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Protein disorder, prion propensities, and self-organizing macromolecular collectives ☆

Liliana Malinovska, Sonja Kroschwald, Simon Alberti *

Max Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstr. 108, 01307 Dresden, Germany

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ABSTRACT

Eukaryotic cells are partitioned into functionally distinct self-organizing compartments. But while the biogenesis of membrane-surrounded compartments is beginning to be understood, the organizing principles behind large membrane-less structures, such as RNA-containing granules, remain a mystery. Here, we argue that protein disorder is an essential ingredient for the formation of such macromolecular collectives. Intrinsically disordered regions (IDRs) do not fold into a well-defined structure but rather sample a range of conformational states, depending on the local conditions. In addition to being structurally versatile, IDRs promote multivalent and transient interactions. This unique combination of features turns intrinsically disordered proteins into ideal agents to orchestrate the formation of large macromolecular assemblies. The presence of conformationally flexible regions, however, comes at a cost, for many intrinsically disordered proteins are aggregation-prone and cause protein misfolding diseases. This association with disease is particularly strong for IDRs with prion-like amino acid composition. Here, we examine how disease-causing and normal conformations are linked, and discuss the possibility that the dynamic order of the cytoplasm emerges, at least in part, from the collective properties of intrinsically disordered prion-like domains. This article is part of a Special Issue entitled: The emerging dynamic view of proteins: Protein plasticity in allostery, evolution and self-assembly.

1. Introduction

1.1. Bringing order to the cytoplasm

Living matter is staggeringly complex. Nothing epitomizes this better than the highly organized structure of the cytoplasm. The cytoplasm of eukaryotic cells is a complex landscape, permeated by a fibrous meshwork of cytoskeletal proteins and compartmentalized into numerous organelles and subcellular domains. What determines the shapes and sizes of these structures, why they form in particular locations, and how their architecture affects cellular function is largely unknown. Despite its complex appearance, however, the cytoplasm is organized by only one process: molecular self-assembly.

A biological structure is self-assembling if it is able to determine its own organization based on the interactions between its constituent components. Thus, the intrinsic properties of these components – their abilities to associate or their affinities for membranes – are the only factors that determine the final architecture of a self-assembling system. A system of disordered components can self-assemble into either static or dynamic structures. In static self-assembly, the structure is the product of a new thermodynamic equilibrium. In dynamic self-assembly, the structure is resulting from a steady state, which is dynamically maintained by dissipative processes. Dynamic structures are characteristic of biological systems and are also known as self-organized [1–4]. They are typically very robust and able to self-repair in response to even severe perturbations. Being decentralized and only reliant on the collective properties of their components, self-assembly and self-organization are simple but also very efficient ways of achieving cellular organization.

In principle, a self-organizing biological system has to fulfill only two requirements: it has to be dynamic to allow the continuous exchange of material and it has to be able to establish and maintain a stable configuration from initially disordered components. Large macroscopic structures, such as mitochondria, the endoplasmic reticulum, or the Golgi, rely on delimiting membranes to maintain their self-organized state. To manage a constant flux of material and retain their integrity over long timescales, they employ the same mechanisms of protein sorting and retrieval. However, despite the importance of membranes in shaping the overall architecture of eukaryotic cells, they are not essential for compartmentalization. Here, we focus on alternative mechanisms for cellular organization that operate in the absence of membranes.

Numerous membrane-less compartments have been identified, and with rising interest their number is likely to increase (Table 1). Examples of such compartments include centrosomes, inclusion bodies, and cytoplasmic RNP granules. Large membrane-free structures, however, are not limited to the cytoplasm. They have also been observed in the nucleus, with nucleoli, Cajal bodies, and PML bodies as prominent

Abbreviations: IDP, intrinsically disordered protein; IDR, intrinsically disordered region; PrD, prion domain; IPOD, insoluble protein deposit; JUNQ, juxtanuclear protein quality control; RNP, ribonucleoprotein

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* Corresponding author. Tel.: +49 351 210 2663; fax: +49 351 210 1209.
E-mail address: alberti@mpi-cbg.de (S. Alberti).

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Table 1
Nuclear and cytoplasmic protein and RNA bodies.

	Name	Other names	Localization	Function/description	Reference
Cytoplasmic bodies	Processing bodies (PBs)	GW (glycine and tryptophan-rich) bodies, Dcp-containing bodies	Cytoplasm of somatic cells	Assemble under stress; store translationally silenced and degrade decay-prone mRNA	[8,11,15,32,34]
	Stress granules (SGs)		Cytoplasm of somatic cells	Form under stress; keep mRNAs of housekeeping genes paused in translation initiation	[6,10,19]
	EGP bodies		Cytoplasm of somatic cells	Intermediate between PBs and polysomes; remodel degradative mRNPs from PBs into translational mRNPs *en route* to translation initiation	[14]
	Germ cell granules	Nuage, *Drosophila melanogaster*: Polar granules or Sponge bodies, *Caenorhabditis elegans*: P granules, mammals: inter-mitochondrial cement, or chromatoid body in spermatocytes	In the cytoplasm of germ cells, associated with nuclear envelope	Partitioned to prospective germ cells where they direct the timing of nascent maternal mRNA translation; probably needed for developmental progression	[18,27]
	Neuronal transport granules	Neuronal RNA granules, Dendritic P-body like structures (dIP-bodies), FMRP granules, Staufen granules	In the cytoplasm of neurons	Transport granules that store translationally repressed mRNA (also rRNA) to prevent translation and decay of mRNA until delivered to specific sites	[7,26]
	Metabolic bodies	Purinosomes	Cytoplasm of somatic cells	Protein storage granules in the quiescent state that serve as reservoirs for reentry into cell cycle when nutrients are available again	[5,28,39]
	Actin bodies		Cytoplasm of somatic cells	Store reorganized F-actin network components in the quiescence phase, which, like in metabolic bodies, can be used for F-actin formation after cell-cycle reentry	[30]
	JUNQ/IPOD = Inclusion bodies		In the yeast cytoplasm in proximity to the nucleus (JUNQ) and located in the peripheral perivacuolar location (IPOD)	Storage of soluble ubiquitinated misfolded proteins in juxtanuclear compartments (JUNQ) and terminally aggregated proteins in peripheral inclusions (IPOD)	[37]
	Proteasome storage granules			Proteasome Cytoplasmic storage reservoirs that are mobilized upon exit from quiescent state	[21]
	Aggresomes		Associated with microtubule organizing center	Forms when proteasome's degradative capacity is exceeded	[17]
	Centrosome/ Spindle pole bodies (SPB)		Mitotic spindle poles	Microtubule organizing center	[16,36]
	U bodies			Sites for assembly & storage of uridine-rich snRNPs (spliceosome)	[23]
Nuclear bodies	Nucleoli (singular: nucleolus)		Forms around actively transcribing ribosomal gene clusters	Function in rRNA transcription, processing and ribosomal subunit assembly	[38]
	Histone locus bodies (HLB)		Associated with chromosomal locus of histone genes	Transcription and 3′-end processing of replication-dependent histone genes	[24,25]
	Cajal bodies (CBs)	Spheres, coiled bodies	Associate transiently with specific genomic loci	Involved in biogenesis of histone, snRNA (spliceosome) and small nucleolar (sno)RNA genes; function in trafficking of snRNPs and snoRNPs	[13,25]
	PML bodies	ALT-associated PML bodies, ND10-, PODs (PML oncogenic domains) or Kr bodies	Associate transiently with specific genomic loci	Induced by DNA damage; to maintain telomeres using an alternative recombination-mediated lengthening mechanism	[35]
	Speckles	Interchromatin granule cluster	Often associated with Cajal bodies	Involved in the storage, assembly and modification of pre-mRNA splicing factors	[33]
	Paraspeckles		Interchromatin space of the nucleoplasm	Regulate gene expression by retaining RNAs in the nucleus	[12]
	Nuclear stress bodies		Nucleoplasm of human cells; frequently adjacent to chromatin blocks	Form in response to heat shock; participate in rapid changes of gene expression through chromatin remodeling and trapping of transcription and splicing factors	[9]
	Clastosome		Nucleoplasm	Form when elevated levels of proteins targeted for proteasome-dependent degradation queue up for proteolysis, recruit additional proteins for the proteasome	[20]
	Cleavage bodies		Adjacent to Cajal bodies	Functions in RNA transcription, splicing, and/or processing; preferentially required during DNA replication; perhaps also for histone gene transcription	[22]
	OPT (Oct1/ PTF/ transcription) domains		Appear in G1 phase next to nucleoli	Sites where particular genes and transcription factors are concentrated	[29]
	Polycomb (PcG) bodies		Associated with heterochromatin; larger foci localized near centromeres	Transcriptional repression complex *e.g.* of Hox genes	[31]