

P016 A putative new role for Presenilin-1 in IL1R-signalling: linking IL1R signalling to Alzheimer's Disease

Baukje M. Elzinga, James C. Powell, Frances Harte,

Ciara Twomey, Justin V. McCarthy

Signal Transduction Laboratory, Dept Biochemistry, Biosciences Institute, University College Cork, Ireland

PS1 is a major catalytic component of the γ -secretase complex that plays a critical role in the cleavage of APP. Recently, γ -secretase has been shown to cleave other type 1 trans-membrane proteins such as Notch, CD44 and NGF receptor. Like NGF receptor, the Interleukin-1 Receptor 1 (IL1R1) is a type 1 trans-membrane receptor and couples to the same signalling pathways (NF- κ B and JNK/P38). Elevated levels of IL1R ligand (interleukin-1 β) in the brain have been associated with neurodegenerative diseases such as Alzheimer's disease. We investigated the involvement of PS1 in IL1R1 processing.

HEK293T cells were transiently transfected with DNA constructs encoding IL1R1, PS1 wild type or dominant negative PS1^{D257A/D385A}. IL1R/PS1-transfected cells were incubated with both the γ -secretase-inhibitor Compound E (CpdE) and with the phorbol ester PMA, a well-known inducer of ectodomain shedding of various receptors. We show that, upon PMA stimulation, the IL1R1 is proteolytically cleaved into a soluble ectodomain (47 kDa), which is secreted into the medium and a residual intracellular C-terminal fragment (CTF, 32 kDa). The CTF is subsequently processed by γ -secretase to generate an intracellular domain (ICD). The production of this ICD was inhibited by the γ -secretase-inhibitor and by expression of the dominant negative PS1^{D257A/D385A} mutant. In this study we show that PS1 affects the IL1R1 processing through its γ -secretase activity. This implies a novel role for PS1 in the IL1R1 signalling pathway.