Human Genome Center

Laboratory of Molecular Medicine
ゲノム医科学分野

Professor	Tatsuhiro Shibata, M.D., Ph.D.	教　授	医学博士	柴　田　龍　弘
Senior Assistant Professor	Atsushi Niida, Ph.D.	講　師	博士(理学)	新井田　厚　司
Assistant Professor	Takahashi Kazuki, Ph.D.	助　教	博士(農学)	高　橋　数　冴

The Laboratory of Molecular Medicine focuses on comprehensive characterization of currently-untreatable diseases including cancer on the basis of molecular genomics and aims to make "breakthroughs for human health" by identifying novel disease-related genes/pathways, including potential therapeutic or preventive targets and biomarkers, and to understand human diseases as heterogeneous but intervention-able "biological systems". This group has also organized the facility for the analysis of next-generation high-performance sequencers.

1. Single-Cell Analysis Reveals a CD4+ T-cell Cluster That Correlates with PD-1 Blockade Efficacy

CD4+ T-cell immunity helps clonal proliferation, migration, and cancer cell killing activity of CD8+ T cells and is essential in antitumor immune responses. To identify CD4+ T-cell clusters responsible for antitumor immunity, we simultaneously analyzed the naïve-effector state, Th polarization, and T-cell receptor clonotype based on single-cell RNA-sequencing data. Unsupervised clustering analysis uncovered the presence of a new CD4+ T-cell metacluster in the CD62Llow CD4+ T-cell subpopulation, which contained multicellular clonotypes associated with efficacy of programmed death-ligand 1 (PD-1) blockade therapy. The frequency of these cells in the peripheral blood significantly correlated with progression-free survival and overall survival of patients with lung cancer after PD-1 blockade therapy. These findings suggest that CD62Llow CCR4-CCR6+ CD4+ T cells form a novel metacluster with predictive potential of the immune status and sensitivity to PD-1 blockade, which may pave the way for personalized antitumor immunotherapy strategies for patients.

2. ICGC-ARGO precision medicine: targeted therapy according to longitudinal assessment of tumour heterogeneity in colorectal cancer.

Colorectal cancer is characterised by high molecular heterogeneity and genomic alterations in common cancer drivers, including RAS, BRAF, and mismatch repair genes, which are routinely assessed to inform precision treatments. However, constant clonal evolution is common and leads to therapeutic resistance. Longitudinal molecular analysis of integrated tissue and liquid biopsies is essential to monitor the molecular evolution of colorectal cancer during the continuum of care and inform sequential adaptive therapies based on real-time genomic changes. We present two patients with metastatic colorectal cancer, who after referral to the Precision Medicine Tumour Board underwent assessment using tumour tissue and circulating-tumour DNA (ctDNA), and responded to targeted therapy based on these molecular profiles.

3. Evolutionary Analysis of Cancer

The process of cancer development by genome mutation can be regarded as the "evolution" of cancer. We have conducted several analyses to elucidate the evolution of cancer. Population genetics has been used to elucidate the evolution of various species. Using the theory of population genetics, we are develop-

ing a method to detect selection related to intratumor heterogeneity (ITH) in cancer. In addition, various genomic mutations occur in cancer, and theoretical analysis can clarify the timing of their mutations in the development of cancer. Using these methods, we have analyzed the evolution of various cancers.

4. Verification of the Effect of Mindfulness Meditation on Heart Rate Variability Using Mobile Health Technology

Mindfulness meditation (hereafter referred to as "meditation") is a modern form of mental training that has been re-edited from traditional Buddhist religious practice to remove its religious overtones. We will examine whether continuous meditation can change heart rate patterns in daily life, based on heart rate data obtained from a smartwatch. For this purpose, we will also collect information on sleep and step counts, collect information on stress and activity status in real time using a smartphone application, and collect information on stress, exercise, sleep, etc. through a post-questionnaire survey, and conduct an integrated analysis of these data. The results obtained from this study will make it possible to objectively measure the effects of meditation on stress reduction using mobile health technology.

Publications

1. Kotani D, Nakamura Y, Fujisawa T, Bando H, Sakamoto N, Johns AL, Park K; ICGC-ARGO, Casolino R, Yoshino T, Biankin AV. ICGC-ARGO precision medicine: targeted therapy according to longitudinal assessment of tumour heterogeneity in colorectal cancer. Lancet Oncol. 2022;23:463-464.
2. Milella M, Luchini C, Lawlor RT, Johns AL, Casolino R, Yoshino T, Biankin AV; ICGC-ARGO. ICGC-ARGO precision medicine: familial matters in pancreatic cancer. Lancet Oncol. 2022;23:25-26.
3. Yachida S, Totoki Y, Noë M, Nakatani Y, Horie M, Kawasaki K, Nakamura H, Saito-Adachi M, Suzuki M, Takai E, Hama N, Higuchi R, Hirono S, Shiba S, Kato M, Furukawa E, Arai Y, Rokutan H, Hashimoto T, Mitsunaga S, Kanda M, Tanaka H, Takata S, Shimomura A, Oshima M, Hackeng WM, Okumura T, Okano K, Yamamoto M, Yamaue H, Morizane C, Arihiro K, Furukawa T, Sato T, Kiyono T, Brosens LAA, Wood LD, Hruban RH, Shibata T. Comprehensive Genomic Profiling of Neuroendocrine Carcinomas of the Gastrointestinal System. Cancer Discov. 2022 Mar 1;12(3):692-711
4. Kogure Y, Kameda T, Koya J, Yoshimitsu M, Nosaka K, Yasunaga JI, Imaizumi Y, Watanabe M, Saito Y, Ito Y, McClure MB, Tabata M, Shingaki S, Yoshifuji K, Chiba K, Okada A, Kakiuchi N, Nannya Y, Kamiunten A, Tahira Y, Akizuki K, Sekine M, Shide K, Hidaka T, Kubuki Y, Kitanaka A, Hidaka M, Nakano N, Utsunomiya A, Sica RA, Acuna-Villaorduna A, Janakiram M, Shah U, Ramos JC, Shibata T, Takeuchi K, Takaori-Kondo A, Miyazaki Y, Matsuoka M, Ishitsuka K, Shiraishi Y, Miyano S, Ogawa S, Ye BH, Shimoda K, Kataoka K. Whole-genome landscape of adult T-cell leukemia/lymphoma. Blood. 2022;139:967-982.
5. Satoh H, Arai Y, Furukawa E, Moriguchi T, Hama N, Urushidate T, Totoki Y, Kato M, Ohe Y, Yamamoto M, Shibata T. Genomic landscape of chemical-induced lung tumors under Nrf2 different expression levels. Carcinogenesis. 2022;43(7):613-623.
6. Liu X, Sato N, Yabushita T, Li J, Jia Y, Tamura M, Asada S, Fujino T, Fukushima T, Yonezawa T, Tanaka Y, Fukuyama T, Tsuchiya A, Shikata S, Iwamura H, Kinouchi C, Komatsu K, Yamasaki S, Shibata T, Sasaki AT, Schibler J, Wunderlich M, O'Brien E, Mizukawa B, Mulloy JC, Sugiura Y, Takizawa H, Shibata T, Miyake K, Kitamura T, Goyama S. IMPDH inhibition activates TLR-VCAM1 pathway and suppresses the development of MLL-fusion leukemia. EMBO Mol Med. 2023 Jan 11;15(1):e15631.
7. Nagane M, Ichimura K, Onuki R, Narushima D, Honda-Kitahara M, Satomi K, Tomiyama A, Arai Y, Shibata T, Narita Y, Uzuka T, Nakamura H, Nakada M, Arakawa Y, Ohnishi T, Mukasa A, Tanaka S, Wakabayashi T, Aoki T, Aoki S, Shibui S, Matsutani M, Ishizawa K, Yokoo H, Suzuki H, Morita S, Kato M, Nishikawa R. Bevacizumab beyond Progression for Newly Diagnosed Glioblastoma (BIOMARK): Phase II Safety, Efficacy and Biomarker Study. Cancers (Basel). 2022 Nov 10;14(22):5522.
8. Kagamu H, Yamasaki S, Kitano S, Yamaguchi O, Mouri A, Shiono A, Nishihara F, Miura Y, Hashimoto K, Imai H, Kaira K, Kobayashi K, Kanai Y, Shibata T, Horimoto K. Single-Cell Analysis Reveals a CD4+ T-cell Cluster That Correlates with PD-1 Blockade Efficacy. Cancer Res. 2022 Dec 16;82(24):4641-4653.
9. Mafficini A, Simbolo M, Shibata T, Hong SM, Pea A, Brosens LA, Cheng L, Antonello D, Sciammarella C, Cantù C, Mattiolo P, Taormina SV, Malleo G, Marchegiani G, Sereni E, Corbo V, Paolino G, Ciaparrone C, Hiraoka N, Pallaoro D, Jansen C, Milella M, Salvia R, Lawlor RT, Adsay V, Scarpa A, Luchini C. Integrative characterization of intraductal tubulopapillary neoplasm (ITPN) of the pancreas and associated invasive adenocarcinoma. Mod Pathol. 2022 Dec;35(12):1929-1943.
10. Oba U, Kohashi K, Sangatsuda Y, Oda Y, Sonoda KH, Ohga S, Yoshimoto K, Arai Y, Yachida S, Shi-

bata T, Ito T, Miura F. An efficient procedure for the recovery of DNA from formalin-fixed paraffin-embedded tissue sections. Biol Methods Protoc. 2022 Jul 26;7(1):bpac014.
11. Tanaka M, Kunita A, Yamagishi M, Katoh H, Ishikawa S, Yamamoto H, Abe J, Arita J, Hasegawa K, Shibata T, Ushiku T. KRAS mutation in intrahepatic cholangiocarcinoma: Linkage with metastasis-free survival and reduced E-cadherin expression. Liver Int. 2022 Oct;42(10):2329-2340.
12. Yamazaki A, Arai Y, Fukuoka K, Nakano Y, Hama N, Nakata S, Makino K, Kuroda JI, Shinojima N, Mukasa A, Mikami Y, Ichimura K, Shibata T, Yokoo H, Nobusawa S. Diffusely infiltrating glioma with CREBBP-BCORL1 fusion showing overexpression of not only BCORL1 but BCOR: A case report. Brain Tumor Pathol. 2022 Jul;39(3):171-178.
13. Kojima N, Arai Y, Satomi K, Kubo T, Matsushita Y, Mori T, Matsushita H, Ushijima T, Yatabe Y, Shibata T, Yonemori K, Ichimura K, Ichikawa H, Kawai A, Yoshida A. Co-expression of ERG and CD31 in a subset of CIC-rearranged sarcoma: a potential diagnostic pitfall. Mod Pathol. 2022 Oct;35(10): 1439-1448.
14. Takami H, Elzawahry A, Mamatjan Y, Fukushima S, Fukuoka K, Suzuki T, Yanagisawa T, Matsushita Y, Nakamura T, Satomi K, Tanaka S, Mukasa A, Saito N, Kanamori M, Kumabe T, Tominaga T, Kobayashi K, Nagane M, Iuchi T, Tamura K, Maehara T, Sugiyama K, Yoshimoto K, Sakai K, Nonaka M, Asai A, Yokogami K, Takeshima H, Narita Y, Shibui S, Nakazato Y, Hama N, Totoki Y, Kato M, Shibata T, Nishikawa R, Matsutani M, Ichimura K. Transcriptome and methylome analysis of CNS germ cell tumor finds its cell-of-origin in embryogenesis and reveals shared similarities with testicular counterparts. Neuro Oncol. 2022 Aug 1;24(8):1246-1258.
15. Shimizu D, Taniue K, Matsui Y, Haeno H, Araki H, Miura F, Fukunaga M, Shiraishi K, Miyamoto Y, Tsukamoto S, Komine A, Kobayashi Y, Kitagawa A, Yoshikawa Y, Sato K, Saito T, Ito S, Masuda T, Niida A, Suzuki M, Baba H, Ito T, Akimitsu N, Kodera Y, Mimori K. Pan-cancer methylome analysis for cancer diagnosis and classification of cancer cell of origin. Cancer Gene Ther. 2022 May;29(5):428-436.
16. Takahashi K. K, Innan H. Frequent somatic gene conversion as a mechanism for loss of heterozygosity in tumor suppressor genes. Genome Res 32:1017-1025, 2022.