

## Research Center for Medical Sciences Radioisotope Research Facilities

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Hiroya Ojiri, *Professor and Director*  
Haruka Minowa, *Assistant Professor*

Tadashi Asakura, *Professor*

### General Summary

The Radioisotope Research Facilities were established to support medical and biological research using radioisotopes. The Facilities also accept the research using nonradioactive isotopes. We have supported researchers by suggesting methods and practical techniques for experiments. Lectures and training courses are held for researchers, medical students, and graduate students. In 2019, the laboratory of this facility was used by 31 researchers from 9 departments and by 10 students of 2 curriculums. Major nuclides used for experiments were  $^{51}\text{Cr}$ ,  $^{125}\text{I}$ ,  $^{14}\text{C}$ , and  $^3\text{H}$ . Education related to radiation is also an interest.

### Research Activities

#### *The mechanism that induced epithelial-mesenchymal transition in proteasome inhibitor-resistant cells*

Ishikawa endometrial cancer cells induced epithelial-mesenchymal transition by acquiring resistance to the proteasome inhibitor epoxomicin (EXM). A decrease in microRNA-200 (miR200) expression induced transcriptional repressor zinc finger E-box-binding homeobox 1 (ZEB1) expression and caused E-cadherin expression to disappear. The regulation of E-cadherin expression by miR200 was also apparent from the fact that introduction of miR200 into EXM-resistant Ishikawa cells suppressed the expression of ZEB1 and restored the expression of E-Cadherin.

In EXM-resistant Ishikawa cells, the expression of dual-specificity protein phosphatase 6 (DUSP6) disappeared, and the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 was enhanced. This increased phosphorylation of ERK1/2 increased expression of FOS like 1, antigen-1 transcription factor (FOSL1). It was found that the expression of miR200 was suppressed by controlling the expression of FOSL1.

On the other hand, CD44 expression was enhanced in EXM-resistant Ishikawa cells, but not cells in non-EXM-resistant Ishikawa cells. When Ishikawa cells overexpressed CD44, DUSP6 expression disappeared. Accompanying DUSP6 disappearance, expression of FOSL1, suppression of miR200 expression, and enhancement of ZEB1 expression were observed.

These results show that in Ishikawa cells without CD44 expression, the phosphorylation level of ERK1/2 was reduced by DUSP6 expression, miR200 was expressed, ZEB1 expression was suppressed, and E-cadherin was expressed with decreased FOSL1 expression. On the other hand, in EXM-resistant Ishikawa cells, CD44 was expressed, and the suppression of DUSP6 expression by CD44 increased the phosphorylation level of ERK1/2 and induced FOSL1 expression. As a result, miR200 disappeared and E-cadherin

expression was suppressed along with ZEB1 expression.

#### *Chemotherapy with curcumin and prodrug curcumin for drug-resistant cancer*

Mutation of the Kirsten ras proto-oncogene, GTPase gene (*KRAS*), which is found in about 40% of intestinal cancers, is thought to be a cause of resistance and causes the activation of the nuclear factor kappa B pathway. This pathway is reported to be inhibited by curcumin, which can thus be an effective drug for oxaliplatin-resistant colorectal cancer. However, conventional oral curcumin has low bioavailability and has difficulty reaching a blood concentration that has a sufficient therapeutic effect. The newly developed prodrug-type curcumin, curcumin monoglucuronide (CMG), succeeded in solving this problem. That is, curcumin is hydrophobic and slightly soluble in water and, so, cannot be administered intravenously, but CMG is water-soluble and can be administered intravenously. A high concentration of curcumin in blood can be achieved by intravenous injection of CMG.

Therefore, the antitumor effect of CMG was examined in a mouse xenograft model in which human colon adenocarcinoma HCT116 cells (*KRAS* mutation/p53 wild type) had been transplanted. As a result, CMG was shown to have remarkable anticancer activity without the weight loss, bone marrow suppression, and liver damage observed with oxaliplatin administration. We also found that CMG, when used in combination with oxaliplatin, had an additive anticancer effect and did not worsen the side effects of oxaliplatin.

#### *Analysis of resistance mechanisms in radiation-resistant organisms*

Tardigrades, which are called water bears, can tolerate extreme environments, including ionizing radiation and dryness. The sludge water bear *Isohypsibius* was isolated from the activated sludge in the Morigasaki Water Reclamation Center, and the terrestrial water bear *Milnesium tardigradum* was isolated from moss collected in Tokyo's Minato Ward. To clarify the radiation-resistant mechanism, tardigrades were irradiated with X-ray at 50 to 200 Gy, and DNA damage was analyzed with the comet assay method.

#### *Measuring and tracing of radioactive fallout in the environment*

The distribution and behavior of radioactive fallout released into the environment by the accident of the Fukushima Daiichi Nuclear Power Plant in March 2011 have been investigated. Environmental samples, such as soil and plants, were collected from Fukushima Prefecture and the Kanto region, and the concentration of radiocesium and radiation images were analyzed with an imaging plate. In indoor dust samples collected from about 40 points within 10 km from the Fukushima Daiichi Nuclear Power Plant the concentrations of  $^{134}\text{Cs}$  and  $^{137}\text{Cs}$  were measured. From the  $^{134}\text{Cs}/^{137}\text{Cs}$  ratio at the time of the accident, the mixing ratios of materials from Units 1, 2, and 3 were obtained. We have obtained important basic data that can be used as a reference when releasing the evacuation order in the difficult-to-return area. Furthermore, we examined a safe, simple, and rapid method of analyzing radioactive strontium in seawater. The analytical method using the strontium adsorbent (Pureceram<sup>®</sup> MAq, Ebara Co./Nippon Chemical Industrial Co., Ltd.) was examined with  $^{85}\text{Sr}$  and  $^{90}\text{Sr}$ . We found that strontium was adsorbed only by stirring without a complicated procedure. This adsorbent can be used for screening sea-

water or purifying contaminated water.

### Publications

**Mezaki Y, Kato S, Nishikawa O, Takashima I, Tsubokura M, Minowa H, Asakura T, Matsuura T, Senoo H.** Measurements of radiocesium in animals, plants and fungi in Svalbard after the Fukushima Daiichi nuclear power plant disaster. *Heliyon*. 2019 Dec 24; **5**(12): e03051. doi: 10.1016/j.heliyon.2019.e03051. eCollection 2019 Dec. PubMed PMID: 32083202; PubMed Central PMCID: PMC7019073.

**Mimoto R, Yogosawa S, Saijo H, Fushimi A, Nogi H, Asakura T, Yoshida K, Takeyama H.** Clinical implications of drug-screening assay for recurrent metastatic hormone receptor-positive, human epidermal receptor 2-negative breast cancer using conditionally reprogrammed cells. *Sci Rep*. 2019 Sep 16; **9**(1): 13405. doi: 10.1038/s41598-019-49775-w. PubMed PMID: 31527634; PubMed Central PMCID: PMC6746954.