Metabolic reprogramming supporting the high proliferation of erythroblasts during ineffective erythropoiesis in β-thalassemia/Hb E disease

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Abstract

Background: β-thalassemia/HbE is caused by mutations in β-globin gene resulting in the absence or reduction of β-globin chains causing an accumulation of excess α-globin chains and generating cytotoxic reactive oxidant species, leading to erythroblast cell death. Ineffective erythropoiesis, characterized by dramatic expansion of erythroblasts and increased erythroblast cell death in bone marrow, is the main cause of anemia in β-thalassemia disease. Metabolism provides energy, building blocks for macromolecule synthesis, and cofactors for antioxidative defense systems. We hypothesized that β-thalassemia erythroblasts might alter their metabolism to cope with increased proliferation and cellular stress. Furthermore, a variation in metabolic gene expression could contribute to different clinical symptoms in β-thalassemia/HbE patients. Therefore, the objective of this study is to investigate the metabolic reprogramming in ineffective erythropoiesis in β-thalassemia/HbE.

Methods: To determine the global gene expression, transcriptomic analysis was performed using bone marrow samples obtained from β-thalassemia/HbE patients with different severities compared to normal controls. To validate the transcriptomics data, the erythroid progenitors were isolated from normal controls and β-thalassemia/HbE patients with mild and severe symptoms and cultured in a two-phase culture system. The expression of metabolic genes during terminal erythropoiesis was further determined by PCR array and RT-qPCR.

Results: Transcriptomic analysis showed the global up-regulation of metabolic genes in glycolysis, TCA cycle, pentose phosphate pathway, ATP, and fatty acid synthesis pathway in β-thalassemia/HbE patients compared to normal controls. The increased expression of enolase1 (ENO1), isocitrate dehydrogenase1 (IDH1), and bisphosphoglycerate mutase (BPGM) was observed in mild compared to severe patients suggesting that mild patients might modulate metabolic flux for cellular stress defense mechanisms resulting in a reduced degree of disease severity.

Conclusions: Our data suggest that metabolic reprogramming during thalassemia erythropoiesis provides energy and macromolecules required for the high proliferation of thalassemic erythroblasts and defense against oxidative stress. This study reveals a new basic knowledge of the metabolism during ineffective erythropoiesis in β-thalassemia/Hb E leading to the discovery of novel drugs or small molecule inhibitors targeting the metabolic enzymes to improve ineffective erythropoiesis and anemia to control disease severity of β-thalassemia/Hb E patients.

Keywords: metabolic reprogramming, metabolic genes, metabolism, ineffective erythropoiesis, β- thalassemia/HbE disease