Trends in Biochemical Sciences

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Review

DSS1/Sem1, a Multifunctional and Intrinsically Disordered Protein

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DSS1/Sem1 is a versatile intrinsically disordered protein. Besides being a *bona fide* subunit of the 26S proteasome, DSS1 associates with other protein complexes, including BRCA2–RPA, involved in homologous recombination; the Csn12–Thp3 complex, involved in RNA splicing; the integrator, involved in transcription; and the TREX-2 complex, involved in nuclear export of mRNA and transcription elongation. As a subunit of the proteasome, DSS1 functions both in complex assembly and possibly as a ubiquitin receptor. Here, we summarise structural and functional aspects of DSS1/Sem1 with particular emphasis on its multifunctional and disordered properties. We suggest that DSS1/Sem1 can act as a polyanionic adhesive to prevent nonproductive interactions during construction of protein assemblies, uniquely employing different structures when associating with the diverse multisubunit complexes.

The Disordered Protein DSS1

DSS1 is a small, 70–90 residue long (depending on the species), phylogenetically conserved eukaryotic protein. The gene was originally linked to split hand/split foot malformation (SHFM), an autosomal dominant limb developmental disorder, characterised by missing digits and fusion of the remaining digits, and therefore named DSS1 for deletion of split hand/split foot 1 [1,2]. However, since deletion of regions near, but not covering the *DSS1* gene, also give rise to SHFM [3], the role of DSS1 in SHFM is unclear. Subsequently, the budding yeast DSS1 orthologue was isolated as a suppressor of various mutants in the exocyst complex, and named Sem1 for suppressor of exocyst mutations 1 [4].

Deletion of DSS1 in *Caenorhabditis elegans* leads to defects in oogenesis, embryonic lethality, and larval arrest [5]. Yeast mutants lacking DSS1/Sem1 display pseudohyphal and temperature-sensitive growth [4,6,7], and are sensitive to canavanine, an amino acid analogue that induces protein misfolding and thus increases the dependency for protein degradation via the **ubiquitin–proteasome system (UPS)** (see Glossary) [7–10]. In fission yeast, the growth defect is suppressed by overexpression of certain other proteasome subunits, suggesting that the phenotype is, at least in part, connected to a structural destabilisation of the **26S proteasome** [7,11].

The sequence of DSS1/Sem1 is enriched in negatively charged residues (33% in fission yeast, 39% in human) and contains three conserved sequence regions. Each of these consists of a few hydrophobic residues flanked by acidic residues, forming a tripartite patch (Figure 1A). DSS1 belongs to the group of **intrinsically disordered proteins (IDPs)**, that is, proteins lacking a defined 3D structure and with specific sequence characteristics [12,13]. It is disordered in its

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Dss1 is a conserved, intrinsically disordered and multifunctional protein.

Dss1 is a component of multiple structurally and functionally diverse protein complexes.

While several disordered proteins have been shown to change shape depending on the binding partner, Dss1 adapts this capability as it associates with different multisubunit protein complexes.

Dss1 molecular functions include targeting, complex assembly, stabilisation, and protection.

Dss1 cellular functions include regulating proteasome assembly, ubiquitin binding, transcription, mRNA export, and DNA repair.

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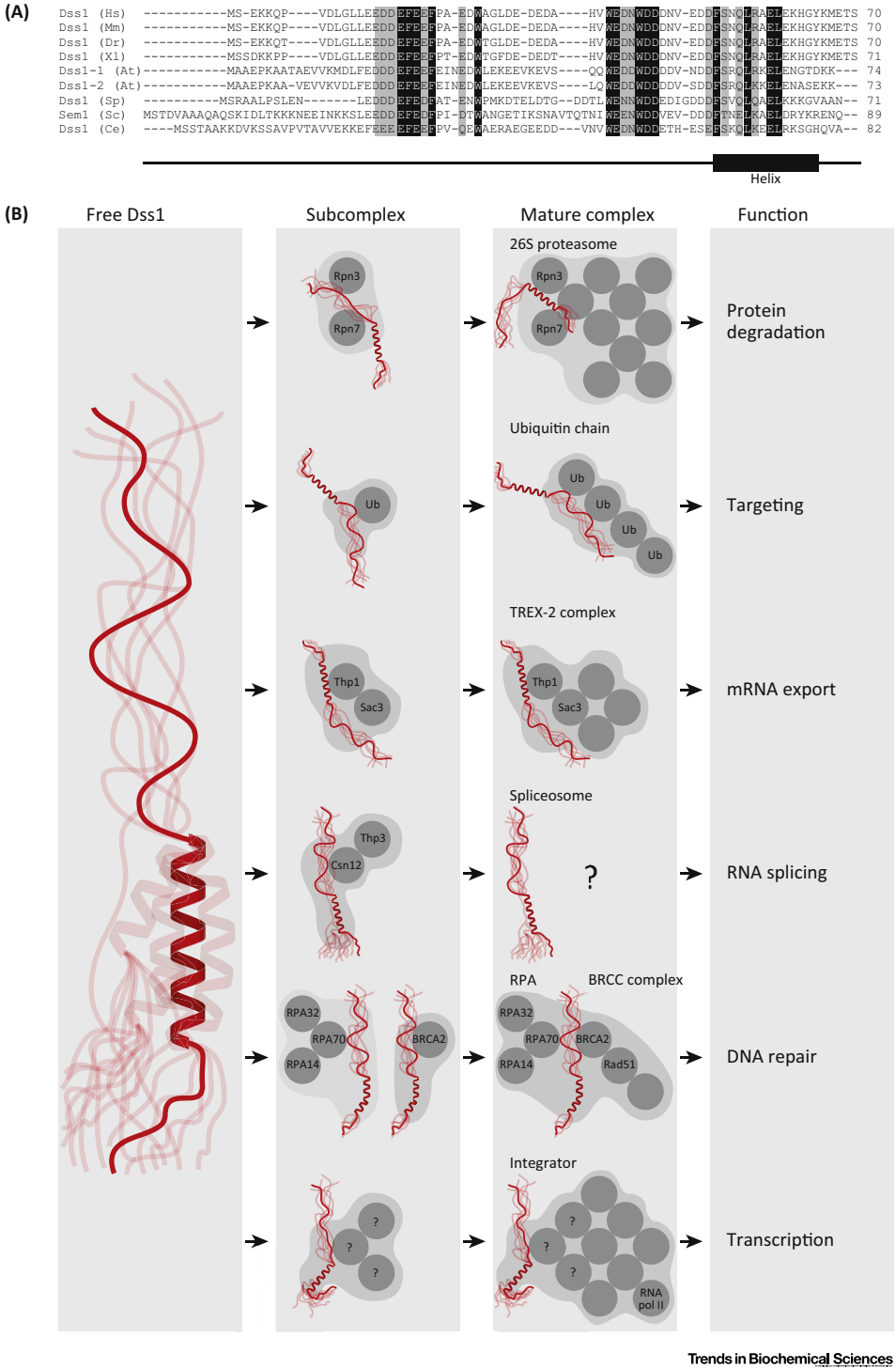

Figure 1. Phylogenetic Conservation of DSS1 and DSS1-Containing Protein Complexes. (A) Multiple sequence alignment of human (Hs), mouse (Mm), zebra fish (Dr), frog (Xl), plant (At), fission yeast (Sp), budding yeast (Sc), and worm (Ce) DSS1. Conserved residues have been shaded (black, identical; grey, conserved). The bar indicates the C-terminal helical region. (B) The known DSS1-binding proteins, protein complexes, and their functions. Often DSS1 binds first to smaller subcomplexes that are later incorporated into larger protein assemblies. Whether this is also the case for DSS1 in the integrator is unknown. It is also unknown whether the DSS1–Csn12–Thp3 complex is incorporated into a larger complex prior to its function in RNA splicing. The disordered nature of DSS1 is illustrated by several copies of the protein shaded in the background.

Glossary

26S proteasome: is a 3 MDa protein complex that mediates degradation of ubiquitylated proteins. It is found in the cytosol and nucleus in all eukaryotic cells.

COP9 signalosome (CSN): is a large protein complex that interacts with cullin–RING ubiquitin ligases and regulates their activity by removing the ubiquitin-like protein Nedd8 from cullins. Note that the DSS1-binding protein CSN12 is not a subunit of the COP9 signalosome. Recently, the DSS1 paralogue CSNAP was shown to be a subunit of the COP9 signalosome.

Eukaryotic translation initiation factor 3 (eIF3): is a protein complex that organises components that initiate translation on the ribosome and thus plays a central role in protein synthesis.

Homologous recombination: is a type of genetic recombination in which a stretch of DNA is exchanged between two similar DNA molecules. The mechanism is widely used by cells as an error-free mechanism to repair double-strand DNA breaks.

Intrinsically disordered protein (IDP) or region (IDR): a protein, or a protein region, that lacks a defined globular fold and exhibits extraordinary conformational flexibility. This results from an underrepresentation of hydrophobic amino acid residues and low sequence complexity. IDPs and IDRs are best described as unstructured ensembles of interchangeable conformations. The length of an IDR varies, but long (more than 30 residues) IDRs are frequent in eukaryotic proteins.

mRNA maturation and export: eukaryotic gene expression involves movement of mRNA transcripts from the site of synthesis in the nucleus to the cytosol, where they can be translated into proteins. Pre-mRNAs transcribed in the nucleus are processed (capped and polyadenylated) and packaged with proteins into messenger ribonucleoprotein (mRNP) complexes. Correctly assembled mRNPs are targeted to nuclear pore complexes for nuclear export into the cytosol.

PCI domain-containing protein complexes: PCI domains are helical regions found in (and named for) subunits of the 26S proteasome, COP9 signalosome (CSN), and