論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	ZHAO WANTONG
論文題名 Title	Expression of Calmodulin and FNDC5 Reverses with Increasing Radiation Dose, Altering Cell Invasion on Pancreatic Cancer Cells （膵臓癌細胞におけるcalmodulinとFNDC5の発現は、放射線量の増加とともに逆転し、細胞浸潤を変化させる）

論文内容の要旨(Abstract of Thesis)

〔目　的(Purpose)〕

It has been reported that the cancer metastatic potential was enhanced by low dose irradiation. However, there is a contradiction in that metastatic potential is suppressed after a certain dose if a sufficient dose is irradiated. In most cases, it can be assumed that cells stop migrating and invading because they undergo apoptosis when irradiated with a sufficient dose, but this may not be the only reason. In this study, we focused on endoplasmic reticulum (ER) stress as one possible solution to the above contradiction. Our previous studies have demonstrated that phosphorylation of eIF2a, which occurs during endoplasmic reticulum stress, suppresses cell invasive capacity. However, the relationship between radiation induced ER stress and cell invasion are not well understood. Therefore, we evaluated the effect of radiation on metastatic potentials of pancreatic cancer cells in vitro and in vivo, focus on ER stress and subsequent pathways.

〔方法ならびに成績(Methods/Results)〕

After 24 hours irradiation, we conducted Matrigel invasion assay to irradiated pancreatic cancer cells. Low dose (0.5 Gy) irradiation was promoted the cell invasion, while 2 or 4 Gy irradiation were not significantly changed the cell invasive capability compared to control. We investigated the expression of p-eIF2α, but its expression was enhanced dose dependently, so there was no relationship between the expression of p-eIF2α and cell invasiveness. Next, we surveyed genes that are related to ER stress and may be associated with invasion assay results via RNA sequencing. We focused on calmodulin from the candidates. Calmodulin and its downstream myosin light chain are known pathways involved in cell motility, and their western blot results and invasion assay trends were consistent. Again, we returned to the RNA sequencing results to search for candidate genes that are opposite to the changes in gene expression of calmodulin. Among them, we focused on Fibronectin type III domain-containing protein 5 (FNDC5). The western blot analysis showed the protein expression of FNDC5 enhanced γ-ray dose dependently. In the case of using calmodulin knock down cells, FNDC5 expression level was no change by γ-irradiation. Next, we investigated the cell invasion on FNDC5 knock down cells. The results showed FNDC5 knock down cells were not inhibited the cell invasion by 2 or 4 Gy irradiation. Irisin, one of the myokines product from FNDC5. Recently, other articles suggested that irisin inhibited the cancer cell growth and motility. Therefore, we also conducted the invasion assay with irisin. Cell invasive capability was suppressed by irisin alone as well as by the combination of γ-ray and irisin compared to controls. The above results were similar for four other different pancreatic cancer cell lines. In animal model, mice irradiated with γ-ray were increased the number of metastatic nodules compared with control. There was no significant difference between irisin injected mice and combination of radiation and irisin injection group. By pathological analysis, micro metastatic square of combination group was reduced compared with irisin injected group.

〔総　括(Conclusion)〕

In conclusion, our data suggest that the combination of irisin and radiation therapy can inhibit the migration and invasion of pancreatic cancer cells through inhibition of CaM. And we identified the Ca2+/CaM or FNDC5 signaling pathway.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本研究によって、放射線照射により膵がん細胞におけるがん転移因子である細胞浸潤能が変化することが示され、そのメカニズムとしてCalmodulinとFNDC5のタンパク発現スイッチングが提唱された。高線量の放射線によって発現が増加するFNDC5の意義として、細胞膜で切断され生成されるミオカインの一種であるIrisinの血中濃度増加を引き起こし、がん転移抑制効果を発揮することを証明した。これらの成果は、依然、治療効果に乏しく生存率が低い膵がんに対する放射線を用いた新たな治療戦略となる可能性を示しており、意義は大きい。よって、学位の授与に値すると考える。