NLRP3 Inflammasome Role in Type 1 Diabetes

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Abstract:
"Diabetes mellitus type 1 is an autoimmune disease which is characterized by the destruction of the pancreatic beta cells that produce insulin by immune cells T lymphocytes and macrophages that invading the islets of Langerhans". A polyprotein called NLRP3 contributes significantly to the inflammation process in the body. Complex protein known as the nucleotide-binding domain, leucine-rich containing family, pyrin domain containing-3 inflammasome that is very important to the process of inflammation. It is made up of the proteins Procaspase-1, NLRP3, and ASC, and its function is to identify pathogens. When a cell is presented with a pathogen-associated molecular pattern, further recognized as a PAMP, or a damage-associated molecular pattern, further recognized as a DAMP, the cell's immune response is triggered (DAMP), the NLRP3 inflammasome is triggered. Caspase-1, when activated, catalysis the conversion of inactive forms of pro-inflammatory cytokines and interleukins (IL-1 and IL-18) into their active metabolic forms, which in turn promotes inflammation. The pathophysiology of type 1 diabetes is affected by the involvement of the NLRP3 inflammasome and also NLRP3 is associated with vast scope of inflammation and immunological conditions. Once immune cells employ Toll-like receptors (TLRs) to identify particular pathogens or endogenous alarm signals, IL-1b is generated as a first-stage indicator of illness. One of the distinguishing features of type 1 diabetes is that auto-reactive T lymphocytes are the cause of the beta cells found in the pancreas that are responsible for insulin production being destroyed. Also, IL-1beta kills beta-cells directly and sends out an inflammatory signal during the disease's initial phases. Those who have just been diagnosed with diabetes mellitus or who have been living with the condition for a long time have increased levels of IL-1b, although treatment may bring these levels down. Moreover, the decreased expression of IL-1RA in islets from donors who did not have diabetes who were subjected to sera from type 1 diabetes patients causes beta-cells that produce insulin to become dysfunctional and eventually die. This further increases the creation of IL-1 beta, which is harmful to beta-cells.

Keywords: NLRP3, inflammasome, IL-1β, T1DM.

Introduction

between 5 and 10 percent of all instances of diabetes are "Type 1 diabetes mellitus (T1DM), which is characterized by severe autoimmune destruction of insulin-producing beta-cells in

the pancreas by T lymphocytes and macrophages invading the islets of Langerhans" [1]. Data suggests that T1DM start and progression are significantly influenced by innate immune system elements, which are predominantly controlled by Toll-like receptors (TLRs) [2]. An initial biomarker of the disease that may aid the beginning of the process and evolution of type 1 diabetes, interleukin-1b (IL-1b, produced by the IL-1B gene), is produced as a result of immune cells' ability to identify particular pathogens or endogenous warning signals through TLRs. This results in the induction of interleukin-1b expression. [2]. The elimination of cells in the pancreas that produce insulin beta cells by auto reactive T lymphocytes is one of the defining characteristics of type 1 diabetes, often known as T1DM. [3]. The specific underlying mechanisms of insulin-dependent diabetes mellitus are not completely understood, it is believed that the pathophysiological process of the disease is influenced by a combination of environmental and hereditary variables. [4-6]. The onset of insulin-dependent diabetes mellitus is affected by both innate and adaptive immunity (7-9). As opposed to adaptive immunity, innate immunity is a generally conserved immunological response that serves as the first layer of protection against an invasion from the outside by microorganisms like bacteria, viruses, and fungus [10, 11]. Previous research has established that the innate immune system is the primary initiator of innate inflammation reactions following stimulation by either external or internal factors, and that it subsequently goes on to stimulate the adaptive immune system through highly conserved "PRRs (pattern-recognition receptors)". When innate sensors detect distinct "PAMPs (pathogen-associated molecular patterns) or DAMPs (damage-associated molecular patterns)", cells of the body's innate immune system set off a cascade of inflammation reactions. [12]. The NLRP3 inflammasome is a polyprotein structure that has a relative molecular mass of which would be around 700,000 Da and performs an indispensable function in the establishment of inflammatory reactions [13]. Procaspase-1, NLRP3, & "ASC (apoptosis-associated speck-like protein with a caspase recruitment domain)" make up the NLRP3 inflammasome [14,15].

NLRP3 INFLAMMASOME COMPONENTS

Procaspase-1, ASC, and NLRP3 are all components within the protein structure known as the NLRP3 inflammasome [16]. The "NLR (Nod like-receptor)" is a family of protein, which includes the member NLRP3, is extensively expressed in dendritic cells, monocytes, and macrophages and is responsible for identifying pathogens. At its C-terminus, NLRP3 has a recognizable "LRR (leucine-rich repeat)" domain found in NLR protein family [17]. Nucleotide-binding domain, commonly referred to as NOD or NACHT, refers to the central portion of NLRP3. The NBD is an NTPase superfamily member that hydrolyzes ATP into GTP. The PYD (pyrin domain), also known as "CARD (caspase recruitment domain) or BIR (baculovirus IAP repeat)" domain, can engage in a variety of inflammatory reactions by attaching to molecules that have identical domain. Consider, for example, the following: the PYD-PYD interaction is used to bind ASC. The NLRP3 inflammasome's adaptor protein is called ASC. ASC has a PYD domain at its N-terminus that is identical to PYD domain in NLRP3, and it has a CARD recruitment domain at its C-terminus that is identical to the CARD domain in procaspase-1. As a consequence, ACS is an adaptor protein with two distinct domains. that interacts to NLRP3 and procaspase-1 via interactions between the PYD-PYD and CARD-CARD domains. The NLRP3 inflammasome effector protein.

identified as Cas-1, cleaves pro-IL-1β and pro-IL-18, which are pro-inflammatory cytokines, into activated versions, IL-1β and IL-18. [18,19]. These cytokines are responsible for inflammation not only because they performs an indispensable function in recruitment and activation more immune cells, but also because they stimulate the production of growth factors, chemokines, and other proinflammatory cytokines (Figure 1). Researchers have discovered a connection between inflammation factors, including the NLRP3 inflammasome, and autoimmunity disorders [20,21].

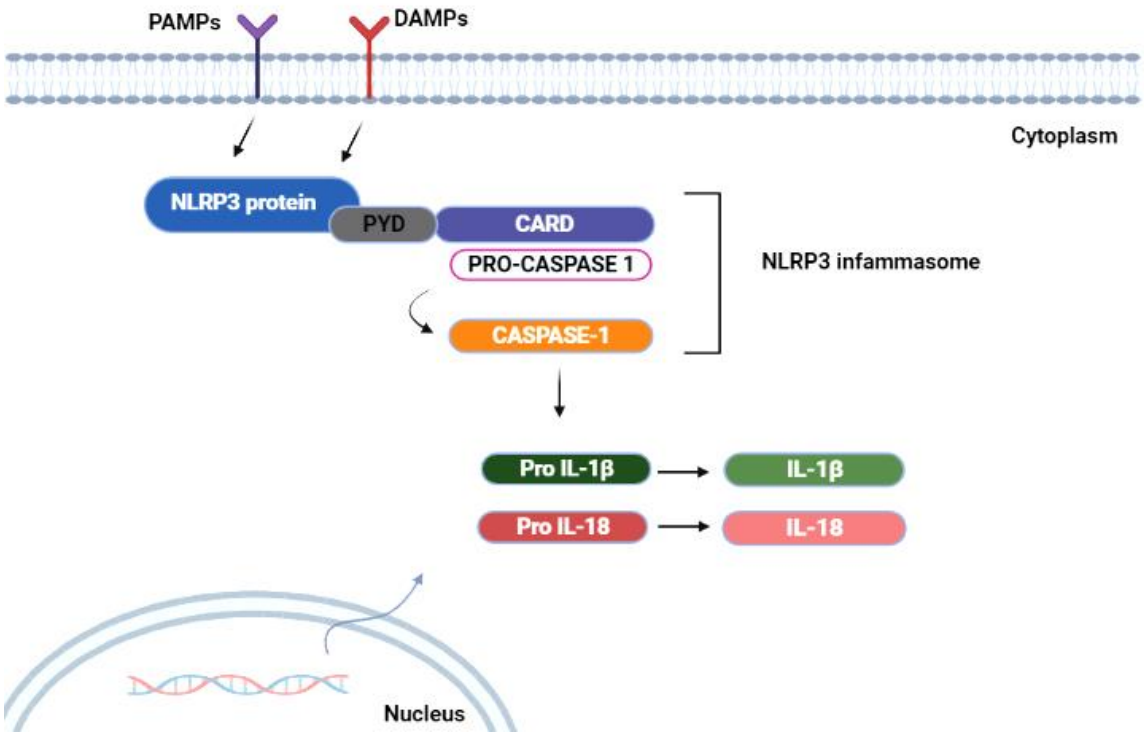

Figure 1: the composition and organization of the NLRP3 inflammasome.

There are three primary constituents that make up the NLRP3 inflammasome.: the "NLRP3 sensor protein, the adaptor protein apoptosis-associated speck-like protein (ASC), and the effector protein caspase-1". NLRP3 activation happen when the cell exposure to PAMPs or DAMPs. When NLRP3 activated, it will interact with ASC via the PYD domain, while pro-caspase-1 binds to ASC through the CARD domain, and they will lead to formation of a large cytosolic complex that ultimately leads to Cas-1 activation. The activated caspase-1 responsible for cleaving the inactive forms of the pro-inflammatory cytokine's interleukins (IL-1β and IL-18) into their biologically active forms, thus promoting inflammation.

The NLRP3 inflammasome is performs an indispensable function into the response of inflammation that is linked to a number of different diseases, one of which is diabetes type 1. In the initiation of NLRP3 inflammasome activation, the assembling of NLRP3 with the adaptor protein ASC and procaspase-1 facilitates the auto-cleavage and maturation of procaspase-1. The activation of caspase-1, which occurs thereafter, inevitably results in a cleavage of pro-IL-1 to produce mature IL-1, a cytokine that attracts other inflammation cells, and it has a deleterious impact on them directly. In addition, the activation of the NLRP3 inflammasome is associated with pyroptosis, a type of programmed cell death that

occurs when a cell is exposed to pathological stimuli. In particular, activation of the NLRP3 inflammasome in pancreatic beta cells can cause the release of IL-1, which can lead to cellular deterioration of β cells and, as a result, the development of type-1 diabetes. In addition to this, the activation of the NLRP3 inflammasome can cause pyroptosis, which can further contribute to the inflammatory response [22,23].

NLRP3 inflammasome activation and regulation:

Within the framework of the NLRP3 inflammasome being activated, the direct binding of various stimuli is unlikely given the structural and chemical dissimilarities amongst the stimuli that have the capability of activating the inflammasome response. According to prevailing thought, the NLRP3 protein recognizes and responds to a shared cellular event that is initiated by diverse stimuli. Despite this, there is no clear consensus on the precise nature of this cellular event. Presently, a widely accepted two-signal model has been put forth in the literature, which posits that the stimulation of the NLRP3 inflammasome needs 2 distinct signals in order to take place. The initial stimulus is triggered by an endogenous or exogenous stimulus triggers the production of NLRP3 and a priming signal. The subsequent activation signal is triggered by another stimulus that initiates the assembly of the NLRP3 inflammasome, which led to the activation of Cas-1, subsequent IL-1β and IL-18 maturation [24].

PRR stimulation by PAMPs or DAMPs sets off the gathering of the components of inflammasome components in the cytosol. The process of activating inflammasomes involves a two-step process. where the first signal, the priming signal, up regulates the expression of inflammasome components and PRRs. This priming step is essential for the inflammasome to respond to the second signal that triggers the formation of inflammasome. Upon recognition of these signals, the NLRP3 inflammasome is formed., resulting in the oligomerization and recruitment of adaptor molecule "apoptosis-associated speck-like protein containing a CARD (ASC)" and procaspase-1. The subsequent auto cleavage and maturation of procaspase-1 lead to the activation of cas-1. Active cas-1 then cleaves the precursor form of pro-inflammatory cytokine pro-IL-1β into mature IL-1β, which is then released to recruit and activate other immune cells and exert direct cytotoxic effects. The exact mechanism of how NLRP3 senses these various stimuli and triggers the inflammasome assembly is still under investigation, but it is believed that NLRP3 recognizes a standard biological response to its triggers [25-27] (**figure2**).

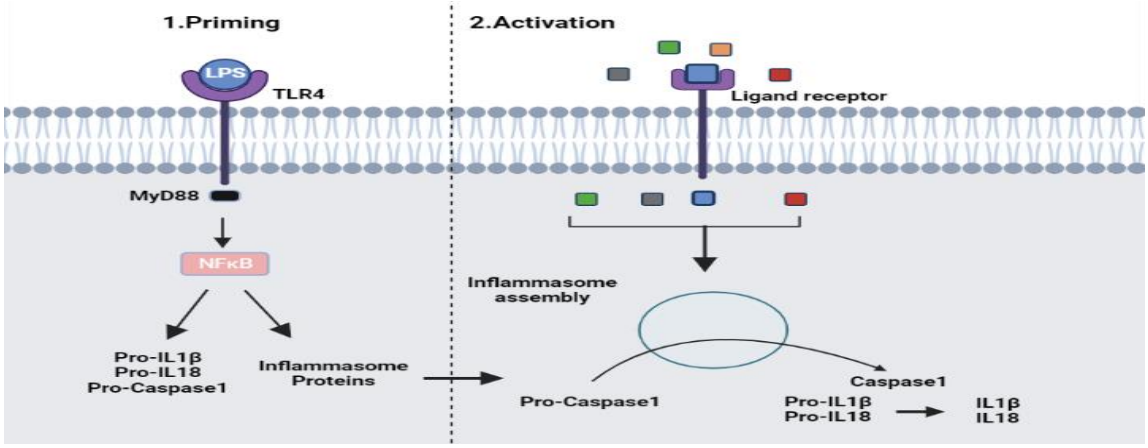

Figure 2: Inflammasome priming and activation Inflammasome.

After PAMP and DAMP ligands have been recognized according to the receptors that are specific to each, such as bacterial Lipopolysaccharides (LPS) recognition by TLR4 pathogen-associated molecular patterns, inflammasome-related genes, such as NLRP3, NLRC4, are transcribed. This "priming" process warns cells about prospective threats and prepares the inflammasome machinery for translation. As further activating signals are recognized, the inflammasome proteins oligomerizes and form a wheel/disk-like shape. The development of these inflammasome complexes allows caspase 1 to be activated from its precursor form, which then activates additional cytokines such as IL-1 β and IL-18. Other caspases, including as Cas 4, 5, 8, and 11, may be activated by inflammasome-associated proteins [28,29].
Inflammation and immunological responses are both mediated by IL-1, which is performs an indispensable function of the host's immune response to a broad diversity of pathogens. On the other hand, an excess of IL-1 production results in persistent inflammation and performs an indispensable function in the development of a broad assortment of inflammatory and autoimmune illnesses [30].

INFLAMMATION OF THE NLPR3 AND TYPE 1 DIABETES:

T1DM is a metabolic condition wherein the body does not have insulin available to control the blood glucose levels. and resulting hyperglycemia as a result of an autoimmune response. Autologous T lymphocytes infiltrate pancreatic islets, causing insulitis and β cell death [31]. In addition to the immune system's adaptive mechanisms, researchers have found that innate immunity also plays a significant role in the pathophysiology of type 1 diabetes. Increasing evidence suggests that the NLRP3 inflammasome and its downstream cytokines, particularly interleukin-1beta, play a crucial role in the pathogenesis of inflammatory diseases, and also responsible for the progression of this disease. Remarkably important element is the NLRP3 inflammasome, which is a multi-protein complex, and it is a part of the innate defense system. It recognizes pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). (DAMPs). The inflammasome, once triggered, holds the responsibility for the development and secretion of pro-inflammatory cytokines, including IL-1b, which is an essential component of the inflammatory reaction. [32,33].
One of the most important contributors cause the onset of diabetic complications of type 1 diabetes is the cytokine IL-1β. It not only attracts proinflammatory cells to the pancreatic islets but also contributes to beta-cell apoptosis through the mediation of cytokines. Moreover, β-cells are particularly susceptible to the deleterious impacts of IL-1β. Furthermore, it acts as an inflammatory signal in the initial stages of type 1 diabetes, which underscores its involvement in the development of the disease [35,36,37]. Higher amounts of IL-1β are found in people with a recent diagnosis of type 1 diabetes as well as people who have had the condition of chronic diabetes mellitus when compared to healthy controls. Nevertheless, IL-1b levels in newly diagnosed type 1 diabetes patients are reduced following therapy [38-40]. Additionally, it has been observed that the expression of "Interleukin-1 receptor antagonist (IL-1RA)" is decreased in islets acquired from non-diabetic donors after they have been subjected to plasma from individuals who have type 1 diabetes. IL-1RA performs an essential function in inhibiting the communication mechanism from working and preventing the interaction between IL-1b and its receptor. The diminished expression of IL-

1RA not only cause beta-cells that produce insulin to become dysfunctional and eventually die, but it also promotes IL-1 β production, which further damages beta-cells [41].
In addition, NOD mice who were pretreated with IL-1RA had lower levels of chemically-induced hyperglycemia, but they did not show any reduction in islet inflammation [42]. On the basis of these results, new therapy techniques that attempt to make the IL-1b activity suppression and have been created to cure or alleviate autoimmune disorders. Some examples of these novel treatment tactics are synthetic IL-1RA and IL-1b traps. In point of fact, following therapy with IL-1RA, individuals with type 1 diabetes had lower insulin needs while maintaining comparable levels of hemoglobin A1c [34,43].
Despite this, there are still certain inconsistencies that need to be resolved. Animal tests using NOD caspase-1.˙/˙ mice demonstrated lower levels of the inflammatory cytokine IL-1, but the incidence of diabetes and susceptibility to streptozotocin remained the same when compared to wild-type NOD mouse models [44]. NOD mice may not necessarily need caspase-1-mediated IL-1b production to develop diabetes. At the very least, this is not required. In vivo experiment conducted on non-obese diabetic (NOD) mice showed that CD4 C T cell-mediated beta-cell death and diabetes were not dependent on the activity of IL-1 and IL-18 [45].
In the NOD mouse model, the NLRP3 inflammasome is essential to the progression of autoimmune diabetes. The development of T1D was postponed and reduced through either the elimination of NLRP3 genes through genetic modification or the administration of NLRP3 inhibitor drugs, and the movement of diabetogenic cells into pancreatic islets was hindered. The IRF1 signaling pathway is probably involved in the down-regulation of chemokine-related gene expression in non-hematopoietic cells caused by NLRP3/ NOD. Recent research showing milder EAE through the decrease in IFN-expressing T helper cells is consistent with NLRP3 deficiency suppressing Th1 responses. T lymphocytes enter pancreatic islets, specific chemokine expression in the islets is necessary. Pancreatic islet cells in both humans and rodents express many chemokine genes, such as CCL2, CCL3, CCL5, and CXCL10. The expression of these chemokines, as well as that of CCL5 and CXCR3, was significantly down-regulated in NOD islets that lack NLRP3, though. This suggests that chemokine gene expression is down regulated and insulitis is decreased as a result of genetic NLRP3 ablation. The lack of IL-1 production and suppressed Th1 responses are likely to be the causes of the down-regulation in NLRP3/ NOD islets [46].

Conclusion:
The NLRP3 inflammasome has been discovered to be correlated, according to the findings of researchers in a number of type 1 diabetes-related processes, such as the migration of pro-inflammatory cells to the pancreatic islets, cytokine-induced β –cell cell death, direct cytotoxic effects on β –, and pyroptosis, that is a specific kind of programmed cell death. The connection between IL-1b and its receptor has been established as a direct causal factor in the progression of type 1 diabetes. In the islets of non-diabetic donors who were exposed to the sera of type 1 diabetes patients, lower levels of the protein called as interleukin-1 receptor antagonist (IL-1RA) were discovered. IL-1RA is an inhibitor of the interaction between IL-1b and its receptor. When IL-1RA is not expressed as much, β –cells that make insulin don't work as well and don't live as long. It also makes more IL-1b, which affects beta-cells even

more. In animal models, there is a correlated relationship between the NLRP3 inflammasome and the onset of type 1 diabetes. For instance, a study with NOD mice showed that IL-1 and IL-18 have nothing to do with the death of beta cells and diabetes caused by CD4+ T cells. Together, these results show how important the innate immune system and the NLRP3 inflammasome are in how type 1 diabetes develops.

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