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## Further Insights into the Hematological Disorders Observed in Shwachman–Diamond Syndrome: mTOR and STAT3 Hyperphosphorylation in CD4<sup>+</sup> and CD8<sup>+</sup> T Cells and Efficacy of Rapamycin Treatment

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### Abstract

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disease which affects 1/168,000 newborns in Italy with a mean of 3.0 new cases/year. SDS is caused by mutations in the Shwachman–Bodian–Diamond syndrome (*SBDS*) gene, which encodes for the homonymous protein SBDS, whose exact function is still unknown. SBDS protein has been reported to play a role in eukaryotic ribosome biogenesis. Thus, SDS is considered a ribosomopathy. The pathology is characterized by multiple–organ impairment involving bone marrow failure, exocrine pancreatic insufficiency, skeletal malformations, hepatic and cognitive disorders. Neutropenia and impaired neutrophil chemotaxis, which in turn cause recurrent infections, are reported in young children. Furthermore, 15–20% of SDS patients develop myelodysplastic syndrome (MDS), with increased risk of acute myeloid leukemia (AML) progression, which represent the main cause of mortality.

However, the exact pathologic mechanism whereby loss of SDBS function could lead to the specific SDS hematological issues remains unclear. We recently reported, for the first time to the best of our knowledge, that the mammalian Target of Rapamycin (mTOR) and Signal Transducer and Activator of Transcription (STAT)-3 pathways are hyper-activated in B cells, PMNs and, mostly, in monocytes obtained from SDS patients (Bezzetti V et al, *Sci Rep* 2016, in press). Since mTOR and STAT3 activation are associated with neutrophil development and AML, this finding could at least partially explain the onset of the hematological issues. Here we show a further Phospho flow analysis of mTOR and STAT3 pathways activation in other lymphocytes subsets, in particular in CD8<sup>+</sup>/CD4<sup>+</sup> T cells and NK cells obtained from five SDS patients. We found that STAT3 S727 is the most phosphorylated site in CD8<sup>+</sup> and CD4<sup>+</sup> T cells (more than twice than the healthy control cells, each). Furthermore, mTOR (S2448) is hyper-phosphorylated in CD8<sup>+</sup> and CD4<sup>+</sup> T cells derived from SDS patients. Median fluorescence intensity shifted from 220 ± 25 (healthy controls) to 405 ± 29 (SDS patients) in CD8<sup>+</sup> T cells and from 350 ± 132 (healthy controls) to 590 ± 150 (SDS patients) in CD4<sup>+</sup> T cells, similarly to results obtained from Monocytes and B cells. NK seems to be less responsive to mTOR/STAT3 activation than B and T cells. Importantly, mTOR inhibitor rapamycin is able to reduce both mTOR and STAT3 activation, with different efficacy, in a cell type-dependent manner. In particular, rapamycin strongly reduces both mTOR and STAT3 S727 phosphorylation in CD8<sup>+</sup> and CD4<sup>+</sup> T cells. Thus, these results suggest a role of mTOR/STAT3 pathways in both myeloid and lymphoid lineages of SDS blood cells. Since several drugs approved by FDA and EMA targeting the JAK-STAT and mTOR pathways have been currently evaluated for the treatment of different forms of hematological malignancies, this work could open a wider scenario into the current SDS therapeutic approaches.

**Disclosures** No relevant conflicts of interest to declare.

- ↩\* Asterisk with author names denotes non-ASH members.

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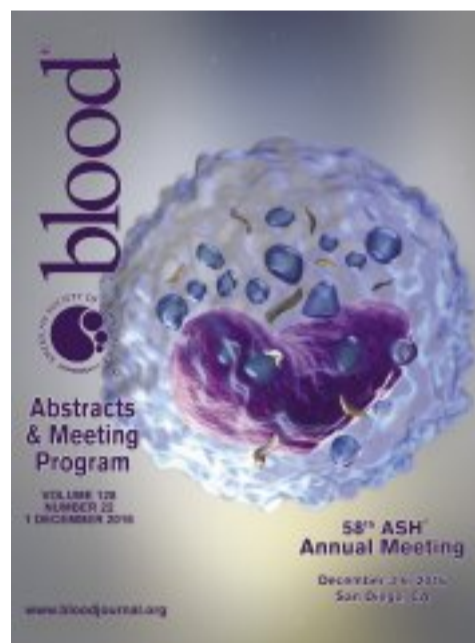
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