRG, see a recent review by Kriegstein and colleagues (Lui et al., 2011). The role of GSK-3 in regulating radial progenitors is now established. Functions related to IPs and oRGs remain to be investigated.

This scaffold supports neuronal migration. Intermediate progenitors in the subventricular zone execute only the final neurogenic division. In addition to radial and intermediate progenitors, there are other types of neural progenitors more prominent in higher species. Importantly, recent studies show existence of a greatly expanded oRG (outer subventricular zone progenitors) in human (Hansen et al., 2010) and mice (Wang et al., 2011). oRG progenitors are located in the outer region of the subventricular zone in rodent. Unlike intermediate progenitors, this type of progenitor can undergo self-renewal as well as symmetric neurogenesis.

EFFECTS OF GSK-3 α AND β DELETION

Recent pharmacological evidence has strongly implicated GSK-3 signaling in the regulation of embryonic stem cell self-renewal (Sato et al., 2004; Umehara et al., 2007; Ying et al., 2008; Bone et al., 2009). Further, DISC1 implicated in some familial cases of schizophrenia and depression, regulates neural progenitor proliferation and may act in part via regulation of GSK-3 activity (Mao et al., 2009). These observations underscore the importance of determining GSK-3 functions in relation to neural progenitor self-renewal and neurogenesis during brain development *in vivo*.

The functions of GSK-3 in mammalian brain development remained unclear because GSK-3 single isoform mutants had not been associated with major brain developmental abnormalities (see above). The results, however, did not exclude possible compensatory effects of one GSK-3 isoform for the other in single null mutant animals (Doble et al., 2007). To explore GSK-3 functions definitively, a recent study pursued a conditional knockout strategy in which a GSK-3 β floxed allele was bred onto GSK-3 α null background to allow tissue specific elimination of GSK-3 signaling

(Kim et al., 2009). This study used a mouse strain expressing Cre recombinase under the control of the neural specifying elements of the nestin promoter (Tronche et al., 1999) to induce recombination around E10 in neuroepithelial cells as they convert to radial progenitors and initiate neurogenesis (Yoon et al., 2008; Yokota et al., 2009). The study conclusively demonstrated that elimination of both GSK-3 isoforms in the developing brain lead to a massive increase in neural progenitor proliferation. This increase was indicated by infolding of the developing cortical wall, major increases in numbers of cells that expressed mitotic markers, and a dramatic expansion of the population of neural progenitors expressing Sox2. GSK-3 double knockout brains showed increased progenitor division, premature re-entry and shortening of the cell cycle.

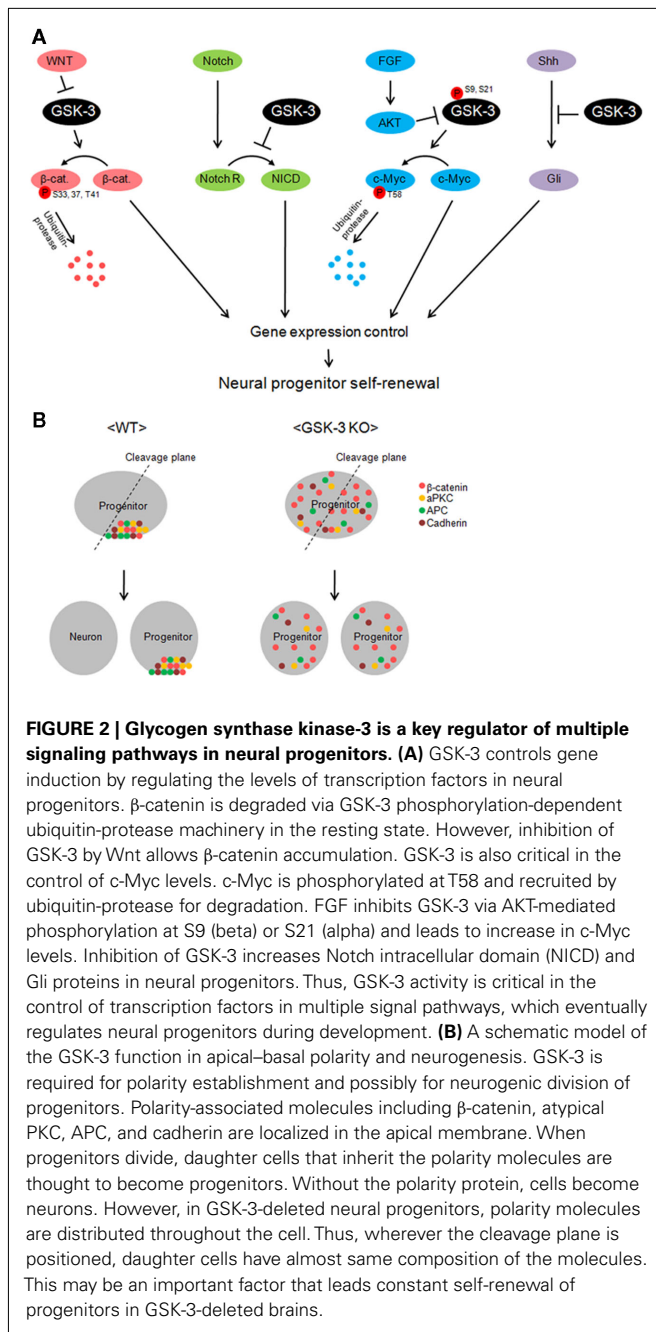
Glycogen synthase kinase-3 deficient cells appeared to be locked into the radial progenitor phase as generation of both intermediate neural progenitors and post-mitotic neurons was markedly suppressed. In contrast to the expansion of Sox2-positive radial progenitors, the population of intermediate neural progenitors marked with Tbr2 was dramatically down-regulated in GSK-3 double knockout brains (Kim et al., 2009). Consistent with this finding, only around one-third of the normal number of neurons was generated in GSK-3 double knockout brains. Although deletion of GSK-3 prevented progression of most cells beyond the radial progenitor phase, a few progenitors were still capable of differentiation as manifested by expression of Tbr2 and markers of post-mitotic neurons. Whether some progenitors can truly progressed independently of GSK-3 signaling or whether the differentiated cells represented a population of radial progenitors that had some persistent GSK-3 proteins due to either late or incomplete deletion of GSK-3 remained unclear.

MECHANISMS ASSOCIATED WITH GSK-3 REGULATION OF NEURAL PROGENITORS

Multiple extracellular signals and intracellular signaling mechanisms that regulate neural progenitor proliferation and differentiation have been identified (reviewed in Corbin et al., 2008). The mechanisms that have received the most attention in the dorsal telencephalon are β -catenin/LEF1 and Notch signaling (Figure 2A). Whether these mechanisms operate independently or are coordinately regulated is an interesting question. GSK-3 has the potential to influence both mechanisms. It is important to emphasize that GSK-3s are also key components in pathways downstream of two extracellular signals, FGF2 and Shh, which also strongly regulate progenitor proliferation in the developing telencephalon (Figure 2A; Vaccarino et al., 1999; Raballo et al., 2000; Komada et al., 2008; Shimizu et al., 2008).

β -Catenin signaling and GSK-3

It is well known that regulation of β -catenin is critical to control of progenitor proliferation in multiple regions of the developing nervous system (Chenn and Walsh, 2002; Machon et al., 2003, 2007; Zechner et al., 2003; Woodhead et al., 2006; Gulacsi and Anderson, 2008). As expected, β -catenin was increased substantially in GSK-3 double knockout brains, consistent with the critical importance of GSK-3 in phosphorylating β -catenin in the destruction complex that mediates canonical Wnt signaling (Kim et al.,



2009). However, stabilization of β -catenin alone may not have fully accounted for the effects of progenitor hyperproliferation in GSK-3 double knockout brains. Although it is difficult to compare studies directly, it appears that the enlarged brain observed upon overexpression of a stabilized β -catenin is associated with a more normal pattern of neuronal differentiation than GSK-3 double knockout brains (Chenn and Walsh, 2002, 2003; Kim et al., 2009). Further, elimination of β -catenin in neural progenitors reduces but does not eliminate progenitor proliferation *in vivo* (Machon et al., 2003; Zechner et al., 2003; Gulacsi and Anderson, 2008). Finally, overexpression of dominant-negative TCF only partially inhibited proliferation in GSK-3 knockout neural progenitors *in vitro* (Kim

et al., 2009). Thus, GSK-3 may regulate self-renewal of neural progenitors by mechanisms in addition to β -catenin signaling.

Notch signaling and GSK-3

Notch signaling is critical to the maintenance and the identity of radial glial cells during development (Gaiano et al., 2000; reviewed in Ohtsuka et al., 2001; Hatakeyama et al., 2004; Yoon and Gaiano, 2005; Mizutani et al., 2007; Shimojo et al., 2008). There are several mechanisms by which GSK-3 may regulate Notch signaling both directly and indirectly (Foltz et al., 2002; Espinosa et al., 2003; Uemura et al., 2007; Hayward et al., 2008; Shimizu et al., 2008; Jin et al., 2009a). For example, GSK-3 β is able to bind and phosphorylate Notch2 *in vitro* and *in vivo* (Espinosa et al., 2003). The GSK-3 α isoform likely has the same function, because the phosphorylation was inhibited by the treatment of Wnt (Espinosa et al., 2003). Thereby, GSK-3 inhibits the transcriptional activation of Notch target genes. Also, β -catenin reportedly enhances the level and transcription activity of Notch1 (Shimizu et al., 2008; Jin et al., 2009b). Meanwhile, there are conflicting studies with regard to the role of GSK-3 in Notch signaling, in which inhibition of GSK-3 using pharmacological drugs or genetic tools decreased NICD levels in neuroblastoma cells (Foltz et al., 2002) and vascular smooth muscle cells (Guha et al., 2011).

Notch signaling was shown to be increased in GSK-3 double knockout brains (Kim et al., 2009). Levels of Notch intracellular domain were markedly enhanced as were levels of the Notch downstream signaling mediators Hes1 and Hes5. Further, immunohistochemical data suggested that most or all of the extra progenitors in GSK-3 double knockout mice express high levels of Hes1 protein, indicative of active Notch signaling in these cells. Levels of Jagged-1, a Notch agonist, were increased in GSK-3-deleted brain lysates, suggesting that the activation of Notch pathway upon GSK-3-deletion requires a Notch agonist. This is different from the activation of β -catenin signal, which is induced in GSK-3-deleted cells in the absence of Wnt ligands (Doble et al., 2007). Overexpression of a dominant-negative Hes1 and pharmacological inhibition of Notch signaling partially inhibited proliferation in GSK-3-deleted progenitors (Kim et al., 2009). Interestingly, Notch signaling levels distinguish radial progenitors from intermediate neural progenitors that have attenuated canonical Notch signaling (Mizutani et al., 2007). Therefore, high levels of Notch signaling in GSK-3 double knockout cells may have suppressed neurogenesis at the stage of radial progenitors such that few cells progress to the stage of Tbr2-positive intermediate neural progenitors. However, whether GSK-3 regulated Notch signaling directly or indirectly via regulation of β -catenin or some other mechanism was not established.

GSK-3 regulation of Myc

GSK-3 is a downstream mediator of FGF/PI3K signaling in neural progenitors (Shimizu et al., 2008). Several recent studies have demonstrated that GSK-3 regulates the stability of Myc family proteins via the PI3K pathway (reviewed in Knoepfler and Kenney, 2006; Bechard and Dalton, 2009; reviewed in Doble and Woodgett, 2009; Otto et al., 2009). It is important to emphasize that GSK-3 can directly regulate the stability of Myc family proteins, independently of β -catenin effects on Myc transcription (Bechard

and Dalton, 2009; reviewed in Doble and Woodgett, 2009; Otto et al., 2009). Interestingly, these effects are thought to be downstream of RTK/PI3K rather than Wnt/Frizzled signaling (reviewed in Knoepfler and Kenney, 2006). Myc family proteins are key elements in the maintenance of neural progenitors by inhibiting differentiation (Knoepfler et al., 2002; Wey et al., 2010). Phosphorylation of c-Myc at T58 thought to be a key to its stability is regulated by GSK-3. The GSK-3-mediated phosphorylation at T58 plays an important role in inducing cell differentiation, as inhibition of the phosphorylation maintains embryonic stem cell pluripotency (Cartwright et al., 2005). This phosphorylation was shown to be eliminated in GSK-3 double knockout brains and the level of c-Myc was increased (Kim et al., 2009). Given the short half-life cycle of c-Myc (~20 min; reviewed in Eilers and Eisenman, 2008), control of c-Myc stability via T58 phosphorylation may be a critical step in GSK-3 regulation of neural progenitor self-renewal.

Myc binds to promoters of many genes including cyclins and regulates their transcription. This traditional role as a transcription factor has been primarily considered in maintaining self-renewal and in inhibiting differentiation of stem cells. But several recent reports suggest that Myc contributes to stem cell maintenance in other ways by globally maintaining the histone acetylation and methylation euchromatin state (Lin et al., 2009; reviewed in Varlakhanova and Knoepfler, 2009; Araki et al., 2011). Whether Myc elicits changes in histone methylation patterns of promoters in neural progenitors and whether GSK-3 is associated with this process remain to be elucidated. Further characterization of functional genomic analysis will likely elucidate Myc functions as epigenetic transcriptional regulator in neural progenitors.

Apical–basal polarity and GSK-3

Cell polarity is a fundamental property of all cells including neural progenitors. GSK-3 is thought to be a key regulator of cell polarity and microtubule-cytoskeleton regulation based on *in vitro* studies (Etienne-Manneville and Hall, 2003; reviewed in Buttrick and Wakefield, 2008). GSK-3 directly binds to polarity-associated proteins including APC (Adenomatous polyposis coli), EB1 (End binding 1), and CLASPs (Cytoplasmic linker-associated proteins) and regulates their activities by phosphorylation. For example, APC and CLASPs promote microtubule stability and their phosphorylation by GSK-3 inhibits microtubule binding, thus destabilizing microtubules (Akhmanova et al., 2001; Zumbunn et al., 2001). Asymmetric cell division results from polarized deposition of polarity proteins and it is required for neurogenic division of radial neural progenitors (Gotz and Huttner, 2005). Apical–basal polarity indicated by the distribution patterns of cell polarity/adhesion proteins including APC, EB1, cadherin, and aPKC was disrupted in GSK-3-deleted developing brains (Kim et al., 2009). Thus, the expansion of the radial progenitor pool and inhibition of neurogenesis in GSK-3-deficient brains may be attributed in part to the dysregulation of polarity-associated proteins (Figure 2B). Localized distribution patterns of apical molecules may be coordinated by GSK-3 regulation of the microtubule apparatus or motor proteins. In this regard, it is notable that elimination of polarity-associated molecules, Lgl1 and α E-catenin results in a major hyperproliferation of neural progenitors (Klezovitch et al., 2004; Lien et al., 2006).

It has also been demonstrated that GSK-3 regulates centrosome reorientation and microtubule spindle formation during cell division (Wakefield et al., 2003; Cheng et al., 2008; Izumi et al., 2008). Dysregulation of centrosome positioning and cleavage planes may favor divisions that result in additional progenitors rather than post-mitotic neurons (reviewed in Higginbotham and Gleeson, 2007). An important implication of these findings is that apical–basal polarity and centrosome positioning may be among of the mechanisms responsible for GSK-3-mediated neural progenitor homeostasis.

DISC1 and GSK-3 signaling

A recent study has shown that GSK-3 binds to DISC1 and that pharmacological inhibition of GSK-3 can mitigate effects of DISC1 shRNA knockdown on neural progenitor proliferation *in vitro* (Mao et al., 2009). DISC1 protein does not have enzymatic activity, rather it functions as a physiological scaffold by interacting with multiple proteins to modulate their functional activities. For example, DISC1 binds to NUDEL (Duan et al., 2007) and girdin (Enomoto et al., 2009), and modulates the activities of these proteins in adult neural progenitors and their progeny. Likewise, DISC1 may serve as an important scaffold to bridge GSK-3 and its regulators in neural progenitors during development.

HOMEOSTATIC CONTROLS IN NEURAL PROGENITORS

During nervous system development, an over-abundance of cells is produced presumably to accommodate the significant loss of cells that fail to achieve functionality. This overproduction allows for remarkable plasticity in nervous system development but requires exquisite inductive coordination. Temporal and spatial regulation of GSK-3 activity during nervous system development must be achieved in order to terminate neural progenitor proliferation and allow differentiation at just the right moment to yield the correct number of neurons. It is remarkable that regulation of the activity of a single kinase provides a powerful and simple mechanism to control neural progenitor homeostasis.

The functions of GSK-3 in radial neural progenitors have been discussed above. However, whether GSK-3 has significant roles in intermediate progenitors and oRGs remains to be elucidated. It will be important to see if GSK-3-deletion also results in self-renewal of these progenitors.

GSK-3 SIGNALING IN NEURONAL MIGRATION

After progenitor proliferation and neurogenesis, post-mitotic neurons migrate to final locations which in the cortex results in proper lamination. There is increasing evidence that GSK-3 may be important in regulating neuronal migration.

Wnt SIGNAL AND NEURON MIGRATION IN *C. ELEGANS*

Recent studies have shown that Wnt family molecules play important roles in controlling anterior/posterior (AP)-directed neuronal cell migration and polarity in *C. elegans* (reviewed in Silhankova and Korswagen, 2007). Multiple Wnt proteins function in parallel as instructive cues or permissive signals to control neuronal migration along the AP axis. EGL-20/Wnt1 is one of the five Wnt proteins of *C. elegans* and specifies posterior direction of Q neuroblast migration (Harris et al., 1996; Maloof et al., 1999). This protein activates a canonical Wnt pathway (β -catenin-dependent)

in the Q neuroblast (Salser and Kenyon, 1992; reviewed in Korswagen, 2002). Accordingly, overexpression of SGG-1, the *C. elegans* GSK-3 β ortholog induced defects in Q cell migration far toward anterior region (Korswagen et al., 2002). Together, these suggest that GSK-3 signaling plays an important role in *C. elegans* neuron migration by negatively regulating Wnt signaling.

Wnt SIGNALING MOLECULES AND NEURONAL MIGRATION IN MICE

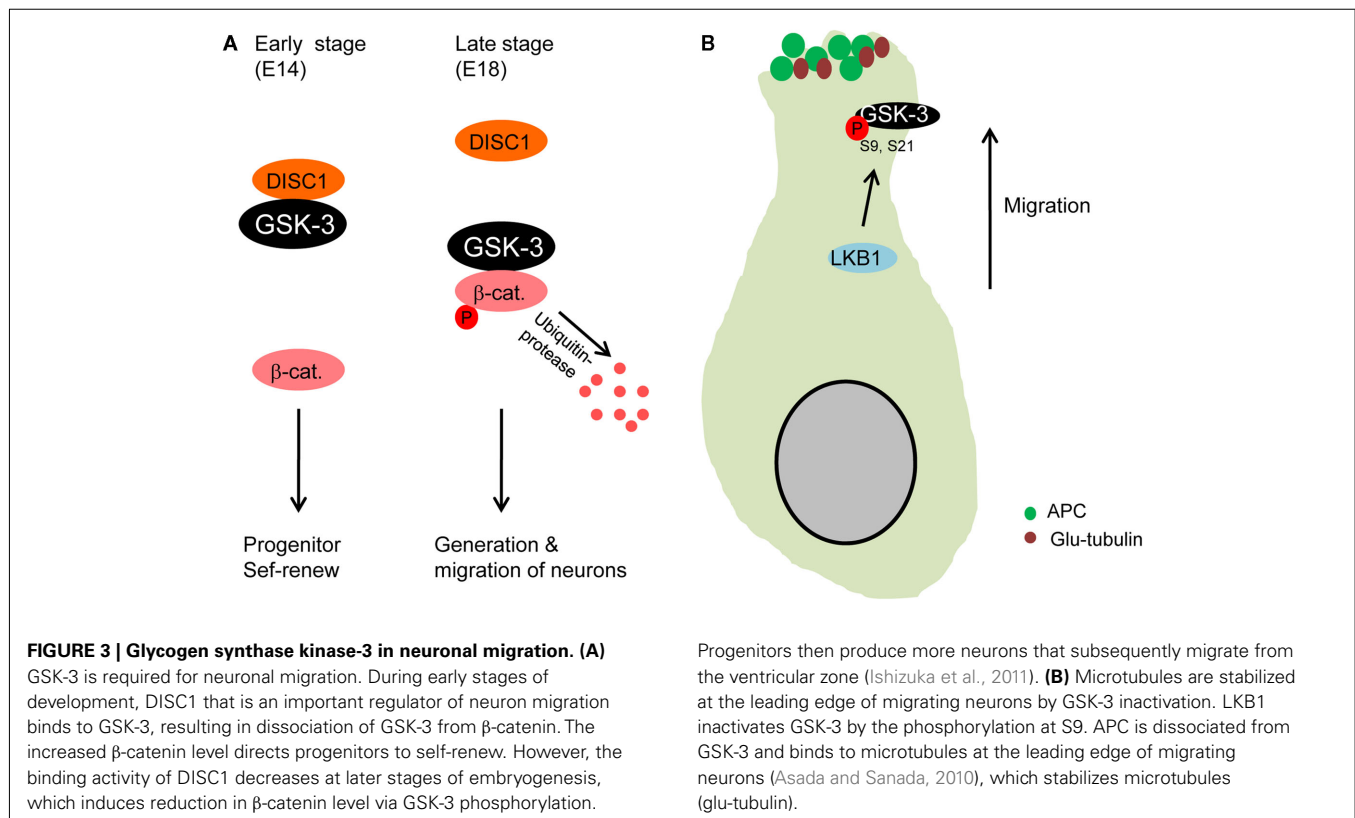
Considerable evidence both direct and indirect now implicates GSK-3 in regulation of neuronal migration in mice. Some evidence has come from functional studies of the GSK-3 target and destruction complex component, APC. In addition to its role in the destruction complex, APC is a microtubule-associated protein and participates in microtubule-based cytoskeleton dynamics (Barth et al., 2008). GSK-3 directly binds to APC and phosphorylates it in order to regulate its activity. APC phosphorylation by GSK-3 dissociates APC from microtubules. A recent study has demonstrated that APC serves an essential function in the maintenance of the polarized radial glial scaffold during mouse brain development (Yokota et al., 2009). Elimination of APC in radial progenitors by conditional gene targeting lead to striking defects in cortical lamination, suggesting an important role for APC in neuronal migration. However, it is not clear whether migration defects were entirely due to disruption of the radial glia scaffold or whether APC regulation of microtubules in neurons also contributed. It will be important to settle this issue with conditional elimination of APC specifically in early post-mitotic cortical neurons.

GSK-3 may also affect neuronal migration via regulation of β -catenin. Several studies have shown that genetic manipulation

of β -catenin by either deletion or overexpression of a stabilized form in mice leads to the disruption of brain and spinal cord formation (Chenn and Walsh, 2002, 2003; Zechner et al., 2003). The malformation is mostly attributed to abnormal neural progenitor development. However, there were also abnormally localized neurons found in the mutant nervous system. Further, a separate study has demonstrated that β -catenin levels in progenitors influenced cortical neuron positioning (Mutch et al., 2009). A caveat of this interpretation is that the abnormal neuronal positioning may be due to a delay in progenitor fate determination. However, the β -catenin mutation studies again strongly suggest potential roles for GSK-3 in neuronal migration.

DISC1 regulates neuronal migration during brain development (Kamiya et al., 2005) and is strongly associated with GSK-3. DISC1 binds to GSK-3 and the interaction interferes with GSK-3 inhibition of the β -catenin signal in neural progenitors, resulting in progenitor proliferation (Mao et al., 2009). Recently, the interaction between DISC1 and GSK-3 has been implicated in control of cortical neuronal migration (Ishizuka et al., 2011). DISC1 bound to GSK-3 tightly during mid-embryonic stage (E14) in which neural progenitor proliferation is active (Figure 3A). But, DISC1 was dissociated with GSK-3 during later embryonic stages (E18) when neuronal migration and neuronal differentiation become dominant. These findings suggest that the DISC1/GSK-3 interaction determines transition of neural progenitor self-renewal to neuronal migration in the developing brain.

Additional relevant evidence about the role of GSK-3 in neuron migration has been recently reported. Radial migration and



placement of cortical neurons were aberrant in GSK-3/nestin-cre mutant mice (Yokota et al., 2010). This study showed that, compared to control brains, fewer deeper layer neurons (Tbr1-positive) were found in the cortical plate of GSK-3 double knockout brains. Substantial numbers of Tbr1 neurons were trapped within the intermediate zone. Yet, GSK-3/nestin-cre mutant brains also show disrupted radial glial development (Yokota et al., 2010). The disruption of radial glial platform may indirectly create radial neuron migration defects in GSK-3/nestin-cre brains. Therefore, elimination of GSK-3 only in neuronal population needs to be done to establish whether or not GSK-3 has a direct role in neuronal migration in developing mammalian brains.

A separate study has recently shown that *in utero* electroporation with active GSK-3 β plasmid into cortical ventricular zone elicits neuronal migration defects (Asada and Sanada, 2010). LKB1 that is an important regulator of neuronal migration in the developing cortex (Asada et al., 2007) mediated GSK-3 β phosphorylation at Serine 9 residue. The phosphorylation induced high levels of APC and Glu-tubulin (stabilized microtubule) at the leading process of neurons, thereby directing centrosomal movement. However, inhibition of the Serine 9 phosphorylation by overexpressing active GSK-3 β (S9A) resulted in very low levels of APC and Glu-tubulin at the leading process of migrating neurons. These results suggest that GSK-3 inactivation via Serine 9 phosphorylation is required for directional migration of cortical neurons by rearranging APC and stabilizing microtubules at the leading process (Figure 3B). An important point of this study is that only sub-population of cortical ventricular cells are manipulated by the gene transfection, leaving surrounding environment including radial glial platform mostly intact.

Although this initial work outlined above has provided valuable information on GSK-3 functions in neuronal migration, it is important now to define the molecular and cellular mechanisms of GSK-3 regulation. For example, GSK-3 may regulate neuronal migration during development by directing gene transcription and/or by rearranging the intracellular cytoskeleton. Results from β -catenin and active GSK-3 overexpression studies strongly suggest that both mechanisms may be significant to GSK-3 regulation in neuronal migration. Defining GSK-3 functions and associated mechanisms has important clinical implications since defects in neuron migration are implicated in a range of neurodevelopmental disorders. Mutations in DISC1 are causative in some cases of schizophrenia.

NEURONAL MORPHOGENESIS

After migration, GSK-3 is critically involved in neuronal morphological development including neurite outgrowth and axon/dendritic specification. The roles of GSK-3 on axon/dendrite development are described well in the article in the same issue from Zhou and Snider.

GLIAL DEVELOPMENT

Although not yet tested, it can be anticipated that GSK-3 will also have important functions related to glial development. IGF1 and FGF2 pathways coordinately control the cell cycle progression of oligodendrocyte progenitors via cyclin D1 expression and

localization (Frederick and Wood, 2004). The turnover of this protein is regulated by GSK-3-dependent proteasome degradation (Diehl et al., 1998). GSK-3 β is phosphorylated in the presence of IGF1 downstream of PI3K/AKT signaling in oligodendrocyte progenitors (Frederick et al., 2007). This suggests that GSK-3 activity is inhibited by IGF1 in oligodendrocyte progenitors, which then enhances the stability and nuclear localization of cyclin D1 protein. Furthermore, inhibition of GSK-3 in postnatal mice by injecting pharmacological inhibitors increased oligodendrocyte differentiation and myelination (Azim and Butt, 2011). This effect was via canonical Wnt signaling stimulating β -catenin. Thus, these findings suggest that GSK-3 may be a crucial to oligodendrocyte differentiation.

Activation of PI3K and inhibition of GSK-3 using lithium promote Schwann cell differentiation (Ogata et al., 2004). This finding suggests that GSK-3 as a downstream of PI3K-AKT pathway is crucial for initiation of myelination during development. It will be important in future work to define aspects of GSK-3 signaling in gliogenesis during neural development that might have additional implications in the context of glial tumors and demyelinating diseases.

SYNAPTIC DEVELOPMENT

Synapses connect neurons to transmit signals and synapse formation is an important step in later stages of development. Recent studies have suggested important functions for GSK-3 in synaptic development. Shaggy, the fly homolog of GSK-3, is present at synapses and negatively influences AP-1-dependent synaptic growth, by modulating the Jun-N-terminal kinase pathway, and regulates presynaptic neurotransmitter release at the larval neuromuscular junction (Franciscovich et al., 2008). In fractionation studies, GSK-3 β is readily detected within the synaptosomal fraction (Hooper et al., 2007). Activation of GSK-3 by transfecting GSK-3 genes in cultured neurons reduces expression and clustering of a synaptic protein Synapsin I (Zhu et al., 2007). In contrast, pharmacological inhibition of GSK-3 activity induces Synapsin I clustering in developing neurons (Hall et al., 2002). Further, GSK-3 activation reduces presynaptic glutamate release by inhibiting the synaptic vesicle exocytosis in response to membrane depolarization (Zhu et al., 2010). GSK-3 β negatively regulates synaptic vesicle fusion events via interfering with Ca²⁺-dependent SNARE complex formation. Finally, in rat, there is strong GSK-3 expression in dendritic spines of cultured hippocampal neurons (Peineau et al., 2007).

Glycogen synthase kinase-3 activity is also implicated in regulation of adult synapses. GSK-3 plays a role in amyloid-induced synaptic alternation and dendritic spine shortening (reviewed in Knobloch and Mansuy, 2008). All these demonstrate that GSK-3 signaling is likely critical to synaptic development, but the precise functions regulated by GSK-3 will require further study.

A recent study has reported functional roles of GSK-3 in the regulation of N-Methyl-D-aspartic acid (NMDA) receptor-dependent synaptic plasticity (Peineau et al., 2008). Activation of GSK-3 mediates NMDA-dependent long term depression (LTD) induction. In contrast, inhibition of GSK-3 activity prevents LTD induction and participates in long term potentiation (LTP)

induction (Hooper et al., 2007). For further information on the roles of GSK-3 in synaptic plasticity and LTP/LTD formation, please refer the review from Collingridge group in this issue.

GSK-3 IN TUMORIGENESIS

DUAL FUNCTIONS OF GSK-3 IN TUMORIGENESIS

Glycogen synthase kinase-3 is associated with neoplastic transformation and tumor development (reviewed in Ougolkov and Billadeau, 2006; reviewed in Luo, 2009). Since GSK-3 negatively regulates oncoproteins such as Myc and β -catenin, it may act as a suppressor of tumorigenesis. Indeed, downregulation of GSK-3 β and upregulation of phospho-GSK-3 β (inactive form) have been found in skin (Leis et al., 2002; Ding et al., 2007; Ma et al., 2007) and mammary tumors (Farago et al., 2005) in mice and humans. Furthermore, overexpression of wild type or constitutively active GSK-3 β inhibits the progression of skin tumors in mice (Ma et al., 2007), while mice overexpressing dominant-negative GSK-3 develop mammary tumors (Farago et al., 2005). The promotion of mammary tumorigenesis by GSK-3 inactivation is accompanied by the accumulation of β -catenin and cyclin D1, suggesting the dysregulation of the Wnt pathway. These findings demonstrate the suppressive role of GSK-3 in tumorigenesis. However, some studies have shown the contrary role of GSK-3, that it may positively regulate tumorigenesis in other types of cancers. Increased GSK-3 levels have been found in human ovarian, colon, liver, thyroid, and pancreatic carcinomas (reviewed in Ougolkov and Billadeau, 2006; reviewed in Luo, 2009). Inhibition of GSK-3 activity by pharmacological inhibitors or RNA interference suppresses proliferation of the human ovarian cancer (Cao et al., 2006), colon cancer (Shakoori et al., 2007), pancreatic cancer (Ougolkov et al., 2005), and prostate cancer cells (Zhu et al., 2011). Conversely, overexpressing constitutively active GSK-3 β induces cell cycle progression of ovarian cancer cells (Cao et al., 2006). Therefore, GSK-3 also functions as a tumor promoter in certain types of tumors. In this case, inhibition of GSK-3 could be an attractive therapeutic strategy for the treatment of ovarian, colon, and pancreatic cancers. Taken together, GSK-3 plays opposing roles as a tumor suppressor or a promoter, depending on cell-types and cellular contexts.

TUMORIGENESIS IN THE NERVOUS SYSTEM

Recent studies suggest important roles of GSK-3 in the formation and maintenance of tumors in the nervous system. Pharmacological inhibition of GSK-3 using the indirubin family reduces growth and invasion of human glioma cells both *in vitro* and in mice (Nowicki et al., 2008; Williams et al., 2011). β -catenin signaling plays an important role in mediating these effects. Another study using a different GSK-3 inhibitor, TDZD-8, has also shown that inhibition of GSK-3 activity suppresses proliferation of mouse glioma cells and induces apoptosis *in vitro* (Aguilar-Morante et al., 2010). The inhibitory effects of TDZD-8 in culture were confirmed in mice, which showed delay in tumor growth after glioma cell injection, and an increase in survival (Aguilar-Morante et al., 2010). Additionally, GSK-3 is involved in the differentiation of human glioma cells (Korur et al., 2009). Interference of GSK-3 activity with siRNA or pharmacological inhibitors induces differentiation of glioma cells. The capacity of GSK-3 in inducing

glioma cell differentiation could be considered for the differentiation therapy that has emerged as a promising treatment tool for brain tumors. However, progression of this idea needs careful assessments, as contrary effects of GSK-3 on glioma differentiation are also reported (Li et al., 2010). GSK-3 also plays a promoting role in the majority of medulloblastoma, the most common pediatric malignant tumor of the central nervous system. Lithium, a clinically available GSK-3 inhibitor, suppresses proliferation of medulloblastoma cells and induces non-apoptotic cell death (Ronchi et al., 2010). Interestingly, the inhibitory effect of GSK-3 is independent of changes in intracellular levels of β -catenin. Together, GSK-3 signaling plays important roles in tumorigenesis and differentiation in the nervous system, and may be a promising target in the establishment of therapeutic strategies. However, before considering clinical application, it is necessary to determine the suppressive and promoting functions of GSK-3 in each tumor type, as both activities have been evident in non-nervous system tumors. This dual role of GSK-3 in tumorigenesis may not be surprising since GSK-3 is involved in multiple pathways and regulates many substrates. Different environments and/or epigenetic programs around different tissues/cells may regulate GSK-3 in different ways, which subsequently influences distinct downstream targets. In this regard, it is important to define and compare GSK-3 signaling mechanisms in each cell-type. This will delineate how the suppressive and promoting activities of GSK-3 are counterbalanced and help to develop therapeutic potentials.

IMPLICATIONS IN NEURODEVELOPMENTAL DISORDERS

Recent studies suggest that changes in GSK-3 activity may be an important aspect of pathophysiologies of neurodevelopmental disorders, including autism spectrum disorders (ASDs), schizophrenia, mental retardation, and bipolar disorders. There are two types of key observations in animal models of neurodevelopmental disorders: (1) The levels and activity of GSK-3 are altered in the brain samples. (2) Pharmacological or genetic inhibition of GSK-3 activity reduces the pathological symptoms. In humans, lithium, a GSK-3 inhibitor is used for controlling abnormal mood changes in patients with bipolar disorders.

ASDs are a spectrum of psychological conditions characterized by abnormalities in social interactions and communication as well as stereotypic behaviors and motor dysfunctions. Neurodevelopmental abnormalities are found in ASD brains. Studies using magnetic resonance imaging and postmortem brains show abnormalities in cortical minicolumn organization and neuron migration in patients with ASDs (Piven et al., 1990; Casanova et al., 2003, 2006). Etiology of autism has yet to be determined. However, recent studies suggest that genetic factors may be the most significant cause for ASDs. Gene linkage studies and array analyses have found multiple ASD-associated genes that encode FMR1 (fragile X mental retardation 1), PTEN (phosphatase and tensin homolog), APC, DISC1, SHANK3 (SH3 and multiple ankyrin repeat domains 3), TSC (tuberous sclerosis), MeCP2 (methyl CpG binding protein 2), and Reelin (reviewed in Abrahams and Geschwind, 2008). All these genes play important roles in functional and anatomical development of the nervous system.

Importantly, GSK-3, a critical regulator in broad aspects of neural development, is associated with many ASD-related genes mentioned above. GSK-3 activity measured by the levels of phospho-GSK-3 is increased in the brains of FMR1-deleted mice (Min et al., 2009; Yuskaitis et al., 2010). Inhibition of GSK-3 activity by treatment with lithium reduces abnormal social behaviors and seizures in the FMR1 mice. Additionally, GSK-3 knock-in mice, in which inhibitory serine 9 (β) and 21 (α) residues are substituted by alanine (McManus et al., 2005), show abnormal social behaviors similar to those of FMR1-deleted mice (Mines et al., 2010). Mice with conditional PTEN deletion in the cortex and hippocampus show macrocephaly and abnormal social interaction (Kwon et al., 2006). The levels of inactive GSK-3 β (phospho-GSK-3 β) are elevated in the brains. Furthermore, recent studies suggest that GSK-3 is a critical downstream mediator of the DISC1 signal. DISC1 regulates proliferation of neural progenitors by modulating GSK-3 activity (Mao et al., 2009). DISC1 directly binds to GSK-3 and participates in the regulation of β -catenin stability. Inhibition of GSK-3 with lithium or overexpression of a stable β -catenin rescues DISC1-deletion effects in neural progenitors. However, whether DISC1 directly controls GSK-3/ β -catenin or serves as a scaffold remains unknown. Together, GSK-3 is associated with genes that are mutated in neurodevelopmental disorders and may play a critical role in the pathogenesis of the diseases. The association of GSK-3 with these genes suggests a therapeutic intervention point in the development of tools for neurodevelopmental disorders.

GSK-3 IN EPIGENETIC CONTROL

Epigenetic control has become an important cell-intrinsic program in the regulation of various processes during neural development. DNA methylation and histone modification (i.e., phosphorylation, acetylation, and methylation) change chromatin structures for transcription factors to gain access to gene promoters (Fischle et al., 2003). Non-coding RNAs also functionally participate in neural development. For example, microRNAs regulate neural progenitor proliferation and differentiation (Aranha et al., 2011; Chen et al., 2011), neural migration (Delaloy et al., 2010), oligodendrocyte differentiation and myelination (Dugas et al., 2010), hippocampal axon growth (Sanuki et al., 2011), and dendritic spine morphogenesis (Lippi et al., 2011).

The role of GSK-3 in epigenetic control has recently been evident. GSK-3 modulates the activity of epigenetic factors. GSK-3 directly phosphorylates histone deacetylase 3 that promotes the death of cortical neurons (Bardai and D'Mello, 2011), suggesting that the neuronal death-promoting activity of GSK-3 could be mediated via an epigenetic mechanism. Pharmacological inhibition of GSK-3 increases methylation at several sites on histone

H3 and histone H4 bound to the promoters of the NF κ B target genes Bcl-2 and XIAP (Ougolkov et al., 2007). This leads to the suppression of NF κ B binding to its target promoters and thereby epigenetic silencing of XIAP and Bcl-2. Additionally, a recent study demonstrates that GSK-3 also participates in epigenetic control by regulating the levels of a DNA methyltransferase. Genetic deletion of both GSK-3 α and GSK-3 β in mouse embryonic stem cells reduces expression of DNA methyltransferase 3a2, which results in hypomethylation and misexpression of the imprinted genes Igf2, H19, and Igf2r (Popkie et al., 2010). Our understanding of this subject is at an initial stage, but the information thus far strongly suggests important roles of GSK-3 in epigenetic control. This field will be expanded by identifying more epigenetic molecules that are regulated by GSK-3.

CONCLUSION

All of the studies discussed here implicate GSK-3 as a multifunctional regulator of neural development. At early stages, GSK-3 serves as a master switch regulating neural progenitor homeostasis and appears to act via regulation of β -catenin as well as other key signaling pathways. It now seems quite clear that after progenitors differentiate into neurons, GSK-3 signaling is also key to neuronal migration and lamination. Although some evidence implicates β -catenin in these processes, GSK-3 regulation of the cytoskeleton via APC and other microtubule-associated proteins may be particularly important. Finally, functions of GSK-3 in neuronal morphogenesis, synaptogenesis, and behavior are only now being defined. Future studies defining cell-type specific effects *in vivo* with a variety of Cre drivers will rapidly enhance our understanding of GSK-3 functions.

A key regulator of GSK-3 function in neural development is an important protein in genetic causes of schizophrenia. Details of GSK-3 regulation by DISC1 have already provided key insights into regulation of key developmental events with important implications to the pathogenesis of some cases of schizophrenia.

Finally, our current understanding of GSK-3 in neural development largely reflects phenotypic characterization of the loss of the protein. It will be important to learn more cellular and molecular mechanisms of GSK-3 signaling related to these striking phenotypes. Further works should distinguish GSK-3 functions between gene induction activity and cytoskeleton regulation and how these processes are linked in various neurodevelopmental events. Also, key to defining GSK-3 functions will be to understand how GSK-3 activity is regulated. Understanding regulation of GSK-3 activity will be a particularly important goal, as we can expect that even relative small changes might have a large impact on important developmental outcomes such as determination of numbers of neurons in the brain.

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