Methods: Using prostate cancer cells, the efficacy of the combination of vorinostat and bortezomib was evaluated in vitro and in vivo. The induction of ER stress and changes in the expression of ubiquitinated proteins and cell-cycle associated proteins were evaluated by western blotting.
Results: Vorinostat in combination with bortezomib induced apoptosis and inhibited the growth of prostate cancer cells synergistically. In a murine xenograft model using PC-3 cells, treatment with the combination inhibited tumor growth effectively. The combination decreased the expression of cyclin D1 and cyclin-dependent kinase 4, and it increased the expression of p21. It induced a marked unfolded protein response and caused the accumulation of ubiquitinated proteins synergistically.
Conclusions: Vorinostat and bortezomib inhibit the growth of prostate cancer cells by enhancing ER stress and ubiquitinated protein accumulation.

Keywords: Ubiquitin, Prostate cancer

J-1119 Combination Therapy of Chemotherapeutic Agents with Telomerase-Specific Oncolytic Adenovirus for Osteosarcomas

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骨肉腫に対するテロメラーゼ依存性腫瘍融解ウイルス製剤と化学療法の併用療法

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Osteosarcomas are the most common malignant bone tumors. Although the multiagent chemotherapy is currently used for the treatment of osteosarcomas, some patients show a poor response to chemotherapy, leading to recurrence and poor prognosis. Therefore, the enhancement of chemosensitivity is required to cure patients with osteosarcomas. We recently developed a telomerase-specific replication-competent oncolytic adenovirus, Telomelysin (OBP-301), and confirmed the antitumor effect of OBP-301 in human osteosarcoma cells. A phase I clinical trial in US has also shown the safety of OBP-301 in cancer patients. In this study, we investigated whether OBP-301 enhances the antitumor effect of chemotherapeutic agents, doxorubicin and cisplatin, that are used for the treatment of osteosarcomas. We used 4 human osteosarcoma cells (HOS, MNNG/HOS, 143B and SaOS2). OBP-301 enhanced the sensitivities to chemotherapeutic agents in human osteosarcoma cells. Combination therapy of chemotherapeutic agents with OBP-301 enhanced apoptotic and autophagic cell deaths. These results suggest that combination therapy of chemotherapy with OBP-301 provides a novel therapeutic strategy for human osteosarcomas.

Keywords: Oncolytic virus, Osteosarcoma

J-1120 Low molecular weight fucoidan extract and anticancer drug synergistically enhance anti tumor effects.

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酵素消化低分子化フコイダン抽出物と抗ガン剤の併用による抗腫瘍増強効果

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Fucoidan is sticky fucose-rich sulfated polysaccharides derived from brown algae such as Konbu or Mozuku. Low molecular weight fucoidan extract (LMWFE) digested by glycosidases exhibited anti-invasion and anti-angiogenesis effects. LMWFE induced apoptosis in cancer cells via both ROS-dependent JNK activation and mitochondria-mediated pathways. LMWFE is now widely used for therapy of terminal cancer patients in Japan. Combined treatment of LMWFE and CDDP caused decrease of cell viability and increase of dead cell numbers in human fibrosarcoma HT1080 cells. The Sub-G1 analysis revealed that dead cells of HT1080 were increased in time- and dose-dependent manners by the combined treatment. Interestingly, LMWFE treatment suppressed the CDDP-induced cell death in human normal fibroblast TIG-1 cells. These facts suggested that LMWFE had not only enhancing effect for cancer cell death by CDDP but also suppressing effect for normal cell death as a side effect of CDDP. In addition, it was suggested that LMWFE induced synergistic cell death by CDDP-induced apoptosis via caspases and MAPK pathways.

Keywords: Fucoidan, Anti cancer drug

Japanese Oral Sessions

Room K-7 Sep. 19 (Wed) 15:00 - 16:00

16J-03 Drug delivery system (1)
ドラッグデリバリーシステム (1)

Chairpersons: Eisaku Kondo (Div. of Oncological Pathol., Aichi Cancer Ctr. Res. Inst.)
Kenji Nakano (Kyushu Univ., Innovation Ctr. for Medical Redox Navigation)
座長：近藤 英作 (愛知県がんセンター研究所　腫瘍病理)
中野 賢二 (九州大学　先端融合医療　レドックスナビ研究拠点)

J-1121 Development of a Novel Drug Delivery System consisting of an Antitumor Agent Tocopheryl Succinate

Susumu Hama, Hiroyuki Tsuchiya, Kentaro Kogure (Dept. of Biophysical Chemistry, Kyoto Pharmaceutical Univ.)

抗癌剤トコフェロールコハク酸を用いた新規ドラッグデリバリーシステムの開発

濱 進、土谷 博之、小暮 健太朗 (京都薬科大学薬品物理化学分野)

α-tocopheryl succinate (TS) has attracted attention as a unique anti-cancer drug for its ability to induce apoptosis in various cancer cells. Furthermore, TS itself readily forms nanovesicles (TS-NVs) and is a prospective tool for use as an antitumor DDS. However, TS-NVs are unstable for encapsulating drugs and delivery to tumor tissue via enhanced permeation and retention effect. Therefore, to improve the stability of vesicles, we developed a novel nanovesicle consisting of TS and egg phosphatidylcholine (TS-EPC-NVs). The stability of vesicles of TS-EPC-NVs was significantly higher than that of TS-NVs. As a result, the *in vivo* antitumor activity of TS-EPC-NVs was more potent than that of TS-NVs. The enhanced antitumor activity of TS-EPC-NVs was found to be due to its effective intratumoral distribution. Moreover, the *in vitro* anticancer efficiency of TS-EPC-NVs increased seven-fold. It is suggested that the improvement is due to homogenous cellular uptake and enhanced cytosolic delivery of the nanovesicles. In conclusion, TS-EPC-NVs represent a novel and attractive drug delivery system.

Keyword: DDS

J-1122 The positive improvement of drug accumulation into tumor using passive targeting carrier

Ikumi Sugiyama, Yasuyuki Sadzuka (Dept. of Advanced Pharmaceutics, Sch. of Pharmacy, Iwate Medical Univ.)

2本鎖ポリエチレングリコール修飾による制癌剤内封受動的ターゲティングリポソームの腫瘍集積

杉山 育美、佐塚 泰之 (岩手医科大学　薬学部 創剤学講座)

[Purpose] Polyethyleneglycol (PEG)-modified liposome as passive targeting controlled behavior using physiological character. In this study, we focused aqueous layer around liposome which was formed by PEG modification, and different double arms PEG (DDA-PEG) was synthesized. DDA-PEG-liposome including doxorubicin was observed antitumor activity and image analysis. [Methods] M5076 ovarian sarcoma cells were inoculated into back of mice and liposome was injected intravenously. For observing distribution of liposome, indocyanine green (ICG) including liposome was injected and took graphics using fluorescent imaging device (Clairvivo OPT, SHIMADZU). [Results and Discussion] Common-liposome decreased tumor size to 34.5 % of control level. DDA-PEG-liposome was more decrease in 65.9 %, this effect was 1.9 times of common. In image analysis, the total count/area of common- and DDA-PEG-liposome were 15.8 and 23.5 at 48 hr, respectively. Moreover, at 24 hr, DDA-PEG-liposome already accumulated into tumor however common-liposome was distributed to liver etc. In conclusion, DDA-PEG-liposome had stronger antitumor activity than common-liposome because it was delivered to targeting site.

Keywords: Liposome, Antitumor activity

J-1123 Antitumor effect and pharmacokinetics of intraperitoneal nanomicellar paclitaxel for peritoneal metastasis

Shigenobu Emoto, Hironori Yamaguchi, Joji Kitayama, Toshiaki Watanabe (Dept. of Surgical Oncology, The Univ. of Tokyo)

ナノミセル化パクリタキセルの腹腔内投与の腹膜播種への抗腫瘍効果と薬物動態

江本 成伸、山口 博紀、北山 丈二、渡邉 聡明 (東京大学腫瘍外科)

Intraperitoneal(IP) paclitaxel(PTX) has been shown to be a promising treatment strategy for peritoneal malignancy. The IP NK105 and PTX-30W -PTX-incorporating micellar nanoparticles- were investigated in animal models of gastric cancer for the improved drug delivery to peritoneal nodules. IP NK105 and PTX-30W significantly reduced peritoneal tumors in a mouse model as compared to PTX-Cre -the conventional paclitaxel formulation with Cremophor, whereas systemic toxicity were similar in the groups. Though NK105 rapidly disappeared from peritoneal cavity, the PTX level in peritoneal nodules at 4 h after IP injection was significantly higher than the PTX-Cre