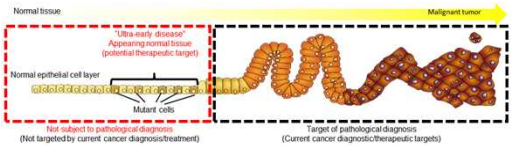
R&D item

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

Progress until FY2023

1.Outline of the project

In this theme, cell biology will explore the role of candidates of 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.

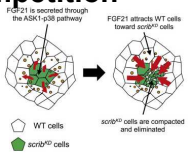


Based on mouse models, normal tissues have multiple mechanisms to eliminate abnormal cells caused by various cellular stresses (cell senescence, bacterial infection, genetic mutation, etc.) to prevent the occurrence of cancer. In addition, changes in metabolism, stem cells, cell adhesion and morphology 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

Network analysis focusing on cell competition and cell senescence

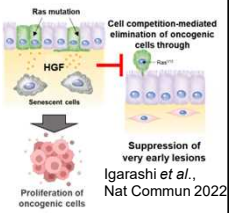


We identified a molecule whose expression increases in the pancreas of a cell competition model mouse. This molecule was expressed in premalignant lesions (ADM) of pancreatic carcinoma in model mice and human clinical samples.

Ogawa *et al.*,Curr Biol 2021

A genetic screen in *Drosophila* identified a group of genes involved in the elimination of cancer mutant or normal cells.

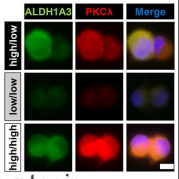
Mutant cells were found to be eliminated from normal cell populations through cell competition by issuing a “kick-me-out” signal to let them out.



We found that elimination of cancer mutant cells by cell competition is suppressed by senescent cells and senolytic drugs are effective in eliminating cancer mutant cells through cell competition. Furthermore, chromatin conformational changes in senescence cells contribute to inflammatory gene expression.

Igarashi *et al.*, Nat Commun 2022

Network analysis focusing on stem cells, cell polarity, and epithelial-to-mesenchymal transition



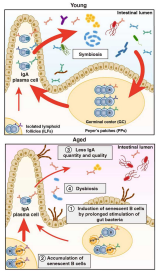
We have found that a cell polarity-related factor is associated with prognosis of pancreatic cancer patients and regulates asymmetric asymmetric division of cancer stem cells.

Kasai *et al.*, BBRC 2023

Using a mouse transplantation model, we identified candidate genes that is involved in ferroptosis resistance, which is involved in the maintenance of cancer stem cells.

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

Network analysis focusing on intestinal flora, cancer immunity, and metabolism



We created a model mouse in which cancer development increases due to the accumulation of senescent cells and identified intestinal bacteria that promote the accumulation of senescent cells and the development of cancer. Furthermore, we discovered that age-related aging of B cells causes disturbances in the intestinal flora.

Kawamoto *et al.*,Nat Cell Biol 2023

We analyzed stresses in the tumor microenvironment that induce the expression of cancer-specific antigens through RNA metabolism and developed simultaneous measurement system for newly synthesized RNA and translation.

We have established a system to detect metabolic changes of amino acids and keto acids in vivo in real time and identified the metabolic pathway of branched-chain amino acids in cancer cells. We found that an inhibitor against chromatin-related factors is effective for leukemia .

3. Future plans

Using the organoids from early lesions of pancreatic cancer, we will clinically verify the usefulness of a molecule whose expression increases in pancreatic precancerous lesions as an early diagnostic marker and investigate the process of cancer onset to reveal the relationship between cellular senescence and intestinal bacteria, metabolic shifts, changes in stem cell characteristics, cell adhesion and morphology