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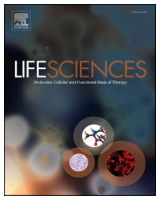

# Exploring the role of the ocular surface in the lung-eye axis: Insights into respiratory disease pathogenesis

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ABSTRACT

Chronic respiratory diseases (CRDs) represent a significant proportion of global health burden, with a wide spectrum of varying, heterogenic conditions largely affecting the pulmonary system. Recent advances in immunology and respiratory biology have highlighted the systemic impact of these diseases, notably through the elucidation of the lung-eye axis. The current review focusses on understanding the pivotal role of the lung-eye axis in the pathogenesis and progression of chronic respiratory infections and diseases. Existing literature published on the immunological crosstalk between the eye and the lung has been reviewed. The various roles of the ocular microbiome in lung health are also explored, examining the eye as a gateway for respiratory virus transmission, and assessing the impact of environmental irritants on both ocular and respiratory systems. This novel concept emphasizes a bidirectional relationship between respiratory and ocular health, suggesting that respiratory diseases may influence ocular conditions and vice versa, whereby this conception provides a comprehensive framework for understanding the intricate axis connecting both respiratory and ocular health. These aspects underscore the need for an integrative approach in the management of chronic respiratory diseases. Future research should further elucidate the in-depth molecular mechanisms affecting this axis which would pave the path for novel diagnostics and effective therapeutic strategies.

## 1. Introduction

Chronic respiratory diseases, the largest contributors to the global mortality rate, constitute a wide array of conditions and pathologies that affect the human pulmonary system. They can primarily be attributed to the widespread exposure to harmful environmental conditions, occupational hazards, and lifestyle-related inhalants [1]. These diseases range from acute infections, such as pneumonia and bronchitis, to

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chronic conditions like asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, interstitial lung disease, pulmonary sarcoidosis, and pneumoconioses, such as silicosis and asbestosis, each presenting unique challenges to understanding their disease pathogenesis, diagnosis and treatment [2]. A significant amount of research has been progressed in elucidating the novel pathways in immunology and respiratory biology to understand these disease conditions, particularly highlighting how these diseases could impact the well-being of individuals beyond the deterioration of the pulmonary system.

One such interesting direction is the elucidation of the "lung-eye axis," which encapsulates the complex and bidirectional crosstalk between respiratory health and ocular well-being. This concept posits the ideology that respiratory diseases may directly and indirectly affect ocular health. Changes and alterations in ocular biology may also reflect the development of lung disease. The interplay between the ocular and pulmonary systems is particularly significant given the eye's exposure to the external environment and its immune privilege status, making it a unique barometer for systemic health, including the state of the respiratory system.

The emergence of the lung-eye axis as a focal point of research is particularly timely, offering novel insights into how diseases that are traditionally confined to the lungs can have far-reaching systemic implications. This axis suggests potential pathways through which respiratory pathogens or the inflammatory responses they elicit can affect ocular tissues, leading to or exacerbating conditions such as dry eye syndrome, uveitis, or retinal diseases. Conversely, ocular findings may serve as early indicators of respiratory diseases, offering a window into the systemic nature of pulmonary pathologies.

The current review aims to explore the lung-eye axis in the progression of respiratory diseases, by focusing on the impact of the environmental triggers overlapping the shared immunological pathways, microbiome, clinical manifestations, and thereby elucidating the potential therapeutic implications. By delving into the interplay between the respiratory and visual systems, the review seeks to expand the current understanding of respiratory diseases, emphasizing a more systemic and integrative approach to disease management and research.

## 2. Approaches to study the lung-eye axis in the development of respiratory diseases

### 2.1. Immunological crosstalk between eye and lung

At the forefront of this axis lies the immune system's role, which is pivotal in respiratory and ocular health. While unique in their physiological contexts, the immune responses in these organs exhibit remarkable parallels in their reaction to pathogens, allergens, and autoimmunity. A central theme to this interconnection is the concept of mucosal immunity. The respiratory tract and ocular surface are lined by mucosal membranes, that serve as the first line of defence against external insults [3]. The mucosal immune system at these sites is characterized by a network of epithelial cells, immune cells, and molecular mediators that work together to maintain homeostasis and combat pathogens [3,4]. Dysregulation in these systems can lead to a cascade of events, potentially linking respiratory diseases with ocular pathologies.

The mucosal immune system in the respiratory tract is adept at responding to inhaled pathogens and allergens. It employs a variety of immune cells, such as macrophages, dendritic cells, and T cells, to initiate and modulate immune responses [4]. The production of specific immunoglobulins, particularly IgA, is crucial in neutralizing pathogens and preventing their adherence to epithelial cells. Similarly, the integrity of the ocular surface is protected by the innate and adaptive immune mechanisms, where the antigens and microbes are systematically removed from the ocular surface through tear film clearance and regular blinking, while the glycocalyx and the tight junctions within the apical cell layers of the conjunctival and corneal epithelia establish an effective physical barrier with capabilities to modulate immune activities. The ocular surface possesses a unique immune apparatus, often called the "eye-associated lymphoid tissue" (EALT) [5]. The EALT is integral in mediating immune surveillance and tolerance, preventing ocular infections while preventing excessive inflammation that could impair vision [5]. Like the respiratory system, it utilizes a range of immune cells and secretory IgA to protect the ocular surface [6].

The crosstalk between these two systems is evident in their coordinated response to systemic immune challenges. For instance, respiratory infections could lead to ocular manifestations, such as conjunctivitis, through systemic inflammatory mediators and immune cell mobilization [7–9]. Conversely, ocular allergies can exacerbate respiratory conditions like asthma, highlighting a reciprocal relationship [10]. This immunological interplay extends to the shared genetic and molecular pathways, as certain cytokines and chemokines are common mediators in both respiratory and ocular immunity. For example, interleukin-6 (IL-6) [11,12] and tumor necrosis factor-alpha (TNF-α) are pivotal in the inflammatory responses in both organs. Additionally, the role of Th1/Th2 balance, a fundamental aspect of systemic immunity, is critical in both respiratory diseases and ocular conditions.

#### 2.1.1. Ocular microbiome and its impact on lung health

The microbiome is a vast ecosystem of microorganisms residing in and around the human body, influencing our overall health in numerous ways [13]. While much attention has been given to the gut microbiome, recent research has unveiled the significance of the ocular microbiome, which refers to the diverse [14,15] community of microorganisms residing in and around the eyes. This ocular microbiome is a relatively unexplored territory but has shown remarkable interconnection with other body parts, including the respiratory system. In this exploration, we delve into the emerging field of ocular microbiome research and its potential impact on lung health.

The ocular surface comprises the conjunctiva and cornea, previously considered a sterile environment. However, advancements in microbiome research have challenged this notion. The ocular surface is now recognised as an apparatus that host a complex microbial community, predominantly composed of bacteria, but also including fungi and viruses such as adenoviruses, orthomyxoviruses, respiratory syncytial viruses, and coronaviruses [7,16].

The bacterial diversity within the ocular microbiome is astonishing [17]. Studies have identified a range of bacteria, with genera like *Staphylococcus, Streptococcus, Corynebacterium, Bifidobacterium, Moraxella, Dolosigranulum,* and *Propionibacterium* being common and predominant inhabitants [18–21]. This diversity may vary among individuals and may be influenced by various factors, such as genetics, environment, and health status. Fungi, particularly yeasts like Candida and Malassezia, have also been detected on the ocular surface [22]. These microorganisms play a crucial role in maintaining microbial balance and contribute to the overall health of the eye. Viruses, including herpesviruses, have also been found to infect ocular tissues, particularly in elderly and immunocompromised individuals [17].

Notably, ocular microbiome possesses several fundamental functions under normal physiological conditions and is a homeostatic ecosystem [14]. However, multiple inflammatory diseases are associated with the imbalance of this homeostasis.

#### 2.1.2. The ocular microbiome-lung health connection

The intriguing connection between the ocular microbiome and lung health lies in the dissemination of microorganisms and their products from the eyes to the respiratory tract thereby impacting lung health in several ways [23–25]. The ocular and respiratory systems are in constant communication through the exchange of immune cells and molecules. Microbes and their products from the eye can travel down the respiratory tract, where they may modulate local immune responses. This interplay can either support or disrupt the immune defence mechanisms in the lungs [7,26].

Ocular dysbiosis, an imbalance in the ocular microbiome, can lead to

chronic inflammation in the eyes. Inflammatory mediators released in response to ocular dysbiosis may not only be confined to the eye but also can potentially travel through systemic circulation and cause lung inflammation [25,27]. Emerging evidence suggests that imbalances in the ocular microbiome may contribute to the development of allergies and asthma [27]. Dysbiosis in the eyes can influence the mucosal immune system's tolerance and may promote hypersensitivity reactions that extend to the respiratory tract [27]. Microbial exchange can therefore occur between the ocular and respiratory systems. Microbes from the ocular microbiome can be inhaled which may colonise the respiratory tract, potentially affecting the lung microbiome's composition and function [24,28].

Interestingly, the secretary IgA is the pivotal antibody which is located at the mucosal lining of the ocular surface and has pleotropic properties that are critical for the maintenance and tolerance of mucosal homeostasis [26]. The inherent anti-inflammatory activity of the secretary IgA aids in neutralizing several toxins or pollutants, bacteria and, viruses. Moreover, IgA promotes the production of interleukin (IL)-10 and affects the maturation of dendritic cells (DCs) [26].

Interestingly, the production of secretory IgA-synthesising B cells in the lacrimal glands is governed by microbiota. Similarly, the lung microbiota regulates the ability of lung dendritic cells (DCs) to induce the production of IgA-mediated immune responses such as Toll like receptor (TLR) activation [29]. These findings suggest that T cell dependent secretory IgA production is critical for protection against pathogens in the eye and lung. Moreover, DCs that positively express surface antibodies such as CD103, CD24 and CD11b are capable of inducing IgA class-switch recombination to activate B cells in lungs via T cell dependent or independent pathways including retinoic acid (a key regulator in lung development and repair) [30] [31–34] and transforming growth factor (TGF)-beta stimulation oriented antigen-specific IgA class switching [29,32]. These findings suggest that, similar to lungs, eye-associated lymphoid tissue alterations in the microbiota may have a role in regulating secretory IgA repertoire. These findings further suggest that the ocular and lung secretory IgA levels may depend on the commensal microbiome, reinforcing the tolerance to both ocular and lung commensals, thus, providing vital tolerance of the ocular and lung axis surface antigens. However, we still need further elucidation about how these mechanisms play a critical role in the homeostasis of microbiota and its impact on immune responses in ocular-lung axis. Nevertheless, understanding the relationship between the ocular microbiome and lung health has important clinical implications.

#### *2.1.3. Altered ocular microbiome and its impact on lung microbiome and lung health*

Growing evidence in immunology has revealed that microbes fundamentally are capable of shaping immunity in humans. In particular, eyes with no signs of ocular distress or infection have a personalised microbiome that differ in their composition and function [35]. Recent studies have demonstrated the translocation of eye commensals to the lungs via the nasolacrimal system ([36,37]. Although, the mechanisms of microbial translocation of eye commensals remain elusive, many factors influencing this process have been proposed [38]. Importantly, ocular dysbiosis can influence the commensals located in the respiratory tract that may contribute to promoting hypersensitivity reactions via inflammatory mediators [27]. These inflammatory mediators that are released in response to ocular dysbiosis may not be confined to the eye but can potentially travel through the systemic circulation and affect the lung microbiome and, thus, its function [25,27,39].

Several studies have shown that lacrimation on the eye surface could promote accumulation of pathogens in the lacrimal ducts that may be transported to the inferior nasal meatus, which serves as a gateway for pathogens and respiratory viruses enabling access to the eye [37]. Furthermore, it is appreciated by few studies that ocular tissues such as cornea and conjunctiva express common proteins or glycoproteins that potentially serve as receptors for numerous pathogens and respiratory viruses [40–43]. Concurrently, several studies have revelated that dysbiosis of the gut microbiome may result in translocation of the intestinal microbes and their metabolites into vascular and lymphatic system, further impacting the eye that is distantly located from the gut [44]. These findings suggest two important propositions; firstly, the pathogens infect the outer surface of the eyes, causing disruption in the ocular microbiome and, thus, employs this site as an access point to reach the respiratory system, further disrupting the lung microbiome. Alternatively, the pathogens infect the respiratory system that may disrupt the lung microbiome and further migrate to eyes via the vascular system thus leading to dysbiosis of the ocular microbiome. These findings provide a valid conclusion that ocular dysbiosis may either impact the lung health or it may lead to lung-gut dysbiosis affecting eyes. However, there is no direct evidence yet in the literature as to how mechanistically they are related especially from the context of the disease. This clearly warrants further investigation.

### *2.2. Eye as the gateway to transmit respiratory viruses*

The eyes and the respiratory system communicate with each other, and this genuinely provides a robust basis for considering eye as a potential gateway to transmit respiratory viruses. Interestingly, studies have revealed that respiratory viruses such as rhinovirus, influenza, and coronavirus -SARS-CoV-2, are capable of primarily targeting the respiratory system. These viruses are transmitted via respiratory droplets of the infected individuals through coughing, sneezing, or by touching the eyes, nose, or mouth. Notably, the conjunctiva of the eye (i.e., outer surface of eye) is exposed to infectious respiratory droplets easily via close contact with infected individuals. A few respiratory viruses such as avian influenza viruses (H7) and human adenovirus D cause highly contagious conjunctivitis or keratitis [7,45]. This further suggests that the conjunctiva is a key gateway of entry for respiratory viruses whereas, conjunctival secretions and tears may contribute to the transmission of viruses [7,45]. Interestingly, several studies have revealed that mucosal lining of the ocular surface including the corneal and conjunctival epithelium, and the upper respiratory tract are linked by the nasolacrimal or tear duct [7]. The mucosal secretions can be partially absorbed by the conjunctiva and cornea but predominantly drained into the nasal cavity through the nasolacrimal or tear duct thus, being transported to lower respiratory tract and gut [46]. Hence, this facilitates the transmission of viruses from eye to respiratory tract and gut mucosa. Moreover, previous studies have revealed that the ocular surface and respiratory tract mucosa commonly share the same receptors for some respiratory viruses such as influenza virus, Respiratory Syncytial Virus (RSV) and SARS-CoV-2 coronavirus [7,47,48]. Studies have shown that ocular tissues such as the cornea and the conjunctiva express various proteins or glycoproteins in common that may serve as receptors for numerous respiratory viruses. These include [41,42] angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) the key receptors for the SARS-CoV-2 coronavirus [40,43] and α2-3- and α2-6-linked sialic acid glycoproteins as the receptors for influenza virus. Although, studies suggest eye as a gateway for viral transmission to lungs the underlying mechanisms that directly contribute to the transmission of various viruses may vary and thus, warrants further elucidation.

## 3. Evidence of respiratory virus transmission via the eye

The eye and the respiratory system are anatomically and functionally interconnected, and this provides a strong rationale for considering the eye as a potential site of respiratory viral infection and viral replication [7]. The nasolacrimal system represents the primary site of physical connection between the eye and the respiratory system. Tears on the eye surface are collected in the lacrimal ducts and are transported to the inferior meatus of the nasal cavity, which serves as an entry point for

respiratory viruses that come in contact with the eye [37]. Furthermore, ocular tissues such as the cornea and the conjunctiva have been reported to express common proteins or glycoproteins that serve as viral receptors for numerous respiratory viruses. These include α2–3-linked and α2–6-linked sialic acid glycoproteins, that function as receptors for many respiratory viruses including the influenza virus [41,42], as well as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), two fundamental entry factors for the SARS-CoV-2 coronavirus [40,43]. For this reason, all major human respiratory viruses either show ocular tropism or cause ocular diseases and complications, albeit to different extents [7]. In this context, two scenarios are possible: (i) the virus infects the eyes, causing ocular complications, and uses this site as an access point to reach the respiratory system; or (ii) the virus infects the respiratory system and migrates to the eyes, causing ocular symptoms. In this section, we will explore these two scenarios using two viruses, RSV and SARS-CoV-2, as examples.

### 3.1. Respiratory syncytial virus (RSV)

RSV, also known as human orthopneumovirus, is a virus that was discovered in 1956 which causes bronchiolitis in infants, colds in adult populations, and often pneumonia in elderly or immunocompromised patients [49,50]. Besides these common respiratory symptoms, conjunctivitis is often observed in patients infected with RSV [7]. In a pioneering study, Hall et al., [51] tested different routes of access for RSV, demonstrating that both the eyes and the nose are equally sensitive to RSV infection in humans [51]. These findings were confirmed by a later study showing that the use of eye-nose goggles significantly reduced the incidence of nosocomial RSV infections compared to the use of face masks only [52]. A decade later, Fujishima and colleagues reported the detection of genomic sequences of the RSV from the conjunctival epithelial cells of patients affected by allergic conjunctivitis (AC), using reverse transcription-polymerase chain reaction (RT-PCR) and Southern blotting [53]. This study was the first to postulate that RSV infection could represent a pathogenetic factor in AC. In a later study, the authors confirmed the tropism of RSV for conjunctival cells by directly infecting primary conjunctival cells collected from healthy patient with RSV and observing the RSV-induced secretion of (IL)-4 in the cell culture supernatant [54]. A further investigation led the authors to confirm that RSV infection of conjunctival epithelial cells is one among the environmental factors contributing to the development of AC [55]. Successively, Bitko and coworkers demonstrated that the cornea is another important site allowing RSV infection [23]. In this study, the authors showed that 60 % of corneal swabs obtained from paediatric patients with acute respiratory symptoms were RSV-positive, and demonstrated that the in vitro infection of primary corneal epithelial cells allowed robust replication of RSV, with concomitant activation of several proinflammatory cytokines [23]. In a later in vivo investigation, the same authors demonstrated, using BALC/c mice, that the ocular instillation of RSV resulted in a respiratory infection which was indistinguishable from the one that was obtained via nasal inoculation [56], thus providing the first direct evidence of eye-to-lung transmission of RSV. This study also showed that the application of ocular anti-cytokine treatment significantly reduced ocular inflammation but failed to reduce viral growth and replication, implying a role of RSV-induced cytokine production in developing ocular symptoms [56]. A more recent systematic review demonstrated that, personal protective equipment (PPE) interventions, including eye protection such as goggles, resulted to be more effective in preventing or limiting nosocomial RSV infections in hospital settings compared to interventions limited to the use of gowns and masks [57].

In summary, the studies examined in this section highlight the ocular tropism of RSV, showing that this virus can infect and replicate in both conjunctival and corneal epithelial cells. These findings also provide direct evidence of transmission of RSV from the eye to the respiratory system, confirming the hypothesis that the eyes represent a viable point of entry for the virus. However, there is no direct evidence in the literature on the migration of the RSV from the lung to the eye, warranting further investigation on the possibility of developing RSV-related ocular manifestations without direct airborne exposure of ocular epithelial tissues to the virus.

### 3.2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 is a novel strain of coronavirus, discovered in 2019, which is the cause of the recent COVID-19 global pandemic [58]. Another member of the same family, the SARS-CoV, was responsible for the 2002–2003 SARS pandemic [59]. Compared to other classes of respiratory viruses such as adenoviruses, influenza viruses, and RSV, coronaviruses have rarely been associated with ocular manifestations [7]. Despite this, direct or indirect contact with the mucous membranes of the eyes is among the primary routes of transmission of the SARS-CoV virus [59], and the lack of usage of eye protection devices such as goggles had been shown to be associated with an increased risk of SARS-CoV transmission from infected patients to healthcare workers during the SARS outbreak that occurred in 2003 in Toronto [60]. With regards to the SARS-CoV-2, even though the use of eye protection was suggested to be an effective way to reduce viral transmission [61], a successive systematic review showed that there are insufficient data to claim the effectiveness of eye protection [62]. More recently, a randomized clinical trial confirmed that the effectiveness of wearing glasses in the prevention of SARS-CoV-2 spread was marginal [63].

The presence of the two main viral entry proteins, ACE2 and TMPRSS2, on both corneal and conjunctival epithelial cells, suggests the potential of these two cell types as entry points for SARS-CoV-2 [40,43]. This, together with reports showing the relative frequency of conjunctivitis and ocular symptoms such as pain, foreign body sensation, tearing, blurred vision [64], and the detection of viral RNA in the tears and conjunctival secretions of SARS-CoV-2 positive patients [65,66], led to further investigation on the ocular tropism of SARS-CoV-2. In a study including 56 SARS-CoV-2-positive patients, Hong et al., demonstrated that ocular complications are relatively common, with 27 % of patients showing aggravated ocular symptoms, of which 11 % were detected before the onset of the disease [67]. Other studies have reported lower incidence of ocular symptoms. In a study conducted on a Polish cohort by Dolar-Szczasny et al., ocular infection by SARS-CoV-2 was found to be infrequent, with only 3 out of 74 SARS-CoV-2 positive patients resulting positive to the ocular swab and showing only mild to moderate ocular symptoms [68]. Similarly, in a study conducted by Gijs and colleagues, SARS-CoV-2 RNA was detected in conjunctival swabs in only 7 % of the enrolled COVID-19 patients [69]. These findings were confirmed by multiple systematic reviews and meta-analyses, that further substantiate the incidence of SARS-CoV-2-associated ocular symptoms to be highly variable ranging between 0 and 32 % [70–74]. Despite this, conclusive evidence of the ocular tropism of SARS-CoV-2 was recently provided by Sen and colleagues, who applied in situ histological hybridization on eye tissues from autopsies of COVID-19 patients to detect the cellular localization of the SARS-CoV-2 virus within the eye [75]. In this study, the viral RNA was detected in several cell types including oligodendrocytes, neuronal cells of both inner and outer layers of the retina, scleral fibroblasts, corneal epithelial cells, and ganglion cells [75]. Furthermore, in an in vivo study involving transgenic mice expressing human ACE2 (hACE2) and wild-type Syrian hamsters, Jeong and coworkers recently shed further light on the ocular tropism of SARS-CoV-2 [76]. Here, hACE2 mice were infected with SARS-CoV-2 through different routes including intranasal (IN), intratracheal (IT), and intraocular (eye drops, ED), whereas, wild-type hamsters were infected via the IN route and by ED. The authors showed that: (i) IN infection in mice resulted in ocular symptoms and retinal inflammation, with production of pro-inflammatory cytokines; (ii) IT infection in mice resulted in the active dissemination of the virus from the lungs to brain and eyes via trigeminal and optic nerves; (iii) ED

infection of both hACE2 transgenic mice and wild-type hamsters did not result in the subsequent lung infection, probably due to the immune function of the tear film that may have contributed to the elimination of the inoculated virus [76]. This was the first ever study that showed the unidirectionality of the SARS-CoV-2 infection route, which proceeded from the lung to the eye via neuronal invasion, in the absence of inverse viral transmission from the eye to the lung [76].

In summary, the studies analysed in this section provide evidence of the ocular tropism of SARS-CoV-2, showing that the virus can infect different tissue types within the eye. However, the reported incidence of ocular symptoms concerning SARS-CoV-2 infection is limited and highly variable. This, together with evidence pointing at the marginal efficacy of eye protection devices in preventing SARS-CoV-2 transmission, suggests that the eye may not be an efficient point of entry for this virus. This is also consistent with the fact that, contrary to what was shown for the RSV, there is no direct proof of eye-to-lung transmission of SARS-CoV-2. On the other hand, the lung-to-eye migration of this virus has been confirmed, which may explain the incidence of ocular complications in certain subset of COVID-19 patients.

## 4. Exposure of the ocular surface to environmental irritants and its impact on lung health

The ocular surface is directly exposed to the external environment, making it vulnerable to various irritants, including pollutants, smoke, and chemical vapours that may trigger various responses, from mild discomfort to significant inflammation [77,78]. While the immediate effects of these irritants on eye health are well-documented, emerging research suggests a potential link between ocular surface irritation and the progression of lung diseases, such as chronic obstructive pulmonary disease (COPD) and asthma.

The proposed mechanisms linking ocular irritation to lung disease progression involve neurogenic inflammation and systemic inflammatory responses [79]. When the ocular surface is exposed to irritants, it can activate trigeminal nerve endings, releasing neuropeptides like substance P, vasoactive intestinal polypeptide (VIP) and calcitonin gene-related peptide (CGRP) [80]. These neuropeptides can initiate and propagate inflammatory responses locally and systemically, potentially affecting the respiratory system.

Moreover, the eye's exposure to environmental irritants can lead to the release of inflammatory cytokines into the bloodstream [81,82], which may contribute to inflammatory processes in the lungs. The ocular surface therefore, acts as a sentinel, and its interaction with environmental irritants can trigger systemic immune responses that exacerbate or contribute to the pathogenesis of lung diseases.

Several epidemiological and clinical studies have supported the link between ocular exposure to environmental irritants and the progression of lung diseases. For instance, populations living in areas with high levels of air pollution exhibit an increased incidence of ocular irritation and respiratory conditions [83]. A clinical study conducted in Indonesia found a positive correlation between exposure to particulate matter (PM2.5) and an increased risk of symptoms associated with dry eye syndrome, alongside a higher prevalence of breathlessness and wheezing when exposed [84]. Experimental studies in animal models have individually demonstrated that exposure to environmental irritants, such as tobacco smoke, can lead to enhanced ocular surface inflammation [88, 89] and could induce or exacerbate lung inflammation [85,86]. However, further experimental studies are essential to highlight the systemic nature of the inflammatory response to environmental irritants, underscoring the potential for ocular irritation to impact lung health.

## 5. Therapeutic interventions and conclusions

The field of ocular microbiome research is in its infancy, and there is a greater extent of information to uncover. Future investigations should focus on the following key points.

(a) Longitudinal Studies: Long-term studies tracking changes in the ocular microbiome and their impact on lung health are needed to establish causality and identify potential therapeutic targets.
(b) Microbial Transfer Mechanisms: Future research should elucidate the mechanisms by which ocular microbes and their products reach the respiratory tract and their consequences on lung health.
(c) Microbiome Interventions: Investigations on the effectiveness of microbiome-based interventions, such as probiotics or microbiome transplantation, in preventing or treating ocular and respiratory diseases should be conducted.
(d) Microbiome Profiling: Standardised methods for profiling the ocular microbiome to enable comparisons across studies and establish a reference database for healthy ocular microbiomes should be developed.

The ocular microbiome is a dynamic ecosystem that plays a crucial yet underexplored role in human health. Its connection to lung health highlights the intricate interplay between different microbiomes within the body. As we delve deeper into this emerging field of research, we can anticipate newer insights and therapeutic strategies that may bridge the gap between ocular and respiratory health, ultimately improving overall well-being.

## CRediT authorship contribution statement

**Venkata Sita Rama Raju Allam:** Writing – review & editing, Writing – original draft, Conceptualization. **Vyoma K. Patel:** Writing – review & editing, Writing – original draft. **Gabriele De Rubis:** Writing – review & editing, Writing – original draft. **Keshav Raj Paudel:** Writing – review & editing, Conceptualization. **Gaurav Gupta:** Writing – review & editing. **Dinesh Kumar Chellappan:** Writing – review & editing. **Sachin Kumar Singh:** Writing – review & editing. **Philip M. Hansbro:** Conceptualization. **Brian Gregory George Oliver:** Writing – review & editing. **Kamal Dua:** Writing – review & editing, Supervision, Conceptualization.

## 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 article.

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