Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
MATERNAL THROMBOCYTOPENIA DUE TO INFLAMMATORY CHANGES IN THE PLACENTA PRECEDES FETAL DEATH ASSOCIATED WITH COVID-19

Akihito Sagara 1, Munekage Yamaguchi 1, Saori Yoshimura 1, Chisato Kodera 1, Takashi Ohba 1, Eji Kondoh 1. 1Department of Obstetrics and Gynecology, Faculty of Life Sciences, Knamoto University

Introduction: Acute coagulopathy, specific placentental change, and fetal death are reported in pregnant women with COVID-19; however, the pathogenesis of them remains unknown. We report two cases of stillbirth in pregnant women with COVID-19 who showed acute coagulopathy and their placentas showed characteristic pathological findings due to COVID-19.

Case: Case 1: A 28-year-old pregnant woman (gravida 3, para 2) who had undergone two cesarean sections had a fever of 39 degree and was positive for SARS-CoV-2 at 26 weeks of gestation. She showed thrombocytopenia and subsequent coagulopathy on day 7, and her fetus was dead on day 9. She underwent a cesarean section after blood transfusion and her coagulability thereafter improved. Case 2: A 35-year-old pregnant woman (gravida 3, para 2) who had no symptoms was positive for SARS-CoV-2 at 20 weeks of gestation. She also presented with thrombocytopenia on day 5. Her fetus was dead, and she went into labor spontaneously and virginally delivered a stillborn baby on day 9. Her coagulability thereafter returned to normal. Placentental histology of both cases showed intervillosus infiltration of histiocytes, necrosis of trophoblast, and fibrin deposition, and the expression of SARS-CoV-2 spike protein was observed in the syncytiotrophoblasts of the villi.

Discussion: Specific placentental changes related to COVID-19 are thought to be the result of an immune response rather than direct infection with SARS-CoV-2. The placentational changes induced by COVID-19 might have caused fetal death. When managing pregnant women with COVID-19, thrombopoenia may be a predictive marker of fetal death following placentental inflammatory changes.

THE PRODUCTION OF ANGIOGENIC AND ANTIANGIOGENIC FACTORS VIA THE ACTIVATION OF PROTEIN KINASE C IN THE PLACENTA OF PREGNANT DIABETIC MICE

Takashi Mitsui 1, Sakurako Mishima 1, Kazumasa Tanii 1, Hisashi Masuyama 1. 1Department of Obstetrics and Gynecology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Objective: Abnormal glucose metabolism during pregnancies is a risk factor for preeclampsia (PE). Disruption of the balance between angiogenic and antiangiogenic factors is linked to PE pathogenesis. The activation of protein kinase C (PKC) is intimately involved in the development of diabetic angiogenic complications and angiogenesis, and might be involved in the production of angiogenic and antiangiogenic factors in the placenta of pregnant women complicated with abnormal glucose metabolism. Therefore, we examined the production of angiogenic and antiangiogenic factors via the activation of PKC in the placenta of pregnant diabetic mice.

Methods: In pregnant diabetic mice (BKS.Cg-Dock7m+/+Leprdb/J) and pregnant control mouse (C57BL/6), blood were collected on day 15.5 of gestation days, and placentas were removed. PKC activity in the placenta was compared. Regarding angiogenic and antiangiogenic factors, soluble fms-like tyrosine kinase-1 (sFlt-1) and placentental growth factor (PIGF) in placentas were measured by quantitative PCR and compared. In addition, sFlt-1 and PIGF in plasma were measured by ELISA and compared between pregnant diabetic mice and pregnant control mice.

Results: PKC activity and mRNA expression of sFlt-1 was significantly increased in the placenta of pregnant diabetic mice compared to pregnant control mice. In plasma of pregnant diabetic mice, sFlt-1 was significantly increased compared to pregnant control mice. Conclusion: The activation of PKC might be involved in the production of angiogenic and antiangiogenic factors in the placenta of pregnant diabetic mice. These changes effect disruption of the balance between angiogenic and antiangiogenic factors, and might be involved in the development of PE in pregnant women complicated with abnormal glucose metabolism.

SUBSETS OF INFILTRATING LYMPHOCYTES AROUND SPIRAL ARTERIES WITH OR WITHOUT REMODELING IN HYPERTENSIVE DISORDERS OF PREGNANCY

Ayako Tateishi 1, Hiyori Kanno 1. 1Department of Pathology, Shinshu University School of Medicine

Objective: Hypertensive disorders of pregnancy (HDP) is assumed to be triggered by incomplete remodeling of the spiral arteries. We examined whether there are any differences in the immune circumstances around spiral arteries between remodeled artery (RA) and non-remodeled muscular artery (MA).

Methods: One hundred seventy three cases of HDP diagnosed at the Shinshu University Hospital between 2008 and 2017 were collected. As 16 cases of control group, during same period, we selected cases of normal course of delivery, and cases of premature birth after 35 weeks without pathological changes and abnormalities in the pregnancy course. We identified spiral artery (SA) in the placential tissue, and classified into acute atherosclerosis (AA), MA, and RA. Infiltrating lymphocytes around these arteries were evaluated for CD3, CD8, and CD56 by immunohistochemistry. Result: AA was observed in 55 cases (31.8%). In HDP cases with AA, the density of CD3+/CD8+ T cells, and CD3+/CD8+ (almost CD4) T cells were higher around AA than that around RA and MA. CD56+ NK cells were more abundant around AA and MA than around RA. In control cases, the density of CD3+/CD8+ ( almost CD4) T cells was higher around MA than that around RA, and there was no difference in CD56+ NK cells. Between HDP cases with AA and control cases, there was no difference in the density of CD3+/CD8-/CD4- T cells and CD56+ NK cells around RA.

Conclusion: Both in HDP cases and in control cases, the density of CD3+/CD8- (CD4-) T cells was higher around non-remodeled spiral arteries such as MA and AA than that around RA. This finding suggests that CD4+ T cell may play a role in SA remodeling.

STRUCTURAL CHARACTERISTICS OF EXOSOMES AND NANOPARTICLES DERIVED FROM TROPHOBLAST CELL LINE BEWO

Shohei Tozawa 1,2, Syunya Noguchi 1, Takanoobu Sakurai 1, Akihide Ohkuchi 1, Hironori Takahashi 2, Hiroiuki Fujirwara 2, Toshihiro Takizawa 1. 1Department of Molecular Medicine and Anatomy, Nippon Medical School; 2Department of Obstetrics and Gynecology, Jichi Medical University

Objective: Exosomes play an important role as carriers for protein and nucleic acid delivery in cell-cell communication. Nanoparticles, non-membranous particles, have recently been reported to function as newly carriers. In this study, we performed morphological and biochemical analysis of exosomes and nanoparticles derived from trophoblast cell line BeWo.

Methods: Exosomes and supernatant fraction were separated from BeWo conditioned medium by the traditional ultracentrifugation method. Nanoparticles were then collected by ultracentrifugation of the supernatant fraction. Structural analyses of exosomes and nanoparticles were performed by electron microscopy and nanoparticle tracking analysis. After total protein and RNA from the samples were extracted, Western blot (exosome marker CD63 and nanoparticle marker AGO2) and real-time PCR (e.g., placenta-specific miRNA mir-517a-3p) were carried out.

Results: BeWo exosomes were round or oval vesicles (average size: 53 nm), while nanoparticles were piling-like, non-membranous particles (26 nm). Exosomes were positive for CD63 but not for AGO2. In contrast,