sFLT1 in preeclampsia: HIF2α, but not HIF1α, is a possible major player in the hypoxic response in trophoblasts of placenta.

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Preeclampsia is known to occur about 5% of pregnancy, and gradually increasing due to a higher aging of pregnant women. Recently, one of the anti-angiogenic molecule, sFLT1, a soluble form of FLT1 (Fms-like tyrosine kinase-1/Vascular Endothelial Growth Factor receptor-1/VEGFR1) was shown to abnormally increased in maternal blood of PE, suggesting that it may be an important player for inducing major clinical problems, hypertension and proteinurea at maternal side, and growth retardation at embryonic side. In 1990, we firstly isolated a new gene in humans, named it as Fms-like tyrosine kinase: Flt-1, and have been working for 30 years on its expression-regulatory mechanism and characteristics of this protein.

To detect sFLT1 in serum, classical ELISA is a little time consuming and high cost. To overcome these problems, we recently developed a simple detection method, new ELISA, using a single anti-sFLT1 antibody and heparin-bearing beads, and showed that severe PE serum has about 6-fold higher sFLT1 compared with those in normal pregnancy similar to the previous reports.

Another important question of PE is the molecular mechanism for the upregulation of sFLT1 in the blood of PE patients. One of the crucial factors are suggested to be hypoxic stress around the placenta. To clarify the factor(s) involved in this process, we used trophoblast-derived tumor cell lines (BeWo, JAR and JEG3) and primary human placental trophoblasts, and examined which transcriptional factor(s) are involved in upregulation of sFLT1. In general, HIF1α is mostly used in hypoxic responses in many tissues and cells. Surprisingly, however, we found that HIF2α, together with HIF1β, plays a major role in the upregulation of sFLT1 in these cells. Thus, our results suggest that HIF2α could be a novel therapeutic target for PE. About one year ago, in cancer research field, new chemical, HIF2α inhibitor Belzutifan (PT2977, MK6482), was approved by the FDA in U.S.A, for the treatment of renal cancer. An appropriate HIF2α inhibitor will hopefully be developed soon for the treatment of PE. We are currently establishing a useful screening system for it.