The Role of Mammalian Target of Rapamycin in the Regulation of Amino Acid Transporters in the Human Placenta

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I. **Roos S**, Powell TL & Jansson T. (2004). **Human placental taurine transporter in uncomplicated and IUGR pregnancies: cellular localization, protein expression, and regulation.** *Am J Physiol Regul Integr Comp Physiol* 287, R886-893.

II. **Roos S**, Jansson NL, Palmberg I, Säljö K, Powell TL & Jansson T. (2007). **Mammalian target of rapamycin in the human placenta regulates leucine transport and is down-regulated in restricted fetal growth.** *J Physiol* 582, 449-459.

III. **Roos S**, Kanai Y, Prasad PD, Powell TL & Jansson T (2008). **Regulation of placental amino acid transporter activity by mammalian target of rapamycin.** *Am J Physiol Cell Physiol; DOI:101152/ajpcell003302008*.

IV. **Roos S**, Lagerlöf O, Wennergren M, Powell TL & Jansson T (2008). **Regulation of amino acid transporters by glucose and growth factors in cultured primary human trophoblast cells is mediated by mTOR signaling.** *Submitted.*

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ABSTRACT

Abnormal fetal growth, which is associated with both perinatal morbidity as well as metabolic diseases in adulthood, is an important clinical problem affecting as many as 15% of all pregnancies. However, to this date, there is no specific treatment of this condition. Fetal growth is intimately linked to the nutrient transport functions of the placenta and placental amino acid transporter activity is known to be altered in cases of abnormal fetal growth. Therefore, detailed information on the mechanisms regulating placental amino acid transporters will increase our understanding of how abnormal fetal growth develops and may provide new targets for therapeutic intervention.

The focus of this study was to identify factors, such as hormones and growth factors, regulating three key amino acid transporters in the human placenta; system L, system A, and system β. The central hypothesis was that mammalian target of rapamycin (mTOR) signaling regulates placental amino acid transporters in the human placenta in response to nutrient availability and growth factors such as insulin and IGF-I. To test this hypothesis, we have used cultured primary trophoblast cells, primary villous fragments, and homogenates, all from the human placenta, to study the regulation of amino acid transport.

We show that the mTOR signaling pathway constitutes an important positive regulator of the placental amino acid transporters system A, system L, and the taurine transporter (system β). Furthermore, we demonstrate that these amino acid transporters are regulated by nutrients, such as glucose, and growth factors, such as insulin and IGF-I, in an mTOR dependent manner. Placental mTOR activity was found to be decreased in intrauterine growth restriction (IUGR), which may explain the down-regulation of placental amino acid transporters in this pregnancy complication.

We propose a model in which placental mTOR functions as a nutrient sensor linking maternal nutrient and growth factor concentrations to amino acid transport in the placenta. Since fetal growth is critically dependent on placental nutrient transport, these data suggest that placental mTOR signaling plays an important role in the regulation of fetal growth.

The regulation of amino acid transport is important not only in the placenta. Our results were obtained in primary human tissue fragments and cells from the placenta, however, we believe that findings in this study are also relevant for other human tissues such as the skeletal muscle and liver. Furthermore, the growth of many tumor cells is dependent on a high expression of amino acid transporters and detailed information on the mechanisms of regulation of these transporters may facilitate the development of new interventions.

Keywords: amino acids, fetal growth restriction, human, mammalian target of rapamycin, membrane transporters, metabolism, placenta, pregnancy, system A, system L, taurine transporter

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