

Marshall (21 Nov., p. 1393), a claim in the legal brief of John Madey is summarized as follows: "nuclear physicists on Duke [University's] faculty who are short of funds are scheming to 'take control of the MFEL [Medical Free Electron Laser] project and to remove Dr. Madey from his position of authority in order to facilitate their nuclear research plans.'" Madey's claim has no basis in fact. It was Madey who encouraged his colleagues at the Duke Free-Electron Laser Laboratory (DFELL) and nuclear physicists from Duke's faculty to work together in order to produce high-intensity gamma-ray beams through Compton backscattering of FEL photons from high-energy electrons using the facilities at the DFELL and using detection systems provided by the Duke faculty. Madey was part of the collaboration and helped spread the news of the first successful gamma-ray production at the DFELL around the world. He was a co-author of the article in *Physical Review Letters* (1) which reported this result.

Madey also encouraged his colleagues at the DFELL and nuclear physicists at the Triangle Universities Nuclear Laboratory (TUNL) to write a proposal with the aim of seeking funds from the Department of Energy (DOE) to support an upgrade of the existing electron storage ring and the existing

accelerator at the DFELL to make it possible to produce gamma-ray beams of higher energy than currently possible with the existing equipment. Such a proposal has recently been submitted to the DOE.

Madey, through his former Associate Director, requested that the TUNL physicists define the space needed in the planned new addition to the DFELL in order to carry out the proposed nuclear research program. Based on mutual agreement with Madey, a "gamma vault" was made part of the new building design.

The Duke University nuclear physicists conduct their research as part of TUNL's basic research program in nuclear physics. TUNL is jointly staffed by nuclear physicists from Duke University, the University of North Carolina at Chapel Hill, and North Carolina State University at Raleigh. The TUNL program has been well funded for more than 25 years by DOE and its predecessors; this funding was recently extended for 3 years at the requested level.

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References

1. V. N. Litvinenko *et al.*, *Phys. Rev. Lett.* **78**, 4569 (1997).

Presenilin Interactions and Alzheimer's Disease

In their article "Genetics of aging" (*Advances in Aging Research*, 17 Oct., p. 407), Caleb E. Finch and Rudolph E. Tanzi cite our observation that the protein β -catenin interacts with the protein presenilin 1 (PS1), as does δ -catenin, a novel member of the *Armadillo* gene family that is expressed specifically in nervous tissue (1). The interaction occurs through the hydrophilic loop region of the PS1 molecule. The most clearly identified roles for presenilin are in development (2) and in promoting the formation of A β peptide (3). Because mutations affect cleavage within the loop region of a presenilin molecule (4), interactions in this region may be critically important in determining the enhanced γ -secretase activity observed in the presence of such mutations.



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With the use of several independent approaches, different investigators have found that PS mutations increase γ -secretase cleavage of the amyloid precursor protein, and thereby increase the formation of the A β peptide, particularly A β 42. Although Finch and Tanzi have noted that interactions between β -catenin and PS may serve as a regulatory step in events preceding apoptosis, the possible link of this interaction to γ -secretase activity may represent a critical step in the pathogenesis of Alzheimer's disease.

Furthermore, β -catenin is a substrate for GSK-3 β , a kinase that is implicated in the pathological phosphorylation of τ protein as it undergoes transformation to a neurofibrillary tangle. Thus, A β formation and τ phosphorylation may both be linked to a common developmental signaling cascade which is initiated by the Wnt ligand. Finch and Tanzi cite the finding that premature aging is associated with attenuated wingless expression in the *Drosophila* antennae (5). Decreased Wnt expression may lead to enhanced GSK-3 β activity and decreased levels of β -catenin. If decreased Wnt expression also contributes to the age-related neurodegeneration of Alzheimer's disease, then β -catenin may serve as an intermediate in regulating the effects of PS on γ -secretase

activity. Destabilization of β -catenin resulting from a decreased Wnt signal may expose the PS loop to enhanced cleavage at a site which can activate γ -secretase. Altered expression of developmental genes in the mature nervous system may result in a gain-of-function, with pathological consequences that lead to age-related impairments.

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References

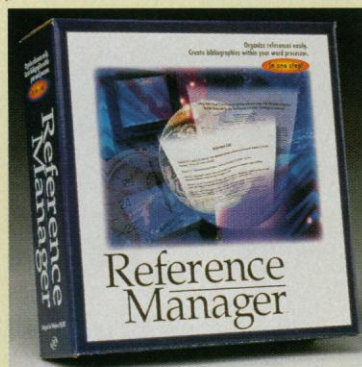
1. J. Zhou *et al.*, *Neuroreport* **8**, 2085 (1997).
2. P. C. Wong *et al.*, *Nature* **387**, 288 (1997); J. Shen *et al.*, *Cell* **89**, 629 (1997).
3. B. De Strooper *et al.*, *Soc. Neurosci. Abstr.* **23**, 117.3 (1997).
4. S. Froelich *et al.*, *Neuroreport* **7**, 297 (1995); T.-W. Kim, W. H. Pettingell, Y.-K. Jung, D. M. Kovacs, R. E. Tanzi, *Science* **277**, 373 (1997).
5. B. Rogina, S. Benzer, S. L. Helfand, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 6303 (1997).

Response: Increasingly, investigators are finding that presenilins are important in many systems and that they appear to mediate aspects of axial skeleton development (1) as well as the processing of the amyloid β pro-

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tein precursor (APP) (2). The large cytoplasmic loop of PS1, which contains the highest density of familial Alzheimer's disease mutations, was shown by Kosik and his colleagues (3) to interact with β -catenin and δ -catenin (in the central nervous system). β -catenin is known to play a role in the Wingless protein metabolic pathway, which can regulate proliferative or apoptotic signaling in response to the Wnt ligand (4). Because the Wingless pathway is mutually inhibitory with the Notch pathway (5), this interaction might help explain how the *Caenorhabditis elegans* presenilin homologue, SEL-12, facilitates the activity of the Notch receptor, LIN-12 (6).

The presenilins are also implicated in apoptosis as substrates for cleavage by caspases subsequent to cleavage by an unidentified enzyme termed "presenilinase" (2, 7). On the basis of these findings, we speculated in our article that interactions of catenins with PS1 may be adversely affected by caspase cleavage, thereby promoting apoptosis. Kosik now suggests that, conversely, the cleavage of PS1 may be influenced by its interaction with β - or δ -catenin and that, in turn, these events may influence the rates of generation of A β 42 from APP and the degree of hyperphosphorylation of τ . This intriguing hypothesis should stimulate heated experimentation.

More fuel may now be added to the fire in view of the recent isolation of the gene S2P, which encodes a zinc metalloprotease required for activation of the sterol regulatory element binding protein (SREBP) via cleavage in its first transmembrane domain (8). SREBP and APP are the only known proteins which undergo intramembrane proteolysis, and this presumably occurs in the endoplasmic reticulum (ER)-cis-Golgi, where the presenilins are localized (9, 10). Thus, Rawson *et al.* (8) suggested that S2P may also be the γ -secretase which cleaves APP to generate A β 42 (g-42). Cleavage of SREBP is regulated in response to cholesterol levels. This regulation is accomplished by a polytopic membrane protein called SREBP cleavage-activating protein (SCAP) which acts as a "sensor" molecule for sterol. Like presenilin, SCAP is predicted to contain eight transmembrane domains and is localized to the ER-cis-Golgi (10). In agreement with Kosik's proposal that protein-protein interactions of the presenilins may influence cleavage of the presenilins as well as γ -secretase cleavage of APP, the presenilins may, like SCAP, also serve as "sensor" molecules, but for the purpose of regulating γ -42 cleavage of APP (10) perhaps in response to catenins or other cellular factors. Indeed, γ -secretase (but not α - or β -secretase) activity is dramatically reduced in neurons taken from PS1 null mice embryos (11). These

data suggest the possibility, that gain-of-function introduced by FAD mutations may cause the presenilins to become more "permissive" for γ -42 cleavage of APP in the ER. If S2P actually is the γ -42 secretase for APP, cholesterol might also be expected to interact with the presenilins for the purpose of regulating γ -42 cleavage of APP and production of A β 42. This would then introduce a most intriguing pathogenic paradigm, because one isoform (APOE- ϵ 4) of apolipoprotein E, the primary transport molecule for cholesterol, is a major risk factor for late-onset Alzheimer's disease (12) and blood cholesterol is elevated in APOE- ϵ 4 carriers.

Alternatively, in accord with Kosik's proposal, the interaction of catenins with the presenilins may directly modulate the cleavage of APP by γ -42. Future experiments aimed at dissecting this fascinating set of potential protein-protein and protein-lipid interactions should greatly contribute to our understanding of the etiology of Alzheimer's disease.

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References

1. P. C. Wong *et al.*, *Nature* **387**, 288 (1997); J. Shen *et al.*, *Cell* **89**, 629 (1997).
2. T.-W. Kim and R. E. Tanzi, *Curr. Opin. Neurobiol.* **7**, 683 (1997).
3. J. Zhou *et al.*, *Neuroreport* **8**, 2085 (1997).
4. V. Korinek *et al.*, *Science* **275**, 1784 (1997); P. J. Morin *et al.*, *ibid.*, p. 1787.
5. J. D. Axelrod, K. Matsuno, S. Artavanis-Tsakonas, N. Perrimon, *ibid.*, **271**, 1826 (1996).
6. D. Levitan and I. Greenwald, *Nature* **377**, 351 (1995).
7. T.-W. Kim, W. H. Pettingell, Y.-K. Jung, D. M. Kovacs, R. E. Tanzi, *Science* **277**, 373 (1997).
8. R. B. Rawson *et al.*, *Mol. Cell* **1**, 47 (1997).
9. D. G. Cook *et al.*, *Nature Med.* **3**, 1021 (1997); T. Hartmann *et al.*, *ibid.*, p. 1016; D. M. Kovacs *et al.*, *ibid.*, **2**, 224 (1996).
10. M. S. Brown and J. L. Goldstein, *Cell* **89**, 331 (1997).
11. B. De Strooper *et al.*, *Soc. Neurosci. Abstr.* **23**, 117.3 (1997).
12. E. H. Corder *et al.*, *Science* **261**, 921 (1993).

Corrections and Clarifications

■ In the Table of Contents of 9 January (p. 147), the order of appearance of the technical comments and their Web addresses was reversed. Thus, "Paleosols and Devonian forests" is located on the Web at www.sciencemag.org/cgi/content/full/279/5348/151a, and "Nucleotide sequence: correction" is located at www.sciencemag.org/cgi/content/full/279/5348/151b



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