【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project : Self-Renewal Capacity of Hematopoietic Stem Cells through the Regulation of Mitochondrial Metabolism

Toshio Suda
(Kumamoto University, International Research Center for Medical Sciences, Distinguished Professor)

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Keyword : Hematopoietic Stem Cells (HSCs), Stem Cell Niche, Mitochondrial Metabolism

【Purpose and Background of the Research】

Ex vivo expansion of HSCs is a long-standing subject in the research field of hematopoiesis, but it has not been realized yet. We hypothesize that HSCs show two types of cell division patterns; self-renewal cell division, which reproduces stem cells, and differentiation division, which produces functioning mature cells.

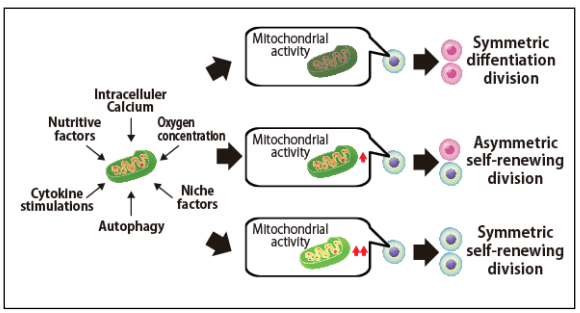
In this project, we will validate how mitochondrial function affects the cell division of HSCs. We have previously shown that oxidative metabolism is critical for the regulation of quiescence and maintenance of HSCs, as well as glycolysis.

Here we will clarify the underlying molecular mechanisms how mitochondria metabolism regulates the stem cell division. We will approach the self-renewal division in HSCs. This project is aiming for the *ex vivo* expansion of HSCs by increasing the self-renewal division by the mitochondrial regulation (see Figure).

【Research Methods】

At first, we will clarify how mitochondrial activation induces the stem cell division and differentiation. We will monitor the mitochondrial mass, membrane potential (MMP) and ROS.

Next, we will clarify how mitochondrial activation is regulated by the HSCs niche. We have previously suggest the following signaling; exogenous adenosine— intracellular Ca^{2+} increase—MMP upregulation—cell division. We will try to connect the missing link in this axis. Especially, to clarify how Ca^{2+} is regulated in HSCs, we will analyze the Ca^{2+} efflux and influx from extracellular compartment and endoplasmic reticulum (ER).



We will analyze the HSC division in MITOL-deficient HSCs, which has abnormalities in mitochondria-ER interaction.

Then, we will examine the quality of mitochondria from the aspect of autophagy/mitophagy. It is interesting to see the regulation of mitochondrial biogenesis and exclusion of damaged mitochondrial in HSCs. We will dissect HSCs of autophagy-defective mice such as ATG7 cKO mice and folliculin (FLCN) cKO mice, in which HSCs are defective. We will analyze the effect of FLCN and downstream signal TFE3 on mitochondria and lysosomal function.

Finally, we challenge to modulate mitochondrial function to increase the self-renewal activity in HSCs and realize the *ex vivo* expansion of HSCs.

【Expected Research Achievements and Scientific Significance】

We will focus on the understanding the mitochondrial function in HSCs. On the basis of these basic data, we will realize the *ex vivo* expansion of HSCs through the mitochondrial modulation.

【Publications Relevant to the Project】

・Ito K, Suda T: Metabolic requirements for the maintenance of self-renewing stem cells. ***Nat Rev Mol Cell Biol*** 141: 243-256, 2014
・Umemoto T, Hashimoto M, Matsumura T, Nakamura-Ishizu A, SudaT: Ca^{2+}-Mitochondrial axis drives cell division in hematopoietic stem cells. ***J Exp Med***, in press. 2018 doi: 10.1084/jem.20180421.

【Term of Project】 FY2018-2022

【Budget Allocation】 140,000 Thousand Yen

【Homepage Address and Other Contact Information】

http:// ircms.kumamoto-u.ac.jp/
sudato@keio.jp