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Fyn in Neurodevelopment and Ischemic Brain Injury

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Abstract

The Src Family kinases (SFKs) are nonreceptor protein tyrosine kinases that are implicated in many normal and pathological processes in the nervous system. The SFKs Fyn, Src, Yes, Lyn and Lck are expressed in the brain. This review will focus on Fyn, as Fyn mutant mice have striking phenotypes in the brain and Fyn has been shown to be involved in ischemic brain injury in adult rodents, and with our work, in neonatal animals. An understanding of Fyn's role in neurodevelopment and disease will allow researchers to target pathological pathways while preserving protective ones.

Keywords

Fyn tyrosine kinase; brain; development; ischemia

Fyn Structure and Regulation

Fyn is a 59kDa protein that is expressed in neurons and glia in the nervous system (1). Alternative splicing produces three Fyn isoforms. FynB, which uses exon 7A, is enriched in the brain (2). In the rodent embryo, Fyn is present in axonal tracts and growth cones, the telencephalon, hippocampal formation, cerebral cortex, and thalamic and hypothalamic nuclei (1, 3). There are elevated Fyn protein levels in white matter beginning at postnatal day 10 that coincides with myelination (3). In the mature brain, Fyn has decreased expression in axonal tracts and is predominantly found in the cerebellum, telencephalon and brain stem (1, 3). Fyn expression and kinase activity increase with development (3, 4).

Fyn shares a similar structure to other SFKs, an N-terminal SH4 domain, unique region, SH3 and SH2 domains, linker regions and a C-terminal kinase domain (Figure 1A). Myristoylation at glycine 2 and palmitoylation at cysteine 3 and 6 allow Fyn to target to the plasma membrane and lipid rafts (5–7). The SH3 domain is a protein-protein interaction module that recognizes proline-rich regions (8) and the SH2 domain recognizes phosphorylated tyrosine (pY) (9). Fyn interacts with a wide range of proteins through these domains (Figure 1B), and thereby regulates various intracellular signaling pathways (10–17).

SFKs exist in active and inactive conformations that are partially driven by phosphorylation of two critical tyrosine residues (Y531 and Y420, numbering according to the amino acid sequence of human Fyn, Figure 2). Y531 is located in the extreme C-terminus. When this residue is phosphorylated, it forms an intramolecular interaction with the SH2 domain. This conformation makes the kinase active site and SH3 domain inaccessible (18, 19). Y420 is located within the activation loop of the kinase domain. When this site is phosphorylated, it activates SFKs and makes the SH3 domain available for protein-protein interactions (20).

The dynamic control of phosphorylation of Y420 and Y531 provides an important level of regulation of Fyn activity and its ability to interact with other proteins. C-terminal Src kinase (Csk) and striatal enriched phosphatase (STEP) are Fyn negative regulators in the mammalian brain. Csk phosphorylates Fyn on Y531, while STEP dephosphorylates Y420 [10]. On the other hand, protein tyrosine phosphatase α (PTP α) activates Fyn by dephosphorylating Y531 (21–23). Once activated, Fyn can phosphorylate substrates in the brain with diverse cellular functions (Table 1). A broad range of substrates and binding partners situate Fyn upstream of many cellular processes in the brain.

Functional role of Fyn in the immature and mature nervous system

Several conclusions about Fyn function in the developing and adult nervous system can be drawn from transgenic mice where Fyn has been deleted, mutated or overexpressed. The Soriano lab generated Fyn null mice that lack expression of all Fyn isoforms (24). Yagi *et al* produced Fyn mutant mice in which the SH2, SH3 and kinase domain are replaced with lacZ, producing a Fyn- β -galactosidase fusion protein that is catalytically inactive (25). A Fyn kinase dead mutant exists which has a point mutant in the ATP binding pocket (K296R) (26). Finally, there are two mouse models that overexpress Fyn in excitatory neurons. Native or constitutively active (Y531F) Fyn is driven by the calcium/calmodulin-dependent protein kinase II α (CaMKII α) promoter where Fyn is overexpressed postnatally in the forebrain (27, 28). Studies using these transgenic mice have implicated Fyn in migration, myelination, synaptic plasticity and the regulation of excitatory and inhibitory receptors.

Neuronal Migration

Development of the neocortex involves the coordinated migration of neurons from the ventricular zone radially toward the pial surface. Fyn is expressed in the leading processes of migratory cortical neurons during corticogenesis (29). On a molecular level, Fyn has been implicated in the Reelin pathway. Reelin is an extracellular molecule that activates signaling cascades eventually leading to “inside-out” layering of neurons in the cerebral cortex, where early-generated neurons are located at a deeper position and later-generated neurons are present superficially (30).

Reelin and the intracellular adaptor protein Dab1 lead to activation of Fyn. Fyn phosphorylates Dab1 that initiates signal transduction cascades critical for neuronal migration (31, 32). Fyn null mice have abnormal stratification of layer II-III neurons with sparing of neurons in the deeper layers (29). Fyn knockout (KO) embryos have an intermediate migration defect, however Fyn Src double KO mice have a *reeler* phenotype

suggesting that both kinases function downstream of Reelin and are necessary for cortical layer formation (33).

In addition, Fyn kinase is reported to be a component of the neural cell adhesion molecule (NCAM) and netrin signaling pathways regulating neurite outgrowth and attraction (34, 35)

Oligodendrocyte Maturation

One function of oligodendrocytes (OL) is myelination of neurons in the central nervous system (36). Fyn null mice have significantly less myelin and OLs. Fyn kinase dead mutant mice are also hypomyelinated, suggesting that Fyn kinase activity is required for myelination (26). *In vitro*, fewer OLs develop in the absence of Fyn and fewer cells are morphologically mature. Fyn KO OLs are insensitive to IGF-1 induced maturation (37). Many of these phenotypes are recapitulated in Fyn KO mice backcrossed to the C57BL/6 background as early as postnatal day 6. These mice show severe hydrocephalus with defects in oligodendrocyte development (38).

Fyn KO mice have decreased myelin basic protein (MBP) throughout development (36). While this may be due to decreased number of OLs, Fyn also regulates MBP at the mRNA level. Activated Fyn phosphorylates RNA binding protein hnRNP A2, which stimulates transport and translation of MBP mRNA (39). These studies suggest that Fyn does not participate in oligodendrocyte migration, but functions in oligodendrocyte maturation and may affect myelin production at transcriptional and translational levels (36).

Synaptic Plasticity

Synaptic plasticity refers to the ability of neuronal connections, synapses, to change over time. One experimental model of synaptic plasticity is long-term potentiation (LTP), in which repetitive stimulation of excitatory synapses leads to a long-lasting increase in synaptic strength (40). Fyn KO mice have impaired LTP in the hippocampus in response to weak intensity tetanus (41). Interestingly, LTP is normal due to Src compensation until 14 weeks of age in Fyn KO mice when compensatory Src expression is reduced and the LTP deficit begins to be observed (27). Mice overexpressing constitutively active Fyn have a lower threshold for LTP in response to a weak stimulus. These studies suggest that Fyn is not required for the initiation of LTP, but rather plays a modulatory role influencing the threshold of LTP induction (42).

In addition to the LTP deficit, Fyn KO mice have impaired spatial memory in the Morris water maze. Anatomically, Fyn deletion results in an abnormal localization and an increased number of granule cells in the dentate gyrus and target cells in CA3 (41). Fyn KO mice also have decreased spine density in the hippocampus at 3 months and 1 year of age (43). These anatomical changes may contribute to aberrant hippocampal function in adult Fyn KO mice.

GABAergic synaptic transmission

Inhibitory neurotransmission is mediated by γ -aminobutyric acid (GABA) through activation of GABA receptors. GABA type A receptors (GABA_AR) are heteropentameric GABA-gated chloride channels that are derived from 19 genes (α 1–6, β 1–3, γ 1–3, δ , ϵ , θ , π , ρ 1–3)

(44). Several lines of evidence suggest that Fyn regulates GABA_AR expression and function.

Fyn KO slices from the olfactory bulb were insensitive to the GABA_AR antagonists, bicuculline and picrotoxin (45). Functional deficits in GABA_A-gated chloride flux are also evident in the cerebellum of Fyn KO mice (46). GABA_AR agonists have hypnotic effects, however Fyn KO mice are less sensitive to the hypnotic effects of $\beta 2/\beta 3$ agonists, but not to an $\alpha 1$ selective agonist (46).

The $\gamma 2$ subunit of GABA_AR is a Fyn substrate (Table 1). Fyn phosphorylates Y365 and Y367 that are within a consensus tyrosine-based endocytosis motif (YGYECL). Phosphorylation at Y365/7 prevents endocytosis of the GABA_AR, leading to increased surface expression of GABA_ARs and synaptic inhibition (47). Homozygotes for the mutation of Y365/7 to phenylalanine (Y365/7F) is embryonic lethal. Heterozygous Y365/7F mice have an increased size of inhibitory synapses and increased miniature inhibitory postsynaptic currents (mIPSCs) in the CA3 region of the hippocampus. Heterozygous mice also have impaired spatial object recognition (48). A recent study also implicated Fyn kinase activity in GABAergic synapse formation downstream of NCAM in postnatal mouse cortex (49).

These studies suggest that Fyn deletion leads to abnormal GABAergic synaptic transmission with behavioral, functional and developmental consequences in different brain regions. Fyn may regulate GABA_ARs specifically via the $\beta 2$, $\beta 3$ and $\gamma 2$ subunits in these different locations.

NMDA Receptor Surface Expression and Cleavage

The *N*-methyl-D-aspartate receptor (NMDAR) is typically a di-heteromeric glutamate receptor composed of an obligatory NR1 subunit and modulatory subunits NR2A-D. NMDARs participate in fast excitatory synaptic transmission (50) and form large multi-protein complexes at synaptic membranes (51). The NR2A and NR2B subunits have multiple tyrosine residues on their C-terminal tails that are phosphorylated by SFKs Src and Fyn (50). Exogenous Fyn upregulates NMDAR currents possibly by tyrosine phosphorylation (52). Fyn-mediated NMDAR tyrosine phosphorylation is also involved in regulation of the susceptibility of kindling and seizure (28).

Fyn deletion results in decreased tyrosine phosphorylation (pY) of NR2B and Fyn overexpression (Fyn OE) leads to elevated pY NR2B. Interestingly, Fyn KO mice have normal levels of pY NR2A, while Fyn OE mice have increased pY NR2A (28). These results suggest that *in vivo* Fyn may preferentially phosphorylate the NR2B subunit of the NMDAR.

In vitro, Fyn phosphorylates seven tyrosine residues on NR2B (53)(Table 1). In the developing cortex, we found that pY1070NR2B, pY1252NR2B, pY1336NR2B and pY1472NR2B expression was highest in synaptic membranes, while pY1336NR2B was also present in extrasynaptic membranes (54). One study reported that pY1252 NR2B is higher in synaptic lipid rafts compared to the post-synaptic density (PSD) (55). While the

physiological function of pY1252 and pY1070NR2B is unknown, pY1336 promotes calpain cleavage of NR2B in response to glutamate exposure *in vitro* (56) and is associated with increased interaction of NR2B with phosphatidylinositol 3-kinase (PI-3K) (57).

Among Fyn-mediated NR2B tyrosine phosphorylation sites, Y1472 has been studied the most extensively. Phosphorylation of Y1472 maintains surface expression and synaptic localization of the NR2B-containing NMDARs as it is within the tyrosine endocytosis motif YEKL (58–60). Although pY1472 leads to increased surface expression and less endocytosis of NR2B, it does not affect excitatory synaptic transmission (59, 60). Interestingly, mice in which Y1472 has been replaced with phenylalanine (Y1472F) have impaired fear-related learning and decreased LTP in the amygdala, but normal LTP and spatial memory in the hippocampus [60]. pY1472 affects NR2B tyrosine phosphorylation, as Y1472F mice have 80% less tyrosine phosphorylation in the amygdala [60] and 70% less in the cortex compared to WT mice [61]. Y1472F mice also have changes in the NR2B complex, with less α -actinin and CaMKII associated with NR2B (60). pY1472 leads to activation of the CaMKII pathway in the amygdala and spinal cord (60, 62). Taken together, these results suggest that pY1472 affects NR2B tyrosine phosphorylation, surface expression, complex formation and downstream signaling cascades.

In summary, Fyn is involved in many processes critical for the development of the brain. Fyn regulates neuronal migration during corticogenesis, oligodendrocyte maturation, myelin production, long-term potentiation, and excitatory and inhibitory neuronal receptors.

Fyn in adult ischemic brain injury

Stroke is a leading cause of death and disability worldwide (63). Preclinical studies in rodents using SFK inhibitors suggest that targeting this kinase family may be protective in ischemic brain injury in humans (64). PP1 (4-amino-5-(4-methylphenyl)-7-(*t*-butyl)pyrazolo[3,4-*d*]pyrimidine) and PP2 (4-amino-5-(4-chlorophenyl)-7-(*t*-butyl)pyrazolo[3,4-*d*]pyrimidine) are ATP-analogues which compete with ATP for the ATP binding pocket of SFKs, thereby decreasing the ability of SFKs to phosphorylate substrates. Both compounds have some selectivity for Fyn among SFKs (65). Experiments using the adult rodent middle cerebral artery occlusion (MCAO) model have shown that PP2 reduces infarct volume and blood brain barrier leakage (66). PP2 protects hippocampal CA1 pyramidal neurons from transient ischemia (67). PP1 decreases infarct volume, edema, neurological deficits and increases survival when given after an ischemic insult (68).

While these inhibitors demonstrate that SFKs contribute to ischemic brain injury, few studies have examined the relative contribution of specific SFKs. Using a permanent MCAO model in adult rodents, Paul *et al* found that Src KO mice have decreased infarct volume compared to control mice. However, brain injury in Fyn KO mice (which are on C57BL/6, 129s hybrid background) did not differ from control C57BL/6 or 129s mice (68). This study would suggest that Src may be more important to the pathogenesis of stroke in adults. However it is unknown how brain injury in Fyn KO mice compares to control mice on a hybrid background. Recently, Du *et al* found in an *in vitro* model of ischemia, oxygen glucose deprivation, that Src or Fyn knockdown leads to decreased apoptotic cell death. Fyn

knockdown with siRNA had a greater neuroprotective effect (69). This study would suggest that Fyn and Src both contribute to injury, and that Fyn may be more important for apoptotic cell death, which is more prevalent in the neonatal brain.

How does Fyn contribute to ischemic brain injury in adult rodents? Consistent with its role as an adaptor protein, Fyn is part of multiple protein complexes that assemble in response to ischemia. It may also phosphorylate proteins implicated in cell death pathways.

Fyn exists in at least three ischemia-induced complexes with the NMDAR, PSD95, L-type voltage gated calcium channel (LVGCC), and SynGAP (Figure 3A). Fyn interacts with NMDAR subunits NR2A and NR2B in response to ischemia (17). While it is unknown whether Fyn directly phosphorylates the NMDAR in this setting, its interaction with the NMDAR coincides with elevated tyrosine phosphorylation (70). Tyrosine phosphorylation of NR2A and the NR2A-Fyn association are enhanced by PSD95 after transient brain ischemia (71). Studies have shown that PSD95 and the NMDAR couple to the neurotoxic nitric oxide signaling pathway and disrupting this interaction is protective (72). It is possible that Fyn may promote this interaction, since the NMDAR and PSD95 are Fyn substrates (Table 1).

Fyn phosphorylates PSD95 at Y523, which leads to upregulation of glutamate receptor channel activity in cultured hippocampal neurons (73). The Fyn-NR2A-PSD95 complex is positively regulated by protein tyrosine kinases and negatively regulated by protein tyrosine phosphatases (71). Two neuroprotective agents, Chinese traditional medicine Sy-21 and lithium, are associated with decreased pY NR2A and decreased formation of the Fyn-PSD95-NR2A complex (74, 75). These results suggest that tyrosine phosphorylation of this complex by Fyn may contribute directly to ischemic brain injury by increasing calcium influx through the NMDAR via PSD95 while also increasing nitric oxide signaling by promoting the NMDAR-PSD95 interaction.

To add another layer of complexity, the Fyn-NR2A-PSD95 complex is enhanced by NMDAR and L-type voltage gated calcium channel (L-VGCC) activity [76]. Fyn interacts directly with the $\alpha 1c$ subunit of L-VGCC during the peak of its tyrosine phosphorylation (77). Fyn also interacts with PSD95 associated GTPase, SynGAP during ischemia. Pei *et al* found that SynGAP tyrosine phosphorylation increases after ischemia, as does its association with Fyn. It is unknown whether Fyn regulates SynGAP phosphorylation or how SynGAP participates in ischemia (16).

Similar to PSD95, PSD93, another member of the membrane-associated guanylate kinase family of proteins, is also found to be a Fyn substrate (78) and interacts with NR2A/NR2B as well as with Fyn (79) in mouse cortex. Interestingly, tyrosine-phosphorylated PSD93 binds to Csk, a negative regulator of SFKs activity, and thereby forms a feedback loop to modulate SFKs-mediated phosphorylation of PSD proteins (78). In adult brain ischemia, PSD93 enhances Fyn/NR2B association and Fyn-mediated tyrosine phosphorylation of NR2B, including NR2B phosphorylation at Y1472, and contributes to brain injury (80). We did not see protection from PSD93 deficiency in neonatal brain hypoxia-ischemia (HI), possibly due to compensation of PSD95 (81). While PSD95 and PSD93 have unique

properties, they may coordinate with Fyn in regulating NMDAR function and downstream signaling in normal neuronal plasticity and in response to pathological conditions.

Taken together, these studies suggest that, as an intrinsic PSD tyrosine kinase and one of the core glutamate receptor kinase, Fyn is involved in phosphorylation and assembly/remodeling of the PSD complexes in response to ischemia in the adult brain. Fyn may phosphorylate several proteins such as PSD95, PSD93, SynGAP and membrane channels leading to increased calcium flux and cell death signaling pathways (Figure 3A). While these studies implicate Fyn in the pathogenesis of ischemic brain injury in adults, much less is known about the contribution of Fyn to ischemic brain injury in neonates.

Fyn in neonatal hypoxic-ischemic brain injury

Neonatal encephalopathy affects 1–6/1000 live births (82). Encephalopathy is derived from the Greek words *enkephalos* (brain) and *pathos* (disease) and refers to a disorder of the brain resulting in global dysfunction. Neonatal hypoxic-ischemic encephalopathy (HIE) is caused by hypoxia-ischemia during the prenatal, perinatal or postnatal periods (82). Neonatal HIE is modeled in postnatal day 7 (P7) and 10 rodents by exposing them to unilateral common carotid artery ligation followed by systemic hypoxia. This leads to injury in the cortex, hippocampus and striatum ipsilateral to the ligation (83–85).

Age-dependent differences in subunit expression and phosphorylation of NMDAR are associated with selective vulnerability of neonatal brain to HIE. While NR2B expression declines with age, tyrosine phosphorylation of NR2B, as well as pY1472NR2B, increase with age (53). By contrast, upregulation of NR2A protein level is paralleled by a decrease of its tyrosine phosphorylation with development (86). HI induced a rapid reduction of NR2A, leaving predominately NR2B tyrosine phosphorylation at P7 in rat brain. At P21, NR2B was reduced after HI and both NR2A and NR2B tyrosine phosphorylation was increased (86). Although it is uncertain whether SFKs are responsible for these phosphorylation events, we found that in the mouse, NR2B and Fyn are expressed at much higher levels at P7 in both synaptic and extrasynaptic membranes than in the adult brain, suggesting the importance of Fyn in regulating NR2B in the developing brain (54). SFKs are activated in response to HI in neonatal mice. SFK activity correlates with elevated NR2A and NR2B tyrosine phosphorylation. Fyn has increased association with NR2A and NR2B in response to injury. Significantly, SFK inhibitor PP2 was protective (87). To address the specific contribution of Fyn, we subjected mice overexpressing Fyn in neurons to neonatal HI. Fyn OE mice have increased brain injury and mortality following injury. This is associated with increased tyrosine phosphorylation of NR2A and NR2B as well as increased calpain activity. NR2B phosphorylation at Y1252 and Y1472 is higher in Fyn OE mice in synaptic fractions (88). These studies are consistent with the adult ischemia literature, namely that Fyn forms a complex with the NMDAR during HI and PP2 is protective (Figure 3B).

Next, we explored the functional consequence of Fyn-mediated NMDAR tyrosine phosphorylation in neonatal HI brain injury. We found that mice with a knock-in mutation of Y1472 to phenylalanine (YF-KI) had less brain injury than WT mice subjected to neonatal HI. This correlated with decreased activity of proteases implicated in apoptotic and

necrotic cell death. Intriguingly, YF-KI mice had reduced superoxide production and decreased expression of NADPH oxidase subunits gp91^{phox} and p47^{phox} *in vivo*. *In vitro*, YF-KI neurons had decreased superoxide generation in response to NMDA without affecting calcium accumulation. Additionally, YF-KI neurons were protected from NMDA and glutamate-induced cell death (61). Taken together, these studies demonstrate that Fyn-mediated phosphorylation of NR2B contributes to cell death, in part, by regulating superoxide-related oxidative signaling during HI and excitotoxicity (Figure 3C).

Given the crucial function of Fyn in neurodevelopment, future investigations of the mechanisms and functional consequences of Fyn-mediated cell death in neonatal HI will accelerate our progress towards developing therapies that selectively target critical signaling nodes mediating brain injury without disrupting normal brain development.

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Figure 1.

Structure of FynB A) Domain structure of FynB including N-terminal myristoylation (Myr) and palmitoylation (Palm) sites as well as regulatory tyrosine residues. B) Fyn binding partners in the unique region (black), SH3 domain (red) and SH2 domain (orange). These are the partners that have been published with demonstrated interactions with specific SH2 or SH3 domain. MAG: myelin-associated glycoprotein; SAP-1: stomach cancer-associated protein-tyrosine phosphatase-1; TRPC-6: transient receptor potential channel member 6

Figure 2.

Inactive and active conformations of Fyn Phosphorylation of Y531 in the C-terminus leads to intramolecular interactions that prevent kinase activity and protein-protein interactions, while phosphorylation of Y420 leads to an open structure that is catalytically active and accessible to binding partners.

Figure 3.

Fyn complexes during ischemia in adult and neonatal rodents A) In response to ischemia in adult rodents, Fyn interacts with two receptors that flux calcium, the NMDA receptor and $\alpha 1c$ subunit of L-type voltage gated calcium channel. PSD95 facilitates the interaction between Fyn and NR2A. Fyn also associates with SynGAP. Additionally, PSD93 interacts with NR2A/NR2B as well as with Fyn. Tyrosine-phosphorylated PSD93 binds to Csk, a negative regulator of SFKs. PSD93 enhances Fyn/NR2B association and NR2B tyrosine phosphorylation in adult brain ischemia. B) Fyn forms a complex with NMDA receptor subunits NR2A and NR2B during neonatal hypoxic-ischemic brain injury. These proteins are tyrosine phosphorylated by Fyn, which strengthens complex formation and likely contributes to pathogenic signaling in the setting of ischemia. C) Phosphorylation of Y1472 NR2B by Fyn mediates cell death by reactive oxygen species (ROS) generation in a calcium independent manner.

Table 1

Direct Fyn substrates in the brain

Substrate	Site(s)	Outcome of phosphorylation	Refs
PTPRT (Protein Tyrosine Phosphatase Receptor T)	Y912	Decreases phosphatase activity Promotes homophilic interactions Inhibits synapse formation	(89)
TrkA receptor	ND	Promotes transactivation of TrkA by G-Coupled Protein Receptors (GPCRs)	(13)
Na _v 1.2	ND	Decreases sodium currents	(90)
γ ₂ subunit GABA _A receptor	Y365, Y367	Prevents clathrin-mediated endocytosis Enhances synaptic inhibition	(48) (47)
NR2A subunit NMDA receptor	ND	ND	(91)
NR2B subunit NMDA receptor	Y932, Y1039, Y1070,Y1109, Y1252,Y1336, Y1472	Y1472: prevents clathrin-mediated endocytosis Y1336: promotes calpain cleavage of NR2B; increased interaction with PI3-K	(91) (53) (58) (56) (57)
TCGAP	Y406	Negatively regulates activity	(92)
p250GAP	ND	Increases association with Fyn	(93)
p190RhoGAP	ND	ND	(94)
Cdk5	Y15	Increases kinase activity Promotes sema3a induced growth cone collapse	(95)
Tau	Y18	Prevents inhibition of anterograde fast axonal transport	(96) (97)
MAP-2c	Y67	Increased interaction with Grb2	(98) (99)
Psd93	Y348	ND	(78)
Psd95	Y523	Increases NMDA receptor currents	(73)
rSLM-1	ND	Prevents splice site selection	(100)
α-synuclein	Y125	ND	(101)
c-Cbl	ND	ND	(102)
N-WASP	Y253	Arp2/3 complex mediated actin polymerization Neurite extension	(103)
Dab1	Y185,Y198	Permits phosphorylation of other Y sites of Dab1 Increases interaction with Fyn Akt activation Degradation of Dab1	(32) (31) (104)