Regulation of Hematopoietic Progenitor Formation in a
Shwachman-Diamond Syndrome Induced Pluripotent Stem Cell Disease Model

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Abstract

Shwachman-Diamond syndrome (SDS) is an inherited bone marrow (BM) failure syndrome, with 90% of SDS patients carrying a mutation in the SBDS gene. Due to limited efficacy or toxicity of the current treatments available, and the otherwise reduced life expectancy of SDS patients, novel therapeutic strategies are critically needed. Since the main morbidity and mortality are related to the blood dyscrasia, studying hematopoiesis may help characterize the hematological phenotype. We hypothesized that the definitive wave of hematopoiesis is markedly impaired, with a post-mesoderm onset. We successfully generated SDS iPSCs that recapitulated the human SDS disease, specifically, the aberrant ribosome profile and reduced blood cell formation. The SDS iPSCs showed a defect in definitive hematopoiesis, with a marked reduction in the hemogenic endothelium population (HE). We did not observe a defect in primitive hematopoiesis. Our study helps shed light on the onset and progression of the SDS hematopoietic phenotype, and provides a platform for the development of novel, potential therapeutic targets, to ultimately improve patient care.