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Review

A Decade Later: Revisiting the TGFβ Family's Role in Diabetes

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In 2010, we published a review summarizing the role of the transforming growth factor-beta (TGFβ) family of proteins in diabetes. At that time there were still many outstanding questions that needed to be answered. In this updated review, we revisit the topic and provide new evidence that supports findings from previous studies included in the 2010 review and adds to the knowledge base with new findings and information. The most substantial contributions in the past 10 years have been in the areas of human data, the investigation of TGFβ family members other than activin [e.g., bone morphogenetic proteins (BMPs), growth and differentiation factor 11 (GDF11), nodal], and the expansion of β-cell number through various mechanisms including transdifferentiation, which was previously believed to not be possible.

Highlights

The members of the TGFβ family, in particular activin, represent promising therapeutic targets for the treatment of diabetes, with emerging roles for additional members such as GDF11, BMPs, and nodal as well.

Species-specific differences exist in the synthesis and function of the TGFβ family members in β-cells and α-cells, with contrasting effects on glucose-stimulated insulin secretion and glucagon secretion.

Expansion of β-cell number in rodent models includes previously known mechanisms such as proliferation and the more current discovery of transdifferentiation as a potential mechanism as well.

Members of the TGFβ family are synthesized in human islets and non-islet tissues and regulate function.

TGFβ Family, β-Cells, and Diabetes

Diabetes continues to be a major public health burden worldwide with no known cure. Diabetes is characterized by a decreased number of functioning pancreatic islet β-cells leading to an inability to control blood glucose levels; therefore, the development of therapeutic strategies that can lead to an increased number of functioning β-cells is of much interest. Historically, research has focused on three potential strategies to achieve an increased number of functioning β-cells [1–4]. The first is β-cell replacement through transplantation of cadaveric islets or human embryonic stem cell (hESC)-derived β-cells. The second is through stimulation of endogenous β-cell replication/proliferation. The third, and most controversial, is through transdifferentiation of endogenous non-β-cells into β-cells. The TGFβ family of growth and differentiation factors have become therapeutic targets of interest due to their emerging roles in the embryonic development of pancreatic tissue and the regulation of glucose homeostasis [5–7].

In 2010, we published a review of the emerging roles for the TGFβ family in pancreatic islet cells [5]. At that time, the evidence clearly supported a role for several members of the TGFβ family, particularly activin, in regulating β-cell development, number, and function. There was evidence that members of the TGFβ family serve a role in the expansion of rodent β-cell numbers through the proliferation and/or incorporation of new β-cells from progenitors in adults. The soluble antagonists of TGFβ family members appeared to have important roles in regulating ligand activity and maintaining homeostasis. Together, the evidence suggested that the coordinated activity of several TGFβ ligands might have important regulatory actions in adult β-cells and raised the possibility of creating new therapies for diabetes based on the development of agonists or antagonists of these ligands. Despite the increasing evidence to support the role of TGFβ family members in pancreatic islet cells, a number of outstanding questions remained unanswered. Since that 2010 review [5], numerous studies have been conducted that address the outstanding questions; therefore, the objective of this

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review is to revisit the evidence and determine whether the following questions have been answered.

(i) Which TGFβ family members and natural antagonists are produced in islets and in which specific cell types? Which ligands have actions on islets, α-cells and/or β-cells? Is the action and biosynthesis modulated by changing physiological conditions?
(ii) Are the observed *in vivo* actions directly on β-cells or dependent on signals from other pancreatic cell types or even non-pancreatic tissues? In other words, are these actions produced by autocrine, paracrine or, endocrine mechanisms of TGFβ family signaling?
(iii) Are these effects functional in all mammalian species and are there species-specific differences?
(iv) Are these ligands produced in human islets and do they have roles in the regulation of β-cell number or function?
(v) Do alterations in TGFβ family signaling produce a lasting change in β-cell proliferation or survival, or increase progenitor cell formation and development to mature β-cells?

The following compares what was known back in 2010 to the new evidence that has since emerged (Figure 1 and Table 1).

TGFβ Family Members, Natural Antagonists, and Signaling Components Are Produced in Rodent Islets and Differentially Regulate Islet Activity Based on Species

The TGFβ family has two subfamilies, the TGFβ-activin subfamily and the BMP subfamily. Action of the ligands from both subfamilies is conducted through the binding of the type I and type II cell surface receptors. The type II receptor activates the type I receptor, which then, on phosphorylation, transduces a signal intracellularly. Mothers against decapentaplegic (Smad) second messengers relay the signal via the serine-threonine kinase actions of the phosphorylated type I receptor. The activated Smads, including Smad1, 2, 3, 5, and 8, form a complex with Smad4. The Smad complex then translocates to the nucleus for the alteration of gene transcription. Additionally, there are inhibitory Smads (Smad6 and 7) that act by blocking the phosphorylation of the signaling Smads. The exact receptors utilized by each subfamily member are as follows: TGFβ signals through a complex of TGFβ receptor II (TβRII) and activin receptor-like kinase receptor 5 (ALK5) (also known as TβR1); activin A signals through activin receptor II B (ActRIIB) and ALK4; activin B uses ActRIIB and either ALK4 or 7; and myostatin and GDF11 use ActRIIA or B combined with either ALK4 or 5. The signal is relayed from these receptors primarily by Smad2 and 3. This is in contrast to the receptors and second messengers utilized by the BMP subfamily. Signal transduction for the BMP subfamily is through a complex of BMPRII or ActRIIA and ALK3 (BMPR1A) or ALK6 (BMPRIB) with Smad1, 5, and 8 as second messengers. Most of these ligands are regulated via extracellular binding proteins specific to the subfamily members. Follistatin (FST) and follistatin like-3 (FSTL3) inhibit activin, myostatin, and GDF11, while noggin and chordin inhibit several members of the BMP subfamily. Taking these findings together, the TGFβ family represents a complicated system of ligands, their receptors, second messengers, and binding proteins, all of which have been found to be present in pancreatic islets [5,8–22].

Historically, most of the literature in this area has focused on activin, but recent studies have provided information about the synthesis and activity of other TGFβ members in islets. Studies in isolated rodent islets have demonstrated that several TGFβ family members, signaling proteins, and antagonists are synthesized in islets and non-islet pancreatic tissues [23–26]. Specifically, activin A, activin B, GDF11, BMP2, BMP3, and BMP4, TGFβ1, TGFβ2, and TGFβ3, FST, FSTL3, and Smad2 and Smad3 are endogenously expressed in both mouse and rat islets [23,24]. Additionally,

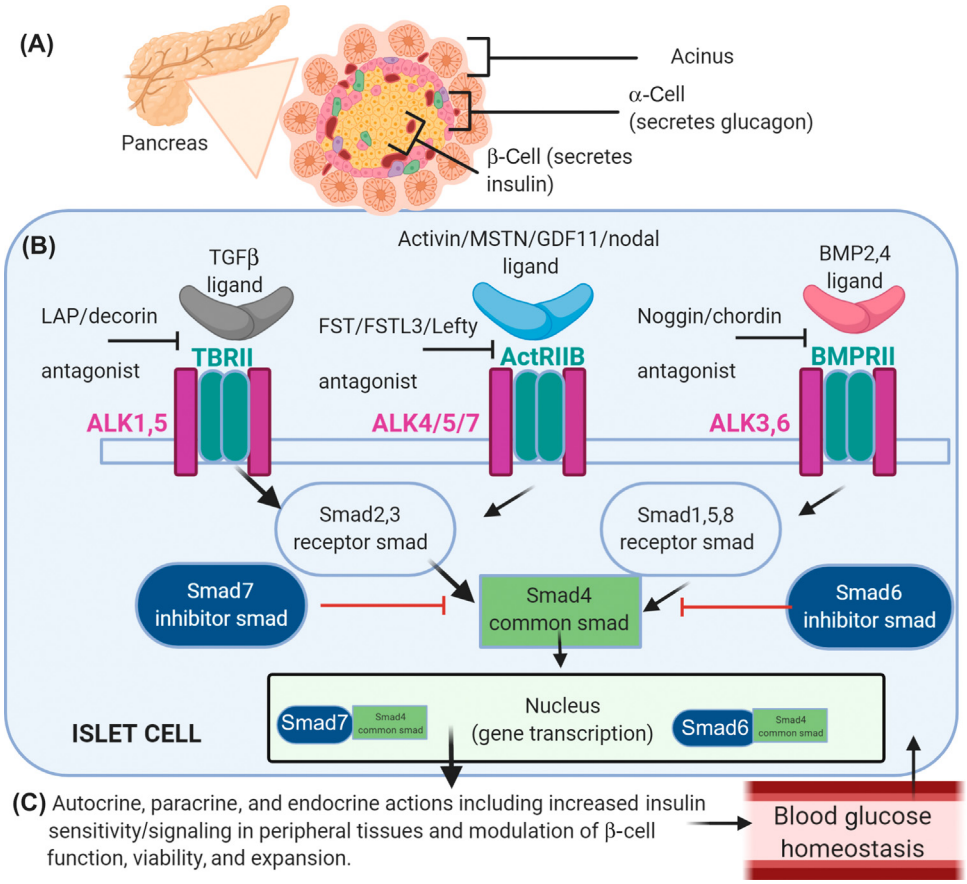

Figure 1. Regulation of Blood Glucose Homeostasis by the Transforming Growth Factor-Beta (TGFβ) Family Members. (A) Illustration of the anatomy of the pancreas with magnification of the microarchitecture of the pancreatic islet. Pancreatic islets are surrounded by exocrine/acinar cells, pancreatic α-cells are located mainly around the periphery of the islet cell, and β-cells are arranged in the core; however, there are some species-specific differences in this microarchitecture. (B) TGFβ ligands, receptors, second messengers, and binding proteins are shown. TGFβ binds to a type II (TBRII) and type I [activin receptor-like kinase receptor (ALK)1,5] receptor complex. Activin/MSTN/growth and differentiation factor 11 (GDF11) bind to a type II (ActRIIB) and type I (ALK4/5/7) receptor complex. Bone morphogenetic protein (BMP)2,4 bind to a type II (BMPRII) and type I (ALK3,6) receptor complex. TGFβ and activin/MSTN/GDF11 signal through mothers against decapentaplegic (Smad)2,3 while BMP2,4 signal through Smad1,5,8. The Smad signaling molecules then form a complex with the common Smad4 and translocate to the nucleus. Smad7 inhibits the Smad2,3/Smad4 complex and Smad6 inhibits the Smad1,5,8/Smad4 complex. LAP/decorin is an antagonist of TGFβ. Follistatin (FST)/follistatin like-3 (FSTL3) is an antagonist of activin/MSTN/GDF11. Noggin/chordin are antagonists of BMP2,4. (C) TGFβ family signaling within the islet cell results in autocrine, paracrine, and endocrine actions that ultimately control blood glucose homeostasis. (A,B) contain mainly information known at the time of the previous review in 2010 [5] and (C) contains new evidence that has emerged since that review. More information on the new evidence can be found in Table 1. This figure was created using BioRender (https://biorender.com/).

less is known about the TGFβ family member nodal, but emerging evidence suggests that nodal is also expressed in rat islets [25]. Interestingly, myostatin is not detectable in rat islets but is the most highly expressed TGFβ family member in mouse islets [24]. Further, a cellular source for the activin proteins in rodents has been identified for activin A (cytosolic and nuclear) and activin B (cytosolic) [24]. Activin A has been found to be colocalized with glucagon in α-cells, as well as colocalized with insulin in some β-cells [24]. Activin B was colocalized mainly with insulin [24].

Table 1. Summary of the Expression Patterns and Actions of the TGFβ Family Members, Natural Antagonists, and Signaling Components in a Species-Specific Manner: New Evidence That Has Emerged Since the Initial *TEM* Review in 2010 [5].

	Mouse	Rat	Human	Refs
Expression in islets	TGFβ ligands (INHBA[a], INHBB[b], GDF11, MSTN, BMP2, 3, 4, TGFβ1, 2, 3), receptors, second messengers, and binding proteins	TGFβ ligands (INHBA, INHBB, GDF11, BMP2, 3, 4, TGFβ1, 2, 3, NODAL), receptors, second messengers, and binding proteins	TGFβ ligands (INHBA, INHBB, GDF11, MSTN, BMP2, 3, 4, TGFβ1, 2, 3, NODAL), receptors, second messengers, and binding proteins [25,33,40] Expression patterns are determined by the microenvironment and whether the islets are functional, cultured, and based on the diabetes status of the donor	[23–26,33]
Autocrine and paracrine actions on islet cell function by TGFβ family members: General control by the TGFβ family members: • GSIS • Calcium flux and calcium channel • kATP channel • ATP production • Expression of β-cell- and α-cell-specific genes • Cell viability	Specific control by: **Activin A** Conflicting results: Negatively regulates GSIS Positively regulates GSIS and ATP production **Activin B** Negatively regulates GSIS and ATP production **GDF11 and BMPs** Positively regulate glucagon secretion Positively regulate GSIS and increase survival of β-cells **Smad2 disruption** Alteration of kATP channel activity resulting in islet hyperplasia and diminished insulin secretion **FST overexpression** Preservation of function through β-cell proliferation	Specific control by: **Activin A** Positively regulates GSIS **TGBb1** Positively regulates GSIS **MSTN** Positively regulates GSIS	Specific control by: **Activin A** Restores GSIS in islets obtained from T2DM donors	[23,24,26–29,31,33]
Action on β-cell expansion by TGFβ family members	Increases β-cell proliferation Generation of β-cells from adult stem cells, hESCs, ductal cells, hAECs, and α-cell to β-cell transdifferentiation		Increases β-cell proliferation	[16,25,26,37–42,44–48]
Endocrine action on other tissue and whole-body glucose homeostasis	Regulation of fat mass (activins/myostatin) Regulation of insulin sensitivity, insulin signaling, and glucose tolerance			[49–56]

[a]INHBA is the gene encoding activin A.
[b]INHBB is the gene encoding activin B.

TGFβ Family Members Regulate Islet Activity through Autocrine and Paracrine Mechanisms

The role of TGFβ family members in the function and survival of isolated pancreatic islets is less clear. In the prior review [5], evidence from several studies was presented to implicate activin and TGFβ1, 2, and 3 in the regulation of adult islet function by enhancing glucose-stimulated insulin secretion (GSIS), but not much was known about the other family members. At that time, the evidence for activin suggested several mechanisms for the ability to regulate islet cells, including increased calcium flux, which is necessary for insulin secretion, as well as through increased expression of β-cell-specific genes and diminished expression of α-cell-specific genes. Updated information supports this evidence and shows that activin A is produced in islets and is secreted where it can act locally on other cell types and increases cell viability [23].

Activin A and B signal through a common set of intracellular components but it is unclear whether they display similar or distinct functions in glucose homeostasis [26]. When comparing the abilities of activin A and B to regulate downstream signaling, ATP production, and GSIS in wild-type mouse islets and β-cells, activin B negatively regulated GSIS and ATP production, while the opposite was found for activin A [26]. Further, overexpression of Smad3 responded preferentially to activin B and resulted in decreased GSIS, but overexpression of Smad2, which preferred activin A, did not [26]. This is in direct contrast to other studies finding positive regulation by activin A in rat islets [24] but not in mouse islets [23,24]. The action of activin A, at least in part, may be modulated through Smad2. Recent evidence has found that if signaling through Smad2 is disrupted in mouse β-cells, ATP-sensitive K^+ (kATP) channel activity is altered and the subsequent result is islet hyperplasia and diminished insulin secretion [27]. By contrast, it has also been found that if FST is overexpressed in the diabetic pancreas, the result is preservation of function through β-cell proliferation [28].

Additional studies have shed light on potential roles for other TGFβ family members as well. In addition to activin A, TGFβ1 and myostatin were found to enhance GSIS in isolated rat islets but not mouse islets and GDF11, BMP4, and BMP7 stimulated glucagon secretion in mouse islets while FST suppressed secretion [23,24]. The mechanism for the regulation of islet cell function by TGFβ1, along with TGFβ2 and TGFβ3, may be through β-cell regeneration, but more evidence is needed. Recombinant GDF11 can restore the function of β-cells, increase survival and, improve morphology after exposure to hyperglycemic conditions *in vitro* and improves glucose homeostasis in mouse models of type 2 diabetes mellitus (T2DM) *in vivo* (both nongenetic and genetic mouse models) [29]. The improvements in metabolic homeostasis appear to be solely attributed to GDF11, while a similar effect of GDF8 was not found in a diet-induced obesity mouse model despite sharing 90% sequence identity [30]. Further, if GDF11 is blocked by the use of an anti-GDF11 monoclonal antibody, the result is β-cell failure and mortality [29]. A potential mechanism for the actions of GDF11 may be through the activation of signaling by the TGFβ/Smad2 and P3K Akt fox01 pathways [29]. BMP pathways have also been found to have a beneficial effect on insulin secretion and glucose homeostasis in a mouse model of islet dysmorphogenesis and nonimmune-mediated lean diabetes [31]. Deletion of the dual BMP and Wnt antagonist Sostdc1 results in improved insulin secretion and glucose homeostasis in a subset of mice versus control after 12 weeks of high-fat diet (HFD) [31]. These effects were attributed to the BMP pathway secondary to altered expression of Bmp-responsive genes in islets without alterations in Wnt target genes [31]. The combined implications of these results indicate that not only does the synthesis differ by species, but the TGFβ family members directly regulate islet function in a species-specific manner as well.

TGFβ Family Members Are Produced in Human Islets and the Function and Modulation of the Family Members Are Dependent on the Physiological Conditions

Data from human islets are relatively sparse and data from T2DM donor islets even more scarce [23,25,32,33]. Recent studies have confirmed that TGFβ ligands, their receptors, second messengers, and binding proteins are produced in human pancreatic islets [23,33] including the lesser known family member nodal [25]. Further, the expression pattern is determined by the microenvironment. Defined transcript expression patterns of activin and the TGFβ family in human islets have been described based on whether the islets were functional, whether they were cultured, and whether they were from a normal donor or a diabetic donor [33]. *INHBA* (the gene encoding activin A) is the most highly expressed of the family members in normal (non-diabetic) cultured islets and the level decreases as the length of time in culture increases [33]. By comparison, freshly isolated human islets (not cultured) showed significantly lower expression of *INHBA* and *FST* and significantly more *INHBB* (the gene encoding activin B),

TGFβ2, and *SMAD2*. Cultured non-functional (little or no GSIS response) human islets (including islets from diabetic donors) also showed significantly lower expression of *INHBA* and significantly greater expression of *TGFβ2* and *FSTL3*.

Several functional roles for the TGFβ family, particularly activin A, in human islets have also been elucidated [23,33]. Similar to the expression patterns, the effect of exogenous activin A on human islets differs based on functional status, culture status, and diabetic status [33]. Addition of activin A to functional cultured human islets from a non-diabetic donor did not result in increased GSIS compared with control, and indeed tended to diminish GSIS [23,33]. By contrast, the exogenous addition of activin A to non-functional human islets from non-diabetic and diabetic donors restored GSIS to normal levels, providing the first direct evidence toward the targeting of activin signaling for therapeutic diabetes drug development [33]. Interestingly, the results in both functional and non-functional islets were reversed by the addition of Fst [33]. This differential effect of activin suggests that the effects are unmasked only when endogenous levels are diminished, whether naturally by increased culture length or when inhibited by an antagonist such as Fst [33]. Further investigation into the mechanism has revealed a dynamic regulatory system involving the modulation of potassium and calcium channels and key target genes involved in function and survival. For insulin secretion to occur, kATP channels must be inactivated and calcium channels must be activated, and these changes occur in response to increasing glucose levels. Human islets from T2DM donors have significantly reduced expression of *GLUT2*, which is thought to be an early sign of β-cell stress, and are consequently insensitive to glucose. Activin A, through Smad2 signaling, can inhibit kATP channels and activate the calcium channel, which leads to insulin secretion [27] in mouse islets. Whether this holds true in human islets is still being investigated; however, preliminary evidence partially confirms this, as activin A has been found to increase the expression of *CACNA1D* and *CACNA1C*, which encode Cav1.3 and Cav1.2, respectively, and are key calcium channels involved in insulin secretion [33]. Further, polymorphisms of *CACNA1D* have been linked to T2DM in the past [34].

Combining the data showing that both non-functioning islets (from non-diabetic donors) and islets from T2DM donors expressed significantly elevated levels of the FSTL3 antagonist in addition to diminished expression of INHBA, strongly suggests that interaction among these TGFβ family members is critical for this dynamic regulatory system. In other words, when islets expressing high levels of endogenous FSTL3 are treated with exogenous activin A, compensation occurs and overrides the inhibition leading to restoration of the intra-islet regulatory loop that controls function. There may be additional mechanisms involved in the role of activin A in maintaining normal physiology in an islet. Isolating and then culturing islets induces the stress-response and prosurvival mechanisms after mechanical and enzymatic stress with subsequent placement in a hypoxic environment. Activin A has been directly linked to the stress response by inducing HIF1α expression and increasing viability in cultured human islets from T2DM [33] and was found to protect islets from cytokine-driven cell death [35]. Therefore, activin A may counteract the acute and chronic alterations that occur in an inflammatory environment. These alterations may include those associated with the development of T2DM in humans. However, little known is known about the *in vivo* actions of the TGFβ family in humans with regard to islet function and blood glucose control. Given the changes that occur based on the microenvironment of cultured islets, *in vitro* data must be interpreted with caution over their applicability to *in vivo* human physiology [33]. One of the few studies available in this area found an association between blood levels of activin A and abnormal glucose regulation in patients with myocardial infarction. Increasing the activin levels appeared to have an anti-inflammatory and antioxidant effect and resulted in a decrease in blood glucose [35]. This underscores that investigation into this protein family and its application to humans is highly relevant.

TGFβ Family Signaling Can Increase Progenitor Cell Formation and Development to Mature β-Cells

The role of activins in the development of the pancreas is fairly well established; however, the role of these proteins, as well as the role of other TGFβ family members, in adult β-cells is still being elucidated. It was clear from the previous review [5] that members of the TGFβ family, in particular activin A, are linked to islet development and may contribute to β-cell proliferation, which is an important mechanism involved in the ability of β-cells to adapt to changes in metabolic demands. Since the last review [5], evidence has been mounting that not only confirms the ability for proliferation, but introduces additional mechanisms for this expansion including the generation of β-cells from hESCs, ductal cells, and human amnion epithelial cells (hAECs) as well as through dedifferentiation with either subsequent proliferation or transdifferentiation. In addition, evidence has solidified a role for TGFβ signaling in the apoptosis of β-cells, in which activation of TGF-β/Smad3 signaling induces β-cell apoptosis [36].

Recent studies have added to the body of knowledge and suggest that TGFβ signaling via Smads has been found to regulate the proliferation of β-cells. In conditional Smad7 knockout mice, proliferation of β-cells is inhibited without any effect on function; conversely, when Smad7 is overexpressed the proliferation is enhanced [37]. Given that Smad7 is an inhibitor Smad and, more specifically, inhibits Smad 2 and Smad3, these findings lend support to an earlier study that found inhibition of TGFβ signaling through Smad3 stimulates β-cell proliferation and, by contrast, β-cell proliferation is suppressed when TGFβ signaling is activated [38]. This regulation by TGFβ is attributed to the impact on p27, a cell cycle regulator and inhibitor of cyclin-dependent kinase (CDK) [16]. The nuclear accumulation of p27 is reduced and the inhibition of CDK subsequently results in β-cell proliferation [38]. There is additional evidence showing a role for repression of the ink4a/arf locus in the subsequent β-cell proliferation that results from the inhibition of TGFβ signaling in mouse and human islets [39]. An emerging area of interest involves the lesser known TGFβ family member nodal and its role in the proliferation of β-cells. Nodal, along with its coreceptor cripto, is present in both embryonic and adult rodent islets; however, while nodal has been found in human β- and α-cells, cripto has not [25]. Nodal stimulates apoptosis in INS-1 cells through the activation of ALK7 signaling with subsequent suppression of Akt signaling and stimulation of Smad2 signaling; however, the role in human islets is less clear [40]. Furthermore, human β-cell proliferation was stimulated by nodal and α-cell proliferation was inhibited [25]. The β-cell proliferation was attributed to the phosphorylation of Smad2 without effects on AKT (also known as protein kinase B) or mitogen-activated protein kinase (MAPK) signaling [25]. Nodal had no effect on apoptosis, differentiation, or viability in human islets [25].

Given that physiological and pathological stresses such as diabetes induce dedifferentiation of β-cells, research has been performed into what molecules may be involved in these processes. Activin A has been found to dedifferentiate β-cells by increasing the number of immature β-cells [23]. Further, activin A has been shown to decrease the gene expression of insulin and other genes directly related to β-cell maturity such as *Pdx1*, *Mafa*, *Glut2* [23]. At the same time, activin A upregulated genes known to be associated with an immature β-cell state such as *Mafb* [23]. This evidence lends support for an activin A suppressive effect on adult β-cell maturation and function via autocrine and/or paracrine actions [23]. By contrast, similar effects in insulinoma cells have been attributed to activin B actions on *Pax4*, a previously unknown target for activin B [41]. The processes of dedifferentiation and proliferation can be linked through Smad2, 3, and 7 which form a network of intracellular TGFβ regulators. These Smads, particularly Smad7, control proliferation after β-cell loss by first inducing a transient dedifferentiated state [42]. Additionally, data have also suggested a previously unknown role for Sel1L-Hrd1 ERAD, which appears to suppress TGFβ signaling leading to the maintenance of β-cell identity without

a change in β-cell survival and proliferation as part of the cytosolic ubiquitin-proteasome system [43].

Recent evidence has also suggested the possibility of generating new β-cells through transdifferentiation [44,45]. Increased activin A and B signaling has been found to result in β-cell expansion through destabilization of the α-cell phenotype (decreased gene expression of α-cell-related genes *Arx*, *GCG*, and *MafB*) and promotion of transdifferentiation into β-cells (increased expression of *Pax4* and *INS*) *in vitro* [44]. These changes were found to be modulated by phosphorylated Smad2 [44]. These results have been further verified *in vivo* through α-cell lineage-tracing technology combined with FSTL3KO mice to label α-cells with YFP [45]. The results showed that ins^+/yfp^+ cells were significantly increased in FSTL3KO mice compared with wild-type littermates [45]. In addition, activin A treatment of isolated islets also led to a significant increase in ins^+/yfp^+ cells [45]. Taken together, the evidence is mounting for the possibility of a role for activin signaling in α- to β-cell transdifferentiation, which may contribute substantially to β-cell mass. This evidence contributes to a new understanding of the plasticity of adult islet cells that has significant implications for the generation of functional β-cells, which can be controlled by local hormonal and/or environmental cues.

Evidence also exists for the differentiation of hESCs and transdifferentiation of non-islet cells into insulin-producing β-cells. Using a chemically defined culture, cooperative signaling from FGF, activin A, and BMP can stimulate hESCs to differentiate into insulin-producing β-cells [46]. Human pancreatic ductal cells exposed to hyperglycemic conditions *in vitro* can also be driven to transdifferentiate into insulin-producing β-cells by a combination of activin A and exendin-4 and reversed hyperglycemia after transplantation into diabetic nude mice [47]. Similarly, a combination of exogenous treatment with activin A and nicotinamide and the ectopic expression of the pancreatic transcription factor pancreatic and duodenal homeobox-1 (PDX1) drove human amnion epithelial cells (hAECs) toward a pancreatic lineage with expression of key genes such as *NKX6.1*, *NEUROD1*, *PDX1*, *SOX17*, and *RFX6* [48]. The TGFβ/Smad pathway has been found to enhance the transcription of *Ngn3*, *miR-375*, and *miR-26a* resulting in the generation of new β-cells from adult stem cells [26].

The TGFβ Family Members Regulate Non-β-Cell Tissues Indirectly Impacting Glucose Homeostasis *In Vivo*

The previous review [5] provided evidence supporting a role for the TGFβ family members in regulating glucose homeostasis while acknowledging the difficulty of being able to distinguish the effects due to developmental alterations versus effects after adulthood is achieved. The clear importance of the roles of the TGFβ family members in adult glucose homeostasis was only revealed in the few studies that blocked signaling after neonatal development. Further, the evidence presented in the previous review suggested that the role of the TGFβ family in maintaining adult glucose homeostasis is not visible until its activity is perturbed [5].

Roles for activin and myostatin in regulating adipose and muscle tissue are emerging. Activin and myostatin have been shown to stimulate proliferation while inhibiting differentiation of primary preadipocytes and preadipocyte cell lines [49]. The activity of activin and myostatin is regulated by the high-affinity antagonists fst and fstl3, therefore serving a role in fat mass and the potential for a subsequent impact on glucose homeostasis. fst is translated as three protein isoforms that differ in their distribution, actions, and biochemically, and FSTL3 has only one isoform. FST288 is the isoform that can primarily be found in tissues while the isoform primarily found in the gonads is FST305. FST and fstl3 are synthesized in mostly the same tissues but not all, suggesting that these inhibitory proteins may share biological actions and also have distinct actions. Since mice

lacking fst do not survive, it has been impossible to investigate the roles of fst in regulating the body composition and glucose homeostasis in adult mice. To explore these potential roles for fst and fstl3, a mouse model was created in which only the FST288 isoform is expressed (FST288-only mice [49]). Another mouse model was created in which this new FST288-only mouse was crossed with the FSTL3KO mouse leading to a double mutant (2xM [49]). Results revealed that differential phenotypes result depending on whether one or two antagonists are eliminated. For instance, perigonadal visceral fat is decreased in both the FSTL3KO mouse and the 2xM mouse, which is interesting given that these mouse models have opposite glucose tolerance and insulin sensitivity. Other studies have revealed that FSTL3 overexpression with subsequent inhibition of both myostatin and activin A leads to enhanced muscular insulin action and protection against the development of insulin resistance and diet-induced obesity [50]. The increase in activin bioavailability by inhibition of antagonists enhances hepatic insulin sensitivity while inducing hepatic steatosis in mice [51] and has been found to increase glucose tolerance in diet-induced obese mice with evidence for fst as a pathological hepatokine [52]. Further, potential clinical significance has been identified in humans who underwent gastric bypass surgery [52]. Improved glycated hemoglobin levels were observed in conjunction with decreased serum levels of fst [52]. Additional clinical relevance is revealed for the TGFβ family in response to exercise in humans [53]. Circulating levels of several family members including activins and FSTs increase after 45 minutes of activity [53]. Activin B has been purported to have a distinct, and potentially opposite, role from activin A in maintaining glucose homeostasis. Since in some studies activin A does not have a stimulatory effect on mouse islets [23,24], it would be expected that activin B would enhance GSIS; however, this was not observed in activin B-null mice [54]. In addition, results from the activin B-null mouse revealed that activin B regulates the composition of islets and the mass but does not serve a role in insulin sensitivity or whole-body glucose homeostasis [54].

Activin A and B are not the only members of the TGFβ family to have been found to serve a role in glucose homeostasis by impacting non-β-cell tissues. BMP4 [55], BMP7 [55], and BMP6 [56] have all been implicated. Antagonistic effects of BMP4 and BMP7 have been elucidated in a mouse model of diabetes, with BMP7 enhancing and BMP4 inhibiting insulin signaling [55]. BMP7 phosphorylates and activates PDK1 and Akt, which subsequently increases the translocation of the glucose transporter GLUT4 and glucose uptake [55]. The antagonistic effects of BMP4 are achieved through activation of the PKC-Φ isoform, which results in insulin resistance [55]. With regard to BMP6, this protein has been found to act on hepatocytes to inhibit glycogenolysis and gluconeogenesis and to act directly on β-cells to increase insulin secretion [56]. These combined actions of BMP6 lead to decreased circulating glucose and lipid levels and increase insulin levels with overall enhanced glucose homeostasis [56].

Members of the TGFβ Family Exert Cellular Functions through Noncanonical Pathways As Well

As previously described, the TGFβ family is a diverse and complex family of proteins that serve many physiological roles beyond glucose homeostasis, including as key regulators of development, the immune system, and cancer [3,57–63]. These functions of the TGFβ family can be performed via canonical (Smad dependent) or noncanonical (Smad independent) pathways. The above description of the role of the TGFβ family in glucose homeostasis has focused on the well-known canonical pathway. There are, however, noncanonical pathways that deserve mention as well, although a comprehensive explanation is beyond the scope of this review. Once a TGFβ ligand binds to its receptor, noncanonical signaling pathways are induced, such as MAPKs, Akt, and phosphoinositide-3-kinase (PI3K) [63–66]. Signaling through the noncanonical pathway can have direct TGFβ biological functions or exert effects through the canonical Smad pathway. Noncanonical signaling downstream effects have been linked to the development of

fibrosis [64], insulin resistance, and T2DM [65,66]. Evidence suggests that inhibition of signaling through MAPKs such as ERK or through PI3K/AKT in the peripheral tissues (skeletal muscle, adipose, liver) can be a potential therapeutic target for the prevention of T2DM by increasing insulin sensitivity [63–66].

Deregulation of TGFβ Signaling in the Context of Cancer-Induced Diabetes

Throughout this review, the focus has primarily been on the role that the TGFβ family plays in glucose homeostasis with type 1 diabetes mellitus (T1DM) and/or classical T2DM in mind, but it is also important to mention deregulation of TGFβ signaling in contexts other than forms of diabetes. There have been several studies linking various types of cancer to the development of diabetes and vice versa. For example, a strong link between T2DM and the subsequent development of pancreatic cancer has been well established [67–84]. In addition, the opposite has proved true. A large percentage of individuals with pancreatic ductal adenocarcinoma (PDAC) develop new-onset diabetes [67]. While the underlying mechanism for this diabetogenic effect is still emerging, evidence is mounting to suggest that the deregulation of TGFβ signaling may be involved [3,85]. PDAC is an incurable, lethal form of cancer and accounts for 85% of all cancers related to the pancreas [67]. It is often difficult to determine which came first, the diabetes or the cancer; however, evidence is starting to emerge to suggest that tumor-secreted molecules may be part of a mechanism that ultimately destroys the β-cells and results in diabetes. Mutations in SMAD4, a tumor suppressor, and the TGFβ type II receptor may be partially responsible for the mechanism by which PDAC triggers the loss of β-cells and the resulting diabetes [85]. As described earlier, the TGFβ family ligand binds to the receptor, initiating the signaling cascade in which Smad2/3 binds to the common Smad4 and then the complex translocates to the nucleus. A mutation in the receptor and/or Smad4 would alter this signaling pathway. Further, beyond their roles in glucose homeostasis, the components of the TGFβ family serve dual roles as both tumor suppressors and tumor promoters [3,62]. TGFβ can inhibit tumor formation by suppressing the proliferation of most normal epithelial cells or via the induction of cell death [3,62]. However, TGFβ can also promote the progression of existing tumors, and cancer cells, including those in PDAC, have been found to secrete TGFβ leading to increased TGFβ signaling [86,87] that results in the loss of β-cells through apoptosis. The new-onset diabetes in individuals with PDAC is distinct from the form of diabetes that develops after pancreatic resection, type 3c diabetes mellitus (T3cDM), which is strictly due to an overall loss of islet cells, and specifically β-cells [67]. However, an interesting finding is that individuals who undergo resection of their PDAC tumor may see a resolution of PDAC-induced diabetes if an adequate β-cell mass remains post-resection [67,69]. This phenomenon lends strong support to PDAC being a diabetogenic cancer. Other factors may also be involved, such as islet amyloid peptide (IAPP), which is a hormone secreted by the β-cells that is associated with insulin resistance, and increased plasma levels of IAPP have been found in individuals with pancreatic cancers [88]. The plasma IAPP levels were significantly reduced after tumor resection [88]. Whether there is a relationship between the deregulation of TGFβ signaling and IAPP remains to be determined, but Hu *et al.* [88] describe in depth the role for both in the development of diabetes in their 2020 publication. The tumor-promoting capabilities of the deregulation of TGFβ signaling must be taken into consideration when contemplating manipulation of this pathway for therapeutic purposes and may have potential as a marker for pancreatic cancer, allowing early detection [89].

Concluding Remarks and Future Perspective

The past 10 years have resulted in a substantial amount of new evidence to support the role of the TGFβ family members, signaling proteins, and antagonists in β-cell regulation and function, as well as illustrating a role in non-islet tissues such as adipose, muscle, and liver (Figure 1 and Table 1). The most substantial contributions in the past 10 years have been in the areas of

Outstanding Questions

What specific molecular pathways are involved in the TGFβ family modification of β-cell function and number?

Do the findings of enhanced β-cell proliferation by TGFβ family members in rodent cells and cell lines translate to the human model, and if not, is it due to the human experimental model currently being used (i.e., the current use of isolated human islets rather than *in vivo*)?

How much functional β-cell mass needs to be restored to completely alleviate diabetes in humans?

Is the observed transdifferentiation an actual physiological process that contributes to functional β-cells in adult humans?

Would new β-cells derived from transdifferentiation be vulnerable to autoimmune attack similar to β-cell destruction occurring in T1DM and is there a marker that can be used to detect this?

human data, the investigation of TGFβ family members other than activin (e.g., BMPs, GDF11, nodal), and the expansion of β-cell number through various mechanisms including transdifferentiation, which was previously believed to not be possible. This new evidence over the past 10 years has provided partial answers to the outstanding questions that remained from the previous review [5]; however, despite all of the new advances in this area, some questions remain (see Outstanding Questions).

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