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Molecular basis of the human ribosomopathy Shwachman-Diamond syndrome

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ABSTRACT

Mutations that target the ubiquitous process of ribosome assembly paradoxically cause diverse tissue-specific disorders (ribosomopathies) that are often associated with an increased risk of cancer. Ribosomes are the essential macromolecular machines that read the genetic code in all cells in all kingdoms of life. Following pre-assembly in the nucleus, precursors of the large 60S and small 40S ribosomal subunits are exported to the cytoplasm where the final steps in maturation are completed. Here, I review the recent insights into the conserved mechanisms of ribosome assembly that have come from functional characterisation of the genes mutated in human ribosomopathies. In particular, recent advances in cryo-electron microscopy, coupled with genetic, biochemical and prior structural data, have revealed that the SBDS protein that is deficient in the inherited leukaemia predisposition disorder Shwachman-Diamond syndrome couples the final step in cytoplasmic 60S ribosomal subunit maturation to a quality control assessment of the structural and functional integrity of the nascent particle. Thus, study of this fascinating disorder is providing remarkable insights into how the large ribosomal subunit is functionally activated in the cytoplasm to enter the actively translating pool of ribosomes.

Contents

Abbreviations: rRNA, ribosomal RNA; rDNA, ribosomal DNA; ITS1, internal transcribed spacer 1; ITS2, internal transcribed spacer 2.

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1. Introduction

Shwachman-Diamond syndrome (SDS, OMIM #260400) is a fascinating autosomal recessive disorder associated with bone marrow failure and an increased risk of transformation to myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML). SDS is also characterised by multiple developmental anomalies including poor growth, exocrine pancreatic insufficiency, skeletal abnormalities (including metaphyseal chondrodysplasia, rib cage dysplasia and osteopenia) and cognitive impairment. However, registry data indicate that the phenotypic spectrum of this rare disease (estimated prevalence of 1 in 77,000 births) is broad (Myers et al., 2014). SDS is most commonly associated with biallelic mutations in the eponymous *SBDS* gene (Boocock et al., 2003), named after the US physician Harry Shwachman, the British ophthalmologist Martin Bodian and the American paediatrician Louis Diamond who reported the syndrome in 1964 (Shwachman et al., 1964). However, Nezelof and Watchi first described SDS as “congenital lipomatosis of the pancreas” in 1961 in two children with exocrine pancreatic insufficiency and leucopenia (Nezelof and Watchi, 1961).

In a French cohort of 102 SDS patients, the cumulative incidence of MDS/AML was 18.8% at 20 years and 36.1% at 30 years of age (Donadieu et al., 2012). Among young adults (18–40 years old) transplanted for MDS who were enrolled in the Center for International Blood and Marrow Transplant Research (CIBMTR) repository between 2005 and 14, 4% were discovered to have germline compound heterozygous mutations in the *SBDS* gene (Lindsley et al., 2017) with concurrent somatic biallelic loss-of-function *TP53* variants. These SDS patients, who were mostly undiagnosed prior to transplant, had a remarkably poor prognosis (median survival of 1.2 years). Thus, loss-of-function *TP53* mutations appear to be biologically important for clonal progression and transformation to haematological malignancy in SDS. Although the incidence is unknown, a limited number of case reports have highlighted a range of solid tumours presenting at a young age in individuals with SDS (Dhanraj et al., 2013; Nakaya et al., 2014; Sack et al., 2011; Sharma et al., 2014; Singh et al., 2012; Verbrugge and Tulchinsky, 2012).

Since the recognition of SDS as a distinct clinical entity in 1961, there have been several key advances in the characterisation of the disease. A major milestone was the identification of biallelic mutations in the *SBDS* gene in 90% of individuals with SDS (Boocock et al., 2003). A second milestone was the discovery that SBDS functions as a cofactor for elongation factor-like GTPase 1 (EFL1) in removing the anti-association factor eIF6 from the subunit joining face of the large (60S) ribosomal subunit in the final step of late cytoplasmic maturation (Finch et al., 2011; Menne et al., 2007; Wong et al., 2011). A third major step was visualising the human SBDS and EFL1 proteins bound to 60S ribosomal subunits carrying endogenous eIF6 using single-particle cryo-electron microscopy (cryo-EM) (Weis et al., 2015). The structures suggest that eIF6 is removed by a cofactor-dependent conformational switching mechanism and allow SDS-associated disease mutations to be interpreted for the first time in a ribosomal context. Finally, the discovery of mutations in the 60S ribosome assembly factor *DNAJC21* (yeast *JJJ1*) in SDS (Dhanraj et al., 2017; Tummala et al., 2016) reveals genetic heterogeneity in this disorder, but supports the original hypothesis that the primary defect in SDS is impaired maturation of the large ribosomal subunit (Menne et al., 2007).

The aim of this review is to discuss the considerable expansion in our understanding of the molecular basis of SDS and to illustrate how elucidation of the function of the genes mutated in this disorder is providing important new mechanistic insights into the fundamental conserved process of ribosome assembly and its quality control. A key remaining challenge is to explain how mutations that affect protein synthesis in all cells cause such tissue-specific abnormalities. Finally, we need to harness new mechanistic insights to develop novel therapeutics that will improve the outcomes for SDS patients and their families.

2. Genetic heterogeneity in Shwachman-Diamond syndrome

In 2003, a positional cloning strategy identified biallelic mutations in the highly conserved *SBDS* gene in the majority of individuals with SDS (Boocock et al., 2003). Pathogenic mutations arise as a consequence of gene conversion due to recombination between *SBDS* and an unprocessed pseudogene located in a distal paralogous duplicon. More than 90% of affected individuals carry one of three common pathogenic SBDS variants on one allele in exon 2: 183_184TA > CT, 258+2T > C, or the combination of 183_184TA > CT + 258 +2T > C. The mutation 258+2T > C disrupts the donor splice site of intron 2, while the dinucleotide alteration, 183–184TA→CT, introduces an in-frame stop codon (K62X). Although most parents of children with SDS are carriers, about 10% of *SBDS* mutations arise de novo (Steele et al., 2014). In addition, more

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