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The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM) is a serious medical problem affecting millions of peoples worldwide, and has a great socio-economic impacts. Cytokines possess a pivotal role in modulation of immune reactions and disease pathogenesis. T-helper type 17 (Th17) cells, an important proinflammatory $CD4^+$ T cell subset secreting interleukin 17 (IL-17), has been embroiled in development of DM. There are recent evidences supporting a definitive role of Th17 cells in the etiology of type 1 diabetes (T1D). In addition, IL-17 has been shown to play a crucial role in inflammation, insulin resistance, and type 2 diabetes (T2D). Recently, small molecules which have been specified to block Th17 cells differentiation are considered as potential therapeutics for the disease. Anti-IL-17 neutralizing antibodies and/or antibodies targeting Th17 cells have been investigated to protect individuals at risk from disease development. In this review we aimed to shed light on the potential role of IL-17 and Th17 cells in both T1D and T2D pathogenesis and future therapeutic strategies.

1. Introduction

Diabetes mellitus (DM) is one of the largest non-communicable global health problems of the current century and considered as metabolic disorders of carbohydrates, lipids, and protein metabolism. Hyperglycemia resulted from insulin deficiency as in type 1 diabetes (T1D) or insulin resistance as in T2D leads to long term clinical complications. Currently, more than 415 million people had diabetes worldwide; a new case of diabetes is diagnosed every two seconds and one patient dies with diabetes every six seconds somewhere in the world [1].

According to the monolithic view, naive $CD4^+$ T-helper (Th) cells can be differentiated into Th1, Th2, Th9, Th17, T-regulatory (Treg) or follicular helper T (Tfh) cells depending on specific cytokine signaling and transcription factors [2]. Both human and murine Th17 cells characterized by expression of transcription factor retinoic acid-receptor-related orphan receptor gamma-T (RORγt) and secretion of IL-17A (henceforth referred as IL-17), IL-17F, and IL-22 as hallmark cytokines [3]. Expression of the IL-23R [4] and the chemokine receptor CCR6 [5] additionally define Th17 subset. Although the phenotype of human Th17 cells does bear many similarities to murine Th17 cells, their differentiation may not be identical. In mouse, naive T cells activated in the presence of TGF-β and IL-6 and begin differentiation toward the Th17 cell subset. IL-6 upregulates IL-21 and IL-23R to further their Th17 development. In the absence of IL-6, TGF-β instead induces Treg cells [6]. Therefore, IL-6, IL-21, IL-23, and TGF-β are the major signaling cytokines involved in murine Th17 cells differentiation, and RORγt is the master regulator. The differentiation process of Th17 cells can be divided into 3 stages: the differentiation stage mediated by TGF-β and IL6, the self-amplification stage by IL-21, and the stabilization stage by IL-23 [7]. However, IL-2, IFN-γ, IL-4, IL-12, IL-27, and retinoic acid can inhibit mouse Th17 polarization [6,8]. On the other hand, IL-23 and/or IL-1 drives differentiation of human Th17 cells that express IL-23R and CCR6. The effects of IL-1 may be enhanced by IL-23 and/or IL-6. Both IFN-γ and IL-12 can inhibit human Th17 polarization [6]. In both human and murine models, Th17 cells have been shown to have a pivotal role in early inflammation and they counteract the inhibitory properties of Treg cells [9,10].

Although fork-head box p3 ($Foxp3^+$) Treg cells have a pivotal role for control of autoimmunity and inflammation [11], Th17 cells could participate in inducing inflammation and autoimmune diseases [12]. The imbalance between Treg and Th17 cells has been shown in many conditions of autoimmune and inflammatory diseases including T1D [13], and the imbalance is exhibited by the expansion of Th17 cells which is accompanying with decreased number or function of Treg cells [14]. The mechanism of how Treg cells regulate Th17 cells response has

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been described by several investigators. Chaudhry et al. reported that responses of Th17 cells is controlled by $CD4^+$ Treg cells through binding of Foxp3 with signal transducer and activator of transcription 3 (STAT3), this is the key factor in Th17 differentiation [15]. In addition, Overexpression of Foxp3 results in a strong reduction of IL-17 gene expression by inhibiting RORγt-mediated IL-17 mRNA transcription by direct interaction of Foxp3 with RORγt [16].

IL-17 appear to be implicated in the pathogenesis of many autoimmune and inflammatory diseases including DM [17]. Although, IL-17 plays a substantial role in the defense against microbial infections through enhanced induction of proinflammatory cytokines and chemokines, it is engaged in many inflammatory disorders such as autoimmune and metabolic diseases as well as cancer [18]. There is a paucity in data concerning the pathogenic role of IL-17 and Th17 cells in development of both T1D and T2D. Therefore, this review was established to highlight on the significant effect of IL-17 in pathophysiology of DM.

2. Implication of IL-17 in pathogenesis of type 1 diabetes

The relative role of Th17 cells in T1D pathogenesis has been suggested in both human and animal models. The investigations have been used IL-17 as a surrogate marker for Th17 activity. Studies used non-obese diabetic (NOD) mice as a T1D model demonstrated that IL-17 and IL-17F expression in the islets of Langerhans are correlated with insulitis [19]. However, IL- 17 deficient NOD mice revealed delayed onset of T1D with reduced insulitis [20]. In another model of autoimmune diabetes, transfer of purified Th17 cells from transgenic mice encourage diabetes in NOD/SCID recipients with similar rates of onset as in transfer of Th1 cells [21]. In such model, Th17 cells transform into Th1-like cells to secrete IFN-γ, and administration of anti-IL-17 did not prevent disease development. It has been concluded that such pathogenic T lymphocytes secrete both IL-17 and IFN-γ [19,22]. Further, treatment with anti-IFN-γ suppress IL-17 secretion in vitro and in vivo [23]. Moreover, high IL-17 transcription level has been correlated with insulitic lesions in NOD mice, and the development of diabetes was associated with high plasma levels of IL-17 in a T-cell receptor (TCR) transgenic NOD mice [24].

In human, the pathogenic contribution of Th17 cells has been correlated with the progression of T1D [25]. Bradshaw et al. reported that circulating Th17 lymphocytes were increased in peripheral blood of long-standing T1D patients [26]. More importantly, circulating $CD4^+$ T cells in T1D patients produce IL-17 when they are activated by β-cell autoantigens including proinsulin, insulinoma-associated protein, and glutamic acid decarboxylase (GAD)-65 peptides [27,28]. In addition, Arif et al. [27] showed marked elevation in IL-17 expression in the pancreas of newly diagnosed T1D patients. Furthermore, circulating lymphocytes of T1D patients showed elevated IL-17 and IL-17F expressions [29].

Investigations that used anti-IL-17 antibodies or IL-17 damping agents showed a positive impact on T1D development in experimental animal models. Jain et al. [30] reported a correlation between reduction in IL-17-producing T cells and protection against diabetes development in NOD mice model. In addition, treatment with IL-17 neutralizing agents, like anti-IL-17 antibodies or IL-25, prevent T1D development in NOD mice, and suppress formation of anti-GAD65 autoantibodies. Such treatment with IL-25 reduce the frequency of autoreactive Th2 and Th17 cells, and increase number of Treg cells that resist disease development [31].

Single nucleotide polymorphisms (SNP) in IL-17 gene have a significant effect on IL-17 production. Espinoza et al. [32] demonstrated that healthy individuals having the A allele of IL-17 197A/G SNP produced high significant levels of IL-17 after in vitro T cells stimulation than those without this allele. In addition, Borilova Linhartova et al. [33] proved the correlation between elevated levels of IL-17 and the A allele of 197A/G SNP. This A allele was marginally linked with increased risk of T1D, and it exhibited a higher affinity for the nuclear factor of activated T cells (NFAT), a master transcription factor involved in the IL-17 regulation [32,34].

2.1. Potential role of Th17 cells and its related cytokines in T1D development

The implication of Th17 cytokines (IL-17 and IL-17F) in trigging T1D and other autoimmune diseases was detected [17]. Pathogenesis of T1D is involved an abnormal activation of several types of immune cells including B lymphocytes, macrophages, dendritic cells (DCs), $CD4^+$ and $CD8^+$ T cells [35]. The precise mechanism described the initiation and progression of β-cell-specific autoimmune process is still unclear. However, there are two suggested pathways that may involve in autoimmune destruction of β-cells in the pancreas (Fig. 1). Upon antigenic stimulation with β-cell autoantigens, activated islet-autoreactive $CD4^+$ T cells could differentiate into either effector Th1, Th2, or Th17 cells, depending on cytokines in the milieu. IL-12 released from antigen presenting cells (APCs) like DCs induces Th1 cells differentiation and enhances Th1 cytokines (IL-2 and IFN-γ) production, leading to breakdown of the immune balance between effector and regulatory cells. Dominant Th1 response (IL-2 and IFN-γ) is correlated with T1D pathogenesis [36]. IL-2 and IFN-γ activate $CD8^+$ pre-cytotoxic T cells (Pre CTL) to develop into effector cytotoxic T cells (CTLs) [37]. In addition, IFN-γ potentiate cytotoxic activities of $CD8^+$ T cells. Effector $CD8^+$ T cells (CTLs) release granzyme and perforin which are toxic to β-cells [38].

Recently, another pathway was suggested via the participation of IL-17 (Fig. 1). Primarily, TGF-β, IL-6, IL-21 and IL-23 are the main cytokine responsible for Th17 cells differentiation and proliferation [7,39]. The precise initiation site of Th17 response at T1D onset is still unclear. However, recent studies indicate that overproduction of proinflammatory cytokines from peri-pancreatic adipocytes (PATs) in early phase of disease could serve as a main driver for immunologic tolerance break and Th17 cells expansion [40]. Nevertheless, triggering factor of inflammatory response in PATs is still elusive. Indeed, adipocytes produce several inflammatory mediators, such as adiponectin, resistin, IL-1β, IL-6, TNF-α, leptin, monocyte chemotactic protein-1 (MCP-1 or CCL2) and macrophage colony-stimulating factor (M-CSF) [41]. Such proinflammatory cytokines have direct effects on islet immunogenicity and islet β-cell survival and apoptosis as well as infiltrations of $CD8^+$ and $CD4^+$ T cells [40]. The death of β-cell lead to priming of autoreactive T cells in pancreatic lymph nodes [42]. In addition, chemokines (such as CCL5, CCL2, CCL21, CXCL9 and CXCL10) are induced in adjacent pancreatic islets and in islet cells in response to proinflammatory stimuli [40,43]. Such chemokines are responsible for recruitment of immune cells at the site of inflammation. In this circumstance, leptin cooperates with IL-6 to promote Th17 differentiation, leading to development of pathogenic Th17 cells [44,45]. Moreover, leptin increases T cell proliferation and Th1/Th17 cytokines secretion and prevents apoptosis through the mammalian target of rapamycin (mTOR) signaling pathway [46,47]. Furthermore, IL-6 and IL-1β together lead islet autoantigen-specific $Foxp3^+$ Treg cell to lose suppressor function and become inflammatory Th17 cells [48]. The vital function of Th17 cells is to induce inflammatory responses via stimulating production of proinflammatory cytokines and chemokines by a variety of immune and nonimmune cells, including monocytes, stromal cells, and adipocytes, which all express IL-17A/F receptors [49]. LeGrand et al. [50] demonstrated that combination of IL-17 with TNF-α induce a higher level of nitric oxide (NO) than the individual cytokine induced alone. In addition, IL-17 act with IL-1β and/or TNF-α to increase prostaglandin-2 production. This suggests that the central function of IL-17 could be to magnify inflammatory responses, as IL-17 alone or synergistic with IFN-γ/IL-1β increase expression of superoxide dismutase-2, nitric oxide synthase-2A, and cyclooxygenase-2 which are implicated in the pancreatic islets inflammation [27,51]. In human