論　文　内　容　要　旨

Characteristic expression of fukutin in gastric cancer among atomic bomb survivors

(原爆被爆者に発生した胃癌における fukutin の特徴的な発現)

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Gastric cancer (GC) is the fifth most common malignancy in the world and the third cause of death for both men and women. Over 60% of GC worldwide occurs in Asian countries including Japan, China, Korea and Vietnam. While radiation is currently widely used in medicine, industry and nuclear power, the effect of radiation on GC development has been estimated on the basis of the Life Span Study (LSS) with excess relative risks (ERRs) per Gy of 1.20 for mortality and 1.32 for incidence. However, Preston et al. estimated that, after exposure at age 30 years, the risk of cancer at age 70 increased by about 35% per Gy for men and 58% per Gy for women. Some studies demonstrated mutations in *TP53* and *BRAF* in atomic bomb survivors, but no study has examined the specific alterations in radiation-associated cancer. In our previous study, we demonstrated that versican and osteonectin genes are expressed at much lower levels in tumor-associated stroma in a group of subjects exposed to a high dose of radiation compared with the group exposed to a low dose. However, these findings cannot completely explain the pathogenesis of radiation-associated GC. We previously performed Escherichia coli ampicillin secretion trap (CAST) using GC cell lines and GC tissue samples and found that the *FKTN* gene is overexpressed in GC. *FKTN*, which encodes fukutin protein, is responsible for Fukuyama-type congenital muscular dystrophy. Fukutin is presumably involved in the glycosylation of alpha-dystroglycan, which is involved in basement membrane formation. Although overexpression of fukutin has been reported in GC, its relationship with radiation exposure has not been studied. In the present study, we performed immunohistochemical analysis of fukutin to elucidate the association between fukutin expression and radiation-associated GC.

This study included formalin-fixed and paraffin-embedded archival tissues from 278 patients with GC who underwent surgery. The patients were treated at Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital (HRCHABSH, Hiroshima, Japan) or Hiroshima University Hospital (HUH, Hiroshima, Japan). The HRCHABSH cohort included 192 GC samples, all from atomic bomb survivors in Hiroshima treated at HRCHABSH. Because these patients were not LSS cohort members, the atomic bomb radiation doses were not estimated. The HRCHABSH cohort patients included directly exposed patients and those not present in Hiroshima city at the time of bombing but who entered the city soon after the bombing (within 2 weeks). They were classified into two groups: exposed at a short distance group (directly exposed patients, exposure distance from the hypocenter of ≤4 km) and exposed at a long distance group (patients not present in Hiroshima city at the time of bombing but who entered the region ≤4 km from the hypocenter within 2 weeks after the explosion). The HUH cohort included 86 GC samples, all from atomic bomb survivors in Hiroshima treated at HUH. The HUH cohort of 86 GC patients were LSS cohort members,

and atomic bomb radiation doses were estimated by the DS02 system. They were classified into two groups according to the levels of exposed radiation dose: the high-dose-exposed group (≥5 mGy) and the low-dose-exposed group (<5 mGy).

Expression of fukutin was first analyzed in the HRCHABSH cohort. All 192 patients were atomic bomb survivors in Hiroshima who developed GC after the bombing and comprised 117 patients in the group exposed at a short distance and 75 patients in the group exposed at a long distance. Patient characteristics, including age at diagnosis, sex, tumor stage, and Lauren classification, did not statistically differ between the two groups. In non-neoplastic gastric mucosa, immunohistochemical analysis revealed weak staining of fukutin in intestinal metaplastic cells, but not in the normal gastric epithelial glands. In contrast, GC tissue showed stronger, more extensive staining of fukutin. In total, 102 (53%) of 192 GC cases were positive for fukutin. We next examined the relationship of fukutin expression to clinicopathologic characteristics. GC cases positive for fukutin were found more frequently in intestinal type GC cases than in diffuse type GC cases ($P = 0.0009$). We previously found that positive fukutin expression is frequently found in CD10-positive GC cases. Thus, we next analyzed association between fukutin expression and CD10 expression. We found that fukutin-positive GC cases were frequently found in CD10-positive GC cases ($P = 0.0001$). In contrast, fukutin expression was not associated with exposure status.

We next analyzed expression of fukutin in the HUH cohort, because the HUH cohort patients were LSS cohort members in which atomic bomb radiation doses were estimated correctly by the DS02 system. All 86 patients were atomic bomb survivors in Hiroshima and comprised 44 high-dose-exposed and 42 low-dose-exposed patients who developed GC after the bombing. Patient characteristics, including age at diagnosis, sex, tumor stage, and Lauren classification, did not statistically differ between high-dose-exposed and low-dose-exposed groups. A total of 58 (67%) of 86 GC cases were positive for fukutin. As with the HRCHABSH cohort, GC cases positive for fukutin were found more frequently in intestinal type GC cases than in diffuse type GC cases ($P = 0.0160$). In this cohort, fukutin expression was associated with exposure status ($P = 0.0001$), but was not associated with CD10 expression.

Although in the first cohort from HRCHABSH, expression of fukutin was not associated with radiation exposure status, the second cohort from HUH showed significant association between fukutin expression and radiation exposure. Because the HRCHABSH patients were not LSS cohort members, the atomic bomb radiation doses may not be correctly estimated. Further studies with a larger cohort with precise radiation dose estimation will help clarify whether fukutin could be a potential biomarker to define radiation-induced GC in atomic-bomb survivors.