

Seung Mi Lee
(J1)



CURRICULUM VITAE

Seung Mi Lee, MD.PhD

Current position

- Clinical Professor, Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea.
- Division Head, Division of Big Data Infrastructure, Department of Data Science Research, Seoul National University Hospital, Seoul, Korea.

Education Carrier

1996/3 – 2002/2	M.D.	Seoul National University, College of Medicine, Seoul, Korea
2006/9 – 2008/8	M.S.	Seoul National University Graduate School
2009/9 – 2011/2	Ph.D.	Seoul National University Graduate School

Medical Training

2002/3 – 2003/2	Intern, Seoul National University Hospital, Seoul, Korea
2003/3 – 2007/2	Resident, Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea
2007/3 – 2009.7	Fellow, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea
2009/8 – 2011/6	Assistant Professor, Department of Obstetrics and Gynecology, Center for Health Promotion and Optimal Aging, Seoul National University Hospital, Seoul, Korea
2011/7 – 2015/8	Assistant Professor, Department of Obstetrics and Gynecology, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea
2015/9 – 2017/2	Assistant Professor, Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea
2017/3 – 2022/2	Associate Professor, Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea
2022/3 – Present	Professor, Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea
2020/4 – 2021/3	Visiting Associate Professor, Department of Biostatistics, Epidemiology & Informatics, The Perelman School of Medicine, University of Pennsylvania

Artificial intelligence in maternal-fetal medicine

Seung Mi Lee, MD, PhD

Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea

Machine learning is a branch of artificial intelligence which focuses the use of data and algorithm to imitate the way that humans learn. With the adoption of machine learning, medical scientists expect higher accuracy/performance and identification of novel contributing factors, compared to traditional statistical method. Recently we have reported that machine learning can be used to better predict adverse pregnancy outcomes.

1. Early prediction of pregnancy complications

Prediction of obstetric complications such as preeclampsia and gestational diabetes in early pregnancy is essential to develop preventive strategies. Using machine learning methods, we have developed prediction model for pregnancy-associated hypertension with the use of clinical variables in early pregnancy, and found that graph-based semi-supervised learning showed the best performance with AUROC of 0.89 in training set and 0.81 in test set. Moreover, the proposed model with graph-based semi-supervised learning showed a higher performance than PIGF measured in early pregnancy.

We also developed an early prediction model for gestational diabetes mellitus with machine learning, and evaluated if non-alcoholic fatty liver disease (NAFLD)-associated factors can increase the prediction model performance. As a result, inclusion of NAFLD-associated factors significantly increased the performance of prediction model.

2. Real-time prediction of intra-operative complications

Various complications can happen during high risk surgery. We tried to predict massive transfusion during surgery, because early prediction of massive transfusion is essential for preparation of blood product and additional medical personnel. We evaluated the performance of real-time prediction model for massive transfusion with intra-operative hemodynamic monitoring data. As a result, a real-time prediction model with intra-operative data significantly outperformed the prediction model with pre-operative variables (AUROC 0.972 vs 0.824). This result showed the possibility of artificial intelligence-assisted clinical decision support systems during surgery.

In conclusion, we showed that machine learning can be used in prediction of pregnancy complications and intra-operative complications with high performance.

Akihiro Kawashima
(J2)



CURRICULUM VITAE

Akihiro Kawashima, MD/PhD

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Education

04/2013-03/2016 Ph.D., Showa University Graduate School
PhD in Medicine

04/1999-03/2005 M.D., National Defence Medical College

Postgraduate training appointments

06/2005-06/2007 resident, National defence medical college hospital

Employment

10/2023 – present Obstetrics ward director, Dept of OBGYN, Showa University

01/2023 – 09/2023 Senior Head Physician, Dept of OBGYN, NTT Medical Center Tokyo

04/2020 – present Lecturer, Dept of OBGYN, Showa University

04/2016 – 03/2020 Associate professor, Dept of OBGYN, Showa University

08/2011 – 03/2013 Member, Dept of OBGYN, Self Defence Forces Central Hospital

07/2009 – 07/2011 Member, Dept of OBGYN, National Defence Medical College

07/2007 – 06/2009 Medical officer, JGSDF Northern Army

Honours and awards

04/2015 Award of the best reviewer of Japan Obstetrics and Gynaecology Research

02/2016 Kamijo Award for distinguished graduates, Showa University Graduate School

04/2019 Japan Society of OBstetrics and Gynaecology Congress Award

Early-Onset Preeclampsia Is Associated with Altered DNA Methylation in the first trimester villi

Akihiro Kawashima, Akihiko Sekizawa

Department of obstetrics and gynaecology, Showa university

Background: Preeclampsia (PE) is thought to be caused by placenta formation failure during early pregnancy. In preeclampsia, asymptomatic placental oxidative stress from early gestation is a precursor to later multi-organ dysfunction in the mother. The lack of reliable methods for early detection limits the opportunities for prevention, diagnosis, and timely treatment. Cell-free DNA (cfDNA) methylation represents biomarker material that can be isolated from the blood plasma in a minimally invasive manner. Although aberrant DNA methylation in cfDNA has been reported for over a decade, its diagnostic accuracy remains unsatisfactory for predicting PE. Using epigenetic biomarkers and digital PCR technology, we have developed a susceptible cfDNA-based screening test to predict early-onset preeclampsia.

Methods: Chorionic villus samples of pregnant women in the first trimester were recruited for this case-control study to extract candidate genes. Genome-wide DNA methylation was quantified using reduced representation bisulfite sequencing in first-trimester chorionic tissue from pregnant women who later developed early-onset preeclampsia with their fetus confirmed of normal female karyotype and gestational age-matched control. To increase the sensitivity and specificity of cfDNA methylation in the subsequent analysis, we removed hypermethylation CpGs in normal blood from differentially methylated CpGs. Next, check whether these methylated genes could be seen in cfDNA before they were diagnosed with early-onset PE. For this, cfDNA samples were obtained from 125 women in the first trimester, ranging from 11 to 13 weeks of gestation. We employed droplet digital PCR to quantify tiny amounts of methylated DNA of candidates in cfDNA. Epigenetic markers for early-onset PE prediction were selected, and a droplet digital methylation-specific PCR (ddMSP) panel with the selected markers was established.

Results: In the first part of our analysis, we collected DNA methylation status of chorionic villus samples at 12 gestational weeks from two pregnant women later progressing to early-onset PE and four gestation-matched controls with normal female karyotype. We identified 841 candidate hypermethylated genes, and through further analysis, we narrowed down the 20 protein-coding genes for the candidate. A ddMSP using these 20 markers was developed, and prediction models were constructed with a dataset containing cfDNA samples from 9 early-onset PE, 23 late-onset PE and 93 controls. The prediction models adopted three methylation markers (ADORA2B, HOXB4 and ZNF714). The dataset's area under the receiver operating characteristic curve for predicting early-onset PE was 0.82.

Conclusions: Our study pointed out that cfDNA methylation alterations of several genes in chorionic villi probably resulted in altered developmental processes and immune dysregulation, contributing to PE. This study provides essential information to refine the clinical and pathological mechanisms of the severe features in placenta-mediated PE.

Chin-Ru Ker 葛菁如
(J3)



CURRICULUM VITAE

Chin-Ru Ker

Director of Obstetrics and Gynecology Department,
Kaohsiung Medical University Gangshan Hospital

Professional Position

Director, Obstetrics and Gynecology Department,
Kaohsiung Medical University Gangshan Hospital
Attending Physician, Maternal Medicine,
Kaohsiung Medical University Hospital
Consultant and Sonographer, Fetal Medicine,
Kaohsiung Medical University Hospital

Education

2021-	Graduate Program in Clinical Medicine, Kaohsiung Medical University Hospital
2019-2020	Fellow, Maternal Fetal Medicine, Kaohsiung Medical University Hospital
2018-2019	Chief Resident, Obstetrics and Gynecology, Kaohsiung Medical University Hospital
2015-2018	Resident, Obstetrics and Gynecology, Kaohsiung Medical University Hospital
2014-2015	Post-graduate Year Training, Kaohsiung Medical University Hospital
2009-2014	Post-baccalaureate Degree, Kaohsiung Medical University

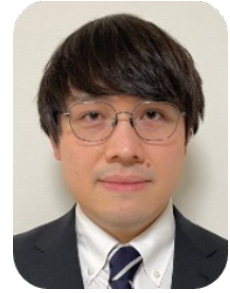
The Aftermath of Emergency Cervical Cerclage

Chin-Ru Ker, MD

Department of OBS&GYN, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

According to the statistics reported by World Health Organization, an estimated 13.4 million babies were born preterm in 2020 and the prevalence rate ranges from 4-16% across countries. In Taiwan, premature babies account for 10-11% of newborn babies every year and the number remained consistent if not gradually increasing over the past decade, despite advances in obstetrics and neonatology medicine. Preterm survivors can have long-term health consequences, which is an area the professionals strive to seek solutions for. Emergency or rescue cervical cerclages for painless cervical dilatation or prolapsed amniotic membrane in second trimester can prolong pregnancy compared to conservative treatment with a wide range of success rate (63-90%). However, pregnancy prolongation does not necessarily translate into take-home healthy babies. The procedure could bring previable babies to extreme preterm infants. Infant mortality is still high after long-term follow ups, in addition to considerable morbidity such as prolonged hospital stay, neurodevelopment delay and sepsis. Who and at what gestations ages would most likely benefit from rescue cerclages at long-term are still unclear and should be investigated. Most current practice guidelines are conservative and leave the decision to receive rescue cervical cerclages to individualized considerations, as described by Royal College of Obstetricians and Gynecologists (RCOG 2022), the Society of Obstetricians and Gynaecologists of Canada (SOGC 2019), the International Federation of Gynecology and Obstetrics (FIGO 2021). Patient selection and pre-procedural consultation become crucial in optimizing the management for these patients, both maternal and fetal. In this session, cases with suboptimal maternal or infant clinical outcomes after “successful” emergency cerclages from Kaohsiung Medical University Hospital (KMUH) will be shared to offer some food for thoughts in critical situations like cervical insufficiency with protruding amniotic membrane.

Satoshi Hosoya
(J4)



CURRICULUM VITAE

Satoshi Hosoya

Assistant Professor, The Jikei University school of Medicine

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Education and Professional Career

- 04/2011-03/2017 A medical student, obtained my MD, The Jikei University School of Medicine, Tokyo, Japan
- 04/2017-03/2019 A junior resident, National Center for Global Health and Medicine, Tokyo, Japan
- 04/2019-present A senior resident, An assistant professor, The Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan
- 04/2020-03/2021 A resident, Center for Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan
- 04/2021-present A graduate student, The Jikei University School of Medicine, Tokyo, Japan
- 04/2021-present A researcher, Center for Regenerative Medicine, National Center for Child Health and Development Research Institute, Tokyo, Japan

Main Research Topic

- Endometrial regeneration using stem cells and the development of a novel regenerative therapy for infertility with the injured endometrium

Honors and awards

- 05/2023 JSOG Congress Award at the 75th annual congress of the Japan Society of Obstetrics and Gynecology
- 12/2022 The Best Poster Award at the 2nd Science symposium by the Japan Society of Regenerative Medicine
- 04/2022-06/2023 Research Fellowship for Young Scientists, Doctoral Course Students 1(DC1), Japan Society for the Promotion of Science (JSPS)
- 03/2019 2019 NCGM The Takaku Prize/The best junior resident of the year, National Center for Global Health and Medicine

Stem cell-based therapy for infertility

Satoshi Hosoya, M.D.

Institution: The Jikei University School of Medicine, Department of Obstetrics and Gynecology

Stem cell-based therapy has been globally expected to be a novel therapeutic strategy for refractory infertility such as Asherman's syndrome and ovarian insufficiency. In Japan, under the Act on the Safety of Regenerative Medicine (ASRM), the current status of the research provision plans is publicly accessible on website. However, as of September 2023, among a total of 183 approved research plans, there had been only 4 clinical trials regarding the field of obstetrics and gynecology (OBGYN) under the ASRM (2.2%), of which two trials targeted endometrial infertility with intrauterine administration of autologous peripheral blood lymphocytes or adipose-tissue derived mesenchymal stem cells. In addition, there is no cell and gene therapy product for infertility with the pharmaceutical approval. Thus, the fact suggests that the research of regenerative medicine for infertility is still in the process of developing in Japan. To overcome the current status, I try to now develop a novel stem-cell based therapy for Asherman's syndrome using menstrual blood-derived stem cells (MenSCs). In our pre-clinical study using a rodent model with injured endometrium, MenSCs from a patient with Asherman's syndrome demonstrated the regenerative efficacy for endometrial infertility through paracrine capacity for tissue repair and angiogenesis. MenSCs have been projected to be a desirable mesenchymal stem cell source due to their easy accessibility, periodic acquisition, beneficial cost-effectiveness, high proliferative ability and low immunological rejection rather than other mesenchymal stem cell sources. Therefore, our research vision is to aim for clinical application of this novel stem cell therapy for endometrial infertility and develop the regenerative medicine in the field of OBGYN. In this conference, I will provide the current status of regenerative medicine regarding OBGYN in Japan and demonstrate our research progress with MenSCs for endometrial infertility.

Chu-Chun Huang 黃楚琚
(J5)



CURRICULUM VITAE

Chu-Chun Huang

Professional Position

- 2015- Attending physician, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, National Taiwan University Hospital, Taipei, Taiwan
- 2021- Assistant professor, Department of Obstetrics and Gynecology, National Taiwan University Hospital, Taipei, Taiwan
- 2022- Secretary General, Taiwanese Society for Reproductive Medicine (TSRM)
- 2022- Chief, Department of Obstetrics and Gynecology, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan

Education and Training

- 1998-2005 M.D., College of Medicine, National Taiwan University
- 2006-2010 Fellowship, Division of Reproductive Endocrinology and infertility, Department of Obstetrics and Gynecology, National Taiwan University Hospital
- 2010-2012 Fellowship, Division of Reproductive Endocrinology and infertility, Department of Obstetrics and Gynecology, National Taiwan University Hospital
- 2013-2020 Ph.D. Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University

Professional experience

- Assisted Reproductive Technologies
- Polycystic ovarian syndrome
- Reproductive endocrinology and infertility
- Fertility preservation

Insights into the pathophysiology and treatment of PCOS

*Chu-Chun Huang, MD. PhD.
National Taiwan University Hospital Yunlin Branch*

Polycystic ovary syndrome (PCOS) is the most common female endocrinopathy, affecting up to 8% to 13% of reproductive-age women and is characterized by chronic anovulation, clinical and/or biochemical hyperandrogenism (HA), and polycystic ovarian morphology that constitute the 3 diagnostic features as per the Rotterdam criteria. The impact on women health is huge and lifelong. They may suffer from irregular menstruation during their adolescence and infertility or subfertility during child-bearing age. These women are also at high risk to develop metabolic syndrome, includes insulin resistance, type II diabetes, dyslipidemia, hyperuricemia, and even more, suffer from increased incidence of endometrial hyperplasia or endometrial carcinoma because of chronic anovulation. A number of pathophysiologic explanations have been proposed, including androgen excess and insulin resistance. Androgen excess favoring visceral abdominal fat disposition facilitates an increased secretion of androgens by the ovaries and/or the adrenal glands. Insulin resistance, a common feature of PCOS, leads to compensatory hyperinsulinemia with diverse effects on adipose tissue and androgen production. However, no single etiology can completely explain the full spectrum of this complex disease and the underlying mechanisms remain unclear. In this section, we will briefly introduce the pathophysiology of PCOS and review the most updated international evidence-based guidelines for PCOS assessment and treatment published in 2023, along with some novel findings from our research works.

Hye Gyeong Jeong
(J6)



CURRICULUM VITAE

Hye Gyeong Jeong, M.D. M.S.

Current Position

Clinical Assistant Professor,
Department of Obstetrics and Gynecology (OB/GY), Korea University Anam Hospital

Education

2010-2014 **Master' s Degree**, College of Medicine, Catholic University of Korea
2020-2022 PhD, Department of Obstetrics and Gynecology, College of Medicine, Seoul National University

Professional Background

2014~2015 Internship, Samsung Seoul Hospital
2015~2019 Residency, Seoul National University Hospital, Dept. of Obstetrics and Gynecology
2020~2022 Fellowship, Seoul National University Bundang Hospital
2022~ Clinical Assistant Professor, Department of Obstetrics and Gynecology, Korea University Anam Hospital

License

March, 2019 Board Certification in OB/GY (issued by Korean Medical Association)
March, 2014 Korean Medical License (issued by Ministry of Health and Welfare)

Investigation for a relationship between vasomotor symptoms and hypothalamus volumetry using magnetic resonance imaging

Hye Gyeong Jeong¹, Nayoung Jeong¹, Sumin Cho¹, Ki-Jin Ryu¹, Woo-Suk Tae², Tak Kim¹, Hyuntae Park¹
¹*Obstetrics and Gynecology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea*
²*Brain Convergence Research Center, Korea University, Seoul, Republic of Korea*

Vasomotor symptoms (VMS) such as hot flushing and night sweating are representative menopausal symptoms commonly experienced by postmenopausal women. It has been revealed that VMS goes beyond simply quality of life and is associated with an increase in symptoms such as anxiety, depression, and insomnia, as well as cardiovascular disease, metabolic disease, and fractures.

In a series of neuroimaging studies in midlife women, VMS were associated with brain health. However, it is unclear whether VMS accounts for changes in brain structure. Voxel-based morphometry (VBM) is a neuroimaging technique that investigates focal differences in the brain region. Our study investigated the association between VMS and VBM findings of the hypothalamus using the three-dimensional reconstruction technique of magnetic resonance imaging among Korean midlife women.

This cross-sectional study included 302 Korean women aged 40-70 years who attended routine health checks including the brain MRI at a single institution from Jan 2010 to Dec 2016. Menopausal vasomotor symptoms were assessed using the results of the Menopause Rating Scale (MRS). Using the axial T1 and T2 MRI of each subject with 6.5 mm slice thickness, the high-resolution T1 MRIs with isotropic 1 mm voxel size were artificially synthesized. Then using the synthesized MRI, subregional hypothalamic volumetry and VBM were performed and correlated with clinical variables.

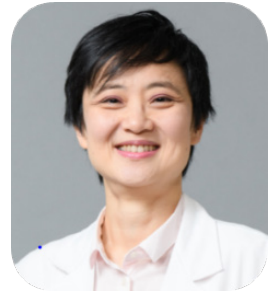
The mean age of the participants was 55.4 ± 5.4 years, and 232 (76.8%) of them were reported to be postmenopausal. Vasomotor symptoms were experienced by 185 (61.3%) of all participants. VMS were negatively correlated with gray matter volume in both hypothalamic areas in VBM (uncorrected $P < 0.05$ with small volume correction in hypothalamic area radius 20 mm). Sub-regional hypothalamic volumetry showed negative relations with vasomotor symptoms score in the amygdala ($r = -0.155$, $p = 0.009$), and hippocampus ($r = -0.169$, $p = 0.004$).

Vasomotor symptoms are associated with the hypothalamus volumetry measured using the synthesized MRI among middle-aged Korean women. These findings suggest that the pathophysiology of menopausal vasomotor symptoms might be closely related to changes in specific areas of the brain, especially the hypothalamus. Further longitudinal studies are needed to confirm our findings.

References

1. Thurston RC et al., Menopausal Vasomotor Symptoms and White Matter Hyperintensities in Midlife Women, *Neurology*. 2023;100(2):e133-e141
2. Monteleone et al., Symptoms of menopause-global prevalence, physiology and implications, *Nature Reviews*. 2018;14:199-215
3. Mosconi L, Berti V, Dyke J, et al. Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. *Sci Rep*. 2021;11(1):10867.
4. Maki PM, Thurston RC. Menopause and brain health: hormonal changes are only a part of the story. *Front Neurol*. 2020;11.

Angel Chao 趙安琪
(J7)



CURRICULUM VITAE

Angel Chao, MD, PhD

Chang Gung Memorial Hospital, Taiwan

Dr. Angel Chao is an Attending within the Department of Obstetrics and Gynecology in Chang Gung Memorial Hospital (CGMH) and Professor at Chang Gung University. She is the Director of Division of Gynecologic Oncology and Head of Gynecologic Cancer Research Center at CGMH. She is board certified in Obstetrics and Gynecology and received her Medical Degree at Taipei Medical University School of Medicine. Dr. Chao performed her Residency and Gynecology Oncology Fellowship Program at CGMH. She is a graduate of The Graduate Institute of Clinical Medical Sciences of Chang Gung University. Dr Chao' s research focuses on translational studies of gynecologic cancer.

Uncovering the molecular landscape of ovarian clear cell carcinoma: towards precision oncology

*Angel Chao, MD, PhD
Chang Gung Memorial Hospital, Taiwan*

Ovarian clear cell carcinoma (OCCC) is a type of epithelial ovarian cancer that more commonly affects women in East Asia. Notably, OCCC is associated with poorer outcomes compared to high-grade serous carcinomas (HGSCs) of the same stage. This can be attributed, in part, to its higher resistance to chemotherapy and the limited identification of molecular targets for treatment. Through the analysis of whole-exome sequencing data, we found that 40% of 104 OCCC samples exhibited tier 1 or 2 clinically actionable molecular targets. Furthermore, we observed that 42% of OCCCs displayed likely biallelic loss of *ARID1A*. Previously unreported mutations in the 5' untranslated regions of *TERT* were associated with poor survival outcomes. OCCC exhibited pervasive and heterogeneous somatic copy number alterations. Clonal evolution reconstruction revealed that early clonal and potentially driver events included mutations in *ARID1A*, *PIK3CA*, *TERT*, *KRAS*, and *TP53*. In this presentation, I will also discuss data of genetic alterations in OCCC from Korea and Japan.

Tatsuya Ishiguro
(J8)



CURRICULUM VITAE

Tatsuya Ishiguro, M.D., Ph.D.

Department of Obstetrics and Gynecology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

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Education

1999 Graduated from Sanjo high school (Niigata, Japan)

2005 Graduated from Niigata University, Medical school (Niigata, Japan)

Professional training and Employment

April 2014-Present Assistant Professor in Niigata University Medical and Dental Hospital

April 2013- March 2014 Medical Staff in Niigata University Hospital

April 2010- March 2013 Research Resident, National Cancer Center Hospital, Research Institute (Tokyo, Japan)

April 2007- March 2010 Senior Resident in Obstetrics and Gynecology, Niigata University Hospital, Niigata City General Hospital, and Tsuruoka Municipal Shonai Hospital (Yamagata, Japan)

April 2005- March 2007 Junior Resident, Niigata University Hospital (Niigata, Japan)

2005 Passed the Examination of National Board

Memberships

Japan Society of Obstetrics and Gynecology

Japan Society of Reproductive Medicine

Japan Society of Gynecologic Oncology

Japan Society of Perinatal and Neonatal Medicine

Japan Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Therapy

Japan Society of Menopause and Women's Health

Japan Society of Gynecologic Oncology

Japanese Cancer Association

Honor & Awards

- 2022 AOFOG Young Gynaecologist Award
- 2020 The University of Niigata President's Award
- 2018 Niigata Medical Association Encouragement Award
- 2017 Japan Society of Gynecologic Oncology Congress Encouragement Award
- 2016 Japan Society of Obstetrics and Gynecology Best Scientific Paper of the Year

Novel therapeutic strategy targeting cancer heterogeneity and metabolism based on a cancer stem cell model

Tatsuya Ishiguro, Niigata University

Objective: Cancerous tissues comprise heterogeneous malignant cells. Cancer stem cells (CSCs), a subpopulation of cells with tumorigenic, self-renewal, and differentiation potential, are instrumental in cancer propagation and proliferation. *in vitro* three-dimensional culture systems derived from human clinical specimens may be a useful platform to develop new therapeutic strategies for refractory cancer. In this study, we introduced a stable cultivation method for gynecological CSCs. Furthermore, we investigated the biochemical characteristics of CSCs to develop an innovative treatment approach targeting CSCs.

Methods: Tumor or ascites samples were obtained from patients treated at the Niigata University or National Cancer Center Hospital. Following enzymatic dissociation of cancerous tissues, cells were cultured in ultra-low-attachment dishes in a serum-free medium. A xenograft model was established after transplantation of stable growing cells. Our study protocol was approved by the Ethics Committee, and all patients provided informed consent.

Results:

1. *in vitro* human gynecological CSCs cultivation:

We successfully established an *in vitro* three-dimensional culture system using ovarian and uterine endometrial cancer specimens. Our three-dimensional cells (tumor-derived spheroids) showed characteristics of CSCs, including *in vivo* tumorigenic and differentiation potential. Spheroid cells and the original cancer shared similar mutation profiles.

2. Investigation of a specific regulatory mechanism underlying CSCs proliferation and a novel treatment approach targeting CSCs:

(1) Ovarian CSCs: Spheroid cells with high expression of aldehyde dehydrogenase (ALDH) activity (ALDH-high cells) showed various CSCs characteristics. Functional analyses using gene knockdown and a chemical inhibitor revealed that ALDH and SOX2 are essential for ovarian CSCs proliferation, whereas SOX2 overexpression inhibits ALDH1A1 and suppresses ovarian CSCs, which suggests feedback regulation of CSCs proliferation; SOX2 and ALDH1A1 form a negative feedback loop.

(2) Uterine endometrial CSCs: ALDH-high endometrial cancer spheroid cells also showed CSCs potential. ALDH activity inhibition reduces endometrial CSCs propagation. Compared with ALDH-low cells, ALDH-high cells showed greater resistance to paclitaxel, and paclitaxel + ALDH inhibitor combination therapy synergistically inhibited endometrial cancer cell progression. High ALDH levels correlated with glycolytic pathway activation and elevated glucose transporter 1 (GLUT1). GLUT1 blockade inhibited characteristics of CSCs, and GLUT1 inhibition synergized with

paclitaxel to block endometrial cancer proliferation. Further analysis showed that the influence of ALDH on mTORC1 is partially channeled through retinoic acid-induced lactate dehydrogenase A (LDHA) activation in the PI3K-Akt-mTORC1 signaling cascade. LDHA inhibition was found to reduce endometrial cancer cell growth, paralleling the effects of mTORC1 inhibition. Curbing mTORC1 bolstered glucose transport via GLUT1 activation.

Conclusion: We established a stable cultivation method for ovarian and endometrial CSCs and observed that ALDH is essential for CSCs propagation in both cancers. ALDH or glycolysis-related inhibitors suppress cancer propagation based on the specific regulatory mechanism underlying ovarian and endometrial CSCs. ALDH or glycolysis-related inhibitors may be useful as novel treatment agents for gynecologic cancers. Our cultivation method may enable screening of patients with high ALDH levels, who tend to respond to these inhibitors. Therefore, this novel approach may be useful to identify patients who are likely to benefit from the therapy.

Jiheum Paek
(J9)



CURRICULUM VITAE

Jiheum Paek

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology
Ajou University School of Medicine, Republic of Korea

EDUCATION

1995-2001 Hanyang University College of Medicine, Seoul, Korea (Doctor of Medicine)
2012-2017 Yonsei University College of Medicine, Graduate School, Seoul, Korea (Ph.D.)

AFFILIATION & POSITION

2002-2006 Resident, Obstetrics and Gynecology, Hanyang University Hospital, Seoul, Korea
2009-2011 Clinical Research Assistant Professor, Division of Gynecologic Oncology, Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, Korea
2011-2017 Assistant Professor, Division of Gynecologic Oncology, Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, Korea
2017-2018 Visiting Scholar, Department of Gynecology Oncology and Robotic Surgery, University of Nevada, Reno School of Medicine, USA
2017-present Associate Professor, Division of Gynecologic Oncology, Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, Korea

Robotic surgery for gynecologic cancers: staying ahead of the curve

The optimal instrumentation and surgical techniques are evolving in the direction of easier minimally invasive surgery (MIS). Since the robotic surgical system in the field of MIS has been introduced, robotic surgery has become a global trend. Robotic surgery has the same advantages as MIS, including less postoperative pain, shorter hospital stays, and shorter recovery times. Moreover, robotic surgery has technical advantages, including improved surgeon dexterity, surgical precision, visualization, and ergonomics. These potential advantages of robotic surgery allow surgeons to perform optimal surgery for treatment in patients with gynecologic cancers as well as benign disease.

In 2018, the results from the Laparoscopic Approach to Cervical Cancer (LACC) trial, a randomized controlled trial, on surgery in early-stage cervical cancer showed that minimally invasive surgery (MIS) had poorer survival outcomes compared to laparotomy. Since then, a great number of regarding studies have been reported and most of them have supported that MIS had poor survival outcome in cervical cancer patients. However, most of the evaluated patients who had MIS had laparoscopic radical hysterectomy, not robotic surgery (RRH). Because robotic surgery, as it is known, has improved surgeons' dexterity and surgical precision, it has been performed popularly for complexed surgical procedures in deep and narrow pelvic cavity instead of laparoscopy or laparotomy. We need to focus on the current trends and controversies of RRH individually. It will provide the future direction of RRH in patients with early-stage cervical cancer.

Endometrial cancer is the most common malignancy of the female reproductive tract in developed countries. Surgery is the most important step in the management of the disease. MIS for endometrial cancer has been shown to offer equivalent survival outcomes with reduced intra- and postoperative morbidity, compared to other surgical approaches. The proportion of endometrial cancers treated through MIS has gradually increased, approaching 90% at high-volume hospitals, which is influenced by the increasing use of robotic surgery. Especially, the implementation of robotic surgery to sentinel lymph node mapping and comprehensive lymph node dissection allow surgeon to perform surgery in endometrial cancer optimally. Although MIS, including robotic surgery, in patients with ovarian cancer has been performed restrictively, the technology of robotic system has potential advantages for primary debulking surgery in early stage disease or metastatectomy in recurrent setting.

In this congress, I will share my opinions regarding the way to stay ahead of the curve for robotic gynecologic cancer surgery with the aim of offering a guide to both experienced and naïve surgeons who plan to learn robotic procedures.