Department of Obstetrics and Gynecology

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General Summary

The main research topics of our department are the development of molecularly targeted agents for gynecologic tumors, including ovarian cancer; clarification of the mechanisms of successful pregnancy; and the development of assisted reproductive techniques. These topics were investigated both experimentally and clinically.

Research Activities

Gynecologic oncology

1. Development of molecular targeting therapy in *ARID1A*-deficient cancers.

ARID1A, SWI/SNF chromatin remodeling complex subunit, has been identified as one of the most frequently mutated genes in human cancers. *ARID1A* mutations rates ranging from 10% to 57% have been identified across multiple tumor lineages, including ovarian clear cell carcinoma. In this study, we identified several compounds as a potential therapeutic targets for *ARID1A*-mutant cancers by screening *ARID1A* wild-type and *ARID1A* knockout cancer cells with an inhibitor kit. To explore the interaction between *ARID1A*-mutant cancers and the compound, we will conduct further assays.

2. Prognostic impact of interleukin-6 expression in stage I ovarian clear cell carcinoma.

In stage I ovarian clear cell carcinoma (OCCC), the prognosis differs according to substage, and predictive biomarkers are needed for stage IC2/IC3 disease. We investigated prognostic factors for stage I OCCC from a clinicopathological perspective with 192 patients, including the expression of ARID1A and IL-6. We calculated overall survival (OS) with respect to 12 clinicopathological parameters. The multivariate analysis indicated that substage classification and IL-6 expression status were associated with poor OS. Loss of ARID1A expression was related with substage, but not with survival. No clear link was found between ARID1A and IL-6 expression. Histological findings showed no prognostic effects. IL-6 molecular stratification may be crucial in optimizing therapeutic strategies for early stage OCCC to improve survival.

3. MicroRNA Gene Expression Signature Driven by *miR-9* Overexpression in Ovarian Clear Cell Carcinoma.

This study aimed to elucidate potential clinical and biological associations of ovarian cancer-related microRNA (miRNA) gene expression profiles in high-grade serous carcinoma and ovarian clear cell carcinoma (OCCC). Global cancer-related miRNA expression analysis identified statistically unique profiles that could discriminate ovarian cancer

histotypes. In OCCC, *miR-9* overexpression may affect pathogenesis by targeting E-cadherin, thereby inducing an epithelial-mesenchymal transition. Therefore, *miR-9* may be a promising therapeutic target strategy for OCCC.

4. Feasibility of reduced port surgery applying Higuchi's transverse incision.

Higuchi's transverse incision is made at a lower position than other incisions and is superior in terms of cosmetic outcomes. We examined the safety and efficacy of novel forms of reduced port surgery for ovarian cysts, patient characteristics and outcomes were compared between multiport laparoscopy and patients and uterine fibroids applying Higuchi's incision. In patients with ovarian cysts who underwent low-position single incision laparoscopic surgery (L-SILS) that was a modified single-port laparoscopy with Higuchi's incision placed in the 2-3cm just above the pubis. Additionally, patients with uterine fibroids who underwent dual-port laparoscopically assisted myomectomy (2P-LAM) and conventional LAM (C-LAM) were investigated. There were no significant differences between L-SILS and multiport laparoscopy in terms of fibroid size, bleeding, duration of hospital stay, or postoperative pain. However, L-SILS demonstrated significantly shorter operative and pneumoperitoneum times. In cases of fibroids, no significant differences were found in size, operative times, pneumoperitoneum times or bleeding. However, hospital stay of 2-P LAM group was shorter than C-LAM statistically. It was suggested that L-SILS for ovarian cysts and 2P-LAM for uterine fibroids are relatively simple and ensure the same safety and efficacy as conventional methods. Therefore, they have potential as novel forms of RPS.

Perinatology

1. Fetal therapy model of myelomeningocele with three-dimensional skin graft using amniotic fluid cell-derived induced pluripotent stem cells.

We generated induced pluripotent stem cells (iPSCs) from patients with Down syndrome and twin-twin transfusion syndrome. We manufactured three-dimensional skin grafts with epidermis generated from keratinocytes derived from iPSCs. For generation of epidermis, we developed a novel protocol using Y-27632 media and epidermal growth factor. The artificial skin was successfully covered over MMC defect sites during pregnancy, implying a possible antenatal surgical treatment utilizing iPSC technology.

2. Prenatal determination of fetal RHD focused on the difference of haplotype.

In Japanese, 80% of fetuses who are RHD negative, RHD loss is caused by RHD gene deletion, and 20% are caused by point mutation or hybrid RHD gene. Thus, many undiagnosed cases are occurred by conventional method. Our approach is focused on the difference of haplotype (single-nucleotide polymorphism combinations) between RHD positive and RHD negative to detect RHD negative specific haplotypes.

3. Elucidation of the role of oxytocin in perinatal brain.

Oxytocin has been reported to affect formation of analgesia, maternity and social behavior. Oxytocin not only induces labor, but also suppresses pain due to labor. We are investigating the effects of oxytocin on changes in neural tissue activity and influence on behavior using Ca-imaging to detect the activity of oxytocin (OXT) receptor in the amygdala using a rat model of the perinatal period.

4. Single cell DNA-sequence of fetal cells in maternal peripheral blood for noninvasive

prenatal diagnosis.
In order to analyze fetal genomic information safely and accurately, we are developing a new method for analyzing fetal DNA at the single cell level using purified circulating fetal cells in maternal peripheral blood. Our method can replace amniocentesis as a diagnostic antenatal test.
5. Investigation of Novel Candidate Genetic Factors Causing Recurrent Abortions in Japanese Women Using Whole-Genome Single Nucleotide Polymorphism Arrays.
High-resolution genome-wide single-nucleotide polymorphism microarray analysis were carried out among Japanese recurrent abortion cases with no obvious anatomical or medical causes. We attempt to analyze the genetic changes which have the potential to be the causative factors of recurrent abortions.
6. Genetic analysis for rare and undiagnosed cases.
Genomic and epigenetic analysis of patients with phenotypes unexplained by conventional chromosome examination may detect novel genetic and epigenetic aberrations. Detailed analysis including, copy number variations, exome analysis and methylation analysis are under examination to detect causative factors in rare cases.

Reproductive endocrinology
1. The utility and issues associated with the use of decision trees in oncofertility patient care.
To identify the utility and issues associated with the use of decision trees in oncofertility patient care, we investigated 35 women who had been diagnosed with cancer but had not begun anticancer treatment. We applied the oncofertility decision tree for women to counsel a consecutive series of women on fertility preservation (FP) options following cancer diagnosis. Oocyte retrieval was performed for 17 patients (48.6%; 36.35±3.82 years). The mean±SD number of cryopreserved embryos was 5.29±4.63. The expected live-birth rate was 0.66. In conclusions, the expected live-birth rate with FP indicated that 1 in 3 oncofertility patients would not expect to have a live birth following oocyte retrieval and embryo cryopreservation. While the decision trees were useful as decision-making tools for women contemplating FP, in the context of the current restrictions on oocyte donation and the extremely small number of adoptions in Japan, the remaining options for fertility after cancer are limited.
2. Study of Awareness of Adoption as a Family Building Option Among Oncofertility Stakeholders in Japan.
Adoption is an option to have a child for the survivor who lost their fertility due to oncologic treatment. However, it remains uncommon in Japan. We provided a questionary survey about adoption to Oncofertility stakeholders. Based on the reported answers, we concluded that doctors have insufficient knowledge about adoption, and survivors lack the self-confidence to even contemplate wanting children. On the other hand, adoption agencies are willing to consider cancer survivors as candidate adoptive parents on terms equal to those used for the general public provided the survivors meet parenting criteria. The present study demonstrated the need for healthcare professionals and reproductive specialists in particular to learn more about adoption and the importance of informing cancer survivors wishing to adopt that their medical history itself is not a hurdle.

Publications

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