Trends in Biochemical Sciences

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Opinion

# Amyloid Fibres: Inert End-Stage Aggregates or Key Players in Disease?

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**The formation of amyloid fibres is a hallmark of amyloid disorders. Nevertheless, the lack of correlation between fibre load and disease as observed, for example, in Alzheimer's disease, means that fibres are considered secondary contributors to the onset of cellular dysfunction. Instead, soluble intermediates of amyloid assembly are often described as the agents of toxicity. Here, we discuss recent experimental discoveries which suggest that amyloid fibres should be considered as disease-relevant species that can mediate a range of pathological processes. These include disruption of biological membranes, secondary nucleation, amyloid aggregate transmission, and the disruption of protein homeostasis (proteostasis). Thus, a greater understanding of amyloid fibre biology could enhance prospects of developing therapeutic interventions against this devastating class of protein-misfolding disorders.**

## Historical Perspective on the Role of Amyloid Fibres in Disease

Amyloid diseases are a group of protein-misfolding disorders defined by the formation and deposition of insoluble protein fibres with a cross-β fold [1,2]. Although well known for their association with neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, amyloid fibres are involved in a range of human conditions, in which misfolded protein aggregates deposit in a localised or systemic fashion [3]. Despite the increasing incidence of amyloidoses in our ageing population, these disorders are remarkably difficult to prevent or ameliorate, since the myriad of misfolded species that can form during amyloid assembly has precluded the precise identification of the originators of toxicity. In addition, many amyloid diseases are exacerbated by ageing due to the reduced efficiency of the proteostasis machinery. This leads to increased protein misfolding and aggregation events that accelerate the decline in protein homeostasis and enhance susceptibility to amyloid toxicity [4,5].

Since their discovery, the pathological role of amyloid fibres has undergone a shifting view; from the original findings implicating fibres as the causative agent of disease [6], to current opinions, which describe fibres as inert end-stage products of aggregation. Several reasons are responsible for this shift in opinion: (i) amyloid fibres, including those comprising amyloid beta $(A\beta)_{1-40/42}$, ∝-synuclein, or islet amyloid polypeptide (IAPP), have been shown to display limited toxicity compared with oligomeric intermediates of their assembly [7]; (ii) the conserved cross-β fold of the amyloid fibre core has emerged as an important functional motif in a range of organisms, including prokaryotes, eukaryotes, and even humans [8,9]; and (iii) amyloid fibres are highly stable thermodynamically, and are among the strongest and stiffest of any known proteinaceous material [10]. Prion fibres, which are structurally homologous to amyloid fibres, are the exception to this current view, and are firmly established as key facilitators of the

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Amyloid fibres are proteinaceous filaments that form as a consequence of protein misfolding. Their formation is linked to over 50 human diseases, including Parkinson's and Alzheimer's diseases, and type 2 diabetes mellitus.

Amyloid fibres are structurally polymorphic even when formed from the same sequence. The structure can alter fibre length distribution, thermodynamic stability, mechanical properties, and biological activity.

Amyloid fibres have several critical roles in disease, facilitating amyloid aggregate transmission, both between cells and, for prion-like species, between individuals.

Amyloid fibres can also sequester core components of the proteostasis network, disrupt membranes, and catalyse or cause the formation of cytotoxic oligomers.

A comprehensive understanding of amyloid fibre biology will advance us towards our goal of therapeutic intervention.

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spreading and infectivity observed in prionopathies [11]. Notably, recent discoveries have also shown that disease-associated amyloid fibres, including fibres formed from Aβ and ∝-synuclein, facilitate the spreading of amyloid *in vivo* [12–14].

Interest in amyloid fibres as disease-relevant agents has undergone a renaissance in recent years. Here, we examine evidence that places amyloid fibres as key players in the persistence, progression, and propagation of amyloid disease through an array of biological activities relevant to the long incubatory periods over which these disorders develop. Thus, an understanding of amyloid fibre structure, dynamics, and biology may help to unravel the complexities of amyloid disease, and pave the way towards developing successful therapies against these disorders.

## Biological Membranes and Fibre-Induced Toxicity

Amyloid formation proceeds, most often, when an unfolded or partially folded precursor partitions into an aggregation landscape in which intermolecular contacts drive the formation of multimeric protein complexes (Figure 1). Under 'normal' physiological conditions, the probability that a protein conformer will aggregate can be enhanced by changes in the cellular environment. This can occur, for instance, during interactions with lipid bilayers, or changes in pH encountered upon entry into endosomes or lysosomes [15,16]. Mutation or truncation of the polypeptide sequence may also render a previously innocuous protein into an aggregation-prone species [17–19]. A variety of structurally diverse oligomeric species can form on or off pathway to the low energy minima occupied by amyloid fibres. These oligomers may initiate a cascade of diverse pathological responses [1].

Although oligomers have been shown to act as the primary deleterious aggregate in cell toxicity assays [7,20,21], several investigations have shown that amyloid fibres also have cytotoxic

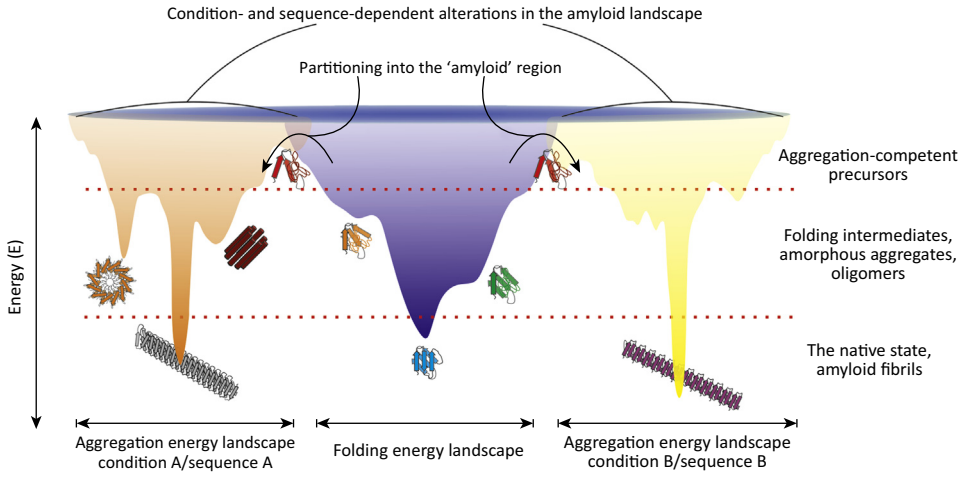


Figure 1. The Energy Landscapes of Protein Folding and Aggregation. Folding of proteins into their functional, native states occurs via the formation of metastable folding intermediates en route to the low-energy native state (blue). Under certain conditions, such as changes in pH, or upon alteration of polypeptide sequence, protein misfolding can occur more frequently (red polypeptides). This creates aggregation-competent monomers that partition into parallel 'misfolding' amyloid landscapes (orange and yellow). The formation of amyloid is driven by intermolecular contacts and generates an array of multimeric protein complexes (oligomers) that precede the formation of highly ordered, low-energy structures known as amyloid fibres. Depending upon the sequence or upon the conditions under which aggregation occurs (condition/sequence A or condition/sequence B), the ruggedness of the folding and amyloid landscapes can be altered. This can affect the probability of molecules misfolding and entering the aggregation landscapes (not depicted here), and/or the stability and structure of fibres and oligomers formed (orange and yellow landscapes). These alterations change the ability of an amyloid fibre and of all species accessible within the particular landscape, to cause cellular dysfunction and degeneration.