News Release

Title

Premalignant pancreatic cells seed stealth metastasis in distant organs

Key Points

○Although metastasis are thought to occur in the late stage of pancreatic cancer, we found that premalignant cells seed metastatic cells in distant organs.

○These premalignant metastasis wears the characteristics of host organs and exists stealthily.

○These findings indicates the possibility of ultimate prevention therapy for metastatic pancreatic cancer.

Summary

Prof. Tomoki Ebata (Division of Surgical Oncology, Department of Surgery) in Nagoya University Graduate School of Medicine (Dean: Dr. Kenji Kadomatsu) and Dr. Junpei Yamaguchi (Lecturer, Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of medicine) revealed that the pancreatic premalignant cells seeded metastasis stealthily in distant organs, where they wore the characteristics of host organs.

Pancreatic cancer is one of the most critical malignancies with the 5-year survival as low as 10%. Pancreatic cancer has been thought to metastasize in their late stage; however, recent reports suggest they metastasize in their relatively early stage. The team utilized the transgenic mouse model to trace the cell fate of premalignant, early malignant, and late malignant cells. As a result, these cells were found to enter the bloodstream and metastasize to the liver; surprisingly, premalignant cells had the highest ability to metastasize. In addition, the metastasized premalignant cells showed the characteristics of hepatocytes, thus they were not distinguishable as metastasis. This type of metastasis was termed as “stealth metastasis”. The stealth metastasis was found in the lung as well, and it developed to malignant tumor. These results revealed that premalignant pancreatic cells seed stealth metastasis to distant organs and eventually develop to manifest metastasis. These findings indicate the possibility of prevention therapy for metastatic pancreatic cancer. This work was published online in *Oncogene* on March 1, 2021.

Research Background

Pancreatic cancer is the 4th leading malignancy in terms of cancer death in Japan and its 5-year survival is as low as 10% (cancer statistics in Japan 2017; Foundation for Promotion of Cancer Research). The most important reason for their poor prognosis is the metastasis, and

we need novel strategy to treat metastasis of pancreatic cancer.

Generally speaking, metastasis is thought to occur at the end stage of malignant disease; however, recent reports suggest that pancreatic and breast cancer disseminate at relatively early stage. Even so, it is still to be clarified how disseminated cells can develop metastatic tumor in distant organs. Thus, it is of great importance to investigate the early dissemination of pancreatic cancer.

Research Results

The mouse models of pancreatic cancer with various stage were employed in this study. Pancreatic cancer (PDAC: pancreatic ductal adenocarcinoma) develops from their precursor lesions (PanIN: pancreatic intraepithelial neoplasms), and we revealed that loss of TFF1 accelerated pancreatic carcinogenesis. Using these models, we investigated four stage of pancreatic cancer (early PanIN, advanced PanIN, early PDAC and advanced PDAC). The pancreatic epithelial cells were labeled with tdTomato and the fate of the cells were traced.

The tdTomato-positive cells were found in the blood, confirming the existence of circulating tumor cells (CTC), and CTC was found most frequently in advanced PanIN models (Figure 1).

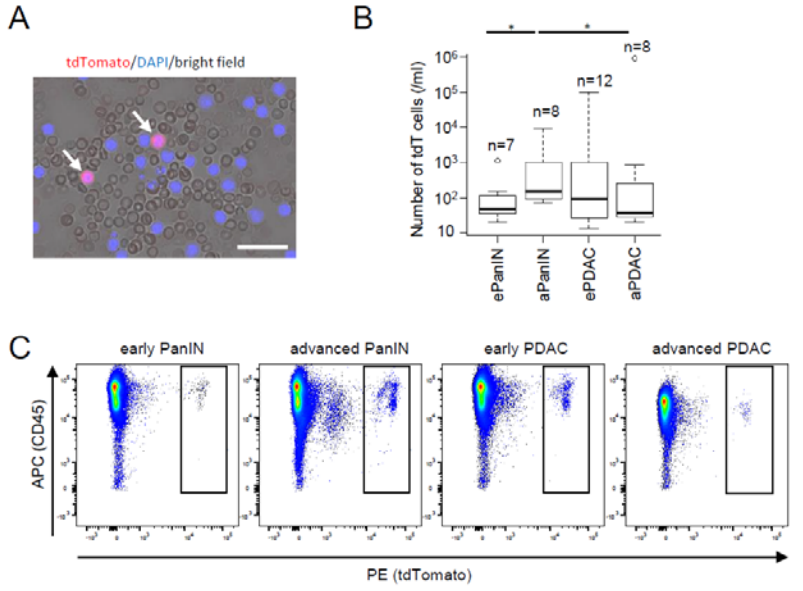

Figure 1. CTC derived from early stage of pancreatic cancer.

Because all mice were harvested at their young age (three-months old), there was no apparent metastasis in the liver; however, abundant tdTomato-positive cells were found in the liver. These cells ware pathologically hepatocytes and could not be recognized as metastatic cells in the usual approach. We termed this type of cells as “stealth metastasis” and further investigated, revealing that they were found most frequently in advanced PanIN model (Figure 2).

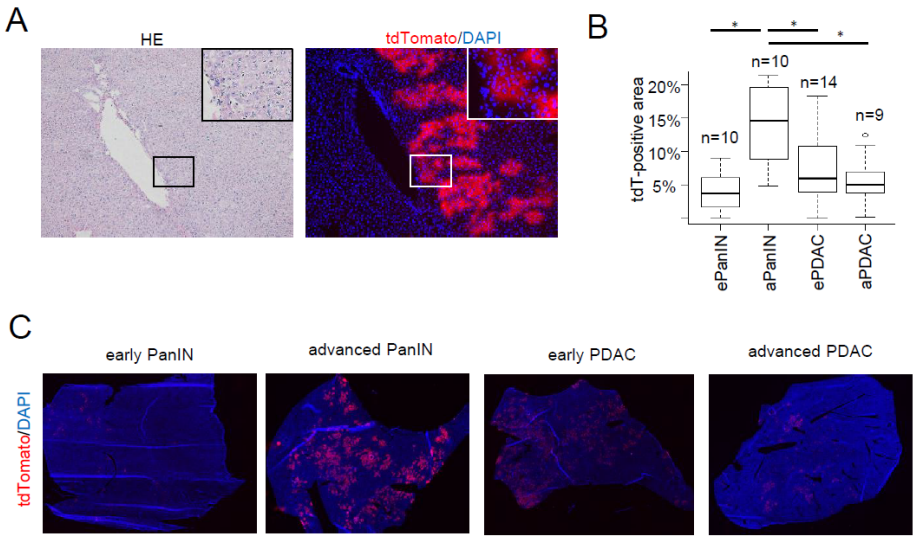

Figure 2. Stealth metastasis in the liver.

The stealth metastasis was found in the lung as well. In addition, this stealth metastasis was found to develop into malignant tumor (Figure 3). These observation suggest that pancreatic premalignant cells metastasize to liver and lung, reside there as stealth metastasis, and develop metastatic tumors (Figure 4).

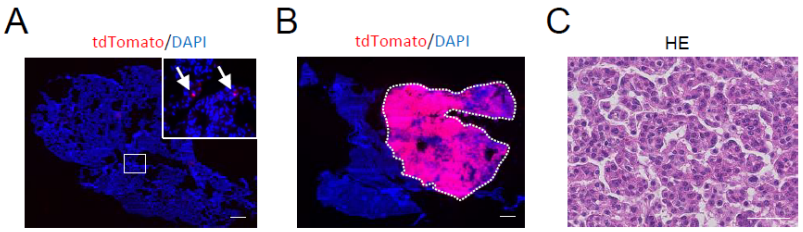

Figure 3. Stealth metastasis in the lung.

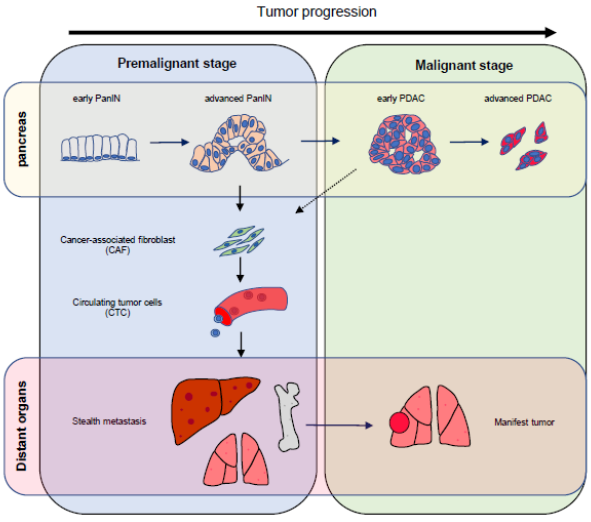

Figure 4. Schema of stealth metastasis.

Research Summary and Future Perspective

Although chemotherapy is only one treatment for the metastatic pancreatic cancer, its effect is very limited, and the rate of adverse event is high. If we can treat them at early stage, when they are stealth metastasis, it could be possible to resect them or prevent their malignant transformation. This team are trying to find specific marker for stealth metastasis and novel treatment to prevent malignant transformation of stealth metastasis.

Publication

Junpei Yamaguchi, Toshio Kokuryo, Yukihiro Yokoyama, Tomoki Ebata, Yosuke Ochiai, and Masato Nagino. Premalignant pancreatic cells seed stealth metastasis in distant organs in mice. Oncogene, In Press.
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Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Onc_210302.pdf