News Release

## Title

A new mechanism of ovarian cancer cells proliferation in peritoneal metastases lesion: Cancer cell-induced adipocyte dedifferentiation process and its involvement in cancer progression

## Key Points

- Ovarian cancer cells show selectivity to the adipocyte-rich tissues such as omentum upon dissemination, and proliferates there at a rate higher than that of the primary lesion, however, there are still a lot of unclear points about the detailed mechanism.
- Ovarian cancer cells promote the dedifferentiation process of omental adipocytes through Wnt signaling and induce omental adipocyte-derived fibroblasts (O-ADF).
- O-ADFs thus generated promote the growth and migration of ovarian cancer cells and contributes to tumor progression at peritoneal dissemination site.

## Summary

A research group consisting of Graduate Student Shohei Iyoshi, Assistant Professor Masato Yoshihara, Professor Hiroaki Kajiyama (Obstetrics and Gynecology), Professor Akihiro Nawa (Bell Research Center, Obstetrics and Gynecology) from the Graduate School of Medicine, Professor Shigehiro Yamaguchi from the Institute of Transformative Bio-Molecules (ITbM), at Nagoya University (Dean: Professor Kenji Kadomatsu) reported a novel mechanism involved in tumor growth at peritoneal metastatic lesions of ovarian cancer (OvCa).

OvCa is the leading cause of death from gynecological malignancies and shows a characteristic mode of progression with peritoneal dissemination. It is known that OvCa cells selectively form disseminated foci at adipocyte-rich tissues such as omentum, and proliferate there to create lesion called “omental cake”, which makes the treatment of OvCa difficult. In this study, the research group focused on the adipocytes, which are abundant in metastatic lesions, and investigated their effects on ovarian cancer cells. They confirmed that addition of malignant ascites to the culture medium of adipocytes or co-culturing with OvCa cells activated the Wnt signaling and induced the dedifferentiation process of omental adipocytes into omental adipocyte-derived fibroblast (O-ADF). The characterization by flow cytometry revealed that O-ADF possess both mesenchymal stem cell and myofibroblast-like features. The research group also found that O-ADF enhances the proliferative and migratory abilities of OvCa cells when co-cultured. Targeting these dedifferentiation processes has potential to be a new therapeutic strategy for advanced ovarian cancer with peritoneal dissemination.

## Research Background

Ovarian cancer (OvCa) is the fifth leading cause of cancer deaths in women and tends to spread within the abdominal cavity. Upon metastasizing into the adipocyte-rich omentum, cancer growth in the omentum exceeds the growth of the primary tumor, and creates a characteristic lesion called “omental cake”. The presence of these disseminated lesions makes the complete surgical resection of the tumor difficult and contributes to the poorer treatment outcomes. Concerning the mechanism of how adipocytes play a role in peritoneal dissemination foci of OvCa, there are still a lot of unclear points.

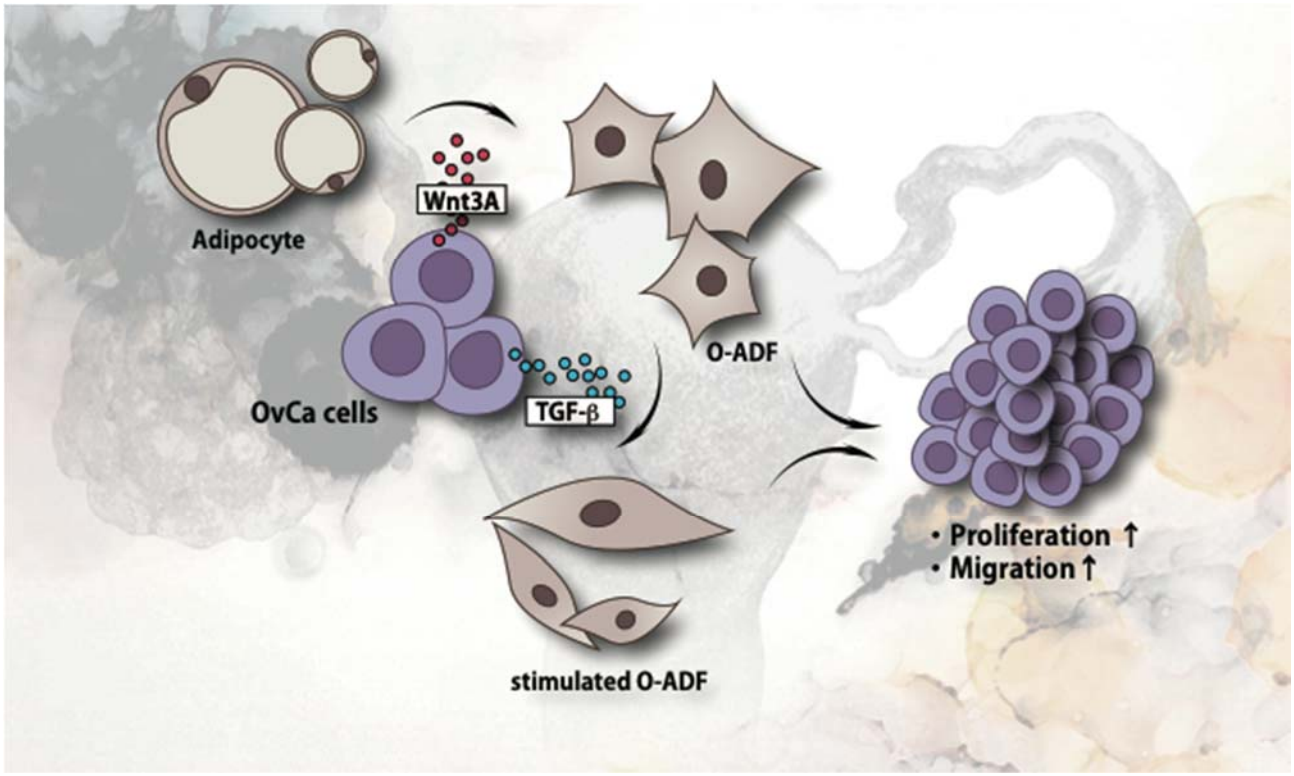
## Research Results

Firstly, the research group confirmed that, when adipocytes obtained from surgically resected omentum were cultured in the presence of malignant ascites, lipid-droplets were fallen out from adipocyte and the fibroblast-like cells appeared. It was also found that this phenomenon is promoted by co-culturing adypocytes with ovarian cancer cells as well. The obtained cells were named as omental adipocyte-derived fibroblasts (O-ADF) and the characterization of O-ADF was then conducted. In flow cytometry analysis, O-ADF showed surface antigen pattern of CD73 +, CD90 +, CD105 +, and α-SMA +, indicating that OADF possess both mesenchymal stem cell and myofibroblast-like features. In addition, from the studies using inhibitors and recombinant proteins, canonical Wnt/b-catenin pathway were determined to be a key signaling pathway involved in the dedifferentiation process of omental adipocytes.

Next, they examined the effect of O-ADF on ovarian cancer cells. It was confirmed that culturing with O-ADF promotes the growth and enhances the migration ability of OvCa cells. Supplementation of TGF-b1, which is known to exit in higher concentration in malignant OvCa ascites, showed further activation of O-ADF and increased these abilities. Upon pathway enrichment analysis with proteomic dataset of the OvCa cells co-cultured with O-ADF, pro-tumoral cellular pathways such as glycolysis/gluconeogenesis, pentose phosphate pathway, and DNA replication were confirmed to be enriched. These tumor supportive roles of O-ADF were also confirmed in vivo by using OvCa disseminated mouse models. From these results, the research group concluded that that O-ADF induced by OvCa cells then contributes to the neoplastic growth of OvCa at adipocyte-rich peritoneal dissemination lesion.

## Research Summary and Future Perspective

Through this study, it is revealed that OvCa cells modify peritoneal environment for their purpose by changing adipocyte at omentum into their supporter and utilize them to grow further. Since this mechanism is different from the target of the currently used treatment option of OvCa, targeting this dedifferentiation process of the adipocytes has a potential to lead a development of new treatment strategy that has additive effects upon standard therapy.




## Publication

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