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Molecular Chaperones, Amyloid-Binding Compounds or Antioxidants?

Perspective on Their Application as Possible Therapeutic Agents in Reduction of Cytotoxicity of Amyloid Oligomers

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Letter to the Editor

It is generally accepted that a broad range of human diseases arises from the failure of a specific peptide or protein to adopt, or remain in, its native functional conformational state, referred as Protein Conformational Diseases (PCDs). The largest group of these misfolding diseases is represented by amyloidoses. Additionally, Present knowledge considers any peptide/protein able to undergo misfolding and aggregation generating intrinsically cytotoxic amyloids [1]. The inhibition of misfolding and oligomerization can be an attractive therapeutic target for these diseases. Among various strategies, application of (structurally unrelated) molecular additives and chaperones is extensively studied. (**a**) Molecular chaperones, such as HSP70 and αB-crystallin, are known to facilitate protein folding, inhibit protein aggregation, and promot disaggregation and clearance of misfolded aggregates inside cells. In case of amyloid aggregation suppressing activity of molecular chaperones, i*n vitro* observations show that chaperones decrease toxicity of oligomers through shielding of the reactive surfaces of toxic protein oligomers, and by formation of larger (and non-toxic) assemblies of oligomers [**1** *and references therein*]. (**b**) Experimental works as well as computational/theoretical studies reveal that small molecules bind to- and stabilize a variety of protein fibrils formed by amylogenic proteins [2]. Also various studies show that small molecules alleviate the toxicity of the amylogenic peptides/proteins to mammalian cells. Since binding sites of synthetic/natural compounds on the fibrils are quite different from the deep hydrophobic cavities/interactions that are believed to be responsible for both correct folding and off-pathway aggregation, the mechanistic effect of small molecules remains to be elucidated. Although, at least, two "aggregation neutralizing mechanisms" for small compounds have been suggested; target fibrils directly or stabilize the native parent proteins. Furthermore, many reports verify that these molecules detoxify fibrils not by targeting toxic oligomers [**2** *and references therein*]. Taking (**a**) and (**b**) into account, although efficient delivery of huge pharmaceutical molecules (such as molecular chaperones, if established) plays as main obstacle of protein-based drug development for amyloidoses, based on generic ability of chaperones to neutralize extracellular misfolded oligomers, they can still be considered as one of the effective strategies to neutralize cell toxicity of (especially extracellular) amyloid species, *in vivo*. Moreover, because continuous screenings have identified a variety of candidate small molecules and due to variety of structure, function, and mechanism of action of these molecules, there is room to design/develop more effective therapeutic interventions against various conformational diseases.

Several determinants of the amyloid cytotoxicity, such as oxidative stress and direct cell membrane–oligomer interaction, have been suggested [3]. Oxidative stress is in fact a primary progenitor of the some amyloid-related neurodegenerative diseases (e.g. Alzheimer's disease, AD and Parkinson's disease, PD), and not merely an epiphenomenon. It has been recently recognized as the most important cause of cell death in Alzheimer's brains [3]. Since some anti-oxidant compounds display strong anti-fibrillogenic activity, a specific inter-connection between oxidative stress and fibrillogenesis can be expected [**3** *and references therein*]. If administered appropriately, a successfully developed "antioxidant therapy" provides the vulnerable, aging neuron with a

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defensive shield against the oxidative cascade of neurodegeneration. More importantly, however, as effective as such therapies may be to those who have yet to enter the neurodegenerative cascade, once significant amounts of oxidative damage accumulate within the cell such that the secondary pathologies become apparent, any hope of reversing the course of the disease remains beyond the scope of simple antioxidant therapy. Nevertheless, ongoing clinical trials should therefore be focused on simultaneous application of molecular chaperones, fibril stabilizers, aggregation inhibitors (no disaggregation inducers) and "oxidative stress" inhibitors as a new generation of amyloidoses therapeutics.

Conflict of Interests

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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