HNF4A and Diabetes
Injury Before Insult?

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One of the distinguishing features of vertebrate development is its highly regulative nature. Following developmental perturbations, vertebrate embryos exhibit a robust ability to compensate and normalize structure. However, such appearances may be deceiving, as it has become clear that relatively mild perturbations in embryonic growth can result in profound metabolic disorders—including diabetes—decades later. This association has important clinical implications, but a complete understanding of the cellular and molecular relationship between embryonic development and adult physiology has been slow to emerge.

The first compelling evidence that intrauterine environment dictates later metabolic outcome was the cohort study of Ravelli et al. (1) of 300,000 men conceived during the Dutch famine of 1944–1945. Embryos exposed to malnutrition during the first half of pregnancy, but not later, had significantly higher rates of obesity at age 19 years, indicating that a nutrient-deprived environment early in development has long-lasting metabolic consequences (1). Human and animal studies have subsequently confirmed a relationship between embryonic environment, particularly intrauterine growth retardation, and later occurrence of type 2 diabetes (rev. in 2,3). Although it was initially postulated that hypothalamic-mediated changes in appetite might underlie adult metabolic derangements, low–birth weight infants were found to also have reduced pancreatic β-cell mass (4). This suggests that the increased risk of type 2 diabtes in low–birth weight babies might be due to developmental deficiencies in β-cell mass, leading to inadequate insulin secretion in the face of age-related increases in demand. These and other findings became embodied in the so-called "thrifty phenotype" hypothesis, which postulates that the embryonic environment forecasts the nutritional state that is likely to exist after birth, thereby leading to permanent changes in β-cell mass and insulin responsiveness (5). Such durable changes in β-cells following nutritional deprivation may be mediated, at least in part, by chromatin remodeling (6).

Recently, genetic determinants of type 2 diabetes have taken center stage (7). It is unknown whether these newly identified disease-modifying genes confer increased risk through developmental or functional mechanisms. But a subset of genes, particularly those responsible for maturity-onset diabetes of the young (MODY), have direct roles in both islet development and β-cell physiology. MODY1 is a disorder characterized by defective glucose-stimulated insulin secretion (8) and is caused by mutations in the gene encoding hepatocyte nuclear factor-4α (*HNF4A*) (9). HNF4α directly regulates genes involved in glucose transport and glycolysis (10). Two groups genetically engineered mice to lack HNF4α in β-cells (HNF4α$^{loxP/loxP}$;Ins-Cre) and found that such animals exhibit normal islet architecture but defective glucose-stimulated insulin secretion in β-cells (11,12). Unexpectedly, one of these studies found that HNF4α$^{loxP/loxP}$;Ins-Cre mice exhibit hyperinsulinemia, glucose intolerance, and mild hypoglcemia (11). This result was surprising both because of the paradoxical relationship between insulin levels and glucose responsiveness and because MODY1 patients with *HNF4A* mutations exhibit the opposite phenotype: hypoinsulinemic hyperglycemia.

Based on these findings, Harries et al. (13) examined 108 newborn infants with *HNF4A* mutations to determine whether they exhibited the same spectrum of metabolic abnormalities as *HNF4A* mutant mice. Remarkably, a subset of newborns with *HNF4A* mutations also had hypoglycemia and/or hyperinsulinemia, despite the fact that adults with the same mutations were expected to develop diabetes. Furthermore, some infants also exhibited fetal overgrowth (macrosomia), likely as a result of fetal exposure to high insulin levels (13). In this issue of *Diabetes*, the same group (14) describes a detailed characterization of human *HNF4A* transcription and genotype/phenotype correlation. *HNF4A* is transcribed from two promoters, P1 and P2, that give rise to nine distinct isoforms through differential exon usage at the 5′ and 3′ ends of the gene. Harries et al. determined that all *HNF4A* transcripts in the adult liver and kidney are derived from P1, whereas all transcripts in the adult pancreas and small intestine are derived from P2 (other parts of the gut utilize both promoters). In the embryonic pancreas, transcripts from both the P1 and P2 promoters were detected. Therefore, within the pancreas, the P2 promoter is utilized by both embryo and adult, whereas the P1 promoter is exclusively embryonic.

By examining the location of *HNF4A* mutations in 190 subjects from 58 MODY families, the authors found an interesting trend: individuals with mutations that affect all *HNF4A* isoforms have an earlier onset of diabetes than those with mutations affecting only P2-derived isoforms or the P2 promoter itself. Based on this statistical finding, the authors propose that mutations that affect only adult transcripts result in milder phenotypes because patients with these mutations are spared the consequence of losing developmentally important P1-derived HNF4α transcripts.

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MODY, maturity-onset diabetes of the young.

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However, there are several alternative explanations for this correlation. Most importantly, the differential effect on protein function of any particular *HNF4A* mutation could outweigh the effect of disrupting P2-derived transcripts during development. Furthermore, HNF4α has critical roles during early embryogenesis and liver development (15,16), and, thus, HNF4α mutations could perturb metabolism through activities in other tissues. Animal models might help resolve some of these questions, although mice with a β-cell–specific deletion of HNF4α do not develop overt diabetes but instead have defects in β-cell proliferation (17).

Thus, at present, the mechanism by which mutations in *HNF4A* cause defective insulin secretion remains unresolved. Likewise, it is unknown why some individuals with *HNF4A* mutations paradoxically develop neonatal hyperinsulinism and macrosomia. Although it is clear that β-cell mass is subject to regulation in adult life (18–20), embryonic cell ablation studies point to the coexistence of limits on pancreatic growth that are imprinted during prenatal life (21). This finding, together with the epidemiologic evidence supporting the "thrifty hypothesis," suggests that autonomous growth constraints established during pancreatic development may lie beneath the normal regulative capacity of β-cells. The hypothesis presented by Harries et al. that *HNF4A* participates in a process of embryonic programming is interesting and warrants further investigation. The next challenge will be to understand how the developmental and physiologic functions of disease-modifying genes conspire to cause diabetes—adding adult insult to an underlying embryonic injury.

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