ejpmr, 2024, 11(1), 435-446

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ROLE OF INFLAMMASOMES IN DIABETES MELLITUS

Himani Dhiman*, Dr. Disha Arora, Dr. Asha Gandhi, Simrata Kaur and Abhishek Yadav

Sri Sukhmani Institute of Pharmacy, Derabassi, SAS Nagar, Mohali, Punjab, India.

***Corresponding Author: Himani Dhiman**

Sri Sukhmani Institute of Pharmacy, Derabassi, SAS Nagar, Mohali, Punjab, India.

Article Received on 20/11/2023 **Article Revised on 10/11/2023** **Article Accepted on 31/12/2023**

ABSTRACT

Inflammasomes are protein complex (multimeric protein complex) oligomers found within the cytoplasm that generate the inflammatory responses within body's innate system. The Nod-like receptor protein 3 is a multimeric complex that found within the cells. They determine the hazard signals and persuade the active caspase-1 to form, as well because of the maturation and unharness of cytokines together with Interleukin-33, Interleukin-18, and Interleukin-1B. Diabetes causes a inferior chronic inflammatory state, that is important for the development of complications. Reactive oxygen organisms, glyco/lipoxidation end products, and cholesterol crystals have all been attributed to DM-related metabolic factors. These metabolic factors are also well-known danger signs that have the potential to regulate the activity of inflammasomes. The intracellular sensing element senses a range of microbic motifs, foreign substance, and set off the expansion and stimulation of Nod like receptors inflammasomes mediators. In this review article, we understand the mechanism of inflammazsomes and its mediators how they cause diabetes.

KEYWORDS: Diabetes mellitus; inflammasomes; interleukins; multimeric protein complex; Nod-like receptor 3 (NLRP3).

INTRODUCTION

India has 77 Million diabetics, making it the world's second-largest country after China, the worldwide range of diabetic patients is predicted to achieve 463 Million by 2020, including 88 million people in Southeast Asia. Diabetes is liable for 1.6 Million deaths worldwide each year.[1] Type 2 Diabetes mellitus is most commonest disorder in all over the world, characterized by when our pancreas is unable to produce enough insulin, there are many factors that may increase the risk of type 2 diabetes i.e Family history, being overweight, inactivity.[2] Most diabetic patients are asymptomatic in the beginning of the disorder, particularly those with type 2 diabetes; however, those with severe high level of glucose and sugar in the blood, and can experience abnormal production of large volume of dilute urine, excess thirst, excess eating, and lack of sharpness of vision.[3] T2DM is also a hidden illness that affects people all over the globe. T1DM, on the other hand, is caused by autoimmune-mediated beta cell death. The islet auto-antibodies are not present in the Type 2 Diabetes mellitus and its normally used in the diagnosis of children.[4-5] Interleukin (IL)-1 has been identified as an important factor in inflammatory mediators that begins and sustains organ pathology in DM.[6] Inflammasomes play a vital role in progression of DM, as they act as loading tools for IL-1B and IL-18. In this article, the role of inflammasomes in the occurrence of DM is described in detail.

Diabetes Mellitus

It is associated with endocrine disorder in which our body is not able to produce enough insulin which is governed by defect in hypoglycaemic agent secretion, hypoglycaemic agent action, or both.[7] Because of the low secretion of insulin and resistance of insulin most tissues, largely fatty tissues and skeletal muscles, receptors present in the pancreas, enzymes, genes are liable for metabolic disease.[8-9] If diabetes is not controlled and not treated, it can cause numbness, insensibility, coma & death either from diabetic acidosis or less commonly nonketotic hyperosmolar hyperglycemic syndrome (HHS).[10] Even though diabetes classification is important because it helps us to know which medications we need to administer, it would be not an easy process although most persons, particularly teenagers, would not comfortably fit into a single class.[11-12] Even after the lack of consistency in clinical trials involving antioxidant properties in diabetic management, the consequences of enhanced reactive oxygen species, insulin resistance, and many endocrine stimuli in the progression, pathogenicity, and associated complications of diabetes mellitus.[13]

Type - 1 Diabetes Mellitus

This type-1 DM occurs due to the destruction of Pancreatic Beta-celll, which affects 5% to 10% of the population. Type 1 diabetes is responsible for 80% to 90% of this type of disease in kids and adolescents.[14] In 2013, 497100 children under the age of 14 were identified with type 1 diabetes globally[15], and in 2019 (age less than 24), the amount of newely diagnosed cases was 210,000.[16-17] Type 1 diabetes is characterized by a T-cell-mediated immune response (insulitis) and also a humoral (B cell) response.[18] Aside from the fact that the purpose of certain antibodies in the spread of the disease pathophysiology is mysterious, auto-antibodies against pancreatic islet cells are indeed a trademark of t1dm.[19-20] Islet cell auto-antibodies, as well as auto-antibodies to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), protein tyrosine phosphatase (IA2 and IA2), and zinc transporter protein (ZnT8A) are among these auto-antibodies.[21-22] Type 1 diabetes is characterised by pancreatic auto-antibodies, which can be detected in the serum of patients months or years before the onset of the disease.[23] The absence of insulin secretion characterises this autoimmune type 1 diabetes, which is more prevalent in children and adolescents.[24-25] In addition to genetic predisposition, many environmental factors have been linked to the development of type 1 diabetes.[26] Polydipsia, polyuria, enuresis, lack of stamina, severe tiredness, polyphagia, rapid weight loss, slow-healing wounds, frequent infections, and blurred vision are some of the signs of type 1 diabetes in children and adolescents with extreme dehydration and diabetic ketoacidosis.[27] Other autoimmune diseases such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anaemia are common among these autoimmune type 1 diabetes patients.[28]

Type 2 Diabetes mellitus

Type 2 diabetes mellitus is accompanied by insulin resistance that can also be followed by a reduction in insulin production.[29] The insulin receptors are thought to be involved in the impaired insulin response of body tissues. The particular flaws are unknown. Type 2 DM is caused mostly by heredity and cultural factors.[30,31] Overweight, reduced activity, bad nutrition, tension, and urbanism are all recognized to play a role in the formation of the disease.

Inflammasomes

Inflammasomes are cellular mechanisms which are activated by cell invasion and allow pro - inflammatory cytokines such as interleukin-1b to develop, allowing immune system responses to be activated. Inflammasomes sensors are hazard proteins found within cells in the body.[32] This inactive protein identifies when cell are damaged or contaminated with microbes. When such proteins are activated by hazard stimuli they begin to emerge inflammasomes. A type of molecular cutter is triggered once inflammasomes are assembled. Another dormant protein is triggered by plucking and punching loops in the cells membranes, while the other latent proteins are triggered by cutting and emitted by the cell to attract inflammatory cells and trigger inflammation.[33] Inflammasomes are multiprotein oligomers that have been located in the immune system's cytoplasm and are responsible for establishing immune reactions.[34] The initiation and configuration of the inflammasome aids proteases action. Among the most essential complex implicated in all of these mechanisms is the inflammasome, which was first discovered by Martinon in 2002.[35] Pro-caspase-1 is recruited to the inflammasome through Apoptosis Associated Speck - like proteins contain a carboxy terminal leucine rich repeat domain, which then scatters Prointerleukin-1L & 18 in to matured interleukin IB & 18.[36] By creating holes in the cell membrane, the inflammasome further facilitates pyroptosis, an inflammatory form of apoptosis controlled via n-terminal region for Gasdermin D.[37] Just an even some of the inflammasomes found so far include Nod like receptor protein – 3 & 1, Nod likr receptor Caspase - 4.

The Nod like receptor protein-3 Inflammasomes is made up of the sensing molecules NLRP3, the associated speck like caspase & Procaspase-1.[38] Nod like structure protein-3 seems to have a Pyrin Domain. Associated speck like caspase proteins also have Pyrin Domain and Carboxy terminal leucine rich repeat domain regions. When Nod like receptor protein-3 is activated, it associates with ASC via PYD, and ASC's CARD domains integrate the CARD domains of pro-caspase-1, forming the NLRP3–ASC–pro-caspase-1 system, also recognized as the NLRP3 inflammasome.[39] The pyrin domain (PYD) is found inside the NLRP3 protein, and the ASC protein also has PYD and CARD regions. When NLRP3 is triggered, it interfaces with ASC through PYD, and ASC's CARD region integrates pro-CARD caspase-1 region, establishing the NLRP3–ASC–pro-caspase-1 system, also recognized as the Inflammasome.[40] Infectious disease with harmful bacteria including Salmonella, Shigella, and Pseudomonasa eruginosa promotes the formation of the Nod like receptor caspase-4 Inflammasomes & resulting Procaspase-1 cleaves, resulting in production of Interleukin-1B & Interleukin-18. By combining ASC streaks, ASC in the NLRC4 system, like NLRP1, facilitates NLRC4-mediated IL-1 and IL-18 production.[42] The NLRP3 inflammasome is the one that has been researched the highest. The NLRP3 inflammasome is activated in macrophages in 2 phases: priming and activation. TLR4 agonists trigger NF-B-mediated NLRP3 and pro-IL-1 production, while PAMPs and DAMPs trigger the triggering process (signal 2), encouraging NLRP3 Inflammasomes aggregation, Caspase– 1 regulated Interleukin – 1B & Interleukin - 18 induction & pyroptosis.[43] In microglia, the NLRP3 inflammasome is triggered in 2 phases: priming and activation. TLR4 stimulants promote NLRP3 inflammasome alignment and caspase-1-mediated Interleukin-1B & Interleukin - 18 releases, as well as

pyroptosis, by inducing NF-B-mediated NLRP3 and pro-IL-1 transmission, whereas PAMPs and DAMPs activate the induction phase (signal 2), encouraging NLRP3 inflammasome alignment and Caspase – 1 resulting Interleukin – 1B & Interleukin - 18 release.[44] Besides that, it has also been proposed that phosphorylation and ubiquitination of NLRP3 during the priming step play important function in Nod like receptor protein - 3 Inflammasomes stimulation.[45] Therefore in study, we review current revelations in Nod like receptor protein-3 Inflammasomes stimulation & antagonists who clearly & explicitly approach nod like receptor protein-3 can provide knowledge through treatment interventions of nod like receptors proteins -3 induced disorders.[46]

The NLR family

The NLRs are a set of 22 genetic mutations. NLRs are composed of three functional entities discovered during in the development of metazoans. At the protein n - terminal NLRs have such a pyrin region, a caspase recruiting site, or a baculovirus inhibiting replicate site.[47] The NLRX1 protein might be an exception because it has a N- terminus with such a domains it does not fit either one of these three, but it has a three-dimensional folds that really is identical. By use of the N-terminal domains as a functional sub classification for both the NLR family is supported by phylogenetic analysis.[48] While structural and functional correlations, the developmental histories of NLR protein and plant R protein tend to be separate and diverging.[49] Nevertheless, the identification of NLR-like variants in at only one nonvertebrate population, the echinoderm sea urchin, suggests that all these genes have such a long evolutionary history, and although their existence in those other metazoan sequences is unclear.[50]

The NLR group is marked by the appearance of a nucleotide-binding and oligomerization (NACHT) region in the centre, accompanied by C-terminal leucine-rich repeats (LRRs) and N-terminal caspase recruitment (CARD) or pyrin (PYD) regions. LRRs are believed to be associated in ligand signaling and autoregulation, while CARD and PYD regions instigate homotypic protein-protein interaction for downstream sensing.[51] Agents of the NLR family are believed to play a role in cytosolic PAMP or DAMP observation. During ligand sensing, NOD1 and NOD2 both identify bacterial cell membrane deterioration items (meso-diaminopimelic acid and muramyl dipeptide [MDP]), oligomerize, and enlist RIP2 via CARD-CARD interactions.[52] The final answer in the formation of NOD1and NOD2 signalosomes is the stimulation of the NF-kB transcriptional activation that regulates pro - inflammatory genes.[53]

The Nod Like Receptor Protein-3 Inflammasomes

The Nod Like Receptor Protein-**3** inflammasome is made up of resistor (Nod Like Receptor Protein-3) and (apoptosis-associated speck; classified as *pycard*), as well as Nod Like Receptor Protein-3 made up of three domains: the amino-terminal pyrin domain (PYD), the main (NACHT regions) & the (CARD). The (NACHT domain) Adenosine triphosphatase behavior needed for NLRP3 self-association and processes, while a LRR domains folds down onto to the NACHT domain to elicit automatic suppression. Amino - Terminal PYD & CARD are the interacting proteins regions of ASC (apoptosis-associated speck). In response to specific stimuli, NLRP3 oligomerizes through homotypic interactions amongst NACHT regions.[54] NLRP3 inflammasomes Obesity, diabetes, as well as other infectious and auto-immune disorders all play a major role.

Activators of Inflammasomes

Cryopyrinopathies (formerly known as cryopyrin) or cryopyrin-related intermittent fever syndrome (CAPS): FCAS (Famllial Cold - induced auto inflammatory syndrome), MWS (MuckleWells syndromes) & NOMID/CINCA (Neonatal Onset Multisystem Inflammatory disorder or chronic infantile neurologic cutaneous and articular syndrome) are all linked to genetic NLRP3 inflammasome stimulation or genetic disposition.[55] FCAS, MWS, and NOMID/CINCA all have varying degrees of disease progression, with FCAS becoming the less serious and NOMID/CINCA seems to be the most serious. Facing phenotypic differences, sporadic consider a different is related to all 3 cryopyrinopathies.[56] While phenotypic variations, all 3 cryopyrinopathies are correlated with neutrophil-dependent inflammation, recurrent colds and skin irritation, neuralgia, and eye infections.[57] NOMID/CINCA can lead to mental problems including rheumatic fever and hearing loss.[58] Although the LRR contains a small proportion of the specific genes mutants, the NBD domains houses the bulk of these. Individual mutants are related to several medical disorders, suggesting the existence of specific altering loci or external conditions.[59] This pattern may indicate that linking to ATP/dATP, a process which regulates inflammasome alignment, is less important. NOMID clinicians' PBMCs establish suicidal tendencies.[60] NOMID clients' PBMCs produce significantly further natural and mediated IL-1.[61] Sudden apoptosis occurs in participant macrophages, which would be linked to an activation of inflammatory mediators, which propagates the inflammatory reaction.[62] Anakinra as well as other IL-1-targeted treatments help to alleviate effects. Nevertheless, a class of CAPS victims, particularly NOMID physicians, has encodified the disease. Even so, a subset of CAPS cases, particularly NOMID patients, have really no mutants in NLRP3, implying that perhaps the illness is characterized by other genes.[63] About this, non-NLRP3 cryopyrinopathies respond similarly to IL-1 system inhibitors Knock-in microphones were created by various companies.[64-65] Extracellular ATP, presumably derived from mitochondria, is recognized by NLRP3 as a damage-Host-derived molecules, that are generally crystal or polymer in configuration and are posted a link to danger, harm, or death of cells, may induce the inflammasome.[66] ATP, monosodium urate (MSU),

calcium pyrophosphate dihydrate (CPPD), saturated fat crystalline, amyloid, hyaluron, and probably glycogen are mostly self-NLRP3 stimulators. The Inflammasome can identify mislocalized organic compounds.[67] For eg, ATP, MSU, and CPPD are normally found throughout the cytoplasm; nevertheless, once they are found within extracellular space, an inflammation response is triggered.[68] When outer membrane lipid crystal, hyaluron, or amyloid are absorbed, a specific reaction is triggered. Caspase-1 is activated in LPS-primery monocytes in an NLRP3-dependent way by the purinergic receptor P2X7 in association with pannexin-1 that is governed by the purinergic receptor P2X7 in connection with pannexin-1.[69] Uric acid is produced by homoeostasis purine metabolic processes throughout cell signaling. Free uric acid from necrotic or contaminated cells and tissues is needed to comprise crystal structure once introduced to the outer membrane.[70] The NLRP3 inflammasome is activated by the presence of ATP or MSU (along with the related CPPD)[71-72], which is involved in a range of disease dysfunctions either intrinsically and extrinsically. Chronic uric acid production and the formation of MSU clusters inside the joint are the hallmarks of arthritis. The accumulation within the joints causes a massive inflammatory reaction defined by IL-1, TNF-, and IL-8.[73] The process through which native macrophages phagocytes particles is known as irritated phagocytes. Assimilation of all these compounds activates the NLRP3 inflammasome, resulting in excruciating pain and neutrophil-mediated joint inflammation. In response to MSU, Nlrp3/ rodents phagocytes does not trigger caspase-1 in situ. Injection of MSU crystal into in the peritoneum of rodents causes a strong neutrophil-mediated inflammatory reaction that seems to be conditional either on the NLRP3 or the IL-1 receptors.[74] Ischemia-reperfusion damage activates the Inflammasome. Using just a bleomycin-induced liver damage in rodents to model ulcerative colitis in patients, Riteau et al. illustrated a task for that kind of mechanism in respiratory inflammation renovating.[75] Additionally, increased ATP levels were observed in bronchoalveolar lavage fluid among patients with primary fibrosis, providing an in situ analog for human disorder Specific induction of a P2X7 receptor or inhibitors of uric acid synthesis in rodents decreased the inflammation activity shown in allergy and respiratory inflammation.[76] Targeting this process can be a secure way of treating asthma attack in patients who've not responded to inhalation treatment with corticosteroids or 2-agonists.[77-78]

Activators of the NLRP3 Inflammasome

Investigators found recently that metallic alloy fragments isolated out of a prostheses joints may activate the Inflammasome, which can lead to sanitary osteolysis. In contrast to exposure to crystalline forms, humans are affected to regular vaccination which contain excipients.[79] Alum is a particle adjunct widely used during vaccines for organisms. These are some of the processes through which alum functions as an adjuvant is its ability to induce IL-1.According to many reports, NLRP3 is implicated in alum-dependent caspase-1 stimulation.[80] Antibody development indicates that the vaccination potency of Nlrp3/ rodents is decreased. Such results indicate that only by detecting alum, the NLRP3 inflammasome may impact the immune responses. But at the other hand, the inference is contestable.[81] In keratinocytes, uv rays and skin allergens will cause the NLRP3 inflammasome. The exact mechanism by which these mechanisms induce cell tissue damage is unclear.[82] By producing endogenous NLRP3 agonists or destroying the process of providing barrier, which allows physiologic microbial moieties to be detected, harm can unintentionally trigger the inflammasomes.[83]

NLRP3 inflammasome activation mechanisms

Ion fluxes

Ca^{2+} signal, Na^{+} Influx, K^{+} & Cl^{-} Efflux, and chloride efflux have mostly known as key things in Nod like receptor protein-3 Inflammasomes induction.[84] It's difficult for NLRP3 to interfere with both the stimulus because there are so many unique NLRP3 inflammasome stimulators.[85] Some many NLRP3 inflammasome mediators have been shown to induce K^{+} efflux, and Intracellular concentration of Potassium lowers the intrinsic activity in Nod like receptor protein-3 Inflammasomes induction.[86] As per recently found an element called (NEK-7) that specifically connect Nod like receptor protein-3, the Inflammasome needs k^{+} Efflux. K^{+} efflux, but at the other hand, is just not restricted towards the stimulation of the Inflammasome.[87] Recent research have already shown that certain molecules, like imiquimodand CL097, may trigger ROS and enhance NLRP3 inflammasome stimulation without requiring k^{+} efflux.[88] Moreover, the stimulation of the NLRP1b inflammasome by *bacillus anthracis* lethal toxin necessitates a reduction in cellular K^{+} ions for inflammasome stimulation and IL-1 induction.[89] As a result, K^{+} efflux plays a role in the role in the regulation of the NLRP3 inflammasome, but this is not unique. So according to studies, Ca^{2+} signal is needed for NLRP3 inflammasome stimulation. Ca^{2+} mobilization inhibition reduces NLRP3 inflammasome stimulation but it has no affect on NLRC4 and AIM2 inflammasome activation.[90] K^{+} efflux appear to be needed for Na^{+} influx-induced NLRP3 inflammasome activation.[91] On the opposite side, the Na^{+} ionophore monensin-induced Na^{+} influx won't result in NLRP3 inflammasome stimulation.[92] As a consequence, the infusion of Sodium ions may not have been needed for NLRP3 inflammasome to be enabled[93] & found the lower Extracellular Cl^{-} concentrations increased Intracellular Cl^{-} Efflux & promoted Adenosine Triphosphate - causes Caspase - 1 stimulation & Interleukin-1 production by increasing intracellular Cl efflux.[94] Cl–channel inhibitors including flufenamic acid, IAA94, DIDS, and NPPB have since been shown to suppress NLRP3 inflammasome modulation and not inflammasomes modulation.[95] Some other ions channel, the chloride

intracellular channel (CLIC), was discovered by Tang et al. to be a VRAC modulator.[96]

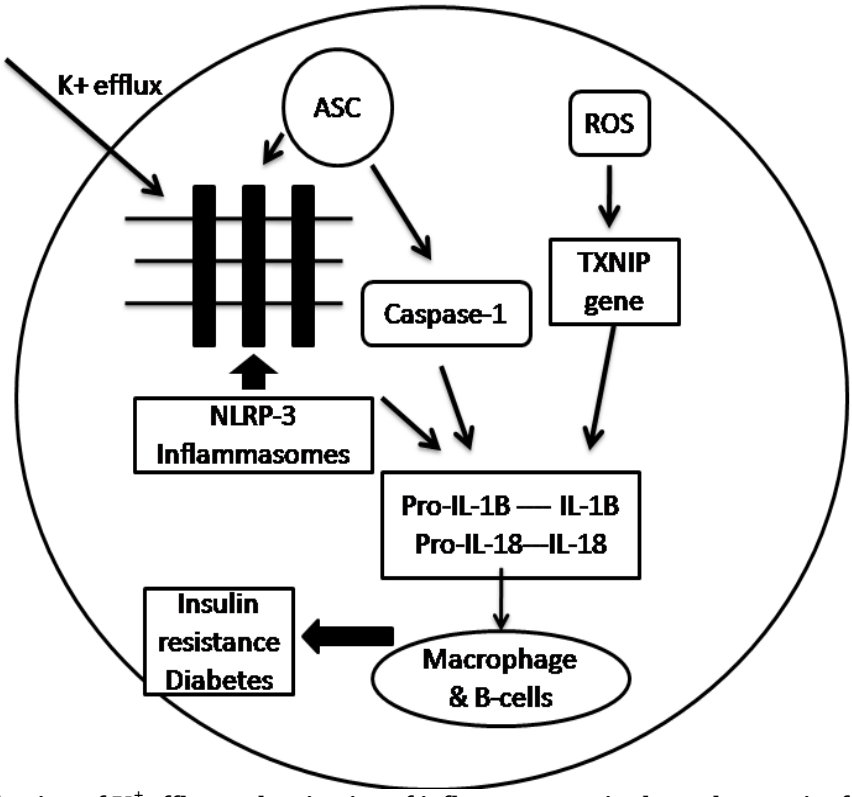

Figure 1: Mechanism of K^+ efflux and activation of inflammasomes in the pathogenesis of diabetes mellitus.

Reactive oxygen species (ROS)

Among the very first factors that activates the NLRP3 inflammasome, particularly in mitochondria.[97] Some NLRP3 inflammasome stimulants can induce mitochondrial Ros production in different cell types, according to many researches. For eg, fatty acids produced by a HFD (High Fat Diet) stimulate the Nod like receptor protein-3 Inflammasomes in AMPK–autophagy–Ros-reliant way.[98, 99] Radical antagonists that inhibit the formation of reactive oxygen species (ROS) prevent the stimulation of the Inflammasome. Several stimulants that induce apoptosis and cellular degradation even enhance mitochondrial depletion, triggering the Inflammasome.[100, 101] In the possession of ROS, though not in the existence of K+, imiquimod, a TLR7 stimulant, can stimulate the Inflammasome; furthermore, cells lacking (NEK7) NIMA related kinase-7 unsuccessful for generate IL-1 in reaction (Immiquimod) activation.[102] ROS-specific antagonists can inhibit NLRP3 inflammasome initiation by interacting with NLRP3 activity during the primary stage, but just not specific NLRP3 stimulation, according to some other reports.[103] The NLRP3 inflammasome was shown to be activated in a mitochondria condition.[104]

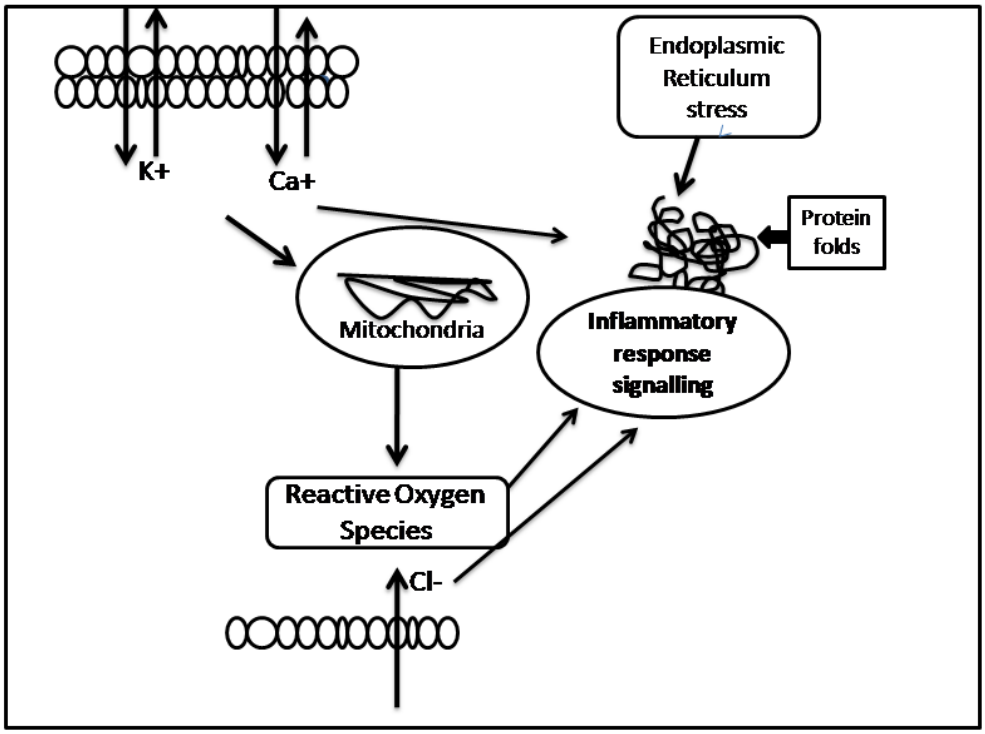

Figure 2: Role of ion fluxes in NLRP3 inflammasomes activation.

Activation in NLRP3 Inflammasome Diabetes

Type 1 Diabetes Mellitus (T1DM) Is Induced by NLRP3 Inflammasome Stimulation.

T1DM is a long-term condition induced through insulin production deficiencies that are primarily induced by autoimmune-mediated pancreatic B-cell degeneration. About 5% to 10% of the nation has type-1 diabetes.[105] T1DM is a type of cellular immune disease. In T2DM, the NLRP3 inflammasome is critical for the development of insulin sensitivity, but its role in autoimmune T1DM is unknown.[106] TLR-mediated innate autoimmune reactions, but at the other hand, appear to perform a significant role in the progression of T1DM, according to growing evidence. TLRs are sequence analysis agents that identify a disease also on substrate of immune system, causing interleukin-1 (IL-1) to be generated.[107] IL-1 has also been suggested as a diagnostic tool for T1DM in its initial stages.[108] As a response, a greater knowledge of IL-1's function in T1DM pathogenesis can contribute to better T1DM therapies. Virus and injury-related cellular pattern components, as well as environmental stimuli, are known to activate NLRP3.[109] Accessing conditions like ATP can also cause mitochondrial damage and cell death by introducing oxygenated DNA Molecules (mDNA) into another cell, which activates NLRP3.[110] In vivo study showed that mDNA raised the volume of Th17/Tc17/Th1/Tc1 cells in pancreatic B cells lymph nodes, encouraging T1DM production, whereas NLRP3/mice had T1DM progression blocked.[111]

The Role of NLRP3 Induction in (T2DM) Development.

T2DM seems to have a world health burden consisting to the different threats it poses, including such heart disease and cancer. As either a result, gaining a deeper knowledge of T2DM's pathophysiology is critical only for creation of new treatments.[112] It has become visible how important insulin homeostasis, insulin, and lipogenesis are already in the pathogenesis of T2DM. The NLRP3 inflammasome regulates the host immune responses by communicating with TXNIP (thioredoxin-interacting protein). NLRP3 inflammasome stimulation seems to have an impact on glycemic control, glucose resistance and gut microbe contacts.[113]

Glucose Tolerance

NLRP3 promotes the production of IL-1B and IL-18. Caspase-1 is made as just a zymogen (an inactive substance that becomes an enzyme until triggered by some other enzyme), that can then be sliced into p20 and p10 (proenzyme 20 and proenzyme 10) subtypes, which can then be integrated into another target metabolite enzyme.[114] An intact caspase-1 hetero-tetramer composed of p10 and p20 sub - units can transform in reactive Prointerlekin-1beta & 18 in to the activated state. As a consequence, IL-1B has also been discovered to have a biological role in glucose production.[115] Although insulin facilitates insulin intake, that enhances macrophage inflammation status, prolonged up - regulation of IL-1B causes an increase in blood sugar levels, which can also be harmful to metabolic processes. This one has been reported that IL-1B enhances glucose uptake into macrophages, but that NLRP3 inflammasomes facilitate IL-1B induction, with insulin exacerbating pro-inflammatory impact, glycogen synthesis, and oxygen radical's behavior.[116] When the tissue's glucose levels get too high, glucose can be excreted unchanged in the urine, preventing the

dangerous and detrimental effects of glucose-induced IL-1B. Immune system such as dendritic cells, macrophages, T cells, and B cells produce IL-18, a pro-inflammatory cytokine. It belongs to Interleukin-1B cytokines group & then was believed to become an IFN inducer. IBS has already been associated with obesity, insulin resistance, and dyslipidemia.[117-118]

Insulin resistance

Patients suffering with diabetes as just a consequence of poor glucose secretions compensate for 90% to 95% of patients. Obesity is a major contributing factor for T2DM, and consuming a progressively nutritious diet will lead to weight gain, that induces insulin sensitivity. Being fat or obese is an important cause factor for T2DM. Obesity is among the reasons which results in the manufacturing of NLRP3 inflammasomes in people with diabetes.[119] It 's getting clearer which role the NLRP3 inflammasome plays in metabolic syndrome insulin sensitivity. Insulin resistance is caused by high levels of IL-1B in obese individuals. The production of NLRP3 inflammasome elements, caspase-1 activity, and IL-1B levels, especially in macrophages, are all elevated in these kind of people's fatty tissue, and all these are linked to insulin sensitivity, metabolic disorders, as well as the intensity of T2DM.[120] The production of IL-1B in pancreatic B - cell is caused by the stimulation of NLRP3 inflammasomes. Besides that, while overweight, metabolic signal molecule including such as glucose, saturated fatty acids (SFA), and uric acid will trigger the Nod like receptor protein-3, obtained by the process of Interleukin-1B & cytokines.[121] While being exposed to an SFA-rich high-fat diet, dendritic cells penetrated fat cells, but these HFD-derived dendritic cell reduced adipose cells insulin sensitivity. In adipose tissue, SFA would function as a biochemical stimulus, causing inflammasome forming and fostering inflammatory disease and insulin sensitivity.[122] SFA has been found to get a significant impact on TLR4-mediated inflammasome stimulation. Through membrane - bound receptor signalling, the AMPK (AMP- activated kinase) signalling process could be triggered by STAT3 (Signal transducer and activators of transcription) active cytokines, which improves fatty acid oxidation in muscle tissue and is successively caused by a high fat diet (HFD).[123] In overweight people with diabetes, obesity was already linked to decreased long term inflammation and raised IL-18 levels.[124]

CONCLUSION

Inflammsomes are essential with in progression of diabetes related long term complications. The NLRP3 inflammasome acts as a loading tool for IL-1B and IL-18. As NLRP3 mediated inflammation begins, cells contain a huge range of pro-inflammatory cytokines, infuriating insulin sensitivity and promoting development of the disease. The detection of the NLRP3 inflammasomes has opened new opportunities for investigation of infectious disorder. The identification of the NLRP3 inflammasomes, that regulate IL-18 and IL-1B, will contribute to a stronger inflammatory disease intervention and rehabilitation strategies. The NLRP3 inflammasome produces IL-1B, which is essential in the production of obesity and heart disease. For both Type 1 and Type 2 diabetes, there are numerous catalysts and a strong connection to chronic inflammation. IL-1B prevents the glucose signaling via trying to reduce dephosphorylation of insulin receptor substrate-1 (IRS-1) and poorly influencing insulin receptor substrate-1 (IRS-1) expression of genes. Inflammatory response and glucose tolerance are both regulated by the (NLRP3) Inflammasome.

To summarize, research into the broad extent of NLRP3-related chronic inflammation is now in its initial phases, and finding inhibition substances which are specific to NLRP3 will probably get the most successful treatment techniques.

REFERENCES

1. American Diabetes Association, Diagnosis and classification of diabetes mellitus. Diabetes Care, 2014; 37(1): S81–S90.doi:10.2337/dc14-s081.
2. https://www.who.int/health
3. F.M Ashcroft, P. Rorsman, Diabetes mellitus and the beta cell: The last ten years. Cell, 2012; 148: 1160–11.doi: 10.1016/j.cell.2012.02.010.
4. N. Esser, S. Legrand-Poels, J. Piette, A.J Scheen, N. Paquot, Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res. Clin. Pract, 2014; 105: 141–150. doi.org/10.1016/j.diabres.2014.04.006.
5. M.E Craig, A. Hattersley, KC Donaghue. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatr Diabetes, 2009; 10(12): 3–12. doi.org/10.1111/j.1399-5448.2009.00568.x.
6. F. Galtier. Definition, epidemiology, risk factors. Diabetes Metab, 2010; 36: 628–651. doi.org/10.1016/j.diabet.2010.11.014.
7. S.I Mannering, A.R. Di Carluccio, C.M Elso, Neoepitopes: A new take on beta cell autoimmunity in type 1diabetes. Diabetologia, 2019; 62: 351–356. doi.org/10.1007/s00125-018-4760-6.
8. A. Nicolucci, A. Maione, M. Franciosi, R. Amoretti, E. Busetto, F. Capani, D. Bruttomesso, P. Di Bartolo, A. Girelli, F. Leonetti, et al. Quality of life and treatment satisfaction in adults with Type 1 diabetes: A comparison between continuous subcutaneous insulin infusion and multiple daily injections. Diabet. Med, 2008; 25: 213–220. doi.org/10.1111/j.1464-5491.2007.02346.x.
9. ME. Craig, A. Hattersley, K.C Donaghue. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatr Diabetes, 2009; 10(12): 3-12. doi.org/10.1111/j.1399-5448.2009.00568.x.
10. F. Galtier. Definition, epidemiology, risk factors. Diabetes Metab, 2010; 36: 628–651. doi.org/10.1016/j.diabet.2010.11.014.

11. Thunander M, Törn C, Petersson C, Ossiansson B, Fornander J, Landin-Olsson M. Levels of C-peptide, body mass index and age, and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden. Eur J Endocrinol, 2012; 166: 1021–1029. doi.org/10.1530/eje-11-0797.
12. Stone MA, Camosson - Stefinovic J, Wilkinson J, de Lusignan S, Hattersley AT, Khunti K. Incorrect and incomplete coding and classification of diabetes: a systematic review. Diabet Med, 2010; 27: 491–497.doi.org/10.1111/j.1464-5491.2009.02920.x.
13. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. Type 2 sdiabetes in children and adolescents. Pediatr Diabetes, 2009; 10(12): 17–32. doi.org/10.1111/j.1399-5448.2009.00584.x.
14. Cakan N, Kizilbash S, Kamat D. Changing spectrum of diabetes mellitus in children: challenges with initial classification. Clin Pediatr (Phila), 2012; 51: 939–944. doi.org/10.1177/0009922812441666.
15. Wilkin TJ. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type I as well as type II diabetes. Int J Obes (Lond), 2009; 33: 716–726. doi.org/10.1038/ijo.2009.97.
16. Canivell S, Gomis R. Diagnosis and classification of autoimmune diabetes mellitus. Autoimmun Rev, 2014; 13: 403–407. doi.org/10.1016/j.autrev.2014.01.020.
17. Lamb MM, Yin X, Zerbe GO, Klingensmith GJ, Dabelea D, Fingerlin TE, Rewers M, Norris JM. Height growth velocity, islet autoimmunity and type 1 diabetes development: the Diabetes Autoimmunity Study in the Young. Diabetologia, 2009; 52: 2064–2071. doi.org/10.1007/s00125-009-1428-2.
18. Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith GJ, Dabelea D. Childhood growth and age at diagnosis with Type 1 diabetes in Colorado young people. Diabet Med, 2009; 26: 961–967. doi.org/10.1111/j.1464-5491.2009.02819.x.
19. Ferrannini E, Mari A, Nofrate V, Sosenko JM, Skyler JS; DPT-1 Study Group. Progression to diabetes in relatives of type 1 diabetic patients: mechanisms and mode of onset. Diabetes, 2010; 59: 679–685. doi.org/10.2337/db09-1378.
20. Robertson RP, Harmon J, Tran PO, Tanaka Y, Takahashi H. Glucose toxicity in beta-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. Diabetes, 2003; 52: 581–587. doi.org/10.2337/diabetes.52.3.581.
21. Vincent AM, Russell JW, Low P, Feldman EL. Oxidative stress in the pathogenesis of diabetic neuropathy. Endocr Rev, 2004; 25: 612–628. doi.org/10.1210/er.2003-0019.
22. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. Diabetes Care, 1996; 19: 257–267. doi.org/10.2337/diacare.19.3.257.
23. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res, 2010; 107: 1058–1070. doi.org/10.1161/circresaha.110.223545.
24. Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther, 2012; 30: 49–59. doi.org/10.1111/j.1755-5922.2010.00218.x.
25. Halban PA, Polonsky KS, Bowden DW, Hawkins MA, Ling C, Mather KJ, Powers AC, Rhodes CJ, Sussel L, Weir GC. β-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. Diabetes Care, 2014; 37: 1751–1758. doi.org/10.2337/dc14-0396.
26. Johansen JS, Harris AK, Rychly DJ, Ergul A. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovasc Diabetol, 2005; 4: 5. doi.org/10.1186/1475-2840-4-5.
27. Kaneto H, Kajimoto Y, Miyagawa J, Matsuoka T, Fujitani Y, Umayahara Y, Hanafusa T, Matsuzawa Y, Yamasaki Y, Hori M. Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity. Diabetes, 1999; 48: 2398–2406. doi.org/10.2337/diabetes.48.12.2398.
28. Nebbioso M, Federici M, Rusciano D, Evangelista M, Pescosolido N. Oxidative stress in preretinopathic diabetes subjects and antioxidants. Diabetes Technol Ther, 2012; 14: 257–263. doi.org/10.1089/dia.2011.0172.
29. Kilic G, Alvarez-Mercado AI, Zarrouki B, Opland D, Liew CW, Alonso LC, Myers MG, Jonas JC, Poitout V, Kulkarni RN, et al. The islet estrogen receptor-α is induced by hyperglycemia and protects against oxidative stress-induced insulin-deficient diabetes. PLoS One, 2014; 9: e87941. doi.org/10.1371/journal.pone.0087941.
30. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am, 2010; 39: 481–497. doi.org/10.1016/j.ecl.2010.05.011.
31. Daneman D. Type 1 diabetes. Lancet, 2006; 367: 847–858. doi.org/10.1016/s0140-6736(06)68341-4.
32. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. BMJ, 2004; 328: 750–754. doi.org/10.1136/bmj.328.7442.750.
33. Kilic G, Alvarez-Mercado AI, Zarrouki B, Opland D, Liew CW, Alonso LC, Myers MG, Jonas JC, Poitout V, Kulkarni RN, et al. The islet estrogen receptor-α is induced by hyperglycemia and protects against oxidative stress-induced insulin-deficient diabetes. PLoS One, 2014; 9: e87941. doi.org/10.1371/journal.pone.0087941.
34. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am, 2010; 39: 481–497. doi.org/10.1016/j.ecl.2010.05.011.
35. Daneman D. Type 1 diabetes. Lancet, 2006; 367: 847–858. doi.org/10.1016/s0140-6736(06)68341-4.

36. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. BMJ, 2004; 328: 750–754. doi.org/10.1136/bmj.328.7442.750.
37. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from, 2001 to 2009. JAMA, 2014; 311: 1778–1786. doi.org/10.1001/jama.2014.3201.
38. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013. doi.org/10.1016/j.diabres.2013.08.003.
39. Prime Group for JDRF. JDRF: Type 1 Diabetes, 2011.
40. Chiang JL, Kirkman MS, Laffel LM, Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care, 2014; 37: 2034–2054. doi.org/10.2337/dc14-1140.
41. Pettitt DJ, Talton J, Dabelea D, Divers J, Imperatore G, Lawrence JM, Liese AD, Linder B, Mayer-Davis EJ, Pihoker C, et al. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. Diabetes Care, 2014; 37: 402–408. https://doi.org/10.2337/dc13-1838.
42. Lawrence JM, Imperatore G, Dabelea D, Mayer-Davis EJ, Linder B, Saydah S, Klingensmith GJ, Dolan L, Standiford DA, Pihoker C, et al. Trends in incidence of type 1 diabetes among non-Hispanic white youth in the U.S., 2002-2009. Diabetes, 2014; 63: 3938–3945.doi.org/10.2337/db13-1891.
43. Vermeulen I, Weets I, Asanghanwa M, Ruige J, Van Gaal L, Mathieu C, Keymeulen B, Lampasona V, Wenzlau JM, Hutton JC, et al. Contribution of antibodies against IA-2β and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. Diabetes Care, 2011; 34: 1760–1765.doi.org/10.2337/dc10-2268.
44. Couper J, Donaghue KC. Phases of diabetes in children and adolescents. Pediatr Diabetes, 2009; 10(12): 13–16. doi.org/10.1111/j.1399-5448.2009.00574.x.
45. Abiru N, Kawasaki E, Eguch K. Current knowledge of Japanese type 1 diabetic syndrome. Diabetes Metab Res Rev, 2002; 18: 357–366. doi.org/10.1002/dmrr.323.
46. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A proposal of three distinct subtypes of type 1 diabetes mellitus based on clinical and pathological evidence. Ann Med, 2000; 32: 539–543. doi.org/10.3109/07853890008998833.
47. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. N Engl J Med, 2000; 342: 301–307. doi.org/10.1056/nejm200002033420501.
48. Imagawa A, Hanafusa T. Fulminant type 1 diabetes--an important subtype in East Asia. Diabetes Metab Res Rev, 2011; 27: 959–964/doi.org/10.1002/dmrr.1236.
49. Shibasaki S, Imagawa A, Hanafusa T. Fulminant type 1 diabetes mellitus: a new class of type 1 diabetes. Adv Exp Med Biol, 2012; 771: 20–23. doi.org/10.1007/978-1-4614-5441-0_3.
50. Imagawa A, Hanafusa T. Fulminant type 1 diabetes mellitus. Endocr J, 2006; 53: 577–584. doi.org/10.1507/endocrj.kr-72.
51. Shimizu I, Makino H, Imagawa A, Iwahashi H, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Maruyama T, et al. Clinical and immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy. J Clin Endocrinol Metab, 2006; 91: 471–476. doi.org/10.1210/jc.2005-1943.
52. Ginsberg H, Kimmerling G, Olefsky JM, Reaven GM. Demonstration of insulin resistance in untreated adult onset diabetic subjects with fasting hyperglycemia. J Clin Invest, 1975; 55: 454–461. doi.org/10.1172/jci107951.
53. Olefsky J, Farquhar JW, Reaven G. Relationship between fasting plasma insulin level and resistance to insulin-mediated glucose uptake in normal and diabetic subjects. Diabetes, 1973; 22: 507–513. doi.org/10.2337/diab.22.7.507.
54. Kraemer FB, Ginsberg HN. Gerald M. Reaven, MD: Demonstration of the central role of insulin resistance in type 2 diabetes and cardiovascular disease. Diabetes Care, 2014; 37: 1178–1181.doi.org/10.2337/dc13-2668.
55. Type 2 diabetes in children and adolescents. American Diabetes Association. Diabetes Care, 2000; 23: 381–389. doi.org/10.2337/diacare.23.3.381.
56. Reinehr T. Type 2 diabetes mellitus in children and adolescents. World J Diabetes, 2013; 4: 270–281. doi.org/10.4239/wjd.v4.i6.270.
57. Druet C, Tubiana-Rufi N, Chevenne D, Rigal O, Polak M, Levy-Marchal C. Characterization of insulin secretion and resistance in type 2 diabetes of adolescents. J Clin Endocrinol Metab, 2006; 91: 401–404.doi.org/10.1210/jc.2005-1672.
58. Saadi H, Nagelkerke N, Carruthers SG, Benedict S, Abdulkhalek S, Reed R, Lukic M, Nicholls MG. Association of TCF7L2 polymorphism with diabetes mellitus, metabolic syndrome, and markers of beta cell function and insulin resistance in a population-based sample of Emirati subjects. Diabetes Res Clin Pract, 2008; 80: 392–398. doi.org/10.1016/j.diabres.2008.01.008.
59. Wei JN, Sung FC, Li CY, Chang CH, Lin RS, Lin CC, Chiang CC, Chuang LM. Low birth weight and high birth weight infants are both at an increased risk to have type 2 diabetes among schoolchildren in taiwan. Diabetes Care, 2003; 26: 343–348. doi.org/10.2337/diacare.26.2.343.

60. Ramachandran A, Snehalatha C, Satyavani K, Sivasankari S, Vijay V. Type 2 diabetes in Asian-Indian urban children. Diabetes Care, 2003; 26: 1022–1025. doi.org/10.2337/diacare.26.4.1022.
61. Sugihara S, Sasaki N, Kohno H, Amemiya S, Tanaka T, Matsuura N; Committee for the Medical Treatment of Childhood-Onset Type 2 Diabetes Mellitus, The Japanese Society for Pediatric Endocrinology. Survey of current medical treatments for childhood-onset type 2 diabetes mellitus in Japan. Clin Pediatr Endocrinol, 2005; 14: 65–75. doi.org/10.1297/cpe.14.65.
62. Pozzilli P, Di Mario U. Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabetes of the adult): definition, characterization, and potential prevention. Diabetes Care, 2001; 24: 1460–1467. doi.org/10.1002/dmrr.426.
63. Hawa MI, Buchan AP, Ola T, Wun CC, DeMicco DA, Bao W, Betteridge DJ, Durrington PN, Fuller JH, Neil HA, et al. LADA and CARDS: a prospective study of clinical outcome in established adult-onset autoimmune diabetes. Diabetes Care, 2014; 37: 1643–1649.
64. Rolandsson O, Palmer JP. Latent autoimmune diabetes in adults (LADA) is dead: long live autoimmune diabetes! Diabetologia, 2010; 53: 1250–1253. doi.org/10.1007/s00125-010-1713-0.
65. Redondo MJ. LADA: time for a new definition. Diabetes, 2013; 62: 339–340. doi.org/10.2337/db12-1171.
66. Leslie RD, Kolb H, Schloot NC, Buzzetti R, Mauricio D, De Leiva A, Yderstraede K, Sarti C, Thivolet C, Hadden D, et al. Diabetes classification: grey zones, sound and smoke: Action LADA 1. Diabetes Metab Res Rev, 2008; 24: 511–519. doi.org/10.1002/dmrr.877.
67. Copps KD, White MF. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. Diabetologia, 2012; 55: 2565–2582. doi.org/10.1007/s00125-012-2644-8.
68. Boura-Halfon S, Zick Y. Phosphorylation of IRS proteins, insulin action, and insulin resistance. Am J Physiol Endocrinol Metab, 2009; 296: E581–E591. https://doi.org/10.1152/ajpendo.90437.2008.
69. Tanti JF, Jager J. Cellular mechanisms of insulin resistance: role of stress-regulated serine kinases and insulin receptor substrates (IRS) serine phosphorylation. Curr Opin Pharmacol, 2009; 9: 753–762. doi.org/10.1016/j.coph.2009.07.004.
70. Cheng Z, Tseng Y, White MF. Insulin signaling meets mitochondria in metabolism. Trends Endocrinol Metab, 2010; 21: 589–598. doi.org/10.1016/j.tem.2010.06.005.
71. White MF. Insulin signaling in health and disease. Science, 2003; 302: 1710–1711. doi.org/10.1126/science.1092952.
72. Farese RV, Sajan MP, Standaert ML. Insulin-sensitive protein kinases (atypical protein kinase C and protein kinase B/Akt): actions and defects in obesity and type II diabetes. Exp Biol Med (Maywood), 2005; 230: 593–605.doi.org/10.1177/153537020523000901.
73. Farese RV, Sajan MP, Yang H, Li P, Mastorides S, Gower WR, Nimal S, Choi CS, Kim S, Shulman GI, et al. Muscle-specific knockout of PKC-lambda impairs glucose transport and induces metabolic and diabetic syndromes. J Clin Invest, 2007; 117: 2289–2301.doi.org/10.1172/jci31408.
74. Morino K, Neschen S, Bilz S, Sono S, Tsirigotis D, Reznick RM, Moore I, Nagai Y, Samuel V, Sebastian D, et al. Muscle-specific IRS-1 Ser-& gt; Ala transgenic mice are protected from fat-induced insulin resistance in skeletal muscle. Diabetes, 2008; 57: 2644–2651.doi.org/10.2337/db06-0454.
75. Copps KD, Hancer NJ, Opare-Ado L, Qiu W, Walsh C, White MF. Irs1 serine 307 promotes insulin sensitivity in mice. Cell Metab, 2010; 11: 84–92. doi.org/10.1016/j.cmet.2009.11.003.
76. Sargis RM. The hijacking of cellular signaling and the diabetes epidemic: mechanisms of environmental disruption of insulin action and glucose homeostasis. Diabetes Metab J, 2014; 38: 13–24.doi.org/10.4093/dmj.2014.38.1.13.
77. Otero YF, Stafford JM, McGuinness OP. Pathway-selective insulin resistance and metabolic disease: the importance of nutrient flux. J Biol Chem, 2014; 289: 20462–20469.doi.org/10.1074/jbc.r114.576355.
78. Ye J. Mechanisms of insulin resistance in obesity. Front Med, 2013; 7: 14–24. doi.org/10.1007/s11684-013-0262-6.
79. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab, 2008; 4: 200–213. doi.org/10.1038/ncpendmet0778.
80. Schwitzgebel VM. Many faces of monogenic diabetes. J Diabetes Investig, 2014; 5: 121–133. doi.org/10.1111/jdi.12197.
81. Kushner JA, Ye J, Schubert M, Burks DJ, Dow MA, Flint CL, Dutta S, Wright CV, Montminy MR, White MF. Pdx1 restores beta cell function in Irs2 knockout mice. J Clin Invest, 2002; 109: 1193–1201. doi.org/10.1172/jci14439.
82. Gusarova V, Alexa CA, Na E, Stevis PE, Xin Y, Bonner-Weir S, Cohen JC, Hobbs HH, Murphy AJ, Yancopoulos GD, et al. ANGPTL8/betatrophin does not control pancreatic beta cell expansion. Cell, 2014; 159: 691–696. doi.org/10.1016/j.cell.2014.09.027.
83. Reardon W, Ross RJ, Sweeney MG, Luxon LM, Pembrey ME, Harding AE, Trembath RC. Diabetes mellitus associated with a pathogenic point mutation in mitochondrial DNA. Lancet, 1992; 340: 1376–1379.doi.org/10.1016/0140-6736(92)92560-3.
84. Chen N, Unnikrishnan I R, Anjana RM, Mohan V, Pitchumoni CS. The complex exocrine-endocrine relationship and secondary diabetes in exocrine

pancreatic disorders. J Clin Gastroenterol, 2011; 45: 850–861. doi.org/10.1097/mcg.0b013e31822a2ae5.
85. Pezzilli R, Calculli L. Pancreatic steatosis: Is it related to either obesity or diabetes mellitus? World J Diabetes, 2014; 5: 415–419.doi.org/10.4239/wjd.v5.i4.415.
86. Larger E, Philippe MF, Barbot-Trystram L, Radu A, Rotariu M, Nobécourt E, Boitard C. Pancreatic exocrine function in patients with diabetes. Diabet Med, 2012; 29: 1047–1054. doi.org/10.1111/j.1464-5491.2012.03597.x.
87. Agostini, L., Martinn, F., Burns, K., McDermott, M.F., Hawkins, P.N., andTschopp, J. (2004). NALP3 forms an IL-1beta-processing inflammasomewith increased activity in Muckle-Wells autoinflammatory disorder. Immunity, 20: 319–325.doi.org/10.1016/s1074-7613(04)00046-9.
88. Fink, S.L., and Cookson, B.T. (2006). Caspase-1-dependent pore formationduring pyroptosis leads to osmotic lysis of infected host macrophages. Cell. Microbiol, 8: 1812–1825.doi.org/10.1111/j.1462-5822.2006.00751.x.
89. Craven, R.R., Gao, X., Allen, I.C., Gris, D., Bubeck Wardenburg, J., McElvania-Tekippe, E., Ting, J.P., and Duncan, J.A. (2009). Staphylococcus aureusalpha-hemolysin activates the NLRP3-inflammasome in human and mousemonocytic cells. PLoS ONE4, e7446. doi.org/10.1371/journal.pone.0007446.
90. Dupont, N., Lacas-Gervais, S., Bertout, J., Paz, I., Freche, B., Van Nhieu, G.T., van der Goot, F.G., Sansonetti, P.J., and Lafont, F. (2009). Shigella phagocyticvacuolar membrane remnants participate in the cellular response to pathogeninvasion and are regulated by autophagy. Cell Host Microbe, 6: 137–149. doi.org/10.1016/j.chom.2009.07.005.
91. Duncan, J. A. et al. Cryopyrin/NALP3 binds ATP/dATP, is an ATPase, and requires ATP binding to mediate inflammatory signaling. Proc. Natl Acad. Sci. USA, 2007; 104: 8041–8046. doi.org/10.1073/pnas.0611496104.
92. Cai, X. et al. Prion- like polymerization underlies signal transduction in antiviral immune defense and inflammasome activation. Cell, 2014; 156: 1207–1222. doi.org/10.1016/j.cell.2014.01.063.
93. Lu, A. et al. Unified polymerization mechanism for the assembly of ASC- dependent inflammasomes. Cell, 2014; 156: 1193–1206. doi.org/10.1016/j.cell.2014.02.008.
94. Boucher, D. et al. Caspase-1 self- cleavage is an intrinsic mechanism to terminate inflammasome activity. J. Exp. Med, 2018; 215: 827–840. doi.org/10.1084/jem.20172222.
95. Schmid- Burgk, J. L. et al. A genome- wide CRISPR screen identifies NEK7 as an essential component of NLRP3 inflammasome activation. J. Biol. Chem, 2015; 291: 103–109. 14.doi.org/10.1074/jbc.c115.700492.doi.org/10.1074/jbc.c115.700492.
96. He, Y., Zeng, M. Y., Yang, D., Motro, B. & Núñez, G. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux. Nature, 2016; 530: 354–357. doi.org/10.1038/nature16959.
97. Shi, H. et al. NLRP3 activation and mitosis are mutually exclusive events coordinated by NEK7, a new inflammasome component. Nat. Immunol, 2016; 17: 250–258. doi.org/10.1038/ni.3333.
98. Bauernfeind, F. G. et al. Cutting edge: NF- kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J. Immunol, 2009; 183: 787–791. doi.org/10.4049/jimmunol.0901363.
99. Tannahill, G. M. et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. Nature, 2013; 496: 238–242. doi.org/10.1038/nature11986.
100. Perregaux, D. & Gabel, C. A. Interleukin-1 beta maturation and release in response to ATP and nigericin. Evidence that potassium depletion mediated by these agents is a necessary and common feature of their activity. J. Biol. Chem, 1994; 269: 15195–15203.
101. Triantafilou, K., Hughes, T. R., Triantafilou, M. & Morgan, B. P. The complement membrane attack complex triggers intracellular Ca2+ fluxes leading to NLRP3 inflammasome activation. J. Cell Sci, 2013; 126: 2903–2913. doi.org/10.1242/jcs.124388.
102. Laudisi, F. et al. Cutting edge: the NLRP3 inflammasome links complement- mediated inflammation and IL-1β release. J. Immunol, 2013; 191: 1006–1010. doi.org/10.4049/jimmunol.1300489.
103. Shimada, K. et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity, 2012; 36: 401–414. doi.org/10.1016/j.immuni.2012.01.009.
104. Zanoni, I. et al. An endogenous caspase-11 ligand elicits interleukin-1 release from living dendritic cells. Science, 2016; 352: 1232–1236. doi.org/10.1126/science.aaf3036.
105. Freeman, L. et al. NLR members NLRC4 and NLRP3 mediate sterile inflammasome activation in microglia and astrocytes. J. Exp. Med, 2017; 214: 1351–1370. doi.org/10.1084/jem.20150237.
106. Duewell, P. et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature, 2010; 464: 1357–1361. doi.org/10.1038/nature08938.
107. Yamasaki, K. et al. NLRP3/cryopyrin is necessary for interleukin-1beta (IL-1beta) release in response to hyaluronan, an endogenous trigger of inflammation in response to injury. J. Biol. Chem, 2009; 284: 12762–12771. doi.org/10.1074/jbc.m806084200.
108. Muñoz- Planillo, R. et al. K+ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. Immunity, 2013; 38: 1142–1153. doi.org/10.1016/j.immuni.2013.05.016.

109. Hornung, V. et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat. Immunol, 2008; 9: 847–856. doi.org/10.1038/ni.1631.
110. Baron, L. et al. The NLRP3 inflammasome is activated by nanoparticles through ATP, ADP and adenosine. Cell Death Dis, 2015; 6: e1629. doi.org/10.1038/cddis.2014.576.
111. Gaidt, M. M. et al. Human monocytes engage an alternative inflammasome pathway. Immunity, 2016; 44: 833–846. doi.org/10.1016/j.immuni.2016.01.012.
112. Martinon, F., Agostini, L., Meylan, E. & Tschopp, J. Identification of bacterial muramyl dipeptide as activator of the NALP3/cryopyrin inflammasome. Curr. Biol, 2004; 14: 1929–1934. doi.org/10.1016/j.cub.2004.10.027.
113. Abdul- Sater, A. A. et al. Cyclic- di-GMP and cyclic-di-AMP activate the NLRP3 inflammasome. EMBO Rep, 2013; 14: 900–906. doi.org/10.1038/embor.2013.132.
114. Sha, W. et al. Human NLRP3 inflammasome senses multiple types of bacterial RNAs. Proc. Natl Acad. Sci. USA, 2014; 111: 16059–16064. doi.org/10.1073/pnas.1412487111.
115. Kailasan Vanaja, S. et al. Bacterial RNA:DNA hybrids are activators of the NLRP3 inflammasome. Proc. Natl Acad. Sci. USA, 2014; 111: 7765–7770. doi.org/10.1073/pnas.1400075111.
116. Schweneker, K. et al. The mycobacterial cord factor adjuvant analogue trehalose-6,6′-dibehenate (TDB) activates the Nlrp3 inflammasome. Immunobiology, 2013; 218: 664–673. doi.org/10.1016/j.imbio.2012.07.029.
117. Gurcel, L., Abrami, L., Girardin, S., Tschopp, J. & van der Goot, F. G. Caspase-1 activation of lipid metabolic pathways in response to bacterial pore-forming toxins promotes cell survival. Cell, 2006; 126: 1135–1145. doi.org/10.1016/j.cell.2006.07.033.
118. Mariathasan, S. et al. Cryopyrin activates the inflammasome in response to toxins and ATP. Nature, 2006; 440: 228–232. doi.org/10.1038/nature04515.
119. Mathur, A. et al. A multicomponent toxin from Bacillus cereus incites inflammation and shapes host outcome via the NLRP3 inflammasome. Nat. Microbiol, 2019; 4: 362–374. doi.org/10.1038/s41564-018-0318-0.
120. Subramanian, N., Natarajan, K., Clatworthy, M. R., Wang, Z. & Germain, R. N. The adaptor MAVS promotes NLRP3 mitochondrial localization and inflammasome activation. Cell, 2013; 153: 348–361. doi.org/10.1016/j.cell.2013.02.054.
121. Franchi, L. et al. Cytosolic double- stranded RNA activates the NLRP3 inflammasome via MAVS-induced membrane permeabilization and K+ efflux. J. Immunol, 2014; 193: 4214–4222. doi.org/10.4049/jimmunol.1400582.
122. Park, S. et al. The mitochondrial antiviral protein MAVS associates with NLRP3 and regulates its inflammasome activity. J. Immunol, 2013; 191: 4358–4366. doi.org/10.4049/jimmunol.1301170.
123. Lamkanfi, M., Malireddi, R. K. & Kanneganti, T. D. Fungal zymosan and mannan activate the cryopyrin inflammasome. J. Biol. Chem, 2009; 284: 20574–20581. doi.org/10.1074/jbc.m109.023689.
124. Kankkunen, P. et al. (1,3)-beta- glucans activate both dectin-1 and NLRP3 inflammasome in human macrophages. J. Immunol, 2010; 184: 6335–6342. doi.org/10.4049/jimmunol.0903019.