FULL TEXT ARTICLE

Diagnosis, Treatment, and Molecular Pathology of Shwachman-Diamond Syndrome

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Shwachman-Diamond syndrome (SDS) is an inherited bone marrow failure syndrome classically associated with exocrine pancreatic dysfunction and neutropenia, with a predisposition toward progressive marrow failure, risk of myelodysplastic syndrome, and leukemia. Most patients carry biallelic mutations in the Shwachman-Bodian-Diamond Syndrome gene, which is an integral component of ribosome maturation and biogenesis. This article reviews the diagnosis, clinical characteristics, and treatment modalities of SDS, and reports advances in the understanding of the molecular pathophysiology of SDS.

Key points

- SDS is a challenging marrow failure disorder with exocrine pancreatic dysfunction and diverse clinical phenotype.
- Ongoing advances in ribosomal biogenesis and cellular function contribute to defining the pathogenesis of the molecular phenotype of SDS, with novel candidate genes recently described.
- Further natural history and collaborative efforts are essential to define disease manifestations, prevent known complications, and ensure new and targeted therapies to ameliorate and prevent malignant transformation.

Introduction

Shwachman-Diamond syndrome (SDS) is an autosomal-recessive inherited bone marrow failure (BMF) disorder characterized by exocrine pancreatic dysfunction, BMF, and predisposition toward myelodysplasia syndrome (MDS) or acute leukemia, particularly acute myeloid leukemia (AML). SDS is rare, with an estimated incidence of 1/76,000. [1] Many different body systems are affected, including the skeletal, cardiac, endocrine, nervous, hepatic, and immune systems, although these are not universally affected in all patients, or even within family cohorts.

SDS is a disorder of ribosomal biogenesis, with approximately 90% of individuals having biallelic mutations in the Shwachman-Bodian-Diamond Syndrome (SBDS) gene located on chromosome 7q11. Although the role of the SBDS protein is yet to be fully established, it is thought to play an integral part in ribosomal maturation, and cellular proliferation and the hematopoietic microenvironment. Recently three additional genes associated with ribosome assembly or protein translation (DNAJC21, ELF1, and SRP54) were reported in association with an SDS phenotype. [2] [3] [4]

There is great phenotypic diversity among individuals with SDS, despite most sharing one or more common allelic mutations within SBDS . Given its rarity, the understanding of the pathogenesis, phenotype, treatment, and outcomes has been limited to case series and reports from new registry studies. Similarly, guidelines on management and treatment are based primarily on expert consensus and small cohort studies. Ongoing large collaborative studies are needed to further define the pathogenesis, treatment, and natural history of SDS to improve clinical practice and promote investigation in novel therapeutic approaches.

This article focuses on the diagnosis, treatment, and molecular pathology of SDS and recent insights into this disease.

Clinical manifestations

Bone marrow and pancreatic dysfunction as described in the most recent consensus guidelines (Box 1 (tbox1)) are the classic clinical features of SDS. In the North American SDS registry, however, only 51% (19 of 37) of those with biallelic SBDS mutations presented with classic findings of neutropenia with steatorrhea. [5] In fact, 14% had no history of cytopenias at initial evaluation. Similarly, the diagnosis

of SDS could not be ruled out in this cohort by absence of pancreatic lipomatosis on imaging, normal fecal elastase levels, or normal skeletal imaging.

BOX 1

Diagnostic Criteria

Biallelic SBDS mutations known or predicted to be pathogenic, or mutations in other SDS-associated genes DNAJC21, ELF1, SRP54 (autosomal dominant)

Clinical Diagnosis

Hematologic features (present on at least two occasions)

- Neutropenia (absolute neutrophil count <1500)
- Anemia or macrocytosis (unexplained by other causes, such as iron/B_{12} deficiency)
- Thrombocytopenia (platelet count <150,000) on at least two occasions
- Bone marrow findings
  - Hypocellularity for age
  - Myelodysplasia
  - Leukemia
  - Cytogenetic abnormalities

Pancreatic features

- Reduced levels of pancreatic enzyme relevant to age
  - Trypsinogen <3 years
  - Isoamylase >3 years
- Low levels of fecal elastase
- Supportive features
  - Abnormal pancreatic imaging with lipomatosis
  - Elevated fecal fat excretion >72 hours

Additional supportive features

- Skeletal abnormalities including thoracic dystrophy
- Neurocognitive/behavioral problems
- Unexplained height less than third percentile
- First-degree family member with SDS

Clinical and molecular diagnostic features of Shwachman-Diamond syndrome
Adapted from **Dror Y, Donadieu J, Koglmeier J, et al. Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. Ann N Y Acad Sci 2011;1242(1):43; with permission.**

Hematologic manifestations

Although the hematologic phenotype of SDS typically manifests with neutropenia other cytopenias are also frequently present. Neutropenia, defined as an absolute neutrophil count less than 1500/μL, is a classic finding in SDS. Neutropenia typically presents in the first year of life, although it can present late (adulthood) or may be absent in a small number of individuals. [5] It is of unpredictable severity and may be intermittent or persistent. Neutrophils may exhibit chemotaxis and migration defects; however, individuals with SDS maintain the ability to form empyema and abscesses in contrast to other disorders of neutrophil chemotaxis. [6] [7] [8] Anemia and reticulocytopenia occur in up to 80% of patients, with a normochromic, normocytic appearance, although occasional macrocytosis has been noted. [9] Thrombocytopenia is variably seen.

Progression to trilineage cytopenia and resulting severe aplastic anemia is a lifelong risk for patients with SDS. The French Severe Chronic Neutropenia Registry reported 41 of 102 SDS patients (40%) developed transient severe cytopenias, with half of these developing progressive severe cytopenias with either hemoglobin less than 7 g/dL or platelets less than 20×10^9 /L. [10]

There are varying reports of malignant transformation to MDS or AML in SDS. The Canadian Inherited Marrow Failure Registry reported a 20% risk (n = 40) of hematologic disease progression (including malignant or clonal myeloid transformation, acquisition of new or additional cytogenetic clones, or worsening of cytopenias) by age 18 years. [11] The Severe Congenital Neutropenia International Registry reported an incidence of 1% per year of MDS/AML in SDS patients and an overall incidence of 8.1% of MDS/AML over 10 years in 37 patients. [12] Risk of malignant transformation may, however, increase with age.

Risk of solid tumor development in patients with SDS remains to be ascertained, with case reports of solid tumors in patients ages 18 to 38, including bilateral breast cancer, central nervous system large B-cell lymphoma, pancreatic adenocarcinoma, and slow progressive dermatofibrosarcoma. [13] [14]

Cytogenetic changes are common in SDS, in the absence of MDS or AML. Common cytogenetic abnormalities associated with SDS include del(20) (q11) and isochromosome 7q (i[7] [q10]). [15] These changes may be transient or persist over time, and may not portend impending malignant transformation to MDS or AML. [16] [17] [18] Whether the maternal or paternal allele bears the del(20) (q) abnormality may affect the hematologic phenotype. Higher hemoglobin levels and red cell counts were observed in patients with paternal deletion of 20(q). [19] The exact mechanism is yet to be elucidated, but may be related to bystander gene loss involving L3MBTL1 and loss of transcriptional repressor activity.

Novel cytogenetic abnormalities in the presence and absence of del(20) (q11) and isochromosome 7q (i[7] [q10]) anomalies were recently reported in a cohort of 91 Italian patients with SDS, including unbalanced structural anomalies of chromosome 7, complex rearrangements of del(20) (q) involving duplicated and deleted portions and unbalanced translocation t(3;6) with partial trisomy of the long arm of chromosome 3 and partial monosomy of the long arm of chromosome 6. [20] Some of these subjects did progress to MDS/AML both with i(7) (q10) or del(20) (q11) (2 of 5) and without (6 of 13). Although significance of infrequent acquired chromosomal changes in SDS remains unclear, additional acquired cytogenetic abnormalities may preempt development of MDS or AML.

The understanding of immune function in SDS is not clear. Individuals with SDS are at risk of a diverse range of infections, including bacterial, viral, and fungal infections, generally believed to be beyond that expected in patients with neutropenia. Defects in humoral (decreased B cell numbers, low IgG levels) and cellular (decreased T-cell proliferation) have been reported in SDS individuals.

Gastrointestinal manifestations

Depletion of pancreatic acinar cells results in the hallmark exocrine pancreatic dysfunction observed in SDS. [21] Disorder of pancreatic function is typically seen within the first 6 to 12 months of life, although the spectrum of disease presentation remains varied. Some patients present with severe pancreatic dysfunction manifested by failure to thrive and malabsorption, whereas others are asymptomatic. [5] [22]

Many patients with SDS and exocrine pancreatic dysfunction spontaneously improve over time, with almost half of patients no longer requiring supplemental pancreatic enzyme therapy despite persistent native secretory enzyme deficiency. [23]

The acinar defect in SDS may be generalized to pancreatic and parotid glands. Serum pancreatic and parotid isoamylase levels are lower in patients with SDS, [24] and compared with other disorders involving pancreatic dysfunction, such as cystic fibrosis, ductal function is normal in SDS. [25] Beyond acinar dysfunction, histologic evidence of duodenal inflammation has been demonstrated on mucosal biopsy of 50% of SDS patients. [26] This enteropathy may contribute to vitamin and mineral deficiencies observed in SDS, with vitamin A, E, selenium, zinc, and copper noted to be low in some patients despite supplemental nutrition and enzymatic replacement. [27] Monitoring of trace elements is essential to maximize nutritional benefit in individuals with SDS.

Other gastrointestinal abnormalities associated with SDS include abnormalities of the liver. Elevation of transaminases and hepatomegaly of unclear cause are often present in early life and resolve spontaneously. [28] Elevated bile acids were reported in one Finnish study in 7 of 12 SDS individuals. [28] There are also reports of hepatic failure of uncertain cause in older individuals with SDS including a 15 year old with cholestasis and fibrosis [29] and one individual in the North American SDS registry in their sixth decade.

Skeletal manifestations

Classical skeletal manifestations of SDS include short stature; progressive metaphyseal dysplasia/thickening of the long bones and costochondral junctions; thoracic abnormalities, such as pectus, asphyxiating thoracic dystrophy, and flared ribs; and delayed development of normally shaped epiphyses and wormian appearance of skull bones. [30] These abnormalities may evolve over time.

SDS is also associated with a low-turnover osteoporosis, and abnormalities of bone health, [31] including low z scores and vertebral compression fractures. Other markers of bone health were abnormal, including vitamin D and K deficiency and associated secondary hyperparathyroidism. It is important to ensure accurate measurement of bone mineral density, because patients with SDS have short stature and may have an incorrectly reported low bone mineral density because of low height z score. [32]

Neurologic manifestations

A wide range of cognitive defects have been noted in individuals with SDS. Areas of limitation have been observed in higher-order language, intellectual reasoning, visual-motor skills, and academic achievement with approximately 20% of SDS individuals meeting the diagnostic criteria for intellectual disability. [33] Attention deficits were also more common in SDS individuals and their siblings than control subjects. Recently Perobelli and colleagues [34] performed questionnaire-based quality-of-life and psychological assessments and showed cognitive impairment varied widely in 65% of younger individuals and 76% of adults from mild to severe and was increased compared with control subjects with cystic fibrosis. Individuals with SDS also reported more social problems, attention deficits, and somatic complaints.

Toiviainen-Salo and coworkers [35] showed decreased brain volume globally in white and gray matter (1.74 L vs 1.94 L; P = .019) in nine individuals with SDS. Booij and colleagues [36] demonstrated a dysregulated dopaminergic system and comparably decreased brain volumes, most evident posteriorly and caudally. Additionally, Perobelli [37] and colleagues were recently able to combine cognitive assessments and MRI neuroimaging in nine individuals with SDS to show cognitive impairment associated with diffuse changes in gray and white matter. Whether these changes signify a static change, a delay in neurocognitive development, or will continue to advance is unknown.

Rarely SDS may mimic neuromuscular disorders, with reports of infants presenting with asphyxia, narrow thorax, and severe hypotonia. [38] Myopathic changes were demonstrated on muscle biopsy with prominent variability in muscle fiber size and abnormal expression of developmental isoforms of myosin.

Other manifestations

Other phenotypes of SDS have been described, including those of the endocrine and cardiac systems. SDS may present with unique endocrine manifestations, including neonatal hypoglycemia, micropenis, and congenital hypopituitarism. [39] Other reports of endocrine dysfunction in SDS describe type I diabetes or growth hormone deficiency. [23] [40] [41] [42] [43] [44] [45] [46] Short stature, however, is a classic finding associated with SDS. [47] Short stature with height z scores less than −1.8, was found in 56% of biallelic SBDS mutation carrying individuals in a small retrospective study (n = 25).

Cardiac abnormalities were seen in 11% of SDS individuals in the French Severe Chronic Neutropenia Registry [48] including congenital heart defects, most of which required clinical intervention. Other abnormalities included cardiomyopathy, occasionally associated with radiation/cyclophosphamide treatments or viral infection.

Patients with SDS may also present in infancy with an eczematous-like rash that does not respond to topical treatments. Less commonly, other skin manifestations may be present, including ichthyosis.

Case reports of sensorineural hearing loss and congenital ear malformations have been reported in children with SDS [49]

Diagnosis and clinical management

The diagnosis of SDS early within the first year of life is often by classic criteria of failure to thrive and feeding difficulties, along with cytopenias and recurrent infections. A high index of suspicion is required in those with nonclassical phenotypes, who may present later in childhood or adulthood. Diagnostic criteria for SDS are summarized in Box 1 (tbox1) . [15] Approximately 90% of SDS individuals carry

biallelic mutations in SBDS . Recently described mutations in ribosomal biogenesis and protein translation involving DNAJC21 , [4] EFL1, [3] and SRP54 [2] suggest novel genetic mutations in small numbers of patients with an SDS phenotype, and the need for continued genetic evaluation for BMF disorders including SDS.

A high index of suspicion is needed in patients who fit the clinical phenotype of SDS yet lack a classical SBDS gene mutation. [50] Marrow dysfunction in the setting of other causes of pancreatic dysfunction, such as Pearson marrow-pancreas syndrome or cystic fibrosis, should be considered. A recent analysis of 1514 patients transplanted for MDS demonstrated 4% of young adults harbored compound heterozygote mutations in SBDS with concurrent TP53 mutations and a poor prognosis. [51]

Comprehensive screening for known disease complications should be pursued in individuals with SDS at diagnosis and regular intervals thereafter (Table 1 (tbl1)).

Table 1
Clinical evaluation for patients with Shwachman-Diamond Syndrome

	Frequency
Hematology	
CBC	Diagnosis, every 3–6 mo or as indicated
Bone marrow aspirate and biopsy	Diagnosis, every 1–3 y or as indicated
Iron, folate, B_{12}	Diagnosis, as clinically indicated
Immunoglobulins and lymphocyte subpopulations	Diagnosis, as clinically indicated
HLA testing	As clinically indicated, impending BMT
Gastroenterology	
Pancreatic enzyme measurement	Diagnosis, as clinically indicated
Fat-soluble vitamins and prothrombin time	Diagnosis, 1 mo after commencement of enzyme therapy, then 6–12 mo as indicated
Hepatic profile	Diagnosis, yearly or as clinically indicated
Pancreatic imaging	Diagnosis
Endoscopy	As clinically indicated
Skeletal system	
Growth evaluation: Height, weight, head circumference	Yearly (more frequently if on GH replacement)
Skeletal survey	Diagnosis, as clinically indicated
Bone densitometry	Adulthood, as clinically indicated
Other evaluations	
Neuropsychological testing	Diagnosis, regular assessment during school years 6–8, 11–13, 15–17 y
Endocrine evaluation (eg, TSH, GH)	As clinically indicated
Auditory testing	As clinically indicated

Abbreviations: BMT, bone marrow transplantation; CBC, complete blood count; GH, growth hormone; TSH, thyroid-stimulating hormone.

Adapted from Dror Y, Donadieu J, Koglmeier J, et al. Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. Ann N Y Acad Sci 2011;1242(1):46–7; with permission.

Monitoring blood counts and bone marrow evaluations is vital to assess for malignant transformation. Neutropenia is common and often intermittent. Most individuals with SDS do not need chronic granulocyte colony–stimulating factor (G-CSF) therapy. Persistent severe neutropenia with severe or recurrent bacterial or fungal infections is an indication for G-CSF therapy. Most SDS individuals have adequate

response with low-dose G-CSF but may range from intermittent to continuous daily dosing. A marrow evaluation including cytogenetics and fluorescence in situ hybridization studies are recommended before starting G-CSF whenever feasible, to avoid potentially promoting abnormal clone growth.

Hematopoietic stem cell transplant remains the only curative therapy for SDS individuals with severe aplastic anemia or malignant transformation. Historically outcomes were poor with high treatment-related mortality using standard myeloablative preparative regimens. [52] Transplant outcomes in the setting of severe aplastic anemia or MDS have significantly improved with the introduction of reduced-intensity regimens. [53] [54] Outcomes for SDS individuals with AML, however, remain poor, highlighting the importance of systematic blood and marrow surveillance. Achieving sustained remission with chemotherapy in the setting of SDS and AML has been challenging, leading to significant toxicity and increased transplant risk. Timely use of hematopoietic stem cell transplant in this setting is essential.

Growth, nutrition, neurodevelopment, and bone health should be monitored regularly for early recognition of areas of concern for prompt intervention. All siblings of an individual with SDS are at risk for SDS regardless of clinical symptoms, [5] and genetic counseling should be offered to patients and family members.

Molecular pathogenesis

The SBDS protein is involved in multiple important pathways including ribosomal maturation, [55] [56] the stromal microenvironment, [57] [58] and mitosis. [59] [60] The crucial role of the SBDS protein in ribosome biogenesis was demonstrated by Finch and colleagues [55] in murine models. EIF6 release from the pre-60S ribosomal subunit results from coupling of GTPase elongation factor-like 1(EFL1) in an SBDS-dependent manner. Association of the 60S ribosomal subunit to the 40S subunit is sterically blocked by EIF6. EIF6 release permits joining of the 60S and 40S subunits and formation of the translationally active 80S ribosome. [61] [62] Mutations in Tif6 , the eIF6 yeast ortholog, reverse the slow growth phenotype of yeast lacking Sdo1 , the SBDS ortholog. [61] In humans SBDS associates with the large 60S subunit but not mature polysomal ribosomes. [63] Half-mers are present in polysome profiles of SBDS-deficient animal models, a pattern caused by defective ribosome joining of the 40S and 60S subunits. [55] These half-mer patterns are not seen in cells from SDS individuals, likely because of low level residual SBDS expression, but they do show impaired ribosome association in vitro . [64] EIF6 knockdown improves ribosome association but not hematopoietic colony formation of SBDS-deficient $CD34^+$ cells from SDS individuals. Additionally, SBDS may have a surveillance role in monitoring conformational maturation of the ribosomal P-site in addition to regulating departure of eIF6. [65]

Biallelic mutations in EFL1 clinically manifest as an SDS-like phenotype and present a novel mutation that may be present in SDS patients without typical mutations in SBDS . Four patients with infantile pancytopenia, exocrine pancreatic insufficiency, and skeletal anomalies were found to have homozygous mutations in EFL1 ; further study of the yeast EFL1 homologue showed that mutations prevent release of cytoplasmic Tif6 from the 60s subunit and prevent the formation of mature ribosomes. [3]

Mutations in DNAJC21 , first reported in four children with BMF and short stature, [66] have also been recently reported in four subjects with a clinical phenotype of BMF, pancreatic dysfunction, and skeletal manifestations. [4] DNAJC21 is ubiquitously expressed and its yeast homolog Jjj1 is also required for ribosome biogenesis through the DnaJ domain and is involved in release of maturation factors from the pre-60S ribosomal subunit, via Arx1/Alb1, with dysfunction of 60S ribosomal subunit biogenesis on deletion of the homologs in yeast.

In and colleagues [67] report their findings that SBDS is required for translation of mRNAs responsible for granulocytic differentiation. Specifically, SBDS is required for efficient translation and reinitiation of C/EBPalpha and C/EBPbeta mRNAs. Furthermore, deregulated mRNA translation results in decreased MYC expression, which may result in loss of hematopoietic progenitor proliferation and contribute to the hematologic phenotype of SDS.

Similarly, novel mutations in SRP54 , a key member of the cotranslation protein-targeting pathway, lead to an SDS-like phenotype. [2] A trio of patients with an SDS phenotype were found to have de novo missense variants in SRP54 , resulting in neutropenia and other SDS features. GTPase activity of the mutated proteins was impaired and the level of SRP54 mRNA in the bone marrow was 3.6-fold lower in patients with SRP54 mutations compared with healthy control subjects. The SDS phenotype with neutropenia was observed in a zebrafish srp54 -knockdown model, indicating this may be a novel mutation in previously SBDS-negative SDS patients.

Additional roles outside of ribosomal maturation have been demonstrated for SBDS . Austin and colleagues [59] demonstrated localization of SBDS to mitotic spindles of primary human marrow stromal cells. Fibroblasts and lymphocytes from individuals with SDS have increased quantities of multipolar spindles, leading to increased genomic instability that is rescued with addition of purified SBDS protein. [59] Addition of the microtubule stabilizing agent taxol improved primary SDS bone marrow hematopoietic progenitor colony formation.

Polymerization of purified microtubules was also increased with addition of recombinant SBDS protein, supporting a direct effect of SBDS on microtubule stabilization. Colocalization of SBDS with centromeres and microtubules of the mitotic spindle and the microtubule organizing center in neutrophils in interphase has also been demonstrated. [60] [68]

In vitro neutrophil proliferation and differentiation are different in SDS compared with control subjects, suggesting an important role for SBDS in myeloid lineage proliferation and division. This was noted in a preleukemic mouse model of SDS, where mesenchymal inflammation resulted in mitochondrial dysfunction, oxidative stress, and activation of DNA damage response systems (particularly toll-like receptor inflammatory signaling) leading to genotoxic stress and evolution of leukemia. [69] These findings suggest inflammatory modulators may present a potential therapeutic approach for prevention of progression to leukemia in susceptible individuals.

SBDS may play a role in energy metabolism within the cell. Ribosomal biogenesis is a high-energy cellular process requiring finely coordinated complex cellular energy production. Ravera and colleagues [70] show impaired oxygen consumption, defective complex IV activity and electron transport defects, and increased cytoplasmic calcium levels in SDS cells. These changes led to an oxidative phosphorylation defect with decreased ATP production. Increased phosphorylation of mTOR was observed in SDS cells, affecting 60s maturation and binding of SBDS and EIF6 possibly to modulate defective ribosome biogenesis through increased cytoplasmic calcium concentration to drive nuclear import of EIF6 . Finally, addition of leucine resulted in improved erythropoiesis, which may represent a therapeutic adjuvant to be tested in future trials.

Bezzerri and colleagues [71] demonstrate loss of SBDS expression is associated with hyperactivation of mTOR and STAT3 pathways. SDS derived EBV-immortalized B cells show constitutive increased activation of mTOR and STAT3 pathways. STAT3 is a key regulator of many cellular processes, and the dysregulation of the mTOR and STAT3 pathways observed in this model may represent putative targets for investigation of commercially available mTOR and STAT pathway inhibitors, which theoretically may benefit neutrophil development and reduce progression to BMF.

SBDS has also been implicated in a variety of other cellular functions including increased reactive oxygen species production, [72] intensified cellular stress responses, [73] Fas-ligand induced apoptosis, [74] and mitochondrial insufficiency. [75] SBDS may also be involved in marrow stromal function. [76] [77] Increased expression of vascular endothelial growth factor-A and osteoprotegerin are seen in SBDS knockdown cell lines, which are known to influence monocyte and macrophage migration, osteoclast differentiation, and angiogenesis. [58] Targeted deletion of SBDS in murine osteoprogenitors resulted in significant marrow abnormalities including lymphopenia, leukopenia, and myelodysplasia in the setting of bony changes. [57] Targeted deletion of Sbds in murine osteoprogenitor cells results in mitochondrial dysfunction and oxidative stress in hematopoietic cells leading to genotoxic stress. This process is driven through p53-S100A8/9-TLR4 signaling and was predictive of evolution to MDS/AML in non-SDS individuals with low risk MDS. [69] Together this suggests that decreased expression of SBDS in stromal cells may alter the hematopoietic microenvironment and favor development of BMF and/or malignant transformation. Normal in vitro function of SBDS-deficient mesenchymal stem cells, however, has been demonstrated by others. [77]

The early embryonic lethality of targeted deletion of murine Sbds results has limited use of this animal model of SDS. [78] Delayed in vitro myeloid differentiation, impaired homing of hematopoietic progenitors, and decreased short-term engraftment is seen after knockdown of murine Sbds with RNA interference in murine bone marrow followed by transplantation. [79] Sbds knockdown in zebrafish morpholinos demonstrated neutrophil loss, skeletal changes, and pancreatic hypoplasia, similar to clinical SDS phenotype. [80] Organ-specific models in mice have shown findings similar to human disease. A pancreas-specific murine knock-in model, created by introducing a missense mutation in Sbds , was smaller overall, with smaller pancreata that show hypoplastic acini and fatty infiltration with decreased zymogen granules but intact islet cells, which is similar to the phenotype of SDS individuals. [81] Zambetti and colleagues [82] most recently developed a conditional Sbds murine knockout under control of a CEBPα-Cre recombinase, allowing for transplantation of Sbds -deficient fetal liver cells into lethally irradiated wild-type recipients. Recipients subsequently developed hypocellular bone marrow and neutropenia similar to the human phenotype. These mice demonstrate activation of p53 with arrest in myeloid differentiation at the myelocyte stage suggesting this phenotype may be mediated by apoptotic pathways. In the short 4-month follow-up, no malignant transformation was observed. Knockdown of SBDS in human embryonic stem cells has been used to develop induced pluripotent stem cells derived from SDS individuals that show enhanced apoptosis with defective hematopoietic differentiation and exocrine pancreatic dysfunction. [83]

Novel gene discovery along with development of animal and induced pluripotent stem cells models allows further evolution in the understanding of the pathogenesis of SDS further elucidating the role of SBDS and other novel proteins in critical cellular pathways, such as ribosome biogenesis, mitosis, and stress response. These exciting scientific advances may lead to putative therapeutic targets and strategies to improve clinical care of individuals with SDS.

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