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Hypothesis

Intrinsically disordered proteins as crucial constituents of cellular aqueous two phase systems and coacervates

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ABSTRACT

Here, we hypothesize that intrinsically disordered proteins (IDPs) serve as important drivers of the intracellular liquid–liquid phase separations that generate various membrane-less organelles. This hypothesis is supported by the overwhelming abundance of IDPs in these organelles. Assembly and disassembly of these organelles are controlled by changes in the concentrations of IDPs, their post-translational modifications, binding of specific partners, and changes in the pH and/or temperature of the solution. Each resulting phase provides a distinct solvent environment for other solutes leading to their unequal distribution within phases. The specificity and efficiency of such partitioning is determined by the nature of the IDP(s) and defines "targeted" enrichment of specific molecules in the resulting membrane-less organelles that determines their specific activities.
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1. Introduction

1.1. Membrane-less organelles and liquid–liquid phase transitions

It is well known that the space inside the cell is crowded and inhomogeneous. Recent studies clearly indicate that the cytoplasm and nucleoplasm of any cell contain various membrane-less organelles, the dynamic assemblies typically containing both RNA and protein, and known as ribonucleoprotein (RNP) granules/bodies, or RNP droplets [1]. These membrane-less organelles form via colocalization of molecules at high concentrations within a small cellular micro-domain. Examples of such organelles include PML bodies or nuclear dots, or PODs [2], perinucleolar compartment (PNC) [3], the Sam68 nuclear body (SNB) [3], paraspeckles [4], nuclear speckles or interchromatin granule clusters [5], nucleoli [6], processing bodies [7], germline P granules [8,9], Cajal bodies (CBs; [10]), centrosomes [11], and stress granules [12]. Being devoid of membrane, these organelles or bodies are highly dynamic, and their components exist in direct contact with the surrounding nucleoplasm or cytoplasm [13,14]. Many of these structures were shown to be just slightly denser than the rest of the nucleoplasm or cytoplasm [15,16]. All this suggests that although these membrane-less organelles may be considered as a different "state" of cytoplasm or nucleoplasm, their major biophysical properties are rather similar to those of the rest of the intracellular fluid [1]. Therefore, these cellular bodies being only slightly denser than the bulk intracellular fluid and being characterized by high level of internal dynamics, can be considered as liquid-droplet phases of the nucleoplasm/cytoplasm [8,12,17–20].

Another important feature that various cellular membrane-less organelles have in common is the mechanism of their formation, which is believed to be related to the intracellular phase transitions [1]. These phase transitions in aqueous media originate from the different effects of macromolecules on the structure and solvent properties of water and are related to the high concentrations of macromolecular solutes. At low concentrations of macromolecules, the solution exists as a single phase, whereas at high concentrations, phase separation occurs [21].

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Table 1
Disorder content in proteins found in various membrane-less cytoplasmic and nucleoplasmic organelles. For each organelle, proteins are arranged according to the decrease in the extent of their disorder evaluated as percentage of the residues predicted to be disordered (i.e., possessing disorder scores above 0.5) by PONDR® VSL2, which is among the more accurate disorder predictors.

Protein name	UniProt ID	Number of residues	PONDR® VSL2 (% disordered residues)	MobiDB (% disordered residues)[a]	Molecular functions (GO terms)[b]
PML bodies [2]					
Speckled 100 kDa protein (Sp100)	P23497	879	77.8	61.0	Protein binding, DNA binding, transcription corepressor, transcription coactivator, protein homodimerization, chromo shadow domain binding, identical protein binding, kinase binding, protein domain specific binding, transcription factor binding
Promyelocytic leukemia protein (PML)	P29590	882	53.1	27.0	Protein binding, DNA binding, transcription coactivator, zinc ion binding, SUMO binding, ubiquitin protein ligase binding, cobalt ion binding, protein homodimerization, protein heterodimerization
Perinucleolar compartment (PNC) [90]					
Nucleolin	P19338	710	86.2	64.9	Protein binding, RNA bonding, telomeric DNA binding, poly(A) RNA binding, identical protein binding, protein C-terminus binding, nucleotide binding
KH-type splicing regulatory protein (KSRP)	Q92945	711	76.2	67.8	DNA binding, poly(A) RNA binding
Ribonucleoprotein PTB-binding 1 (Raver1)	Q8IY67	606	74.2	45.4	Poly(A) RNA binding, nucleotide binding
CUG binding protein-2 (CUG-BP2)	O95319	508	60.4	15.6	Poly(A) RNA binding, RNA binding, nucleotide binding
Ribonucleoprotein PTB-binding 2 (Raver2)	Q9HCJ3	691	54.0	25.0	Poly(A) RNA binding, nucleotide binding
CUG binding protein-1 (CUG-BP1)	Q92879	486	50.0	21.6	BRE binding, poly(A) RNA binding, nucleotide binding, protein binding, translation repressor, nucleic acid binding, mRNA binding, RNA binding
Polypyrimidine tract-binding protein (PTB)	P26599	531	40.7	18.6	Poly(A) RNA binding, protein binding, nucleotide binding, RNA binding, pre-mRNA binding, poly-pyrimidine tract binding
Polypyrimidine tract-binding protein 3 (Rod1)	O95758	552	39.3	19.0	Poly(A) RNA binding, RNA binding, nucleotide binding,
Sam68 nuclear body (SNB) [3]					
Sam68 like mammalian-1 (SML1)	Q5VWX1	349	82.5	63.6	Poly(A) RNA binding, poly(U) RNA binding, protein binding,
Src associated in mitosis 68 kDa protein (Sam68)	Q07666	443	79.7	66.1	Poly(A) RNA binding, poly(U) RNA binding, protein binding, poly(A) binding, SH3/SH2 adaptor activity, DNA binding, RNA binding,
Sam68 like mammalian-2 (SML2)	O75525	346	68.2	54.3	Poly(A) RNA binding, RNA binding, protein binding
Paraspeckles [4,91]					
Polypyrimidine tract-binding protein-associated-splicing factor or splicing factor, proline- and glutamine-rich (PSF or SFPQ)	P23246	707	79.8	74.5	Poly(A) RNA binding, core promoter binding, transcription regulation sequence-specific DNA binding, protein binding, nucleotide binding
Paraspeckle protein 1 (PSPC1)	Q8WXF1	523	75.7	52.2	Poly(A) RNA binding, core promoter binding, protein binding, nucleotide binding
Non-POU domain-containing octamer-binding protein or 54 kDa nuclear RNA- and DNA-binding protein (NONO or P54NRB)	Q15233	471	76.9	56.1	Poly(A) RNA binding, core promoter binding, protein binding, nucleotide binding, identical protein binding
Nuclear speckles or interchromatin granule clusters [5,92]					
Transformer-2 protein homolog α (TRA2A)	Q13595	282	80.5	72.3	Nucleotide binding, poly(A) RNA binding
Transformer-2 protein homolog β (TRA2B)	P62995	288	79.5	72.6	Nucleotide binding, poly(A) RNA binding, mRNA binding, protein binding
Arginine/serine-rich domains-containing splicing factor, suppressor-of-white-apricot (SFSWAP)	Q12872	951	79.2		RNA binding
Nuclear inhibitor of protein phosphatase 1 (NIPP-1)	Q12972	351	69.5	64.7	DNA binding, RNA binding, protein binding, endonuclease activity, ribonuclease E activity, protein phosphatase type 1 regulator activity, protein serine/threonine phosphatase inhibitor activity
Threonine-proline repeats-containing splicing factor 3B subunit 1 (SF3B1)	O75533	1304	39.1	29.8	Chromatin binding, protein binding, poly(A) RNA binding
Nucleoli [6]					
Ribosomal proteins, many of which are known to be highly disordered [93]					rRNA binding, structural constituent of ribosome
Processing bodies or P-bodies					
Proline-rich nuclear receptor coactivator 2 (PNRC2)	Q9NPJ4	139	97.1	81.3	Protein binding
Trinucleotide repeat-containing gene 6A protein (TNRC6A)	Q8NDV7	1,962	96.5	79.9	Protein binding, poly(A) RNA binding, nucleotide binding
Eukaryotic translation initiation factor 4E transporter (EIF4ENIF1)	Q9NRA8	985	93.3	57.5	Protein binding, poly(A) RNA binding, protein transported activity
CCR4-NOT transcription complex subunit 3 (CNOT3)	O75175	753	80.5	58.3	Protein binding
LIM domain-containing protein 1 (LIMD1)	Q9UGP4	676	69.8	50.3	Protein binding, zinc ion binding, transcription corepressor activity

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