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ABSTRACT
Reversible protein phosphorylation is a common and important form of protein posttranslational modification which determines the proteins’ activities, substrate specificity and inhibitions or degradations, depending on the specific amino acid residue, or combination of residues, being targeted. While protein phosphorylations by kinases have been well studied, the importance of protein dephosphorylation by phosphatases has emerged over the past two decades in numerous cell functions, including cell cycle, development, regulation of signal transduction pathways, mitochondrial fusion and fission and disease states of cells. So far, there are five classes of phosphatases: tyrosine-specific phosphatases, serine/threonine specific phosphatases, dual specificity phosphatases, histidine phosphatase and lipid phosphatase. The subject of this review, Protein Phosphatase 2 (PP2, aka PP2A), is a member of the serine/threonine specific phosphatases which dephosphorylate a wide range of proteins including many of the phosphatases and kinases. In eukaryotic proteins, 86 and 12% are phosphorylated on Ser and Thr, respectively and the reversible phosphorylation of these proteins is key to their dynamic functions. The research done on PP2A has exploded in recent years and there are many excellent detailed reviews each with a specific PP2A topic. This article presents a brief overview of PP2A functions in four aspects: Their substrate specificity, roles in Tau hyperphosphorylation, roles in mitochondria fusion and fission and nine examples of their roles in neuronal functions.

Keywords: PP2A, Substrate Specificity, Tau Hyperphosphorylation, Mitochondria Fusion and Fission, Neuronal Functions

1. INTRODUCTION
1.1. General structure of PP2A
The heterotrimeric holoenzyme PP2A is made up of a scaffolding subunit (A), a variable regulatory subunit (B) and a Catalytic subunit (C). In vertebrates, there are two isoforms each of the A and C subunits but at least 15 different isoforms of the B subunit (Slupe et al., 2011). The two isoforms of the A and C subunits are more conserved while the more diverse regulatory B isoforms can be grouped into four families: B (PR55), B’ (PR 61), B” (PR72) and B”’(PR93/PR110) (Slupe et al., 2011). The A subunit contains 15 tandem repeats of the Huntington-Elongation-A subunit-TOR (HEAT) motif (Hemmings et al., 1990; Walter et al., 1989) which are important for the assembly of the heterotrimeric holoenzyme. The C subunit was shown to interact with the HEAT repeats 11-15 (Ruediger et al., 1992; Xing et al., 2006). Each of the four families of the B subunits was found to have their particular docking sites which overlap but are mutually exclusive in different parts of the A subunit (Strack et al., 2002). For example, a B (PR55) subunit interacts with Heat repeats 1-10 with repeat 1 being absolutely required (Nobumori et al., 2012) while a B’ (PR61) regulatory subunit interacts with HEAT repeats 2-8 (Cho and Xu, 2007; Xu et al., 2006). In addition to the A-B subunit interaction, the carboxy terminus of the catalytic C subunits was shown to interact with the surface groove formed between the A and B’ (PR61) subunit (Xu et al., 2006). That interaction was found to be mediated through a highly negatively
charged region of the surface groove (Cho and Xu, 2007). Thus, the three subunits of PP2A have tight and specific interactions among each other. From now on, PP2A refers to the trimeric holoenzyme. PP2A/B or simply B refers to the B subunit without specific information on which isoform. B (PR55) refers to an uncharacterized isoform of the first B subunit family. Bα refers to the alpha subunit of B (PR55) while Bδ is the delta subunit of B’ (PR61). The same notation terminology applies to PP2A/A and PP2A/C.

1.2. Substrate Specificity of PP2A

PP2A is ubiquitously expressed and found to dephosphorylate a wide array of substrates. Its substrate specificity was poorly understood until Strack et al. (1998) showed that substrate specificity of PP2A can be determined by the three B (PR55) isoforms (Bα, Bβ and Bγ) they studied. As more isoforms are found, the number of possible combinations among the A, B and C subunits increases to over sixty possible different trimeric PP2As. However, that number of combinations may not be specific enough for its diverse substrates. Slupe et al. (2011) summarized experimental evidence to suggest the presence of five determinants for PP2A’s substrate specificity in which the presence of the many different B subunits for selective holoenzyme assembly is one important determinant. The activation of a specific PP2A by phosphorylation and methylation of the C subunit and phosphorylation of the B subunit is another determinant. The third one is through protein inhibitors being expressed under specific conditions. The fourth determinant is substrate recruitment by the regulatory B subunit through distal low-affinity interactions to increase the local substrate concentration. The fifth one is substrate interactions near the catalytic site to enhance the dephosphorylation of the specific substrate. Besides these five determinants, there are many PP2A binding partners which also contribute to the specificity of PP2A activities (Janssens and Goris, 2001).

1.3. Regulations of PP2A

The diverse PP2As are regulated by extracellular signals. How does a cell respond to a sudden change in external stimulus that leads to the expression of a specific PP2A for its specific signaling pathway? Janssens et al. (2008) reviewed the possibility for such a temporal increase in the expression of a specific B subunit followed by the swapping of the B subunit into existing PP2A heterotrimers. The advantage of such a mechanism would be to generate a temporal change in the expressions of PP2A by increasing the production of a specific B subunit without an equal and corresponding increase in the production of A and C subunits. In their review, the phosphorylation and methylation states of three of the six highly conserved amino acids in the C terminal of the C subunit were shown to determine which B subunit is being selected. In addition, the activities of PP2A can also be modulated by its regulators, e.g., alpha 4, through its C subunit (Nanahoshi et al., 1998; Chen et al., 1998; Kloeker et al., 2003). Tap42, an orthology of alpha4, was recently found to interact with PP2A in vivo in Drosophila wing imaginal disc (Wang et al., 2012). The authors showed that a mutant of PP2A/C subunit partially rescued the phenotypes and lethality caused by RNAi knockdown of Tap42. Thus, it is likely that the defect caused by Tap42 knock down in the wing imaginal disc of Drosophila is mediated through the PP2A/C activity.

2. PP2A’S ROLE IN PHT-TAU HYPERPHOSPHORYLATION

2.1. Neurotoxicity of the Phosphorylated Microtubule-Associated Protein Tau

Phosphorylation of Serine-Proline (SP) and Threonine-Proline (TP) residues within the microtubule-associated protein Tau (MAPT) by proline-directed kinases is a striking feature of Tau observed from patients with Alzheimer’s disease and other Tauopathies (Lee et al., 1991; 2001; Goedert et al., 1994; Gong et al., 2005). However, Tau hyperphosphorylation at specific sites can be caused by up-regulation of kinases, down-regulation of phosphatases and both. Several kinases have been shown to phosphorylate Tau, including Extracellular Signal-Regulated Kinases (ERKs) Or Microtubule-Associated Protein Kinases (MAPK) (Drewes et al., 1992; Goedert et al., 1992b), glycochen synthase kinase-3 or GSK3 (Hanger et al., 1992; Mandelkow et al., 1992), CDKS (Baumann et al., 1993; Kobayashi et al., 1993; Paudel et al., 1993), CDC2 kinase (Ledesma et al., 1992) and proline-directed protein kinases (Vulliet et al., 1989). It has been demonstrated that PP2A and PP2B are able to dephosphorylate Tau (Goedert et al., 1992a; Drewes et al., 1993; Harris et al., 1993; Gong et al., 1994). The phosphorylation of specific amino acid residues in normal Tau reduces the ability of these proteins to bind to microtubules, rendering them to bind to each other to form paired helical filaments (hence the name PHF-Tau) and subsequently neurofibrillary tangles. Thus, it is crucial to know these SP/TP sites and which specific kinases and phosphatases are involved.
2.2. The Roles of PP2A in Tau Hyperphosphorylation

The first group to suggest that phosphatases played a role in PHF-Tau formation is likely to be Matsuo et al. (1994). This group examined the phosphorylation of the human adult Tau from brain biopsies, autopsy-derived human fetal Tau and rapidly processed rat Tau. They found all three tissues contained phosphorylated Taus that were indistinguishable from that of Tau obtained from Alzheimer’s Disease (AD) brain. In the case of the human adult Taus obtained from brain biopsies, they were phosphorylated at the same sites as PHF-Tau; sites that could be dephosphorylated easily and efficiently by endogenous phosphatases. Matsuo’s group therefore suggested that it was unlikely that kinases hyperphosphorylate Tau in AD patients. Rather, it was the down regulation of phosphatases in AD patients allowing persistent phosphorylation of Tau.

Which subunits of PP2A are responsible for Tau dephosphorylation? Both Bα regulatory subunit (Xu et al., 2008) and B’δ (PR61δ) (Louis et al. 2011) have been shown to dephosphorylate Tau. Xu et al. (2008) studied the interactions between Bα and purified recombinant human Tau protein from bacteria. They identified the amino acid residues found in Bα that are important for Tau interactions. Furthermore, Louis et al. (2011) showed that B’δ (PR61δ) was highly expressed in neural tissues. They used knockout mice lacking B’δ (PR61δ) to show that there was a co-relation between the progressive phosphorylation of the pathological Tau epitopes and the impaired sensorimotor functions. Most recently, Sontag et al. (2012) showed that Tau and MAP2 competed for binding to and were dephosphorylated by Bα. They suggested that Bα is part of MAP2 and Tau signaling scaffolds to coordinate the action of key kinases and phosphatases involved in modulating neuronal plasticity. Although there is much evidence to suggest Bα subunit to be primarily involved in Tau dephosphorylation, the complexity of the system has yet to be elucidated. Currently, PP2A abnormalities have been reported in AD patients including decreased protein levels of the A and B subunits, reduced methylation but increased phosphorylation of the C subunit and up-regulation of the PP2A inhibitors (Torrent and Ferrer, 2012).

Many of the SP/TP sites found in Tau have been identified to be neurotoxic when they are phosphorylated, thus the term “disease-associated” sites (Otvos et al., 1994; Goedert et al., 1994; 1995; Jicha et al., 1997; Zheng-Fischhofer et al., 1998; Shea and Cressman, 1999). To do a systemic analysis of the correlation between SP/TP phosphorylation and disease severity, Augustinack et al. (2002) used 11 monoclonal antibodies that recognize particular phosphoepitopes of Tau and checked the phosphorylation state of these sites in tissues obtained from AD patients. They were able to identify the phosphorylation of specific sites during the formation of (a) pre-neurofibrillary tangle (pT231, pS262 and pT153), (b) intra- (pT175/181, pS262/pS356, pS422, pS46, pS214) and (c) extra-neuronal neurofibrillary tangles (pS199/pS202/pT205, pT212/pS214 and pS396/pS404). They concluded that specific phosphorylation of these SP/TP sites leads to conformational changes of these filaments at different stages of the cytopathological progression in the patients. The elucidation of specific PP2A abnormality and the corresponding specific SP/TP sites being affected is needed for a thorough understanding of PP2A’s roles in Tau hyper-phosphorylation.

2.3. Drosophila Model of Tau Hyperphosphorylation

To study the toxicity of the hyperphosphorylated Tau in vivo, Wittmann et al. (2001) generated a Drosophila Tauopathy model by expressing wild-type and mutant forms of human Tau in Drosophila melanogaster. They found neurodegeneration occurred in the transgenic flies without the neurofibrillary tangle formation. Later on, Steinhlub et al. (2007) used the Drosophila photoreceptors as a model to study five known neurodegenerative-disease related SP/TP sites and found that no single Tau SP/TP site promoted neurotoxicity, suggesting that phosphorylation of multiple sites worked together to promote neurodegeneration. They further showed that blocking phosphorylation of all 14 SP/TP sites in Tau by mutating them to alanine markedly inhibited Tau-induced neurodegeneration in Drosophila. Meanwhile, a pseudophosphorylated Tau generated by mutating all SP/TP sites to glutamate was found to be significantly more toxic than TauWT (Khurana et al., 2006; Dias-Santagata et al., 2007; Fulga et al., 2007). The question regarding which combinations of the SP/TP sites are important at different stages of the Tau-induced neurodegeneration in Drosophila remains to be worked out. For a more detailed review of Drosophila models of Tauopathies, please refer to Gistelinck et al. (2012).
3. PP2A’S ROLE IN MITOCHONDRIAL FUSION AND FISSION

Among many functions, mitochondria buffer calcium, sequester cell death-inducing molecules and provide energy for various cell activities. Thus mitochondrial dysfunction will lead to various cellular problems which are implicated in various neuropathologies. In cells, particularly in neurons, mitochondria are highly dynamic organelles that constantly move, divide and fuse together. These events are regulated by the Dynamin-related Protein 1 (Drp1) (Wilson et al., 2012), the mitofusins MFN1 and MFN2 and Optic Atrophy type I (OPA1) (Kanamaru et al., 2012).

The roles of phosphatases on neuronal functions were not well studied until the late-1990s largely due to the lack of understanding that phosphatases are, like kinases, substrates specific. Holmes et al. (1999) found a trinucleotide repeat expansion in the promoter region of the human B gene (PPP2R2B which encodes a B subunit of PP2A) in the human brain cDNA of neurodegenerative disorder spinocerebellar ataxia type 12. Since trinucleotide repeat expansion was found in several human neurodegenerative disorders, including spinocerebellar ataxia type 1 (Ashley and Warre, 1995; Paulson and Fischbeck, 1996), the finding implicated that mis-regulated B gene expression may be one of the possible causes of spinocerebellar ataxia type 12. At around the same time, more B subunits were found and the idea that specific phosphatase may be involved in specific neurodegenerative diseases emerged.

The story of a specific B subunit involved in mitochondria function came from Dagda et al. (2003). They found that expression of the neuronal-specific Bβ2 isoform was induced during neuronal differentiation. They then showed that Bβ2 contained a unique N-terminal which was sufficient to target green fluorescent protein to the mitochondria. Later on, Dagda et al. (2005) demonstrated that full-length Bβ2 interacted with the mitochondrial import complex, but was arrested at the Outer Mitochondrial Membrane (OMM). Although the location of the induced Bβ2 had been identified, the substrate remained elusive. One of the good candidates was dynamin-related GTPase Drp1 because it had been known to be involved in mitochondrial fission (Smirnova et al., 1998; Otsuga et al., 1998) and the subsequent causes of neurodegeneration. Later on, Dickey and Strack (2011) showed that Bβ2-mediated dephosphorylation of Drp1 at S656 led to mitochondrial fragmentation. The kinases and phosphatases involved in reversible Drp1 phosphorylation as well as their phosphorylation and dephosphorylation sites were mostly found in the late 2000. So far, there are at least four known Ser phosphorylation sites found in Drp1 that are shown to play roles in mitochondrial fusion and fission. Phosphorylation of two of them, S585 (Taguchi et al., 2007) and S600 (Han et al., 2008), activates Drp1 and induces mitochondrial fission. Phosphorylation of the other two, S637 and S656, inhibits Drp1 and prevents mitochondrial fission. The story of the S656 is interesting: PKA is the kinase for S656 phosphorylation in Drp1 but both PP2B (Cribbs and Strack, 2007) and PP2A/Bβ2 (Dickey and Strack, 2011) were reported to be responsible for S656 dephosphorylation. The PP2B-mediated dephosphorylation of Drp1 S656 was demonstrated to drives cardiomyocyte apoptosis during ischemia-reperfusion (Wang et al., 2011) while the PP2A’s role on Drp1 was revealed to play roles in neuronal developmental processes. It is likely that a cohort of other signaling molecules accompanying the activation of each of the two phosphatases determines the cell fate.

Like kinases, the phosphorylation state of phosphatases is important for their activities and/or their localization. Merrill et al. (2012) worked out the phosphorylation sites found in PP2A that regulate its activities. They showed that phosphorylation of three N-terminal serines, S20-S22, render the neuron specific Bβ2 cytosolic while dephosphorylation allows Bβ2 to translocate to the OMM where it will dephosphorylate S656 of Drp1 and activate it to induce mitochondria fragmentation.

4. THE MECHANISMS OF PP2A’S NEURONAL FUNCTIONS ARE STILL POORLY UNDERSTOOD

Although PP2A has been known to dephosphorylate a wide array of substrates including cytoskeletal proteins, receptors and ion channels and transcription factors, the in vivo mechanisms underlying the protein phosphatases’ cell functions are poorly understood. To illustrate this point, some of the neuronal functions of PP2A are shown in Table 1. The first four studies use either brain tissues from rats or Drosophila photoreceptors. The remaining five studies mainly employ cell lines. In most of the cases listed, the in vivo signaling cascades underlying the functions being regulated are not known. The study of PP2A’s physiological functions have been known to be difficult, partly because in vivo knockdown would lead to lethality of the organisms or multiple signal transductions being affected (Wang et al., 2012).
Table 1. Nine examples of the neuronal functions of PP2A

<table>
<thead>
<tr>
<th>Subunit of PP2A</th>
<th>Organism and/or specific cells</th>
<th>Substrate</th>
<th>Functions being regulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PP2A/B subunit (Koh, 2011)</td>
<td>Rat brain tissues and Hippocampal-derived HT22</td>
<td>Not studied</td>
<td>Cerebral Ischemic injury</td>
</tr>
<tr>
<td>2. PP2A/C subunit (Lu et al., 2009)</td>
<td>Drosophila photoreceptors</td>
<td>CaMKII</td>
<td>PDA generation</td>
</tr>
<tr>
<td>3. PP2A/C subunit (Wang et al., 2008)</td>
<td>Drosophila photoreceptors</td>
<td>INAD</td>
<td>Response deactivation</td>
</tr>
<tr>
<td>4. PP2A/C subunit (Zhu et al., 2010)</td>
<td>Rat brain tissues and the dissociated hippocampal neurons</td>
<td>Collapsin Response Mediator Protein-2 (CRMP2)</td>
<td>Axonogenesis</td>
</tr>
<tr>
<td>5. Bγ (Strack, 2002)</td>
<td>PC6-3 cells</td>
<td>Stimulating the MAP kinase cascade downstream of the TrkA NGF receptor but upstream or at the level of the B-Raf kinase</td>
<td>Neurofilament expression and neurite outgrowth</td>
</tr>
<tr>
<td>6. B′, Bα and Bδ (Kanegan et al., 2005)</td>
<td>PC12 cells</td>
<td>Akt and MEK1</td>
<td>B′ regulates Akt signaling while Bα and Bδ regulate ERK pathway</td>
</tr>
<tr>
<td>7. B′β and B′δ (Kanegan and Strack, 2009)</td>
<td>PC12 cells</td>
<td>TrkA receptor</td>
<td>Promote neurotogenesis and differentiation</td>
</tr>
<tr>
<td>8. B′β (Saraf et al., 2007)</td>
<td>PC6-3 cells and rat midbrain slides</td>
<td>Tyrosine hydroxylase</td>
<td>Catecholamine synthesis</td>
</tr>
<tr>
<td>9. Bβ subunit (Dickey and Strack, 2011)</td>
<td>Cultured rat hippocampal neurons</td>
<td>Drp1</td>
<td>Suppresses dendritic outgrowth and facilitates synapse formation</td>
</tr>
</tbody>
</table>

One way to resolve that problem would be to have inducible, tissue-specific drivers to knockdown a particular B subunit in a time and tissue-specific manner to avoid premature lethality of the organism. Moreover, it is possible that the most dominant phenotype may show upon a very transient knockdown of a particular PP2A subunit. Such an approach may allow the separation of the causal relationship when more than one signaling cascade is involved.

Koh (2011) studied the expression level of the B subunits of PP2A (PP2A/Bs) after surgically induced cerebral ischemic injury, with sham-operated adult male rats as control. Western blot analysis showed that the expression of PP2A/Bs was reduced in brain tissues collected 24 h after the induced injury. In addition, PP2A/Bs expression was also reduced in glutamate exposure-induced neuronal cell death in a hippocampal-derived cell line. Taken together, Koh suggested that the decreased expression of PP2A/Bs after ischemic brain injury can mediate neuronal cell death. The antibody used in this study was not specifically targeted for a particular B subunit and therefore provided only an overall evaluation of the PP2A/Bs function without specific mechanisms.

Roles of PP2A/C in Drosophila photoreceptors. Drosophila photoreceptors are specialized neurons which undergoes a phototransduction cascade that transduces light into electrical signals. The activation and deactivation of photoreceptor pigment, rhodopsin R1, is critical for photoreceptor function. Rapid activation of rhodopsin is required for a fast response and a complementary rapid deactivation is necessary for good temporal resolution wherein a photoreceptor can distinguish two separate stimuli that come one right after another. Drosophila photoreceptors enhance the temporal resolution at several levels but not all of them involve PP2A. Arrestin 2 is involved in the deactivation of metarhodopsin (the activated rhodopsin isomer) while INAD is most likely involved in deactivation of the light activated TRP channels. Both Lu et al. (2009) and Wang et al. (2012) used a PP2A/C subunit mutant which is encoded by the microtubular star (mts) gene in Drosophila to study the roles of PP2A at these two levels. Lu et al. (2009) showed that in the mts mutant, CaMKII activity was increased due to its hyperphosphorylation. The result was that arrestin 2, a CaMKII substrate, was also hyperphosphorylated. Photoreceptors carrying the mts mutation are less likely to generate a prolonged response with blue light stimulus. Thus, Lu et al. (2009) showed that in vivo regulated phosphorylation of arrestin 2 by CAMKII, with its activities regulated by PP2A, is important for the efficient deactivation of metarhodopsin. Wang et al. (2012) used the mts mutant to study the deactivation of the photoreceptor response in Drosophila. INAD is a multi-PDZ domain protein that was shown to organize the signaling molecules for a fast, orchestrated response activation and deactivation. The kinase that
phosphorylates INAD is the eye-specific PKC, ePKC. An ePKC mutant was shown to have very slow response deactivation, leading to a poor temporal resolution of successive stimuli. Wang et al. (2012) showed that PP2A dephosphorylated INAD and the mutant mts rescued the PKC’s defect of slow response deactivation. Thus, reversible phosphorylation of INAD is important for response deactivation. To further understand the mechanisms of the two processes, it would be important to know if two different B subunits of PP2A are involved in the two studies.

Zhu et al. (2010) found that PP2A/C is enriched in the distal axon of the hippocampal neurons. Upregulating PP2A/C by treating the hippocampal neurons with D-erythro-S resulted in the formation and elongation of the functional axons. To understand how, they showed that PP2A dephosphorylated Collapsin Response Mediator Protein-2 (CRMP2), which had previously been shown to be important for axonal polarization and outgrowth. To further understand the mechanisms of the two processes, it would be important to know if two different B subunits of PP2A are involved in the two studies.

Strack (2002) studied the roles of BY on the differentiation of PC6-3 cells, an inducible neuronal subline of PC12 cells. Once induced by Nerve Growth Factor (NGF), the PC6-3 cells become neuronal and their survival depend on NGF. Strack showed that transient expression of plasmids containing the regulatory BY subunit in PC6-3 cells, but not other PP2A regulatory subunits, promoted neuritogenesis and cell differentiation. Moreover, PC6-3 cells containing FLAG-tagged BY, with a tetracycline-inducible promoter, underwent growth arrest and neurofilament expression when treated with tetracycline. Strack checked the activities of Raf, Mitogen-activated protein Kinase (MEK) and Extracellular signal-Regulated Kinase (ERK) activities and found that they were being dephosphorylated by B family rather than the B’ family subunits. RNAi silencing of PP2A/Ba and Bb subunits led to hyperactivity of ERK. Kanegan and Strack (2009) later reported that B’β and B’δ recruit the heterotrimer PP2A into the NGF-TrkA receptor to dephosphorylate and potentiate the activities of the NGF receptors specifically. This in turn leads to the activation of the Ras-Akt pathway to promote neuritogenesis and differentiation of PC12 cells.

Tyrosine Hydroxylase (TH) is the rate-limiting enzyme in catecholamine synthesis which is essential for the production of neurotransmitters in dopaminergic neurons. Saraf et al. (2007) identified PP2A/B’β as a specific TH phosphatase in the catecholamine-secreting PC6-3 cells as well as in rat brain. They showed that inducing B’β expression decreased TH activity while silencing the endogenous B’β increased TH activity in the PC6-3 cells. They further showed that PP2A/B’β, but not other regulatory subunits, directly dephosphorylated TH in vitro. They then examined TH phosphorylation in the dopaminergic cell in the substantia nigra and found that TH phosphorylation was higher in the processes than in somata. Moreover, PP2A/B’β was only found in the neuronal cell body. These results are consistent with the idea that TH is inactivated in the cell body and therefore catecholamine synthesis is confined to axonal terminals.

The role of Drp1 on the dynamic fusion and fission of mitochondria has been well studied. Dickey and Strack (2011) studied the effects of reversible phosphorylation of Drp1 at a conserved Serine residue, S656, on dendrite and synapse development in cultured rat hippocampal neurons. They showed that hippocampal neurons co-transfected with PKA/AKAP1 displayed increased mitochondrial length and enhanced dendritic outgrowth but decreased synapse number and density. On the other hand, when co-transfected with PP2A/Bβ, the same neurons exhibited mitochondrial fragmentation and depletion of mitochondria from dendrites, stunting dendritic outgrowth but augmenting synapse formation. These actions were abolished when construct S656A were used indicating that S656 was essential for the observed effects. Thus, reversible phosphorylation of

S656 of Drp1 determines dendrite and synapse development in these neurons.

5. CONCLUSION

The importance of PP2A is reflected by the increasing number of publications relating protein dephosphorylation to human neurodegenerative diseases such as AD and Parkinson’s disease, as well as the therapeutic strategies targeting PP2A’s expression or activities. This review sampled some of the research the author is more familiar with and is therefore quite limited in its scope. In a short time span of about twenty years, the role of PP2As has evolved from that of a ubiquitously expressed, non-specific enzyme to function as players in specific mechanisms, with its particular binding partners and confined in well-defined cellular compartments or domains, being expressed in finely controlled ways and found to play roles in a vast number of signal transduction pathways, each with its own unique features.

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6.1. Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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