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Commentary

Commentary on Giralt et al.: PTK2B/Pyk2 overexpression improves a mouse model of Alzheimer's disease

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A B S T R A C T

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most common cause of dementia and the 6th leading cause of death. Although research has revealed significant information about AD, much is yet to be discovered about the precise biological changes that cause AD and how the disease could be prevented, slowed, or stopped. Accumulating evidence suggests the involvement of the non-receptor proline-rich tyrosine kinase 2 (Pyk2) in AD, but the downstream signaling events triggered by this protein and their implications on the pathology of the disease were unclear until recently. A recent paper by Giralt et al. used genetically depleted and overexpression mouse models to elucidate the role of Pyk2 in AD. Here, we discuss the findings presented in this paper in light of previous information and hypotheses, and suggest interpretations and explanations for this surprising and unexpected phenotype.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most common cause of dementia and the 6th leading cause of death, afflicting more than 5 million people at all ages in the USA and more than 35 million people worldwide. In addition to human suffering, the advances in medicine that lead to longer life expectancy, together with the long duration of illness before death from AD contribute significantly to the public health impact of AD and present both social and economical burden.

The clinical dementia of AD is coupled to a distinct pathology, with neuritic plaques consisting amyloid beta (Aβ) peptide and neurofibrillary tangles consisting of aggregates of hyper-phosphorylated Tau protein. Loss of synaptic density represents another invariant feature of the disease that appears to precede overt neuronal degeneration. Although research has revealed significant information about AD, much is yet to be deciphered about the precise biological changes that cause AD, why it progresses more quickly in some than in others, and how the disease can be prevented, slowed, or stopped (Alzheimer's Association, 2017).

The gene encoding proline-rich tyrosine kinase 2 (Pyk2) was recently found as a new susceptibility locus of late-onset Alzheimer's disease in several genome-wide association studies (GWAS), supporting a critical role for Pyk2 in AD (Chan et al., 2015; Kamboh et al., 2012; Lambert et al., 2013; Li et al., 2016; Lin et al., 2017). The *Drosophila* homolog of Pyk2 was recently identified as a strong Tau toxicity suppressor in a high-throughput screen. The human Pyk2 binds directly to Tau in vitro, and co-localizes with hyper-phosphorylated, oligomeric Tau in hippocampi of Pyk2 and Tau transgenic mice as well as in brains of AD patients (Dourlen et al., 2017; Li and Gotz, 2018).

A critical early step in AD is the process by which extracellular Aβ oligomers interact with the neuronal surface protein PrP^C to trigger Fyn phosphorylation and activation leading to downstream pathology. In addition to phosphorylating Tau and *N*-methyl-D-aspartate receptors (NMDARs) in post-synaptic AD neurons, activated Fyn also phosphorylates and activates Pyk2 (Kaufman et al., 2015; Li and Gotz, 2018). Significant increase in phosphorylation of Pyk2 was also observed in brain lysates from amyloid precursor protein/presilinin1 (APP/PS1) mice, a common mouse model for AD (Kaufman et al., 2015). Despite accumulating evidence suggesting the involvement of Pyk2 in AD, the downstream signaling events triggered by Pyk2 and their implications for the pathology of the disease were unclear until present.

Recently, Giralt et al. evidenced that overexpression of Pyk2 in the hippocampi of AD mice improved their memory and learning due to a decrease in Src cleavage and consequent decrease in the formation of a neurotoxic form of Src kinase. In this commentary, we will briefly review past and present knowledge of Pyk2 signaling in AD with the intent to place the findings of Giralt et al. within a more general context.

2. Pyk2 in Alzheimer's disease: expectations versus reality

The non-receptor tyrosine kinase Pyk2 is highly expressed in the central nervous system and is activated in response to increase in intracellular and extracellular calcium levels, neuronal membrane

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depolarization, hyperosmolarity, and activation of protein kinase C (PKC) (Lev et al., 1995; Menegon et al., 1999). Pyk2 is involved in the induction of long-term potentiation (LTP) through the phosphorylation and activation of Src and Fyn, that phosphorylate the NMDAR subunit GluN2B at tyrosine 1472, leading to exocytosis of GluN1-GluN2B receptors to synaptic membranes as well as to calcium influx through NMDAR, which further activates Pyk2 (Huang et al., 2001). Moreover, Pyk2 activation results its translocation to postsynaptic membranes via association with the post-synaptic density protein 95 (PSD-95), which recruits Pyk2 to NMDAR. This association is essential for Pyk2 activation and for the induction of LTP (Bartos et al., 2010). A recent publication by Giralt et al. using Pyk2 knockout mice confirmed that Pyk2 is essential for LTP and consequent spatial memory acquisition, as well as for the modulation of dendritic spine density and organization of post-synaptic regions (Giralt et al., 2017).

The metabotropic glutamate receptor 5 (mGluR5) is a transmembrane receptor that links extracellular glutamate levels to calcium mobilization, protein translation in dendrites, and tyrosine kinase signaling. The cellular prion protein (PrP^C) binds to mGluR5 and initiates intracellular signaling as a response to glutamate binding. Consequently, mGluR5 changes conformation, dissociates from PrP^C, and activates downstream synaptic signaling. Binding of Aβ oligomers (Aβo), which are highly produced in AD, to PrP^C prevents the conformational change in mGluR5 and its dissociation from PrP^C followed by its activation, and scaffolds it in a pathological conformation. Aβo binding and Aβo-PrP^C-mGluR5 complex formation also leads to Pyk2 autophosphorylation and activation and to its dissociation from the PrP^C-mGluR5 complex (Haas et al., 2016), suggesting a role for Pyk2 in the pathogenesis of the disease (Fig. 1).

It has long been assumed, based on the extensive evidence described above and on human genetic data, that Pyk2 has a critical role in AD and that deletion of Pyk2 should improve the prognosis and/or symptoms of the disease (Haas et al., 2016; Haas and Strittmatter, 2016; Kaufman et al., 2015; Xu et al., 2012). In their work, Giralt et al. used an APP/PS1 transgenic mouse model that co-expresses five familial AD mutations (5XFAD) and rapidly develops amyloid plaque pathology reminiscent of that found in human AD (Oakley et al., 2006). The authors demonstrate that, although Pyk2 autophosphorylation and activation were naturally decreased in these mice, no additive behavioral phenotype that is related to memory and learning was observed following breeding of these mice with a complete Pyk2 knockout mouse. Human genetic data demonstrate a role for PTK2B in late onset AD risk, but a relationship of *PTK2B* genetic variation to the rate of decline in AD is not defined. As the animal experiments of Giralt et al. relate to rate of decline in the setting of strong over-expression of Aβo-forming mutants, they may not bear directly on the human *PTK2B* variant genetic risk for late onset AD. Additionally, data regarding the human minor allele of *PTK2B* associated with increased AD risk suggest increased expression from this allele (Chan et al., 2015). This argues that *PTK2B* expression increases AD risk in human, rather than reducing it. Overall, it may be crucial to reassess the role of Pyk2 activation versus suppression in AD using human samples or additional mouse models, given the unexpected published results with animal experiments as described in Giralt et al.

To increase Pyk2 autophosphorylation and activation in the 5XFAD mice, the authors injected a neuronal specific recombinant adeno-associated virus (AAV) expressing wild-type (WT) Pyk2 into the hippocampus. Overexpression of Pyk2 rescued the long-term memory of the mice, but did not affect their associative memory. Pyk2 plays an important role in hippocampal synaptic functions, specifically in post-synaptic recruitment and clustering and in NMDAR activation. The authors suggest that the functional deficit in Pyk2 in 5XFAD mice contributes to their synaptic alterations and that overexpression of Pyk2 improves behavioral deficits by rescue of these synaptic alterations. These results confirm previous data from the same group suggesting that Pyk2 is essential for learning and memory within the healthy brain (Giralt et al., 2017).

The authors note that a postulated protective role for Pyk2 overexpression is unexpected and in the opposite direction indicated by previous studies of Tau models and of Aβo signaling. It may be beneficial to note that Pyk2 effects need not be monophasic with regard to protein levels or timing. Different conclusions by Giralt et al. versus previous studies may derive from biphasic Pyk2 response curves, such that greatly elevated Pyk2 expression, as shown in the current study, produces opposite responses than physiological elevation or suppression. Alternatively, acute versus chronic assays following Pyk2 manipulation may result in different outcomes.

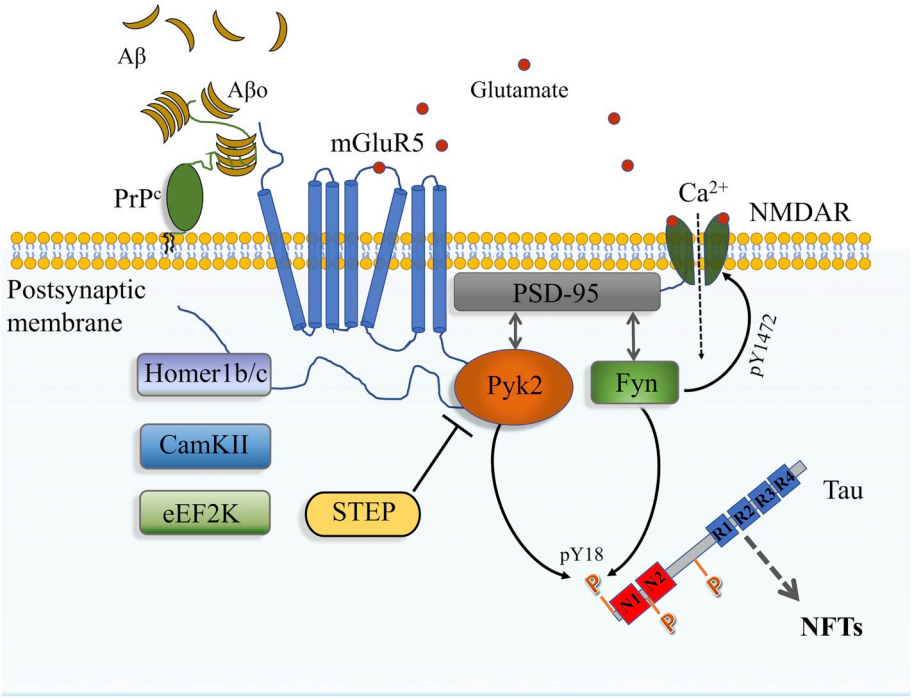

Fig. 1. Aβ-induced Pyk2 signaling in AD. Binding of Aβo to PrP^C prevents its dissociation from mGluR5 and scaffolds the complex in a pathological conformation, which signals via a complex containing Homer, CamKII, eEF2K, and Pyk2, which is recruited to the post-synaptic membrane by PSD-95. Complex formation leads to Pyk2 autophosphorylation and phosphorylation by Fyn and consequently to activation of Pyk2 and its release from the complex. Inactivation of Pyk2 is performed by the tyrosine phosphatase STEP, which can reverse the pathological effect of activated Pyk2 in AD. Both activated Fyn and activated Pyk2 can tyrosine phosphorylate Tau on tyrosine 18 (pY18), which contributes to Tau aggregation and formation of neurofibrillary tangles (NFTs). Activated Fyn can further tyrosine phosphorylate the NR2B subunit of NMDAR, which leads to extracellular calcium influx and consequent activation of Pyk2, as well as to dendritic spine loss and synaptic dysfuction, which contribute to AD pathology.

3. The critical role of Tau

Amyloid plaques and neurofibrillary tangles are the main characteristic lesions in the brain of AD patients. While Aβ deposition is an early event that is widely explored, how Tau tangles subsequently form is still a scientific conundrum. It is now becoming clear that Tau can undertake a multitude of roles beyond its most established function of axonal microtubule stabilization, such as maintaining neuronal structural integrity, axonal transport, and signaling within and between neurons (Guo et al., 2017).

The *Drosophila* homolog of Pyk2 was recently identified as a strong Tau toxicity suppressor in eye roughening and in wing blister assays in Drosophila. The human Pyk2 binds directly to Tau in vitro, and co-localizes with hyper-phosphorylated, oligomeric Tau in the hippocampi of Tau transgenic mice as well as in brains of AD patients (Dourlen et al., 2017).

Using a new mouse model with neuronal expression of human Pyk2, Pyk2/tau double transgenic mice, and biochemical assays, Li and Gotz have recently demonstrated that Pyk2 co-localizes, interacts with, and tyrosine phosphorylates Tau both in vitro as well as in mouse brains. The authors then used Fyn transgenic and knockout mice to further demonstrate that the activity of Pyk2 towards Tau is controlled by Fyn kinase (Li and Gotz, 2018).

In their work, Giralt et al. used the APP/PS1 transgenic mouse model that contains five familial AD mutations leading to massive production of Aβo and a rapid accumulation of amyloid plaques. These transgenic mice recapitulate the major features of AD amyloid pathology and, as such, represent a useful model of Aβo-induced neurodegeneration (Oakley et al., 2006).

In light of the critical role of Pyk2 in Fyn-mediated regulation of Tau pathology, and considering the absence of mutant Tau in the 5XFAD mouse model, the lack of synaptic and consequent behavioral phenotypes in 5XFAD/Pyk2-KO mice could be explained by the lack of clear Tau pathology in these mice (Huttenrauch et al., 2017) and consequently the absence of Tau-Pyk2 interaction, which is a critical contributor to disease pathology. It would be worthwhile to explore the effect of genetic depletion of Pyk2 using an AD mouse model that more closely represents late-onset non-familial AD pathology, such as the 3XTg-AD transgenic mouse model, that harbors mutations in PS1, APP, and Tau (Oddo et al., 2003).

4. FAK family kinases in Alzheimer's disease: a dynamic duo?

The focal adhesion kinase and its homologous FAK-related proline-rich tyrosine kinase 2 define a distinct family of non-receptor tyrosine kinases that exhibit approximately 48% amino acid sequence identity, common phosphorylation sites, and a similar domain structure. Although FAK is expressed in most cells, Pyk2 exhibits a more restricted expression pattern with strongest expression in the central nervous system and in hematopoietic cells (Lev et al., 1995). FAK is a major intracellular signaling component of integrin-mediated cell adhesion (Sieg et al., 1999) and plays a role in signaling pathways mediated by growth factor receptors. PYK2, on the other hand, is activated by a variety of extracellular cues including agonists of G protein–coupled receptors, increase in intracellular Ca^{+2} concentration, inflammatory cytokines, and stress signals, as well as integrin-mediated cell adhesion (Lev et al., 1995; Sieg et al., 1999).

FAK and Pyk2 are predominantly expressed in neurons, however they exhibit different developmental patterns, partially different cellular and spatial distribution in the brain. They are activated by different extracellular stimuli and execute distinct regulatory effects on various aspects of neuronal development processes and neuronal function. The different expression patterns during development and in adult brain, together with distinct localization in cultured neurons and in vivo in the brain suggest that FAK may be important for axon pathfinding during brain development while Pyk2 may be involved in regulating synaptic plasticity and other functions in the adult brain (Girault et al., 1999; Menegon et al., 1999; Xiong and Mei, 2003). The similarities and differences between FAK and Pyk2 properties in neurons and in brain raise the question of specificity and possible redundancy of their functions in these systems.

It has previously been demonstrated that Aβo treatment of primary human and rat cortical cultures leads to association of Fyn with FAK and consequent increase in FAK tyrosine phosphorylation and activation (Williamson et al., 2002). Activation of FAK was also observed in the olfactory bulb of AD patients, where dysfunction is considered as an early event in disease prognosis (Lachen-Montes et al., 2016). These accumulating evidence suggest that FAK may have a compensatory role for Pyk2 in AD, and that the lack of synaptic and behavioral phenotype in the 5XFAD/Pyk2-KO mice in the current study by Giralt et al. may be explained, at least in part, by a compensation from FAK, which develops over a long period of time in which Pyk2 is totally and persistently eliminated. In agreement with this idea, Giralt et al. did not observe a learning and memory phenotype in their older Pyk2-KO mice, which were used as control in this study, despite a significant phenotype in 4-month-old Pyk2-KO mice in their previous study (Giralt et al., 2017), further supporting the development of FAK-mediated compensatory role over time. A closer examination of FAK levels and phosphorylation in the 5XFAD/Pyk2-KO mice used in this study may resolve this enigma.

5. Pyk2 and the β-amyloid theory

Giralt et al. demonstrate that levels of Aβ plaques are decreased in 5XFAD/Pyk2-KO mice and increased in 5XFAD overexpressing Pyk2. Moreover, Pyk2 and Aβ co-localize in the neuropil zone but not in plaques, suggesting proximity of Pyk2 to sites of Aβ production. Based on this, the authors suggest that Pyk2 contributes to amyloid plaque formation through modulation of Aβ production.

It was recently demonstrated by Grossi et al. that inhibition of Pyk2 reduces levels of intracellular calcium via disrupting its release from the endoplasmic reticulum reservoir (Grossi et al., 2017). Furthermore, Small et al. evidenced that increased intracellular calcium levels lead to activation of γ-secratase, an APP processing enzyme (Small et al., 2010). Increased activity of γ-secratase leads to excessive processing of APP and further release of toxic and aggregating amyloid forms outside of the cell (Fig. 2). This model further supports the findings of Giralt et al. and their conclusion regarding the connection between Pyk2 expression levels and amyloid plaque production and deposition. Examination of intracellular calcium dynamics in 5XFAD/Pyk2-KO mice and comparison to 5XFAD mice that contain intact Pyk2 could further confirm this suggested model.

6. The Src connection

Although the *PTK2B* gene is genetically associated with late-onset AD, whether and how the protein Pyk2, which is encoded by this gene, is involved in the disease was not known until recently. A major goal of the work presented in Giralt et al. was to elucidate the downstream signaling events triggered by Pyk2 and their implications for the pathology of the disease.

Using cultured cortical neurons and an in vivo rat model of ischemic stroke, Houssain et al. had previously demonstrated a calpain-mediated cleavage of Src kinase at its N-terminal region. This cleavage generates a 52 kDa Src fragment that lacks the myristoylation motif and unique domain and re-localizes from the plasma membrane into the cytosol, where it induces excitotoxic neuronal death via negative regulation of the pro-survival kinase PKB/Akt (Hossain et al., 2013).

While no change in Fyn kinase protein expression or activation was observed in 5XFAD mice lacking or overexpressing Pyk2, Giralt et al. noticed an increased amount of cleaved Src product with neurotoxic properties in their Pyk2-KO, 5XFAD, and 5XFAD/Pyk2-KO mice.

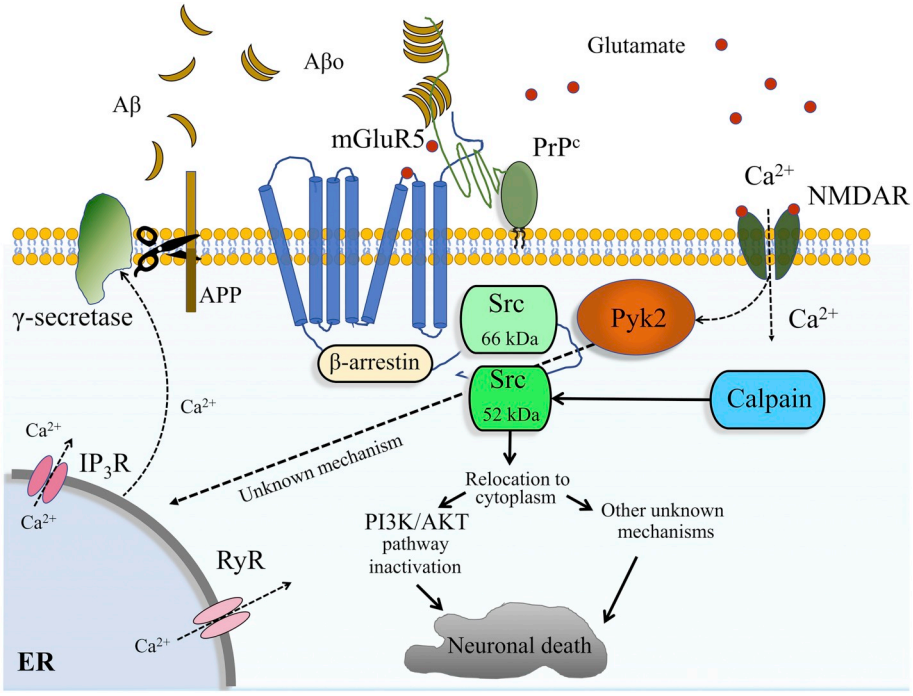

Fig. 2. Pyk2 regulates neurotoxicity in AD by controlling calpain-mediated Src cleavage. Activation of Pyk2 by the Aβo-PrP^C-mGluR5 complex leads to recruitment and activation of Src, which phosphorylates the NR2B subunit of NMDAR and results excessive influx of extracellular calcium. Calcium further activates Pyk2 and calpain, which cleaves Src and releases a 52 kDa fragment into the cytosol. The truncated Src fragment facilitates neurotoxicity and neuronal death in part by inactivating PKB/Akt. Activated Pyk2 also leads to release of calcium from the endoplasmic reticulum, which activates γ-secretase and induces APP processing and consequent excessive production of Aβo and plaques.

Interestingly, overexpression of Pyk2 in the 5XFAD mice significantly decreased the appearance of this cleaved Src form. The authors conclude that a decrease in Pyk2 levels and/or autophosphorylation triggers the appearance of the short form of Src that has potential cytotoxic properties. The authors further claim that the appearance of this fragment may contribute to the consequences of decreased Pyk2 activity and signaling in 5XFAD mice, and that overexpression of Pyk2 corrects the 52 kDa levels and consequently toxic effects and behavior (Fig. 2). The exact mechanism by which Pyk2 regulates calpain-mediated Src cleavage is a subject for future investigation, and may be related to the ability of Pyk2 to regulate intracellular and extracellular calcium influx in cells.

7. Conclusions

It has long been hypothesized that Pyk2 has a critical role in the prognosis and pathology of AD, but whether and how this kinase participates and regulates disease symptoms was unclear until recently. Giralt et al. had pioneered a research that used genetic knockout and overexpression AD mouse models to demonstrate the critical role of Pyk2 in AD. Moreover, they describe for the first time a novel mechanism by which Pyk2 inhibits calcium- and calpain-mediated cleavage of Src kinase and consequent maintenance of neuronal cell survival.

Contradictory to hypotheses and expectations in the field, no change in behavioral phenotype was observed in AD mice depleted of Pyk2, however a significant phenotype was observed following Pyk2 overexpression in hippocampus neurons. The authors suggest that these findings may imply that increasing, rather than decreasing, Pyk2 levels and activation in AD may improve the cognitive decline and disease pathogenesis. As differences in observations and conclusions may result from the specific mouse model and/or methods used, the findings described in Giralt et al. may benefit from validation by other laboratories and other methods.

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