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

Broad Section I

Title of Project : Mechanism and Regulation of Stem Cell Fates by the Branched-Chain Amino Acid Metabolism in Cancer

ITO Takahiro
(Kyoto University, Institute for Frontier Life and Medical Sciences, Professor)

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【Purpose and Background of the Research】

Understanding the basic operating rules of tissue stem cells is the holy grail of biology because it will provide great insights into fundamental cellular processes including development, aging and oncogenesis and as such holds cast clinical implications and therapeutic potential for multiple diseases in the era of regenerative medicine. Recent studies have clearly demonstrated that metabolism affects stem cell behaviors in many animal tissues. Extracellular factors and cell-cell interactions elicit intracellular signaling that regulates cellular metabolism, which modulates how the dividing cells react and respond to such external stimuli to change their cell fates. In vertebrate tissue stem cells, cell fate decision has a critical role in homeostasis and diseases. The two daughter cells of a stem cell can either stay as stem cells (self-renewal) via a symmetric cell division or become committed to produce multipotent progenitors (commitment), and the decision directly regulates how many stem or functioning mature cells are generated. Imbalance between self-renewal and commitment could lead to a variety of physiologic dysfunctions such as aging, dystrophy and cancer. While we have learned a great deal about how growth factors and signaling cascades can affect stem cell proliferation, we have very limited knowledge of the mechanisms by which metabolism regulates the cell fate decisions in stem cells. In this context, we have been investigating how metabolic changes affect cell fates and found that the metabolism of the branched-chain amino acids (BCAAs), i.e. valine, leucine and isoleucine, plays a significant role in cell fate regulation in cancer. The proposed research is aimed at molecularly interrogating how BCAAs and the associated metabolic pathways modulate cell fates in myeloid leukemia as well as other solid tumors.

【Research Methods】

In order to define the underlying molecular mechanisms for stem cell maintenance by BCAAs, we will investigate how these amino acids maintain uncommitted cell fate. Our preliminary transcriptome analysis suggested that increased BCAA flux by a BCAA transaminase BCAT1 affects several differentiation pathways and thus we plan to compare protein and mRNA expressions after BCAT1 gene inactivation. This analysis will uncover mRNA targets that are regulated by elevated BCAAs. We will also examine if BCAA-derived metabolites modulate cellular responses via post-transcriptional modifications such as histone acylations and regulate expressions of cell fate genes. We will conduct our molecular analysis mainly using mouse models of myeloid leukemia and examine whether the same pathway operate in other stem cell systems of normal hematopoietic stem cells and solid tumors such as breast cancer. Together, we will be able to understand how BCAAs enhance self-renewal and maintain stem cells in malignant and normal tissue stem cells.

【Expected Research Achievements and Scientific Significance】

Cancer has primarily been studied in the context of oncogenic mutations and dysregulated cell growth. Our study is original and unique in that we seek to understand the biology of stem cells from the perspective of altered metabolism and its impact on cell fate decision. While metabolic shifts in cancer have become a central subject in the field, glycolysis and carbon metabolism have been the major focus and the patho-physiologic roles of amino acid metabolism have not been defined in detail. Importantly, very little is known about the causative relationship between the essential nutrients BCAAs and disease progression, and therefore we propose to study the regulatory roles of BCAA metabolism in cell fate decision in cancer. In sum, our study will not only clarify a novel regulatory mechanism of self-renewal but also help determine whether the BCAA metabolism is a rational and effective therapeutic target for controlling disease progression in human cancers.

【Publications Relevant to the Project】

- Hattori A, Tsunoda M, Konuma T, et al., Cancer progression by reprogrammed BCAA metabolism in myeloid leukemia. ***Nature*** 545:500-504 (2017).
- Zimdahl B, Ito T, et al., Lis1 regulates asymmetric division in hematopoietic stem cells and in leukemia. ***Nat Genet*** 46:245-52 (2014).
- Ito T, Kwon HY, Zimdahl B, et al., Regulation of myeloid leukaemia by the cell fate determinant Musashi. ***Nature*** 466:765-8 (2010).

【Homepage Address and Other Contact Information】

https://cellfate.infront.kyoto-u.ac.jp/