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FIELD OF VISION

Betatrophin: A liver-derived hormone for the pancreatic β-cell proliferation

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Abstract

The pancreatic β-cell failure which invariably accompanies insulin resistance in the liver and skeletal muscle is a hallmark of type-2 diabetes mellitus (T2DM). The persistent hyperglycemia of T2DM is often treated with anti-diabetic drugs with or without subcutaneous insulin injections, neither of which mimic the physiological glycemic control seen in individuals with fully functional pancreas. A sought after goal for the treatment of T2DM has been to harness the regenerative potential of pancreatic β-cells that might obviate a need for exogenous insulin injections. A new study towards attaining this aim was reported by Yi *et al*, who have characterized a liver-derived protein, named betatrophin, capable of inducing pancreatic β-cell proliferation in mice. Using a variety of *in vitro* and *in vivo* methods, Yi *et al*, have shown that betatrophin was expressed mainly in the liver and adipose tissue of mice. Exogenous expression of betatrophin in the liver led to dramatic increase in the pancreatic β-cell mass and higher output of insulin in mice that also concomitantly elicited improved glucose tolerance. The authors discovered that betatrophin was also present in the human plasma. Surprisingly, betatrophin has been previously described by three other names, *i.e.*, re-feeding-induced fat and liver protein, lipasin and atypical angiopoeitin-like 8, by three independent laboratories, as nutritionally regulated liver-enriched factors that control serum triglyceride levels and lipid metabolism. Yi *et al* demonstration of betatrophin, as a circulating hormone that regulates β-cell proliferation, if successfully translated in the clinic, holds the potential to change the course of current therapies for diabetes.

Key words: Type 2 diabetes mellitus; Insulin resistance; Liver-derived betatrophin; Pancreas β-cell regeneration

Core tip: Yi *et al* have characterized a secreted protein named betatrophin that potently regulates β-cell proliferation. Evidently, betatrophin is identical to re-feeding-induced fat and liver protein, lipasin and atypical angiopoeitin-like 8, all of which were characterized as regulators of lipid homeostasis, by three independent groups of investigators. Yi *et al* were the first to demonstrate that hepatic expression of betatrophin in mice caused a dramatic surge in proliferation of the pancreatic β-cells with a concomitant improvement of their glucose tolerance. The discovery of a circulating hormone that specifically targets β-cell proliferation is a promising development towards a better clinical management of diabetes.

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COMMENTARY ON HOT TOPICS

Chronic obesity associated type 2 diabetes mellitus (T2DM) is emerging as a global healthcare crisis (World Health Organization Global Infobase: data on over-

weight and obesity mean body mass index, healthy diets and physical inactivity; www.who.int/mediacenter/). If the present trends continue nearly 350 million people worldwide will develop T2DM by the year 2030[1]. Insulin resistance in the skeletal muscle and liver accompanied by a "burnt-out" pancreas, as judged by its functional decline and reduced numbers of β-cells, is a hallmark of diabetes[2-4]. The underlying etiology of insulin resistance largely reflects a combination of chronic tissue inflammation and pancreatic β-cell failure[3,5]. Current therapies for the treatment of T2DM commonly include insulin sensitizers (*e.g.,* metformin and pioglitazone), with or without insulin secretagogues (*e.g.,* glyburide), or injectable insulin[6]. Decades of clinical experience have proven that current drug regimens to manage T2DM rarely achieve the physiological glycemic control elicited by a fully functional pancreas[6]. As a consequence, the cardiovascular, renal and neurological complications of poorly controlled blood sugar continue to be a major challenge in the management of T2DM[6].

A long sought after but unrealized goal of treatment of T2DM is to replenish the loss of β-cell mass in the diabetic pancreas to restore normal glycemic control. Therefore, in recent years much effort has been focused on the physiological and pathological mechanisms that regulate the biogenesis, survival and apoptosis of the pancreatic β-cells. The pancreatic mass and β-cell numbers increase rapidly during embryogenesis and in the neonatal period, but the rate of replication of β-cells slows down dramatically in adult rodents and humans[7-9]. This is in contrast to a number of physiological (*e.g.*, gestation-induced diabetes) and pathological (*e.g.*, obesity-associated T2DM or pancreatic injury) states of insulin resistance during which pancreatic β-cells elicit enhanced rates of proliferation[8]. These observations have prompted a number of investigators to search for and identify a plethora of cell-intrinsic (*e.g.*, cyclin D1/D2; CDK-4, nuclear factors of activated T cells, Menin and p53) and systemic [glucagon-like peptide-1, glucose-dependent insulin-tropic polypeptide, leptin, adiponectin, interleukin (IL)-1, IL-6, tumor necrosis factor-1, fibroblast growth factor-21 and serotonin] factors that are presumed to control β-cell proliferation[8]. However, based on a rigorous functional assessment of the varied factors purported to control β-cell proliferation it is apparent that most of these factors lack sufficient potency and/or β-cell specificity for them to be warranted as serious candidates for drug development.

A number of recent observations in murine models of insulin resistance and obesity (*e.g.*, leptin-deficient *ob/ob* mice) appear to offer a way out of the current predicament. It has been reported that in a number of murine models of severe insulin resistance there is an apparent increase in pancreatic mass. The increased pancreatic mass seen under these conditions have re-ignited a search for systemic factor that might control proliferation of β-cells. The strongest evidence in favor of a putative factor(s) produced by the liver and released in circulation originally came from Ronald Kahn's laboratory[10,11]. Using liver-specific insulin receptor knockout (LIRKO) mice, these authors reported the induction of a humeral factor involved in crosstalk between liver and pancreatic islets to trigger β-cells to multiply. Subsequently, El Ouaamari *et al*[12] applied the techniques of parabiosis, tissue transplantation, and *in vitro* islet culture in LIRKO mice to provide additional evidence for a non-neural and non-cell-autonomous factor(s) capable of inducing β-cell proliferation.

A parallel line of investigation in another model of obesity and insulin resistance also hinted at the existence of inter-organ metabolic communication between liver and pancreas. It had been suspected for some time that the livers of obese animals elicit enhanced activation of mitogen-activated protein kinase (MAPK) pathway. To investigate if MAPK signaling was involved in inter-organ relay of information between liver and pancreas, Imai *et al*[13] expressed a constitutively active extracellular regulated kinase (ca-ERK) in the livers of mice. Consistent with their hypothesis, ERK activation in the liver induced an obesity-associated metabolic signal(s) that was relayed *via* neuronal circuits to induce pancreatic β-cell proliferation. A number of additional studies have also hinted at the existence of a circulating factor(s) that might induce β-cell proliferation[10,14]. These tantalizing observations in experimental models of obesity notwithstanding, the identity of the putative liver-derived molecule(s) responsible for increased pancreatic β-cell mass and their implications for humans remain elusive. Apparently, Yi *et al*[15] were inspired by the tantalizing observations in LIRKO or ca-ERK mice to mount a systematic search for a putative liver-derived pancreatic β-cell growth factor produced in insulin resistance states.

Yi *et al*[15] began by co-opting a previously described model of insulin resistance in rat caused by infusion of S961, an insulin receptor (IR) antagonist peptide[16]. The authors delivered S961 by an osmotic pump and noted that S961 infusion caused dose-dependent peripheral insulin resistance and hyperglycemia that were accompanied by a dose-dependent surge in plasma insulin. These findings led the authors to posit that the observed surge in plasma insulin in mice most likely resulted from a compensatory increase in the numbers of pancreatic β-cells as a direct result of S961-induced insulin resistance. The authors experimentally tested this hypothesis and stained pancreatic sections of normal and S961-treated mice with specific antibodies to assess cell division [*e.g.*, Ki67 and Proliferating Cell Nuclear Antigen (PCNA)]; insulin- and nuclear Nkx6.1-specific antibodies were used to specifically stain the β-cells in the pancreatic islets. The histological assessments of pancreas from control and insulin-resistant mice were further complimented by quantitative polymerase chain reaction (qPCR) to measure expression of cell cycle specific genes (*e.g.*, cyclins, CDKs and E2Fs). Based on these analyses the authors concluded that S961 infusion-mediated insulin resistance in mice was accompanied with a potent (about 12-fold) and preferential

induction of cell proliferation.

Since a direct exposure of pancreatic islets to S961 did not cause β-cell proliferation, Yi *et al*[15] reasoned that the IR antagonist acted by altering gene expression in insulin sensitive tissues, other than pancreas, and potential inter-organ relay of signals indirectly impinged on the mechanism of pancreatic β-cell proliferation. To test this hypothesis, the authors analyzed global gene expression in untreated control and S961-treated liver, adipose tissue, skeletal muscle and pancreatic β-cells. The analyses of gene expression by microarrays revealed that a number of mRNAs were specifically induced in the liver and white adipose tissue (WAT) of S961-infused mice. Yi *et al*[15] chose a candidate gene from microarray analysis for more detailed *in silico* and experimental studies. They discovered that betatrophin mRNA was specifically induced by S961 in the liver and WAT of mice but not in skeletal muscle and pancreatic β-cells. The authors expressed exogenous betatrophin in the liver and detected the recombinant betatrophin protein in the serum. Interestingly, an *in silico* analysis of the putative betatrophin gene/transcript revealed that these had been annotated by other names in the mouse and human genomes. It became obvious from these analyses that *Gm6484* (gene) and EG624219 (protein) as annotated in the mouse genome and *C19orf80* (gene) and TD26 (hepatocellular carcinoma-associated protein), annotated in the human genome described the same genetic entity[17].

Yi *et al*[15] noted that the expression of betatrophin mRNA was the most abundant in the liver and WAT of mice. Similarly, the expression of betatrophin was more than 250-fold higher in the human liver compared with WAT, heart, brain, pancreas or skeletal muscle. The authors extended their observations in S961-infused mice by exploring the expression of betatrophin in a number of other well-studied murine models of insulin resistance. Consistent with their hypothesis that betatrophin expression was a compensatory response to insulin resistance, Yi *el al*[15] observed that the livers of *db/db* and *ob/ob* mice expressed 3-4-fold higher levels of betatrophin mRNA. Similarly, a about 20-fold surge in hepatic expression of betatrophin mRNA was seen in mice during gestation, a time known to be associated with insulin resistance, accompanied with pancreatic β-cell expansion. Based on these observations the authors concluded that a state of insulin resistance was specifically involved in the induction of betatrophin gene expression. This conclusion was further bolstered by authors' observation that regeneration response of pancreas after its exposure to diphtheria toxin did not lead to induction of betatrophin.

As predicted by *in silico* analysis, Myc-tagged betatrophin expressed in Hepa1-6 or 293T cells behaved as a secreted protein, as judged by its intracellular location in vesicle-like structures, and its presence in the culture medium. Similarly, the hepatic expression of Myc-tagged betatrophin led to its appearance in circulation and was accompanied by a robust increase in the rate of replication of β-cells (17 to 33-fold). To examine the specificity of betatrophin action on β-cells, Yi *et al*[15] stained pancreatic sections with Ki67- and PCNA-specific antibodies, and used qPCR to quantify expression of cyclins, *CDKs*, *E2F1* and *E2F2* genes. These studies revealed that exogenous hepatic expression of betatrophin was highly specific for β-cell proliferation since no other exocrine or endocrine cell types in the pancreas underwent multiplication. Thus, betatrophin appears to be a *bona fide* pancreatic β-cell specific hormone.

Yi *et al*[15] experimentally assessed the authenticity and normalcy of the newly formed β-cells by a number of criteria. They observed that pancreatic islets from control and betatrophin-expressing mice elicited similar glucose induced insulin secretion. The insulin tolerance tests in control and betatrphin-producing mice showed that they were similarly insulin sensitive. The normal insulin sensitivity of the betatrphin-expressing mice was in a sharp contrast to the situation seen in S961-infused mice that elicited robust insulin resistance. Finally, Yi *et al*[15] discovered that mice with forced expression of betatrophin elicited lower fasting glucose levels and had improved scores on glucose tolerance tests. These observations are consistent with the authors' conclusion that betatrophin, a hormone capable of inducing β-cell proliferation, is specifically produced by the liver under conditions of insulin resistance. Furthermore, the functional phenotype of the newly made β-cell in response to a forced expression of betatrophin appeared to be normal.

The discovery of a circulating hormone capable of inducing β-cell proliferation fulfills a cherished goal of many investigators engaged in T2DM research[14]. My commentary on the publication of Yi *et al*[15], would not be complete without a few words about the re-discovery of betatrophin in its current guise and it molecular characterization by three other names by three independent laboratories. Thus, the discovery of so-called *RIFL* (re-feeding induced fat and liver) was reported as an adipocyte-enriched insulin target gene with a role in lipid metabolism[18]. A related strategy to analyze differential gene expression by RNA-seq expression experiments in the liver and WAT of fasted and high fat-fed mice, lead Zhang[19] to discover *lipasin* as a nutritionally regulated inhibitor of lipoprotein lipase that was involved in regulating serum triglyceride levels. Finally, Quagliarini and co-authors characterized angiopoitin-like 8 (ANGPTL8) protein, a member of angiopoitin-like family of proteins[20] that was shown to regulate postprandial fatty acid metabolism; apparently, ANGPTL8 could not carry out this function in the absence of its association with ANGPTL3, a paralog of ANGPTL8[21]. In retrospect, it is obvious that betatrophin, RIFL, lipasin and ANGPTL8 are one and the same gene/protein. However, all three reports that preceded Yi *et al*[15] had described these genes as regulators of fatty acid metabolism and lipid homeostasis. In light of these observations the question of how mechanistically betatrophin exerts its pleiotrophic actions in different tissues under physi-

ological and pathological conditions becomes even more urgent[17]. The current progress notwithstanding, a fuller understanding of the varied functions attributed to betatrophin/RIFL/Lipasin/ANGPTL8 must be clarified before full therapeutic implications of Yi *et al*[15] findings are realized.

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