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HOT TOPICS

Disease-modifying pharmacological approaches to correcting basal forebrain cholinergic neuronal (BFCN) dysfunction and degeneration

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Degeneration of the basal forebrain, the primary source of cholinergic innervation in the brain, occurs in age- and neurodegenerative disease-related cognitive disorders, including Alzheimer's disease (AD) where BFCN degeneration may be a major driver of disease progression [1]. Further, a recent publication demonstrated BFCN loss underpins gait dysfunction in Parkinson's disease, arguing that therapeutically targeting the cholinergic system could also address certain motor aspects of neurodegenerative disease [2]. Recent evidence also indicates correcting BFCN dysfunction, leading to physiologic release patterns, could be expected to have better efficacy than compensating for BFCN dysfunction with cholinesterase inhibitors [3]. These findings, combined with the limited effects of anti-amyloid therapies on AD progression, have renewed interest in disease-modifying approaches to treat BFCN dysfunction

A critical pathogenic event in the development of BFCN dysfunction and degeneration is impaired nerve growth factor (NGF) signaling that deprives cholinergic neurons of the neurotrophic support for proper functioning and survival [4]. NGF signaling is transduced by endocytosis and retrograde trafficking of a maturing Rab5-"signaling endosome" containing the NGF receptor, TrkA to initiate a transcriptional program. Basal forebrain cholinergic neurons, with axonal projections throughout the cortex, are particularly vulnerable to disruption of this

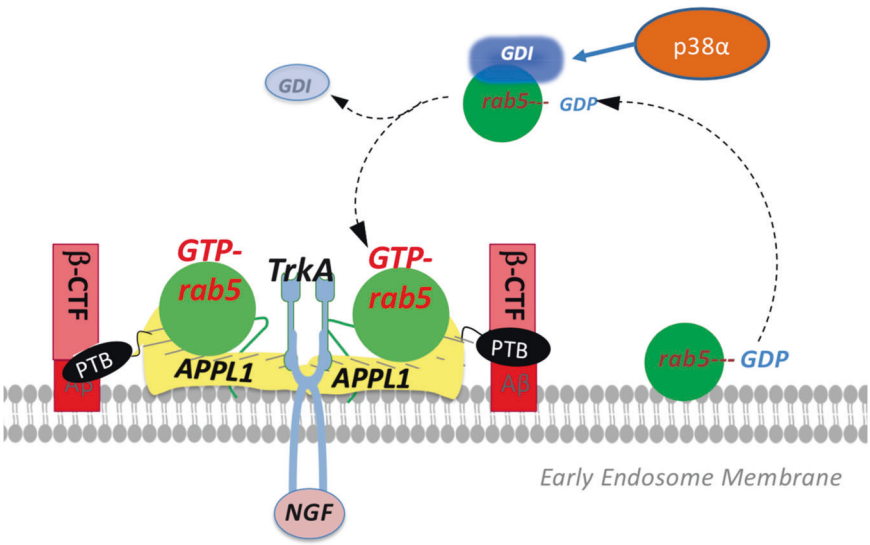

Fig. 1 Inhibition of p38α kinase activity represents a pharmacological lever to modulate molecular mechanisms underlying cholinergic neurodegeneration. See text and Ref. [4]. Aβ amyloid-beta cleavage product of amyloid precursor protein (APP). APPL1 adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1, β-CTF "beta-carboxyl-terminal fragment" of APP, GDI GDP dissociation inhibitor, GDP guanosine diphosphate, NGF nerve growth factor, p38α alpha isoform of p38 MAP kinase. PTB phosphotyrosine binding domain, Rab5 a GTPase, TrkA tropomyosin receptor kinase A, high affinity NGF receptor.

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retrograde signaling process from distant synaptic connections back to the cell body. Rab5, a GTPase, is a master signaling molecule normally regulating endocytosis and endosome function. Both Rab5 hyper-activation, induced by the ß-CTF proteolytic fragment of APP (Fig. 1), and lowered rates of recycling from endosomes impair these processes, partly due to enlargement of endosomes, which slows their retrograde transport and trophic signaling, and induces cholinergic atrophy deficits in Down syndrome (DS) mouse models, which recapitulate AD pathology in the basal forebrain. Rab5 activity is also strongly influenced by AD causative and risk genes. A key piece of the mechanistic puzzle was the demonstration that hyperactivating rab5 directly in vivo in rab5 overexpressing transgenic mice causes BFCN degeneration, establishing rab5 as a therapeutic target for BFCN dysfunction [5].

The therapeutic potential of targeting the neurodegenerative process in BFCNs is underscored by the knowledge from animal studies that the apparent "degeneration" of BFCNs does not reflect cell death; rather, there is a loss of cholinergic phenotype, functional properties, and cell volume, all of which can be reversed with direct infusion of NGF to the basal forebrain [6]. That is, pharmacologically restoring NGF signaling has the potential to reverse disease progression. As the alpha isoform of p38 mitogen-activated-protein kinase (p38α) is a major regulator and activator of Rab5, it has been hypothesized that inhibition of p38α would be a pharmacological approach to restore NGF signaling and treat diseases associated with BFCN dysfunction [4]. Accordingly, an oral p38α kinase inhibitor, neflamapimod, has been studied preclinically in the DS mouse model and in a phase 2a clinical study in dementia with Lewy bodies [4, 5], a context where BFCN dysfunction and degeneration is considered to be the primary driver of disease expression and progression. Results from these studies are expected to be published in a peer-reviewed journal in the coming year.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

JJA is CEO of, and shareholder in EIP Pharma Inc., the company that is developing neflamapimod as a treatment for DLB. The other author declares no competing interests.

ADDITIONAL INFORMATION

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