

Erythroid Differentiation and Heme Biosynthesis Are Dependent on a Shift in the Balance of Mitochondrial Fusion and Fission Dynamics

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Abstract

Erythropoiesis is the most robust cellular differentiation and proliferation system, with a production of $\sim 2 \times 10^{11}$ cells per day. In this fine-tuned process, the hematopoietic stem cells (HSCs) generate erythroid progenitors, which proliferate and mature into erythrocytes. During erythropoiesis, mitochondria are reprogrammed to drive the differentiation process before finally being eliminated by mitophagy. In erythropoiesis, mitochondrial dynamics (MtDy) are expected to be a key regulatory point that has not been described previously. We described that a specific MtDy pattern occurs in human erythropoiesis from EPO-induced human CD34⁺ cells, characterized predominantly by mitochondrial fusion at early stages followed by fission at late stages. The fusion protein MFN1 and the fission protein FIS1 are shown to play a key role in the progression of erythropoiesis. Fragmentation of the mitochondrial web by the overexpression of FIS1 (gain of fission) resulted in both the inhibition of hemoglobin biosynthesis and the arrest of erythroid differentiation, keeping cells in immature differentiation stages. These cells showed specific mitochondrial features as compared with control cells, such as an increase in round and large mitochondrial morphology, low mitochondrial membrane potential, a drop in the expression of the respiratory complexes II and IV and increased ROS. Interestingly, treatment with the mitochondrial permeability transition pore (mPTP) inhibitor, cyclosporin A, rescued mitochondrial morphology, hemoglobin biosynthesis and erythropoiesis. Studies presented in this work reveal MtDy as a hot spot in the control of erythroid differentiation, which might signal downstream for metabolic reprogramming through regulation of the mPTP.

Author keywords

cell differentiation

erythropoiesis

fission and fusión

mitochondria

permeability transition pore

stem cell