SYSTEMATIC REVIEW

The Role of the NLRP3 Inflammasome in Type 1 Diabetes: Insights From a Systematic Literature Review of Rodent Studies

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ABSTRACT

Introduction: Type 1 *Diabetes mellitus* (T1DM) is an autoimmune disease characterized by the destruction of pancreatic β-cells, necessitating lifelong insulin therapy. The rising incidence of T1DM imposes a significant economic burden worldwide, particularly in countries like Malaysia with high diabetes rates. The NLRP3 inflammasome, crucial for regulating inflammation, has emerged as a potential therapeutic target for T1DM due to its involvement in immune dysfunction and tissue damage. This study reviews existing literature and experimental data to clarify the NLRP3 inflammasome's role in T1DM development and progression. **Materials and methods:** We conducted a systematic search across five electronic databases (Scopus, Science Direct, Sage Journals, Wiley Online Library, and SpringerLink) from 2000 to 2024 using keywords such as "NLRP3," "inflammasome," "rat," "rabbit," and "mice." Data were extracted using a predefined Excel template, covering study objectives, rodent models, NLRP3 inflammasome treatment, findings, and limitations. A systematic review approach was used to analyze and synthesize the results- **Results:** The review highlights a consistent upregulation of NLRP3 inflammasome activity in T1DM, suggesting its role in disease pathophysiology. Studies on NLRP3 inhibitor compound (MCC950), showed promising results in reducing neurovascular remodeling, improving cognitive function, and enhancing survival rates post-stroke in diabetic animals. Additionally, NLRP3 inhibition facilitated alveolar bone healing in diabetic rats, indicating its potential in tissue repair and regeneration. **Conclusion:** Targeting the NLRP3 inflammasome offers a promising strategy for managing T1DM. However, further research is needed to understand its mechanisms fully and to develop therapeutic strategies that improve patient outcomes and address T1DM-related complications.
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INTRODUCTION

Type 1 *Diabetes mellitus* (T1DM) is a prevalent autoimmune condition that typically appears in infancy. It results in the destruction of pancreatic β-cells, necessitating lifelong insulin therapy (1). About 10% of all *Diabetes mellitus* cases are classified as type 1, and its incidence is rising (2). This autoimmune disorder is often diagnosed in childhood and requires ongoing insulin administration due to the loss of pancreatic β-cells (3).

Residual β-cells have been noted in individuals with longstanding T1DM. However, clinical symptoms often appear only after a substantial reduction in both the number and function of these β-cells. At this point, maintaining glucose homeostasis becomes impossible, leading to hyperglycemia, which presents with symptoms like frequent urination, intense thirst, and weight loss (3). The occurrence of this condition exhibits an annual rise of around 3% and can lead to the development of debilitating micro- and macrovascular problems. Therefore, T1DM is a financial burden on society as a whole, and on individuals and their families, it is much more of a hardship (4).

Malaysia has among the world's highest prevalence rates of diabetes, resulting in an economic cost of about $600 million (5). Between 2011 and 2019, the incidence of diabetes increased substantially, with the incidence rate increasing from 11.2% to 18.3% (6). In 2019, Malaysia had over 3.6 million people who were diagnosed with diabetes, and nearly half of these cases (49%) remained undiagnosed. With a diabetes incidence rate of 31.3%, it is estimated that approximately 7 million Malaysians aged 18 and older will be impacted by the disease by 2025. The general health of the population is put in jeopardy because of this enormous vulnerability. 7.3% to 23.8% of the population in Malaysia has DM,

according to published studies (5).
T1DM is a persistent autoimmune condition distinguished by the removal of insulin-positive pancreatic beta-cells by the action of autoreactive T lymphocytes (7). Individuals diagnosed with T1DM need lifelong insulin treatment given the substantial adverse impacts of diabetes on individuals and society, it is crucial to investigate or enhance the possible therapies for the condition (8).

In response to bacterial infection or cell injury, the cytosol becomes home to a protein complex known as an inflammasome (9). During the construction of the inflammasome, active caspase-1 is produced from inactive procaspase-1 (10, 11). The NLRP3 inflammasome has undergone thorough investigation and is widely acknowledged as the most thoroughly researched inflammasome responsible for the development and release of interleukin 1-beta (IL-1β) and IL-18 (12).

This process transforms the precursor cytokines pro-IL-1 and pro-IL-18 into their mature and biologically active forms, IL-1 and IL-18, respectively. Conversely, excessive activation of the NLRP3 inflammasome can result in pathological conditions marked by increased inflammation and unintended damage to the host organism (15). Inflammasomes, such as the nucleotide-binding oligomerization domain (NOD)-like receptor pyrin domain 3 (NLRP3), are protein complexes located in the cytoplasm that regulate the host's immune responses. Several causes which include urbanization, population expansion, population aging, and rising obesity rates, all contribute to the upward trend (16).

Inflammation occurs at different stages of the progression of T1DM and may be impacted by the genetic makeup of individuals, hence contributing to the heterogeneity of the illness (17). This process leads to the conversion of cytokine precursors pro-IL-1 and pro-IL-18 into their mature and biologically active forms, IL-1 and IL-18. However, excessive activation of the NLRP3 inflammasome can cause pathological conditions with excessive inflammation and damage to the host (18). Signaling from both internal and external pathogens that activate the NLRP3 intracellular receptor leads to the formation and activation of the NLRP3 inflammasome. This inflammasome consists of caspase-1, an adaptor protein, and apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) (19).

The inflammasome, responsible for regulating inflammation and the immune response, is tightly controlled by interactions among these three proteins (20). The involvement of the NLRP3 inflammasome in various autoimmune diseases, including experimental autoimmune encephalomyelitis (EAE), inflammatory bowel disease (IBD), and type 1 *Diabetes mellitus* (T1DM), has been well-documented. The NLRP3 inflammasome can be activated by several upstream signals, such as potassium efflux, chloride efflux, calcium influx, lysosomal damage, mitochondrial dysfunction, and ROS production (21). There is a suggestion that the activation of NLRP3 is associated with oxidative stress (22). NLRP3, a subcellular multiprotein complex present in the central nervous system (CNS), is triggered by various internal and external stimuli. In the end, cell death is promoted by this activation, which results in the creation of IL-1β, IL-18, and caspase-1 (22).

Additionally, studies have shown that obese individuals have increased caspase activity in monocytes. Palmitate has been observed to activate caspase 4/5, resulting in the release of inflammatory cytokines. This suggests that targeting caspases could be a promising approach for reducing inflammation related to obesity (8). Furthermore, inhibiting NLRP3 with MCC950, a specific NLRP3 inhibitor, may offer protection against neuroinflammation resulting from damage to the inner ear or retina (22).

The research question posed is: "What role does the NLRP3 inflammasome play in the development and progression of type 1 *Diabetes mellitus* (T1DM), and how can it be targeted to enhance treatment approaches?" This study seeks to explore the involvement of the NLRP3 inflammasome in T1DM, with a particular emphasis on its effects on inflammation and immune response regulation. Given the rising prevalence of T1DM globally, gaining a comprehensive grasp of the factors that drive its growth is essential for the creation of successful treatment strategies.

This study aims to clarify the role of NLRP3 inflammasome activation in inflammatory processes associated with T1DM models and its potential as a therapeutic target. By analyzing research and experimental data, the study seeks to provide insights into how NLRP3 inflammasome activation connects to T1DM pathophysiology. The findings are expected to inform the development of new treatment strategies focused on reducing inflammation and preserving pancreatic beta-cell function.

Unlike previous reviews, this study systematically examines data from rodent models to explore the translational potential of targeting the NLRP3 inflammasome in T1DM. By comparing different models and treatment approaches, we aim to outline promising strategies for managing T1DM-related inflammation, offering new insights that could guide future clinical research. Rodent models play a vital role in studying T1DM due to their genetic and physiological similarities to human immune responses. They allow for controlled investigation of disease mechanisms, including inflammasome activation. However, while rodent studies provide valuable insights, these models have limitations in fully replicating human T1DM

pathology, especially regarding the complexity of immune responses and genetic diversity seen in human populations. Acknowledging these limitations is crucial as we interpret the findings and consider their applicability to human therapeutic strategies.

MATERIALS AND METHODS

This section describes the four main components used in the current research: PRISMA, resources, systematic review process, and data extraction and analysis.

Prisma

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) is a well-established protocol for systematically reviewing literature. These publication guidelines are vital for providing researchers with the necessary information to evaluate and assess the quality and comprehensiveness of a review. Additionally, PRISMA emphasizes the assessment of randomized trials in its reports, which may also serve as a foundation for presenting systematic reviews in other research fields. PRISMA is commonly employed in medical research to determine the specific criteria for including or excluding participants in a study. Furthermore, PRISMA analyses a comprehensive scientific literature collection at a specific moment, enabling a precise search for phrases related to NLRP3 inflammasome in T1DM. In addition, the utilization of PRISMA allows for the encoding of information related to forthcoming assessments of environmental management (23).

Search Strategy

The search strategy employed keywords including 'NLRP3,' 'inflammasome,' 'T1DM,' 'rat,' 'rabbit,' and 'mice,' combined to capture a broad range of studies focused on inflammasome activation in rodent models of T1DM. Databases such as Scopus, ScienceDirect, Sage Journals, Wiley Online Library, and SpringerLink were chosen due to their extensive biomedical and experimental research coverage, ensuring an inclusive search across relevant studies.

The process of systematically reviewing and selecting articles

The technique of systematically reviewing and choosing relevant publications for the present investigation involved two primary steps. The initial phase involves identifying keywords, which is then followed by looking for associated and comparable phrases using resources Open Athens, Sultan Abdul Samad Library, Universiti Putra Malaysia.

Significantly, the ongoing research project effectively obtained a combined total of 501 articles from the five databases where we found 179 instances when the searches overlapped. As mentioned before, a manual search was performed on other databases using similar terms, which yielded an additional 5 articles. A total of 506 articles were obtained during the initial phase of the systematic review procedure.

The main goal of the first screening round was to remove duplicate material. During this stage, three papers were excluded, and 327 articles were reviewed in the next phase based on specific inclusion and exclusion criteria set by the researchers. Articles were included if they investigated the role of the NLRP3 inflammasome in T1DM, were published between 2000 and 2024, and used rodent models to examine inflammasome activation. Studies were excluded if they lacked empirical data, focused solely on human models without discussing translation to animal models, or were review articles, conference proceedings, or book chapters. These criteria were applied to ensure relevance and consistency in evaluating inflammasome activity in rodent models of T1DM

Initially, the focus was on selecting journal articles, leading to the exclusion of other types of publications such as systematic reviews, reviews, meta-analyses, meta-syntheses, book series, books, book chapters, and conference proceedings. Additionally, the research was limited to publications from the past 24 years (2000 to 2024). In total, 497 publications were discarded based on these criteria.

n the third step, known as the eligibility phase, a total of 18 articles were carefully selected. During this phase, the titles, abstracts, and key content of these articles were thoroughly reviewed to confirm they met the inclusion criteria and were relevant to the study's objectives. Consequently, 97 papers were excluded from the study due to their lack of empirical data or their focus on hard sciences rather than specifically addressing the NLRP3 inflammasome in T1DM.

However, it should be noted that no database is perfect or comprehensive including five electronic databases, namely Scopus, Science Direct, Sage Journal, Wiley Online Library, and SpringerLink database through a comprehensive systematic search. This initial search was performed from 2000 till 2024. The development of keywords arose from a review of existing works of literature. The references list of the included study was vetted manually using manual searches. Each of the identified cases was thoroughly verified for the presence of the original report. Researchers should expand their search method by utilizing a greater number of databases to enhance the probability of acquiring pertinent articles.

Data extraction with analysis

This study employed an integrative review approach, which involves analyzing and synthesizing different types of research designs, including qualitative, quantitative, and mixed methods. This process can involve converting data from one form to another, such as turning qualitative data into quantitative data or the

other way around.

Data were systematically extracted into an Excel template with the following categories: study objectives, rodent models used, specific NLRP3 inflammasome components investigated, treatment approaches, main findings, and study limitations. This structured extraction method facilitated consistent data synthesis across studies, enhancing reproducibility. To systematic investigation was done before the screening procedure, and any duplicates were removed. Following the extraction of data, we conducted a thorough consistency check to rectify any observed inconsistencies..

RESULTS

Scientific publications trend

A total of 501 publications were retrieved by electronic database searches, reference searches, and examination of the reference lists of included research. Additionally, a list of the included studies was obtained using the citation tool of Google Scholar. Following the identification of duplication, publications that were found to be duplicates were excluded. After a thorough screening method, only 18 unique studies were selected. This is illustrated in Figure 1. Table I comprises observational research conducted on rats, encompassing individual investigations that investigate the role of T1DM and its

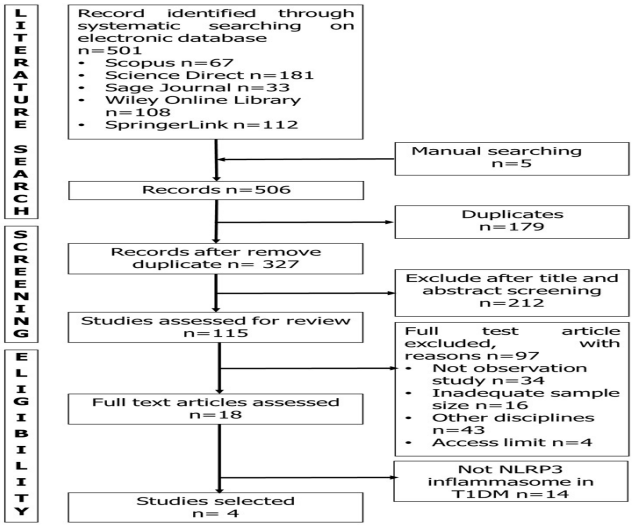

Figure 1: Flowchart depicting the selection process for the systematic review. A total of 506 records were identified through database and manual searches, with 327 records remaining after duplicates were removed. Following title and abstract screening, 115 studies were assessed, resulting in 18 full-text articles reviewed. After exclusion criteria were applied, 4 studies were selected for final analysis.

Table I: Summary of Studies Investigating the Role of the NLRP3 Inflammasome in T1DM.

Author (s)	Study objective	Rodents	NLRP3 Inflammasome	Treatment	Findings	Limitations
Huawei Liu et al. (2017) (24)	1. To investigate the signaling pathways of NLRP3 and NLRP1 inflammasomes in the progression of T1DM. 2. To assess the levels of NLRP3, NLRP1, caspase-1, and IL-1β expression in peripheral blood mononuclear cells (PBMCs) and granulocytes (GCs) of patients with T1DM.	Mice	NLRP3, NLRP1, Caspase-1, IL-1β	IRAK-M$^{-/-}$	1. The expression of IL-1β mRNA showed a favourable correlation with levels of NLRP3, NLRP1, and Caspase-1. 2. In STZ-treated NOD mice, IRAK-M deficiency accelerates the development of T1DM.	1. This work does not discuss future research on the involvement of the NLRP3 and NLRP1 inflammasome signaling pathways in the advancement of autoimmunity, which might improve our understanding of the development of T1DM.
Xiaohan Wu et al (2019) (25)	1. To determine the impact of NLRP3 inflammasome on the development of atrial remodeling and atrial fibrillation (AF) caused by diabetes mellitus (DM). 2. To investigate if the use of an NLRP3 inflammasome inhibitor, GLB, may mitigate these effects.	Rabbits	NLRP3 Gal-3, TGF-β1, IL-1β, IL-18	Glibenclamide (GLB)	1. GLB demonstrated anti-atrial and antiarrhythmic effects without impacting blood glucose and insulin levels. 2. The levels of NLRP3 protein and the activity of caspase-1 enzyme were considerably higher in the DM group compared to the control group. However, GLB treatment reduced these levels. 3. The activity of the NLRP3 inflammasome was increased in the atrial cardiomyocytes of diabetic rabbits and showed clear evidence of left atrial fibrosis, although GLB successfully mitigated the observed alterations. 4. The DM group showed a larger occurrence of AF along with longer IACT and AERPD, which was reduced by treatment with GLB.	1. The trials did not investigate the impact of RA remodeling on AF, nor did we analyze electrophysiological processes at the cellular level. 2. There is a dearth of data about atrial ionic channel activity. The study did not examine the association between various doses and the impact of GLB. Ultimately, a particular modification of the NLRP3 model in the atria, would be ideal for demonstrating the activation of NLRP3 that contributes to the development of atrial fibrillation (AF). Further research is required for future investigation.

CONTINUE

Table I: Summary of Studies Investigating the Role of the NLRP3 Inflammasome in T1DM. (CONT.)

Author (s)	Study objective	Rodents	NLRP3 Inflammasome	Treatment	Findings	Limitations
Hao Li et al (2019) (26)	To examine the impact of inhibiting the NLRP3 inflammasome using a lentiviral short hairpin RNA (shRNA) that targets NLRP3 on the repair of alveolar bone defects in diabetic rats.	Rats	NLRP3	shRNA lentivector treatment	1. To indicate that suppressing the NLRP3 inflammasome might enhance the repair of alveolar bone defects in diabetic rats. 2. The positive impact may be associated with a decrease in the production of proinflammatory cytokines and an increase in the expression of genes related to bone formation in individuals with high blood sugar levels.	
Rebecca Ward et al (2019) (27)	To identify the function of NLRP3 activation in diabetes situations regarding vasotrophic (un)coupling following hypoxic insult to neurons and endothelial cells.	Rats	NLRP3	MCC950	1. Inhibiting NLRP3 with MCC950 improves neurovascular remodeling, cognitive function, and mortality in diabetic rats. 2. Inflammasome NLRP3 is upregulated in the hippocampus after diabetes and stroke.	1. Further investigations are required to determine the potential benefits of administering MCC950 therapy to these particular individuals rather than the therapeutic approach for treating cognitive impairment in individuals with diabetes and stroke.

relationship to the NLRP3.
The study was classified using meta-analysis and systematic review as the levels of evidence, with each classification being based on the year of publication in increasing order. All selected articles were categorized in the "included" section. Although a few components lacked ratings, such as adverse effects identification and demographic information reporting from clinical presentation sites, most of the articles included explicit clinical information, demographic characteristics, comparable exposures for patients and controls, and satisfactory statistical analysis. This suggests that the literature is of high quality.

The study revealed that the NLRP3 and NLRP1 inflammasome signaling pathways are linked to the onset and progression of T1DM, acting as protective factors during the early stages of the disease. Furthermore, the data supporting the validity of the NLRP3, including its reliability and relationships with other variables, has not been showing. Therefore, more research was necessary to get longitudinal measurements of the NLRP3 inflammasome to validate the results.

Furthermore, four studies were identified (24-27). To investigate the signaling pathways of NLRP3 inflammasomes in the progression of T1DM, and to assess the levels of NLRP3, NLRP1, caspase-1, and IL-1β expression pathways.

Investigation findings
Additionally, NLRP3 and NLRP1 were notably reduced in T1DM patients experiencing diabetic ketoacidosis (DKA) compared to those without DKA who were under normal management. Later, a positive correlation was observed between the expression levels of IL-1β mRNA and the levels of NLRP3, NLRP1, and Caspase-1 (27). Furthermore, in vitro expression of caspase-1 and IL-1β decreased with downregulation of NLRP3/NLRP1 but increased with overexpression of NLRP3/NLRP1. Impaired glucose tolerance and an early and fast onset of T1DM were features of the IRAK-M/NOD mice. Compared to IRAK-M+/+NOD mice, the pancreas and lymph nodes of IRAK-M/NOD mice exhibited significantly higher mRNA expression levels of NLRP3, NLRP1, Caspase-1, and IL-1β (27).

This research indicates that in our trials using type 1 diabetes animals, GLB demonstrated anti-atrial remodeling and antiarrhythmic effects, while having no impact on blood glucose and insulin levels (26). The activity of the NLRP3 inflammasome was elevated in the atrial cardiomyocytes of diabetic rabbits. Additionally, the researcher noted the occurrence of left atrial fibrosis in the diabetic group, but found that GLB significantly reduced these changes. In the DM group, a greater occurrence of AF was seen along with prolonged IACT and AERPD. However, treatment with GLB resulted in a decrease in AF incidence. Furthermore, the levels of left atrial proteins such as Gal-3, TGF-β1, serum IL-1β, and IL-18 were increased in diabetic animals, but GLB was able to lower these levels. (26).

Observations of alveolar bone healing following NLRP3 RNAi revealed that rats with diabetes had decreased healing of alveolar bone defects, as evidenced by less new bone production in the defect location compared to normal healing (25). The findings suggest that there is increased activation of the NLRP3 inflammasome and generation of IL1β in the alveolar bone defect in the presence of diabetes. However, this effect may be suppressed by administering shRNAs that specifically target NLRP3 (25). Impact of NLRP3 RNA interference on factors associated with bone formation Phrase

RUNX2 and OCN are recognized as significant genes that indicate the formation of bone tissue. Therefore, we examined their expression in the region of the alveolar bone defect in rats using qRT-PCR and western blot analysis (25).

The research findings indicate that diabetes increases NLRP3 inflammasome activation, a process that is further exacerbated by stroke. Additionally, MCC950, an NLRP3 inhibitor, improves survival, cognitive function, and vascular integrity in diabetic animals after a stroke (24). It also raises BDNF levels in hippocampal neurons, especially following hypoxic injury, though it does not enhance reduced endothelial BDNF levels in diabetic conditions. This study is the first to suggest that MCC950 could be used as a therapeutic option to prevent neurovascular remodeling and reduce cognitive decline in diabetic patients after a stroke (24).

DISCUSSION

In this study, we investigated the complex relationship between the NLRP3 inflammasome and the development of T1DM. Our results support previous research showing that the NLRP3 inflammasome is crucial in regulating the inflammatory responses linked to T1DM [7, 8]. By analyzing various animal models and clinical studies, we have demonstrated a consistent upregulation of NLRP3 inflammasome activity in T1DM subjects, suggesting its involvement in disease progression [14]. This observation aligns with the notion that dysregulated immune responses contribute to the destruction of pancreatic beta cells, leading to insulin deficiency characteristic of T1DM [15].

Furthermore, our study sheds light on the potential therapeutic implications of targeting the NLRP3 inflammasome in T1DM management. The administration of NLRP3 inhibitors, such as MCC950, demonstrated promising outcomes in mitigating neurovascular remodeling, improving cognitive function, and enhancing survival rates in diabetic animals following stroke [16]. These findings underscore the therapeutic potential of modulating NLRP3 inflammasome activity to attenuate inflammatory processes associated with T1DM complications, thereby improving patient outcomes and quality of life [17].

Moreover, our investigation into the effects of NLRP3 inhibition on alveolar bone healing in diabetic rats provides valuable insights into the role of the inflammasome in tissue repair and regeneration [19]. The observed enhancement of bone formation and reduction of inflammatory cytokine production following NLRP3 inhibition suggest a potential avenue for therapeutic intervention in diabetic bone disorders [20]. These findings highlight the multifaceted impact of NLRP3 inflammasome activation on various organ systems beyond the pancreas, underscoring its relevance in the context of T1DM complications.

Differences in inflammasome activation and outcomes across rodent studies may stem from species- and strain-specific immune characteristics. For example, certain rodent strains exhibit heightened immune responses or differing susceptibilities to pancreatic inflammation, which could influence NLRP3 activity and the overall inflammatory response. Understanding these variations is essential for interpreting findings and assessing translational relevance to human T1DM.

Although our study offers valuable insights, several limitations should be acknowledged. First, most of the evidence is derived from animal models, which may not completely reflect the complexity of human T1DM pathology. While these models provide important information about disease mechanisms, applying these findings to clinical practice should be done with caution. Second, our analysis mainly concentrated on the role of the NLRP3 inflammasome in T1DM development, potentially neglecting the contributions of other inflammasome complexes and inflammatory pathways. Lastly, the heterogeneity across included studies, such as differences in rodent models, methodologies, and outcome measures, which may affect comparability. Additionally, publication bias may be present, as studies with positive or significant findings are more likely to be published, potentially skewing our understanding of NLRP3's role in T1DM.

Future studies should aim to comprehensively explore the interplay between different inflammasomes and cytokine cascades in T1DM development and progression. Additionally, the heterogeneity of T1DM phenotypes and the influence of confounding variables such as age, genetic predisposition, and environmental factors pose challenges to data interpretation and generalization. Future research could explore the roles of other inflammasomes, such as AIM2 or NLRP1, in T1DM to understand their contributions to disease pathogenesis. Additionally, investigating related inflammatory pathways or cytokines could provide a more comprehensive picture of the immune dysregulation in T1DM and identify alternative therapeutic targets. Addressing these limitations through well-designed clinical studies with large sample sizes and rigorous methodology will be essential for advancing our understanding of T1DM pathophysiology and developing targeted therapeutic interventions.

CONCLUSION

In conclusion, our study adds to the expanding evidence linking the NLRP3 inflammasome to the development and complications of T1DM. By clarifying the inflammasome's role in regulating inflammatory responses and tissue damage related to T1DM, our findings lay the groundwork for developing targeted treatments that aim to modulate inflammasome activity

and improve patient outcomes. Continued research in this field holds promise for deepening our understanding of T1DM pathogenesis and uncovering new approaches for managing and preventing the disease. This research on targeting the NLRP3 inflammasome could indirectly benefit insulin production strategies by highlighting mechanisms that may alleviate the inflammatory destruction of pancreatic β-cells in T1DM. By potentially preserving endogenous insulin production, this approach could reduce dependence on synthetic insulin and contribute to more cost-effective diabetes management, a pressing need given the rising cost of insulin globally. While targeting the NLRP3 inflammasome shows promise, it is essential to consider the potential for unintended consequences, such as promoting malignancy or impacting hereditary diabetes susceptibility. Further research should closely monitor any adverse effects, ensuring therapeutic interventions are safe and mitigate rather than exacerbate long-term health risks.

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