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Interleukin-13: A Pivotal Target Against Influenza-Induced Exacerbation of Chronic Lung Diseases

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Abstract

Non-communicable, chronic respiratory diseases (CRDs) affect millions of individuals worldwide. The course of these CRDs (asthma, chronic obstructive pulmonary disease, and cystic fibrosis) are often punctuated by microbial infections that may result in hospitalization and are associated with increased risk of morbidity and mortality, as well as reduced quality of life. Interleukin-13 (IL-13) is a key protein that regulates airway inflammation and mucus hypersecretion. There has been much interest in IL-13 from the last two decades. This cytokine is believed to play a decisive role in the exacerbation of inflammation during the course of viral infections, especially, in those with pre-existing CRDs. Here, we discuss the common viral infections in CRDs, as well as the potential role that IL-13 plays in the virus-induced disease pathogenesis of CRDs. We also discuss, in detail, the immune-modulation potential of IL-13 that could be translated to in-depth studies to develop IL-13-based therapeutic entities.

Keywords: IL-13, chronic respiratory diseases (CRDs), asthma, COPD, cystic fibrosis, COVID, IL-33, eosinophils, innate lymphoid cells (ILC2s)

Introduction

Chronic respiratory diseases (CRDs) is a term which is used to describe pulmonary disorders such as asthma, chronic obstructive pulmonary disease (COPD), lung fibrosis, respiratory tract infections and lung cancer[1, 2]. Among these, respiratory tract infections, caused primarily due to seasonal influenza, are considered to be one of the main triggers of morbidity and mortality. The World Health Organization (WHO) has reported that respiratory tract infections are one of the leading causes of mortality, accounting for up to half a million deaths every year across the globe[3]. It is well-reported that alterations in inflammatory or pro-inflammatory cytokine levels are closely linked with the progression of CRDs[4, 5]. Among the type-2 cytokines; interleukin (IL)-13 has been well studied in CRDs[6]. It is noteworthy that airway inflammation in CRDs like asthma is dependent on the interactions of IL-4 and IL-13 with IL-4Rα[5]. Interestingly, mice infected with plaque-forming units of influenza virus A (H1N1) have shown significantly ($p<0.01$) higher levels of IL-13 expression in their lungs[7]. The viral load in the lungs during an influenza A virus (IAV) infection may even reach a million-fold and exert a proportional increase in the severity of CRDs. Over time, CRDs may cause bronchiolisation of the alveoli, mucus overproduction with higher mRNA expression of mucin (*Muc5ac*) and IL-13. In contrast, airway hyper-reactivity was attenuated by blocking IL-13 production in IL-13-deficient mice[8]. The current review we discuss the association between IL-13 and CRDs such as asthma, COPD and lung fibrosis and the potential role that IL-13 plays in the viral infection-induced disease pathogenesis of CRDs. However, due to lack of literature/scientific evidence, we did not discuss the link between IL-13 in virus-induced disease pathogenesis of lung cancer.

Methodology and literature search

This is a narrative review on the crucial roles of IL-13 in CRDs and the role of IL-13 in the viral

infection-induced disease pathogenesis of CRDs. We searched PubMed and Google Scholar with relevant keywords for instance, “IL-13 [AND] Asthma”, “IL-13 [AND] Viral Infection-induced Asthma”; IL-13 [AND] Cystic Fibrosis”, “IL-13 [AND] Viral Infection-induced Cystic Fibrosis”; IL-13 [AND] COPD”, “IL-13 [AND] Viral Infection-induced COPD”. We then short-listed the relevant articles for further discussion in the review.

Influenza virus infection-induced asthma complications and role of IL-13

Asthma is a global health burden that affects nearly 350 million individuals in all parts of the world. In regards to the extent and duration of disability, asthma is the 14th most critical disorder in the world[9]. People with asthma have reduced quality of life caused by its physical, as well as psychological and social effects. Asthma is a non-communicable, complex, chronic, multifactorial disorder of the conducting airways. The key characteristic features of asthma include airway hyper-responsiveness (AHR), airway inflammation and recurrent reversible airway obstruction[10, 11]. The primary structural changes during asthma include hypertrophy of the airway smooth muscle (ASM), resulting in airway wall thickening, epithelial damage, sub-basement membrane fibrosis and mucus metaplasia (collectively known as airway remodeling)[10]. Asthmatic patients typically experience wheezing, chest tightness, breathlessness, and coughing. The countries with the highest prevalence of asthma (10-20%) include Latin and North America, Australasia, Europe and South Africa[9]. The annual healthcare expenditure for the management of asthma in the United States of America was reported to be approximately $15 billion[12]. Although, the exact cause of asthma in an individual is often hard to identify, a wide array of factors is known to contribute towards the pathogenesis of asthma. The major factors attributing to asthma include, genetic, environmental factors, cigarette smoke, and stress to name a few[13].

Alongside genetic and environmental factors, common seasonal viruses such as, influenza are known to play a significant role in worsening the various aspects of asthma, including AHR[14]. Virus-induced respiratory tract infections account for almost 80% of the acute asthma exacerbations in children and 60% in adults[15-17]. Notably, respiratory tract infections caused by influenza is of utmost importance, as asthmatic patients are at a higher risk of developing influenza due to an impaired inflammatory response. Viral infections often lead to accelerated degradation of the characteristic features of the disease, resulting in significant morbidity and even mortality[18].

Influenza virus contributes to the pathophysiology of asthma by modulating the processes associated with airway inflammation. These include, bronchial hyperresponsiveness and mucus hypersecretion. The respiratory epithelium acts as a site for viral replication, and its invasion triggers innate and adaptive immune response inducing the release of several pro-inflammatory cytokines and chemokines associated with the pathophysiology of asthma. These inflammatory mediators include, IL-1, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), leukotriene, RANTES (Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted), eosinophil cation protein, histamine, myeloperoxidase, and elevated carbon monoxide (CO) levels[19-25]. For instance, an increase in the levels of IL-8 and myeloperoxidase in nasal aspirates of asthmatic patients during viral infection was correlated with the severity of symptoms and onset of asthma exacerbation[21]. Similarly, elevated exhaled CO concentration and reduction in peak expiratory flow rate in patients infected with influenza are considered as some of the key markers in the development of viral-induced asthma exacerbation[25].

Classically, allergen-specific T-helper type 2 (TH2) cells that are present in the airways of almost all asthmatic patients are largely known to be associated with the developmental features

of asthma[26]. Activation of such cell types results in the production of major cytokines such as, IL-4, IL-5, IL-9 and IL-13 that are essentially involved in the pathogenesis of the disease[27]. However, with respect to influenza-induced asthma, there are several questions that remain to be answered: i) what is the precise mechanism that causes acute asthma after infection with influenza virus?; ii) does TH2 paradigm play a fundamental role in influenza-induced asthma attacks?; OR iii) are there other types of cells that can cause asthma exacerbation due to influenza infection?

The relationship between viral infection and asthma remains controversial. Several epidemiological studies have reported the protective role of viruses in the development of allergy and asthma[28-30]. Nevertheless, recent experimental and clinical observations suggest a detrimental role of viral infection in asthma. Lately IL-13, a pleiotropic cytokine, has been recognized as one of the driving forces that causes viral infection along with virus-induced AHR and airway inflammation[31, 32]. It has been reported that the susceptibility of human airway epithelial cells to viral infection rises due to IL-13 induced mucous cell metaplasia[33]. Unregulated levels of IL-13 have been reported in bronchial tissues and also in cells of bronchoalveolar lavage fluids collected from asthmatic patients[34, 35]. IL-13 is known to be the central mediator that can induce AHR independently[36, 37]. Besides increasing AHR, IL-13 is also associated with enhancing the infiltration of eosinophil, structural modifications in the contractile apparatus of ASM, mucous metaplasia, and polarization of macrophages[32].

Tsitoura *et al.,* demonstrated that induction of influenza-A virus in a murine model of allergic asthma prompted the development of AHR[38, 39]. Enhanced AHR was reported to be due to the activation of allergic-specific TH cells and concurrent production of pro-inflammatory mediators such as, immunoglobulin (IgE), IL-4, IL-5, IL-13, and IFN-γ. However, interestingly, AHR persisted in spite of neutralizing IL-4 and IL-5 in the same model system, suggesting a

substantial role of IL-13 in influenza-induced AHR development in asthma[38, 39]. On the other hand, IFN-γ may have dual effects on IL-13 modulated-inflammatory signaling in the lung. For instance, in a mouse model of airway mixed T-cell inflammation, IFN-γ was negatively correlated with AHR and blocking of IL-13 resulted in reduction of AHR and goblet cell hyperplasia but not inflammation[40]. This becomes especially relevant in people with asthma who demonstrate a mixed Th1/Th2 inflammatory response where IFN-γ and IL-13 play critical roles, respectively.

It is evident from clinical findings that IL-13 plays an essential role during influenza-induced asthma. Hence, additional mechanisms/pathways that can elevate the level of IL-13 may also account for respiratory viral infection-induced exacerbation of asthma. The involvement of distinct cell types other than allergen-specific TH cells has been reported to play a central role during influenza-induced asthma[31]. Chang et al. reported that mice infected with influenza virus resulted in the activation of NLRP3 inflammasome which resulted in substantially higher production of IL-33 by alveolar macrophages[41]. This process in turn activated natural helper cells [cells of the non-T-cell, non-B cell innate lymphoid type] leading to much more production of IL-13. A two-fold increase in the levels of IL-33 was recorded in bronchoalveolar lavage fluid from mice infected with H3N1 influenza virus compared to resting mice[41]. Moreover, the presence of natural helper cells in the lungs of mice infected with H3N1 virus was found to be the key cellular source for the production of IL-13. Importantly, an improvement in AHR in IL-13-deficient mice clearly displays the significant role played by this cytokine during influenza-induced asthma. There is evidence that IL-13 also modulates airway pathology in asthma. Specifically, IL-13-induced IgE secretion results in airway structural changes but does not promote TH2 cell differentiation[42]. In addition, IL-13 induces AHR and mucus overproduction by activating STAT6 in lung epithelium[43].

Influenza virus predominantly adheres on the surface of epithelial cells, which is followed by the process of viral replication, invasion, and the release of viral RNA. The presence of influenza virus within the cells induces the release of several inflammatory mediators including, IL-33. IL-33 plays a major role in the recruitment and activation of many cell types that have been linked to the development of asthma. These include T-cells, natural killer T cells, eosinophils, mast cells, macrophages and natural helper cells[32]. Additionally, the requirement of IL-33 signaling receptor, IL-1 receptor-like 1 (IL1RL1), also called as ST2, was also found to be vital for the development of AHR in influenza infected mice[41]. In response to IL-33, these cell types are known to produce large amounts of IL-13 leading to AHR and a decline in other features of asthma (Figure 1).

The role of IL-13 in influenza virus-associated exacerbations in cystic fibrosis

Cystic fibrosis (CF) is a progressive, autosomal recessive disorder among the caucasian ancestry. CF is mainly caused due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, that encodes a protein responsible for the transportation of chloride ions across the cells[44]. CF is a multi-organ mutilation disease, however, the predominant cause for mortality and morbidity is mainly due to complications associated with the lung[45]. Dysfunction of the CFTR gene in the lung epithelial cells causes a progressive abnormal loss of hydration of the airway surface[46]. This results in dysregulated mucus plugging that drives an altered inflammation, mainly dominated with an increased infiltration of neutrophils, airway structural damage, airway obstruction and bronchiectasis, which is commonly associated with increased pathogen growth and persistent lung function deterioration[47].

Research has largely been conducted to show the importance of T-helper type 1 and 17 (TH1/TH17) dependent inflammation and associated the increase in infiltration of the neutrophils in the pathogenesis of CF[48, 49]. A very few studies have reported TH2-associated inflammation in CF disease progression[50, 51]. Lack of CFTR gene in the monocyte-derived macrophages in CF patients; or deletion of CFTR gene using the CFTR inhibitors in the healthy macrophages failed to polarize to macrophage M2 phenotype in the presence of IL-13/IL-4 resulting in the failure of post-translational expression of IL-13 receptor A1 (IL-13RA1) on the macrophages[51]. Recently Anja *et al*. reported the importance of the involvement of innate lymphoid cells 2 (ILC2) in CF pathogenesis[52]. The study demonstrated that ILC2 expressing chemokine receptor 6 in the blood stream are chemo-attracted to the CF inflamed lung tissue in the presence of C-C Motif Chemokine Ligand 20 (CCL20), whereby, they induce type 2 inflammation via the production of IL-4 and IL-13 and induce tissue remodeling[52]. These factors further drive CF disease progression. On contrary, it is interesting that TH17 cells express functional IL-13 receptors which can attenuate the IL-17 production[53, 54], a critical cytokine that can promote inflammation and lung infection in CF[55]. The importance of IL-13 in the pathogenesis of pulmonary CF was also been reported in earlier studies. The BAL cells and peripheral blood mononuclear cells from CF patients had increased expression of IL-13 mRNA which may actively or passively be involved in lung function deterioration and increased AHR[56]. Furthermore, IL-13 not only mediates the eosinophilic inflammation and AHR, but also involved in epithelial cell damage, which is an important characteristic feature of CF. This is due to the stimulation of the mucociliary epithelial cells with IL-13, which reduces its differentiation and decreases the ciliary beat frequency further leading to epithelial damage and airway obstruction[57]. In a murine model of bleomycin-induced pulmonary fibrosis, Belperio et al. demonstrated an interaction between IL-13 and chemokine C10. It was reported that neutralization of IL-13 results in attenuation of pulmonary fibrosis and levels of C10. Similarly,

neutralization of C10 attenuated pulmonary fibrosis and intrapulmonary macrophage numbers, suggesting IL-13 as a potent inducer of C10 [58].

Dysregulated inflammation and persistent lung damage in the pathogenesis of CF leads to declined local host defenses. These factors further result in an altered microbiome of the lungs[59, 60]. This is associated with the acquisition of new flora and impaired bacterial clearance which further increase the rate of infection and pulmonary exacerbations[61]. The exacerbations associated with pulmonary CF are characterized by increased sputum production, dyspnea and lung obstruction, which cause a decline in the quality of life, increased morbidity and mortality[62, 63]. Infectious exacerbations associated with pulmonary CF are mainly associated with the bacterial species namely, *Staphylococcus aureus*[64], *Pseudomonas aeruginosa*[65] and *Burkholderia cepacia*[66]. However, infections induced by respiratory viruses, for example, influenza A and B, respiratory syncytial virus (RSV), parainfluenza virus (PIV) types 1 to 4, rhinovirus, metapneumovirus, coronavirus and adenovirus also play a major role in the pathogenesis of CF associated exacerbations[67-69].

The involvement of respiratory viruses in CF exacerbation episodes have been previously reported. However, the impact on the etiology has not been studied properly. Of all the major viruses, influenza and RSV associated infections have demonstrated a significant rise in morbidity of CF patients[70]. Earlier studies have reported the rise in exacerbations rates in CF patients during the flu season. They also demonstrated a positive correlation between the sputum influenza virus and increased exacerbation episodes in the pathogenesis of CF[70, 71]. Influenza-associated exacerbations are also associated with a significant decline in the lung function, especially FEV1 levels in CF patients[72].

Earlier studies have demonstrated that, mice infected with H3N1 influenza virus develops AHR[41]. In addition, an increased proportion of influenza A virus has been observed in a mouse model with an increased number of inflammatory cells and mucus accumulation[73]. Furthermore, several other studies have also reported on the activation of ILC2 cells that promote the induction of TH2 associated inflammatory mediators during influenza virus infection[74] suggesting that IL-13 plays a significant role in the development of inflammation and AHR in influenza virus infection.

Although, no studies have been reported to understand the role of IL-13 in influenza virus-associated CF exacerbations. Previous studies demonstrated that influenza infection may cause a progressive decline in the chloride ion channels, CFTR, which is an important chloride ion channel regulator, along with epithelial sodium channels (ENaC) on the airway epithelium, which are involved in sodium resorption and chloride ions secretion in the airway fluid homeostasis[75]. Aberrant disruption in these channels leads to dehydration of the airway epithelium, which is further associated with the alveolar epithelial damage, increased mucus accumulation, and altered bacterial colonization. These are the principal observations found in the initiation of CF. The damaged epithelium leads to the release of epithelial-derived innate cytokines like, IL-33/ST2 axis[76] which plays a major role in the activation of the ILC2 cells. This may also promote the recruitment of T lymphocytes and induce the release of the various TH2 cytokines including, IL-4, IL-5 and IL-13 (Figure 1)[77]. These cytokines plays a major role in mucus accumulation and a decline in the lung function, which further worsen the symptoms in CF patients.

The role of IL-13 in influenza virus-induced exacerbations in chronic obstructive pulmonary disease (COPD)

COPD is one of the leading causes of morbidity and mortality globally. COPD is commonly associated with chronic inflammation, emphysema and poorly reversible air flow obstruction[78, 79]. The chronic inflammation intervened with the pathogenesis of COPD is mainly TH1 driven, and associated with the infiltration and activation of neutrophils and macrophages. These release various inflammatory mediators and proteases causing irreversible airway tissue damage and impaired elastic recoil of the lung[1, 80, 81]. Although, cigarette smoke and other exposures are considered to be the major risk factor[82], various other genetic factors also play a major role in the pathogenesis of this disease. While COPD is considered as a heterogenous chronic airway disease, exacerbations further worsen the symptoms of COPD. These exacerbations affect the patients with COPD, making them non-responsive to the standard treatment, thereby, impacting the quality of the life, increasing the morbidity and incurring increased healthcare costs.

Majority of COPD exacerbations are associated with infections, especially of viral origin. This has been implicated as the major trigger for exacerbations in COPD, which is observed in almost 50% of the total cases[83]. The predominant viruses implicated in COPD exacerbations include, rhinoviruss, influenza, parainfluenza, and adenovirus. These viral pathogens cause both upper and lower respiratory tract infections [84]. Virus-associated COPD exacerbations have been linked to influence various etiological factors including, persistence of inflammation characterized by excess inflammatory responses, irreversible airflow obstruction, abnormality in gas-exchange potential, mortality and morbidity[85]. Inflammation associated with viral COPD exacerbations are primarily neutrophil and TH1 associated, with an increase in the levels of various TH1 and proinflammatory cytokines that are involved in the upregulation of IL-8, interferon gamma (IFN)-γ, IL-6, TNF-α, GM-CSF and various metalloproteases (MMPs) including, MMP9 and MMP12 in the airways[86]. In addition, previous reports suggest the existence of IL-13-IL-17 axis, primarily through inhibition of IL-17A and IL-21 production by

cultured Th17 cells[87]. This is primarily due to IL-13 mediated reductions in the expression of IL-10 and increase in IL-17A production in murine model[54]. Furthermore, IL-13-induced gene expression of MMP-2, 9, 12, 13, 14 and protein expression of cathepsins B, S, L, H and K was reported to induce emphysema in transgenic mice model[88]. These findings were confirmed via treatment with MMP or cysteine proteinase antagonists that significantly reduced emphysema and inflammation, suggesting critical role of IL-13 as a potent stimulator of MMP and cathepsin-based proteolytic pathways in the lung[88].

Influenza is the second most detected viral pathogen associated with COPD exacerbations which could be co-infected with bacterial pathogens, such as, *Streptococcus pneumonia,* which further increases the risk of mortality or morbidity in COPD patients[89]. Co-infection of influenza with this bacteria may supress the immune responses against the bacteria, and may also promote its adhesion via increasing the pneumococcal adhesion molecules like, influenza neuraminidase[90]. Influenza infection may also promote neutrophil apoptosis which mediates neutrophil dysfunction[91]. It also inhibits the phagocytic function of the macrophages[92] which obstruct the bacterial clearance in the airways. This may further complicate the health status of COPD patients.

Although COPD and associated viral exacerbations are considered as neutrophilic dominant, a positive correlation between other immune cells namely, eosinophils[93, 94], ILC2[95, 96] and COPD exacerbations have been reported in various studies. Eosinophilia in the airways of COPD has been reported in various studies, which on activation, secrete various toxic mediators that may include, leukotrienes, eosinophil peroxidase (EPX), and various TH2 inflammatory cytokines, namely, IL-4, IL-5 and IL-13 promoting lung injury and airway obstruction[97]. Earlier reports using transgenic mice have reported that eosinophil derived IL-13 promotes

emphysema via stimulating the alveolar macrophages to release MMP-12 and induces airway space enlargement[97]. Another study using the IL-13 transgenic mice showing over expression of IL-13 resulted in the induction of various metalloproteases like, MMP-2, MMP-9, MMP-12, MMP-13, MMP-14; cathepsins like B, S, L, H, and K, all of which promote emphysema, mucus metaplasia and increased lung inflammation[88]. Similarly, a recent study by Prajakta *et al*., demonstrated robust infiltration of eosinophils in the lung tissues of influenza/smoke mouse-exacerbation model of COPD. This was found to be mediated via the IL-33/ST2 axis[98] suggesting the role of eosinophils in the pathogenesis of influenza associated COPD exacerbations.

ILC2 are another subset of innate immune cells that have a key role in the pathogenesis of COPD. A previous study reported an increase in the blood TH2 cytokines and TH2/TH1 imbalance during acute exacerbations of COPD. This was associated with the expansion and activation of ILC2 in patients with acute COPD exacerbations[96]. Moreover, another study reported that resident ILC2 in the lungs of mice infected with influenza A virus (IAV) produced significant amount of IL-13, which may be responsible for the contribution of virus-induced AHR[99]. ILC2 upon activation in the presence of IL-33/ST2 axis were able to secrete different TH2 cytokines namely, IL-5 and IL-13 that promote lung deterioration and induce various disease compartments of COPD. These may include, infiltration of the eosinophils, fibrosis, AHR, mucus secretion and airway remodelling in the pathogenesis of COPD[96], suggesting an association between ILC2 and the accumulation of eosinophils in the pathogenesis of COPD (Figure 1)

Anti-IL-13 therapies

For Asthma:

Recent scientific breakthroughs and technological advancements have paved way for novel individualized therapies to block specific inflammatory pathways using monoclonal antibodies (mAbs) for the management of asthma.

Tralokinumab is one of the human mAbs that neutalises IL-13 and has been trialled to assess its efficacy in asthmatic patients. In initial clinical trials[100] and a Phase II placebo-controlled study[101], intravenous administration of tralokinumab was reported to be safe with no serious adverse effects in patients with severe uncontrolled asthma. Similar safety profiles were reported in two phase III clinical trials with tralokinumab STRATOS 1 (NCT02161757), and STRATOS 2 (NCT02194699)[102]. However, the effect of tralokinumab in reducing asthma exacerbation rates were found to be inconsistent in both STRATOS 1 and STRATOS 2 studies.

Additional recent double-blind, randomised, placebo-controlled Phase II, MESOS (NCT02449473) trail reported that tralokinumab did not significantly affect bronchial eosinophil count, blood eosinophil count or sputum eosinophil count and therefore, ineffective for eosinophilic asthma control[103]. Collectively, efficacy of tralokinumab as a treatment is questionable and further trails are warranted to clearly define its role in the management of asthma.

Lebrikizumab is another anti-IL-13 mAb which in initial trials showed promising results in asthmatic patients and improved lung function and decreased exacerbation rate[104]. However, similar to tralokinumab, in a subsequent phase III trial (NCT01868061), Lebrikizumab failed to

reduce the asthma exacerbation rate alongside exhibiting serious adverse effects including aplastic anaemia and eosinophilia[104]. Similar findings were reported in another phase III trial (NCT02104674) where improvement in lung function was not observed after lebrikizumab treatment[105].

Collectively, the results from a recent meta-analysis of five studies (n=3476) investigating the efficacy of anti-IL-13 antibodies (lebrikizumab and tralokinumab) showed that individuals with uncontrolled asthma receiving anti-IL-13 antibodies demonstrated significant improvements in hallmark features of diseases, including reduction in asthma exacerbation, improved FEV1 and Asthma Quality of Life Questionnaire (AQLQ) scores, as well as reduction in rescue medication use, when compared to placebo. Moreover, the authors found that patients with higher Periostin levels receiving the anti-IL-13 antibody exhibited lowest risk of asthma exacerbations[106]. However, it may be possible to achieve more favourable and persistent disease-mitigating effects with a combinatorial anti-IL-13 and anti-IL-4 therapy.

For CF:

Interestingly, administration of tralokinumab (anti-IL-13 antibody) significantly reduced the aberrant lung remodelling and promoted lung repair and epithelial integrity in a humanised experimental mouse model of pulmonary fibrosis[107]. The results indicate that IL-13 could be a potential and promising therapy in individuals with IPF showing prominent lung remodelling, thus, progressing rapidly from the time of diagnosis.

For COPD:

The experimental murine study suggests a crucial role for MMP-12 and eosinophils, (*via* the release of Il-13/IL-4) in perpetuating lung inflammation and airspace enlargement (indicative of

emphysema)[97] thus, warranting focussed investigation into the potential of anti-IL-13 therapies in patients with emphysema.

Overall, the results obtained from these trials have raised questions on the efficacy of anti-IL-13 mAbs and their use as treatments. Specific targeting of IL-13 may not be sufficient and future trials should focus on utilising a group of mAbs that inhibit other inflammatory markers that play similar role like IL-13 in the pathophysiology of CRDs. Greater emphasis should be given on long-term efficacy and safety of these biological agents.

Influenza and COVID-19

A comparative study among patients with influenza and patients with COVID-19 found that the patients with COVID-19 exhibited lower cytokine storms than patients with influenza. Interestingly, while the relative abundance of IL-13 in patients with influenza was 1, the relative abundance of IL-13 in patients with COVID-19 was 0.57[108]. A similar trend was observed in another study, where the immunohistochemistry analysis of human lung tissue expressions showed a significant increase in the levels of IL-13 ($p = 0.007$) among H1N1 patients, as compared to COVID-19 patients[109]. In contrast to the prevailing assumption of high cytokine-bursts in COVID-19, it was observed that there were no significant changes in IL-13 levels among healthy control and COVID-19 patients (with mild and severe disease condition)[110]. Considering the spectrum of immune responses, these studies suggest that individual with COVID-19 infections are less inflamed than patients with influenza infections.

Limitations and future directions

Although, in the present review we have clearly demonstrated the critical role played by IL-13 in the influenza virus-associated exacerbations in various CRDs based on the existing evidence, it possesses certain limitations. The major limitation of the current review is the availability of limited literature, further research is warranted in elucidating the role of IL-13 in the neutrophil dominant viral exacerbations associated in CRDs like CF and COPD. The role of the CFTR gene mutations in virus-associated exacerbations were poorly understood and needs further investigation. Secondly, the complex interplay via which IL-13 plays key roles during the pathogenesis of CRDs has been clearly investigated in the review however, with respect to the viral-induced exacerbations, this was not extended further considering the limited availability of the existence literature.

Summary and conclusions

In summary, the increasing burden of CRDs have grown into a global health challenge for the healthcare communities around the world. Moreover, frequent viral infections in these vulnerable patients pose a huge risk *vis-à-vis* management of the disease. In addition, these factors exert an immense economic and societal burden. A relatively novel and crucial cytokine, IL-13, has shown to play an important role in the pathogenesis of CRDs, particularly, in conjunction with viral infections which has been shown to result in persistent lung damage. Although IL-13 seems to be pivotal in perpetuating the inflammatory cascade in the lungs in course of a viral infection and underlying chronic diseases, it remains to be established, pre-clinically and pre-clinically, whether blocking IL-13 alone could impart the positive outcomes. Thus, the regulation of IL-13, and the IL-13 mediated immune functionality need to be teased out in focussed *in-vivo* models to develop novel treatments for yet incurable lung diseases. In-depth future-focussed studies are

warranted to dissect the underlying cellular and molecular mechanisms, that could be targeted therapeutically to mitigate exaggerated inflammation and ongoing lung pathologies in CRDs.

Author contribution:

Conceptualization: MDS, SDS, KD; **Writing-original draft:** MDS and VRA; **Writing-review and editing:** All Authors

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FIGURE LEGEND

Figure 1. Role of IL-13 in influenza-induced exacerbations in chronic respiratory diseases Influenza associated exacerbations in various chronic respiratory diseases like, asthma, cystic and COPD promote epithelial damage and secrete various innate immune cytokines like IL-33 from the damaged epithelial cells. IL-33 further acts on the ST2 receptor of the innate lymphoid cells (ILC2) promoting the secretion of IL-13, which is involved in various functions namely, goblet cell hyperplasia, airway smooth muscle cell proliferation, collagen deposition, bacterial colonisation, and eosinophilia. These factors result in increased airway remodelling, airway hyper-responsiveness, and decline in lung function further reducing the quality of life. These detrimental reasons may lead to an increase in mortality and morbidity.

CREDIT AUTHOR STATEMENT

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