Thrombopoietin as an expansion factor for hematopoietic stem cells

Toshio Suda

Kumamoto University, Japan

Cellular metabolism in hematopoietic stem cells (HSCs) is an area of intense research interest, but the metabolic requirements of HSCs and their adaptations to their niches during development have remained largely unaddressed. Distinctive from other tissue stem cells, HSCs transition through multiple hematopoietic sites during development. This transition requires drastic metabolic shifts, insinuating the capacity of HSCs to meet the physiological demand of hematopoiesis. In this review, we highlight how mitochondrial metabolism determines HSC fate, and especially focus on the links between mitochondria, endoplasmic reticulum (ER), and lysosomes in HSC metabolism.

In order to gain a detailed understanding of regulating HSC quiescence, we will focus on Thpo (Thrombopoietin)-Mpl (Receptor) signaling. We analyzed *Thpo*$^{-/-}$ and *Thpo*$^{fl/fl}$*;AlbCre*$^{+/-}$ HSCs in detail. *Thpo*$^{-/-}$ HSCs were apoptotic and impaired in mitochondria bioenergetics. *Thpo*$^{fl/fl}$*;AlbCre*$^{+/-}$ HSCs exhibited a similar HSC phenotype yet with a lesser extent of damage. Administration of Romiplostim restored mitochondria function and induced quiescence in *Thpo*$^{-/-}$ HSCs. Moreover, *Thpo*$^{-/-}$ HSCs did not exhaust and exhibited reconstitution potential even after continuous stimulation with Romiplostim. Our data reveal that a subpopulation of HSCs which escape Thpo-deprivation acquiesce quiescence through Thpo-Mpl signaling in a dose-dependent manner which process involves the modification of metabolism.