ELSEVIER

Blood 142 (2023) 3825–3826

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

101.RED CELLS AND ERYTHROPOIESIS, EXCLUDING IRON

STK10 Mutation Block Erythropoiesis in Acquired Pure Red Cell Aplasia Via Down-Regulated the Ribosome Biosynthesis

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Background: Acquired pure red cell aplasia (PRCA) is anemia associated with the absence of erythroblasts and characterized by persistent and easy recurrence. However, the underline mechanisms of acquired PRCA remain obscure, and the role of gene mutation in the pathogenesis of acquired PRCA was not elucidated yet.
Aims: To identify gene mutations in acquired PRCA patients and their possible effects on the origin of the disease.
Methods: Blood and buccal genome DNA extracted from thirty newly diagnosed patients with acquired PRCA were detected with whole exome sequencing. The candidate genes with high frequency in acquired PRCA but the low frequency in 1000 normal genomes which may affect protein function were selected. The pGreen-CMV-puro system was employed to generate lentivirus expressing short hairpin RNAs to target the candidate genes, and stable transfected K562 cell lines with silenced candidate genes were constructed. The erythroid and megakaryocytic differentiation was evaluated for the transfected K562 cell lines either by benzidine staining hemoglobin and CD235a expression or CD41 expression on the cell surface. STK10 gene was selected which affects the erythropoiesis. The influence of the STK10 gene on the expression of p53 mRNA/ protein was also detected. The RNA sequencing in STK10 silenced K562 cells was performed and KEGG enrichment was analyzed. Next, ribosome RNA synthesis was detected, and ribosome proteins and p53 signaling pathway were also detected by western blotting.
Results: Through whole exome sequencing in patients with acquired PRCA, we confirmed that STK10 gene mutation is common in acquired PRCA patients, the mRNA/protein expression of STK10 was reduced and p53 increased in the bone marrow of the patients in which the gene mutated. Furthermore, the silence of the STK10 gene through the lentiviral vector harboring short hairpin RNAs in K562 cells could inhibit the erythropoiesis after being induced by Hemin. Whereas, CD41 expression was similar in STK10 silenced K562 cells to control K562 cells after being inducted by phorbol 12-myristate 13-acetate. We performed RNA sequencing in STK10 silenced K562 cells. KEGG enrichment analysis of differentially expressed ribosome biosynthesis pathway and p53 signaling pathway was affected. 28S and 18S in ribosome RNA synthesis impaired in these STK10 silenced K562 cells through RNA electrophoresis. Further, through the western blotting test in STK10 silenced K562 cells, we found ribosome proteins expression down-regulated and p53, phospho-p53 and p21 expression up-regulated due to STK10 mutated.
Conclusion: STK10 gene mutation is common in patients with acquired PRCA and causes the reduction of mRNAs and protein expression in the mutated patients. The underlying research revealed STK10 gene mutation could affect the ribosome biosynthesis pathway and down-regulated the ribosome protein level, contributing to the abnormal erythropoiesis. This research elucidated the pathogenesis of PRCA, which may provide evidence for precise diagnosis and exploring potential therapeutic targets in patients with acquired PRCA.
Keywords: pure red cell aplasia, mutation, erythropoiesis, STK10, ribosome biosynthesis

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-189722