MS42 Solving Structures Through Combination of Reciprocal and Direct Space Methods

MS42-05

Multi-methodological approach to solve SBDS protein involved in the molecular mechanism of Shwachman Diamond Syndrome

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Abstract

The Shwachman-Diamond Syndrome (SDS, OMIM #260400 and #617941) is an autosomal recessive disease that affects many parts of the body, including bone marrow, pancreas, bones, immune and central nervous systems [1], with an increased risk of progression to myelodysplastic syndrome [2]. In most cases (90%), SDS is associated with mutations in the Shwachman-Bodian-Diamond Syndrome gene (SBDS, OMIM gene #607444), located in chromosome 7q11 and encoding for a protein, named SBDS, structurally organized into three highly conserved domains [2–4]. SBDS is required for the assembly of mature ribosomes and ribosome genesis. Together with the Elongation Factor Like-1 EFL1 (OMIM gene #617538) [5], SBDS triggers the GTP-dependent release of eIF6 (eukaryotic initiation factor 6) from 60S pre-ribosomes in the cytoplasm [2,6,7], thereby activating the ribosomes for translation competence by allowing 80S ribosome assembly and by facilitating eIF6 recycling to the nucleus, where it is required for 60S rRNA processing and nuclear export. In this mechanism, SBDS acts as the nucleotide exchange factor (GEF) for EFL1[8,9], increasing its affinity for GTP over GDP [6]. In this presentation, we aimed to show the *Archaeoglobus fulgidus* SBDS (AfSBDS) protein structure solved by the crystallographic method (data collected at the Diamond Light Source beamline I24) [10], as well as the conformations of the protein (both archaeal and yeast orthologues) in the solution obtained small-angle X-ray scattering (SAXS) technique (data collected at the Diamond Light Source beamline B21) [10, 11]. Furthermore, starting from the observation that SBDS single-point mutations, localized in different domains of the proteins, are responsible for an SDS phenotype, we carried out the first comparative Molecular Dynamics simulations on three SBDS mutants [manuscript in preparation].

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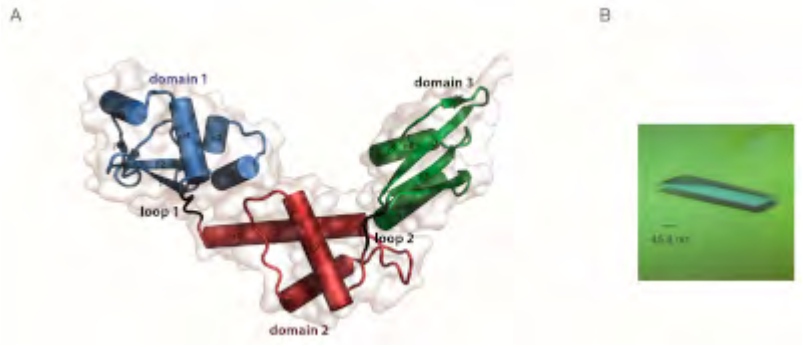
Crystallographic model of SBDS and its crystal



Ensemble of SBDS conformations obtained by SAXS