Alzheimer disease

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genes, which affect antigen processing and presentation. It is therefore appropriate that such genes are usually inherited as a coordinated set, given that both class I and class II gene products, many of which are encoded in the MHC, play on the same pool of T cell receptors.

Incidentally, many other regions of the genome also appear to be in linkage disequilibrium, indicating that subtle epistatic effects at linked loci may be widespread. The order of genes in the human genome appears to us fairly random, but this may be illusory. New gene pairings are forged and subjected to selection as species are formed, and pairing of genes in different species may be advantageous rather than simply fortuitous.

We may be beginning to understand how DR2a keeps the DR2b rottweiler in check and how obedience training of T cells by exposure to antigen may be beneficial. But how, in treating multiple sclerosis, do we throw the aggressive DR2b dog a juicy bone? Strategies designed to target and eliminate specific T cells might provide a lead.

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Alzheimer disease: presenilin springs a leak

Sam Gandy, Mark K Doeven & Bert Poolman

Presenilins are thought to contribute to Alzheimer disease through a protein cleavage reaction that produces neurotoxic amyloid-β peptides. A new function for presenilins now comes to light—controlling the leakage of calcium out of the endoplasmic reticulum. Is this a serious challenge to the 'amyloid hypothesis' of Alzheimer disease?

Several proteins are believed to be essential for the pathology of Alzheimer disease. Two of these proteins—presenilins—are involved in a cleavage reaction that generates key protein fragments, known collectively as amyloid-β peptides. According to this "amyloid hypothesis"[1], the clumping in the brain of one especially sticky form of amyloid-β peptide, amyloid-β42, is thought to define the final common pathway toward all forms of Alzheimer disease.

These molecular events have been recognized for years, but now a twist emerges. In a recent issue of *Cell*, Tu *et al.*[2] challenge the prevailing view of presenilin biology. They provide evidence that presenilins, in addition to their cleavage function, also form ion channels responsible for a normal trickle of calcium—known as the 'calcium leak current'—out of a storage depot in the endoplasmic reticulum and into the cytoplasm.

It's not clear whether alterations in calcium handling contribute to the pathology of the disease, although the new findings are in sync with previous studies hinting that this could be the case[3,4]. Also unclear is the relationship of altered calcium handling to the biology or pathology of amyloid-β. But the new findings should provoke a flurry of follow-on experiments evaluating whether or not the calcium leak data fit into the amyloid hypothesis.

Presenilin-1 and presenilin-2 are highly homologous, polytopic membrane proteins that were discovered about ten years ago through standard positional cloning strategies aimed at identifying the genetic bases of the most common forms of early-onset familial Alzheimer disease[1,5]. Each presenilin was later found to form a protein-conducting pore, lined by the active site of the proteolytic activity that generates the C termini of amyloid-β peptides, an activity informally known as 'γ-secretase'.

Cleverly, order is maintained between the secretase function of presenilin and its apparent role in calcium handling: it is the endoplasmic reticulum–localized, unprocessed zymogen form of presenilin that acts as a calcium channel. The protease function of presenilin is only revealed in later compartments (such as the *trans*-Golgi network, endosome and plasma membrane) after the assembly of N- and C-terminal presenilin fragments together with three essential partners (nicastrin, Aph1 and Pen2) necessary to form the minimal functional γ-secretase (**Fig. 1**) (refs. 1,5).

Dual-function pores conducting both proteins and ions are not unprecedented, as such activities were characterized in the early 1990s by Simon and Blobel[6]. This is the first time, however, that presenilins have been formally proposed to play roles in both protein processing and ion conductance. It is also true that membrane proteins have in the past been artifactually identified as ion channels when, in fact, their main physiological function is the transport of some other substance (for example, the misidentification of P-glycoprotein as a chloride channel[7]).

Tu *et al.*[2] suggest that pathogenic missense mutations in the presenilin-1 gene cause loss of the normal endoplasmic reticulum calcium leak current, so that endoplasmic reticulum calcium levels are elevated in the resting state whereas cytosolic levels are normal or even low. Then, when cells are exposed to some stimulus that causes endoplasmic reticulum calcium channels to open, those excess endoplasmic reticulum calcium stores are disgorged into the cytosol. Excessive cytosolic calcium is a well-known mediator of neuronal death, as has long been appreciated in studies of excitotoxicity.

The authors also examine a mutant presenilin informally known as PS1Δ9 because it lacks the ninth exon. They report that this channel leaks calcium out of the endoplasmic reticulum to an excessive extent under basal conditions. PS1Δ9 is unusual in some other respects as well: it is active as a protease without being cleaved into N- and C-terminal fragments (NTF and CTF), and patients with this mutant protein have especially large deposits of amyloid-β (ref.

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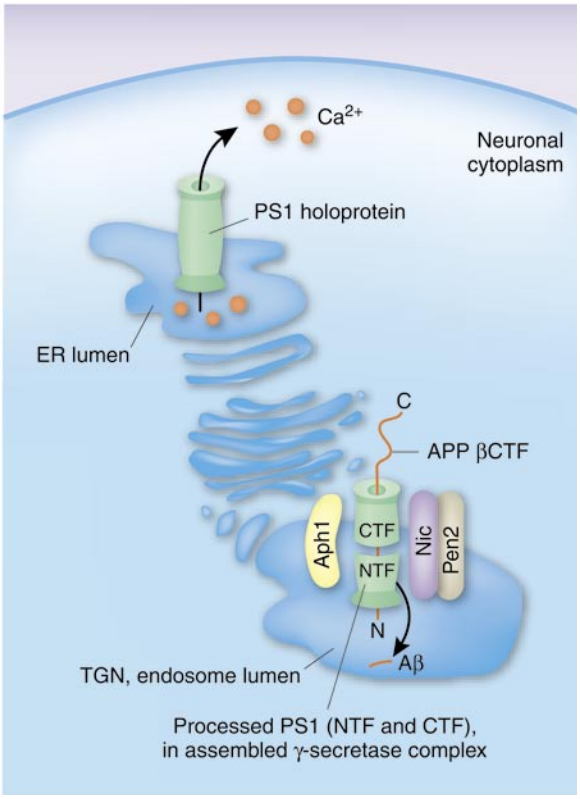

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Figure 1 Calcium, amyloid-β, presenilin and Alzheimer disease. Presenilin holoproteins modulate calcium leakage from the endoplasmic reticulum (ER), whereas their cleaved derivatives (PS1 NTF for presenilin N-terminal fragment; CTF for C-terminal fragment) assemble with partners (Aph1, Pen2, and nicastrin (Nic)) to form the functional protease complex (γ-secretase), which is concentrated in the *trans*-Golgi network (TGN) and endocytic system. γ-Secretase cuts β-cleaved C-terminal fragments (βCTFs) of the amyloid precursor protein (APP), releasing amyloid-β peptide (Aβ), indicated in orange. Aβ is initially localized in the TGN lumen (dark blue), endosome lumen (dark blue) or both, but is rapidly released from the cell through the constitutive secretory pathway.

8) that were nicknamed "monster plaques"[8]. In culture, PS1Δ9 generates an especially high ratio of amyloid-β42 to amyloid-β40, but this may be due to a deficiency in the generation of amyloid-β40 (ref. 9).

Calcium is no newcomer to the study of Alzheimer pathogenesis or of presenilin action. In the mid-1980s, Gibson and Shelanski independently reported disturbances in calcium metabolism in fibroblasts cultured from biopsies of the skin from patients with Alzheimer disease, including (but not confined to) patients with presenilin mutations[3]. The signal-transduction abnormalities in these skin cells seemed to be attributable to some poorly understood disturbance of calcium homeostasis, leading to the proposal of the "calcium hypothesis of Alzheimer disease"[10]. In the mid-1990s, several groups studied some of these same fibroblasts and found changes in amyloid-β in their conditioned media[11,12].

Meanwhile, a substantial literature has accumulated over the past decade indicating a link between presenilins and calcium. More than 100 papers from six separate laboratories[4] link presenilins to some role in calcium homeostasis. Clearly, the Tu *et al.* claim that presenilins direct most calcium leak current is cause for reflection.

Assuming that the results are confirmed, one question has the greatest clinical significance: which phenomenon is more important for pathology, calcium or amyloid-β? (**Fig. 2**). Conceivably, disturbed endoplasmic reticulum calcium leakage and aberrant amyloid-β metabolism might be tightly linked.

Is accurate γ-cleavage required for proper endoplasmic reticulum calcium leakage? This seems unlikely, because Oh and Turner were unable to demonstrate any alterations in intracellular calcium stores after pharmacological inhibition of γ-secretase function[13]. Alternatively, can calcium control amyloid-β metabolism? Here the answer is clearly "yes."

Calcium perturbation has been shown to dynamically modulate amyloid-β release, in both positive and negative directions[4,14]. Perhaps abnormal endoplasmic reticulum calcium leakage sets up a cytoplasmic signal transduction environment that enhances amyloid-β release. Normally, one important source of cytoplasmic calcium in neurons is its entrance through voltage-gated calcium channels after electrical depolarization. Because neurotransmission and depolarization regulate physiological amyloid-β release[5,14], one can easily imagine that pathological increases in cytoplasmic calcium could do the same.

An extensive clinicopathological and biochemical correlation study of mutant presenilin phenotypes could help resolve whether calcium or amyloid-β is more important for the pathogenesis of Alzheimer disease. Although over 100 pathogenic mutations in the presenilins have been identified, relatively few of them have been studied in detail. Abnormalities in amyloid-β42/amyloid-β40 ratios associated with presenilin mutations are barely detectable in some cases, and in at least one family, a mutant presenilin incapable of generating amyloid-β can apparently cause familial Alzheimer disease[8].

In contrast (and also surprisingly), a few families with hereditary dementia and presenilin mutations have recently been reported to be entirely devoid of amyloid-β pathology[15]. The presence of presenilin mutations, familial dementia and an apparent amyloid-β–independent neuropathological phenotype may incriminate calcium and exculpate amyloid-β in the pathophysiology of at least some mutant presenilin disease.

Nonetheless, when formulating a global definition for Alzheimer disease, one must keep in mind that primary endoplasmic reticulum calcium leak failure is clearly not necessary to cause Alzheimer disease. The first pathogenic mutations discovered to cause amyloid-β pathology were found not in presenilins but in the amyloid precursor protein[1,5]. These mutations are localized within or around the amyloid-β domain, and they are sufficient to cause the complete clinical and pathological picture of Alzheimer disease. Notably, however, extracellular amyloid-β oligomers can apparently induce cytoplasmic calcium disturbances[16]. Perhaps particular patterns of calcium dysregulation and amyloid-β mismetabolism set up a vicious cycle in which toxicity from each provokes higher levels of the other.

Another question raised by the data of Tu *et al.* is whether the newly described endoplasmic reticulum calcium leak dysfunction can provide a parsimonious explanation for all the reported aberrancies in calcium metabolism attributed to presenilin mutations[4]. The answer here is, "No, at least not obviously." Fingering presenilin as an endoplasmic reticulum calcium leak channel does not immediately bring clarity to the existing literature on presenilin and calcium.

In the final analysis, clinical trials will be required to resolve the most critical issue—that is, whether calcium handling or amyloid-β is the better therapeutic opportunity in common, so-called 'sporadic' forms of Alzheimer disease. Perhaps we will need to target both to arrest the disease completely.

To date, the experience with Alzheimer therapeutic trials aimed at calcium has been limited to compounds that block L-type voltage-dependent calcium channels.

These drugs were apparently ineffective, but perhaps other calcium-modulating compounds, specifically targeting endoplasmic reticulum pools of calcium, would yield a more favorable outcome. In light of the fresh insights from Tu *et al.*, the good news is that we already know a great deal about calcium pharmacology—enough to give us a substantial head start if, indeed, the "calcium hypothesis of Alzheimer's"[10] is back to stay.

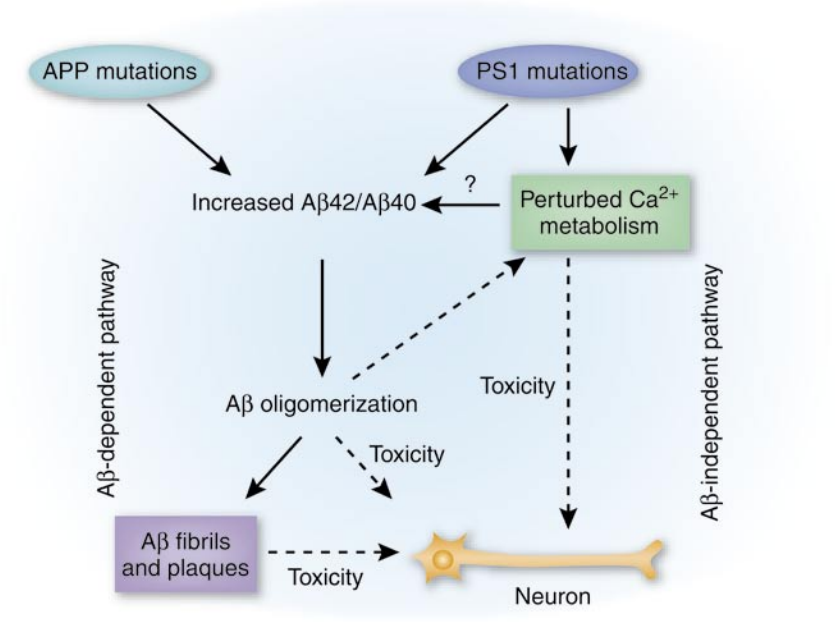

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Figure 2 Potential steps leading from familial Alzheimer mutations (APP mutations, PS1 mutations) to neurotoxicity and neurodegeneration, via either Aβ-dependent (left) or Aβ-independent (right) pathways. Proximate mediators of toxicity (Aβ oligomers, calcium) are connected to the cartoon neuron using dashed arrows.

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Alzheimer disease: BACE1 branches out

An enzyme that helps generate clumps of amyloid-β in the brains of people with Alzheimer disease also has a role in myelinating axons, according to a study in *Science* (doi: 10.1126/science.1132341). The findings sound a cautionary note for ongoing efforts to develop drugs to inactivate this enzyme.

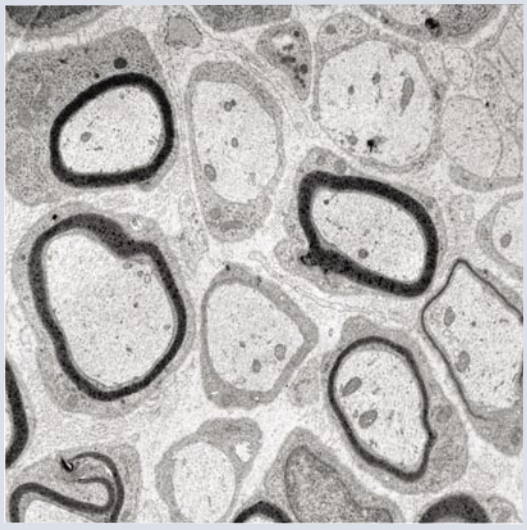
The enzyme, BACE1 (beta-site amyloid precursor protein–cleaving enzyme 1), is required to cleave amyloid-β from a larger precursor. (After BACE1-mediated cleavage, the presenilin-containing complex γ-secretase makes the final cleavage, liberating amyloid-β.)

Michael Willem *et al.* found that BACE1 seems to be required for processing a signal, the EGF-like factor neuregulin 1,that activates receptors on Schwann cells. Activation of these receptors is required for myelination.

One observation supporting this hypothesis was that animals deficient in BACE-1 had myelin defects in the peripheral nerves. Shown is a cross-section of the sciatic nerve of an 8-day-old BACE1-deficient mouse; myelin sheath in black. The myelin is thinner than in wild-type mice and some axons lack myelin altogether.

Peripheral nerve myelination occurs early in life, so it is unclear how BACE1 inhibition might affect older animals. Whether BACE1 also has a role in myelination of the central nervous system is also unclear.

—Charlotte Schubert



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