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

Broad Section I

Title of Project： Analysis of the malignant progression of tumors affected by tumor angiogenesis

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Keyword：tumor, angiogenesis

【Purpose and Background of the Research】

It has been elucidated that merely VEGF signal inhibition has limitation for effective suppression of tumor growth. It has been widely accepted that new blood vessel formation in tumor is induced by sprouting angiogenesis under VEGF/VEGFR system; however, in our research, we will elucidate another mechanism of neovascularization in tumor (Fig. 1). Moreover, we will elucidate the mechanism how malignant progression of cancer cells such as epithelial-mesenchymal transition and contrary phenomenon is induced by angiocrine signals from endothelial cells (Fig. 2) based on the achievement of novel mechanism of vascular remodeling by endothelial stem cells.

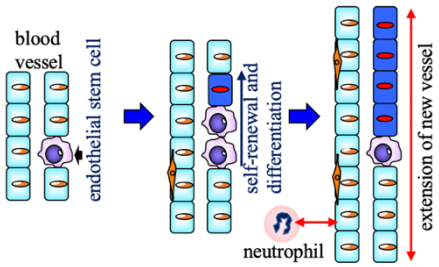

Figure 1 Molecular analysis of 'extension' type angiogenesis

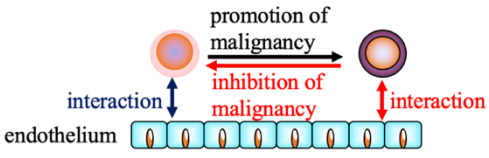

Figure 2 Elucidation of angiocrine signals in cancer

【Research Methods】

Our research can be divided into two plans. One is molecular analysis of new blood vessel formation induced by extension of pre-existing blood vessels regulated by endothelial stem cells and neutrophils (Fig. 1). The other is molecular mechanism of angiocine regulation in promoting malignant progression of cancer cells (Fig. 2). In the plan 1, we will analyze blood vessel formation in tumor which shows resistance against VEGF signal inhibitors, especially focused on the quality and quantity differences of neutrophils and endothelial stem cells. In the analysis, we will observe the time course of new blood vessel formation three dimensionally by real-time imaging using two photon microscopy. Here, we will observe the involvement of endothelial stem cells for new vessel formation by lineage tracing of these cells. In research plan 2, among molecular cues from tumor endothelial cells, we will elucidate molecular function of two molecules which are already isolated as molecules regulating malignant progression of cancer cells or inhibition of malignant change of cancer cells.

【Expected Research Achievements and Scientific Significance】

Our research shed light on the understanding malignant tumor microenvironment by analyzing the interaction of cancer cells and blood vessels. Molecular mechanism of malignant progression of cancer cells or tumor vascular formation has been independently analyzed so far. Our research will be performed to elucidate tumor malignancy in association with vascular formation. Our research will develop novel methods for cancer therapy by the suppression of interaction of cancer cells and endothelial cells.

【Publications Relevant to the Project】

- Naito H, et al. TAK1 Prevents Endothelial Apoptosis and Maintains Vascular Integrity. **Dev Cell** *48*, 151-166 (2019).
- Kidoya H, et al. Regnase-1-mediated post-transcriptional regulation is essential for hematopoietic stem and progenitor cell homeostasis. **Nat Commun**. *10*, 1072 (2019).
- Wakabayashi T, et al. CD157 Marks Tissue-Resident Endothelial Stem Cells with Homeostatic and Regenerative Properties. **Cell Stem Cell** *22*, 384-397 (2018).

【Term of Project】 FY2020-2024

【Budget Allocation】 151,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://st.biken.osaka-u.ac.jp/