Learning from the Failure of Alzheimer’s disease clinical trials: Is the amyloid hypothesis discredited?

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The latest estimates identify 5.4 million Americans as victims of Alzheimer’s disease (AD), and the percentage of people dying of this serious scourge has increased by an astounding 66% between 2000 and 2008 whereas other serious illnesses such as stroke, HIV-AIDS and cardiovascular disease have declined substantially [1]. This highlights the lack of approaches to prevent, slow and treat AD. In the meantime, investigators have formulated numerous drugs to treat AD that were based on neuroprotection and on the basis of the amyloid hypothesis [2-7]. Many of these treatments were also successfully tested in animal models of AD that express familial AD (FAD) mutant forms of the human β amyloid protein (Aβ) precursor (APP) [7]. Unfortunately, most of these studies have failed to show clinical improvement or protection in AD patients. This has resulted in a disillusionment and even hostility against the amyloid hypothesis [8-11], which in its simplest and broadest sense states that Aβ derived from APP forms toxic aggregates that trigger a cascade of events, including deposition of the microtubule-associated protein tau (MAPT) as neurofibrillary tangles (NFTs), to induce synaptic loss followed by neurodegeneration to cause dementia [12]. This theory has been supported by a core set of findings that have been reproduced in a number of laboratories that FAD mutations on APP and another set of membrane proteins termed presenilins (PS1 and PS2) preferentially increase the levels of longer 42/42 aa forms of Aβ (Aβ42/43), while the normally predominant form (Aβ40) may or may not be altered [13-15]. This fits well with other studies showing that Aβ42 self-associates to form aggregates (oligomers and larger fibrils) more readily than does Aβ40. Further, a large body of literature also demonstrates that soluble Aβ oligomers are neurotoxic in vitro and cause defects in memory and long-term potentiation (LTP) in animal models [16-20]. Despite the large consensus, one has to recognize that there are several gaps in our understanding of neurodegeneration in AD and the pathway is poorly replicated in transgenic animal models, as none of these models show the sequence of synaptic loss followed by NFT formation and neurodegeneration observed in AD [21].

The key problem in AD cannot be the simple toxicity of Aβ, given the high level of its conservation across species, but the fact that this metabolite, and potentially others sharing clearance pathways, accumulates to toxic levels in disease [12]. One of our preliminary unpublished observations is that monomeric Aβ accumulates to very high levels in several AD brain regions, supporting the notion that there may be multiple toxic protein metabolites that accumulate and cause the disease. Aβ accumulation is fostered by FAD mutations and possibly other metabolic and environmental factors that influence its clearance and maintenance pathways. It is interesting to note that even in humans, FAD mutations do not uniformly cause degeneration in all regions of the brain but show clearly affected regions with high amyloid and NFT load [22,23]. The fact that we fail to see the same degeneration sequence in transgenic mice despite expression of FAD mutant proteins and observing Aβ deposition therefore does not discredit the amyloid hypothesis, but points to our general ignorance of the mechanisms of neurodegeneration induced by this pathway. Furthermore, multiple hits may be involved with early hits sensitizing the system followed by secondary later hits that precipitate the disease. For example lead exposure is known to induce APP expression, but the expression returns to baseline after maturation unless challenged by a second exposure. Both exposures are essential to induce the hyperepression, which may increase late life Aβ load as described by the LEARn (latent early-life associated regulation) model [24].

On a positive note, both transgenic and nontransgenic cellular and animal models have provided biochemical support for clinically observed risk factors for AD, such as cholesterol, isoprenoids, lead, copper, inflammation, diabetes and homocysteine, and therefore facilitate our understanding of genetic and environmental modulation of the homeostasis of Aβ. These are known to induce other neurodegenerative diseases, such as age-related macular degeneration (AMD), diabetic retinopathy, renal failure and cardiovascular diseases, although these diseases do not necessarily co-occur with AD, possibly because they employ different protective mechanisms and express different target subsets [25-30].

Some risk factors may influence the disease by multiple mechanisms. For example, we find that homocysteine impairs insulin degrading enzyme that degrades Aβ, while methionine, a precursor of homocysteine and a methyl group donor for DNA and histone methylation can regulate expression of APP and histone methylation can regulate expression of APP and its processing enzymes, dephosphorylation of MAPT by PP2A and synthesis of choline, affecting multiple steps in Aβ accumulation pathway [31-33]. Given that most drugs can have multiple unknown activities and targets, one needs to also stop attributing toxicity to known pathways such as Notch and test for toxicity in multiple systems including effects that are target-dependent to establish safety and study efficacy of treatment in multiple model systems. Understanding the pathways that modify Aβ accumulation rather than waiting for deposition may yield targets for safe intervention to modify disease risk before it leads to the system to breakdown [34]. After the symptomatic disease stage,

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brain damage may be irreversible and may be maintained by other unidentified intermediates.

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References