Role of Interleukin-6 in Type 1 Diabetes Mellitus (Review of Articles)

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ABSTRACT

Type one diabetes mellitus (T1DM) is an autoimmune condition wherein islet cells of pancreas are damaged, necessitating extrinsic insulin therapy for the remainder of life. T1DM affects kids and teenagers and accounts for roughly 5-10% of diabetes cases. Cytokines are low-molecular-weight extracellular molecules that serve as immune modulators which cause β cells impairment in T1DM patients by generating nitric-oxide. Comprehending and controlling autoimmune inflammatory factors, on the contrary, may aid in treating or even avoiding disease advancement. Interleukin-6 (IL-6) is a versatile mediator that have an influential purpose in inflammation besides autoimmune conditions and one of variables implicated in autoimmune inflammation. This cytokine, however, was demonstrated to play a significant function in metabolic control, notably homeostasis of glucose.
Objective of this review is to demonstrate the contribution of interleukine-6 in T1DM etiology.

Keywords: cytokine, diabetes mellitus, autoimmunity.

دور الإنترلوكين ٦ في داء السكري من النوع الأول (مقالة استعراضية)

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الخلاصة

داء السكري من النوع الأول (T1DM) هو مرض مناعي ذاتي يتم فيه تدمير خلايا جزيرة البنكرياس، مما يتطلب علاجًا خارجيًا بالأنسولين لمدى الحياة. و يؤثر داء السكري من النوع الأول على الأطفال والمراهقين ويمثل ما يقرب من ٥-١٠ ٪ من حالات مرض السكري. السايتوكينات هي عبارة عن بروتينات خارج الخلية منخفضة الوزن الجزيئي تعمل كوسيط للاستجابة المناعية و تسبب إصابة خلايا بيتا البشرية في مرضى داء السكري من النوع الأول عن طريق إنتاج اوكسيد النيتريك. من ناحية أخرى، قد يساعد فهم أسباب التهاب المناعة الذاتية وإدارتها في علاج أو حتى منع تطور المرض. انترلوكين-٦ هو سايتوكين متعدد الوظائف يلعب دورًا في الأمراض الالتهابية المزمنة وأمراض المناعة الذاتية وهو أحد المتغيرات الضالعة في التهاب المناعة الذاتية. ومع ذلك ، فقد ثبت أن هذا السايتوكين يلعب دورًا مهمًا في تنظيم التمثيل الغذائي ، وخاصة استتباب الجلوكوز.
الهدف من هذه المراجعة هو إظهار دور الإنترلوكين-٦ في التسبب في مرض السكري من النوع الأول.

الكلمات المفتاحية: سايتوكين، داء السكري، المناعة الذاتية.

INTRODUCTION

Type 1 diabetes (T1DM), is an autoimmune illness defined as the damage of insulin-secreting cells in the pancreas by T lymphocytes, leading to an extreme insulin deficiency. These T lymphocytes become triggered in consequence to autoantigens found in the islets, causing T1DM to develop. Among the islet autoantigens is insulin that causes T-lymphocyte activation, generation of inflammatory cytokines, and development of diabetes [1].

Autoimmune diabetes has a complex pathogenesis that encompasses both genetic susceptibility and environmental factors, such as viruses and toxins [2]. Immune cells such as CD4+ as well as CD8+ T lymphocytes infiltrate the

pancreas, following a brief autoimmune assault by anti-islet antibodies [3]. According to studies, cytokines have a substantial function in the initiation of T1DM development, elevated circulatory values of pro-inflammatory interleukins manufactured by mononuclear cells in autoimmune diabetes cases firmly imply a role for a bothered balance among pro-inflammatory mediators as interleukin-6 and anti-inflammatory interleukins as transforming growth factor-β in the emergence of autoimmune diabetes [4]. Inflammation mediators including interleukin-6, have recently been associated with the establishment of T1DM in a variety of investigations.

Interleukin-6

Interleukin-6 (IL-6) is a multifunctional protein that has a function in chronic inflammation and autoimmune illnesses, it is one of the variables implicated in autoimmune inflammation. Numerous types of cells, particularly stromal and immune system cells, with neutrophils besides monocytes, becoming key producers of IL-6 following viral as well as bacterial infection [5]. IL-6 is a soluble cytokine that influences inflammation, immunologic response, besides cell regeneration [6].

Patients with rheumatoid arthritis, lupus, and sclerosis have high IL-6 blood and tissues quantities, which frequently correlate with clinical outcomes , it was also shown that animals lacking IL-6 are resistive against neuroinflammation [7], and IL-6 receptor (IL6R) inhibition constrains collagen triggered arthritis [8], implying the involvement of IL-6 in autoimmunity. In addition, it was found that, anti–IL-6R antibody tocilizumab's had efficacy in treating rheumatoid arthritis besides systemic juvenile arthritis.

IL-6 Signaling

The pathway where interleukin-6 signals predominantly is JAK/STAT, after IL-6 attaches to the cell surface IL-6 receptor, glycol-protien130, the ubiquitous sensor subunit for the IL-6 group of cytokines, is recruited and dimerized [9]. JAK family kinases are activated by gp130 dimerization and phosphorylate tyrosine residues on the protein, the MAPK and STAT transcription factors one and three pathways are triggered by sequential docking of the phosphatase SHP2 (Src homology 2 domain–containing tyrosine phosphatase 2) besides STAT1 and STAT3 (Figure 1). STAT proteins that were phosphorylated undergo dimerization and transmit to the nucleus, wherein they promote targeted transcriptional activity [10].

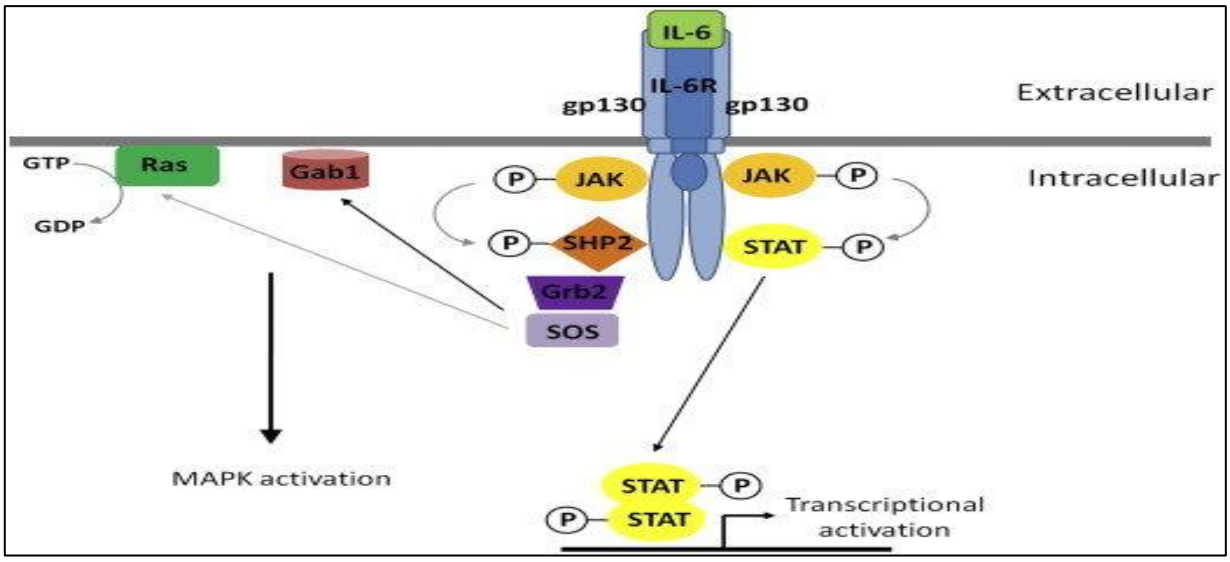

Figure 1: Diagram showing IL-6 signaling events.

A distinctive aspect of IL-6 physiology is a signal strategy known as trans-signaling, allowing cells without membrane-attached IL-6R (mbIL-6R) to be stimulated. Interaction of gp130 with IL-6 complex besides a solvable version of IL-6 receptors results in this method of IL-6 signaling. While minor amounts of solvable IL-6R protein are generated through IL-6R spliced version translation, the majority of IL-6R is produced by enzymatic processing of the IL-6R exterior domain from surface of the cell, this is known as shedding [11]. The primary enzyme that drives IL-6R shedding has been identified as A disintegrin and metalloproteinases-17 (ADAM-17) [12]. The IL-6R/gp130/STAT3 pathway is linked to the harmful effects of IL-6 in autoimmune disorders; signaling

through this route is required for development of T-helper 17 cells as well as the control of T-regulatory cells formation via forkhead box P3 (FOXP3) expression inhibition. In addition, IL-6-brought STAT3 phosphorylated can promote T effector (Teff) cell resistant to Treg cell repression [13].

Biological Influence of IL-6 on Immunity

The powerful interleukin IL-6 contribute to a large variety of biological activities and immunological responses and this cytokine is significant pathogenetic mediator in autoimmune illnesses as rheumatoid arthritis, demonstrating that IL-6 pathway dysregulation is a typical hallmark of autoimmunity [14].

Interleukine-6 stimulates the distinction of naive CD4 T lymphocytes, which is critical in the link between the acquired and innate immune reactions. Additionally, IL-6 in association with TGF-beta, is mandatory for T-helper 17 cell formation from CD4 T cells [15]. TGF-beta-brought Treg differentiation is likewise inhibited via IL-6 [16]. IL-6 similarly increases T-follicular helper-cell development along with the manufacture of IL-21, which controls the production of immunoglobulin in general and IgG4 production in particular. It has been also shown that continuous over synthesis of IL-6 causes hypergammaglobulinemia and autoantibody production because it can stimulate B cells to differentiate into antibody-creating plasma cells [17]. Furthermore, IL-6 can trigger atherogenesis via inducing adhesion molecules, monocyte-endothelial contacts, and inflammatory injury [18]. Involvement of IL-6 in vascular inflammation similarly observed in study [19] that show increased fat peroxidation in rodents who upregulates IL-6, indicating that high IL-6 concentrations in the blood linked to the onset of atherosclerosis and vascular inflammation . In mice, anti–IL-6 treatment greatly reduces inflammation [20].

IL-6 in Type 1 DM

Interleukin-6 is a versatile interleukin with several functions in various tissues, it was first established as a vital factor of the immune response. This cytokine, however, shown to have a significant function in metabolic control, particularly glucose homeostasis [21]. Furthermore, IL-6 acts as an insulin secretion regulator by acting as a stimulating cytokine [22]. Among the most essential hormones is insulin in maintaining balance of glucose, also its effect is determined by its secretion, target tissue sensitivity, and clearance. There has been various research on the influence of IL-6 on insulin levels and release [23].

Interleukin-6 act as inflammatory marker because it affects insulin release either directly or indirectly via acceleration of free lipid synthesis, as well as glucose homeostasis. Moreover, the IL-6 gene might participate in T1DM susceptibility [24]. Moreover, by encouraging B lymphocyte development and activating killer T cells, IL-6 might cause actual damage to cells of the pancreas [25]. Mediators of inflammation, as IL-1 and TNF-alfa, are essential cytokines in the development of type one diabetes, derived from macrophages and causing the release of IL-6 as a result of a series of biological events [26].T1DM was studied using the normal - weight diabetes (NOD)/Wehi animal model, blocking IL-6 resulted in a significantly lower incidence of diabetes, according to one report [27].

Interleukin-6 acts as an insulin secretion regulator by acting as a stimulating cytokine, according to previous studies, low levels of IL-6 can stimulate insulin release whereas large levels decrease insulin production [28]. Furthermore, the IL-6 gene may have a role in T1DM susceptibility [24]. IL-6 influences inflammatory, immune, and various cells include cells in the pancreas, skeletal muscles and fat cells, since it can communicate via cell wall attached (cis-signaling) and liquid (trans-signaling) IL-6 sensors [29]. Increased IL-6 levels are significant diabetes risk influence, and this cytokine impairs β cell function alone or in conjunction with IL-1β [30].

Interleukin-6 receptor membrane abundance, that is linked to phospho-STAT3 quantities, is a significant predictor of greater IL-6 responsiveness in T1DM. Furthermore, decreased ADAM17 activation of IL-6R sheddase in diabetics T lymphocytes suggested a mechanical relationship between T1DM and increased IL-6 responses. The time from diagnosis was inversely associated to IL-6–brought STAT3 phosphorylation, demonstrating an IL-6 signal mismatch might be used to diagnose earlier disease[14]. Increased IL-6 levels have been linked to diabetes, according to studies, which is concerned with patient subgroup analysis based on their age, disease duration, and ethnicity, one study show that in children with T1DM, certain mediators were rapidly raised in hyperglycemia, and remain elevated for periods following hyper-glycemia. Elevated oxidative and inflammation damage cytokine levels are hypothesized to mediate endothelial changes that underlie the emergence of long-time diabetes vascular complications [31].

Adults with T1DM have increased levels of proinflammatory mediators in the blood, that may be extremely produced by elevated glucose level[32].

Circulating monocyte-derived cytokines have been found to be higher in diabetes patients' blood and that at the outset of clinical disease, diabetic people had greater blood levels of Interleukin-6 than matched controls [1]. Additionally, Monocytes were investigated in atherosclerosis and glycemia regulation in long-term diabetic individuals, in diabetic people, stimulation causes an increase in release of cytokines from monocytes, in contrast to the controls [33].

It was found that T1DM is divided into two gene expressing groups, one is characterized by elevated pro-inflammatory interleukin generation, include IL-6 [34]. Another study found that monocytes obtained directly from T1DM patients' blood released the pro-inflammatory mediators interleukin-1 and interleukin-6 [35].

Insulin is an autoantigen that causes potentially dangerous memory cells to produce interleukin-6 and interleukin-10 in vitro [36]. T helper-1 cells and their cytokine products outnumber T helper 2 cells and cytokine products. The Th-2 and Th-1 subsets are out of balance, this permits Interleukins of kind 1 to start a chain of inflammatory responses on the islet, includes the stimulation of monocytes and causing them to release proinflammatory mediators. By increasing nitric oxide generation, these mediators exert cytotoxicity or cytocidal influences on pancreatic islets [36].

The proinflammatory mediators may have major functions in the development of T1DM, either alone or in combination, prior to the creation of significant pancreatic β-cell devastation, TNF-α besides IL-1β values could employed as indications of ongoing autoimmunity aggressiveness towards tissues [37]. IL-6 levels in T1DM blood conveyed to rise in several researches [38,39], this indicate its contribution in the etiopathogenesis of T1DM. Elevated glucose quantities in cultured monocytes were demonstrated to boost IL-6 production in cell culture studies [40].

CONCLUSIONS

T-cell reactivity to IL-6 is higher in T1DM patients, partly due to an increase in IL-6R activation, Diabetes can be aggravated by a malfunctioning IL-6 response through a variety of mechanisms, such as changed T lymphocytes activity, implying that people who have T1DM might gain from an IL-6-specific treatment approach like the presently investigated Tocilizumab. Higher IL-6 levels are also likely to correctly represent the condition of T1DM patients, increased IL-6 concentrations may suggest changed metabolic activity, and IL-6 bioavailability may be a potential marker for early diagnosis of T1DM development as well as progression.

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