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.

Robert W. Wallace

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

the report includes recent data by Sharp and coworkers showing an overall lack of correlation between the number of US patents and competitive advantage. For example, Roche ranks first in R&D expenditure as a percentage of sales, is in the top five in number of US patents (1990–1994), but had only one top selling brand in 1993.

By contrast, the Sharp study puts Glaxo in the 11th place in terms of R&D expenditure as a percentage of sales, with less than half the number of patents Roche owns, and yet it ties with Merck in producing six top-selling drugs in 1993.

Potential of Human Genome project

Part of the pressure to patent stems from the promise of the Human Genome Project, which is expected to generate about 100,000 genes by the year 2000. Pharmaceutical and biotech companies consider patenting to be critical in using the human genome to develop new therapeutic and diagnostic products; Thomas points out that about three quarters of patented human DNA sequences have been granted to industry, compared with about 17% granted to public institutions [S. Thomas *et al. Nature* (1996) 380, 387–388].

Surprisingly, that study also shows that about half the world total of human DNA patents have been issued by the European Patent Office, and of these, 70% belong to the US or Japan; and more than 80% of European patents are company-owned. By contrast, a mere 16% of human DNA patents have been granted by the US Patent Office; the result of a backlog of applications in the US, Thomas suggests.

Information-intensive research

Another reason for the increasing pressure is the development of information-intensive types of research found in the newer areas of biotech, such as genomics, gene therapy and combinato-rial chemistry. Genomics companies, for example, generate thousands of cDNA sequences when using the 'expressed-sequence-tag' method to screen for abnormal gene expression. Because of the number of sequences generated, genomics companies have filed for patents containing hundreds of cDNA sequences expressed in particular tissues. For example, two firms, Human Genome Sciences and Incyte have filed for US patents containing hundreds of sequences from disease-specific libraries. By comparison, Thomas notes, human DNA sequence patents have on average contained about three sequences per patent over the past ten years.

Forging alliances for exclusivity

Large corporations, particularly European multinationals, have formed an increasing number of alliances with genomics companies in recent years in an attempt to gain exclusivity over genomic information. In the first half of 1995, multinationals concluded agreements with genomics firms worth over $400 million, Thomas notes. The $125 million alliance with Human Genome Sciences resulted in 125 of SB's 452 patent filings between 1992 and 1995.

Conclusion

Europe continues to lag behind the US in attracting R&D investment and developing new markets, and Thomas calls for a harmonized EU patent directive, a European 'grace period' like that found in the US, although he points out that the US 'first-to-invent' principle puts small biotech firms at a disadvantage.

The full article, 'Intellectual property rights in biotechnology' (ISSN 1354-3776) includes five tables with information on ownership of human DNA sequence patents worldwide, top companies in terms of R&D expenditure, public and private sector organizations ranked by patent ownership, classification of human gene patents and predicted US sales of biotech-related drugs in 2003. The report is published by Ashley Publications, 1st Floor, The Library, 1 Shepherds Hill, Highgate, London, UK N6 5QJ. Tel: +44 181 347 5030; fax: +44 181 347 5040, www:http://biomednet.com/ashley/ashley.htm.

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