A standard model of Alzheimer’s disease?

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ABSTRACT

The recent Research Framework proposed by the US National Institute on Aging and the Alzheimer’s Association (NIA-AA) recommends that Alzheimer’s disease be defined by its specific biology rather than by non-specific neuropathological and syndromal features. By affirming markers of abnormal Aβ and tau proteins as the essential pathobiological signature of Alzheimer’s disease, the Framework tacitly reinforces the amyloid (Aβ) cascade as the leading theory of Alzheimer pathogenesis. In light of recent evidence that the cascade is driven by the misfolding and templated aggregation of Aβ and tau, we believe that an empirically grounded Standard Model of Alzheimer’s pathogenesis is within reach. A Standard Model can clarify and consolidate existing information, contextualize risk factors and the complex disease phenotype, identify testable hypotheses for future research, and pave the most direct path to effective prevention and treatment.

An international workgroup commissioned by the US National Institute on Aging and the Alzheimer’s Association (NIA-AA) recently recommended that Alzheimer’s disease be distinguished by its core pathobiology rather than by nonspecific features such as its signs, symptoms, and neurodegenerative sequelae [1]. Intended specifically for research purposes, the Framework classifies Alzheimer’s as a unique biological cause of dementia, and identifies the two proteincous hallmarks of the disease – profuse accumulations of aberrant Aβ and tau – as its defining biomarkers. This biological definition substantiates the enduring explanatory power of the Aβ (amyloid) cascade hypothesis of the pathogenesis of Alzheimer’s disease [2,3], and, placed in the mechanistic context of protein misfolding and seeded self-assembly [4], signals that an evidence-based Standard Model of Alzheimer’s Disease is possible. Loosely analogous to the venerable Standard Model of particle physics, which succinctly summarizes the best current knowledge of the basic properties of matter and energy [5], a Standard Model of Alzheimer’s disease can present to the scientific and lay communities a clear and concise representation of Alzheimer’s disease that is grounded in our most compelling empirical understanding of the biology of the disorder.

The Aβ cascade and the prion paradigm

The Aβ cascade hypothesis, formally proposed in 1992 [2], posits that the misfolding and multimerization of Aβ incites tauopathy along with other neurodegenerative and compensatory sequelae [3]. Genetic, pathologic, and biomarker evidence affirms an instigating role of Aβ in Alzheimer’s disease [6,7], although tauopathy is essential to the complete disease phenotype [3,8]. At the molecular level, extensive research indicates that the Aβ cascade is driven by the nucleated self-assembly of misfolded Aβ and tau, a phenomenon closely resembling the auto-propagation of misfolded prion protein (PrP) in spongiform encephalopathies such as Creutzfeldt-Jakob disease [4,9,10].

The NIA-AA research framework

In the NIA-AA Research Framework, a categorical pathobiological diagnosis of Alzheimer’s disease includes two disease-specific markers – multimerized Aβ (A) and abnormally phosphorylated, multimerized tau (T) – along with numerous neurodegenerative sequelae (N) that can also occur in other brain disorders, and thus are not specific to Alzheimer’s disease [1]. Accordingly, the Aβ-tau nexus is obligatory for the biological designation of Alzheimer’s disease, but the
fully manifest disease includes nonspecific pathological sequelae that contribute to cognitive impairment, and therefore are useful biomarkers of the progression and severity of the illness [1]. Together, Aβ, tau and neurodegeneration comprise the A/T/[N] biomarker classification system for Alzheimer’s disease [1,11].

The NIA-AA Research Framework is not meant to supplant clinical diagnosis, but rather to enhance and focus research on the core pathological features of Alzheimer’s disease. By defining the disease as a singular biological cause of dementia, the Framework distinguishes Alzheimer’s unambiguously from other neurocognitive disorders. In addition, it incorporates the long, pre-symptomatic period during which the disease quietly propagates through the brain [12]. The contribution of comorbid conditions to cognitive failure, particularly in advanced old age, is acknowledged, but the biological definition explicitly specifies the attributes that together classify Alzheimer’s as a unique disease entity: the intracerebral accumulation of abnormal Aβ and tau.

A standard model?

In our view, the basic biology of Alzheimer’s disease is now sufficiently well-understood that a consolidation of the Aβ cascade hypothesis, the NIA-AA Research Framework, and the prion paradigm constitutes the foundation for a Standard Model of the disease. The mechanistic core of the Model is the seeded multimerization of abnormal Aβ and tau (Figure 1). While the A/T/[N] biomarker scheme does not assume a sequence of events [1], the order of progression is important for strategic therapeutics; genetic and experimental evidence supports the contention that Aβ-proteopathy begets tauopathy, but not vice versa [3]. In this regard, it should be noted that most analyses of the temporal link between Aβ and tau have relied on histologically detectable lesions in the brain – Aβ plaques and tau tangles. However, a growing body of evidence indicates that small, cryptic oligomeric assemblies of the proteins are likely to be important in the disease [3,13–18], and these may not entirely overlap temporally, spatially, or functionally with the obvious proteineous deposits [8].

Risk factors in the Model promote the corruption and accumulation of Aβ. These include rare, causative mutations in the genes encoding the Aβ-precursor protein (APP) or the enzyme complexes that liberate Aβ from APP (presenilins 1 and 2), as well as numerous genetic, environmental and physiological influences that increase, to varying degrees, the likelihood that disease will ensue. The nonspecific pathologic sequelae of the Aβ cascade include such phenomena as inflammation, dysproteostasis, loss of neurons and their connections, and several others (Figure 1). Importantly, the set of sequelae partially overlaps with the set of risk factors; in other words, a given risk factor may also arise in response to the Aβ cascade. Persuasive evidence indicates that inflammation (for example) is a risk factor for Alzheimer’s disease, but Aβ plaques themselves can cause focal inflammation. Consequently, a
positive feedback loop may develop in which neurodegenerative sequelae continually reinforce the proteopathic cascade and thereby exacerbate the disease state.

A practical advantage of the Standard Model is that it presents a clear, evidence-based concept of Alzheimer’s disease to both the scientific and lay communities, in which confusion about the disease is inconsistent with recent advances in knowledge. The model places the complexity of Alzheimer’s disease in the clarifying context of a straightforward yet impactful phenomenon – seeded protein self-assembly. Although complexity has been invoked as evidence against the Aβ cascade, in actuality, the elaborate and somewhat variable disease phenotype simply reflects the variety of compensatory and degenerative consequences of the Aβ-tau nexus.

A theoretical benefit of the Model is that it formalizes the integration of Aβ-proteopathy and tauopathy into a common paradigm, something long acknowledged by many Alzheimer researchers, but which remains the source of occasional debate (see, e.g. [19–21]). The Model also serves as an explicit paradigm for testing alternative assumptions about the interrelationships among Aβ, tau, neurodegeneration, and cognition [1]. The Model is not meant to be immutable, but rather to stand as an unambiguous, evidence-based representation of the pathobiology of Alzheimer’s disease that can be augmented and challenged as new information arises.

**Future directions**

The foundation of a Standard Model of Alzheimer’s Disease is now reasonably well-defined, but many issues remain to be resolved (see Box). One is the existence of cognitively normal people with abundant Aβ-plaques; whether this is an early stage of Alzheimer pathogenesis or a benign form of Aβ-amyloidosis is likely to be settled soon by longitudinal analyses of Aβ and tau in living subjects. Another open question is the nature of the mechanistic relationship between Aβ and tauopathy. For example, does aberrant Aβ induce tau misfolding and multimerization directly (by cross-seeding), indirectly (by stressing cells in the brain), or are Aβ proteopathy and tauopathy individually acted upon by a common risk factor [22]? From a therapeutic standpoint, it will be critical to determine whether tauopathy is continually driven by Aβ proteopathy, or whether, once instigated, tau multimerization propagates independently. More information is needed also on the phosphorylation pattern of tau in Alzheimer’s disease compared to other forms of tauopathy, and whether this is linked in some way to Aβ. On a broader level, it will be informative to identify cellular and genetic mechanisms on which diverse risk factors converge to promote Alzheimer’s disease, as has been done for putative viral risk factors [23].

The Standard Model makes no a priori assumptions about the relative pathogenicity of different states of Aβ and tau, such as their molecular architecture, aggregation state, or chemical modifications, but these phenomena influence the disease and thus require further scrutiny [24,25]. It is increasingly clear, for instance, that Aβ can form many different kinds of assemblies, or polymorphs, and not all of them are equally pathogenic. The Model also accommodates the potential role of the small, diffusible oligomeric assemblies of Aβ and tau that are thought to be particularly injurious [3,13–18], although the details of the origin, composition, size, distribution, and bioactivity of these heterogeneous and dynamic assemblies in the Alzheimer brain are still indefinite. Moreover, the relationship between oligomers and large amyloid deposits remains ambiguous; for example, do the deposits protect the brain by sequestering toxic oligomers, or can they generate new oligomers via processes such as fragmentation and/or secondary nucleation [26]?

Finally, a lingering obstacle to acceptance of the Aβ cascade hypothesis has been the failure of clinical trials for Alzheimer’s disease, particularly those targeting Aβ. An important practical prediction of the Standard Model is that altering key elements of the Aβ cascade will impede the onset or progression of dementia. A reasonably persuasive case can be made that many clinical trials to date have foundered due to imperfect targets, poor timing, and/or flawed agents [3]. Furthermore, given the extended preclinical phase of Alzheimer’s disease and the presence of substantial pathology at the onset of detectable dementia [12], a definitive clinical test of the Standard Model may need to block the Aβ cascade early on, before significant damage has occurred. Several prevention trials of agents designed to inhibit Aβ proteopathy are underway in people who are at high risk of developing Alzheimer’s disease, but who will not yet have shown clear signs of cognitive decline [27–29]. It is hoped that early intervention will at least delay dementia in these subjects, although the time-frame for effective prevention has not yet been established, and the efficacy of some of the agents currently being tested is questionable [3]. However, a rare, inherited polymorphism in Aβ that lowers the likelihood of developing dementia [30] fosters optimism that, given the right treatment at the right time, success is possible.
Conclusions

The physician Lewis Thomas once articulated two general principles of human disease: 1) ‘It is necessary to know a great deal about underlying mechanisms before one can really act effectively’; and 2) ‘for every disease there is a single key mechanism that dominates all others’ [31]. Recent years have witnessed a surge of illuminating research on the pathobiology of Alzheimer’s disease, and the single key mechanism that has emerged is the seeded self-assembly of anomalous Aβ and tau. Many of the risk factors for Alzheimer’s disease as well as the nonspecific neurodegenerative sequelae are viable therapeutic targets, and research should continue to clarify their involvement in the disease. The Aβ-tau nexus, however, is central to disease-specific diagnosis, prevention and treatment. More broadly, the basic principles underlying the Standard Model may extend well beyond Alzheimer’s disease, given growing evidence for the seeded self-assembly of specific proteins in many other neurodegenerative and systemic disorders [32].

Abbreviations

Aβ  Amyloid-β  
APP  Aβ-precursor protein  
A/T/[N]  Aβ/Tau/Neurodegeneration biomarker classification system for Alzheimer’s disease  
Ca²⁺  calcium ions  
NIA-AA  National Institute on Aging and the Alzheimer’s Association  
P  phosphorylated  
PrP  prion protein  
US  United States

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Box: Open questions

What is the mechanistic link between Aβ proteopathy and tauopathy?  
Are seeding potential and toxicity mechanistically separable in the case of Aβ or tau (as has been shown for prion disease [33])?  
How do molecular architecture, aggregation state, and/or post-translational cleavage or chemical modifications influence the seeding potential and toxicity of Aβ and tau?  
What is the precise nature of proteopathic oligomers in the brain?  
What is the relationship between oligomers and larger polymers of Aβ and tau?  
What is the role of chaperone proteins, lipids, or other molecules in the misfolding, propagation, and/or toxicity of Aβ and tau?  
What governs the selective vulnerability of cells and tissue compartments to Alzheimer’s disease?  
What cellular and molecular functions are lost or gained, and how do these contribute to the disease?  
How do the proteopathic agents spread from one region to another?  
How do genetic, environmental and physiological risk factors impel the Aβ cascade, and do these converge onto common cellular and genetic mechanisms?  
What are the phenotypic similarities and differences between autosomal dominant and idiopathic Alzheimer’s disease?  
How do high-pathology but cognitively normal people fit in the Model?  
Are co-morbid conditions, when present, causally linked to Aβ or tau?  
How does advancing age – a universal risk factor for neurodegenerative diseases – facilitate the corruption and persistence of Aβ and tau?

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