Host Laboratory:
Laboratory of Molecular Target Therapy of Cancer, Department of Medical Genome Sciences, The University of Tokyo
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Research in our Laboratory

The recent development of molecular targeted therapies drastically improved the cancer treatments, however we are still facing problems to surmount in prevention and therapy of cancers. Cancer metastasis and drug resistance are the major obstacles for the cancer therapies. Especially, because of its complexity and the absence of anti-metastasis drug, it is still underway to manage the metastasis.

In our laboratory, we aims to understand the basis of cancer metastasis and drug resistance, to identify possible targets, to clarify the function of molecular targets, and ultimately to develop an effective molecular-targeted therapy for cancer. We have studied and identified multiple factors which are deeply related to cancer metastasis. Among them, we identified Aggrus/podoplanin as a metastasis-inducing factor (1). Aggrus/podoplanin promotes metastasis by its activity to aggregate platelets around cancer cells, and the cell-platelets aggregates results in increasing the frequency of embolization in the microvasculature and protecting from immunological assaults. To target the Aggrus-mediated metastasis via platelet aggregation, we developed the neutralizing anti-Aggrus antibody and its humanized chimeric one that interferes with the binding of Aggrus-CLEC-2, a platetet receptor (2,3) and attenuates the lung metastasis of Aggrus-positive cancer cells in vivo. We anticipate Aggrus as a therapeutic target for developing new anti-metastatic drug.

As another pillar of our research, we are focusing on the identification of the resistant mechanism against molecular targeted therapy especially in the non-small-cell lung cancer (NSCLC), and the development of the therapeutic strategies to overcome the resistance. We have identified multiple resistant mechanisms to molecular targeted therapies, such as crizotinib or second generation ALK inhibitors, using *in vitro* and *in vivo* models as well as clinical specimens from the patients. In addition, we identified the molecular targets and drugs to overcome the resistance (4,5).

Proposal for exchanged students in this program

- Analysis of molecular mechanisms in metastasis-inducing factors.
- The importance and the function of Aggrus for the cancer cell survival in early metastasis.
- Identification of the mechanism of drug resistance in NSCLC cells

Possible training skills

- Cell manipulation and cell growth assay - Molecular biological techniques - Gene engineering and sequencing analysis – primary culture from the tumor specimen etc.

Related publications

1. Kato Y, Fujita N, et al., Molecular identification of Aggrus/T1alpha as a platelet aggregation-inducing factor expressed in colorectal tumors. ***Journal Biological Chemistry***, 278, 51599-51605 (2003).
2. Takagi S., Fujita N. et al., Platelets promote tumor growth and metastasis via direct interaction between Aggrus/Podoplanin and CLEC-2. ***PLoS ONE***, **8,** e73609 (2013).
3. Takagi S., Fujita N. et al., Expression of Aggrus/podoplanin in bladder cancer and its role in pulmonary metastasis. ***International Journal of Cancer***, 134, 2605-2614 (2014).
4. Katayama R., Shaw AT, Engelman JA, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. ***Science Translational Medicine*** 4, 120ra117 (2012).
5. Friboulet L, Li N, Katayama R, Fujita N, Shaw, AT, Engelman JA et al, The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer ***Cancer Discovery***, in press (2014).