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Pin1 and Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is an immense and growing public health crisis. Despite over 100 years of investigation, the etiology remains elusive and therapy ineffective. Despite current gaps in knowledge, recent studies have identified dysfunction or loss-of-function of Pin1, a unique *cis-trans* peptidyl prolyl isomerase, as an important step in AD pathogenesis. Here I review the functionality of Pin1 and its role in neurodegeneration.

Introduction

Alzheimer's disease remains among the fastest growing, most debilitating and costly diseases in the western world. The search for etiology has consumed scientists and physicians since its description by Alois Alzheimer in 1907-1911. He identified a constellation of pathology consisting of neuronal loss, brain atrophy, amyloid plaques and intracellular tangles that was distinct from syphilitic brain syndromes prevalent at the time. In 1984, plaques were purified [1] and the major component identified as a 39-44 amino acid peptide [2, 3]. The predicted amyloid precursor consisted of 695 amino acids and showed characteristics of a cell-surface, glycosylated receptor. The so-called amyloid precursor protein (APP) was ubiquitously expressed in multiple, alternatively spliced mRNAs and translated as isoforms of 564, 695, 717 and 770 amino acids, depending on the tissue [4, 5]. Ultimately 2 paralogs denoted amyloid precursor like protein 1 and 2 (APLP1 and 2) were also identified [6]. APP's transcriptional and post-transcriptional responses were sensitive to outside-in cytokine driven signaling and mimicked typical acute phase responses [7]. Over time, Aβ42 and related species accumulate, especially in aged individuals or those homozygous for APO E4 [8], carrying germline, APP mutations at or near the Aβ42 cleavage sites [3], trisomy 21 (Down's Syndrome)[9], presenilin 1/2 mutations [10], or traumatic brain injuries [11]. Soluble, oligomerized Aβ42 reaches toxic levels and damages neurons and synaptic connections, inhibits plasticity, enhances the accumulation of intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, and activates microglia and astrocytes which release cytokines, chemokines, reactive oxygen species and nitric oxide. Over years, this toxic environment causes synaptic loss, mitochondrial and metabolic failure with deposition of hyperphosphorylated tau, neuronal cell death, chronic gliosis and ultimately brain atrophy. Reduced blood flow due to classic atherosclerosis or intravascular amyloid deposition commonly amplifies and accelerates these events.

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As AD evolves, many proteins show changes in expression, distribution or function. The vast majority are associated rather than causal events and have not been shown to drive neuronal dysfunction or death. The breadth of change in afflicted neurons reflects many dysregulated signaling pathways that are evoked. Given that reality, protein(s) with involvement in multiple pathways, especially signaling cascades should be carefully considered as etiologic drivers of AD. Pin1 is one such molecule.

Pin1

Pin1 is a ubiquitously expressed, 18KD *cis-trans* prolyl isomerase. It was identified in 1996 with a yeast-2 hybrid screen for Never in Mitosis Associated (NIMA-1) kinase interactors [13]. Pin1 deletion pevented cell-cycle progression and is lethal in yeast [13, 14]. It is very highly conserved eukaryotic homolog to bacterial *parvulin*, yeast *Ess1* and drosophila *DoDo*. Pin1, Ess1 and Dodo share a bipartite structure with a 40 amino acid, N-terminal, type IV WW domain connected via a flexible linker to a ~120-125 amino acid isomerase domain [12]. These homologs are functionally interchangeable as Pin1 or *dodo* complements deleted *Ess1* in yeast [13, 14]. The WW-domain contains 2 essential and conserved tryptophans which mediate binding to Ser/Thr-Pro or pSer/pThr-Pro dipeptides [15-17] and positions the isomerase domain for the conversion of the WW binding target from *cis* to *trans* or the reverse. Pin1 mediated isomerization is ~1000 fold faster if the Ser/Thr are phosphorylated [18]. Notably bacterial parvulin lacks the WW targeting domain as does a Pin1 mammalian ortholog Par14/17. Pin1 along with FKBP and cyclophilin constitute the so-called immunophilin superfamily and share *cis-trans* prolyl isomerase activity. However, FKBP and cyclophilin target X-Pro dipeptide bonds rather than only pSer/Thr-Pro. Much controversy remains concerning the functions of FKBP and cyclophilins in yeast but the latest data suggests their deletion greatly reduces growth and viability [19]. Nevertheless, Pin1 is the only known enzyme with pSer/Thr-Pro selectivity which probably accounts for its very high conservation over hundreds of millions of years of evolution.

The Ser/Thr-Pro dipeptide in *cis* is the target for the so-called proline-directed kinases (PDKs) which includes MAPKs (p38, Erk and JNK), CK1/2, GSK3 and CDKs among others. The *cis-trans* conversion mediated by Pin1 is possible because the planar Pro can exist either *cis* or *trans* to the N-terminal Ser/Thr. The conformation around this peptide bond has relevance as PDKs and opposing phosphatases show selective activity towards either the *cis* or *trans* isomer [18, 20]. For example, *cis* but not *trans* tau is progressively phosphorylated by GSK3 at Thr231-Pro232 as AD evolves [21] which is opposed by PP2A which favors the *trans* form. The final conformation of the bond plays a key role in a variety of other protein functions including susceptibility to degradation, localization, activity and protein-protein interactions [22]. Not surprisingly, total pS/T modifications are very prevalent and constitute approximately 96% of the entire AD brain phosphoproteome [23, 24] while 2/3rds of identified pS/pT sites in axon growth cones precede a Pro [25]. Once phosphorylated, Pin1 catalysis increases the cis-trans conversion rate by 10^3 to 10^6 fold from spontaneous [26]. Trans pSer/Thr-Pro can be attacked by PP2A and other phosphatases that typically prefer pSer/Thr-Pro this isoform [27]. Because the rate of spontaneous, nonenzymatic interconversion is so slow, once isomerized and dephosphorylated, protein targets are essentially locked for their lifespan into the trans conformation. Conversely,

in the absence of Pin1, *cis* pSer/Thr-Pro tau cannot be converted to *trans* and efficiently attacked by PP2A, leading to accumulation, microtubule toxicity, mitochondrial and axonal catastrophe and eventual neurodegeneration [28, 29]. Therefore, Pin1 activity is absolutely critical for transmitting PDK initiated signaling and maintaining cellular phospho-proteome homeostasis at Ser and Thr sites. Dysregulation of the phosphoproteome is increasingly seen as a driver of AD pathology [30].

Pin1 is ubiquitously expressed throughout all tissues but shows highest levels in reproductive organs and brain (https://www.proteinatlas.org/ENSG00000127445-PIN1/tissue). However, expression alone can be deceptive as Pin1 activity varies dramatically between cells and tissues. Activity is very low in quiescent peripheral immune cells such as lymphocytes and eosinophils despite ample expression [31] but constitutively active in neurons [32, 33] where it can be found in the axon growth cone, dendritic spines, soma and nucleus. In the immune system, isomerase activity is very rapidly (seconds to minutes) upregulated by lectin, cytokine and chemokine driven, outside-in signaling which alters Pin1 phosphorylation (see below). Conversely, at synapses, isomerase activity can be transiently suppressed by glutamatergic [33] or Aβ42 signaling [34]. These data demonstrate that Pin1 has both generic as well as cell-specific and possibly organelle-specific functions. Pin1 is often highly expressed in epithelial, CNS and hematopoietic cancers, likely facilitating cell-cycle progression and growth which is often associated with poor prognosis [35]. Conversely, Pin1 inhibition can disrupt tumor cell proliferation and enhances apoptosis suggesting it may be an attractive target for combination anti-cancer therapy [36-38].

Not surprisingly, the regulation of Pin1 is complex but mostly focused on post-translational events. Pin1 is the target of multiple kinases and at least 1 phosphatase which alter Pin1 activity, localization and half-life. PKA [39] and Aurora A [40] phosphorylation at Ser 16 disrupts WW domain-target interactions, essentially silencing Pin1 activity and blocking cell-cycle progression while COT and RSK phosphorylation at the same site do not reduce proliferation [41]. These divergent conclusions likely reflect differences in analytical endpoints rather than solely based on the effects of these kinases on Pin1-WW mediated target binding. DAPK1 phosphorylation of Ser71 [42] inhibits activity, possibly by interfering with the phosphate binding domain in the isomerase domain [43]. As such DAPK1 activators have shown some promise as anti-cancer agents [44]. Ser 111 is phosphorylated in healthy neurons [23][24] and required for activity but dephosphorylated by calcineurin after Aβ42 outside-in signaling [34]. C113 can be oxidized, blocking isomerase activity and increasing Pin1 cytoplasmic localization at the expense of nuclear [45]. Ser 108, 115, 147 and 154 moieties have been reported as phosphorylation sites although the biological role of these modifications have not been elucidated. Finally, Pin1 can also be acetylated [46], sumoylated [47], ubiquitinated [48] and methylated [49], again with uncertain significance.

Pin1 and Alzheimer's disease

Pin1 was first implicated in AD pathogenesis in 1999 [50]. The Lu laboratory reasoned that hyperphosphorylated tau, the main component of paired helical filaments (PHF) and neurofibrillary tangles (NFTs), a common and established feature of evolving AD, would be

regulated by Pin1 due to its repetitive pS/T-P motifs. Further support for this hypothesis was the observation that tau normally undergoes cycles of phosphorylation/dephosphorylation during cell-cycle progression and can be detected with MPM-2, a phospho-specific mAb that identifies a subset of mitotic phospho-proteins [51] previously shown to bind to Pin1. Accumulation of hyperphosphorylated tau, PHFs and NFTs would therefore be predicted if there was a Pin1 loss-of-function in evolving AD. The Lu lab was able to show by in vitro binding and antibody competition assays that Pin1 interacted only with pT231, one of several possible Pin1 recognition sequences in ptau. Other groups have subsequently implicated T212 as a second Pin1 binding site [52]. Biological relevance was established by demonstrating Pin1 bound to PHFs derived from AD brain but did not bind to tau from normal brain [50]. Immunohistochemistry showed that Pin1 was largely colocalized with PHFs in the cytoplasm in AD brain tissue [50]. While total Pin1 was not significantly different in AD brain, the available, soluble fraction was reduced by ~5 fold with a corresponding increase of Pin1 in the insoluble fraction.

Interestingly the maintenance of phosphorylation at T212 and T231 promoted phosphorylation at multiple additional sites including S199, S396, S400 and S404 in neurons treated with Aβ42 or okadaic acid, a potent PP2A inhibitor [53]. These results suggested that failure of Pin1 to isomerize ptau and enable PP2A mediated dephosphorylation of T231 and possibly T212, leads to a cascade of additional and toxic phosphorylation events that further promote PHF formation. Wild type neurons treated with the Pin1 inhibitor juglone, or Pin1 knockout neurons both showed increased pT231 tau content after exposure to Aβ42 or oxidation [54]. The logical inference from these studies is that Aβ42 or oxidation induces tau phosphorylation at T231 or T212. Pin1 binds with high affinity to these sites and mediates a *cis-trans* conversion of the intervening peptide bond. Presentation of the phosphate group now in *trans* allows PP2A to remove the group, prevent tau hyperphosphorylation and maintain tau functionality. Failure to do so creates a pro-phosphorylation milieu that predisposes to tau toxicity both directly as PHFs and NFTs and as a sink to remove Pin1 from the soluble fraction.

These data point to the critical role of Pin1 expression but more precisely, to the maintenance of Pin1 isomerase activity to prevent AD related, tau phenotypes. pTau mediated neurodegeneration is not seen uniformly across the entire brain, however. The entorhinal cortex, hippocampus and neocortical pyramidal neurons are particularly affected while cerebellum and other brain regions are typically spared [55, 56]. Even within highly susceptible regions such as the hippocampus, involvement is often nonuniform. Selective loss of Pin1 activity could explain the regional or subregional vulnerability of distinct brain regions to excess ptau or Aβ42 mediated signaling. Indeed, Pin1 expression was inversely correlated to NFT formation in the hippocampus with the most affected regions showing the least expression [57]. Similarly, the Allen Brain Atlas ISH data shows that Pin1 mRNA levels are the lowest in the most vulnerable regions of the brain including hippocampus and entorhinal cortex but approximately double in the cerebellum and cerebellar cortex. The biological or physiological underpinnings for these differences are not known. Thus, low Pin1 expression strongly correlates with the presence of tau pathology.

Critical in vivo evidence for Pin1's role in tau pathology and AD came from analysis of germline Pin1 KO mice [58]. These animals were developed by Uchida's group in Japan in a mixed 129/Sv and C57L/B6 background through the insertion of a silencing *neo-TK* cassette into the Pin1 gene [59]. The mice developed normally but post-starvation cultures of $Pin1^{-/-}$ MEFs were unable to reenter the cell cycle despite refeeding. *Drosophila* lacking the Pin1 homolog *dodo* also developed normally [14]. These data suggest the presence of proteins capable of complementing at least some of Pin1's functionality (see discussion of Immunophilins above). Nevertheless, neuroanatomic and biochemical analysis by Lu's laboratory of the Pin1 KO mice demonstrated age dependent and regional accumulation of ptau, PHFs and eventual neurodegeneration that closely resembled that seen in tau or tau mutant overexpressing mice [60, 61]. Motor and behavioral defects were also observed at 9-10 months of age while western blotting and immunohistochemistry showed dramatically increased MPM2, AT8, AT180 and Alz50 staining, indicative of hyperphosphorylated tau. Murine Aβ42, while normal at 6 months of age was increased ~30% at 15 months of age. Therefore, the 2 major proteins pathologically implicated in AD evolution – ptau and Aβ42 – were significantly elevated in Pin1 null mice. The only potential caveat to these results is the mixed 129/Sv and C57L/B6 background of the Pin1 KO mice [59]. Once in a stable, pure C57L/B6 background, the phenotypes of the germline KO changed with loss of germ cells and profound infertility making breeding very difficult [62, 63]. Despite breeding fertile, heterozygous pairs, viable $Pin1^{-/-}$ offspring were rare, consistent with profound defects in cell-cycle progression and mitosis seen in vitro in Pin1 null MEFs [55]. Notably, there has not been a published reassessment of CNS phenotypes in the pure bred, germ-line Pin1 knockout mouse.

Nevertheless, the impact of Pin1 on AD pathogenesis was further clarified by evaluation of the phenotypes of progeny from germline, mixed background Pin1 KO mice and an AD model, Tg2576. The latter were among the first AD mouse models which was engineered to produce high levels of mutant (double mutation (K670N/M671L)), human APP695 and equally robust (~14 fold compared to human AD patients) Aβ42 [64]. Tg2576 develop normally but begin to show cognitive impairment at approximately 6 months of age which progressively worsens. By 11-13 months of age, animals show numerous Aβ42 plaques, modest vascular amyloid and diffuse oxidative damage but no evidence of tau pathology (e.g. NFTs) or neurodegeneration [65]. Dendritic spine loss occurs by 4.5 months in the CA1 [66] with reduced LTP compared to wild-type controls [67]. Insoluble Aβ42 levels in the compound mice ($Pin1^{-/-}$ x Tg2576) [68] were unchanged in young animals but rose significantly higher by 6 months of age compared with Tg2576 littermates. Soluble Aβ40 and Aβ42 were also unchanged as was neurodegeneration. The latter was unexpected as Pin1 null mice independently show tauopathy and neurodegeneration [58]. These data suggest the 50% C57/Bl6 genotype contributed by Tg2576 sufficiently altered the progeny such that tauopathy was modulated.

How Pin1 loss enhanced insoluble Aβ42 production in the compound mice was first explored *in vitro* in N18 neuroblastoma cells. Thr668-Pro669 of the APP intracellular domain is phosphorylated by cdc2 kinase during the cell cycle [69], although additional kinases and multiple other sites in APP have also been identified [70]. Binding studies and NMR spectroscopy revealed phosphorylation dependent binding to and *cis* to *trans*

isomerization of this site by Pin1. Once in *trans*, APP processing favored so-called α-cleavage which occurs on the cell surface and prevents Aβ42 production. In the absence of Pin1, APP processing was more endosomal [71-73] and became more amyloidogenic with greater production of Aβ42. In vitro studies confirmed that APP processing was heavily influenced by Pin1 which drove α-cleavage when present and β−γ cleavage when absent [68]. However, the conclusion that isomerization of APP at Thr668-Pro669 was responsible for these observations has been controversial as knock-in mice with Ala substituted for Thr668 did not show changes in APP processing [74, 75] compared to wild type. As the intracellular domain of APP (AICD) interacts with Fe65, Mint/X-11 and other trans factors which are transported to the nucleus after cleavage [76, 77], the effects ascribed to Thr668 phosphorylation and subsequent Pin1 isomerization may be incorrect. Alternatively, the effects of Pin1 may be indirect through the activation/suppression of other proteins which then influence APP processing or Aβ42 production and subsequent oligomerization. For example, a variety of kinases including typical PKC, CamKII [34, 78], DAPK1 [79, 80] and GSK3β [81] all phosphorylate the AICD and all interact with Pin1 [82, 83]. PKC [32], DAPK1 [42] and CamKII [82] also regulate Pin1 through phosphorylation (see above discussion). Therefore, data suggests bidirectional regulation of Pin1 by/to kinases which influence Pin1 activity and the number of phosphorylated, Pin1 targets based on kinase activity. This complexity must be clarified to better establish Pin1's role in the regulation of APP processing and Aβ42 production in the brain of normal individuals or AD patients.

The appearance of hyperphosphorylated tau is typically late in human AD and in the absence of tau mutation, follows years of CNS exposure to gradually rising levels of soluble, multimeric Aβ42 [84, 85]. A consistent early result of Aβ42 exposure is a progressive loss of synapses and dendritic spines which presumably underlies the clinical appearance of mild cognitive impairment (MCI) in patients or reductions in LTP and elevations in LTD in slices from AD model mice or WT slices exposed to exogenous Aβ42 [86, 87]. In addition to dysregulated Ca^{2+} fluxes [88, 89] Aβ42 induces oxidative stress [89, 90], possibly through the induction of catalase or the attack by metalloproteins [91]. Pin1 contains a critical active site sulfhydryl (C113) which is oxidized in the brain of both MCI and AD patients [92, 93]. The finding of extensive oxidation early in disease is consistent with mouse data and suggests a pathognomonic role for Pin1 in AD development. While changes in Pin1 function were not experimentally demonstrated in these studies, it is likely isomerase activity was negatively affected by C113 oxidation. These results also show that Pin1 is sensitive to outside-in Aβ42 signaling, suggesting blockade of this pathway might preserve Pin1 activity and attenuate AD pathology [94].

Pin1 is also subject to a variety of other post-translational modifications that affect its activity, stability and location. These include phosphorylation, sumoylation, acetylation and ubiquitination. In the context of AD, dysregulation of these regulatory cascades, induced by Aβ42 or ptau can have substantial downstream effects on Pin1 functionality. The WW-domain can be phosphorylated at Ser16 by a variety of kinases including PKA [39], Aurora A [40], Ribosomal S6 kinase 2 (RSK2) [95] and COT/Tpl2 [96]. Consistent with an *in vivo* role, Ser16 phosphorylation is very elevated in AD brain or *in vitro* in cells overexpressing tau [97]. As Ser16 is located nearly in the center of the WW domain, the introduction of a large, negatively charged phosphate would be expected to interfere with ligand recognition

and binding. Indeed, this has been clearly demonstrated for PKA mediated phosphorylation at this site [39]. However, subsequent studies have argued that Ser16 phosphorylation mediated by RSK2 or COT had a positive, not negative effect on Pin1 binding to targets [95] [96] [41]. These studies focused on the downstream biological outcome coincident with Ser16 modification without explicitly demonstrating how these modifications directly affected Pin1 binding to partners or isomerase activity. We and others [39] have found that Ser16Glu substitution blocks WW domain binding and thus prevents Pin1 mediated isomerization of targets. This was well illustrated by the profound blockade of endogenous Pin1 function and the induction of apoptosis by the expression of dominant-negative WW domain fragments containing Ser16Ala but not by Ser16Glu [39].

Other Pin1 posttranslational modifications have been identified including phosphorylation at Ser65 by Plk1 [98], Ser71 by DAPK1 [42] and Ser138 by MLK3 [99]. Plk1 [100] and DAPK1 are overexpressed in AD neurons [42] while MLK3 [101] is activated by Aβ42, making the action of all three kinases relevant to AD pathobiology. Phosphorylation at Ser65 prevents sumoylation while modification at Ser71 suppresses Pin1 activity. Ser138 phosphorylation has the opposite effect and is associated with increased Pin1 activity and nuclear localization. Using proteomics, we recently [34] identified a number of novel Pin1 PTMs induced by multimeric Aβ42 signaling. Intact and translationally functional synaptoneurosomes were isolated by percoll gradient centrifugation from mouse brain and exposed briefly (10 min) to physiologic concentrations (100 nM) of multimeric Aβ42. This brief exposure time and concentration were sufficient to completely block Pin1 activity [34] suggesting signaling triggered inhibitory, post-translational modifications. We did not establish the lowest, effective Aβ42 concentration for this effect. Pin1 immunoprecipitants were analyzed for differences in protein interactors as well as PTMs. Particularly notable changes after Aβ42 treatment included the dephosphorylation of Pin1 at Ser111, Ser147 and Ser154 as well as a strong association of Pin1 with calcineurin (CaN, PP2B). Of note, recent phosphoproteomics has confirmed these data in MCI and AD brain [23, 24]. CaN is among the most abundant phosphatases in brain and plays a critical role in plasticity and memory [102, 103]. Aβ42 signaling is known to upregulate CaN activity in cells [104, 105] and CaN expression in patients and AD animal models is elevated [105, 106]. Conversely, CaN normalization restores synaptic plasticity [107], dendritic spine density [108] and learning and memory [109, 110]. However, complete knock-down of CaN inhibited working memory [111] and synaptic plasticity [112] demonstrating that normal brain function requires CaN expression and activity within a tightly controlled range.

The above data from other labs and our co-immunoprecipitation results suggested Pin1 activity could be regulated by CaN and Aβ42 signaling which would further establish and enlarge the pathobiological relevance of Pin1 in AD. We investigated that possibility by generating single and multiple Ser to Glu and Ser to Ala mutants in Pin1 at position 111, 147 and 154 and introducing them into neurons, synaptoneurosomes or tumor cell lines. While most experimental work has utilized Ser111 mutants due to its proximity to the Cys 113 active site, we have observed similar data with multiple mutants as well. After transduction or transfection, Ser111Glu mutants were entirely resistant to inhibitory Aβ42 signaling and retained full activity while Ser111Ala mutants were isomerase dead [34]. Treatment of cells or synaptoneurosomes with FK-506, a potent and specific CaN

inhibitor fully rescued wild type Pin1 activity after Aβ42 treatment but had no effect on Ser111Glu activity nor did it rescue isomerase null Ser111Ala mutants. To minimize off target effects, FK506 was employed at its IC_{50} (~5 nM) and experiments were repeated with cyclosporin and yielded similar results. Therefore, we concluded that Aβ42 signaling induced dephosphorylation by CaN at Ser111 of Pin1 leading to loss of isomerase activity. This is the first report of Pin1 regulation by a phosphatase but as DAPK1, PKA, MLK3, Plk1 and PKMζ [32], all influence Pin1 function, stability or location, phosphatases must also play an opposing role in the control of Pin1. Whether CaN is the only phosphatase opposing these kinases is unknown. Based on the cell and tissue specific regulation of Pin1, I suspect different phosphatases will be important in different cell types. Second, the effects were quite rapid with activity blockade within minutes. This suggest that in early, evolving AD as the concentration of soluble, multimeric Aβ42 rises to an inhibitory level, Pin1 will be less active. Phosphoproteomics have revealed ~50% reductions in pSer111 content in the cortex of MCI patients although there was partial rebound in many full-blown AD cases [23, 24] As discussed above, the loss of Pin1 will directly contribute to the accumulation of hyperphosphorylated tau and the initiation of neurodegeneration (Fig 2). Thus Pin1 loss-of-function can be viewed as a bridge between Aβ42 signaling and tau hyperphosphorylation.

In order to establish other pathophysiologic effects of Pin1 suppression by Aβ42 and CaN signaling, we assessed dendritic spine density. Spines are lost early in AD progression and correlate with memory and learning reductions [113, 114] [86]. Spine counts are significantly reduced in patients with early AD (MCI) [115, 116], correlate well with cognitive losses, appear before tauopathy and are recapitulated in AD mouse models that overexpress Aβ42 [66]. We hypothesized genetic ablation of Pin1 would mirror Pin1 suppression seen in AD or mouse models induced by Aβ42 and help establish if Pin1 was essential for spine maintenance in AD. Indeed, dendritic spine counts in cultured DIV21 neurons were reduced by ~35% either after Pin1 KO or after 1 h of Aβ42 treatment of wild-type cells [34]. In both cases, spines were rescued after delivery of exogenous Pin1. Consistent with the synaptoneurosome data above, pretreatment with FK506 completely blocked Aβ42-mediated spine loss but only in neurons with Pin1 expression [34]. These data established that Pin1 was a critical target for Aβ42-CaN signaling in spines. When WT Pin1 was replaced with Pin1 Ser111Glu or Ser111Ala mutants, cells with Ser111Glu were also fully resistant to Aβ42-mediated spine loss irrespective of CaN blockade with FK506. As expected, Ser111Ala mutants failed to rescue Aβ42-mediated spine loss irrespective of CaN blockade. These data collectively demonstrated that Pin1 activity was required to maintain dendritic spines, that Pin1 suppression by CaN-Aβ42 signaling, driven by Ser111 dephosphorylation was a necessary and sufficient step in initiating spine loss and that FK506 could potentially be repurposed to normalize CaN activity, blunt Aβ42 signaling and preserve Pin1 function in early AD.

We also evaluated the effects of acute Pin1 KO in adult mice. Floxed mice were injected with AAV-Cre-GFP or control AAV-GFP into hippocampus or entorhinal cortex. Mice were harvested at various times thereafter which revealed KO neurons in the injected regions exhibited ~ 40% loss of synapses by 6 DPI which remained constant but reduced over time [34] (Fig 1). Both entorhinal cortex (EC) and hippocampus showed significant architectural dysruption, cell death and astro-glial proliferation by 12 DPI which progressively worsened,

leaving both the hippocampus and EC entirely defaced by 40 DPI (Fig 2). As observed in the Pin1 germ-line KO mice, ptau was readily detected with anti-AT8 antibody after Pin1 silencing (Fig 2) but unlike the prior observations where ptau elevation appeared at 9-10 months of age, ptau appeared within 40 DPI after conditional KO. These data suggest that KO of Pin1 in adult mice has different and possibly accelerated phenotypes than observed after germ-line KO. The very rapid cell death is notable and suggests loss of Pin1 triggered acute events through an unknown mechanism along with slower, ptau dependent neurodegeneration observed at 40 DPI. As Pin1 has been implicated in intrinsic and extrinsic apoptosis pathways [117-119] as well as proinflammatory cytokine production [17] in the peripheral immune system, it is tempting to speculate activation of these pro-death pathways in neurons and/or astrocytes-glia after Pin1 KO. Other plausible causes include axonal [33] or dendritic dysfunction [34][116, 120] secondary to Pin1 loss with subsequent retrograde cell death. Regardless, the mechanism of cell death elicited by Pin1 KO is likely to be one relevent to and seen in AD neurons.

We recently evaluated if CaN inhibition with the FDA approved, transplant antirejection drug, FK506 could reduce/block AD pathologies (Stallings, N et al. submitted, 2022). Short-term, generally high dose FK506 has restored plasticity [108] and reduced Aβ42 burden in AD model mice [121]. Interestingly, solid organ recipients who received FK506 showed significantly reduced AD incidence than age-matched recipients treated with mTOR inhibitors or an age-matched, nontransplanted population [106]. We hypothesized that low-dose FK506 capable of normalizing CaN activity in the brain would prevent Pin1 inhibition by Aβ42 signaling while leaving peripheral immunity intact. To test this, FK506 time release pellets were implanted subcutaneously into 3 month-old APP/PS1 mice. Pellets were designed to release ~1 mg FK506/kg body weight to maintain drug at <10 nM plasma for 3 months. Mass spectroscopy analysis showed mice had somewhat higher levels for the first month which dropped and remained at target for the last 2 months of treatment. Behavioral testing at 6 months showed treated mice performed as well as untreated controls in the Morris Water Maze. Neuropathology revealed increased synaptic connections and dendritic spines, and reductions in microglial activation and Aβ42 plaque content. CaN and Pin1 activity was normalized in treated APP/PS1 mice while splenocytes activated with phorbol ester and ionophore showed normal IL-2 mRNA expression. An open label, human trial in MCI patients (NCT04263519) was recently initiated but has been delayed due to COVID.

Plasticity and Pin1

As AD evolves, synaptic plasticity declines [86, 122, 123]. This has been ascribed to synaptic dysfunction and later synaptic loss due to escalating soluble, multimeric Aβ42 levels and likely accounts for early, clinically detectable reductions in learning and memory that occur in MCI patients [124]. While Pin1 had been localized to the cytoplasm and nucleus, we showed by western blotting, Pin1 activity assay, immunofluorescence and immuno-EM that Pin1 was also highly expressed and highly active in post-synaptic dendritic spines [32]. Pin1 was likely translated in situ as glutamate treatment of intact neurons increased spine localized Pin1 by 3 fold in ~30 minutes. As most forms of long-term memory and learning require glutamate-induced, de novo, dendritic spine protein synthesis [125], we evaluated if Pin1 KO affected this process. Translationally active SN from WT

and Pin1 KO mice were pulsed with S-35 methionine before glutamate/glycine treatment [32]. WT preparations showed a consistent, transient 40-60% increase in overall dendritic protein synthesis which was suppressed entirely by anisomycin. Pin1 KO SN however showed constitutively elevated protein synthesis which was unaffected by glutamate but quantitatively similar to that seen in WT SN after glutamate. Similar observations have been observed in *FMR*$^{-/-}$ SN after mGluR5 activation [126, 127]. These data suggested that glutamaturgic signaling transiently inhibited Pin1 activity, permitting a temporary upregulation of dendritic protein sythesis. Isomerase assays confirmed this and revealed complete and very rapid suppression of Pin1 activity due to Ser16 phosphorylation by PKCζ or PKMζ [32]. We also showed that under basal conditions, Pin1 interacted with hyperphosphorylated eIF4E, 4E-BP1 and 4E-BP-2, providing a molecular link to translation initiation and regulation. While it was not determined at the time, involvement of CaN or another phosphatase would presumably reactivate Pin1 while the protein degradation machinery would reduce Pin1 content on the post-synaptic side to basal levels.

Paradoxically, while Pin1 loss/inhibition is clearly associated with evolving AD and diminishing cognition and reduced expression in spines [128], hippocampal slices from young, germ-line Pin1 KO mice [58][63] show normal E-LTP but elevated, anisomycin sensitive, L-LTP when elicited with a train of four, high frequency burst stimuli [32]. A similar phenotype was seen in FKBP KO mice [129] which showed elevated phosphorylation of mTOR and S6 Kinase which are upstream of 4E-BP1 and eIF4B, respectively, suggesting FKBP also participates in dendritic protein synthesis. Conversely, cyclophilinD KO mice showed impaired short-term memory which could be replicated in WT mice by cyclosporine infusion [130, 131]. However, cyclophilinD KO in the context of an AD model improved cognitive function [131]. In aggregate these data suggest that the entire class of immunophilins/prolyl isomerases participate in the positive and negative regulation of synaptic plasticity via control of activation dependent, de novo protein synthesis. Whether enhanced L-LTP or cognition are maintained as Pin1 or FKBP KO mice age has not been formally assessed but given elevated ptau and cell death, adult germ-line KO mice must show loss of plasticity.

Stimulation capable of inducing L-LTP increases the numbers and maturity of dendritic spines [132, 133], presumably reflecting alterations in the spine proteome. Pin1 contributes to cognition and memory by playing a role in the maintenance and structure of dendritic spines. Adult WT mice treated with Pin1 inhibitors or Pin1 germline KO mice showed an increased density of mature, mushroom-shaped, dendritic spines [134]. Such a phenotype would be consistent with elevated L-LTP discussed above. Loss of Pin1 derepressed PSD95, increasing synaptic NMDA-R content and currents. Additional recent reports have confirmed the Pin1-PSD95 interaction on the post-synaptic side and downstream effects of isomerization on synaptic NMDA-R and AMPA-R expression and currents [135]. However, Pin1 likely interacts with multiple sites on PSD95 with opposing effects on the latter’s abundance, turnover and function. Interestingly, overexpression of Pin1 reduced spine numbers, demonstrating that deviations in Pin1 expression and presumably function was detrimental to normal physiology. Nevertheless, if valid, these observations suggest Pin1 loss should mitigate, not worsen cognitive decline in evolving AD.

These unexpected results encouraged us to generate conditional mice with floxed Pin1 alleles [34]. Cre-mediated loss of Pin1 in P1, DIV21-24 neurons or the hippocampus of adult, floxed mice caused significant reductions in dendritic spines within 6 days and eventual cell death *in vivo* [34](Fig 1). Neuronal cell death was associated with the accumulation of hyperphosphorylated tau (Fig 1), as seen in late-stage AD. Thus, these results resemble those observed in Tg2576 AD mice lacking Pin1 [68]. Why Pin1 germ-line or chemical KO enhances spines but Cre-mediated excision has the opposite effect remains unclear. Pin1 inhibitors and possibly siRNAs are never fully specific and observations after their use could be partially attributable to off-target effects. The germ-line Pin1 KO mice have extremely poor fertility due to cell-cycle arrest. Those that are born must have compensated for Pin1 loss, possibly by overexpression of another prolyl isomerase, again creating nonphysiologic phenotypes.

Pin1 and neuroinflammation

Cross-talk between neurons and supporting cells, especially astrocytes and microglia, is critical for normal brain function and homeostasis. Microglia are CNS-resident myeloid cells whose function includes responses to infection and support of neuronal plasticity. Neurons and microglia produce IL-33 which activates microglia to phagocytize dendritic spines, intact neurons and extracellular matrix [136]. Loss of detectable IL-33 accompanies AD evolution [137] while exogenous IL-33 antagonized AD pathology and cognitive defects [138]. In response to Aβ42, microglial TLRs [139] and NLRs [140] become activated with the production of proinflammatory cytokines [141, 142], NO, chemokines [143] and ROS capable of interfering with neuronal function and viability [144-146]. In animal models or patients with AD, IL-1, TNFα, IFNα/β, IL-6, GM-CSF, IL-12 and IL-23 are detectable or upregulated [147].

Innate and humoral cytokine production in the peripheral immune system is heavily reliant on both transcriptional and post-transcriptional control systems [148-150]. These include TLR/IRAK/IRF7 dependent transcription [150], reduced mRNA decay and increased translation. Pin1 binds to IRAK1 and is required for the elaboration of type 1 IFN in dendritic cells after TLR7/9 activation by IL-1 receptor signaling [151]. Post-transcriptional regulation is often mediated by sequence or conformation specific mRNA binding proteins which interact with highly conserved cis elements such as AUUUA repeats [152, 153] or stable stem-loop structures [154]. Pin1 has been implicated in post-transcriptional control of cytokine production by activated T cells [155]), eosinophils [31, 156-158] and neutrophils [159]. Pin1 also mediates NF-kB activation after cytokine or LPS [160, 161]. Usually outside-in signaling simultaneously activates quiescent Pin1 and triggers phosphorylation of Ser/Thr-Pro sites of cognate mRNA binding protein enabling their isomerization and change of function [17]. Macrophages employ many of the same regulatory schema suggesting that microglia would as well. However, one notable difference is that the component cells of the brain (neurons, astrocytes and microglia) express active Pin1 under basal or homeostatic conditions while cells in the periphery require outside-in signaling. It is tempting to speculate that upon neuronal or potentially microglial/astrocytic activation induced by Aβ42 [34], glutamate [31], ptau (Stallings, O'Neal and Malter, unpublished observations) or hypoxia transiently inhibit Pin1, leading to stabilization of proinflammatory cytokine

mRNAs and their translation. This suggests that in chronic disease such as AD, there would be a smoldering but gradually increasing proinflammatory environment due to the relentless accumulation of Aβ42 and ptau along with autocrine glial activation by previously released cytokines such as TNF and IL-1 [162].

Pin1 and Neuronal Cell Death

Apoptosis is one of the main cell death pathways active in advanced AD although autophagic and necrotic cell death also occur [163, 164]. Extrinsically triggered apoptosis involves death receptor and caspase 8 cleavage while intrinsic pathways increase mitochondrial membrane permeability through BCL-2 proapoptotic family member activation [165]. Both extrinsic and intrinsic apoptotic pathways are activated in evolving AD and genes associated with death are increased in expression at the expense of pro-survival pathways [164]. Pin1 has been reported to interact with FADD and caspase 8 of the extrinsic pathway [117] and Bax and cIAP [118] of the intrinsic pathway. In both scenarios, active Pin1 was pro-survival and prevented the initiation of caspase cleavage and apoptosis. Pin1 can also act upstream on critical pro-survival regulators including p53 and p73 [166], MAPK [167], survivin [168], Fbw7 [169], ataxia telangiectasia and Rad3-related (ATR) [170]. Therefore, loss of Pin1 can directly accelerate apoptotic cell death through multiple mechanisms. Pin1 has also been implicated in autophagic [171] , necroptopic [172] and necrotic [173, 174] neuronal cell death.

It is well known that AD progressively involves distinct brain regions which likely accounts for the characteristic and sequential clinical manifestations. The disease likely starts in the EC, next affecting the adjacent hippocampus and eventually spreading to the temporal cortex [175]. How and why AD starts and spreads along this consistent path is poorly understood. The EC accumulates ptau as NFTs early in AD with corresponding neuronal loss [176]. While detailed analysis of Pin1 protein levels and activity in different brain regions during AD evolution is yet to be done, EC Pin1 mRNA expression is among the lowest in the brain, closely followed by hippocampus and neocortex [Allen Brain Atlas, https://human.brain-map.org/]. These data suggest that regional AD vulnerability correlates with Pin1 expression.

Summary and Perspectives

A variety of in vitro and in vivo biochemical, molecular, neuroanatomic, behavioral and physiologic evidence implicates Pin1 loss, a *cis-trans* prolyl isomerase, as a key determinant in the erosion of higher cognitive function and eventual neuronal cell death characteristic of Alzheimer's disease. Pin1's involvement in multiple pro-survival and homeostatic signaling cascades places it uniquely in many patho-biologically relevant pathways that are dysfunctional in AD. The identification of Aβ42-CaN as a rapid, potent, inhibitory signal clarifies how Pin1 activity, along with potential contributions from germ-line SNPs [177, 178] or somatic mutations [179] can be gradually lost and lead to early synaptic disease manifesting as MCI as well as later tau pathology, neurodegeneration and full-blown AD.

Clearly preservation of Pin1 activity could antagonize AD progression [88]. Since AD, as is cancer, typically a disease of the aged, Pin1 activation could inadvertently accelerate tumor development or progression [35], a undesirable outcome. This suggests Pin1 targeted therapy should ideally be focused on the CNS and be titratable with the goal of activity normalization. Such an approach would require lipophilic therapeutics capable of penetrating the blood-brain barrier and concentrating in the brain. At present, there are no direct Pin1 agonists that meet these criteria. However, interference with known, inhibitor modulators of Pin1 such as DAPK1 [38, 44] or the Aβ42-CaN signaling cascade [88][110] [100] are viable options. The former phosphorylates Ser71 while the latter dephosphorylates Ser111 and possibly Ser147 and Ser 154. Low nM DAPK1 inhibitors [180] have been developed and used to attenuate PTZ-induced epilepsy [181] and proposed for AD as well [182]. FDA approved agents FK506 and cyclosporine target CaN. The latter are lipophilic, penetrate the BBB, accumulate in the brain, show excellent target selectivity and potency and have a well-documented, long-term safety profile. Other options include RAGE receptor inhibitors which have shown safety and efficacy in preclinical models of ARDS [183]. Antibodies which target tau have also failed in phase II clinical trials sponsored by Roche, Lilly and AC Immune [184]. Anti-*cis*-ptau and a few other anti-tau antibodies are entering early phase clinical trials. Interestingly, anti-Aβ42 antibodies which fit some of the above criteria, while often effective for clearing fibrillar and plaque Aβ42 in animal models and some patients, have almost uniformly failed to significantly alter AD evolution [185]. Of note, these agents have usually not significantly altered the total brain burden of Aβ42 [171]. This suggests that antibody treatment may have left enough residual Aβ42 to continue CaN activation and suppress Pin1. Despite our improved understanding of AD pathogenesis, substantially more investment and research are needed to identify effective therapeutics for this crippling disease.

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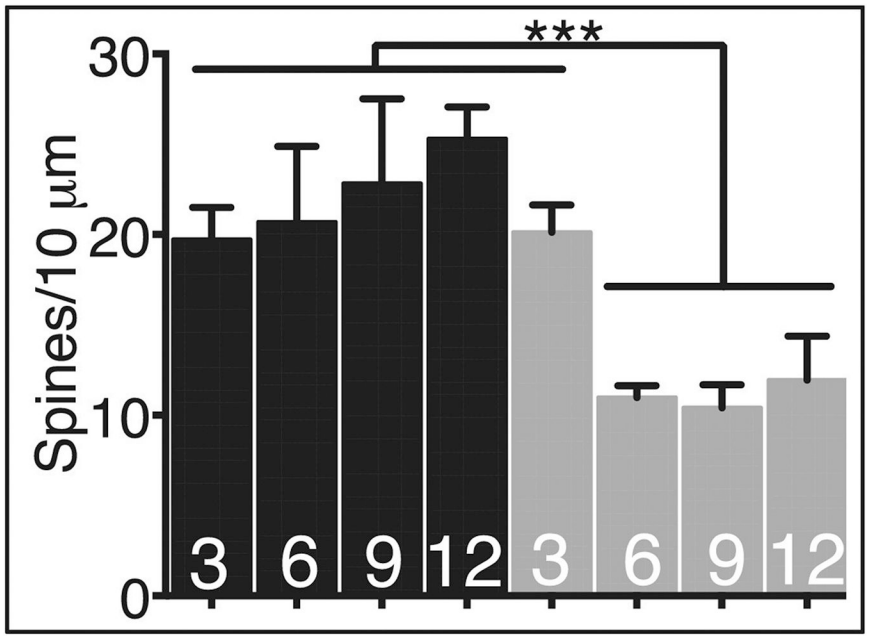

Fig 1.

Pin1 is required for spine maintenance in vivo. 2 months old Pin1$^{fl/fl}$ mice were injected in the hippocampus with AAV-GFP (black bars) or AAV-GFP-Cre (grey bars) at equal titer and synaptophysin positive spines counted 3–12 days thereafter, denoted along X axis. ***$P <$ 0.001 between groups.

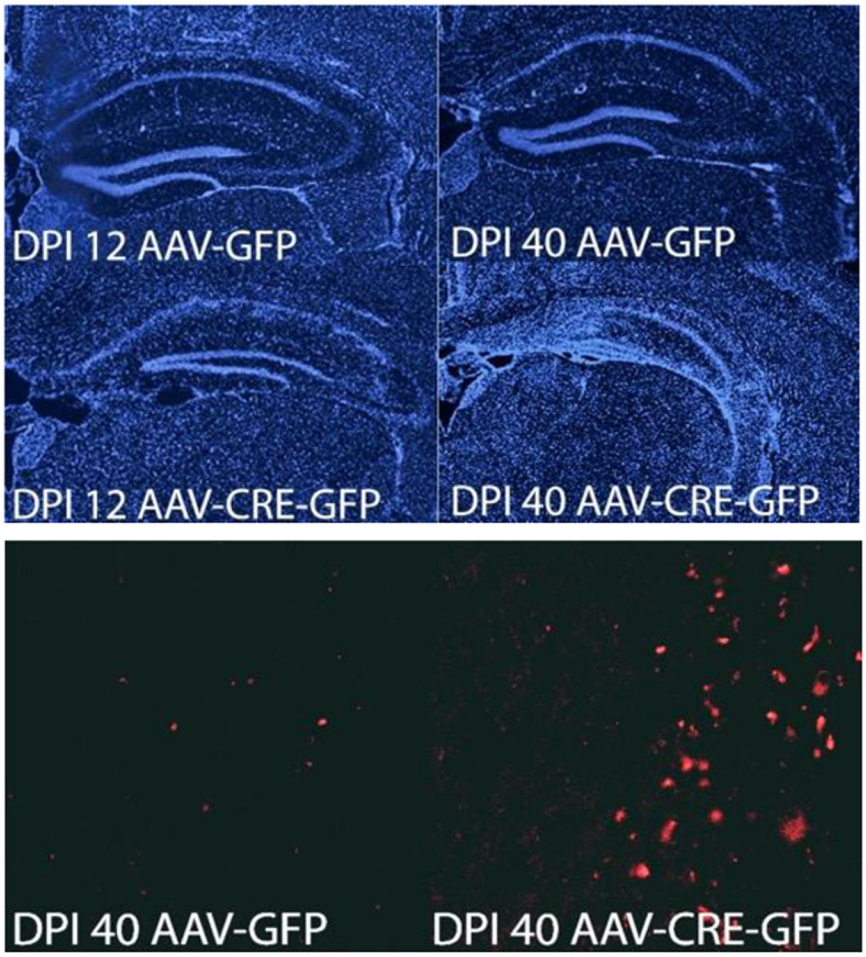

Fig 2.

Loss of Pin1 causes neuronal cell death and AT8 immunoreactivity in the hippocampus. $Pin1^{fl/fl}$ mice were injected in the hippocampus with AAV-GFP-Cre or AAV-GFP, prior to sacrifice after 12 or 40 days. Top 4 images stained with DAPI (blue), bottom 2 images stained with anti-AT8 (red, 40X).