Putting presenilins centre stage

Introduction to the Talking Point on the role of presenilin mutations in Alzheimer disease

Genetic analysis of autosomal dominant Alzheimer disease has identified the amyloid precursor protein (APP) and the presenilins as its pathogenic loci (Rogaeva, 2002). APP is normally cleaved by γ -secretase into the APP intracellular domain (AICD) and the 40-residue amyloid β peptide (A β 40) or, less frequently, the 42-residue A β 42. Analyses of blood plasma from mutation carriers shows that all of the pathogenic mutations cause an increase in the A β 42/A β 40 ratio, suggesting that they alter the position of the γ -secretase cleavage of APP (Scheuner *et al*, 1996; Haass & Selkoe, 1993). Gene-ablation studies and focused mutagenesis experiments by De Strooper, Wolfe and their colleagues (De Strooper *et al*, 1998; Wolfe *et al*, 1999) shows that the presenilins—along with other accessory proteins (Edbauer *et al*, 2003)—form the γ -secretase complex. This work is a good example of how genetic analysis can give direct mechanistic insight into the pathogenesis of an important disease. In the Talking Point in this issue of *EMBO reports*, De Strooper and Wolfe separately outline their views concerning the precise molecular details of the γ -secretase cleavage reaction and discuss the ways in which mutations might affect this process (De Strooper, 2007; Wolfe, 2007). In many ways, these papers make it clear how much we have learned about γ -secretase and intramembranous cleavage in general. In addition, they also clearly delineate what we do not know, and this clarity about the 'known unknowns' makes the articles particularly useful.

We do not know what these mutations do to the cleavage reaction. A consensus seems to be emerging that the mutant presenilins lead to slower acting γ -secretase, although why this should result in more A β 42 and less A β 40 is not clear; Wolfe and De Strooper discuss some alternatives. It is important to remember that their arguments concern the effect of mutations on the rate of cleavage per molecule of γ -secretase rather than the overall rate; clearly, presenilin hemizygosity would reduce the overall rate of cleavage but would not affect the rate of cleavage per molecule of γ -secretase. Understandable confusion over this important distinction has perhaps led to some of the controversy about the precise effects of the mutations (Fig 1). A full understanding of the effects of the mutations on the cleavage reaction awaits the difficult task of obtaining a high-resolution image of wild-type and mutant γ -secretase. Some limited progress has been made towards achieving this goal (Lazarov *et al*, 2006). γ -secretase cleavage has turned out to be considerably more complex than predicted, with the discovery of a multi-cut mechanism and many other important substrates besides APP, including Notch (Levitan & Greenwald, 1995). It is clear that detailed understanding of the

mechanism of the γ -secretase cleavage reaction will be important for cell biology in general, as well as for deciding exactly what strategy to take in modulating γ -secretase as a therapeutic target. One important gap in our knowledge concerns the molecular effects of presenilin mutations on, for example, Notch metabolism: do the mutations alter the cleavage site in the same way as they alter APP cleavage? This question is important both for our understanding of the basic biology of the process and for therapeutic reasons; however, we do not yet have the molecular tools to provide an answer. If they do alter the processing of Notch—and other substrates—is this important for Alzheimer pathogenesis, as some have suggested (Beglopoulos & Shen, 2006; Sambamurti *et al*, 2006)?

We have certainly come a long way in our quest to understand Alzheimer pathogenesis and this mission has yielded revelatory knowledge of regulated intramembranous cleavage. However, as with all genuine advances, more questions have been raised than answered. The articles by Wolfe and De Strooper constitute a high-level debate and update of these issues.

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