Mechanisms of pathogenesis of emerging adenoviruses [version 1; referees: 2 approved]

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Abstract
Periodic outbreaks of human adenovirus infections can cause severe illness in people with no known predisposing conditions. The reasons for this increased viral pathogenicity are uncertain. Adenoviruses are constantly undergoing mutation during circulation in the human population, but related phenotypic changes of the viruses are rarely detected because of the infrequency of such outbreaks and the limited biological studies of the emergent strains. Mutations and genetic recombinations have been identified in these new strains. However, the linkage between these genetic changes and increased pathogenicity is poorly understood. It has been observed recently that differences in virus-induced immunopathogenesis can be associated with altered expression of non-mutant viral genes associated with changes in viral modulation of the host innate immune response. Initial small animal studies indicate that these changes in viral gene expression can be associated with enhanced immunopathogenesis in vivo. Available evidence suggests the hypothesis that there is a critical threshold of expression of certain viral genes that determines both the sustainability of viral transmission in the human population and the enhancement of immunopathogenesis. Studies of this possibility will require extension of the analysis of outbreak viral strains from a sequencing-based focus to biological studies of relationships between viral gene expression and pathogenic responses. Advances in this area will require increased coordination among public health organizations, diagnostic microbiology laboratories, and research laboratories to identify, catalog, and systematically study differences between prototype and emergent viral strains that explain the increased pathogenicity that can occur during clinical outbreaks.
Introduction

Human adenoviruses (HAdVs) are non-enveloped, double-stranded DNA viruses of the genus Mastadenovirus in the *Adenoviridae* family. There are seven different species of HAdV (HAdV-A to -G), with over 50 serotypes (numbered consecutively from 1) and 70 distinct genotypes. Different clinical manifestations of infection are, in part, due to the tissue tropism of each species (see Ghebremedhin’s review). Thus, HAdVs infect the upper or lower respiratory tracts (species B, C, and E), conjunctiva (species B and D), or gastrointestinal tract (species F and G). Species A–F circulate globally and can cause limited outbreaks of infection. HAdV outbreaks usually occur in closed populations (e.g., hospitals, long-term care facilities, and military installations). Most HAdV infections are diagnosed in children younger than 4 years old. Young children and immunosuppressed adults are more susceptible to HAdVs and are more likely to have more severe infections. HAdV outbreaks might also occur in healthy populations, but since most such infections are self-limited, they are rarely detected by public health surveillance. However, severe pneumonia can occasionally occur and be fatal in immunocompetent patients. The reasons for such severe illness in otherwise healthy patients are unknown.

The existence of over 70 distinct genotypes among the more than 50 serotypes of HAdV suggests ongoing changes in the viral genome as one mechanism of evolutionary diversity. HAdV serotypes are differentiated based on antibody neutralization assays. Genotypes are determined by either restriction endonuclease analysis (REA) or viral genome sequencing. Whereas REA is useful for rapid analysis, it is limited to finding changes in restriction digest patterns. Whole viral genome sequencing combined with bioinformatics provides more precise information on the nature of each new genotype that is discovered. In addition to random mutations, new adenoviral genotypes also result from homologous recombination. Studies by Lukashev et al. on clinical isolates of HAdV-C showed that recombination events are common among circulating adenoviruses. Recombination requires co-infection of the same cell with different viral types. These recombination events usually occur between members of the same species (e.g., HAdV-B with another HAdV-B strain). Interspecies HAdV recombination increases the rate of molecular evolution and results in novel HAdVs that could theoretically have increased viral fitness, altered cell tropism, and increased virulence. However, HAdV recombination usually goes unnoticed because of the self-limited nature of the infections. It is only when mutations or recombinations result in a more pathogenic HAdV genotype that causes outbreaks of more severe disease that the effects of these genetic changes are realized.

Increased pathogenesis associated with emergent adenovirus outbreaks

There are several examples of outbreaks of respiratory illness resulting in fatalities that have been observed with emerging strains of HAdV. Whereas many cases of severe, HAdV-induced respiratory illness have occurred in patients with underlying and in some cases immunocompromising conditions, there also have been outbreaks of infections among those with no apparent pre-existing risk factors. This review will focus on issues relating to the outbreak of viral strains and not an extensive review of possible variations in host defense against infection.

HAdV-3/7 (a recombinant strain) caused an outbreak of acute respiratory infection with fatal outcomes in otherwise healthy infants in Portugal in 2004. HAdV-7 has 27 different genotypes that have been associated with fatal disease in immunocompetent patients and tend to be more virulent than other serotypes. A new genotype of HAdV-14, HAdV-14p1, was identified first in US military populations and then in civilian populations, with outbreaks of respiratory illness of varying severity, including fatal infections. HAdV-14p1 is now the main HAdV-14 strain circulating worldwide. Between 2005 and 2013, there were cases of febrile respiratory illness and fatalities in Germany caused by a new genotype of HAdV-21, HAdV-21a. In 2006 in China, a novel HAdV genotype, HAdV-55, was isolated in outbreaks of severe pneumonia and acute respiratory distress syndrome (ARDS). Israel experienced an outbreak of HAdV-55 in 2016. HAdV-55 is an intertypic recombinant of HAdV-11 and HAdV-14, with the backbone of HAdV-14 and a partial hexon of HAdV-11. When compared with patients with subclinical infections, patients with severe HAdV-55 infections showed significantly higher levels of blood IL-17, CD4+ T lymphocytes and higher levels of serum IFN-γ, IFN-α2, IL-4, and IL-10. Why some of these emergent strains induce more intense immune responses and more severe immunopathogenesis in some patients than in others is unclear.

One theory about why these emergent strains cause outbreaks is that the mutations have altered the hexon, fiber, or penton (HAdV structural proteins) that are the targets for neutralizing antibodies, allowing the virus to escape pre-existing herd immunity. Reduced immunogenicity resulting from changes in viral structural proteins and associated with immune escape has been proposed as an explanation for outbreaks involving emerging strains of group D that cause epidemic keratoconjunctivitis (EKC). Some of these emerging EKC strains were observed to induce increased cytokine and chemokine expression and neutrophil infiltrates in a mouse model of conjunctivitis. In other studies, it was proposed that some emerging EKC strains might be more pro-inflammatory because of the lack of expression of an immunomodulatory RGD domain (integrin ligand) in the viral structural penton base. Pursuit of such relationships between viral structural protein sequence and function will be required to more completely define their role in increased viral immunopathogenesis.

Linkage between human adenovirus gene expression and the host immune response

Infection with HAdV turns on a robust innate immune response, resulting from a wide array of viral effects on cellular pathways. Cellular entry of HAdV triggers strong proinflammatory responses. The presence of the viral genome induces the cellular inflammasome through the activation of Toll-like receptor signal transduction pathways, resulting in the activation of interferon responses and other proinflammatory cellular defenses. Viral genome replication induces cell death responses that could kill the host cell before completion of maximal HAdV replication. However, HAdVs have evolved defenses mediated by virally encoded proteins that control the cell death response and repress many of the proinflammatory pathways.
responses and antiviral effects of host innate immune defender cells that would otherwise limit viral spread, immunopathogenesis, and infection transmission. The functions of such anti-cell-death and immunomodulating HAdV gene products have been best characterized in the HAdV-C species viruses, HAdV-2 and HAdV-5 (see below). Bioinformatic data suggest that the functions of these gene products are similar to those in other HAdVs but not all of these genes are found in every HAdV species.

The adenoviral gene E1A is expressed early after infection, helps drive the cell cycle to increase the efficiency of viral replication, and is necessary for the efficient expression of other viral genes\textsuperscript{35,36}. E1A also represses both NF-κB-dependent transcription (the major mediator of proinflammatory gene expression) and IFN-stimulated genes, thereby suppressing early inflammatory responses induced by viral entry\textsuperscript{37-40}.

Products of the EIB gene, 19K and 55K, work together to block E1A-induced cell death (apoptosis), and 55K also blocks IFN-stimulated gene expression and other antiviral cellular innate immune reactions\textsuperscript{41-46}. It would be predicted from these reported immunorepressive effects of E1B 55K that its expression during viral infection would reduce lung inflammation and related cytokine production and that deletion of the EIB 55K gene would result in a virus that would cause greater inflammation than wild-type (E1B 55K\textsuperscript{+}) Ad5 during infection. However, the opposite has been reported. Lung infection of either cotton rats (permissive for Ad replication) or mice (nonpermissive) with an EIB 55K-deleted Ad5 has been reported to induce less inflammation than infection with wild-type (E1B 55K\textsuperscript{-}) Ad5 and to induce lower levels of lung TNFα and IL-6\textsuperscript{47,48}. Our studies revealed that human cells dying from infection with wild-type Ad5 or an EIB 55K-deleted Ad5 mutant virus (H5d338) were highly and equally repressive for macrophage activation responses\textsuperscript{49}. These apparent inconsistencies in the immunoregulatory effects of E1B 55K protein will require further study.

The E3 transcription unit encodes several viral proteins that can alter the innate and adaptive immune responses to HAdV infection\textsuperscript{51}. E3-19K glycoprotein (E3-19Kgp) represses cell surface expression of MHC class I molecules and ligands for the NK cell activating receptor, NKG2D, protecting infected cells from targeting by host killer cells\textsuperscript{52,53}. There have been varying results of studies of E3-19Kgp expression in determining the host inflammatory response to viral infection. Initial reports indicated that mutant HAdVs lacking the expression of E3-19Kgp induced increased lung inflammatory responses in infection-permissive cotton rats\textsuperscript{54}. Those results suggested that the E3-19Kgp repression of cell surface MHC antigens might reduce inflammation and the generation of virus-specific cytotoxic T lymphocyte (CTL) responses. However, subsequent studies in mice did not find that E3-19Kgp expression during viral infection reduced either virus-specific CTL generation or lung inflammation but suggested that E3B gene products 14.7K, 10.4K, and 14.5K are involved in the repression of the amplitude of the host mononuclear cell inflammatory response in the lung\textsuperscript{55}. The E3 proteins 14.7K, 10.4K, 14.5K, and 6.7K work together to block TNF-induced apoptosis and also play a role in repressing NF-κB-dependent inflammatory responses\textsuperscript{55-59}. Whereas the E1A and EIB genes are conserved among HAdV species, the E3 genes vary markedly. In some strains, one or more of the E3 genes are absent, and in others there are novel E3 genes\textsuperscript{60}.

Bioinformatic methods can predict mutations within the more conserved viral genes but might not reveal altered expression of these gene products or the consequences of varying levels of viral gene expression.

**Loss-of-function human adenovirus phenotype associated with increased immunopathogenesis**

A novel function of the HAdV-2/5 E1B 19K protein has been described that is associated with the repression of macrophage-mediated inflammatory responses to HAdV-infected cells\textsuperscript{61}. When cells dying as a result of HAdV-5 infection are co-cultured with activated macrophages, the virally infected cells repress pro-inflammatory cytokine production by the macrophages. Deletion of the E1B 19K gene from HAdV-5 results in infected cells that fail to repress and, in the case of some cytokines, enhance the pro-inflammatory responses of activated macrophages. These studies show that, even after HAdV-induced cell death, the virus can still have an impact on the host’s innate immune response. This finding suggested that emergent strains of HAdV that induce increased proinflammatory responses and immune-mediated disease manifestations such as ARDS might have a defect in the expression or function of the viral E1B 19K protein.

HAdV-14p1 has induced global outbreaks for the last 10 years. Sequencing of HAdV-14p1 showed only a 0.3% difference from the prototype HAdV-14 deWit strain, with limited mutations in coding regions\textsuperscript{62}. In nearly all of the HAdV-14p1 outbreaks, there were cases of severe respiratory illness and ARDS that occasionally resulted in death. ARDS causes severe impairment of gas exchange and lung mechanics that are induced by acute lung injury. The inciting event can be a physical injury but in many cases involves either a bacterial or a viral infection. Alveolar macrophages play a key role in both initiating and resolving inflammatory responses associated with ARDS by modulating the expression of IL-1β, IL-6, IL-8, TNF-α, and other pro-inflammatory cytokines\textsuperscript{63}.

Studies of the \textit{in vitro} effects of HAdV14-p1 on cultured human cells showed no increase in either cell infectivity or viral replication as compared with the prototype strain\textsuperscript{64}. Lam \textit{et al.} showed that infection of primary human bronchial epithelial cells with HAdV14-p1 resulted in increased expression of IP-10 and I-TAC, two chemokines implicated in ARDS, and speculated that these are potential virulence factors induced by HAdV14-p1 infection\textsuperscript{65}. We observed that HAdV-14p1 infection of human cells results in a marked reduction in E1B 20K expression (the E1B 19K homolog of HAdV-14p1) at the level of transcription, resulting in the formation of larger viral plaques and increased spread of cell pathology in tissue culture compared with the prototype deWit strain of HAdV-14\textsuperscript{66}. Furthermore, HAdV-14p1-infected human cells either failed to repress or induced increased proinflammatory cytokine expression from human alveolar macrophages, whereas cells dying from infection with the prototype HAdV-14 strain repressed macrophage production of the same cytokines. In a
Syrian hamster model of adenoviral pneumonia, HAdV-14p1 induced intense, multifocal inflammatory infiltrates compared with minimal inflammatory responses to the prototype strain\(^6\) (Figure 1). The sequence of the \(EIB\) 20K gene of HAdV-14p1 was essentially unchanged when compared with the prototype strain (one silent point mutation)\(^6\) and would not be predicted to alter \(EIB\) gene transcription. We postulated, therefore, that one mechanism by which outbreaks of highly virulent HAdV can induce increased lung immunopathology involves loss-of-function phenotypes that result from low-level expression of a normal \(EIB\) 20K gene product.

The critical threshold hypothesis of HAdV outbreak strain immunopathogenesis

As a result of this observation, we speculate that there is a “critical threshold” level of expression of \(EIB\) 19/20K that sustains normal Ad14p1 replication and transmission in the human population but fails to convey immunorepressive activity to virally infected cells, resulting in increased proinflammatory cytokine responses and lung injury. This phenotype contrasts with (1) the mild pathogenesis and illness severity associated with the “prototype level” of viral gene expression associated with HAdV-14 (deWit) infection and (2) the reduced infectivity, transmission, and pathogenesis that would occur if the \(EIB\) 19/20K gene were deleted or rendered nonfunctional by mutation (the equivalent of an \(EIB\) 19/20K gene knockout) (Figure 2).

These observations raise the possibility that there might be other evolutionary changes in HAdV gene expression that could fit with the “critical threshold” hypothesis of adenoviral pathogenesis (Figure 2). Thus, there might be other emergent HAdV strains that induce increased host inflammatory responses (or increases in other parameters of viral pathogenesis) as a result of a reduced expression of otherwise normal viral genes below a critical threshold. In such cases, conventional sequencing studies might not reveal the genetic mechanism(s) of increased viral pathogenesis, since the viral gene that mediates the pathogenic phenotype (the “effector gene”) might be unchanged in sequence but altered in expression because of mutations and functional differences in another viral regulatory gene (the “activator gene”) or sequences (e.g., enhancer element). It is well established that HAdV encodes key gene products, especially the \(EIA\) gene family of proteins, that have transcriptional control effects on other viral genes, such as \(EIB\) 19/20K\(^3\). Therefore, it is theoretically

Figure 1. Comparative lung pathology induced by infection with prototype strain Ad14 (wild type, wt) vs. the outbreak strain, Ad14p1. Lungs were harvested from infected hamsters at 7 days after intratracheal viral inoculation (5 × 10\(^9\) plaque-forming units per animal). A&B, hematoxylin and eosin (H&E)-stained lung section macroscopic comparison, showing minimal peribronchial changes in wt Ad14-infected lung (A) vs. marked peribronchial infiltrates in Ad14p1-infected lung (B). C&D, H&E comparisons at 10X magnification. Green, yellow, and red arrows indicate perivascular, alveolar, and peribronchial inflammation, respectively, in wt Ad14-infected lung (C) vs. Ad14p1-infected lung (D). Adapted with permission from American Society of Microbiology. Copyright © American Society for Microbiology, [Journal of Virology, volume 90(1), 2016, pages 497-505 and doi: 10.1128/JVI.01790-15].
possible that evolutionary changes in the interactions between such viral activator genes or enhancer elements and their targeted viral effector genes could explain the increased pathogenesis of some outbreak strains of HAdV.

**Future studies of the mechanisms of enhanced pathogenesis of outbreak strains of HAdV**

Public health surveillance is needed to continue to identify new outbreak strains of HAdV that can cause unusually severe illness. These epidemiological and clinical studies must be coupled with new research approaches in order to understand both the reasons for increased transmission and the mechanisms of increased pathogenicity and virulence of outbreak strains. Sequencing and bioinformatics studies can predict changes in the viral genes and encoded structural proteins – hexon, penton, and fiber – that might result in a change in the sensitivity of the emerging virus to neutralizing antibodies that pre-existed in the population. But formal studies of cross-neutralization of outbreak strains compared with the previously circulating prototype strains, using banks of human sera or virus-induced antisera from animals, would be required to determine whether mutation-related changes in structural protein epitopes could explain the increased transmission of these emerging HAdVs.

Studies will also be needed to more stringently compare the viral “fitness” (i.e. the in-host replication capacity) of the emergent HAdV to their respective prototype strains. It can be assumed that the emergent strains would not succeed in causing outbreaks of infection if they were not at least as fit as the parental strains. However, the question of whether changes in the basics of viral infection, replication, and promulgation have provided any advantage to the outbreak strains that might explain their emergence as a clinically relevant entity would require study of the steps in viral replication, including interactions between viruses and cell surface receptors, viral replication rates, and viral spread from cell to cell.

With the discovery of the immunomodulatory activity of HAdV-infected cells on macrophages, it will be important to continue to develop new in vitro model systems to answer questions about how virally infected cells alter the functional activities of other components of the innate and adaptive immune responses to infection. For example, do outbreak HAdV strains that can cause more severe clinical illness induce different virus-infection-related changes in cytokine and chemokine production from other immune cells, such as dendritic cells, T cells, B cells, and NK cells? Do the outbreak strains and the cells they infect alter other immune cell functions such as cellular proliferation, chemotaxis, cytotoxic activity, and antibody production? Answers from these and other in vitro studies could provide insights into the possible mechanisms of both the increased success of outbreak strains in avoiding immune surveillance and the increased immunopathogenesis and related organ-specific disease manifestations of infection.

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**Figure 2. “Critical threshold” viral gene expression model of emergent adenoviral immunopathogenesis.** When expression of the adenoviral “effector” gene is normal (left gray bar, Prototype human adenovirus [HAdV]), viral replication and infectivity (green line) are at the rates associated with prototype virus infection, and pathogenesis and illness severity (red line) are mild. Conversely, when viral effector gene expression falls below the critical threshold needed for normal viral replication and infectivity, as would be observed with a gene knockout (KO) virus (right gray bar, Ad Gene KO), there would be inadequate virus generated for infection transmission and little (or no) pathogenesis and no clinical illness. With more virulent, emergent adenoviral strains, expression of the adenoviral effector gene would fall below the normal expression level observed with the prototype strain but would stay above the critical threshold expression level needed for viral replication, infectivity, and infection transmission. Because of the loss-of-function phenotype of the emergent virus that would result from reduced expression of the effector gene, there would be reduced infection-related immunomodulation and, consequently, increased virus-induced immunopathogenesis and more severe clinical illness.
Understanding the translational relevance of in silico and in vitro studies of comparative changes in parameters of infection and immune response of emergent vs. prototype HAdV strains will require advances in animal model development. Currently, Syrian hamsters and cotton rats are the only virus-replication-permissive small animals available for in vivo studies of HAdV infection and pathogenesis. Cotton rats are expensive and difficult to manipulate and maintain in experimental settings. Syrian hamsters are less expensive and easier to use for a variety of studies of viral infection and related pathology. There have been limited hamster-specific reagents available to identify and characterize immune cell types, cytokines, and chemokines at sites of infection and systemically; however, more such reagents are becoming available. Furthermore, the recent description of the use of the CRISPR/Cas-9 system to make a STAT-2 knockout Syrian hamster provides increased options for the use of this animal model for detailed genetic and immunological studies. It remains to be determined whether HAdV infection of Syrian hamsters will recapitulate the full spectrum of disease manifestations observed in humans and how such animal model studies will correlate with the results of in vitro studies using primary human cells.

Not all humans infected during outbreaks of infection with emergent strains of HAdV develop severe illness. Studies of variations in human immune and non-immune responses to outbreak Ad strain infection might be revealing but are limited by the small numbers of people involved and the short durations of these outbreaks. Furthermore, there has been no clear correlation between disease severity and genetic or other predisposing factors of those who have developed severe manifestations of infection. Since viral immunopathogenesis appears to be one determinant of disease severity, studies of differences in the host immune response to infection might provide guidance for future studies of key differences between infections with previously circulating prototype strains and emergent strains of virus at the interface with the host immune response. Progress in developing this understanding will be challenged by the episodic nature of new outbreaks, the relatively small numbers of patients involved in each outbreak, and the limited coordination of such studies at the national and international level.

Coordination between epidemiological studies and laboratory studies of HAdV replication and pathogenesis will require a concerted effort to isolate, identify, genetically characterize, store, and distribute new outbreak strains. The trend in clinical microbiology laboratories is toward the molecular diagnosis of viral respiratory pathogens and away from viral isolation in cell culture. Therefore, emerging diagnostic technology is more likely to result in decreased, not increased, availability of viral isolates for banking, characterizing, and distributing to research laboratories. Since outbreaks of HAdV are usually limited, are not major public health hazards, and are often recognized in hindsight, it is likely that there will continue to be limited resources available to support the public health and laboratory systems needed for advances in HAdV research. These challenges will have to be addressed to make progress in understanding the epidemiology and biology of emerging HAdV infections.

Competing interests
The authors declare that they have no competing personal or financial interests.

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The referees who approved this article are:

1  Hans-Gerhard Burgert, Warwick School of Life Sciences, University of Warwick, Coventry, UK
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2  David Ornelles, Department of Microbiology & Immunology, Wake Forest School of Medicine, Winston-Salem, NC, USA
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