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TOPIC HIGHLIGHT

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B7-H4 as a protective shield for pancreatic islet beta cells

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Abstract

Auto- and alloreactive T cells are major culprits that damage β-cells in type 1 diabetes (T1D) and islet transplantation. Current immunosuppressive drugs can alleviate immune-mediated attacks on islets. T cell co-stimulation blockade has shown great promise in autoimmunity and transplantation as it solely targets activated T cells, and therefore avoids toxicity of current immunosuppressive drugs. An attractive approach is offered by the newly-identified negative T cell co-signaling molecule B7-H4 which is expressed in normal human islets, and its expression co-localizes with insulin. A concomitant decrease in B7-H4/insulin co-localization is observed in human type 1 diabetic islets. B7-H4 may play protective roles in the pancreatic islets, preserving their function and survival. In this review we outline the protective effect of B7-H4 in the contexts of T1D, islet cell transplantation, and potentially type 2 diabetes. Current evidence offers encouraging data regarding the role of B7-H4 in reversal of autoimmune diabetes and donor-specific islet allograft tolerance. Additionally, unique expression of B7-H4 may serve as a potential biomarker for the development of T1D. Future studies should continue to focus on the islet-specific effects of B7-H4 with emphasis on mechanistic pathways in order to promote B7-H4 as a potential therapy and cure for T1D.

Key words: Diabetes mellitus; Autoimmunity; Transplantation; Co-stimulation blockade; Biomarker

Core tip: Onset of type 1 diabetes is driven by defects in immune regulation, resulting in β-cell autoimmunity. However, there may be mechanisms inherent to the β-cell that may prevent or slow development of autoimmunity and progression of disease. One such factor is B7-H4, which acts at the islet-immune interface to defend β-cells from autoimmune diabetes and to protect transplanted islet allografts.

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INTRODUCTION

Pathophysiology of diabetes, current therapies and their limitations

Diabetes mellitus affects 382 million people world-wide today, and this number is expected to increase by 55% by 2035[1]. Diabetes is a chronic metabolic disease which stems from insufficient production of insulin by pancreatic β-cells and/or inability of the body to respond to insulin. There are two major forms of diabetes-type 1 diabetes (T1D), and type 2 diabetes (T2D). While differing in their pathogenesis, both types of diabetes result from failure and/or loss of insulin-producing β-cells that eventually translate to a state of chronic hypergly-

cemia[2-4]. Persistently high blood glucose concentrations are associated with this disease, which result in both acute metabolic conditions such as diabetes ketoacidosis and long-term vascular complications such as diabetic retinopathy, nephropathy, and neuropathy[2,4,5]. These devastating complications lead to enormous socioeconomic burdens, mandating a pressing need to find a cure.

There are both differences and similarities in mechanisms by which β-cell injuries occur in T1D and T2D. T1D has been identified as an autoimmune disease in which insulin-producing β-cells are destroyed by targeted immune attack in genetically susceptible individuals. It is believed that environmental events initially trigger the recruitment of $CD4^+$ and $CD8^+$ T cells to the islets of Langerhans and mount continuous attacks against autoantigens on β-cells, resulting in β-cell death[4,5]. T2D, closely linked to aging and obesity as well as a certain level of genetic susceptibility, is characterized by insulin insensitivity due to insulin resistance in peripheral tissues, which leads to β-cell stress[4,6,7]. T1D and T2D overlap in β-cell stress and death pathways despite differences in initiating triggers[3]. One such common pathway is endoplasmic reticulum (ER) stress, which can activate downstream signaling cascades collectively known as the unfolded protein response (UPR)[3]. Various conditions such as nutrient deprivation, inflammation, alterations in oxidation-reduction balance and elevated levels of glucose and lipids can all lead to accumulation of unfolded proteins in the ER lumen. In response to this ER stress, the UPR serves as a compensatory mechanism to restore ER homeostasis by increasing the protein folding capacity of the ER and muting protein translation[8-10]. However, chronic ER stress can shift the UPR towards a pro-apoptotic state[8,9]. In T2D, increased demand on insulin production due to progressive insulin resistance, combined with exposure to increased levels of glucose and fatty acids, induces prolonged β-cell ER stress, thus triggering cell death *via* apoptotic pathways[6,7,11]. Growing evidence also implicates ER stress as one of the factors that contribute to T1D[8,12,13]. Pro-inflammatory cytokines secreted by infiltrating immune cells in the islets of T1D patients could induce apoptosis *via* signal transducers such as STAT-1 and nuclear factor-kappa B[3,14,15], and cytokines could also negatively impact ER homeostasis and cause UPR dysregulation, which contributes to β-cell demise[3,16,17]. Knowledge of overlapping β-cell injury mechanisms between T1D and T2D can provide valuable insight into pathogenesis of diabetes, guiding rational development of therapeutics that target instigators of both T1D and T2D.

Treatments for diabetes have been designed to address glycemic control and alleviate diabetic complications. Depending on the severity of insulin resistance, management of T2D can be achieved through lifestyle and diet modifications. Commonly used pharmacological agents for T2D include insulin sensitizers, insulin secretagogues, incretin-based therapies, and insulin analogues[11]. Most T1D patients still rely on exogenous insulin injection to maintain euglycemia. However, stringent monitoring of blood glucose level is needed and the use of exogenous insulin carries the risk of hypoglycemic episodes that can be life-threatening.

In search of the elusive "cure" of diabetes, it would be desirable to halt the autoimmune attacks on β-cells, or to prevent it altogether. Current on-going clinical trials for T1D are focusing on using immunomodulation strategies to delay disease onset and preserve β-cell function in full blown diabetes. Examples of these drugs include anti-CD3 (teplizumab) and anti-CD28 (rituximab), antibodies to inhibit autoreactive T cells and B cells. CTLA4-Ig (abatacept), an inhibitory molecule for T cells, also showed promise in previous clinical trials to prolong insulin production in newly-diagnosed T1D patients[18].

Transplantation of insulin-producing tissue also provides a therapeutic option for diabetes. Whole pancreas transplantation yields better glycemic control compared with insulin injections, but subjects patients to major surgery with associated risks, and is therefore only offered to patients with severe diabetic complications. Islet cell transplantation is a relatively safe and fast alternative, in which islets isolated from cadaveric donors are infused into the liver *via* the hepatic portal vein[19,20]. With the development of the Edmonton Protocol, islet cell transplantation has become a reproducible, standardized procedure in multiple medical centers around the world which improves glycemic control[19,21]. Patients who received islet cell transplantation also showed markedly reduced diabetic retinopathy and nephropathy compared with patients who were treated with conventional medical therapy[20,21]. Even though insulin independence declined during prolonged follow up, partial graft function was maintained in 80% of the patients, as measured by C-peptide secretion[21]. Despite ongoing improvements in islet transplantation, eventual graft dysfunction, failure, and rejection remain a challenge[19,20].

The limited success of β-cell protection in various studies has attracted interest to novel β-cell immunoprotective strategies. In the following we review recent findings that suggest the negative co-stimulatory molecule B7-H4 has unique functions in the pancreatic islets that carries the potential to act as not only as a natural but also a therapeutic "shield" for β-cells during the development of diabetes and following pancreatic islet transplantation, as well its prospective role as a novel biomarker for T1D.

B7-H4: A NOVEL IMMUNE-REGULATORY MOLECULE

B7-H4, also known as B7x, was identified in 2003, and belongs to the B7 family of immunoglobulins[22-24]. Genomic B7-H4 is encoded on the *VTCN1* gene, which is located on chromosome 1 and 3 in human and mouse, respectively[24]. Given that mouse and human share 87% amino acid identity, B7-H4 is a highly evolutionarily conserved molecule. Mature B7-H4 is a 50-80 kDa transmembrane protein consisting of one IgV and one IgC

region, which are encoded on exons Ⅲ, Ⅳ, and part of Ⅴ[22-24]. Like other members of the B7 family, it is up-regulated on the cell membrane of activated antigen presenting cells, and acts to modulate the immune response[22-24]. Upon binding to a putative yet unidentified counter-receptor on T cells, B7-H4 acts as a negative co-signaling molecule to inhibit T cell proliferation and cytokine production. One proposed mechanism of action is that B7-H4 arrests cell cycle progression of T cells at the G_0/G_1 phase[23]. Since T cell activation is dependent on the presence of co-stimulatory signals, the suppressive nature of B7-H4 highlights its therapeutic potential in autoimmune diseases.

Interestingly, B7-H4 exhibits a unique mRNA profile. Unlike other B7 molecules, B7-H4 mRNA is expressed in multiple peripheral tissues such as the spleen, lung, liver, and pancreas[23]. Protein expression of B7-H4 in peripheral tissues is minimal, and its role is subject of much debate[23,25,26]. It is possible that B7-H4 undergoes tight post-transcriptional or post-translational regulation that limits its protein expression in those tissues. It remains unclear what roles B7-H4 play in the periphery, and whether it has functions that are independent of its effect on T cells. We and others have shown that the pancreas expresses moderate level of B7-H4, especially in the endocrine cells[25,27]. This raises the question of what the specific functions of B7-H4 are in pancreatic islets, and suggests the intriguing possibility that activity of B7-H4 is not limited to immune-modulation. For the purpose of this review, we will focus on the existing evidence which indicates that B7-H4 plays an essential role in islet autoimmunity and islet allotransplantation, and report data from cancer studies which alludes to other non-immune functions of B7-H4. All of the roles, known and potential, are shown in Table 1, which are classified as autoimmunity modulator, allograft protection, UPR modulation, and biomarker of β-cell immunity. This manuscript extends beyond previous reviews of B7-H4 by highlighting the importance of endogenous B7-H4 expression in β-cells, suggesting that the B7-H4 pathway for treating T1D may be more advantageous than other co-stimulatory molecules.

B7-H4 AS A PROTECTIVE SHIELD FOR β-CELLS IN T1D

Regulation of autoreactive T cells in autoimmune diseases can be achieved through various methods, such as regulatory T cell (Treg) therapy, interleukin (IL)-2 pathway manipulation, tolerance induction with antigen administration, and co-stimulation blockade[28]. As a negative co-signaling molecule, B7-H4 has the potential to down-regulate autoreactivity in autoimmune diseases such as T1D. While B7-H4 deficiency itself does not cause autoimmune diseases, various studies showed that B7-H4 plays an important role in inhibition of auto-reactive T cells in diseases such as experimental autoimmune encephalomyelitis, and rheumatoid arthritis[22,27]. Genome-wide association studies have also uncovered certain Single Nucleotide Polymorphisms within the B7-H4-encoding *VTCN1* gene as disease-causing in the context of diabetes, further implicating B7-H4 as a potential regulator of T1D[29].

Immunosuppressive functions of B7-H4 was confirmed in experimental T1D models using B7-H4-immunoglobulin (B7-H4 Ig), a recombinant protein derived from fusion of the immunoglobulin constant region to the extracellular domain of B7-H4[30,31]. Both intraperitoneal injections of B7-H4 Ig and cell-associated B7-H4 inhibited proliferation and cytotoxicity of $CD4^+$ and $CD8^+$ T cells *in vitro*[22-24,32]. Juvenile NOD mice treated with B7-H4 Ig exhibited significantly later onset as well as reduced incidence of diabetes[31]. This coincided with a reduction in proliferation and activation of both $CD4^+$ and $CD8^+$ subsets of T cells in the islet infiltrates[31]. In support of this, our preliminary findings suggested that β-cell specific over-expression of B7-H4 in transgenic NOD mice significantly decreased T1D incidence compared with wild type NOD mice (unpublished data). In conjunction with its preventive role in the onset of autoimmune diabetes, B7-H4 reversed incidence of established T1D. Return of glycemic control was observed in newly-onset diabetic NOD mice following B7-H4 Ig injections[33]. Conversely, adoptive transfer of diabetogenic T cells into B7-H4 deficient mice resulted in more exacerbated disease than wild-type controls[27]. It was hypothesized that B7-H4 did not have an effect on recruitment of immune infiltrates during the pre-diabetic stage, but rather, it prevented the progression of insulitis to overt diabetes by arresting severe insulitis at 12 wk of age in NOD mice[27,31]. This modulation of immune status at later stage of disease may be associated with down-regulation of the Th1 cells, which are widely accepted as key mediators of autoimmune diseases[31].

Mechanistic studies examining the role of B7-H4 showed that it was able to limit autoreactive CTLs, and suppressed secretion of inflammatory cytokines in the periphery[33]. For instance, levels of Th17-associated cytokines, IL-6, and IL-23, were reduced in B7-H4 treated animals[33]. This reduction was concomitant with a decrease in Th17 cells, a subpopulation of $CD4^+$ T cells that produce IL-17, IL-17F, IL-21, and IL-22, and have been implicated in various autoimmune conditions[34,35]. IL-17 is an inflammatory cytokine that may stimulate the production of other inflammatory cytokines, and is present at high levels in autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis[36-38]. Importantly, elevated Th17 cells were found in NOD mice as well as T1D patients, and were suggested to be a contributing factor to the pathogenesis of autoimmune diabetes[39-41]. One mechanism by which Th17 cells were proposed to act in T1D patients was to cause a disturbance in the ratio of T effective cell (Teff)/Treg cells, which shifted the adaptive immune response to allow development of T1D[42]. Additionally, Th17 cells were able to convert to a Th1 phenotype and stimulated cytotoxic T lymphocytes (CTL) to further contribute to autoimmunity[39]. Consistent with roles of B7-H4 in islet

Table 1 Evidence for immune regulatory and β-cell autonomous roles of B7-H4 in experimental/human diabetes

Role	Model	Summary of findings	Application	Ref.
Autoimmune modulator	NOD mouse	B7-H4 Ig inhibits development of, and reverses newly-onset autoimmune diabetes	Prevents/ reverses T1D	[31,33]
Allograft protection	NIT cell line	B7-H4 transfected NIT cells promote β-cell allograft survival	Suppresses islet graft rejection	[44]
	Mouse	Adenoviral-transduced B7-H4 donor islets enhanced islet allograft survival, and promotes donor-specific tolerance		[43,46]
	Mouse	B7-H4 transgenic islets improve islet allograft survival	Preserves β-cell mass in T1D/T2D	[51]
Non-immune dependent UPR and cell survival regulator	Pancreatic carcinoma-derived cell lines	B7-H4 knock-down increases cell apoptosis		[56]
	Renal carcinoma tissues and cancer cell lines	Human intracellular B7-H4 is identified as a cytoplasmic-nuclear shuttling protein that contains a NLS		[57]
	Mouse	B7-H4 modulates UPR in isolated pancreatic β-cells		Unpublished
Biomarkers of β-cell immunity	Mouse	B7-H4 RSS0.2 mRNA splice form is correlated with different stages of T1D	Detects β-cell autoimmunity	Unpublished
	Human	Reduced B7-H4 expression and B7-H4/insulin colocalization is detected in pancreata of T1D patients		[25]
	Human	Elevated sB7-H4 is present in RA and newly-onset T1D patients		[61,62]

T1D: Type 1 diabetes; NOD: Non-obese diabetic; UPR: Unfolded protein response; NLS: Nuclear localization signal.

autoimmunity, pancreata of B7-H4 deficient mice expressed significantly enhanced production of IL-17 and interferon (IFN)-γ, while islet-specific over-expression of B7-H4 led to a dramatic reduction in IL-17 and IFN-γ[27]. *In vitro* studies showed that cultured splenocytes displayed less affinity toward a Th17 phenotype when incubated with B7-H4 Ig, and sequestering of B7-H4 restored Th17 polarization[33]. This effect was dependent on increased IFN-γ production by the splenocytes, suggesting that inhibitory effect of B7-H4 on Th17 cell differentiation was due to stimulation of IFN-γ release[27,33]. However, it seemed that inhibition of Th17 cells by B7-H4 did not shift the Teff/Treg ratio towards Teff cells, neither did it act to expand the Th2 cell population, which is classically known as the anti-inflammatory T cell phenotype[27]. It is possible that the reduction in Th17 cells may potentially reduce the pathogenic Th1 phenotype that contributes to autoimmunity.

In summary, B7-H4 has been demonstrated to have functionality in both arresting and reversing newly-onset T1D in rodent models, and thus shows great promise as a preventative measure and a potential treatment for the disease. Current evidence suggests that B7-H4 prevents progression of severe insulitis to overt diabetes, in part, by suppressing mediators of autoimmunity such as Th1 and Th17 cells. Further research will help clarify the upstream signaling events leading to the observed beneficial effects and may significantly advance our ability to harness the potential of B7-H4 as a therapeutic for T1D.

B7-H4 INDUCES DONOR SPECIFIC TOLERANCE IN ISLET TRANSPLANTATION

B7-H4 also promotes the viability of islet grafts, and thus has significant potential for improving clinical islet transplantation as a treatment for diabetes[43-46]. Transplanted islets face many overlapping forces that conspire to limit graft function and survival, ranging from mechanical stress during isolation procedures to adverse effects of immunosuppressive drugs post-transplantation. During islet isolation and transplantation, conditions of hypoxia and nutrient deprivation collectively induce oxidative stress, ER stress and apoptosis, resulting in a decline in functional β-cell mass[47]. In the case of T1D patients, islet grafts not only encounter autoimmune surveillance, but also experience rejection mediated by alloreactive T cells. This process occurs due to priming of $CD4^+$ T cells by alloantigens presented by MHC molecules on antigen presenting cells. Activated $CD4^+$ T cells then promote the differentiation and proliferation of $CD8^+$ T cells, which attack the donor tissue. Current immunosuppressive regimens for islet transplant recipients consist mostly of tacrolimus (FK506), sirolimus (rapamycin), and mycophenolate mofetil (MMF)[20,21,48]. Generalized side effects of these drugs include increased risks for infection and malignancy, hypertension, lung toxicity, and cardiac damage. Tacrolimus has been linked to nephrotoxicity, which can be especially damaging to recipients who are at risk for diabetic nephropathy[19]. Importantly, studies have demonstrated that these drugs induced islet cell apoptosis and impaired islet function based on their mechanisms of action[19,49]. For instance, tacrolimus and sirolimus inhibit calcineurin and mammalian target of rapamycin, both of which are involved in insulin signaling and secretion[49,50]. It is therefore critical to identify novel therapeutics that offers immune-protection with minimal level of toxicity and side effects. B7-H4 is a molecule which can suppress autoimmunity as well as modulating alloreactivity, which makes it a perfect candidate for islet cell transplantation especially in T1D patients[45].

Initial investigation into the role of B7-H4 on allograft rejection demonstrated that B7-H4 protected NIT cells, a functional NOD-derived β-cell line, from injury[44]. Survival of NIT cells allotransplanted into diabetic mice was prolonged by B7-H4 transfection[44]. This was associated with reduced proliferation of recipient splenocytes,

decreased production of IFN-γ, and increased Tregs in the spleen[44]. The protective effect of B7-H4 in allotransplantation was further observed in B7-H4 adenoviral-transduced islets and B7-H4 transgenic islets. Local overexpression of recombinant B7-H4 adenovirus (Ad)-B7-H4 in intact mouse islets preserved original β-cell function and endogenous glucose responsiveness at both basal and high glucose conditions[43]. Furthermore, mice who received islets transduced with (Ad)-B7-H4 demonstrated longer allograft survival with significantly reduced infiltrates compared with control recipients[43]. Elevated Tregs and reduced cytotoxic T cells were observed in transduced islet grafts, further suggesting that B7-H4 may alter the immune environment at the graft site to induce tolerance[43]. Similarly, B7-H4 transgenic islets promoted islet allograft survival, concurrent with migration of Tregs to the graft site[51]. Tregs are known to secrete IL-10, an anti-inflammatory cytokine, and can also induce IL-10 secretion in APCs[52]. IL-10 suppresses Th1 phenotype, thus inhibiting Th1 effector cells such as $CD8^+$ T cells. In addition, Tregs also stimulated B7-H4 expression on monocytes and other APCS[52], which may act as negative co-signals to restrain T cell reactivity against donor antigens. These studies demonstrated that allotransplantation outcomes can be largely influenced by T cell co-signaling molecules, where Tregs played an important role in B7-H4 induced tolerance.

Interestingly, B7-H4 is able to achieve donor-specific tolerance rather than general unresponsiveness towards foreign antigens. When the primary B7-H4-transduced islet graft was removed and replaced with a secondary graft from the same donor mouse strain, graft survival was higher compared with a secondary graft from a third-party donor strain[46]. Isolated splenic leukocytes from recipient mice showed decreased IL-2 levels due to reduced number of IL-2 secreting cells[46]. However, no differences were observed in Tregs between mice that received same donor strain islets compared with those transplanted with third party strain islets[46]. It is possible that while Tregs are central to establishment of allograft tolerance, they may not be the main contributors to the maintenance of the secondary graft. Conceivably, B7-H4 can act on other pathways to affect IL-2 secretion and induction of donor-specific tolerance, however, this avenue of research is yet to be explored.

B7-H4 AS A DIRECT MODULATOR OF THE UNFOLDED PROTEIN RESPONSE AND CELL DEATH

The ubiquitous expression of B7-H4 in peripheral tissues has led to speculations regarding its role independent of the immune system. In support of this, studies on cancer cells reported elevated expression of B7-H4 in the cytoplasm and cell membranes from breast, uterus, and pancreas cancer cells[53-55], and its expression was correlated with tumor progression. It has been speculated that up-regulation of B7-H4 may help cancer cells evade immunosurveillance as well as being a direct tumorigenic factor independent of the immune system[56,57]. Consistent with these hypotheses, Zhang *et al*[57] demonstrated that human B7-H4 contains a nuclear localization sequence that allows B7-H4 to shuttle between the cytoplasm and the nucleus, and may regulate transcription of genes involved in cell apoptosis. Qian *et al*[56] also showed *in vitro* B7-H4 gene silencing in pancreatic cancer cells led to reduced proliferation rate and an increase in cell apoptosis that correlated with increased expression of the pro-apoptotic Bax protein and caspase activation. B7-H4 may thus play a central role in survival and apoptosis, but the exact mechanisms by which it facilitates disease progression remain an area of active investigation.

Specifically in the β-cells, endogenous B7-H4 may regulate stress *via* other cell-autonomous signaling pathways. Data from our lab suggested that *in vivo* administration of B7-H4 Ig affected the age-dependent expression of key UPR genes in the islets of NOD mice (unpublished). Notably, additional *in vitro* experiments on islets from transgenic islets with β-cell specific B7-H4 expression suggested that B7-H4 can modulate β-cell UPR signaling and may thus affect the ability of pancreatic islets to adapt to ER stress (unpublished data). In conjunction with the evidence from tumor cells, these findings support the intriguing possibility that B7-H4 also has non-immune-mediated roles in maintaining β-cell function and survival, and highlight promising new avenues for future research.

SPECIFIC EXPRESSION OF B7-H4 AS A POTENTIAL NOVEL BIOMARKER FOR T1D

While the end result of T1D is significant loss of islet β-cells that warrants the need for life-long insulin replacement, progression to end-stage diabetes occurs in several stages[58,59]. The initial step is development of islet autoimmunity, which manifests as presentation of autoantibodies to putative antigens such as GAD, ZnT8, IA-2, and insulin. Measurements of these autoantibodies have proven useful for predicting diabetes. However, after the initiation of islet autoimmunity, they are no longer able to offer consistent information regarding disease progression. From the time of autoimmunity onset to clinical diabetes there is a relatively long pre-diabetic stage. This is a critical time for therapeutic intervention, as there is theoretically still adequate functional β-cell mass at this stage of dysglycemia to preserve sufficient endogenous insulin secretion that obviates full blown T1D[60]. It is therefore vital to develop reliable markers for monitoring β-cell loss and characterizing each stage of T1D in order to determine the efficacy of therapeutic interventions associated with each stage.

In the prediction of autoimmunity, B7-H4 has been proposed to serve as a candidate biomarker for rheumatoid arthritis (RA)[55,61]. Serum samples indicated that levels of soluble B7-H4 protein (sB7-H4) in patients diagnosed with RA were significantly higher than those in

healthy donors[61]. In addition, elevated levels of sB7-H4 were associated with increased disease severity[61]. Our results showed a trend of higher sB7-H4 in diabetic children, though not statistically significant. This data agreed with a more recent study, which confirmed that sB7-H4 were elevated in newly-onset T1D patients[62]. Previous characterization of the B7-H4 gene using human multiple cDNA panels demonstrated that there are two major versions of B7-H4 transcripts from the pancreas tissue: A full-length (2.0 kb) transcript which is shared with other organs, and a shorter (1.2 kb) transcript version which is specific for pancreas[23,24]. We have also detected the presence of an additional 0.2 kb B7-H4 mRNA splicing species (RSS0.2) in the serum of T1D patients (unpublished data). Moreover, preliminary studies showed that high levels of circulating B7-H4 RSS0.2 were correlated with newly-onset T1D (< 1 year), while intermediate levels of this mRNA splice form were observed in patients with longer-term disease (1 year), and the lowest levels were found in patients with late stage T1D (2-5 years). This suggests that sB7-H4 and unique B7-H4 splice forms may serve as a novel biomarker for determining various stages of T1D.

In the human pancreas B7-H4 is more abundantly expressed in the islets than the exocrine tissue at both mRNA and protein level[25,27]. Recently, Cheung *et al*[25] showed that altered B7-H4 expression occurred in T1D and insulinoma. Multi-fluorescence immunohistochemical analyses revealed moderate expression of B7-H4 in non-diabetic pancreatic islets, significantly reduced protein expression in T1D islets, and high expression in insulinoma tumor cells[25]. Furthermore, correlation analyses demonstrated B7-H4 co-localization with insulin in both human and mouse islet[25,27]. Interestingly, the B7-H4/insulin co-localization was dramatically reduced in both T1D islets and insulinomas compared with non-diabetic islets[25]. It is possible that the reduced association between B7-H4 and insulin may reflect diseased islet states, agreeing with the observation that B7-H4 protein and mRNA expressions in islet β-cells and in sera may be useful as indicators of islet dysfunction and β-cell death/loss in the progression of T1D.

CONCLUSION

B7-H4 is the newly-identified member of the B7 immunoglobulin family commonly associated with co-stimulatory or inhibitory signals for T cells. Even though the putative receptor for B7-H4 on activated T cell is yet to be identified, its marked ability to suppress and reverse autoimmune diabetes has been demonstrated in various cellular and animal models. Furthermore, B7-H4 can induce donor-specific tolerance in islet allografts, which holds great promise as an adjunct for modern paradigms of immunosuppression. In the pancreas a relative abundance of B7-H4 in β-cells alludes to novel functions in the pancreatic islets, and ongoing work hints at important roles of endogenous B7-H4 for β-cell health and function. Of note, B7-H4 also displays a unique expression profile unlike that of other B7 family members, and variations in its protein and mRNA splicing species may act as potential biomarkers for T1D. Further research into both the immune-regulatory and β-cell-autonomous roles of B7-H4 promises to elucidate its contributions to β-cell health and survival, thus identifying it as a novel β-cell protective shield for patients suffering from diabetes.

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