Rare diseases but common problems: Shwachman Diamond Syndrome from genetics to therapy through the combination of nanoscale techniques

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Shwachman-Diamond Syndrome (SDS) is a ribosomopathy with a wide spectrum of clinical presentations [1] associated with the loss of function of Shwachman-Bodian-Diamond Syndrome (SBDS) protein [2] and as we described for the first time [3], the Elongation Factor-Like 1 (EFL1).Together, these proteins remove the anti-associationfactor eIF6 from the surface of the pre-60S ribosomal subunit to promote the formation of mature ribosomes. Due to the lack of knowledge of the molecular mechanisms responsible for SDS pathogenesis, current therapy is nonspecific and focuses only at alleviating the symptoms. For that reason, we studied [4] the interaction mechanism of the proteins in solution and demonstrated that binding SBDS*EFL1 consists of two independent and cooperative events, with domains 2–3 of SBDS directing the initial interaction with EFL1, followed by docking of domain 1. In solution, both proteins exhibited large flexibility and consisted of an ensemble of conformations, as demonstrated by Small Angle X-ray Scattering (SAXS) experiments [4, 5]. SAXS is a powerful technique for structural investigation of macromolecules in solution as for nanoparticles in solution or in solid state. Building on the recent observation that EFL1 single-point mutations clinically manifest as SDS-like phenotype, we carried out comparative Molecular Dynamics (MD) simulations on three mutants, T127A, M882K and R1095Q and wild type EFL1 [6] combining with SAXS experiments. This study supports the notion that EFL1 function is governed by an allosteric mechanism involving the concerted action of GTPase domains and can help point towards new approaches to SDS treatment.

References

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