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Research Interests

Mouse genetics, organoid, microscopy imaging, microenvironment, metastasis

Education

1982- 1986	Faculty of Veterinary Medicine, Hokkaido University
1986- 1988	Hokkaido University Graduate School of Veterinary Medicine (MS)

Professional Career

1988- 1991	Staff Scientist, Chugai Pharmaceutical Co. Ltd.
1992- 1997	Staff Scientist, Banyu Tsukuba Research Institute (Merck)
1997- 1999	Research Associate, Merck Research Laboratories, USA
2000- 2005	Associate Professor, Kyoto University Graduate School of Medicine
2005 - present	Professor, Cancer Research Institute, Kanazawa University
2017 - present	Professor, Nano Life Science Institute (WPI-NanoLSI), Kanazawa University

Scientific Activities

1992- 2005	Mouse genetics studies for chemoprevention of intestinal tumorigenesis
2005 - present	Mouse genetics and organoid research for gastrointestinal cancer malignant progression

Honors

2012	JCA-Mauverynay Award, Japanese Cancer Association
2013	Achievement Commendation of Kanazawa University, Kanazawa University
2015	The Commendation for Science and Technology, MEXT
2020	Ishikawa Television Award, Ishikawa TV Broadcasting Co. Ltd

Publications

1. Nakayama M, Hong CP, Oshima H, Sakai E, Kim SJ, and Oshima M. Loss of wild-type p53 promotes mutant p53-driven metastasis through acquisition of survival and tumor-initiating properties. Nat Commun, 11: 2333. 2020.
2. Takeda H, Kataoka S, Nakayama M, Ali MAE, Oshima H, Yamamoto D, Park JW, Takegami Y, An T, Jenkins NA, Copeland NG, and Oshima M. CRISPR-Cas9 mediated gene knockout in intestinal tumor organoids provides functional validation for colorectal cancer driver genes. Proc Natl Acad Sci USA, 116: 15635-15644, 2019.
3. Oshima H, Kok SY, Nakayama M, Murakami K, Voon DC, Kimura T, and Oshima M. Stat3 is indispensable for damage-induced crypt regeneration but not for Wnt-driven intestinal tumorigenesis. FASEB J, 2019.

Polyclonal metastasis of colorectal cancer

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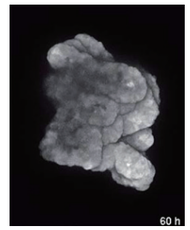
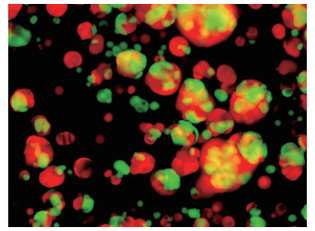
Colorectal cancer (CRC) is a leading cause of cancer-related death globally, and the majority of cancer-related deaths are caused by metastasis. It is therefore important to predict metastatic ability of the primary cancers to establish a clinical strategy. The accumulation of driver mutations is responsible for development and malignant progression of colorectal cancer, and comprehensive genome research has identified driver genes that are frequently mutated in CRC. Using genetic mouse models, we have constructed mouse models and established intestinal tumor-derived organoids carrying various combinations of driver mutations, Apc (A), Kras (K), Tgfbr2 (T), Trp53 (P), and Fbxw7 (F). Comprehensive phenotype analyses revealed that AT and AP mutation combinations cause submucosal invasion, AKT and AKP combinations induce advanced malignant phenotype like epithelial-mesenchymal transition (EMT), and AKTP and AKTPF acquire highly metastatic ability from the spleen to liver [1-3], which is consistent with the established concept of multistep tumorigenesis based on Darwin evolution. However, a unique concept for metastasis, polyclonal metastasis, has recently been proposed. We therefore examined the mechanism of polyclonal metastasis by labeled the intestinal tumor-derived organoids with Venus and tdTomato. When non-metastatic (Non-M) cells are transplanted into the spleen with malignant metastatic (MM) cells, they form chimeric metastatic foci in the liver. Importantly, MM cells, but not Non-M cells, induce niche generation surrounding disseminated tumor clusters, and such microenvironment consisting of macrophages and αSMA-expressing cells promotes the colonization of Non-M cells. These results indicate that non-metastatic cells can metastasize via the polyclonal mechanism using the microenvironment that is generated by malignant cells.



AKTP organoids



AKTP and AP chimeric spheroids
for spleen transplantation

References

[1] Oshima H, Nakayama M, Han TS, Naoi K, Ju X, Maeda Y, Robine S, Tsuchiya K, Sato T, Taketo MM, and Oshima M. Suppressing TGF-β signaling in regenerating epithelia in an inflammatory microenvironment is sufficient to cause invasive intestinal cancer. **Cancer Res**, 75: 754-765, 2015.

[2] Nakayama M, Sakai E, Echizen K, Yamada Y, Oshima H, Han TS, Ohki R, Fujii F, Ochiai A, Robine S, Voon DC, Tanaka T, Taketo MM, and Oshima M. Intestinal cancer progression by mutant p53 through the acquisition of invasiveness associated with complex glandular formation. **Oncogene**, 36: 5885-5896, 2017.

[3] Sakai E, Nakayama M, Oshima H, Kouyama Y, Niida A, Fujii S, Ochiai A, Nakayama KI, Mimori K, Suzuki Y, Hong CP, Ock CY, Kim SJ, and Oshima M. Combined mutation of Apc, Kras and Tgfbr2 effectively drives metastasis of intestinal cancer. **Cancer Res**, 78: 1334-1346, 2018.