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Pancreatic islet hepatocyte growth factor and vascular endothelial growth factor A signaling in growth restricted fetuses

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ABSTRACT

Placental insufficiency leads to intrauterine growth restriction (IUGR) and a lifelong risk of developing type 2 diabetes. Impaired islet development in the growth restricted fetus, including decreased β-cell replication, mass, and insulin secretion, is strongly implicated in the pathogenesis of later life type 2 diabetes. Currently, standard medical management of a woman with a pregnancy complicated by placental insufficiency and fetal IUGR is increased fetal surveillance and indicated preterm delivery. This leads to the dual complications of IUGR and preterm birth – both of which may increase the lifelong risk for type 2 diabetes. In order to develop therapeutic interventions in IUGR pregnancies complicated by placental insufficiency and decrease the risk of later development of type 2 diabetes in the offspring, the mechanisms responsible for impaired islet development in these cases must be determined. This review focuses on current investigations testing the hypothesis that decreased nutrient supply to the IUGR fetus inhibits an intra-islet hepatocyte growth factor – vascular endothelial growth factor A (HGF – VEGFA) feed forward signaling pathway and that this is responsible for developmental islet defects.

1. Intrauterine growth restriction and the pancreatic islet

1.1. Clinical aspects of intrauterine growth restriction (IUGR)

Placental insufficiency and intrauterine growth restriction (IUGR) complicate approximately 4–8% of pregnancies (Platz and Newman, 2008). IUGR is best defined as a failure of the fetus to reach its genetic potential size. The distinction between IUGR patients and those that are simply small for gestational age (SGA) based on their genetic make-up has important implications for short and long term morbidities (Von Beckerath et al., 2013). There are a variety of causes of IUGR, including maternal and placental diseases, as well as idiopathic cases. In the majority of cases, however, decreased placental nutrient and oxygen transfer to the fetus are important pathophysiological features. Current medical management includes close fetal monitoring and delivery of the fetus when the risks associated with continued development in a compromised intrauterine environment are felt to be greater than the risks of induced preterm birth (Zeitlin et al., 2000). This leads to serious complications for the baby including increased perinatal mortality as well as serious short and long term morbidities (Rosenberg, 2008). One of the most worrisome long term consequences of IUGR is an increased risk for developing type 2 diabetes later in life (Hales and Barker, 2001). The development of type 2 diabetes requires both insulin resistance and an inability of the pancreatic β-cell to compensate for this insulin resistance by increasing insulin secretion (Kasuga, 2006). Therefore, the development of the pancreatic islet and β-cell has been the subject of intense investigation (Green et al., 2010). Despite this, gaps in our understanding of the pathogenesis of IUGR limit specific therapies available for women whose pregnancies are complicated by placental insufficiency. Nutritional strategies have produced variable results, including some that actually increased the severity of fetal growth restriction and were associated with higher fetal mortality rates (Brown et al., 2011; Rush et al., 1980). Development of better therapies holds the promise of improving fetal growth, prolonging pregnancy, and decreasing the risk in the offspring of developing adult diseases like diabetes later in life. This review will highlight some of the recent work aimed at understanding the pathophysiology of impaired islet development during IUGR which might inform the design of these improved therapies.

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1.2. Placental insufficiency and impaired pancreatic islet development

In humans, severe placental insufficiency results in persistently decreased oxygen and nutrient transfer to the fetus, including amino acids and notably leucine, as early as the end of the second and beginning of the third trimester. In fact, the degree of impairment in leucine transfer to the fetus directly correlates with the severity of fetal growth restriction in cases of placental insufficiency (Jansson et al., 1998, 2002; Paolini et al., 2001; Marconi et al., 1999). Severe placental insufficiency also results in decreased fetal glucose stimulated insulin secretion when tested during percutaneous umbilical cord blood sampling (Nicolini et al., 1990), and reduced pancreatic islet vascularity and β-cell mass (Van Assche et al., 1977). This contrasts with a morphological analysis of pancreases from less severely growth restricted patients in which no difference was found in β-cell mass (Béringue et al., 2002). The differences between the Van Assche and Beringue studies highlight the important distinction between IUGR fetuses who fail to reach their genetic growth potential due to placental insufficiency from those who are simply small for gestational age based on their genotype (Von Beckerath et al., 2013). This distinction is even more critical to consider when one realizes that there are genetic mutations which result in decreased fetal insulin secretion, decreased fetal growth, and a higher risk for developing diabetes in later life. Loss of function mutations in the gene encoding glucokinase is an important example of such a mutation (Spyer et al., 2001).

1.3. Animal models to study impaired pancreatic islet development during placental insufficiency

While we know some of the structural and functional islet defects that result from IUGR, in humans the mechanisms underlying impaired islet development in IUGR remain unknown. In order to determine these mechanisms, animal models must be used. One such model organism is the pregnant sheep, in which several models of placental insufficiency have been developed (Green et al., 2010; Morrison, 2008). Of these sheep models, one of the best characterized in terms of impaired islet development also is the most severe sheep placental insufficiency model of IUGR available (PI-IUGR) (Green et al., 2010). Experimental placental insufficiency and fetal growth restriction in the PI-IUGR model is established by exposing pregnant sheep to elevated ambient temperatures beginning on approximately days 35–42 of gestation (normal sheep gestation is approximately 148 days) and ending between 105 and 115 days of gestation. Impaired placental function is evident as early as days 95–105 (Limesand et al., 2013; de Vrijer et al., 2006). Decrements in umbilical blood flow, oxygen and nutrient transfer to the fetus, and fetal anabolic hormone concentrations become more prominent as gestation progresses and are associated with asymmetric fetal growth restriction (de Vrijer et al.,. 2004; Limesand et al., 2007; Brown et al., 2012; Galan et al., 2005; Regnault et al., 2007).

Pregnant sheep, and this model in particular, offer several advantages for determining the mechanism by which placental insufficiency impairs fetal islet development and function of the β-cell. These advantages include both similarities to human placental insufficiency and technical features which allow for complex *in vivo* and *in vitro* fetal studies (Green et al., 2010; Jansson et al., 1998; Paolini et al., 2001; Van Assche et al., 1977; Nicolini et al., 1990; Barry and Anthony, 2008; Barry et al., 2008; Brown et al., 2012; Limesand et al., 2005, 2006; Ross et al., 1996; Rozance et al., 2015; Thorn et al., 2013). Development of the human and sheep fetal endocrine pancreas is similar. The transition of pancreatic progenitor cells into more differentiated endocrine cells with mature secretory products, formation of pancreatic islets, and replication of existing endocrine cells within the islet occur at the same gestational stages in both human and sheep fetuses (Green et al., 2010). In addition to developmental similarities, technical advantages include the ability to isolate fetal islet endothelial cells to 95% purity (Rozance et al., 2015). For the current review the most important similarities between human IUGR and our sheep PI-IUGR model are decreased nutrient supply to the fetus including amino acids and leucine, decreased fetal insulin concentrations and glucose stimulated insulin secretion, and decreased islet size and β-cell mass (Green et al., 2010; Limesand et al., 2005, 2006; Ross et al., 1996; Rozance et al., 2015; Thorn et al., 2013). Interestingly, while pancreatic islets are smaller and β-cell insulin content is lower, isolated pancreatic islets from PI-IUGR fetal sheep actually secrete a higher fraction of the cellular insulin present when tested *in vitro* compared to normal fetal sheep (Limesand et al., 2005, 2006). In fact, in the *in vivo* condition hypoxemia and hypercatecholinemia in the fetus play a major role in the suppression of insulin secretion in the PI-IUGR fetus and once the adrenergic signaling is blocked the PI-IUGR islets actually become hyper responsive to glucose stimulation (Rozance et al., 2009; Leos et al., 2010). Fetal hypoxia and hypercatecholinemia in pregnancies complicated by fetal growth restriction (Greenough et al., 1990) might set up the formerly IUGR fetus for increased postnatal insulin secretion leading to apparent hyperinsulinemic hypoglycemia in a subset of these patients once normoxia is established and catecholamine concentrations return to normal (Arya et al., 2013).

In fact, unlike the fairly consistent finding of decreased fetal insulin concentrations and secretion in IUGR, studies of insulin concentrations in the early postnatal period are quite variable (Collins and Leonard, 1984; Collins et al., 1990; Bazaes et al., 2003; Hoe et al., 2006; Wang et al., 2007). As formerly IUGR infants age the incidence of increased adiposity and insulin resistance increases (Hofman et al., 1997; Ong et al., 2000; Mericq et al., 2005). This complicates interpretation of insulin secretion measurements in children and young adults who experienced IUGR, because of the hyperbolic relationship between insulin secretion and insulin sensitivity (Kahn et al., 1993). However, studies that accounted for insulin sensitivity showed impaired insulin secretion in children and young adults who had IUGR during fetal life (Li et al., 2001; Jensen et al., 2002).

2. Hepatocyte growth factor (HGF) and vascular endothelial cell growth factor A (VEGFA) in the pancreatic islet

2.1. HGF and VEGFA in normal islet development

There has been increasing interest in the role of the pancreatic vasculature and paracrine signaling between the β-cell and endothelial cells. The paracrine signals most studied in this context are hepatocyte growth factor (HGF) produced by the endothelial cell and vascular endothelial growth factor A (VEGFA) produced by the β-cell, though they are often studied in isolation from each other. Genetic manipulations that increase islet HGF or VEGFA signaling also increase adult islet vascularity, β-cell mass, and/or insulin secretion (Dai et al., 2003; Garcia-Ocana et al., 2000, 2001; Lammert et al., 2001). When islet HGF or VEGFA signaling is decreased, adult animals develop reduced islet vascularity, β-cell mass, insulin secretion, glucose intolerance, and diabetes (Dai et al., 2005; Kamba et al., 2006; Lammert et al., 2003; Brissova et al., 2006; Mellado-Gil et al., 2011; Reinert et al., 2013). Most currently available literature regarding islet HGF and VEGFA signaling does not directly address the pathogenesis of impaired islet development during placental insufficiency. Furthermore, published studies primarily used genetic and pharmacological inhibition or activation of HGF and