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Consensus Statement
β-cell Failure in Type 2 Diabetes:
Postulated Mechanisms and Prospects for Prevention and Treatment

Short title: **β-cell Failure in Type 2 Diabetes**

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Objective: This report examines the foundation of β-cell failure in type 2 diabetes and suggests areas for future research on the underlying mechanisms that may lead to improved prevention and treatment.

Participants: A group of experts participated in a conference on October 14-16, 2013 cosponsored by The Endocrine Society and the American Diabetes Association. A writing group prepared this summary and recommendations.

Evidence: The writing group based this report on conference presentations, discussion, and debate. Topics covered include genetic predisposition, the foundations of β-cell failure, natural history of β-cell failure, and impact of therapeutic interventions.

Conclusions: β-cell failure is central to the development and progression of type 2 diabetes. It antedates and predicts diabetes onset and progression, is in part genetically determined, and often can be identified with accuracy even though current tests are cumbersome and not well standardized. Multiple pathways underlie decreased β-cell function and mass, some of which may be shared and may also be a consequence of processes that initially caused dysfunction. Goals for future research include: 1) Impact the natural history of β-cell failure; 2) Identify and characterize genetic loci for type 2 diabetes; 3) Target β-cell signaling, metabolic, and genetic pathways to improve function/mass; 4) Develop alternative sources of β-cells for cell-based therapy; 5) Focus on metabolic environment to provide indirect benefit to β-cells; 6) Improve understanding of the physiology of responses to bypass surgery; 7) Identify circulating factors and neuronal circuits underlying the axis of communication between the brain and β-cells.

Two major pathophysiologic abnormalities underlie most cases of type 2 diabetes (T2D): 1) insulin resistance and 2) defects in pancreatic β-cell function. The current consensus is that both are essential components in disease pathogenesis even if their relative importance, the precise temporal sequence of events, and underlying mechanisms vary considerably in different populations and individual patients.

In October 2013 The Global Partnership to Accelerate Diabetes Research, cosponsored by The Endocrine Society and The American Diabetes Association, assembled international experts (see Appendix) to inform the global health research agenda by reviewing the state of the science and identifying pressing research needs related to β-cell dysfunction in T2D. The major issues addressed and outcomes of their discussion follow.

Genetics and Epigenetics

Powerful evidence for a genetic component to T2D (1) has driven extensive efforts to identify genetic variants contributing to risk. Monogenic forms of diabetes such as Maturity-Onset Diabetes of the Young (MODY) have proven to be natural models for understanding mechanisms underlying insulin secretion defects; genes discovered through family-based approaches are important regulators of insulin secretion and β-cell development. Findings that neonatal diabetes is most commonly due to activating mutations in genes encoding the ATP-sensitive potassium channel subunits Kir6.2 or SUR1 and can be treated with high-dose sulfonylureas despite being insulin-dependent also provide a compelling case for genetic evaluation of monogenic diabetes with therapeutic and prognostic implications (2-6). Exome-wide and whole genome sequencing approaches will expand current capacity to study these disorders.

Genome-wide association studies (GWAS) using high density genotyping arrays have transformed understanding of the genetic architecture of T2D (7). At the time of writing, over 60 genetic loci have been convincingly associated with T2D, the great majority in some way involved in β-cell biology, underscoring the importance of β-cell dysfunction in T2D pathogenesis (8, 9). GWAS data must be interpreted with great caution until the precise genes in the loci associated with T2D have been identified and the impact of specific variants on β-cell function is more clearly understood, as exemplified in a recent enigmatic study on the possible

protective effects against T2D of loss-of-function mutations in *SLC30A8* (encoding the islet zinc transporter ZnT8) (10). In any case, these variants explain only a small proportion of total genetic risk (11). Studies are underway based on exome and whole genome sequencing technology to identify low-frequency, high-impact variants accounting for a greater component of risk (12). Other novel approaches have been proposed, but genetic discovery models to date have largely been simple case-control studies of this complex metabolic disorder (13). It is furthermore evident that other factors that influence gene expression contribute towards the complexity of T2D, specifically epigenetic mechanisms and microRNAs (miRNAs).

Epigenetic mechanisms refer to functional changes to the genome that do not involve any alteration in nucleotide sequence. Such mechanisms (e.g. DNA methylation and histone modifications) can be active during fetal as well as postnatal and adult life, and impact the level of expression of select genes associated with T2D (14). While the epigenome may be dynamic and change due to environmental exposure, modifications may also be stable and inherited, making epigenetics a potentially important pathogenic mechanism. The possibility that the environment can alter the pancreatic islet epigenome and subsequently affect β-cell function and diabetes pathogenesis is specifically reflected in human and animal studies linking an impaired intrauterine environment and resulting low birthweight to an increased risk for postnatal metabolic disease, with decreases in β-cell proliferation, mass, and insulin secretion in the face of documented epigenetic modifications in key β-cell genes (15, 16). In addition, a low protein diet *in utero* alters the epigenetic profile of *HNF4A* in rodent islets, associated with impaired islet function, findings supported by human studies (17, 18).

Studies of pancreatic islets from non-diabetic donors (19, 20) and from patients with T2D (21) have identified epigenetic modifications in genes that potentially affect β-cell function. Such studies of human pancreatic islets together with *in vitro* studies of clonal β-cells further suggest that hyperglycemia alters DNA methylation of *PDX1* and *INS* (22-25). DNA methylation mainly occurs on cytosines in CpG dinucleotides, and approximately 50% of single nucleotide polymorphisms (SNPs) associated with T2D introduce or remove a CpG site. These CpG-SNPs are associated with differential DNA methylation, gene expression, alternative splicing events, and hormone secretion in human pancreatic islets, suggesting strong genetic-epigenetic interactions (26).

It has also been suggested that histone modifications in human islets contribute to reprogramming α to β cells, possibly due to the large number of bivalent marks in α cells (27). Lipid treatment also alters the activity of enzymes responsible for histone modifications in clonal β-cells, in parallel with decreased glucose-stimulated insulin secretion (28). Other recent studies indicate that histone deacetylases (HDACs) contribute to cytokine-mediated β-cell damage, suggesting HDAC inhibition as a possible diabetes treatment (29).

MicroRNAs are a class of small non-coding RNA molecules that modulate gene expression by binding to specific target mRNAs to prevent their translation and/or promote degradation. It has been suggested that altered miRNA expression may contribute towards β-cell failure in T2D and that these molecules may serve as biomarkers for the disease (30).

Genetic and environmental stressors likely modulate miRNA expression, altering cellular phenotypes. Specific miRNAs are critical to pancreatic β-cell development, function, and adaptive turnover. Individual miRNAs are highly represented in β-cells (31), impacting function and mass both positively and negatively. For example, knockout of miR-375 promotes progressive hyperglycemia in mouse models due to decreased insulin content and progressive loss of β-cell mass (32). There is increasing interest in the modulation of miRNA expression and a recent study has revealed an epigenetic mechanism in islets from patients with T2D (33).

***Looking to the future*:** Elucidating a full picture of genetic risk for diabetes is an increasingly daunting prospect. This will require insight and expertise from investigators in a wide range of fields that complement the specific skills of diabetes-focused researchers. Clearly extensions of "conventional GWAS" are highly desirable, including evaluation of genetic models beyond single genes, coupled with more sophisticated quantitative measures of β-cell function. A major barrier is the lack of large-scale, population-based samples with high quality metabolic measurements of β-cell function, together with a dearth of explanations for how discovered T2D genes actually mediate diabetes risk.

Studies on epigenetics and miRNAs are distinctive in going beyond statistical associations to integrate multiple pathways to identify function, but they are in their infancy. Understanding factors altering the expression of miRNAs and the epigenome in pancreatic islets and β-cells from prediabetic and T2D subjects and, further, developing selective small molecules that target epigenetic enzymes to improve β-cell function and/or treat diabetes is essential.

Environmental modification could influence both miRNAs and epigenetics, and a provocative question is whether such modifications can be used to predict β-cell failure risk. Finally, combining epigenetic and genetic research to integrate the entire body of data will be necessary to explain the "missing" heritability in diabetes.

The foundation of β-cell failure; dysfunction, dedifferentiation, or death?

β-cell loss in response to nutrient excess and stress was traditionally felt to occur exclusively via β-cell death. While β-cell death might be a final common pathway in T2D's natural history, more recent evidence indicates a more complex situation in which β-cells can initiate several alternative responses to avert irreversible loss, suggesting the potential for earlier intervention. Mouse studies led by Accili and coworkers have shown that β-cell dysfunction due to Fox01 deficiency during pregnancy and aging is primarily associated with β-cell dedifferentiation, rather than death (34). This finding revisits an earlier one (35) suggesting β-cell dedifferentiation during disease development, although additional experimentation is needed to determine whether cells lose their defining β-cell characteristics temporarily; revert to an immature fetal or neonatal-like state with impaired glucose-stimulated insulin secretion that reinitiates expression of fetal hormones; or indeed revert to an undifferentiated progenitor state. Relevance to human diabetes remains to be established.

Oxidative stress can inactivate key islet transcription factors, producing "stunned" β-cells that temporarily stop responding to glucose and storing normal amounts of insulin (36, 37). Emerging evidence in mice also shows considerable plasticity within islets, allowing intra-islet cell conversions but only in the face of extreme β-cell destruction (38). The similarity between α and β-cell transcriptomes in mice and humans supports this model, as does the discovery that hormone gene promoters in different islet cell types present similar methylation patterns.

A challenge in understanding β-cell failure is elucidating key elements responsible for their function and survival, including their apparently unique vulnerability to environmental changes. Here clonal cell lines selected for characteristics such as secretory defects after high glucose exposure or susceptibility to cytokine-induced death have proved useful (39). Insights have also come from studying the unique substrate metabolism of β-cells, chiefly those focusing on the link between pyruvate cycling and glucose-induced insulin secretion (40). Studying the transcriptional control of replication is yet another way in which basic models may provide

valuable translatable information and ultimately generate hypotheses for evaluation in primary β-cells *in vitro* and *in vivo* (41).

Many physiologic stressors (Figure 1) impact β-cell function in the environment of metabolic overload and insulin resistance commonly found in human obesity-linked T2D. While β-cells initially respond by activating compensatory pathways to improve the insulin secretory response, eventually they initiate several pathological programs that synergistically promote β-cell dysfunction and, ultimately, death. To understand and intervene in disease progression, ongoing investigations are exploring which of the following pathological conditions, or β-cell stressors, are initiated first and which might represent the most effective intervention points.

Endoplasmic reticulum (ER) stress appears to arise when markedly increased insulin production to meet metabolic demand necessitates increasing flux through the rough ER, with stress evident in the unfolded protein response (UPR) that chaperones newly synthesized proinsulin along the secretory pathway. Such changes may promote β-cell secretory dysfunction and, under chronic challenge, apoptosis. While ER stress may play a key role in the pathogenesis of certain forms of monogenic diabetes, its role in common T2D remains unclear.

Metabolic and oxidative stress, primarily from obesity's excessive nutritional state, leads to β-cell damage associated with glucotoxicity, lipotoxicity, and glucolipotoxicity (42). An emerging concept is a link between oxidative stress and observed DNA damage leading to altered transcription factor expression. Although β-cells are uniquely geared for efficient oxidative metabolism—both to provide energy via ATP production and to generate secondary signaling mechanisms—markedly increased glycolytic flux in hyperglycemia may underlie dysfunction. Moreover, because β-cells lack certain antioxidant enzymes that dispose of reactive oxygen species (ROS), increased ROS production may promote dysfunction and even apoptosis. Mishandling of excessive cholesterol commonly seen in T2D, with accumulation in β-cells, could perhaps impair secretion (43).

Amyloid plaques, which characterize islets in T2D, consist mainly of islet amyloid polypeptide (IAPP). In chronic hyperglycemia/hyperlipidemia, (pro)IAPP synthesis increases in β-cells, parallel to proinsulin, and can reach threshold levels that allow proapoptotic IAPP oligomers to form (44) that induce IL-1β release to recruit macrophages and enhance local islet inflammation (45).

Inflammation. Whether increased local islet inflammation, well-established in T2D pathogenesis (46), results from a janitorial macrophage infiltration to clear damaged islet β-cells and/or an innate inflammatory response remains unresolved. What has become clear, however, is that anti-inflammatory therapies (i.e. IL-1beta antagonism) can preserve some β-cell functional mass in T2D (47).

Islet integrity/organization is often disrupted in T2D pathogenesis, potentially perturbing cell-cell communication within islets. This may contribute to poorly regulated secretion of insulin and also glucagon, perhaps contributing towards hyperglucagonemia that exacerbates hyperglycemia in T2D. In addition, loss of islet integrity could diminish the β-cell incretin response.

***Looking to the future*:** β-cell demise is a multifactorial process involving many stressors. It remains unclear which pathway is disrupted first, and this may actually depend on the individual. Regardless of the initiation event, a feed-forward loop becomes induced that is difficult to stop. Given the likely molecular crosstalk and convergence between the pathways, targeting a single molecule could have beneficial effects by blocking multiple stressor pathways. Recent studies have offered novel insight into pathways activated within β-cells to cope with stress. Novel therapies that exploit these natural defense mechanisms to prevent or reverse β-cell failure in T2D may be possible. It is postulated that if β-cell dysfunction is not ameliorated by effective therapy, with time there is loss of β-cell identity through dedifferentiation, and ultimately death. This sequence suggests the need to intervene as early as possible in the course of disease.

Natural history of β-cell failure

Impaired insulin secretion assessed by oral or intravenous glucose tolerance testing and hyperglycemic clamp studies is seen in pre-diabetes as well as early in disease, with reduced secretion negatively correlated with glycemia (48). Although declines in β-cell mass and function are not well-correlated, presumably because function depends greatly on diabetic milieu, climbing glucose levels and deteriorating β-cell function are tightly correlated (49). While β-cell function appears to decline progressively, insulin secretion defects seem at least partially reversible, especially early in disease.

Family history and obesity are major risk factors for both youth and adults. In youth, a family history of T2D is also associated with a high-risk for decreased insulin sensitivity and response, and increased proinsulin-to-insulin ratio (50). Impaired glucose tolerance (IGT) in youth is characterized by β-cell dysfunction manifested in impaired first-phase, but preserved second-phase, insulin secretion relative to sensitivity. However, youth with IGT are no more insulin resistant than normal glucose tolerance (NGT) peers if matched for body composition and fat topography (51). Once treated with metformin after progressing to T2D, youth show a greater rate of treatment failure than adults (52).

β-cell mass increases during the first decade of life due to proliferation during the first five years (53, 54), stabilizing during adolescence with considerable variation (3-5 fold) unrelated to age or BMI. β-cell mass in T2D likewise varies, overlapping with that of normal individuals (55-57), although current data suggest a 20-60% reduction (58). Currently, measurements of human β-cell mass rely entirely on post-mortem, cross-sectional assessments; inability to assess mass non-invasively via imaging or biomarkers impedes determining temporal changes. Furthermore, histomorphometric measurement of β-cell area, volume, or mass is often imprecisely defined and complicated by technical inconsistencies (59). Importantly, too, because insulin sensitivity may vary as much as ten-fold in humans, variations in β-cell mass may be linked to individual insulin sensitivity. Thus, an individual with low insulin sensitivity and T2D may have a higher than "normal" β-cell mass that is functionally reduced, suggesting that *de facto* variation might be considerably reduced if corrected for insulin sensitivity.

Looking to the future: Marked variation in degree of β-cell loss in T2D could potentially be reconciled by adopting standardized approaches to quantification using area, volume, and/or mass in available pancreases. It would be enormously helpful to be able to measure beta cell mass in humans with non-invasive techniques. Many approaches have been and are being examined as has recently been reviewed (60). One promising approach is to use fluorescent exendin-4 derivatives, which should bind preferentially to beta cells (61, 62). However, a major issue concerns how much sensitivity and precision can be achieved by any non-invasive approach. A desirable goal might be to be able to measure changes in beta cell mass as small as 5% because such changes are expected to be important for beta cell function.

Given the difficulty of studying human β-cells, well-defined clinical phenotypes

correlated with β-cell defects and/or non-invasive imaging or biomarkers defining proliferation and death in pancreatic samples could help elucidate the discordance between functional and morphometric assessments, as well as identify changes indicating early β-cell failure in high-risk individuals (63).

Standardizing methodologies measuring β-cell function, and defining approaches for specific clinical questions, may also facilitate cross-study comparisons. Currently β-cell function is variably assessed using fasting indices derived from insulin and glucose values, dynamic testing with oral glucose or standardized meals, and responses following intravenous glucose infusions (64). Interpreting β-cell function in the context of glycemia and concurrent insulin resistance is critical in clinical studies evaluating therapeutic efficacy. Other features of potential interest include sustainability and durability of treatment effects during and after therapy.

Impact of therapeutic interventions

Interventions to prevent and treat diabetes by improving β-cell function are based on the premise that β-cell dysfunction can be reversed. This appears true for at least some portion of the pathogenesis spectrum, but limits of reversibility remain unexplored. Available data suggest that in established diabetes effects on β-cell function are not sustained following withdrawal of active therapies; whether this is true at earlier stages of diabetes or in pre-diabetes is unknown.

In the Diabetes Prevention Program (DPP), greater baseline β-cell function and insulin sensitivity contributed independently to the restoration of normal glucose tolerance following lifestyle changes (65, 66). Improvements in β-cell function also appear to play a role in pharmacologic approaches to prevention and treatment. Interventions in the TRIPOD/PIPOD (troglitazone and pioglitazone) and ActNOW (pioglitazone) studies, for example, significantly improved oral Disposition Index. Moreover, changes such as regression to IGT, maintenance of NGT, or progression to diabetes were proportional to insulin secretion response (67). GLP-1-based therapies magnify glucose-stimulated insulin secretion, as seen with significantly improved β-cell function in T2D following short-term infusions of GLP-1 (68, 69) and longer-term treatments with DPP-4 inhibitors (70) and GLP-1 receptor agonists (71, 72) However, while augmented insulin production as assessed with glucose- and arginine-stimulation continues during active treatment and is of clinical value, none of these agents has produced a meaningful, persistent change following therapy withdrawal (71, 73).

New evidence suggests that Roux-en-Y gastric bypass surgery (RYBG) exerts antidiabetic effects in part via β-cell functional improvements. RYGB is unique among weight-loss surgery approaches to diabetes for producing marked improvements in metabolic status, including disease remission in at least 80% of patients (74). The overall benefit clearly has a basis in the direct effects of weight loss, with attendant reduction in insulin resistance, and acute caloric restriction (75, 76). However, many lines of evidence demonstrate glycemic benefits independent of weight (77), including changes in β-cell function (78). Although studies to date have not clearly dissected changes in insulin sensitivity from changes in β-cell function, augmented GLP-1 secretion amplifies RYGB's antidiabetic effects on pancreatic islets (79), and post-RYGB hyperinsulinemic hypoglycemia may involve β-cell hypertrophy or neogenesis as well (80, 81). The observation that the strongest predictor of diabetes remission is duration of diabetes and insulin use prior to surgery (82) rather than weight regain also suggests underlying β-cell health as a limiting factor for RYGB's antidiabetic benefits.

Novel mechanisms of action and targets in β-cells such as fatty acid receptor activation, glucokinase activators, fractalkine, betatrophin, and β-secretase2 (BACE2) inhibitors continue to emerge, adding to the potential approaches to alter the natural history of diabetes. For decades it has been known that relieving hyperglycemia can itself improve insulin secretion and restore metabolic control, at least temporarily. Recently, aggressive early interventions with insulin therapy in newly diagnosed T2D (83), with targeted anti-inflammatory therapy using an IL-1beta antagonist (84), and with GLP-1 receptor agonists (85), have demonstrated that β-cell dysfunction can be reversed temporarily. However, durability of these effects following therapy withdrawal remains challenging. To date these responses have been evaluated only in established diabetes; whether they can alter the natural history of β-cell failure earlier in disease progression is unknown.

***Looking to the future*:** Numerous pathophysiologic pathways contributing to progressive β-cell failure have been identified as viable targets for intervention. However, no studies have established whether one pathogenic pathway dominates or can serve as a single major target. Moreover, different pathophysiologic processes may be active at different stages of progression, and optimal targets may shift accordingly. For example, early hyperglycemia may activate multiple pathophysiologic processes, including inflammation, amyloid accumulation,

dedifferentiation, apoptosis, and genetic alterations; whether any one target is optimal or sufficient at this stage remains undetermined. Further, there may also be a stage of pathogenesis beyond which therapeutic interventions cannot sufficiently enhance β-cell function, making treatments targeting other aspects of metabolic dysregulation relatively more valuable. Interventions targeted by stage of pathogenesis or combinatorial approaches may be required to preserve or restore β-cell function.

Summary and Conclusions

Progressive loss of β-cell function is central to the development and progression of T2D. Deterioration of β-cell function antedates and predicts diabetes onset and progression, is genetically determined, and can be predicted with accuracy even though current tests are cumbersome and not well standardized. There is, however, continued debate surrounding the relative contributions of decreased function or mass to clinically manifest β-cell dysfunction. This leads to confusion that extends beyond semantics and that will not be resolved until there are precise non-invasive methods to relate changes in β-cell mass and function over time. Multiple pathways underlie decreased β-cell function and mass, some of which may be shared, with reduction in mass perhaps a consequence of processes that initially caused dysfunction. In addition, the concept of β-cell dedifferentiation in T2D has regained favor. Even in the late stages of the disease, residual β-cells remain, and their number is possibly underestimated due to absence of markers of β-cell identity in dedifferentiated cells (86).

To date, most genes suggested by GWAS as associated with T2D are also associated with reduced β-cell function in the non-diabetic population, and are known to be expressed in β-cells and implicated in their development, function, or survival. However, many of these genes are also expressed in other tissues where their dysfunction may disturb glucose homeostasis and thereby, indirectly, β-cell function. Other genetic variation associated with diabetes, both common and less common, will be identified as the power of genetic studies increases; the challenge will be to turn this information into new biological insights. The study of epigenetic changes in the β-cell in T2D is likely to provide important new insight as well, but these studies are severely limited by the small number of islets available from patients with T2D and the difficulties separating cause and effect in hyperglycemia

A variety of interventions including weight loss, insulin, thiozolidenediones, and anti-inflammatory drugs can improve β-cell function temporarily, with improved glucose control, and these outcomes are certainly of value to patients. However, the limited number of clinical studies with appropriate protocols indicate that existing therapy does not arrest progression of β-cell dysfunction in T2D let alone reverse it, with the possible exception of gastric bypass surgery.

The group identified areas for future research that would improve our understanding of β-cell failure in T2D, hopefully leading to more effective prevention and the development of treatment with more durable beneficial effects on β-cell function than is possible today. Goals of future research are presented in Table 1.

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Author Contributions

P.A.H., K.S.P., D.W.B., M.A.H., C.L., K.J.M., A.C.P., C.J.R., L.S. and G.C.W. wrote the manuscript. P.A.H. is the guarantor of this work.

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Appendix

Participants in the meeting "β-cell Failure in T2D" held on October 14-16, 2013 were the following:

Meeting Series Steering Committee:

Robert H. Eckel, MD, University of Colorado
Ele Ferrannini, MD, University of Pisa, Italy
Steven E. Kahn, MB, ChB, VA Puget Sound Health Care System and University of Washington

Meeting Co-Chairs:

Philippe A. Halban, Ph.D., University of Geneva, Switzerland
Kenneth S. Polonsky, M.D., University of Chicago

Session Co-Chairs:

Donald W. Bowden, Ph.D., Wake Forest University
Robert L. Hanson, M.D., M.P.H., National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health*
Lori G. Sussel, Ph.D., Columbia University
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Meredith A. Hawkins, M.D., Albert Einstein College of Medicine

Kieren J. Mather, M.D., Indiana University

Speakers:

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Silva A. Arslanian, M.D., University of Pittsburgh
David E. Cummings, M.D., University of Washington
Stefano Del Prato, M.D., University of Pisa, Italy
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Rebecca A. Simmons, M.D., University of Pennsylvania
Markus Stoffel, M.D., Ph.D., Swiss Federal Institute of Technology (ETH), Switzerland
C. Bruce Verchere, Ph.D., University of British Columbia, Canada

* Unable to attend due to US government shutdown

Fellows:

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Andrea Giuseppe Daniele, M.D., Ph.D., University of Texas, Health Science Center

Daniel T. Meier, Ph.D., University of Washington, Seattle

Sara Michaliszyn, Ph.D., Children's Hospital of Pittsburgh

Marcel H.A. Muskiet, M.D., VU University Medical Center, The Netherlands

Anders Olsson, Ph.D., Lund University Diabetes Centre, Sweden

Richard Oram, M.D., University of Exeter, United Kingdom

Lane Jaeckle Santos, Ph.D., University of Pennsylvania

Marta Seghieri, M.D., University of Pisa, Italy

Sam Stephens, Ph.D., Duke University

Clara Westwell-Roper, M.D./Ph.D. Candidate, University of British Columbia, Canada

Table

Table 1: **Goals of future research:** The meeting participants identified the following major goals for future research focused on understanding, preventing and reversing β-cell failure in T2D.

1. Impact the natural history of β-cell failure, and slow the rate of progressive deterioration in function/mass.
2. Identify and characterize additional genetic loci for T2D, and define their impact on β-cell function.
3. Target β-cell signaling, metabolic, and genetic pathways to improve β-cell function/mass. Suggested targets: glucose metabolism, transcription factors and miRNAs, epigenetic changes, inflammation, growth and differentiation, and amyloid deposition.
4. Develop alternative sources of β-cells for cell-based therapy.
5. Focus on metabolic environment, insulin resistance, and obesity to benefit β-cells indirectly.
6. Improve understanding of the important and unexpected physiology of responses to bypass surgery as the basis for new therapy and to identify patients most likely to benefit from surgery.
7. Identify circulating factors and neuronal circuits underlying the axis of communication between the brain and β-cells.

Figure Legend

Figure 1. **Stressors on the β-cell in the pathogenesis of T2D**. In the excessive nutritional state found in obesity, hyperglycemia and hyperlipidemia develop, increasing metabolic load coupled with concurrent inherent insulin resistance and chronic inflammation. The pancreatic islet response to this new environment is likely variable among individuals with differing genetic susceptibility but may include inflammatory stress, ER-stress, metabolic and oxidative stress (e.g., glucotoxicty, lipotoxicity, and glucolipotoxicity), amyloid stress, and loss of islet cell integrity. If untreated, these interrelated stressors increase with time, promoting β-dysfunction (coupled with increased glucagon secretion), and ultimately loss of β-cell mass and possibly dedifferentiation that mark the onset of T2D.

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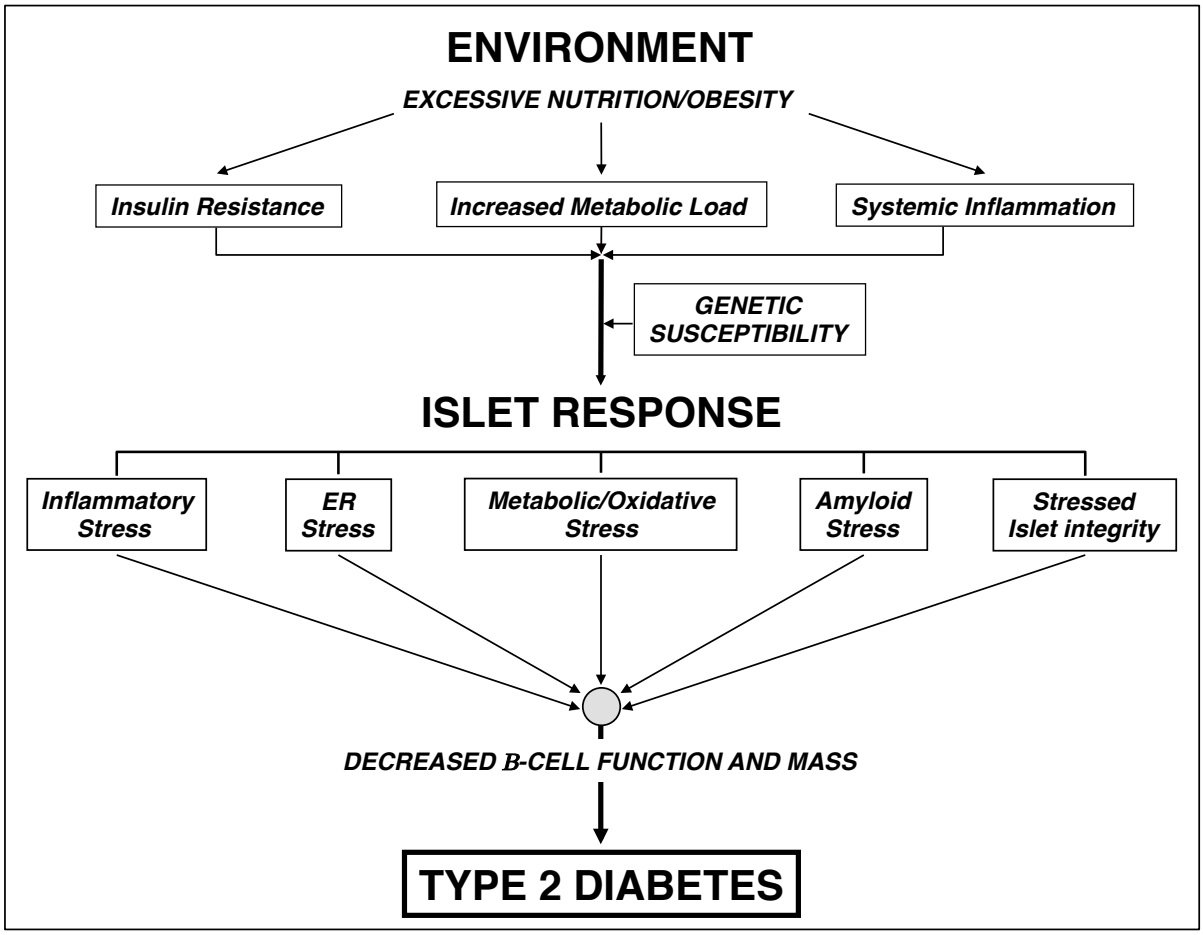
ENVIRONMENT
EXCESSIVE NUTRITION/OBESITY
Insulin Resistance
Increased Metabolic Load
Systemic Inflammation
GENETIC SUSCEPTIBILITY
ISLET RESPONSE
Inflammatory Stress
ER Stress
Metabolic/Oxidative Stress
Amyloid Stress
Stressed Islet integrity
DECREASED B-CELL FUNCTION AND MASS
TYPE 2 DIABETES