

 NEURODEGENERATIVE DISEASE

# Inhibiting $\beta$ -secretase where it matters

$\beta$ -amyloid is a key peptide in the pathogenesis of Alzheimer's disease. Whether it is forming plaques or in soluble form,  $\beta$ -amyloid is thought to be responsible for the neurotoxicity and neurodegeneration that characterizes the disease. By cleaving  $\beta$ -amyloid precursor protein (APP),  $\beta$ -secretase is one of the main enzymes responsible for producing  $\beta$ -amyloid. The authors of a study published in *Science* show that a membrane-anchored version of a  $\beta$ -secretase inhibitor reduces the enzyme's activity more effectively than a free inhibitor both *in vitro* and *in vivo*.

Efforts to develop treatments for Alzheimer's disease have largely focused on decreasing the production of  $\beta$ -amyloid — by preventing

APP processing — or increasing  $\beta$ -amyloid degradation. Many of the  $\beta$ -secretase inhibitors that have been developed so far prevent APP from binding to the enzyme's active site, but neglect the fact that the main location of enzyme activity is in endosomes. This might explain the poor results obtained with some inhibitors in cellular assays.

Here, the authors coupled a sterol moiety, by solid-phase synthesis, to the carboxyl terminus of a  $\beta$ -secretase inhibitor to anchor the compound to cellular membranes and make it competent for endosome internalization. In cultured cells, this membrane-anchored inhibitor was up to five times more effective at inhibiting  $\beta$ -cleavage of APP than the free inhibitor. Interestingly, this increase in efficacy was not observed when the sterol group was linked to the amino terminus of the inhibitor, suggesting that the effect is orientation specific.

Fluorescent labelling experiments demonstrated that the sterol-linked inhibitor was endocytosed and accumulated in endosomes. Concentrations as low as 0.1  $\mu$ M were sufficient to block  $\beta$ -cleavage of APP, although an increase in  $\alpha$ -cleavage, which precludes the formation of toxic  $\beta$ -amyloid, was observed. This result indicates that the membrane-anchored inhibitor specifically targets  $\beta$ -secretase and that it does not inhibit APP processing by  $\alpha$ -secretase.

It has previously been shown that cholesterol- and sphingolipid-rich membrane domains, known as lipid rafts, are important sites of amyloidogenic APP cleavage. So, coupling the  $\beta$ -secretase inhibitor to a sterol anchor could have the added advantage of targeting the drug specifically to these sites. Indeed, when the inhibitor was coupled to other membrane anchors that have less affinity for lipid raft microdomains, such as oleyl or myristyl anchors, its activity was greatly reduced. This effect was attributed to an enhancement of the interaction between the compound and active  $\beta$ -secretase at these sites.

Finally, the authors showed that the sterol-linked inhibitor reduced  $\beta$ -amyloid toxicity and increased survival in a fly model of Alzheimer's disease and decreased  $\beta$ -amyloid production in a mouse model of the disease, highlighting the importance of targeting the inhibitor to the appropriate cellular compartment for therapeutic efficacy. As the authors suggest, this could be a useful strategy for developing drugs that target other proteins that are localized on particular membrane domains or intracellular compartments.

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**ORIGINAL RESEARCH PAPER** Rajendran, L. *et al.* Efficient inhibition of the Alzheimer's disease  $\beta$ -secretase by membrane targeting. *Science* **320**, 520–523 (2008)

