Establishing a Recurrence Prevention Measure for Colorectal Cancer After Radical Surgery by Targeting the Tumor Microenvironment

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Molecular therapies targeting active mutations in driver genes have been ongoing worldwide since the genome medicine initiative was declared by Barack Obama, the former president of the United States. However, the limitations of targeting actively mutated genes necessitate the identification of alternative approaches to cancer treatment. To address the challenges posed by the untargetable and diverse passenger mutations in the genomes of epithelial cancer cells, our research has focused on identifying interstitial cells and genes within the tumor microenvironment that support oncogenesis or cancer progression.

Previously, we reported the abundant expression of VEGFR-1 in hematopoietic progenitor cells (HPCs), which promoted gastric cancer cell metastasis (Clin Cancer Res, 2008). Additionally, we demonstrated the clinical significance of ID1 derived from bone marrow endothelial progenitor cells in gastric cancer (Br J Cancer, 2009).

In colorectal cancer, our research has concentrated on epigenomic mutations as early diagnostic markers. We explored colorectal cancer-specific, malignant cell-specific, and prognosis-recurrence significantly correlated methylated genomic regions using a large-scale public methylation database. As a result, we identified three methylated genes and demonstrated their clear clinical utility as predictive markers for metastasis and recurrence. By deconvolving cells expressing GPC6 using public scRNA-seq data from 15 samples of stage IV colorectal cancer (primary tumors, liver metastases, and blood), we found that GPC6 was not expressed by cancer cells in the recurrent lesions but by cancer-associated fibroblasts (CAFs).

Furthermore, through the machine learning pipeline DeepCOLOR applied to single-cell data, we identified cells co-localized with GPC6 (highly methylated) low-expression CAFs and their crosstalk genes. The results revealed that GPC6 (highly methylated) low-expression CAFs secrete CCL2, which activates downstream CCR2 signaling in CD8 T cells and contributes to the formation of metastatic lesions.

We have already confirmed the safety of the CCL2-targeting inhibitor propagermanium in investigator-initiated clinical trials. In the future, the "pre-metastatic niche" composed of GPC6 (highly methylated) low-expression CAFs and CD8 T cells via CCL2 may serve as a novel therapeutic target.

CV.

Education and career:

1991 Graduated from the Medical College of Oita

1991 Dept of Surg II, Kyushu University (Resident)

1994 Dept of Surg, Medical Institute of Bioregulation Kyushu University (Research Fellow)

1997 Medical Doctor, PhD authorized by Kyushu University

1997 Kimmel Cancer Inst, Thomas Jefferson Univ., Philadelphia (Research Fellow)

2000 Dept of Surg, Medical Institute of Bioregulation Kyushu University (Research Associate)

2011 Dept of Surg, Kyushu University Beppu Hospital (Associate Professor)

2012 Professor of the Dept of Surg, Kyushu University Beppu Hospital

2023 Director of Kyushu University Beppu Hospital - At present.

Japan Agency for Medical Research and Development (Program Officer)

Certification:

Instructor and Specialist, certified by the Japanese Society of Surgery

Instructor and Specialist, certified by the Japanese Society of Gastroenterological Surgery

Certified Physician, certified by the Japanese Society of Breast Cancer

Membership:

Japanese Cancer Association (Board)

Japanese Society of Surgery (Council 25th District)

Japanese Society of Gastroenterological Surgery (Board)

The Japanese Society for Gastrointestinal Carcinogenesis (President of the Board)

The Japanese Association for Metastasis Research (Board)

American Association of Cancer Research (USA) (Active member)

Journal Contribution:

Associate Editor; Cancer Science (Japan)

Deputy Editor-In Chief; Annals of Gastroenterological Surgery (Japan)

Awards：

Incitement Award of the Japanese Cancer Association (2004)

Young Researcher's Award, Ministry of Education, Sci. and Technol in JPN (2006).

Prize for encouragement in Research by the Japan Medical Association (2011)

The Ohara Prize the Japanese Society for Gastroenterological Carcinogenesis (2018)

The Annals of Gastroenterological Surgery Award (2019)

The Takeda Foundation Award (2020)

Takashi Tsuruo Award, The Japanese Association for Molecular Target of Cancer (2022)