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Can We Accelerate the Path towards Therapy for Amyloid-Related Diseases?

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Aging is a growing problem in the developed and developing world. As life span has been increasing steadily over the last few decades and a large percentage of people live into the 9th and 10th decade of their life, the prevalence of aging-related diseases has been growing steadily, posing new challenges to healthcare systems and economies around the world. These changes have come about thanks to large strides in medical development, which allow people to survive diseases that used to be major causes of mortality in the past. Though antibiotic-resistant bacterial strains are a growing threat, most common infectious diseases can be treated effectively and many can be cured. Multiple types of cancers that used to be considered as a death sentence a decade or two ago, now can be treated and often cured. AIDS is significantly more manageable today than it was a decade ago. However, with the increase in life span, a class of diseases, for which currently there is no cure, has emerged as a major threat particularly among the elderly – diseases called amyloidoses, which are characterized by aberrant protein folding and aggregation.

Prominent examples of such diseases are Alzheimer's disease (AD), Parkinson's disease (PD), and type-2 diabetes (T2D). In each of these diseases and in all amyloidoses, certain proteins, which otherwise are part of normal physiology, undergo abnormal folding and self-associate with each other forming first water-soluble, and later insoluble, toxic aggregates. Though it is difficult to formally prove that this abnormal process is what causes disease (rather than resulting from the disease), multiple lines of evidence support the view that the protein aggregates are either the cause or are important mediators of the ensuing pathology. Consequently, many academic laboratories and pharmaceutical companies have been dedicating substantial resources into understanding the details of the aberrant aggregation process and attempting to stop it. But are all these efforts spent in directions that make sense?

The history of scientific discovery contains multiple examples of individuals or small groups who had to battle with dogma. Copernicus, Newton, the Wright brothers, and several recent Nobel laureates come to mind. The problem with dogma is that we tend to accept it without questioning. We all accept today that the earth is round, that it revolves around the sun and not vice versa, and that machines can fly in the air, yet originally people who proposed or perpetrated these "radical" ideas found themselves ridiculed, if not persecuted.

I believe that dogma exists in research related to the search for compounds that prevent formation of, modulate, and/or dissociate toxic protein aggregates. According to the dogma, similar to typical drugs, these compounds should be able to recognize their target's three-dimensional structure and bind to it with high affinity and specificity. The way a key fits into a lock. This model has worked well for many traditional drugs and drug targets. Therefore, it is expected to work in the combat against amyloidoses. However, in my opinion, this model is unlikely to yield successful drugs for the most devastating amyloidoses because the self-aggregating proteins that cause or mediate the pathology do not have well-defined, three-dimensional structures.

This is not true in all cases, though. Some of the offending proteins do have well-defined, three-dimensional structures *before* they undergo abnormal folding and aggregation. Consequently, Kelly and co-workers have shown that the abnormal process can be prevented by small molecules that strategically bind to key pockets in the three-dimensional structure and stabilize the protein sufficiently to prevent it from undergoing into abnormal folding and aggregation [1].The drug tafamidis meglumine (European trade name Vyndaqel®), which uses this mechanism, recently has been approved for the treatment of familial amyloid polyneuropathy, one of several rare diseases caused by aberrant aggregation of the protein transthyretin, a carrier of thyroxin and retinol [2]. Some other proteins associated with aberrant aggregation and disease have a stable structure before undergoing amyloidogenic transformation, which ostensibly can be stabilized by a similar strategy [3]. But the proteins that form toxic aggregates in AD, PD, T2D, and a number of other amyloidoses are naturally unstructured. Thus, although we can make a key, it has no lock to fit into.

So what is the alternative? Is there another way? For a while, attempts have focused on the structures formed by these amyloidogenic proteins, which *are* stable, namely the cross-β structure of the insoluble amyloid fibrils formed by virtually all amyloidogenic proteins. These efforts did not result in therapeutically viable solutions, probably both because the fibrils turned out not to be the key toxic aggregates, and because many of the compounds actually aggregated themselves into colloids that could sequester the fibrils but were unlikely to prevent the harmful effect of the real culprit – water-soluble, non-fibrillar oligomers [4].

The growing recognition that the evasive oligomers were the most toxic species and the primary effectors of pathology has positioned them as the new key target of therapeutic efforts. The oligomers are all metastable, which means that they have a limited half-life and they are held together by relatively weak forces. Nevertheless, clearly, structural elements responsible for this metastability must exist and if they can be elucidated, they can direct drug design and discovery efforts. Elucidating these structural elements is a tremendous challenge and the focus of many research groups worldwide. The difficulty lies in the very metastable nature of the oligomers. Not only do the key structures populate only a fraction of the conformational ensemble, but inevitably, the oligomers exist in dynamically changing mixtures. The locks for which we are searching for a key are morphing constantly in an ocean of other, similarly morphing locks. How then can we identify the most important structures in this ocean?

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I obviously do not have all the answers, but I believe that the solution will include several important components. First, efforts should be focused on identifying those key structural elements in the toxic oligomers, not in the unstructured monomers or the fibrils, and characterizing the impact of these elements on both the self-association process and the toxic activity of the oligomers must be done side-by-side. One without the other is not sufficient.

Second, those of us in this research field know that in recent years, not a week goes by without another report of yet another compound that modulates protein aggregation to some extent. But despite the constant accumulation of such reports, we are still searching in the dark because in the vast majority of cases, we do not understand why or how the particular compound interacts with the target protein and affects its aggregation. I posit that efforts should be refocused away from searching more compounds, which often are simply derivatives of those discovered previously, and dedicated to detailed understanding of what specific forces mediate the interaction, what the specific impact on the assembly process is, and how and why this affects the toxicity of the offending protein.

Finally, several lines of evidence show that the malleable oligomer structures are shared among amyloidogenic proteins, in sharp contrast to the restricted, unique configurations of most "normal" proteins, suggesting that the same level of specificity cannot be achieved when targeting these oligomers. But ostensibly this very difference can be used as a sufficiently distinctive feature for identification of compounds that would specifically affect the metastable amyloid oligomers and not the stable structure of globular proteins. Following this non-traditional line of thinking, we recently showed that compounds that theoretically bind to almost any protein can effectively modulate the aggregation of amyloidogenic proteins and prevent the toxicity of their oligomers *in vitro* and *in vivo* without causing toxicity or interfering with normal physiologic processes [5,6]. I believe that focusing attention, effort, and funding on detailed understanding of the molecular and atomic interactions mediating the aberrant self-association of amyloidogenic proteins, and looking for out-of-the-box-strategies for deciphering the interactions between the toxic oligomers of these proteins and for non-traditional compounds selected or designed to target these specific interactions will accelerate the discovery and development of efficacious, disease-modifying drugs for major amyloidoses.

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