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Amyloid in neurodegenerative diseases: Friend or foe?

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Abstract

Accumulation of amyloid-like aggregates is a hallmark of numerous neurodegenerative disorders such as Alzheimer's and polyglutamine disease. Yet, whether the amyloid inclusions found in these diseases are toxic or cytoprotective remains unclear. Various studies suggest that the toxic culprit in the amyloid folding pathway is actually a soluble oligomeric species which might interfere with normal cellular function by a multifactorial mechanism including aberrant protein-protein interactions. Molecular chaperones suppress toxicity of amyloidogenic proteins by inhibiting aggregation of non-native disease substrates and targeting them for refolding or degradation. Paradoxically, recent studies also suggest a protective action of chaperones in their promotion of the assembly of large, tightly packed, benign aggregates that sequester toxic protein species.

Keywords

amyloid; polyglutamine; huntingtin; neurodegenerative disease; molecular chaperone

1. Introduction

Protein misfolding and the accumulation of amyloid aggregates are prominent features in a vast array of human diseases including numerous neurodegenerative disorders [1]. An amyloid fibril is an insoluble, highly ordered aggregate and the major component of extracellular plaques found in Alzheimer patient's brains. Amyloid fibrils are defined by a cross-β structure where the β sheets run perpendicular to the fibril axis [2]. Amyloid can be distinguished from other disordered aggregates by several properties including insolubility in ionic detergent, protease resistance, and recognition by diagnostic indicator dyes such as Congo Red [3]. Intracellular inclusions which exhibit similar characteristics are usually termed amyloid-like [2], but for the purposes of this review we will refer to amyloid plaques, fibrils, and amyloid-like aggregates all as amyloid unless otherwise noted. It remains highly controversial whether the amyloid deposits found in patients with amyloid disorders is the root problem as researchers first thought or if, as increasing evidence suggests, the large inclusions serve a protective cellular function [4, 5].

Amyloid diseases are associated with a broader family termed protein conformational diseases, coined by Carrell and Lomas in 1997. They proposed that each disease occurs via a similar mechanism that involves the abnormal folding and aggregation of specific disease associated proteins causing a toxic gain of function [6]. However, the precise reason behind aggregation of a disease protein causing toxicity remains unclear. An equally challenging enigma in neurodegenerative amyloidoses is the cause of selective vulnerability of certain

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neuronal populations. Each neurodegenerative disorder affects a specific subset of neurons even though the disease associated protein is often present in many cells throughout the brain and the rest of the body [7]. This phenomenon may be a result of interactions between an array of intracellular factors which have both positive and negative influences on the cells ability to buffer accumulation of potentially toxic proteins [8, 9]. It has been suggested that subtle differences in the expression pattern of broad networks of protein homeostatic factors influence the fate of disease proteins and may account for selective vulnerability [10, 11]. Yet, the components that make up such collectives of protective or harmful interactions remain ambiguous. Herein, we discuss mechanisms for amyloid toxicity and explore how molecular chaperones act to modulate the proteotoxicity associated with formation of intracellular amyloid aggregates.

2. Formation of toxic species in amyloid diseases

Although numerous neurodegenerative diseases are associated with the presence of amyloid-like aggregates, the toxic culprit in the aggregation pathway leading to amyloid formation remains elusive. Some researchers suggest that the inclusion bodies found in amyloid diseases (bottom, right in Fig 1) are the toxic species [12], yet there is often a negative correlation between neurotoxicity and existence of large amyloid aggregates[13, 14]. Accumulating literature suggests that a soluble, pre-fibrillar species of the disease protein (Soluble Oligomers in Fig 1) causes cytotoxicity and the fibrillar aggregates may be part of a cytoprotective mechanism whereby toxic species are sequestered [4, 5].

How is a normally folded protein converted to a cytotoxic amyloid-like conformer? The conformation of soluble proteins is dynamic. Native proteins often “breath” and sample partially unfolded non-native states which leads to transient folding intermediates [15]. The equilibrium between native and non-native conformers is shifted toward the non-native state via mutation or upon aging and/or stress [10]. Non-native protein conformers are subject to action of protein quality control (PQC) machines and are partitioned towards refolding, degradation or aggregation (Fig 1). The capacity of a cell to efficiently manage non-native protein conformers can impact cellular life or death [16]. Although it is clear that directing a natively folded protein towards amyloid formation is linked to disease, the exact conformation of the species causing the primary toxic insult is still unknown. There are many neurodegenerative disorders characterized by amyloid inclusions, but some of the most highly studied are Alzheimer’s Disease (AD) and polyglutamine diseases such as Huntington’s Disease (HD). Below, we will discuss studies directed towards elucidating what the toxic amyloidogenic species might be in these two diseases.

2.1. Oligomeric amyloid assembly

The structural transition from a non-native fold to a pre-fibrillar conformation occurs via nucleated polymerization [15, 17]. The nucleation step of this process begins very slowly, perhaps due to an unfavorable energy barrier. After nucleation, however, polymerization occurs much more rapidly as the folding intermediate is capable of serving as a template or seed for further conformational switching [17]. Interestingly, it appears that all proteins which form amyloid may proceed through the same intermediate steps [18]. In this section, we will review recent advances in amyloid biology which suggest that there are common features in the mechanism for toxicity of structurally distinct proteins; these studies also highlight the toxic nature of soluble intermediates in the amyloid assembly pathway.

2.1.1. Polyglutamine diseases: Huntington’s Disease—Polyglutamine (polyQ) diseases are a very well studied, yet enigmatic, subset of neurodegenerative disorders. These diseases are characterized by amyloid inclusions where the disease protein contains an expanded polyQ tract [19]. HD occurs when Huntingtin (Htt) has a polyQ tract expanded

beyond 33 residues. Disease onset is associated with cleavage of an N-terminal exon 1 fragment containing the expanded polyQ tract from Htt. This is followed by nuclear accumulation of the cleaved fragment even though the wildtype form of Htt is localized mainly to the cytosol [20, 21].

Although aggregation intermediates have been hard to identify, polyQ length dependent formation of Htt oligomers has indeed been demonstrated both *in vivo* and *in vitro* [22, 23]. Indeed, much evidence supports the hypothesis that there may be an inverse relationship between Htt toxicity and aggregation. For instance, expression of Htt with an expanded glutamine stretch in cultured striatal neurons causes aggregation in a manner that does not correlate with cell death. In fact, suppression of intranuclear Htt inclusion formation is accompanied by increased cell death [14]. While this study analyzed a total population of cells, Arrasate et al designed a series of experiments where they followed individual neurons. During the lifetime of the cells, the group tracked survival, Htt load, and Htt inclusion formation. This inventive experimental setup revealed that neuronal death correlates with increased polyQ expansion length and amount of diffuse Htt within the cell. Additionally, Htt inclusion body formation reduced the amount of soluble Htt thereby increasing neuronal survival [24]. These studies provide fundamental insight which supports the idea that the toxic Htt species is soluble rather than large intranuclear inclusions.

2.1.2. Alzheimer's Disease—Like HD, the formation of amyloid containing plaques was long assumed to be the causative agent of neurodegeneration in AD. However, there are accumulating data that suggest that the toxic species is actually a soluble form of the disease causing protein [25, 26]. The disease associated protein in AD is amyloid precursor protein (APP). Amyloid aggregation in AD occurs with cleavage of APP fragment into Aβ42 which accumulates in extracellular amyloid plaques [27]. Aβ amyloid plaques found in human brains of AD patients have a low correlation with severity of AD [28]. A recent study using a mouse model of AD strongly supports the toxic oligomeric hypothesis [25]. AD symptoms were decreased upon reduction of insulin growth factor signaling which correlated with formation of tightly packed Aβ aggregates. As seems to be the case with Htt, Aβ apparently may undergo oligomerization into a soluble, toxic conformer which can be sequestered by protective cellular pathways into larger benign aggregates.

In AD, the toxic soluble oligomer has been identified in various ways. Injection of medium containing Aβ monomers and oligomers, but lacking amyloid fibrils, was able to inhibit hippocampal long-term potentiation (LTP) in rats [4]. Pretreatment of the sample in order to destroy Aβ monomer followed by injection still resulted in decreased LTP. In another *in vivo* study, rats were injected with an oligomer specific antibody which was able to block inhibition of LTP [26]. Altogether, these *in vivo* results suggest that Aβ oligomers mediate toxicity or nucleate the formation of a toxic protein species. Soluble intermediates in the amyloid assembly pathway for Aβ have a structure in common with other amyloidogenic proteins as evidenced by a structural specific antibody [18]. Importantly, this observation links different amyloid diseases to a common soluble amyloid conformation which seems to correlate with toxicity. Thus, various amyloid associated neurodegenerative disorders are apparently caused by a population of harmful oligomeric conformers which have common toxic properties.

2.2 Interaction surfaces of toxic amyloid species

A broad array of protein interaction partners can affect aggregation both positively and negatively, composing a vast protein homeostasis network which needs to be balanced to maintain cell viability [10]. For example, aberrant protein-protein interactions can interfere with the normal function of various transcription factors, such as CREB Binding Protein and

TATA Binding Protein, leading to transcriptional dysregulation [29, 30]. Htt and various amyloid disease proteins might also deplete and/or inactivate other necessary cellular factors. These include but are not limited to ubiquitin proteosome machinery [31], ER associated degradation (ERAD) machinery [16], numerous glutamine or glutamine/asparagine (Q/N) rich proteins [32, 33], and large proteins predicted to be highly unstructured which may act as hubs or scaffolds [34]. In addition, coiled-coil (CC) domains were recently suggested to regulate aggregation and toxicity of Q/N rich amyloid proteins [35]. Increased CC propensity in regions of proteins that contain polyQ was found to increase occurrence of aggregation and toxicity. It's possible that the CC structure may be an interaction domain which mediates the nucleation event for pre-fibrillar β-rich amyloid to occur in polyglutamine diseases. Furthermore, there may be distinct chaperone machineries regulating the formation of the CC domain, imparting another level of control over the system. Although we are just beginning to understand mechanism for 'nucleation' of amyloid assembly, it seems that the nature of protein interactions are able to dictate how a non-natively folded protein is handled within the cell.

Yeast prions provide an extremely useful example of interaction surfaces affecting nucleation and toxicity of amyloid forming proteins. Prions are self-propagating proteinaceous particles [36] which, in yeast, are amyloid-like heritable genetic elements passed from mother to daughter cell [37]. Prion proteins can exist in their natively folded conformation or in their amyloid-like prion conformation. For instance, Rnq1 and Sup35 are the proteins which form [RNQ^+] (also called [PIN^+]) and [PSI^+] prions, respectively. The [RNQ^+] prion serves as a prime example of a protein which affects conformation of another protein. When [RNQ^+] comes into contact with another amyloidogenic protein such as Sup35, the prion allows the interaction partner to assume its amyloid conformation, in this case [PSI^+] [38, 39]. The Rnq1/Sup35 interaction is normally very weak, but nonetheless Rnq1 can serve as a nucleator of amyloid conversion and assembly [40]. In the context of HD, when Htt is expressed in yeast, toxicity only occurs in the presence of [RNQ^+] [41]. Thus, Rnq1 serves as a nucleation factor not only for other yeast prions, but also for other amyloidogenic disease associated proteins. Htt assembly could actually be relocalized to the nucleus by tagging Rnq1 with a nuclear localization signal [42]. Relocalizing Htt assembly to the nucleus hindered amyloid assembly resulting in the accumulation of a soluble Htt species. This correlated with enhanced Htt-induced cell death. Consequently, the specific location of amyloid conversion impacts cytotoxicity perhaps by influencing aberrant protein-protein interactions that might disrupt the essential cellular functions mentioned above. While [RNQ^+] as well as already templated amyloid proteins can serve as nucleators for amyloidogenic proteins, further studies are needed to discover other cellular factors with this capability.

From all of these studies combined, we deduce several things. First, there seems to be a common mechanism of amyloid toxicity even though different disease proteins misfold and aggregate in specific, disease dependent, neuronal subpopulations. The primary amino acid sequence, which is different for each individual disease protein, may play a role in selective vulnerability. Second, the common amyloid toxicity mechanism seems to stem from soluble oligomeric species which may be the toxic culprit in various neurodegenerative amyloidosis. Finally, though it remains unclear whether the soluble amyloid is a folding intermediate or an off-pathway conformer, the toxic soluble species in various amyloid associated neurodegenerative disorders must adopt a β-rich structure [43, 44]. The toxic β-rich structure may expose surfaces amenable to aberrant intracellular interactions, but when packaged into large benign aggregates, these surfaces may be hidden.

3. Suppression of amyloid proteotoxicity by molecular chaperones

Molecular chaperones are a crucial part of PQC and work by maintaining the proper folding status of proteins within a cell. Chaperones recognize misfolded conformers which are then targeted for refolding, aggregation, or triaged towards degradation. They play a vital role in protecting the cell from conformational diseases such as amyloidogenic neurodegenerative disorders. Chaperones do this by either suppressing the initial oligomerization of disease proteins and disassembling disease protein aggregates or stimulating the conversion of toxic amyloid assembly intermediates into benign aggregates [5, 45–47]. In other words, chaperones can either inhibit or promote aggregation but the end goal is to eliminate the toxic soluble species.

3.1 Chaperone dependent suppression of aggregation

The Hsp40/Hsp70 system is a well characterized molecular chaperone machine that recognizes non-native disease proteins and prevents aberrant aggregation. Hsp40 functions as a co-chaperone by binding non-natively folded proteins and delivering them to Hsp70 for refolding [48]. The diversity of Hsp40s polypeptide binding domain provides amazing substrate specificity to the Hsp70 [49, 50]. Various Hsp40/Hsp70 machineries act in different ways towards distinct disease protein substrates. This chaperone machinery has been highly studied as a mechanism which inhibits amyloid-like aggregate assembly of disease proteins [51, 52]. In yeast, overexpression of Hsp70, Ssa1, or Hsp40, Ydj1, alters aggregation of mutant Htt by preventing fibrillization [45]. Additionally, elevated expression of Ydj1 reduced aggregation and toxicity of Q/N rich amyloid aggregates [53]. Likewise in cell culture, increasing the amount of Hsp40 and Hsp70 has been shown to decrease formation of polyQ disease protein aggregates as well as alleviate toxicity [54, 55]. Thus it seems that the Hsp40/Hsp70 machinery may act to hold the disease protein in a soluble conformation in order to prevent accumulation of a toxic intermediate or byproduct of the amyloid aggregation pathway.

Molecular chaperones can also antagonize accumulation of amyloid assemblies by acting later in the folding pathway via solubilization of already formed aggregates. Hsp104, an AAA ATPase protein remodeling factor in yeast, is required for propagation of yeast prions via shearing of large amyloid-like aggregates into smaller seeds [38, 56]. Utilizing its solubilization activity, overexpression of Hsp104 in a yeast HD model was able to effectively fragment amyloid-like aggregates of expanded-polyQ Htt [57]. There is no Hsp104 in higher eukaryotes, however, exogenous expression of the chaperone in worm and rat models demonstrates that it retains its functional activity. Expression of Hsp104 in *C. elegans* reduced expanded polyQ protein aggregation and assuaged developmental delay [58]. Presence of Hsp104 in rats was also able to suppress toxicity and alter distribution of expanded polyQ proteins [59]. Though these are just a few examples, the Hsp40/Hsp70 and Hsp104 machines clearly can protect cells from amyloid disease proteins by suppressing aggregation thereby inhibiting formation of a toxic soluble species.

3.2 Chaperone mediated aggregation

Molecular chaperones are also able to reduce the buildup of toxic oligomeric conformers via packaging of these assemblies into larger benign amyloid-like aggregates. Work in yeast provides an excellent basis for understanding chaperone mediated amyloid assembly. In a [RNQ+] yeast background, elevation of Rnq1levels results in toxicity [5]. At normal levels, Rnq1 exists predominately as high molecular weight, SDS insoluble species in these studies. Moderate overexpression of Rnq1 to toxic levels causes accumulation of a lower molecular weight, SDS soluble pool. As in HD and AD, these studies suggest that the toxic Rnq1 species might be a smaller soluble species and the large SDS insoluble aggregates are a

benign product. Further substantiating this hypothesis, co-expression of Rnq1 with the Hsp40 co-chaperone, Sis1, suppressed toxicity and promoted Rnq1 assembly into large amyloid-like aggregates [5]. Elevating the levels of Rnq1 in a [RNQ+] cell saturates the [RNQ+] biogenesis pathway and results in the accumulation of toxic aberrant Rnq1 conformers. Co-expression of Sis1 may then alleviate toxicity by increasing [RNQ+] assembly into large SDS insoluble aggregates. Evidence towards this hypothesis also comes from the observation that Sis1 binds directly to [RNQ+] specifically in its prion conformation and is required for prion propagation [60]. Thus Sis1 acts as a PQC factor to promote aggregation in order to prevent accumulation of toxic soluble species of Rnq1 (Letter C in Fig 1).

Chaperone machinery has also been shown to promote aggregation of human amyloidogenic substrates. A human Hsp40, Hdj2, has been shown to increase aggregation of expanded polyQ Htt in Cos-7 cells [61]. In conjunction with Hsp40/Hsp70 machinery, the chaperonin complex, TRiC, also alters amyloid aggregation while suppressing polyQ-mediated toxicity as shown in *C. elegans* [62], yeast [63], and cell culture [64]. These studies demonstrate that depletion of TRiC leads to accumulation of a toxic, soluble, oligomeric Htt species. In fact, Behrends et al. utilized size exclusion chromatography to show that toxic Htt oligomers exhibited a molecular weight of approximately 200 kDa. TRiC, in conjunction with Ssa1 and Ydj1, was able to shift the toxic soluble oligomers into non-toxic 500 kDa aggregates [63]. Thus, promotion of protective aggregation seems to be a mechanism whereby cells eliminate cytotoxic pools of Htt oligomer. Altogether, these studies demonstrate that molecular chaperones protect cells from proteotoxic insult by targeting misfolded proteins away from toxic oligomeric states; chaperones either enhance assembly into fibrillar benign aggregates, or disassemble the oligomers into soluble monomeric forms which can be properly folded [65]. Incredibly, chaperones are able to carry out these opposing activities, both of which lead to promotion of a healthy and functional folding state of non-native proteins in the cellular milieu.

3.3 Chaperone assisted protein degradation

Chaperones also mediate clearance of proteotoxic substrates via degradation of non-native proteins. When molecular chaperones cannot repair a misfolded protein, it can be targeted for degradation either via the ubiquitin proteosome system or autophagy. CHIP (carboxy terminus of Hsc70-interactin protein) is an E3 ligase which mediates transfer of polyubiquitin chains to misfolded substrates, but also has inherent chaperone activity and acts as an Hsp70/Hsc70 co-chaperone [66, 67]. Indeed, CHIP has been shown to play a role in chaperone mediated degradation of expanded polyQ disease proteins. When CHIP was overexpressed, ubiquitination and turnover of polyQ disease substrates such as Htt increased, resulting in suppression of polyQ aggregation and cell death [68, 69]. CHIP's chaperone activity is necessary in order to observe this suppression. Elevated Hsc70 levels increased CHIP's ability to suppress aggregation and cell death, thus CHIP works cooperatively with Hsc70.

Autophagy is another cellular clearance mechanism for neurodegenerative amyloid proteins which is independent of the ubiquitin-proteosome system. Autophagy, literally meaning "self-eating", is a cellular process that involves compartmentalizing bulk cytosol, including cell components and proteins, which is sent to lysosomes to be degraded [70]. When autophagy was suppressed in mice via inhibition of ATG5, even without the presence of disease causing proteins, the mice displayed characteristics of neurodegeneration [71]. As a result, this study suggests that neuronal cells are constantly challenged by the formation of misfolded proteins and autophagy is required for the removal of these proteins. In the absence of this pathway, misfolded proteins accumulate and disrupt normal cellular function. In the context of neurodegenerative diseases, expanded polyQ disease proteins

have indeed been shown to be degraded via autophagy [72]. Furthermore, recent evidence suggests that mutant Htt can specifically be targeted to autophagosomes by acetylation [73]. Altogether, these studies establish that degradation, which can also be chaperone mediated, is a crucial mechanism by which neurodegenerative disease associated proteins are cleared from the cell.

4. Concluding Remarks

Normal PQC is crucial to cell viability because it maintains the balance of non-native proteins targeted towards refolding or degradation. A shift in this equilibrium can be highly detrimental to the cell, leading to death. Specific mechanisms of proteotoxicity caused by misfolded protein accumulation remain unclear, but many cellular processes have been implicated. Neurodegenerative disorders characterized by amyloid inclusions seem to be caused by a multifactorial mechanism which may be centered around titration and inactivation of essential cellular components in processes such as transcription [74], degradation via the ubiquitin proteosome [31], and ER associated degradation (ERAD) [16] among others. Aberrant interactions arising from exposed hydrophobic surfaces within the amyloidogenic disease protein [33, 75] and/or mislocalization [42] can lead to cell death.

Not all cell types are equally affected by a single amyloidogenic protein, however. The equilibrium between a native and non-native conformation is cell type specific, and not all cell types equally respond to the same protein misfolding event. Some cell types may be less equipped than others and therefore unable to clear toxic amyloid species. Cellular mechanisms for clearance of these toxic amyloid species include chaperone dependent suppression or promotion of aggregation, chaperone dependent turnover, and clearance via autophagy.

Although chaperone machinery can partition misfolded proteins between these various pathways, some proteins are able to escape normal PQC mechanisms and cause havoc within the cell. By gaining a better understanding of the affinities of non-native proteins for chaperones versus their propensity to aggregate, we may shed light upon exactly how those proteins can escape PQC machinery. Cellular environment seems to play a major role here. Upon cellular stress, it has been well documented that the environment within the cell shifts in order to avoid accumulation of misfolded protein species. Over time, these PQC pathways become less efficient. If the balance between refolding, degradation, and protective aggregation pathways is jeopardized then cytotoxic protein conformers are able to accumulate. Specific cell types may or may not be unable to respond accordingly by upregulating an alternative pathway to compensate for the stress. Thus, future research in the realm of amyloid diseases should focus on defining the protein networks within cells that help protect against that fate. In the long term, identification of protective cellular factors and how these networks are integrated and regulated will help us better understand exactly how amyloid causes disease.

Abbreviations

htt	huntingtin
HD	Huntington’s disease
AD	Alzheimer’s disease
CC	coiled-coil
polyQ	polyglutamine

IB	inclusion body
APP	amyloid precursor protein
FRET	fluorescence resonance energy transfer
LTP	long-term potentiation
PQC	protein quality control
ERAD	ER associated degradation
Q/N	glutamine/asparagine

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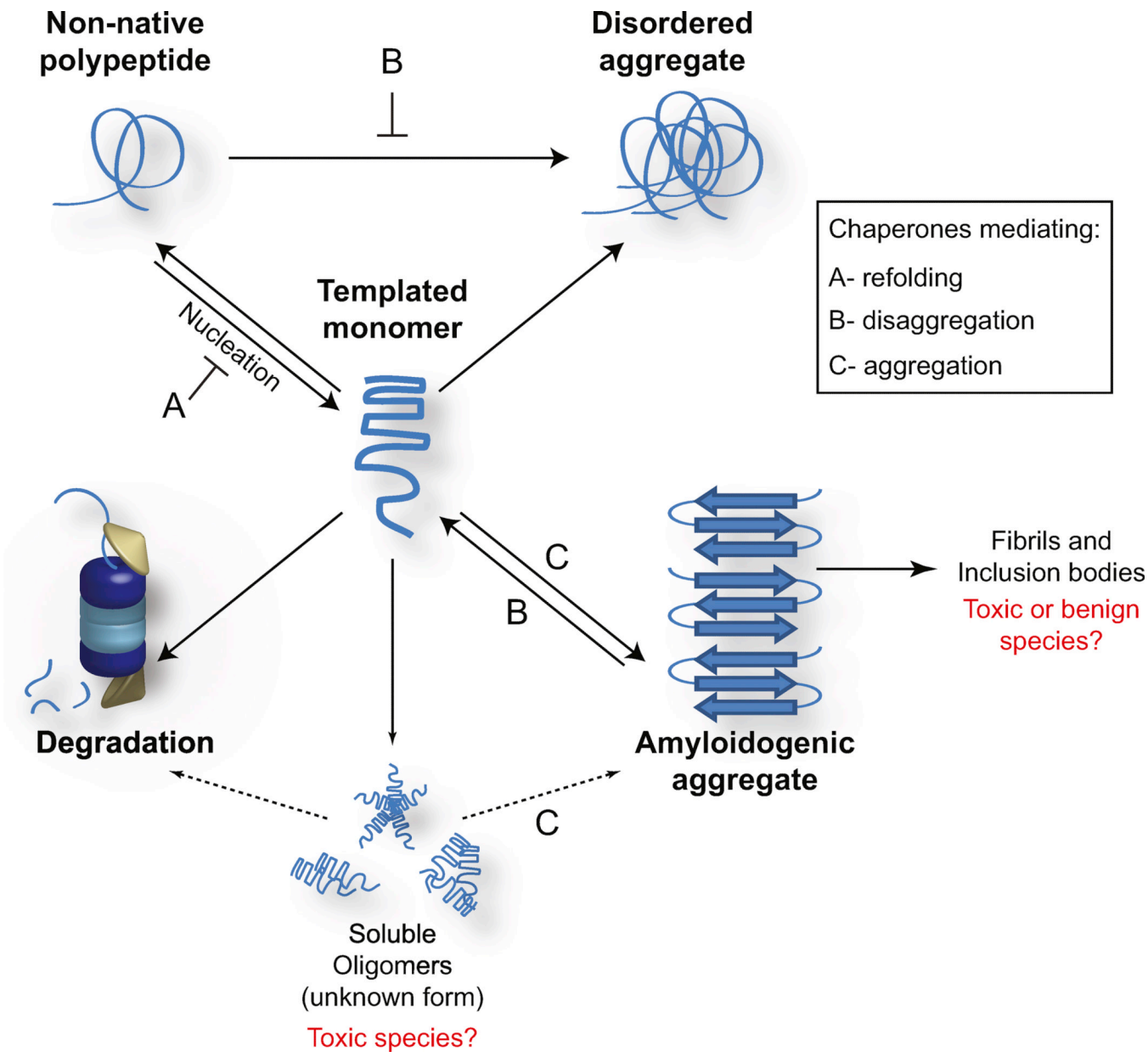

Figure 1.

Protein folding and amyloid formation. Non-native proteins can be partitioned into several conformational fates including refolding, ordered or disordered aggregate formation, and degradation. Amyloid is a type of very structured (or ordered) aggregate and forms through a poorly understood pathway. Sometimes a protein comes into contact with another surface that influences how it folds, but exactly how this occurs remains unclear. This interaction could be called nucleation since the newly "templated" monomer can now influence other monomers to adopt the same conformation. Following nucleation, possible small oligomeric species or amyloidogenic aggregates can assemble although the structure of this species is unknown. Molecular chaperones act at various points in the amyloid formation pathway to influence how the non-native protein is handled, as designated with letters A–C.