0031-3998/03/5304-0537
PEDIATRIC RESEARCH

Vol. 53, No. 4, 2003
Printed in U.S.A.

RESEARCH NEWS

Understanding Fetoplacental Growth Through Transgenic IGF Models

A review of: Crossey PA, Pillai CC, Miell JP 2002 Altered placental development and intrauterine growth restriction in IGF binding protein-1 transgenic mice. J Clin Invest 110:411–418

BARBRA DE VRIJER
TIMOTHY R.H. REGNAULT
RUSSELL V. ANTHONY

RECENT UNICEF STATISTICS indicate that 14% of newborns worldwide weigh less than 2.5 kilograms at birth, and it is thought that this may well be an underestimate due to the lack of birth weight data in developing countries. Of this group of small for gestational age infants, 70–80% display an asymmetrical fetal growth restriction (FGR), generally a result of placental insufficiency. Interest in the development of these FGR fetuses has been enhanced by retrospective human clinical studies that suggest consequences into adult life, including a higher incidence of hypertension and diabetes, presumably as a result of impaired oxygen and nutrient transport *in utero* (1). The insulin-like growth factors, IGF-I and IGF-II, and the interactions with their binding proteins (IGFBPs) play important roles in regulating placental and fetal development (2). Recently, the role of IGFBP-1 in the development of the placenta and its pathological role in preeclampsia has been examined in a mouse model of decidual IGFBP-1 overexpression (3).

An important aspect of early placental development is trophoblast invasion and its regulation by IGFBP-1. The overexpression of decidual IGFBP-1 in the report of Crossey *et al.* (2002) confirms that IGFBP-1 has marked effects early in pregnancy (3). Early deficits in fetal growth are overcome as gestation advances, occurring as placental weights increase. Increased placental weights, however, do not result in fetal weights greater than control fetuses at e17.5, suggesting possible alterations in placenta metabolism and function. Potential interactions between decidual IGFBP-1 overexpression and IGF-I and IGF-Type I receptor expression await further study.

While overexpression studies provide insight into tissue-specific activities, comparisons made to human disease states such as pre-eclampsia must carefully consider the pathology of that disease. For example, in the report of Crossey *et al*. (2002), it is suggested that elevated IGFBP-1 levels play a pathological role in the development of pre-eclampsia (3). However, a recent study highlighted that term pre-eclamptic basal plate decidua contains significantly less IGFBP-1 mRNA (4), suggesting that reported increases in maternal circulating concentrations of IGFBP-1 in late-gestational pre-eclampsia are not of decidual origin. Furthermore, low levels of IGFBP-1 have been suggested to predict the onset of pre-eclampsia as early as week 16 of human pregnancy (5).

In addition, possible species differences need to be taken into account. In primates, decidual IGFBP-1 expression is normally high in early pregnancy, regulating the actions of trophoblastic IGF-II at the fetomaternal interface during implantation and placental development. However, decidual expression of the IGFBPs is absent in rodents, and expression is limited to the myometrium. IGFBP-1-like actions observed in rodent pregnancy have been attributed to decidual α_2-macroglobulin, which can also bind IGFs (6).

Discrepancies which exist between data from human pregnancies and those derived from transgenic animal models highlight the difficulty in extrapolating between species in terms of explaining aspects of FGR and pre-eclampsia. However, these models do provide an excellent starting point from which to study the role peptides play in specific components of placental invasion and function, and their role in the cascade of events that finally results in disease.

1. Barker DJ, Bull AR, Osmond C, Simmonds SJ 1990 Fetal and placental size and risk of hypertension in adult life. BMJ 301:259–262
2. Han VK, Bassett N, Walton J, Challis JR 1996 The expression of insulin-like growth factor (IGF) and IGF-binding protein (IGFBP) genes in the human placenta and membranes: evidence for IGF-IGFBP interactions at the feto-maternal interface. J Clin Endocrinol Metab 81:2680–2693
3. Crossey PA, Pillai CC, Miell JP 2002 Altered placental development and intrauterine growth restriction in IGF binding protein-1 transgenic mice. J Clin Invest 110:411–418
4. Gratton RJ, Asano H, Han VK. 2002 The regional expression of insulin-like growth factor II (IGF-II) and insulin-like growth factor binding protein-1 (IGFBP-1) in the placentae of women with pre-eclampsia. Placenta 23:303–310
5. DeGroot CV, O'Brien TJ, Taylor RN 2002 Biochemical evidence of impaired trophoblast invasion of decidual stroma in women destined to have pre-eclampsia. Am J Obstet Gynecol 175:24–29
6. Correia-da-Silva G, Bell SC, Pringle JH, Teixeira N 1999 Expression of mRNA encoding insulin-like growth factors I and II by uterine tissues and placenta during pregnancy in the rat. Mod Reprod Develop 53:294–305

Department of Pediatrics
Division of Perinatal Medicine
University of Colorado Health Sciences Center
Aurora, Colorado, U.S.A.
Russell.Anthony@UCHSC.edu

DOI: 10.1203/01.PDR.0000063362.91000.AB