Clinical metabolic understanding of human erythropoiesis

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In a recent study, Lyu and colleagues pointed out that physiological erythropoiesis requires a metabolic switch from initial glutamine catabolism to later anabolism *(1)*. Glutamine synthesis in differentiating red blood cells is catalyzed by glutamine synthetase (GS), a ubiquitously expressed enzyme requiring glutamate and ammonia as substrates. This reaction was demonstrated to be essential for detoxifying the four ammonia molecules released from the porphobilinogen deaminase reaction during heme biosynthesis. In the study, impairment or enhancement of GS activity were shown to have detrimental or beneficial effects on erythropoiesis, respectively, including in the case of β-thalassemia.

From a theoretical-metabolic point of view, the finding that sodium phenylbutyrate treatment improved erythropoiesis in mice with erythroid GS deficiency suggests that glutamine deficiency itself is not detrimental for red blood cells differentiation, as sodium phenylbutyrate acts as a glutamine scavenger *(2)*. The previous observation that exogenous glutamine can act as precursor of alpha-ketoglutarate required for heme biosynthesis during late erythropoiesis is also in agreement *(3)*.

From a clinical-metabolic point of view, here we report first evidence of impaired erythropoiesis in one patient with inherited GS deficiency, an ultra-rare very severe inborn error of metabolism reported only in very few patients so far *(4)*. A selective impairment of erythropoiesis during pediatric age was observed in one of the reported GS deficient patients *(5)*, with acutely progressive anemia (hemoglobin drop from 12.7 to 6.0 g/dl, reference 11.5-13.9). Interestingly, the patient was not anemic in neonatal and infantile period, suggesting unaffected fetal erythropoiesis. It could be argued that during fetal life, when erythropoiesis occurs mainly in the liver, urea cycle enzymes (expressed in the fetal liver from 13 weeks of gestation) *(6)* may address detoxification of ammonia from heme biosynthesis instead of GS, allowing quasi-normal early erythropoiesis in patients with inherited GS deficiency. According to the findings by Lyu and colleagues, the impact of inherited GS deficiency on erythropoiesis would then become clinically evident at a later point in life.

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