D5 Medical & Life Science Seminar (Elective 2 credits)

Academic Year 2018 "International Biomedical Research Seminars"

Title: # Purine metabolism in the divisions of hematopoietic stem cells.

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Date: **November 7, 2018 (Wednesday)**

Time: 17:30 –

Venue: IRCMS 1F Meeting Lounge

Abstract

Cellular metabolism is an area of recent intense research interest. However, the metabolic requirements and adaptations of stem cells and their niches remain largely unaddressed. We have analyzed hematopoietic stem cell (HSC) metabolism using metabolomics approaches. With step-wise differentiation of stem cells, the cell metabolism associated with each differentiation stage may be very different. We show that quiescent HSCs predominantly utilize glycolytic pathways under the control of hypoxia inducible factor (HIF) 1a, while proliferating HSCs use oxidative phosphorylation and purinergic metabolism to obtain the energy. It is well-known that HSCs are dormant in hypoxic areas and not rich in the mitochondria mass – a hallmark of oxidative phosphorylation for energy production. However, under the stress hematopoiesis such as thrombopoietin (Thpo) administration, mass cytometry (CyTOF) revealed enhanced mitochondria metabolism accompanying by the change in the HSC subpopulation.

To elucidate the mechanism underlying the transition of cell cycle state in HSCs, we analyzed the change of mitochondria in HSCs after BM suppression induced by 5-fluoruracil. We found that HSCs initiate cell division after exhibiting enhanced mitochondrial membrane potential ($\Delta\Psi_m$) as a result of increased intracellular Ca^{2+} level. Although further activation of Ca^{2+}-mitochondria pathway led to loss of HSCs after cell division, the appropriate suppression of intracellular Ca^{2+} level by exogenous adenosine or Nifedipine, a Ca^{2+} channel blocker, prolonged cell division interval in HSCs, and simultaneously achieved both cell division and HSC maintenance. Collectively, our results indicate that the Ca^{2+}-mitochondria pathway induces HSC division critically to determine HSC cell fate.

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