decreased the production of sFlt-1 protein in the placentas of pre-eclampsia-like diseased mice.
Conclusion: r-TM as an anticoagulation therapy has the potential for the medical treatment of recurrent miscarriage and fetal growth restriction due to improved angiogenic factors. Additionally, r-TM treatment has the potential for the recovery of placental insufficiency and preeclampsia.

S-03.
THE PRODUCTION OF ANGIOGENIC AND ANTIANGIOGENIC FACTORS VIA THE ACTIVATION OF PROTEIN KINASE C IN THE PLACENTA UNDER HIGH-GLUCOSE CONDITIONS

Takashi Mitsui, Sakurako Mishima, Akiko Ohira, Kazumasa Tani, Jota Maki, Shoko Tamada, Eriko Eto, Kei Hayata, Hisashi Masuyama. *Department of Obstetrics and Gynecology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayam, Japan*

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. In high-glucose conditions such as a diabetes, a large amount of glucose incorporated into cells activate protein kinase C (PKC). The activation of 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 under high-glucose conditions.
Methods: In the human trophoblast cell line HTR-8/SVneo cultured with high-glucose conditions, PKC activity was examined. Regarding angiogenic and antigenic factor, the mRNA expressions of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) were examined by real-time RT PCR. In pregnant diabetic mice (KK/TaJcl) and pregnant control mice (C57BL/6), placentas were removed on day 15 of gestation days, and blood were collected. PKC activity in placentas were compared between pregnant diabetic mice and pregnant control mice. Regarding angiogenic and antiangiogenic factors in plasma, sFlt-1 and PlGF were measured by ELISA and compared between pregnant diabetic mice and pregnant control mice.
Results: In high-glucose conditions, PKC activity was increased, and mRNA expressions of sFlt-1 and PlGF were also significantly increased. In placentas of pregnant diabetic mice, PKC activity was significantly increased. sFlt-1 was significantly increased in plasma of pregnant diabetic mice compared to pregnant control mice.
Conclusion: The activation of PKC might be involved in the production of angiogenic and antiangiogenic factors in the placenta under high-glucose conditions. 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.

S-04.
AUTOPHAGY SUPPRESSION CAUSED BY ATG4B OVEREXPRESSION LEADS TO PREECLAMPSIA WITH FETAL GROWTH RESTRICTION

Tae Kusabiraki, Akitoshi Nakashima, Aiko Aoki, Shigeru Saito. *Department of Obstetrics and Gynecology, University of Toyama*

Objective: Poor placentation is a common feature between fetal growth restriction without PE (FGR) and preeclampsia with FGR (PE w FGR). However, no one knows the differences between them in the pathophysiology. We aim to study the autophagy status in placental tissues.
Methods: Phosphorylated p62 (p-p62), an autophagy failure marker, and ATG4B, a protease that processes pro-LC3 paralogues, were immunostained in placental tissues obtained from normal pregnancies (NP), FGR, PE w/o FGR and PE w FGR. Two trophoblast cell lines, and human placental tissues were used.
Results: Bafilomycin A1, an autophagy inhibitor, increased p-p62 protein levels in placental tissues. Immunohistochemical analysis showed that the rate of p-p62 was significantly higher in PE w FGR than the other groups in EVT and syncytiotrophoblast cells, suggesting the autophagy inhibition in the PE w FGR placentas. To further clarify the mechanism of autophagy inhibition in PE w FGR, autophagy-related proteins were comprehensively compared among PE w FGR, FGR, and NP by western blot. Remarkable upregulation was seen in ATG4B as well as p-p62 in PE w FGR. Finally, overexpression of ATG4B introduced by adenovirus vector completely blocked the activation of autophagy in a dose-dependent manner in TCL1 cells.
Conclusion: ATG4B has been reported to contribute to the activation of autophagy so far. This study, however, newly found that overexpression of ATG4B led to autophagy suppression in human trophoblasts. In addition, autophagy was more inhibited in PE w FGR than FGR. For our future tusk, autophagy activation, by which ATG4B is downregulated in placental tissues, might develop a specific-treatment for PE w FGR.