【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (Comprehensive fields)

Title of Project : Regulatory Mechanisms of Tumor Microenvironment

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Research Area : Integrated Science and Innovative Science, Comprehensive fields, Oncology, Tumor biology

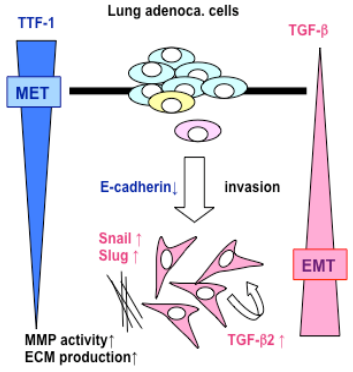
Keyword : Tumor microenvironment, Signaling, Pathology, Development/Differentiation

【Purpose and Background of the Research】

Tumor microenvironment is composed of fibroblasts, inflammatory cells, immune cells, and blood and lymphatic vascular cells. In this project, we will elucidate the roles of TGF-beta family proteins and some transcription factors, including Snail and Prox1, in induction of epithelial-mesenchymal transition (EMT), differentiation of cancer-associated fibroblasts (CAFs) and their interaction with cancer stem cells, and regulation of homeostasis of blood and lymphatic vasculatures. Through these studies, we will uncover the molecular mechanisms of invasion and metastasis of cancer, and try to develop new strategies for treatment of cancer. For these purposes, we will study 1) the mechanisms of EMT induced by TGF-beta. We also study 2) the roles of growth factors and transcription factors in the induction of CAFs, 3) molecular mechanisms of angiogenesis and lymphangiogenesis and identification of novel lymphangiogenic molecules using diffuse-type gastric cancer models, and 4) identification of BMP-target genes involved in angiogenesis and lymphangiogenesis.

【Research Methods】

1) Regulation of TGF-beta-induced EMT. We will find molecule(s), which are downstream components of Ras signaling and cooperatively act with TGF-beta for induction of EMT. We also identify Snail-target genes involved in EMT using Panc1 and A549 cells, and study mechanisms of action of TTF-1, focusing on the Smad-binding sites on the Snail promoter.



2) Induction of CAFs and their functional characterization. We will investigate the functional properties of CAFs induced by FGF, TNF-alpha, or HGF using various technologies.
3) Regulation of angiogenesis and lymphangiogenesis. We will study the mechanisms of (lymph)angiogenesis using diffuse-type gastric cancer models in mice. We also study the function of novel Prox1-binding protein(s) in lymphangiogenesis.
4) Functions of BMPs in tumor microenvironment. We will identify novel BMP-9 target genes in endothelial cells by ChIP-Seq. We also study the function of BMP-9 in lymphangiogenesis.

【Expected Research Achievements and Scientific Significance】

This project will facilitate the establishment of novel strategies for treatment of cancer. Since cancer therapy targeting tumor micro-environment may not induce critical side effects, findings obtained in this project may become useful in the future. Since studies on micro-environment are important not only for cancer progression but also for normal developmental processes, our project may also be valuable for biological processes other than cancer.

【Publications Relevant to the Project】

1) Ikushima H, Miyazono K. (2010) TGF-beta signalling: a complex web in cancer progression. Nat Rev Cancer. 10 (6): 415-24.
2) Komuro A, et al. (2009) Diffuse-type gastric carcinoma: progression, angiogenesis, and transforming growth factor beta signaling. J Natl Cancer Inst. 101 (8): 592-604.

【Term of Project】 FY2010-2014

【Budget Allocation】 167,400 Thousand Yen

【 Homepage Address and Other Contact Information】

http://beta-lab.umin.ac.jp/