β-Cell–Specific Gene Repression: A Mechanism to Protect Against Inappropriate or Maladjusted Insulin Secretion?

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What makes β-cells unique is their continuous responsibility to produce, store and release the required amount of insulin to keep blood glucose normal. This is no trivial task because daily insulin demands fluctuate acutely (as happens during meals) or chronically (e.g., the adaptation to obesity or pregnancy). Moreover, normal blood glucose has two borders that need continuous protection. Insufficient insulin secretion should be avoided as this leads to hyperglycemia. Moreover, insulin excess causes hypoglycemia, a situation that jeopardizes brain function. Therefore, the optimal amount of β-cell activity is needed for normal health and this depends on an adequate plasticity of the functional β-cell mass (1). This Perspective examines the idea that protection of the two borders of blood glucose requires a genetically programmed β-cell phenotype with two unique faces (Fig. 1). The first depends on transcription factors that activate expression of specific proteins that mediate β-cell function. The second face depends on β-cell–specific repression of a small set of genes. We start to understand how expression of the latter genes may impair normal β-cell function. The best examples of expression of such “disallowed” genes in β-cells lead to inappropriate insulin release (2).

HOW ISLET-SPECIFICALLY REPRESSIONED GENES WERE IDENTIFIED

The idea of “disallowed” β-cell genes originated from studies on glucose phosphorylation, the first flux-generating step of glucose signaling in β-cells. Four different genes encode for enzyme isoforms that can catalyze this step, but only glucokinase (hexokinase 4) is expressed in mature β-cells, whereas the other hexokinases, in particular hexokinase 1, are profoundly repressed (3). Evolution has favored a developmental program based on repression of low Km hexokinases in maturing β-cells because this prevents insulin release in the fasted state, when circulating glucose is low (2). Another “disallowed” gene in β-cells is Mct1 (Slc16a1) (4). The encoded protein is a monocarboxylate transporter that facilitates diffusion of lactate and pyruvate across the plasma membrane of most cells in order to sustain ATP production by anaerobic glycolysis. In β-cells, however, MCT1 protein needs to be very low in order to prevent inappropriate insulin release triggered by circulating pyruvate. In a rare genetic disease called exercise-induced hyperinsulinism a mutation in the Mct1 promoter leads to MCT1 production in β-cells, causing hypoglycemia (4).

These examples suggested that other proteins could also be repressed in β-cells in order to allow normal insulin release. In order to find genes that are preferentially or specifically expressed in mouse islets, we compared the mRNA expression profiles of freshly isolated islets with a panel of 20 other mouse tissues (Fig. 2A) (5). On the basis of these comparisons, we calculated a tissue specificity score for each of the expressed mRNA species in the panel. This resulted in a distribution plot shown for islets in Fig. 2B for the collective transcriptome. The rightmost category contains a group of genes that are preferentially or specifically expressed in pancreatic islets, insulin 1 and insulin 2 and the other islet hormone genes being examples. On the basis of this information, we further studied some of these genes in detail (6–8). Unexpectedly, at the extreme left of the same plot there is a category of mRNA species that are significantly more expressed in all tissues in the panel than in islets (5). This result further illustrated the idea that large differences exist between tissues in the expression level of ubiquitously expressed genes (9). We confirmed the result by a Bayesian approach based on the intersection-union test (5) and found a largely overlapping set of genes that are islet-specifically repressed. In order to get an overall error rate of 0.05 for the total of 17,344 tested genes, the intersection-union test was performed with multiple comparison correction resulting in a significance level of 3 × 10⁻⁶ for individual tested genes. The used strategy was applicable to any tissue in the panel, indicating that tissue-specifically repressed genes may have a broad biological significance that still largely needs to be defined. The chosen strategy for finding tissue-specific gene repression was also applied to the liver as baseline instead of islets (5), and this resulted in the identification of liver-specifically repressed genes as the mirror situation of liver-specific genes (Fig. 2C). Thus, we can draw the conclusion that the specialized phenotype of any particular cell type may not only reflect expression of tissue-specific genes but also an opposite phenomenon of cell type–specific gene repression.

We next considered potential artifacts that may give false-positive or false-negative results. One source of false positives is transcript variation. Indeed, it is possible that a gene is truly expressed in all tissues, but that it forms one transcript variant that is not produced in islets. The probe set that would measure this variant would generate data suggesting that the gene is not expressed in islets. To investigate this possibility, we repeated the analysis with exon-oriented Affymetrix Gene microarrays and found good overlap with the results obtained with 3’UTR-oriented Affymetrix 430 2.0 arrays (Fig. 3). False-positives can also
result from common cell types that are present in the tissue panel but that are artifically excluded in the baseline tissue. This is important for collagenase-isolated islets because a possible artifact is that circulating blood cells are washed out. We shortened the collagenase isolation to 3 min digestion followed by several sedimentation steps at 1 x g in order to obtain ex vivo RNA (10). As a result, significant amounts of blood cells were still present, and abundant erythrocyte and lymphocyte mRNA signals (e.g., a- and b-globins, Lyc6 genes) were in the range of the tissues panel. More false-positives of this type are expected when purified b-cells are compared with the tissue panel. On the other hand, when islets are used instead of pure b-cells, false-negatives occur because repression in b-cells is masked by high expression in contaminating exocrine cells and/or non-b-cells. This point was illustrated before by measuring hexokinase 1 in purified pancreatic b-cells and acinar cells (3). In order to assess this contamination effect, we measured mRNA expression for islet-repressed genes in fluorescence-activated cell sorter-purified b-cells and obtained even lower signals (5). Together, the approach with a tissue/organ reference panel requires properly isolated islets as a baseline. In order to refine the search for genes that are selectively repressed in b-cells, a new reference panel with other purified primary cell types will be needed.

**ISLET-SPECIFIC GENE REPRESSION STARTS WHEN b-CELLS MATURE**

Progress in regenerative medicine brings closer the idea of replacing the functional b-cell mass in patients with type 1 diabetes with an alternative source of cells (11). Considering the hypothesis of Fig. 1, it may be important to understand how normal b-cells mature not only in terms of b-cell--specific function and specialized metabolic signaling (12) but also in terms of avoiding inappropriate insulin release. Together with Susan Bonner-Weir and Frederic Lemaigre, we observed that tissue-specific repression of genes unfolds in parallel with tissue-selective gene expression, both in neonatal rat islets and in fetal liver (5). One example is the important crossroad of pyruvate metabolism (Fig. 4): b-cell maturation can be measured both as increased pyruvate carboxylase expression and repression of lactate dehydrogenase. In adult b-cells, pyruvate carboxylase is abundant and lactate dehydrogenase deeply repressed, explaining anaplerosis and lack of anaerobic glycolysis (13). For the liver, metabolic specialization favors ketogenesis over ketone body oxidation, which is in agreement with liver-specific repression of OXCT1 as opposed to high expression of HMGCS2 (5).

The regulators that are responsible for the reciprocal time course of preferentially expressed and disallowed genes when b-cells mature need to be further defined. It is possible that overlap exists in the transcription factors that activate/repress in a context-dependent manner. Genomewide analysis of the histone code in islets and other mouse tissues indicates that activation and repression marks for gene transcription arise when b-cells differentiate (14). In agreement with this idea, trimethylation of lysine-27 of histone 3, a mark for polycomb-mediated gene inactivation, is high in the gene promoter region of Ldha, Mct1, and other repressed islet genes in the mouse (5). Posttranscriptional regulation by microRNAs could further contribute to tissue-specific repression as is suggested by experiments in the maturing liver where miR-122 repressed OXCT1 mRNA (5). We further predicted that other tissue-specifically repressed microRNAs can be targeted by microRNA isiforms, which are abundant in the tissue where mRNA repression occurs (5). For Mct1 and b-cells, experimental evidence was indeed provided for repression via miR-29 (15), but a developmental context still needs to be established. Both histone modifications and microRNA’s create a multitier mechanism of islet-specific repression of genes.

One important area of further research is the possible failure of islet-specific gene repression in diabetes. Very little is known about this subject in human diabetes. In animal models, however, detailed information is known for Ldha. In a pioneering article, Jonas et al. (16) showed that significant upregulation of Ldha mRNA is the result of chronic exposure of isolated rat islets to hyperglycemia. Laybatt et al. (17) then showed that this derepression of the Ldha gene in islets also occurs in vivo in diabetic animals, and that this loss of repression is paralleled by a loss of expression of the b-cell transcription factors PDX1, NKX6-1, and PAX6. As the epigenetic marks of the Ldha-gene in the adult mouse islets are strongly repressed (5), it is of interest to understand how derepression occurs. One possibility is that PDX1, NKX6-1, or PAX6 (or a combination of these) act as repressors of the Ldha gene so that reduced expression of these factors causes both loss of b-cell maturation and derepression of the Ldha-gene.

Another issue that needs to be better understood is why some genes need to be specifically repressed in b-cells. For most of these genes, we can only speculate how repression
contributes to β-cell function. Some may protect against excessive β-cell growth or inappropriate secretion of insulin, whereas others might reduce insulin production by interfering with the work of normal β-cell proteins. It should be emphasized at this stage that, although there is reasonable amount of evidence to support the concept of inappropriate insulin release, the idea of protection against excessive β-cell growth is more speculative and needs to be further investigated. In the next two sections, we will discuss the idea that at least some of the genes in Table 1 and Fig. 3 would, when not repressed, cause either inappropriate insulin release or rates of insulin release induced by physiological stimuli that are poorly adjusted to physiological demands.

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**FIG. 2. Tissue-specific repression of gene expression.**

A: The phenomenon was discovered by performing genome-wide mRNA expression analysis of total mRNA extracted from freshly isolated islets as compared with 20 different tissues from the same mice. For all transcripts that are expressed in one or more tissues, statistical analysis allows to search for islet-specifically repressed genes (5). B: One way to visualize such genes is to plot for all transcripts the distribution of the sum score of significant comparisons (20 comparisons made between islets and members of the panel and for each comparison a score of −1, 0, and +1 when the transcript is less, equally, or more abundant in islets, respectively). The category with a sum score of −20 contains the islet-specifically repressed genes. C: The same concept can be applied to other tissues and organs such as the liver (5). At the left side of this cartoon, a liver-specific gene is shown with high expression (green) in contrast with background mRNA expression (red) in the rest of the organism. This situation is mirrored by a liver-specifically repressed gene such as *Oxct1*, for which mRNA is abundant in all tissues (green) except in the liver (red). This gene encodes a key enzyme of ketone body breakdown, whereas the liver is a ketone body-exporting tissue.

**FIG. 3. Islet-specifically repressed genes in the mouse.** Data are from Thorrez et al. (5) and represent mean mRNA expression signals ± SEM for 14 genes that were identified with two different types mRNA expression arrays as being specifically repressed in isolated islets as compared with a panel of mouse tissues. Islet expression levels are black and white bars, and mean tissue panel expression are dark and light gray bars. Dark shades, Affymetrix 430 2.0 array (oriented to the 3' UTR of transcripts); light shades, Affymetrix Mo Gene 1.0 arrays (probes oriented to all exons). GA, gene array.
In most other cell types, MCT1 and LDHA ensure anaerobic glycolysis during hypoxia. Production and cellular efflux of lactate and pyruvate maintains ATP production, even when mitochondrial oxidation is low. In contrast, β-cells exhibit an aerobic glycolysis (13) and contain low amounts of LDHA (23) and MCT1 (24). This is explained by the fact that the Mct1 and Ldha genes are deeply and islet-specifically repressed (5). The rationale of this repression is illustrated by in vitro experiments and by a human genetic disease. Forced expression of MCT1 in INS1 cells caused pyruvate-stimulated insulin release, while overexpression of both MCT1 and LDHA were needed for lactate-stimulated release (25). In exercise-induced hyperinsulinemia, inappropriately high levels of circulating insulin are found shortly after physical exercise or after pyruvate injection (26). These patients have mutations in the Mct1 promoter (4), and it is believed that such mutations destroy regulatory site(s) that allow repression in mature β-cells. From an evolutionary standpoint, such inappropriate insulin release would seem problematic because the struggle for life usually requires exercise; when this would lead to hypoglycemia it would impair the brain’s ability to plan a survival strategy. Although other cell types need MCT1 and LDHA to adapt metabolism to hypoxia, it remains to be understood how β-cells can cope with insufficient oxygen supply when these genes are not expressed. Very high blood flow rates may protect against hypoxia. Indeed, islet tissue represents less than 1% of pancreatic mass but receives 6% of pancreatic blood flow; when calculated per minute and per gram tissue, islet blood flow is among the highest in the organism (27). However, local variations in islet oxygenation exist in the normal pancreas, and it was recently proposed that the poorly oxygenated islets represent a functional reservoir (28). This could indicate that, in addition to other aspects of heterogeneity among individual β-cells (29), normal pancreatic β-cells may differ in the degree of repression of islet-specifically repressed genes, but there is no experimental evidence to support this idea.

In addition to LDHA, two other enzymes—catalase and ornithine aminotransferase—are selectively repressed in mouse islets (Fig. 3), but a direct influence of this repression on insulin release has not been demonstrated so far. For many years it has been known that rodent β-cells contain very low levels of catalase (30), and this lack may explain the great sensitivity of β-cells for oxidative stress (31). Catalase recovers hydrogen peroxide (H₂O₂) to water and oxygen. An interesting difference exists with glutathion peroxidases (Fig. 4) because the latter enzymes require NADPH. Because NADPH levels in β-cells strongly depend on glucose metabolism (21), it is possible that the accumulation of H₂O₂ at low glucose levels may serve to prevent inappropriate insulin release. However, it should be mentioned that the role of repression of catalase to allow physiological control of insulin release is hypothetical because mice with overexpression of a catalase transgene in β-cells did not have abnormal insulin release (32). This could still mean that if repression of catalase prevents inappropriate insulin release, the conditions under which this might occur have not yet been identified. Another possibility that needs perhaps further investigation is that low catalase in β-cells could allow the buildup of oxidative stress at chronic low glucose in order to favor β-cell apoptosis (33). One can only speculate about the profound repression of ornithine aminotransferase (OAT) in β-cells. In the liver, this enzyme connects arginine and glutamate metabolism (34), and congenital enzyme deficiency causes hyperammonemia and blindness due to gyrate
atrophy of the choroid and retina (35). Lack of this mitochondrial enzyme in β-cells could for instance help prevent anaplerosis of amino acid carbon into the Krebs cycle when circulating amino acids rise without an elevation of blood glucose, such as occurs after a protein-rich carbohydrate-depleted meal.

### ISLET-SPECIFIC GENE REPRESSION TO PREVENT MALADJUSTED INSULIN SECRETION INDUCED BY PHYSIOLOGICAL STIMULI

In addition to inappropriate insulin release, the amount of secretion after physiological stimuli can be maladjusted to the amounts that are needed. One can speculate about the possibility that islets repress expression of growth promoting genes in order to prevent the pancreatic β-cell mass from expanding too much. This hypothesis can be made on the basis of the observation that several genes shown in Table 1 and Fig. 3 are linked to cell proliferation in general from expanding too much. This hypothesis can be made on the basis of the observation that several genes shown in Table 1 and Fig. 3 are linked to cell proliferation in general and β-cell proliferation specifically in some recent studies. LIM-domain only 4 (Lmo4) encodes a transcriptional regulatory protein that is responsible for multiple protein-protein contacts in the nucleus. LMO4 overexpression is found in mammary gland tumors and pancreatic cancer. LMO4 silencing resulted in G2/M arrest of the cell cycle, interfering with a mitotic signaling pathway that depends on activation of ErbB2, a member of the epidermal growth factor–receptor tyrosine kinase family (36).

Another example of a widely expressed gene that stimulates cell proliferation is Cxcl12, also known as stromal cell–derived factor-1. The encoded protein is a small chemokine that binds primarily to CXC receptor 4 (CXCR4) leading to enhanced β-cell proliferation triggered by the activation of the protein kinase Akt and WNT signaling (37). In a recent study, Habener and colleagues (38) propose that Cxcl12 expression is present in the neonatal pancreas but declines to undetectable levels at 2 months of age. Interestingly, the expression of Cxcl12 in mature β-cells could be boosted by β-cell injury, and the authors propose that this reactivation may be an essential component of the capacity of rodent β-cells to regenerate after injury (38).

Perhaps the same is true for Pdgfra, the gene that encodes the platelet-derived growth factor receptor α polypeptide, a widely expressed tyrosine kinase receptor that stimulates cell proliferation in many tissues. A pioneering study on growth factor receptors indicated that overexpression of PDGF β-receptor stimulated β-cell replication, whereas cotransfection with the PDGF α-receptor limited this growth response (39). However, more recent work by Kim and colleagues (40) indicated that a crucial stimulatory alpha-type platelet-derived growth factor receptor (PDGFRA)-dependent pathway for pancreatic β-cell growth exists. One of the key observations in this study was that PDGFRA expression in mouse and human islets declines with age in a manner that may explain the loss of β-cell replicative potential in older individuals. An interesting aspect of the study is that forced overexpression of the receptor in PDGFRA-transgenic mice led to a phenotype with three times higher β-cell mass, significantly lower postprandial blood glucose, and improved glucose tolerance (40). It will be interesting to see how these mice tolerate the fasted state.

Four more genes listed in Table 1 influence proliferation, but the link to islet biology is uncertain. Insulin-like growth factor binding protein 4 (Igfbp4) is highly expressed in many tissues, and encodes a small secreted protein that regulates insulin-like growth factor 1; in some circumstances this protein can promote cellular growth (41). Rho GDP dissociation inhibitor 2 (Arhgdib) plays a role in tumor growth and metastasis (42). The same applies to intera (globulin) inhibitor H5 (Itih5) that acts as a tumor suppressor that stabilizes the extracellular matrix and prevents tumor metastasis (43).

A special case among the islet-specifically repressed genes is mothers against decapentaplegic (MAD) homolog 3 (Drosophila) (Smad3), because the maladjustment that needs to be avoided is insufficient insulin release triggered by normal stimuli. In many tissues, SMAD3 is a key factor in the fibrotic response to chronic injury accompanied by transforming growth factor β receptor stimulation (44). In pancreatic β-cells, however, SMAD3 binds to the E2-box of the insulin promoter so that it represses insulin gene transcription (45). Low expression of Smad3 in β-cells

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**TABLE 1**

Function of mouse islet-specifically repressed genes

| Gene    | Name                                                      | Function                        | Reference |
|---------|-----------------------------------------------------------|---------------------------------|-----------|
| Arhgdib | p GDP dissociation inhibitor 2                            | Proliferation                   | (42)      |
| Cat     | Catalase                                                  | Degradates H$_2$O$_2$           | (30)      |
| Cxcl12  | Chemokine (C-X-C motif) ligand 12                         | Proliferation after injury      | (37)      |
| Igfbp4  | Insulin-like growth factor binding protein 4              | Proliferation                   | (41)      |
| Itih5   | Inter a (globulin) inhibitor H5                           | Proliferation                   | (43)      |
| Ldha    | Lactate dehydrogenase A                                   | Inappropriate insulin release   | (25)      |
| Lmo4    | LIM domain only 4                                         | Proliferation                   | (36)      |
| c-Maf   | Avian musculoaponeurotic fibrosarcoma (v-maf) oncogene homolog | Proliferation                   | (48)      |
| Oat     | Ornithine aminotransferase                                | Interconversion of arginine, proline, and glutamate | (35)      |
| Pdgfra  | Platelet-derived growth factor receptor, α polypeptide    | Proliferation                   | (40)      |
| Slc16a1 | Monocarboxylic acid transporter member 1                   | Inappropriate insulin release   | (4)       |
| Smad3   | MAD homolog 3 (Drosophila)                                | Fibrosis after injury; repressor of insulin gene | (44,45) |
| Zfp36l1 | Zinc finger protein 36-like 1                             | mRNA binding protein            | (49)      |
| Zyx     | Zyxin                                                     | Apoptosis                       | (50)      |
may therefore beneficial to allow normal control of the insulin gene by PDX1 and other β-cell transcription factors, resulting in normal insulin biosynthesis after glucose stimulation. Although Smad3 seems to be an exception to the model presented in Fig. 3, it forms a unifying theme together with Cxcl12 and Pdgfra: the idea that wound healing factors that aid to the regeneration response in other tissues need to be restrained in β-cells in order to keep circulating insulin levels in the normal range. One could argue that, as long as β-cells are properly controlled by glucose, an increased β-cell number would not be a risk factor for hypoglycemia. It is conceivable however that the newly replicated β-cells in adult pancreata start as immature cells that are not properly controlled by metabolic coupling factors, analogous to what was found in neonatal β-cells (12). In particular, further investigation is needed to assess when newly formed β-cells (that arise in models of enhanced β-cell proliferation or β-cell neogenesis) repress genes that would predispose to inappropriate or maladjusted insulin release.

FROM ISLET-SPECIFIC REPRESSION IN MICE TO “DISALLOWED” HUMAN β-CELL GENES

In this article we have discussed the available evidence for the idea that a genetically programmed phenomenon of islet-specific gene repression contributes to the avoidance of inappropriate insulin release. Moreover, as some of the islet-specifically repressed genes encode proteins that stimulate β-cell proliferation, one can speculate that another level of protection against excess circulating insulin is the avoidance of a too high pancreatic β-cell mass. More research is needed in order to better understand how each of the islet-specifically repressed genes contributes to the phenotype of normal β-cells. Is the function of the encoded protein really detrimental for β-cells, so that we can call the gene “disallowed” in β-cells (2)? Or do we measure the extreme end of a stochastic distribution of mRNA expression levels among tissues, in the sense that β-cells can work normally with very low levels of gene expression but would also functionally tolerate higher expression levels?

The distinction between these two possibilities can perhaps be made by measuring the consequence of forced gene expression experiments, either by transfection in vitro or by transgenic mice. When consequences of forced expression experiments in β-cells are significant, it will be relevant to better understand the precise development of the repressive machinery during β-cell maturation. Another aspect that needs further study is whether or not mouse data of islet-specific repression can be extrapolated to human β-cells. As was shown before for glucose transport (46) and oxygen radical-induced repair (47), major differences can exist between rodent and human islets. At the level of tissue panels, we found reasonable overlap for genes that are tissue-specifically repressed in mice and humans, but islets were not included in the analysis (5).

When repression in β-cells is evolutionarily conserved, as appears to be the case for MCT1, the important conclusion is that two faces of the mature phenotype of human β-cells are needed to protect against excursions across the borders of normoglycemia. Further studies of this novel concept will be necessary to understand the true identity of primary β-cells; this knowledge will help research efforts aiming at the generation of β-cells from stem cells. Finally the protection against maladjusted insulin release by restraining growth and wound repair gene signaling in β-cells needs further investigation as novel insight might contribute to understanding the problem of a low functional β-cell mass in patients with type 2 diabetes.

ACKNOWLEDGMENTS

Studies of islet-specifically repressed genes in the laboratory of the authors are financially supported by the Juvenile Diabetes Research Foundation (JDRF Grant 2006-182), the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (FWO Grant G.0672.12), the Belgian Science Policy (Interuniversity Attraction Poles Program [PAI 640]), and the Katholieke Universiteit Leuven (GOA/2009/10).

F.S. researched data and wrote the manuscript. L.V.L. and M.G. researched data and reviewed and edited the manuscript. L.G. and G.d.F. contributed to discussion and reviewed and edited the manuscript. A.S. researched data, contributed to discussion, and reviewed and edited the manuscript. K.L. researched data, wrote the manuscript, and contributed to discussion. F.S. is the guarantor of the integrity of the data and the accuracy of the data analysis.

The authors thank Dr. Susan Bonner-Weir and Dr. Gordon Wexler (Joslin Diabetes Center, Boston, MA) and Timo Otonkoski (Biomedicum Stem Cell Centre, University of Helsinki, Helsinki, Finland) for insightful discussion and comments after reading the manuscript; and Lieven Thorrez and Stefan Lehnert (Katholieke Universiteit Leuven, Belgium) for making Figure 2C.

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