Goal2 Realization of ultra-early disease prediction and intervention by 2050.

Challenge toward the Control of Intractable Cancer through Understanding of Molecular, Cellular, and Interorgan Networks

Here begins our new MIRAI

**MOONSHOT** RESEARCH & DEVELOPMENT PROGRAM

R&D Theme

Technology development for the creation of innovative diagnostic and treatment concepts based on understanding of the onset process of cancer

Progress until FY2022

1.Outline of the project

In this theme, cell biology will explore the role of candidate sof early diagnosis markers and therapeutic targets revealed from the multi-hierarchical data of intractable cancer patients . We are developing the experimental system and technology necessary to evaluate its validity.
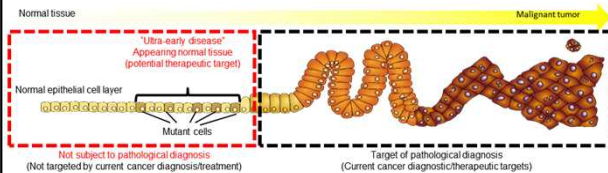
Based on mouse models, normal tissues have multiple mechanisms to eliminate abnormal cells caused by various cellular stresses (cell senescence, bacterial infection, genetic mutation, etc.). to prevent the occurrence of cancer. In addition, changes in metabolism, stem cells, cell adhesion and morphology are central characteristics of cancer cells. It is necessary to know when these cancer development process occur.

In addition to model mice and cancer cell lines, we use clinical specimens containing early-stage lesions, and patient organoids as experimental systems. We are working to understand the process and create new diagnostic and treatment concepts.

2. Outcome so far

We created a model mouse that can induce cell competition in the pancreas, and identified molecules whose expression increases during cell competition. This molecule was expressed in premalignant lesions (ADM) of pancreatic carcinoma model mice and also expressed in ADM from human pancreatic cancer clinical samples.

Mutant cells were found to be eliminated from normal cell populations through cell competition by issuing a "kick-me-out" signal to let them out. A genetic screen identified a group of genes involved in the elimination of cancer mutant or normal cells.

We found that elimination of cancer mutant cells by cell competition is suppressed by senescent cells. We found that senolytic drugs are effective in eliminating cancer mutant cells through cell competition.

Igarashi *et al.*, Nat Commun 2022
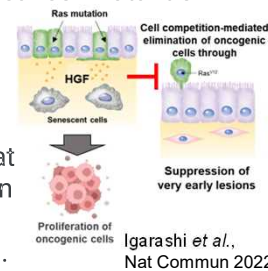
We created a model mouse in which cancer development increases due to the accumulation of senescent cells over time, and using this model, we identified intestinal bacteria that promote the accumulation of senescent cells and the development of cancer. In addition, we constructed an analysis system using human biological samples.

We analyzed the mechanism that various cellular stresses in the tumor microenvironment induce the expression of cancer-specific antigens through changes in RNA metabolism.

We have established a system to detect metabolic changes of amino acids and keto acids in vivo in real time. Using this, we identified the metabolic pathway of branched-chain amino acids (BCAA) in cancer cells.

Using a mouse transplantation model, we narrowed down candidate genes that are suspected to be involved in ferroptosis resistance, which is involved in the maintenance of cancer stem cells.

We have successfully identified new molecules and networks that control the asymmetric division of cancer stem cells in refractory breast cancer.

We found the mechanism of filamentous process formation and vascular mimic formation, which are correlated with the prognosis of patients with pancreatic cancer and lung adenocarcinoma.

3.Future plans

Molecules with increased expression in pancreatic cancer precancerous lesions (ADMs) are candidate markers for early diagnosis of pancreatic cancer and valuable research tools for understanding pancreatic precancerous lesions. It can be expected that In the future, we will proceed to verify the clinical usefulness of this molecule at early-stage pancreatic cancer lesions. We will also use clinical samples, including organoids, to study the relationship between cellular senescence and intestinal bacteria, metabolic shifts in cancer, changes in stem cell characteristics, changes in cell adhesion and morphological changes.

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