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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

Inactivating somatic mutations of genes that encode subunits of the switch/sucrose non-fermentable chromatin remodeling complex have attracted much interest in cancer cells. We performed the screening analysis with an inhibitor kit and cancer cells in which the AT-rich interactive domain 1A gene (*ARID1A*) was of the wild type or had been knocked out. The results identified the compounds as a potential therapeutic target for *ARID1A*-mutant cancers. To explore the interaction between *ARID1A*-mutant cancers and the compound, we will perform further assays.

2. A noninvasive diagnosis of ovarian clear cell carcinoma

The aim of this study was to establish a noninvasive diagnostic procedure for ovarian clear-cell carcinoma (CCC) by evaluating circulating tumor DNA and Pap smear-derived DNA from patients. We successfully demonstrated that our noninvasive digital polymerase chain reaction-based method of diagnosis can be used to detect gene amplification or mutation or both in circulating tumor DNA/Pap smear-derived DNA from ovarian CCC.

3. Interleukin 6 expression and its relationship with clinicopathological features including *ARID1A* expression in stage I CCC of the ovary

We aimed to identify the interleukin 6/*ARID1A* expression signature associated with patient characteristics in stage I CCC by means of immunohistochemical analyses. Interleukin 6 expression is likely a useful prognostic marker in stage I CCC.

4. Identification of the function of *FOXL2* mutation in granulosa cell tumor of the ovary

We addressed a drug-screening method using the granulosa cell line inducible with the wild-type or mutant forkhead box L2 gene (*FOXL2*) to establish novel treatments specific for this mutation. We found that the transforming growth factor β pathway is involved in tumor growth.

5. MicroRNA gene expression signature driven by overexpression of microRNA-9 in ovarian CCC

This study aimed to elucidate potential clinical and biological associations of ovarian cancer-related microRNA gene expression profiles in ovarian high-grade serous carcinoma and CCC. In CCC, overexpression of microRNA-9 may affect pathogenesis by targeting E-cadherin.

Perinatology

1. Novel nonsense mutation in *NLRP7* associated with recurrent hydatidiform mole

This study aimed to clarify the genetic and epigenetic features of recurrent hydatidiform mole in Japanese patients. This report is, to our knowledge, the first of a Japanese case of recurrent hydatidiform mole with a novel homozygous nonsense mutation of the NLR family pyrin domain containing 7 gene (*NLRP7*) and a specific loss of maternal DNA methylation of differentially methylated regions.

2. Increased expression of perforin, granzyme B, and C5b-9 in villitis of unknown etiology

Villitis of unknown etiology is associated with fetal growth restriction. This is, to our knowledge, the first report to assess villous injury, especially from the viewpoint of villous apoptosis, in a placenta with villitis of unknown etiology. An activated perforin/granzyme pathway and C5b-9 are suggested as possible mechanisms of apoptosis.

3. Antenatal treatment of myelomeningocele with 3-dimensional skin by using induced pluripotent stem cells

Myelomeningocele is a congenital abnormality resulting in exposure of the spinal cord to amniotic fluid. We obtained stem cells from amniotic fluid and induced differentiation into a skin lineage to create biomaterial. We developed a novel fetal therapy by using biomaterial that can be transplanted less invasively.

4. Single-cell DNA sequencing of fetal cells in maternal peripheral blood for noninvasive prenatal diagnosis

To develop a new risk-free method for obtaining precise genetic information from fetuses, we attempted to purify the fetal nucleated red blood cells in maternal peripheral blood and to develop the method for single-cell DNA sequencing with these fetal cells.

5. Exploring the unknown genetic causative candidate factors of recurrent abortions in Japanese women by using high-resolution whole-genome single-nucleotide polymorphism microarray analysis

To detect unknown genetic causative candidate factors of recurrent abortions in the Japanese, we performed high-resolution whole-genome single-nucleotide polymorphism microarray analysis in cases of recurrent abortion with no anatomical or medical causes in Japanese women and attempted to find genetic changes that are possible causative factors for recurrent abortions.

6. Noninvasive prenatal diagnosis of fetal sex and rhesus D status with circulating cell-free DNA

We attempted to develop a method to detect fetal sex and the rhesus D blood type with circulating cell-free DNA in maternal peripheral blood. Moreover, we assessed whether the method can be introduced as a clinical examination and whether the same protocol

can be adapted to prenatal examinations for other diseases and the phenotypes of fetuses.

Reproductive endocrinology

1. Investigation of the relationship between the optimal storage duration and the fertility of mouse ovary: Basic research for clinical application of ovarian transport

In Europe ovarian tissue is often transported overnight before being frozen, but the maximum storage time when ovaries are transported to increase fertility has not been investigated. This study aimed to clarify the relationship between the optimal storage duration and fertility. The study's results suggest that prolonging the ovarian storage time reduces fertility in mice. Thus, to minimize damage, ovaries should be frozen immediately after being harvested or should be transported as rapidly as possible.

2. Psychosocial care for oncofertility patients in Japan

Psychosocial care should be established for oncofertility patients who seek fertility preservation. We interviewed several healthcare providers working on oncofertility at Northwestern University (Evanston, IL, USA). A patient navigator is clearly recognized as the person for first contact from oncologists. A patient navigator provides patients with initial information about oncofertility. A psychologist cooperates closely with the patient navigator and provides psychological counseling to patients in a timely manner. We recognized that human resources, such as reproductive psychologists, cultivated by Japanese society for reproductive psychology, might play an important role. We examined the utility of decision trees for decision-making in Japan by using our data about oncofertility patients. The results showed that a social environment including the donation of oocytes or sperm, adoption, and other practices, should be prepared.

Publications

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