

P018 A Novel Role for Presenilins in NGF-signalling: Relevance to the Pathogenesis of Alzheimer's Disease.

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Presenilin's have long been established as playing a perfunctory role in the pathogenesis of Alzheimer's Disease, being critically involved in γ -secretase cleavage of APP. It's now emerging that presenilin-1 (PS1) is a multifunctional protein involved in many other cell signalling events, including cleavage of type I integral membrane proteins such as E-cadherin, Erb4 and more recently the Nerve Growth Factor receptor (NGFR).

We have identified a novel function for PS1 as a component of the NGFR-signalling complex whereby PS1 specifically interacts with the TNF receptor-associated factor 6 (TRAF-6) adapter protein. Within PS1 we have mapped residues involved in the PS1-TRAF-6 interactions and subsequent site directed mutagenesis of these two residues attenuates the interaction between PS1 and TRAF-6.

We have also demonstrated that PS1 is involved in cleaving the NGFR following ectodomain shedding, and thereby modulates signalling events arising from these receptors. Disruption of the PS1-TRAF-6 interaction had no proximal defects in γ -secretase processing of the NGFR. In addition to identifying a PS1-TRAF-6 interaction, we also show that in human 293T cells and rat PC12 cells, PS1 and TRAF-6 are recruited in an NGF dependent manner to the NGFR. This defines a novel role for presenilins in mediating NGFR signalling events.