Pathogenesis of Alzheimer's Disease

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Abstract

Alzheimer disease (AD) is a clinically progressive decline in cortical function involving memory and executive function and pathologically defined by two hallmark lesions, the senile plaque and the neurofibrillary tangle. Nearly 30 years ago, these hallmark lesions were purified and their protein constituents identified by quantitative analysis, which led in turn to a substantial expansion of knowledge, as well as optimism about the ultimate success of targeted therapy. Unfortunately, despite copious facts of new knowledge of the biochemical cascades that produce these protein abnormalities, there has been no meaningful progress toward disease modification for AD, a disease only found in humans. The repeated failures in this regard have been attributed to tardiness in intervention rather than instead an overdue need for a paradigm shift. The ruling theories for AD pathogenesis have their root in lesion removal. We argue that the lack of progress may instead reflect the evolving concept that pathological

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lesions, be they plaques, tangles, or soluble low-n protein species, signify mechanisms of neuroprotection, in response to a decade-long adaptation to an aging-hostile environment. The lesions themselves may similarly be a manifestation of neuroprotection, and likewise the targeting of such lesions as the offending agents is done at the very real risk of disrupting homeostasis and the body's attempt at fighting disease. Rather than simply shifting the same ideas and interventions to an earlier age or stage of disease, a broadening of the scope of treatment efforts to working with rather than against the biological processes of the brain, and the realities of repeated negative data, should be accepted both in theory and in practice.

Keywords
Aβ • Alzheimer disease • Amyloid-beta • Tau

1 Introduction

Alzheimer disease (AD) is complex and heterogeneous, differing in many respects from case to case, including age at onset, clinical signs and symptoms, presence or absence of various and numerous risk factors, extent and distribution of neuropathology, and genetic alterations including germline mutation and susceptibility alleles. Numerous hypotheses and the treatment implications inherent in them are not unexpected, although the success in treatment has, to date, been absent. Whether or not this failure reflects the complexity of the disease, the now numerous failures in the face of almost limitless knowledge of biochemical facts suggest that prevailing paradigms are significantly, if not fatally, flawed and not salvageable by overlooking theoretical flaws (Castellani et al. 2008a, b, 2009; Castellani and Smith 2011).

Presently, standard thought equates protein constituents of insoluble pathological lesions or their assembly intermediates with toxicity (Hardy and Higgins 1992). AD brains, for example, accumulate neurofibrillary tangles (the major discovery made by Alzheimer in 1906), which are comprised of phosphorylated tau disposed in insoluble fibrils, and those fibrils are derived from soluble tau species which are toxic to neurons in vitro). Thus, the protein "cascade" that produces phosphorylated tau is deleterious (Spires-Jones et al. 2009). Alternatively, one could say that AD brains accumulate amyloid plaques, which contain amyloid beta-protein (AβP) in insoluble fibrils of "amyloid"; the amyloid is itself derived from soluble toxic intermediates of Aβ, which are toxic to neurons. The cascade that produces these soluble intermediates is therefore inherently deleterious (Selkoe 2008). In addition, often included in discussions of toxic soluble intermediates is a direct attack on the synapse, closing the loop so to speak on the process in that lesions are tied directly to cognition, although the degree of separation from the in vivo environment is unclear (Tanzi 2005). To be sure, much work needs to be done (Benilova et al. 2012).

2 Amyloidosis in the Brain

Aβ was initially identified through purification of insoluble pathological lesions – senile plaque cores and cerebral vasculature involved by amyloid angiopathy (Glenner and Wong 1984; Masters et al. 1985). Subsequent identification of Aβ as a metabolic product of amyloid β-protein precursor (AβPP), its localization to the long arm (q) of chromosome 21, the identification of familial AD kindreds with pathogenic AβPP mutations, and the increased AD pathology in Down's syndrome patients who carry an extra copy of chromosome 21 produced a compelling argument in favor of the so-called amyloid cascade as the pathogenic mediator of disease (Castellani et al. 2008a). The cascade was further substantiated by the characterization of presenilin proteins, part of the notch signaling complex with γ-secretase activity (see below) and therefore inherently amyloidogenic.

Aβ is derived from AβPP, an integral membrane protein on chromosome 21q21 (Vetrivel and Thinakaran 2006; Wilquet and De Strooper 2004; Ling et al. 2003). Full expression of AβPP produces a cytoplasmic tail, a transmembrane domain, and a large extracellular domain, although only a fraction of newly synthesized AβPP molecules reach the cell surface. AβPP further exists as multiple alternatively spliced isoforms, three of which predominate: two isoforms AβPP770/751 contain the Kunitz protease inhibitor domain (exon 7) within the extracellular portion and are the predominant forms in cells other than neurons; AβPP695 is devoid of the Kunitz protease inhibitor domain and is the predominant form in neurons.

Cleavage of AβPP by either α-secretase or β-secretase produces soluble N-terminal fragments AβPP, and C83 and C99 membrane-bound C-terminal fragments, respectively. Further cleavage by γ-secretase leads to the release and secretion of nonpathogenic p3 peptide (previous α-secretase cleavage) and Aβ (previous β-secretase cleavage). Moreover, depending on the precise site of γ-secretase cleavage, different lengths of Aβ are produced, varying from 38 to 43 amino acids. The 42-amino acid form, Aβ42, has a greater tendency to form fibrils in vitro compared to other forms, has a tendency to deposit in brain parenchyma in the form of plaques relative to other species, and has traditionally been regarded as the "pathogenic" Aβ species. Aβ40 is generally considered benign as well as the principle component of Aβ that is deposited in cerebral vessels in cerebral amyloid angiopathy, particularly cerebral amyloid angiopathy type 2, which tends to spare cortical capillaries. Aβ42 synthesis and deposition represents the basis for the amyloid cascade hypothesis and therefore the theoretical underpinning of most clinical trials attempted to date.

The constituents and cell biology of γ-secretase have proven a challenge, although these questions were answered in part with the appearance of familial early-onset AD linked not to AβPP mutations but to so-called presenilins 1 and 2, presenilin 1 mutations being much more common. Presenilin mutations markedly increase Aβ deposits as well as phospho-tau accumulation in affected patients (Citron et al. 1997; Duff et al. 1996; Scheuner et al. 1996) and have been linked to γ-secretase activity (Maiorini et al. 2002). On the other hand, despite the presumption of presenilin as an important component of the multimeric secretase

complex, the biochemical mechanism of presenilin action is largely unknown. During development, presenilins appear to cleave a transmembrane protein termed notch, which in turn is a transcriptional activator of gene involvement in cellular differentiation (De Strooper et al. 1999). PS1 and PS2 have also been found to be involved in a range of biological processes, including cell adhesion, G-protein-mediated signal transduction, and unfolded protein response (Baki et al. 2001; Smine et al. 1998; Niwa et al. 1999) (Baki et al. 2001; Smine et al. 1998; Katayama et al. 1999; Niwa et al. 1999). Nicastrin has also been shown to interact strongly with the presenilins and appears to be required for normal notch signaling in *Caenorhabditis elegans* (Yu et al. 2000).

APP cleavage with generation of Aβ fragments also differs as a function of cellular subcompartment. At the cell surface, AβPP is proteolytically processed, primarily by α-secretases, resulting in shedding of the majority of the extracellular domain. Rapid and efficient internalization is mediated by a "YENPTY" internalization motif (Vetrivel and Thinakaran 2006). Once endocytosed, AβPP may be recycled to the cell surface, degraded, or further processed. β-site AβPP cleaving enzyme-1 (BACE1) appears to act on AβPP in late Golgi/TGN and endosomes, as indicated by the acidic optimal pH of BACE1. γ-secretase complex activity on the other hand takes place in multiple cellular compartments including ER, Golgi, and plasma membrane; the last is thought to comprise only a small fraction of the γ-secretase activity.

A key question that has existed since the elucidation of AβPP is the normal cellular function of this molecule, which is unresolved. One candidate ligand, secreted neuronal protein F-spondin, is implicated in neuronal sprouting and development. F-spondin binds AβPP as well as APLP-1 and APLP-2, which may interfere with β-secretase cleavage and cell signaling effected by the cytoplasmic domain (Wilquet and De Strooper 2004). AβPP has been suggested to serve as a receptor for intracellular transport of synaptic vesicles through interaction with kinesin and microtubules (Kamal et al. 2001). Both AβPP and the low-density lipoprotein receptor-related protein have been shown to bind the adaptor protein Fe65 via their cytoplasmic domains which increases AβPP proteolytic processing (Pietrzik et al. 2004). Interestingly, both LRP and AβPP are also γ-secretase substrates after cleavage and removal of their extracellular domains. A role of AβPP in heavy metal binding and as an antioxidant may also be an important role with direct implications in the disease process when dysfunctional (Cho et al. 2010).

In brief, the fundamentally toxic Aβ42, otherwise a product of normal cellular metabolism, is thought to be overproduced in disease resulting in neurodegeneration, or so the amyloid cascade theory postulates. Support for this comes principally from Mendelian diseases with pathogenic AβPP mutations leading to extensive Aβ deposits and early-onset disease. In vitro toxicity of Aβ42 peptides is considered further evidence for the cascade, although toxicity lies within narrow conditions, irrelevant to brain physiology in terms of toxicity. Despite the commonly held notions, whether or not Aβ42 is toxic in vivo remains to be elucidated. On the other hand, a role of Aβ42 in neuroprotection, which is made intuitively difficult by prevailing ideas, has been demonstrated (Nunomura et al. 2006). The significance of

this cannot be understated, given again that the overwhelming majority of clinical trials accept Aβ42 toxicity as fact. The first major and somewhat infamous phase II active immunization approach (AN-1792) may have been the most informative of all trials to date given the now long-term follow-up. The evidence is now clear that removal of Aβ from the brain in mild to moderate AD has no major cognitive benefits. Moreover, the two individuals studied who had almost complete removal of Aβ plaques progressed to dementia at the same rate as placebo, and each expiring with a mini-mental status score of 0. This effectively answered the question of whether dementia progresses in the face of Aβ removal from the brain whether it be fibrillar amyloid or oligomers (Holmes et al. 2008) and objectively speaking leaves considerable doubt as to whether Aβ42 is toxic at all. Yet the enthusiasm for anti-Aβ42 therapy is seemingly undaunted and is now progressing toward earlier intervention, based on perhaps an equally flawed notion that failure to reverse mild to moderate dementia means that intervention was too late, something for which there is no evidence whatsoever.

2.1 Does Aβ Correlate with Clinical and Anatomic Indices of Disease?

While the above question data seems to have closed the case on whether Aβ causes dementia (the lag in acceptance of this evidence notwithstanding), the relationship between Aβ pathology and disease has been the subject of a number of studies prior to the AN-1792 trial, and indeed the data indicate unambiguously that the correlation between Aβ and clinical disease is imprecise at best (Castellani and Smith 2011). An early study in the 1960s showed an overall tendency toward increased disease severity with plaque burden (Blessed et al. 1968; Giannakopoulos et al. 2003), although numerous subsequent studies have refuted this concept (Giannakopoulos et al. 2003; Braak and Braak 1991; Arnold et al. 1991). At present, it is accepted that amyloid burden overall correlates poorly with disease severity, and the distribution of Aβ tends to be diffused throughout the neocortex with no meaningful region specificity. Diffuse deposits of amyloid also occur in the striatum and cerebellar cortex late in disease (Montine et al. 2012), with no discernible selectivity in terms of loss of function subserved by these regions. Relative to neocortical Aβ, it is of some interest that medial temporal allocortical tissue involved in memory processing shows decreased Aβ (Arnold et al. 1991), something that gets little attention in the literature. Given the role of ApoE in facilitating fibrillogenesis of Aβ, it is also interesting that the extent of neocortical Aβ deposits shows variable correlation in the literature with ApoE susceptibility alleles, including ε4 (Berg et al. 1998; Nunomura et al. 2001).

A relatively new paradigm that is more functional than structural has emerged, in part, in response to the growing realization of the imprecise relationship between Aβ and clinical disease and to the clinical trials that have effectively removed Aβ and have not altered the neurodegenerative process. It is now suggested that soluble low-n Aβ oligomers cause synaptic damage and functional neurologic deficits (Selkoe 2008).

Experimental studies involving injection of conditioned medium, derived from oligomer-secreting APP V717F Chinese hamster ovary cells, into rat lateral ventricle, demonstrated alterations in long-term potentiation (LTP) that was related to low-n oligomers per se and not monomers (Walsh et al. 2002). LTP alteration was also shown in vitro in hippocampal mouse slices, along with concomitant changes in cell cycle signaling cascades and behavioral abnormalities. Here again, however, there is a premature juxtaposition of nakedly artificial experimental data and human brain function, separated from each other by so many degrees of relevance that irrelevancy is the only logical conclusion. This is in addition to lack of insight into those soluble species that are the most toxic and to the overall lack of reproducibility of many of the studies (Benilova et al. 2012). The implication is nevertheless present that these soluble low-n species, which are in vitro elaborations that cannot be directly measured or even reproduced between laboratories, are attacking the synapse, which is also not directly assessed either clinically or pathologically, and, moreover, that this combination is the true substrate for cognitive decline, even with implications for so-called mild cognitive impairment. Again, with these data in mind, the failure of treatment efforts is expected and leaves us in urgent need of a reorganization of the way AD pathogenesis is viewed by the medical and scientific communities.

3 Phosphorylated Tau

When the subject of the findings by Alzheimer is discussed by way of introduction to pathogenesis, it is often stated that amyloid plaques were a key discovery. The fact of the matter is that plaques were discovered some 15 years prior to Alzheimer's description, which he knew at the time, and in fact plaques were a known accompaniment of senile dementia. The first description of the neurofibrillary tangle (NFT), however, can be attributed to Alzheimer (Castellani and Smith 2011; Alzheimer 1907). It is also interesting to note that Alzheimer devoted ten sentences and two paragraphs to his initial description of the NFT, compared to only two sentences to the senile plaque (Alzheimer 1907; Wilkins and Brody 1969), suggesting that the NFT was the more intriguing, or at least novel, lesion for him. Alzheimer and his contemporaries were nevertheless hesitant to draw conclusions regarding disease pathogenesis and were more consumed with the age of onset and clinical signs which differed from "senile dementia," a known condition at that time (Moller and Graeber 1998).

Neurofibrillary tangles received relatively little attention in subsequent years, until the advent of electron microscopy (Terry et al. 1964) and, more importantly, the advent of modern molecular techniques which allowed NFT purification and identification of tau protein as a major protein component (Grundke-Iqbal et al. 1986). The enthusiasm for tau phosphorylation as a primary process in AD, however, has always been blunted by the absence of genetic linkage and the association of TAU mutations with the frontotemporal dementia clinicopathological phenotype, rather than the AD phenotype (Cairns et al. 2007). For this reason,

more than any other, phospho-tau is regarded as downstream to Aβ in terms of the pathogenic process, despite greater fidelity in its association with clinical disease (see below).

Tau is the major protein component of neurofibrillary pathology. Similar to the situation with Aβ, knowledge of tau has expanded considerably since it was purified and molecular species elucidated from the insoluble lesions. We now know that the phosphorylated tau is a major protein component of neurofibrillary pathology, which in turn promoted the study of tau in copious detail.

The tau gene is comprised of over 100 kb and contains 16 exons (Hernandez and Avila 2007). Upstream of the first exon are consensus binding sites for transcription factors. Alternative splicing of tau nuclear RNA in the adult brain involving exons two, three, and ten results in six tau isoforms. These six isoforms in turn differ in the presence of either three of four repeats of 31 or 32 peptide residues in the C-terminal region (exon 10). This peptide repeat region also comprises the microtubule-binding domain and therefore has direct implications in tau pathophysiology. Moreover, tau isoforms differ in the expression of zero, one, or two inserts encoded on exons two and three. The relative amounts of these tau isoforms as well as their phosphorylation status change during development; 3-repeat tau with no inserts is expressed in the fetus and early postnatal infant, while heterogeneous isoforms are expressed in the adult brain. This switch in RNA splicing also corresponds to an overall reduction in tau phosphorylation. Tau is relatively abundant in neurons but is present in all nucleated cells given. Its major physiologic function appears to be in binding microtubules and in stabilizing microtubule assembly for polymerization.

In disease, tau is abnormally hyperphosphorylated at proline-directed serine/threonine phosphorylation sites, including Ser-202/Thr-205 (AT8 site), Ser-214 and/or Ser-212 (AT100 site), Thr-231 and/or Ser-235 (TG3 site), and Ser-396/Ser-404 (PHF-1 site). In addition, alternative tau splicing differs according to pathological phenotype, such that tau accumulation in AD is a mixture of 3R and 4R tau, Pick disease tends to be 3R tau, corticobasal degeneration and progressive supranuclear palsy tend to be 4R tau, and so-called argyrophilic grain disease accumulates small inclusions comprised of 3R tau.

Does phospho-tau correlate with clinical and anatomic indices of disease? In spite of the fact that tau tends to appear in the cortex subsequent to Aβ and is generally considered a secondary or downstream phenomenon (Nelson et al. 2009), it is interesting that neurofibrillary pathology correlates closely clinical signs (Braak and Braak 1991) and much more closely than Aβ deposits. Phosphorylated tau deposition, for example, has a striking tendency to involve memory circuitry early in disease as well as in the aging process (Giannakopoulos et al. 2003; Arnold et al. 1991). It is also remarkable that abundant neocortical neurofibrillary pathology is virtually always associated with clinical signs of AD (Nelson et al. 2009, 2012), whereas extensive neocortical Aβ deposits are often seen in aged individuals in the absence of significant cognitive impairment or evidence of neuronal loss. In other words, heavy tau "burden" is generally incompatible with preserved cerebral function, while heavy amyloid burden often is not.

The role of phosphorylated tau in functional disease is progressing in a manner very much similar to Aβ. Recent studies, for example, indicate that insoluble tau accumulation is somewhat benign, while oligomeric phospho-tau intermediates may be more toxic and may be toxic at the specific level of the synapse (Santacruz et al. 2005). Also similar to Aβ studies, support for this concept is limited to highly experimental models (Stokin et al. 2005; Yoshiyama et al. 2007). The results highlight the growing theme that insoluble pathological lesions, and in this case NFT formation is a late stage nontoxic event, and that attention might be better directed toward upstream soluble tau intermediates. That the entire process, from changes in synthesis of soluble species, to putative soluble assembly intermediates, to insoluble pathological lesions, has yet to be embraced as a response to an underlying pathogenic process is remarkable. With recent multiple failures of the cascade concept, testing of biological alternatives is long overdue.

4 Conclusion

Current hypotheses of AD pathogenesis encompass copious and sophisticated data, but nevertheless have their origin in hallmark pathological lesions described more than a century ago. The literature is now contradictory on whether hallmark lesions are best considered manifestations of neurotoxicity or instead insoluble epiphenomena to the more important events involving soluble, toxic intermediates and the synapse, events ironically that cannot be directly observed, and are based on in vitro elaborations which have proven challenging to reproduce between laboratories and have not passed the test of relevance to the human brain. More likely, and based on now considerable evidence, pathological lesions as well as their constituent proteins of whatever species, be they monomeric, oligomeric, or insoluble fibrils, can be tied to molecular pathogenesis on the basis of disease expression, or a host response. This response is likely fundamentally adaptive over a long period of time and more in line with Darwinian theory. Targeting of such lesions, or any individual protein as part of a putative pathogenic cascade for that matter, should be entertained only with considerable care, if not the sober realization that it will more likely do more harm than good, as has been demonstrated in abundance. As the pathogenesis of AD continues to be elucidated, a broadening of the focus, rather than the perseveration on a very narrow set of principles, appears to be needed.

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