UKE Paper of the Month April 2015
J Clin Invest (2015) 125(4):1726-38

Progesterone and HMOX-1 promote fetal growth by CD8+ T cell modulation
María Emilia Solano, Mirka Katharina Kowal, Greta Eugenia O'Rourke, Andrea Kristina Horst, Kathrin Modest, Torsten Plösch, Roja Barikbin, Chressen Catharina Remus, Robert G. Berger, Caitlin Jago, Hoang Ho, Gabriele Sass, Victoria J. Parker, John P. Lydon, Francesco J. DeMayo, Kurt Hecher, Khalil Karimi, Petra Clara Arck

ABSTRACT: Intrauterine growth restriction (IUGR) affects up to 10% of pregnancies in Western societies. IUGR is a strong predictor of reduced short-term neonatal survival and impairs long-term health in children. Pla-cental insufficiency is often associated with IUGR; however, the molecular mechanisms involved in the pathogenesis of placental insufficiency and IUGR are largely unknown. Here, we developed a mouse model of fetal-growth restriction and placental insufficiency that is induced by a midgestational stress challenge. Compared with control animals, pregnant dams subjected to gestational stress exhibited reduced progesterone levels and placental heme oxygenase 1 (Hmox1) expression and increased methylation at distinct regions of the placental Hmox1 promoter. These stress-triggered changes were accompanied by an altered CD8+ T cell response, as evidenced by a reduction of tolerogenic CD8+CD122+ T cells and an increase of cytotoxic CD8+ T cells. Using progesterone receptor– or Hmox1-deficient mice, we identified progesterone as an upstream modulator of placental Hmox1 ex-pression. Supplementation of progesterone or depletion of CD8+ T cells revealed that progesterone suppresses CD8+ T cell cytotoxicity, whereas the generation of CD8+CD122+ T cells is supported by Hmox1 and ameliorates fetal-growth restriction in Hmox1 deficiency. These observations in mice could promote the identification of pregnancies at risk for IUGR and the generation of clinical interventional strategies.

STATEMENT: *In the present publication, we unveiled novel pathways underlying the pathogenesis of IUGR, such as reduced progesterone levels, low placental Hmox1 expression, epigenetic alterations of the Hmox1 promoter and a dichotomous response of CD8+ T cell subsets. We introduced a mouse model of fetal-growth restriction triggered by prenatal stress challenge, which allowed us identify the hierarchical in-teraction of these pathways in the pathogenesis of IUGR. These novel insights have pivotal clinical implications, as the detection of low levels of progesterone or a skewed CD8+ T cell response prior to the onset of IUGR in human pregnancies could allow the early identification of pregnancies at risk for IUGR. Once these pregnancies are identified, therapeutic interventions aiming to prevent or ameliorate IUGR can be envisioned, such as progesterone supplementation to restore placental HMOX-1 expres-sion.*

BACKGROUND: Whilst the findings presented here were largely generated by Dr. Solano in the Laboratory for exp. Feto-Maternal Medicine under the supervision of Prof. Petra Arck, the present insights would not be available to this extent without the support of UKE collaborators from various interdisciplinary are-as. These local collaborators were based at the Institute of Experimental Immunology and Hepatology and the Department of Diagnostic and Inter-ventional Radiology. Some of the hormonal assessments were performed in international collaborations, including scientists at the Baylor College in Houston, TX, and the University of Edinburgh. The study was funded by research grants provided by the German Research Foundation, the Werner-Otto Foundation and the Foundation for Research and Science in Hamburg.