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Hypothesis for the cause and therapy of neurodegenerative diseases

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ABSTRACT

The cause and therapy of neurodegenerative diseases remain unsolved puzzles. These diseases are correlated with presence of beta sheet-rich amyloid assemblies. Here, I derive and assemble puzzle pieces to obtain a loose end-tying hypothesis for cause with direct implications for therapy. I use the following extrapolations to find connectable puzzle pieces: (a) the traditional extrapolation that amyloid/amyloid precursors cause disease, (b) a recent extrapolation that amyloid-forming proteins, some of which are virus protein homologs, are components of an empirically obscure innate immune system that counters insults, including those by both viruses and bacteria, (c) a new extrapolation that various insults produce assemblies with structural features in common and that amyloid-forming, innate immune system proteins recognize these features and, then, counter insults by co-assembly, (d, 1) a second new extrapolation that beta sheet is a common structural feature and is extended during insult-neutralizing co-assembly and (d, 2) an appendix, derived from studies of phages T3 and T4, that most insult-produced assemblies are obscure to current biochemical analysis. The hypothesis is the following. One function of amyloid-forming proteins is non-classical innate immunity to biological insults. This immunity works via beta sheet-extending co-assembly of amyloid-forming proteins with beta sheet-containing insult products. For example, co-assembly with beta sheet-containing viral assembly intermediates inhibits virus production. Amyloid-forming proteins cause neurodegenerative disease when errant, typically overproduced. Other innate immunity systems sometimes exacerbate symptoms. This hypothesis suggests the following therapy, based on manipulating Nature's chemistry. First, conduct directed evolution to obtain low-pathogenicity, chronic symptom-producing viruses with assembly intermediates that co-assemble with and destabilize both amyloid and amyloid sub-assemblies. Then, infect patients with these viruses.

Introduction

Neurodegenerative disease mechanism and therapy are puzzles that have evaded solutions. Furthermore, solutions do not appear to be on the horizon with current strategies. A new perspective appears to be needed. I will propose a perspective and hypothesis that lead to the novel conclusion that therapy should be based on manipulating Nature's chemistry via directed evolution, rather than using human-design chemistry.

Neurodegenerative diseases are correlated with presence of cell-damaging amyloid assemblies. However, the normal, non-disease-causing function(s) of these assemblies, and sometimes of unassembled amyloid-forming proteins, is not known [1–5]. This statement includes Alzheimer disease [1], Parkinson disease [2], ALS [3], Huntington disease [4] and prion-associated diseases [5]. Here, I derive a hypothesis by assembling connectable puzzle pieces via extrapolations from data. I use four puzzle pieces, two newly derived here.

Taking ALS as an example, one might look for puzzle pieces by asking why this disease sequentially spreads from one motor nerve to another. Possible answers include [1] virus infection and [2] self-activation of the synthesis of a toxic molecule.

Indeed, ALS resembles an ultra-slow polio, a disease caused by virus infection [6]. But, self-activation of the synthesis of a toxic molecule is also possible. In early work on bacterial viruses (also called bacteriophages or phages), most investigators thought, although incorrectly, that phages were self-activating bacterial proteins [7].

Origin and foundation of the hypothesis

First and second puzzle pieces

Self-activation of the synthesis of a toxic molecule(s) is, however, the most reasonable explanation, based on (a) correlation of amyloid/amyloid sub-assembly presence with neurodegenerative disease and (b) low-to-zero inter-organism transmission [1–5]. My first extrapolation/puzzle piece (summarized in Fig. 1) is the conventional one, although

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Puzzle Pieces Obtained Via Extrapolation

1. Either amyloid or, more likely, an amyloid sub-assembly causes disease.
2. A previous extrapolation is correct in proposing that amyloid proteins work as part of an innate immune system that counters biological and physical insults. Disease is caused by malfunction of this system.
3. The various insults produce structures with limited variability (common structural features). These features are used as targets by amyloid-forming proteins to initiate insult-countering co-assembly.
4. Beta sheet is a common structural feature, found, for example in (typically obscure) replication intermediates of most viruses.

Fig. 1. The puzzle pieces are summarized. The four extrapolations involved are separately re-stated.

not universally accepted [1], that this correlation is not accidental and that either amyloid or, more likely, an amyloid sub-assembly causes disease. But, this extrapolation leads one to ask what are the normal functions, if any, of amyloid-forming proteins. These proteins undergo a change in secondary/tertiary structure (to be called a change in state) when they assemble to form amyloid [1–5]. The data suggest that at least Alzheimer disease amyloid-forming protein (Aβ, a cleavage product) and prions are descended from viral proteins. This raises the possibility that these proteins inhibit viral propagation [review [8]]. Historically, the assumption is that disease-causing, amyloid-forming proteins do not have functions when they are in the amyloid-forming state; protein misfolding is the major theme [1–5].

However, this assumption is not always correct because bacteria produce amyloids that have functions. These functions include formation of external fibers [curli, for example, in the case of *Escherichia coli* [9]] needed for formation of biofilms. Mechanisms exist to inhibit intracellular (toxic) formation of bacterial amyloid and the typically more toxic, smaller amyloid sub-assemblies [10].

Obtaining the next puzzle pieces begins with the following previous [8] extrapolation. In addition to pre-amyloid state functions, amyloid-forming proteins have amyloid state function. This latter function is within a (thus far empirically obscure) system of innate immunity. After beneficial activation within this system, amyloid-forming proteins act to counter external insults by both microbes and physical traumas. Neurodegenerative diseases occur after beneficial activation, when non-beneficial hyper-synthesis and, sometimes, misfolding of these innate immunity proteins occur. Erroneous self-countering (a) sometimes is the source of this malfunction [8] and (b) produces self-activation of synthesis. Thus, this previous hypothesis provides a simple explanation for the progression of ALS. The initially beneficial activation provides a simple explanation for the previously observed [11], broad-based correlation of Alzheimer disease with infections by viruses, bacteria and fungi.

Therefore, my second puzzle piece is the accepting of this previous, relatively recent extrapolation (Fig. 1). This extrapolation is independent of further conformational change that can (a) be construed as misfolding and (b) exacerbate the disease via its propagation (template toxicity), as shown for an amyloid of ALS [3], as well as Aβ [1] and prions [5].

Third and fourth puzzle pieces (new)

However, the number of innate immune system proteins of this type cannot possibly be as high as the number of different insults. In Ref. [8], this problem is anticipated by proposing that the amyloids adapt, via conformational changes, to various insults. But, the observed amyloid-producing conformational changes have limited variability and are biased toward beta sheet structure [1–5].

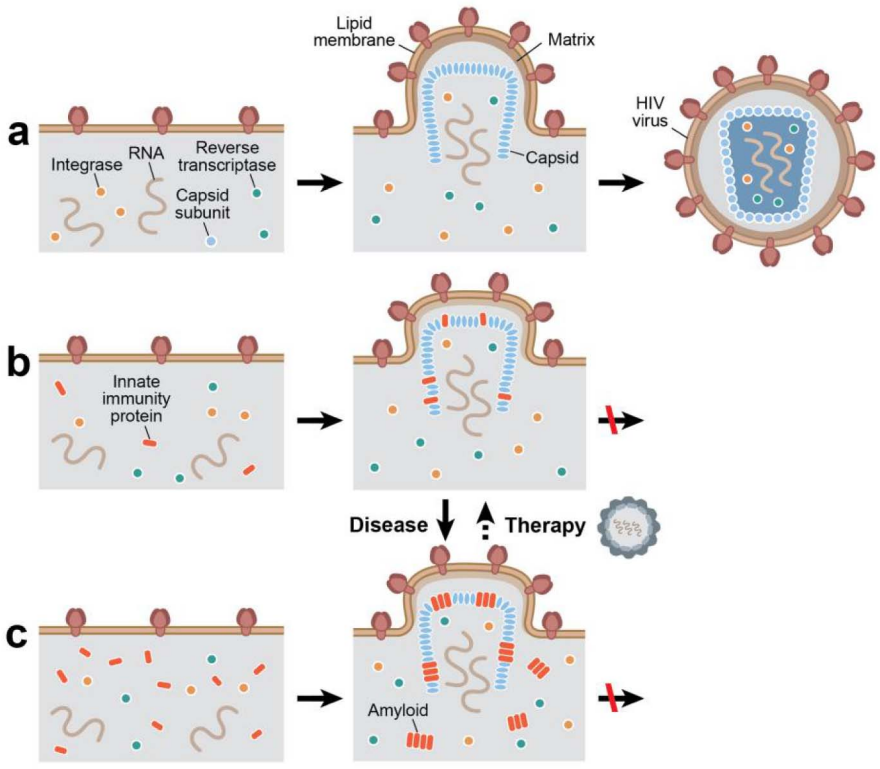

Fig. 2. An example is given of the proposed mechanism for responding to an insult caused by a virus. (a) A virus subassembly converts to a virus. HIV is chosen as the example [19,20]. (b) An innate immunity protein (red) counters this conversion by co-assembly with a beta sheet-rich intermediate of the capsid protein (light blue). This intermediate is currently hypothetical for most viruses. (c) The innate immunity protein forms amyloid precursors and amyloid when it co-assembles with itself, typically in a mistaken attempt to counter itself. The result in (c) is formation of toxic assemblies that cause neurodegenerative diseases. The proposed therapy is based on a virus that converts condition (c) back to a condition approximating (b), except for formation of a less stable (disposable) version of the amyloid and its sub-assemblies. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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