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Treating Diet-Induced Diabetes and Obesity with Human Embryonic Stem Cell-Derived Pancreatic Progenitor Cells and Antidiabetic Drugs

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SUMMARY

Human embryonic stem cell (hESC)-derived pancreatic progenitor cells effectively reverse hyperglycemia in rodent models of type 1 diabetes, but their capacity to treat type 2 diabetes has not been reported. An immunodeficient model of type 2 diabetes was generated by high-fat diet (HFD) feeding in SCID-beige mice. Exposure to HFDs did not impact the maturation of macroencapsulated pancreatic progenitor cells into glucose-responsive insulin-secreting cells following transplantation, and the cell therapy improved glucose tolerance in HFD-fed transplant recipients after 24 weeks. However, since diet-induced hyperglycemia and obesity were not fully ameliorated by transplantation alone, a second cohort of HFD-fed mice was treated with pancreatic progenitor cells combined with one of three antidiabetic drugs. All combination therapies rapidly improved body weight and co-treatment with either sitagliptin or metformin improved hyperglycemia after only 12 weeks. Therefore, a stem cell-based therapy may be effective for treating type 2 diabetes, particularly in combination with antidiabetic drugs.

INTRODUCTION

The International Diabetes Federation estimates that up to 95% of the ~380 million people worldwide who are affected by diabetes suffer from type 2 diabetes (International Diabetes Federation, 2014). Thus, the potential impact of a novel treatment for type 2 diabetes is enormous. Despite obvious differences in the pathogenesis of type 1 and 2 diabetes, both diseases are characterized by impaired glucose homeostasis resulting from insufficient insulin production by pancreatic beta cells. In type 1 diabetes, beta cell destruction by the immune system is rapid and extensive, causing severe insulin deficiency. In contrast, beta cell failure in type 2 diabetes occurs gradually over time and is associated with peripheral insulin resistance. Clinical studies have shown that patients with type 2 diabetes also have reduced beta cell mass (Butler et al., 2003; Yoon et al., 2003) and declining beta cell function during the progression from pre-diabetes to overt diabetes (Weyer et al., 1999; Ferrannini et al., 2005). Therefore, treatment strategies for type 2 diabetes should be aimed at restoring beta cell mass and/or function, in addition to improving insulin sensitivity (Halban, 2008; Kahn et al., 2014).

Transplantation of cadaveric human islets can restore insulin-independence in patients with type 1 diabetes (Shapiro et al., 2000; Ryan et al., 2001), but this approach has not been actively pursued for type 2 diabetes, likely due to the inadequate supply of donor islets, risk of immunosuppression, and perceived hurdle of insulin resistance. The obstacle of an insufficient cell supply may be overcome with the use of human embryonic stem cells (hESCs). We previously demonstrated that hESC-derived pancreatic progenitor cells reversed hyperglycemia in a mouse model of type 1 diabetes characterized by severe beta cell destruction and insulin deficiency (Rezania et al., 2012, 2013; Bruin et al., 2013). However, the efficacy of this stem cell-based therapy for treating hyperglycemia in an obesogenic and insulin-resistant environment, such as in type 2 diabetes, has not been reported. Based on evidence that intensive insulin therapy improves insulin sensitivity, glycemic control, and beta cell function in patients with type 2 diabetes (Weng et al., 2008; Kramer et al., 2013), we hypothesized that hESC-derived insulin-secreting cells may also be effective for this patient population.

Our first aim was to establish a model of type 2 diabetes in immunodeficient mice that would be compatible with xenotransplantation. Different strains of rodents have widely variable susceptibility to high-fat diet (HFD)-induced obesity and/or hyperglycemia (Srinivasan and Ramarao, 2007; Svenson et al., 2007; Hariri and Thibault, 2010). Moreover, insulin resistance, a hallmark feature of type 2 diabetes (Kahn et al., 2006), is thought to be driven primarily by obesity-associated inflammation (reviewed in Kalupahana et al., 2012; Osborn and Olefsky, 2012), and

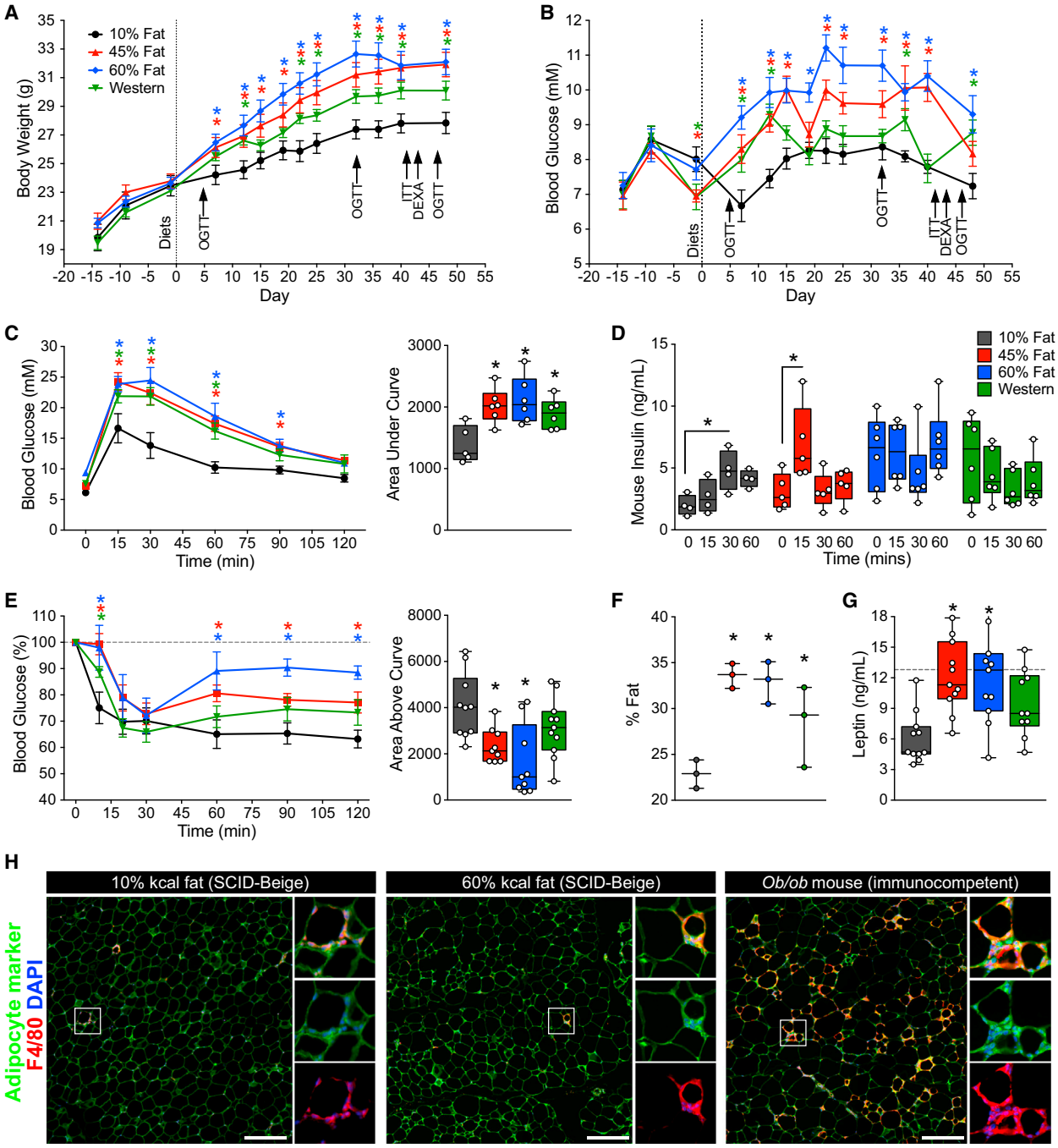

Figure 1. SCID-Beige Mice Rapidly Develop Obesity, Fasting Hyperglycemia, Glucose Intolerance, and Insulin Resistance Following Exposure to HFDs

(A and B) Body weight (A) and fasting blood glucose levels (B) were measured during a 14-day acclimation period on normal chow and for 51 days following administration of one of the following diets: 10% fat (black; n = 11 mice), 45% fat (red; n = 11 mice), 60% fat (blue; n = 11 mice), or Western diet (green; n = 11 mice).

(C and D) Blood glucose (C, raw values and area under the curve) and plasma mouse insulin levels (D) were assessed during an oral glucose tolerance test (OGTT; n = 4–6 mice per group) on day 47. See Figure S1 for OGTTs at days 5 and 32.

(E) An insulin tolerance test (ITT) was performed on day 42 (n = 9–11 mice per group). Glucose levels are presented as a percentage of basal glucose levels (at time 0) and the area above the curve was calculated using 100% as the baseline.

(F) Adiposity (% fat) was assessed by DEXA at day 43 in a subset of mice (n = 3 mice per group).

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