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news

Specific enzyme identified that snips APP into β-amyloid

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Researchers in Texas have discovered a novel mechanism by which enzyme action cleaves amyloid precursor protein (APP) to produce β-amyloid, the protein fragment responsible for the tangled plaques that are a major feature of Alzheimer's disease (AD). 'Understanding the biochemistry of this step in the disease process should enable us to discover ways of blocking the cleavage and therefore, perhaps, of treating AD', comments senior author Gang Yu (Center for Basic Neuroscience, University of Texas, Southwestern Medical Center, Dallas, TX, USA).

It was already known that the enzyme γ-secretase was responsible for APP cleavage but this large and complex molecule has many other functions in the cell and many of them are essential, therefore blocking the entire enzyme is not a feasible strategy. Yu's group has shown that one part of γ-secretase, nicrastin, is directly involved in β-amyloid production. 'Nicrastin has two functions: its ectodomain is a receptor that recognizes the short amino-terminal stubs generated by ectodomain cleavage of type I transmembrane proteins; its transmembrane region plays a role in assembling the γ-secretase complex', explains Yu. The ectodomain binds the new amino terminus that is generated upon proteolysis of the extracellular APP domain and the APP substrate is recruited into the γ-secretase complex [1].

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'This is an interesting study', comments Claudio Soto, Distinguished Professor of Neurology and Director of the Protein Misfolding Disorders Laboratory (University of Texas Medical Branch, Galveston, TX, USA). 'The findings reported are very exciting and open a whole new possibility for drug discovery in Alzheimer's disease', he says. He regards the article as also very important scientifically, because until now the role of nicastrin in the γ-secretase complex or how the substrates were recognized was not clear.

Yu further reports that it was possible, *in vitro*, to block the free amino terminus of APP. 'This addition of purified nicastrin ectodomain or mutations in the ectodomain, all markedly reduce the binding and cleavage of substrate by γ-secretase', he says. This evidence, he points out, suggests that designing or screening for compounds or antibody derivatives that specifically or preferentially block the binding of the N-terminus of γ-secretase-cleaved APP to the nicastrin ectodomain could prove to be a strategy that might lead to new drug therapies for AD.

'For drug discovery, if you want to block a protease, it is probably easier to target the active site of the enzyme, which in this case is most likely presinilin 1,' he adds. However, this approach is very likely to run into problems of specificity and side-effects, because the protease always has more than one substrate. Bart De Strooper (Center for Human Genetics, Leuven, Belgium) notes that the γ-secretase complex also cleaves at least 30 other type I membrane proteins, including Notch, a key signaling component during embryonic development. 'In the case of γ-secretase almost all inhibitors reported have tremendous side-effects due to the inhibition of the processing of other important substrates, such as Notch. So, if nicastrin is the receptor recognizing the substrates, it may be feasible to identify lead compounds exclusively targeting the cleavage of APP.' Nevertheless, concludes Soto, 'this will surely be a challenging task.'

References

1 Shah S. *et al.* (2005) Nicastrin functions as a secretase-substrate receptor. *Cell* 122, 435–447

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