Corruption of cellular prion protein signaling is at the cross-road of Alzheimer, Parkinson, prion diseases and Amyotrophic Lateral Sclerosis: identification of the kinase PDK1 as a broad therapeutic target to combat amyloid-based neurodegenerative diseases.

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Neurodegenerative diseases such as Alzheimer's (AD), prion (PrD), Parkinson's (PD) diseases and Amyotrophic Lateral Sclerosis (ALS) are characterized by the accumulation in the central nervous system of β-sheet enriched neurotoxic amyloid proteins: the amyloid-β peptides (Aβ) in AD, the scrapie prion protein (PrP^{Sc}) in PrD, the α-synuclein in PD, and mutant of superoxide dismutase 1 (SOD1) in some forms of ALS. The mechanisms by which these amyloid proteins accumulate in the brain and exert their toxicity still remain elusive. Even if these pathologies display distinct etiologies and clinical manifestations, it is more and more suspected that these diseases may share common pathocascades. With the perspective to design potent therapies to treat these disorders, the identification of those common neurodegenerative pathways represent an important biomedical challenge.

The laboratory revealed for the first time the occurence of common mechanisms of neurodegeneration between PrD and AD. Both PrP^{Sc} and Aβ interact with the normal cellular prion protein (Prp^{C}) at the plasma membrane of neurons, which corrupts PrP^{C} protective signaling function. Such a PrP^{Sc}/Aβ interaction with PrP^{C} notably impacts on PrP^{C} coupling to the 3-Phosphoinositide-Dependent protein Kinase-1 (PDK1), which overactivated, causes the internalization of TNFα converting enzyme (TACE α-secretase), thus neutralizing TACE neuroprotective cleavage activity (Pietri et al., 2013, Alleaume-Butaux et al., 2015).

Our current work extends the repertoire of amyloid proteins that corrupt the PrP^{C}-PDK1-TACE pathways by showing that pathological α-synuclein (PD) or $SOD1^{G93A}$ (ALS) also interact with PrP^{C} and provoke PDK1-mediated TACE impairment. Internalized TACE is uncoupled from one of its substrates, TNF-α receptors (TNFR), which accumulate at the neuron cell surface, rendering "Parkinson" or "ALS" neurons hypersensitive to TNF-α inflammatory stress, a strong component of these neurodegenerative diseases. The inhibition of PDK1 relocates TACE back to the plasma membrane where it recovers its neuroprotective cleavage activity, protecting "Parkinson" and "ALS" neurons from neuroinflammation. The protective effect of PDK1 inhibition is currently tested in PD and ALS mouse models.

This work supports the view that deregulation of the PrP^{C}-PDK1-TACE pathway is a trait of neurodegeneration common to several unrelated amyloid-based neurodegenerative diseases and posit PDK1 as a potential therapeutic target with broad spectrum to combat these diseases.

References :

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