would be useful for discriminating between the influence of $CD34^+$ cells and that of neovascularization on the overall neurogenic capacity of the dentate gyrus and forebrain SVZ. It may also provide insight into the possibility of recruiting neural stem cells from these regions for brain repair. This information would be particularly relevant in regard to the experimental group that also received erythropoietin, as this treatment has been shown to enhance both angiogenesis and neurogenesis (13). The current study suggests that one mechanism accounting for the functional recovery resulting from cord blood cell delivery works through the enhancement of angiogenesis around the site of degeneration. This finding provides a note of optimism for developing therapeutic strategies for stroke. Taguchi et al. provide an important piece of the puzzle, but there remains much to be determined about the mechanisms involved and the specific role of neurogenesis in brain recovery from stroke before a comprehensive picture will emerge on how to treat this old problem (17).

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Unlocking the secrets of the pancreatic β cell: man and mouse provide the key

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Failure of the pancreas to secrete sufficient insulin results in type 2 diabetes, but the pathogenesis of pancreatic β cell dysfunction is still poorly understood. New insights into β cell failure come from defining the genes involved in rare genetic subtypes of diabetes and creating appropriate animal models. A new mouse model of transient neonatal diabetes mellitus emphasizes that both the number of β cells and their function are critical for insulin secretion and may be regulated by imprinted genes (see the related article beginning on page 339).

The regulated secretion of insulin by the pancreatic β cell maintains blood sugar concentrations within a narrow physiological range. In over 150 million people worldwide, however, pancreatic β cells fail to secrete adequate insulin, usually in the presence of increased insulin resistance, which results in type 2 diabetes (T2D). Understanding the pathways that result in β cell dysfunction at a physiological and molecular level is critical for improved understanding and treatment of T2D.

Learning from rare genetic subtypes of diabetes

How can we study the pancreatic β cell in humans when these cells are not readily accessible? Accidents of nature in which a single gene defect results in severe β cell dysfunction, causing diabetes, offer the chance of gaining new insights into this disease if the responsible gene can be defined. The best example of such research has been the use of positional cloning to demonstrate that heterozygous mutations of the genes encoding the hepatic transcription factors

Nonstandard abbreviations used: hydatidiform mole–associated and –imprinted transcript (*HYMAI*); P1-derived artificial chromosome (PAC); transient neonatal diabetes mellitus (TNDM); type 2 diabetes (T2D); Z finger protein that regulates apoptosis and cell cycle arrest (*ZAC*).

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Table 1
Comparison of the clinical features and pathophysiology related to glucose regulation in human TNDM with the transgenic mouse model, TNDM29

Human TNDM	**In utero**	**Neonatal (0–3 mo)**	**Early childhood (0.5–4 yr)**	**Late childhood/ adolescence/early adulthood (4–25 yr)**
Phase of the disease		Neonatal diabetes	Apparent remission	Relapse of diabetes
Features in humans	Greatly reduced growth in utero; birth weight typically less than 2nd percentile	Marked hyperglycemia (>20 mmol/l) usually diagnosed in first week of life Needs insulin treatment Reduction in insulin dose during infancy typically discontinued at 3 months	Normal glucose tolerance	≈ 2/3 of individuals develop diabetes with some residual endogenous insulin secretion Mean age of diagnosis is 14 years (range, 4–25)
Pathophysiology in humans	Probable insulin deficiency in utero reduces insulin-mediated growth	Marked insulin deficiency at birth Subsequent progressive improvement in endogenous insulin secretion	Normal insulin secretion	Loss of first phase insulin secretion (as seen in type 2 diabetes)
TNDM29 mouse	**Embryonic (day 14.5 after conception)**	**Neonate (days 2–8)**	**Juvenile (1.5–2 mo)**	**Adult (6–10 mo)**
Features in mouse	Impairment of development of all pancreatic endocrine cell types Birth weight normal	Hyperglycemia during both fasting and after glucose challenge	Normal glucose tolerance	Normal fasting but hyperglycemia after glucose challenge
Pathophysiology in mouse	Reduced levels of transcription factors: Pdx1, Ngn3, Pax6	β cell dysfunction Insulin secretion reduced relative to hyperglycemia	Normal insulin secretion	β cell dysfunction Reduced insulin secretion with glucose challenge
β cell mass relative to WT	Reduced ~ 2-fold; reduced β cell number	Similar to WT	≈2-fold increase in β cell number	Similar
Total insulin content of pancreas relative to WT		Reduced	Similar to WT	Similar
Possible synthesis of findings	Reduced development of all endocrine cells including β cells	Compensatory increase in β cell number begins but is not adequate, as insulin synthesis is reduced and secretion is abnormal despite normal β cell mass	Increased β cell mass compensates for reduced insulin synthesis and secretion	Compensatory increase in β cell mass is not maintained, which results in reduced β cell function

HNF-1α and HNF-4α cause early-onset diabetes (1, 2). Subsequent studies have allowed the unraveling of a previously unexpected transcription factor network that is crucial to the maintenance of normal β cell development and function (3) and also involved in the susceptibility to T2D (4, 5). Although genetics provided the initial breakthrough, subsequent careful animal and molecular biological studies were needed to elucidate the underlying mechanism.

Transient neonatal diabetes: a disorder of imprinting in humans

Now, studies of the molecular genetics of transient neonatal diabetes mellitus (TNDM) in humans and mice have been combined to give new insights into the development and physiology of the β cell. TNDM is a rare condition (affecting approximately 1 in 600,000 live births) that is characterized by a unique clinical course (6). Affected babies have low birth weight, and high blood-glucose values are detected in the first week of life — features of low pancreatic insulin secretion in utero and after delivery, respectively. Initially, insulin treatment is needed, but by 12 weeks, endogenous insulin secretion has usually improved sufficiently to allow its discontinuation. Patients remain in apparent remission for many years, but 2/3 of them will subsequently develop diabetes, usually in adolescence. Their diabetes at this stage, despite their age and lack of obesity, is similar to T2D, with a loss of first-phase insulin secretion (7).

The first major clue to the etiology of this disappearing and reappearing diabetes came from genetic analysis implicating abnormalities of an imprinted locus on chromosome 6 (8). Three interrelated genetic mechanisms have been found to cause most TNDM (reviewed in ref. 6): (a) inheriting 2 copies of the paternal chromosome 6 (paternal uniparental isodisomy of chromosome 6); (b) paternally inheriting a duplication of 6q24; or (c) a mater-

nal methylation defect within this region. These data are consistent with TNDM resulting from biallelic expression rather than the normal paternal monoallelic expression that results from methylation and hence inactivation of the maternally inherited allele. There are 2 overlapping imprinted genes with maternal allele silencing in the TNDM locus: *ZAC* (Z finger protein that regulates apoptosis and cell cycle arrest) and *HYMAI* (hydatidiform mole–associated and –imprinted transcript) (9). Overexpression of one or both of these genes could be responsible for the TNDM phenotype.

New insights from the mouse model TNDM29

This genetic information has allowed an excellent rodent model of TNDM to be created. Ma and colleagues, in this issue of the *JCI* (10), describe a transgenic mouse (TNDM29) with overexpression of a P1-derived artificial chromosome (PAC) containing the complete *ZAC* and *HYMAI* human genes. In keeping with the observation that TNDM in humans only results from the paternal inheritance of the duplication of 6q24, offspring generated by paternal transmission of the overexpressing PAC, but not maternal transmission, were hyperglycemic as neonates. The glycemia changes in TNDM29 mice mirrors those in TNDM in humans, with remission and normal glucose tolerance in juvenile mice followed by relapse and glucose intolerance in adulthood (Table 1).

The initial studies of the TNDM29 transgenic mice have already suggested possible underlying mechanisms for the recurring β cell failure. The most fascinating findings in the TNDM model are the marked changes in β cell number compared with wild-type mice and the relationship of these changes in β cell number to the varying glucose tolerance and insulin secretion (Table 1). In the pancreata of the early embryonic TNDM29 transgenic mice, there was a marked reduction in the number of β and other pancreatic endocrine cells. This effect was probably mediated, at least partially, by downregulation of critical pancreatic transcription factors Pdx1, Ngn3, and Pax6. In late gestation and early postnatal life, there was a rapid increase in pancreatic β cell mass in the TNDM29 mouse, achieved primarily by an increased number of β cells (either through increased proliferation or decreased apoptosis), which help at least in part to compensate for the low initial number of β cells. Despite this, in the early neonate, the total insulin content of the pancreas was still reduced, and the animal was hyperglycemic as a result of inadequate insulin secretion. The number of β cells continued to increase and by 2–3 months (juvenile) was approximately twice the number observed in wild-type mice, although the total insulin content of the pancreas was unchanged, which suggests that each β cell contains less insulin. The increased number of β cells enabled normal glucose tolerance. However, the compensatory increase in β cell mass was not maintained, and adult TNDM29 mice had a β cell mass similar to that in wild-type animals. The glucose tolerance of the adult animals deteriorated and was characterized by reduced early insulin secretion. A key result is that disordered imprinting, like mutations in transcription factors (4), has led to both altered development and altered function of β cells.

New directions

As with all good science, these studies have raised more questions than they have answered. Why is the insulin deficiency less severe in mouse than human? Does the phenotype result only from the overexpression of *ZAC*, a potent cell cycle regulator, or is increased expression of *HYMAI* — an apparently untranslated mRNA of unknown function — also needed? Does the rapid increase in β cell mass in late intrauterine and early postnatal life represent secondary compensatory mechanisms, or is it directly mediated by *ZAC/HYMAI*? Is it the failure of β cell function as an adult a consequence of rapid compensation in early life? If the latter scenario is true, there could be parallels with fetal exposure to hyperglycemia in utero resulting in glucose intolerance as an adult. Again, the combination of human genetics and a resultant mouse model offers the opportunity for discovery of many more of the secrets of the pancreatic β cell.

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