Developmental cognitive deficits including X-linked mental retardation (XLMR) can be caused by mutations in P21-activated kinase 3 (PAK3) that disrupt actin dynamics in dendritic spines. Neurodegenerative diseases such as Alzheimer disease (AD), where both PAK1 and PAK3 are dysregulated, may share final common pathways with XLMR. Independent of familial mutation, cognitive deficits emerging with aging, notably AD, begin after decades of normal function. This prolonged prodromal period involves the buildup of amyloid-β (Aβ) extracellular plaques and intraneuronal neurofibrillary tangles (NFT). Subsequently region dependent deficits in synapses, dendritic spines and cognition coincide with dysregulation in PAK1 and PAK. Specifically proximal to decline, cytoplasmic levels of actin-regulating Rho GTPase and PAK1 kinase are decreased in moderate to severe AD, while aberrant activation and translocation of PAK1 appears around the onset of cognitive deficits. Downstream to PAK1, LIM kinase inactivates coflin, contributing to coflin pathology, while the activation of Rho-dependent kinase ROCK increases Aβ production. Aβ activation of dyn disrupts neuronal PAK1 and ROCK-mediated signaling, resulting in synaptic deficits. Reductions in PAK1 by the anti-amyloid compound curcumin suppress synaptotoxicity. Similarly other neurological disorders, including Huntington disease (HD) show dysregulation of PAKs. PAK1 modulates mutant huntingtin toxicity by enhancing huntingtin aggregation, and inhibition of PAK activity protects HD as well as fragile X syndrome (FXS) symptoms. Since PAK plays critical roles in learning and memory and is disrupted in many cognitive disorders, targeting PAK signaling in AD, HD and XLMR may be a novel common therapeutic target for AD, HD and XLMR.

Alzheimer Disease

Alzheimer disease (AD) is the most prevalent neurodegenerative disease of aging but has many common mechanisms with other neurodegenerative diseases. AD is characterized clinically by progressive cognitive decline and pathologically by prodromal accumulation of neuritic plaques containing amyloid-β (Aβ) protein and neurofibrillary tangles containing tau protein aggregates comprising paired helical filaments. Proximal to cognitive decline, there is a selective loss of synapses, especially excitatory synapses and vulnerable neurons in networks required for learning and memory. Synaptic loss is accelerated at early stages of AD clinical symptoms and is more closely related to cognitive deficits than neuronal loss or amyloid buildup.1,2 Although soluble aggregated Aβ forms called β-amyloid-derived oligomers (ADDLs) or Aβ oligomers, including dimers, trimers and dodecamers (12-mer or Aβ*56) are implicated in synaptic dysfunction and loss in AD patients and AD animal models6-10 and Aβ immunoneutralization rescues synaptic defects in AD animal models,7,8 there are major gaps in our understanding the mechanisms controlling synaptic loss in AD and other neurodegenerative diseases, which remain under active investigation. Here we explore the potential overlap of dysregulation in PAK kinases that cause mental retardation, with synaptic deficits in other neurodegenerative diseases, which link GTPases to cytoskeletal reorganization and to nuclear signaling.

The RAC/CDC42-activated kinase PAK1 is a key regulator for actin cytoskeleton and dendritic spine morphogenesis. We first reported a loss of PAK1 and PAK3 in cytoplasm of AD brain specimens, as well as in AD animal and cellular models, suggesting PAKs might play crucial roles in dendritic spine/synapses loss and cognitive deficits in AD.9 Synaptic plasticity is dependent on the regulation of the actin cytoskeleton in dendritic spines.10-12 The regulation of F-actin cytoskeleton involves various actin-binding proteins and the molecular regulators of actin dynamics by membrane receptors and their downstream signaling cascades. In particular, Rho family GTPases, Rho, RAC and CDC42, play a

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Alteration of PAKs in AD

Cognitive decline has been directly linked to the synaptic dysfunction, especially to synapses, postsynaptic and dendritic spine loss in AD and mental retardation (MR) syndromes. A primary role of dendritic spine defects in MR has been demonstrated by the discovery of multiple mutant X-linked MR genes. These MR genes reveal a clustering of proteins in the postsynaptic pathways regulating spine actin assembly and disassembly and spine morphogenesis. PAK3 is one of these MR genes and missense mutation in PAK3 causes severe X-linked nonspecific MR. Animal models of MR syndromes created using the AID (auto-inhibitory domain) of PAK1, which blocks PAK1–3, or knockout of its downstream LIM-kinase both show defects in dendritic spines and cognition. These observations suggest the essential role of the PAK1–3/LIM-kinase pathway in regulating synaptic plasticity.

Similar to MR, in AD, postsynaptic and dendritic spine defects are an early event in memory circuits and therefore spatiotemporally situated to play a critical role in cognitive deficits. For example, although the overall estimate of neuronal loss in AD hippocampus ranges from 5–40%, albeit with higher losses in CA1, overall loss of postsynaptic proteins on Westerns from whole hippocampus, such as the actin-regulating developmentally-regulated brain protein (drebrin), have been found to reach 70–95%. Selective drebrin loss results from an attack on excitatory synapses since drebrin regulates actin assembly and drebrin-dependent actin filaments in dendritic filopodia govern synaptic targeting of PSD-95 and dendritic spine morphogenesis. Two major neuronal isoforms of PAK exist in the brain, PAK1 and PAK3. Normally, both show diffuse distribution in cell bodies and dendrites. However, in AD brain, significant losses of PAK1 (35% ± 6) and PAK3 (55–69%) were observed in hippocampus, while PAK3 was also significantly decreased in AD temporal cortex (63–77%). However, the loss of PAK1’s kinase activity clearly exceeds that of its protein level. The auto-phosphorylated PAK1 at Ser141, an index of activity, was reduced by 73% in AD temporal cortex. In addition, PAK1 also showed aberrant activation in AD, and this activated PAK1 was translocated from cytoplasm to membrane, probably to granular structures in a complex with its activators, GTPases RAC/CDC42. An increase in the total protein level of PAK1–3 at early stages of AD but a reduction of both total and cytoplasmic phospho-PAK in late-stage severe AD was observed by Nguyen and collaborators. Moreover, a similar reduction and sub-cellular translocation of PAK1 was observed in a transgenic AD mouse model. Similarly, cytoplasmic phosphoPAK1 (pPAK) was significantly reduced in a triple transgenic mouse model of AD that develops both plaque and tangle pathology and this loss of pPAK, and cognitive deficits were improved by dietary docosahexaenoic acid (DHA). Since PAK1–3 defects are sufficient to cause cognitive deficits, these data suggest that dysregulation (hyper-activation) of PAK1 followed by a loss of soluble pPAK may also play an important role in dendritic spine/synapse loss and cognitive deficits in AD.

To characterize the likely mechanism behind the cytoplasmic PAK deficits in AD, cultured hippocampal neurons were treated with β-amyloid (Aβ) oligomers, where we then observed a rapid abnormal PAK activation/ translocation followed by subsequent loss of cytoplasmic pPAK. This aberrant activation was accompanied by a rapid loss of F-actin and dendritic spines unlike the response to normal activation of PAK1 by RAC/CDC42. The wild-type PAK1, but not its kinase–dead mutant (K299A), prevented the pathological changes in spines, providing evidence that functional PAK1 recruitment and signaling is blocked by Aβ exposure. In addition, it has been observed that fibrillary Aβ42 treatment of hippocampal neurons can also activate PAK1. These results suggest that β-amyloid species could be the primary elements responsible for PAK dysfunction in AD. These results also indicated that PAK1 has a significant functional role in neuronal plasticity, many important functions can be compensated by PAK3 and aberrant and chronic PAK1 activation should be considered “bad” in AD and Huntington disease (HD) that will be discussed later.

Since PAK1 aberrant activated at early stages of AD, inhibition of PAK1 could reverse, partially reverse or delay clinical signs in AD. However, since PAK1 and PAK3 were eventually lost at late-stage severe AD, this dynamic alteration of PAK at different AD
stages may also limit PAK inhibitors as a consistent drug for AD therapy.

RAC/PAK1/LIMK/cofilin signaling pathway in AD. The regulation of actin cytoskeletal dynamics is through the phosphorylation of cofilin at Ser 3 by LIM-Kinase (LIMK), in a pathway where PAK1 activates LIMK. The PAK/LIMK signaling inactivates cofilin, which depolymerizes actin filament (F-actin). Our data suggest this may enable other proteins, for example, drebrin, to bind and regulate actin in postsynaptic spines. Pathologic intracellular inclusion bodies (Hirano bodies) containing cofilin and smaller actin rods decorated by other actin-binding proteins are prominent features in the hippocampus and cortex of AD brains. We have observed that confocal co-labeling of pPAK and cofilin in AD hippocampus show cells with different stages of pPAK and cofilin pathologies; for instance, some cells exhibit increasingly intense cofilin labeling associated with progressively decreased diffuse pPAK accompanied by granular structure staining (Fig. 1A). The severe pPAK and cofilin pathologies in AD are associated with the reduction in the dendritic spine actin-regulating protein drebrin (70–95%). This is consistent with the hypothesis that translocation and loss of the cytosolic pPAK can lead to local pathology related to cofilin aggregation, drebrin loss and synaptic defects observed in AD brain.

Cofilin labeling in and around Aβ plaques is also observed in AD model APPswt transgenic mouse hippocampus. Triple labeling of pPAK (green), cofilin (red) and Aβ plaques (blue with 10G4 antibody) in Tg' mouse hippocampus indicated intense central-plaque pPAK staining sometimes associated with local cofilin puncta (Fig. 1B), similar to that observed in AD hippocampus. In addition, a large 62% loss in drebrin was also observed in these mice. Therefore, pPAK and cofilin pathology and severe drebrin loss are found in both AD and aged AD APPswt mice, suggesting that the dysregulation of PAK/LIMK/cofilin signaling pathway might play a significant role in the regulation of synaptic defects and memory deficits in AD. Both Aβ oligomers and fibrillar Aβ42 treatment of hippocampal neurons can activate PAK1, which in turn activates LIMK1 in vitro. In addition, Heredia et al. (2006) observed that fibrillar Aβ could activate LIMK1 and induce ADF/cofilin phosphorylation in cultured neurons, suggesting LIM kinase is required for the neurotoxicity of Aβ. They also demonstrated that in AD brain, the number of pLIMK-positive neurons was significantly increased in those regions affected with AD pathology. Collectively, these data suggest dysregulation of the RAC/PAK1/LIMK/cofilin signaling pathway occurs in AD brain.

Rho/ROCK/LIMK/cofilin signaling pathway in AD. ROCKs, Rho-activated Ser/Thr kinases, are implicated in Rho-mediated actin reorganization. For the maintenance of synaptic balance, ROCK mediates signals to retract the growth cones and dendritic spines via its downstream target LIMK. Recent studies have found that ROCKs can induce the processing of APP to the toxic Aβ42 species and inhibitors of ROCKs, such as statins and certain NSAIDs, can significantly suppress this amyloidogenic APP processing. Our earlier study also found that chronic orally administered ibuprofen, the most commonly used non-aspirin NSAID, fed to a mutant APPswt transgenic AD mouse model resulted in significant reductions of Aβ deposits, with ROCK inhibition in vitro are higher than the low micromolar levels we have measured in brain. One of the ROCK effectors, CRMP-2 (collapsin response mediator protein-2) displays a prominent hyperphosphorylation in AD, but CRMP-2 can also be phosphorylated by known tau kinases, GSK3β and Cdk5. These observations suggest aberrant ROCK and downstream CRMP2 signaling could also play a role in AD pathogenesis.

Petrosos et al. (2008) observed that Aβ increases while a ROCK inhibitor prevents the RhoA-GTP response and CRMP-2 phosphorylation observed in cultured neuroblastoma cells. RhoA and phospho-CRMP-2 levels are increased in neurons surrounding amyloid plaques in the cerebral cortex of the APPswt mice. These observations support the hypothesis that Aβ increases the Rho GTPase activity via ROCK2 activation that enhances CRMP-2 phosphorylation to inhibit neurite outgrowth and synapse formation. Since the RhoA/ROCK pathway also activates ADF/cofilin-mediated actin depolymerization via LIMK, dysregulation of the Rho-ROCK/LIMK/cofilin signaling pathway may also play a role in the pathogenesis of synaptic defects in AD.

In addition, although conventionally angiotensin receptors serve to regulate vasodilation and blood pressure, AT2 receptors linked to RhoA inhibition are found on neurons and have been implicated in X-linked mental retardation and the regulation of actin dynamics in dendritic spines. The possibility of using selective AT2 receptor agonists to modulate synaptic plasticity and potentially treat AD has been recently reviewed.

Connecting NMDA receptors, FYN and PAK signaling in AD. The Rho family interacts with N-methyl-D-aspartate receptors (NMDARs). NMDARs are a subtype of ionotropic...
NMDARs are directly anchored to the αβ for FYN. Oligomer and fibril toxicity. This suggests that Several PAK. These observations on the NMDA oligomer-induced effects on dendritic spine and synaptic marker loss in cultured neurons.

Thus cross-talk between NMDARs and the Rho family via calcium signaling to activate RAC/PAK occurs during synaptic plasticity underlying new synapse formation.

NMDARs subunit NR2A and NR2B mRNA levels are decreased in hippocampus and entorhinal cortex from AD brains. It was also found that decreased protein subunits of NMDARs, for example NR2B as well as the scaffold PSD-95 and activated z-CaMKII occur in postsynaptic density preparations of APP[V717I] AD transgenic mice. This was associated with impaired NMDA-dependent long-term potentiation (LTP), a major cellular mechanism required for learning and memory and with decreased NMDA- and AMPA-receptor currents in hippocampal CA1 region. These observations on the NMDA receptor link to RAC/PAK appear directly relevant to in vitro studies that show NMDA receptors mediate Aβ oligomer-induced effects on dendritic spine and synaptic marker loss in cultured neurons.

Figure 2. Proposed Rho family pathways involved in actin disorganization in AD pathogenesis. Both β-amyloid (Aβ) oligomers and fibrillar amyloid can activate ROCK and PAK1, which in turn activates LIMK1 and induces cofillin phosphorylation to mediate actin depolymerization. ROCKs can also induce the processing of APP to the toxic Aβ species and inhibitors of ROCKs, such as NSAIDs, can significantly suppress this amyloidogenic APP processing. Curcumin may indirectly inhibit PAK1 activity via suppressing Aβ oligomer and fibril toxicity. This suggests that dysregulation of Rho-ROCK/LIMK/cofilin and RAC/PAK/LIMK/cofilin signaling pathways might play a significant role in the regulation of synaptic defects and memory deficits in AD pathogenesis. In addition, one of the ROCK effectors, CRMP-2 (collapsin response mediator protein-2) displays a prominent hyperphosphorylation in AD, and CRMP-2 can be phosphorylated by known tau kinases, GSK3β and Cdk5. Furthermore, NMDA receptors mediate Aβ oligomer-induced effects on dendritic spine and synaptic marker loss though SRC family tyrosine kinase FYN link to PAK. FYN activation has been implicated in soluble Aβ oligomer induced LTP defects in vitro, and synaptotoxicity and cognitive deficits in APP transgenic mice.

Actin disorganization synaptic dysfunction and synapse loss

Several PAK inhibitors such as TAT-PAK18, IPA-3 and PF-3758309 have been developed for the therapy of mainly non-brain solid tumors. These inhibitors block the growth of PAK1-dependent solid tumor cells selectively without affecting the growth of normal cells. However, the most potent inhibitors fail to pass the BBB. Thus, it is rather unlikely that this class of drug would be useful for AD therapy.

Further, since PAK signaling plays a critical role in synaptic plasticity, learning and memory, there could be limitations for inhibiting PAK1 as a direct drug target for AD or other brain diseases. Despite this caveat, based on the dynamic alteration of PAK1 in different AD stages, PAK1 inhibitors might be still useful for AD intervention to block abnormal PAK1 activation and translocation, albeit with a narrow therapeutic window. One can also (and perhaps more safely) target the upstream Aβ oligomers. We found that a pleiotropic natural compound, curcumin, inhibited Aβ-induced PAK1 activity suppressing persistent phospho-PAK translocation to granules in CA1 neurons evaluated in aged APPswe Tg2576 mice. Curcumin also
suppressed punctate anti-Aβ staining and pPAK translocation induced by Aβ42 oligomers in cultured hippocampal neurons. Since curcumin has been reported as an effective anti-amyloid and anti-Aβ oligomer agent in vivo and in vitro, curcumin’s activity on PAK1 is likely through the reduction of upstream Aβ aggregates. Curcumin is an anti-cancer drug with logP=-2.5 (XLogP3-AA = 3.2), consistent with BBB permeability; however, curcumin alone has a very poor bioavailability and has to be encapsulated with liposomes or formulated for clinical application, for example for good oral absorption.

In 2011, a Gonzalez-Billault group found that fibrillar Aβ42 can activate LIMK, through RAC/CDC42 and PAK1, leading to the inactivation of coflin. Furthermore, a coflin phosphatase called Slingshot (SSH), which antagonizes LIMK, blocks the neuro-cytotoxicity of fibrillar Aβ42. In short, fibrillar Aβ42 block coflin’s F-actin severing activity through the SRC-Tiam1-RAC/CDC42-PAK1-LIMK signaling pathway, and SSH could reverse this neurodegenerative pathway. Thus, in principle an SSH activator, in addition to a water-soluble (aminohexyl) derivative of SRC family kinase inhibitors such as PP1 and PP2, or PAK1/LIM kinase blockers, could be useful candidates for oral therapy, particularly for early stage AD.

Although neither the potent PAK1 blocker IPA-3 nor the PAK1 inhibitor PF-3758309 is available on the market for neurodegenerative diseases, several natural PAK1 blockers are inexpensively available. One of them is berberine chloride, which has been shown to ameliorate spatial memory impairment in a rat Aβ infusion model of AD.

Huntington Disease

Huntington disease (HD) is an autosomal dominant progressive neurodegenerative disorder that prominently affects the basal ganglia, leading to clinically significant motor function, cognitive and behavioral deficits. HD is caused by an expanded CAG repeat encoding a polyglutamine (polyQ) tract in exon 1 of the HD gene Htt coding for huntingtin (htt). Normal HD alleles have 37 or fewer glutamines in this polymorphic tract, more than 37 of these residues cause HD. A polyQ repeat expansion of more than 37 units as observed in HD results in a very large protein (> 348 kDa) of 3,145 or more amino acids aggregated in HD. The length of the CAG tract is directly correlated with disease onset, with longer expansions leading to earlier onset of HD. The onset age in HD patients with CAG repeats below 60 units varies considerably.

Although the hallmark of HD is motor disability that features chorea, HD and AD patients share many of the same clinical manifestations. These include behavioral and psychiatric disturbances (including depression and apathy) in the early stages of the diseases, as well as cognitive defects in later stages that result in forgetfulness, impaired judgment, disorientation and confusion. Cognitive deficits in patients with HD are usually less severe than in AD.

Currently, the exact mechanisms of cellular toxicity caused by mutant htt are not completely understood. A number of studies have shown that wild-type htt reduced the cellular toxicity of mutant huntingtin in vitro and in vivo and protects neurons with a mechanism that involves inhibition of procaspase-9 processing or caspase 3. Wild type htt also prevents PAK2 cleavage by caspase-3 and caspase-8, which activates PAK2 by releasing a constitutively active C-terminal kinase domain that mediates cell death. Thus, it has been proposed that loss-of-function of htt might contribute to neuronal toxicity resulting from the polyQ expansion. In contrast, genetic and transgenic data argue that the primary toxicity caused by the mutation of the HD gene is via a gain-of-function caused by intracellular aggregates of mutant htt protein. It remains unclear whether the toxic effects of this protein are due to loss of function or soluble monomers, or oligomers or insoluble species. In this respect, the same questions arise with AD and tau aggregates. And as with AD, PAK1 appears to modulate toxic pathways in HD.

Recently, PAK1 was identified as an htt interactor that modifies mutant htt (muthtt) toxicity. PAK1 promoted soluble mutant huntingtin self-interaction that enhances toxicity in HD cellular models, suggesting PAK1 may play an important role in HD pathogenesis. PAK1 co-localized with muthtt aggregates in cell models and in human HD brains. PAK1 overexpression not only enhanced the aggregation of muthtt, but also promotes soluble wild-type htt (wt htt)-wt htt, wt htt-muthtt and muthtt-muthtt interactions. Moreover, PAK1 overexpression enhanced htt toxicity in cell models and neurons in parallel with its ability to promote aggregation, while PAK1 knockdown suppressed both aggregation and toxicity. Interestingly, overexpression of either kinase-dead or wild-type PAK enhanced both aggregation and toxicity of muthtt protein. The domains of PAK1 that bind htt also facilitate oligomerization/aggregation, and no enhanced toxicity was observed with PAK1 domains that do not bind htt. More importantly, PAK1 also enhances dimerization of wt htt, but this does not lead to any large or toxic aggregates. This suggests that PAK1 plays a key role in enhancing htt htt interactions in a way that synergizes with the effects of the “sticky” expanded polyQ tract to enhance aggregated muthtt toxicity.

In addition, the PAK-interacting exchange factor (α PIX/Cool2) was also identified as a novel htt interacting protein. Similar to PAK1, α PIX binds to both the N-terminal region of wt htt and muthtt, and colocalizes with muthtt in cells where it accumulates in the muthtt aggregates. Deletion analysis suggested that the dbl homology (DH) and pleckstrin homology (PH) domains of α PIX are required for its interaction with htt. Overexpression of α PIX enhanced muthtt aggregation by inducing SDS-soluble muthtt-muthtt interactions. Conversely, knocking down α PIX attenuated muthtt aggregation. These findings suggest that α PIX plays an important role in muthtt aggregation, and targeting PAK1 or α PIX could be a useful strategy for HD therapy (Fig. 3).

X-Linked Mental Retardation

Mental retardation (MR) is characterized by significantly impaired cognitive function affecting 2-3% of the population in Western countries. Unlike AD and HD, MR often occurs before...
Dysfunction of PAK might be involved in the pathogenesis of both forms of XLMR, because mutations in the PAK3 gene were found in nonsyndromic X-linked mental retardation (MRX) and inhibition of PAK activity was found to rescue symptoms of fragile X syndrome (FXS) in FXS mouse models.

PAK3 and related pathways and the pathogenesis of MRX. Recent studies have found that physiological activation of synaptic RAC/PAK signaling is defective in a mouse model of fragile X syndrome (FXS) and inhibition of PAK activity in this model directly ameliorated several cellular and behavioral deficits, including FXS-related abnormalities present at the levels of synaptic morphology, synaptic plasticity and behavioral abnormalities such as locomotor activity, stereotypy, anxiety and trace fear conditioning. This observation suggested that defects of PAK signaling might directly contribute to human FXS pathogenesis.

FXS is the most common inherited form of mental retardation with an estimated incidence of 1 in 4,000 males and 1 in 6,000–8,000 females. FXS is caused by the expansion of the CGG repeat in the 5-untranslated region of the fragile X mental retardation 1 (FMR1) gene located on the X chromosome. The length of the CGG is the major genetic factor to determine FXS or the carrier status of individuals. Usually, individuals with > 200 CGG repeats are classified as having FXS-associated cognitive deficits and abnormal cortical dendritic spines. This expansion of the CGG repeats in the X-linked FMR1 gene results in the silencing of transcription of the gene to cause the loss of the FMR1 protein (FMRP) and clinically to present the fragile X syndrome phenotype.

FMRP is a selective RNA-binding protein that is mainly expressed in the brain and gonads where it is mostly confined to the cytoplasm. Several studies have shown that FMRP plays a critical role in regulating mRNA translation, transport and stability. In neurons, FMRP regulates the local translation of a subset of mRNAs at synapses in response to activation of Gp1 metabotropic glutamate receptors and possibly other receptors essential processes for learning and intellectual development. However, in the absence of FMRP, dysregulated mRNA translation leads to altered synaptic function and loss of protein synthesis-dependent synaptic plasticity. Patients with FXS display long, thin and immature dendritic spines, which are similar to the dendritic spine morphology of FMR1 knockout (KO) mice. FMR1 KO mice also showed similar behavioral defects to those found in human FXS such as anxiety, hyperreactivity to auditory stimuli, impaired motor coordination and impairment in spatial learning. Thus, the interaction of Rho GTPases with missense mutation; another is missense mutation; suggesting a direct link between PAK3 and related pathways and the pathogenesis of MRX.

PAK in fragile X syndrome. Recent studies have found that physiological activation of synaptic RAC/PAK signaling is defective in a mouse model of fragile X syndrome (FXS) and inhibition of PAK activity in this model directly ameliorated several cellular and behavioral deficits, including FXS-related abnormalities present at the levels of synaptic morphology, synaptic plasticity and behavioral abnormalities such as locomotor activity, stereotypy, anxiety and trace fear conditioning. This observation suggested that defects of PAK signaling might directly contribute to human FXS pathogenesis.

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PAK with FMRP and the defects of synaptic RAC/PAK signaling in FMR1 KO mice suggest a direct link between altered PAK function and defective synaptic plasticity in human FXS. FMRP has also been implicated in regulation of APP expression via mGluR5 and mGluR5 antagonists currently used to treat FXS, lower Aβ and audiogenic seizures in vivo.95-97 Since mouse models of FXS (FMR1 KO) recapitulate the cellular and behavioral phenotypes observed in human FXS, the genetic rescue of the phenotypes of FXS by inhibiting PAK activity suggest that targeting PAK signaling pathway could be a potential therapeutic strategy for development of new drugs for FXS.

In conclusion, evidence from genetic, biochemical and animal data suggest that normal learning and memory require functional PAK and related pathways that are disrupted with the major dementia of aging (AD) as well as with HD and fragile X and other syndromes with developmental cognitive deficits. Preliminary preclinical data suggest that PAK inhibition may be an interesting approach for the treatment of AD, HD and fragile X syndrome based on abnormal PAK activation in these diseases. PAK inhibitors are hypothesized to exert beneficial effects on improving cognitive impairment via modulation of dendritic spine morphology and/or synaptic function. This suggests that abnormal PAK activation contributes to symptoms in several neurological diseases and raises the possibility of common treatment strategies that correct PAK dysregulation.

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