

Yamato Fukui
(Y11)



The role of uterine EZH2-PRC2-H3K27me3 axis in embryo implantation

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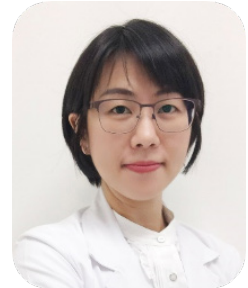
Objective: Trimethylation on lysine 27 of histone H3 (H3K27me3) is a major epigenetic modification to silence gene expressions and polycomb repressive complex 2 (PRC2) induces H3K27me3. Enhancer of zeste homolog 2 (Ezh2) is a core molecule in PRC2 to exert H3K27 methylations (Ezh2). Our recent RNA-seq analysis of mouse endometria in peri-implantation period showed that H3K27me3-targeting genes are highly enriched in differentially expressed genes during implantation transition, indicating the possible roles of PRC2-H3K27me3 in the process of successful pregnancy. This study aimed to clarify the unappreciated roles of Ezh2-PRC2-H3K27me3 axis in the uterus during the peri-implantation period by analyzing human and mouse endometrial tissues.

Methods: Human peri-implantation endometrium was collected from patients with recurrent implantation failure (RIF) and their fertile controls. RNA-seq analyses of the human endometria were performed between the two groups. Mice with deletion of Ezh2 in the whole uterus (UKO mice) and in the epithelium (EKO mice) were generated. Reproductive phenotypes of UKO and EKO mice were analyzed in detail.

Results: RNA-seq analyses of the human endometria revealed that EZH2 and PRC2-H3K27me3-targeting genes are more dysregulated in the human endometrium of patients with RIF compared to the fertile controls. UKO mice exhibited severe subfertility, whereas fertility of EKO mice was normal, suggesting that stromal Ezh2 has a significant impact on female fertility. Tissue analyses of peri-implantation uteri showed that UKO mice have embryo invasion defects. RNA-seq and ChIP-seq analyses revealed that H3K27me3-related dynamic gene silencing is canceled by Ezh2 deletion, and the gene expression of cell-cycle regulators is dysregulated in Ezh2-deleted uteri. Uterine Ezh2 deficiency also caused the sustained proliferation of the epithelium and reduced terminal differentiation of the stroma, suggesting epithelial defects and stromal differentiation in the Ezh2-deficient uterus.

Conclusion: Our findings indicate that the EZH2-PRC2-H3K27me3 axis is critical to preparing the endometrium for the blastocyst invasion into the stroma in mice and humans.

Caroline Lim 林嘉玲
(Y12)



To assessment of chronic endometritis in infertile women with prior implantation failure

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Objective: To investigate the association of chronic endometritis (CE) in infertile patients with or without prior implantation failure (IF) by assessment of CD138, a plasma cell marker.

Methods: We prospectively enrolled a total of 191 CE treatment cycles (involving 152 patients) from January 2021 to February 2022 at Changhua Christian Hospital. After excluding 25 treatment CE cycles with non-compliance or incomplete data, the study ultimately included 166 CE treatment cycles. These cycles were further categorized based on patients' age, previous history of implantation failure, and endometrial sampling pathology report.

Result: Among 166 CE treatment cycles, 56.2% (77/137) was diagnosed as chronic endometritis in prior-implantation failure, and 62.1% (18/29) was diagnosed without prior implantation failure history. The prevalence of CE was higher in cycles with non-prior IF than in those without in the group under 38 years [73.1% (19/26) vs. 53.2% (50/94), $P=.69$]. The cured chronic endometritis in prior-IF and non-IF groups were comparable to those in the non-CE groups [Prior-IF: implantation rate (50% vs 45%, $P=0.56$); Non-prior IF: implantation rate (47.4% vs 27.3%, $P=0.28$)]. The pregnancy outcomes were also comparable to those in the non-CE group if transferring with good quality embryo. Furthermore, there was a 5% reduction in the miscarriage rate in the Cured CE group compared to the CE-negative group; however, no statistically significant difference was found between these two groups.

Conclusion: Chronic endometritis is significantly associated with prior implantation failure in women under 38 years old, but not in aged 38 or older. Importantly, CE with antibiotic treatment significantly improves pregnancy outcomes, especially in patients with a history of prior IF. The evaluation of CE in IF remains inconclusive and requires further investigation.

Isabel Hsu 許嘉樺
(Y13)



The Mid Luteal Progesterone Level and Ratio of Progesterone and Estradiol is Predictive of Pregnancy Outcome in Frozen Embryo Transfer Cycles

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Objective: To investigate the serum P4 level and P4/E2 ratio at mid luteal phase in the prediction of pregnancy outcome in frozen embryo transfer (FET) cycles.

Materials and Methods: This is a retrospective study including 308 women aged 32 to 42 years old undergoing frozen embryo transfer in artificially prepared endometrium with hormone replacement therapy (FET-HRT) cycles conducted between January 01, 2019 and December 31, 2021. The serum E2 and P4 levels at Day 10 of the luteal phase (5 days after blastocyst transfer) and serum P4 level on the day of the pregnancy blood test (12 days after blastocyst transfer) were investigated. Patients with donated oocytes, history of recurrent pregnancy loss, uterine anomalies including endometrial polyps and intrauterine adhesions, untreated hydrosalpinx, thin endometrium, <7mm, and transfer of more than one day 5 blastocyst were excluded. The FET-HRT cycles consisted of oral estradiol valerate with a total daily dosage of 4 to 8mg, taken twice a day starting on day 3 of the cycle, and vaginal micronized progesterone with a total daily dosage of 800mg, administered twice a day starting 5 days before ET. Statistical analysis was conducted by performing logistic regression and t-tests with SPSS. Optimal cutoff value of serum P4 level and P4/E2 ratio in the mid luteal phase for predicting pregnancy outcome was identified with receiver operating characteristic (ROC) curve assessment.

Result: The clinical pregnancy rate was 43.8%, live birth rate was 26.6%, and miscarriage rate was 16.9%. The mid luteal serum P4 level is significantly correlated with pregnancy outcome. According to the ROC curve with AUC of 0.63, the optimal cutoff value of D10 serum P4 level was 16.8 ng/mL for prediction of pregnancy in FET-HRT cycles. Moreover, mid luteal serum P4/E2 ratio is also significantly correlated with pregnancy outcome in FET-HRT cycles. The optimal cutoff value of D10 serum P4/E2 ratio was 0.08 for prediction of pregnancy in FET-HRT cycles, as shown by the ROC curve with AUC of 0.61.

Conclusion: Serum P4 level and P4/E2 ratio in the mid luteal phase are predictive of pregnancy outcome in FET-HRT cycles. Further studies should be conducted to investigate whether or not adding progesterone supplementation can improve pregnancy outcome when mid luteal serum P4 level and P4/E2 ratio are below the optimal cutoff values.

Ming-Ju Wang 王敏如
(Y14)



Diminished ovarian reserve does not impact oocyte and embryo performance in women \leq 40 years old

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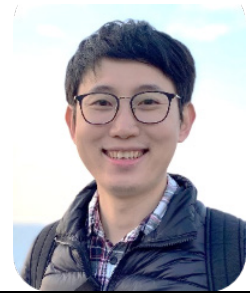
Objective: To retrospectively investigate whether diminished ovarian reserve (DOR), as measured by serum anti-müllerian hormone (AMH), impacts oocyte quality and embryo performance in the cleavage or blastocyst stage or not.

Materials and Methods: We retrospectively reviewed 1707 women aged \leq 40 years who underwent 1862 IVF/ICSI cycles and divided patients into two groups: DOR included the patients with AMH levels lower than 1.2 ng/ml, and non-DOR included the patients with AMH values above \geq 1.2 ng/ml. Ovarian stimulation response till fertilization condition and fresh transfer outcomes were compared between the two groups.

Result: The cancellation rate was significantly higher in the DOR group than in the non-DOR group (12.6% vs 2.2%, $p < 0.001$). The MII oocyte retrieval and available embryos were significantly higher in the non-DOR group than in the DOR group. There were no significant differences in the implantation rates (IR), miscarriage rate (MR) and live birth rate (LBR) in cleavage transfer (IR:20.90% vs 21.59%, $p = 0.787$; MR:18.8% vs 22.3%, $p = 0.543$; LBR:29.3% vs 30.9%, $p = 0.686$) and blastocyst transfer (IR:43.92% vs 44.09%, $p = 0.819$; MR:6.7% vs 15.8%, $p = 0.486$; LBR:48.1% vs 45.1%, $p = 0.758$) between the two groups.

Conclusion: Ovarian reserve, measured by circulating AMH, is correlated with cycle cancellation rate and predicts the recovery of oocytes and available embryos after conventional ovarian hyperstimulation but not oocyte or embryo quality.

Chi-Ting Lai 賴祈廷
(Y15)



The early evolution of gut microbiome in infants born after in vitro fertilization and its association with concurrent oral microbiome

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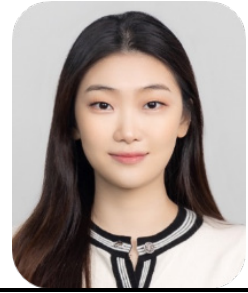
Objective: To investigate the evolution of gut microbiome and its association with concurrent oral microbiome in early infantile life of babies born after in vitro fertilization.

Materials and Methods: A longitudinal cohort study was conducted with a total of 15 babies enrolled during 2019~2022 in a single medical center. Stool samples were collected consecutively in the first five days after birth and oral specimens from saliva and buccal mucosa were obtained within one week after delivery. All three samples continued acquisition at the end of 1st, 2nd, 4th and 6th months. The microbiota of stool, saliva and buccal mucosa were investigated by 16S rRNA gene profiling. Alpha diversity was calculated for comparison of microbial complexity at different time points and from various sampling sites. The abundance trends of the shared genera between oral and gut ecosystems were analyzed to investigate their correlation.

Result: Enterobacteriaceae rapidly surpassed other gut pioneers (Bacteroides, Prevotella and Ruminococcaeae) and sustainably dominated this ecosystem through the time. Meanwhile, Bifidobacterium gradually rose in abundance since the 1st month after delivery. The compositions of salivary and buccal mucosal microbiome were similar in majority. Streptococcus were dominant among oral species at all times, while Veillonella and Gemellaceae were late colonizers. There were rises in the alpha diversity of stool and salivary microbiota as infants' age increased, particularly after weaning commenced, but that was not apparent in buccal mucosa. The alpha diversity of stool microbiota before weaning was closer to that of buccal mucosa but lower than saliva. Most of the gut and oral microbiota evolved independently, whereas the oral Rothia, Prevotella and Veillonella were involved in the development of gut microbiota as seeding species.

Conclusion: This study offered a piece of knowledge on the distinctive constitution and evolution of gut and oral microbiome as well as their mutual correlation in different postpartum stages. Besides, the demonstration of oral seeding species affecting gut microbiota might provide new therapeutic strategies in treating early life intestinal dysbiosis.

Jaekyung Lee
(Y16)



Catheter-Directed Sclerotherapy for Endometrioma; studies over the years and future prospectives

Objective: To review studies conducted for catheter-directed sclerotherapy(CDS) on patients with endometrioma and future prospectives.

Methods: Retrospective, observational study. Electronic medical records and images of patients with endometrioma who underwent CDS from August 2014 to December 2022 at Severance Hospital were obtained. Cyst diameter, laterality, AMH level, and CA- 125 level before and after 1 month, 6 months, 1 year, 2 years, and 3 years of sclerotherapy were obtained.

Results: Early study, with 14 participants that was published in 2018, evaluated the short-term effect of CDS revealed the decrease in mean endometrioma size, pain symptom, CA-125 level with no recurrence, complication and change in serum AMH level. In 2020, a study compared 51 patients who had laparoscopic ovarian cyst enucleation for endometrioma and 20 patients who had CDS for endometrioma. The hospital stay was shorter with CDS than with surgery. There was no significant difference in serum AMH levels before and after CDS, but there was a significant decrease in serum AMH in the surgery. Thus, we hypothesized that CDS for endometrioma would be beneficial for patients with endometrioma who are at high risk for ovarian damage when laparoscopic surgery is performed. These indications would include patients with already decreased ovarian reserve before treatment, patients with recurrent endometrioma who had prior surgery, and patients with large sized endometrioma. In 2022, we published an article that analyzed 14 patients with AMH level less than 2.0ng/mL, who are at risk for decreased ovarian reserve, who underwent CDS for endometrioma. The mean cyst size on ultrasonography and serum CA-125 levels decreased 6 months after CDS. All patients reported a decreased visual analog scale score for dysmenorrhea. However, the difference in serum AMH levels before and after CDS was statistically insignificant. Also, we evaluated the effect of CDS in patients with recurrent endometrioma and compared with patients with primary endometrioma. There was no significant difference in delta value of AMH after sclerotherapy in both groups at each follow- up period. Also, this result was consistent when stratified by laterality, preprocedural AMH level, and initial size of endometrioma. No case of recurrence was reported in both groups.

Conclusion: CDS for endometrioma is efficacious in relieving symptoms related to endometrioma, and CA-125 level without having deleterious effect on ovarian reserve. It is also proven its safety in patients who are at high risk for ovarian damage when laparoscopic surgery is performed, such as patients with already decreased ovarian reserve before treatment, patients with recurrent endometrioma who had prior surgery. Current studies are in progress with focus on its effect in patients with large sized endometrioma and prospective patient group.

Gyul Jung
(Y17)



Advantages of vNOTES (vaginal Natural Orifice Transluminal Endoscopic Surgery) gynecologic procedure using da Vinci SP

Advancements in gynecologic surgery over the past few decades have transitioned from conventional open procedures to minimally invasive techniques such as laparoscopy, including single-port approaches. vNOTES (vaginal Natural Orifice Transluminal Endoscopic Surgery) represents an innovative and novel surgical technique utilizing a single incision through the vagina, resulting in a scar-less abdomen. This approach is described as versatile, facilitating various gynecologic procedures, including benign myoma/adenomyosis surgery, hysterectomy, ovarian/tubal surgery (oophorectomy, cystectomy), endometrial and uterine cancer surgery, as well as sentinel lymph node surgery for endometrial cancer. The da Vinci SP (dvSP) robotic surgical system emerges as a key player in enhancing vNOTES procedures. In comparison to the da Vinci Xi, dvSP is designed for a single incision, featuring three robotic arms and one camera. This design allows for a more focused and streamlined approach, providing a better view of the camera. The dvSP demonstrates effectiveness in targeting smaller and deeper areas within the abdominal cavity, supported by stronger arm power. This capability is pivotal for achieving precision in gynecologic surgeries, particularly when accessing specific anatomical structures requires advanced maneuverability. This abstract highlights some advantages of vNOTES surgery using dvSP, showcasing its impact on the field of gynecologic surgery. A video demonstration accompanies this abstract, offering a visual insight into the demonstrated advantages.

Yeong Eun Choi
(Y18)



Spatial Transcriptomic for Investigating Tumor Budding and Immune Microenvironment Dynamics in Uterine Cervical Cancer

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Background: Tumor budding (TB), characterized by small clusters of tumor cells, is recognized as an adverse histomorphological biomarker in uterine cervical cancer. While TB likely exhibits epithelial-mesenchymal transition traits, the biological characteristics of TB within the tumor-immune microenvironment (TIME) remain unexplored. This study aimed to investigate the biological properties of TB and its interaction with the coordinated immune cells in cervical cancer.

Method: We employed GeoMx digital spatial profiling (nanosttring) on tissue microarrays containing 34 cases of uterine cervical cancer to analyze transcriptomic expression within TB histology in the context of the TIME. Of these cases, 24 demonstrated high TB (≥ 4 peripheral TB/10HPFs), while 10 had low TB. To specifically assess transcriptional changes related to the TIME, we examined cytokeratin-positive (PanCK+) and immune cell-positive (CD45+ and CD68+) compartments within each region of interest (ROI) separately.

Results: A set of significantly intersecting genes was selected. As an overview, we visually represented 44 genes in unsupervised clustered heatmaps per compartment, TB status, and disease progression. We identified a subset of distinct genes through differential gene expression linked to disease recurrences, persistently exhibiting their distinctive biological characteristics even in cases with low TB. Pathway enrichment analysis was conducted using Wikipathways databases. Enrichment scores revealed coordinated transcriptomic alterations in the epithelial and immune cell segments of most TB histology AOIs from patients with disease recurrence. These alterations included the activation and regulation of the complement cascade, interleukin-4 and interleukin-13 signaling pathways, keratin dysregulation, and lipid metabolism. Specific gene sets exhibited distinct changes and coordination across TB histology and TIME contexts, suggesting their potential as significant biomarkers for predicting disease recurrence.

Conclusion: Through the application of DSP, we conducted a comprehensive multi-region transcriptomic profiling to unravel the biological properties and contributions within specialized tumor budding histology regions within the TIME of cervical cancer.

Kentaro Ishida
(Y19)



A Retrospective Analysis of the Efficacy of Bevacizumab Maintenance on the Histopathological Mesenchymal Subtype of High-grade Serous Ovarian Carcinoma

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Objective: High-grade serous ovarian carcinoma (HGSC) is classified into four transcriptome subtypes (mesenchymal, immunoreactive, proliferative, and differentiated) by the Cancer Genome Atlas project. Recently, we have developed a new histopathological classification for HGSC, which corresponds to the transcriptome subtypes. These are Mesenchymal Transition (MT), Immune Reactive (IR), Solid and Proliferative (SP), and Papillo-Glandular (PG) types. Although bevacizumab (Bev) extends the prognosis in high-risk patients, its impact on these specific histopathological subtypes has not been explored. Therefore, this study aims to evaluate the prognostic efficacy of Bev maintenance therapy, specifically in the MT and mesenchymal subtypes.

Methods: We retrospectively reviewed medical records for advanced HGSC patients treated at our hospital from 2012 to 2017. These patients were divided into two groups: those who received standard chemotherapy with or without Bev. The histopathological classification was performed using hematoxylin and eosin-stained slides of HGSC. The overall survival (OS) and progression-free survival (PFS) were evaluated to compare the efficacy of standard chemotherapy with or without Bev in the MT or non-MT subtypes. Additionally, we analyzed the ICON7 dataset (GSE140082), which includes gene expression subtype annotations, to determine Bev's survival impact across these subtypes.

Results: Of the 50 patients included, 25 were in the MT and 25 in the non-MT subtype. The MT subtype showed a longer OS in the Bev group (n=9) than in the standard chemotherapy group (n=16) ($p=0.049$; median, not reached(NR) vs 34 months; HR=0.058; 95% CI=0.0038-0.8771). However, no significant differences in OS were observed in the non-MT subtype ($p=0.12$; median, 41 months vs NR; HR=5.389; 95% CI=0.49– 59.5). In the GSE140082 dataset, among 43 advanced HGSC patients with the mesenchymal subtype, a better OS was noted in those treated with Bev (n=20) compared to standard therapy (n=23) ($p=0.037$; median, NR vs 26.4 months; HR=0.23; 95% CI=0.059– 0.859). In 149 patients with non-mesenchymal patients, bev (n=77) also extended OS ($p=0.02$; median, NR vs 34 months; HR=0.52; 95% CI=0.275– 0.981) than standard therapy (n=72), suggesting that bev had more efficacy on the mesenchymal subtype in terms of lower HR.

Conclusion: Bev prolonged the survival of high-risk patients with the MT and mesenchymal subtype.

Shao-Jing Wang 王韶靖
(Y20)



Outcomes of “sandwich” chemoradiotherapy compared with chemotherapy alone for the adjuvant treatment of FIGO stage III endometrial cancer

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Objective: To analyze and compare outcomes of adjuvant chemoradiotherapy in patients with International Federation of Gynecology and Obstetrics (FIGO) stage III endometrial cancer (EC) patients using the “Sandwich” sequence and chemotherapy (CT) alone.

Methods: From, 2005 to, 2019, we retrospectively reviewed 80 patients with FIGO stage III EC who received treatment at our institute. We analyzed 66 patients who had undergone complete surgical staging followed by adjuvant treatment with sandwich chemoradiotherapy (39 patients) and CT alone (27 patients). The 5-year overall survival (OS), progression-free survival (PFS), and disease-specific survival (DSS) were calculated using the Kaplan– Meier method. Additional prognostic factors were analyzed using Cox proportional hazards regression.

Results: Herein, the analysis was conducted using 66 patients with a median follow-up period of 50 and 85 months in the sandwich and CT-alone arms. Comparing the sandwich sequence and CT-alone groups, the 5-year OS and PFS were 87% vs. 70% ($p = 0.097$) and 77% vs. 65% ($p = 0.209$), respectively. The sandwich therapy conferred an improved 5-year DSS (92% vs. 70%, $p = 0.041$) and a lower local recurrence rate (0% vs. 11%, $p = 0.031$). In multivariable analyses, grade 3 histology and deep myometrial invasion were independent risk factors for 5-year OS and DSS. The sandwich sequence was a positive predictor for 5-year DSS (hazard ratio [HR] = 0.23, $p = 0.029$). The sandwich arm demonstrated higher acute hematologic toxicity than the CT-alone arm. CT dose delay/reduction and treatment completion rates were similar in both groups.

Conclusion: For patients with stage III EC, postoperative sandwich chemoradiotherapy appears to offer a superior 5-year DSS and local control with tolerable toxicity when compared with CT alone.