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Recent Developments in Islet Biology: A Review With Patient Perspectives

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Key Messages
- High-throughput omics studies are advancing our understanding of islet biology and of disease profiling, enabling more precise treatment options.
- Stem cell–derived islet cells are a promising source of insulin-producing cells to treat type 1 diabetes (T1D) and advanced type 2 diabetes (T2D).
- There is little data to suggest coronavirus disease-2019 (COVID-19, now COVID) has had a direct effect to cause new cases of T1D or T2D.
- New mechanisms of glycolysis and mitochondrial biology that impact insulin secretion are highlighted.
- Circulating lipids modify islet cell function.

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Abstract
Navigating the coronavirus disease-2019 (COVID-19, now COVID) pandemic has required resilience and creativity worldwide. Despite early challenges to productivity, more than 2,000 peer-reviewed articles on islet biology were published in 2021. Herein, we highlight noteworthy advances in islet research between January 2021 and April 2022, focusing on 5 areas. First, we discuss new insights...
New Insights Into Mechanisms of Insulin Secretion

The pancreatic β cell and the process of insulin secretion has been one of the most intensely studied areas in biomolecular diabetes research for decades. Despite these efforts, fundamental mechanisms of energy coupling in functioning β cells and their impairment in diabetes are still incompletely understood. In what follows, we provide some background on our current understanding of the process of insulin secretion and highlight some of the exciting recent advances in this area.

Glucokinase: A viable target for diabetes treatment?

Insulin is released from pancreatic β cells after a meal, stimulated by glucose and other secretagogues, including fatty acids and amino acids (1,2). Appropriate insulin secretion in response to a rise in plasma glucose is essential for maintaining normoglycemia (3). After the entry of glucose into β cells, glucose is oxidized initially in glycolysis, which is initiated by phosphorylation of glucose by glucokinase (GCK). Oxidation of glucose and other nutrients results in elevation of the adenosine triphosphate (ATP)/adenosine diphosphate (ADP) ratio, closure of ATP-sensitive K⁺ channels, cell depolarization, and the influx of Ca²⁺, allowing insulin granule mobilization and exocytosis (4). Although classically attributed to oxidative phosphorylation in mitochondria, emerging evidence suggests that the critical increase in ATP to ADP may be generated by plasma membrane-associated pyruvate kinase (5). As GCK activity initiates this cascade, small-molecule GCK activators, such as MK0941 and AZD1656, were developed to promote insulin secretion in the context of insulin insufficiency. In phase 2 clinical trials, GCK activation in patients with type 2 diabetes (T2D) provided only transient glycemic control, and subjects unexpectedly had an increased risk of hyperlipidemia, steatosis, and hypertension (6-8). Although complete inhibition of GCK can cause both hypo- and hyperglycemia (9), Omori et al developed a model of GCK haploinsufficiency in db/db mice to help clarify these observations (10). GCK⁻/⁻ db/db mice have enhanced glucose-stimulated insulin secretion (GSIS) associated with increased β-cell mass and decreased oxidative stress–related genes, consistent with previous work wherein the GCK inhibitor MH restored insulin secretion in...
db/db islets (11). Taken together, these results suggest that decreased GCK-facilitated glucose influx and resulting metabolism and insulin secretion (also known as “β-cell rest”) may preserve β-cell mass and support earlier studies showing long-term benefits of resting the β-cell function (12,13). Thus, partial inhibition of GCK could limit the exhaustive failure of β cells that contributes to the onset of T2D.

Mitogen-activated protein kinase–kinase (MEK)/extracellular signal–regulated kinase (ERK) and the β cell

In addition to glycolysis, the phosphorylation cascade featuring MEK and ERK is another fundamental signalling pathway that regulates β-cell growth, survival and proliferation (14). In β cells, MEK/ERK signalling activation promotes GSIS and cell survival (15). Consistent with this, a 2021 study showed that diet-induced obese mice harbouring a compound deletion of both Mek1 and Mek2 genes had impaired β-cell function and reduced proliferation (16). This work features the first metabolic consequences of MEK/ERK loss in β cells, whose depletion reduces GSIS associated with enrichment of cytoskeletal genes altered during exocytosis. However, this work contrasts with previous work demonstrating that pharmacologic inhibition of MEK improves glucose homeostasis in insulin-resistant ob/ob mice (17). Furthermore, known pro-survival and proliferative roles of enhanced MEK/ERK signalling may be associated with increased risks of cancer (18), limiting the attractiveness of MEK/ERK as therapeutic targets.

Mitochondrial function and insulin secretion

Nutrient oxidation in mitochondria is critical to β-cell function, and numerous factors linked to mitochondrial dysfunction result in impaired insulin secretion. Previous work showed that attachment of small ubiquitin-like modifier (SUMO) to protein targets is associated with preservation of β-cell survival and mass, but at the cost of β-cell function (19). Recent studies showed that the enzymes sentrin-specific proteases 1 and 2 (SEN1P1 and SENP2), which catalyze the removal of SUMO from SUMOylated protein targets (20), can rescue compromised β-cell function associated with excess SUMOylation. Redox signals from mitochondria activate SENP1, and SENP1 knockout in β cells reduces GSIS and incretin receptor activation and results in impaired glucose tolerance in mice on a high-fat diet (21). Knockout of SENP2 in β cells also impairs insulin secretion, and this is accompanied by alterations in mitochondrial size and function, which can be restored by reconstitution of SENP2 (22). Beneficial actions of deSUMOylation were related to the activation of voltage-gated K⁺ channels that govern Ca²⁺ influx to trigger insulin exocytosis (23,24). These data contradict previous work showing that deletion of the SUMO ligase UBC9 and consequent reduction in its SUMOylated targets reduce GSIS (25), increase blood glucose levels, and worsen insulinitis (26). These discrepancies indicate that the relationship between SUMOylation in β cells and insulin secretion is still unclear.

14-3-3ζ and β-cell function

The 14-3-3 protein family is ubiquitously expressed in mammalian cells and has been implicated in metabolism (27) by binding to phosphorylated cargo and influencing their subcellular localization (28). Deletion of the 14-3-3ζ gene improves glucose tolerance in association with elevated glucagon-like protein-1 (GLP-1) synthesis and release (29). The link between 14-3-3ζ and β-cell secretory function is further elucidated in a recent study by Mugabo et al, wherein β-cell–specific 14-3-3ζ knockout resulted in increased insulin secretion accompanied by upregulated mitochondrial respiration (30). Interestingly, the level of 14-3-3ζ mRNA expression is inversely associated with insulin–secretory capacity in T2D. Identifying relevant cargo for 14-3-3ζ will be an important next step in explaining how the deletion of 14-3-3ζ promotes β-cell function.

Cardiolipin

Insulin secretion is also affected by alterations in mitochondrial membrane components. Phospholipids play an integral role in maintaining the architecture of the mitochondrial membranes and support mitochondrial respiration (31). The enzyme tafazzin alters the content and structure of cardiolipin, a phospholipid in the inner mitochondrial membrane required for oxidative phosphorylation (32). Cole et al generated tafazzin knockout mice by in utero doxycycline administration to mice carrying a doxycycline-inducible tafazzin-specific short hairpin RNA, showing that islets with reduced tafazzin levels had an altered profile of cardiolipin species, compromised mitochondrial function, and reduced basal insulin secretion (33). The authors also noted upregulation of genes associated with pancreatic fibrosis and impaired β-cell function in tafazzin knockout mice. These results support the importance of maintaining the structural integrity of mitochondria for β-cell function.

Is insulin signalling in β cells essential for glucose homeostasis?

Autocrine feedback of insulin on β cells can negatively regulate insulin secretion. In support of this finding, Skovsø et al showed that β-cell deletion of the insulin receptor caused initial insulin hypersecretion and increased GSIS, followed by development of insulin resistance (34). These results contradict a previous β-cell insulin receptor knockout study demonstrating that insulin receptor deletion caused significant glucose intolerance and impaired GSIS (35). Differences between the studies likely stem from the genetic strategy used, specifically that Cre-recombinase expression driven by the rat insulin promoter in tissues outside the β-cell compartment could influence glucoregulation in tissues outside the islet. As technology advances, we can address such controversies and clarify the role of insulin action on the islet and in whole animal physiology (36,37).

Gene deletion strategies for the β cell

A significant barrier to studying insulin secretion in vivo has been off-target effects associated with genetically targeted β cells in mice (38). Genetic elements responsive to exogenous drugs, including tamoxifen or tetracycline, are 2 popular ways to control transgene expression. However, new work has revealed that introducing a tetracycline-controlled transactivator protein in β cells can reduce insulin content and/or insulin secretion, even in the absence of drug (39). Although the authors illustrated the effective and specific targeting of β cells using the “Tet-Off” model, their study highlights the importance of using comprehensive genetic cohort controls, a message now being echoed in the field of islet biology (38,40).

Tracking live insulin release in the mouse

A major recent advance is the development of methods to visualize insulin secretion in vivo, a longstanding challenge (41). These optical imaging techniques rely on tracking zinc, which is released together with insulin, using a zinc indicator for monitoring induced exocytotic release, or ZIMIR (41). Recently, ZIMIR was used to track insulin release in live mice using HaloTag, an enzyme derived from a bacterial protein that covalently attaches
to a synthetic ligand containing a haloalkane group. Using a ZIMIR molecule modified to contain a HaloTag substrate in transgenic mice expressing HaloTag protein targeted to the β-cell surface, researchers successfully generated a β-cell-specific Zn\(^{2+}\) reporter. The plasma membrane–targeted HaloTag ZIMIR successfully detected insulin release from individual islet β cells in intact pancreas with high spatiotemporal resolution (42). They also developed a new cell-permeable, pH-insensitive fluorescent zinc tracker, ZIGIR, which emits 100-fold increased complexing with Zn\(^{2+}\) compared to a synthetic ligand containing a HaloTag substrate in transgenic mice expressing HaloTag protein targeted to the β-cell surface, researchers successfully generated a β-cell-specific Zn\(^{2+}\) reporter. The plasma membrane–targeted HaloTag ZIMIR successfully detected insulin release from individual islet β cells in intact pancreas with high spatiotemporal resolution (42). 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and loss of ATP synthase. Transcriptomic analysis revealed that knockdown of Plin2 in human β-like EndoCβH2-Cre induced a profile of endoplasmic reticulum (ER) stress and reduced static GSIS, despite an increase in insulin content (63). Treatment with the ER stress inhibitor tauroursodeoxycholic acid restored normal insulin content and GSIS. Consistently, knockout of the lipid droplet protein FIT2 in β cells increased expression of ER stress genes, reduced expression of genes implicated in exocytosis, and diminished GSIS (61). Treatment with the saturated fatty acid palmitate also reduced FIT2 protein and induced ER stress in MIN6 insulinoma cells (61). These recent studies demonstrated how β-cell lipid droplets play an indispensable role in mitochondrial and ER homeostasis in the β cell to preserve insulin secretion.

Harnessing Omics Analyses As a Tool to Study Diabetes

The last decade has seen an explosion of information about biologic systems driven by high-throughput technologies, such as genomics, proteomics, and metabolomics. Collectively referred to as “omics,” these comprehensive approaches can be used to understand the genetic, and molecular alterations involved in islet dysfunction on a system scale. In the past year, several groups used omics and multi-omics tools to better understand the molecular causes of islet dysfunction in diabetes.

Mitochondrial health and protection from diabetes

Causal links between changes in cellular metabolism and impaired β-cell function remain poorly understood. You et al sought to identify key changes in the whole islet proteome associated with metabolic health using mice fed chow or a high-fat diet as a model of diet-induced obesity and T2D (64). Comparative proteomic analyses revealed a strong link between proteins associated with mitochondrial function and metabolic health, underscoring the importance of mitochondria in β-cell compensation to nutrient excess.

Exocrine pancreas in T1D

The development of new high-throughput technologies has enabled the creation of single-cell RNA sequencing (scRNA-seq), a tool used to map and quantify cell transcriptomes (65). Fasolino et al generated and analyzed scRNA-seq data from human pancreatic islets to examine the pathogenesis of T1D (66). They found major histocompatibility complex class II (MHC II) expression was enriched in the ductal cells of individuals with T1D. MHC class II receptors facilitate antigen presentation to CD4+ T cells and are typically expressed by antigen-presenting cells, such as dendritic cells (67). Interestingly, the expression profiles of ductal cells isolated from people living with T1D were similar to those of a subtype of dendritic cells that promotes immune tolerance (66,67). This suggests that the ductal cells of individuals with T1D may have a role in negatively regulating CD4+ T-cell activity. Fasolino et al complemented these transcriptomic analyses with spatial data from image mass cytometry and showed that ductal cells from individuals with T1D were surrounded by dendritic and CD4+ T cells, further supporting their argument that ductal cells play a protective role in regulating the T-cell response in T1D.

Transcription factors related to islet health and diabetes

scRNA-seq sequencing and transcriptomic analyses can also be used to develop comprehensive profiles of transcription factors expressed in islets of individuals with or without diabetes. Shrestha et al used scRNA-seq to identify the transcriptomic profiles of mature α and β cells. They found that most mature α cells coexpress high levels of ARX and MAFA, whereas the most mature β cells highly express MAFA and MAFB (68). This characterization of coexpression of transcription factors in mature endocrine cells can be used to understand pathways responsible for coordinating hormone secretion within pancreatic islets. Moreover, scRNA-seq shows the heterogeneity of endocrine cells within the islet. The in-depth transcriptomic profile using single-cell RNA sequencing can be used to understand what a healthy and mature endocrine cell entails on a molecular level, and how this profile shifts when cells undergo stress and dysfunction. For example, Green et al found that inducing ER stress in β cells leads to an unfolded protein response, causing β cells to upregulate the production of ER chaperones and downregulate the production of β-cell-specific proteins (e.g. MAFA, PAX4, and PDX1), thus altering their identity (69). The loss of these transcription factors leads to a more immature β-cell phenotype, potentially causing dysregulated insulin production and secretion.

Using multi-omics to create comprehensive disease profiles

To better characterize endocrine cell identity and function in the islet, Wigger et al combined transcriptomic, metabolomic, and proteomic signatures to create a comprehensive biomarker profile of diabetes (70). Individuals with T2D had greater heterogeneity within their islet-cell transcriptomic and proteomic profiles than normal subjects. Like Fasolino et al, their analysis also underscored the notion that mitochondrial dysfunction is a key event in diabetes pathogenesis, with mitochondrial genes YMEL1, MRPL12, and ACADS downregulated in T2D. Their analyses also revealed an upregulation of ALDOB, a marker of β-cell precursors, along with elevated sphingolipids and reduced phospholipids in islets of subjects with T2D (70). These observations align with previous data (71), suggesting that changes in lipid populations can be used as an indicator of diabetes. Last, Wigger et al integrated transcriptomics and lipidomics data to determine the relative importance of changes in gene expression and plasma lipids in determining variations in glycated hemoglobin (A1C), a measure of long-term glycemia (70).

Multi-omics has also been used to create a more detailed profile for those at risk of developing T1D. In contrast to the profile for T2D, Alcazar et al used lipidomics and metabolomics to confirm multiple previous potential biomarkers of T1D onset. Lipidomic analyses revealed that individuals at high risk for T1D have increased levels of lysophosphatidylcholine, a phospholipid that promotes insulin secretion (72,73). Metabolomic analyses also showed an increase in pyruvate levels in these individuals. Accumulation of pyruvate due to inflammation is a characteristic of T1D, preventing further oxidation in the Krebs cycle (72). The work also identified a reduction in alanine levels in individuals at risk for T1D that may serve as a compensatory mechanism to combat T1D-associated hypoglycemia through inhibition of the AMP-kinase pathway. Moreover, transcriptomic analyses demonstrated an overall increase in the expression of microRNAs associated with T1D and β-cell dysfunction (72,74). Taken together, combining multi-omic analyses has the potential to identify biomarker signatures of diabetes, which can ultimately lead to the generation of new targets for therapies, and treatment. Moreover, the creation of comprehensive molecular profiles for healthy individuals, individuals with diabetes, and individuals at high risk for diabetes will help in our
Emerging omics technologies

Two notable techniques that will undoubtedly expand the utility of multi-omics technologies include single-nucleus RNA (snRNA) sequencing and deep machine learning. Basile et al demonstrated that snRNA and scRNA sequencing data from nuclei or cells (from frozen or freshly isolated human islet graft samples) had similar sequencing efficiency. scRNA sequencing also successfully identified all cell types in pancreatic islets and may be a faster and cheaper alternative to scRNA sequencing (75). Turki et al visualized single-cell gene-regulatory networks from 224 human donors and, after training of several deep learning architectures, demonstrated that deep learning can differentiate gene-regulatory networks in individuals with T2D and those without diabetes (76). Although preliminary, these advancements in multi-omics technologies demonstrate their potential to improve the efficiency of studies surrounding molecular mechanisms of islet function.

Omics technologies will continue to generate comprehensive data sets that provide novel mechanistic insights into the etiology of T1D and T2D. Furthermore, with more widespread use and enhanced scale, these approaches even raise the possibility of more personalized diagnoses and treatment approaches.

Advancements in Cellular Replacement Therapy

To achieve normoglycemia, people living with T1D require frequent injections of insulin throughout the day, delivered manually or via insulin pump. Although life saving, this standard-of-care approach fails to restore ideal glycemic control, which can lead to vascular complications, retinopathy and nephropathy. Exogenous insulin also has the inherent risk of inducing severe hypoglycemia (77). Thus, researchers are exploring various alternative strategies to improve glucose homeostasis in T1D, and at the forefront of this effort is cellular replacement therapy.

Outcomes in clinical islet transplantation

Since its introduction in the late 1980s, several groups have investigated the clinical outcomes of islet transplantation (78–80). A recent study by Lablanche et al showed outcomes of 31 islet graft recipients 10 years after intraportal islet transplantation. As determined by detectable circulating C-peptide levels, 52% of recipients had functional islet grafts 10 years after islet transplantation (81). Compared with pretransplant measures, the patients lowered their average A1C level (7.2% vs 8.0%) and required less daily exogenous insulin, and 74% of them were protected from severe hypoglycemic episodes, showing that long-term efficiency is possible with transplant strategies. Although clinical islet transplantation was successful in some patients, recent studies (78,81–84) confirm previous conclusions that islet transplantation is not yet a viable solution for all individuals living with T1D (82,83). Following the Edmonton protocol, 79% of islet transplant recipients achieved insulin independence, which decreased to 20% at 10 years (76) due to poor islet engraftment. Additional confounding factors have been donor insufficiency and the need for lifelong immunosuppression (82).

Enhancing islet vascularization and engraftment in preclinical models

In addition to limited cell sources, clinical islet transplantation is burdened by acute islet cell death in the peri-transplant period. The initial loss of ~70% of islets severely compromises long-term success and is mainly attributed to poor engraftment and an inflammatory response at the intraportal site (82). As such, there is a major drive to improve angiogenesis and reduce local inflammation. One recent approach by Nalbach et al generated prevascularized islet organoids by fusing native microvascular fragments with rodent islets, enabling local release of angiogenic growth factors by these vessels (85). Compared with islets alone, prevascularized islet organoids showed significantly accelerated and improved vascularization. Moreover, streptozotocin-induced diabetic mice become normoglycemic after receiving subtherapeutic numbers of prevascularized islet organoids under the kidney capsule. Aghazadeh and colleagues implanted stem cell–derived islet-like cells in the subcutaneous space of mice (86) and found that cells preincorporated with microvessels enhance engraftment in immunodeficient, streptozotocin-induced diabetic mice and reduce time to normoglycemia by half (87–89). These promising preclinical findings suggest that incorporating microvascular fragments could significantly improve engraftment and early graft survival, irrespective of cell source.

As virtually all clinical islet transplants are delivered to an intraportal hepatic site, efforts to improve islet engraftment within the liver are ongoing. Recently, Alwahsh and colleagues’ innovative approach preconditions the hepatic site through local delivery of fibroblast growth factor 7 (FGF7), which promotes hepatocyte proliferation (90). They encapsulated FGF7 within a biodegradable polymer and fabricated optimally sized micro-particles that sequester exclusively to the liver after codelivery with islets via the portal vein. This release system provides an initial 24-hour local burst of FGF7, supporting engraftment by increasing immediate islet “trapping” and vascularization by increasing vascular endothelial growth factor (91). As such, mice that received islets codelivered with FGF7 microparticles had more engrafted islets and increased vascularization 72 hours posttransplant compared with mice receiving islets alone. Seventy-five percent of streptozotocin-induced diabetic mice receiving FGF7 microparticles displayed normoglycemia at 30 days posttransplant with a noncurative mass of islets. The findings highlight the utility of hepatic engraftment while demonstrating the feasibility of localized peptide delivery. Beyond this application, localized drug delivery could also help to alleviate the need for lifelong systemic immunosuppression after islet transplantation, which has been demonstrated recently in preclinical models (92–95).

Stem cell–derived β cells: The islet alternative

To address the limited availability of islet donors, a central focus of many islet researchers is to generate β-like cells in vitro via controlled differentiation of human stem cells. Recently, 2 proof-of-concept studies reported breakthrough findings using a population of stem cell–derived pancreatic islet cells that included β cells (96,97). In these clinical trials, researchers implanted 15 and 17 subjects with T1D, respectively, with stem cell–derived endoderm cells contained in subcutaneous macro-encapsulation devices. These devices possess pores previously shown necessary for graft vascularization, function, and survival. As the pores are large enough to allow flux of immune cells,
Does COVID put people at risk for new-onset diabetes?

T1D: Despite early warnings of a potential surge in T1D diagnoses in 2020 (111) fueled by concerns over immune dysregulation linked to COVID (112), recent evidence suggests no causal link between COVID diagnosis and new-onset T1D (113–115). One study indicated that the increased severity of T1D symptoms reported during the pandemic were not due to the SARS-CoV-2 infection itself, but instead may have been exacerbated by pandemic-related delays in doctor and hospital visits (116). Similar conclusions can be drawn from literature meta-analyses considering the bidirectional effects of T1D and COVID (117,118).

T2D: A large-cohort study of US veterans suggested that men are more susceptible than women to incident (or new-onset) T2D diagnosis after a positive COVID test (119). Another study suggested that COVID patients are 40% more likely to develop primarily T2D up to 1 year after diagnosis (120). At particular risk are individuals with obesity, who have a more than doubled risk of developing T2D after having COVID. However, there are major caveats associated with that study. First, the subjects were older, most were White males, and many were already at higher risk for developing diabetes (due to elevated body mass index and blood pressure). Second, some people in the control group were not tested for COVID if they were asymptomatic. Third, pre-existing cases of diabetes may have coincidentally been detected because subjects sought medical care for COVID. Thus, despite limited evidence and few well-controlled prospective studies, the theory that SARS-CoV-2 infection is associated with worsening of T2D symptoms and increased incidence of new diabetes diagnosis after infection remains widely reported, including by the US Centers for Disease Control and Prevention (121). In addition, there was some limited concern over the possibility that COVID vaccines alone could trigger new-onset diabetes. Although 2 case studies featuring 1 patient each revealed a diabetes outcome after vaccination against SARS-CoV-2, this has not been widely reported (122,123).

COVID outcomes with pre-existing diabetes and immunosuppression: As both T1D and T2D are associated with inflammatory states, some have suggested that pre-existing diabetes could be a risk factor for poorer COVID outcomes that appear to be mediated by an exaggerated inflammatory response to the virus (124). Concerns were also raised for how requisite immunosuppression for solid-organ transplant, including islet transplant, may place individuals at greater risk for severe disease and even death after a COVID diagnosis (125), leading to recommendations for prioritization of these individuals for immunization, booster shots, and other treatments.

In all scenarios, the high prevalence of COVID infection and high uptake of immunization mean that it is now difficult to find unexposed comparator populations. The inability to adequately control for confounding effects of social determinants of health is a major limitation. Finally, given the long preclinical phases of both T1D and T2D, proximity to COVID infection more likely represents undiagnosed pre-existing or incipient diabetes. Taken together, the available data indicate that concerns over a potential causal relationship between SARS-CoV-2 infection and islet function with new-onset or pre-existing T1D or T2D are largely unfounded.

Discussion

In the past year, greatly expanded islet and diabetes research has advanced our knowledge of the biology of the healthy islet, the

Impact of Severe Acute Respiratory Syndrome—Coronavirus-2 (SARS-CoV-2) on Diabetes: An Update

Early reports on COVID suggest a potential causal link between SARS-CoV-2 infection and new-onset diabetes, raising various concerns for at-risk individuals, particularly those recently diagnosed with diabetes. Indeed, concerns were raised about increased susceptibility, the potential for worsened COVID symptoms and outcomes in patients with pre-existing diabetes and lower efficacy of vaccinations. Many of the initial reports conflated T1D and T2D and did not adequately consider the influence of age and comorbidities. In 2021–2022, this picture became clearer, and there is currently little compelling evidence to support a direct association between COVID and development of either T1D or T2D.

SARS-CoV-2 and direct infection of the islet

A potential connection between diabetes and COVID stems from evidence that SARS-CoV-2 can directly infect endocrine cells of the pancreatic islet in vitro (104–108). However, additional work suggests that infection of pancreatic endocrine cells by SARS-CoV-2 is unlikely, as viral receptor expression seems localized primarily to ductal cells and blood vessels (109). Recent work has confirmed that islet cells and pancreatic acinar cells can express the cell-surface receptor angiotensin-converting enzyme 2 (ACE2) and be infected by SARS-CoV-2 and related coronaviruses in vitro, yet this did not have deleterious functional consequences. Last, although SARS-CoV-2 can access the brain via neuronal trafficking, current data indicate that the virus is unlikely to disturb glucoregulation by causing pancreatic endocrine dysfunction during natural infection (110).
effects of disease on islet function, and the usefulness of preclinical models. In this review we have highlighted progress in our understanding of the mechanisms of insulin secretion and β-cell lipid metabolism, while following up on the rapidly evolving impact of COVID, the benefits of multi-omics strategies, and new developments in islet transplantation.

Despite the ongoing pandemic, islet biology research continues to challenge current theory, expanding our understanding of extracellular and intracellular signalling and the use and storage of fuel in the β cell. Research this year has expanded knowledge of signalling pathways, elaborated on mitochondrial roles in β-cell function, and reinforced the importance of well-designed preclinical models for diabetes research. Such improvements in mechanistic understanding have set the stage for future therapeutics.

This year also saw studies aimed at improving replacement therapies and diagnostic procedures currently being used in clinic. Advances in islet transplant vascularization and the prospect of stem cell-derived transplantation may have potential to vastly increase availability and success of these therapies for people currently living with T1D, and potentially some people with T2D. Using omics to identify circulating biomarkers as a tool to accurately classify patients with T1D or T2D could eventually reshape the way we approach individual treatment. Seeing the light at the end of the COVID pandemic, research has yet to provide solid evidence of SARS-CoV-2—inducing diabetes. Although SARS-CoV-2 may infect islet cells, recent data show that COVID is not likely the cause of new-onset T1D or T2D. Research focus in 2021 shifted from the impact of COVID on diabetes back to mechanistic and therapeutic advances. This momentum re-institutes our hope to develop a more thorough understanding of diabetes pathophysiology and to highlight the impact of basic biomedical research in developing promising therapeutics to treat T1D and T2D.

Lay Summary

For well over 100 years, our understanding of insulin secretion and how islet dysfunction contributes to the development of diabetes has been evolving. In this lay summary, we discuss recent and how islet dysfunction contributes to the development of diabetes and observed a reduced number and function of β cells, whereas others reduce GCK activity and cause hyperglycemia (9). After glucose enters the β cell, it is broken down to generate a key cellular energy source called ATP, which triggers insulin release. Emerging evidence suggests that the ATP/ADP ratio influenced by pyruvate kinase triggers a series of events that culminate in insulin secretion (9).

After glucose enters a β cell, a protein called glucokinase modifies it to remain inside the cell and avoid escaping into circulation (4). This modification by glucokinase is the critical first step in the breakdown of glucose to generate ATP. Drugs that ramp up glucokinase activity enhance insulin secretion from the islet and are currently in development as potential therapies. However, in early clinical trials, although the drugs successfully maintained a normal blood glucose level for up to 6 months, the ability to regulate blood glucose level was not sustained in the longer term. In addition, human subjects with T2D treated with glucokinase (GCK) activators experienced a greater risk of high blood pressure and circulating blood fats (6–8).

These unwanted effects prompted Omori et al to study the effect of deleting 1 of the 2 copies of the GCK gene from β cells in diabetic mice. Surprisingly, the mice had more β cells, higher insulin secretion, and reduced signs of cell stress. These data suggest that lowering the levels of GCK may let β cells “rest” between meals. This may be important in preserving the number of β cells in the pancreas (10).

These observations support earlier studies showing long-term benefits of resting the β cell to restore the capacity of β cells to secrete insulin. The role of GCK in humans is complex, as some mutations can enhance insulin release causing hypoglycemia, whereas others reduce GCK activity and cause hyperglycemia (9). Although turning GCK off completely does not improve diabetes symptoms, treatments that partially inhibit GCK may limit exhausted failure of β cells and are worthy of further study.

Role of growth proteins MEK/ERK in the β cell

As glucose is used to generate energy within the β cell, signals throughout the cell are engaged. MEK and ERK are enzymes called protein kinases, which add a phosphate molecule to other proteins in the cells, in a cascading fashion, whereby many downstream target proteins receive a phosphate molecule, which leads to their activation or inhibition. Although the MEK/ERK phosphorylation relay is known to be critical for regulating cell growth, survival, and replication in other cell types (14), turning on these 2 proteins in β cells promotes insulin secretion and β-cell survival (15). Further insight into the significance of MEK/ERK activity in β cells was shown in a recent study. Researchers deleted the MEK gene from the β cells (and not from other cells in the body) of mice with diabetes and observed a reduced number and function of β cells, attributing these effects to structural changes inside the cell (16). Conversely, others have used drugs that inhibit MEK in mice with diabetes and showed improvements in blood glucose management (17). It is unclear whether stimulating MEK/ERK helps in diabetes, but care will be required because this may be associated with unwanted cell growth and even cancer (18). Future work should be done that is directed toward identifying the specific proteins that MEK/ERK act on in the β cell that are critical for impacting insulin secretion.

Update on Fundamental Pathways Involved in Insulin Secretion

Glucokinase: A useful target for diabetes treatment?

An increase in blood glucose is a key trigger for release of insulin from the β cell. The breakdown of glucose into cellular energy components by the mitochondria (i.e., “the powerhouse of the cell”) is an important regulator of insulin secretion (126).

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Mitochondrial function and insulin secretion

Mitochondria are miniature organs within cells and known as the furnace or "powerhouse of the cell," and their role in breaking down nutrients to be used to generate cellular energy is critical for β-cell function. Mutations in any gene that reduce mitochondrial function in β cells are typically associated with reduced insulin secretion. Previous work has shown that the E2 SUMO-conjugating enzyme (UBC9), which adds a protein tag called SUMO, is associated with preserving β cells. Decreasing SUMOylation (i.e. removing some of these tags) in β cells can impair their antioxidant capacity, leading to cell death and high blood glucose levels (19,25). Recent studies in mice showed that the enzymes SENP1 and SENP2, which remove the SUMO tag from target proteins, are closely linked to actions of the mitochondria, and their activity can improve β-cell function. Signals from mitochondria activate SENP1 and the loss of SENP1 in β cells of obese mice reduces insulin secretion, leading to higher blood glucose (21). Similarly, the deletion of SENP2 from β cells leads to impaired secretion of insulin accompanied by changes in mitochondrial size and activity (22). The beneficial effects of having intact SENP1 and SENP2 in insulin secretion contradicted earlier work showing that the SUMO tag would promote insulin secretion (25). The roles of SUMO and the enzymes that remove it from targets are complex and yet to be fully understood.

14-3-3 protein and β-cell function

A family of proteins called 14-3-3ζ act as important carriers that coordinate many processes related to how cells send and receive information (127). Earlier work has shown that deleting 1 of the 14-3-3 family members, namely 14-3-3ζ, from all tissues in the mouse improved blood glucose levels by increasing levels of incretin hormones that stimulate β-cell function (29). To confirm that the main effect of deleting 14-3-3ζ was due to improved β-cell function, researchers selectively eliminated the 14-3-3ζ gene only in β cells, which resulted in improved insulin secretion in the mouse due to enhanced mitochondrial function and energy production (30). Conversely, increased levels of 14-3-3ζ in a mouse model of T2D were found to be associated with a decrease in insulin secretion. Further insight is needed into the proteins that 14-3-3ζ interacts with to help coordinate insulin secretion.

Cardiolipin

Cardiolipin is a fat molecule found in the inner membrane of mitochondria and is required for proper energy production, including the conversion of glucose to ATP. The protein tafazzin is known to alter both the structure of cardiolipin and total mitochondrial cardiolipin content (32). Recent work has shown that blocking the activity of tafazzin alters cardiolipin, thereby resulting in compromised mitochondrial energy production, which in turn decreases insulin secretion and increases damage and scar formation in the pancreas (33). These results point to the importance of maintaining mitochondrial structural integrity for proper β-cell function.

New mouse models to study how insulin affects islet function

Insulin is produced by β cells to stimulate glucose uptake by other tissues, but, as the β cell has receptors for insulin on its own surface, insulin can also affect how the β cell works (35–37). Precisely how this works and whether it is important in diabetes is controversial. In a new study, researchers deleted the insulin receptor genes from β cells in the mouse to study what happens when insulin can no longer control β-cell function (34). In the study, β cells without insulin receptors secreted more insulin, but the animals became insulin resistant, so blood glucose levels increased—which is very similar to what is believed to be a major underlying cause of T2D in people. These recent results show that a re-evaluation of the role of the insulin receptor and of insulin action in the β cell is necessary.

Genetically modified mice: Models to study T1D and T2D

A significant challenge in the islet biology field is being able to activate or inhibit important genes and their protein targets in β cells and only β cells. One recent study (39) outlined the drawbacks with current genetic strategies for studying β-cell function and provided a roadmap for tackling them. The study showed that researchers' standard techniques—where a switch to control the gene of interest is inserted—are problematic. The process of inserting the switch on its own is enough to unintentionally reduce insulin content and secretion. Unless researchers account for this, their conclusions regarding the relevance of their gene in diabetes may be incorrect. For example, this was a problem with earlier studies of insulin receptors on β cells, which have now been clarified using more precise and sophisticated techniques (described in the previous section). This serves as an important reminder that studying β-cell function in mice is challenging and requires careful experimental design.

Tracking insulin release in live mice

A major advancement has been the development of tools to view insulin release in a live animal. These imaging techniques track the location of zinc, which is packaged together with insulin and thus released together with insulin after a meal. A fluorescent marker, ZIMIR, which binds specifically to zinc, has been used to measure insulin release (41). Chen and colleagues expanded this technique to record insulin release in live mice (42). They achieved this by delivering a fluorescent tag to the surface of the β cells, thereby allowing for live tracking of the zinc release from the islet in its normal context. They also developed a fluorescent granule zinc indicator, ZIGIR, which can measure changes in β-cell mass and the number of β cells in the whole pancreas of living mice. These imaging tools will be essential in studying diabetes in live animals and increasing our understanding of the islet β-cell function.

Metabolism and Storage of Fats: Impact on Release of Insulin

The importance of blood glucose levels is widely appreciated in the context of diabetes research. However, controlling the transport of fats, both those from the diet and those derived from stores in fat tissues, is important for controlling the development of insulin resistance and reducing the risk of diabetes complications. People living with T2D can have higher levels of fats in the blood before and after a meal than people without diabetes (128). High levels of blood triglycerides, the most common type of body fat, can be predictive of T2D, and this has been suggested to impede the β cell's ability to respond to glucose and release insulin (45). Furthermore, the specific combination of fats in the blood of infants and children may have some predictive value in development of T1D (43,44). Improving our understanding of how fats contribute to the pathophysiology of both T1D and T2D is of significant interest.

Fat transporters and their impact on insulin release

Excess body fat and fat within the liver can send signals to the pancreas through the blood using fat transporters. Fat transporters assist the movement of fats from the blood to target cells. Cells will then use fats as a source of energy. Excessive body fat breakdown or excess fat storage in the liver increases the release of fat.
transplantation into the blood (48,50). Recent studies in cells and mice have shown that these fat transporters can reduce the pancreas’ ability to release insulin (51,54). Interestingly, when excess fats are in the blood, one of these fat transporters, fetuin-A, can be released from insulin-secreting cells in the pancreas and cause self-induced inflammation (54). Long-term inflammation can cause dysfunctional problems in insulin-releasing cells (54,55).

β cells store fat to adapt to stress

Although the breakdown of fat can trigger pancreatic β cells to secrete insulin, glucose metabolism must be the primary trigger for insulin-secreting cells to maintain normal blood glucose levels (129). It is currently unknown whether high levels of fat in the blood can reduce the survival of β cells in the islet. Studies in cells showed that high levels of certain fats can cause damage or death to β cells (46). One recent study showed that antioxidants, natural body-produced chemicals that protect cells from damage, can improve β-cell survival after exposure to excess fat (46). Because these experiments were done with isolated cells, they will require testing in the mouse and then in humans (47). A study in mice suggested that the pancreas may be able to store excess fats, which may help avoid the toxic effects of the fats to maintain insulin secretion (58). Furthermore, another study in mice showed that β cells can keep insulin output tied to the breakdown of sugar and not fat, even when excess fat is present (59).

Lipid droplets: Essential to keep insulin-secreting cells healthy

Human β cells store fats in packages called lipid droplets. Until recently, it was thought that mouse β cells did not do this (60). However, 3 recent studies demonstrated that critical components in the structure and formation of lipid droplets are needed to maintain insulin secretion in response to glucose administration in mice and isolated β cells (61–63). Interestingly, one study showed that saturated fats decreased the amount of important components in the formation of lipid droplets, but unsaturated fat did not (61). These studies will lead to an improved understanding of how individual fats impact islet cells differently.

Harnessing Large-scale Analyses as Tools to Study Diabetes

Advances in technology have made it possible to study the molecular events that underlie diabetes. Techniques analyzing large-scale biologic data, such as proteomics (to determine what proteins are present in a sample), transcriptomics (to determine what genes are turned on), and metabolomics (to determine what molecules involved in metabolism are present)—collectively termed “omics”—can be used to gain significantly more detail about the changes that occur in T1D, prediabetes, and T2D.

Using omics data to characterize mouse models in diabetes research

Proteins are complex molecules involved in many important processes in our cells. Proteomics can be used to answer how abundance of proteins in a cell responds to stressful conditions by analyzing and quantifying all the proteins within a cell. You and colleagues aimed to identify changes in islet protein levels in different types of mice in response to a regular and high-fat diet, and showed that mice with normal blood glucose, normal blood pressure, and minimal fat tissue had higher levels of the proteins that contribute to normal cellular energy production present in their islets (64).

Using omics data to identify potential markers of diabetes in humans

Analyzing genes at the single-cell level can lead to a world of discovery beyond what we previously imagined. Gene switches are proteins responsible for turning genes “on” or “off” within the individual cells of the islet. The activity of these gene switches is vital in regulating the glucose levels in our body. Using a technique called “single-cell RNA sequencing,” researchers can look at changes in what genes are being turned on in individual cells. Learning more about how changes in the levels of these genes affect the development and function of islet cells may lead to the design of more effective therapies and treatments for people with diabetes. β-cell failure is a critical event in the development of diabetes, as these cells will no longer be able to secrete insulin. Cellular stress is a known contributor to β-cell failure (130,131). Using single-cell RNA sequencing, Groen and colleagues found that inducing stress in β cells leads to the loss of gene switches critical for normal β-cell function (69), disrupting insulin production and increasing blood glucose levels. Beyond studying β cells in a state of dysfunction, it is equally important to understand what genes are active when a β cell is healthy and fully functioning. Shrestha and colleagues found a combination of specific gene switches that distinguish healthy and mature pancreatic endocrine cells from unhealthy ones (68).

Using omics data to understand immune cell activity

In T1D, a person’s own immune cells attack their β cells. Dendritic cells are immune cells that can contribute to β-cell destruction by turning on helper T cells (67), which help other immune cells perform better. One major role of dendritic cells is to sample their environment, and “eat” cells and other materials (e.g., bacteria) in their surroundings, process them, and present the processed pieces to helper T cells. T-helper cells, in turn, then determine whether to activate or suppress an immune response. Dendritic cells use a specialized protein called MHC class II to do this (67). Using single-cell RNA sequencing, Basu et al. found that cells that line the pancreatic ducts of patients with T1D have higher levels of this specialized protein (66). Interestingly, this work also suggests that an unappreciated role of duct cells may be to reduce the autoimmune destruction of β cells by T cells.

Using multi-omics to generate more comprehensive T1D and T2D profiles

Studying all proteins, genes, and fats in cells in parallel can help form a more comprehensive picture of how diabetes starts and progresses. This approach is called “multi-omics.” Multi-omics can be used to create more comprehensive and distinct molecular profiles that best describe individuals without diabetes, individuals as they progress toward diabetes, and individuals who live with diabetes. Wigger and colleagues created a biologic profile for individuals with T2D and found that the activity of genes that play a role in processing fat and producing cellular energy was different in β cells from people with and without T2D (70). Moreover, people with T2D had higher levels of a marker of immature β cells, suggesting that β cells revert to a less functional version of themselves under the stressful conditions of T2D. As we need fully functioning, mature β cells to precisely regulate blood glucose levels, Wigger et al. identified major changes that accompany the transition to T2D.

Multi-omics has also been used to create a molecular marker that identifies people who are at risk of developing T1D. Alcaraz and colleagues analyzed several metabolites (molecules created when the body breaks down food or other chemicals) and discovered that individuals at high risk for developing T1D had increased levels of a molecule called pyruvate, which is typically used as a fuel...
to drive insulin secretion. Normally, insulin secretion helps to regulate pyruvate levels (72). These individuals also had lower levels of an amino acid called alanine, a characteristic of individuals living with T1D, which helps to combat low blood glucose. The authors analyzed carriers of genetic information called “micro-RNAs” and found that certain microRNAs associated with both T1D and β-cell failure were higher in people at high risk for T1D. Combined multi-omic analyses have the potential to create a comprehensive biologic profile of disease. More precisely classifying what type of diabetes people may have (beyond just T1D or T2D) made possible by these new approaches can help clinicians and other health-care professionals provide optimal care and personalized medicine to improve overall health outcomes.

Emerging technologies

To advance multi-omics technologies, scientists have explored various options to better characterize islet function and diabetes. Basile and colleagues proposed single-nucleus RNA sequencing as a more economical and less time-consuming alternative for single-cell RNA sequencing (75). The nucleus is the compartment in cells where genetic information, DNA, is stored. RNA represents temporary copies of DNA that the cell uses to make protein. Single-nucleus RNA sequencing is like single-cell RNA sequencing in that it analyzes the temporary RNA copies of DNA. However, single-nucleus RNA sequencing only looks at RNA in the nucleus instead of individual cells. Although preliminary, the authors showed that single-nucleus RNA sequencing could be as effective as single-cell RNA sequencing in fresh and frozen islet samples from human donors, which will make this technique easier to use with all samples available. Meanwhile, Turki and colleagues brought together multi-omics approaches and artificial intelligence to create a new method that efficiently generates a profile of individuals with and without diabetes (76). The authors “trained” a computer program to recognize patterns within networks of genes linked to biologic processes in both individuals without diabetes and those with T2D. This program was successfully able to distinguish gene networks based on their diabetes status. Although more work must be done to perfect this technology, the findings point to new possibilities in accelerating data analysis.

Advancements in Treatments for Diabetes

Using cell therapies such as islet transplantation to replace insulin treatment for people with T1D has been an area of interest and focus for researchers and people living with diabetes. There has been much progress made in the field of islet transplantation and β-cell replacement throughout the COVID pandemic. Major successes, such as improving the ability to make insulin-producing cells from stem cells and supporting blood vessel growth around transplanted islets, may one day lead to a more efficient, feasible, and sustainable T1D therapy.

Evaluating islet transplantation

Islet transplantation involves taking islets that make insulin from a deceased donor without diabetes and administering them into a person with T1D so that they can once again produce their own insulin. The safety and effectiveness of islet transplantation has been studied since the 1980s (78–80), but success was not truly achieved until 2000. One recent study followed islet recipients for 10 years after islet transplantation (81). Over half of the patients who received islet transplants had improved blood glucose levels compared with those before transplantation. The recipients required fewer daily insulin injections, and episodes of severely low blood glucose levels were prevented in 75% of recipients. Together, these studies show that islet transplantation could be a useful way to treat T1D in the future.

Although islet transplantation has been successful in some patients for a few years after receiving surgery, this approach still has challenges. In 2 studies, most recipients still required low doses of daily insulin injections after islet transplantation (78,81). Therefore, islet transplantation is not yet a cure for T1D (82,83). There is also a shortage of islet donors, and, if an individual receives an islet transplant, they will be required to take lifelong medication to suppress their immune system to prevent the rejection of transplanted islets. Discovering ways to improve islet transplantation effectiveness and feasibility are being explored by scientists globally.

Improving transplant cell survival and early blood vessel growth

One current issue with islet transplantation is that about 70% of islets are initially lost after the transplant procedure (82). This is caused by inflammation and delayed blood vessel growth (i.e. lack of blood supply) around the islets, which is harmful to islet survival and reduces the long-term success of this treatment. Recent approaches in mice addressed this poor blood supply by combining islets with fragments of blood vessels to promote early blood vessel development (85). These combinations improved early blood vessel growth and increased the efficiency to restore normal blood glucose levels in mice with diabetes even when a smaller dose of islets was used. The same approach was used to support the function of stem cell–derived β cells to produce insulin and restore normal blood glucose levels in mice with diabetes (88). Alwahsh and colleagues found that release of a chemical that promotes blood vessel growth in the vicinity of the transplant site was another way to improve early blood vessel growth and islet survival in mice (90). These promising and successful approaches in mice have the potential to be used in humans by improving the early survival of transplanted islets and reducing the number of islet cells needed to restore blood glucose control. This may allow more people living with T1D to be treated with islet transplantation in the future.

A new cell source for transplantation

Stem cells are specialized cells that can become any cell type in the body. To address the limited availability of islet donors, intensive research is being performed to understand how to convert stem cells into fully mature, insulin-producing cells. Recently, 2 studies showed that devices with insulin-producing cells made from stem cells transplanted into individuals with T1D were safe, well-tolerated, and produced no serious side effects in all 32 study participants (96,97). For the first time, it was shown that insulin-producing cells made from stem cells could produce insulin in humans after a meal (96)—although there was no clear impact on their blood glucose levels. With more research being done on improving the production of insulin-producing cells from stem cells (99,103), these findings suggest that stem cell therapy could be a potential therapeutic option to treat T1D in the future.

Impact of COVID on Diabetes: An Update

Early reports on COVID-19 (or COVID) raised several questions: Were people with diabetes at increased risk to contract COVID? Were they more likely to have severe outcomes? Would vaccination be less effective? Could COVID trigger new cases of diabetes? The use of dexamethasone (a steroid), which causes high blood glucose levels, as a key treatment for severe COVID was a further complicating factor. These suggestions caused substantial distress for people living with diabetes. As time has passed, the consensus emerging in newer reports has not supported a direct causal link between acute SARS-CoV-2 infection and an increase in diagnoses
of either T1D or T2D, as discussed in what follows. However, further research on postacute infection (long COVID) and the risk of developing diabetes will be required to fully appreciate the impact of SARS-CoV-2 (120).

SARS-CoV-2 and the islet

Early suggestions of a potential link between COVID and diabetes resulted from observations that the virus that causes COVID, SARS-CoV-2, may infect hormone-producing cells in the pancreatic islet (105–107,132). To begin the process of infection, SARS-CoV-2 binds to ACE2, a protein found on the cell’s surface. However, a recent comprehensive study evaluating both normal human pancreatic tissues and tissue from subjects with COVID argued that infection of β cells by SARS-CoV-2 was unlikely due to a lack of receptors to facilitate entry (108). Consistently, another study of subjects with COVID confirmed that only a small percentage of pancreatic hormone—producing cells have ACE2 on their surface. However, there was a presence of virus in some patients (108), suggesting that SARS-CoV-2 can infect pancreatic endocrine cells in some circumstances. However, additional studies have demonstrated that infection does not impair the β cell’s ability to secrete insulin (110). Therefore, current data indicate that it is unlikely that SARS-CoV-2 during a natural infection could have any adverse effect on blood glucose management by impairing islet cell health (108–110).

Does COVID put people at risk for new-onset diabetes?

**COVID and T1D risk:** Despite early reports warning of a potential surge in T1D diagnoses due to an attack of SARS-CoV-2 on the immune system (111,112), the bulk of the evidence now indicates that there is likely no direct connection between contracting COVID and new-onset T1D (113–115,117,118). One report suggested the number of new T1D diagnoses in persons <18 years of age increased during the pandemic, and furthermore that respiratory infection due to causes other than SARS-CoV-2 was not associated with an increased risk for T1D (121). However, access to health care may explain the observed increased incidence severity of diabetic ketoacidosis (i.e., acid buildup in the blood)—that is, delays in hospital visits resulting from pandemic-related restrictions to hospital access and not to SARS-CoV-2 directly (116).

**COVID and T2D risk:** From March 2020 to March 2021, a large study involving US veterans showed that men, but not women, were more susceptible to new-onset T2D diagnosis after a positive COVID test, concluding that veterans who contracted COVID were 40% more likely to develop primarily T2D within 1 year (119). At particular risk were individuals with obesity, who were found to be twice as likely as subjects without obesity to develop T2D after having COVID. However, there were significant caveats to interpretation to these results, including that the subjects were older and were generally Caucasian men, many with metabolic risk factors like elevated body mass index and high blood pressure. Also, some people in the control group were not tested for COVID if they did not show any of its symptoms, so an infection could have been missed. Third, existing cases of diabetes may have only been detected after subjects sought medical care for COVID. Because many of the risk factors for diabetes are also risk factors for COVID, care is required when considering whether COVID is the causal factor.

**COVID outcomes with pre-existing diabetes or immunosuppression**

Sources that include the US Centers for Disease Control and Prevention have stated that SARS-CoV-2 infection (like any infection or inflammatory disease) is associated with worsening symptoms of diabetes, and that persons with diabetes and metabolic disease are at increased risk for more severe COVID (133). Much of this seems to be related to the presence of comorbidities and/or complications of diabetes (e.g., heart or kidney disease) rather than diabetes per se. It has been difficult to work out whether high blood glucose levels cause worse outcomes since dexamethasone, a common treatment for severe COVID, can itself cause high blood glucose levels. It is widely recognized that observational studies are not good at clarifying the root cause. Concerns were also raised over how immunosuppressive drugs taken by recipients of organ transplants, including pancreatic islets, may place them at greater risk for severe disease and even death after a COVID diagnosis (125). Risk for bacterial, but not viral, infections is increased in people with high blood glucose levels. The autoimmunity that triggers T1D is not known to reflect a deficient immune system—and concerns about increased risk for those with T1D to contract COVID have not been substantiated. Nevertheless, many suspect that pre-existing diabetes could be a risk factor for poorer outcomes when presented with the SARS-CoV-2 virus (124). Others have highlighted the impact of social determinants of health as an underappreciated aspect, such that vulnerable populations have a higher risk for both diabetes and COVID.

A related concern has been the potential for COVID vaccines to trigger new-onset diabetes. Although this has not been widely reported, there were 2 case studies that had a single patient reporting a diabetes outcome after vaccination against SARS-CoV-2 (122,123). Nevertheless, given the high uptake rates, almost all cases of new diabetes will be in those who have received a COVID shot in the preceding months. Diabetes (both T1D and T2D) may be present for months and years before any symptoms, so new cases being diagnosed close to COVID infection may represent unmasking of the disease rather than a new problem resulting from the infection. Large-scale longitudinal studies will allow researchers to obtain valuable data regarding potential relationships between SARS-CoV-2 infection, vaccination, and new-onset diabetes.

**Patient Partner Perspectives**

The codevelopment of research priorities for researchers and individuals living with diabetes or supporting disease management as caregivers is a powerful way to incorporate different streams of disease-based knowledge. Together, researchers and patient partners have explored significant findings from the past year, reflected on the real-world impact, expressed concerns, revealed their preferences regarding where new research priorities should be set, and described the experience of partnering with basic research scientists.

**What new research findings are you most excited about?**

Collective response: We are very excited about the advancements in treatments for diabetes. Stem cell therapy, without the need to take immunosuppressive drugs, has the potential to be an incredible future therapy option to treat T1D. Harnessing omics data as a tool to study diabetes and the study of insulin production and β-cell function in genetically modified mice seem like promising research areas. The interaction between fat storage and its impact on the pancreas’ ability to release insulin is of great interest:

I'm excited about the omics data research. It would be exciting if one day it's possible to identify in living humans what their molecular profile is before developing diabetes. (N. Zoe Hilton)
The most exciting prospects are with stem cell research, which would permit β-cell transplants and not require immune system suppressants. (Tom Weisz)

What are your current worries or fears regarding research directed toward diabetes?

Collective response: We are concerned about the length of time research takes to go from the lab to an available treatment option. Even with research advancements, we worry about the health inequities that arise because new treatments are often too expensive for most people to afford. Access to medical research needs to be improved and we need to ensure that research findings are disseminated to marginalized demographics and those living in rural or remote communities:

My current worries are that I will not be able to benefit from this research in time given the number of years that I have been living with diabetes. (Sylvie Dostie)

That the funding for further research will be limited. (MaryAnn Maloney)

I’m afraid that there will never be a cure for a silent killing disease. (Anna Di Giandomenico)

What new discoveries/advancements/topics would you like to see be a priority in diabetes research in the next 3 to 5 years?

Collective response: Although we are a diverse group of patient partners working together on this project, we are all hopeful for the same thing—a cure for everyone living with diabetes. Many feel that stem cell therapy should be a priority, as it could provide the cure for T1D. However, research should also be focussed on what causes the autoimmune attack and how we can prevent it. Research on T2D in people without metabolic risk factors, and customized, personalized treatment options should also be a priority in research. Studies need to focus on preventing and treating complications, including micro- and macrovascular issues. We also believe that there needs to be a greater focus on translational research to apply scientific advances from the lab directly to those living with diabetes:

I would like more research done on medications for treating both type 1 and type 2 diabetes, such as drugs that increase glucokinase activity and enhance insulin secretion. (Matt Larsen)

The concept of stems cells becoming insulin-producing cells is quite fascinating and, if done right, antirejection drugs would not be needed. (Christina Marie Mulchandani)

I hope to see increased collaboration between basic science researchers and people living with diabetes in order to ensure that new research is meeting the diverse needs of people with diabetes. (Marley Greenberg)

What was your experience like being a patient partner connecting with basic researchers?

Collective response: Collaborating as partners on this project provided us with the opportunity to engage with the researchers, ask questions relevant to us, co-create our own research questions, and create a patient-led commentary integrated into the manuscript. Advocating on behalf of others living with diabetes is empowering and helps to ensure that research priorities are relevant to those living with the condition. We found the experience informative, inclusive, and enjoyable, and we are grateful for the opportunity:

In terms of improvements, applying a bottom-up, qualitative approach to research by using patient partnerships early on in the research-generation process may be beneficial to help bridge the gap between knowledge gained through research, and its application in policy and practice. (Christine MacGibbon)

I have enjoyed seeing the wide range of patient partners that are included in this project as I think it’s critical to have patients from different backgrounds collaborate in research projects to identify what health outcomes are most important to us individually and across groups. (Adhiyat Najam)

I loved it. I felt extremely privileged to understand the process, see the commitment and the open mind of the research team. (Farida Mersali)

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Author Contributions

L.B., V.B., M.E.A.C., J.H., N.Z.H., E.M.J., K.L., C.A.A.L., I.S., J.W., and P.A.S. drafted and edited the manuscript. A.D.G., S.D., M.G., M.L., M.A.M., C.M., F.M., C.M.M., A.N., and T.W. edited the lay manuscript and provided patient perspective. D.G. edited the lay manuscript and collated patient perspectives. M.E.A.C. prepared the graphical abstract. J.L.E., E.E.M., and R.A.S. designed the project, edited the manuscript, and provided project oversight.

References

1. Campbell JE, Newgard CB. Mechanisms controlling pancreatic islet cell function in insulin secretion. Nat Rev Mol Cell Biol 2021;22:142–58.
2. Komatsu M, Takei M, Ishii H, Sato Y. Glucose-stimulated insulin secretion: A nested perspective. J Diabetes Invest 2013;4:511–6.
3. Pfeifer MA, Halter JB, Porte Jr D. Insulin secretion in diabetes mellitus. Am J Med 1981;70:579–88.
4. Matschinsky FM, Wilson DF. The central role of glucokinase in glucose homeostasis: A perspective 50 years after demonstrating the presence of the enzyme in islets of Langerhans. Front Physiol 2019;10:148.
5. Lewandowski SL, Cardone RL, Foster HR, et al. Pyruvate kinase controls signal strength in the insulin secretory pathway. Cell Metab 2020;32:736–750.e5.
6. Meininger GE, Scott R, Alba M, et al. Effects of MK-0941, a novel glucokinase activator, on glycemic control in insulin-treated patients with type 2 diabetes. Diabetes Care 2011;34:2560–6.
7. Wilding JP, Leonsson-Zachrisson M, Wessman C, Johnsson E. Dose-ranging study with the glucokinase activator AZD1656 in patients with type 2 diabetes mellitus on metformin. Diabetes Obes Metab 2013;15:750–9.
8. Matschinsky FM. GKAs for diabetes therapy: Why not clinically useful drug after two decades of trying? Trends Pharmacol Sci 2013;34:90–9.
9. Osbak KK, Colclough K, Saint-Martin C, et al. Update on mutations in glucokinase (GCK), which cause maturity-onset diabetes of the young, permanent
neonatal diabetes, and hyperinsulinemic hypoglycemia. Hum Mutat 2009;30:1512–26.

10. Omori K, Nakamura A, Miyoshi H, et al. Glucokinase inactivation paradoxically ameliorates glucose intolerance by increasing β-cell mass in db/db mice. Diabetes 2021;70:917–31.

11. Jahaz L, Perkin KB, Durr AM, et al. Reducing glucokinase activity restores endogenous pulsatility and enhances insulin secretion in islets from db/db mice. Endocrinology 2018;159:3747–60.

12. van Raalte DH, Verchere CB. Improving glycaemic control in type 2 diabetes: Stimulate insulin secretion or prevent beta-cell rest? Diabetes Obes Metab 2017;19:1205–13.

13. Boland BB, Brown Jr C, Boland ML, et al. Pancreatic β-cell: an adaptive signaling hub of 14-3-3: Emerging mechanisms of regulation and counterregulatory metabolic responses. J Lipid Res 2019;60:734–40.

14. O’Neill E, Kolch W. Conferring specificity on the ubiquitous Raf/MEK signaling pathway. Br J Cancer 2004;90:283–8.

15. Lawrence M, Shao C, Duan L, McGlynn K, Cobb MH. The protein kinases ERK1/2 and their roles in pancreatic beta cells. Acta Physiol (Oxf) 2008;192:11–7.

16. Ikishima YM, Awazawa M, Kobayashi N, et al. MEK/ERK signaling in β-cells functionally regulates β-cell mass and glucose-stimulated insulin secretion to maintain glucose homeostasis. Diabetes 2021;70:1519–35.

17. Banks AS, McAllister FE, Camporez JP, et al. An ERK/Cdk5 axis controls the diabeticogenic actions of PPARα. Nature 2015;517:391–5.

18. McCubrey JA, Steelman LS, Chappell WH, et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta 2006;1773:1263–80.

19. MacDonald PE. A post-translational balancing act: The good and the bad of 14-3-3. Nature 2013;500:33–41.

20. Li D, Chen S, Bellomo EA, et al. Imaging dynamic insulin release using a fluorescent zinc indicator for monitoring induced exocytotic release (ZIMIR). Proc Natl Acad Sci USA 2011;108:21063–8.

21. Chen S, Huang Z, Kidd H, et al. In vivo ZIMIR Imaging of mouse pancreatic islet cells shows oscillatory insulin secretion. Front Endocrinol (Lausanne) 2021;12:613964.

22. Niinistö S, Eurlund I, Lee HS, et al. Children’s erythrocyte fatty acids are associated with the risk of islet autoimmunity. Sci Rep 2021;11:36327.

23. Hakola L, Eurlund I, Currie M, et al. Serum fatty acids and risk of developing islet autoimmunity: A nested case-control study within the TRIGR birth cohort. Pediatr Diabetes 2021;22:577–85.

24. Sánchez-ArchiJona AR, Cruciani-Guglielmacci C, Roujeau C, et al. Plasma triacylglycerols are biomarkers of β-cell function in mice and humans. Mol Metab 2021;54:101355.

25. Yung JHM, Yeung LS, Iovovic A, et al. Prevention of lipotoxicity in pancreatic islets with gammainohydroxylate. Cells; 2022:11.

26. West CG. Glucolipotrophins, β-cells, and diabetes: The emperor has no clothes. Diabetes 2020;69:273–8.

27. Prentice KJ, Saksi J, Robertson LT, et al. A hormone complex of FABP4 and nucleoside kinases regulates islet function. Nature 2021;600:720–6.

28. Yin L, Cai W, Chang XY, et al. Association between fatty-A levels with insulin resistance and carotid intima-media thickness in patients with new-onset type 2 diabetes. Diabetology 2014;2:962–70.

29. Wang H, Gao J, Su JB, et al. Serum fatty acid-binding protein 4 levels and responses of pancreatic β-cells and x-cells in patients with type 2 diabetes. Diabetol Metab Syndr 2021;13:70.

30. Mukhuty A, Fouzder C, Kundu R, Fett-A excess expression amplifies lipid induced apoptosis and beta-cell damage. J Cell Physiol 2022;237:352–50.

31. Mukhuty A, Fouzder C, Mukherjee S, et al. Palmitate induced Fett-A sequestration from pancreatic β-cells: An interesting phenomenon from clinical and disease perspectives. PLoS One 2008;3:e1765.

32. Prentice KJ, Saksi J, Robertson LT, et al. A hormone complex of FABP4 and nucleoside kinases regulates islet function. Nature 2021;600:720–6.

33. Yin L, Cai W, Chang XY, et al. Association between fatty-A levels with insulin resistance and carotid intima-media thickness in patients with new-onset type 2 diabetes. Diabetology 2014;2:962–70.

34. Wang H, Gao J, Su JB, et al. Serum fatty acid-binding protein 4 levels and responses of pancreatic β-cells and x-cells in patients with type 2 diabetes. Diabetol Metab Syndr 2021;13:70.

35. Mukhuty A, Fouzder C, Kundu R, Fett-A excess expression amplifies lipid induced apoptosis and beta-cell damage. J Cell Physiol 2022;237:352–50.

36. NestaK S, Cuozzo F, Valioria K, et al. Prolyl-4-hydroxylase 3 maintains β-cell function and metabolism during fatty acid excess in mice. JCI Insight 2021;6:e140288.

37. Tong X, Liu S, Stein R, Imai Y. Lipid droplets’ role in the regulation of β-cell function and β-cell demise in type 2 diabetes. Endocrinology 2022;163:e4007.

38. Zheng X, Ho QWC, Chua M, et al. Destabilization of β-cell FIT2 by saturated fatty acids alter lipid droplet numbers and contribute to ER stress and diabetes. Proc Natl Acad Sci USA 2021;119:e2113074119.

39. Mukhuty A, Liu S, Promets CH, et al. Perilipin 2 downregulation in β cells impairs insulin secretion under nutritional stress and damages mitochondria. JCI Insight 2021;6:e144341.

40. Tong X, Stein R. Lipid droplets protect human β-cells from lipotoxicity- induced β-cell death and cell dysfunction. JCI Insight 2022;7:103099.

41. Wuyu G, Nabihglo B, Diaz-Vegas A, et al. Proteomic pathways to metabolic disease and type 2 diabetes in the pancreatic islet. iScience 2021;24:103099.

42. Wang Z, Gerstein M, Snyder M. RNA-Seq: A revolutionary tool for transcriptomics. Nat Rev Genet 2009;10:57–63.

43. Fasoldino M, Schwartz GW, Patil AR, et al. Single-cell multi-omics analysis of human pancreatic islets reveals novel cellular states in type 1 diabetes. Nat Metab 2022;4:284–99.

44. Fucikova J, Palova-Jelinkova L, Bartkova J, Spisek R. Induction of tolerance and immunity by dendritic cells: Mechanisms and clinical applications. Front Immunol 2019;10:2393.

45. Sánchez-ArchiJona AR, Cruciani-Guglielmacci C, Roujeau C, et al. Plasma triacylglycerols are biomarkers of β-cell function in mice and humans. Mol Metab 2021;54:101355.
100. Nair GG, Liu JS, Koylew AS, et al. Recapitulating endocrine cell clustering in human pancreatic islets: A novel deep learning application. Comput Biol Med 2021;132:104257.

101. Van der Heide V, Jangra S, Cohen P, et al. Limited extent and consequences of pancreatic SARS-CoV-2 infection. Cell Rep 2022;38:110508.

102. Yang D, Bartsy T, Lithovius V, et al. Functional, metabolic and transcriptional maturation of human pancreatic islets derived from stem cells. Nat Biotechnol 2022;40:1042–52.

103. McCarthy MJ, Weir A, Bishop J, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: A cohort study of the total populations of Scotland and Canada. Lancet Diabetes Endocrinol 2021;9:82–93.

104. Hollstein T, Schulte DM, Schulz J, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: A case report. Nat Med 2020;2:1021–4.

105. Müller JA, Grosse R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab 2021;3:149–65.

106. Zayed S, El-Huniedy W, Hamad M, Mohammad AK, Elaraby E, Hacham MY. Expression profile of SARS-CoV-2 host receptors in human pancreatic islets revealed upregulation of ACE2 in diabetic donors. Biochemistry (Basel) 2020;5:215.

107. Steenbold C, Richter S, Berger I, et al. Viral infiltration of pancreatic islets in patients with COVID-19. Nat Commun 2021;12:3534.

108. Kusmarts e A, Wu W, Syed F, et al. Expression of SARS-CoV-2 Entry factors in the pancreas of normal organ donors and individuals with COVID-19. Cell Metab 2020;32:1041–1051.e6.

109. van der Heide V, Jangra S, Cohen P, et al. Limited extent and consequences of pancreatic SARS-CoV-2 infection. Cell Rep 2022;38:110508.

110. Dilek S, Gurbuz F, Turan I, Cellaoglu C, Yuksel B. Changes in the presentation of newly diagnosed type 1 diabetes in children during the COVID-19 pandemic in a single tertiary center in south-eastern Turkey. Pediatr Diabetes 2021;22:543–9.

111. Nielsen-Saines K, Li E, Olivera AM, Martin-Blaís B, Bultû Y. Case Report: Insulin-dependent diabetes mellitus and diabetic keto-acidosis in a child with COVID-19. Front Pediatr 2021;9:628810.

112. Ni A, Jüttner A, Kergoët Y, et al. Does COVID-19 predispose patients to type 1 diabetes mellitus? Clin Pediatr Endocrinol 2022;31:33–7.

113. McKeigue PM, Cunningham S, Blackburn L, et al. Relation of incident type 1 diabetes to recent COVID-19 infection: Cohort study using e-health record linkage in Scotland. Diabetologia 2022;65:220385.

114. Messiou A, Jhaveri S, Shetarsh S, et al. Anti-SARS-CoV-2 antibodies in newborn type 1 diabetes in children during pandemic in Belgium. J Pediatr Endocrinol Metab 2021;34:1319–22.

115. Salmo H, Hennonen S, Haskaback J, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. Arch Dis Child 2022;107:180–5.

116. Baddou SK, Aurangabadkar G, Kuchay MS. New onset type 1 diabetes and COVID-19. Diabetes Metab Syndr 2020;14:2211–7.

117. Holahkoo GA, Trishler R, Hyyppä LA, Povirková TM, Boluvi K. Diabetes mellitus in COVID-19 patients: Verdict or not? Wiad Lek 2020;73:2672–6.

118. Wander PL, Lowy E, Beste LA, et al. The Incidence of diabetes among 2,777,768 veterans with and without recent SARS-CoV-2 infection. Diabetes Care 2022;45:782–8.

119. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: A cohort study. Lancet Diabetes Endocrinol 2022;10:31–21.

120. Barrett CE, Koyama AK, Alvarez P, et al. Risk for newly diagnosed diabetes in COVID-19 patients: Verdict or not? Wiad Lek 2020;73:2672–6.

121. Sluchanko NN. Recent advances in structural studies of 14-3-3 protein complex: A review. J Mol Struct 2021;1204:128005.

122. Chung DS, Lee SC, Jung H, et al. Expression of SARS-CoV-2 spike protein in human pancreatic islets. J Mol Struct 2021;1204:128035.

123. Tang X, He B, Liu Z, Zhou Z, Li X. Fulminant type 1 diabetes after COVID-19 infection: Linkage in Scotland. Diabetologia; 2022:dc220385.

124. Wiederholt M, Møller P, Costa S, et al. COVID-19 in solid organ transplant recipient: Experience from a tertiary center in southern Turkey. J Pediatr Endocrinol Metab 2021;34:1303–7.

125. Kusmarts e A, Wu W, Syed F, et al. Expression of SARS-CoV-2 Entry factors in the pancreas of normal organ donors and individuals with COVID-19. Cell Metab 2020;32:1041–1051.e6.

126. Kusmarts e A, Wu W, Syed F, et al. Expression of SARS-CoV-2 Entry factors in the pancreas of normal organ donors and individuals with COVID-19. Cell Metab 2020;32:1041–1051.e6.

127. Sluchanko NN. Recent advances in structural studies of 14-3-3 protein complex: A review. J Mol Struct 2021;1204:128005.