Proteolytic Pathways in Parkinson Disease

A hallmark of Parkinson Disease (PD) is the presence in the brain of intracellular protein inclusions of α-synuclein termed Lewy bodies or Lewy neurites. Until a few years ago α-synuclein was thought to be an intracellular protein. More recently, it was demonstrated that α-synuclein is also a secreted protein and that, importantly, it can spread from cell-to-cell in a prion-like mechanism. However, the mechanisms that regulate the turnover of extracellular α-synuclein are unknown. In collaboration with Kostas Vekrellis’ Group at the Biomedical Research Foundation of the Academy of Athens, we showed that cell-secreted α-synuclein forms are resistant to direct proteolysis by kallikrein-related peptidase 6 (KLK6), an extracellular enzyme known to cleave recombinant α-synuclein efficiently. This differential susceptibility of the endogenous vs the recombinant α-synuclein to KLK6 proteolysis appears to be partially due to the association of naturally secreted α-synuclein with lipids. We also found that extracellular α-synuclein can be cleaved by KLK6 indirectly through activation of a secreted metalloprotease. These findings provide the first evidence that physiological modifications affect the biochemical behavior of secreted α-synuclein and that a proteolytic cascade may be involved in its catabolism (Ximerakis M, Pampalakis G et al. FASEB J 2014), thus, providing novel insights into mechanisms and potential targets for therapeutic intervention. Using our recently generated Klk6 knockout mice and established transgenic models for PD, we are currently investigating the role of KLK6 in the turnover of extracellular α-synuclein and α-synuclein fibrils and their propagation in vivo.

Schematic representation of differential proteolytic processing of recombinant and naturally secreted α-synuclein forms. The serine protease KLK6 cleaves recombinant α-synuclein (solid green line) but is unable to cleave cell-secreted α-synuclein. The catabolism of secreted α-synuclein could be mediated by a proteolytic activation cascade, in which KLK6, on its activation, activates an as yet unidentified metalloprotease, which in turn promotes the proteolysis of extracellular α-synuclein (dashed green arrows).

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