“Cancer Models” from the Pathological View

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Many cancer models, either in vitro or in vivo, have been developed actively in order to elucidate and understand the mechanisms of the carcinogenesis and progression of human cancers. Such models include cell lines, *in vitro* three-dimensional culture model as spheroid, organoid, animal cancer xenograft model, human cancer xenograft model and patient-derived xenograft (PDX) model and the like. Meanwhile, in the construction of cancer models, to make the cancer model itself are not becoming the objectives but the real objectives of the models are to deepen the knowledge and comprehension on the intended system (pathology of cancers), and furthermore the drug discovery based on the animal models is the further objective. When we develop and utilize an animal model derived from human tissue, we have to clarify the objectives of the model and utilize it appropriately based on the comprehension of its advantage and defect.

The pancreatic cancer is one of the representative intractable cancers which is difficult to diagnose in its early stage and of which the prognosis is very poor even after the diagnosis. Our clinic-pathological studies revealed that the characterization of nerve infiltration. To clarify the clinical significance of the nerve infiltration, we tried and found that the genetically engineered mouse pancreatic cancer model did not match for the study, because the location of pancreas and the relation to the nerve are definitely different between human and mouse. We constructed a model for the nerve infiltration in which human pancreatic cancer cells are xenotransplanted in the immune deficient mouse sciatic nerve. As a result, it was observed that the transplanted cancer cells aggressively invaded toward the proximal side similarly as in cases of human pancreatic cancer. Additionally, rapid loss of body weight of the mouse similar to the cachexia and cancerous pain were observed. To confirm these phenomena in patients with pancreatic cancer; therefore we researched into the treatment using the animal model. IL-6 highly produced by human pancreatic cancer cells at the nerve invading region site strongly affects the promotion of pancreatic cancer development resulting in cancer pain and the cachexia. Similar clinical manifest is observed in pancreatic cancer patients. With an aim of drug discovery, we tried to verify the inhibition of these phenomena both in animal and clinical trials with anti-IL6 receptor antibody. We couldn’ t verify the efficacy of antibodies in a clinical trial, since we couldn’ t find an appropriate marker to select patients,.

Based on our experiences, the comprehension of pathological condition using models is different from that of the development of therapeutic method. The construction of appropriate cancer model depending on its objective is important on understanding the pathological condition of cancer patients or the development of treatment. New models in which integration of *in vitro* and *in vivo* information obtained from both in animal models and human cancers may appear. New cancer model based on the deeper comprehension of cancer and the human body is expected.

[Awards]

2018 President of the 29th Annual Meeting of Japanese Society for Gastroenterological Carcinogenesis, Tokyo.
2017 President of the 106th Annual Meeting of Japanese Society of Pathology, Tokyo
2006 Pathology award, Japanese Society of Pathology
2004 Research grant award, The Princess Takamatsu Cancer Research Fund.
1999 Baerz prize, Boehringer Ingerheim
1997 Tamiya prize, Foundation for Promotion of Cancer Research
1996 Young scientific award of the Japanese Cancer Association
1996 Pathology Research award of Japan Science Academy

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2. Nerve invasion distance is dependent on laminin gamma2 in tumors of pancreatic cancer. Mitsunaga S. et al. Int J Cancer. 2010;127(4):805-19.
3. Neural invasion induces cachexia via astrocytic activation of neural route in pancreatic cancer. Imoto A, et al. Int J Cancer. 2012;131(12):2795-807
4. Prognostic impact of M2 macrophages at neural invasion in patients with invasive ductal carcinoma of the pancreas. Sugimoto M et al. Eur J Cancer. 2014;50(11):1900-8.
5. Neural Invasion Spreads Macrophage-Related Allodynia via Neural Root in Pancreatic Cancer. Miura T et. al. Anesth Analg. 2018;126(5):1729-1738.

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1988 Experimental Pathology, Medical School of Hannover, West Germany
1991 Pathology Division, National Cancer Center Research Institute
1998~2016 Pathology Division, Research Center for Innovative Oncology, National Cancer Center
2002~ Professor, Laboratory of Cancer Biology, Integrated Bioscience, The University of Tokyo
2013~2018 Deputy Director, National Cancer Center Research Institute
2016~ Director, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center