Do mutated presenilin genes cause Alzheimer's?

Because Alzheimer's is such a complex disease, it has been very difficult to devise molecular strategies for drug discovery. Most of the discovery efforts so far have focused on developing CNS drugs that selectively modulate neurotransmitters known to improve cognitive function. Attacking the disease at its root has been difficult, because a firm biochemical or genetic lead for the cause of the disease has remained elusive. However, this situation is rapidly changing.

Just last year, the presenilins, a new gene family thought to be associated with early-onset familial Alzheimer's disease, were discovered [*Nature* (1995) 375, 754–760; *Science* (1995) 269, 973–977]. In a recent paper, D. Scheuner at Case Western Reserve University (Cleveland, OH, USA) and a large consortium of researchers from both academia and industry have linked the mutated presenilin genes to the pathology of the disease. They report that the mutant genes cause the overproduction of an altered form of amyloid β-protein, which makes up the amyloid senile plaques in the brains of those afflicted with Alzheimer's [*Nat. Med.* (1996) 2, 864–870]. Such plaques in brain cells are associated with all forms of Alzheimer's disease, and are believed to be one of the early causative events in the development of the disease.

In the normal brain amyloid precursor protein is processed to generate an amyloid β-protein containing 40 amino acids (Aβ-40), but in Alzheimer's patients there is an abundance of an amyloid β-protein containing 42 residues (Aβ-42). The recent investigation found that plasma from subjects with the mutated presenilin genes contains high concentrations of the Aβ-42 protein, whereas only small amounts of this form of the amyloid protein is found in subjects with the wild-type presenilin genes. Elevated levels of the Aβ-42 protein were also present in media from fibroblast cell lines with the mutant presenilin genes.

The Aβ-42 protein is much more susceptible to aggregation than its Aβ-40 counterpart. Scheuner and colleagues propose that the mutated genes promote the formation of the Alzheimer's senile plaques by causing the overproduction of the Aβ-42 amyloid protein, which then spontaneously aggregates and forms plaques. They go on to propose that it is either the senile plaques themselves or a soluble protein aggregate containing the Aβ-42 amyloid protein that is the trigger for Alzheimer's disease.

The mechanism by which the presenilin gene family coaxes the overproduction of the Aβ-42 protein remains to be determined. The current evidence suggests that the presenilin proteins are involved in intracellular trafficking of membrane vesicles. The suggestion is made that their mutant cousins may cause a subtle alteration of the presentation of the amyloid precursor protein to its cleavage enzyme during membrane processing, resulting in the formation of Aβ-42 instead of the normal protein.

Undoubtedly, extensive biochemical detective work is under way to confirm or deny this hypothesis. If it turns out to be correct, the door may be opened to a rational approach for drug discovery. A membrane-active drug that would restore the normal cleavage pattern of the amyloid precursor protein might be very useful to treat those who have the mutant pre-senilin gene and are showing signs of elevated plasma Aβ-42, a possible early sign of Alzheimer's disease.

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Intellectual property rights in biotechnology

The role of patents in the development of biotechnology is the subject of a recent report [*Exp. Opin. Ther. Patents* (1996) 6(9), 845–854] by Sandy M. Thomas of the University of Sussex. The article is divided into two sections: the first addresses legal development relating to biotechnology patents in the United States, illustrating how the US has shaped worldwide patent policy; the second section discusses quantitative patent data, suggesting that while the number of patents may not correlate directly with commercial success, companies are under increasing pressure to secure them, particularly in information-intensive areas of biotechnology.

With biopharmaceutical products coming onto the market in ever-growing numbers, companies are under increasing pressure to obtain patents on their inventions. Yet

