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Beyond Autoantibodies: The Predictive Power of Pro-Inflammatory Cytokines in Type 1 Diabetes Pathogenesis

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ABSTRACT

Type 1 diabetes (T1DM), an autoimmune disorder marked by a characteristic dysfunction of insulin-secreting beta-cells in the pancreatic islets. This destructive process is not a simple event but a chronic inflammatory cascade, propelled by immune cells including T-lymphocytes and macrophages that release potent signaling molecules known as pro-inflammatory cytokines.

This review delves into the growing body of evidence that implicates specific inflammation promoting mediators, that include Interleukin-1β (IL-1β), Tumor Necrosis Factor-α (TNF-α) and Interferon-γ (IFN-γ), as master regulators of beta-cell death. We explore how modern analytical techniques allow for the precise mapping of these cytokine patterns in the blood, revealing a dynamic and ongoing disease process long before clinical symptoms appear. By weaving together findings from clinical and preclinical studies, this article argues that profiling these inflammatory signals provides a crucial real-time, functional readout of autoimmune activity. This complements the traditional, static measurement of autoantibodies. We conclude by discussing the significant potential of integrating cytokine data into existing models to create more robust risk stratification tools and to pave the way for interventions that could intercept the disease pathway before critical beta-cell mass is lost.

Keywords: Pro-inflammatory cytokines; β cells; Type 1 diabetes; Reactive oxygen species

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune endocrinopathy characterized by the selective destruction of pancreatic β-cells, resulting in an absolute deficiency of endogenous insulin. Consequently, this leads to progressive hyperglycemia and confers a significant predisposition to diabetic ketoacidosis (DKA) (1). Although this condition can develop at any age, it is most frequently diagnosed in children, particularly between five and seven years old or just before puberty, and it occurs more often in males.

Insulin deficiency, along with elevated blood glucose, precipitates symptoms such as fatigue, unexplained weight loss, excessive thirst (polydipsia), increased appetite (polyphagia), and frequent urination (polyuria) (2). When insulin is insufficient, glucose cannot penetrate cellular membranes, resulting in higher glucose concentrations in both the blood and urine, which subsequently leads to the depletion of fluids and caloric reserves (3,4). As the disease progresses, extremely low insulin levels trigger the breakdown of lipids, which may generate ketone bodies. These compounds accumulate in the circulatory system and can lead to metabolic acidosis, which is partially mitigated by respiratory alkalosis resulting from hyperventilation. If left untreated, these compensatory mechanisms can fail, potentially culminating in grave complications such as cerebral edema, confusion, loss of consciousness, coma, or death (5,6).

The development of T1DM is also modulated by several exogenous factors that exert significant influence. The resulting events trigger an autoimmune response in which immune cells target the pancreatic islets. This leads to localized inflammation, characterized by insulitis, and eventually results in β-cell destruction. Pro-inflammatory cytokines are released from a diverse range of immune cells, including T lymphocytes, dendritic cells, and macrophages (7,8). These cytokines further exacerbate β-cell degeneration and amplify immune-mediated responses. This review highlights the critical significance of these inflammatory mediators in the pathogenesis and progression of T1DM (9).

Pro-inflammatory Cytokines and their functions

Pro-inflammatory cytokines are generated by immunologically active cells, notably T helper (Th) cells and activated macrophages. These cytokines are crucial mediators of inflammatory responses and are proteins, peptides, or glycoproteins secreted by specialized immune cells (10,11). They act as modulators of inflammatory processes, pathogenic incursion, tissue trauma, and the resulting immune responses. Several key pro-inflammatory mediators, specifically interleukin (IL)-1 and tumor necrosis factor (TNF), possess the potential to exacerbate disease pathogenesis by amplifying inflammation, thereby manifesting as events such as nociception, pyrexia, tissue degradation, and sustained inflammation. These effects are attributable to immune cell dysregulation and subsequent tissue damage (12, 13).

Systemic defenses such as inflammation and fever are primarily driven by pro-inflammatory cytokines. These responses represent two crucial defense mechanisms in the body's battle against pathogens, serving to strengthen innate immunity. Interestingly, under certain circumstances, these cytokines can also function as growth factors (14). Some of the key pro-inflammatory cytokines contributing to this process include IL-1β, IL-6, and TNF-α, all of which play pivotal roles in inflammation and pain.

IL-1β, which is produced by macrophages, is also found in sensory neurons and serves a critical function in the host's immunological defense against infection and tissue damage (15). Similarly, IL-6 is rapidly produced in response to pathogenic infections and tissue damage. Furthermore, IL-6 enhances immune function, stimulates blood cell production, and triggers acute-phase responses. In addition,

IL-6 may also act as a pro-inflammatory agent and participate significantly in the pathogenesis of several autoimmune diseases (16). TNF-α, on the other hand, is found in both neurons and glial cells. It is a complex cytokine that not only promotes inflammation but also induces cell death and interferes with several cellular signaling pathways (17). Each of these cytokines plays a multifaceted role in our immune response, demonstrating the intricate balance that our bodies strive to maintain between fighting off disease and controlling inflammation (18).

Engaging in physical exercise has been shown to stimulate the production of several key cytokines that promote inflammation and are involved in inflammatory processes observed alongside tissue injury and fever (19). Elevated levels of these cytokines have been associated with several pathological conditions, including atherosclerosis, tissue damage, immune cell infiltration, and cancer. Such inflammatory processes may also increase the risk of stroke (20). Furthermore, imbalances in these inflammatory agents may contribute to the development of depression and other neurological disorders (21). Therefore, maintaining an optimal equilibrium between inflammatory and anti-inflammatory cytokine profiles is extremely important for overall health (22, 23).

Pathological Consequences of Pro-inflammatory Cytokines Dysregulation

It is widely established that pro-inflammatory cytokines initiate and control inflammation. An increase in their concentration can accelerate this process, resulting in tissue damage, fever, and the development of chronic disease (24). In severe cases, overproduction can precipitate life-threatening conditions, including cytokine storm (25).

Studies have linked heightened cytokine activity to various inflammatory conditions, including cystic fibrosis, reduced insulin sensitivity in muscle cells, and several adverse events in normal kidney physiology, where overproduction of pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6 drives renal dysfunction through a multifaceted pathogenic cascade (26,27,28). Hemodynamically, these cytokines tilt the vasoregulatory balance toward vasoconstriction by amplifying endothelin-1 and angiotensin II while suppressing nitric oxide, thereby reducing afferent arteriolar flow and glomerular filtration (29). Simultaneously they increase endothelial permeability and adhesion molecule expression, which promotes leukocyte infiltration, capillary leak, and proteinuria (30). This inflammatory milieu extends into the tubulointerstitium, where activated immune cells release reactive oxygen species and proteases that directly damage tubular epithelia (31). Persistent cytokine signaling induces epithelial-to-mesenchymal transition and stimulates fibroblast proliferation, leading to progressive extracellular matrix deposition, interstitial fibrosis, and tubular atrophy (32). Concurrently, cytokines like TNF-α disrupt podocyte cytoskeletal integrity and downregulate slit diaphragm proteins such as nephrin and podocin, causing foot process effacement and sustained proteinuria, which further perpetuates tubular injury and local inflammation (33). Moreover, cytokine-driven activation of the intrarenal renin-angiotensin system generates a positive feedback loop, as angiotensin II both exacerbates intraglomerular hypertension and stimulates additional cytokine release, creating a vicious cycle of oxidative stress, structural remodeling, and functional decline (34). This cycle transforms an acute inflammatory response into a self-sustaining pathological process, ultimately culminating in fluid-electrolyte imbalances, impaired excretion, and progressive nephron loss characteristic of chronic kidney disease (27, 28).

In the kidneys, pro-inflammatory cytokines disrupt the activity of potassium ions (K^+) by hindering the normal function

of transporters and ion channels (35). For example, they alter the behavior of potassium channels, which in turn, impacts the movement of water and solutes across epithelial tissues, ultimately negatively affecting kidney cell function (36). When kidney proximal tubule cells are exposed to lipopolysaccharides, they release cytokines, enhance inflammation (37). Furthermore, interferon-gamma (IFNγ) prolongs the inflammatory response and activates the pS K^+ channel (38). Additionally, transforming growth factor-beta 1 (TGF-β1) stimulates calcium-dependent potassium channels (KCa3.1), which may contribute to kidney fibrosis and its associated complications (39).

In cystic fibrosis, hyperactive inflammation caused by pro-inflammatory cytokines injures lung tissue. This exaggerated immune response, along with the accumulation of immune cells, impairs the lungs' ability to fight bacterial infections, consequently, increasing the likelihood of infections in patients (40). A significant number of individuals with Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) deficiency—approximately 40–70% of cases—exhibit asthma-like symptoms (41). Upregulated expressions of TNF-α, IL-8, and IL-13, together with CFTR-deficient T-helper cells, contribute to a pro-inflammatory environment that enhances airway smooth muscle contraction (42,43).

Pro-inflammatory cytokines also contribute to impaired insulin signaling in skeletal muscle. During infection, cytokines like TNF-α are released and interfere with insulin-dependent glucose uptake, resulting in insulin resistance (44). This mechanism is largely implicated in the pathophysiology of Type 2 Diabetes Mellitus (T2DM) and muscle wasting due to heightened protein breakdown. Cytokines like IL-1 reduce the efficiency of protein synthesis in muscle cells, contribuing to increased muscle loss (45). Furthermore, persistent pro-inflammatory activity can hinder glucose absorption following meals, leading to glucose intolerance and insulin resistance (46,47).

Role of Pro-inflammatory Cytokines as predictor in T1DM

The autoimmune attack on pancreatic β-cells in TIDM is largely influenced by dysregulation of cytokines (48). To fully understand this complex process, we need to explore how immune system problems interact with genetic predispositions and environmental factors. Gaining insights into these complex interactions could lead to the development of novel therapeutic strategies and improved outcomes for patients with T1DM. Genetic components, particularly the human leukocyte antigen (HLA) variants DR3/DR4-DQ8, significantly increase T1DM risk by disrupting antigen presentation, which undermines immune tolerance (49). Furthermore, non-HLA genetic variants, including Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22) and Interleukin 2 Receptor Subunit Alpha (IL-2Rα), contribute to the disorder by interfering with immune signaling pathways, leading to imbalances in cytokine levels (50,51).

Environmental factors like viral infections—specifically enteroviruses—trigger innate immune responses, resulting in the production of pro-inflammatory cytokines. Such mediators contribute to the immunological destruction inflicted on β-cells in T1DM. To fully comprehend this complex mechanism, it is crucial to explore the interaction among genetic predispositions, immune system dysfunction, and environmental influences. Such research could pave the way for more effective treatment strategies, potentially improving outcomes for individuals diagnosed with T1DM (52,53).

Certain genes, such as HLA-DR3/DR4 and DQ8, influence how antigens are presented, which raises the risk of immune tolerance failure and the development of T1DM (54). In addition, non-HLA genes like PTPN22 and IL2Rα disrupt immune signaling pathways, contributing to greater cytokine dysregulation (55). Furthermore, viral infections and other environmental factors activate innate immune responses, resulting in the induction of pro-inflammatory cytokine production (56).

Research suggests that the heightened inflammation seen in T1DM, which exacerbates β-cell destruction, is largely driven by the activation of as-yet-unidentified regulatory regions within cytokine genes (57). This overproduction of pro-inflammatory cytokines may be associated with genetic predispositions, epigenetic changes, or imbalances in the immune system. These factors can trigger the activation of enhancers and promoters within these regulatory regions (58).

Investigating the regulatory framework of β-cells provides important insights into T1DM by analyzing how pro-inflammatory cytokines are expressed. Researchers are currently focusing on enhances—DNA regions that respond to specific signals—and linking them to regulatory elements within human islets to better understand the β-cells cell transcriptome, proteome, and chromatin structure (59). Recent evidence suggests that the β-cell responsiveness to cytokines is modulated by both newly identified regulatory regions and established elements that are governed by islet-specific transcription factors (60). These novel cis-regulatory elements are frequently located in genomic areas associated with T1DM, underscoring the significance of an enhanced activity in response to cytokines within human β-cells. This research highlights how β-cells adapt to pro-inflammatory environments and suggests a connection between genetic variations linked to T1DM and the enhancers that respond to different stimuli in the islets (61,62,63).

THE ROLE OF PRO-INFLAMMATORY CYTOKINES IN T1DM PATHOGENESIS

Pro-inflammatory cytokines play a central role in the autoimmune destruction of pancreatic β-cells, significantly impacting the development of T1DM (64). These cytokines are mainly produced by immune cells, but stressed β-cells can also release them, creating an inflammatory environment that further aggravates β-cells dysfunction and promotes cell death (65,66). Current research aims to identify the mechanisms that drive autoimmunity in T1DM, as fully understanding these processes is essential for improving disease knowledge and developing effective treatments. Recent studies have highlighted the important roles of DCs and macrophages, as well as genetic factors like the HLA-DR3/DR4-DQ8 alleles in shaping the immune response (66). These immune cells present β-cell antigens to T lymphocytes and release cytokines—including IL-1β, interferon-alpha (IFN-α), and TNF-α (65,66). The key mechanistic insights and their individual roles with recent evidence are summarized in Tables 1 and 2).

In T1DM, pro-inflammatory cytokines drive the inflammatory response. Activated macrophages release IL-1β, which stimulates β-cells to generate nitric oxide (NO) and reactive oxygen species (ROS). These molecules cause oxidative stress and damage to mitochondria (67,68). Furthermore, TNF-α promotes β-cell death (apoptosis) and recruits more immune cells, further exacerbating the inflammatory condition (66,67).

IFN-α, which is typically triggered by viral infections, boosts T cell activity and increases the expression of major histocompatibility complex (MHC) class I molecules on the surface of β-cells. This makes the β-cells more visible and vulnerable to attacks by the immune system (69). At the same time, pro-inflammatory cytokines stimulate the release of chemokines such as C-X-C Motif Chemokine Ligand 10 (CXCL10) that attract more immune cells to the pancreatic islets, fueling the ongoing cycle of inflammation (70,71).

These cytokines create feedback loops that keep inflammation going in T1DM. For example, IL-1β promotes the production of more inflammatory mediators, such as TNF-α and IL-6, further amplifying the inflammatory response (72,73).

Induction of diabetogenic T cell responses

Autoreactive CD4+ and CD8+ T

lymphocytes often called diabetogenic T cells play a key role in destroying the insulin-producing β-cells in the pancreas. TNF-α contributes to this process by increasing the expression of MHC class I and II molecules in islet cells, which helps recruit immune cells to the area, enhances cell adhesion, and promotes the proliferation of endothelial cells, T cells, and antigen-presenting cells (APCs). In addition, CD8+ T lymphocytes release TNF-α, which directly triggers β-cell destruction (74).

When DCs present additional autoantigens, they trigger CD8+ T lymphocytes to produce IFN-γ and TNF-α. This activation increases the expression of Fas and MHC class I molecules on β-cells, speeding up their destruction and amplifying the T-cell-mediated autoimmune response (75). Furthermore, the inflammatory environment created by diabetogenic T cells created damaged β-cells even after the initial release of antigen, prolonging the autoimmune response (76, 77).

More research is needed to better understand the roles played by CD8+ T lymphocytes. DCs, natural killer cells, and macrophages in the TNF-α mediated destruction of β-cells a process that is facilitated by CD4+ T lymphocytes.

Pro-inflammatory cytokines and the third signal

ROS serve two roles: they act as agents of oxidative stress and also as secondary messengers in immune signaling (78). They are essential for the development of adaptive immunity, as they initiate intracellular signaling pathways involving key regulators like nuclear factor kappa B (NF-κB), mitogen-activated protein kinase pathways (MAPK), and activator protein 1 (AP-1). These pathways boost the production of inflammatory mediators, including the TNF-α and IL-1, mainly in DCs and macrophages (79). In T1DM, these cytokines contribute to β-cell death while also helping to establish adaptive immune responses. As a result, ROS and pro-inflammatory cytokines from innate immunity work together to connect innate and adaptive immunity (80, 81).

A key area of T1DM research focuses on understanding how T cells differentiate into β-cell-specific effectors and how they influence disease progression. As mentioned earlier, ROS and pro-inflammatory cytokines play a major role in shaping adaptive immunity. Additionally, ROS participates in reduction-oxidation (REDOX) signaling, which enhances the effects of inflammatory cytokines in adaptive immune responses (82). IL-12 and type I interferons (IFN-α/β) are essential for the cytotoxic function of mature CD8+ T cells, while IL-1 primarily affects the effector response of CD4+ T cells. Both IL-12 and IFN-α/β also regulate genes involved in effector functions (such as telomerase, FasL, and IFN-γ), activation markers (including CD25, OX40, and 4-1BB), and survival factors (like serine proteases) (83, 84).

Research shows that IL-12 and IFN-α/β help maintain and enhance gene expression by promoting chromatin remodeling, a process that is essential for CD8+ T cell differentiation through the third signal mechanism (85). Without these cytokines, transcription levels drop (86). Similarly, IL-1 acts as a third signal for CD4+ T cells, while ROS-mediated IL-12 and IFN-α/β support memory formation, cytolytic activity, and clonal expansion in CD8+ T cells (87). Importantly, the combination of IL-1, antigen, and co-stimulation significantly boosts CD4+ T cell proliferation (88, 89, 90).

RECENT TECHNOLOGIES FOR IDENTIFYING PRO-INFLAMMATORY CYTOKINES IN T1DM

Studying the roles and interactions of cytokines in T1DM requires identifying and measuring pro-inflammatory cytokines. They serve as important biomarkers, offering a window into the inflammatory and autoimmune processes that occur before clinical symptoms develop. Because their presence in serum or tissues reflects immune system activation, they are

valuable for identifying individuals at risk, tracking disease progression, and evaluating how well treatments are working. Studies have demonstrated that β-cell destruction linked to insulitis is associated with higher levels of key inflammatory cytokines, including TNF-α, IFN-γ, and IL-1, as well as other immune mediators like TNF-β, IL-2, IL-6, and IL-12 (91,92).

In addition, monoclonal antibody therapies targeting pro-inflammatory cytokines represent promising avenues for managing T1DM. These interventions work by neutralizing key inflammatory mediators—such as IL-1β, TNF-α, and IFN-γ and by modulating autoreactive T cell activity. This helps reduce inflammation, protect β-cell function, and potentially slow disease progression. These strategies focus on the immune components, cytokine networks, and signaling pathways involved in the autoimmune attack on β-cells and the resulting inflammatory processes (90,91,92). Ongoing improvements in cytokine detection technologies are helping to refine these antibody-based therapies and develop more effective prevention strategies.

RNA Sequencing

Comprehensive analysis of cytokine gene expression in T1DM can be effectively conducted using RNA sequencing (RNA-Seq), a cutting-edge high-throughput technique for transcriptome profiling (93,94,95). Previously, oligonucleotide arrays served as the main method for detecting a broad array of transcripts. However, this approach depended on both target messenger RNAs (mRNAs) and their complementary probes, which limited its capacity to identify only known transcripts (93,94). Recently, RNA-Seq has emerged as a powerful alternative, allowing the detection of all transcripts associated with diabetes progression (89). This encompasses those expressed in human pancreatic islets, splice variants present under normal conditions, and those upregulated in response to inflammatory cytokines such as IL-1β and IFN-γ (90,92).

Genome-wide association studies (GWAS) have discovered 29,776 transcripts in human islets and about 20% of changes in transcript expression are influenced by pro-inflammatory cytokines (96). Quantitative analyses using Enzyme-Linked Immunosorbent Assay (ELISA) have revealed that chemokines were the cytokines most significantly altered at the protein level (97). More than 90% of eukaryotic transcript genes can undergo alternative splicing, often resulting in various isoforms (98). Pro-inflammatory cytokines can impact the function of splicing genes by altering specific cellular signaling pathways, which in turn contributes to tissue-specific splicing patterns. By combining RNA-Seq with sophisticated bioinformatics tools, researchers can identify alternative promoter usage, skipped exons, and retained introns in distinct splice variants (99,100).

Mauvais-Jarvis F. Single cell regulatory architecture of human pancreatic islets suggests sex differences in β cell function and the pathogenesis of type 2 diabetes.

Real Time Quantitative Polymerase Chain Reaction

The highly sensitive technique known as Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR) was employed to quantify the mRNA expression levels of various inflammatory cytokines. Because RT-qPCR is highly reproducible, it can work with very small cell samples, a major advantage in immunology, where cytokines are often produced in tiny amounts and found in specific locations (101). Furthermore, traditional PCR techniques can accurately assess the initial quantities of mRNA transcript copies. The single-step amplification and detection process of PCR enables the rapid generation of extensive data. These features make qPCR a widely trusted, sensitive, and accurate method for quantifying c cytokine mRNA levels (102,103).

Enzyme-Linked-Immuno-Sorbent-Assay

In T1DM, pro-inflammatory cytokines

play a significant role in the autoimmune obliteration of pancreatic β-cells, and ELISA constitutes an essential methodology for monitoring their elevated concentrations. This analytical technique employs enzyme-labeled antibodies to identify and quantify cytokines released during the decline of pancreatic β-cells, thus enabling the examination of secreted cytokines in culture supernatants or serum. Pro-inflammatory mediators, including TNF-α, IL-1β, and IFN-γ, demonstrate patterns that parallel those observed in autoantibodies (102,103).

The immunometric double-antibody sandwich ELISA methodology incorporates a capture-antibody alongside an enzyme-linked detection antibody, which ensures high specificity for the precise identification of target cytokines. However, the reliability of this method depends largely on the quality of the antibodies used. While the technique gives accurate results, it has some drawbacks, namely, it is time-consuming, can only analyze only one sample at a time, and has a limited dynamic range, meaning samples with very high cytokine levels must be diluted before testing. As the number of patients requiring cytokine testing grows, these limitations become more challenging (104). The multiplex array a more advanced protein detection method based on ELISA principles solves these problems by allowing multiple cytokines to be measured at once, significantly improving efficiency and throughput (102, 105).

Sensitive Cytokine Enzyme-Linked Immunospot

The Cytokine Enzyme-Linked Immunospot (ELISPOT) assay is a sophisticated method used to quantify how peripheral blood mononuclear cells (PBMCs) respond to islet autoantigens in healthy individuals by producing pro-inflammatory cytokines, such as IFN-γ. In this context, IFN-γ serves as a crucial pro-inflammatory effector molecule. The granzyme pathway in the pancreatic islets allows CD8+ T cells to develop into effector cells that can specifically target and harm human β-cells (106).

The islet-specific CD8+ T cell IFN-γ ELISPOT test, or ISL8SPOT assay, is carried out ex vivo on unfractionated PBMCs without requiring previous in vitro expansion. This assay is a useful and effective method because it can use both fresh and frozen samples and only needs 10 milliliters of blood (107,108).

Gene Expression in Human Islet

The islets of Langerhans, which comprise about 2% of the adult human pancreas, are vital for hormone secretion, including insulin, glucagon, and somatostatin, all of which are crucial for maintaining metabolic homeostasis. Damage or dysfunction of these islets may lead to diabetes. To investigate the transcriptome of human pancreatic islets in response to pro-inflammatory stimuli and cytokines like IFN-γ and IL-1β, researchers utilize reverse transcription combined with RNA-Seq. This method allows for an in-depth analysis of the transcriptome, including splice variants, and is instrumental for future genetic and functional studies (107,109).

Research indicates that approximately 60% of genes linked to T1DM are expressed in both the immune system and human pancreatic islets, with cytokines playing a pivotal role in regulating many of these genes. Both genetic factors and environmental influences can trigger immune responses targeting β-cells, leading to the production of islet antibodies (IA). Inflammatory cytokines and chemokines can activate immune pathways, potentially resulting in tissue damage. Recent studies highlight that gene expression occurs not only in immune cells but also within the islets and functioning β-cells, as most of the genes associated with T1DM reside in human islets. Exposure to pro-inflammatory cytokines alters the expression of several critical genes in islets, underscoring their contribution to the immune-mediated destruction of β-cells (108,109).

Monocyte Isolation

Monocytes are vital components of the

immune system, as they migrate from the bloodstream into various tissues, where they undergo differentiation into pro-inflammatory DCs or macrophages (110, 111). Macrophages serve a pivotal function in host immune defense mechanisms by facilitating the clearance of apoptotic cells, producing essential growth factors, and identifying pathogens through their array of recognition receptors (112). Dendritic cells, on the other hand, are responsible for directing the adaptive immune response during inflammatory inflammation, helping to ensure it proceeds and resolves properly (113). Monocytes, macrophages, and DCs are key immune cells that secrete inflammatory cytokines and chemokines, which help immune cells communicate with each other. The Cytokines Panel Blood Test is an important diagnostic tool that measures inflammation by quantifying key biomarkers, including IL-1β, IL-6, IL-8, and TNF-α. Increased levels of these cytokines can lead to tissue damage, making regular monitoring essential (114). Recent investigations examining the blood of individuals diagnosed with T1DM have provided important insights into the immune processes involved in the disease. Monocytes derived from T1DM patients exhibit an enhanced propensity to polarize naïve $CD4^+$ T cells toward a Th17 phenotype, driving the differentiation of these T cells into IL-17-producing effectors. Furthermore, these activated monocytes secrete elevated levels of inflammatory cytokines, includingIL-1β and IL-6, which promote Th17 differentiation and function (115). Moreover, monocytes from T1DM patients elicit a more robust response from memory T cells that produce IL-17, as compared to monocytes obtained from healthy subjects (116). This enhanced comprehension of monocyte–T cell crosstalk in T1DM may pave the way for the formulation of novel therapeutic strategies aimed at disrupting this pathogenic interaction (113).

Limitation

Investigating pro-inflammatory cytokines in individuals diagnosed with T1DM presents notable challenges as well as valuable opportunities to better understand the disease. Elevated levels of cytokines such as IL-1β, TNF-α, and IFN-γ are commonly detected in a variety of inflammatory, viral and autoimmune disorders. While this overlap makes it difficult to link these cytokines specifically to T1DM, it also highlights the need for more precise diagnostic tools that can distinguish T1DM from other conditions (117).

The development of highly sensitive assays is essential for the precise quantification of cytokines at low concentrations in human serum, and adherence to stringent protocols for the preparation and preservation of plasma samples is paramount. Minimizing freeze-thaw cycles is particularly critical, as such processes can introduce variability and affect the reliability of cytokine measurements.

The investigation of dysregulated cytokine networks represents a compelling domain of research; however, it is crucial to recognize that cytokines can influence β-cell apoptosis through both pro-inflammatory and anti-inflammatory mechanisms.

Table 1: Pro-inflammatory Cytokines in Type 1 Diabetes

Key Mechanistic Insights	Contributing Cytokines	Key Supporting Studies
Direct beta cell cytotoxicity	IFN-γ, TNF-α, IL-1β, IL-17	Kumar & Subramaniyam, 2015 (127)
Th17 cell differentiation/ maintenance	IL-6, IL-17, IL-21, IL-23	Costa et al., 2010 (126) Singh et al., 2013 (128) Kumar & Subramaniyam (127), Huang Xiangli, 2020 (129)
Immune cell recruitment (Chemokines)	MCP-1, MIP-1α, MIP-1β, RANTES	Lohmann et al., 2002(125)
Macrophage/dendritic cell activation	GM-CSF, IFN-γ, TNF-α	Singh et al., 2013 (126) Kumar & Subramaniyam, 2015(127)

Table 2: Pro-inflammatory Cytokines in Type 1 Diabetes Mellitus: Individual Roles and Recent Evidence

Cytokine	Pro-inflammatory Roles in Type 1 Diabetes Pathogenesis	Recent Evidence/ Clinical Correlates
IFN-γ (Interferon-gamma)	o Key effector cytokine secreted by autoreactive CD4+ and CD8+ T cells o Synergizes with IL-1β and TNF-α to induce β-cell apoptosis o Upregulates Fas and MHC Class I expression on β-cells; activates macrophages	Serum levels surge around time of seroconversion in at-risk children (130)
IL-1β (Interleukin-1 beta)	o Secreted by macrophages and dendritic cells; amplifies islet inflammation o Activates pro-apoptotic NF-κB signaling in β-cells o Induces iNOS → nitric oxide production → oxidative stress o Impairs insulin secretion; synergizes with IFN-γ and TNF-α	Represses GDF15 expression in human islets (131) Higher levels correlate with pathogenic Th17 cell responses in T1D patients (132)
IL-2 (Interleukin-2)	o Expands effector T cells and NK cells o Can promote inflammatory T cell responses o Essential for Treg survival and function (dual role)	Inversely correlated with β-cell function in newly diagnosed children (133)
IL-6 (Interleukin-6)	o Promotes migration and inflammatory responses of effector T cells o Elevated in T1DM patients; positively associated with BMI o Supports Th17 differentiation from naïve $CD4^+$ T cells	Inversely correlated with β-cell function in children (133) Therapeutic blockade being explored (NCT02293837) (135) Promotes Th17 differentiation (134)
IL-17 (Interleukin-17)	o Secreted by Th17 cells; promotes inflammation and β-cell destruction o Recruits neutrophils and amplifies local islet inflammation o Positively correlated with BMI in LADA patients	IL-17F surges around seroconversion in at-risk children (130) Th17 cells and IL-17A elevated in T1D patients (132)
IL-21 (Interleukin-21)	o Promotes Th17 differentiation; supports DC and Tfh migration o Promotes B cell autoantibody production o Key pro-inflammatory cytokine in diabetogenic immunity	Surges around seroconversion in at-risk children (130) Therapeutic blockade in clinical trial (NCT02443155) (136) Promotes Th17/Tfh differentiation (134)
IL-23 (Interleukin-23)	o Essential for Th17 maintenance and effector function o Higher secretion in LADA vs. T1D after GAD65 stimulation	Surges around seroconversion (130) Th17 cells correlate with IL-23 in T1D patients (132) Supports pathogenic Th17 cells (134)
TNF-α (Tumor Necrosis Factor-alpha)	o Directly cytotoxic to β-cells (especially when secreted by CD8+ T cells) o Activates endothelial cells → enhances leukocyte homing to islets o Upregulates MHC molecules; synergizes with IFN-γ o Activates dendritic cells and macrophages	Inversely correlated with stimulated C-peptide over 12 months in children (137) TNF-α at diagnosis predicts 6-month C-peptide decline (133) Promotes inflammatory T cell responses (134)
GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor)	o Upregulated at onset of young-age T1D o Enhances dendritic cell and macrophage function o Amplifies antigen presentation and inflammation	Dual microparticle delivery (GM-CSF + TGF-β1) reduced T cell proliferation and inflammatory cytokines in preclinical models (138)

For instance, studies utilizing murine models have demonstrated that immune mediators such as IL-4, IL-13, and IFN-γ can either worsen or protect against T1DM, depending on the circumstances (118). This complexity accentuates the importance of continued research into the diverse functions of cytokines in β-cell destruction, which will augment our understanding of T1DM and facilitate the development of more efficacious therapeutic strategies (91).

THE COMPLEX ROLE OF ANTI-INFLAMMATORY CYTOKINES IN T1DM

Anti-inflammatory cytokines also play a key role in type 1 diabetes. While cytokines like IL-1β and TNF-α drive β-cell death, anti-inflammatory cytokines such as IL-10 and TGF-β help regulate the immune response and may limit tissue damage (119).

For example, IL-10 is thought to be protective in several ways. It can increase the number of regulatory T cells, which help keep the immune system in check and it promotes a more balanced immune reaction by shifting the response toward a T-helper 2-type profile while reducing harmful T-helper 1-type cytokines (120). However, the IL-10's effects depend heavily on the situation. When IL-10 is overproduced directly inside the islet cells of NOD mice, it can paradoxically accelerate diabetes. This may be due to increased stress on the β-cells, suggesting that location and concentration matter (121). This highlights the dual nature of IL-10: depending on the biological context, it can be either protective or pro-inflammatory (122,123). For instance, systemic delivery of IL-10 using gene therapy helped prevent diabetes after islet transplantation, whereas blocking IL-10 early in life reduced the development of insulitis. (124,125). These findings suggest that IL-10 is a key immunoregulator. It works by suppressing harmful CD4+ and CD8+ T cells and reducing the production of inflammatory cytokines from dendritic cells, which helps lower overall pathogenic T-cell responses (124). In addition, IL-10 helps promote protective antibody responses, particularly of the IgG1 type (125).

Beyond T-cells, other immune cells are also involved. B cells that produce IL-10 play an essential role in controlling the disease. These regulatory B cells can suppress autoreactive T-cells in laboratory experiments and have been shown to prevent diabetes progression in living models (128). Emerging evidence also suggests that these IL-10-producing B cells can help induce regulatory T cells, possibly through a mechanism involving TGF-β. This may explain why increased IL-10 levels from B-cells have been found in the islet cells of mice that remained normoglycemic for longer periods (129).

CONCLUSION

In summary, reviewed here shows that pro-inflammatory cytokines offer a powerful new way to understand type 1 diabetes. Rather than seeing it simply as a condition marked by the presence of autoantibodies, we can now recognize it as a disease driven by active, ongoing inflammation. This is where cytokine profiling becomes so valuable. Autoantibodies have been useful for decades as reliable markers to identify people at risk, but they are essentially scars from past immune attacks, they tell us that something happened, but they do not tell us what is happening now. Cytokines, on the other hand, provide real-time updates from the immune system. When we detect elevated levels of molecules like IL-6, IFN-γ, or TNF-α, or when we spot certain inflammatory pathways activated inside immune cells, we are witnessing the disease process as it unfolds. These signals do more than just confirm risk; they reveal the specific inflammatory environment that may either protect or destroy β-cells, and they may even give clues about how quickly a person might progress from being at risk to developing symptoms.

This deeper understanding allows for smarter, more personalized early interventions. Instead of using the same broad approach for everyone, we can design strategies that target the specific inflammatory drivers at work in each individual. For someone whose profile shows intense cytokine activity, the goal might be to calm that particular storm before it causes irreversible damage. This could mean protecting β-cells from attack or dialing down the activity of the immune cells that are fueling the fire. The old approach of simply monitoring at-risk individuals and waiting to see what happens may soon be behind us. By weaving cytokine profiling into routine clinical care, we move closer to a future where we can step in at exactly the right moment with exactly the right tool, one that may help preserve insulin production and, ultimately, prevent type 1 diabetes.

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