**Forum**

Disentangling a Bad Reputation: Changing Perceptions of Amyloids

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Historically, amyloids were perceived as toxic/irreversible protein aggregates associated with neurodegenerative disorders including Alzheimer’s and Parkinson’s diseases. Recent papers are challenging this perception by uncovering widespread cellular roles for physiological amyloidogenesis. These findings suggest that the amyloid-fold should be considered, alongside the native-fold and unfolded configurations, as a physiological and reversible protein organization.

The Dark Past of Amyloids

Amyloidogenesis is a biochemical process whereby soluble proteins assemble into insoluble and fibrillar aggregates known as amyloid fibrils. In humans, amyloidogenesis and amyloid fibrils have almost exclusively been associated with debilitating disorders because researchers have linked approximately 25 amyloid-forming proteins to common neurodegenerative diseases, most notably β-amyloid and α-synuclein in Alzheimer’s and Parkinson’s diseases, respectively. This strong pathological connection has fueled the pervasive view that amyloid aggregation is inherently toxic and detrimental to normal cellular function. Overall, this singular portrayal of amyloids has given this protein conformation a bad reputation as an irreversible and non-physiological cellular endpoint of disease-causing protein misfolding [1].

The prevailing view that an amyloid-fold is undesirable has resulted in decades of work dedicated to understanding how proteins can avoid conversion to the amyloid state under physiological settings. Despite most proteins having intrinsic aggregation propensity [1], many have proposed that amyloidogenic events are rare because the amyloid-prone segments of proteins are effectively concealed, either buried during the folding process or guarded against by chaperones [2]. Others have reported models of high kinetic barriers to aggregation or evolutionary selection against aggregation-prone segments [3]. In each of these models, cells are thought to possess a complex suppressive strategy to counter the inherent propensity of proteins to adopt the amyloid state, with amyloid diseases arising as an unfortunate consequence of breaching these protective safeguards. Conceptually, the literature implies that the amyloidogenic propensity of proteins is a conundrum that evolution has failed to solve during the elaboration of functional proteins, in other words an unavoidable flaw of polypeptide assembly.

In recent years a new narrative has emerged, one that depicts amyloids as a physiological protein organization instead of solely as an outcome of pathological aggregation.

Introducing Functional Amyloids

The notion that amyloids are exclusively pathological in human was first challenged by Fowler and collaborators [4]. They showed that Pmel17 proteins assume an amyloid-fold to accelerate the covalent polymerization of reactive small molecules into melanin biopolymer that protects against cytotoxic insults. This groundbreaking work was followed by the discovery of human functional amyloids involved in hormone storage [5] and the regulation of kinase activity [6]. The diversity of mammalian functional amyloids was expected to grow to become as common as they are in lower organisms [7]. However, most authors maintain that mammalian cells likely exploit the amyloid-fold only in highly specialized circumstances and under strict regulatory surveillance to avoid its inherent toxic effects [2,3]. The recent identification of systemic physiological amyloidogenic programs that exploit the broad fibrillation propensity of proteins requires us to reconsider the rarity of amyloids in cellular settings and the relationship between the amyloid state and toxicity in mammals.

Physiological Amyloidogenesis and Cellular Dormancy

Recently, several groups have provided evidence that cells activate physiological amyloidogenesis to induce cellular dormancy, an adaptive state that temporarily shuts down key metabolic pathways in response to harsh environmental conditions. For example, human cells enter dormancy following the assembly of nuclear amyloid bodies (A-bodies), which are induced by extracellular stressors [8]. A-bodies are composed of hundreds of heterogeneous proteins and display amyloid-like biophysical properties, highlighting that amyloidogenesis is not limited to a few specialized polypeptides. Heat-shock chaperones can efficiently disaggregate A-bodies, establishing the reversible nature of these physiological amyloids. Likewise, the RAS–MEK pathway regulates protein amyloidogenesis to induce tumor cell dormancy [9], and amyloid-like aggregation of Xvelo in the Balbiani body is linked to a dormant state in Xenopus...
Amyloids Represent a Solid-State Organization of Cellular Matter

Phase transition of matter between gas, condensed liquid, and solid states are ubiquitous in nature and occur predominately as a function of temperature. Recently, scientists have come to understand that a dynamic continuum of material states also exists within a cellular environment. Analogous to molecules in the physical world, intracellular macromolecules can undergo phase transitions from gas-like monomers to liquid droplets, producing a diverse range of granular bodies such as stress granules and P-bodies that are important to cellular organization [12]. Phase transition of proteins to solid state was originally observed in in vitro systems whereby proteins form hydrogels and fibrils under experimental settings [12]. The dynamic nature by which physiological amyloid-like structures, such as A-bodies, assemble and disaggregate fits into the phase transition conceptual framework in vivo. We posit that physiological amyloid-like bodies represent a solid-state macromolecular organization in a cellular context, highlighted by several unique biophysical features, most notably protein immobilization [8,11] (Figure 1). Unlike highly-mobile molecules with gas- or liquid-like properties, solid-state proteins are immobile because they do not exchange between binding sites, a property of the amyloid-fold. Whether the amyloid-fold represents the only form of cellular solid-state protein organization remains to be determined. Nonetheless, these studies remind us that nature can take advantage of different states of matter for cellular organization by reversibly transitioning macromolecules between a gas-like state, liquid assemblies, and solid-state structures.

References


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Figure 1. Dynamics of Intracellular Phase Transition. Analogue to phase transitions that occur in nature, such as the transitions between vapor (evaporation on a hot day), water (rainy afternoon), and ice (frozen lake in winter), physiological amyloidogenesis illustrates phase transition in a cellular context. As a protein transitions from a gas to liquid to solid states we observe higher-affinity interactions and a significant reduction in protein mobility, as measured by FRAP (fluorescence recovery after photobleaching). Recovery occurs rapidly for GFP-tagged proteins in the gas state, slower in the liquid state, and not at all in the solid state. Black circle represents the bleach point.