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Inflammasomes – Fighting the enemy from within
(Inflamasomas – atacando al enemigo desde adentro)

Joselyn Rojas

Instituto de Inmunología Clínica, Facultad de Medicina, Universidad de los Andes, Mérida - Venezuela.

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Resumen

Los inflamasomas son un grupo de proteínas que participan en el sistema de detección y erradicación intracelular, siendo un aspecto fundamental del sistema inmune innato. Las proteínas involucradas pertenecen a la familia de proteínas CATERPILLER las cuales contienen un dominio de reclutamiento de caspasas, pirina, dominio de unión a nucleótidos y repeticiones de leucina. Actualmente, hay 4 tipos de inflamasomas descritos y se han considerado parte de un abanico de eventos dentro del fenómeno de defensa: a) NLRP1 el cual activa a Caspasa-1 y Caspasa-5; b) NLRC4, acoplado a NAIP5 para la activación de Caspasa-1; c) NLRP3, el inflamasoma prototipo, el cual produce Caspasa-1; y d) AIM2, funcionando como sensor de ADN. La siguiente revisión discute la información más reciente de los subtipos de inflamasomas, su influencia en la polarización de la respuesta inmune y su participación en la patogenia de enfermedades metabólicas como diabetes y aterosclerosis.

Palabras clave

Inflamasomas, caspasas inflamatorias, defensa ante microorganismos intracelulares, polarización de la respuesta inmune, inmunometabolismo.

Abstract

The inflammasomes are a group of proteins that participate in the intracellular detection and eradication system, being an important piece in the innate immune system. The proteins involved belong to the CATERPILLER family of proteins which contain a caspase recruiting domain, pyrin, a nucleotide binding domain and leucine repeats. Currently, 4 types of inflammasomes are described and are part of an array of events within the defense phenomena: a) the NLRP1 which activates Caspase-1 and Caspase-5; b) NLRC4, that coupled with NAIP5 relates to Caspase-1 activation; c) NLRP3, the prototype inflammasomes, which produces Caspase-1; and d) AIM2 that functions as a DNA sensor. The following review discusses the current information regarding each subtype of inflammasomes, its influence in the immune response and their role in the pathogenesis of metabolic diseases like diabetes and atherosclerosis.

Keywords

Inflammasomes, inflammatory caspases, intracellular microorganism defense, immune response polarization, immunometabolism.

Introducción

Evolution has granted higher vertebrate members with an efficient immune system which relies not only in an innate "seek and destroy" arrangement (dendritic cells, macrophages, neutrophils, eosinophil, and NK), but also in an adaptive mechanism to provide specific targets of destruction and long-lasting memory of such killing specificities (B and T cells). Even though, mainstream research was focused on the adaptive system for a long period of time, the discovery and characterization of Toll-like receptors in humans and other mammalians challenged the coined concept of "non-specific innate system". The Pattern Recognition Receptors (PRR) provide the cell with an array of complex proteins which are capable of activation of coagulation and complement pathways, inflammation, opsonization and induction of apoptosis, all mediated through the detection of Pathogen-Associated Molecular Patterns (PAMPs) – highly conserved

✉ **Autor de correspondencia:** Joselyn Rojas, Insituto de Inmunología, Edificio Louis Pasteur, al lado del IAHULA, Merida 5101, Venezuela, e-mail: rojas.joselyn@gmail.com

molecular signatures which work as beacons for microbial pathogens and stress signals from injured cells (1). The acquisition of PRR throughout evolution secured the interaction and recognition of PAMPs allowing the detection of infection, but the downside of the system is that PAMPs are not solely expressed in pathogenic microorganisms, it´s actually shared with commensal microflora (2-7). PRR can be classified in three groups (8): those which are assembled in the plasma membrane (like CD14, MARCO, among others), the intracellularly assembled (such as NODs and PKR), and the soluble forms (for example C-reactive protein and mannan-binding lectine). The purpose of this review is to dissect the molecular basis associated with the inflammasomes mediated by intracellular PPRs and their role in modulating normal immune response and metabolic diseases.

The Inflammasomes

Martinon et al. (9) published back in 2002 about a super molecular protein complex which was capable of activating caspase-1 and caspase-5, which were enzymes required for the final processing and cleavage of pro-IL-1β and pro-IL-18. In this first description, the authors explain that the complex requires caspase-1 and capase-5 recruitment, the coupling with the proteins ASC and NALP1. Of course, this first characterization has evolved over the past 9 years, thanks to several findings within the NLR family. The capability for activating proinflammatory caspases is not restricted to NLRP1/NALP1, in fact, NLRP3 and NLRC4/IPAF are also considered inflammasomes pathways for IL-1β, as well as inductors of autophagy and cell death (10-12); see Figure 1. The main role on inflammasomes is to serve as immune guardians of the cytosol, acting as sentinels by identifying intracellular pathogens through PAMPs and immediately inducing an inflammatory response.

Ting´s laboratory (13) began working on the characterization of the genes associated with the peculiar family of proteins CATERPILLER, which stands for CARD, Transcription Enhancer, R(purine)-binding, Pyrin, Lots of LEucine Repeats (LRR) (See Figure 2). The current nomenclature established that the family should be named NLR for Nucleotide-binding domain and Leucine-rich Repeats (15). According to phylogenetic and functional characteristics, 22 human genes have been characterized dividing them in 4 groups (15-16): a) the CIITA subfamily/NLRA, comprising one member containing a CARD domain, the signaling molecule CIITA (class II major histocompatibility complex transactivator) which activated the transcription of the MHC class II genes; b) the NLRB subfamily, with NAIP (Neuronal Apoptosis Inhibitory Protein); c) the CARD containing subfamily/NLRC, encompassing NLRC3 (NOD3), NLRC4 (IPAF), NLRC5 (NOD27), NOD1 and NOD2; and d) the NALP subfamily/NLRP, which has 14 members characterized by the presence of Pyrin, NATCH, NAD and LRR. There is a fifth subfamily, labeled NLRX, which has one member – NLRX1 – with no strong homology to the N-terminal domain, separating it from the other members of the family.

Inflammatory Caspases

The enzymes called caspases (Cysteine-ASPartic proteASES) can be divided into 2 groups according to the final function of their action: a) proapoptotic caspases, also classified into 2 subsets, the initiator caspases (Casp-2, -8, -9 and -10), and the effector caspases (Casp-3, -6 and -7); and b)

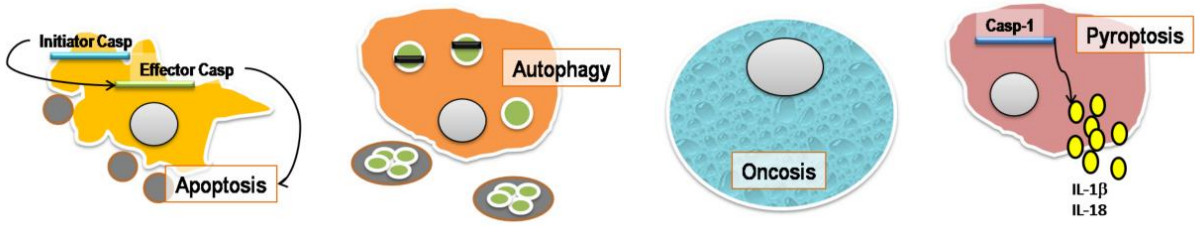

Figure 1. Mechanisms of cell death related to Inflammasomes. Apoptosis is associated with the production of effector caspaces which generate vacuolization and apoptotic bodies. Another form of celular death, autophagia, which is basically the degradation of cellular components in autophagy vesicles. Both mechanisms are considered not inflammatory. The swelling of the cell, blebbing, and membrane permeability control failure leads to a prelethal state called Oncosis, which precedes death by Necrosis. This process is *per se* not inflammatory, but cellular debris released induces anti-inflammatory response to begin its removal. Finally, Pyroptosis is a form of apoptotic cel death Casp-1 dependent, which can be theoretically induced by any of the inflammasomes, since their main product is the pro-inflammatory cytokine IL-1β which not only induces cell componet lysis, but is also related to degradation of glycolitic enzymes, proving to use several mechanisms to secure cell death. Adapted from Labbé et al. (12).

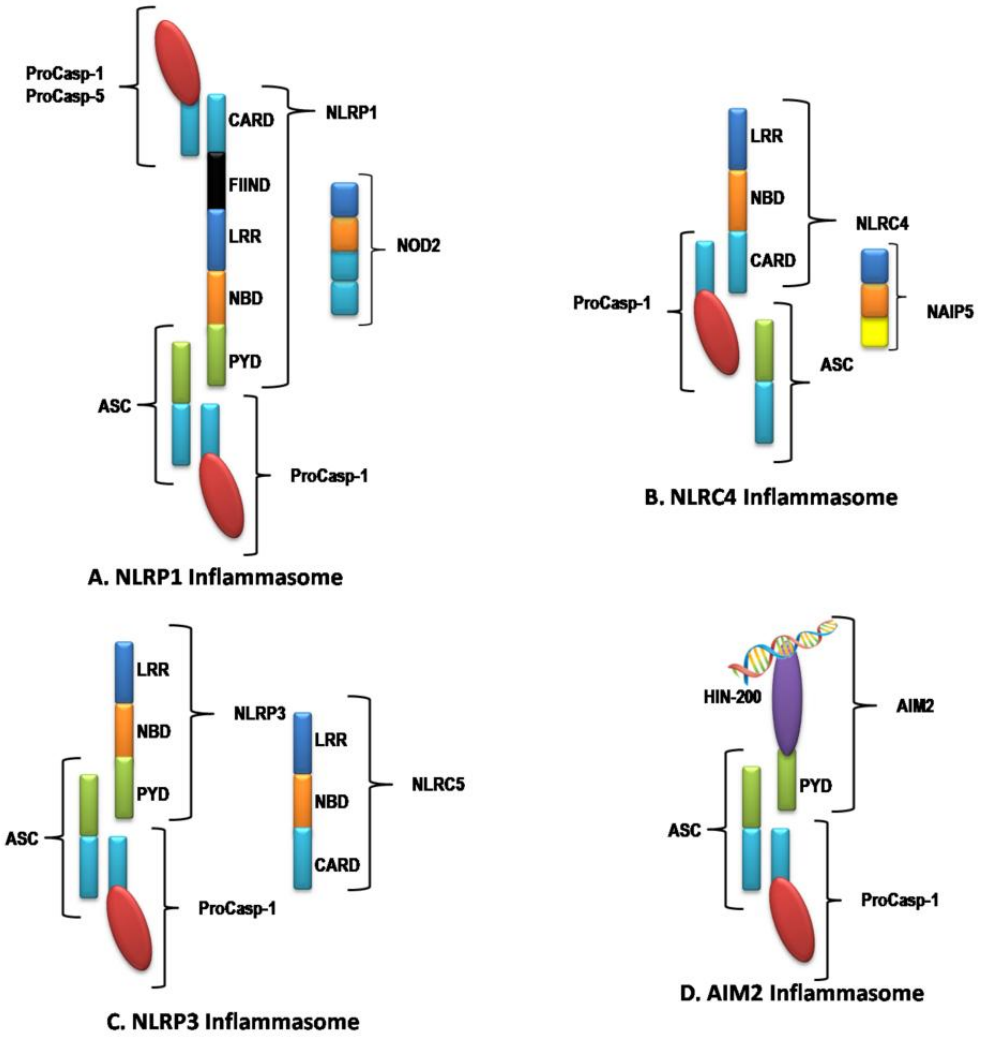

Figure 2. The diagram shows the different domains being assembled for each inflammasome. A – NLRP1 using a CARD domain in both termini of the protein, allowing for Casp-1 and Casp-5 activation. B – NLRC4 which is suspected to couple with NAIP5 (a Birci1e containing protein –yellow box) to modulate Casp-1 activation. C – NLRP3 showing its novel proposed interaction with NLRC5 for full activation of the complex. D – AIM2 and its 2-faced binding domains, PYD to recruit ASC and HIN-200 which allows DNA binding. Adapted from Kersee et al. (14).

inflammatory CARD-containing caspases, with Casp-1, Casp-4, and Casp-5 being related to inflammasomes and IL-1β and IL-33 formation (17). Caspases 11 and 12 are known modulators of Caspase-1 activity (18), where Casp-11 is required for proper inflammasome activation in the presence of LPS but is dispensable during *L. monocytogenes* infection, while Casp-12 is the natural inhibitor molecule, limiting damage to cells during severe infection and stopping unwarranted activity of the inflammasome to prevent situations like those observed in Familial Cold Urticaria and CINCA (Chronic Infantile Neurological Cutaneous Articular syndrome).

NLRP1 Inflammasome

The NLRP1 protein is expressed in blood immune cells, even overlapping with NLRP3, but the difference of expression lies in their distribution in epithelial cells (19). The first is absent from stomach and intestinal epithelia, while both are expressed in lung and endometrium serving as a danger sensing structure in these tissues. Other sources of NLRP1 are testis, oligodendrocytes and neurons. Even though it belongs to the Casp-1 inflammasomes it differs from the others because it has a FIIND motif and a CARD domain in its C-terminal portion, elements that are absent in the rest of the groups (20). Moreover, this C-

terminal CARD domain can interact and activate Casp-5 (21). In a steady-state, NLRP1 is inhibited by direct interaction with anti-apoptotic molecules Bcl-2 and Bcl-XL, behaving in a dose-dependent manner, reaching inhibition of ATP binding to the NATCH domain of the inflammasome (22). Several activators have been proposed, yet the protein is capable of binding muramyl dipeptide (MDP), using NOD2 along this pathway, activating a structural 3D modification in NLRP1 which allows binding of ATP and oligomerization. One of the most important danger patrolling activities of NLRP1 is the ability to induce pyroptosis in the presence of Anthrax lethal toxin. This secreted factor from *Bacillus anthracis* is known to cleave mitogen activated protein kinase kinase (MAPKK), blunting the MAPK/Erk1/2 pathways which is involved in survival (23). Pyroptosis is a form of cell death in which the effector caspase is in fact Caspase-1 and not Caspase -3, -6 or -7, being an inflammatory kind of death due to the effect of IL-1β. Newman et al. (24) reported that lethality form anthrax infection in rat depends on the chromosome 10 locus of NLRP1. Furthermore, Moayeri et al. (25) reported that mouse resistance to infection depended on the expression of toxin responsive (Nlrp1bS/S) or non-responsive (Nlrp1bR/R) alleles in neutrophils and macrophages. This toxin responsive phenotype allows for pyroptosis to occur after release of cathepsin B from the lysosomes ("lysosomal membrane permeabilization"), using this form of cell death as the mechanism of destruction of the agent (26).

NLRP3 Inflammasome

Just as NLRP1 expression, NLRP3 is expressed in immune cells, including B and T cells. Nevertheless, it is also observed in non-keratinizing keratinocytes from mouth, esophagus, ectocervix, vagina and urinary tract (19). Also, NLRP3 has been observed in skin keratinocytes, which suggests that this type of inflammasome is related to injury by ultraviolet light and similar agents (19). The ASC protein coincides with the expression pattern of NLRP3, although it is not exclusive since it´s also observed in spinal cord, trophoblast, tubule epithelium from kidney, colon, Leydig cells in testis, hair follicle and eccrine sweat glands in the skin (22). Arrays of stimuli are known to induce this superstructure, such as *Staphylococcus aureus*, *Listeria monocytogenes*, *Mycobacterium marinum*, *gonococcus*, *E. coli*, *Candida albicans*, LPS, MDP, nigericin, amongst others (21).

Several issues have been raised with this superstructure, modulation of the expression of Nlrp3 and activation mechanisms. It has been suggested that NLRP3 inflammasome assembly needs priming for proper oligomerization. Bauernfeind et al. (27) reported that NF-κB signals are a necessary checkpoint for NLRP3 activation, inducing Nlrp3 expression. Moreover they state that macrophages acquire NF-κB signals from other PRRs, probably Toll-like receptors, sending the signal to the nucleus to start transcription. As for the activation mechanisms, various classical models have been proposed (20): extracellular ATP and K^+ efflux, pore forming devices, and crystal activators. In an exemplary review, Tschopp and Schroder (28) describe the 3 mechanisms proposed of NPLR3 activation in the light of new information, giving emphasis in the new proposed role for ROS in the activation pathway. Briefly, the (a) channel model refers to an ATP-mediated activation which relies in K^+ efflux through the opening of the P2X2 ATP-gated ion channel; explaining how pore-forming toxins like the α-toxin of *S. aureus* (29) and nigericin (*Streptomyces hygroscopicus*) (30) induce pyroptosis. In the (b) lysosome rupture model, the release of cathepsin B from the failed phagocytosis triggers inflammasome activation. The last model involves the (c) production of Reactive Oxygen Species (ROS) and modulation of inflammasome activation.

The synthesis of ROS has been observed in virtually all NLRP3 inductors, thus suggesting that they play a part in the activation process. Further evidence comes from the observation that thioredoxin (TRX) interacts with NLRP3 (31). The thioredoxin system (32) has 2 enzymes at play, the TRX and thioredoxin reductase. Both proteins work in a circuit to reduce several potentially damaging substances, including hydrogen peroxide, oxidized gluthation, and other oxidized molecules. They are also known to inhibit apoptosis signal-regulating kinase 1 (ASK1) playing a role in the survival related to antioxidant substances (33). Zhou et al. (31) proposes that redox imbalance is one of the inductors of IL-1β production in inflammatory diseases, including type 2 Diabetes (34). The suggested mechanism involves the dissociation of thioredoxin-interacting protein (TXNIP) from its complex with TRX, in a ROS dose-dependent manner, allowing TXNIP to bind NLRP3. Now, in spite of evidence supporting the ROS theory, there are studies that seem to differ. Such is the case of van de Veerdonk et al. (35) who published that patients with mutations in the p47-phox subunit of the NAPH Oxidase complex (chronic granulomatous diseases - CGD) had enhanced IL-1β production, especially after being challenged with uric acid crystals, suggesting a modulating role (perhaps inhibition) in inflammasome activation. In fact, van Bruggen et al. reported that

NLRP3 activation is independent of NOX1-4 (36). In this same line of investigation, Meissner et al. (37) demonstrated that Casp-1 activity and IL-1β production was elevated in patients with asymptomatic CGD, concluding that ROS production is more likely to dampen or blunt NLPR3 inflammasome.

NLRC4/IPAF Inflammasome

Once thought to be the only one of its family to form an inflammasome, this protein has a CARD domain, which enables it to recruit Casp-1, but it requires ASC for full activation (19). This type of inflammasome is known for its activation in the presence of flagellin and type-III and type-IV secretion system from several bacteria including: *S. typhimurium*, *P. aeruginosa*, *S. flexneri*, *L. monocytogenes* (38) and most importantly *L. pneumophila* (39) due to the activation of Casp-7 and the restriction of lung infection (40). It has been recently shown that NLRC4 and NLRP3 induce the Casp-1-dependent cleavage and activation of the DNA damage sensor poly(ADP-ribose) polymerase 1, which is considered the hallmark for apoptosis, shedding more light into the mechanisms of pyroptosis (41).

AIM DNA sensing Inflammasome

Absent In Melanoma 2 (AIM2) is a pyrin-containing protein which is part of the interferon-inducible HIN-200 family, capable of recognizing double-stranded DNA (18). Bürckstümmer et al. (42) identified AIM2 as a cytoplasmatic DNA sensor, able to recruit ASC and its "speckles" (agglomerates), and to induce IL-1β production in monocytes, creating an inflammasome which is ASC dependent but NLRP3 independent. This finding was further supported by the work of Fernandes-Alnemri et al. (43), proposing that when viral DNA is located in unstable phagosomes NLRP3 is activated, but when DNA escapes the phagosome it is sensed directly through AIM2, inducing the activating cleavage of Casp-1 (44). This form of foreign DNA sensing is essential to the defense of intracellular bacteria and DNA viruses as has been observed in knock-out animal models (45) which show susceptibility to *L. monocytogenes* (46) and *F. tularensis* (47).

NLRC5 Inflammasome

Current findings indicate that this novel inflammasome is capable of interfering with antiviral responses. Benko et al. (48) reported that NLRC5 is mainly expressed in myeloid and lymphoid lineages, being involved in the blunting of type-I interferons and NF-κB pathways, while inducing IL-10 when LPS was applied to the model. In fact, it inhibits the phosphorylation of IKK and RIG-I/MDA5, limiting type-I responses while enabling NF-κB and early response elements like TNF-α and IL-6 (49). Moreover, it has been shown that viral infection NLRC5 is induced, being associated with JAK/Stat and INF-γ pathways, offering a beneficial effect during viral infection (50). Kumer et al. (51) reported that NLRC5 controls the synthesis of IL-1β, which was later associated to 3D interaction with NLRP3 through the NATCH domain, concluding that NLRC5 cooperates with the assembly of NLRP3 (52).

Polarization of the Immune Response

It has been suggested that IL-1β is crucial for the proper immune response against several microorganisms, including *Mycobacterium tuberculosis* with the activation of NLRP3 (53), *Francisella tularencis* (54) and *Listeria monocytogenes* (55) with the induction of AIM2 inflammasome. Recent findings also provide evidence of the modulatory aspects of inflammasome regarding polarization of the immune response, whether it is T_H1, T_H2 or even T_H17 (Figure 3).

Immune responses

IL-18 is a known T_H1 response modulator, which is able to induce TNF-α, IL-1β, INF-γ, Fas Ligand and several chemokines in T and NK cells (56), and in fact, IL-12 acts in conjunction with IL-18 and IL-1β to induce INF-γ in T effector cells, assuring the promotion of a T_H1 response and its proinflammatory phenomena (57). Nevertheless, if IL-18 is secreted without the influence of an IL-12 driven response, it can stimulate a Th2 response with allergenic inflammation, putting it central stage in the decision-making aspect of the response (58). In the animal model for experimental autoimmune encephalomyelitis (EAE), NLRP3 inflammasome is an important modulator of INF-γ and IL-17 production, controlling Th1 and Th17 cell production (59). The EAE is an experimental model for multiple sclerosis, determined by the presence of autoreactive T cells which can be differentiated towards Th1 cells if influenced by IL-1β, IL-12, IL-18 and INF-γ, while the Th17 cells are induced by IL-1β, IL-6 and TGF-β. Meng et al. (60) published an animal model which had a gain-of-function mutation in NLRP3 similar to the one found in the Meckell-Wells Syndrome, reporting that the mice had increased skin neutrophil infiltration and an enhanced Th17 response and autoinflammation. Moreover, knock-out models

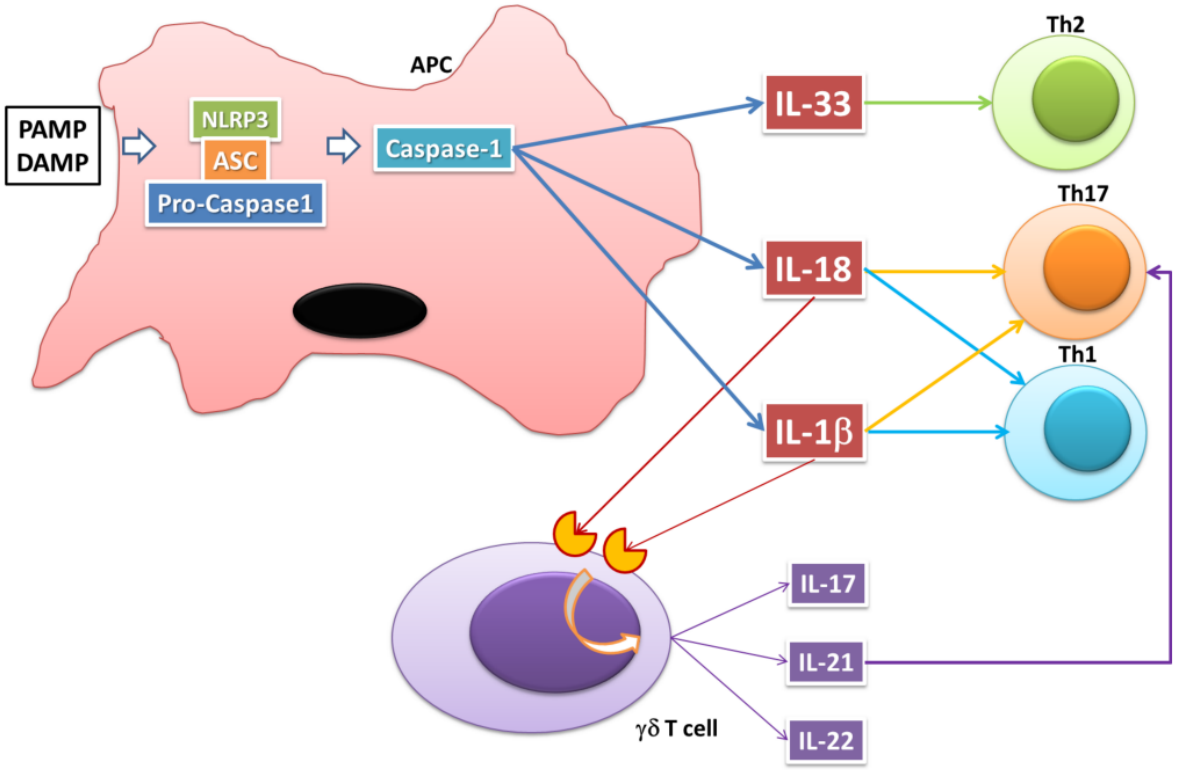

Figure 3. Polarization of the immune response by Inflammasome (NLRP3). The diagram shows the influence of the inflammatory caspases on the differentiation of T cell subsets. It also requires de participation of γδ T cells which aid in the differentiation of T_H 17 by the production of IL-21. Adapted from Dungan et al. (62).

for Nlrp3$^{-/-}$, IL-1β$^{-/-}$, IL-18$^{-/-}$ and Casp1$^{-/-}$ revealed that all of these elements are key factors in demyelination, which prove them to be important in neuroinflammation (61). The T_H17 response involves the participation of γδT cells and iNKT, which under the influence of IL-1β and IL-18 synthetize IL-17, IL-21 and IL-23, and in turn, these cytokines drive the Th17 differentiation (62). Finally, γδT cells also secrete IL-17 when IL-23 and IL-1β or IL-18 are acting upon them. The microenvironment of this reaction is then commanded by IL-17, inducing neutrophil recruitment, secretion of lipocalins and calgranulins, secretion of metalloproteinases, being regarded as a proinflammatory milieu (62-63). Given the importance of IL-1β and IL-18 in the T_H1/T_H17 response, it´s no wonder that mutations or hyperactivation stimuli are central in the development of autoimmunity, such as observed in models of EAE which demonstrate potential pharmaceutical target (64), type 1 Diabetes Mellitus (65), Cryopyrin-associated periodic syndromes (66), nephritic lupus (67), and even asthma (68). As for the T_H2 response, it has been shown that NLRP3 inflammasome is activated in dendritic cells and modulates the induction of Th2 lymphocytes in the lung, having a role in the control of the expression of Th2 cytokines, like IL-5, IL-13, IL-33 and thymic stromal lymphopoietin, and even in the eosinophilic recruitment, events mediated by the IL-1β axis (69). In fact, the adjuvant property of aluminum-based vaccines relies on inflammasome recognition and activation, which induces IL-1β, IL-18 and IL-33 in macrophages (70), concluding that inflammasomes are essential for humoral adaptive immune response (71).

Intestinal tolerogenic environment

The influence of gut microbiota in the maintenance of a tolerogenic microenvironment and physical integrity of the intestinal epithelial barrier has been subject of intense analysis, due to the ample implications of the concept, from proper absorption of food to the local symbiosis with the commensal bacteria. Even though, proinflammatory caspases have been associated with defense, they are also involved in tissue repair processes. In their experimental model,

Duapul-Chicoine et al. (72) used dextran sodium sulfate (DSS) to damage the colonic epithelium and evaluate the local response in knock-out mice for Casp1$^{-/-}$ and Nlpr3$^{-/-}$. The deficient mice showed intestinal bleeding, shortening and fibrotic changes in the colon, weight loss and increased mortality compared to the wild type mice. They propose that the Caspase-1 axis is essential to control inflammation, intestinal injury and local microbiota. These results correlate with those reported by Zaki et al. (73) who applied a similar methodology, and observed that after treatment with DSS commensal bacteria dispersed systemically with concomitant massive colonic leukocyte infiltration. Among the NLPRs associated with colonic ecology, are the NLRP6 and NLRP12 inflammasomes, assembled by the recruitment of ASC and processing of pro-IL-1β and pro-IL-18; these superstructures are relatively new in their description (74). Elinav et al. (75) described the role of NLRP6 inflammasome in the integrity of the epithelial barrier and its role in the maintenance of microbiota, finally modulating aspects of the tolerogenic microenvironment. In this publication, the authors proposed that the assembly of such inflammasome is driven by the detection of danger signals which alert of the loss of integrity of the colonic epithelial with the subsequent production of IL-18. In fact, Normand et al. (76) reported that NLRP6-coupled inflammasome is involved in the selfrenewal of the intestinal epithelium, acting as a negative regulator in colonic myofibroblast. Models deficient of Nlrp6$^{-/-}$ showed altered expression of Wnt/β-catenin proteins, probably related to dysregulation of Casein kinase ε which stabilizes β-catenin, and upregulation of the SMARCC1 transcription factor (SWI/SNF family of proteins). Since the expression of NLRP6 gene is controlled by PPAR-γ, the use of agonists to target this transcription factor in inflammatory bowel diseases or even in colorectal cancer is a potential pharmacological therapy (77).

Metabolic sensing

As a final consideration within the immune response polarization and modulation, there is growing evidence that suggests that type 2 diabetes, gout and even atherosclerosis can be considered as part of the autoinflammatory spectrum of diseases, due to the recruitment and assembly of NLRP3 inflammasome in these clinical syndromes (79). Insulin resistance and adipose derived inflammation have been recently linked to activation of inflammasome via ceramide sensing in macrophages and adipocytes, inducing the production of IL-1β and IL-18, with the subsequent elevation of IFN-γ, a local T_H1 driven response with enrichment of CD44+CD62L- T cells, and M1 macrophage activation that results in enhanced lipolysis, insulin resistance and glucose intolerance (78). Moreover, Stienstra et al. (80) evaluated the effect the Nlrp3$^{-/-}$, ASC$^{-/-}$ and Casp1$^{-/-}$ knock-out models and overfeeding, reporting that this deficiency protects against obesity induced by high-fat diet, confirming its role in the pathogenesis of obesity. Other metabolic traits were reported, such as lower levels of monocyte chemoattractant protein and resisting accompanied with higher levels of leptin, conferring a gene expression controlling property to this superstructure. Macrophage has been the main signaled culprit in the common metabolic diseases (81), and the understanding of NLRP3 inflammasome has shed some light in the matter, especially after the fact that glyburide – an anti-hyperglycemic drug – is known to inhibit cryopyrin assemble via microbial, DAMP or crystal pathways, blunting IL-1β secretion (82). On a final note concerning the adipocyte, the B cell has also taken part in the chronic inflammation milieu with the production of IgG2c pathogenic antibodies, derived from antigenic presentation within the adipose tissue necrotic sites (82), and it has supported the finding that in insulin resistant subjects several autoantibodies can be detected. This result conveys that in chronic overnutrition, there is an adaptive humoral response within the adipose tissue and it modulates the worsening of the insulin signaling (83).

In type 2 diabetes and β cell dysfunction, there is compelling data that suggests that NLRP3 inflammasome is fundamental in the deleterious effect observed in chronic hyperglycemia and oxidative stress. Hyperglycemia triggers an accelerated metabolism within the β cell mitochondria, which enhances the production of reactive oxygen species (ROS), which dissociate the heterodimer TXNIP from thioredoxin, allowing the former to induce the assembly of NLRP3 inflammasome and production of IL-1β (34) (see Figure 4). This creates a proinflammatory T_H1 driven microenvironment that enhances β cell dysfunction and cell death via NF-κB/MAPK induced CHOP pathway (84), but it is blunted in knock-out models for Nlrp3$^{-/-}$ and ASC$^{-/-}$ (85), Txnip$^{-/-}$ and Nlrp3$^{-/-}$ (86) or in experiments using IL-1β receptor antagonist (87); in the 3 scenarios previously mentioned, insulin sensitivity was enhanced alongside β cell increased survival and maintenance of glucose tolerance even in presence of a high-fat feeding state.

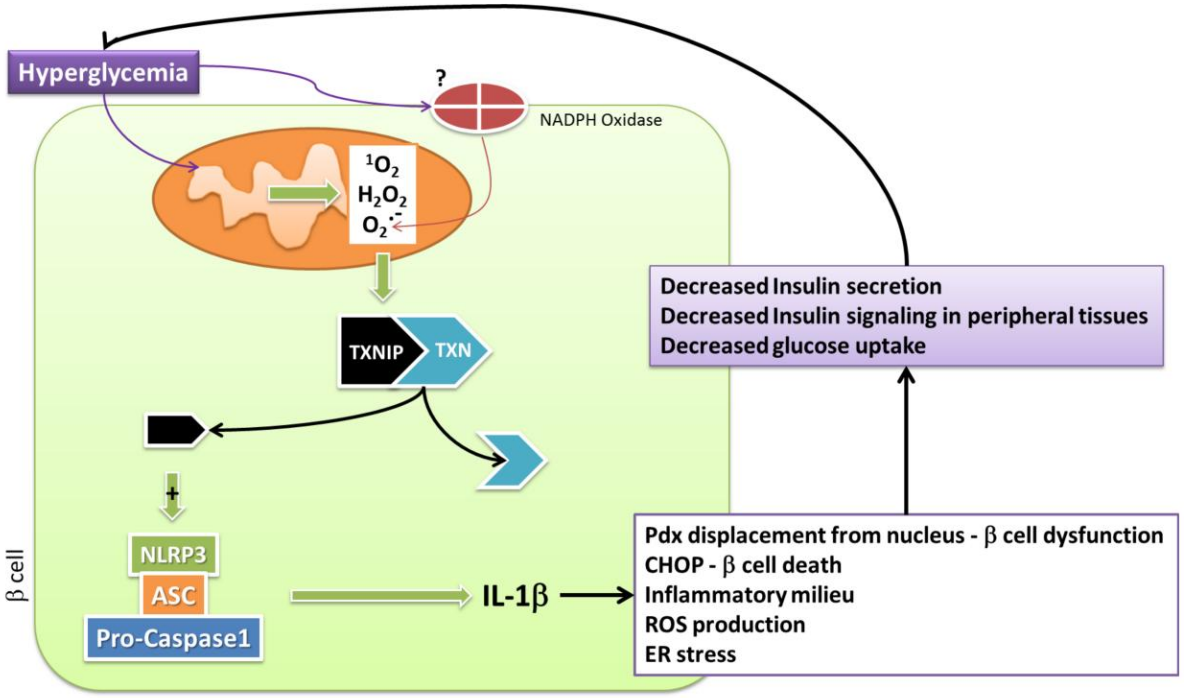

Figure 4. Role of Inflammasome activation during hyperglycemia and type 2 diabetes. The increase of ROS induces the separation of TXNIP from TXN, allowing the first to induce the NLRP3 inflammasome and increase the production of IL-1β. This inflammatory caspase is related to β cell death, diminished insulin secretion and ultimately, the enhancement and perpetuation of hyperglycemia. Adapted from Schroder et al. (34).

It has been known for quite a long time that atherosclerosis is an inflammatory disease, and various reviews have dwelled on this subject (88-90). In several models, the role of cholesterol has been essential for the development of the atherosclerotic plaque and the surrounding inflammatory milieu which renders it susceptible to rupture. Duewell et al. (91) reported in 2010 that cholesterol crystals were able to activate the NLRP3 inflammasome in phagocytes, inducing an acute inflammation site within the vessel; and these results were able to be reproduced even in animal models low-density lipoprotein receptor (LDLR) deficient, suggesting that the formation of foam cells is not the only way that cholesterol contributes to atherosclerosis. In fact, Rajamäki et al. (92) reported that human macrophages were able to engulf cholesterol crystals, inducing a dose-dependent IL-1β secretion. The crystals were able to activate the assembly of the NLRP3 machine via destabilization of the lysosome membrane and cathepsin B leakage to the cytoplasma. Moreover, cholesterol crystals are known to induce the oxidative stress-responsive transcription factor NF-E2-related 2 (Nrf2), and together prompt the synthesis of IL-1β, proposing a common pathway for oxidative stress and metabolic stress signals in the maintenance of vascular inflammation (93).

As for the case of the inflammatory disease gout, the monosodium urate crystals (MSU) are the main culprit concerning joint inflammation, pain and deformation. The macrophages phagocytize MSU and in exchange induce ROS production, ATP secretion and activation of the P2X7R, activating the NLRP3 inflammasome (94-95). Moreover, MSU can activate TLR2 and TLR4 and also inducing IL-1β (96). Even though MSU are the main pathogenic signal, not all patients with hyperuricemia develop gout, and the pain crisis are often associated with heavy meals or alcohol consumption. In this regard, Joosten et al. (97) reported that there is a synergistic effect between stearic acid and MSU, partially explaining the relationship between metabolic events triggering a gout attack. Finally, MSU are not exclusive for gout, since they are also associated with the activation of fibroblastic-like synoviocytes in rheumatoid arthritis, inducing the secretion of IL-6, CXCL8, and MMP-1 (98), and this effect is subject to modulation of polymorphisms associated with cryopyrin and CARD8 (99).

As a final note, I have to highlight the fact that several other molecules can trigger inflammasome assembly and are known as inflammasome activation disorders and they include: pseudogout, silicosis, asbestosis and Alzheimer´s disease (100). This doesn´t downplay the genetically defined inflammasome dysregulation disorders, which comprise the Familial Mediterranean fever, Cryopyrin-associated periodic syndromes, and Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (100). The analysis of these syndromes has shed light on the mechanistics involved in the activation disorders, providing groundwork to develop new pharmaceutical targets to control such diseases.

Concluding remarks

The abrupt abundance of data concerning this branch of the innate immune system, the inflammasomes, has offered answers to long-ago asked questions while creating new ones. Needless to say, this modifies the common concept that the innate system lacked specificity and memory and challenges the complexity of it. It requires a very specialized system that can survey, detect and initiate a destruction signal in the gut while canvasing over 10^{11} bacteria per gram of colonic content (101). This is no small task, and evolution has granted the permanence of several surveillance systems, and this includes the inflammasomes. These superstructures not only participate in the defense system against bacteria, fungi and viruses, but have also been involved in oncogenic control. Diane Mathis and Steven Schoelson recently published (102) that a merge in two classical fields have occurred while the vast knowledge concerning inflammasomes was being gathered, and that field is Immunometabolism. Diseases like type 2 diabetes, atherosclerosis and gout have been subject of extensive and multidisciplinary research, and this included immunology when the diagnostic criteria included low grade inflammation (103). From that moment on, the complex relationship between immune cells and endocrine systems has received growing attention, not only because it offers a more complete and integrated view of the pathogenesis of the diseases, but also because it offers another group of potential pharmacological targets.

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