Islet amyloid and type 2 diabetes: overproduction or inadequate clearance and detoxification?

Dhananjay Gupta and Jack L. Leahy

Division of Endocrinology, Diabetes and Metabolism and Department of Medicine, University of Vermont, Burlington, Vermont, USA.

A hallmark of type 2 diabetes is the reduction of pancreatic islet β cell mass through induction of apoptosis and lack of regeneration. In most patients, β cell dysfunction is associated with the presence of extracellular amyloid plaques adjacent to β cells and intracellular toxic oligomers that are comprised of islet amyloid polypeptide (IAPP). In this issue of the *JCI*, three independent research groups reveal that a functional autophagy system normally prevents the accumulation of toxic IAPP oligomers in human IAPP–expressing murine models. Furthermore, mice expressing human IAPP but deficient for β cell autophagy through genetic deletion of the autophagy initiator ATG7 developed β cell apoptosis and overt diabetes. Together, these studies indicate that autophagy protects β cells from the accumulation of toxic IAPP oligomers and suggest that enhancing autophagy may be a novel target for prevention of type 2 diabetes.

Type 2 diabetes mellitus and the pancreatic islet β cell

Type 2 diabetes mellitus is a complex metabolic disorder that is comprised of defective insulin action in the periphery as well as within the liver and adipose tissue. Numerous cross-sectional and prospective studies have shown that what determines whether a person develops diabetes resides within their pancreatic β cells (1, 2). Insulin resistance is common in our modern society due to extenuating factors, including obesity, poor dietary and lifestyle habits, disordered sleep, and emotional stress. However, β cell compensation, the normal biological counter response of hyperinsulinemia, prevents most individuals from becoming diabetic. In turn, a defining feature of those at risk for type 2 diabetes is a defective β cell compensation response, with subtle β cell dysfunction evident even when blood glucose is still in the normal glucose tolerance range (1–3). As metabolic demands exceed an individual's capacity for β cell compensation, glucose levels rise along with the onset of a multidimensional pathogenic response in β cells that is likely driven by glucotoxicity, lipotoxicity, ER and oxidative stress, inflammation, and dedifferentiation. Once the pathogenic cascade is initiated, there is a progressive loss of β cell mass and function that results in worsening hyperglycemia and a waning response to therapy, which are both typical of this disease.

Research into the mechanisms that promote β cell dysfunction has been performed mostly in isolated cells, cell lines, or animal models, given the inability to perform pancreas biopsies on healthy subjects for clinical research purposes. While these models are useful to probe the biology of the β cell pathogenic processes, it remains unclear which β cell dysfunction–promoting mechanism is most active for induction of the inadequate β cell compensation in human type 2 diabetes. Studies performed with isolated islets from brain-dead pancreas donors and pathological pancreas specimens — from nondiabetic and type 2 diabetic subjects — have provided evidence that supports multiple pathways for β cell dysfunction. Unfortunately, these studies lack the ability to identify the initial steps in this process that occur before the onset of diabetes and directly cause the β cell dysfunction. It is clear that both reduced β cell mass and lowered insulin secretory function are elements of the β cell pathophysiology of type 2 diabetes. Furthermore, a defective β cell compensation system, which predisposes patients to type 2 diabetes, is operative well before the diagnosis of abnormal blood glucose values by current criteria (1, 2). As such, the hunt continues for mechanisms for β cell dysfunction that are independent of hyperglycemia.

Islet amyloid

Pancreatic sections from patients with type 2 diabetes have revealed the presence of extracellular amyloid plaques adjacent to shrunken and distorted β cells (4). These plaques are made up of the 37 amino acid β cell–specific protein islet amyloid polypeptide (IAPP, also referred to as amylin). IAPP is packaged in insulin granules in which it is processed from proIAPP to mature IAPP and cosecreted with insulin in a 1:100 molar ratio. β Cell–secreted IAPP functions along with insulin to control postprandial glucose levels by slowing gastric motility that also has a subtle effect to promote satiety. Indeed a pharmacological analog of IAPP, pramlintide, has the same gastric slowing effect and is in clinical use for patients with diabetes. Due to the presence of IAPP-containing plaques in virtually all individuals with type 2 diabetes, IAPP accumulation has been a highly studied mechanism for the lowered β cell mass in type 2 diabetes.

In the 1980s, interest in these amyloid plaques grew after studies of the events leading to type 2 diabetes in nonhuman primates revealed a similar time frame for the appearance of islet amyloid and hyperglycemia. Amino acids 20–29 within human and

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nonhuman primate IAPP are responsible for its amyloidogenic properties; however, in rodent IAPP, proline substitutions at positions 25, 28, and 29 render the protein nonamyloidogenic (5). Several lines of transgenic mice that produce human IAPP have been created, many of which exhibit islet amyloid accumulation, β cell apoptosis, and reduced β cell mass, along with the development of glucose intolerance or frank diabetes. Recent debate has focused on whether small intracellular oligomers of IAPP or the extracellular plaques themselves are cytotoxic. The general consensus is that the intracellular toxic oligomers are causative (4), while the plaques are a more secondary effect. This hypothesis was advanced by the development of immunohistochemistry antibodies specific for toxic oligomers and the demonstration of the presence of small toxic IAPP oligomers in pancreas sections from individuals with type 2 diabetes; however, several key issues remain to be addressed. For example, circulating levels of IAPP are higher in individuals with obesity and normoglycemia that in those with type 2 diabetes, but the nondiabetic subjects have no detectable β cell IAPP oligomers or plaques. Stated another way, why does IAPP oligomerize in the context of type 2 diabetes? Additionally, can anything be done to intervene in this process?

Autophagy protects β cells against IAPP toxic oligomers

Three separate studies in this issue of the *JCI* have provided insight into how β cells are normally protected against IAPP oligomerization. All three groups generated human IAPP–expressing mice with a β cell–specific deficiency of the autophagy initiator ATG7 and revealed that autophagy-dependent packaging of monomeric or unprocessed IAPP dimers or trimers into p62-associated vacuoles allows autophagosomes to dispose of these molecules, keeping them nontoxic. These studies also showed that activity of this detoxification system was increased when a high-fat diet was used in the mice with hyperexpression of human IAPP to mimic the β cell compensation response to obesity and insulin resistance. In contrast, β cell–specific autophagy blockade in human IAPP–expressing mice markedly reduced the presence of p62 vacuoles in β cells and resulted in the diffuse cytoplasmic presence of toxic IAPP oligomers, along with a relative or absolute reduction of β cell mass and the induction of glucose intolerance or overt diabetes.

Each individual study presents unique features that support a model of autophagy-induced detoxification of IAPP. Shigihara et al. (6) demonstrated that the proliferation rate of β cells in vitro and in vivo is lowered when autophagy is defective, suggesting that autophagy regulates β cell division; however, they did not provide a mechanism for this effect. Rivera et al. (7) showed that the IAPP present in p62-dependent vacuoles is exclusively nontoxic IAPP fibrils and did not identify insulin within the p62 inclusions. Moreover, Rivera and colleagues determined that enhanced oxidative stress induces β cell apoptosis in the human IAPP–expressing autophagy-deficient mice through reduction of nuclear factor erythroid-2–related factor 2 (NRF2), which induces antioxidant enzyme expression. As such, the current study by Rivera et al. has identified another IAPP-related β cell pathogenic mechanism in addition to extensive evidence from this laboratory that ER stress is induced in β cells in response to toxic oligomers of IAPP (8). Kim et al. (9) demonstrated that administration of trehalose, a pharmacologic agent that enhances autophagy, partially reverses diabetes-associated phenotypes and reduces toxic oligomer accumulation in β cells of human IAPP–expressing autophagy-deficient mice on a high-fat diet.

Caveats and considerations

Autophagy is a key regulatory system in cells for the removal of damaged or unneeded proteins and organelles and the degradation of aged proteins in order to recycle amino acids (10). There is an abundance of prior work that indicates that autophagy is important for normal β cell function (11, 12) and autophagy activity is increased in β cells from humans with type 2 diabetes (13); therefore, the results of these three studies are not surprising. It is still not clear how and when during the course of type 2 diabetes development this autophagy-dependent detoxification system might be overcome, allowing toxic IAPP oligomers to form. The animal models used by all three research groups were based on a severe disruption of autophagy in β cells through genetic knockout. While useful for probing the biological action of a protein, the physiologic relevance of such models remains obtuse in terms of understanding the real-world variability of β cell autophagic activity. Studies that suggest aging (14) and high-fat diets (15), which are both known risk factors for type 2 diabetes, lower β cell autophagy activity have potentially important implications. A better understanding of the impact of environmental and genetic factors on the autophagy system is needed.

There are many additional mechanisms that have been proposed for β cell dysfunction and death in type 2 diabetes, including ER stress, oxidative stress, and autoimmune damage, all of which have been linked to IAPP toxicity (7, 8, 16). While it is tempting to try and connect the dots through a single, unified mechanism, all of these proposed pathways of β cell dysfunction have been recapitulated and extensively studied in rodent models of diabetogenic systems, such as high-fat feeding and partial pancreatectomy, or through genetic modification. Given the absence of rodent IAPP oligomerization, these mechanisms of reduced β cell function clearly do not require IAPP activation.

Notwithstanding these cautions, the papers by Rivera et al. (7), Shigihara et al. (6), and Kim et al. (9) raise exciting possibilities. For example, patients with type 2 diabetes have an increased risk of Alzheimer's disease, suggesting a common pathogenesis. Disordered neuronal autophagy has been described in Alzheimer's (17), such that a widespread alteration in the clearance of amyloidogenic proteins may explain the association between these two diseases and is an important issue for further investigation. Additionally, autophagy has been reported to be critical for normal regulation of cellular lipid storage (18) and hepatic function (19); therefore, it should be considered that a more generalized effect of altered autophagy results in the metabolic profile of type 2 diabetes. Finally, the most exciting possibility is that autophagy activators could be used to intervene in the development of type 2 diabetes (20).

In summary, there is no debate that IAPP oligomers and amyloid plaques are present in β cells of individuals with type 2 diabetes or that cytoplasmic IAPP oligomers in cellular systems and animal models are toxic. However, acceptance of

the hypothesis that IAPP oligomer formation and subsequent plaque development are a major cause of type 2 diabetes will require a better understanding of when this pathogenic mechanism is activated and what modulates its destructive potential. These current studies may have provided an important clue by shifting the focus away from the biology of how IAPP oligomers cause β cell destruction to probing for defects within the protective system against the formation of toxic IAPP oligomers.

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Address correspondence to: Jack Leahy, University of Vermont College of Medicine, Colchester Research Facility, 208 South Park Drive, Colchester, Vermont 05446, USA. Phone: 802.656.2530; E-mail: jleahy@uvm.edu.

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