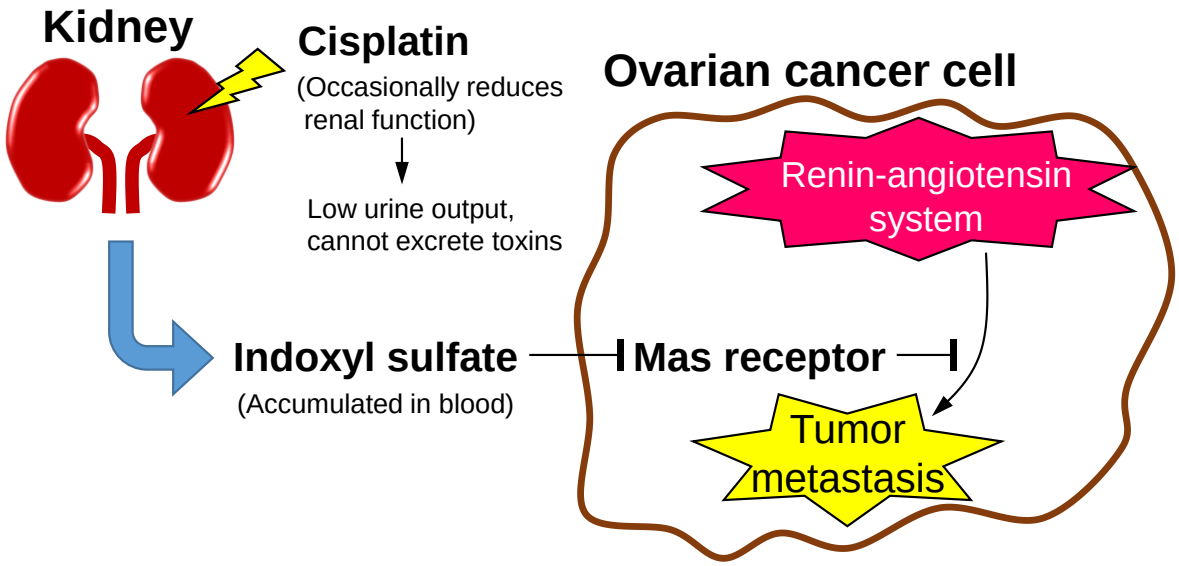

Indoxyl sulfate accumulated in blood inhibits the function of Mas receptor in ovarian cancer cells (above figure).
However, activation of the Mas receptor by the drug suppressed the metastatic process (infiltration) of ovarian cancer cells.

Title

Indoxyl sulfate promotes metastatic characteristics of ovarian cancer cells via arylhydrocarbon receptor-mediated downregulation of the Mas receptor

Summary

It has been found that chemotherapy-induced ovarian cancer metastasis may be suppressed by activating a molecule called Mas receptor by the team led by Specially Appointed Professor Akihiro Nawa and Visiting Researcher Shinichi Saito (R&D Department, Medical Corporation Kishokai) at Nagoya University Graduate School of Medicine Graduate School of Medicine, Obstetrics and Gynecology Industry-Academia Collaborative Research Laboratory, and collaborators including Professor Hiroaki Kajiyama at Nagoya University Graduate School of Medicine, Department of Obstetrics and Gynecology. In recent years, it has become clear that chemotherapy occasionally induces cancer metastasis, but the mechanism is not well understood. This time, various studies have been conducted with the following hypothesis: when the kidney function deteriorates due to the side effect of cisplatin used in chemotherapy, a toxin called indoxyl sulfate (IS), which is normally excreted from the kidney, accumulates in the blood, and the action of IS promotes ovarian cancer metastasis. The results showed that cisplatin-treated mice had decreased renal function and increased blood IS levels. Moreover, in ovarian cancer model mice treated with IS, cancer cells were observed to spread over a wide area in the abdominal cavity [**Figure 1**]. The molecular mechanism of metastasis induction

by IS was investigated by focusing on a molecule called Mas receptor, which has been reported to act suppressively on the growth and/or lymph node metastasis of various cancers. The results showed that IS reduced the expression of Mas receptor in ovarian cancer cells. Moreover, it was found that IS increases the infiltration ability of ovarian cancer cells, and the increase in infiltration ability due to IS is suppressed by activating Mas receptor.

This study elucidated a part of the mechanism of cisplatin-induced ovarian cancer metastasis. Since uremic toxins including IS are carried throughout the body by the bloodstream, the results of this study may be applicable to chemotherapy for cancers other than the ovary. The results of this research were published online in the Nature Research Scientific Journal, Laboratory Investigation on January 10, 2023.

Key Points

- Recent studies have shown that chemotherapy occasionally induces cancer metastasis, but the detail is not clear.
- In mice treated with cisplatin, which is used in ovarian cancer chemotherapy, renal function was reduced and indoxyl sulfate was accumulated in the blood. Furthermore, it was found that administration of indoxyl sulfate to ovarian cancer model mice promoted the metastasis of ovarian cancer cells to the abdominal cavity.
- Indoxyl sulfate was found to increase the infiltration ability of ovarian cancer cells. It was also found that IS reduces the expression of a molecule called Mas receptor in ovarian cancer cells. Activation of Mas receptor with a drug suppressed the increase in infiltration ability caused by indoxyl sulfate.
- It has been suggested that activation of Mas receptor may suppress ovarian cancer metastasis after chemotherapy.

Research Background

It is said that about 90% of deaths from solid tumor are caused by metastatic diseases, and the presence or absence of metastasis can be said to be a turning point in the prognosis of life. Chemotherapy for ovarian cancer works well in the primary site, but has no inhibitory effect on cancer metastasis, and on the contrary, recent studies have increasingly revealed that chemotherapy may induce cancer metastasis. However, the mechanism is not well understood.

Cisplatin, an anticancer drug used in chemotherapy for ovarian cancer, may reduce kidney function as a side effect. Normally, when food is ingested, waste products are excreted as feces and urine after nutrients are absorbed, but when renal function is extremely low, waste products that should be excreted

as urine (“uremic toxins”) will be accumulated in the blood. It is well known that the accumulation of indoxyl sulfate (IS), a typical uremic toxin, increases the risk of death from stroke and heart failure, but its association with cancer has been poorly studied. Moreover, the effect of IS on ovarian cancer metastasis was completely unknown.

This time, we hypothesized that if renal function declines due to the side effect of cisplatin, IS will accumulate in blood and IS will promote the metastasis of ovarian cancer.

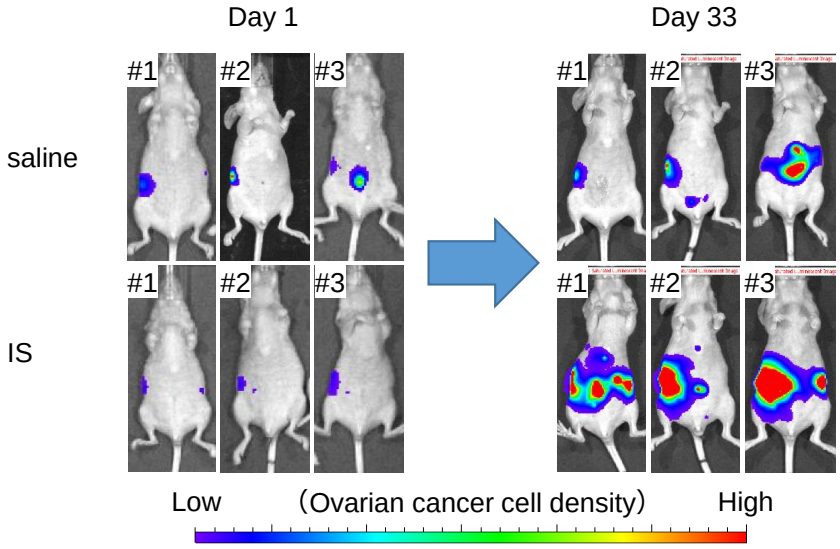

Figure 1. Tumor growth in ovarian cancer model mice

Research Results

The renal function and IS concentration in blood of cisplatin-administered mice were measured weekly, and it was found that the renal function was lower and the IS concentration was higher than that of control mice for at least one month. Moreover, when IS was administered to ovarian cancer model mice every 3 days for 1 month, it was observed that cancer cells spread over a wider area of the abdominal cavity than control mice [Fig. 1].

Regarding the molecular mechanism of ovarian cancer progression, the research group led by Professor Kajiyama reported that an endocrine regulatory system called ”renin-angiotensin system” is activated in various gynecological cancers (cervical cancer, endometrial cancer, villous cancer) including ovarian cancer, which promotes cancer growth, invasion and angiogenesis. This time, on the contrary, we focused on a molecule called Mas receptor, which is a molecule that inhibits the activation of renin-angiotensin system and has been reported to suppress the growth and lymph node metastasis of various cancers. As a result, it was found that IS reduces the expression of Mas recetptor in ovarian cancer cells. Moreover, IS was found to increase the infiltration ability of ovarian cancer cells, and the increase in infiltration ability caused by IS was

suppressed by angiotensin-(1-7), the Mas receptor activating molecule. In addition, it was found that IS requires a molecule called arylhydrocarbon receptor, reactive oxygen species, and signal transducers and activator of transcription 3 to reduce the expression of Mas receptor.

Research Summary and Future Perspective

Previous studies on the induction of cancer metastasis by chemotherapy have shown that anticancer drugs directly alter the properties of cancer cells. On the other hand, this study showed that anticancer drugs reduce renal function, thereby indirectly altering the properties of cancer cells. This is the first report showing an indirect induction of cancer metastasis by anticancer drug.

According to the European Uremic Toxin Research Group (EUTox), there are more than 100 types of uremic toxins. Since uremic toxins including IS are carried throughout the body by the bloodstream, which may affect the progression of cancers other than the ovaries. It is expected that this research result will lead to further research on the effect of uremic toxins in the progression of various cancers and to the development of new therapeutic strategies that do not cause cancer metastasis.

Publication

Journal: Laboratory Investigation (January 10, 2023)
DOI: 10.1016/j.labinv.2022.100025
Title: Indoxyl sulfate promotes metastatic characteristics of ovarian cancer cells via arylhydrocarbon receptor-mediated downregulation of the Mas receptor
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