Review Article

Novel Inflammasomes and Type II Diabetes, Intestinal Inflammation and Psoriasis as Newly Inflammasome-Related Diseases

Michael C. Heymann and Sigrun R. Hofmann*

University Hospital Carl Gustav Carus, Dresden, Germany

Abstract

Inflammasomes are multiprotein complexes representing an activating platform for caspase-1. This enzyme processes the cytokines IL-1β, IL-18 and others into their bioactive variants leading to an inflammatory cascade. Mutations responsible for defects in inflammasome regulation cause severe autoinflammatory disorders.

This review provides a short summary of new insights in the autoinflammatory field including the association of inflammasomes to diabetes, intestinal inflammation as well as psoriasis and communicates the ideas of two novel inflammasomes, recently discovered.

Introduction

During the last decade our knowledge of how cells sense potential critical substances and pathogens has improved significantly. First, the discovery of membrane-bound Toll-like receptors (TLRs), recognizing non-self structures and enabling the cell to sense extracellular and endosomal pathogen-associated molecular patterns (PAMPs), "revolutionized" our understanding of the innate immune system [1-3]. The detection of intracellular pattern-recognition receptors (PRRs), including NOD-like receptors (NLRs) [4], recognizing host-derived danger signals (danger associated molecular patterns, DAMPs), C-type lectin receptors (CLRs) [5,6] and RNA-sensing RIG-like receptors (RLRs) [7], further extended the image of pathogen recognition [8]. Exploring signal transduction from these receptors toward the nucleus led to the discovery of so called inflammasomes [9], a family of intracellular multiprotein complexes, also described as caspase-1 activating platforms. Inflammasomes oligomerize in the cytoplasm of innate immune cells to cleave and activate pro-inflammatory cytokines such as IL-1β and IL-18. These multiprotein complexes consist of a characteristic scaffold protein, namely NLRP1 (NOD-like receptor family, pyrin domain containing 1), NLRP3, NLRC4 (NLR family CARD (Caspase activation and recruitment domain) domain-containing protein 4) or AIM2 (Absent in melanoma 2). Besides that, the small adapter protein ASC (Apoptosis-associated speck-like protein containing a caspase recruitment domain) and the pro-inflammatory enzyme procaspase-1 are the other typical components of inflammasomes [10]. The NLRC4 inflammasome also can bind procaspase-1 directly, because NLRC4 has a CARD domain itself and does not necessarily need ASC [11]. Other studies claim that ASC may function as a stabilising or promoting supporter for inflammasome activity [10,12].

After the recognition of an activating signal, protein-protein-interactions via pyrin-domains (PYD) between the scaffolding protein and ASC, as well as via CARD-domains between ASC and procaspase-1 lead to the establishment of the multiprotein complex. This promotes the autoproteolysis of procaspase-1 and thus the activation of an enzymatically functional caspase-1. The activated heterotetrameric caspase-1 can subsequently cleave non-active pro-interleukin-1β (pro-IL-1β) and pro-IL-18 into its active mature variants IL-1β and IL-18 [13-15]. IL-1β and IL-18 secretion activates T-cells, stimulates their proliferation and differentiation and thus creates an appropriate answer of the immune system against the harmful substances or pathogens [16]. Other cytokines, which have been shown to be cleaved

by caspase-1, are IL-33 [17-19] and finally IL-1F7, which seems to be an anti-inflammatory molecule [19,20]. A short overview on the mechanisms of IL-1β and IL-18 activation is provided in Figure 1.

To date, four characteristic inflammasomes have been described. The NLRP1 inflammasome is activated by components of the bacterial cell wall, specifically muramyl dipeptid (MDP) [21] and the anthrax lethal toxin [22], the AIM2 inflammasome by cytoplasmic dsDNA [23], and the NLRC4 inflammasome mainly by flagellin [24,25]. In contrast, NLRP3 gets activated by a variety of different stimuli including MDP [26], toxins like nigericin [27] or alpha-toxin of *S. aureus* [28], live bacteria and bacterial RNA [29], viruses [30], fungi like *Candida* [31-33], but also DAMPs like asbestos [34], alum [35], ureat crystals [36], extracellular ATP [27], UV-radiation [37] or K+ efflux [38]. Eventually, to activate inflammasomes, cells have to be primed via TLRs [39,40]. This priming step causes the activation of NF-kB (nuclear factor kappa-light-chain-enhancer of activated B-cells) and thus boosts the production of pro-IL-1β and pro-IL-18. In a second step, activators of inflammasomes as non-self signals can be sensed and the inflammatory cascade is initiated. Notably, there is an ongoing controversial discussion among scientists whether certain microbial derived NLRP3-inflammasome-activators only play a role in priming the cells via TLRs and therefore are no real activators. How such a wide range of particles, substances and pathogens leads to NLRP3 activation remains unclear. Some authors claim reactive oxygen species (ROS), which are produced by mitochondria in response to cell stress, to be the transmitter for NLRP3 activation [41]. Others postulate that inhibition of ROS only prevents the priming step of inflammasome dependent inflammation and not inflammasome activation itself [42]. Another mediating process could be lysosomal rupture which goes along with

*Corresponding author: Dr. med. Sigrun R. Hofmann, Department of Pediatrics, University Hospital Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany, Tel:+49-351-458-18125; Fax:+49-351-458-6333; E-mail: sigrun.hofmann@uniklinikum-dresden.de

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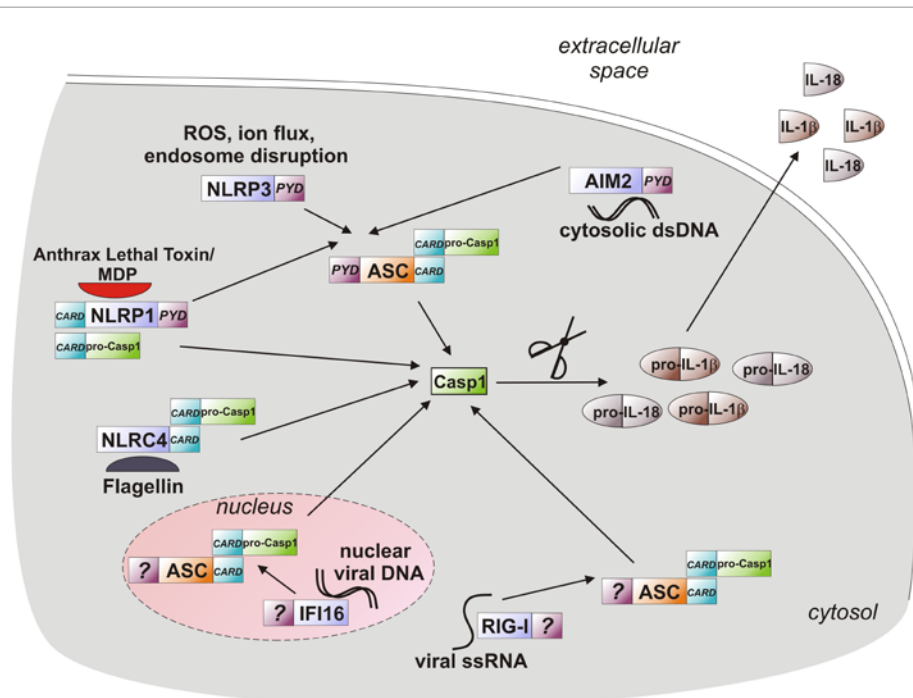
Figure 1: The inflammasomes in IL-1β and IL-18 activation. Certain danger signals and pathogens trigger the assembly of a multiprotein complex called the inflammasome. Inflammasomes consist of a scaffolding protein, in particular NLRP1, NLRP3, NLRC4, AIM2, and recently discovered RIG-I and IFI16, of ASC and of procaspase-1. NLRP1 and NLRC 4 can also bind procaspase-1 directly. The assembly is responsible for autoproteolysis and thereby activation of caspase-1 which subsequently can cleave the non-active inflammatory cytokines pro-IL-1β and pro-IL-18 into their mature and biologically active variants.

ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CARD, caspase activation and recruitment domain; Casp1, enzymatically active caspase-1; dsDNA, double stranded deoxyribonucleic acid; IFI16, interferon gamma-inducible protein 16; IL-18, interleukin-18; IL-1β, interleukin-1β; MDP, muramyl dipeptide; NLRC4, NLR family CARD domain-containing protein 4; NLRP1, NOD-like receptor family, pyrin domain containing 1; NLRP3, NOD-like receptor family, pyrin domain containing 3; pro-Casp1, procaspase-1; PYD, pyrin domain; RIG-I, retinoic acid inducible gene-I; ROS, reactive oxygen species; ssRNA, single stranded ribonucleic acid.

the release of cathepsin into the cytoplasm [35,40]. However, obviously more studies are needed to shed light into the darkness of NLRP3 activation steps.

Autoinflammation and inflammasome associated diseases

Based on the discovery of mutations in *MEFV* and *TNFRSF1A* genes in patients with recurrent periodic fevers more than ten years ago, the concept of autoinflammation has been introduced by the groups of McDermott and Kastner [43]. Starting from the disease-associated gene, the discovery of the underlying molecular mechanisms and inflammatory pathways has stimulated research enormously. IL-1β has been rediscovered as a central cytokine in these human diseases.

A continuous spectrum of monogenic recurrent fever syndromes is caused by mutations of NLRP3 or cryopyrin which are collected in the group of the so called cryopyrin associated periodic syndromes (CAPS) [44]. Those include neonatal-onset multisystem inflammatory disease (NOMID), as the most severe disease entity, the Muckle Wells Syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS), as less affected variant [44]. Patients do not only suffer from recurrent fever episodes but also from conjunctivitis, inflammation of the skin and the joints, and, in the case of NOMID, also from inflammation of the meningi as well as the inner ears and additionally from bony epiphyseal hyperplasia [44].

Depending on mutations in the pyrin-encoding gene *MEFV* the Familian Mediterrean Fever (FMF) is probably the most frequent monogenic inflammasome-associated disease. Pyrin is a negative

regulator for the PYD-PYD-interactions between inflammasome core proteins like NLRP3 and the adaptor protein ASC [45-48]. Interestingly, Chae and colleagues [49] postulated that gain of function mutations in *MEFV* cause severe inflammation dependent on ASC but independent of NLRP3 [49].

Several advances in the study of monogenic auto-inflammatory syndromes recently have occurred including the discovery of the deficiency of the IL-1 receptor antagonist (DIRA) in humans [50,51]. This disease entity leads to a severe neonatal inflammation presenting as osteolytic bone lesions and pustular skin lesions [50]. It has also been shown that loss of function mutations in the IL-10 receptor gene lead to early-onset enterocolitis [52].

These autoinflammatory diseases have been defined by McGonagle and McDermott as a "self directed inflammation, whereby local factors at sites predisposed to disease lead to activation of innate immune cells, including macrophages and neutrophils, with resultant target tissue damage." [53]. Additionally, there is usually a great association with exogenous stimuli, a lack of autoantibodies and the periodic characteristics [19]. It is important to emphasize that not every disease accompanying inflammation can be associated with either autoinflammation or autoimmunity. It is more likely that diseases with ambivalent background and pathogenesis are classified as a mixture of both [53]. An overview on autoinflammatory diseases is given in Table 1 [19,44].

During the past few years more and more immune disorders

Familial Mediterranean fever (FMF)	Urate crystal arthritis (gout)
Familial cold autoinflammatory syndrome (FCAS)	Behçet's syndrome
TNF receptor-associated periodic syndrome (TRAPS)	Pericarditis
Neonatal-onset multi-inflammatory disease (NOMID)	PAPA syndrome
Deficiency of the interleukin-1–receptor antagonist (DIRA)	Blau's syndrome
Muckle-Wells syndrome (MWS)	Sweet's syndrome
Normocomplementemic urticarial vasculitis	Type 2 diabetes
Hyper IgD syndrome (HIDS)	Majeed syndrome
Chronic recurrent multifocal osteomyelitis (CRMO)	Cherubism
Systemic-onset juvenile idiopathic arthritis (soJIA)	FCAS2
Mevalonic aciduria	Early-onset enterocolitis (IBD)
Macrophage activation syndrome (MAS)	Anti-synthetase syndrome
Schnitzler's syndrome	Adult-onset Still's disease

The family of autoinflammatory diseases

Table 1: Autoinflammatory diseases.

became explored that had not yet been associated with inflammasomes, but have now been affiliated into the big family of autoinflammatory diseases.

Diabetes and inflammasomes

The link between obesity and diverse metabolic diseases is known for a long time. One important complication of obesity is the higher risk of developing diabetes and atherosclerosis. For both diseases it has been shown recently, that they are IL-1β-mediated autoinflammatory diseases. Obesity-related factors like hyperglycemia [54], cholesterol crystals [55], free fatty acids [56] and ceramides [57] are triggers for inflammasome activation, leading to the release of the proinflammatory cytokines IL-1β and IL-18.

The pathomechanism underlying the failure of pancreatic beta cell function in patients with type II diabetes is a chronic inflammatory process. It has been shown that this insulitis is driven by glucose, free fatty acids, but also IL-1β [58-60]. In addition, the expression of interleukin-1-receptor antagonist is decreased in beta cells from type II diabetes patients leading to IL-1β-mediated inflammation and beta cell death. These processes are mediated and reinforced by infiltrating macrophages [61]. Neutralization of IL-1β or blockade of IL-1 receptor will prevent this vicious cycle of IL-1β autostimulation and correct beta-cell dysfunction and insulin production in type II diabetes. In a clinical trial, Larsen and colleagues [60] showed that the blockade of IL-1β and IL-1α with anakinra improved glycemia and beta-cell secretory function in type II diabetes patients and reduced markers of systemic inflammation. A long lasting inflammatory and metabolic remission was still found 39 weeks after withdrawal of anakinra [60].

Several investigations followed this clinical trial. Stienstra and colleagues [62] demonstrated that caspase-1 is upregulated during adipocyte differentiation and directed these cells toward adipocytes being less sensitive to insulin. This differentiation is mediated by IL-1β which displays the connection to the inflammasomes. A higher grade of activity of the inflammasomes could lead to more IL-1β and thus to a lower level of insulin sensitivity. In contrast, mice deficient in caspase-1 (Casp1$^{-/-}$) were more insulin sensitive as compared to wild-type animals, and the use of a caspase-1 inhibitor in wild type adipocytes raised the sensitivity to insulin. Additionally, the adipocytes of Casp1$^{-/-}$ mice and of NLRP3$^{-/-}$ mice differentiated to more metabolically active and insulin sensitive types [62].

Furthermore, Owyang and colleagues [63] fed mice with a high fat diet (HFD), resulting in elevated glucose levels, less glucose tolerance and reduced insulin secretion. Those symptoms were prevented when the mice were treated with the IL-1β antibody XOMA 052. Moreover, beta cell apoptosis was decreased and beta cell proliferation was enhanced [63].

The relation between diabetes and inflammasomes was further investigated by Vandanmagsar and colleagues [57]. They found that weight loss of obese individuals decreased the expression of NLRP3 in the adipose tissue and moreover reduced inflammation and promoted insulin sensitivity. They also showed that NLRP3$^{-/-}$ mice had no obesity-induced inflammation in the liver and fat depot, and that NLRP3 depletion led to extended insulin signalling. Additionally, this paper described that lipotoxicity-associated ceramide could activate NLRP3 and thus result in caspase-1 activation and IL-1β maturation, that could cause inflammation and insulin deregulation [57]. Of course other substances typically increased in obese individuals, like oxidized low density lipoprotein (LDL) [64] as well as cholesterol [55], may interact with the inflammasome mechanism and interfere in insulin signalling.

In the past it has been shown that pancreatic cells from type II diabetes patients show amyloid deposits [65]. Therefore, several groups explored the role of islet amyloid polypeptide (IAPP) in diabetes patients [66,67]. IAPP did not only activate NLRP3 inflammasome but also caspase-1 and ASC speckle formation [68]. The subsequent IL-1β production impaired viability and functionality of beta cells. This may not be the causal reason for diabetes manifestation alone but could contribute to the decline of the beta cells and, due to that, the insufficient insulin signalling. Masters and colleagues also reported that glucose metabolism was necessary for NLRP3 activation by IAPP and that LPS as well as minimally modified LDL as a TLR4 agonist were able to realize the priming step [68].

Another study [69] revealed that certain polymorphisms of the NLRP3 gene (SNP rs12150220) are associated with a higher risk of type I diabetes. In addition, there are increasing preclinical data implying IL-1β as mediator of pancreatic beta-cell destruction in type I diabetes [70]. Furthermore, clinical trials with IL-1β blockade have been initiated in patients with new-onset type I diabetes to eventually preserve residual beta-cell function [71,72].

Taken together, adipocyte function and insulin sensitivity are regulated by inflammasomes, and caspase-1 inhibition or IL-1β blockade may represent a novel therapeutic target.

Considering the large number of people who will be affected by type II diabetes in the next decades, estimations range to at least 300 million people in the year 2025 [73], it is absolutely essential to investigate and finally discover the pathogenesis of this disease and to find out, which role the inflammasomes play in this context.

Inflammasomes in intestinal inflammation and tumorigenesis

Another interesting subject, connected to inflammasomes, is the intestinal inflammation. Several papers have been published during the last few years dealing with the effect of diverse inflammasome components or the inflammasome dependent cytokines on colitis and colitis associated cancer (CAC). Notably, the results are not only differing but sometimes oppositional, which implies a controversial discussion concerning the role of the inflammasomes during colitis and CAC.

The participation of the inflammasomes and the inflammasome

dependent cytokines IL-1β und IL-18 in colitis is already evident for some years. In 2002, Tamura and colleagues [74] found, that an IL-18 polymorphism is significantly associated with Crohn's disease [74], a chronic inflammatory bowel disease, which alters cytokine production and homeostasis of host microorganisms in the intestinal tract [75]. IL-18 represents a very important part in protecting and renewing epithelial tissue [76]. Besides IL-18, which gets cleaved and thus activated by caspase-1, NLRP3 SNPs were also identified as a risk factor for developing Crohn's disease [77].

Colitis and CAC can be studied using dextran sodium sulfate (DSS) or DSS + azoxymethane (AOM) respectively as stimulating noxa [8]. Considering the above mentioned results, Allen and colleagues [78] induced colitis in different knockout mice, using the DSS system. They demonstrated, that NLRP3$^{-/-}$, ASC$^{-/-}$ and Casp1$^{-/-}$ animals developed a more severe colitis and to a higher extent CAC compared to wild type animals. NLRP3 deficient mice showed the less severe inflammatory reaction compared with the other knockout animals. One possible pathophysiological explanation, why these different knockouts increased the susceptibility to colitis, might be impaired apoptosis and thus weakened repair and renewal of epithelial cells, altered intracellular signalling and of course a faster and unimpeded growth of tumor cells. Accordingly, Dupaul-Chicoine and colleagues [79] found, that Casp1$^{-/-}$ mice showed impaired tissue repair, more severe inflammation and a higher mortality rate, when they were treated with DSS compared with wild type animals. ASC$^{-/-}$ mice were also affected, but to a lower extent. The scientists argued that caspase-1 contributes to healing and repair of the mucosal tissue, thereby inhibiting penetration of epithelial cells by intestinal microbes [79]. Correspondingly, recent studies revealed, that epithelial cells in the gastrointestinal tract of NLRP3$^{-/-}$ mice showed a lower proliferation rate during acute colitis. Furthermore, the epithelial tissue was more permeable, hence bacteria as well as leukocytes could penetrate easier into the colon mucosa [80]. Zaki and colleagues also showed that treating NLRP3 deficient mice with 4 % DSS led to more than 80 % mortality, whereas only 20 % of the wild type mice did not survive this treatment. Using only 3 % DSS increased the survival of both but demonstrated the more severe colitis-associated complications, NLRP3$^{-/-}$ mice suffered from. They showed more rectal bleeding, a higher loss of weight, increased inflammation, and more necrotic lesions in the infected tissue in addition to shortened colon length. In this study, ASC$^{-/-}$ mice and Casp1$^{-/-}$ mice were comparable with the NLRP3 deficient animals [80]. At molecular levels, the decreased secretion of IL-18 played the most important role in these knockout animals. When NLRP3$^{-/-}$ mice were provided with recombinant IL-18, the symptoms during colitis were less severe compared to non treated animals [80].

Although the contribution of flagellated microbes like *Shigella* and *Salmonella* to gastrointestinal infections raises the potential for NLRC4 to be responsible for colonic inflammation [12,24,81], the scientists could not show any significant involvement of this inflammasome in colitis or CAC [78].

Hu and colleagues [82] used the DSS + AOM model to induce CAC. Caspase-1 deficient mice showed enhanced tumor growth due to an impaired control of proliferation and apoptosis of the epithelial cells. Interestingly, between NLRP3$^{-/-}$ mice and wild type animals no differences concerning tumorigenesis or colitis were detected. In contrast, a higher tumor rate and a more aggressive tumor expansion were observed in NLRC4$^{-/-}$ mice [82]. These data lead to the assumption, that intrinsic alterations in the epithelial tissue like gene expression or apoptosis control are responsible for the more aggressive tumor expansion in caspase-1 and NLRC4 deficient mice [82].

In total contrast to the so far introduced studies, Bauer and colleagues [83] postulated, that NLRP3 deficient mice supplied with 2 % DSS survived the colitis whereas 27% of the wild type population died. Additionally, NLRP3$^{-/-}$ showed fewer leukocyte infiltrates in the colonic tissue, less pro-inflammatory cytokine secretion and less tissue damage [83]. Moreover, DSS-treatment of macrophages led to IL-1β production which not only depended on caspase-1, ASC and NLRP3, but also on lysosome maturation and ROS [83]. Remarkably, the pharmacological inhibition of caspase-1 with pralnacasan rescued from the severe colonic inflammation observed in wild type animals after DSS administration [83].

These facts demonstrated a completely different function of NLRP3 inflammasome in colitis. Whereas other studies postulated a preventive role of the inflammasomes, whether NLRP3 or NLRC4, by supporting the homeostasis of the epithelial tissue, Bauer and colleagues suggest a pro-inflammatory character which supports the development of a colitis and CAC after DSS treatment [83].

The recent data disclose the necessity for more studies in this relatively new field of research. The contribution of the inflammasomal components and the inflammatory cytokines IL-1β and IL-18 to colitis and CAC is undisputable. But in which direction mutations or deficiencies in certain components push colonic inflammation is still unclear. On the one hand, different concentrations of DSS administered to the animals for colitis induction could lead to different results. On the other hand, differing genetic background, variable microfloral environment in the animal facilities and a different gender of the animals could also contribute to the contradictory outcomes of the studies mentioned [79].

Especially the effects of the experimental conditions on the colonic microbiota could give more reasons for opposing results. Elinav and colleagues [84] found, that NLRP6 seems to be a regulator of microbiotic homeostasis in the gut, which is among others relying on the housing conditions and co-housed mice. In short: NLRP6 inflammasome-deficient mice suffering from colitis induced by exposure to DSS developed spontaneous intestinal hyperplasia and inflammatory cell recruitment. If they were co-housed with wild type mice, they may transfer their colonitic activity to the healthy individuals negatively affecting their physical state [84]. Additionally, mice deficient in NLRP6, ASC, caspase-1 or IL-18 showed an altered gut microbial ecology as well as an increased susceptibility towards DSS induced colitis [84]. The latter may be due to the disproportional overgrowing by certain bacteria species which might also act as an initiatory incident in inflammatory bowel diseases.

Inflammasomes and psoriasis

Besides diabetes and colitis, another inflammatory disease was recently related to inflammasomes. Dombrowski and colleagues [85] studied keratinocytes from patients suffering from psoriasis. This is a chronic inflammatory disease of the skin, which affects about 2 % of the worldwide population [86]. However, the exact number is differing between various countries. In India 0.7 % of the population is affected, whereas in the United States 4.6 % of the people are suffering from psoriasis [86]. Scientists could show that higher amounts of cytosolic DNA and the inflammasomal scaffolding protein AIM2 were detectable in psoriatic skin sections [85]. Additionally, keratinocytes produced more IL-1β after transfection of poly (dA:dT) due to the activation of the AIM2 inflammasome. For this activation via DNA, the cells had to be primed with interferon-γ (IFN-γ) or tumor necrosis factor-α (TNF-α) previously. In addition, the cells secreted more active caspase-1 after they were primed with IFN-γ or TNF-α [85].

Furthermore, an anti-inflammatory effect of LL37 is described in this paper. LL37 is the human variant of the anti-microbial cathelicidine. Previously, LL37 was supposed to have a pro-inflammatory effect due to its DNA binding capacity and hence its potential to activate TLR9 [87]. Additionally, significantly more LL37 was found in psoriatic lesions compared to healthy skin [87]. Surprisingly, LL37 led to a reduced release of AIM2-dependent IL-1β. This could possibly be due to its positive charge what raises its capacity to bind DNA. Binding the cytosolic DNA to LL37 after its penetration into the cell inhibits AIM2 sensing of the cytosolic DNA. Therefore, the AIM2 inflammasome is not activated with the result that caspase-1 remains inactive and IL-1β is not processed [85]. Interestingly, vitamin D, which endogenously controls LL37, is used therapeutically in psoriasis patients [88]. Considering the great number of people suffering from this inflammatory skin disease, the contribution of the AIM2 inflammasome to psoriasis pathogenesis and maintenance implies a new therapeutic potential.

New inflammasomes: RIG-I inflammasome

Retinoic acid inducible gene-I (RIG-I), as one of the RNA-sensing RIG-like receptors (RLRs), is responsible for recognizing RNA-viruses. Its ligand is ssRNA, more precise 5' triphosphate RNA (3pRNA) [89,90], indicating RIG-I as the counterpart to the dsRNA identifying RLR melanoma differentiation-associated antigen 5 (mda5) [91,92]. RIG-I may also sense short dsRNA fragments, for instance when the artificial mda5 ligand polyinosinic-polycytidylic acid was used in a short variant [93,94].

Recent studies revealed more functions of RIG-I than known. This RLR is commonly known for its important role in virus infections by inducing interferon (IFN) pathways besides TLR signalling [95]. This is realized via interaction with mitochondrial antiviral-signalling protein (MAVS) and subsequent signalling pathways including TNF receptor-associated factor 3 (TRAF3) and TRAF6, inhibitor of NF-κB kinase-ε (IKKε), and IFN response factor 3 (IRF3) and IRF7 [92]. Additionally, a complex consisting of RIG-I, MAVS, CARD9 and B-cell lymphoma/leukemia 10 (Bcl-10) is responsible for activation of NF-κB as an important pro-inflammatory transcriptional factor [96].

Besides these functions of RIG-I, Kim and colleagues [97] reported that caspase-1 decreased the level of intracellular RIG-I depending on its enzymatic activity [97]. Moreover, they demonstrated a physical interaction between RIG-I and procaspase-1 reliant on the CARD domain and the helicase domain of RIG-I but independent of the CARD domain of procaspase-1 [97], what may lead to the assumption that an active caspase-1, not bearing the card domain anymore, is also capable of binding RIG-I. Furthermore, the scientists postulated a putative interaction between ASC and RIG-I based on immunoprecipitation studies [97].

Relying on these results, Poeck and colleagues [96] studied the role of RIG-I in IL-1β maturation. They could show IL-1β activation after stimulating cells with vesicular stromatitis virus (VSV) or transfecting 5' triphosphate RNA. This activation was depending on caspase-1 activation and was abrogated when RNA without a 5' phosphate residue was used [96]. Additionally, they observed that IL-1β maturation after RIG-I-stimulation was absent in cells of ASC⁻/⁻ mice whereas cells of NLRP3⁻/⁻ mice showed no different secretion pattern of IL-1β [96]. This phenomenon was elucidated after immunoprecipitation studies that revealed an interaction between ASC and RIG-I after VSV-infection, although this interaction became apparent in uninfected cells, too [96].

Summarizing these recent data, the existence of a postulated RIG-I-inflammasome becomes very likely [92,96,98]. Triggered by 3pRNA or short dsRNA, RIG-I does not only function as an interferon stimulator but also as a sensor responsible for IL-1β production. By boosting the NF-κB-pathway via MAVS, pro-IL-1β is produced, which subsequently gets cleaved by activated caspase-1. This activation is facilitated by the assembly of a complex consisting of at least RIG-I, ASC and caspase-1 [92,96]. Considering these RIG-I mediated pathways, this viral RNA sensor provides the first priming signal for IL-1β-activation by interfering with the NF-κB-activation and importantly also the second activating signal by forming the inflammasome as an IL-1β activating platform [92]. However, it is also possible that RIG-I supports a so far unknown and NLRP3-independent inflammasome [98] and thus may be indirectly responsible for IL-1β-maturation.

IFI16 as a nuclear inflammasome

A recent study provided evidence that another protein is involved in caspase-1 activation. Kerur and colleagues [99] investigated the role of interferon gamma-inducible protein 16 (IFI16) [100] in inflammasome establishment and IL-1β processing.

Virus derived dsDNA in the cytoplasm is sensed by AIM2, and subsequently caspase-1 activation and IL-1β maturation create an appropriate immunological answer [23]. The question remained how cells can sense viral DNA in the nucleus. In sera as well as in lesions of patients infected with the nuclear replicating Kaposi sarcoma-associated herpesvirus (KSHV), IL-1β levels are elevated. Additionally, de novo infected endothelial cells or human THP-1 cells produced higher amounts of pro-IL-1β and secreted more biological active mature IL-1β [99]. This IL-1β upregulation went along with the activation of caspase-1. Interestingly, UV-inactivated KSHV, which can still penetrate the cell regularly but cannot lead to a nuclear phase of the infection anymore [101], could only activate caspase-1 shortly after internalisation most probably via recognition of the DNA in the cytoplasm by AIM2. In contrast, functional virus capable of infecting the cell latently allowed a longer activation [99]. Importantly, the scientists could also reveal a speckled co-localisation of IFI16, ASC and caspase-1 in the nucleus of infected cells 2 hours post infection (p.i.). The staining changed to a more perinuclear pattern at later time points beginning at 8 hours p.i. Immunoprecipitation studies showed an interaction between ASC and IFI16 after infection with KSHV, whereas ASC and AIM2 only interacted shortly after internalisation of the virus. Eventually, immunofluorescence studies showed a co-localisation of IFI16 and the KSHV genome in the nucleus. Knockdown of ASC or IFI16 with shRNA decreased caspase-1 activation by 60% or 85% respectively [99].

These data are in contrast with previous publications, where no interaction between IFI16 and ASC were observed [23,102]. However, the latter scientists focused on cytoplasmic localisation of the stimulation and the detection. Yet, there is the possibility of a mechanism how cells sense viral DNA in the nucleus. Kerur and colleagues [99] provide first indication that IFI16 could be a putative component of a nuclear inflammasome responsible for defending viral pathogens.

Conclusion

Inflammasomes have been discovered as important players in the defence of pathogens and threatening substances. Plenty of activators have been described during the last years which enhanced our knowledge concerning many different diseases enormously. Nonetheless, more and more improvements accompany our research. It will be a challenging task to further reveal the association of the inflammasomes with different diseases beyond characteristic monogenic autoinflammatory

syndromes. Additionally, the family of inflammasomes still seems to be incomplete. The discovery of new components of the multiprotein complexes or even completely new inflammasomes may further advance our understanding of autoinflammation and autoimmunity helping us to create new models of cellular signalling, to uncover so far unknown networks and eventually find novel treatments and therapies for our patients.

Acknowledgements

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