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Ocular Tropism of Respiratory Viruses

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SUMMARY

Respiratory viruses (including adenovirus, influenza virus, respiratory syncytial virus, coronavirus, and rhinovirus) cause a broad spectrum of disease in humans, ranging from mild influenza-like symptoms to acute respiratory failure. While species D adenoviruses and subtype H7 influenza viruses are known to possess an ocular tropism, documented human ocular disease has been reported following infection with all principal respiratory viruses. In this review, we describe the anatomical proximity and cellular receptor distribution between ocular and respiratory tissues. All major respiratory viruses and their association with human ocular disease are discussed. Research utilizing *in vitro* and *in vivo* models to study the ability of respiratory viruses to use the eye as a portal of entry as well as a primary site of virus replication is highlighted. Identification of shared receptor-binding preferences, host responses, and laboratory modeling protocols among these viruses provides a needed bridge between clinical and laboratory studies of virus tropism.

INTRODUCTION

Respiratory viral infections represent the most common cause of acute illness and physician visits in the United States, with disease ranging from mild influenza-like symptoms to life-threatening pneumonia (1). Shared features between the principal viruses associated with human respiratory disease include high transmissibility, global distribution, mucosal sites of infection, and several overlapping symptoms. While human infection with respiratory viruses generally causes an acute but transient and resolving upper respiratory tract illness, progression to lower respiratory disease is possible, especially among individuals with compromised immune systems or other comorbidities. Respiratory viruses are typically spread by inhalation of virus-containing aerosols expelled by infected individuals or by direct or indirect contact with virus-contaminated fomites on environmental surfaces (1, 2). However, the epithelia of the human eye represent an additional mucosal surface which is similarly exposed to infectious aerosols and contaminated fomites (3, 4). Viruses which are generally considered respiratory pathogens are nonetheless capable of causing ocular complications in infected individuals and establishing a respiratory infection following ocular exposure (Table 1). It is important to keep in mind that our use of "respiratory viruses" in this review encompasses a diverse range of pathogens, of which ocular disease is but one of many potential complications.

Despite the anatomical proximity between ocular and respiratory tissues and documented reports of ocular disease following infection with most known respiratory viruses in humans, studies of respiratory pathogens and their role in ocular disease have been underrepresented in the literature. Our knowledge is incomplete regarding the properties which confer an ocular tropism to particular respiratory viruses or virus subsets and the mechanisms which allow ocular exposure to viral pathogens to cause a respiratory infection. To appropriately control and treat disease presenting with ocular complications, a more rigorous understanding of the relationship between the development of ocular symptoms and respiratory disease is critical. In the sections below, we present a summation of ocular findings following respiratory virus infection in humans and the current innovations in laboratory modeling which will allow for a greater analysis of the properties which govern virus tropism.

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TABLE 1 Principal respiratory viruses known to cause ocular disease in humans

Virus	Subtype(s)[a]	Tropism in humans	Ocular disease in humans	Reference(s)
Adenovirus	Species D	Ocular	Frequently associated with epidemic keratoconjunctivitis	5–7
	Species B, C, E	Respiratory	Occasional simple acute follicular conjunctivitis or pharyngeal conjunctival fever	1, 8
Influenza virus	H7	Ocular	Conjunctivitis	9, 10
	H1, H3, H5	Respiratory	Rare but documented ocular complications	1, 11, 12
Respiratory syncytial virus	NA	Respiratory	Occasional reports of conjunctivitis concurrent with respiratory illness	13–16
Coronavirus	NL63	Respiratory	Rare reports of conjunctivitis	17, 18
	SARS	Respiratory	Not reported	19
Rhinovirus	NA	Respiratory	Rare but documented ocular complications	20–22
Human metapneumovirus	NA	Respiratory	Rare but documented ocular complications	23, 24

[a] NA, not applicable (indicates that there is no association with any given subtype/serotype with ocular complications in humans).

ANATOMICAL AND HOST RECEPTOR LINKS BETWEEN OCULAR AND RESPIRATORY SYSTEMS

There are several properties which permit the eye to serve as both a potential site of virus replication as well as a gateway for transfer of virus to extraocular sites to establish a respiratory infection. This is achieved primarily by the nasolacrimal system, which provides an anatomical bridge between ocular and respiratory tissues (Fig. 1) (4, 25). The lacrimal duct collects tear fluid from the ocular surface and transports it to the inferior meatus of the nose, facilitating the drainage of virus from ocular to respiratory tract tissues in a replication-independent manner, thus serving as a conduit for virus-containing fluid exchange between these sites (3, 26–28). When placed on the eye, fluid can be taken up by the conjunctiva, sclera, or cornea, but the majority of liquid is drained into the nasopharyngeal space or swallowed; absorption of tear fluid through the epithelial lining of the lacrimal duct is also possible (29). This allows drainage of immunizing agents to nasal tissue following topical ocular administration as well as the spread of intranasally administered solutions to the conjunctival mucosal surface (28, 30). The lining of nasolacrimal duct epithelial cells with microvilli additionally permits both secretion and reabsorption of tear fluid components (31). Linkage of the ocular mucosal immune system (composed of the conjunctiva, cornea, lacrimal glands, and lacrimal drainage system) with nasal cavity-associated lymphoid tissue in the nasolacrimal ducts further supports the immunological interdependence between ocular and respiratory tract tissues (28). Despite the presence of antimicrobial peptides present in tear film, numerous viral agents have been detected in the tear fluid of symptomatic, chronic, and asymptomatic individuals (4, 32–36), underscoring the potential for ocular involvement following respiratory virus infection.

Beyond the anatomical linkage of ocular and respiratory tract tissues, the structure and distribution of cellular receptors in these systems likely contribute to the tissue tropism of respiratory viruses. Host epithelial cell glycoproteins bearing terminal sialic acids (SA) are distributed throughout the human respiratory tract and ocular tissue (Fig. 1) (reviewed in reference 37) and serve as the cellular receptor for several respiratory viruses. In humans, α2-6-linked SA dominate in the nasal mucosa and trachea, whereas α2-3-linked SA are found at greater abundance in lower respiratory tract tissues and ocular tissue (37–39). Interestingly, the epithelium of the human lacrimal sac and nasolacrimal duct, which bridge ocular and respiratory tissues, express a diverse variety of lectin-binding sites, including both types of SA; α2-6-linked SA have been detected on both epithelial and goblet cells of the lacrimal duct, and α2-3-linked SA are restricted to epithelial cells (31). While the terminal SA linkage represents a critical determinant of tissue tropism and host range for influenza viruses, the composition of internal sugars of the glycan receptor can also influence receptor specificity (40, 41).

The pattern of cellular receptor distribution in ocular and respiratory tract tissues generally agrees with the tropism of numerous respiratory viruses. Human influenza viruses prefer α2-6-linked SA, and as such, their replication is typically restricted to the upper respiratory tract, whereas avian influenza viruses preferentially bind α2-3-linked SA and are capable of efficient replication in lower respiratory tract tissue, where these receptors are most prevalent. The abundance of α2-3-linked SA on the corneal and conjunctival epithelium may partially govern the tropism observed with select influenza virus subtypes, although it has been shown that both human and avian influenza viruses can bind to human ocular tissue, demonstrating that receptor binding preference is not the sole determinant of this property (3, 42). Similarly, the tissue distribution of cellular receptors may partially govern the tropism of adenoviruses (Ad). Generally, adenoviruses which exhibit a respiratory tropism use CD46, desmoglein-2 (DSG-2), or the coxsackievirus and adenovirus receptor (CAR) as a cellular receptor (43–45), while adenovirus serotypes which exhibit an ocular tropism use α2-3-linked SA and GD1a glycans present on the human ocular surface as host cellular receptors (46, 47), although the bread tissue distribution of these receptors indicates a role for additional tropism determinants. Furthermore, the location of angiotensin-converting enzyme 2 (ACE2), the cellular receptor for severe acute respiratory syndrome (SARS) coronavirus, on cardiac and pulmonary tissue likely contributes to the severe respiratory disease associated with this virus (48–50). The continued identification of the cellular receptors utilized by respiratory viruses will allow for a greater understanding of the permissiveness of ocular tissue to infection with these agents (51). Collectively, it appears that the presence of permissive receptors can

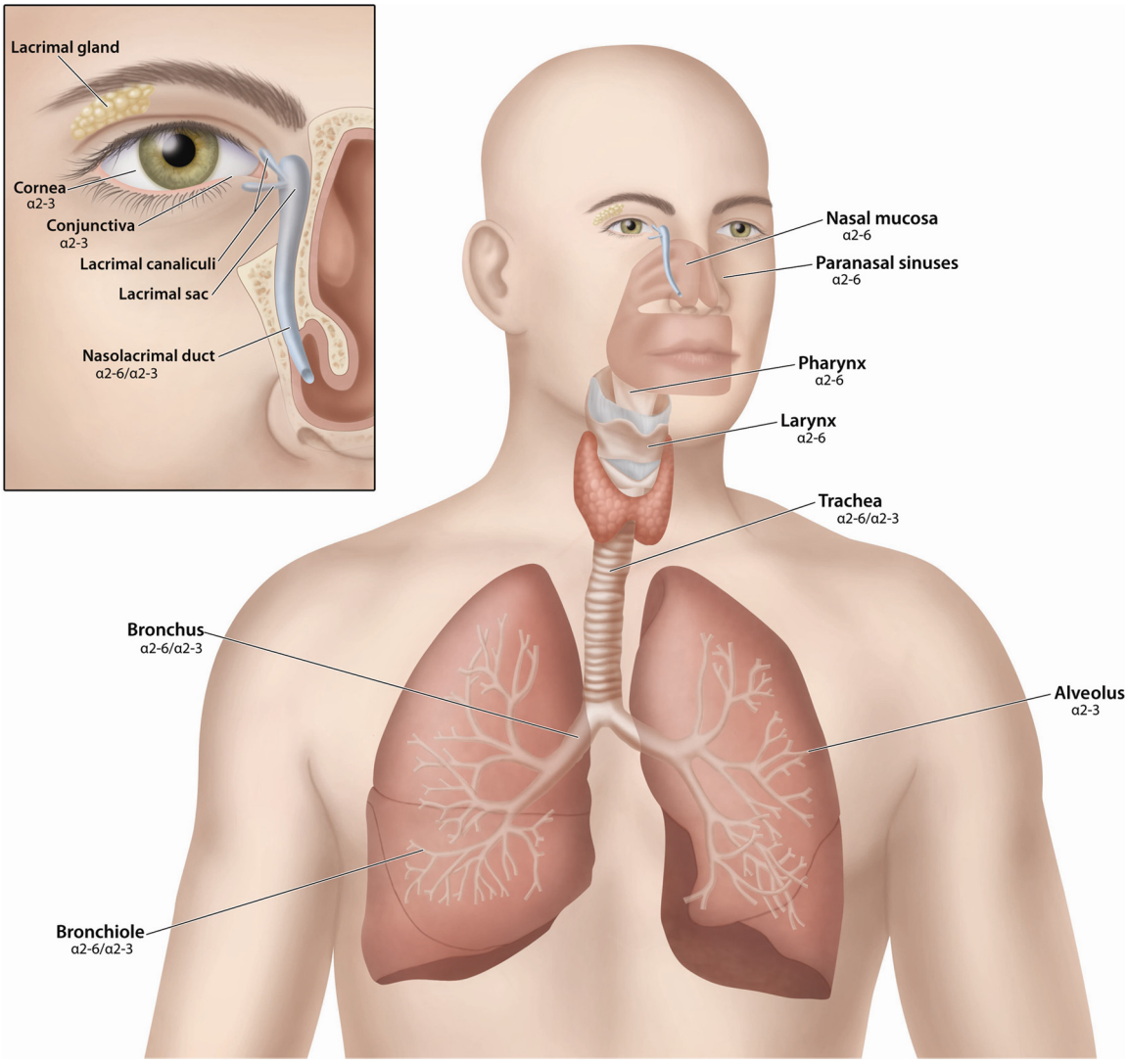

FIG 1 Distribution of sialic acids in human ocular and respiratory tract tissues. Major components of human ocular and respiratory tissues are depicted, with the predominant α2-6- and/or α2-3-linked glycans expressed on epithelial cells identified where known (see references 37 and 3). While these sialic acids are predominantly employed by adenovirus and influenza virus, additional cellular receptors and the viruses which utilize them are discussed in the text.

contribute to the tropism of a virus to ocular tissue but does not restrict respiratory viruses from using the eye as a portal of entry to gain passage to extraocular tissues to establish a productive infection.

Despite the body of work that has been focused on an understanding of the distribution of viral receptors present on the ocular epithelium, further research is needed to better understand the contribution of sialylated ocular mucins to host defense of these pathogens (3). While there is great heterogeneity of mucins and secretory peptides synthesized and secreted by discrete regions and cell types within the human ocular surface and nasolacrimal ducts (29), the potential contribution of this localized distribution to viral infection is not well understood. The identification of differences in the spatial arrangement of α2-3- and α2-6-linked sialic acids on purified human ocular mucins highlights the potential importance of receptor distribution in mucosal antimicrobial defense in this tissue (52). Examination of the structural topology and length of surface glycans present on human ocular tissue may also shed light on fine receptor differences present on this surface which influence the tropism of select virus subtypes, as was previously shown for respiratory tissues (40, 53). Due to the potential of zoonotic spread of select respiratory viruses to humans, it is prudent to extend the study of these properties in relevant nonhuman species (54).

OCULAR MODELS OF RESPIRATORY VIRUS INFECTION

While it is acknowledged that some respiratory viruses exhibit an apparent ocular tropism, and uncommon but documented ocular complications can occur following infection with respiratory-tropic viruses (Table 1), it has only been with the use of experimental *in vitro* and *in vivo* laboratory models that these anecdotal observations have been confirmed. The development of continuous ocular cell lines and the use of primary human ocular cell types have provided researchers the opportunity not only to study the permissiveness of discrete locations within the human eye to respiratory virus infection (Fig. 2) but also to elucidate the role of

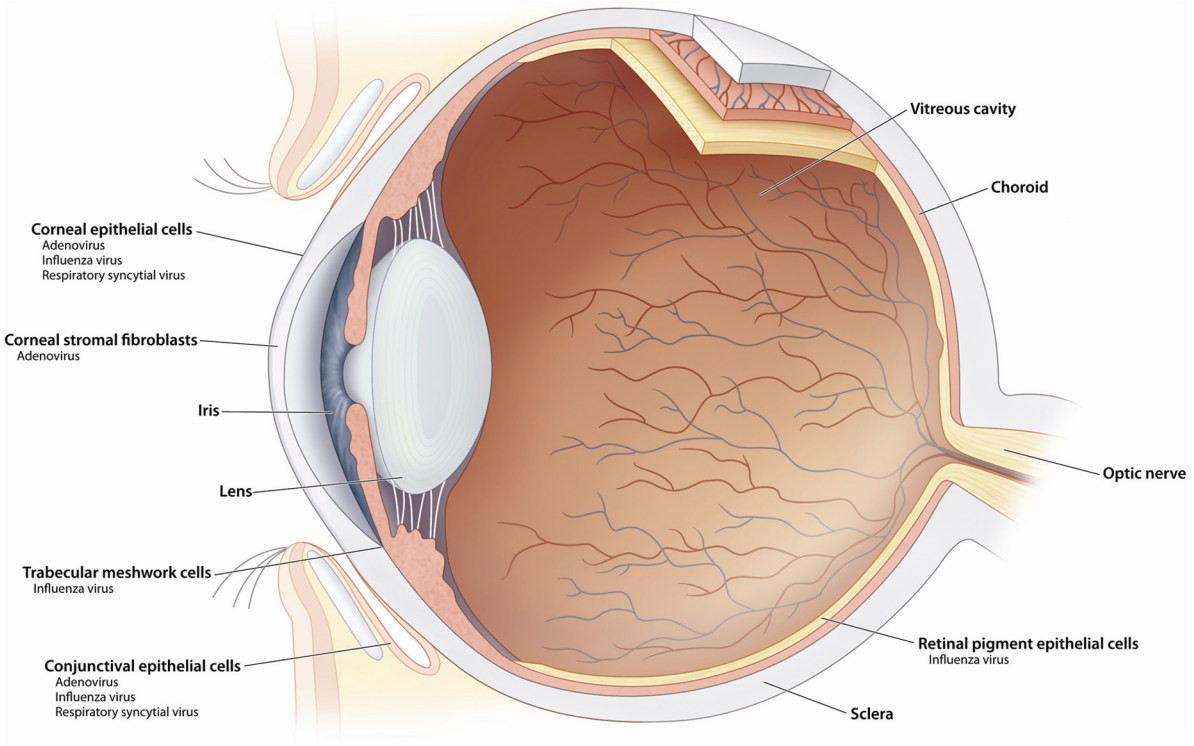

FIG 2 Location of human ocular cell types permissive to respiratory virus infection. Cell types of the human eye previously shown to support viral replication of adenovirus (75, 92, 93, 95), influenza virus (55, 58, 122), and respiratory syncytial virus (56, 131) are depicted.

host responses present in these sites following viral infection (55–57). With their increased tissue complexity, human and mammalian model *ex vivo* cultures have also furthered our understanding of virus-host interactions (58–60). These studies have yielded crucial information for the identification of prospective targets for immunomodulatory agents to mitigate conjunctival symptoms (61–63).

Unlike *in vitro* systems, *in vivo* mammalian models allow for the coincident study of multiple anatomical locations following viral infection, providing greater insight into the capacity for virus to disseminate from the site of inoculation to systemic tissues. Furthermore, mammalian models are ideally suited to study the effect of concurrent viral infections, an important parameter to understand, as the simultaneous presence of multiple respiratory viral pathogens has been detected in patients with keratoconjunctivitis (64, 65). While host restrictions limit the permissiveness of some viruses to select species, these models have nonetheless provided valuable information (Table 2). Mouse models, used extensively to study herpesvirus keratitis, have further been adapted to study ocular complications from numerous viral respiratory diseases (27, 66, 71, 80). The rabbit has long been used for the assessment of eye irritation and has since been utilized to study ocular disease following respiratory virus infection (65, 73, 81). The ferret has been recognized as an appropriate experimental model for studies involving the visual system and has been employed to study ocular inoculation of respiratory viruses (26, 72, 82–84). As described below, these and other species have provided a greater understanding of how respiratory viruses cause ocular disease.

In the following sections, we discuss respiratory viruses which have caused documented ocular disease in humans, both viruses for which an ocular tropism has been accepted as well as those viruses for which only sporadic and rare instances of conjunctivitis or other ocular complications have occurred following virus exposure. Laboratory studies which have studied the capacity of these respiratory viruses to cause disease following ocular exposure, employing both *in vitro* and *in vivo* models, are highlighted. Despite the great diversity of respiratory viruses represented below and the differing incidence of ocular disease inherent between individual viruses, numerous shared properties of how these respiratory pathogens interact with the eye become apparent.

HUMAN RESPIRATORY VIRUSES WITH DOCUMENTED OCULAR COMPLICATIONS

Adenoviruses

Human adenoviruses, members of the family *Adenoviridae*, are nonenveloped, double-stranded DNA viruses with over 50 known serotypes divided into at least six subgroups (85, 86). Adenoviruses are most commonly associated with respiratory illness in humans, ranging from mild to acute respiratory disease, but are capable of causing a diverse range of clinical symptoms depending on the serotype, including gastroenteritis and ocular disease, with or without respiratory involvement (6). Species A, B, C, E, and F adenoviruses utilize CD46, DSG-2, or CAR as a cellular receptor and generally cause respiratory disease in humans (with the exception of species F, which is associated with gastroenteritis), while species D viruses bind to α2-3-linked SA and GD1a glycans and exhibit an ocular tropism (46, 47, 87). Human disease with species D adenoviruses, notably of serotypes 8, 19, and 37, has frequently been associated with epidemic keratoconjunctivitis

TABLE 2 Summary of experimental ocular inoculation of respiratory viruses in mammalian models[a]

Species	Virus	Inoculation route	Virus detection p.i.	Clinical sign(s) p.i.	Reference(s)
Mouse	Adenovirus (species D)	Intrastromal inoculation	Low titer in eye	Stromal opacification and inflammation	66–68
	Influenza virus (H7)	Dropwise onto corneal surface with or without scarification	Predominantly eye, lower titer in nose and lung	Comparable to intranasal inoculation[b]	58
	Influenza virus (H5N1, H1N1)	Dropwise onto corneal surface with or without scarification	Predominantly nose and lung or not at all	Comparable to intranasal inoculation	58, 69–71
	RSV	Dropwise onto corneal surface following scarification	Eye and lung	Comparable to intranasal inoculation	27
Ferret	Influenza virus (H7)	Dropwise onto corneal surface	Ocular, respiratory, intestinal tract tissue	Comparable to intranasal inoculation, ocular signs rarely reported	26, 72
	Influenza virus (H5N1)	Dropwise onto corneal surface	Ocular, respiratory, intestinal tract tissue	Comparable to intranasal inoculation	26
	Influenza virus (H1N1, H3N2)	Dropwise onto corneal surface	Ocular, respiratory, intestinal tract tissue	Comparable to intranasal inoculation	26
Rabbit	Adenovirus (species C)	Intrastromal inoculation followed by scarification and topical administration	Ocular	Subepithelial corneal infiltrates similar to EKC in humans	73–75
Cotton rat	Adenovirus (species C and D)	Intrastromal inoculation followed by scarification and topical administration	Ocular	Subepithelial corneal infiltrates similar to EKC in humans	76–78

[a] p.i., postinoculation.
[b] Clinical signs of influenza A virus subtypes following intranasal inoculation are reviewed in reference 79. Generally, ocular inoculation with influenza virus and RSV results in a 1- to 3-day delay in onset of clinical signs compared with intranasal inoculation.

(EKC), a highly contagious and severe ocular disease, which can progress to hemorrhagic conjunctivitis (5, 6). Adenovirus-caused EKC spreads readily by direct or indirect contact, even from asymptomatic patients, with a high potential for nosocomial spread (88–91). However, ocular disease has been documented following human infection with over half of all identified adenovirus serotypes, typically simple acute follicular conjunctivitis, which is generally mild and limited to the conjunctiva, or pharyngeal conjunctival fever, which presents with both cold-like symptoms and conjunctivitis, although the development of severe ocular disease with these serotypes is possible (8).

Much of our understanding of the ocular tropism of adenoviruses has come from *in vitro* studies using human ocular cell types. Multiple regions of the human eye are permissive to adenovirus infection, including corneal and conjunctival epithelial cells and corneal stromal fibroblasts (75, 92–95) (Fig. 2). Mirroring the tropism observed in humans, Ad37 viruses bind to and infect human ocular cells more efficiently than respiratory cells, likely due to the ability of EKC-causing species D serotypes to use specific membrane protein receptors present on ocular but not respiratory cell types (46, 47, 96). Beyond receptor restrictions, species D serotypes have been shown to be more resistant to defensin-like chemokines in human conjunctival cells than serotypes more frequently associated with respiratory disease (93). Infection of human ocular cell types with species D viruses has further shed light on the kinetics of cytokine induction and NF-κB activation, which play a role in the inflammation present during adenoviral keratitis (57, 95). Collectively, these and other studies have identified several critical receptors and inflammatory mediators which contribute to the ocular tropism of adenoviruses and represent candidate targets for future therapeutic development (97–100).

While the high degree of species specificity of adenoviruses has posed a challenge for *in vivo* studies of these pathogens, the establishment of mammalian models has furthered our ability to study adenovirus-induced ocular disease. Ocular inoculation of cotton rats with Ad5 or Ad8 results in a course of disease generally similar to that of human infection with these serotypes (78). Rabbits have also been widely used as a model for adenovirus ocular study, notably for species C viruses, with the duration and titer of virus shedding from the eye being comparable to those of human infection (73–75). Mouse models of ocular Ad37 inoculation, while not fully possessing all the hallmarks of human disease, nonetheless recapitulate many ocular immunopathologic features present in human Ad37 keratitis and have furthered our understanding of immunological mediators via the use of knockout mice (66–68). These small-mammal models have proven useful in the evaluation of numerous potential antiviral and other therapeutic agents against ocular adenovirus infection, which are especially needed as there is currently only limited virus-specific therapy and no vaccine available for adenovirus-caused ocular disease (8, 63, 76, 77, 101).

Orthomyxoviruses

Influenza A viruses belong to the family *Orthomyxoviridae* and possess 8 negative-sense RNA segments, which encode at least 13 known proteins (102). Serologically distinct virus subtypes are formed by the presence of the viral surface glycoproteins hemagglutinin (HA) and neuraminidase (NA); 16 HA and 9 NA subtypes have been identified in wild water birds, the natural host for all influenza A viruses. Seasonal influenza viruses (subtypes H1 to H3) cause a highly transmissible respiratory illness in humans, resulting in >300,000 deaths worldwide each year (103). Avian

influenza viruses of the H5, H7, and H9 subtypes have additionally caused human infection in recent years, with highly pathogenic H5 viruses frequently associated with severe disease and death (11). The great majority of human infections with avian and human influenza A viruses result in respiratory disease, but additional symptoms (including ocular and gastrointestinal complications) have been documented (104). Notably, >80% of all human infections with subtype H7 viruses have presented with conjunctivitis (9, 10). Documented cases of conjunctivitis following H7 virus infection in both Europe and North America have occurred by numerous exposure routes, including close direct physical contact with infected poultry, possible eye abrasions with contaminated material, ocular exposure to splashed liquid containing virus, and exposure of the face and eye to aerosolized virus following sneezing of an infected animal (9). Select H7 viruses have been associated with concurrent ocular and respiratory disease in humans (105); interestingly, many H7 influenza viruses have been found to be partially adapted to recognize α2-6-linked sialic acids, the receptor preferred by human influenza viruses and present in human upper respiratory tract tissues (106–109). Several cases of H7 virus infection in humans resulting in respiratory illness in the absence of ocular complications further underscore the spectrum of disease possible with viruses within this subtype (10, 110, 111).

While infrequent, ocular complications have been documented following human infection with influenza virus subtypes that are more commonly associated with respiratory illness. Concomitant conjunctivitis and respiratory disease have been reported among individuals infected with or exposed to H5N1 viruses (11, 112–114), and seasonal and 2009 H1N1 influenza viruses have also sporadically caused ocular complications following human infection (12, 104, 115, 116). The occurrence of rare adverse events following seasonal influenza virus vaccination, including the onset of oculorespiratory syndrome and the rejection of corneal transplants in vaccine recipients, underscores the importance of studying the ocular environment in the framework of influenza virus infection and vaccination (117–120). In this context, a recent study demonstrated transocular spread of aerosolized live attenuated influenza virus vaccine (LAIV) to nasopharynx tissue in experimentally exposed individuals (121). These reports illustrate the ability of a diverse range of influenza A viruses to use the eye as a portal of entry in the absence of a recognized tropism for this tissue.

Several *in vitro* and *ex vivo* studies have been conducted to examine the permissiveness of ocular cell types to influenza virus infection and to identify those properties which confer the ocular tropism demonstrated for the H7 virus subtype. Human corneal and conjunctival epithelial cells support the productive replication of select influenza viruses, as do retinal pigment epithelial cells and trabecular meshwork cells located in the interior of the eye (55, 59, 122). Generally, avian H5 and H7 influenza viruses replicate more efficiently and to higher titers in these cells than human and swine influenza viruses (55, 123). Differential patterns of cytokine production and NF-κB signaling following H7N7 virus infection in human corneal and lung epithelial cells suggest that tissue-specific host responses may contribute to the ocular tropism observed with this virus subtype (55).

To assess the ability of influenza viruses to replicate in ocular tissue as well as spread to the respiratory tract following ocular exposure, we and others have established mammalian models to study the pathogenesis of influenza virus following ocular inoculation (Table 2). Ocular inoculation of mice with influenza A viruses generally mirrors the ocular tropism observed in humans: H7 influenza viruses replicate more frequently and to higher titers in the eye, whereas H5N1, seasonal, and 2009 H1N1 influenza viruses are detected at a lower frequency in respiratory and not ocular tissues or are unable to use this route to establish infection (58, 69–71, 124). In contrast, ferrets mount a productive respiratory virus infection following ocular inoculation with both avian and human influenza viruses (26, 72). While macroscopic ocular signs are generally not common following influenza virus inoculation by the intranasal route in laboratory species, conjunctivitis has been reported following experimental inoculation of dogs and mice with H5N1 virus and of ferrets with H7N3 virus (72, 125). Concurrent ocular and respiratory disease has been documented for a diverse range of species infected with influenza virus subtypes not associated with human disease (126–128), underscoring a need to monitor the incidence of ocular symptoms during viral surveillance. While future studies are needed to identify the particular molecular determinants that confer the ocular tropism observed for viruses within the H7 subtype, these reports demonstrate that the eye and surrounding conjunctiva represent a permissive port of entry for all influenza virus subtypes.

Paramyxoviruses

Respiratory syncytial virus. Respiratory syncytial virus (RSV) is a nonsegmented negative-strand RNA virus of the family *Paramyxoviridae*. This highly transmissible respiratory pathogen can infect cells of the upper and lower respiratory tract and is a major cause of pediatric respiratory disease worldwide, resulting in up to 100,000 hospitalizations of infants and children annually (103, 129). Infection can occur following respiratory or ocular exposure, likely following direct contact with infectious secretions or self-inoculation (16). Febrile upper respiratory tract illness is a primary clinical feature, with acute lower respiratory tract infection being present disproportionally in infants and young children (129). While not a routine clinical feature, conjunctivitis is not infrequently reported in concert with RSV infection, and RSV has been isolated from clinical samples (superficial cells and tears) with allergic conjunctivitis (13, 14). The reduction of nosocomial spread of RSV following the use of eye protection further demonstrates that ocular tissue is a portal of entry for RSV (15).

In vitro and *in vivo* studies have advanced our understanding of the role of RSV in ocular disease. Human corneal and conjunctival epithelial cells are permissive to RSV infection, and RSV infection of ocular epithelial cells results in the production of numerous cytokines and chemokines involved in ocular inflammation, notably the activation of NF-κB signaling (56, 130, 131). The establishment of a murine model of ocular RSV inoculation demonstrated experimentally the ability of this virus to both use the eye as a gateway to mount a respiratory infection as well as replicate specifically in ocular tissue (27, 56). Bovine and sheep isolates of RSV have caused conjunctivitis with mild respiratory disease in lambs and cattle (132–135), highlighting the ability of this virus to cause ocular complications in nonhuman species. Several potential approaches to mitigate ocular inflammation following RSV infection are under investigation, including anticytokine treatments and the use of protein inhibitors (27, 136, 137). Considering the high burden of disease associated with this virus in humans, even a low level of documented ocular disease following

RSV infection indicates a public health need to better understand this property.

Other paramyxoviruses. Human metapneumovirus (hMPV) was first discovered in 2001 and is second only to RSV as the causative agent of acute pediatric respiratory disease (138, 139). Clinical manifestations of hMPV disease typically range from mild respiratory disease to pneumonia. Similar to human infection with RSV, conjunctivitis has been reported infrequently in patients with hMPV, often in combination with otitis (23, 24). Several mammalian models have been established to study hMPV respiratory disease, but none have reported ocular signs following infection with this virus (reviewed in reference 140). In contrast to rare reports of ocular disease following hMPV infection in humans, avian pneumoviruses frequently cause both respiratory and ocular disease in turkeys (141, 142). Further study is needed to better understand the potential of hMPV to cause ocular disease or use the eye as a portal of entry to establish a respiratory infection.

Measles virus causes a febrile rash illness that is accompanied by cough, coryza, and conjunctivitis (143). Although measles causes a systemic infection, it is spread by the respiratory route, with the initial infection targeting lymphoid cells present in the lung (144). In many countries, measles is effectively controlled by vaccination programs. However, measles remains a major public health problem in developing countries, where it is responsible for approximately 139,000 deaths annually (145). Corneal ulcerations often follow measles infections in malnourished children, and measles blindness is the single leading cause of blindness among children in low-income countries; accordingly, measles virus can be detected in ocular tissue (146–155). It is worth noting that measles-rubella vaccine is now used worldwide, so the same vaccine used to protect children from measles also protects from rubella infection. Rubella virus, a member of the family *Togavirus*, causes a relatively mild disease in children and adults, but if a woman is infected during pregnancy, the child is often born with congenital rubella syndrome, which can lead to deafness, heart disease, and cataracts (156–158). Therefore, measles-rubella vaccine can prevent two significant causes of blindness or visual impairment in developing countries. Demonstrating experimentally the ability of these viruses to cause ocular complications, measles retinopathy and keratitis have been observed in the hamster model, and rubella virus has been found to replicate in both *in vitro* and *in vivo* ocular models (159–163).

Coronaviruses

Human coronaviruses (HCoV) are enveloped, single-stranded RNA viruses, which (with the exception of severe acute respiratory syndrome [SARS]) generally cause mild upper respiratory tract infections in humans (164). Among coronaviruses which have circulated in the human population, two were identified in the 1960s (HCoV-229E and HCoV-OC43), and two others (HCoV-HKU1 and HCoV-NL63) were identified recently (18, 164, 165). HCoV isolates are highly transmissible and are a frequent cause of common colds in all age groups (1). Similar to other human respiratory coronaviruses, HCoV-NL63 typically causes both upper and lower respiratory tract infections, notably in young children and immunocompromised adults, but conjunctivitis has been reported in select cases (17, 18, 166, 167). An association between HCoV-NL63 infection and Kawasaki disease (a systemic vasculitis of childhood for which presentation with bilateral conjunctivitis is one criterion for diagnosis) has been reported; however, a definitive link of HCoV-NL63 as the etiologic agent of this disease has not been established (166, 168). It is therefore unclear if the presentation of conjunctivitis in HCoV-NL63-infected patients is attributed to the coronavirus itself or rather represents a manifestation of disease caused by an unrelated pathogen or disease.

In contrast to other human coronaviruses, SARS-associated coronavirus, first identified in 2003, is a viral pneumonia capable of rapid progression to severe disease and death (19, 169). The virus is transmitted primarily via direct or indirect contact with mucous membranes of the eyes, nose, or mouth (19). Eye or mucous membrane exposure to body fluids and a lack of wearing eye protection were both associated with an increased risk of SARS coronavirus transmission from infected patients to health care workers during the 2003 Toronto SARS outbreak (170), demonstrating the potential for virus transmission following exposure of unprotected eyes to this respiratory pathogen. While ocular symptoms have not been reported following virus infection, SARS coronavirus was detected by reverse transcription (RT)-PCR in tear samples from three probable cases, using conjunctival swabs collected during the early phase (within 9 days) of symptom onset (171). However, several other studies could not detect SARS coronavirus in tears and conjunctival scraping samples collected from confirmed SARS patients, and eyes of confirmed patients with SARS coronavirus did not demonstrate ocular manifestations of disease following ophthalmic examination (172, 173); further study is required to determine if this discrepancy is attributable to false-negative results or the timing of sample collection (174). Despite inconclusive evidence of SARS coronavirus replication in ocular samples, these studies nonetheless underscore the eye as a potential portal of entry for this virus (175).

Numerous animal models have been established to study respiratory disease following SARS coronavirus infection (reviewed in reference 176), with most models demonstrating evidence of virus infection but without the severe acute pulmonary illness present in humans. While mild respiratory disease was present in several of these models, conjunctivitis was reported in ferrets infected with SARS (84). Unlike SARS and HCoV-NL63 infection in humans, nonhuman coronaviruses frequently cause ocular disease following intraocular or oronasal inoculation in numerous species, including mice, cats, rats, and pigs (177–180). Collectively, these studies indicate that while ocular complications are not a frequent manifestation of coronavirus infections in humans, ocular exposure may represent a meaningful route of entry for this virus. Further study of virus infectivity specifically within ocular tissues would allow for a better understanding of the permissiveness of nonrespiratory tissues to this virus.

Picornaviruses

Rhinoviruses represent a highly contagious respiratory illness of the family *Picornaviridae* with approximately 100 identified serotypes. The most typical symptoms from rhinovirus infection in humans include runny nose, congestion, sore throat, chills, and fever. Initiation of virus infection occurs following deposition of virus in the nose or eye and transport of virus by mucociliary transport to the back of the throat, where lymphoepithelial cells in the adenoid area contain intracellular adhesion molecule 1 (ICAM-1), the cellular receptor for >90% of rhinovirus serotypes (21, 181). ICAM-1 is expressed constitutively at low levels

throughout the body, including the ocular epithelia, and was shown to be upregulated during ocular inflammation (182). Several studies have demonstrated that experimental inoculation of virus into the conjunctiva results in human rhinovirus infection, likely due to the spread of the virus inoculum to the nose via the nasolacrimal duct (22, 183–185). However, experimental transocular exposure to aerosolized rhinovirus did not result in a productive infection, suggesting that self-inoculation or direct contact of contaminated material with ocular tissue is a more likely mode of ocular exposure to rhinovirus resulting in human infection (186). Reports of rhinovirus replication in conjunctival tissue itself have been rare but documented and were not associated with a particular virus serotype (20). Only recently have small-mammal models become available to study rhinovirus pathogenicity *in vivo* (187); future research will allow for a better understanding of how rhinoviruses use the eye as a portal of entry to establish respiratory disease.

Isolated reports of ocular complications concurrent with upper respiratory infection have been documented following infection with other viruses of the family *Picornaviridae* (188, 189). In particular, ophthalmic infection with enterovirus 70 and coxsackievirus A24 has been associated with acute hemorrhagic conjunctivitis, and echovirus serotypes EV11 and EV19 were responsible for outbreaks of enterovirus uveitis in infants (189, 190). Interestingly, many of these viruses utilize α2-3-linked SA as a cellular receptor (37), warranting closer examination to determine if human ocular tissue represents a permissive cell type for these viruses.

CONCLUSIONS

There are numerous other viral respiratory pathogens for which documented ocular complications have been sparse or nonexistent. For example, the human parainfluenza viruses have been detected in conjunctival cells isolated from patients with keratitis and from nasal swabs collected from children presenting with conjunctivitis and upper respiratory tract illness (64, 191). While Newcastle disease (caused by avian paramyxovirus serotype 1) is a contagious and potentially lethal virus primarily in poultry (192), inadvertent human exposure (most frequently resulting from direct ocular exposure to infected material) has resulted in transient conjunctivitis (193, 194). BK virus, a member of the family *Polyomaviridae*, which typically presents with nonspecific upper respiratory tract infection, was associated with bilateral atypical retinitis in one immunocompromised patient (195). Collectively, it is evident that numerous respiratory viruses, of both human and zoonotic origins, are capable of using the eye as both a site of virus replication as well as a portal of entry to mount a productive respiratory infection.

While some virus subgroups exhibit a preferential tropism for ocular tissue and others only sporadically cause ocular symptoms, there are many commonalities between respiratory viruses in regard to virus dissemination from ocular tissue and host responses following viral infection of ocular cells. Adenoviruses and avian influenza viruses both exploit the presence of α2-3-linked sialic acids present on the ocular epithelium for receptor-dependent entry into this tissue; several other respiratory viruses with documented cases of ocular disease also display this binding preference (3). Similarities in the elicitation of host responses to influenza virus, RSV, and adenovirus infection of corneal and conjunctival epithelial cells, notably with regard to the induction of the NF-κB pathway, provide insight into potential shared mechanisms of inflammation following virus infection (55–57, 196). While the mammalian species used to model ocular infection differ somewhat between viruses, shared protocols for virus inoculation, tissue harvesting, and sample manipulation underscore the ability to use advances from research with other respiratory pathogens with ocular complications or with pathogens such as herpes simplex virus, for which abundant data using a murine model are available, as a resource when further building on existing and nascent *in vitro* and *in vivo* ocular models of virus infection (80, 197, 198).

Great strides have been made in our understanding of the ocular tropism of respiratory pathogens, but there is substantial work that still needs to take place for a fuller understanding of the properties which confer this tropism and how best to prevent and treat human ocular disease caused by these etiologic agents. Additional analysis of viral growth kinetics and host responses and analysis of progeny virions following the simultaneous *in vitro* infection of human respiratory and ocular cell types would further identify tissue-specific differences that contribute to tropism (55). The majority of antiviral agents available for viral conjunctivitis are used to treat herpesvirus and not adenovirus infection; the development of antiviral agents which target ocular disease caused by RNA viruses is urgently needed (63). While individuals with ocular disease following infection with a respiratory virus are prescribed antiviral agents specific for that pathogen (such as the use of oseltamivir following an outbreak of H7N7 influenza virus in The Netherlands in 2003, which manifested largely as conjunctivitis), the efficacy of existing antiviral treatments as they pertain specifically to treatment of ocular complications requires further study (10, 199). Future research evaluating the efficacy of existing vaccines and antivirals against respiratory viruses in the context of ocular exposure will better address these questions. Regardless of the complexities which contribute to the incidence of ocular disease, the studies described in this review support recommendations which advise for the benefit of wearing eye protection during potential exposure to respiratory pathogens, even when these viruses are not frequently considered to possess an ocular tropism (200–202). Concurrent infection with multiple viral pathogens is not uncommon in humans, and epidemiological studies which demonstrated that the occurrence of one virus in the community can influence the prevalence of another demonstrate the interrelatedness of these agents (64, 203); only by studying these pathogens in a larger context will we best understand the public health threat posed by these viruses and how best to prevent and treat complications.

APPENDIX

Relevant articles were identified by searches of PubMed (1957 to 2012) with the terms "ocular," "cornea," "conjunctivitis," or "eye," combined with the associated disease terms "respiratory virus," "influenza," "adenovirus," "respiratory syncytial virus," "RSV," "coronavirus," "SARS," "NL63," and "human metapneumovirus" and the laboratory modeling terms "ferret," "mouse," "rabbit," "cotton rat," "*in vitro*," and "*ex vivo*." Additional relevant articles were identified by cross-referencing Google Scholar, references from relevant articles, and personal files. English language articles were reviewed.

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