INTRINSICALLY DISORDERED PROTEINS
2017, VOL. 5, NO. 1, e1327757 (15 pages)
https://doi.org/10.1080/21690707.2017.1327757

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COMMENTARY

Paradoxes and wonders of intrinsic disorder: Stability of instability

Vladimir N. Uversky[a,b]

[a]Department of Molecular Medicine and USF Health Byrd Alzheimer Research Institute, Morsani College of Medicine, University of South Florida, Tampa, FL, USA; [b]Institute for Biological Instrumentation, Russian Academy of Sciences, Pushchino, Moscow Region, Russia

ABSTRACT

This article continues a series of short comments on the paradoxes and wonders of the protein intrinsic disorder phenomenon by introducing the "stability of instability" paradox. Intrinsically disordered proteins (IDPs) are characterized by the lack of stable 3D-structure, and, as a result, have an exceptional ability to sustain exposure to extremely harsh environmental conditions (an illustration of the "you cannot break what is already broken" principle). Extended IDPs are known to possess extreme thermal and acid stability and are able either to keep their functionality under these extreme conditions or to rapidly regain their functionality after returning to the normal conditions. Furthermore, sturdiness of intrinsic disorder and its capability to "ignore" harsh conditions provides some interesting and important advantages to its carriers, at the molecular (e.g., the cell wall-anchored accumulation-associated protein playing a crucial role in intercellular adhesion within the biofilm of *Staphylococcus epidermidis*), supramolecular (e.g., protein complexes, biologic liquid-liquid phase transitions, and proteinaceous membrane-less organelles), and organismal levels (e.g., the recently popularized case of the microscopic animals, tardigrades, or water bears, that use intrinsically disordered proteins to survive desiccation).

ARTICLE HISTORY
Received 10 April 2017
Accepted 10 April 2017

KEYWORDS
conformational stability; intrinsically disordered protein; liquid-liquid phase transition; membrane-less organelle; protein-protein interaction

Introduction

Recent years clearly witnessed increased penetrance of the intrinsic disorder concept into the different branches of protein science.[1-7] Because of their lack of stable structures, exceptional spatiotemporal heterogeneity, outstanding conformational plasticity, ability to be precisely controlled and regulated, and capability to conduct and juggle multiple jobs, intrinsically disordered proteins (IDPs) and hybrid proteins possessing ordered domains and intrinsically disordered protein regions (IDPRs)[8] are specialized in unique biologic functions,[1-7,9-38] which are extending far beyond mostly catalytic activities traditionally assigned to the proteins within the "one gene – one structure – one function" paradigm.[1,3,10-12,18,39-41] In fact, among intrinsic disorder-based biologic functions are regulation of various cellular pathways, binding promiscuity, involvement in diverse signaling processes, and participation in cell protection, protein protection, controlled cell death, and cellular homeostasis.[1-7,10-41] Several recent studies (mostly of computational nature) revealed that IDPs are very common in various proteomes, with the proteome content of IDPs being typically an indicator of both evolution and adaptation to the environment.[1,18,42-46] In fact, the percentage of IDPs in proteomes is increasing from bacteria and archaebacteria, to fungi, and to eukaryotic organisms, thereby reflecting the evolutionary importance of intrinsic disorder.[42,44-46] On the other hand, the role of disorder in adaptation to the environment can be illustrated by the fact that the salt, pH, and/or temperature-tolerant bacteria and Achaea typically contain more IDPs than their mesophilic and salt/pH-sensitive counterparts.[31,47]

Many aspects related to the structure, conformational behavior and functionality of IDPs look rather strange from the viewpoint of "traditional" ordered proteins.[48,49] To give a brief outlook of various paradoxes and wonders of intrinsic disorder, a series of short comments on different unusual features of IDPs was started in the *Intrinsically Disordered Proteins* journal. The first comment in this series was dedicated to the introduction of the "prevalence of exceptionality" paradox, where a progression was shown in

CONTACT Vladimir Uversky vuversky@health.usf.edu Department of Molecular Medicine, University of South Florida, 12901 Bruce B. Downs Blvd. MDC07, Tampa, Florida 33612, USA.

understanding of the natural abundance of IDPs from the early days, when they were taken as rare exceptions, to the current days, when the prevalence of IDPs/IDPRs in various proteomes and biological processes is well accepted.[50] In the second comment, the "complexity of simplicity" paradox was introduced to indicate how the multilevel simplicity of IDPs ranging from the reduced amino acid αbet and simplified sequences containing multiple sequence repeats to their structural primitivity and inability to spontaneously fold into the ordered structures is translated into the exceptional structural and functional complexity of disorder carrying proteins.[51] This article continues the aforementioned series by introducing the "stability of instability" paradox.

Intrinsic disorder from the traditional viewpoint of protein conformational stability

A set of specific non-covalent interactions (conformational forces) of different nature, such as hydrogen bonds, hydrophobic interactions, electrostatic interactions, van der Waals interactions, etc., is responsible for the ability of a typical globular/ordered protein to have a unique 3-D structure For ordered proteins, the presence of the "protein folding" code was proposed, where, under the physiological conditions, the correct folding of a globular protein into its unique biologically active structure is determined by its amino acid sequence.[52] The presence of unique and stable structure in ordered proteins implies that it can be cooperatively unfolded into a random coil-like conformation under the variety of conditions.[53-56] Such unfolding process of a small, single domain, globular protein is typically described by a sharp sigmoidal curve representing a case of the all-or-none transition, where a cooperatively unfoldable unit includes the whole protein molecule; i.e., no intermediate states can be observed in the transition region. In fact, based on the analysis of the urea- or guanidinium chloride-induced unfolding transitions in ordered globular proteins it has been concluded that the steepness of the corresponding unfolding curves (that can be expressed as the difference in the numbers of denaturant molecules 'bound' to the initial and final states in the denaturant-induced transitions, $\Delta\nu_{eff}$) depends strongly on whether a given protein has a rigid tertiary structure (i.e., it is ordered) and undergoes the O→U transition from ordered (O) to unfolded (U) state or exists as a molten globule (MG) and undergoes the MG→U transition.[57,58] For example, for a protein with the molecular mass of 30 kDa, $\Delta\nu_{eff}^{O\rightarrow U} = 23.1$, whereas $\Delta\nu_{eff}^{MG\rightarrow U} = 8.2$.[59]

Inasmuch the ability of an ordered protein to fold into unique 3D-structure is encoded in its sequence, the lack of rigid globular structures in IDPs/IDPRs is also encoded in the specific features of their amino acid sequences, such as enrichment in the disorder-promoting residues (Pro, Arg, Gly, Gln, Ser, Glu, Lys, and Ala) and depletion in the order-promoting amino acids, such as Cys, Trp, Tyr, Phe Ile, Leu, Val, and Asn.[18,60-66] Obviously, due to their highly biased amino acid sequences IDPs/IDPRs might possess some unusual conformational responses to changes in their environment. Although the denaturant-induced unfolding of a native molten globule is a low cooperativity transition that can be described by a shallow sigmoidal curve,[59,67] due the low content of the residual structure in native pre-molten globules or native coils their denaturant-induced structural changes are typically non-cooperative and seen as monotonous feature-less curves.[59] In other words, from the traditional view of protein conformational stability, IDPs/IDPRs are characterized by low structural stability, which is reflected in low steepness of their unfolding transitions induced by strong denaturants or even in the complete lack of the sigmodal shape of these unfolding curves.[59] This structural instability is supported by the well-known fact of high sensitivity of IDPs/IDPRs to proteolytic degradation.[68-77]

High resilience of intrinsic disorder

Although lacking stable structure, possessing non-cooperative unfolding behavior, and showing high sensitivity to proteolysis, one of the most intriguing biophysical properties ascribed to highly disordered proteins is their extraordinary resilience, where an IDP can sustain exposure to the extremely harsh environmental conditions, being able either to keep its functionality under these extreme conditions or to rapidly regain it after returning to normal conditions.[48,49] An illustrative example of such behavior is given by a "funny protein" prothymosin α,[48] which triggered my interest to the intrinsically disordered proteins by its unusual ability to be unharmed by the prolonged exposure to harsh conditions (activity of the protein was not affected by boiling for a few days).

Because of its highly biased amino acid composition (no aromatic or cysteine residues and overall low hydrophobicity level compensated by extremely high (~60%) content of charged residues), prothymosin α behaved as a highly disordered coil-like chain, thereby providing illustration of the "one cannot break what is already broken" concept.[78]

Prothymosin α is not an exception, and several other extended IDPs, such as p21, p27, α-synuclein, and phosphodiesterase γ subunit, were shown to possess high resistance toward heat denaturation and aggregation, being virtually unaltered by heating to 90°C.[78-88] Curiously, this resistance to thermal aggregation has been used for purification of these proteins,[83,89-92] and the indifference to heat treatment was proposed as an analytical tool for evaluation of the abundance of extended IDPs in various proteomes.[93,94]

Furthermore, extended IDPs, being characterized by high percentages of charged residues and low overall hydrophobicity, do not undergo large-scale structural changes at low pH[95] and remain soluble under these extreme conditions.[78,96] Furthermore, a careful analysis of proteins which do not precipitate during perchloric acid (PCA) or trichloroacetic acid (TCA) treatment of cell extracts revealed that many of these proteins are totally unstructured.[97]

In contrast to this remarkable pH resistance of IDPs, ordered proteins commonly undergo denaturation or unfolding in solution with extreme pH.[98-101] Since ordered proteins contain high fractions of hydrophobic residues, their pH-denatured or unfolded conformations contain numerous solvent exposed hydrophobic residues, which are normally buried inside the folded structures. This exposure of hydrophobic residues defines the "stickiness" of the partially folded pH-induced conformations of globular proteins, leading to their aggregation and precipitation. Based on these observations it has been suggested that indifference to acid treatment represents one of the characteristic properties of extended IDPs that can be used for the isolation of extended IDPs. In fact, it was shown that substantial enrichment of IDPs in the soluble fraction can be achieved after the acid treatment, and, therefore, such PCA/TCA pretreatment can be exploited to develop standard protocols for isolating and studying IDPs on a proteomic scale.[97]

Besides being highly resistant to the exposure to harsh environmental conditions (high temperature or extreme pH values), extended IDPs are also characterized by the "turned out" conformational response to the changes in their environment, where they gain some structure under conditions resulting in denaturation or even unfolding of ordered proteins, such as heat, extreme pH, and desiccation.[18,48,59] For example, the temperature-induced formation of secondary structure (and not partial unfolding, which is typical of ordered globular proteins) was reported for α-synuclein,[102] 636–771 fragment of caldesmon,[88] γ-subunit of phosphodiesterase,[103] the extracellular domain of nerve growth factor,[104] α_s-casein,[105] and many other IDPs. Furthermore, complete reversibility and independence on protein concentration was reported for these heat-induced partial folding of IDPs, indicating the intramolecular nature of this structural transition. These structure-forming potential of elevated temperatures was attributed to the peculiarities of the amino acid compositions of the extended IDPs (namely, their overall low level of hydrophobicity) leading to their "turned out" response to heating: higher temperatures caused the increase in strength of the hydrophobic interaction, leading to a stronger hydrophobic attraction, which is the major driving force for protein folding.[48,49,102]

Similar "turned out" response to changes in pH was reported for several extended IDPs, such as prothymosin α,[78] α-synuclein,[102] pig calpastatin domain I,[106] histidine rich protein II,[107] naturally occurring human peptide LL-37,[108] and several other extended IDPs. Here, partial folding of extended IDPs (which are characterized by the high net charge at neutral pH) in solutions with extremely high or low pH values can be attributed to the minimization of the overall net charge, thereby decreasing charge-charge intramolecular repulsion and permitting hydrophobic-driven collapse to the partially-folded conformation.[48,49]

Some biological uses of the "stability of instability" of intrinsic disorder

There are multiple way of how Nature is using stability of instability paradox introduced in this article. Sections below provide description of several cases where sturdiness of intrinsic disorder provides remarkable benefits to individual proteins (bacterial accumulation-associated protein, Aap), as well as serves as means for the mechanical regulation of the macroscopic properties of the networks formed by the

neurofilament proteins, assembly of stable complexes (e.g., elastin), liquid-liquid phase transitions residing at the core of the formation of various membraneless organelles, and defines desiccation stability of organisms.

Die-hard proline-rich extended stalk of the bacterial accumulation-associated protein

Since IDPs and IDPRs possess specific and rather unusual (from the viewpoint of ordered proteins) structural properties,[48,49] it is not too surprising to find that they are uniquely suitable for orchestrating some surprising (again, from the viewpoint of ordered proteins) functions.[109-111] One of the illustrative examples of such atypical function is given by an intrinsically disordered C-terminal portion of the cell wall-anchored (CWA) accumulation-associated protein (Aap) that plays a crucial role in the intercellular adhesion within the biofilm of *Staphylococcus epidermidis*.[112] Aap is one several staphylococcal CWAs that are anchored to the peptidoglycans located at the surface of bacterial cell.[113] This multifunctional protein contributes to both the primary attachment phase and the establishment of intercellular connections by forming fibrils on the cell surface.[112] Structurally, Aap consists of multiple repetitive blocks. For example, besides the globular lectin domain, the N-terminally located A-domain of Aap contains 11 short (16-residue-long) A-repeats. This A-domain is responsible for the initiation of the biofilm and is proteolytically removed to promote biofilm accumulation and growth.[112] The B-repeat superdomain, which follows the A-domain, contains 5–17 nearly identical 128-residue-long B-repeats that are used in the Zn^{2+}-mediated antiparallel self-assembly responsible for the intercellular adhesion.[114,115] Finally, the C-terminal tail of Aap includes a 135-residue-long proline/glycine-rich region (PGR) containing a set of 18 nearly identical AEPGKP repeats followed by the LPXTG motif that is used for the sortase A-mediated covalent linkage of Aap to the peptidoglycan layer of the bacterial cell wall.[116] Recent comprehensive multilevel biophysical analysis of the structural properties and conformational behavior of the PGR domain of Aap revealed that this intrinsically disordered region is highly extended (e.g., in SDS-PAGE experiments, PGR migrated as a species with an apparent molecular mass more than 10-fold higher than predicted, and in SEC and SLS experiments, this domain also showed very large R_h values (37.06 ± 1.1 Å and 38.39 ± 0.9 Å according to SEC and DLS analyses, respectively) that were noticeably exceeding those expected for native coil of the molecular mass of 13.2 kDa (30.2 Å) consistent with a highly elongated shape), likely due to the very high content of the polyproline type II (PPII) helical structure.[117] Importantly and rather unexpectedly, PGR showed remarkable sturdiness and was able to resist temperature-induced compaction and solvent-induced α-helix formation.[117] It was hypothesized that this ability of the PGR to keep an extended state irrespectively of the environmental conditions helps this region in fulfilling its biologic function as an extended stalk that pushes Aap out and away from the bacterial cell wall.[117]

Phosphorylation controllable expansion and collapse of the neurofilament network

Neurofilaments are the crucial constituents of the neuronal cytoskeleton that play several pivotal roles in supporting the axon structure and controlling its diameter.[118] Morphologically, neurofilaments are 10 nm wide bottlebrush-like filaments assembled from the 3 intermediate filament proteins, the light or lowest (~70kDa), the medium or middle (~150kDa), the heavy or highest chains/subunits (~210kDa) and designated as NF-L, NF-M, and NF-H, respectively.[119,120] The neurofilament backbone is assembled from the N-terminal head and rod domains of NF-L, NF-M, and NF-H that are ~100 and ~300 residue long respectively and are rather similar among the NF-L, NF-M, and NF-H proteins. The C-terminal tails of these proteins are highly disordered and serve as entropic bristles protruding outwards the neurofilament body, providing means for the bottlebrush topology of the neurofilaments, and mediating the inter-filament interactions and controlling the neuronal cytoskeletal organization.[121-123] These tails of the neurofilament proteins differ from each other by their length and amino acid composition. For example human NF-L, NF-M, and NF-H proteins contain 147, 504 and 613 residues, respectively.

The C-tails of NF-M and NF-H undergo extensive phosphorylation mostly at the serine residues located within the Lys-Ser-Pro (KSP) repeat motifs that results in the dramatic changes of their charge distributions (e.g., dephosphorylated NF-M and NF-H C-tails have

total charges of −46 and −7, whereas, total charge of their completely phosphorylated forms are −87 and −97, respectively).[124,125] It was expected that charge alterations induced by phosphorylation of these C-tails could play a role on controlling changes in the inter-filament spacing, the axonal caliber, and protein transport.[122,126-129] This is because phosphorylation would increase electrostatic repulsion between the excess charges thereby promoting lateral extension of neurofilament tails. This hypothesis was proven to be wrong by a recent comprehensive analysis of physico-chemical and mechanical properties of phosphorylated and dephosphorylated composite filaments containing NF-L assembled with either NF-M (NF-LM), NF-H (NF-LH), or both (NF-LMH).[125] Although, the macroscopic properties of the networks formed by the neurofilament proteins, such as expansion, orientation, and stress response, were shown to be dramatically modulated by phosphorylation, the structural and mechanical modifications caused by phosphorylation were strongly neurofilament composition-dependent, with phosphorylation being able to lead to either neurofilament network expansion or collapse.[125] The found expanding-collapsing effects of phosphorylation on the neurofilament network were caused by the dual nature of the phosphorylation-introduced interactions, which depend on the protein sequence and could be repulsive or attractive.[125] Therefore, the actual consequences of the extensive phosphorylation could be more complex than the naïve expectations of the increased electrostatic repulsion due to the phosphorylation introduced excess negative charges. Instead, there is a possibility of the phosphorylation-driven electrostatic attraction between the highly disordered regions that could graft unexpected structural and mechanical properties to the assemblies of intrinsically disordered proteins.[125]

Making sturdy complexes

One of the illustrative examples is given by utilization of intrinsic disorder in assembly of large multiprotein complexes, where highly flexible IDPs/IDPRs serve as *assemblers*[130] or molecular glue cementing protein complexes.[131] In fact, mutual folding of intrinsically disordered protomers is crucial for the formation of so-called 2-state protein complexes, where the protomers are intrinsically disordered in their unbound forms and undergo the binding-induced folding at the complex formation.[132-135]

Structurally, the protomers of protein complexes formed via the 2-state mechanism, where binding and folding occur concomitantly, are characterized by very large per-residue interface and surface areas.[134] As a result, protomers in such complexes do not have a simple globular structure (i.e., structure that defines the smallest accessible area), but possess very unusual, mostly non-globular shapes.[136,137] Resulting complexes are characterized by sophisticated, highly intertwined structures, where different parts of one protomer penetrate to the multiple binding pockets of different protomers. Therefore, IDPs participating in the formation of the 2-state proteins can be considered as a molecular glue or cement that becomes rigid once the complex forms and thereby serves as a crucial means for stable complex formation.[131] The idea of using flexible disorder for making sturdy complexes is illustrated by elastin, which is a self-assembling intrinsically disordered protein of elastic fibers found in the extracellular matrix and constituting an essential part of different elastic tissues in animals (e.g., connective and vascular tissue, lungs, and skin).[138] The major biological function of elastin relies on its ability to elastically extend and contract in repetitive motion when hydrated.[139-143] Although monomers of elastin are highly disordered, random coil-like polypeptides,[138,144-147] because of the formation of the elastic supramolecular complexes, this protein has been shown to be one of the longest lasting proteins in the body, possessing a half-life of about 74 y.[148]

Liquid-liquid phase transitions and membrane-less organelles

Eukaryotic cells contain numerous proteinaceous membrane-less organelles (PMLOs) that are commonly found in cytoplasm and nucleus of eukaryotic cells and represent an intricate solution of the cellular need to facilitate and regulate molecular interactions by chemically isolating target molecules in specialized compartments in a reversible and controllable way.[149-151] PMLOs are also known as ribonucleoprotein (RNP) granules/bodies, or RNP droplets since they typically contain both RNAs and proteins.[152] PMLOs are observed as spherical micron-sized droplets,[153] structural integrity of which is not supported by encapsulation in the membrane. They are just slightly denser than the rest of the cytoplasm or nucleoplasm,[154,155] exhibit liquid-like behavior, such as dripping, relaxation to spherical

structures upon fusion, and wetting,[156-159] and, therefore, are classified as liquid-droplet phases of the nucleoplasm/cytoplasm.[156-161] These organelles have unique morphologies, are characterized by specific distribution patterns, and have specific sets of resident proteins. Importantly, the biogenesis of PMLOs is entirely controlled and mediated by protein–protein, protein–RNA, and/or protein–DNA interactions.[162] The list of currently known cytoplasmic PMLOs includes centrosomes,[163] germline P-granules (germ cell granules or nuage),[156,164] neuronal RNA granules,[165] processing bodies or P-bodies,[166] and stress granules.[159] The nuclear PMLOs are more numerous and include Cajal bodies (CBs),[167] chromatin,[168] cleavage bodies,[169] histone locus bodies (HLBs),[170] nuclear gems (Gemini of coiled of Cajal bodies),[171,172] nuclear pores,[173] nuclear speckles or interchromatin granule clusters,[174] nuclear stress bodies (nSBs),[175,176] nucleoli,[177] Oct1/PTF/ transcription (OPT) domains,[178] paraspeckles,[179] PcG bodies (polycomb bodies containing polycomb group proteins),[180] perinucleolar compartment (PNC),[181] promyelocytic leukemia nuclear bodies (PML nuclear bodies) or nuclear dots (PODs),[182] and the Sam68 nuclear body (SNB).[181]

PMLOs are believed to be generated as a result of biologic liquid-liquid phase transitions (LLPTs), which is one of several forms of protein condensation (crystallization, liquid-liquid phase separation, aggregation, or gelation). Although crystallization, aggregation, and gelation are typically irreversible processes, PMLOs are formed as a result of reversible LLPTs under the physiologic conditions of living cells. It was shown experimentally for some PMLOs, such as nuages,[153] P-granules,[183] nucleolus,[184] and RNA granules,[185] computationally validated for several nuclear and cytoplasmic PMLOs,[186] other "assemblages,"[187,188] and generalized for all PMLOs and complex biological coacervates that their formation might be critically dependent on specific IDPs.[149-151]

Mechanistically (besides the obvious prerequisite to be present in high enough concentrations), the most important properties of the constituents capable of successful liquid-liquid phase separation are their flexibility (fluidity) and multivalency, which are the characteristic features of RNA/DNA (which are commonly found in PMLOs) and IDPs or hybrid proteins containing ordered domains and IDPRs. In fact, nucleic acid binding is one of the disorder-specific functions of proteins, and some IDPs are known to possess mosaic structure with alternating regions of opposite charges. Furthermore, many IDPs and IDPRs are highly charged, have highly repetitive sequences, contain multiple low complexity regions, and often possess disorder-based interaction motifs such as molecular recognition features (MoRFs),[22,189,190] AIBSs (binding sites identified by ANCHOR algorithm),[191,192] or short linear motifs (SLiMs)[193] that can be used by IDPs in formation of various complexes and assemblages. All this suggests that IDPs or hybrid proteins containing IDPRs can serve as potential players in liquid-liquid phase separation causing formation of PMLOs.[149-151]

Sturdy IDPs to the rescue! intrinsic disorder and organismal desiccation resistance

In line with the idea that sturdy IDPs characterized by remarkable conformational stability could have crucial importance for the sturdiness at the organismal level is a recently popularized thought-provoking case of the microscopic animals, tardigrades that use IDPs to survive complete desiccation.[194] Tardigrades (which are also known as water bears, space bears, pudgy wudgies, or moss piglets) are water-dwelling, 8-legged, segmented micro-animals characterized by the prodigious desiccation tolerance and the ability to survive a vast array of environmental extremes (e.g., exposure the vacuum and solar radiation of outer space for 10 full days).[195] They also can remain in the dehydrated state for up to 20 y and resume normal life, when external conditions become favorable again.[196] Being discovered more than 250 years, this micro-animals and the molecular mechanisms of their exceptional die-hardiness remained an enigma till recently, when it has been revealed that at the molecular level, the exceptional desiccation tolerance of tardigrades is attributed not to certain saccharides (e.g., trehalose) typically found in many anhydrobiotic organisms, but to the high contents of a set of tardigrade-specific IDPs (TDPs), which are either constitutively expressed at high levels or dramatically upregulated by desiccation.[194] These TDPs are found in multiple tardigrade species, and, being heterologously expressed in both prokaryotic and eukaryotic systems, are sufficient to promote desiccation tolerance in these heterologous systems. The protective role of TDPs in the tardigrade desiccation was attributed to the ability of these proteins to vitrify; i.e., to form a glass-like matrix that physically prevents

denaturation and aggregation of other cellular proteins and also preclude membrane fusion.[194]

The finding that TDPs are crucial for the ability of the members of the animal kingdom to survive during extreme desiccation concur with the previous work on the plant desiccation resistance that was shown to be critically dependent on several specific IDPs, such as late embryogenesis abundant (LEA) proteins and dehydrins (which are members of the Group II LEA proteins).[197-199] However, the protective role of LEA proteins (which in addition to plants can be found in bacteria, nematodes, and shrimps) was attributed to their ability to suppress desiccation-induced protein aggregation via formation of a 'molecular shield', a physical barrier, between the neighboring proteins. Therefore, the ability of TDPs to vitrify represents a novel intrinsic disorder-based molecular mechanism of protection of biologic material from desiccation.[194]

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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