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Clinical spectrum and molecular pathophysiology of Shwachman-Diamond syndrome

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Abstract

PURPOSE OF REVIEW—Shwachman Diamond syndrome (SDS) is an inherited bone marrow failure and cancer predisposition syndrome that affects multiple organ systems. Mutations in the *SBDS* gene are found in the majority of patients, but the molecular function of the SBDS protein product remains unclear. Here, we review recent progress in the clinical and molecular characterization of SDS.

RECENT FINDINGS—Emerging data support a multifunctional role for the SBDS protein. Current studies indicate that SBDS functions in 60S large ribosomal subunit maturation and in mitotic spindle stabilization. Recent data suggest it may also affect actin polymerization, vacuolar pH regulation and DNA metabolism. SBDS loss results in both hematopoietic cell-intrinsic defects as well as marrow stromal abnormalities.

SUMMARY—SDS is a multisystemic disease arising from defects in a protein that participates in several essential cellular processes. Elucidating the molecular function of SBDS will provide important insights into how defects in ribosome biogenesis and mitotic spindle stabilization result in hematopoietic failure, cancer predisposition, and abnormalities.

Keywords

bone marrow failure; leukemia; neutropenia; ribosome; mitotic spindle

INTRODUCTION

Shwachman Diamond Syndrome (SDS) is an autosomal recessively inherited bone marrow failure syndrome originally characterized by neutropenia and pancreatic dysfunction [1,2]. Further studies reported that the hematopoietic defect is not confined to neutropenia, but can also affect red cells and platelets. SDS patients have an increased risk of developing bone marrow aplasia, myelodysplastic changes, and leukemia (reviewed in [3]). Additionally, patients may manifest abnormalities in multiple other organs, most notably in the bones, liver, heart and immunologic system.

In 2003, *SBDS*, a gene highly conserved in eukaryotes and archaeobacteria, was found to be mutated in patients with SDS [4]. Since then, *SBDS* mutations have been identified in approximately 90% of patients who manifest the clinical characteristics of the syndrome. Proteomic data implicated SBDS in RNA metabolism and ribosomal function [5,6]. The *S. cerevisiae* ortholog, Sdo1p, interacts with the ribosomal assembly protein Tif6p to regulate maturation of the 60S large ribosomal subunit and its joining to the 40S subunit to form the mature ribosome [7]. Consistent with a role in ribosomal function, human SBDS is concentrated in the nucleolus and co-sediments with the 60S large ribosomal subunit.

Furthermore, SDS patient cells are more sensitive to inhibition of rRNA transcription[8,9]. Additional functions for SBDS in mitosis are supported by data demonstrating that SBDS also localizes to the mitotic spindle, binds and stabilizes purified microtubules in vitro, and loss of SBDS leads to aneuploidy when mitotic checkpoints are inactivated[10]. A role for SBDS in chemotaxis has been postulated based on the observation that SBDS localizes to the pseudopods in *Dictostyleum* [11] and SDS patient neutrophils exhibit impaired chemotaxis in vitro, though whether this is a direct or indirect effect of SBDS loss remains to be clarified [12]. How the SBDS protein carries out these disparate functions is unclear since the precise molecular function(s) of the *SBDS* protein product remains to be deciphered.

Here we briefly highlight some of the most recent advances (focusing on those published in the past eighteen months) in our understanding of the clinical spectrum of SDS and of the molecular function of the SBDS protein. For additional background, several prior comprehensive reviews are available ([3,13,14]).

CLINICAL SPECTRUM

The complete spectrum of SDS clinical manifestations remains to be characterized. Recent clinical studies have provided a clearer picture of the progression of marrow disease in SDS [15, 16, 17, 18, 19, 20], and better characterized its neurocognitive [21] and hepatic [22] symptoms.

Hematologic manifestations

Much of the information on the prevalence and natural history of SDS has been derived from cohort and cross-sectional studies. The relative estimated allele frequencies of SDS (~1/140 –from an estimated incidence of 1 in 76,538 live births, based on the relative frequency to cystic fibrosis patients in patients with pancreatic failure[23]) and Fanconi Anemia (FA) (1/100–1/300)[24,25], suggests that SDS is likely more common than currently recognized. In the NIH registry, SDS (7%) is the fourth most common IBMFS, behind FA (27%), dyskeratosis congenita (DC) (20%), and Diamond Blackfan Anemia (DBA) (25%)[15]. In the Canadian Inherited Marrow Failure Study, SDS (27%) and FA patients are equally represented, and less than only DBA patients (31%), but more than severe congenital neutropenia (SCN) (8%) and DC (6%)[16]. In the Israeli Inherited Bone Marrow Failure Registry, SDS comprise a smaller proportion of patients - FA 52%, SDS 2% - but this population based registry may be skewed by the increased incidence of FA in the Ashkenazie Jewish population[17,24]. As with any Registry study, referral biases may affect the relative frequencies of the different syndromes enrolled.

As in FA or DC, the marrow disease in SDS can progress, leading to aplastic anemia, myelodysplastic syndrome or acute myelogenous leukemia. The definition of MDS in SDS patients was not consistent between studies thus generalizations are difficult. Previous estimates of the rate of transformation to MDS or AML gave rates of 18.8% at 20 years and 36.1% at 30 years from a group of 55 SDS patients in the French registry[26]. Similarly, the crude rate of MDS/AML of SDS patients was approximately 1%/year from a limited number (22) of SDS patients in the Severe Chronic Neutropenia International Registry[27]. In comparison to the other IBMFS tracked by the Canadian registry, the cumulative rate of transformation for SDS (18%) was intermediate between FA (41%), and DC (13%), SCN (10%), and DBA (0%)[16]. In contrast, none of the 17 SDS patients in the NIH registry, nor any of the 3 in the Israeli registry developed MDS or AML[15,17]. Importantly, while the median age of the NIH SDS patients was 14 years old[15], those SDS patients in the Canadian study that transformed did so at a median age of 20 years[16], and those in the French cohort transformed at a median age of 19.1 years, with most occurring after 20

years[26]. These data indicate that the pace and likelihood of malignant transformation in SDS is lower than that in FA.

In addition to developing clonal myeloid disease such as MDS and AML, SDS patients also have a propensity to acquire characteristic cytogenetic clones that may persist without immediate further evolution of their marrow disease. Notably, clones of isochromosome i(7)(q) may wax and wane for years without malignant transformation [28]. Using microsatellite analysis, Minelli and colleagues determined the parental origin of the isochromosome 7 clones present in 8 patients who were compound heterozygotes for mutations in *SBDS*. All eight patients carried the c.258+2T>C allele, which disrupts the donor splice site in intron 2 and leads to a truncated protein, but allows the production of a small amount of full-length protein, as well as an allele that introduces an in-frame premature stop codon. In all eight cases, the isochromosome was derived from the parental chromosome containing the splicing mutant. This result suggests that the selective advantage of cells having three copies of an allele with partial expression of *SBDS* may give rise to the i(7)(q) clones[18].

Two recent reports provide additional insights into the natural history of a second commonly seen cytogenetic abnormality in SDS - del(20)(q11q13)[19,20]. The first describes two patients who developed del(20)(q11q13) clones at age 12 years, and whose clones persisted for over six years without progression to MDS or AML. In one patient, the positive clones progressively increased over six years until all marrow cells were positive. The authors detected del(20q) cells in all hematopoietic lineages from both patients, leading them to conclude that the del(20)(q11q13) clones arose in a totipotent cell which retains its ability to differentiate despite the abnormal karyotype[19]. The second is a report of the cytogenetic findings of a cohort of 37 SDS patients, 18 of whom developed abnormal cytogenetic clones. All of the clones involved either chromosome 7 or chromosome 20. Of the chromosome 7 abnormalities, 10 were isochromosome i(7q)(10), one was a deletion del(7)(q22q32), and one had additional materials add7(p?). Of the six chromosome 20 clones, all began as del(20)(q11), but two developed subclones with additional alterations. The patients had been followed for 3 months to 9 years and at the time of the report, eight were stable, four had increased, and 1 had decreased; only the patient with the add7(p?) clone developed MDS. Importantly, no AML developed despite the fact that all the del(20)(q11) clones included a region commonly deleted in MDS and AML. Thus, the acquisition of either isochromosome i(7)(q11) or the deletion del(20)(q11) is likely a relatively benign event, rather than a herald of imminent progression to MDS or AML. Furthermore, the acquisition of the abnormal cytogenetic clones appear to be an age-related phenomenon in SDS patients as the frequency of such clones increase with age – they were present in 4/17 patients below 10 years, 8/14 between 10 and 20, and in 4/4 of those older than 20 years[20].

Neurocognitive impairment

Although SDS was first described over 45 years ago, due to its rarity and phenotypic variability, its clinical spectrum is still being fully characterized. In follow up to prior reports of neurocognitive impairment in SDS patients[29], Kerr and colleagues performed systematic neuropsychological assessments of the largest cohort of SDS patients to date. Thirty four children with SDS from Canada and the United States were compared with 13 siblings and with 20 patients with cystic fibrosis. Although SDS patients exhibited a wide range of abilities – from severely impaired to very superior in some measures – as a group, SDS patients generally had significant impairments in intelligence, language abilities, perceptual skills, and academic achievement. On measures of attention, SDS patients scored lower than CF patients, but not sibling controls. The authors note that 1 in 5 SDS patients met the diagnostic criteria for intellectual disability (<2nd percentile), and that the proportion (6%) of the children with diagnosed with pervasive developmental disorder is much higher

than the expected number (1/165)[21]. This study highlights an underappreciated facet of SDS, suggests a role for *SBDS* in neurodevelopment, and raises the importance of early neurocognitive assessment and intervention.

Hepatopathy

In addition to pancreatic insufficiency, SDS patients may manifest additional gastrointestinal alterations, most prominently in the liver (reviewed in [3]). The liver manifestations were further characterized in a cohort of 12 SDS patients in a population based study from Finland[22]. Consistent with previous reports, they found that elevated transaminases and hepatomegaly occurred early in life, but normalized over time. In contrast, more than half of the patients had elevated bile acid levels at the time they were tested for the study. The authors also provide a longitudinal assessment of liver imaging changes, showing that hepatomegaly was present only in patients younger than 3 years of age, but that all three patients older than 30 years old had developed hepatic microcysts. Thus, it appears that the elevated transaminases and hepatomegaly present in some young SDS patients resolve over time, but cholestasis may persist, and hepatic microcysts may develop in older patients[22].

MOLECULAR PATHOPHYSIOLOGY

SBDS appears to be a multifunctional protein implicated in several important cellular pathways. There is accumulating evidence for its role in ribosomal function [30, 31, 33-36] as well as in microtubule binding [37] and actin polymerization [38]. Moreover, several recent studies posit additional functions [36, 39, 40]. In mouse models, deficiency of *SBDS* expression in marrow osteoprogenitor cells leads to hematologic and skeletal abnormalities [41].

RNA Metabolism and ribosomal function

Recent studies provide additional insights into SBDS structure and further illuminate its interaction with RNA. Ng et al solved the crystal structure of the *Methanothermobacter* SBDS to 1.75 angstrom resolution and de Oliveira et al determined the structure of human SBDS by solution NMR[30,31]. Both groups describe a tripartite domain structure consisting of an amino terminal (NT) FYSH domain, a central three-helical domain, and a carboxy-terminal (CT) ferredoxin-like domain, linked by flexible connectors, similar to that previously determined for *Archaeoglobus fulgidus*[6,30-32]. NMR studies indicated that the NT domain is the site of RNA-SBDS interactions, and moves independently of domains II and III, which act as one unit[31]. Additionally, the budding yeast ortholog, Sdo1p, was shown to co-immunoprecipitate with a number of rRNA species and their processing intermediates[33]. In human, methanobacter, and yeast systems, RNA binding does not appear to be sequence specific, though there may be increased affinity for poly AU tracts in the human and yeast, and with GC-rich sequence in yeast[31,33].

Because both SDS and DBA have been linked to ribosomal dysfunction, Moore et al compared the effect of yeast models of DBA (*RPL33A*) and SDS (*SDO1*) on the ribosome. Both mutants exhibit a selective decrease in the 60S large ribosomal subunit and an accumulation of half-mer polysomes containing stalled 48S initiation complexes, but the defect in SDS appears to be downstream to that of DBA. Unlike the DBA model, where incompletely assembled ribosome precursors are rapidly degraded, in SDS, 60S particles accumulate in the nucleoplasm[34]. These results support the role previously posited for Sdo1p in Tif6p recycling and the maturation and joining of the 60S ribosomal subunit [7], although half-mer polysomes were not observed in the earlier study.

Further evidence of a link between SBDS and ribosomal function or RNA metabolism comes from expression microarray and protein interaction studies. Gene expression profiles in SDS patient bone marrow cells show that the most deregulated genes cluster among pathways known to be defective in bone marrow failure syndromes was that for translation [35]. The *Methanothermobacter* SBDS co-purifies with ribosomal subunits Rpl1, 2, 14 [30]; similarly FLAG-tagged human SBDS interacts with a number of ribosomal subunits, two heterogeneous nuclear ribonucleoproteins, a nucleolar RNA helicase, and nucleolar proteins nucleophosmin and nucleolin [36]. In the yeast two-hybrid assay, Sdo1p partners with Rpl3p, translation elongation factor Eft2p, nucleolar protein Nip7p, the RNA helicase Prp43p and two of its interaction partners, Spp382p/Ntr1p and Asc1p [33].

Non-RNA functions

Recent investigations also provide additional evidence that SBDS plays roles aside from ribosome maturation and RNA metabolism. Orelia and Kuijpers examined the localization of SBDS in neutrophils, CD34⁺ hematopoietic progenitor cells, and adherent and leukemic cell lines. They found that SBDS is present in the nucleus, perinuclear area, and cytoplasm. Consistent with the previously demonstrated mitotic function of SBDS [10], they also found that SBDS co-localizes with microtubules, microtubule organizing centers, and centrosomes in both primary hematopoietic progenitors and various cell lines, and that SBDS binds microtubules in vitro [37]. Additionally, in activated and adherent neutrophils and a leukemic cell line, SBDS co-localizes with F-actin and Rac2 in cellular protrusions [38], similar to that described for *Dictyostelium* during chemotaxis [11], and F-actin polymerization is disturbed and its polarization delayed in SDS patient neutrophils in response to chemoattractants [38]. Thus, these data support a role for SBDS in both microtubule and actin-dependent cellular processes.

Other recent studies implicate SBDS in additional possible functions. A yeast two-hybrid screen identified an interaction between the C-terminus of SBDS with the cytosolic portion of CLN3, the transmembrane protein mutated in juvenile neuronal ceroid lipofuscinosis (Batten disease). This interaction was confirmed by co-immunoprecipitation and immunofluorescence in mammalian cell lines, and in the yeast model with Btn1p (the yeast CLN3 ortholog) and Sdo1p [39]. Although the function of *CLN3/BTN1* is not well understood, *BTN1* plays a role in vacuolar pH regulation. Interestingly, deletion of *SDO1* alters vacuolar pH and the level of vacuolar ATPase proteins, an effect that is reversed by *TIF6* mutants that suppress the *sdo1* Δ slow growth phenotype [39]. Second, FLAG-tagged human SBDS also co-purified with proteins involved in DNA metabolism, including DNA-PK, RPA1, histones, and XRCC5 [36]. These papers suggest that SBDS may play previously unsuspected roles in vacuolar pH regulation and DNA metabolism.

Previous studies described a role for SDS in both marrow hematopoietic cells [42, 43] and in marrow stromal cells [42]. Unexpected insights on SBDS function in the marrow stroma were elicited from the examination of mice wherein expression of Dicer1, an RNaseIII endonuclease required for microRNA biogenesis and RNA processing, was knocked down specifically in osteoprogenitor cells. This resulted in reduced *SBDS* expression in osteoprogenitor cells and an increased rate of myelodysplasia and myeloid leukemia. Furthermore, selective deletion of *SBDS* in mouse osteoprogenitors results in mice exhibiting bony abnormalities, leucopenia and lymphopenia, increased marrow vascularity, micromegakaryocytes, and dysplastic (though not decreased) neutrophils [41]. Given the skeletal anomalies associated with SDS, a role for SBDS in osteoprogenitor cells is intriguing. Furthermore, these results suggest that normal hematopoiesis requires proper *SBDS* expression in stromal cells. Interestingly, expression microarray analysis of *SBDS*-depleted human cell lines identified VEGFA and osteoprotegerin, two secreted proteins that

affect osteoclast differentiation and vascular formation, as the most significantly upregulated genes [40]. The impact of SBDS on human marrow stromal function in vivo remains unclear since patients with SDS have not manifested high rates of engraftment failure during hematopoietic stem cell transplant (reviewed in [44]). The long term follow up of SDS patients who have undergone stem cell transplant may provide important clues to the clinical impact of stromal cell *SBDS* expression on hematopoiesis.

CONCLUSION

Careful descriptions of the natural history of SDS, and of its effect on multiple involved organs are providing crucial information for counseling patients and families on outcomes and treatments choices, as well as for timely assessments and interventions.

The SBDS protein participates in numerous key cellular functions, though its precise molecular functions remain to be elucidated. How these apparently different functions of SBDS contribute to disease pathogenesis remains an important area of investigation.

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Key points

1. SDS is likely more common than currently recognized
2. Some cytogenetic changes in SDS do not in isolation signal imminent progression to MDS or leukemia
3. The pace and likelihood of malignant transformation in SDS appears lower than that in FA
4. Neuro-cognitive impairment is common in SDS
5. SBDS protein has multiple functions