

## **$\gamma$ -Secretase and Presenilins: Not Just for A $\beta$ and Alzheimer's Anymore**

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For most people, the presenilins are familiar from their roles in Alzheimer's disease (AD) pathogenesis. Not only are Presenilin 1 and 2 (PSEN1 and PSEN2) often mutated in patients with familial AD, but the role of presenilins as components of the  $\gamma$ -secretase proteolytic complex also makes them essential for the production of A $\beta$  peptides from APP. However, the biological roles of the presenilins extend well beyond APP processing. Evidence for a more extensive list of functions is seen in the fact that the PSEN1 knockout is embryonic lethal (Wong et al., 1997), while the phenotype of the APP null mouse is mild (Zheng et al., 1995).

As noted in the text,  $\gamma$ -secretase is a complex of four polypeptides with an aspartyl protease activity (Small, et al., 2010). The  $\gamma$ -secretase complex has the unusual property of working on membrane proteins and producing intramembranous cleavages in a select set of proteins (Hass, et al., 2009). There may be more than 90 type I integral membrane protein substrates of  $\gamma$ -secretase (Leo et al., 2011). There is no clear consensus sequence for cleavage and the example of APP indicates that  $\gamma$ -secretase cleavages can be imprecise, yielding multiple distinct fragments. There is nonetheless selectivity, which may be based on conformation of the transmembrane domain. The functional significance of  $\gamma$ -secretase cleavage is uncertain for many of these substrates, but known functions include signaling and regulation of protein functions. Several of these substrates are of particular interest.

The best-known  $\gamma$ -secretase substrates after APP are notch and its ligands, delta and jagged (Woo, et al., 2009). Notch is a four member gene family in humans that plays an important role in neurogenesis, neurite growth, and differentiation. Notch is also implicated in synaptic plasticity as well as learning and memory. Notch is subject to multiple regulatory

proteolytic events. The critical one is  $\gamma$ -secretase cleavage following ligand binding to release the notch intercellular cytoplasmic domain (NICD), which translocates to the nucleus and binds DNA to regulate transcription. The notch ligands Delta and Jagged are also substrates for  $\gamma$ -secretase (Lleo et al., 2011). The loss of notch signaling is considered to be a major barrier to the use of  $\gamma$ -secretase inhibitors for treatment of Alzheimer's. However, other substrates that may also present complications.

There are other receptors important for differentiation of cells in the nervous system that are processed by  $\gamma$ -secretase. Two receptors of particular interest are ErbB4 and some members of the Ephrin receptor family (Lleo et al., 2011). Both are receptor tyrosine kinases (see chapter 26) that play key roles in the nervous system. ErbB4 and its ligands, the neuregulins, are important for control of glial development and myelination (Newbern et al., 2010). The Eph/Ephrin pathway plays important roles in synaptic development and plasticity (Lai et al., 2009). Several Eph receptors (A4, B2 and B4) as well as some of their Ephrin ligands (B1, B2) can be processed by  $\gamma$ -secretase. As with APP and Notch, the action of  $\gamma$ -secretase on these receptors is to generate an intracellular cytoplasmic domain involved in signaling either to modulate transcription or through Rac1.

LDL receptor related proteins are particularly interesting substrates given the identification of ApoE4 as a major risk factor for late onset Alzheimer's disease (Bu, 2009). Several of the family members (LRP1, ApoER2, VLDL and megalin can be processed by  $\gamma$ -secretase (Lleo et al., 2011). Much like APP and Notch, cleavage of LRP1 gives rise to an intracellular cytoplasmic domain that can be translocated to the nucleus and affect transcription (Bu, 2009). LRP1 and ApoER2 also interact with APP, while ligand ApoE can bind A $\beta$ . The extent to which LDL receptor processing by  $\gamma$ -secretase contributes to AD pathology is a matter

of speculation at present.

Although these examples touch on only a fraction of the substrates cleaved by the presenilins and  $\gamma$ -secretase, they illustrate the complexities of presenilin biology in the brain. For example, some familial AD mutations of PSEN1 can differentially affect processing of some of substrates, but not others. Consistent with this, a recent report identified a  $\gamma$ -secretase activating protein (GSAP) that selectively enhances APP processing and A $\beta$  production without altering Notch processing (He et al., 2010). Before  $\gamma$ -secretase inhibitors can be used to treat AD, we need to understand the biology of these proteases. Such information may provide new strategies as well as imposing constraint on therapeutics.

### References

- Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer's disease: Pathways, pathogenesis and therapy. (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review). *Nature Reviews. Neuroscience*, *10*(5), 333–344. 10.1038/nrn2620.
- Hass, M. R., Sato, C., Kopan, R., & Zhao, G. (2009). Presenilin: RIP and beyond. (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review). *Seminars in Cell & Developmental Biology*, *20*(2), 201–210. 10.1016/j.semcdb.2008.11.014.
- He, G., Luo, W., Li, P., Remmers, C., Netzer, W. J., Hendrick, J., et al. (2010). Gamma-secretase activating protein is a therapeutic target for Alzheimer's disease. *Nature*, *467*(7311), 95–98. (doi: nature09325; pii: 10.1038/nature09325).
- Lai, K. O., & Ip, N. Y. (2009). Synapse development and plasticity: Roles of ephrin/Eph receptor signaling. (Research Support, Non-U.S. Gov't Review). *Current Opinion in Neurobiology*, *19*(3), 275–283. 10.1016/j.conb.2009.04.009.
- Lleo, A., & Saura, C. (2011).  $\gamma$ -secretase substrates and their implication for drug development

in Alzheimer's disease. *Current Topics in Medicinal Chemistry* (11) (in press).

Newbern, J., & Birchmeier, C. (2010). Nrg1/ErbB signaling networks in Schwann cell development and myelination. (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review). *Seminars in Cell & Developmental Biology*, 21(9), 922–928. 10.1016/j.semcdb.2010.08.008.

Small, D. H., Klaver, D. W., & Foa, L. (2010). Presenilins and the gamma-secretase: Still a complex problem. (Research Support, Non-U.S. Gov't Review). *Molecular Brain*, 3, 7. 10.1186/1756-6606-3-7.

Wong, P. C., Zheng, H., Chen, H., Becher, M. W., Sirinathsinghji, D. J., Trumbauer, M. E., et al. (1997). Presenilin 1 is required for Notch1 and Dll1 expression in the paraxial mesoderm. *Nature*, 387(6630), 288–292. 10.1038/387288a0.

Woo, H. N., Park, J. S., Gwon, A. R., Arumugam, T. V., & Jo, D. G. (2009). Alzheimer's disease and Notch signaling Research Support, Non-U.S. Gov't Review). *Biochemical and Biophysical Research Communications*, 390(4), 1093–1097. 10.1016/j.bbrc.2009.10.093.

Zheng, H., Jiang, M., Trumbauer, M. E., Sirinathsinghji, D. J., Hopkins, R., Smith, D. W., et al. (1995). beta-Amyloid precursor protein-deficient mice show reactive gliosis and decreased locomotor activity. *Cell*, 81(4), 525–531. (doi: 0092-8674(95)90073-X; pii).