Abstract

Diamond-Blackfan anemia (DBA) is a rare congenital bone marrow failure syndrome characterized by deficient development of erythroid progenitors and accompanied by a variable set of developmental defects. About 25 % of patients have mutations of the small ribosomal subunit protein *RPS19,* and the precise mechanism of single aminoacidic mutations of RPS19 protein in the pathology of Diamond-Blackfan anemia remains largely unknown. To understand the interaction between of genotype and phenotypic variability we have created a mouse model with homozygous mutation in a highly conserved arginine 67 ($Rps19^{R67\Delta/R67\Delta}$).

Mouse model with this mutation display many of the same phenotypical trades as patients with DBA. We decided to focus on hematopoiesis and erythropoiesis in this mouse model and tried to characterize those processes. We discovered that $Rps19^{R67\Delta/R67\Delta}$ mice similarly to DBA patients suffer from anemia and that the erythropoiesis process is disrupted at the stage of proerythroblasts. We also observed changes in hematopoiesis in stages as early as multipotent progenitors.

The role of p53 protein as a modifier of DBA phenotype is well known. We created mouse model with p53 depletion to assess the role of p53 protein in relation with mutation in *Rps19*. $Rps19^{R67\Delta/R67\Delta}Trp53^{-/-}$ mice show no signs of DBA, thus the mutation in *Trp53* acts as rescue of the phenotype. Erythropoiesis and hematopoiesis of those mice remains unchanged compared to wild-type mice. Using transcriptomic analysis of adult bone marrow cells and E14.5 fetal livers from $Rps19^{R67\Delta/R67\Delta}$ mice we identified a small set of genes – transcriptional targets of p53 signaling pathway, associated with DBA phenotype, whose expression was not upregulated in the $Rps19^{R67\Delta/R67\Delta}Trp53^{-/-}$ mice model, highlighting the significance of p53 signaling pathway in DBA pathogenesis.

Keywords