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The regulation of inflammasome activation and inflammasome-dependent cytokine expression by IL-1 blockade

Abstract

Many autoinflammatory disorders are caused by a dysregulation of inflammasomes. This leads to a divergent expression pattern of inflammasome-dependent cytokines IL-1β and IL-18. Although IL-1 blockade is very effective in many autoinflammatory disorders, and has significantly improved quality of life, the molecular pathways by which the symptoms are inhibited remain incompletely understood. The canonical activation of the inflammasome is characterized by a two-signal cascade, consisting of increased expression of inflammasome components caused by recognitions of pathogen associated molecular patterns (PAMPs), damage associated molecular patterns (DAMPs) or homeostasis-altering molecular processes (HAMPs) as the first signal, and a second signal of recognition of such signals by the inflammasome itself leading to its activation. Noncanonical activation of the inflammasome can be acquired via activation of caspase-8. On a posttranscriptional level inflammasome activation can be regulated by processes such as phosphorylation and deubiquitination. Inflammasome activation leads to cleavage of pro-IL1β, pro-IL18 and gasdermin D, leading to pyroptosis and an proinflammatory response. Despite the canonical cleavage of pro-IL1β and pro-IL18 by caspase-1, also other proteases from different immune cells are able to cleave the immature proteins into pro-inflammatory molecules. Although pro-IL-18 is constitutively expressed in many cell types, in contrast to pro-IL-1β, much remains unknown about the specific homeostatic functions of IL-18 and its role in (the persistence of) autoinflammatory diseases. Hence, it is not known how IL-1 blockade can contribute to the silencing of the whole inflammasome pathway when just one component is inhibited. Here, we review the current knowledge of inflammasome activation and IL-1β and IL-18 processing, as well molecular mechanisms of inflammasome-dependent cytokine regulation by IL-1 blockade.

Laymen summary

Autoinflammatory disorders are diseases that are primary caused by the innate immune system and more specifically by changes in the inflammasome activation. The inflammasome is a complex of multiple proteins that, once activated, will cleave the immature form of the inflammatory mediators IL-1β and IL-18 into biologically active proteins. Cleavage of the inactive precursors of IL-1β and IL-18 is mainly done by the protein caspase-1, which is part of the inflammasome complex. These proteins will be released from the cell, bind to their receptors and aggravate the inflammatory reactions, resulting in clinical symptoms such as fever and ultimately organ damage. The inflammasome is normally activated by a two-signal cascade. Signal 1 consists of binding of danger signals such as microbial molecules to the immune cells which leads to an increased expression of inflammasome components. Binding of other danger signals to the inflammasome results in activation of the inflammasome and is considered as signal 2. The inflammasome can also be regulated by modifying the different components of the inflammasome with phosphate or ubiquitin molecules. Phosphorylation or the removal

of ubiquitin generally leads to an increased activation, whereas removal of the phosphate groups or the addition of ubiquitin leads to an inhibition of the inflammasome. Autoinflammatory disorders are often treated with biological drugs that target IL1, which have significantly improved the quality of life of these patients. IL-1 blockade not only neutralizes IL-1, but also seems to decrease the production and secretion of IL-1β and IL-18. However, the exact mechanisms by which IL1 blockade inhibits inflammasome activation remains unclear. This review will cover the current knowledge of inflammasome activation and IL-1β and IL-18 processing and will give an overview of what is known about the modulation of inflammasome activation by IL-1 blockade.

Introduction

Autoinflammatory disorders (AIDs) are characterized by uncontrolled episodes of inflammation mainly caused by activation cells and molecules of the innate immune system. Disorders that are caused by autoinflammation can be either monogenetic hereditary disorders, or multifactorial disorders. In many autoinflammatory disorders the autoinflammation is in some way caused by dysregulation of inflammasomes, leading to an aberrant expression of IL-1β (1). IL-1 blockade is a very effective therapy in those disorders (1).

Examples of monogenetic hereditary disorders are familial Mediterranean fever (FMF), TNF-receptor associated periodic syndrome (TRAPS), the cryopyrin associated periodic syndrome (CAPS), hyperimmunoglobulinemia D (HIDS), mevalonate kinase deficiency (MKD), Blau syndrome, deficiency of the IL-1-receptor antagonist (DIRA), and pyogenic arthritis with pyoderma gangraenosum and acne (PAPA) syndrome (2). CAPS belongs to the intrinsic inflammasomopathies, referring to hereditary autoinflammatory disorders that are caused by mutations of proteins that are a part of the inflammasome (2). FMF, HIDS, DIRA, PAPA syndrome, and MKD are examples of extrinsic inflammasomopathies, meaning that the mutations are found in proteins that associate with the inflammasome (2).

Systemic Juvenile Idiopathic Arthritis (sJIA) and adult-onset Still's Disease (AOSD) belong to the multifactorial autoinflammatory disorders, which are diseases of which the genetic and environmental factors still need to be fully elucidated. Recently also gout, pseudogout, type II diabetes, Schnitzler syndrome and atherosclerosis have been linked to dysregulated inflammasome activation (1,2). sJIA (and its adult counterpart AOSD) is an example of a complex auto-inflammatory disease in which increased understanding of underlying disease mechanisms, has led to both the identification of potential (diagnostic) biomarkers like IL-18, S100A8 (MRP8), S100A9 (MRP14) and S100A12 and to improve therapeutic strategies. However, the exact etiopathogenesis is still far from elucidated (3–7). Neutrophils, macrophages, monocytes and natural killer (NK) cells are all involved in the disease progression, but which cell type is dominant in the onset of sJIA remains unknown (8–10). Finally, macrophage activation syndrome (MAS) and sJIA-associated lung disease (sJIA-LD), severe complications that occur in some patients with sJIA and AOSD, are incompletely understood (11,12).

Although autoinflammatory disorders are caused by the innate immune system, the adaptive immune system can also get involved resulting in a more complex, and often refractory disease course (13,14). Together with IL-6 and TGF-β, IL-1β is able to promote Th17 differentiation (15,16). Patients with sJIA also have higher levels of IL-17A produced by γ/δ T cells compared to healthy controls, which partially normalized after administration of IL-1 blockade (17). In fact, healthy γ/δ T cells cultured in medium from sJIA patients or medium enriched with IL-1β, IL-18, and S100A12 also showed increased IL-17 expression (17). Furthermore,

IL-18 in synergy with IL-12 was found to promote Th1 differentiation (18). In the last decade, the concept of trained immunity has gained attention.

To better understand how the inflammasomes are dysregulated in AIDs and how come IL-1 blockade is so effective in many patients, this review describes (in short) the mechanisms of inflammasome activation, and how blockade of the IL-1 pathway regulates the activation of different inflammasomes and the processing of inflammasome-derived cytokines.

Mechanisms of inflammasome activation

The inflammasome comprises a complex of proteins that, once assembled, will activate cytokines that induce inflammation. In the last decades, different inflammasomes have been described. During an infection, the inflammasome is activated by a two-signal cascade (canonical activation), initiating eradication of the pathogen (19). Signal 1 is recognition of pathogen associated molecular patterns (PAMPs), damage associated molecular patterns (DAMPs) or homeostasis-altering molecular processes (HAMPs) by a Toll-like receptor (TLR), leading to an upregulated expression of the different components of the inflammasome (20). Signal 2 is the activation of the inflammasome, predominantly by DAMPS, such as reactive oxygen species (ROS), heat shock proteins (HSPs), hyaluronan fragments, ATP, uric acid, DNA, cathepsin B, cholesterol crystals, and the potassium efflux. However, many PAMPs can directly activate inflammasomes as well. Posttranscriptional modifications to the inflammasome components such as phosphorylation and ubiquitination can not be defined as signal 1 or 2 per se, but regulate activation by modulation of inflammasome response to signal 2. Activation of the inflammasome will lead to maturation of cytokines such as IL-1β and IL-18 that will activate other pro-inflammatory pathways. The inflammasomes are named after the pattern recognition receptor (PRR). Nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 1 (NLRP1), NLRP3, NLR family CARD domain containing 4 (NLRC4), Pyrin, and absent in melanoma 2 (AIM2) are the most well known described inflammasomes (21,22). As of yet, also other members of the NOD-like receptor (NLR) family and the pyrin and HIN domain (PYHIN) family are thought to form an inflammasome, but their exact functions remain unknown (22).

The NLRP3 inflammasome

The NLRP3 (also known as NALP3) inflammasome is the best studied inflammasome and is linked to hereditary AIDs such as CAPS (2). NLRP3 binds with an amino-terminal pyrin domain (PYD) to ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD)) (19). ASC binds with a CARD domain to procaspase-1 (19). Many such complexes bind together, resulting in conformational changes that lead to proteolytic cleavage of pro-caspase-1 into the cysteine protease caspase-1 (19). This protein will then cleave pro-IL-1β and pro-IL-18 into active IL-1β and IL-18 and will release the N-terminal part of gasdermin D. Gasdermin D is a pyroptosis regulator which belongs to the family of pore-forming proteins and is important for the secretion of mature IL-1β and IL-18 (23). Caspase-1 activity is also known for induction of pyroptosis, a proinflammatory type of cell death (24).

The transcription of NLRP3 can be induced by a diverse range of stimuli, such as PAMPs and DAMPS as mentioned before, but also by proteins such as IL-1β and TNFα, (25,26). On a posttranscriptional level, interleukin-1 receptor-associated kinase 1 (IRAK1) and IRAK4 have been implicated in activation of the NLRP3 inflammasome by phosphorylation, whereas BRCA1/BRCA2-containing complex subunit 3 (BRCC3) showed to induce activation of NLRP3 by deubiquitination (27–31). The vitamin D receptor (VDR) was recently found to inhibit the

function of BRCC3, thereby indirectly inhibiting the inflammasome activation (32). A20, another deubiquitinating enzyme, was found to be a negative regulator of NLRP3 activation and showed to protect against arthritis (33). A recent review describes different (de-)ubiquitination enzymes that play a role in NLRP3 activation (34). Human monocytes are also capable of alternatively activating the NLRP3 inflammasome (35). LPS directly activated the TLR4 – TIR-domain-containing adapter-inducing interferon-β (TRIF) – receptor-interacting serine / threonine-protein kinase 1 (RIPK1) – Fas associated via death domain (FADD) – caspase-8 signaling pathway, leading to activation of NLRP3 and subsequently cleavage of pro-IL-1β into IL-1β (35). Examples of regulators of NLRP3 inflammasome activation are double-stranded RNA-dependent protein kinase (PKR), guanylate-binding protein 5 (GBP5), platelet-activating factor (PAF) and NIMA related kinase 7 (NEK7) (36–41). PKR and GBP5 have both shown to be positive regulators of NLRP3 inflammasome activation, although their role remain controversial (36,37,42,43). PAF and NEK7 are also positive regulators and required for NLRP3 inflammasome activation but not for NLRC4 and AIM2 inflammasome activation (38–41). Potassium efflux and calcium influx were required for activation of the NLRP3 inflammasome by PAF, but presence of the PAF-receptor (PFAR) was indispensable (41). The potassium efflux channel that contributes to NLRP3 inflammasome activation has long remained elusive, but was recently found to be TWIK2 (also known as potassium channel subfamily K member 6 (KCNK6)) (44). NEK7 binds with its catalytic domain to the carboxy-terminal leucine-rich repeat (LRR) domain of NLRP3, but potassium efflux is necessary for the interaction (38). The interaction between NEK7 and NLRP3 most likely provide the conformational change that is necessary for the association of the complete inflammasome, however, the exact mechanism remains unclear. ATP can induce NLRP3 inflammasome activation by binding the P2X7 receptor (45). This receptor is also known for its role in cytokine and chemokine release, including IL-1β (46). Bruton tyrosine kinase (BTK), which is known for its role in X-linked agammaglobulinemia, was found to act as a physiological inhibitor of the NLRP3 inflammasome, by binding to the NLRP3 protein and thereby inhibiting the formation of the inflammasome (47). Finally, a genetic polymorphism in the inositol-triphosphate 3-kinase C (ITPKC) gene which was associated with Kawasaki's disease, was found to induce a higher expression of NLRP3 by a contributing to a dysregulated intracellular calcium level leading to an increased production of IL-1β and IL-18 (48).

The NLRC4 inflammasome

Research over the last decade has shown that genetic variants in components of the NLRC4 inflammasome can also contribute to autoinflammatory disorders and recurrent MAS episodes, including variants of unknown significance (VUS) in the NLRC4 protein (49–52). The NLRC4 inflammasome can be activated by flagellin and proteins of the type III secretion system of bacteria that are recognized by both functional isoforms of the NLR family apoptosis inhibitory protein (NAIP) protein (53–55). Conformational changes in the NAIP protein will facilitate binding to NLRC4, inducing its oligomerization. NLRC4 activation can be regulated by phosphorylation in murine macrophages by Protein Kinase C (PKCδ) or Leucine Rich Repeat-containing Kinase-2 (LRRK2) (56,57). A recent study showed that Sirtuin3 (SIRT3) also influences NLRC4 activation by deacetylation of the protein (58). Furthermore, β-arrestin, a regulator of G protein–coupled receptor signaling, also played an important role in facilitating the oligomerization of the NLRC4 inflammasome (59). NLRC4 can activate procaspase-1 indirectly via binding to ASC, but also by directly binding to procaspase-1 (60). The NLRC4 inflammasome was also found to recruit and activate the pro-apoptotic procaspase-8 (61). Besides cleaving pro-IL-1β, pro-IL18 and gasdermin D in their functional counterparts, NLRC4 has also been reported to induce expression of the IL-1R via NF-κB (62).

Functions of IL-1β and IL-18 and regulation of their expression and action

The IL-1 cytokine family consists of the proteins IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-37, IL-38, IL-1 receptor antagonist (IL-1Ra) and IL-36 receptor antagonist (IL-36Ra) (63). IL-37 and IL-38 have anti-inflammatory functions, IL-1Ra and IL-36Ra are antagonists, whereas the other cytokines activate pro-inflammatory pathways. In this review we will mainly focus on the inflammasome-dependent IL-1 family members IL-1β and IL-18. Both cytokines are produced as pro-cytokines and need to be cleaved at their N-terminal to become active. The most dominant protease that cleaves both pro-cytokines is caspase-1, but both pro-cytokines can be cleaved by a variety of other proteases in different cell types and tissues (63,64). Caspase-1 also cleaves gasdermin D, from which the N-terminal part forms pores. It was found that although IL-1β and IL-18 lack an export signal peptide, they both are be released from the cell by the pores created by the cleaved form of gasdermin D (23,35).

IL-1β is released from hematopoietic cells, generally only during an inflammatory response. IL-1β binds the receptor IL-1R1 and the co-receptor IL-1RAcP to activate pro-inflammatory pathways, whereas binding to IL-1R2 does not result in activation. IL-1Ra is the natural antagonist of IL-1β, also able to (competitively) bind to IL-1R1, resulting in decreased activation of pro-inflammatory pathways. IL-1β is normally hardly detectable in serum, probably due to its short half-life and the neutralizing properties of IL-1Ra and IL-1R2. IL-1β is known for inducing its own production (65,66). The conventional way for IL-1β cleavage and release from the cell is via the NLRP3 inflammasome. Cleavage via the inflammasome is achieved by caspase-1, however also caspase-8, chymase released by mast cells or neutrophil-released cathepsin G, proteinase 3 and neutrophil elastase have already shown to process pro-IL1β to its active form, independently of the inflammasome (67–73). A recent study also showed that in murine macrophages multiple cathepsins can mediate IL-1β cleavage (74). Moreover, a recent study showed that IL-1β was released from dendritic cells (DCs) independent of the NLRP3 inflammasome after interaction of the DC with the invariant Natural Killer T (NKT) cell via Fas-Fas ligand interaction (75). Multiple studies investigated the role of murine caspase-11 in the activation of IL-1β, but much less is known about the human homologs caspase-4 and caspase-5. Capase-4 can physically interact with and thereby induce caspase-1 activity to cleave pro-IL-1β (76). When caspase-4 was inhibited during infection with the dengue virus serotype-2 (DENV-2) in human macrophages, the production of IL-1β was reduced (76). Induction of the production of IL-1β by caspase-4 and -5 is also supported in other studies where these proteins where found to be responsible for the one-step non-canonical activation of the NLRP3 inflammasome in human monocytes and where caspase-4 mediated non-canonical inflammasome activation is induced by gram-negative bacteria (77–79). The Ubiquitin E2 Conjugase UBE2L3 was found to ubiquitinate K48 at pro-IL1β to induce degradation of pro-IL1β (80). During inflammation, UBE2L3 is an indirect substrate for caspase-1 and is subsequently degraded (80). Macrophages that were deficient for the deubiquitinase POH1 showed an increased production of IL-1β, therefore POH1 is a negative regulator of inflammation (81). Another recent study showed that binding of K11-linked, K63-linked and K48-linked ubiquitination chains to IL-1β is important in the regulation of its activity (82).

IL-18, often in synergy with IL-12, is best known for it's ability to induce the expression of IFN-γ, the induction of Th1 proliferation and the activation of NK cells (83). Solitary IL-18 is capable of inducing Th2 proliferation, contributing to allergic inflammation (83). Pro-IL18 is cleaved by caspase-1 after activation of the NLRP3 inflammasome, but it can also be cleaved by mast cell derived chymase and granzyme B derived from NK and NKT cells, although chymase-cleaved IL-18 shows only 20% biologic activity (84,85). Moreover, caspase-8 is most likely a pro-IL18 processing enzyme, although cleavage is induced independent of the inflammasome (86). Finally, IL18 processing and release was induced upon incubation with proteinase-3 and

LPS, but direct cleavage by proteinase-3 could not be proved (87). IL-18 binds to the receptor IL-18Rα and the co-receptor IL-18Rβ and IL-18 binding protein (IL-18BP) functions as a natural inhibitor. In contrast to IL-1β, IL-18 is easily detected in serum. Pro-IL-18 is constitutively expressed in blood monocytes, macrophages, dendritic cells from healthy subjects as well as in endothelial cells, keratinocytes, and intestinal epithelial cells throughout the gastrointestinal tract (83,88). Despite being constitutively expressed, TLR4, TLR2, or TLR7 ligands can cause a further prolonged upregulation of IL18 mRNA levels (89). In contrast, IL-1β expression declines directly after induction (89). In addition, IL-18 was found to induce Fas ligand in Kupffer cells and was found to be responsible for skin and liver damage in murine CAPS, which could explain the hepatic damage that is occurring in AIDs (90,91). Production of IL-18, but not IL-1β, requires cooperative TLR and IFNα/β signaling in human monocytes (92). IL-18 is also important for the expression of cell adhesion molecules, chemokines and nitric oxide (88). Although a homeostatic role for IL-18 is suspected because of its constitutive expression, the exact function still needs to be elucidated. However, a reduced level of IL-18 expression caused by NLRP3 or caspase-1 deficiency in mice led to an increased colorectal tumor burden, suggesting that IL-18 is necessary to prevent cancer (93).

Does IL-1 blockade interfere with inflammasome activation?

IL-1 blockade has proven to be very effective in AIDs. Most inflammatory markers will decrease, although in some cases IL-18 protein expression remains high even in clinically inactive disease (50). IL-1 blockade diminishes the pro-inflammatory effect of IL-1β binding to its receptor. However, this does not explain the relief of all clinical and laboratory symptoms of patients with AIDs, therefore there is most likely another form of indirect regulation that is involved in inhibiting the inflammatory mechanisms. The molecular pathways by which the systemic symptoms are inhibited are still unclear. At this moment, anakinra, canakinumab and rilonacept are approved therapies in different AIDs and some data is known about the molecular mechanisms besides blocking the IL-1 pathway (Figure 1).

Anakinra is an IL-1 receptor antagonist, resembling the human IL-1Ra but lacking the post-transcriptional glycosylation. It is approved for different AIDs and included in several guidelines for treating sJIA and AOSD as a first line therapy, both in the US and Europe (94). It binds the IL-1R1 and blocks the subsequent inflammatory pathway. Due to it's short serum half-life of 4-6 hours it needs to be administered daily. In sJIA, anakinra reduced inflammatory markers such as C-reactive protein (CRP), ferritin, IL-18, S100A12 and S100A8/A9 already within a month (95). The human IL-1Ra has four isoforms of which three lack a signal peptide and are retained intracellularly (96). It has previously been shown that type one of the intracellular IL-1Ra (IL-1Ra1) is able to decrease IL-1 gene expression, without altering the pro-inflammatory signal by IL-1β (97). IL-1Ra1 directly binds to the third component of the COP9 signalosome complex (CSN3) in keratinocytes which is involved in the regulation of degradation of proteins belonging to the pro-inflammatory p38 MAPK pathway (98). Another study in intestinal epithelial cells likewise showed that IL-1Ra1 inhibited the p38 MAPK phosphorylation and nuclear translocation of nuclear factor κB (NF-κB), resulting in a decreased expression of IL-6 and IL-8 (99). Anakinra was found to reduce inflammasome activity by activating superoxide dismutase 2 (SOD2) in murine macrophages leading to a protection from mitochondrial oxidative stress (100). Prevention of SOD2 degradation by anakinra was achieved by association of SOD2 with deubiquitinase USP36 at the level of CSN3, suggesting that anakinra has the same properties as IL-1Ra1 and thus can bind more targets than the IL-1R (100). However, it is not likely that anakinra is transported into the cell while it contains an export signal. Thus, it is unknown how anakinra, like IL-1Ra1, can associate with CSN3. SOD2

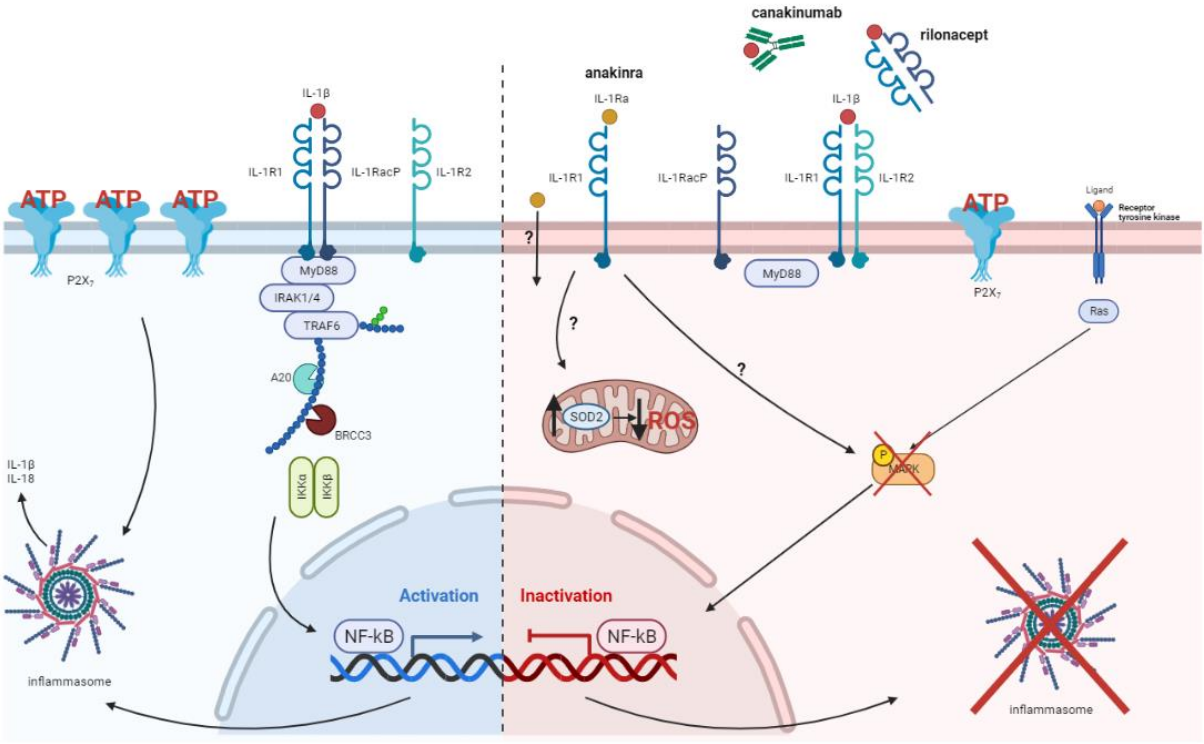

Figure 1 ***Mechanism of activation and blockade of the IL-1 pathway****. IL-1 pathway activation will lead to induction of NF-κB and subsequently to transcription of inflammasome components and pro-IL1β and pro-IL18. A disturbed P2X7-IL1β axis will result in activation. Inhibition of the IL-1 pathway will quench the IL-1 pathway and inhibition of NF-κB, but also to increase of SOD2 and a decrease in ROS, as well as a restored P2X7-IL-1β axis. Image created with Biorender.com*

knockdown resulted in oxidative damage and an increased NLRP3 inflammasome activation (101). Anakinra also inhibited inflammasome activity by restoring autophagy in chronic granulomatous disease (CGD) and cystic fibrosis (CF) (62,102). Furthermore, anakinra also attenuated acute liver injury in mice specifically by blocking IL-1R1 (103). In patients with Schnitzler's syndrome, the loss of Th1, Th2 and Th17 cells was reversed upon treatment with anakinra (104). IL-1 blockade with anakinra in a patient with AOSD resulted in normalization of activated peripheral T lymphocytes (105). Blocking IL-1 in mice with CGD also resulted in a decreased neutrophil recruitment, Th17 responses and restored expression of autophagy genes (102). A case report about Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) syndrome showed a dysregulated P2X7-IL1β axis which was resolved when the patient was treated with anakinra (106).

Canakinumab is a human monoclonal antibody specific against IL-1β. It was approved in the US for sJIA and in Europe for AOSD (94). It can be used to avoid the daily injections of anakinra due to is significantly longer half-life of 21-28 days. Canakinumab resulted in a rapid resolve of symptoms and inflammatory markers in sJIA (107,108). However, a study on atherothrombosis revealed that after inhibition of IL-1β, the risk of an auto-inflammatory reaction caused by IL-18 and IL-6 remains, which suggests that canakinumab might be less effective in the inhibition then anakinra of the inflammatory pathways (109). This might be due to the additional effect anakinra has on inhibiting the inflammasome and mitochondrial damage. Finally, rilonacept is a human dimeric fusion protein of the extracellular domains of both IL-1R1 and IL-1RAcP which targets both IL-1α and IL-1β and also has a significantly longer half-life of 67 hours compared to anakinra. Its safety and efficacy was shown in sJIA (110,111). For both canakinumab and rilonacept there are currently no other molecular effects than inhibiting the inflammatory response known.

As of yet, there is limited data available on how IL-1 blockade can inhibit the inflammasome expression and activation. Anakinra showed to inhibit inflammasome activation by preventing mitochondrial damage (62,100,102). The other types of IL-1 blockade, however, are not investigated yet for a role in ROS inhibition. Treatment of AIDs with IL-1 blockade have shown to inhibit the processing of the inflammasome-dependent cytokines IL-1β and IL-18. The exact mechanism responsible for quenching the inflammasome activation when just one component (IL-1β) of the inflammasome pathway is inhibited remains elusive. It is not known yet how IL-1 inhibition also affects both transcription and processing of IL-18, and why IL-18 expression is inhibited after IL-1 blockade in some patients but not in others. There is no data yet available on the exact mechanism of IL-1 blockade affecting the regulation of inflammasome-dependent processing of IL-1β and IL-18 and will be studied in future studies.

Discussion

In the last decades we gained more knowledge about the pathogenesis of AIDs as well as the molecular mechanisms behind inflammasome activation and IL-1β and IL-18 processing and functions. IL-1 blockade has immensely improved the outcome of IL-1 dependent AID and the quality of live of many patients. IL-1 blockade decreases the downstream pro-inflammatory pathway by quenching the signal cascade of the IL-1R, but how IL-1 blockade is mechanistically able to regulate the expression and processing of inflammasome-dependent cytokines needs to be elucidated. Anakinra resulted a decreased mitochondrial stress, normalization of peripheral T lymphocytes, decreased neutrophil recruitment and restored expression of autophagy genes. However, it is not yet fully known how IL-1 blockade specifically interferes with the inflammasome activation and subsequently with the cytokine maturation. Earlier studies revealed that the intracellular IL-1Ra1 also regulates the pro-inflammatory response by reducing mitochondrial damage by ROS and inhibiting nuclear translocation of NF-κB (97–99). Anakinra was found to decrease mitochondrial damage at the same level as IL-Ra1, however, it contains a export signal peptide and is most likely not transported into the cell (100). How anakinra is able to provoke the same effect IL-1Ra1 is remains elusive. Recently, single-nucleotide polymorphisms (SNPs) found in sJIA patients in the promotor of the IL-Ra gene showed a strong correlation with IL-1Ra expression, as well as a correlation between presence of homozygous IL-1Ra high expression alleles and the response to anakinra therapy, showing the relevance of the molecular mechanisms of IL-1Ra in the regulation of pro-inflammatory response (112). Furthermore, it remains unclear how IL-1 blockade is mechanistically responsible for the rapid decline in expression of other pro-inflammatory cytokines such as IL-18, and why this decrease is not seen in all cases. IL-1 blockade definitely results in quenching the IL-1 pathway because of a lack of stimulation, resulting in loss of the positive feedback loop of IL-1β transcription (113). How this mechanism is responsible for the decreased expression of the inflammasome components and how IL-1 blockade affects the maturation of IL-18 remains elusive. Even though patients with a constitutively high IL-18 expression respond very well clinically to IL-1 blockade, they are more at risk of developing MAS. Interestingly, not all AID patients respond very well to IL-1 blockade and thus new therapies need to be developed. MAS825 is a novel bispecific antibody against IL-1β and IL-18 and is now being studied in phase 2 in patients with a NLRC4 gain-of-function (GOF) mutation (114).

In conclusion, this review summarized the current knowledge on inflammasome activation, IL-1β and IL-18 processing and the regulation of the inflammasomes and the inflammasome-dependent cytokine by IL-1 blockade. It remains important to unravel the exact molecular mechanisms of IL-1 blockade so that better treatments can be offered to patients with AIDs and side-effects and complications can be restricted or even prevented.

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