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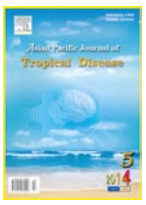

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IL-17A plays an important role in induction of type 2 diabetes and its complications

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PEER REVIEW

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Comments

In general, this article presents a systematic review of current knowledge about the role of IL-17A in the pathogenesis of T2D. The authors provide a scientific interpretation of data from various scientific studies. This article raises several important questions, for instance, about therapeutic potential of IL-17A in inflammation and autoimmune diseases.
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ABSTRACT

Type 2 diabetes (T2D) is the most prevalent metabolic disease worldwide. Previous studies revealed that immune responses, genetic factors, and inflammatory processes played important roles in the pathogenesis and complications of T2D. It has been documented that some people who have T2D are suffering from serious organ-specific pathophysiological conditions including nephropathy and retinopathy. The mechanisms responsible for progression of the disease and its long-term complications are yet to be clarified. IL-17A as a pro-inflammatory cytokine has a dual function, inducing early immune responses against infections and participating in autoimmunity and destructive inflammatory conditions. Therefore, the aim of this review was to address the recent information regarding the status and association of IL-17A with T2D and its related disorders.

KEYWORDS

IL-17A, Type 2 diabetes, Immune responses, Long-term complications

1. Introduction

It has been established that the frequency of diabetes mellitus is increasing globally and type 2 diabetes (T2D) is the most prevalent type of diabetes[1]. Previous studies demonstrated that the genetic and environmental parameters were associated with T2D[1-3]. Several organ-specific disorders including nephropathy and retinopathy are also relatively frequent following T2D[3,4]. It has been suggested that T2D and its complications are immune-dependent conditions that alter patterns of cytokine expression[3,5]. The recent studies revealed that cytokines played crucial roles in T2D with or without nephropathy and retinopathy[6]. IL-17A is a potent pro-inflammatory cytokine with dual effect including induction of early innate immune responses against infections (beneficial) and participation in autoimmune and inflammatory diseases (harmful)[7]. The role of IL-17A in immunological disorders including

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systemic lupus erythematosus[8], multiple sclerosis[9], graft rejection[10], asthma[11], nephrotic syndrome[12] and type 1 diabetes[13] has been well documented. The key roles of IL-17A as the main cytokine in autoimmune disorders rise questions concerning the impacts of the cytokine on the pathogenesis of T2D and its complications. Therefore, the aim of the current review article was to collect recent information regarding role of IL-17A and its cell producer, Th17, in T2D and its associated complications.

2. IL-17A: source, gene and function

It has also been established that IL-6 in parallel with TGF-β and IL-1β induces Th17 development as the main cell producer of IL-17A and IL-23 playing key roles in the cell maintenance[14]. Furthermore, in an autocrine manner, IL-21 leads to Th17 amplification[15]. Expression of the two transcription factors called RORγt and RORα, which induce Th17 differentiation, increases following IL-6, TGF-β, IL-21 and IL-1β stimulation[16]. IL-21, IL-22, IL-26, IL-17A and F are expressed by Th17 via the above mentioned transcription factors[16]. Moreover, Th17 has a positive feedback interaction with innate immunity via the effects of IL-6 and IL-1 on Th17 development and IL-17A promotes innate immune cells to produce IL-6 and IL-1[17]. IL-17A is a homodimeric 35 kDa protein[18] consisting of 23 and 122 amino acids related to signal peptide and main chain respectively[19]. IL-17 receptor (IL-17R), a type I cell surface receptor, has three variants including IL17RA, IL17RB, and IL17RC expressed on the several target cells[20]. IL-17A plays dual roles, beneficial and harmful, in immune responses against infection[21] and autoimmunity respectively[22]. IL-17A activates the JAK1, JAK2, PI3K and NF-κB pathways which up-regulate inflammatory gene expression[23]. Increased expression of IL-17A in immune-related diseases including T2D and its complications raised a hypothesis that this cytokine may contribute to pathogenesis of the disease. Hence, the next section addresses the current information regarding the roles and mechanisms of IL-17A in inducing T2D as well as its related disorders.

3. IL-17A and T2D

IL-17A is a potential inflammatory cytokine which contributes to several autoimmune and inflammatory diseases including T2D[24]. Several studies showed that IL-17A could be considered as a potent inducer of T2D. For example, our previous study revealed that the serum levels of IL-17A were increased in the Iranian T2D patients[3]. Interestingly, Zeng *et al*. (2012) have shown that the ratio of T regulatory/Th17 cells was decreased in patients with T2D[25]. The results suggested that Th17 played important roles in the pathogenesis of T2D. Furthermore, increased expression of IL-17A mRNA was seen in the gingival biopsies of patients with T2D suffering from chronic periodontitis[26]. Another study revealed that Th17 peripheral blood cells of T2D patients were increased compared with healthy controls[27]. The elevated activation of Th17 signature genes has also been reported[27]. Based on the aforementioned studies, it appears that IL-17A contributes to T2D pathogenesis, but the main responsible mechanisms are unclear yet. A recent study suggested some probable mechanisms regarding the role of IL-17A in the pathogenesis of T2D as follows: Ohshima *et al*. (2012) demonstrated that IL-17A played a crucial role in the pathogenesis of insulin resistance induced by angiotensin II type 1 receptor[28]. Interestingly, it has been evidenced that angiotensin II type 1 receptor/ligand interaction lead to an increase in the production of renal nitric oxide (NO) in the diabetic nephropathy[29]. NO production, as an active free radical, results in a renal tissue damage[29]. Hence, it appears that IL-17A induces type 2 complications via induction of free radicals production. Previous reports indicated that hypertension was another disorder which could occur after T2D[30] (Figure 1). Madhur *et al*. (2010), showed that IL-17A was critical for inducing hypertension and vascular dysfunction, as common disorders in T2D, through angiotensin II pathway (Figure 1)[31]. Moreover, the effective roles of IL-17A in induction of atherosclerosis, as an another complication in T2D, by up-regulation of angiotensin II type 1 receptor have been reported[32]. Angiotensin II type 1 receptor activation also results in extracellular matrix remodeling through activation of metalloproteinases (Figure 1). Previous investigations revealed that IL-17A activated the JAK1, JAK2, PI3K and NF-κB pathways via its corresponding receptors[23]. Furthermore, Saleh *et al*. (2009) demonstrated that STAT3 was critical for IL-17-mediated inflammatory chemokine expression[33]. Therefore, it seems that STAT3 plays crucial roles in IL-17A cell signaling. On the other hand, previous reports revealed that JAK2/STAT3/SOCS-1 signaling pathway was crucial to hepatic insulin resistance[34]. It has also been established that STAT-3 signaling is involved in beta-cell apoptosis[35]. Several studies have also demonstrated that STAT3 activation leads to insulin resistance in the hepatocytes and skeletal muscle[36-38]. It has been documented that high plasma levels of amino acids lead to insulin resistance via STAT3 pathway[38]. Furthermore, another study reported that IL-17A induced fibrosis as well as apoptosis in the liver cells by this pathway[39]. Moh *et al*. (2008) also reported that STAT3 inactivation contributed to the pathogenesis of insulin resistance[40]. STAT3 also suppresses the gluconeogenic gene expression in the liver[41]. Therefore, based on aforementioned studies, it appears that IL-17A participates in the either induction of T2D or its complications. Interestingly, previous investigations revealed that the activation of the JAK2/STAT3 pathway occured during generation of beta cells[42] and inhibition of STAT3 significantly decreased beta cell-specific markers at the mRNA levels[42]. Therefore, it may be concluded that JAK2/STAT3 pathway is essential for normal generation and functions of beta cells, but its ectopic expression under effects of IL-17A/IL-17R interaction can lead to the aforementioned disorders.

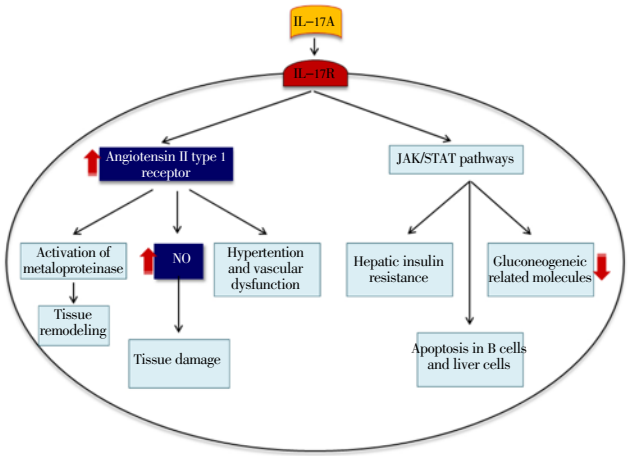

Figure 1. Immunopathogenesis of IL-17A in T2D and its complications. IL-17A/IL-17A receptor (IL-17R) interaction leads to upregulation of angiotensin II type 1 receptor, which results in activation of metalloproteinases, hypertension and vascular dysfunction, and enhanced production of renal NO. IL-17A/IL-17A receptor (IL-17R) interaction also activates JAK/STAT pathways, which lead to hepatic insulin resistance, beta and liver-cell apoptosis, and downregulation of gluconeogeneic related molecules.

4. Conclusion

Based on the published studies concerning IL-17A and T2D, it may be concluded that IL-17A plays a key role in the development of T2D and its related disorders via upregulation of several inflammatory molecules including angiotensin II type 1 receptor and JAK2/STAT3 pathway-related molecules. Future studies can shed more light on this field and improve our knowledge of the main mechanisms responsible for the regulation of Th17 function. Accordingly, immunotherapy methods to limit hepatic and pancreatic tissue damage may be modified.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

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Comments

Background

T2D is a chronic metabolic disease and the most common form of diabetes. The prevalence of T2D has increased dramatically and 1.6 million cases diagnosed each year in the United States. IL-17A is a cytokine playing an important role in both host defense against infections and chronic inflammatory diseases including psoriasis, psoriatic arthritis, and rheumatoid arthritis.

Research frontiers

This review summarizes recent publications regarding the role of this cytokine (IL-17A) in T2D and its complications. It is a clear and concise review that shows a link between immune system and diabetes.

Related reports

Several studies have demonstrated that high levels of IL-17A are associated with chronic inflammatory and autoimmune diseases. Honkanen J *et al.* (2010), showed that IL-17 immunity is upregulated in human type 1 diabetes, suggesting the role of IL-17 in the pathogenesis and therapy of type 1 diabetes.

Innovations & breakthroughs

To the best of my knowledge, there is no informative review article about the role of IL-17A in T2D. This article presents the recent knowledge about T2D and IL-17A. The authors have also collected up-to-date references.

Applications

This review provides an overview of recent studies on how IL-17A affects T2D and its complications. Researchers including immunologists and biochemists may find it helpful to read this before conducting their studies in this field.

Peer review

In general, this article presents a systematic review of current knowledge about the role of IL-17A in the pathogenesis of T2D. The authors provide a scientific interpretation of data from various scientific studies. This article raises several important questions, for instance, about therapeutic potential of IL-17A in inflammation and autoimmune diseases.

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