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Role of inflammasome in severe, steroid-resistant asthma

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ABSTRACT

Purpose of review: Asthma is a common heterogeneous group of chronic inflammatory diseases with different pathological phenotypes classified based on the various clinical, physiological and immunobiological profiles of patients. Despite similar clinical symptoms, asthmatic patients may respond differently to treatment. Hence, asthma research is becoming more focused on deciphering the molecular and cellular pathways driving the different asthma endotypes. This review focuses on the role of inflammasome activation as one important mechanism reported in the pathogenesis of severe steroid resistant asthma (SSRA), a Th2-low asthma endotype. Although SSRA represents around 5–10% of asthmatic patients, it is responsible for the majority of asthma morbidity and more than 50% of asthma associated healthcare costs with clear unmet need. Therefore, deciphering the role of the inflammasome in SSRA pathogenesis, particularly in relation to neutrophil chemotaxis to the lungs, provides a novel target for therapy.

Recent findings: The literature highlighted several activators of inflammasomes that are elevated during SSRA and result in the release of proinflammatory mediators, mainly IL-1β and IL-18, through different signaling pathways. Consequently, the expression of NLRP3 and IL-1β is shown to be positively correlated with neutrophil recruitment and negatively correlated with airflow obstruction. Furthermore, exaggerated NLRP3 inflammasome/IL-1β activation is reported to be associated with glucocorticoid resistance.

Summary: In this review, we summarized the reported literature on the activators of the inflammasome during SSRA, the role of IL-1β and IL-18 in SSRA pathogenesis, and the pathways by which inflammasome activation contributes to steroid resistance. Finally, our review shed light on the different levels to target inflammasome involvement in an attempt to ameliorate the serious outcomes of SSRA.

1. Introduction

1.1. Severe, steroid-resistant asthma (SSRA)

Asthma is a common heterogeneous group of chronic inflammatory diseases. It is characterized by airway hyper-responsiveness, inflammation, remodeling, and reversible airflow limitation due to occupational or environmental exposure to microbes, industrial products, or allergens (Chanez, 2005; Fahy, 2001). Asthma is heterogeneous in terms of the underlying cause, severity, and treatment responsiveness. Accordingly, the different pathological phenotypes of asthma are classified based on the various clinical, physiological, and immunobiological profiles of patients. The two major asthma phenotypes are non-atopic or "intrinsic" asthma and atopic or "extrinsic" allergic asthma. Early-onset atopic asthma is most prevalent during childhood and into young adulthood, whereas the non-atopic form predominates among older age groups. Other phenotypes include aspirin-exacerbated respiratory disease (AERD), obesity-associated, and smoking-associated asthma (Kuruvilla et al., 2019).

The common therapy for asthma is inhaled corticosteroid (ICS) (Chung et al., 2014; Wang et al., 2020a). ICS therapy is composed of synthetic highly lipophilic glucocorticoids that rapidly diffuse into airway cells upon inhalation. Following their binding to cytosolic glucocorticoid receptors (GRs), glucocorticoids activate and trigger the formation of GR homodimers (Barnes, 2014; Ito et al., 2006a). The GRα isoform mediates the anti-inflammatory effects, and the GRβ isoform acts as its dominant inhibitor (Oakley et al., 1999). Importin-α and importin-13 transport the homodimers into the nucleus, where they

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bind response elements in promoter regions of responsive genes (Tao et al., 2006). The interaction of GR homodimers with transcriptional co-activators like the cyclic adenosine monophosphate response element (CREB)-binding protein (CBP) results in the acetylation of core histones associated with anti-inflammatory glucocorticoid response genes and further induces the transactivation of these genes. Also, activated GR homodimers can interact with CBP proteins already complexed with promoter regions of pro-inflammatory genes, such as nuclear factor (NF)-κB and activator protein (AP)-1, thus leading to their trans-repression by inhibiting histone acetylation (Barnes, 1995, 2011; Horwitz et al., 1996). Importantly, the recruitment of the enzyme histone deacetylase (HDAC)2 acts as a key transcriptional co-repressor and mediates the anti-inflammatory activity of GRs (de Ruijter et al., 2003; Ito et al., 2006b).

However, asthmatic patients may respond differently to treatment despite similar clinical symptoms. Hence, asthma research is becoming more focused today on deciphering the molecular and cellular pathways driving the different asthma endotypes. An appropriate classification system of the inflammatory endotypes will help in identifying biomarkers and managing asthma in a personalized manner *via* making use of the expanding repertoire of biological agents. Asthma endotyping is based on the dominant $CD4^+$ T-cell response. The multiple subsets of $CD4^+$ T-cell promote different inflammatory pathways. Moreover, eosinophils and neutrophils are among the most important immune cells contributing to asthma pathogenesis. As such, inflammation can be eosinophilic, neutrophilic, or a mix of both (Eder et al., 2006; Fahy, 2015; Israel and Reddel, 2017). Eosinophilic asthma is typically associated with Th2 lymphocytes, whereas neutrophilic airway inflammation is strongly linked to Th1/Th17-mediated responses (Hansbro et al., 2013; Kim et al., 2010; Park et al., 2021; Ro et al., 2019; Simpson et al., 2007; Thorburn and Hansbro, 2010). Hence, considering $CD4^+$ T-cell response and the involvement of eosinophils and neutrophils, corticosteroid-dependent asthma is classified into two major endotypes: Th2-high (eosinophilic) and Th2-low (non-eosinophilic) (Wenzel et al., 1999). Eosinophilic asthma is considered mild to moderate in severity and patients with this subtype respond well to corticosteroid therapy. However, it is worth noting that glucocorticoid insensitivity has also been described in patients with persistent eosinophil inflammation (Peters et al., 2019). On the other hand, neutrophilic airway inflammation is severe and resistant to steroid treatment (Ntontsi et al., 2017). Based on the updated diagnostic criteria, severe steroid-resistant asthma (SSRA) in adults is defined as ineffectiveness in achieving >15% improvement in forced expiratory volume in 1 s after 14 days of oral steroid treatment (Adcock et al., 2008; Barnes and Adcock, 2009). SSRA represents around 5–10% of asthmatic patients, the majority of asthma morbidity and more than 50% of asthma associated healthcare costs with clear unmet need (Kuruvilla et al., 2019; Lang, 2015; Wang et al., 2010). Thus, effective treatments for SSRA are urgently needed given the heterogeneity of the disease and the involvement of various immunological, inflammatory, and molecular mechanisms which impede the development of one effective therapy. For that purpose, deciphering the molecular and cellular mechanisms underlying SSRA pathogenesis is crucial to identify targets for personalized treatment.

SSRA is attributed to a multitude of factors including but not limited to obesity, air pollution, smoking, and infectious agents like *Chlamydia pneumonie* and *Haemophilus influenzae*. In addition, different molecular and cellular mechanisms contribute to the pathogenesis of SSRA such as Th17 inflammatory response, phosphoinositide-3-kinase (PI3K) signaling, TLRs and inflammasomes, exosomes, and microRNAs (Hansbro et al., 2017). Furthermore, neutrophilia in SSRA occurs due to the IL-23-Th17-IL-17-ILC3 pathway, delayed apoptosis of neutrophils caused by epithelial cell-derived cytokines and growth factors, impaired apoptosis of neutrophils induced by corticosteroid treatment, ineffective macrophage efferocytosis of neutrophils, reduced lipoxin levels, altered airway microbiome and upregulated inflammasome/interleukin (IL)-1β response and p38/MAPK activity (Yokoyama). In this review, we will focus on the role of pyroptosis and inflammasome activation in the pathogenesis of SSRA in an attempt to decipher additional levels for disease intervention.

1.2. Inflammasomes and pyroptosis

Inflammasomes are cytosolic oligomeric protein complexes of the supramolecular organizing centers composed of NLRs or absent in melanoma 2-like receptors (AIM2), adapter protein apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1 (CASP-1) (Martinon et al., 2002; Proell et al., 2013). Five proteins have been confirmed to assemble inflammasomes and promote CASP-1 activation: NLRP1, NLRP3 and NLRC4, AIM2, and pyrin. Other less-well characterized pathways include NLRP6, NLRP7, NLRP12, retinoic acid-inducible gene I (RIG-I; also known as DDX58), and interferon-γ (IFNγ)-inducible protein 16 (IFI16) (Broz and Dixit, 2016). The NLRP3 inflammasome (also called NALP3, PYPAF1, or cryopyrin) is the best characterized and has been widely implicated in various inflammatory diseases (Martinon et al., 2002; Schroder and Tschopp, 2010; Stutz et al., 2009). Theoretically, two separate events are required for inflammasome assembly and activation. First, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are recognized by several types of pathogen recognition receptors (PRRs), including endocytic (e.g., macrophage mannose receptor), secreted (e.g., mannose-binding lectin) or signaling PRRs [e.g., RIG-I-like receptors (RLRs), toll-like receptors (TLRs), and nod-like receptors (NLRs)] (Eisenbarth and Flavell, 2009). Following their binding to PRRs, PAMPs such as LPS and microbial molecules like dsDNA and ssRNA upregulate the expression of the inflammasome (Bauernfeind et al., 2009). DAMPs such as extracellular ATP, potassium efflux, and monosodium urate crystals act as a second signal and activate the assembled inflammasome (Schroder and Tschopp, 2010; Stutz et al., 2009). Further, reactive oxygen species (ROS) are also considered activators of the inflammasome through mitogen-activated protein kinases (MAPKs) and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) (Cruz et al., 2007; Harijith et al., 2014). The inflammasome activation results in autocatalysis of pro-caspase-1 and activation of caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 into their active forms (IL-1β and IL-18) (Schroder and Tschopp, 2010; Hornung and Latz, 2010).

In addition, members of the gasdermin family of pore forming proteins are also cleaved by caspase-1, with GSDMD being one of the most characterized members (Bergsbaken et al., 2009; Jorgensen and Miao, 2015; Lieberman et al., 2019; Lu et al., 2020). This results in the release of inflammatory cytokines in an inflammatory cell death pathway termed as "pyroptosis". Pyroptosis or programmed necrosis was initially discovered in macrophages. Later, research revealed that various immune and non-immune cells as well as healthy and malignant cells can undergo pyroptosis (Fink et al., 2008; Shi et al., 2017). Although pyroptosis is an important event during innate immunity to kill pathogens and intracellular bacteria as well as to promote adaptive immunity, yet it is reported to contribute to the pathogenesis of different diseases such as cancers, cardiovascular, pulmonary, and autoimmune disorders (Liang et al., 2020a; Xia et al., 2019; Zeng et al., 2019; Wang et al., 2020b). Despite that inflammasomes are implicated in the canonical pathway of pyroptosis, yet they are complemented by the non-canonical pathway, which targets CASP-11 in mice and CASP-4 and/or CASP-5 in human cells (Baker et al., 2015; Kayagaki et al., 2011, 2015).

However, it is important to highlight that pyroptosis is not a simple process, and its relationship with inflammasome activation, GSDMD cleavage, and IL-1β and IL-18 release can vary in different cell types and in the presence of different stimuli. For instance, in neutrophils, inflammasome activation and IL-1β release have been reported in the absence of pyroptosis (Liu et al., 2014; Chen et al., 2014). Moreover, it is not always that two signals are needed for the release of IL-1β and an alternative NLRP3 inflammasome pathway independent of pyroptosis

has been described in primary PBMCs to be sufficient for IL-1β release upon LPS stimulation only (Gaidt et al., 2016). Interestingly, macrophage pyroptosis independent of IL-1β or IL-18, has also been reported for bacterial clearance by phagocytic neutrophils (Miao et al., 2010, 2011). In addition, the absence of GSDMD in BMDMs treated with canonical inflammasome inducers delayed rather than prevented pyroptosis (Kayagaki et al., 2015). Further, blocking caspase-1 with cell-permeable inhibitors delayed cell death but did not completely prevent it in nigericin-treated THP-1 cells (O'Brien et al., 2017). This implicates that other cell death pathways can take over as an alternative to pyroptosis and that the players involved in the different cell death pathways such as apoptosis, autophagy, and necroptosis can cross talk (Bertheloot et al., 2021). These findings make defining pyroptosis, inflammasome activation, the involvement of gasdermins and the release of cytokines challenging and more complex.

2. Role of inflammasome in SSRA

2.1. Inflammasome activation

Well known activators of the NLRP3 inflammasome are elevated during asthma including Charcot-Leyden crystals, apolipoprotein E, and uric acid (Braga et al., 2017; Gordon et al., 2019; Kool et al., 2008; Rodriguez-Alcazar et al., 2019). Eosinophilic airway inflammation is exacerbated by IL-1β released by monocyte-derived macrophages upon NLRP3 activation in response to Charcot-Leyden crystals which are formed spontaneously from galectin-10 proteins upon eosinophil lysis (Rodriguez-Alcazar et al., 2019). S100A12, released by eosinophils, induces degranulation of tissue mast cells (Yang et al., 2007), and can as well activate NLRP3 inflammasome and induce MUC5AC production by airway epithelial cells, in vitro (Kim et al., 2018). The levels of apolipoprotein E released by macrophages from bronchoalveolar lavage fluid are elevated in response to house dust mite (HDM) exposure (Gordon et al., 2019). Furthermore, HDM induces abundant production of uric acid by the human airway epithelial cells (Huff et al., 2017). However, uric acid potently induces Th-2 lymphocyte immunity in an NLRP3-independent manner through PI3K-δ (Kool et al., 2011). This was further supported by another study on wild type and NLRP3-deficient mice where no differences were detected in the key features of acute or chronic ovalbumin induced allergic airway disease, including eosinophilic airway inflammation, mucus hypersecretion, and AHR (Allen et al., 2012).

In Th2-high or Th2-low SSRA, NLRP3 inflammasome activation, IL-1β release and the consequent downstream signaling contribute significantly to disease pathogenesis (Kim et al., 2017a; Simpson et al., 2014). Regarding Th2- high SSRA, one study demonstrated that IL-1β and IL-1α induced pulmonary eosinophilia and allergic lung inflammation in mice (Qi et al., 2017). However, the production of IL-1β and IL-1α was mediated by caspase-8 rather than caspase-1/11. In this context, it is worth mentioning that caspase-8 can act as a positive modulator of the NLRP3-dependent caspase-1-IL-1β signaling pathway (Antonopoulos et al., 2015). In another study on experimental steroid-insensitive airway hyperresponsiveness induced by obesity, eosinophilic inflammation in airway tissue was shown to be associated with NLRP3 inflammasome activation (Pinkerton et al., 2022). This was further correlated with an increase in Th2 cytokines, IL-5 and IL-13, in the sputum of asthmatic patients. Interestingly, in the murine model of high fat diet-induced obesity and ovalbumin-induced asthma, inhibition of NLRP3 inflammasome responses reduced steroid-insensitive airway hyperresponsiveness yet had no effect on IL-5 or IL-13 responses. However, depleting IL-5 and IL-13 reduced obesity-induced NLRP3 inflammasome responses and steroid-insensitive airway hyperresponsiveness in the same mouse model (Pinkerton et al., 2022). This indicates the upstream role of IL-5 and IL-13 in activating the NLRP3 inflammasome in the context of obesity induced asthma.

The inflammasome pathway's involvement in disease pathogenesis has also been highlighted by several studies in Th2-low SSRA. Sputum transcriptomics used in the U-BIOPRED cohort revealed that neutrophil accumulation is characterized by inflammasome-associated gene signature (Rossios et al., 2018). However, NLRP3 is not the only involved inflammasome during asthma. The mRNA expression of NLRP1 and NLRC4 inflammasome sensors is also increased in the sputum of patients with neutrophilic asthma (Rossios et al., 2018). Sputum macrophages of neutrophilic asthmatics were shown to exhibit elevated expression of TLR-2, TLR-4, NLRP3, caspase-1, caspase-4, caspase-5, and IL-1β, compared to other groups. Similarly, sputum neutrophils showed strong immunoreactivity for NLRP3 and caspase-1 via immunocytochemical analysis. This was accompanied by increased protein levels of IL-1β in the sputum that correlated with IL-8 levels (Simpson et al., 2007, 2014). Further, the NLRP3 inflammasome is linked to the downstream production of GM-CSF and CCL-20 (Fujii et al., 2001; Reibman et al., 2002, 2003) *via* IL-1R1 signaling (Hirota et al., 2015). Another study using *Chlamydia*- and *Haemophilus*-induced mouse models of severe, steroid-resistant allergic airway disease (AAD) demonstrated elevated NLRP3 and IL-1β expression (Kim et al., 2017a). In addition, the expression of NLRP3 and IL-1β was positively correlated with neutrophil numbers in patients' sputum and negatively correlated with airflow obstruction and asthma in a cohort of stable asthmatics, the majority of which were on inhaled corticosteroid therapy. Consequently, depletion of neutrophils suppressed IL-1β-induced, steroid-resistant AHR in *Chlamydia* and *Haemophilus* respiratory infection–mediated, ovalbumin-induced severe, steroid-resistant allergic airway disease mouse model (Kim et al., 2017a). This highlights a significant role for neutrophilic inflammation in the pathogenesis of IL-1β-induced steroid-resistant disease.

Although these studies demonstrated the elevation of NLRP3 expression in steroid resistant asthma (SRA) models in the airway epithelium and infiltrating leukocytes, yet the detailed mechanism underlying the involvement and activation of the inflammasome NLRP3 and the consequent IL-1β release observed in severe neutrophilic asthmatic airway inflammation is not clear. In this regard, few studies revealed some mechanisms that activate NLRP3 inflammasome during asthma. For instance, PI3K-δ signaling was demonstrated to be an important activator of NLRP3 inflammasome during HDM-induced allergic responses and fungus-induced severe allergic airway inflammation. The effect of PI3K-δ is mediated by nuclear translocation of NF-κB and mitochondrial ROS generation. Therefore, the inhibition or knockdown of PI3K-δ reduced the increase of NLRP3 protein levels as well as its activation (Kim et al., 2020). Another possible mechanism of NLRP3 activation is the LTB_4 receptors BLT1 and BLT2 which play an important role in the stimulation of the NLRP3 inflammasome and IL-1β synthesis in HDM/LPS-driven neutrophilic airway inflammation (Kwak et al., 2021). Also, excess generation of mitochondria ROS and alteration of mitochondrial DNA induced steroid-resistant neutrophilic asthmatic features through the activation of NLRP3 inflammasome in mice (Kim et al., 2014). It is worth mentioning that the non-canonical pathway of pyroptosis is also implicated in asthma pathogenesis where caspase-4/5/11-induced pyroptosis in human and murine macrophages was associated with allergic airway inflammation (Zaslona et al., 2020).

Further research is needed to reveal other possible mechanisms or signaling pathways involved in inflammasome activation during severe asthma and to determine whether a similar mechanistic pathway underlies the different asthma endotypes especially that NLRP3 can also exhibit a regulatory role in allergic airway diseases. This was demonstrated in HDM-induced model of asthma where NLPR3-dependent caspase-1 pathway reduced IL-33 responses (Madouri et al., 2015). IL-33 is a member of IL-1family; however, unlike IL-1β and IL-18, IL-33 does not require posttranslational processing for its secretion and is released passively in its active full-length form upon cellular damage (Cayrol and Girard, 2009; Dinarello, 2009; Ghayur et al., 1997; Lefrancais et al., 2012; Thornberry et al., 1992). Interestingly, the cleavage of the N-terminal portion of IL-33 by the inflammasome

complex and caspases-1, -3 and -7, inactivates IL-33 (Luthi et al., 2009; Talabot-Ayer et al., 2009). Accordingly, the NLRP3 inflammasome exhibits a contrasting regulation on IL-33 and IL-1β (Saikumar Jayalatha et al., 2021). These findings reflect the controversial role of the NLRP3 inflammasome in the pathogenesis of asthma in general and in SSRA in particular, hence highlighting the need to better define its function.

2.2. Pyroptosis in SSRA

GSDMD-dependent pyroptosis has been reported to drive excessive inflammatory response, macrophage depletion and airway remodeling in a variety of pulmonary diseases (Orning et al., 2019) such as pulmonary fibrosis (Liang et al., 2020b), acute respiratory distress syndrome (ARDS) (Kovarova et al., 2012; Yang et al., 2016), and asthma (Kim et al., 2017a; Panganiban et al., 2018). Furthermore, genome wide association studies identified several candidate genes potentially involved in asthma pathogenesis among which ORMDL3/GSDMD locus on chromosome 17q21 was found to be associated with childhood onset asthma (Moffatt et al., 2010). Another gasdermin family member being GSDMB; whose cleavage by caspase-1 induces pyroptosis; is highly linked to asthma pathogenesis *via* inducing the activation of TGF-β and 5-lipooxygenase pathways. This leads to the spontaneous increase in AHR, airway remodeling, and airway smooth muscle mass in the absence of airway inflammation (Das et al., 2016). Moreover, multiple coding variants in the GSDMB gene are associated with reduced asthma risk with the splicing variant, rs11078928, abolishing its pyroptotic activity (Panganiban et al., 2018; Chao et al., 2017).

2.3. IL-1β & IL-18

IL-1β is a major inflammatory cytokine released during pyroptosis and several studies showed that its release contributed to severe asthma pathogenesis. NLRP3 inflammasome-mediated IL-1β release is a well-documented and known feature of macrophages (Schroder and Tschopp, 2010), which are elevated in the Chlamydia SRA model, but also neutrophils have been reported to release IL-1β *via* this pathway (Karmakar et al., 2015, 2016). In this regard, Wright et al. confirmed the contributory role of neutrophils to IL-1β release in patients with severe neutrophilic asthma whereby collected sputum exhibited elevated levels of neutrophil extracellular traps (NETs) and extracellular DNA (eDNA). In turn, high eDNA levels were associated with increased CXCL8, IL-1β and NLRP3 gene expression, collectively contributing to heightened innate immunity (Wright et al., 2016). Furthermore, via an unknown mechanism, NETs released by activated neutrophils in severely asthmatics airways may activate the inflammasome in resident macrophages and monocytes leading to IL-1β secretion (Lachowicz-Scroggins et al., 2019). In addition, neutrophil-derived proteases can also activate any extracellular pro–IL-1β, enhance and amplify the initial caspase-1–mediated activation (Afonina et al., 2015), and further contribute to IL-1β–driven inflammation. In turn, IL-1β signaling promotes the recruitment of neutrophils into the lungs by inducing the expression of the pro-neutrophil chemokines, CXCL1 and CCL5 (Mahmutovic Persson et al., 2018). In addition, in vitro experiments showed that IL-1β alone may transiently influence epithelial barrier function, and both IL -1β and IL -17A may increase mucin expression, thus suggesting a mechanistic link between increased inflammasome -Th17-related axis and impaired barrier function (Tan et al., 2019). As a clinical translation of these findings, the release of IL-1β was shown to be strongly linked with inhaled corticosteroid insensitivity (Kim et al., 2017a; Simpson et al., 2014). Furthermore, the expression of IL-1R1 and its accessory protein (IL-1RAcp) strongly reduced the neutrophil counts in the sputum of asthmatic subjects compared with controls, and decreased the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity in asthma (Evans et al., 2018).

Unlike IL-1β whose level is well documented to be elevated during SSRA, the role of IL-18 in asthma pathogenesis is rather controversial with no clear consensus of whether IL-18 is increased or decreased or even has a defined role in disease pathogenesis (Birrell and Eltom, 2011). Nonetheless, IL-18 can enhance the innate immunity as well as affect both Th1 and Th2 type responses by inducing IFN-γ production from Th1 cells and IL-4 and IL-13 production in T cells, natural killer (NK) cells, NK T cells, mast cells, and basophils (Birrell and Eltom, 2011). In addition, IL-18 genetic variants were shown to be significantly associated with asthma severity resulting in higher transcriptional activity and expression of IL-18 in the serum and in LPS stimulated monocytes (Harada et al., 2009).

3. Role of pyroptosis in inducing steroid resistance during severe asthma

Despite recent advances in the development and clinical application of biologics in treating asthma (Hansbro et al., 2013; Asquith et al., 2011; Foster et al., 2013), corticosteroids remain fundamental to successful asthma management and controlling the frequency and extent of disease exacerbations (Bucala, 2012; Rhen and Cidlowski, 2005). Therefore, researching the underlying mechanisms which contribute to steroid resistance during severe asthma is an essential need. However, prior to reviewing the literature regarding the role of pyroptosis and inflammasome activation in inducing steroid resistance during severe asthma, it is important to define the two types of GC resistance among asthmatic patients. Type 1 resistance is cytokine-induced or acquired, the former being associated with polymorphisms that lead to an overproduction of certain cytokines, and the latter is due to chronic exposure to corticosteroids (Wan et al., 2012). Type 2 or primary cortisol resistance affects all tissues and is associated with mutations in the GR gene (Rodriguez et al., 2016).

Several mechanisms were shown to contribute to steroid resistance during asthma. For instance, changes in the cellular microenvironment, which is associated with the secretion of proinflammatory molecules, stand to play an important role in steroid resistance in severe asthmatic patients given the significance of GC signaling in inflammatory diseases (Barnes and Adcock, 2009; Rodriguez et al., 2016). Among the inflammatory mediators released, overexpression of IL-2 and IL-4 reduces the translocation and binding affinity of GRs in some target cells (Rodriguez et al., 2016). On the other hand, TNF-α phosphorylates GRs via JNK, leading to glucocorticoid-response-element binding (Bruna et al., 2003). Moreover, other cytokines, such as IL-17, increase the expression of GRβ, thus producing a dominant-negative effect on GR signaling (Vazquez--Tello et al., 2010). Moreover, oxidative stress which attenuates HDAC2 can impair GR activity (Adcock et al., 2005). Furthermore, GC-resistant asthma patients exhibit overactivation of the transcription factor AP-1, which binds GRs and inhibits its cellular function (Rodriguez et al., 2016).

However, during SSRA, the exact mechanism that links pyroptosis and inflammasome activation to steroid resistance is not well defined. It has been suggested in murine model of steroid-resistant allergic airway disease that exaggerated NLRP3 inflammasome/IL-1β activation critically contributed to glucocorticoid resistance (Kim et al., 2017b). One possible explanation can be attributed to the role of IL-1β in Th17 cell differentiation and IL-17 production (Chung et al., 2009), especially since asthmatic patients resistant to glucocorticoids show increased Th17 cells and IL-17A levels (Alcorn et al., 2010). In the same context, the adoptive transfer of Th17 cells in mice has resulted in the development of steroid insensitivity (Vazquez-Tello et al., 2010; McKinley et al., 2008). Another study found that IL-17A synergizes with dexamethasone in inducing colony-stimulating factor 3 (CSF 3) in both human airway smooth muscle cells and fibroblasts through transcriptional and post-transcriptional regulation. This effect is further increased in the presence of TNF-α and has been associated with glucocorticoid resistance (Ouyang et al., 2020). Moreover, an additional inhibitory effect mediated by IL-17 could be *via* activating the PI3K pathway and decrease in HDAC2 activity (Zijlstra et al., 2012). Interestingly, IL-17

was shown to be positively correlated and colocalized with the pyroptotic markers NLRP3, caspase-1, GSDMD, and IL-1β in the nasal mucosa of CRSwNP patients. Furthermore, IL-17A–induced pyroptosis contributed to steroid resistance by affecting GRα and GRβ expression, and the inhibition of pyroptotic proteins partially abolished IL-17A–induced steroid resistance in hNECs (Li et al., 2022). Furthermore, the activation of the TLR-4/MyD88 pathway in murine pulmonary macrophages triggered by IL-27 and IFN-γ, inhibits GR nuclear translocation and results in steroid resistance (Li et al., 2010). Therefore, the inflammatory cell death pathway or pyroptosis including inflammasome activation could be an important target for managing steroid resistance, especially in severe asthma with type I acquired GC resistance. Inflammasome activation and pyroptosis during SSRA are presented in Fig. 1.

4. Targeting inflammasome activation in SSRA

Inflammasome activation in macrophages and epithelial cells plays a role in asthmatic airway inflammation and is considered an important target for therapy. Some of the inflammasome inhibitors reported in the literature are the potent and highly selective NLRP3 inhibitor MCC950 or CRID (cytokine release inhibitory drug) (Coll et al., 2015) which prevented airway hyperresponsiveness and inflammation in a mouse model of severe asthma by lowering the expression of IL-1β, Th2 cytokines, and chemokines released from eosinophils, neutrophils, and macrophages (Rossios et al., 2018). Interestingly, estrogen was found to suppress allergen-induced airway inflammation in mice by inhibiting the transcription and activation of NLRP3 (Cheng et al., 2019). Traditional herbs having inhibitory effects on the NLRP3-caspase-1 interaction were also used in treating asthma (Tomani et al., 2018). Moreover, other inhibitors were used in experimental SSRA such as ac-YVAD-cho (a selective caspase-1 inhibitor) or neutralizing anti-IL-1β monoclonal antibody (Kim et al., 2017a). These treatments were effective for suppressing aberrant IL-1β responses and led to the suppression of steroid-resistant neutrophilic inflammation and airway hyperresponsiveness in allergic airway disease. Further, the administration of recombinant IL-1β to the airways of naïve mice or mice with steroid sensitive AAD resulted in the induction of steroid-resistant neutrophilic inflammation and airway hyperresponsiveness. Currently, several commercially available drugs target the IL-1 pathway, such as anakinra (IL-1RA that binds to IL-1R1), canakinumab (a human monoclonal IgG1 antibody for blocking IL-1β), rilonacept (a soluble decoy fusion protein that competitively binds to IL-1R) and gevokizumab (a humanized monoclonal anti-IL-1β) (Borthwick, 2016). Two clinical trials (NCT03513458 and NCT03513471) examined the effectiveness of anakinra on mitigating allergic inflammation during the early and late phases of allergic asthma (University of North Carolina Chapel Hill, 2018a; University of North Carolina Chapel Hill, 2018b). However, these studies were withdrawn since the risk of inhaled allergen challenge and anakinra treatment outweigh the benefits to participants. Another clinical trial on canakinumab was completed and showed to be safe, well tolerated, and lowered late asthmatic response by 28% (Novartis, 2007). This highlights the paradox of translating pre-clinical research into successful treatment to be used in the clinic, mainly due to the complexity and heterogeneity of asthma. Hence, more research is warranted to gain a deeper understanding on the role of the inflammasome pathway in SSRA so as the benefits of anti-IL-1 biologics outweigh their risks. On the other hand, treatment with dexamethasone significantly lowered the protein expression of NLRP3, pro-caspase-1, and cleaved caspase-1 in lung tissue. Also, Th2 cytokines BALF and lung tissue were reduced (Kim et al., 2017a). However, it is worth

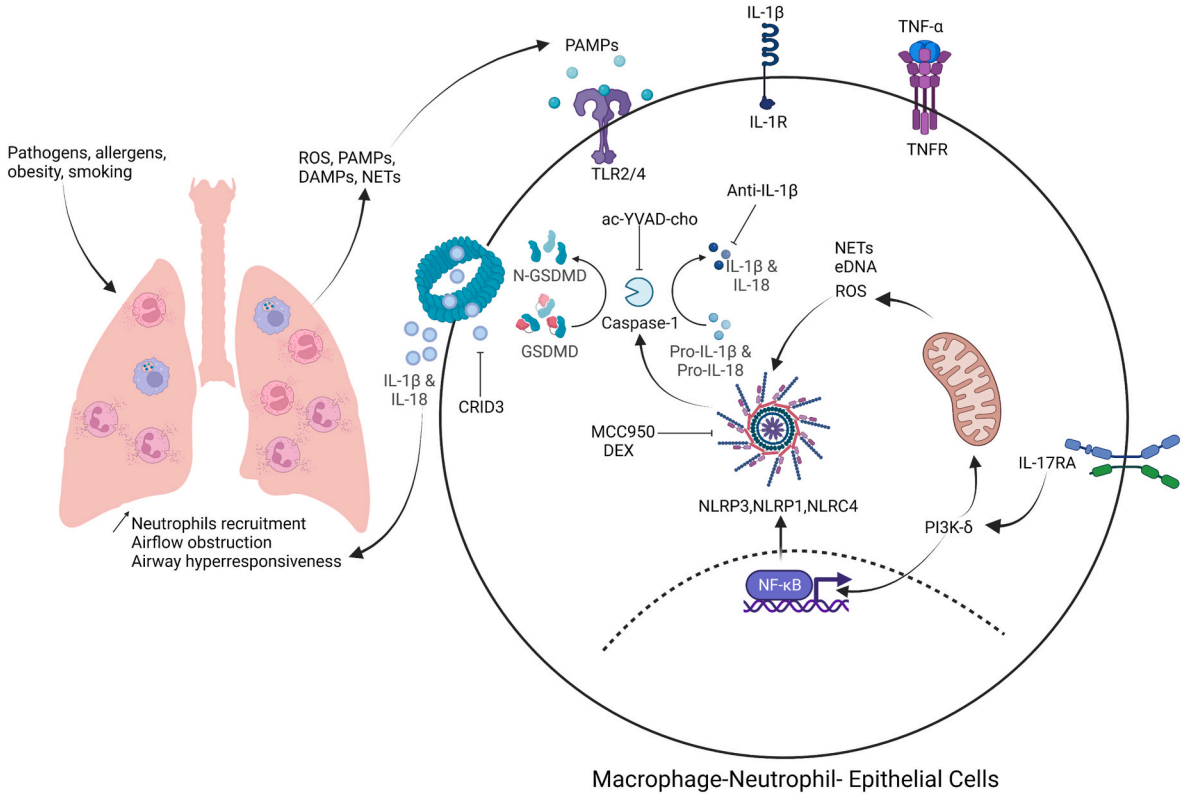

Fig. 1. Inflammasome activation and pyroptosis during SSRA. This figure summarizes the reported literature on signaling pathways leading to inflammasome activation during SSRA. These pathways involve IL-17, PI3Kδ, ROS production, eDNA, NETs and ROS. The activation of the inflammasome results in the release of chemokines and inflammatory mediators that attract more neutrophils and contribute to airway hyperresponsiveness. Several inhibitors such as MCC950 (CRID), ac-YAD-cho and anti-IL-1β act at different levels such as the NLRP3 inflammasome, caspase-1 and IL-1β respectively and were shown to reduce inflammation. PAMPs: pathogen associated molecular Patterns, DAMPs: damaged associated molecular patterns, ROS: reactive oxygen species, NETs: neutrophil extracellular traps, eDNA: extracellular DNA, DEX: dexamethasone.

highlighting the role of dexamethasone in enhancing the expression and function of NLRP3 in human monocytes (THP-1) and monocyte-derived macrophages (THP-M) (Busillo et al., 2011). This might be part of the early innate immunity against pathogens. Hence, the mechanism through which dexamethasone regulates NLRP3 inflammasome is context dependent and requires more investigation, especially in the case of chronic administration during severe asthma. Epigenetic regulations by micro-RNAs stand to be another important regulator of NLRP3 inflammasome activity. MicroRNAs miR-9, miR-21, and miR-126 have been defined as molecular mechanisms in the process of steroid-resistance (Kim et al., 2017b; Li et al., 2015; Mei et al., 2019). As such, the deletion of miR-223 promotes the expression of NLRP3 mRNA and protein, thereby enhancing airway inflammation and the production of pro-inflammatory cytokines (Bauernfeind et al., 2012).

5. Conclusions and gaps in knowledge

Given the heterogenicity of asthma, it is important that diagnosis is not merely dependent on patient characteristics but also closely considers the underlying pathology and drivers of the disease to be able to tailor the treatment regimen in a more specific manner for a particular endotype. As such, the involvement of the inflammasome and pyroptosis is one unique mechanism that poses a new target for treatment, especially for SSRA. However, it is worth emphasizing that despite the reported contribution of inflammasome activation to the pathogenesis of certain asthma subtypes, the molecular mechanism of involvement and the way it affects the function of different immune cells or alters signaling pathways involved in airway inflammation and steroid resistance is not yet fully elucidated and requires further research.

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Human and animal rights and informed consent

No experiments involving humans or animals were performed for this manuscript.

CRediT authorship contribution statement

Bariaa A. Khalil: Conceptualization, Writing – original draft, Writing – review & editing. **Narjes Saheb Sharif-Askari:** Conceptualization, Writing – original draft, Writing – review & editing. **Rabih Halwani:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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