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Current perspectives on the role of Interleukin-1 signaling in the pathogenesis of Asthma and COPD

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) cause significant morbidity and mortality worldwide. In the context of disease pathogenesis, both asthma and COPD involve chronic inflammation of the lung and are characterized by the abnormal release of inflammatory cytokines, dysregulated immune cell activity and remodeling of the airways. To date, current treatments still only manage symptoms and do not reverse the primary disease processes. In recent work, interleukin (IL)-1α and IL-1β have been suggested to play important roles in both asthma and COPD. In this review, we summarize overwhelming preclinical evidence for dysregulated signaling of IL-1α and IL-1β contributing to disease pathogenesis and discuss the paradox of IL-1therapeutic studies in asthma and COPD. This is particularly important given recent completed and ongoing clinical trials with IL-1 biologics that have had varying degrees of failure and success as therapeutics for disease modification in asthma and COPD.

INTRODUCTION

The morbidity and mortality associated with asthma and chronic obstructive pulmonary disease (COPD) results in a substantial economic and social burden around the world, that is still rising[1-3]. More effective therapeutics are clearly needed to not only manage chronic inflammatory symptoms in asthma and COPD, but resolve the underlying disease pathologies. While there is overwhelming preclinical evidence of the involvement of various immune mediators in the pathogenesis of asthma and COPD, these have not been successfully translated into therapies yet. One such important mediator is the major master-regulatory cytokine, interleukin (IL)-1.

While asthma and COPD are both characterized by chronic airway inflammation and airway remodeling[4], the master cytokines involved are substantially different for each disease[5, 6]. This notwithstanding, IL-1 that has been shown to be involved in many aspects of inflammation in asthma and COPD [7-13]. In asthmatics in response to triggers such as allergens or exercise, IL-1 is released as an immune mediator or damage associated molecular pattern (DAMP) together with other master-cytokines; thymic stromal lymphopoietin (TSLP) and granulocyte monocyte-colony stimulating factor (GM-CSF) within the airways, resulting in eosinophilia, immunoglobulin (Ig)-E switching[14] and T_H2 inflammation (IL-4, IL-9, IL-13)[14-17]. In COPD, damage from inhaled noxious particles, such as cigarette smoke (CS)[18], also causes IL-1 release, along with other master-cytokines; tumor necrosis factor (TNF)-α, IL-6, and IL-8/CXCL8 to cause neutrophilia, macrophage activation, T_H1 and T_C1 cell responses[19-25]. In addition, IL-1 signaling is directly involved in various aspects of airway remodeling. This includes, smooth muscle activation and airway hyperresponsiveness (AHR) in asthma[26, 27] as well as chronic mucus hypersecretion (CMH)[28, 29] and abnormal extracellular matrix (ECM) protein production in both diseases[9, 30, 31].

The existence of a common mediator for the pathogenesis asthma and COPD such as IL-1 might explain why epidemiological studies show that both diseases may coexist, or evolve into each other termed Asthma and COPD Overlap Syndrome (ACOS)[32]. For example eosinophilic airway inflammation is found in some COPD patients, and associates with greater steroid-mediated reversibility of airflow obstruction[4]. On the other hand, neutrophilic inflammation in severe asthmatics is associated with steroid-resistance[32]. Interestingly, IL-1 signaling has been

shown to be associated with both eosinophilic and neutrophilic inflammatory profiles in both diseases [12, 33]. These inflammatory profiles forms the basis of different disease sub-phenotypes in addition with factors such as aetiology (allergic/non-allergic), syndrome type (e.g. ACOS) and disease severity for asthma and for COPD, different overlaps of disease presentations, including small airway disease[34], emphysema[35] and the COPD-asthma phenotype (ACOS)[36]. Of note, the expression of IL-1 receptor (IL-1R) 1 and other signaling molecules of the IL-1 pathway in sputum were found to be important predictors of frequent exacerbations in asthma and COPD patients[37].

The heterogeneity in disease sub-phenotypes presents a substantial hurdle for research into curative therapies and underlies the importance for understanding the roles of a common master-regulators such as IL-1. Although this is known and well understood in the field, there is limited data on the levels of IL-1 in patients stratified into various specific disease sub-phenotypes of asthma and COPD.

There are different commercially available drugs to regulate IL-1 signaling, including IL-1 receptor antagonists, humanized monoclonal antibodies, and soluble decoy fusion proteins that block the IL-1 pathway in disease[38, 39]. However, the few clinical trials that have assessed the use of IL-1 therapeutics in asthma and COPD have largely failed to yield positive results. This raises important questions about the paradox of translating important preclinical research in diseases such as asthma and COPD into successful therapeutics. Hence, this review will specifically examine and summarize current knowledge on the biology and contribution of IL-1 to the pathogenesis of asthma and COPD, further we assess the paradox of the failed clinical trials and evaluate the implications and usefulness of therapeutically targeting this cytokine.

Regulation of IL-1 signaling within the lung

In the lung, IL-1 is primarily produced by the airway epithelium and macrophages[40], and its expression can be induced to varying degrees by lung fibroblasts, neutrophils, and T cells[9, 39, 41]. IL-1 denotes two variant cytokines, IL-1α and IL-1β, with closely related polypeptides which are part of a larger family of 7 agonists (including: IL-18, IL-33, IL-36α, IL-36β and IL-

36γ). IL-1α and IL-1β are encoded by different genes, and are synthesized as 31kDa precursor molecules with missing leader sequences. Pro-IL-1α is biologically active, but can undergo cleavage by calpain, a cysteine protease activated by calcium, to generate an additional biologically active 18kDa mature form. On the other hand, pro-IL-1β is not biologically active and requires activation through cleavage by caspase-1 (IL-1β converting enzyme), which occurs after processing by the nucleotide-oligomerization binding domain-like receptor protein (NLRP) 3-inflammasome complex to generate a biologically active 17kDa mature IL-1β[42]. The inflammasome is activated when pathogen associated molecular patterns (PAMPs) or DAMPs (e.g. ATP) released upon cell-damage or death, activate pattern recognition receptors (PRRs) such as toll-like receptor (TLR)4 and the P_2X_7 purinergic receptor[43]. In various animal studies it has been shown that inflammasome activation is directly involved in inflammatory, fibrotic or emphysematous responses to inhalation-related insults within the lung, including allergens (in asthma) and noxious agents e.g ozone, alum and bleomycin modeling fibrosis and/or emphysema[44-46].

Despite differences in activation, IL-1α and β bind individually to the same IL-1 receptor 1 (IL-1R1)[40]. The binding of IL-1α/β to IL-1R1 forms the IL-1R1-complex, activating signaling through the classical toll interleukin receptor (TIR)/myeloid differentiation primary response 88 (MYD88) pathway **(Figure 1).** This signaling pathway significantly overlaps with the TLR pathway and is shared between most members of the IL-1 family. This pathway specifically leads to the nuclear translocation of transcription factors, such as p38 mitogen-associated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), activator protein (AP)-1 and NF-κB, that promote the expression of a wide variety of inflammatory cytokines and growth factors[47-50] (**Figure 1**).

The signaling of IL-1α/β is regulated at various levels by anti-inflammatory family members and receptors **(Figure 2)**. Compared to IL-1R1, the decoy IL-1R2, is a biologically inert receptor that can also bind IL-1α/β and prevent signaling[40, 51]. The IL-1 receptor antagonist (IL-1RA) is an anti-inflammatory family member that competes for the IL-1R1 binding site and regulates the function of IL-1α/β[42]. In line with this, various studies have shown a lower expression of IL-1R2 and IL-1RA in asthma and COPD causing an increased IL-1 activity due to the lack of adequate anti-inflammatory regulation[11, 52-54]. In addition, the

activity of IL-1 can also be regulated by epigenetic factors. Increased methylation of the *IL1R2* gene locus is associated with a lower expression of the anti-inflammatory IL-1R2, which may add to increased IL-1 activity in asthmatics[52]. Short interfering RNAs such as microRNAs (miRNA), also regulate IL-1 signaling. In particular, miR-149 and miR-146a do not only have altered expression in COPD but also influence IL-1 signaling in COPD[55, 56]. As an example, we have shown that miR-146a-5p binds to and down-regulates the expression of IRAK-1, a mediator in the IL-1 pathway to inhibit lung fibroblast responses to IL-1α[57]. Hence a balance between IL-1 signaling and its regulation in the lung is not only essential for normal immune defense, but is also important in the pathogenesis of diseases such as asthma and COPD.

IL-1α and IL-1β, master-regulators in the lung immune defense

In the lung, IL-1α and β are essential for the immune defense against various inhaled noxious agents such as nanoparticles (silica and titanium dioxide)[58, 59], ozone[46, 60], particulate matter (PM)[61], CS[62] and pathogens such as respiratory viruses[63]. In the lungs, IL-1 is released early to drive the inflammatory response as evidenced in a mouse model of acute silica exposure. Here, IL-1α was released in the first hours after challenge and peaked after 6-12 hours, to stimulate the release of inflammatory mediators including IL-1β, 24 hours later[58].

The airway epithelium is the structural barrier which forms the first part of innate immunity in the lungs, and constitutively produces and stores IL-1α primarily as a membrane-associated form[42, 64]. IL-1α can also be rapidly shuttled into the nucleus to initiate transcription[40]. In apoptotic conditions, IL-1α translocates into the nucleus and remains bound to chromatin. However in necrotic conditions, such as during cellular damage caused by inhaled noxious particles, IL-1α is released and acts as an 'alarmin' or DAMP[58]. Thus, upon exposure of the airway epithelium to inhaled noxious particles (smoke) or allergens, IL-1α and β are among the initial immune mediators released[58]. This induces inflammation by activating the synthesis and release of a wide variety of chemokines and growth factors[49, 65]. In addition, recruited alveolar macrophages are also responsible for the release of high concentrations of IL-1α/β[8]. The receptors for IL-1 are found on most immune and structural cells of the lung and IL-1 acts in concert with other innate cytokines (e.g. TNF-α) to activate master-transcription factors of inflammation such as NF-κB and AP-1 to activate innate and adaptive immunity[39].

IL-1α/β signaling can also contribute to repair, remodeling, and fibrosis of the lung[39]. Using a co-culture model, we have shown that airway epithelial-derived-IL-1α regulates the production of inflammatory cytokines and ECM proteins by lung fibroblasts[62]. Specifically, airway epithelial-derived-IL-1α stimulated inflammatory cytokine release (CXCL8, IL-6) and suppressed the expression of ECM proteins (collagen Iα1 and fibronectin) by lung fibroblasts. IL-1α also suppressed the production of the classical pro-fibrotic cytokine, transforming growth factor (TGF)-β in lung fibroblasts[62]. Other studies have revealed a possible counteractive interaction between IL-1 and TGF-β, which may play a role in fibrosis and airway remodeling. Specifically, TGF-β supports the survival of pro-fibrotic myofibroblasts by inhibiting IL-1β-induced apoptosis[66], while IL-1β inhibits TGF-β1-dependent fibroblast-myofibroblast transformation[67]. This interaction points to a balance between IL-1 and TGF-β signaling in the lungs during repair processes that may be disrupted due to abnormal remodeling in asthma and COPD. Cross-talk between the endoderm and mesoderm-derived cells may provide a mechanism whereby the mesenchymal lung tissue is primed to respond to inflammation and prevented from uncontrolled ECM production. This is supported by data demonstrating that IL-1β at low and high concentrations is a major inducer of cyclooxygenase-2 (COX-2) and prostaglandin (PG)E2 in human lung fibroblasts, which inhibits increased fibroblast proliferation. However, at moderate concentrations, IL-1β induces accelerated fibroblast proliferation, demonstrating a concentration-dependent biphasic effect of IL-1β induced lung fibroblast proliferation[68]. This shows that both the temporal release and concentration of IL-1 maybe essential for specific-IL-1 driven responses within the lung micro-environment. However in lung diseases such as asthma and COPD, the global activity and release of IL-1 is increased and this could serve as a target for IL-1-specific therapeutic studies.

IL-1 in asthma pathogenesis

In asthma, IL-1 plays an important role in the pathogenesis of different molecular phenotypes of the disease. IL-1α and β are known to contribute to T_H2 inflammation in asthma through the activation and recruitment of eosinophils, mast cells, dendritic cells (DCs) and other inflammatory cells like neutrophils in neutrophilic asthma[12, 69]. IL-1α/β concentrations are increased in sputum and bronchial lavage (BAL) fluid from symptomatic asthma patients

compared to asymptomatic asthmatics[70-72]. In a study by Busse and colleagues, an increased IL-1β concentration together with IL-6 and CCL20 was found in the sputum of older patients with more severe asthma and was associated with increased neutrophil counts compared to younger patients with less severe asthma[73]. Liu *et al*, also found increased IL-1α concentrations in the BAL fluid of asthma patients who had a T_H2/T_H17 low-phenotype together with increased neutrophilia[74]. In addition, IL-1β concentrations were increased in both T_H2/T_H17-predominant patients who had increased eosinophilia and T_H2/T_H17 low-phenotype asthma patients[74]. This increased production originates from the airway epithelium and macrophages as demonstrated by Sousa *et al.* who showed an increased protein expression of IL-1β and IL-1RA in these cells from atopic asthmatic patients compared to normal control individuals[11]. These findings of elevated IL-1 levels and the discovery that IL-1R1-IL-1 signaling contributes to airway inflammation and remodeling have raised interest in the potential for targeting the IL-1R1 therapeutically in asthma[69].

Several *in vitro* and *in vivo* studies have assessed the link between allergen triggers and increased levels of IL-1 in asthma. When stimulated with house dust mite (HDM), an asthma allergen, airway epithelial cells released IL-1α and IL-1β to stimulate IL-6, GM-CSF and IL-33, both in an autocrine manner and from immune cells such as monocytes [12, 75, 76]. IL-1β–dependent control of the hypoxia induced factor (HIF)-1α is involved in CMH in asthma through the overexpression of MUC5AC, an important mucin in bronchial epithelial cells[28]. Using bronchial air-liquid interface (ALI) cultures, it was also determined that an autocrine TLR4-dependent-IL-1α production stimulates GM-CSF and IL-33 to recruit dendritic cells involved in asthmatic T_H2 inflammation and allergic sensitization[12]. In *in vivo* studies, Willart *et al*. exposed IL-1R-knock-out mice to HDM and found that they were protected against T_H2 inflammation compared to air-exposed mice[12]. In an ovalbumin (OVA) sensitization mouse model, deletion of IL-1α/β expression strongly attenuated AHR with decreased T-cell-proliferation and inflammation and loss of B-cell IgG1 and IgE production[77]. Conversely, knocking out the anti-inflammatory IL-1RA caused an increased AHR response and T-cell cytokine production[77]. In addition, IL-1R1 knock-out and administering IL-1α/β neutralizing antibodies in a toluene disocyanate-induced asthma mouse model significantly reduced AHR and abrogated various inflammatory features of asthma. This included decreased IgG1, airway

epithelium hyperplasia, lymphocyte influx, eosinophilia, along with decreased IL-4 and vascular adhesion molecule (VCAM)-1 production[78].

To further dissect the role of IL-1 in specific phenotypes of asthma, Schmitz *et al.* investigated IL-1R1-knock-out in a mild *in vivo* asthma model with low-dose OVA challenges with no adjuvant. While IL-1R1 signaling was dispensable in more severe models, in this mild asthma model, it led to a robust reduction in goblet cell hyperplasia, T_H2-cell proliferation and dysregulated IgE-responses[13]. Apart from the regulation of T_H2 inflammation, IL-1 also activates and causes the proliferation of group 2 innate lymphoid cells (ILC2) that promote the release of T_H2 cytokines independent of T_H2-cells in allergic asthma [79, 80]. Here, IL-1β in the presence of IL-12 was shown to potentiate ILC2 switching in an *in vivo* mouse model[80]. IL-1β signaling is also crucial for glycolysis-mediated inflammatory responses in an allergic mouse model. IL-1α/β administration led to increased glycolytic flux and an increase in genes of glycolytic mediators such as lactate dehydrogenase A[81]. In addition, IL-1-induced TSLP and GM-CSF release in airway epithelium were mediated by increased glycolysis[81]. This suggests a potential link between energy metabolism and IL-1-pro-inflammatory responses in the airways.

Various *in vivo* models have also demonstrated a critical role of the NLRP3-inflammasome complex in asthma activated in response to inhaled allergens[82]. In allergic HDM and OVA-models without an alum adjuvant, NLRP3-inflammasome activation and subsequent IL-1β release is essential for allergic airway inflammation[83, 84]. In these models, deletion of NLRP3 caused an abrogation of eosinophil recruitment and T_H2-inflammation[83, 84]. Mechanistically, inflammasome activation has been attributed to the activity of DAMPs (e.g. ATP and uric acid) released after allergen exposure in the airways[85]. More recently, a non-typeable *Haemophilus influenzae* and *Clamydia muridarum* infection was used to demonstrate a crucial role for the NLRP3-inflammasome and IL-1β signaling in an OVA mouse model of steroid resistant asthma[86]. Specifically, inhibition of IL-1β and the NLRP3-inflammasome led to suppression of important characteristics of steroid resistant asthma, including neutrophil influx and non-responsive AHR[86]. Translating these findings to the clinical setting, inflammasome activation and release of active IL-1β in patients with neutrophilic asthma was strongly linked with inhaled corticosteroid insensitivity[86-88]. Further, the expression of IL-1R1 and its accessory protein (IL-1RAcp) strongly correlates with neutrophil

counts in the sputum of asthmatics compared to controls[89]. There is also a strong correlation between increased IL-1R1 (and IL-1RAcp) expression and a reduced ratio of Forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) in asthma. This indicates that IL-1-induced neutrophilia may have a prominent contributory role in airflow obstruction in asthma[89].

IL-1 signaling also contributes to sub-epithelial airway remodeling, as it has been implicated in airway smooth muscle (ASM) sensitization in asthma[26]. In addition, IL-1RA and the soluble decoy IL-1R2, abrogates both IL-5 and IgE-dependent ASM contraction[26]. A combined stimulation of IgE, IL-5 and IL-1β causes an enhanced production of IL-1 in human ASM cells[26]. This can synergistically act with TNF-α in an autocrine manner, to stimulate production of IL-6 and GM-CSF from ASM cells[27]. We have also shown in preliminary work using a 3-dimensional collagen 1 gel assay that both IL-1α and β inhibit the ability of lung fibroblasts to repair and remodel fibrillar collagen I[90]. Such a response has potential implications for the effect of an increased production of IL-1α/β on collagen repair in the airways of asthmatic patients[90]. However, compared to the body of work supporting the role of IL-1 in allergic airway inflammation, more studies are needed to determine the specific mechanisms by which IL-1 contributes to airway remodeling in asthma.

A decreased activity of anti-inflammatory IL-1 regulators due to an underlying genetic predisposition has been shown to cause increased IL-1 activity in asthma patients[52]. The presence of an A2 allele in the *IL1RN* gene (encodes for IL-1RA) is associated with non-atopic asthma in a Japanese population, and correlates with a lower serum concentration of IL-1RA[53]. Furthermore, a gain-of-function single nucleotide polymorphism (SNP) in the *IL1A* gene is associated with reduced lung capacity in asthmatic children from Brazil[91]. Gagné-Ouellet and colleagues also showed an epigenetic regulatory component may be involved in IL-1 dysregulation in asthma. Here, increased DNA methylation of the *IL1R2* promoter negatively correlated with IL-1R2 mRNA expression in atopic and asthmatic subjects compared to controls[52]. This led to lower expression of the anti-inflammatory decoy IL-1R2 receptor in asthmatics and increased IL-1 activity[52].

The studies reviewed in this section point to not only an increased production and activity of IL-1 in asthmatic patients and a functional role in animal models, but also a genetic

component that may predispose asthmatics to down-regulate anti-inflammatory regulators of increased IL-1 activity. This could inform pharmacogenomic studies of IL-1 therapeutics in asthma.

IL-1 in the pathogenesis of COPD

Increased expression and release of IL-1 plays a role in different phenotypes that make up COPD, including small airway disease and emphysematous destruction. Specifically, mRNA and protein levels of IL-1α and IL-1β are increased in the serum, lung biopsies, sputum and BAL fluid of COPD patients compared to healthy controls irrespective of smoking status[7, 8, 10, 92]. The increased level of IL-1β in particular has been associated with an increased NLRP3-inflammasome activation in COPD patients[93]. The levels of IL-1 may also help to differentiate COPD phenotypes. Increased levels of IL-1β have been observed in the serum of patients during acute exacerbations of COPD (AECOPD), compared to stable COPD patients, healthy smoking and non-smoking controls[33]. This increased release of IL-1β in AECOPD is positively correlated with the number of pack-years, percentage neutrophil counts and C-reactive protein (CRP) in the serum, while negatively correlating with FEV_1[33]. In addition, mRNA levels of the NLRP3-inflammasome were found to be increased in peripheral blood mononuclear cells and bronchial biopsies from AECOPD patients compared to control smokers[94].

The plasma levels of IL-1β negatively correlates with FEV_1 and pack-year number in COPD patients[54]. The proposed source of these elevated levels of IL-1β are the airway epithelium and macrophages, which highly express IL-1β in the lungs of COPD patients[54]. IL-1β also acts on these same cells, expressing IL-1R1 in an autocrine manner to stimulate CXCL8 and GM-CSF release[8]. These then recruit and maintain neutrophils, one of the major cell-types involved in airway inflammation in COPD[95].There is also a corresponding dampening of the inhibitory activity of IL-1, as concentrations of IL-1RA and IL-1R2 are decreased in sputum and plasma of COPD patients compared to non-smoking controls[54]. Thus IL-1 release not only correlates with smoking status, but also with lung function decline, indicating its important role in COPD pathogenesis.

To understand the mechanisms underlying the increase of IL-1 in COPD, *in vitro* and *in vivo* models have been used. Increased expression and release of IL-1 *in vitro* from the airway epithelium and macrophages have been shown after exposure to CS, other noxious particles such as particulate matter and various infectious agents (e.g. H1N1, LPS, polycytidylic acid (poly(I:C))[29, 61, 62, 96, 97]. Further, various *in vivo* studies using CS-exposure in mice have found increased release of IL-1α and IL-1β. CS exposure causes increased concentrations of IL-1α and pro-IL-1β in the bronchoalveolar space and lung parenchyma through a TLR4/MyD88 dependent mechanism[98]. IL-1R1 knock-out and IL-1α/β neutralization (with an antibody) in mice led to protection against CS-induced inflammation in the lung due to decreased inflammatory cytokines in lung homogenates compared to wild-type mice[7]. CS-induced lung inflammation was shown to be NLRP3-inflammasome and caspase-1 independent indicating a dependence on IL-1α, but not IL-1β signaling[7]. In another study, caspase-1 knockout and administration of neutralizing antibodies in mice, showed CS-induced lung inflammation and neutrophil influx is dependent on IL-1α, but not IL-1β[8]. In this and another study, IL-1 signaling has also been linked to viral induced inflammation as IL-1 inhibition attenuated H1N1 influenza induced inflammation after CS exposure[8, 29]. This leads to a significant reduction in inflammatory mediators and MUC5AC expression with decreased numbers of neutrophils and macrophages[29]. In support of these findings, Nikota *et al*, showed that an exaggerated IL-1α production is crucial for CS-induced neutrophilia through a CXCR2-dependent mechanism upon infecting mice with a non-typeable *Haemophilus influenza* strain[99]. Compared to the selective role of IL-1α over IL-1β reported in the models above, other studies have shown an increased activation of the NLRP3-inflammasome and IL-1β release[93]. Noxious agents such as PM10 and CS exposure in the airway epithelium *in vitro* and in mice activates IL-1R1 and the NLRP3-inflammasome leading to the release of IL-1β and other mediators such as GM-CSF and CCL20 which cause neutrophilia and activation of DCs in COPD[61, 100]. The differences in the release of IL-1α and/or β in various models need further studies for clarification and maybe due the different times of cytokine release[58].

IL-1 signaling *in vivo* is also involved in airway remodeling and emphysema in COPD. Knock out of IL-1R1 and IL-1β neutralization in mice not only protected against emphysema after a 6-month CS exposure, but also caused a complete protection from CS-induced small

airway remodeling[30]. Added to this, Lappalainen and colleagues showed that over-expression of IL-1β in mice lung epithelium leads to a robust inflammatory phenotype accompanied by emphysema and airway remodeling[9]. This was mediated through increased production of matrix metalloproteinase (MMP)-9 and -12, neutrophil chemoattractant KC, and macrophage inflammatory protein (MIP)-2[9]. Together, these studies indicates that IL-1α/β signaling is implicated in CS and infection-induced chronic inflammation, airway remodeling and emphysema and either interacts with or affects almost all known mediators and disease processes involved in COPD.

To further highlight the complexity of IL-1 signaling in the COPD pathogenesis, multicellular co-culture models have been used to reveal its crucial role in dysregulated cellular communication, leading to aberrant repair processes in the lung. Here, IL-1 signaling has been shown to be the main driver of a disturbed epithelial-fibroblast communication in the lung epithelial-mesenchymal trophic unit (EMTU) in COPD[62]. Through the use of an *in vitro* co-culture model, we found that CS-exposure caused COPD-derived airway epithelial cells to produce increased levels of IL-1α that stimulated lung fibroblasts to release inflammatory mediators, such as CXCL8, while suppressing lung fibroblast-ECM expression[62]. Lung fibroblasts are the major cells involved in matrix turnover, and ECM suppression could play a significant role in COPD in terms of both emphysematous tissue destruction and the most recently understood early loss of small airways[101]. Our findings are in line with Suwara *et al*, who showed that epithelial damage, either via thapsigargin to simulate endoplasmic reticulum (ER) stress or H_2O_2 to induce reactive oxidative species (ROS), caused an increased release of IL-1α[97]. Further, conditioned medium from damaged bronchial epithelium induced an IL-1α-dependent release of pro-inflammatory mediators CXCL8 and IL-6 from lung fibroblasts[97]. This effect was amplified after stimulation with the viral mimic, poly (I:C)[97]. Hill *et al*, corroborated these findings by showing that poly I:C and rhinovirus stimulation causes an epithelial-derived-IL-1α-dependent release of CXCL8 and IL-6 from lung fibroblasts in a polarized EMTU model[102]. Since viral infections have been associated with exacerbations in COPD, the involvement of IL-1 signaling in a disturbed cellular cross-talk associated with both CS- and viral-induced acute inflammation demonstrates a prominent role for IL-1 in not only stable COPD but also during exacerbations.

Our co-culture studies also highlighted the role of disturbed epigenetic regulation of the IL-1 pathway in contributing to aberrant epithelial-fibroblast communication in COPD pathogenesis. miR-146a is a known suppressor of IL-1 signaling, which is induced in lung epithelial and mesenchymal cells after IL-1 stimulation, acting as an anti-inflammatory regulator[103-105]. We reported lower induction of miR-146a-5p in COPD-derived lung fibroblasts compared to controls upon co-culture with airway epithelial cells[57]. This miR-146a-5p induction was epithelial-IL-1α-dependent, and the lower expression in lung fibroblasts from COPD patients was associated with the SNP rs2910164 (GG allele), which caused reduced expression of mature miR-146a-5p[106]. Thus we proposed that dysregulated epigenetic control of IL-1 in COPD fibroblasts may lead to an exaggerated IL-1-mediated inflammatory response and as such contribute to abnormal repair in COPD[57](**Figure 3)**.

These studies show the involvement of IL-1 as a master-regulator in the complex interplay of mediators that are dysregulated in COPD disease pathogenesis. In addition, a unique role of IL-1 in aberrant cellular communication and repair in the EMTU may provide an explanation for the molecular mechanisms involved in small airway disease in COPD.

The paradox of IL-1 targeted therapeutics for asthma and COPD

The studies presented here demonstrate that IL-1α and β are clearly involved in the disease pathogenesis of asthma and COPD **(Figure 4).** However, this wealth of data has failed to translate into successful therapeutics for asthma and COPD. Interestingly, IL-1 is not the only mediator that has failed to be translated into successful therapies. Examples of failed therapeutics against important mediators in COPD include, anti-IL-5 (Benralizumab)[107], anti-IL-17 (CNTO6785)[108], anti-CXCR2 (MK-7123)[109] , anti-TNF-α (Etanercept)[110], anti-MMP9/12 (AZD1236)[111] and the neutrophil elastase inhibitor (AZD9668)[112]. In asthma, the anti-IL-13 antibody (Tralokinumab, CAT-354) failed across 6 clinical trials[113] and the humanized anti-IL-4 monoclonal antibody (Pascolizumab, SB 240683) also had no therapeutic benefit[114]. Although Benralizumab effectively blocks IL-5 for the treatment of severe eosinophilic asthma, this effect is only partial and the disease burden in some patients is unaffected[115]. In addition, administration of the inhaled IL-4/IL-13 antagonist Pitrankinra, at

different doses (1mg, 3mg or 10mg given twice daily for 12 weeks) failed in clinical trials comparing the entire asthma patient population to the placebo control[116]. However, the 10mg dose of Pitrankinra significantly attenuated exacerbation rates in the asthma patients with specific SNPs (rs1029489GG and rs8832GG) in the gene encoding the receptor for IL-4 (IL-4Rα)[116]. This showed that understanding the pharmacogenomics and careful stratification of patient cohorts might be the way forward for clinical trials. This stratification could be informed by studies such as those in Japan[53] and Brazil[91] that found associations between non-atopic asthma and lower serum levels of IL-1RA caused by 2 alleles in the *IL1RN* gene and a gain-of-function SNP in the *IL1A* gene associating with reduced lung capacity in asthmatic children respectively. In addition to this, the failure of these therapies could be due to functional redundancies between the major inflammatory mediators involved in both diseases[117]. Again, the failure to translate IL-1 therapies from the lab to bedside, may be due to the fact that IL-1 release is triggered by different allergens, noxious and infectious agents in both diseases and its signaling is involved in and has different roles in most phenotypes of both diseases. Hence, the development of IL-1 therapies may need specific preclinical disease models that carefully mimics these specific roles to aid in therapeutic studies. In these preclinical models, the interaction between IL-1 and other major mediators such as TGF-β [66, 67] which is discussed could also be studied to determine if there might be a net protective role of IL-1 in disease.

Currently, commercially available drugs targeting the IL-1 pathway include, 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 the IL-1 receptor), and Gevokizumab (a humanized monoclonal anti-IL-1β)[39]. Of these drugs, significant success has been shown in the use of the Anakinra in the management of gouty and rheumatoid arthritis as well as cyropyryrin-associated periodic syndrome (CAPS), a genetic auto-inflammatory disease[118-120]. The human monoclonal antibody for IL-1β (Canakinumab), is also effective for treating most auto-inflammatory disorders including CAPS, TNF receptor-associated periodic syndrome (TRAPS) and familial Mediterranean fever[38, 118]. In the large Canakinumab anti-inflammatory thrombosis outcome study (CANTOS) trial, COPD as a confounder was not associated with incident lung cancer cases and drug allocation. Canakinumab was effective at reducing concentrations of IL-6 and high-sensitivity-CRP in trial participants leading to a significant reduction of lung cancers[121].

The monoclonal anti-IL-1R1 (MEDI8968), has been assessed for different inflammatory diseases including COPD, type 2 diabetes and osteo-arthritis[117, 122]. An anti-IL-1α IgG1 monoclonal antibody (Bermekimab, Xilonix) is also currently in various trials (Phase 2–3) for diseases including colorectal and lung cancers, diabetes mellitus type 2 (DM2), acne vulgaris, and atopic dermatitis[118]. In addition, evidence supports a role for targeting the inflammasome (responsible for IL-1β production) as a therapeutic strategy in chronic inflammatory diseases such as asthma and COPD. The use of compounds such as the inflammasome inhibiting P_2X_7 receptor antagonist (AZD9056) has been investigated in other inflammatory diseases such as rheumatoid arthritis[39, 118].

To date, a few clinical trials have looked at the possibility of treating asthma and COPD with IL-1 biologicals (see Table 1 for an overview). The problem with some of these trials has been the lack of adequate end-points to aid in assessing the impact of these studies on disease pathogenesis. In addition to adequate end-points, the critical involvement of IL-1 in co-morbidities of asthma such as atopic dermatitis as well as hypertension, DM2 and obesity for both diseases present a unique cohort of patients in which IL-1 treatments can be assessed[123, 124]. Again, since IL-1 has been strongly associated with exacerbations in both diseases, clinical trials could be undertaken in specific patients who are prone to a higher rate of exacerbations[37]. This is noteworthy since IL-1 is a prominent cytokine released during infections of the airways which is a major trigger of exacerbations[29, 86, 99]. Also, since IL-1 is released as one of the main prominent initial mediators in response to various noxious particles, clinical trials could be designed to target early disease in asthma and COPD. In line with this, there are two ongoing clinical trials to assess the effectiveness of Anakinra as a rescue treatment for airway inflammation in allergic asthma either through an early or late phase administration after allergen challenge[125, 126]. With regards to COPD, clinical trials involve patients with moderate to severe disease. However, recent evidence has demonstrated that up to 41% of the smallest conducting airways are already lost in mild COPD patients[101], indicating that treatment strategies and trials need to be focused on early disease.

In a randomized double-blind placebo-controlled trial presented as a conference abstract, patients with mild asthma were given 10 mg/kg of Canakinumab twice, with a 15 day interval between the first and second dose, and an allergen challenge test was performed on the start date

and day 28[128]. The results of this trial was positive and showed a significant reduction of circulating levels of IL-1β with a reduced rate of late phase asthma response compared to pre-treatment[38, 128]. For COPD, a phase 1/2 clinical trial assessed the pharmacokinetic properties of Canakinumab, but findings were inconclusive as statistical data related to the trial were not provided[129]. It was also reported that administration of 400mg of the P_2X_7 antagonist, AZD9056 once a day for 4 weeks did not change lung function in moderate to severe COPD patients[130]. However there were no further details on this report. A double-blind placebo controlled trial of the humanized monoclonal IL-1R1 antibody (MEDI8968) in COPD patients failed to reach its primary endpoint of reducing the rates of moderate and acute exacerbations[117]. In this trial, the projected annual rate of moderate/severe AECOPD (1.27) in the placebo group estimated in the initial power calculation was higher than the actual observed rate of 0.78. Hence, although there was a 32% reduction in exacerbation rate, this fell short of the 40% reduction in exacerbations needed to reach statistical significance. Moreover, although administration of MEDI8968 consistently reduced blood neutrophil counts in addition to CRP and fibrinogen levels in COPD patients compared to controls, clinical surrogate markers were used to assess levels of circulating IL-1[117]. Again, pulmonary levels of the administered drug were not assessed. Although this does not prove that the lung was under-dosed, it can also not be concluded that the lung was properly dosed. Future, larger and adequately powered trials that assess the pulmonary effects of IL-1 therapeutics are therefore needed to provide a clearer picture of the role of IL-1 therapeutics in the treatment of COPD.

Future trials and studies to target IL-1 inhibition should consider that although both IL-1α and β are involved in asthma and COPD pathogenesis, the roles of these two cytokines may be different under particular disease triggers. As an example, mouse studies in both asthma and COPD have shown early IL-1α release independent of IL-1β could be a key initiator of disease pathogenesis. However, currently available commercial biologicals do not specifically target IL-1α, although the anti-IL-1α IgG1 monoclonal antibody (Bermekimab) is currently in various trials (Phase 2–3) for other diseases. Thus, current studies or trials that are directed towards targeting the activity of IL-1α also and not only IL-1β, may provide more promising therapeutic potential in both COPD and asthma. As IL-1 strongly associates with increased neutrophilia in both diseases and is associated with disease exacerbations[37], this may serve as an example of a

specific disease phenotype in which IL-1 together with other master-cytokines could be biomarkers for responder populations and biologicals could be further investigated.

As with the blockade of various other master-regulatory cytokines, blocking the IL-1 pathway in chronic diseases such as asthma and COPD raises concerns about off-target effects that may occur due to IL-1's important role in normal immune functions of the body. As seen in most cytokine therapies, the number of occurrences of routine bacterial infections have been reported to be increased with IL-1 blockade[118]. However, compared to other anti-cytokine therapies such as anti-TNF treatment for inflammatory diseases, there is virtually a complete lack of opportunistic infections following anti-IL-1 therapy[118]. In line with this, Anakinra is remarkably safe in chronic inflammatory diseases such as arthritis, where patients have been on daily doses for over 10 years[131, 132]. Thus, clinical trials for anti-IL-1 therapy in asthma and COPD need to be carefully planned with the right dosing and targeting of proper disease phenotypes to minimize any off-target effects on the normal immune defense within the lung.

CONCLUSION

In this review, we demonstrated clear evidence for a role of IL-1α and β in the disease pathogenesis of asthma and COPD. However, a major unanswered question is, how do these two closely related cytokines that bind to the same receptor and activate the same pathway drive divergent inflammatory processes in asthma and COPD? Further studies are needed to determine how different environmental triggers can stimulate differential IL-1α/β signaling in asthma and COPD. Although a few trials have reported varying data targeting the function and activity of both IL-1α and IL-1β, there is the need for better stratification and targeting of specific disease cohorts in future trials. The use of specific antibodies against IL-1α and IL-1β and lung-specific biomarkers may also be worth examining in future trials to determine if targeting these cytokines is a promising therapeutic approach for asthma and COPD patients.

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Intervention	Disease	Phase	NCT Number	Status	Expected Outcome	Results	Reference
ASTHMA							
Drug – Anakinra (Recombinant Human IL-1 Receptor Antagonist – Late Phase Administration)	Allergic Asthma	1 & 2	NCT03513458	Ongoing	Examine Anakinra effectiveness to rescue allergic inflammation	NA	[125]
Drug – Anakinra (Recombinant Human IL-1 Receptor Antagonist - Early Phase Administration)	Allergic Asthma	1 & 2	NCT03513471	Ongoing	Examine Anakinra effectiveness to rescue allergic inflammation	NA	[126]
Drug - ACZ885 (Canakinumab)	Late Asthmatic response (LAR)	NA	NA	Completed	NA	ACZ885 was safe well tolerated and lowered LAR by 28%	[128]
COPD							
Drug - MEDI8968 (IL-1R1 Monoclonal antibody)	COPD	2	NCT01448850	Completed	NA	Failed to reach primary endpoint of reducing moderate and acute exacerbation rate	[117]
Drug – ACZ885 (Canakinumab)	COPD	1 & 2	NCT00581945	Completed	NA	Statistical analysis not provided	[129]
Drug – AZD9056 (P_2X_7 antagonist)	COPD	2	NA	Completed	NA	No significant changes on lung	[130]

						function in COPD patients after a 400mg, 4 week UID treatment.	

Table 1. A Summary of clinical trials of IL-1 biologics in asthma and COPD

Figure Legends

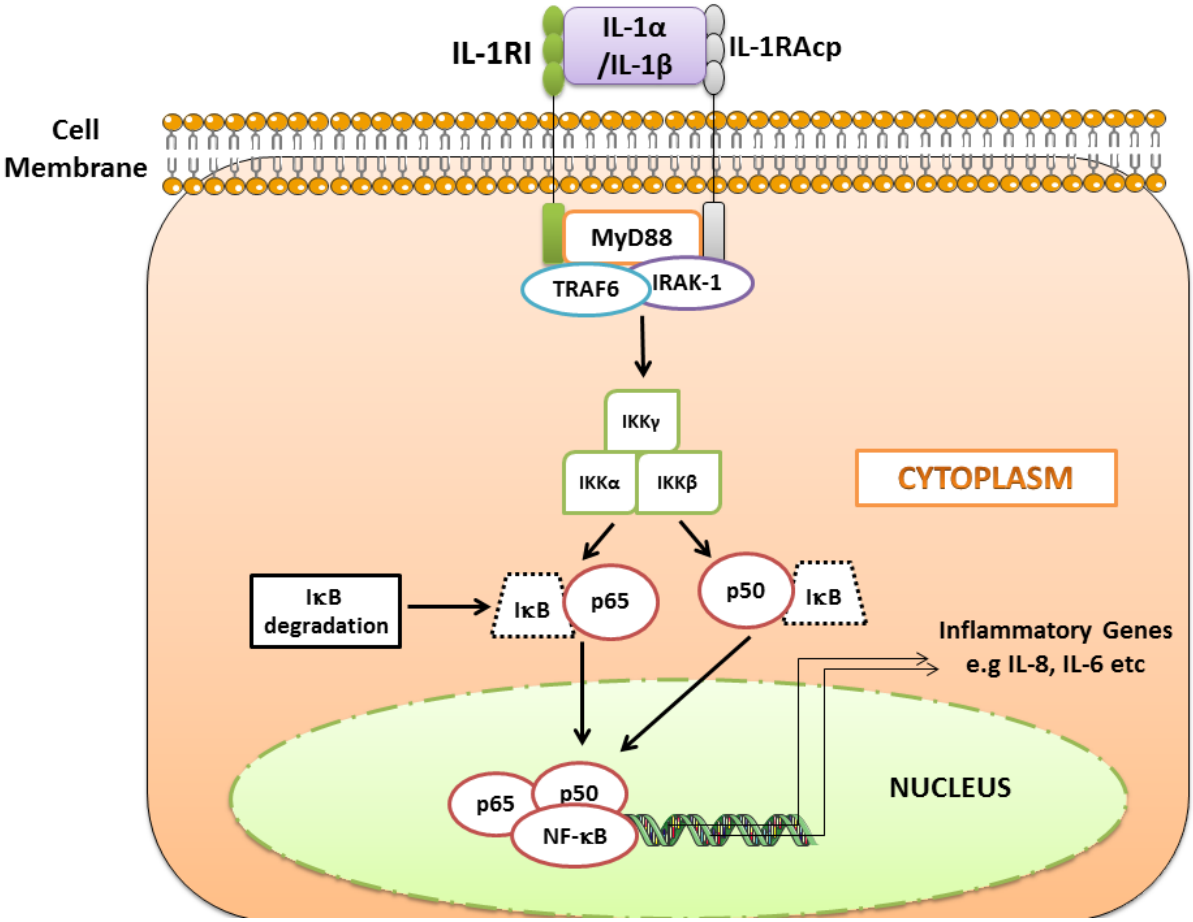
Figure 1. Classical IL-1 signaling. IL-1α and IL-1β both share the same receptor IL-1 receptor (IL-1R)-1. The binding of IL-1α or IL-1β individually to IL-1R1 causes a formation of a receptor complex with the IL-1R accessory protein (IL-1RAcp). The formation of this receptor complex leads to the recruitment of the adaptor Myeloid differentiation primary response gene 88 (MYD88) which leads to the further recruitment of IL-1R associated kinase (IRAK)-1 and tumour necrosis factor (TNF) receptor associated factor (TRAF)-6. This leads to the phosphorylation of inhibitory-κ B kinase (IKK) -α, IKK-β and IKK-γ that leads to the degradation of inhibitory-κ B kinase, the translocation of the nuclear factor-κ (NF-κ) B subunits p65 and p60 into the nucleus and the transcription of various inflammatory genes. Other nuclear transcription factors that may be activated include activator protein-1 (AP-1), c-June N-terminal kinase (JNK) and p38 mitogen-associated protein kinase (MAPK).

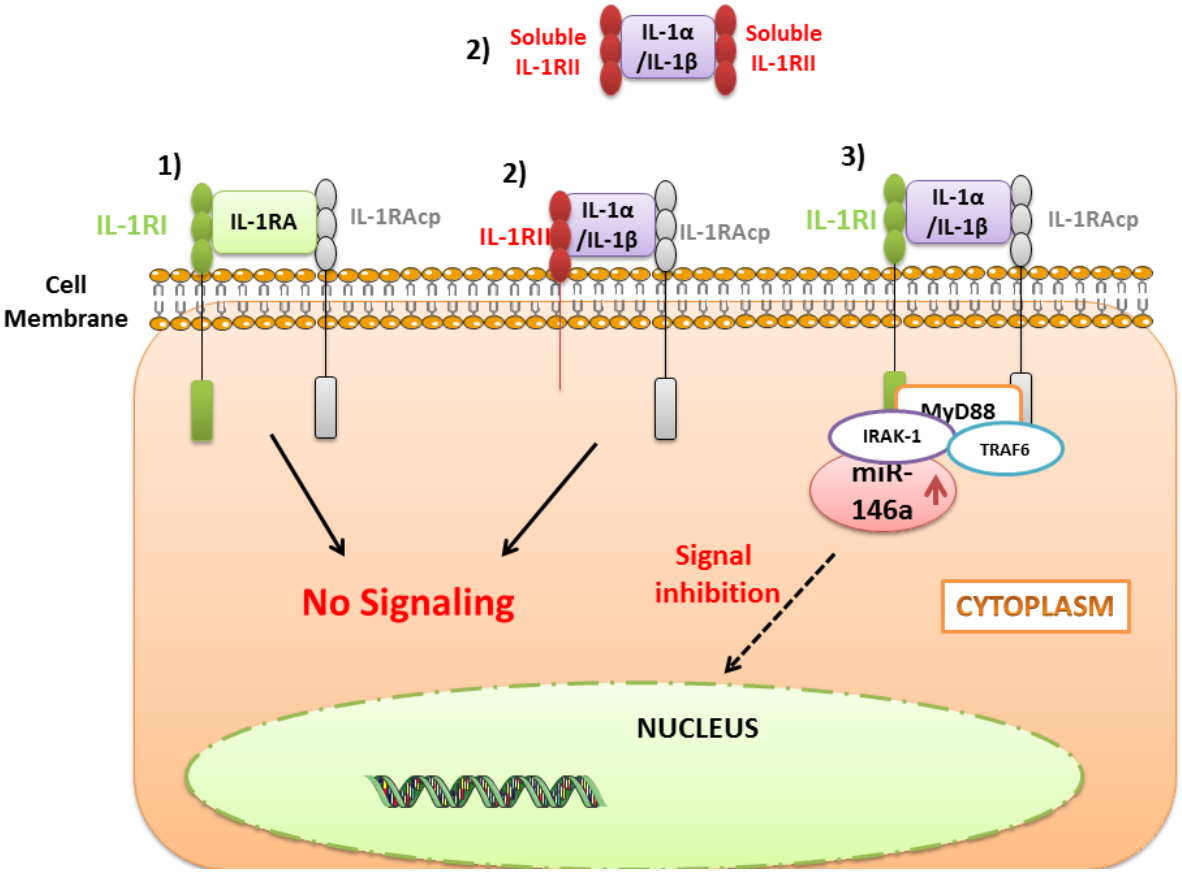
Figure 2. Regulation of IL-1 signaling. The regulation of IL-1 signaling includes anti-inflammatory family members and epigenetic mechanisms such as miRNA regulation. 1) The IL-1 receptor antagonist (IL-1RA) competes with IL-1α and IL-1β and binds to the IL-1R1 receptor to prevent IL-1 signaling. 2) The IL-1 receptor (IL-1R) II is a decoy receptor that can form either a homodimer resulting in a soluble form which can bind extracellular IL-1, or forms a heterodimer with IL-1RAcp which is found at the membrane surface but lacks a cytoplasmic domain that can initiate IL-1 signaling. 3) IL-1 signaling can also be controlled by epigenetic mechanisms such as the increased expression of miR-146a which binds and down-regulates IRAK-1 and TRAF-6 to prevent biological signaling.

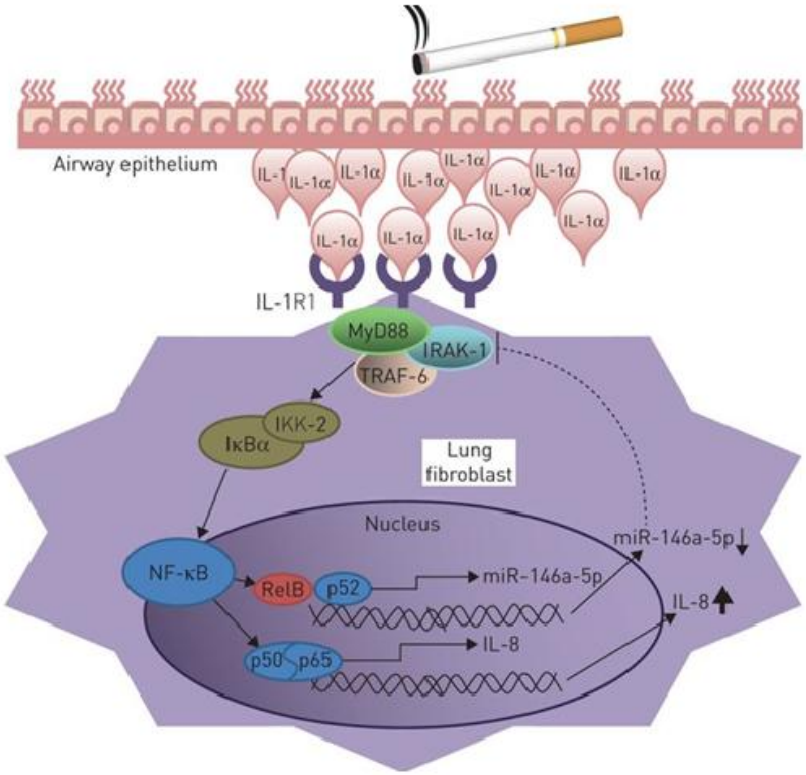
Figure 3. Decreased miR-146a-5p induction contributes to increased lung fibroblast-mediated CXCL8 release in COPD. Airway epithelial-derived interleukin (IL)-1α release after cigarette smoke exposure causes an induction of miR-146a-5p expression in addition to CXCL8 release from lung fibroblasts (solid lines). MiR-146a-5p regulates the inflammatory properties of IL-1 by binding to and down-regulating the expression of IL-1 receptor (IL-1R)-associated kinase (IRAK)-1 downstream of the IL-1 pathway in a feedback loop (dotted line) to dampen the NF-κB activation and the inflammation. However, the IL-1α-induced increase in miR-146a-5p expression in COPD-derived fibroblasts, is lower compared to fibroblasts derived from control individuals. This leads to a dampened feedback inhibition of NF-κB activation and an exaggerated pro-inflammatory response due to an increased production of airway epithelial-derived IL-1α from COPD patients. (Adapted from reference[57]).

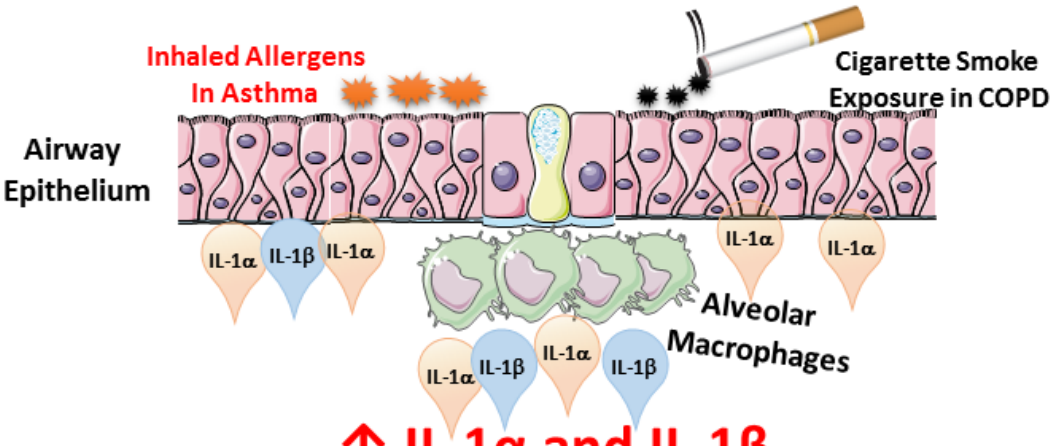
MyD88: myeloid differentiation primary response gene 88; TRAF: tumour necrosis factor receptor-associated factor; IKK: IκB kinase.

Figure 4. Summary of contributory role of IL-1 signaling in the pathogenesis of asthma and COPD. A schematic representation of the various processes in the pathogenesis of asthma and COPD influenced by IL-1 signaling


IL-1RI
IL-1α
/IL-1β
IL-1RAcp
Cell
Membrane
MyD88
TRAF6
IRAK-1
IKKγ
IKKα
IKKβ
CYTOPLASM
IκB
degradation
IκB
p65
p50
IκB
Inflammatory Genes
e.g IL-8, IL-6 etc
NUCLEUS
p65
p50
NF-κB


2)
Soluble IL-1RII
IL-1α /IL-1β
Soluble IL-1RII
1)
IL-1RI
IL-1RA
IL-1RAcp
2)
IL-1RII
IL-1α /IL-1β
IL-1RAcp
3)
IL-1RI
IL-1α /IL-1β
IL-1RAcp
Cell Membrane
MyD88
IRAK-1
TRAF6
miR-146a
No Signaling
Signal inhibition
CYTOPLASM
NUCLEUS


Airway epithelium
IL-1α
IL-1R1
MyD88
IRAK-1
TRAF-6
IKK-2
IκBα
Lung fibroblast
Nucleus
NF-κB
RelB
p52
p50
p65
miR-146a-5p
IL-8



↑ IL-1α and IL-1β

ASTHMA

Airway Inflammation

↑ T_H2 Allergic Sensitization & cell proliferation
↑ T cell cytokines e.g. IL-4, IL-5
↑ IgE and IgG1 production from B cells
↑ Group 2 Innate Lymphoid Cells
↑ IL-33, GM-CSF, TSLP from Airway epithelium
↑ Glycolytic flux and an increase in glycolytic mediators such as lactate dehydrogenase A, linked to airway inflammation
↑ Eosinophilia
↑Lymphocyte influx
↑Neutrophil influx in Steroid Resistant Asthma

Airway Remodeling

↑ Hyperplasia of the airway epithelium
↑Airway smooth muscle sensitization
↑ Airway Hyper-responsiveness
↑ Sub-epithelial airway remodeling
↑ Non-responsive AHR in steroid resistant asthma
↑Hypoxia induced factor (HIF)-1α and MUC5AC, Role in Mucus Hypersecretion

COPD

Airway Inflammation

↑ CXCL8, IL-6, GM-CSF, CCL20, TNF-α, MCP-1, MIP-1α, MIP-1β, MIP-2 DAMPs e.g. Heat shock protein (HSP) 70 produced by airway epithelium, other structural and immune cells
↑ Systemic inflammation in COPD e.g. C-Reactive Protein
↑ ICAM-1
↑Influx and Maintenance in Neutrophils and Macrophages
↑ Activation of Dendritic Cells
↑Lymphocyte aggregates

Airway Remodeling

↑ MUC5AC, Mucus hypersecretion
↑ MMP-9 , MMP-12
↓Controls Fibroblast ECM expression
↑Emphysema
↑ Airway wall remodeling measured by Airway wall thickening and Collagen fiber thickening