use them for combinatorial therapy with gemcitabine in order to down-regulate expression of HSP27, and up-regulate the sensitivity to gemcitabine of pancreatic cancer cells (19).

In order to down-regulate HSP27 expression, we need to try the combined therapy of gemcitabine with HSP27. KRIBB3 {[5-(5-ethyl-2-hydroxy-4-methoxyphenyl)-4-(4-methoxyphenyl) isoxazole]} is a synthetic agent. This agent inhibits HSP27 phosphorylation (20). Since phosphoryration of HSP27 is increased in gemcitabine-resistant cells, inhibition of phosphorylation by using KRIBB3 may be useful for combined therapy with gemcitabine for gemcitabine-resistant pancreatic cancer cells.

Besides the role of HSP27 in drug resistance, increased levels of HSP27 in cancer tissues including gastric, head and neck, renal and prostate cancer have been reported (21-24). What is the role of increased HSP27 expression in cancer tissues? Anti-apoptosis activity of HSP27 is necessary for cancer cells suffering from stress including anticancer drugs, oxidative stress and irradiation. Cancer cells are defended from apoptosis induced by stress by up-regulation of HSP27. HSP27 also has a role in the progression of cancer. Song *et al.* showed increased HSP27 expression in metastatic hepatocellular carcinoma tissues (25). Cancer cells overexpressing HSP27 had increased metastatic capacity (26, 27). On the other hand, HSP27 depletion induces the cells to undergo apoptosis and down-regulates tumor progression in prostate cancer cells (28). Not only mature cancer cells, but also cancer stem cells were reported to show increased HSP27 expression. Wei *et al.* reported up-regulation and phosphorylation of HSP27 in breast cancer stem cells, and silencing of HSP27 in these cells reduced cancer stem cell-like features, including the epithelial–mesenchymal transition (29).

These reported features of HSP27 show that the control of HSP27 is very important in the treatment of cancer cells, not only from the view of gemcitabine-resistance, but also with regard to cancer progression and cancer stem cell-like features.

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F. 研究発表

F-1. 論文発表

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