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REVIEW

The role of GSK3beta in the development of the central nervous system

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Abstract **Glycogen synthase kinase 3β (GSK3β) is a multifunctional serine/threonine kinase. It is particularly abundant in the developing central nervous system (CNS). Since GSK3β has diverse substrates ranging from metabolic/signaling proteins and structural proteins to transcription factors, it is involved in many developmental events in the immature brain, such as neurogenesis, neuronal migration, differentiation and survival. The activity of GSK3β is developmentally regulated and is affected by various environmental/cellular insults, such as deprivation of nutrients/trophic factors, oxidative stress and endoplasmic reticulum stress. Abnormalities in GSK3β activity may disrupt CNS development. Therefore, GSK3β is a critical signaling protein that regulates brain development. It may also determine neuronal susceptibility to damages caused by various environmental insults.**

Keywords development, differentiation, neurogenesis, proliferation

Introduction

Glycogen synthase kinase 3 (GSK3) is a multifunctional serine/threonine kinase. Originally found in mammals, and homologs have been found in all eukaryotes (Grimes and Jope, 2001; Doble and Woodgett, 2003). GSK3 was named for its ability to phosphorylate, and thereby inactivate glycogen synthase, a key regulatory molecule in the synthesis of glycogen. There are two highly homologous forms of GSK3 in mammals encoded by distinct genes, GSK3α (51 kDa) and GSK3β (47 kDa). GSK3 is an important component of diverse signaling pathways involved in the regulation of cell fate, protein synthesis, glycogen metabolism, cell mobility, transformation, proliferation and survival (Grimes and Jope, 2001; Doble and Woodgett, 2003; Luo, 2009a). Despite a high degree of similarity and functional overlap, these isoforms are not functionally identical and redundant. Between these isoforms, GSK3β is better studied and highly expressed in the CNS; evidence indicates that GSK3β plays a prominent role in the CNS. It is now known that GSK3β regulates diverse early events of neuronal development, such as neurogenesis, neuronal migration, differentiation and survival in the immature brain. This review discusses studies on the role of GSK3β in the developing CNS.

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GSK3β signaling

Regulation of GSK3β activity

GSK3β is constitutively active in resting cells and undergoes a rapid and transient inhibition in response to a number of external signals (Grimes and Jope, 2001; Doble and Woodgett, 2003). GSK3β activity is regulated by site-specific phosphorylation. Full activity of GSK3β generally requires phosphorylation at tyrosine 216 (Tyr216), and conversely, phosphorylation at serine 9 (Ser9) inhibits GSK3β activity. Phosphorylation of Ser9 is the most common and important regulatory mechanism. Many kinases are capable of phosphorylating Ser9, including p70 S6 kinase, extracellular signal-regulated kinases (ERKs), p90Rsk (also called MAPKAP kinase-1), protein kinase B (also called Akt), certain isoforms of protein kinase C (PKC) and cyclic AMP-dependent protein kinase (protein kinase A, PKA) (Grimes and Jope, 2001; Kaytor and Orr, 2002). In opposition to the inhibitory modulation of GSK3β that occurs by serine phosphorylation, tyrosine phosphorylation of GSK3β increases the enzyme's activity. Studies of tyrosine

phosphorylation of GSK3β are relatively sparse. Stimulation of pGSK3β (Tyr216) is reported to be mediated by alterations in intracellular calcium levels and a calcium-dependent tyrosine kinase, proline-rich tyrosine kinase 2 (PYK2) or by Fyn, a member of the Src tyrosine family (Hartigan and Johnson, 1999; Lesort et al., 1999; Hartigan et al., 2001; Sayas et al., 2006). pGSK3β (Tyr216) is also subject to the regulation of mitogen-activated protein kinase kinase (MEK1/2) (Takahashi-Yanaga et al., 2004). It has been suggested that GSK3β tyrosine phosphorylation may be regulated by autophosphorylation (Cole et al., 2004).

GSK3β can be activated without apparent changes in phosphorylation of Tyr216 and Ser9 (Baltzis et al., 2007). Regulation of GSK3β may also be mediated by its subcellular localization. Some substrates of GSK3β, such as Tau, are cytosolic, whereas others, notably several transcription factors, are nuclear. Thus, GSK3β must be located in both compartments to regulate these proteins. Diehl et al. (1998) report an increase in nuclear GSK3β during the S phase of the cell cycle. Proapoptotic stimuli cause the translocation of Tyr216-phosphorylated GSK3β to the nucleus (Bhat et al., 2000). Identification of a nuclear localization sequence (NLS) in GSK3β shed light on the mechanisms underlying its shuttling between cytosolic and nuclear compartments (Meares and Jope, 2007).

Substrates of GSK3β

More than 40 proteins are directly subjected to GSK3β regulation. These proteins have diverse cellular functions, including glycogen metabolism, transcription, translation, cytoskeletal regulation, cell differentiation, proliferation, transformation and apoptosis (Grimes and Jope, 2001; Manoukian and Woodgett, 2002; Luo, 2009a). Substrates of GSK3β can be divided into three major groups, namely, metabolic/signaling proteins, structural proteins and transcription factors. The proteins belonging to the first group include acetylCoA carboxylase, amyloid precursor protein, APC tumor suppressor protein, ATP-citrate lyase, Axin, cyclic AMP-dependent protein kinase, cyclin D1, eIF2B, glycogen synthase, insulin receptor substrate-1 (IRS-1), myelin basic protein, NGF receptor, protein phosphatase 1, protein phosphatase inhibitor-2 and pyruvate dehydrogenase. The structural proteins include dynamin-like protein, microtubule-associated protein 1B (MAP1B), microtubule-associated protein 2 (MAP2), neural cell-adhesion protein (NCAM), neurofilaments, spindle-associated protein Astrin, ninein and Tau. GSK3β-targeted transcription factors are AP-1 (Jun family), β-catenin, C/EBPα, CREB, glucocorticoid receptor, HSF-1, Myc, NFAT and NF-κB.

β-catenin is probably the most well-known substrate of GSK3β. Since β-catenin is an essential component of Wnt signaling, GSK3β is critically involved in the Wnt system. The Wnts are a family of secreted, cysteine-rich and glycosylated protein ligands that signal by activating the Frizzled family of membrane-bound receptors. Wnt signal transduction causes nuclear translocation of β-catenin and ultimately results in the activation of genes regulated by the T cell factor (TCF)/lymphoid enhancer factor (LEF) family of transcription factors. In the absence of Wnt signals, free cytoplasmic β-catenin is incorporated into a cytoplasmic complex that includes Axin, GSK3β and adenomatous polyposis coli (APC). This enables GSK3β to phosphorylate β-catenin and results in ubiquitin-mediated degradation of β-catenin (Doble and Woodgett, 2003; Ille and Sommer, 2005). Wnt signaling inactivates GSK3β and prevents it from phosphorylating β-catenin, thus stabilizing β-catenin in the cytoplasm. As β-catenin accumulates, it translocates into the nucleus where it binds to TCF/LEF and increases their transcriptional activity. Thus, GSK3β must be inactivated for Wnt signaling to proceed, and the presence of active GSK3β inhibits Wnt signaling. The Wnt signaling pathway is an integral component of embryonic development and is involved in morphogenesis and patterning, differentiation processes and lineage decision events during both central and peripheral nervous system development (Patapoutian and Reichardt, 2000; Ille and Sommer, 2005; Malaterre et al., 2007). Therefore, the effect of GSK3β on development may be associated with Wnt signaling. Adiditionally recent studies indicate that GSK3β is a crucial component of cell signaling pathways controlled by disrupted in schizophrenia 1 (DISC1), partitioning defective homolog 3 (PAR3) and PAR6. The role of these pathways in neural development and the involvement of GSK3β have been reviewed elsewhere (Hur and Zhou, 2010).

GSK3β in neuronal development

The expression of GSK3β in the developing brain

Although GSK3β is widely expressed in all tissues, it is particularly abundant in the CNS (Woodgett, 1990). In the developing brain, GSK3β is predominantly expressed in neurons and barely detectable in astrocytes (Leroy and Brion, 1999; Takahashi et al., 2000). Leroy and Brion (1999) show that the expression of GSK3β in the developing rat brain is highest from 18 days of embryonic life up to 10 days of postnatal life (PD10). The expression decreases thereafter and is lowest in the adult; strong GSK3β immunoreactivity is localized in developing neurons, but is only weakly detected in layers containing neuroblasts. During development and in the adult, GSK3β is detected in the perikarya and proximal part of dendrites. In the embryo, an intense GSK3β immunoreactivity is also observed in axonal tracts. This axonal immunoreactivity has markedly decreased by PD10 and is absent at PD20 as well as in the adult (Leroy and Brion, 1999). Similarly, Takahashi et al. (2000) show a high expression of GSK3β in the rat brain during the first two weeks of postnatal life; GSK3β levels peak at PD8-11, and its expression decreases significantly at PD20. Coyle-Rink et al.

(2002) examine the expression of GSK3β in the developing mouse brain. As in the rat brain, a strong GSK3β expression is observed in the mouse brain during the first two postnatal weeks and then the level of GSK3β drastically decreases after PD18.

GSK3β and cell proliferation

GSK3β is expressed more abundantly in postmitotic neurons than cycling neuroblasts in the developing brain (Leroy and Brion, 1999). Neuronal overexpression of a constitutively active GSK3β induces microcephaly (Spittaels et al., 2000; 2002). This suggests that GSK3β activity may negatively regulate the proliferation of neural precursors and neurogenesis. Cui et al. (1998) show the inhibition of GSK3β can promote the proliferation of cerebellar granule neuron progenitors *in vitro*, suggesting the activation of GSK3β may suppress the division of neuronal precursors. Knoepfler and Kenney (2006) also used an *in vitro* model of cerebellar granule neuron progenitors to show GSK3β activation inhibits cell cycle progression, and the inhibitory effect of GSK3β is mediated by phosphorylating and destabilizing N-Myc. Inhibition of GSK3β enhances the proliferation of neural progenitor cells (Nedachi et al., 2011). GSK3β is implicated in adult hippocampal neurogenesis (Boku et al., 2009). Lithium, an inhibitor of GSK3 enhances the proliferation of adult dentate gyrus-derived neural precursor cells in culture (Boku et al., 2009). GSK3β inhibitor, SB216763 enhances hippocampal neurogenesis (Guo et al., 2011). Under most circumstances, the proliferation and differentiation of neural precursor cells are mutually exclusive during brain development. Fibroblast growth factor 2 (FGF2) promotes neural precursor cell proliferation and concurrently inhibits differentiation. FGF2 inactivates GSK3β and induces β-catenin nucleus accumulation which enhances the proliferation of neural stem/precursor cells while concurrently inhibiting their differentiation in culture (Shimizu et al., 2008). Similarly, Jin et al. (2005) show that FGF2-stimulated proliferation of cortical neural progenitor cells is mediated by GSK3β inactivation. According to some studies, however, GSK3β activity appears necessary for cell cycle progression. Maurer et al. (2007) show that inhibition of GSK3β by SB216763, a specific GSK3β inhibitor, suppresses proliferation while promoting neuronal differentiation in neural stem cells isolated from the adult rat subventricular zone. GSK3β activation by serum and potassium withdrawal induces the expression of several cell cycle regulating proteins, such as cyclin D1, cyclin E, transcription factor E2F-1 and the phosphorylation of retinoblastoma protein (Rb) in cultured cerebellar granule cells (Yeste-Velasco et al. 2007). In some tumor cells, inhibition of GSK3β results in cell cycle arrest and apoptosis (Luo, 2009a).

Multiple mechanisms are involved in GSK3β regulation of cell proliferation. First, GSK3β may regulate mitogenic transcription factors. The activity of some mitogenic transcription factors, such as AP-1 and NF-κB, is inhibited by GSK3β activation (Ma et al., 2007; Luo, 2009a; Grimes and Jope, 2001). Secondly, GSK3β may inhibit cell cycle progression by interacting with cell cycle regulatory proteins, such as cyclin D1 and D2 (Diehl et al., 1998; Huang et al., 2007). Thirdly, GSK3β may directly regulate spindle microtubule assembly and accurate chromosome segregation by interacting with the spindle-associated protein Astrin, a substrate for GSK3β (Cheng et al., 2007).

GSK3β and neural migration

During development of the CNS, neuronal cells undergo directional movements to specific sites in response to extracellular signals and establish proper connections to other cells. Cell migration in the direction of extracellular cues is mediated by actin and microtubule cytoskeletons. GSK3β regulates the dynamics of microtubule cytoskeletons in response to extracellular cues (Ciani and Salinas, 2007; Barth et al., 2008), and therefore is an important signaling component that links extracellular signals to cytoskeletal components and governs neuronal migration. Evidence supports that GSK3β plays an important role in neuronal migration. For example, Chen et al. (2009a) demonstrate that GSK3β activity is essential for laminin-mediated neurite growth and neuronal migration in the developing cerebral cortex. Asada and Sanada (2010) show that GSK3β is critical for centrosomal forward movement and neuronal migration in the developing neocortex.

GSK3β regulates neuronal migration through its interaction with structural or signaling proteins. For instance, MAP1B, a neuron-specific microtubule-associated protein, is a substrate of GSK3β; it is implicated in the control of the dynamic stability of microtubules and in the cross-talk between microtubules and actin filaments in neurons (González-Billault et al., 2004). GSK3β-dependent MAP1B phosphorylation is required for Reelin-regulated neuronal migration *in vivo* and *in vitro* (González-Billault et al., 2004). Platelet activating factor (PAF) induces apoptosis and inhibits the migration of cerebellar granule neurons in a GSK3β-dependent manner*;* GSK3β inhibitors block these effects of PAF (Tong et al., 2001). Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase found in focal adhesion events and plays important roles in cell adhesion, spreading and migration (Hanks et al., 2003). It is shown that GSK3β regulates cell spreading and migration through the phosphorylation of FAK at selected serine sites (Bianchi et al., 2005). Aspartyl (asparaginyl)-beta-hydroxylase (AAH) regulates cell motility by catalyzing post-translational hydroxylation of proteins involved in cell migration, such as Notch and Jagged (Carter et al., 2008). AAH is a substrate of GSK3β and GSK3β-mediated phosphorylation induces AAH degradation, resulting in retarded cell motility (Carter et al., 2008).

Microglia plays a prominent role in the brain's inflammatory response to injury or infection by migrating to affected

locations and secreting inflammatory molecules. GSK3 inhibitors reduce the migration of microglia in cultured mouse hippocampal slices (Yuskaitis and Jope, 2009). The regulation of GSK3β on microglia migration may underlie its role in inflammatory responses to injury in the CNS.

GSK3β and neuronal differentiation

Neurons are highly polarized cells that contain a single long axon and multiple dendrites. Initial differentiation of neurons is to establish neuronal polarity. Polarization occurs when one of the multiple neurites emerging from the cell body initiates a phase of rapid elongation, becoming the axon; the remaining neurites will develop as dendrites. Rearrangement of the neuronal cytoskeleton provides support for the dramatic morphological changes that occur during neuronal polarization and neurite outgrowth. GSK3β plays a critical role in regulating neuronal polarity (Etienne-Manneville and Hall, 2003; Arévalo and Chao, 2005; Jiang et al., 2005; Yoshimura et al., 2005; Gärtner et al., 2006; Vohra et al., 2007). Several microtubule-associated proteins (MAPs) important for neuronal polarity and axonal outgrowth, such as Tau and MAP1B, are substrates of GSK3β (Barth et al., 2008). The potential mechanisms for GSK3β regulation of neuronal polarity have been discussed in a review by Hur and Zhou (2010).

GSK3β also regulates the maturation and neurite outgrowth in neurons. Neuronal overexpression of a constitutively active GSK3β causes a delayed postnatal maturation and differentiation of neurons in the mouse brain (Spittaels et al., 2000, 2002). In *in vitro* models of neuronal development, inhibition of GSK3β by selective inhibitors or molecular approaches is shown to promote neurite outgrowth; in contrast, activation of GSK3β causes neurite retraction (Muñoz-Montaño et al., 1999; Orme et al., 2003; Castelo-Branco et al., 2004; Sayas et al., 2006; Dill et al., 2008; Chen et al., 2009b). Lysophosphatidic acid induces neurite retraction in differentiated neuroblastoma cells via GSK3β activation (Sun et al., 2011). WW domain-containing oxidoreductase (WWOX), a putative tumor suppressor induces neurite outgrowth and differentiation of SH-SY5Y neuroblastoma cells by repressing GSK3β activity (Wang et al., 2011). In addition, inactivation of GSK3β mediates a leptin-induced increase in the size of axonal growth cone in developing mouse cortical neurons (Valerio et al., 2006). GSK3β also negatively regulates the differentiation of neural stem cells. Inhibition of GSK3β by SB216763 inhibits proliferation while promoting neuronal differentiation in neural stem cells isolated from the adult rat subventricular zone (Maurer et al., 2007). Inactivation of GSK3β is also beneficial for axonal regeneration after a spinal cord lesion (Dill et al., 2008).

On the other hand, some reports demonstrate that GSK3β activity is necessary for neurite outgrowth and axonal extension. For example, lithium or other GSK3β inhibitors are shown to reduce neurite outgrowth and axon elongation rates in primary cultures of rat hippocampal neurons and sensory neurons (Takahashi et al., 1999; Owen and Gordon-Weeks, 2003). The complex effects of GSK3β on neuronal differentiation are demonstrated by studies using PC12 cells. PC12 cells are rat pheochromocytoma cells that are extensively used to study the cellular/molecular mechanisms of neuronal differentiation. PC12 cells differentiate into neuronal-like cells by extending neurites and expressing neurotransmitters in response to neurotrophic factors such as NGF and bFGF. There are conflicting reports on the effect of GSK3β in PC12 cell differentiation; GSK3β activity can either negatively or positively regulate neurite outgrowth of PC12 cells (Goold and Gordon-Weeks, 2001, 2005; Trivedi et al., 2005; Seng et al., 2006; Zhou et al., 2008; Zhang et al., 2009).

The effect of GSK3β on neuronal differentiation appears to be mediated by its interaction with microtubule-associated proteins, such as MAP1B which is essential for neuronal polarization, migration neurite outgrowth and axon elongation (Gonzalez-Billault et al., 2001; Owen and Gordon-Weeks, 2003). GSK3β phosphorylation of MAP1B acts as a molecular switch regulating the control that MAP1B exerts on microtubule dynamics in growing axons and growth cones (Trivedi et al., 2005). Besides MAP1B, GSK3β may interact with other proteins that participate in regulating neuronal differentiation. For example, E2F1 transcription factor is a key downstream target of the retinoblastoma tumor suppressor protein (pRB) and is involved in neuronal differentiation. NGF-induced GSK3β/E2F1 interaction facilitates E2F1 degradation, increasing neurite outgrowth in PC12 cells (Zhou et al., 2008). NGF promotes the interaction between GSK3β and MRP2, an actin binding protein in PC12 cells; the interaction enhances neurite outgrowth (Seng et al., 2006).

GSK3β and neuronal survival

Apoptosis has been recognized to be an essential process during neural development and naturally occurring neuronal death plays a substantial developmental role in the building of neural circuitries (Madalosso et al., 2005). It is generally assumed that about half of the neurons produced during neurogenesis die before completion of CNS maturation; this process affects nearly all classes of neurons (Lossi and Merighi, 2003). GSK3β is an important modulator of apoptosis (Grimes and Jope, 2001; Kaytor and Orr, 2002; Beurel and Jope, 2006). Lucas et al. (2001) use transgenic mice that conditionally overexpress GSK3β to demonstrate the link between GSK3β activity and neurodegeneration. They show that overexpression of GSK3β to specific regions of the brain in mice results in neuronal death which is characteristic of apoptosis in these regions (Lucas et al., 2001). This is supported by studies using various *in vitro* models which show overexpression of GSK3β in neurons is sufficient to trigger neuronal cell death; in contrast,

expression of an inhibitory GSK3β binding protein or a dominant interfering form of GSK3β reduces neuronal apoptosis (Pap and Cooper, 1998; Crowder and Freeman, 2000; Hetman et al., 2000; Song et al., 2002). Although there is a lack of evidence regarding direct regulation of GSK3β on naturally occurring neuronal death during brain development, *in vitro* studies suggest that GSK3β plays a role in the death/survival of neural precursors or immature neurons. For example, the activation of GSK3β promotes apoptotic signaling in cultured neural precursor cells (NPCs) derived from embryonic mouse brains subjected to two common apoptotic conditions, trophic factor withdrawal and genotoxic stress (Eom et al., 2007). Lithium, an inhibitor of GSK3β, is shown to have an opposing effect on neuronal survival depending on the developmental status of the neuron; it induces apoptosis in immature cerebellar granule cells, but promotes survival of mature neurons (D'Mello et al., 1994).

GSK3β may be activated and induces neuronal death in response to various environmental/cellular stresses, such as deprivation of trophic factors, oxidative stress and endoplasmic reticulum (ER) stress (Bhat et al., 2000; Hetman et al., 2000; Song et al., 2002; Chen et al., 2004; Koh et al., 2005; Brewster et al., 2006; Eom et al., 2007; Lee et al., 2007; Takadera et al., 2007). Relatively low levels of GSK3β overexpression, which alone do not induce apoptosis, greatly facilitate pro-apoptotic signaling and promote apoptosis (Bijur et al., 2000). The expression of GSK3β is developmentally regulated; therefore, the status of GSK3β may play an important role in the susceptibility of the developing brain to environmental insults. For example, we have demonstrated as well as other studies that ethanol-induced death of neurons is mediated at least partially by the activation of GSK3β in the developing brain, and lithium can protect neurons from ethanol-induced neurodegeneration (Liu et al., 2009; Luo, 2009b; Saito et al., 2010; Ke et al., 2011). We further show that manipulation of GSK3β activity in neurons can alter neuronal susceptibility to ethanol toxicity (Liu et al., 2009).

GSK3β activation during neuronal death is commonly mediated by deregulation of phosphorylation at Ser9. Bhat et al. (2000) report that pro-apoptotic stimuli (nerve growth factor withdrawal, ischemia or staurosporine treatment) increase Tyr216 phosphorylation of GSK3β and induce its nuclear translocation. Multi-mechanisms underlie GSK3β regulation of neuronal survival/death. It has been suggested that GSK3β promotes cell death caused by the intrinsic apoptotic pathway, but inhibits the death receptor-mediated extrinsic apoptotic signaling pathway (Beurel and Jope, 2006). The intrinsic apoptotic signaling cascade can be induced by numerous stimuli that cause cell damage, such as DNA damage, oxidative stress and endoplasmic reticulum (ER) stress. The intrinsic apoptotic signaling pathway causes the disruption of mitochondria, leading to cell destruction. Other potential contributory mechanisms are also evident. It is suggested that GSK3β-induced phosphorylation of Tau may destabilize microtubules which contributes to cytoskeletal collapse associated with apoptosis (Tsukane et al., 2007); GSK3β-mediated phosphorylation of pyruvate dehydrogenase may impair Krebs cycle activity, reducing cell viability (Hoshi et al., 1996). Effects of GSK3β on neuronal survival may be mediated by modulation of transcription factors. It is shown that GSK3β activity is required for AP1-dependent expression of pro-apoptotic Bim, and inhibitors of GSK3β block AP-1 activation and protect neurons from apoptosis (Hongisto et al., 2003). Activation of GSK3β is shown to antagonize NF-κB-mediated neuronal survival, resulting in decreased cell viability (Sui et al., 2006). GSK3β binds to p53 and promotes p53-induced apoptosis (Watcharasit et al., 2003). Mixed lineage kinase 3 (MLK3) is a mitogen-activated protein kinase kinase kinase member that activates the c-Jun N-terminal kinase (JNK) pathway. GSK3β-dependent MLK3 phosphorylation mediates neuronal death caused by NGF deprivation (Mishra et al., 2007). Additionally, the effect of GSK3β on neuronal survival may be regulated by translational control. Translation initiation factor 2B (eIF2B) is a substrate of GSK3β. GSK3β phosphorylates and inhibits eIF2B, resulting in translational suppression and programmed cell death (Pap and Cooper, 2002). Finally, GSK3β may directly modify the activity of pro-apoptotic proteins. For example, it has been demonstrated that GSK3β directly phosphorylates pro-apoptotic Bax and promotes its mitochondrial localization during neuronal apoptosis (Linseman et al., 2004). In addition to the direct effect on neurons, GSK3 may contribute to neuronal injury by modulating brain inflammation. Excessive neuroinflammation contributes to neurodegeneration. GSK3β activation promotes the production of inflammatory molecules and microglia migration, which together make GSK3 a powerful regulator of inflammation (Jope et al., 2007).

Conclusions

GSK3β is primarily localized in neurons of the developing CNS and its expression is developmentally regulated. GSK3β regulates diverse developmental events in the immature brain, including neurogenesis, neuronal migration, differentiation and survival. GSK3β is sensitive to external signals and its activity is readily altered by various environmental/cellular insults, such as deprivation of nutrients/trophic factors, oxidative stress and endoplasmic reticulum stress. Therefore, GSK3β not only plays an essential role in CNS development, it may also determine neuronal susceptibility to damages caused by various environmental insults.

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