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Adenovirus infections and lung disease

Shizu Hayashi and James C Hogg

Adenovirus, particularly its E1A protein, has been investigated in the pathogenesis of chronic obstructive pulmonary disease (COPD). High levels of E1A DNA were found in the lungs of COPD patients, where its expression increased with disease severity. In lung epithelial cells, E1A increased intercellular adhesion molecule-1 and interleukin-8 expression, as well as nuclear factor- κ B activation, in response to inflammatory stimuli. In addition to regulating the mediators that promote emphysema, E1A upregulates transforming growth factor- β 1 expression in bronchiolar epithelial cells and transforms lung epithelial cells to express mesenchymal markers. These results support its additional role in the airway remodeling process reported in COPD.

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Introduction

From their first identification as a distinct viral agent in 1953 [1] to the present today, adenoviruses are recognized as etiologic agents of the respiratory and gastrointestinal tracts, eye, kidney and, more recently, of other organs as a consequence of solid organ and bone marrow transplantations with their associated immunosuppression. This review focuses on these viruses as respiratory pathogens, particularly group C adenoviruses as significant infective agents of the lower respiratory tract. Whereas most adenovirus infections are mild and self-limiting, considerable morbidity and even death can occur in the pediatric population, in military recruits and in immunocompromised individuals [2]. Adenovirus persistence or latency supports the possibility that, as a consequence of immunosuppression, the otherwise quiescent virus, either in the recipient host or in the transplanted donor organ, is reactivated to cause more serious disease. The paucity of treatment options to control these infections emphasizes

the urgent need for well-controlled clinical trials of the therapeutic modalities currently in development.

Besides disease caused by infective virus, latent infections in which the adenoviral E1A protein is expressed in the absence of replicating virus have been postulated to play a role in the pathogenesis of chronic obstructive pulmonary disease (COPD), for which cigarette smoking accounts for less than 20% of the risk of developing disease (reviewed in [3]). This review summarizes evidence supporting this hypothesis from lung tissue of COPD patients, from an animal model and from lung epithelial cells, in which the mechanisms by which E1A could enhance the inflammatory response in lungs of patients to promote emphysema have been studied [3]. More recent advances in our understanding of these mechanisms are presented, as well as results supporting the role of adenovirus E1A in the airway remodeling observed in COPD.

Adenovirolgy

Adenoviruses are non-enveloped icosahedral double-stranded DNA viruses that infect a wide range of vertebrates [2,4^{*}]. Human adenoviruses comprise 51 serotypes that are classified into six groups, A to F, according to sequence homology and oncogenicity when injected into rats. Each group has its own preferred site(s) of infection and mainly causes mild disease in immunocompetent individuals at these sites [2,4^{*},5] (Table 1). The most common human adenoviruses are those that belong to group C [6], which predominantly infect the upper respiratory tract. This group, along with groups B and E, which infect the lower respiratory tract, causes clinical symptoms ranging from mild pharyngitis to acute respiratory disease.

The icosahedral capsid of adenovirus is composed of hexon and penton proteins [2,4^{*},5]. The fiber protein that protrudes from the 12 vertices formed by the penton bases has a knob domain that serves as a ligand for receptors on the host cell. The knob domain of group A, C, D, E and F adenoviruses attaches to the coxsackie B virus and adenovirus receptor on the host cell surface, whereas that of group B viruses, except for serotypes 3 and 7, attaches to CD46 [7]. This binding facilitates further interactions between the penton base and members of the integrin family, predominantly α ν β $_{1,3,5}$, which are required for internalization of the virus. The details of adenovirus internalization, including fiber shedding, endocytosis, and release from endosomes with loss of the penton bases, are reviewed in [4^{*}] and [8]. The viral capsid is directed by microtubules to the nuclear pore,

Table 1**Classification of human adenovirus^a**

Group	Serotypes	Major site(s) of infection	Associated disease
A	12,18,31	Intestine	Gastroenteritis
B	3,7,11,14,16,21,34,35,50	Lung, urinary tract	Acute respiratory disease, pharyngitis, pneumonia, pharyngoconjunctival fever, acute hemorrhagic cystitis
C	1,2,5,6	Upper respiratory tract	Pharyngitis, pneumonia
D	8–10,13,15,17,19,20,22–30,32,33,36–39,42–49,51	Eye	Epidemic keratoconjunctivitis
E	4	Respiratory tract	Acute respiratory disease, conjunctivitis
F	40,41	Intestine	Gastroenteritis

where nuclear import of the hexons results in the release of the viral DNA into the nucleus for its transcription, replication and packaging. Once in the nucleus, E1A, the product of the first viral gene to be expressed, activates the expression of other viral genes required for viral replication and does so, not by binding directly to the promoters of these genes, but by interacting with cellular transcription factors and other regulatory proteins necessary for the transcription of the genes [8]. This capacity of E1A to bind host transcriptional regulators and thus regulate not only viral genes but also genes of the host cell [8] is relevant to its role in the pathogenesis of COPD (see below).

Both persistent adenovirus infections (with shedding of replication-competent virus) and latent infections have been reported, particularly in lymphocytes where viral DNA in the absence of infectious virus was detected (reviewed in [2]). It has not been tested whether genes of the E3 region, which are also expressed early in the viral life-cycle and assist in subverting the host immune response against the virus [5,8], affect this persistence, nor have other possible mechanisms been investigated.

Adenovirus and lung disease

Adenovirus infections occur frequently as documented by the presence of antibodies to one or more adenovirus serotypes in approximately 50% of infants and nearly 100% of adults [9–11]. In the face of these infections,

disease in immunocompetent individuals is uncommon and rarely fatal owing to potent innate and adaptive immune responses. However, in the susceptible minority, particularly the pediatric age group, military recruits and those immunosuppressed either for transplantation and cancer or by HIV infection, disease is more common (Table 2, Figure 1).

Pediatric population

In children younger than five years of age, who are more vulnerable as this is probably a primary infection, adenovirus causes up to 5% of acute respiratory disease. Serotypes most commonly found are 1, 2, 5 and 6 from group C and 3 from group B [6,11]. Adenovirus accounts for 10% of pneumonias in this population [2] and the serotypes isolated from the lungs include 1, 2, 3, 5, 7 [12] and 21 [13,14]. *In situ* hybridization showed that alveolar and bronchiolar epithelial cells are infected by adenovirus in pneumonias [15] (Figure 2). Other less common respiratory consequences of adenovirus infection reported in this age group include bronchiolitis [14,16,17], post-infectious bronchiolitis obliterans [18*] and, when combined with or preceded by measles infection, bronchiectasis [19,20].

Military recruits

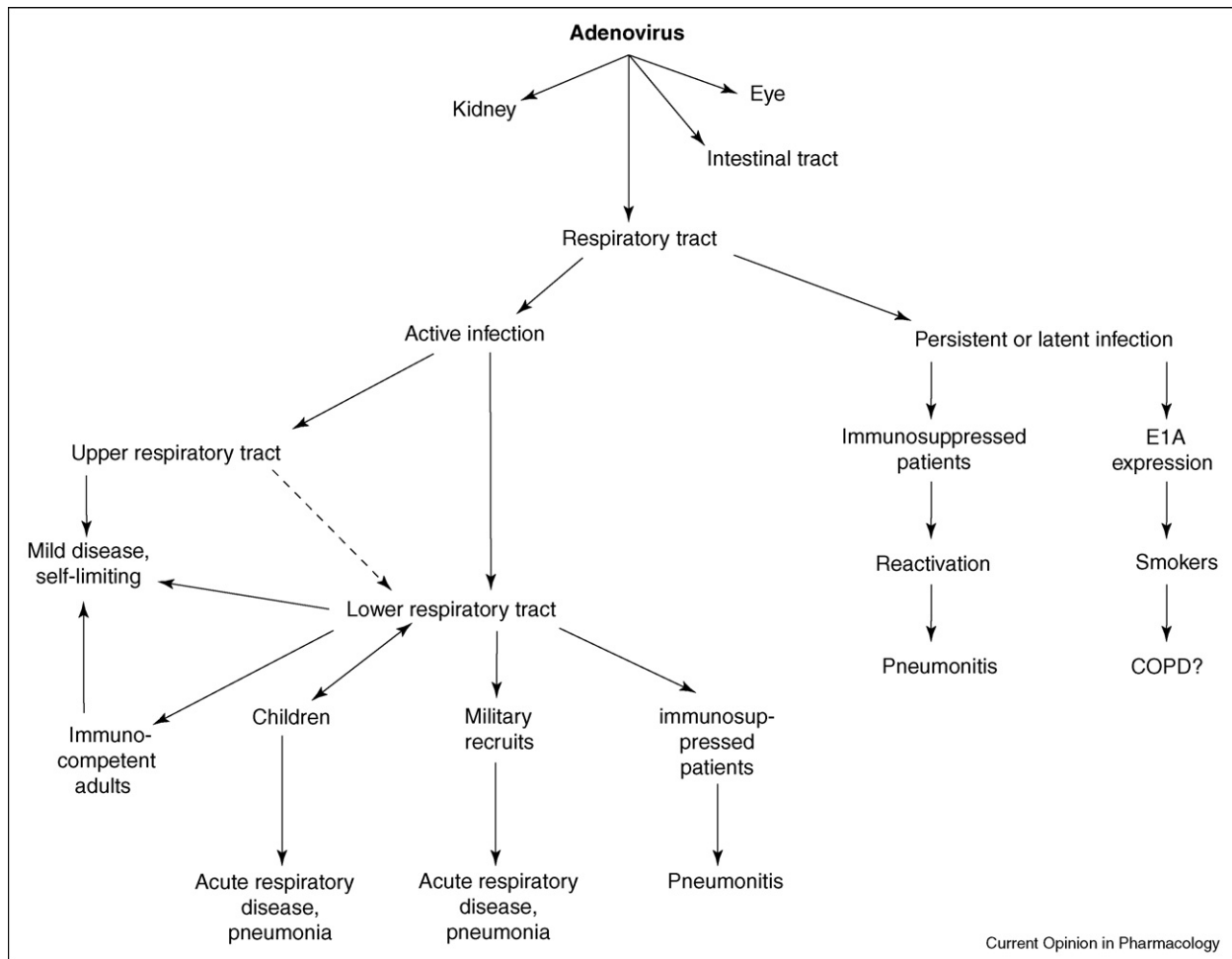
Adenovirus infections were reported in military recruits soon after the discovery of this virus [9,21]. Fatigue, stress and crowded living conditions contribute to the spread of

Table 2**Adenovirus serotypes and lung disease in susceptible populations.**

Respiratory disease patient group	Serotypes reported	References
Pediatric and childhood age		
Acute respiratory disease	1,2,3,5,6	[11]
Pneumonias	1,2,3,5,7,21	[12–14]
Bronchiolitis	Not determined	[14,16,17]
Post-infectious bronchiolitis obliterans	Not determined	[18*]
Military recruits		
Acute respiratory disease	3,4,7,21	[22–25]
Immunocompromised patients		
Pneumonitis ^a	1,2,5,6,31,34,35	[29,31**]

^a Predominantly in bone marrow transplant and cancer patients.

Figure 1



Respiratory consequences of adenovirus infections.

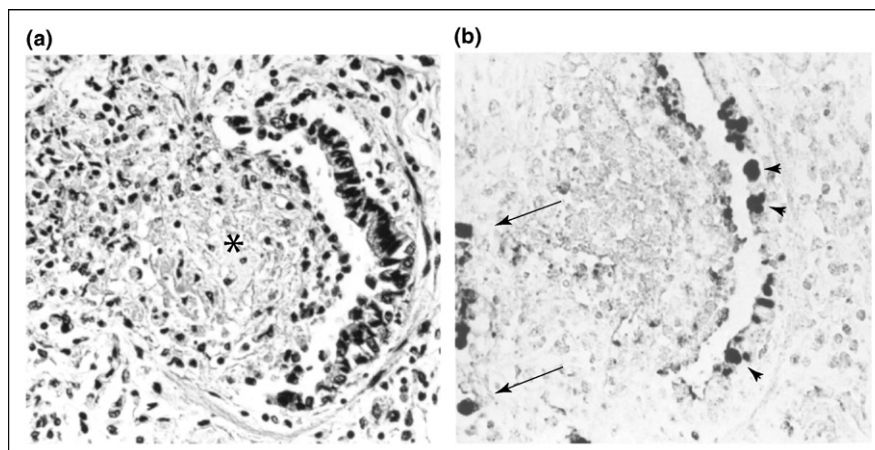
an epidemic form of infection; the serotypes most prominent are 4 and 7 and, less frequently, 3 and 21 [22–25]. Susceptibility to these serotypes of group B and E adenoviruses is consistent with the fact that immunity to group C adenovirus had already been acquired in early childhood. Effective vaccines against adenovirus 4 and 7 were developed [26] but discontinued after 1996; as a result, infections continue to be a problem in this population [27,28].

Immunocompromised patients

Adenovirus infections and the associated morbidity and mortality in immunocompromised patients are a growing concern, particularly with increases in the number of individuals undergoing solid organ and bone marrow transplantations, as well as in those with AIDS and malignancies (reviewed in [29,30,31]). In transplant patients, vulnerability to adenovirus infection is greatest in the pediatric population, and incidents of infection and severity of disease are both higher in allogeneic versus

autologous transplants. The adenovirus source can be a primary infection, reactivation of a persistent or latent infection in the recipient (see above), or possibly, in the case of transplant patients, transmission from the donor. Pneumonitis, which develops from infection mainly by group C adenoviruses (Table 2), has the worst prognosis for survival along with hepatitis and meningoencephalitis. In lung transplant recipients, adenovirus was associated both with respiratory failure, leading to death or graft loss, and with the diagnosis of necrotizing bronchocentric pneumonia or obliterative bronchiolitis. Although most patients eventually clear the virus, treatment for those with adenoviremia, a predictor of a fatal outcome, is limited to antiviral drugs. More recently, less severe outcomes of viremia in adult patients were reported (see Update). Cidofovir, an inhibitor of the viral DNA polymerase, and its lipid ester show some promise. Various modes of immunotherapy, including adenovirus-specific cytotoxic lymphocytes, are currently being investigated.

Figure 2



Histological preparations of adenovirus pneumonia in a pediatric patient. **(a)** Section stained with hematoxylin-eosin showing bronchial lumen partially filled with an organizing inflammatory exudate (*). **(b)** *In situ* hybridization with an adenovirus probe of a serial section of the lung in **(a)** showing virus-positive epithelial cells lining the bronchioles (arrowheads), as well as in the parenchyma (arrows). Original magnification: x250. Reproduced with permission from [15].

Adenovirus E1A and COPD

COPD pathophysiology and etiology

COPD is defined by the irreversible airflow limitation measured as the volume of air that can be forcibly expired from the lungs in one second and its ratio to the forced vital capacity [32]. The key determinants limiting airflow are an increase in the resistance of small conducting airways less than 2 mm in diameter [33–35] and emphysematous destruction of the lung elastic recoil force available to drive expiratory flow [36]. COPD is currently the fourth leading cause of death in the world (The Global Burden of Disease; URL: http://www.who.int/mip/2003/other_documents/en/globalburdenofdisease.pdf), and further increases in its prevalence and mortality are predicted [37]. The major risk factor is the inhalation of toxic particles and gases, primarily from tobacco smoking [32]. Respiratory infections in early childhood are also associated with reduced lung function and increased respiratory problems later in life [38], which could lead to COPD.

Why adenovirus as a pathogen in COPD?

The potential of childhood respiratory infections to be risk factors for COPD led to investigations of adenoviruses owing to their ability to commonly produce respiratory infections in early childhood. Unlike other common childhood respiratory viruses such as rhinovirus, respiratory syncytial virus, the parainfluenza viruses, influenza and coronavirus, which are all RNA viruses, adenovirus has a double-stranded DNA genome. This confers the potential for persistence in the nuclei of infected cells and even the possibility of integrating into the chromosomes of the host cell. This notion is supported by the persistent or latent infections reported above. Furthermore, group C

adenoviruses were chosen as a target for study because these serotypes (1, 2, 5 and 6) are largely ubiquitous in children [2,6]. Besides predominance of this group in upper respiratory tract infections (Table 1), its association with pneumonias in infants (Table 2) is evidence that it also infects the lower respiratory tract.

Adenovirus E1A in COPD

Studies showed that lungs of COPD patients who were asymptomatic for viral infections harboured more group C adenovirus E1A DNA than those of controls with a similar history of smoking [39]. In addition, they showed that E1A protein was expressed in alveolar and bronchiolar epithelial cells in these lungs [40] and that this E1A protein expression, as well as the expression of the inflammatory marker intercellular adhesion molecule (ICAM)-1 and the number of inflammatory cells, increased with disease severity in these patients [41]. A role for adenovirus infections in COPD was further supported by studies in guinea-pigs: after the initial acute infection with adenovirus 5 had subsided and viral replication ceased, E1A DNA and protein continued to be detected in alveolar and airway epithelial cells, and bronchiolitis persisted [42]. Short-term [43] and chronic exposure [44] to cigarette smoke at this time increased the number of inflammatory cells and caused emphysema-like changes, respectively, compared with uninfected animals.

How does E1A increase inflammation in COPD?

As discussed above, E1A has the capacity to regulate gene transcription of the host cell. To determine whether this is the basis of the relationship between E1A and increased lung inflammation in COPD, both A549 cells (a model of

alveolar epithelial cells) and primary bronchiolar epithelial cells expressing adenovirus 5 E1A were developed ([45] and [46], respectively). In both cell-types, the presence of E1A increased ICAM-1 [45,46] and interleukin (IL)-8 expression [46,47] in response to lipopolysaccharide (LPS) stimulation, but not that of other inflammatory mediators; these increases were accompanied by increased binding activity of the transcription factor nuclear factor- κ B (NF- κ B) [46,48], which binds to the promoters of the ICAM-1 and IL-8 genes. That E1A affects the promoters of these genes is supported by evidence of increased ICAM-1 promoter-driven reporter gene expression in the presence of E1A [46,49]. These results suggest that E1A regulates the expression of specific mediators in response to LPS through a common mechanism. Moreover, these mediators promote increases in the number of neutrophils in the lungs of COPD patients (reviewed in [46]), with IL-8 serving as a potent neutrophil chemoattractant, and ICAM-1 as a ligand for the adhesion receptor on neutrophils. Recent site-directed mutagenesis studies showed that, of the two NF- κ B binding sites in the ICAM-1 promoter, the one most proximal to the transcription start site was essential for increased expression when E1A was present (E Ogawa *et al.*, abstract in *Am J Respir Crit Care Med* 2003, 167:A401). As a result, chromatin immunoprecipitation assays were designed to investigate whether E1A interacts with the proteins of the transcription complex that assembles at this site to promote transcription of the ICAM-1 gene. In both A549 and bronchiolar epithelial cells stimulated with LPS, the presence of E1A increased the binding of NF- κ B, the coactivator p300 and RNA polymerase II to this promoter; E1A was also present at this site (K Morimoto *et al.*, abstract in American Thoracic Society International Conference, May 18-23, 2007). Expression of both the ICAM-1 and IL-8 genes was also increased by E1A in response to stimulation with environmental particulate matter < 10 μ m (PM₁₀) and, again, increased gene expression was associated with activation of NF- κ B [50,51]. Taken together, these results suggest that, in lung epithelial cells, adenovirus E1A regulates the expression of mediators relevant to the pathogenesis of COPD by interacting with transcriptional regulators at the promoters of these genes, and that regulation of this response to inflammatory stimuli (i.e. bacteria or environmental pollutants) could play a role in the emphysematous destruction of the lung in COPD.

In addition to modulating inflammatory mediator expression in lung epithelial cells, adenovirus E1A upregulates the expression of transforming growth factor- β 1 and connective tissue growth factor [52], two factors important in extracellular matrix deposition. These results suggest that E1A can also promote the process of peripheral airway remodeling that occurs in COPD [53]. Studies using guinea-pig cells demonstrated that E1A transforms peripheral lung epithelial cells into cells with a

more mesenchymal phenotype [54^{*}], such as myofibroblasts that are active in tissue repair, thereby further supporting a role for E1A in airway remodelling.

Conclusions

This review emphasizes the significance of adenovirus as a respiratory pathogen, even to the present day. Although the molecular mechanisms that maintain its persistence or latency have not been elucidated, this viral reservoir remains a major source of disease-causing agents in immunosuppressed individuals, for whom promising treatment options with antiviral drugs such as cidofovir and its lipid ester to limit the impact of newly established infections are being developed. Latent infections could also be the source of adenovirus E1A in lungs of COPD patients (Figure 1), although integration of viral DNA needs further investigation. Therapies for latent adenovirus infection in COPD have not yet been developed. Although exacerbations of COPD are treated successfully by glucocorticoids, this therapy does not prevent the continued chronic decline in lung function in this disease. Furthermore, results from a guinea-pig model showed that allergic lung inflammation is steroid resistant in the presence of a latent adenovirus infection [55,56]. Whether adenovirus confers a similar resistance to inflammation caused by bacterial infections has not been studied; however, unravelling how E1A augments the expression of inflammatory and growth-promoting mediators in lung cells could provide insights into new treatments for COPD.

Update

More recently, adenovirus was detected by PCR in plasma from 18 out of 80 (22.5%) adult lung transplant recipients, with a median time to detection of 134 days post-transplant and low mean viral loads of 180 copies/ml of plasma [57^{*}]. These patients were either asymptomatic or had self-limited febrile syndromes despite no change in immunosuppression or specific anti-viral therapy. The authors note that, in contrast to previous findings of adenoviral pneumonitis in lung transplant patients, the isolated episodes of low-level viremia reported here are self-limited and do not trigger acute rejection or a decline in pulmonary function.

Acknowledgements

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