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p38-MAPK and CDK5, signaling pathways in neuroinflammation: a potential therapeutic intervention in Alzheimer's disease?

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Alzheimer's disease (AD), the most common type of dementia, affects millions of people worldwide, putting a significant strain on healthcare infrastructure and societal resources. AD is characterized by the build-up of amyloid-beta (Aβ) plaques and neurofibrillary tangles containing hyperphosphorylated tau protein. These pathological features cause neuroinflammation, vascular dysfunction, and ultimately, neuronal death and cognitive decline (Long and Holtzman, 2019). Two critical signaling pathways, the mitogen-activated protein kinase (MAPK) family and cyclin-dependent kinase 5 (CDK5), have been implicated in the pathogenesis of AD. There are three primary subfamilies within the MAPK family, namely extracellular signal-regulated kinases, c-Jun N-terminal kinases, and p38 MAPKs. Of these, p38α MAPK is particularly involved in neuroinflammation and vascular dysfunction, processes that are integral to the progression of AD. CDK5, a serine/threonine kinase primarily expressed in the central nervous system, has crucial roles in neuronal migration, synapse formation, and synaptic plasticity. However, aberrant activation of CDK5 has been linked to various neurodegenerative diseases, including AD.

Recent advancements suggest a potential interplay between the p38 MAPK and CDK5 signaling pathways, providing a novel therapeutic intervention in AD. The roles of these pathways have been validated using advanced techniques like single-cell sequencing and neuroimaging, adding more depth to our understanding. The advancement of novel therapies targeting these pathways, such as small molecule inhibitors and gene therapies, has shown promising results in preclinical studies and early-phase clinical trials. This perspective will summarize the molecular interconnections between p38 MAPK and CDK5, providing our personal viewpoint on the relevance of specifically directed and/or multiple simultaneous signal abrogation in future treatment strategies.

p38-MAPK's role and impact in AD: The MAPKs are a pivotal class of serine/threonine protein kinases that manage numerous cellular functions, including cell growth, differentiation, survival, and apoptosis (Guo et al., 2020). In the context of AD, the p38 MAPK signaling pathway has a significant impact, especially in neuroinflammation, being a critical factor in the disease progression. For example, its activation within microglia has been identified as a significant contributor to the upregulation of proinflammatory cytokines, via nuclear factor kappa B dependent-signaling pathway, particularly in response to Aβ or Toll-like receptor ligands.

Vascular dysfunction is another critical aspect of AD pathophysiology, with evidence also suggesting the involvement of the p38 MAPK signaling pathway. Specifically, this pathway stimulates aberrant endothelial cell activation, increasing gap-junctions and impacting the permeability of the blood-brain barrier (BBB) promoting immune cell transmigration, barrier dysfunction, and subsequently escalating micro-environmental neuroinflammation (Wang et al., 2020)

CDK5 and aberrant signaling associated with acute and chronic neuroinflammation: CDK5 is an atypical cyclin-dependent kinase that helps to maintain the functional integrity of the neurovascular unit (NVU) and the BBB, by regulating vascular patency and neuroglial activity. However, its hyperphosphorylated, dysregulated activation, particularly through p25-CDK5 preferential binding, compromises the NVU's structure, impairs the normal physiological status of the glial vascular unit, and predisposing an individual to AD (Ao et al., 2022).

Quan et al. (2019) showed that lentiviral upregulation of CDK5 increased Aβ production and concomitant apoptosis in primary rat hippocampal neurons in a peroxisome proliferator-activated receptor γ-dependent mechanism, whilst Pao et al. (2023) inhibited CDK5/p25 activity using a novel peptide, blocking this interaction and consequently protecting CA1 hippocampal neurons from gliosis and cell death in a p25-inducible murine model. Most recently, both the concept of vascular aberration and neuroinflammatory alignment with AD have been supported by increasing recognition of the correlation between inflammatory cytokine expression and signaling, and the development of neurocognitive disturbances. Wong-Guerra et al. (2023), recently described this, indicating the importance of the cyclic microglial activation pathways perpetuated by the interleukin-6 (IL-6)-CDK5/p35 axis (**Figure 1**).

CDK5-p38-MAPK interactions in AD: To define the role of CDK5 in mediating inflammatory activation within the central nervous system, we should understand more fully, the complex signaling interactions within individual critical components of the NVU. Recently, Posada-Duque et al. (2021) eloquently summarised the current knowledge pertaining to the importance of CDK5 in maintaining competent NVU and BBB function through control of vascular patency and neuroglial activity. They further described how aberrant overactivation, associated with p25-CDK5 preferential binding compromises the integrity of the NVU, predisposing to potential development of AD. Finally, they contemplated the therapeutic strategies that could protect or improve neuroplasticity by blocking the hyperphosphorylation of CDK5. Two decades ago, Otth et al. (2003) first showed a correlation between phosphorylation of p38, CDK5

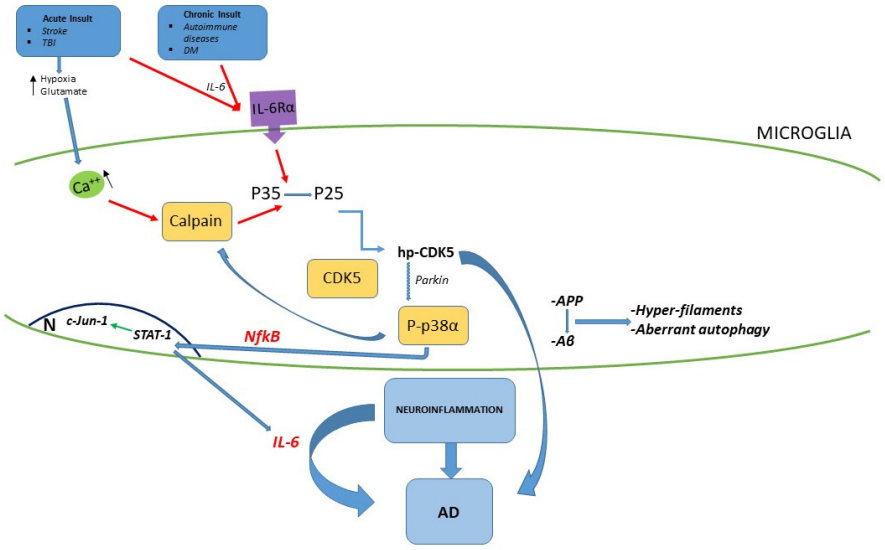

Figure 1 | **Legend-microglial CDK5 pathway signaling through MAP kinase P38 in microglia.**
Although systemic inflammation results in IL-6 (and other cytokines)-mediated p38 phosphorylation and nuclear c-Jun transcription factor-thus perpetuating inflammation through transcription and translation of additional TNF/IL-1β, NO, etc., the impact of calpain with calcium from brain trauma is distinct and the CDK5-mediated neurodegenerative activity synergizes with its p38-mediated signaling to submit a plethora of aberrant messages to the nearby neurons, resulting in dysfunction. Therefore, hyperphosphorylation of CDK5 appears to be acritical and partially distinct from the inflammatory signaling cascade. However conventional inflammatory stimulation of p38 MAPK could recycle calpain-CDK5 activity and in addition, perpetuate glial-mediated neuroinflammatory damage. Created with Microsoft PowerPoint. Aβ: Amyloid-beta; AD: Alzheimer's disease; APP: amyloid precursor protein; CDK5: cyclin-dependent kinase 5; DM: diabetes mellitus; hp-CDK5: hyperphosphorylated cyclin-dependent kinase 5; IL-6: interleukin-6; IL-6Rα: interleukin-6 receptor alpha; N: nucleus; Nfκβ: nuclear factor kappa beta; STAT-1: signal transducer and activator of transcription-1; TBI: traumatic brain injury; TNF: tumor necrosis factor.

overactivation, their co-immunoprecipitation, and expression of Aβ in neuritic plaques of a transgenic murine model of dementia. Quintanilla et al. (2004) demonstrated that exogenous addition of IL-6 to rat hippocampal neurons caused CDK5-dependant increase p38 phosphorylation concomitant with tau phosphorylation. These early studies first indicated a strong relationship between these molecules, induction of inflammation, and dementia.

Recently, He et al. (2022) provided evidence that modulation of CDK5 could reduce microglial expression of IL-6, as well as other pro-inflammatory markers (tumor necrosis factor α and IL-1β) in a rat model of intracerebral hemorrhage, indicating a probable role for CDK5 in microglial neuroinflammatory response to injury. Using a rat model of thermal hyperalgesia, Fang-Hu et al. (2015) effectively reduced tumor necrosis factor-α/microglia mediated inflammatory pain by blocking CDK5-p38 signaling, whilst Tomov et al. (2019) inhibited CDK5 using roscovitine, and successfully protected intracerebral dopaminergic grafts from rejection by abrogating local micro-environmental microglial recruitment and activation. The above studies indicate the importance of microglial-induced neuroinflammation in brain disease and reflect the key role of CDK5 in controlling inflammatory status through MAPK signaling, thereby suggesting an important contribution during dysregulation associated with dementia/AD, and possibly other neurocognitive disorders.

Since calpain is the primary stimulator for p35 conversion to p25 during calcium deregulated, and other neuroinflammatory associated injury, it is necessary to characterize its relationship to neuronal microglial inflammation, (the source of the majority of neuroinflammation), and associated signaling pathways. Current evidence suggests that astrocyte reactivity is dependent upon calpain-induced p38-MAPK signaling mediated by p25-CDK5. p38-MAPK activation is also associated with decreased synaptic activity, neuronal dysfunction, and neurodegeneration, therefore, regulation of the calpain-p38-p25-CDK5 axis could represent an important neuroprotective strategy. In addition to triggering the inflammatory cascade in neuroglia, aberrant CDK5 activity has direct neurotoxic effects, for example stimulating p38 phosphorylation and reactive oxygen species formation in the presence of glutamate or Aβ, whilst in diabetic mice exposed to high glucose, increased cleavage of p35 by calpain resulted in caspase-3 dependant neuronal apoptosis, which was protected by pre-treatment with the CDK5 inhibitor roscovitine, concomitant with reduction in p38-MAPK expression (**Figure 1**).

Potential therapeutic approaches in AD targeting CDK5 mediated p38 MAPK activation: Combination therapy, targeting both CDK5 and alternatively activated p38 MAPK pathways that promote glial-induced local neuro-inflammation, could prove to be an effective therapeutic strategy. Given the multifaceted roles these kinases play in AD, a combined inhibition approach might enhance therapeutic effectiveness, minimize side effects, and prevent drug resistance. Blocking p38α signaling could synergistically abrogate feed-forward stimulation of further calpain activity, in addition to nuclear transcription associated with neuroinflammatory cytokine production, and ultimately Aβ dissolution. An example of this multi-kinase inhibition approach is HSB13. This compound, part of the 1,4-benzoxazines class, has demonstrated protective effects against neurodegeneration in a Drosophila model of AD. HSB13 operates by inhibiting a range of kinases associated with AD progression, including glycogen synthase kinase 3, cyclin-dependent kinases (CDKs) 1, 2, and 5, and p38 MAPK. The inhibition of these kinases, identified via kinase profiling analyses, suggests a mechanism through which HSB13 confers its neuroprotective effect.

Future perspectives: Future research should focus on overcoming these challenges, refining our understanding of these kinases in the context of AD, and perfecting the pharmacological strategies aimed at their modulation. With continuous advancements in drug discovery, gene therapy, and our increasing understanding of neurodegenerative processes, we should identify more effective treatment strategies against AD. The focus on CDK5 and p38 MAPK reflects the growing recognition that combating AD will require multifaceted therapeutic strategies that target not just a single molecule or process, but the intricate network of biological systems, and in particular the key or primary signaling units that contribute to disease progression.

One of the critical goals should be to block aberrant microglial stimulation associated with either systemic or brain localized trauma. However, since normal glial communication with the glial vascular unit and NVU, is required for maintenance of BBB function and neuronal synaptic activity, silencing of primary cell signaling pathways is not an acceptable form of therapeutic. Therefore, the selection of more specific intermediates, or indeed a pathway set such as calpain-CDK5-p38α as described above, where cycling and feedback can result in chronic activation and incremental neurodegenerative effects, e.g. specific agonists like calpain and IL-6, could synergistically and more effectively protect against neuroinflammatory associated dementia.

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