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

Study on the Mechanisms of the Induction of Mesenchymal Cancer Cells and Their Plasticity and Diversity

Principal Investigator	The University of Tokyo, Graduate School of Medicine, Distinguished University Professor MIYAZONO Kohei　Researcher Number:90209908
Project Information	Project Number : 23H05486　Project Period (FY) : 2023-2027 Keywords : Invasion/metastasis, cell signaling, tumor microenvironment

Purpose and Background of the Research

●Outline of the Research

Highly malignant cancer cells often show characteristics of mesenchymal cells. Mesenchymal cancer cells (MCCs) are induced by epithelial-mesenchymal transition (EMT), in which cytokines such as TGF-β and EMT-inducing transcription factors (TFs), e.g., Snail and Slug, play central roles. MCCs are involved in cancer invasion and metastasis; they are also resistant to anti-cancer drugs and show cancer stem cell-like phenotype. MCCs are characterized by their diversity and plasticity, and lose their mesenchymal properties under certain conditions. In this research project, we conduct basic research on MCCs in pancreatic cancer, oral cancer, and glioblastoma (GBM), to develop innovative treatments for intractable cancers through understanding the molecular characteristics of MCCs.

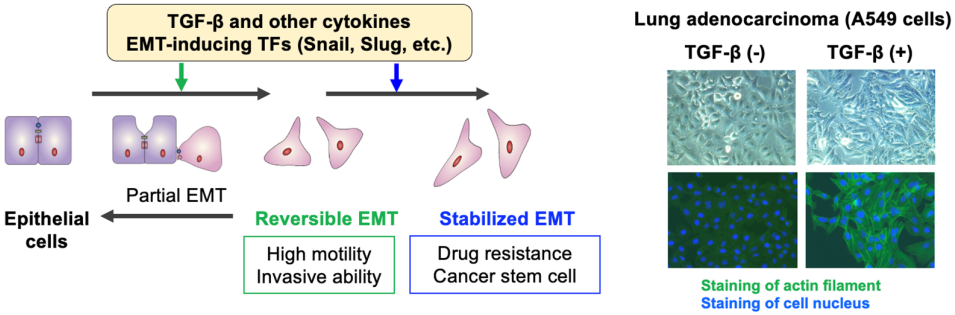

Figure 1. EMT. The process of EMT initially results in reversible mesenchymal cells. Prolonged stimulation with TGF-β induces the stabilized mesenchymal cell phenotype.

●Background leading to the conception of this research project

Paradox of TGF-β action in pancreatic cancer: Accumulation of gene abnormalities in epithelial cells leads to progression of pancreatic cancer. KRAS activated by gene mutation induces EMT together with TGF-β at early stages in pancreatic cancer. At later stages, abnormalities in SMAD4 are observed in 50% of cases. Since SMAD4 is a mediator of TGF-β signaling, TGF-β fails to induce EMT, when the SMAD4 gene is abnormal; but contrary to expectations, pancreatic cancer progresses further. The mechanism of this phenomenon is still a mystery.

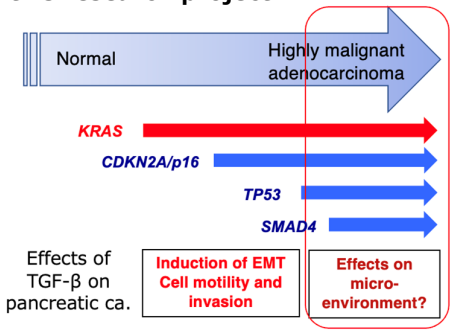

Figure 2. Abnormalities of oncogenes (red) and tumor-suppressor genes (blue) and the roles of TGF-β in progression of pancreatic cancer.

Two distinct types of MCCs in oral cancer: EMT in oral cancer cells is induced by the Slug-mediated pathway (classical pathway); in addition, we have found a novel, Slug-independent EMT-inducing pathway. The novel EMT-inducing pathway is mediated by a keratin-associated protein (KRTAP2-3). We will elucidate the characteristics of the two types of MCCs, and how they play roles in progression of oral cancer.

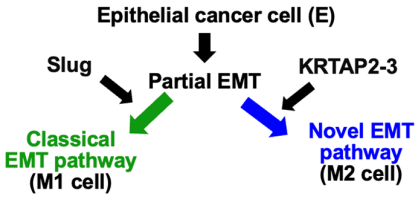

Figure 3. EMT-inducing pathways in oral cancer

Cancer cells in the mesenchymal (MES) subtype of GBM: GBMs are classified into several subtypes based on their gene expression profiles. The MES type GBM is a highly malignant type with resistant to chemo- and radiotherapy. MES-GBM cells are derived from proneural (PN) GBM cells; we have shown that a TNF receptor superfamily protein called HVEM plays critical roles in the MCCs in GBM, and that regulation of the functions of HVEM and its related proteins may be a new strategy for treatment of malignant GBM.

Expected Research Achievements

●Roles of MCCs in advanced cancer

When epithelial cells undergo EMT, they acquire invasive ability and start to metastasize. They adhere to vessel walls in distant organs, and some surviving cells extravasate to form metastasis. A variety of MCCs form metastasis by interacting with each other and by exhibiting plasticity. They further interact with the microenvironment, evading immune surveillance, and acquire resistance to anti-cancer drugs, leading to further progression of cancer. Thus, MCCs play important roles in various steps of cancer metastasis.

●Development of cancer therapies targeting MCCs

Since MCCs play important roles in various steps of cancer progression, they may be important targets for cancer therapy. This research project aims to elucidate the induction mechanism of MCCs and compare their characteristics in some cancers. We have already identified some molecular targets for cancer therapies; we wish to gain basic knowledge for the development of new strategies for cancer therapies.

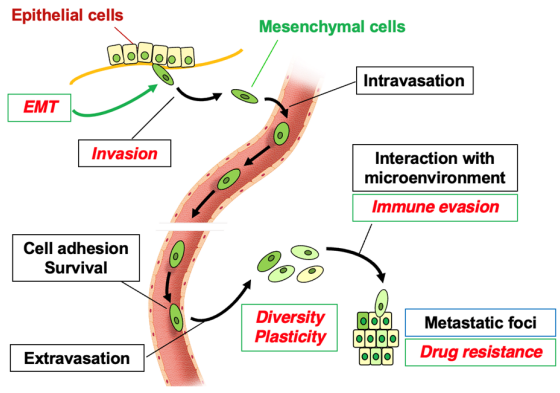

Figure 4. Role of MCCs in cancer invasion and metastasis

● Impact of the project to social life

✓ We elucidate the diversity and plasticity of MCCs, one of the ultimate phenotypes of intractable cancer, to understand the characteristics of highly malignant cancer.
✓ We contribute to the development of new innovative cancer therapies by elucidating the characteristics of MCCs at the molecular level.

Homepage Address, etc.	http://beta-lab.umin.ac.jp (Homepage of Miyazono lab)