

News Release

Title

Novel intraperitoneal treatment with non-thermal plasma-activated medium inhibits metastatic potential of ovarian cancer cells

Key Points

○Plasma-activated medium inhibits the initial step of the dissemination of ovarian cancer cells onto mesothelial cells *in vitro*.

○ROS in Plasma-activated medium could suppress cancer cell migration and invasion through inhibiting the MAPK/MMP pathways.

○Plasma-activated medium prohibits peritoneal metastasis of ovarian cancer cells in a mouse model.

Summary

This work is mainly from the team of Hiroaki Kajiyama (Associate professor, Department of Obstetrics and Gynecology) and Fumitaka Kikkawa (Professor, Department of Obstetrics and Gynecology) in Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, M.D., Ph.D.), in collaboration with Masaaki Mizuno (Professor, Center for Advanced Medicine and Clinical Research) in Nagoya University Hospital (Director: Naoki Ishiguro, M.D., Ph.D.) and Masaru Hori (Director and Professor, Plasma Medical Science Global Innovation Center) and his team members from Nagoya University Graduate School of Engineering (Dean: Yushu Matsushita, Ph.D.). Non-thermal plasma has been focused on as a novel medical practice. There have been a number of reports showing the effect of plasma-activated liquids on cell death of ovarian and gastric cancers and glioblastoma brain tumor cells in Nagoya University. However, there are only few reports demonstrating the anti-tumour effects of PAM in an animal model reflecting pathological conditions and the accompanying mechanism. In the clinic, peritoneal metastasis is quite an issue for ovarian cancer patients and a big obstacle for treatment. In this study, it is found that Plasma-Activated Medium presents anti-metastatic ability to ovarian cancer both *in vitro* and *in vivo*. These promising findings suggest new strategies of using plasma treatment for ovarian cancer patients, especially with peritoneal metastasis. The paper was published on the journal of Scientific Reports on July 20, 2017.

Research Background

Ovarian cancer is considered as the most malignant disease among gynaecological cancers. The current treatment for the advanced ovarian cancer patients is debulking surgery followed by platinum-based chemotherapy. However, due to rapid metastasis to the peritoneum, the patients have a poor prognosis with the present treatments and the 5-year survival rate is less than 50%. Recently, Non-thermal plasma has been focused on as a novel medical practice for

wound healing, blood coagulation and cancer therapy. Plasma-activated medium (PAM), a sub-branch of plasma medicine, has shown anti-tumour effects in ovarian and gastric cancers and glioblastoma brain tumor cells in Nagoya University. However, there are only few reports demonstrating the anti-tumour effects of PAM in an animal model reflecting pathological conditions and the accompanying mechanism. So in this study, the effect of PAM against ovarian cancer metastasis is investigated both *in vitro* and *in vivo*, with underneath mechanism well elucidated.

Research Results

In both wound-healing assay and transwell assay, PAM inhibited the migration and invasion abilities of ovarian cancer cells. Furthermore, in the co-culture system by planting cancer cells onto human peritoneal mesothelial cells to mimic the human peritoneum environment, PAM prevented cancer cells implantation onto mesothelial cells. The underneath mechanism study showed that PAM repressed MMP-9 expression, via down-regulating the phosphorylation of MAPK key components JNK1/2 and p38 by ROS produced by plasma in PAM. Moreover, the *in vivo* mouse model showed that peritoneal metastasis of ovarian cancer was alleviated by PAM intraperitoneal treatment, resulting in better survival rate than those without treatment.

Research Summary and Future Perspective

From these results, we concluded that PAM inhibited metastasis of ovarian cancer cells both *in vitro* and *in vivo*, resulting in prolonged survival in a mouse model. This inhibition was due to repression of MMP-9 expression, which was dependent on the attenuation of the phosphorylation of JNK1/2 and p38 MAPK. These findings might predict a new clinical strategy for ovarian cancer therapy involving the use of PAM via intraperitoneal administration in the future.

Publication

Nakamura, K., Peng, Y., Utsumi, F., Tanaka, H., Mizuno, M., Toyokuni, S., Hori, M., Kikkawa, F. and Kajiyama, H. Novel intraperitoneal treatment with non-thermal plasma-activated medium inhibits the metastatic potential of ovarian cancer cells. *Scientific Reports*, July 20, 2017.

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