Dichotomous roles of co-stimulatory molecules in diabetes mellitus

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ABSTRACT

Numerous studies have established the importance of immune dysfunction in the development of diabetes mellitus, including type1 and type2 diabetes, and it is worth noting that T cell activation acts a key role in the pathogenesis of loss of β cell mass, adipose inflammation and insulin resistance. Regarding as an important checkpoint in the process of T cell activation, co-stimulatory molecules interaction between antigen present cells and T cells have been identified the critical role in the development of diabetes mellitus. Thus, blockage of co-stimulatory dyads interaction between antigen present cells and T cells was supposed to a potential of therapeutic strategies. However, studies also showed that inhibition or deletion of some co-stimulatory molecules do not always reduce the development of diabetes, and even exacerbate the disease activity. Here, in this context, we highlight the dichotomous role of co-stimulatory molecules interaction in the pathogenesis of diabetes.

INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycemia, which is resulted from the loss of β cell mass or loss of insulin sensitivity [1–3]. Long-term improper control of blood glucose homeostasis predisposes patients to the development of diverse complications such as diabetic retinopathy [4], nephropathy [5], neuropathy [6], foot ulcers [7], and cardiovascular diseases [8]. Now it is well-accepted that abnormal immune response including both innate and adaptive immunity plays a critical role in the development of β cell destruction and insulin resistance, although the underlying mechanisms remains elusive [9–11]. The co-stimulatory molecules are important regulators of immune activation via providing second signal for T cells activation [12]. Therefore, most studies have shown that interaction of co-stimulatory molecules exhibits a pathogenic role in autoimmune diseases [13–15]. Remarkably, B7/CD28 interaction is the vitally important second signal [16–18]. However, increasing evidence has suggested that some co-stimulatory signaling pathways may have a protective role in diabetes pathogenesis. Here, we review dichotomous role of these co-stimulatory molecules serve complicated roles in diabetes mellitus, especial B7/CD28.

Co-stimulatory molecules and diabetes

When the body encounters foreign antigens or endogenous danger signals, immune response usually initiates. The innate immune cells, especially the professional antigen present cells (APCs), play a crucial role in uptaking and processing pathogenic substance present the antigen to T cells through MHC molecules [12, 18], which results in cellular and humoral immunity. In addition to presenting antigens to T cells, APCs also express co-stimulatory molecules which are regulated by the exogenous pathogens or endogenous alarmins [such as high mobility group protein 1 (HMGB1), heat shock protein 70 (HSP70) as well as interleukin-33 (IL-33)], providing the second signal for T cell activation [19]. The second signal is initiated by the interaction between co-
stimulatory molecules expressed on the APCs and their corresponding ligands on the surface of T and B cells [20]. Like the neural synapse, the co-stimulatory dyads form an immunological synapse which is very important for the T or B cells activation [21]. In the absence of the second signal, the interaction of antigen-MHC complex with TCR or BCR, also known as the first signal, is insufficient to activate the T cells or B cells, leading to T cell and B cell anergy or apoptosis [20]. A number of co-stimulatory molecules have been identified, among which CD28/B7, CD40L/CD40, PD-1/PD-L1 and ICOS/ICOSL are the best-characterized co-stimulatory dyads involved in the immune synapse and immune cells activation.

Type 1 diabetes mellitus (T1DM) is the consequence of the autoimmune-mediated diabetic insulin-producing β cells damage and loss [3]. Inflammatory autoreactive T cells, escaping from central and peripheral tolerance, recognize pancreatic islet antigens, can be activated in the pancreatic lymph nodes. Activated T cells then migrate to local pancreatic islet and induce an inflammatory microenvironment, recruiting macrophage and neutrophil infiltration and leading to pancreas islet damage and injury [22]. Of note, obesity-associated inflammation is widely believed to play a key pathogenic role in the development of obesity-induced insulin resistance and type 2 diabetes mellitus (T2DM). Innate immune activation typified by infiltrating macrophages is deemed to represent important mediators of obesity-related complications [11, 23, 24]. Keeping with previous reports, our recent work also demonstrated that a critical role acted by adipose macrophages in T cells immune responses during this process [25].

The co-stimulatory molecules mediating the interaction between T cells and APCs have been linked to the development of abnormal immune response [20]. Therefore, inhibition of co-stimulatory molecules interaction has been suggested to modulate T cell activation. Lots of studies have indicated a protective role of co-stimulatory inhibition in the development of many disease, such as experimental allergic encephalomyelitis (EAE) [26–29], allograft transplantation [30–32], arthritis [33, 34], and hypertension [35, 36]. Furthermore, the abnormal immune response induced by co-stimulatory molecules also result in β cell loss and insulin resistance in T1DM and T2DM [9, 22, 37]. Thus, dampening inflammation induced by autoimmune response become a potential therapeutic method in diabetes. However, increasing evidences suggest a protective role by some co-stimulatory molecules dyads in diabetes pathogenesis. Below we review the complicated roles of co-stimulatory molecules dyads in the development of diabetes.

**Role of B7/CD28 in diabetes**

Two signals are required for full activation of naive CD4+ T lymphocytes as described [20]. T cell will be anergy or undergo apoptosis in the absence of second signal [38]. Therefore, co-stimulation inhibition shows a great therapeutic potential in immune-mediated diseases. B7 molecules, including B7-1 (CD80) and B7-2 (CD86), are the best-characterized co-stimulatory molecules and mainly expressed on APCs such as dendritic cells (DCs), B cells, and macrophages [17]. Nevertheless, Study have shown that B7-2 might be more important in the initiation of immune responses, as its expression is rapidly up-regulated when APCs encounter endogenous damage alamin or foreign bodies, yet B7-1 is up-regulated in the later phase during the immune response [39, 40]. Through binding its specific receptor CD28, B7 activates protein kinase C0 (PKC0) and RAS guanyl nucleotide-releasing protein (RASGRP) [41, 42], which promotes T cell activation, proliferation, and anti-apoptosis. Of note, the co-inhibitory receptor CTLA-4 also shares the ligands (B7-1 and B7-2) with CD28 [40]. Generally, CTLA-4 is highly expressed in activated T cells, which is the self-control for preventing excessive immune response by binding to B7-1 or B7-2 [29, 43]. This co-inhibitory receptor CTLA-4 attracts increasing attention, because of its potential in immune regulation and higher binding affinity compared with CD28. CTLA-4 Ig has been used in the treatment of autoimmune disease [29, 33] and transplant rejection [44, 45]. Overall, the opposing roles of CD28 and CTLA4 are considered a prototypical immune checkpoint for the immune response through competing pro- and anti-inflammatory effects.

Interestingly, studies have demonstrated that basal B7-1 and B7-2 expression is also necessary to prevent autoimmunity by sustaining regulatory T (Treg) cell populations [46–49]. In our previous investigation, we also elucidated a homeostatic role of B7-mediated co-stimulation in diet-induced obesity using CD80/CD86 double knockout (B7 KO) mice and investigated the relevance of this process in humans with obesity and IR [50]. Our results suggested an essential role for B7 in maintaining Tregs and adipose homeostasis and may have important implications in immunotherapies targeting co-stimulation in type 2 diabetes.

As is well-known, interaction between B7 and CD28 promotes inflammation, while there is difference between the function of B7-1 and B7-2. In the development of type 1 diabetes in the NOD mouse, a distinct regulation of B7-1 and B7-2 were observed. At the onset of insulitis, mice treated with CTLA4 Ig or a blocking B7-2 antibody did not develop diabetes. However, there is no significant effect when CTLA4 Ig or a blocking B7-2 antibody administered late. Consistently, a delayed development of diabetes was seen in B7-2 knockout NOD mice, where islet-reactive CD4 T cells were defective. In contrast to the effect of B7-2 inhibition, B7-1 neutralization or gene deficiency causes exacerbation of disease, the lack of B7-1 significantly accelerated the development of disease accompanied by enhanced expansion, survival,
and effector function of islet specific T cells in periphery [51, 52]. Furthermore, B7-1 deficiency mice showed a significant reduction in immunosuppressive Tregs cells [52]. These results suggest that B7 may play complicated role in the development of autoimmunity. Likely, in our previous study, expression of B7-1 and B7-2 was negatively correlated with the degree of IR and adipose tissue macrophage infiltration in both humans and mice. Furthermore, instead of promoting inflammation, ablation of CD80/CD86 by double gene knockout defects Tregs development and proliferation in mice, and exhibits enhanced adipose macrophage inflammation and IR under high-fat diet feed. Conversely, adoptive transfer of Tregs reversed IR and adipose inflammation in B7 KO mice [50]. Taken together, above studies of B7/CD28 co-stimulatory molecules show a complicated role in development of immune-mediated disease, including diabetes.

**Beneficial roles of B7/CD28 in diabetes**

Although B7/CD28 co-stimulation participates in the induction and progression of autoimmune diseases, it has also been demonstrated that B7/CD28 co-stimulatory molecules interaction is substantial for Tregs development and proliferation. To examine the role of B7/CD28 in the development of EAE, CTLA-4 Ig was administrated to the mice. Unexpectedly, B7 blockade with CTL1-4 Ig exacerbated disease signs and exhibited more severe CNS inflammation and demyelination, which was associated with the increased inflammatory cytokines IL-17 and IFN-γ [29]. Similarly, in our previous study, CD80/CD86 was found to be essential for Tregs development and proliferation in obese mice and human, instead of promoting inflammation [50]. Furthermore, a subpopulation of CD4+ T subsets, characterized by low CD28 expression, is resistant to apoptotic signals and lives longer in vivo [53, 54]. The CD4 + CD28- T cells shows an atherogenic and plaque-destabilizing property [55–59]. It is well known that the diabetes patients are at high risks of atherosclerosis. Therefore, these T cell subpopulations were investigated in diabetes patients. When compared with non-diabetic individuals, T2DM patients with proliferative diabetic retinopathy showed a higher percentage of CD4 + CD28- population [60]. A study showed that CD4 + CD28- T cells potentially drive the severity of the disease through producing IL-17, and IL-17 expression of CD4 + CD28- T cells was regulated by NKG2D. In addition, when compared to non-diabetic individuals, CD4 + CD28- NKG2D + T cells subpopulation is increased in T2DM patients [61]. Shi B et. al showed that advanced glycation end products (AGEs) effectively enhanced these subset T cells proliferation in patients with T2DM, and the higher level of CD4 + CD28- T cells is closely associated with the status of macrovascular atherosclerosis in patients with T2DM [62]. Similarly, by means of ultrasound image to analyze the atherosclerotic plaque in the common carotid artery (CCA), CD4 + CD28- lymphocytes reveals a positive correlation with the number of atherosclerotic plaques within the CCA. In a clinical follow-up observation, CD4 + CD28- T cells are correlated with the occurrence of a first cardiovascular event and with a worse outcome after an ACS in DM patients [63]. These data revealed that the expression of CD28 molecules on CD4 + cell is vital for immune homeostasis in T2DM.

Furthermore, lack of B7/CD28 interaction also results in a limited numbers of regulatory T cells and aggressive disease progression in the T1DM NOD mice [64]. Treg cells were markedly decrease in the B7-1/ B7-2-deficient and CD28-deficient NOD mice [49]. Additionally, the percentage of CD4 + CD28 + T cells and IL-2 production were also decreased along with aging, which resulted in inspired Tregs function in NOD mice [65]. Recently, multipotent stem cells received huge attention in the treatment of many diseases due to its immunoregulatory and tissue repair functions [66–70]. In a clinical trial, the C-peptide levels, median glycated hemoglobin A1C (HbA1C) values, and the median daily dose of insulin were markedly improved in T1DM patients treated with cord blood-derived multipotent stem cells. Study also showed that the improvement was associated with increased expression of CD28, ICOS and the number of Tregs [71]. This study sustains the concept that CD28 plays an immunoregulatory function. Keeping with above reports, B7-1 gene knockout NOD mice showed a diminished amount and expansion in Tregs, accompanied by increased survival and amplification of auto reactive T cells [52]. Bour-Jordan H et.al further demonstrated that B7-1 overexpression on B cells completely protected NOD mice from developing diabetes [72]. These studies suggest a protective role of B7/CD28 in the development of diabetes.

**The pro-inflammation of B7/CD28 in diabetes**

As is well-known, the interaction between B7 and CD28 is critical for the second signal of T cell activation and promotes inflammation [18]. In a case report, the patient with T2DM showed a dramatic improvement in insulin resistance when blockage CD28 activity by CTLA4-Ig infusion [73]. Furthermore, high glucose conditions promoted podocytes to express B7-1 both in vitro and in vivo. Treatment with CTLA4-Ig inhibited the apoptosis of podocytes, leading to an improvement of urinary albumin excretion and kidney pathology in these animals. Besides, the B7-1 expression is also up-regulated in podocytes from kidney biopsy specimens of T2DM patients [74]. Moreover, the expression of B7-2 has also been shown to increase in gestational diabetes mellitus (GDM) patients [75, 76]. Although not statistically significant (probably due to the small sample size),
Schliefsteiner et al. reported that there was an increase of B7-2 in parallel with proinflammatory cytokines IL-1β and IL-6 in patients with GDM [76]. The expression of CD28, the binding partner of B7, was also increased in the peripheral T cells from patients with GDM [77].

A single-nucleotide polymorphisms (SNPs) analysis demonstrated that CD28 might contribute to the risk of T1DM [78]. In addition, a recent study showed that mice deficient for CTLA-4 or treated with anti-CTLA-4 antibody exhibited spontaneous follicular T cells (Thf) differentiation by enhancing the strength of CD28 ligation with B7-1 and B7-2 [79]. IL-21, a critical cytokine in autoimmunity, can promote autoimmune response through up-regulating B7-2 on B cells [80]. These studies showed a great potential of B7/CD28 in the treatment of autoimmune diseases. Indeed, a marked reduction of spontaneously activated CD4 T cells and islet-specific CD4 T cell expansion and enhanced CD4 T cell death were observed in B7-2 knockout NOD mice. Interestingly, a significant reduction of Treg was not seen in the peripheral compartments of B7-2 KO mice [81]. Contrary to the inflammatory characteristic of CD4 + CD28- subset T cell, a CD8 + subpopulation with lower expression of CD28 exhibits an anti-inflammatory function [82]. In the peripheral blood mononuclear cells from juveniles with T1DM, CD8 + CD28- T cell subset was significantly reduced and correlated with disease duration. Moreover, CD8 + CD28- subpopulation was also significantly lowered in multiple sclerosis patients as well [83]. In the absence of Tec family kinase ITK, a CD28 downstream signaling molecule, there was a profound diminishment of islet-infiltrating inflammatory cells in mice with T1DM [84].

Taken together, B7/CD28 co-stimulation has divergent effects on the pathogenesis of diabetes mellitus in the different context of disease, which leads to a great barrier for the therapeutic method in diabetes. While not only complicated role of B7/CD28 dyad, many other co-stimulatory molecule dyads also exhibit a dichotomous role in the pathogenesis of diabetes. Below, we discuss some other co-stimulatory molecules that play an essential role in diabetes development.

**Complicated role of other co-stimulatory molecules in diabetes**

**ICOS**

Inducible co-stimulator (ICOS), a member of the CD28 family, is expressed after T cell activation [85]. The deletion of ICOS in T cells results in a decreased production of the Th1 cytokine IFN-γ without affecting the numbers of regulatory T cells. ICOS plays a considerable role in the induction of the autoimmune-mediated diabetes [86]. However, there was also a study reporting that the absence of ICOS exacerbates the disease activity in experimental models of diabetes by ablating Treg function [87]. This difference might be caused by the different function of ICOS on different cells, which leads to discrepant outcome.

**B7-H4**

A member of the B7 family, is expressed on the cell membrane of APCs and up-regulated when they activated by exogenous and endogenous stimulator [88, 89]. However, its specific receptors remain unknown. Previous study showed that B7-H4 deficiency increased the incidence and severity of EAE and collagen-induced arthritis (CIA) [90–92]. Furthermore, B7-H4 inhibits allograft rejection and decreases lymphocyte proliferation [93]. Recent studies also indicate a suppressive function of B7-H4 in the development of diabetogenic autoimmunity. An increased level of soluble B7-H4 (sVTCN1) was detected in T1DM patients, which is correlated with the aggressive pace of disease. The sVTCN1 lost its immunosuppressive function on inhibiting diabetogenic T cells. Therefore, inhibiting the cleavage of membrane B7-H4 may serve as a potential therapeutic strategy [94, 95]. Independent of inhibiting the recruitment of activated CD4 + and CD8 + T cells to islets, B7-H4 Ig treatment significantly postponed the disease onset and reduced incidence of diabetes in NOD mice due to a transient increase of Treg cells population [96]. Furthermore, β cell-specific B7-H4 overexpression protected against allograft rejection [97]. Unexpectedly, endogenous B7-H4 showed a defect in inhibitory costimulation, but augments the activation of diabetogenic T cell during T1D development [95]. Further study should be carried out to address the exact role of B7-H4 in the immune modulation during the development of diabetes.

**CD40/CD40L**

The costimulatory molecule CD40 and its ligand CD40L (CD154) are expressed by T cells, B cells, APCs, pancreatic islet β cells, and pancreatic ductal cells [12, 98]. In T1DM animal model NOD mice, blockage of CD40L during early diabetes ameliorates spontaneous disease onset, resulting from the decreased number of auto-reactive T cells [99–101]. In parallel with T1DM, CD40-CD40L interactions showed a pro-inflammatory role of in adipose tissue inflammation. Deletion of CD40L protected against weight gain, adipose tissue inflammation, hepatosteatosis, and insulin resistance after high-fat diet feeding [102–105]. However, it has been demonstrated that CD40-/- mice on high-fat diet displayed increased weight gain, impaired insulin secretion, and upregulated pro-inflammatory cytokines compared to the wild type mice. Further data revealed that the expression of pro-inflammatory cytokines inhibited by CD40 activation only found in T cells, but not in B cells or macrophages. This study provided the evidence
that protective effect of CD40 was closely associated with CD40 signaling on T cells, which improved adipose tissue inflammation and metabolic complications [106]. These data suggest CD40L/CD40 also plays a complicated role in the development of obesity.

4-1BB/4-1BBL

As a member of the TNF receptor superfamily, 4-1BB provides a co-stimulatory signal through binding to its ligand 4-1BBL [12,107]. 4-1BB is expressed on adipocytes and macrophages, and is upregulated by obesity-related factors [108]. 4-1BB and/or 4-1BBL agonists activate inflammatory signaling molecules in adipocytes and macrophages [109]. In consistency, 4-1BB deficiency protects against HFD-induced obesity, glucose intolerance, and fatty liver disease though decrease adipose infiltration of macrophages/T cells, and tissue levels of inflammatory cytokines [110]. Unexpectedly, anti-4-1BB scFv transgenic NOD mice developed more severe diabetes than their non-transgenic littermates, as evidenced by earlier onset, faster diabetic process, and higher mortality rate [111].

CONCLUSIONS

Heretofore, although lots of basic and clinical studies of co-stimulatory molecules have been investigated in the pathogenesis of diabetes, the roles and mechanisms remains ill defined. Due to the complicated and dedicated micro-environment of disease, contradictory role of co-stimulatory dyads is often observed in the development of diabetes. The possible reasons for the contradictory roles of co-stimulatory dyads in diabetes mellitus might be as follow: 1) The basal expression of co-stimulatory molecules such as B7-1 and B7-2 is required to prevent heightened inflammatory response by sustaining Treg populations; 2) The expression of different co-stimulatory molecules may be regulated differentially by a variety of inflammatory cytokines during the process of diabetes; 3) Different co-stimulatory molecules have distinct effects on different cell populations, which leads to discrepant outcomes; 4) The source (exogenous versus endogenous) of co-stimulatory molecules such as B7-H4 might affect their functions on immune activation; 5) In addition, the intervention methods to block co-stimulatory molecules (eg. Antibody-mediated neutralization and administration of recombinant fusion proteins) might affect the function of other co-stimulatory molecules. For example, CTLA-4 depletion also promotes the ligation between B7 and CD28. Therefore, further studies are required to fully understand the pathophysiological roles of co-stimulation in diabetes and develop immunomodulatory therapeutics against the inflammatory process in metabolic disease.

Author contributions

L.H.D., J.C. and J.X.Z designed, prepared and revised the manuscript. X.Q.R. and J.X.Z. were involved in the preparation and critical intellectual revision of the paper.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest within this manuscript.

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