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Neuropathology

Aph-1a is required for presenilin-dependent γ -secretase complex assembly and enzymatic activity in mammals.

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Recent studies indicate that Aph-1 along with Nicastrin and Pen-2 are essential components of the presenilin-dependent γ -secretase complex. Aph-1 has two mammalian homologues called Aph-1a and Aph-1b. To examine the *in vivo* function of *Aph-1a*, we generated *Aph-1a* knock out mice. The development of *Aph-1a* null embryos was dramatically retarded by embryonic day 9.5 as compared to littermate controls. *Aph-1a*^{-/-} embryos exhibited defects in patterning of somites and neural tube, distention of pericardial sac and abnormalities in vascular morphogenesis of the yolk sac. These defects observed in *Aph-1a*^{-/-} embryos resemble those of *Notch1* null or *Presenilin* null embryos. Moreover, secretion of A β peptides in immortalized *Aph-1a*^{-/-} fibroblasts were significantly reduced, accompanied by decreased levels of total and mature Nicastrin, PS1, as well as Pen-2 when compared to control cells. Our results establish that Aph-1a is necessary for assembly of γ -secretase complex and enzymatic activity in mammals.