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Murine Adenoviruses: Tools for studying adenovirus pathogenesis in a natural host

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Abstract

Small laboratory animals are powerful models for investigating *in vivo* viral pathogenesis of a number of viruses. For adenoviruses (AdVs), however, species-specificity poses limitations to studying human AdVs (HAdVs) in mice and other small laboratory animals. Thus, this review covers work on

naturally occurring mouse AdVs, primarily mouse adenovirus type 1 (MAdV-1), a member of the species *Murine Mastadenovirus A*. Molecular genetics, virus life cycle, cell and tissue tropism, interactions with the host immune response, persistence, and host genetics of susceptibility are described. A briefer discussion of MAdV-2 (member of species *Murine Mastadenovirus B)* and MAdV-3 (member of species *Murine Mastadenovirus C*) is included. We report the use of MAdVs in the development of vectors and vaccines.

Keywords

Mouse adenovirus, viral pathogenesis, PKR, Ly6, alpha-defensins, host susceptibility to viruses, immunoproteasome, adenovirus vaccines, adenovirus vectors

Abbreviations

AdV, adenovirus
CAR, coxsackie-adenovirus receptor
Chr, Chromosome
CNS, central nervous system
CR, conserved region
Cul, Cullin
dpi, days post infection
E, early
EnAd, enadenotucirev
GlcNAc, N-acetylgucosamine
IFN, interferon
INR, initiator
L, late
MAdV, mouse adenovirus
MHC, major histocompatibility complex
MLP, major late promoter
MMP, matrix metalloproteinase
NK, natural killer
PGE_2, prostaglandin E_2
QTL, quantitative trait locus

RGD, Arg-Gly-Asp

VA, virus-associated

Introduction

Study of animal adenoviruses is of importance both because of the fundamental knowledge gained from comparative biology with human adenoviruses and because of the ability to study the pathogenesis of an adenovirus in its natural host using experimental infections, which is not possible for human adenoviruses. Moreover, adenovirus species-specificity limits the use of small animal models for study of human adenovirus pathogenesis. The ease and relative low cost of studying mice in the laboratory is augmented by the wealth of genetically distinct inbred strains of *Mus musculus* and the ability to make transgenic mice to test the functional importance of mouse genes for virus infection. These are coupled with a rich supply of immunological reagents for studying the mouse host response.

Mouse adenovirus MAdV-1 (Ad-FL) [1] was among the first non-primate adenoviruses identified in the 1950s and 1960s, along with canine hepatitis virus, CAdV-1 [2]; fowl AdV-1 (CELO)[3] and bovine AdV [4]. MAdV-1 has a tropism for endothelial cells and cells of the monocyte/macrophage lineage, and it also infects astrocytes [5-7]. MAdV-1 infects tissues throughout the mouse, and the highest levels of virus are found in the brain, spinal cord, and spleen after intraperitoneal infection [5, 6, 8]. MAdV-1 causes encephalitis in susceptible mice [6, 8, 9], myocarditis [10-12] and respiratory infection [13, 14]. A second mouse adenovirus, MAdV-2 (K87) was isolated from faeces of laboratory mice in Japan in 1966 [15]. Both in cultured cells and in mice, MAdV-2 has a tropism for cells of the intestinal tract, but it does not cause apparent disease in mice [15-17]. MAdV-1 and -2 were isolated from laboratory mice, whereas a third type of mouse adenovirus, MAdV-3, was isolated from a liver from a striped field mouse, *Apodemus agrarius* [18]. MAdV-3 has a primary tropism for cardiac tissue, and it is present at high levels in myocardium, not in the brain, and at lower levels in most other organs [18]. MAdV-3 is genetically more similar to MAdV-1 than to MAdV-2.

The MAdV types discovered to date seem to have low significance as natural pathogens, and only a limited number of prevalence studies in the wild [19-21] and in commercial or research colonies [22-26] have been performed. These studies indicate a moderate serologic prevalence of MAdV-2 with considerable site-to-site variability. More recently, virome profiling studies have added more insights and provided evidence for new rodent adenoviruses [27-29]. The “murine” adenoviruses that have been characterized to date do not infect infant rats [30], and thus this review covers only mouse adenoviruses.

MAdVs have similarities and differences compared to human adenoviruses (HAdVs) that will be discussed below. We include comparisons of molecular genetics and gene expression, cell and tissue tropism, and viral persistence. The MAdV-mouse host system enables studies of viral pathogenesis that have no direct comparison to HAdV studies. We also discuss the use of MAdVs for vaccines and gene delivery vectors. Readers are also directed to previous reviews of mouse adenoviruses [31, 32] for additional historical perspectives and further details.

Mouse adenovirus type 1

Isolation, physical, and molecular genetic properties

MAdV-1 was isolated by Hartley and Rowe when they were establishing Friend mouse leukemia virus in culture, and they subsequently isolated it from Swiss mice in a mouse colony, designating it "M.Ad. virus strain FL" [1]. The virus has physical and serologic properties like HAdVs [1, 31], and infected mice transmit the virus to uninoculated cage contacts, but there is no apparent transmission through the air or via bedding from cages of infected mice [1, 33]. MAdV-1 has subsequently been studied in cell culture and mice. One isolate of MAdV-1 is in the American Type Culture Collection (Cat. no. VR550), deposited by Steven Larsen; we and others from 1981 onward have used an isolate obtained directly from Dr. Larsen, referred to as "standard." These two isolates have minor molecular and pathogenetic differences [34], and it is not known which strain (if either) was used prior to 1981.

MAdV-1 has a 30,944 bp double-stranded genome with 93 nt inverted terminal repeats [34-36]. The complete sequence is available as NC_000942.1 [37]. Another entry with in silico-derived annotations of the same sequence is AC_000012.1 [38]; it has some predicted genes not in agreement with published experimental evidence (e.g., in silico E1A annotation does not match transcription mapping and cDNA sequencing data) [31].

In broad terms, the genome structure of MAdV-1 is similar to that of HAdV-5. It encodes genes with sequence and functional similarity to HAdV early (E) regions 1 - 4, a major late promoter with a tripartite leader, and late (L) genes encoding the major virion proteins and proteins involved in morphogenesis [reviewed in 31]. The gene arrangement is like that of HAdVs. A terminal protein is associated with the 5' end of each end of the genome [36]. In fine details, there are some differences between HAdVs and MAdV-1 in gene expression and function. For example, MAdV-1 does not encode virus-associated RNA (VA RNA) [37], which in HAdV infections counteracts the host protein kinase R (PKR) antiviral response [39].

Instead of two major isoforms of the E1A protein found in HAdV-5, MAdV-1 only has one 200 aa protein, corresponding to the larger (289 aa, "13S") HAdV-5 protein [40]. Although its overall sequence similarity to HAdV E1A proteins is low, it has about 40% similarity to conserved regions 1 (CR1), CR2, and CR3. MAdV-1 E1A has functional similarity to HAdV E1A: it interacts with cellular proteins pRb and p107 via its CR2 domain and is involved in the regulation of cell proliferation of quiescent cells [41]. MAdV-1 E1A, like HAdV E1A, interacts with a component of the Mediator transcriptional complex, Sur2, now known as Med23, through the E1A CR3 domain [42]. This finding enabled the demonstration that Med23 is required for efficient replication of adenoviruses, which was unable to be tested directly using HAdVs.

Transcription mapping has not been done for MAdV-1 E2, but the predicted proteins have good sequence similarity with the three HAdV E2 proteins, which are involved in viral DNA synthesis. The DNA polymerase, DNA binding protein, and pTP, which is involved in protein priming of DNA synthesis, have 33-57% sequence similarity to HAdV proteins [37, 43].

MAdV-1 E3 is distinct from the E3 regions of HAdVs. There are three mRNAs encoded that share 5' and 3' termini but differ in splicing of the third exon, such that the three predicted proteins share amino terminal sequences but have different carboxyl terminal domains [44]. Only one of the MAdV-1 E3 proteins is detected in wild-type virus-infected cells, the E3 gp11K protein [45]. As is true of the HAdVs, the E3 region of MAdV-1 is involved in viral pathogenesis [45, 46]. MAdV-1 E3 functions are not directly comparable to those of HAdVs, however. For example, one of the first viral immune evasion strategies identified for any virus is downregulation of class I major histocompatibility complex (MHC) antigens on the surface of infected cells by HAdV-2 [47]. This function of HAdV E3 gp19K is not mimicked by MAdV-1 infection [48]. The MAdV-1 E3 proteins do not have sequence similarity to other known proteins.

Unlike the E4 mRNAs of HAdVs, which are 5' and 3' coterminal, the MAdV-1 E4 mRNAs have different 5' ends but share 3' ends [49]. Predicted proteins have sequence similarity to HAdV-2 E4orf6 (34K protein) (MAdV-1 protein originally identified as orf a/b), E4orf3 protein (MAdV-1 orf a/c), E4orf2 and E4orf6/7 (MAdV-1 orf d) [34, 49]. Little has been reported about function of the MAdV-1 E4 proteins. However, when E4orf6 is introduced into human cells by transfection, it coimmunoprecipitates with Cullin 2 (Cul2), Elongin C, and MAdV-1 E1B 55K protein [50]. Importantly, mouse p53 is degraded when it and MAdV-1 E4orf6 and E1B 55K protein are coexpressed, indicating that E4orf6 (together with E1B 55K) functions as a ubiquitin ligase.

The major late promoter (MLP) of MAdV-1 has features like the HAdV-1 MLP, including a TATA box and an inverted CAAT box, but it lacks a sequence that binds the transcription factor USF and it lacks the initiator (INR) sequence [51]. At late times, the MLP is functional in MAdV-1-infected cells, as demonstrated by RNAse protection assays of infected cell RNAs. MAdV-1 late mRNAs have a typical tripartite leader structure (C. Coombes, J. Boeke, L. Gralinski, and K. Spindler, unpublished).

Receptor studies indicate that the mouse coxsackie-adenovirus receptor (CAR) homolog of the human CAR used by many HAdVs as the attachment receptor is not used by MAdV-1 [52]. Transfection of mouse CAR into Chinese hamster ovary cells does not increase attachment of virus relative to untransfected cells, and purified HAdV-5 fiber knob does not compete with MAdV-1 binding. MAdV-1 penton base protein does not have an Arg-Gly-Asp (RGD) sequence that in HAdVs is important for interaction with entry receptors. However, the MAdV-1 fiber knob has an RGD motif in a sequence of the knob that represents an insertion relative to HAdV-1 fiber sequences [53]. This RGD sequence plays a role in MAdV-1 infection of cultured fibroblasts. Competition studies indicate that the fiber knob is the viral attachment protein. Cell surface heparan sulfate is important for infection, and α_v integrin acts as a primary receptor for MAdV-1. MAdV-1 associates with factor X and factor IX, but this does not result in increased cellular attachment, unlike the case for HAdV [54].

MAdV-1 Pathogenesis – Tropism, Adaptive Immune Responses

In contrast to HAdVs, which have an epithelial tropism, MAdV-1 primarily infects endothelial cells and monocytes/macrophages, and astrocytes can also be infected [5-8, 55, 56]. The virus causes a pantropic infection; high levels of virus found in the central nervous system (CNS) lead to increased permeability of the blood-brain barrier, accompanied by altered tight junction-protein expression and encephalitis [5, 6, 8, 56-58]. MAdV-1 CNS infection is characterized by viral brain loads that correlate with disease severity and induction of matrix metalloproteinase (MMP) activity [7, 59]. Enzyme activity of MMP2 and MMP9, which are induced in brains during microbial infection or neurological disease, is increased in mice and cultured cells upon MAdV-1 infection. This is not accompanied by increases in MMP mRNA levels, indicating that the MMP activation is a posttranscriptional event. MAdV-1 does infect epithelial cells and infects the respiratory tract when inoculated intranasally, and neonatal mice are more susceptible than adults to respiratory infection [13, 14]. MAdV-1 also causes myocarditis that is accompanied by myocyte and endothelial necrosis when inoculated intraperitoneally or intranasally [10-12]. Many mouse primary cell types, cell strains, and established cell lines can support MAdV-1 replication in vitro, including fibroblasts (3T6, 3T12 and L929) [35, 60], endothelial cells (MBMEC) [57],

pre-adipocyte cells (3T3-L1) [61], epithelial cells (LA-4, MLE-12 and MLE-15; J.B. Weinberg, unpublished), cardiac myocytes [12] macrophages/monocytes [55], and tumor cells such as lung adenoma (LA-4), renal adenocarcinoma (RAG) [48] and rectal carcinoma (CMT-93) cells [62].

Mice infected with MAdV-1 develop adaptive immune responses, both cell-mediated and humoral. These responses are important for host survival, because RAG-$1^{-/-}$ mice and SCID mice (deficient in T cells and B cells) are more susceptible to infection than wild-type mice [56, 63]. Virus-specific cytotoxic T cells can be detected 4 days post infection (dpi), peak at 10 dpi, and then decrease in numbers [64-67]. Studies with immunodeficient mice have shown that T cells are required for long-term survival of infection and contribute to immunopathology during the acute phase of infection [68]. CD8 T cells, but not CD4 T cells, are required for efficient clearance of MAdV-1 from the lungs and for virus-induced inflammation and weight loss [69]. These effects of CD8 T cells are not mediated exclusively by IFN-γ, perforin or Fas/FasL [69, 70]. MAdV-1-induced humoral responses have been studied in outbred and inbred mice. Sublethal infection of outbred mice leads to high neutralizing antibody titers two weeks after infection that increase for a year before declining [71]. Infection of inbred mice leads to B cell proliferation in the spleen 10 days post infection, stimulating predominantly IgG2a antibody [72-74]. Using B cell-deficient mice, Moore et al. showed that B cells help prevent disseminated MAdV-1 infection, and they produce T cell-independent antiviral IgM [63]. In studies using a model in which mice are made immunodeficient by cyclophosphamide, humoral immunity is important for protection from MAdV-1 disseminated infection, and survival correlates with presence of MAdV-1-specific antibodies [75].

MAdV-1 Pathogenesis – Innate Immune Responses

The innate immune response to MAdV-1 infection is dependent on immune cells and cytokines. Macrophages are infected by the virus [5, 55]. Peritoneal and splenic macrophages from infected mice express viral early and late genes, and peritoneal macrophages produce infectious virus [5, 55]. However, the level of virus production is low, suggesting that replication is inefficient or only some cells can produce virus. Bone marrow-derived macrophages and CD11c+ cells (predominantly dendritic cells) infected ex vivo express MAdV-1 mRNAs and proteins [55]. Depletion of macrophages by clodronate liposome treatment increases MAdV-1 infection severity [55]. Macrophages are thus targets and effectors in MAdV-1 infection. In contrast, depletion of mice of their natural killer (NK) cells either genetically or biochemically does not alter MAdV-1 brain viral loads, indicating that in contrast to other viral infections, NK cells are not required for control of MAdV-1 infections in the brain [76].

Interferons (IFNs) are major antiviral cytokines. In vitro, wild-type MAdV-1 infections are resistant to the effects of type I and type II IFN [77]. In contrast, E1A mutant infections are sensitive to both types of IFN, and expression of E1A in the absence of other viral gene products rescues vesicular stomatitis virus from the effects of type I IFN. The results indicate that MAdV-1 uses E1A to inhibit expression of IFN-stimulated genes. IFNγ is not a major antiviral cytokine in MAdV-1 respiratory infection or myocarditis [12, 78]. However, it is necessary for cardiac inflammation induced by intranasal infection of neonatal mice [12]. The virus replicates in both neonates and adult mice, but only neonates develop myocarditis, and there is higher IFN-γ expression in neonates compared to adults. Thus IFN-γ is a proinflammatory mediator in adenovirus-induced myocarditis. IFN-γ is important for the induction of the immunoproteasome, an inducible form of the proteasome involved in protein degradation and generation of peptides for major histocompatibility complex class I presentation [79]. Intranasal inoculation of MAdV-1 results in significantly increased immunoproteasome activity in the lung and heart compared to uninfected mice [80], and this is dependent on IFNγ. The immunoproteasome is important for survival of neonatal mice infected with MAdV-1 [60].

The role of interleukin 1β (IL-1β) in MAdV-1 encephalitis was examined in mice lacking the IL-1 receptor. IL-1β is a proinflammatory cytokine that contributes to inflammation in the CNS. Surprisingly, the lack of IL-1 signaling in the mutant mice results in increased mortality and inflammation during MAdV-1 infection compared to control mice; this is accompanied by an increase in transcription of type I IFN-stimulated genes [81]. Thus IL-1β, although pro-inflammatory, protects mice from some of the pathogenic effects of MAdV-1 CNS infections. A similar result is found in herpes simplex virus 1-induced encephalitis, in which IL-1β acts synergistically with tumor necrosis factor alpha [82].

IL-17 is another proinflammatory cytokine; it is produced by a subset of helper T cells known as Th17 cells. Pulmonary infection of mice by MAdV-1 results in increased IL-17 mRNA and protein compared to uninfected mice [83]. IL-17 knockout mice have less recruitment of neutrophils to the lung than wild-type mice, but peak viral loads, clearance of virus, and protective immunity do not differ. This indicates that the Th17 responses during respiratory infection are not required for viral control or for pulmonary inflammation.

Prostaglandin E_2 (PGE_2) is a lipid mediator that increases during many viral infections, and it can have effects on many immune cell types. Production of PGE_2 increases during MAdV-1 respiratory infection, promoting production of a variety of cytokines [84]. However, mice deficient in PGE_2 production do not differ from wt mice in virus replication, virus-induced lung inflammation, or protective immunity.

Alpha-defensins are short antimicrobial peptides with antibacterial activity [85]. These peptides can also neutralize viruses, and α-defensin binding to HAdV-5 blocks in vitro infection by stabilizing the capsid and preventing uncoating of the virion [86-88]. In vivo evidence that defensins are a protective host response for adenovirus infection comes from study of MAdV-1 infection of mice lacking functional enteric α-defensin processing [62]. When mice lacking functional α-defensins in their small intestine are orally infected with MAdV-1, there is a dose-dependent increase in susceptibility compared to wild-type control mice. However, when the mice are infected intraperitoneally, there is no difference between mutant and wild-type mice, indicating that the defensin protective effect is specific to the small intestine. The effect is not dependent on the host intestinal microbiota. Viral loads in the defensin-deficient mice are higher in brain, spleen, and ileum only at late times after infection, suggesting that rather than directly delaying viral dissemination, α-defensins act indirectly to protect orally infected mice. Histological and humoral response assays indicate that the adaptive immune response to MAdV-1 infection, particularly the neutralizing antibody response, is delayed in the absence of functional α-defensins.

A major innate response to virus infection is PKR activation. PKR is an interferon-stimulated kinase that is activated by binding to double-stranded RNA produced in infections by DNA and RNA viruses [89-92]. Activation of PKR leads to phosphorylation of eukaryotic translation initiation factor eIF2a, which halts protein synthesis [93, 94]. Viruses have evolved a variety of ways to circumvent this antiviral host response, including inhibiting PKR phosphorylation, sequestering PKR, dephosphorylating eIF2a, and degrading PKR [95]. HAdVs encode VA RNAs that sequester PKR by binding it as a monomer, preventing its autophosphorylation/activation [96]. However, MAdV-1 does not encode a VA RNA [37], and it circumvents the antiviral PKR response by a mechanism not previously shown for DNA viruses. MAdV-1 degrades PKR in multiple cell types infected in vitro [97]. PKR degradation has not been previously observed for DNA viruses. Inhibiting the proteasome blocked MAdV-1-induced PKR degradation, indicating that the degradation likely proceeds by a proteasomal mechanism. The viral gene(s) involved in PKR degradation have not been identified, but the data point towards an early viral gene.

MAdV-1 Pathogenesis – Persistence and Host Genetics of Susceptibility

Like HAdVs, MAdV-1 persists in the host after acute infection [32, 33, 98]. MAdV-1 is detected in brains, spleens, and kidneys of outbred mice up to 55 weeks after intraperitoneal infection [33], and in urine for up to two years [71]. After intranasal inoculation, MAdV-1 viral genomes can be detected in

the hearts of inbred mice at 9 weeks post infection [12]. This persistence in the heart can lead to cardiomyocyte hypertrophy. It is not known whether MAdV-1 also persists in lymphocytes, as has been found for HAdVs [99-101], including in lymphocytes of the gut lamina propria [102].

Different strains of outbred and inbred mice differ in their susceptibility to MAdV-1 [6, 8, 9]. Adult SJL/J mice are highly susceptible to the virus, whereas other inbred strains, such as BALB/cJ, are resistant [9]. The H-2^s haplotype of SJL/J mice is not associated with susceptibility, which was shown to be a quantitative trait [103]. Genetic mapping using an interstrain backcross identified a major quantitative trait locus (QTL) on mouse chromosome (Chr) 15, *Msq1*^{SJL}, that accounts for a significant portion of the total trait variance between SJL/J and BALB/cJ strains. Fine mapping localized the QTL to a region of Chr 15 that encodes genes of the hematopoietic cell surface-expressed LY6 family [104]. Further mapping was unable to identify specific *Ly6* genes involved in MAdV-1 susceptibility (Spindler, unpublished), but interestingly, *Ly6E* is among other IFN-stimulated genes shown to enhance the replication of several enveloped viruses, by targeting a late viral entry step [105, 106]. Interval-specific congenic mice for the *Msq1*^{SJL} locus were used to examine the contribution of the locus to disease phenotypes of intraperitoneally infected mice [9, 58, 104]. The locus is responsible for a subset of the physiological phenotypes that correlate with MAdV-1-induced encephalitis. Disease phenotype differences between the congenic mice and parental SJL mice indicate that there are additional host genes involved in CNS disease in mice.

Mouse adenoviruses type 2 and 3

The genomic sequence of MAdV-2 (HM049560.1) has been determined and compared to those of MAdV-1 and MAdV-3 (EU835513.1) [18, 37, 107, 108]. Phylogenetic analyses showed that the three mouse AdVs have a close common ancestor, but MAdV-1 and MAdV-3 are closer to each other than to MAdV-2. Strikingly, although the number of predicted genes is almost the same, the MAdV-2 genome size of 35,203 bp is considerably larger than the genomes of MAdV -1 and MAdV-3 (30, 944 and 30,570 bp, respectively). This is mainly due to larger genes and ORFs in MAdV-2, although there are also some differences in the number of ORFs for the early regions E1, E3 and E4. A peculiar feature was noted when analyzing the leader sequence of the late mRNA transcripts: in MAdV-1 and -3, as in most AdVs, the leader consists of three spliced sequences (tripartite sequence), whereas in MAdV-2, it is a bipartite leader sequence [109]. A bipartite leader is also found in fowl adenovirus type 10 [110]. It has been hypothesized that MAdV-2 is a genuine mouse adenovirus that has continuously coevolved with *Mus musculus*, whereas MAdV-1 may have switched to this host from some other species and is still in an

adaption process, including remodelling of the genetic content [107]. This could also explain the elevated pathogenicity of MAdV-1 in the house mouse.

The receptors for MAdV-2 and -3 are not known. Just as in MAdV-1 and -3, no RGD motif is found in penton base of MAdV-2 [107]. However, the RGD motif present in the fiber knob of MAdV-1 and -3 is lacking in the fiber knob of MAdV-2, which has little sequence identity (10-16%) to adenovirus fibers of known structures. A high-resolution crystal structure of the carboxy-terminus of the MAdV-2 fiber reveals a domain with the typical adenovirus fiber head topology and a domain containing two triple β-spiral repeats of the shaft domain [111]. The fiber head contains a monosaccharide N-acetylglucosamine (GlcNAc) binding site that allows binding to GlcNAc-containing mucin glycans, potentially representing a target in the mouse gut. As reported for MAdV-1, mouse CAR does not serve as receptor for MAdV-2 or -3. Studies with mouse CAR-transfected B16 melanoma cells did not reveal increased MAdV-2 or -3 infection (M. Bieri and S. Hemmi, unpublished). This is consistent with the fact that few of the residues important for CAR binding are conserved in the MAdV-2 fiber head [111]. Competition studies with recombinant MAdV-2 fiber knob demonstrated that fiber knob is the attachment protein [111, 112], paralleling competition results for MAdV-1 fiber knob discussed above [53]. However, the receptors for MAdV-1 and MAdV-2 on cultured cells are not the same, because purified MAdV-2 fiber knob does not inhibit MAdV-1 infection [112].

As discussed above, enteric α-defensins have potent antiviral effects on in vivo and in vitro MAdV-1 infection. For enteric MAdV-2, α-defensins have the opposite effect and enhance infection of mouse colon CMT-93 cells and stem cell-derived small intestinal enteroids [112]. The enteroid experiments accurately predicted increased MAdV-2 shedding in the faeces of wild type mice compared to mice lacking functional α-defensins. These results are in line with in vitro findings for human enteric viruses and suggest that some viruses have evolved to use these host α-defensin proteins to enhance their replication.

MAdVs as vaccines and vectors

Only a few studies to date have used wild-type or recombinant MAdVs for therapeutic approaches. This may be due in part to the relatively fastidious growth of the viruses and the difficulty in generating recombinant vectors. Robinson et al. engineered an oncolytic MAdV-1 in which a small deletion in the E1A rendered the protein deficient for binding to pRb, thereby resembling the human AdVΔ24 vector that has been shown to replicate selectively in cancer cells defective for the pRb pathway [113]. This MAdV-1 was engineered to express the immune stimulatory GM-CSF and tested in

immunocompetent syngeneic tumor models. Compared to the parental vectors, the MAdV-1 vector with GM-CSF was more effective in reducing tumor growth in the low immunogenic Pan02 tumor model and induced a greater systemic antitumor immune response. This system represents substantial progress for testing armed oncolytic viruses, since oncolytic HAdVs cannot productively infect mouse cells, and effects of immunostimulatory transgenes on overall virus potency, virus dissemination, and vector safety cannot be readily assessed in immunocompromised models, such as nude or SCID mice.

Genetically modified mouse cells (and possibly mice) capable of supporting HAdV replication represent an alternative immunocompetent mouse model. They would have the advantage that the vast number of oncolytic HAdV vectors could be tested directly. Initial studies showed that coinfection of HAdV-C5 and MAdV-1 or heterologous overexpression of HAdV-C5 L4-100K can partially complement late protein expression, which has been identified as a bottleneck for HAdV-C5 replication in mouse cells [114]. A second detailed complementation study used the HAdV-B-derived oncolytic virus, enadenotucirev (EnAd), in coinfections either with MAdV-1 or with EnAd viruses containing 24 different MAdV-1 ORFs [113, 115]. These transcomplementations with MAdV-1 genes failed to rescue EnAd replication. Thus, the mechanisms preventing productive replication of HAdVs in mouse cells seem to vary for the different HAdV species, and more work needs to be done to understand and overcome these hurdles.

Oral replication-competent vaccines against HAdV-4 and -7 have long been used to immunize the US military against severe respiratory infection caused by these viruses [116]. MAdV-1 has recently been examined as a model to study oral replication-competent adenovirus vaccines in vivo in a natural host [117]. Intranasal, intraperitoneal, and natural MAdV-1 infection generate neutralizing antibodies [1, 6, 60, 63]. Oral infection of C57BL/6 mice, which have intermediate susceptibility to MAdV-1 [104], leads to a systemic infection with moderate bowel pathogenesis and antiviral neutralizing-antibody responses [62]. In the MAdV-1 vaccine study, when BALB/c mice, which are more resistant to MAdV-1 infection [104], were inoculated orally, there was only a subclinical infection that also generated a virus-specific neutralizing-antibody response [62, 117]. Although clinical signs of disease were not seen after oral infection of the BALB/c mice, sporadic shedding of virus in faeces occurred, as measured by qPCR. Importantly, oral immunization with MAdV-1 protected against homologous virus challenge, similar to the HAdV-4 and -7 immunizations, with generation of an adaptive immune response. However, the oral administration of MAdV-1 alone led to a systemic infection, even at low doses. Whether this occurs in humans is not known; the authors note that the HAdV oral vaccines have been primarily used on a specific population of young, healthy adults. It would be interesting to test whether the enteric MAdV-2

gives rise to similar levels of neutralizing antibodies, perhaps in the absence of systemic spread. The findings of disseminated infection after MAdV-1 oral infection should be considered if HAdVs are developed for broader vaccination.

Conclusions and Perspectives

Mouse adenoviruses are important because they enable study of adenoviruses in their natural hosts. Studies of mouse adenoviruses have revealed tropisms and pathologies distinct from those seen in HAdV infections. They have also increased our knowledge of adenoviral pathogenesis and revealed new mechanisms of virus response to the host response in the "arms race" between viruses and cells. While humanized mouse models [118] and organoid systems [119, 120] may enable study of HAdV pathogenesis, their complexity and costs may limit their use. Study of mouse adenovirus pathogenesis in its natural host, with all the benefits of mouse genetics and immunological reagents, will continue to advance our understanding of viral-host interactions.

Display items, Figures, Tables

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