

P017 Phosphorylation of Presenilin 1 regulate binding and turnover of beta-catenin.

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Presenilin 1 (PS1) is an essential component of the gamma-secretase-complex involved in the intramembrane cleavage of type I membrane proteins. In particular, processing of C-terminal stubs of beta-amyloid precursor protein leads to the formation of amyloid beta-peptide. Within the cytoplasmic loop domain of PS1, serines 353 and 357 have been identified as phosphorylation sites for glycogen-synthase-kinase-3-beta (GSK3beta).

We show that PS1 is phosphorylated at Ser353 and Ser357 in stably transfected Hek293 cells and by GSK3beta *in vitro*. We demonstrate that phosphorylation at these sites induces a structural change of the hydrophilic loop domain. This leads to a strong decrease in the binding to beta-catenin. Cells stably transfected with a Ser353/357Asp mutant, which mimics phosphorylated PS1, show a marked increase in the cytoplasmic pool of beta-catenin as compared to cells expressing PS1wt. Cells transfected with PS1 Ser353/357Asp have a decreased turnover of beta-catenin.

The interaction of beta-catenin and PS1 is regulated by GSK3beta-dependent phosphorylation of the large hydrophilic loop resulting in a structural change of this domain. The phosphorylation of both PS1 and beta-catenin by GSK3beta suggests a synergistic mechanism to regulate beta-catenin turnover and signalling.

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