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Skeletal Muscle of the Fetus: A Window on the Cellular Basis of Intrauterine Growth Restriction

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Intrauterine growth restriction (IUGR) is a vexing problem in translational science. Small babies are at greater risk for cardiac and cardiometabolic disease later in life (1). We trust that having a better understanding of the biological underpinnings of IUGR will increase the likelihood that we can manipulate fetal growth rate in utero and avoid the morbidities associated with low birth weight. Recent work by Stremming, Jansson, Powell, Rozance, and Brown in the current edition of this journal ("Reduced Na+K+-ATPase activity may reduce amino acid uptake in IUGR fetal sheep muscle despite unchanged ex vivo amino acid transporter activity") reveals that IUGR is associated with changes in cellular ATP utilization and transmembrane ion gradients that could explain reduced muscle growth in the IUGR fetus (2). Skeletal muscle of the IUGR fetus has a lower intracellular ATP content and a lower cellular Na/K ATPase activity. Decreased cellular amino acid uptake is a downstream effect of the decreased Na/K ATPase activity.

The model of IUGR used in this study is a well-established model of early pregnancy heat stress exposure in the sheep (3). Exposure of the pregnant ewe to a limited period of increased environmental heat changes the course of development of the placenta, effectively reducing the size and exchange capacity. This model of IUGR is characterized by a mild fetal hypoxia relative to an unmanipulated pregnancy, reduced amino acid and glucose flux from mother to fetus, and asymmetric growth restriction of the fetus (increased ratio of brain/body weight at birth). Because the model produces an apparent nutrient-restricted IUGR, it is likely to be an accurate model of IUGR in the human, which is also thought to be nutrient-restricted.

Skeletal muscle accounts for a substantial fraction of fetal body weight and glucose and oxygen utilization in late gestation. Because muscle development and growth are such a large proportion of fetal somatic growth overall, the cellular basis of metabolism and growth in fetal muscle is an important window on mechanisms of IUGR. For that reason, pharmacologic manipulation of the cellular physiology of the developing muscle could hold the key to effective therapeutics for IUGR. The question of mechanism with regard to the availability of substrate as an influence on the rate of fetal growth is an important translational question. The present work of Stremming, et al., is consistent with a direct influence of reduced oxygen/substrate supply on the metabolism (and therefore the rate of growth) of muscle, but is also consistent with an indirect endocrine effect of reduced

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circulating concentrations of Insulin-like Growth Factor-1 (IGF-1) (4). Exogenously administered IGF-1 increases fetal somatic growth patterns both prenatally and postnatally in the sheep (5), and may work in part by adjusting Na/K ATPase activity in fetal muscle. The mechanism of growth restriction in IUGR may be a complex interplay between direct and endocrine modulators of cellular function, and a combination of short- and longer-term responses. Nevertheless, a focus on the myocyte gives us a window through which we can better understand the cell biology of growth restriction in a tissue that is quantitatively important to overall fetal growth.

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