form an organizer. However, once the node is ablated, node gene expression is induced in these cells and a new node is formed[3]. Thus the node itself may be producing an inhibitor of node induction. Furthermore, in the periphery of the embryo, the ability to respond to the node-inducing signals is lower than in the centre. Joubin and Stern attribute the latter effect to the lateral expression of bone morphogenetic proteins (BMPs), more TGF-β-like molecules. The region of combined *BMP-2*, *BMP-4* and *BMP-7* expression forms a peripheral ring surrounding the node. Adding BMP-4 to a primitive-streak graft prevents the induction of *chordin*, a node marker[3], and a graft of the mid-primitive streak to the lateral area pellucida is able to induce *chordin* expression only when accompanied by cells expressing the BMP antagonist Noggin.

In the central domain of the chick embryo, another BMP-related molecule appears to have a similar function. Antidorsalizing morphogenetic protein (ADMP) is a BMP-related protein that is expressed in the *Xenopus* organizer but, contrary to the dorsalizing activity of organizer genes, exerts a ventralizing activity[11]. *ADMP* is expressed in the chick Hensen's node as well, and ADMP-expressing cells have an inhibitory activity in a node-induction assay[3]. So *ADMP* is a good candidate for mediating the negative feedback exerted by the node.

It is interesting that, in both the centre and the periphery of the chick embryo, a BMP-like protein acts to inhibit node induction. Vg1, a major activator of node genes, is also a TGF-β-related protein. It still needs to be resolved at what level these two signals interact. Other inhibitors may be at work too. Expression of *Frzb1*, a Wnt antagonist, has been detected in the organizer[12]; it is possible that, in parallel to ADMP, Frzb1 acts as an inhibitor of the Wnt signal.

Gastrulation is a highly complex developmental process in which massive and complex cell movements are coordinated with graded inductive signals to form the three germ layers. The organizer, orchestrating these molecular/cellular events, has been conserved through evolution, so that despite the highly divergent fertilization modes, egg structure and early developmental strategies found amongst vertebrates, the post-gastrula embryos converge to form a relatively similar embryonic morphology. Joubin and Stern's results[3] emphasize the synergistic requirement for Vg1 and Wnt signalling for induction of the organizer across vertebrate species. But the source of these signals and the modes in which the organizer is maintained appear to vary, pointing to the induction of the organizer as the point of convergence between these developmental programmes. Refining our molecular understanding of these processes, and further studies of other vertebrate embryos, will advance our ability to distinguish between the conserved and the group-specific aspects of this process. □

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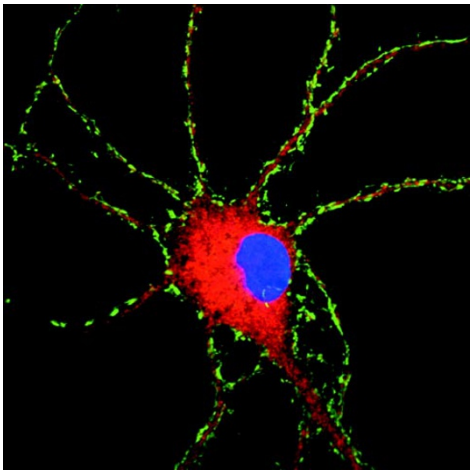
The case against presenilin-1



W. ANNAERT

Certain mutations in the *presenilin-1* gene cause the neurodegenerative disorder Alzheimer's disease. These same mutations also cause increased secretion from neurons of Aβ4(1–42), one form of the neurotoxic amyloid-β peptide (Aβ), which is probably the main contributor to the extracellular senile plaques characteristic of the brains of Alzheimer's patients. Presenilin-1 is clearly important in generating Aβ, but what exactly does it do?

Aβ is generated within neurons from a larger precursor, the amyloid precursor protein (APP), by a series of cleavage events. The cleavage enzymes have not been identified yet, but are known hypothetically as α-, β- and γ-secretase. Researchers have speculated that presenilin-1 might actually be the elusive γ-secretase, but a problem has been that presenilin-1 and APP seem to be found in different places within neurons. Annaert and colleagues (*J. Cell Biol.* **147,** 277–294; 1999) have now taken steps to tackle this question.

First, the authors showed that the active form of presenilin-1 is, as thought, located mainly in the early compartments of the secretory pathway — the endoplasmic reticulum (ER), the ER–Golgi intermediate compartment, and the early Golgi itself. But it isn't found in later compartments, as shown here — little overlap is seen between staining for presenilin-1 (red) and synaptobrevin-II (green), a marker of synaptic vesicles. (The nucleus is shown in blue.) Then, Annaert *et al.* showed that APP 'stubs', generated by the initial, α-/β-secretase-mediated cleavage, are found in the same compartments as presenilin-1. Finally, they made use of APP mutants that become stalled at different points in the secretory and internalization pathways. One APP mutant, for example, is trapped in the ER, and, in neurons that carry clinical mutations in presenilin-1, this mutant is processed to Aβ4(1–42) and secreted in higher quantities than the wild-type peptide.

Despite these results, it still isn't certain whether presenilin-1 is indeed γ-secretase. On the one hand, rather than being γ-secretase itself, presenilin-1 might instead control trafficking of APP or γ-secretase, and Annaert *et al.*'s results are compatible with this idea. But now we know that presenilin-1 and APP are found in the same places, the argument that presenilin-1 and γ-secretase are one and the same is certainly strengthened.

AMANDA TROMANS