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Orphan amyloid diseases

Alzheimer's disease (AD) is thought to affect ~10% of people over the age of 65 and ~50% of people over 85. It is not the only disease that involves the abnormal deposition of proteins into structures known as amyloid (meaning starch-like) plaques. However, we rarely hear about the 17 or so other diseases that are recognized as involving amyloid. Why not? Most likely because those diseases affect fewer people (hence the designation 'orphan') and are, consequently, much less attractive to the biotechnology and pharmaceutical research industry, which has focused a major effort on the more highly populated AD market in recent years.

Amyloid fibrils are formed by proteins that are primarily β-sheet in structure, and thus the various amyloid diseases are likely have some basic similarities. Nevertheless, it is not widely appreciated that a large variety of different proteins — including lysozyme, immunoglobulin proteins, the amyloid-β protein and transthyretin (TTR) — can cause problems in many different parts of the body, and therefore that the specific details of each disease are likely to be somewhat different. It is hoped that research on AD may prove useful for developing therapies against all of the other amyloid diseases, but this may not universally prove to be the case. The paper on page 312 of this issue of *Nature Structural Biology* highlights some of the orphan amyloid diseases — ones that are caused by abnormal deposition of the protein TTR.

TTR is named for its function: it is a backup transporter (trans) for the hormone thyroxine (thy), and it is the primary transporter of the retinol binding protein (ret). TTR forms a tetramer, which can bind thyroxine, and thyroxine stabilizes tetramer formation. The monomeric form of TTR, rich in β-sheet, forms amyloid fibrils, and the diseases known as senile systemic amyloidosis (SSA) and familial amyloid polyneuropathy (FAP) involve TTR amyloid deposition in various tissues[1–3].

FAP can be caused by mutations in TTR that destabilize the tetramer, resulting in a higher concentration of fibril-forming monomers. However, even wild type TTR can be problematic; SSA appears to result from deposition of TTR mainly in the hearts of elderly patients. It is interesting to note that TTR deposits are usually not found in the brain — only in the heart and the peripheral nervous system. This is probably because TTR is the major carrier of thyroxine in the cerebral spinal fluid, where thyroxine-mediated stabilization of the tetramer likely results in a lower concentration of monomeric TTR, and hence less fibril formation in the brain. In contrast, in blood plasma, where the major thyroxine carrier is thyroxine-binding globulin, TTR is often devoid of thyroxine, and dissociation to fibril-forming monomers is probably more common. It has been proposed that small molecules that stabilize the TTR tetramer but lack the hormonal effects of thyroxine may prove to be useful drugs for treating FAP and SSA, and the paper on page 312 addresses this possibility.

SSA, which is associated with wild type TTR, mainly affects the elderly, whereas FAP, which is associated with mutations in TTR, can begin earlier in life, in the 30s or 40s. FAP has been most commonly observed in Portugal and Sweden, where mutations in the TTR gene were

first identified in the 1980s. There have also been recent suggestions that TTR mutations may be fairly prevalent in African Americans, affecting ~4% of that population[4]. This prevalence suggests that TTR amyloid deposition could be a more widespread problem than previously thought; in fact it could be the unrecognized cause of many cardiac troubles.

FAP is notable for its highly variable penetrance and clinical expression, an indication of as yet unidentified additional genetic factors in TTR-mediated disease. In many cases, nerves and vessels in the extremities are first affected, with symptoms including numbness, lack of feeling in the toes and fingers, burning sensations, leg weakness, and bruising of the face as the result of protein deposition around fragile blood vessels. Later, the nerves that affect the gastrointestinal tract and blood pressure regulation may be affected, and cardiomyopathy may occur. FAP can result in death within 10 years of diagnosis.

There is a treatment for patients with TTR-associated FAP, but it is a fairly drastic one: a liver transplant. Since TTR is mainly produced by the liver, transplanting an organ containing a wild type TTR gene should, in theory, prevent or slow progression of FAP. The first liver transplant to treat FAP occurred in Sweden in 1990, and since then many such transplants have been performed, with a good degree of success[5]. In many cases, patients saw not only a halt in disease progression, but also some degree of amyloid clearance and some abatement of disease symptoms after the transplant. These results suggest that clearance of TTR amyloid can occur, and consequently, that perhaps an effective drug would only have to slow fibril formation just enough to allow the rate of clearance to overtake the rate of deposition.

Despite the fact that FAP, SSA, and AD all involve amyloid deposition, it is clear that the TTR-based amyloid diseases differ from AD in many important details. AD primarily affects the brain and is associated with a different protein, amyloid-β, which is a proteolytic cleavage product of the amyloid precursor protein (APP). Although it is widely thought that amyloid deposition may be the primary event in AD, this has not been strictly shown, and there have been no treatments that lead to the clearance of amyloid deposition and improvement of the disease symptoms to support this causal hypothesis. Nevertheless, much circumstantial evidence, including genetic mutations that lead to an increase in amyloid-β accumulation, supports amyloid deposition as the cause of AD. Thus, much research has concentrated on preventing amyloid-β deposition in the brain, including developing drugs to inhibit the proteins (known as secretases) that cleave APP into the fibril-forming amyloid-β fragment.

Since the AD research is highly focused on the details of amyloid-β processing and deposition, the results may not directly help with the development of therapies for other amyloid diseases, such as those caused by TTR. Instead, therapies targeted toward the specific processing and deposition mechanisms of the other amyloid-forming proteins may be needed. In other words, although the overall goal of preventing amyloid deposition or accelerating amyloid clearance may be the same in the treatment of all amyloid diseases, the means of achieving those goals may be quite different in each case.

A recent industry financial report by Stephen Scala of SGCowen Securities, dated February 16, 2000, estimates that the current AD market (~15 million people worldwide) is ~$1.1 billion and could be $2.4 billion by 2003. So, it is not surprising that many of the big names in the pharmaceutical industry — such as Bristol-Myers Squibb, Eli Lilly, Glaxo Wellcome, Johnson & Johnson, Merck, Pfizer and Schering-Plough — have invested in AD research. We can hope that the millions of dollars pouring into AD research will also aid and encourage work on the less well known amyloid diseases. Their markets may be smaller, in terms of the financial bottom line, but they are just as large in terms of devastation to the individual.

1. Koo, E.H., Lansbury, P.T. Jr. & Kelly, J.W. *Proc. Natl. Acad. Sci. USA* **96**, 9989–9990 (1999).
2. Kelly, J.W. *Curr. Opin. Struct. Biol.* **8**, 101–106 (1998).
3. Miroy, G.J. *et al. Proc. Natl. Acad. Sci. USA* **93**, 15051–15056 (1996).
4. Jacobson, D.R. *et al. N. Engl. J. Med.* **336**, 466–473 (1997).
5. Coelho, T. *Curr. Opin. Neurol.* **9**, 355–359 (1996).