PrPP PDK1
Targeting the PDK1 kinase to protect neurons from the toxicity of several unrelated amyloids

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Starting from prion diseases, we uncovered a neurodegenerative cascade that is common to prion and Alzheimer's (AD) diseases. Pathogenic prions (PrPSc) or neurotoxic beta-amyloid (Aβ) peptides of the Alzheimer trigger the overactivation of the 3-phosphoinositide-dependent kinase-1 (PDK1), which in turn promotes the phosphorylation and internalization of the α-secretase TACE (ADAM17). Internalized TACE is uncoupled from three main substrates (i) the normal cellular prion protein PrPC favoring the replication of PrPSc in prion diseases, (ii) the amyloid precursor protein APP enhancing the production of Aβ in AD, and (iii) TNFα receptors that accumulate at the plasma membrane and render diseased neurons highly sensitive to TNFα toxicity [1-2].
Deregulation of the PDK1-TACE pathway by PrPSc or Aβ originates from the interaction of PrPSc/Aβ with PrPC at the cell surface of neurons and corruption of PrPC protective signaling function [3].
We recently showed that PrPSc also corrupts the PrPC-PDK1-TACE-APP pathway at the root of Aβ accumulation within a prion-infected context. Accumulated Aβ does not impact on prion replication nor infectivity. Aβ, however, displays seedable properties as it can deposit and form Aβ plaques in the brain of prion-infected mice, but only when a seed of trimers of Aβ is co-transmitted with PrPSc. Importantly, brain Aβ deposition accelerates the death of prion-infected mice [4]. The inhibition of PDK1 is sufficient to target TACE back to the plasma membrane of prion-infected or Alzheimer's neurons, where it recovers its protective cleavage activity. This permits to rescue a normal sensitivity to TNFα, to lower the PrPSc and Aβ amyloid loads, and to limit the deposition of Aβ and formation of Aβ plaques.

Consequently, the inhibition of PDK1 counteracts motor deficits and prolongs the survival of prion-infected mice and reduces memory and cognitive impairments in AD mouse models. These results posit PDK1 as a therapeutic target to combat both prion and Alzheimer's diseases, which is also supported by a rise in PDK1 activity and reduced TACE α-secretase activity in the postmortem brain of AD subjects [1,2,4].

Beyond prion and Alzheimer's diseases, our current work indicates cross-disease implication of the PrPC-PDK1- TACE pathocascade in Parkinson's disease and the amyotrophic lateral sclerosis and defines PDK1 as a broad therapeutic target to fight against all these unrelated amyloid-based neurodegenerative diseases.

References:
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