

sion over more than 40 weeks. It was demonstrated that, following liver gene transfer, transcriptional initiation was only from the liver-specific promoter, and that splicing of the primary transcript and processing of RNA and protein were normal. Gene transfer with increasing doses of this vector resulted in very high and stable α_1 -antitrypsin serum levels that so far are unparalleled by gene transfer with any other tested combination of strong viral promoters and the α_1 -antitrypsin cDNA. Significantly, the high serum α_1 -antitrypsin levels that would be considered supraphysiological in humans were not accompanied by any significant hepatotoxicity. Gene transfer with the same dose of a first-generation vector carrying an α_1 -antitrypsin expression cassette led to hepatic damage that was morphologically characterized by liver cell necroses and infiltration by granulocytes and was accompanied by significantly elevated liver enzymes in the serum. Improved expression and decreased toxicity with high-capacity adenoviral vectors were confirmed with another vector that carried the murine leptin cDNA under the control of a viral promoter. Taken together, these results indicate that high-capacity adenoviral vectors will be useful for functional studies on gene transfer and likely also for somatic gene therapy because of their improved safety and expression profiles. Their increased capacity for foreign DNA is a significant advantage over first and second generation adenoviral vectors.

See also: Adenoviruses (Adenoviridae): General features; Latency; Persistent viral infection; Vectors: Animal viruses.

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Animal Viruses

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History

Members of the adenovirus family (*Adenoviridae*) can be recognized in virtually every class of vertebrate animals (Table 1). However, not all of the family members contain the same common antigen and initially two genera have been established each of them being characterized by a common (or group) antigen. The genus *Mastadenovirus* comprises viruses isolated from mammals (humans, monkey, cattle, pig, sheep, horse, dog, goat, tree shrew, deer, whale, mouse, etc.) whereas the *Aviadenovirus* genus contains viruses isolated from avian species (chicken, turkey, goose, pheasant, duck, etc.). The organization of the genome, though normally rather conserved within a genus, differs considerably between the two genera. Recently, strong evidence (based on genomic organization and phylogenetic analysis; Fig. 1) supported the establishment of a third genus incorporating several bovine adenoviruses (BAVs), the ovine adenovirus isolate 287 (OAV287) and the egg drop syndrome (EDS) virus which (lacking the genus-specific common antigens) had been recorded as 'atypical' members of the *Mastadenovirus* or *Aviadenovirus* genera. The proposed name of this possible third genus is *Atadenovirus* (referring to the characteristic AT-rich genome rather than the host animal taxon). The candidate BAV serotypes (4 to 8) of this proposed genus do not fit clearly into the *Mastadenovirus* genus and are presently separated as subgroup 2 from the subgroup 1 BAVs which obviously belong to the mastadenoviruses. A number of adenoviruses isolated from (or only detected in) lower vertebrate hosts (fish, frog, snake, chameleon, crocodile, etc.)

Table 1 Adenovirus infections detected in animal species

	<i>Types</i>	<i>Affected organs</i>	<i>Evidence</i>	<i>DNA sequence</i>
<i>Fish</i>				
Cod	?	Epidermis	EM	–
Dab	?	Epidermis	EM	–
<i>Amphibians</i>				
Leopard frog	frog 1	Kidney	Isolated	Partial
Common frog	?	Liver	Isolated	–
<i>Reptiles</i>				
Corn snake	?	Liver, kidney, spleen	Isolated	?
Royal python	?	?	Isolated	–
Boa constrictor	?	Liver	Isolated	–
Jackson's chameleon	?	Trachea, esophagus	EM	–
Nile crocodile	?	Liver, intestine	EM	–
<i>Birds</i>				
Chicken	FAV-1	Egg (CELO)	Isolated	Full
	FAV-2–12	Trachea, liver	Isolated	Partial (3)
Quail	FAV-1	Bronchial epithelium	Isolated	–
Guinea fowl	FAV-1	Lung, pancreas, spleen	Isolated	–
Pigeon	FAV-2	Liver, intestine	Isolated	–
Crow	?	Healthy	Serology	–
Goose	Goose 1–3	Liver, intestine	Isolated	–
Turkey	turkey 1–3	Respiratory	Isolated	–
	HEV	Intestine, spleen, kidney	Isolated	Partial
Pheasant	MSDV	Spleen	Isolated	–
Duck	duck 1	Egg (EDS)	Isolated	Full
Muscovy duck	duck 2	Liver	Isolated	–
Wild duck, coot, grebe	duck 1	Healthy	Serology	–
Herring gull	?	Bursa of Fabricius	EM	–
Common murre	?	Kidney	EM	–
Cockatiel	?	Liver	EM	–
Rose-ringed parakeet	?	Bronchial epithelium	EM	–
Amazon parrot		Liver, intestine	EM	–
Emu	?	Intestine	EM	–
Ostrich	FAVs	Trachea, lung, intestine, pancreas, kidney	Isolated	–
American kestrel	?	Liver	EM	–
<i>Mammals</i>				
Platypus	?	?	EM	–
Brush tail possum	?	Intestine	EM, serology	–
Mouse	MAV-1–2	Lung, intestine, kidney	Isolated	Partial
Wild meadow vole	?	?	Serology	–
Syrian hamster	MAV-1?	Intestine, liver	EM, serology	–
Ground squirrel	?	Kidney	Isolated	–
Guinea pig	?	Lung	EM, PCR	Partial
Rabbit	?	Intestine	Isolated	–
Dog	CAV-1	Liver, CNS	Isolated	Full
	CAV-2	Resp	Isolated	Full
Fox	CAV-1	CNS	Isolated	–
Black bear	CAV-1	Kidney, liver	Isolated	–
Black panther	?	Liver	LM	–
Cat	?	Resp, intestine	Serology, PCR	Partial
California sea lion	CAV?	Liver	EM	–

Table 1 Continued

	<i>Types</i>	<i>Affected organs</i>	<i>Evidence</i>	<i>DNA sequence</i>
Sei whale	?	Intestine	Isolated	–
Horse	EAV-1–2	Resp, intestine	Isolated	Partial (2)
Swine	PAV-1–5	Lung, intestine, CNS	Isolated	Partial (5)
Cattle	BAV-1–10	Lung, intestine	Isolated	Partial (8)
Sheep	OAV-1–6	Liver, intestine, kidney,	Isolated	Partial (2)
	BAV-2	Resp	Isolated	
	OAV287		Isolated	Full
Goat	caprine 1–2	Intestine, CNS	Isolated	–
Llama	?	Lung, liver	Isolated	–
Red deer	?	Lung	EM	–
Fallow deer	BAV-6	Lung	Isolated	–
Mule deer	BAV?	Lung, blood vessels	Isolated	–
African buffalo	BAVs	Healthy	Isolated	–
Caribou	BAVs	Healthy	Serology	–
Tupaia (tree shrew)	TAV-1–2	Resp, intestine, kidney	Isolated	Partial
Monkeys (African green, baboon, macaque, owl, rhesus, squirrel, vervet)	SAV1–20	Conjunctiva, resp, lung, intestine, pancreas, kidney	Isolated	Partial (12)
Chimpanzee	SAV-21–27	Resp, intestine, kidney	Isolated	Partial (6)

Abbreviations. BAV, bovine adenovirus; CAV, canine adenovirus; CELO, chicken embryo lethal orphan; EAV, equine adenovirus; EDS, egg drop syndrome; FAV, fowl adenovirus; HEV, hemorrhagic enteritis virus; MAV, murine adenovirus; MSDV, marbled spleen disease virus; OAV, ovine adenovirus; OAV287, OAV isolate 287; PAV, porcine adenovirus; SAV, simian adenovirus; TAV, tupaia adenovirus; CNS, central nervous system; intestine, gastrointestinal tract; resp, respiratory organs; EM, electron microscopy; LM, light microscopy; PCR, polymerase chain reaction; partial, partial sequences (can be very short; in parentheses the number of sequenced serotypes); full, the complete genome is sequenced.

have as yet no genus attribution – mainly because of the lack of comparative data.

Properties of the Virion

The virion has an icosahedral capsid of diameter 75–90 nm and a core containing the viral DNA and basic proteins. The capsid has 252 capsomers; 240 of them are at the faces and on the edges of the icosahedral capsid, surrounded by six others and hence called hexons. The remaining 12 capsomers are located at the apices and, being on the axes of fivefold symmetry, are surrounded by five hexons and termed pentons. The proximal hexons are further defined as peripentonal hexons. These peripentonal hexons and pentons can be detached from the remainder of the capsid by a variety of treatments and it appears that the remaining 180 hexons are cemented together in 20 groups of nine via another structural component, polypeptide IX in mastadenoviruses. However, in the aviadenoviruses and in the members of the proposed third genus, protein IX is missing. The pentons are characteristic of the *Adenoviridae* and have a dumb-bell shape with a (penton) base and a protruding

knobbed fiber. The fiber is of variable length, the largest so far described being visualized on an equine adenovirus of length 50 nm. Several bovine adenoviruses also have considerably longer fibers than human adenoviruses and sometimes these are bent. Most of the aviadenoviruses have two fibers normally of very different sizes (varying from 8.5 to 47 nm) attached to the same penton base. High-resolution x-ray crystallography of the hexon and image reconstruction from cryoelectron micrographs of human adenoviruses have provided a detailed understanding of virion structure and all studies of animal adenovirus so far completed have indicated that they will in general conform to these same structural parameters. Thus it has been demonstrated that avian adenoviruses possess a terminal protein covalently linked to the 5' termini of the virus DNA and that animal virus hexons possess a similar spectrum of type, subgroup and group specificity already noted in the human viruses. In the studied members of the *Aviadenovirus* and the proposed third genus, however, besides the above-mentioned protein IX, a structural component protein V is also missing. Moreover, in the OAV287 and in the EDS virus (candidate members of the third

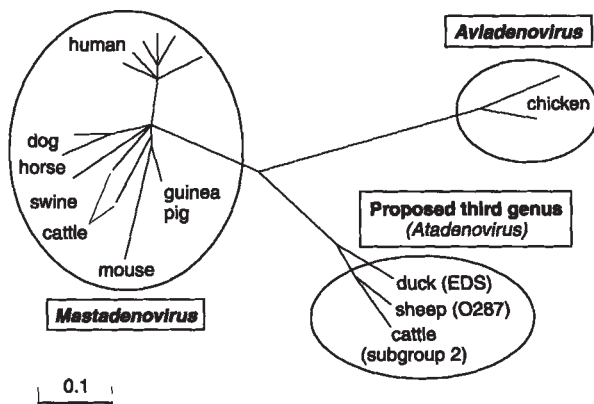


Figure 1 Genetic distance between adenoviruses isolated from different animal species resulting from the phylogenetic analysis of 23 known hexon gene amino acid sequences. The unrooted phylogenetic tree was generated by distance matrix analysis: PROTDIST and FITCH of the PHYLIP v3.5c program package of J. Felsenstein (<http://evolution.genetics.washington.edu/phylip.html>). The length of the branches indicates the phylogenetic distance between the different viruses, the scale bar represents 10% mutations. The virus types composing the two existing and third (proposed) genera are circled. The original sequence alignment and the alignment edited for the calculations are available at <http://www.vmri.hu/~harrach>. From the hexon gene of the guinea-pig adenovirus only a short sequence was available and therefore only preliminary conclusions could be drawn for this virus type. The tree was visualized using the TreeView program of R. Page (<http://taxonomy.zoology.gla.ac.uk/rod/treeview.html>) and the Windows Metafile was edited in Microsoft Word 7.0 for demonstrating the discussed new (three cluster) grouping of the adenoviruses of different hosts. Similar clustering was obtained by the analysis of protease gene (either amino acid or nucleic acid) sequences.

genus), the occurrence of new, homologous open reading frames (ORFs) encoding putative structural proteins termed 28K or 24K, respectively, were observed. In OAV287, the presence of the 28K protein in the virion was confirmed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE).

Properties of the Genome

Adenoviruses have a linear double-stranded DNA genome with inverted terminal repeats (ITRs) of varying length and all animal adenoviruses studied have conserved this feature. Aviadenviruses appear to have about 17% of their total weight as DNA and a molecular weight of $28\text{--}30 \times 10^6$ which is slightly greater than that of human adenoviruses. Compared to the long genome of aviadenoviruses exceeding 44 kb, mastadenoviruses have a genome length of 31–36 kb, and the DNA of the members of the proposed third genus is shorter in the range 28–33 kb. There is

very limited base homology between the genomes of viruses of the different genera. Within a genus however, as a rule, more significant base homologies have been detected among the DNAs of different serotypes of the same host species. Cattle, sheep and chicken seem to be exceptions in this respect, since these animal species can apparently be infected with unrelated adenoviruses from different genera (no DNA homology could be detected by DNA hybridization between bovine adenoviruses belonging to the *Mastadenovirus* genus or to the proposed new genus).

Besides the four entirely sequenced human adenoviruses (types 2, 5, 12 and 40), there are five animal adenoviruses with completely sequenced genomes: canine adenovirus types 1 and 2 (mastadenoviruses), fowl adenovirus 1 (aviadenovirus), and OAV287 and EDS virus (proposed third genus). Many further partial sequences are available (or to be published soon) from different hosts, such as ovine adenovirus type 3, porcine adenovirus types 1 to 5, BAV-1, 2, 3 and 10, mouse adenovirus type 1, equine adenovirus types 1 and 2, tree shrew (tupaia) adenovirus, fowl adenovirus types 8 and 10, turkey hemorrhagic enteritis virus, and BAV-4, 6, 7 (candidate members of the proposed new genus) etc. (see Table 1).

The data in hand in relation to regulatory events and the sequence data available for the animal adenoviruses suggest that genome organization of the mastadenoviruses should be generally similar to that already discerned for the human adenoviruses. The only real differences between the members of the *Mastadenovirus* genus can be seen in the content of the E3 region, which has a different number and entity of genes even in the different types of human adenoviruses. To date, the shortest E3 region was found in the murine adenovirus (MAV) type 1 and BAV-10 (only one but a different gene in each), whereas the longest was described in the subgenus B human adenoviruses (eight E3 genes in type 35, and possibly nine in type 3). The aviadenoviruses and the members of the proposed new genus, however, have strikingly different genomic organization especially at the two ends of their genomes mainly concerning the early regions. Although the genes of the structural proteins (apart from the missing proteins V and IX) and their location and organization in the middle part of the genome is very similar to that of the mastadenoviruses, apparently there is no recognizable E1A region in the aviadenoviruses and in the candidate members of the proposed genus. Similarly, the region contained between the pVIII and fiber genes (at the conventional location of the E3 region) has no similarity to the E3 of mastadenoviruses. Furthermore, in the aviadenoviruses, no E1B region has been identified. The corresponding region in the members

of the candidate new genus is also very divergent from the mastadenoviruses and needs further characterization. There are several additional ORFs found on the right hand end of the genome, which are homologous only among the members of the aviadenoviruses or proposed new genus, respectively.

Apparently, most human and chimpanzee adenoviruses encode two RNA polymerase III-transcribed low-molecular-weight 'virus-associated' (VA) RNAs which are important in efficient translation of late virus mRNAs. In the twelve monkey adenoviruses which have been examined, however, there is only one VA RNA. The avian adenoviruses also code for a single VA RNA but this is much shorter (90 compared to 160 nucleotides (nt)) and does not exhibit sequence homology with the human VA RNA species; nevertheless, its predicted secondary structure is similar. The location of the VA RNA in aviadenoviruses (CELO) at the far right hand part of the genome is also different from that in mastadenoviruses. In the EDS virus a VA RNA similar to that of CELO virus and located at the far right end of the genome has been described.

Properties of Virus Proteins

Most of the proteins encoded by human adenovirus prototype strains have been well-characterized and, as mentioned, the animal adenoviruses of the *Mastadenovirus* genus seem to be similar. The aviadenoviruses and the proposed new genus show differences in the number of the structural proteins: the lack of protein V and IX, and the existence of several new, yet uncharacterized proteins (28K in OAV287, or 24K in EDS virus). Most avian adenoviruses also have an additional fiber protein (see earlier) coded by a second gene, but a similar phenomenon also occurs in human adenovirus types 40 and 41. The most distinctive feature of the CELO virus polypeptide composition appears to be the increase in the amount of core polypeptides present and it has been suggested that these may be needed to neutralize the negative charge of the DNA which is 30% larger than human adenovirus DNA.

Physical Properties

Virions have a molecular weight of $\sim 170 \times 10^6$ – 185×10^6 , sedimentation value $\sim 560S$ and a density in CsCl of 1.32 – 1.35 g/cm^{-3} . As noted earlier, aviadenoviruses appear to have larger genomes and this is reflected in the physical properties of the virions. Virus infectivity is resistant to lipid solvents and is relatively acid stable.

Replication

In the animal adenoviruses (so far examined) and which belong to the *Mastadenovirus* genus the genome organization appears to be broadly similar to that of the human adenoviruses. The early regions E1A and E1B are similarly located at the left hand end of the genome and E3 at around 80 map units. All three of these transcription units are transcribed in the rightward direction and a region corresponding to E4 transcribed (as in the human viruses) in the leftward direction has also been detected. In the avian adenoviruses and the members of the new proposed genus, however, an E1A region could not be identified. Moreover, in OAV287, BAV-6 and EDS a supposedly nonessential region tentatively called 'E3' (because it was proven to be deletable in OAV287) is located after the E4 region and is transcribed in the leftward direction. The role of this region in the replication is not known and neither is the role of the unidentified open reading frames of the aviadenoviruses at the right-hand end of their genome. Analogous findings to human adenoviruses with respect to the mechanisms of virus DNA replication have been established with a number of animal virus systems (e.g. avian and murine adenoviruses). Thus all the sequences of the ITRs from animal adenoviruses contain sequences at nucleotides 8–15, consistent with the termini being the origins of DNA replication. Other aspects of the molecular biology of the animal mastadenoviruses have so far indicated that they appear to conform with that already established in much more detail for the human adenoviruses, while the lack of the E1A region in the avian and candidate third genus adenoviruses raises interesting questions about the early events in their replication.

Host Range and Virus Propagation

Animal adenoviruses generally can be readily propagated in a range of epithelial cells derived from tissues of their own species, although some adenoviruses can also replicate in other tissue cell lines. There is a wide variation in their ability to replicate in cells from other species, e.g. ovine adenoviruses can be propagated in bovine and porcine cells as well as ovine, but murine adenoviruses are more restricted to mouse cells, preferably mouse embryo cells. Aviadenoviruses can only replicate in avian cells, doing best in cells from the homologous species. Although the animal adenoviruses appear to be specific to their original host, there are some reports on isolation of bovine adenoviruses from sheep, buffalo, and deer. On the other hand, restriction enzyme fragmentation, DNA hybridization and limited sequencing suggested that

BAV-9 clearly belongs to subgenus C of human adenoviruses. These observations leave open the possibility that the isolation of BAV-9 could be an artifact (laboratory contamination). On the other hand group C human adenoviruses can perhaps establish infection in cattle. Nevertheless, HAV-5 is also capable of replication in bovine cell cultures or even in cell lines with similar efficiency as in human cells. Similarly to human adenovirus types 40 and 41, the hemorrhagic enteritis virus of turkey can be propagated in live animals or in transformed cell lines only. BAV serotypes 4 to 8 and 10 are also restricted to primary or low-passage number bovine testicular or endothelial cells.

Genetics and Evolution

Complete sequence data are available from five animal adenovirus genomes, and numerous partial sequences have been determined recently (Table 1). Sequence data along with restriction enzyme patterns have been used in some cases (e.g. bovine and avian adenoviruses) for the confirmation of groupings based on serological results. More importantly, however, these sequence data also make possible the examination of the phylogenetic relationships among adenoviruses. Initially, the ITRs present at the termini of the virus DNA were used for comparisons, whereas nowadays the DNA and predicted amino acid sequences of selected viral proteins available from many different adenovirus types provide useful data for comparative taxonomy. For example, on the basis of serological crossreactivity and similarities in restriction enzyme cleavage patterns, several simian adenoviruses could previously be allocated into four (A, B, C, E) out of the six known human subgenera. Comparison and phylogenetic analysis of the VA RNAs of human and simian adenoviruses further defined their close relationship and possible common origin. Phylogenetic analyses based on reasonably large data sets comprising those possibly most restricted to their host species (sequences of the hexon or the protease genes are most appropriate) consistently resulted in the obvious separation of three clusters corresponding to the two accepted, and the third proposed genera (Fig. 1). The subgenus classification of HAVs, and the general similarity of adenoviruses isolated from the same host was also confirmed.

Several interesting aberrations could be observed among adenoviruses isolated from cattle or sheep. BAVs apparently belong to two different genera and the isolate OAV287 is definitely more closely related to subgroup 2 BAVs (the proposed new genus) than to OAV-3. On the other hand, OAV-3 and BAV-2 are clustered together, whereas other subgroup 1 BAVs

(BAV-1 and -3) are further from BAV-2. Although as its name indicates, BAV-2 was first isolated from cattle, it has in fact also been isolated from sheep with an equal or higher frequency, and might therefore genuinely be an ovine adenovirus. Another questionable virus concerning its host and evolutionary origin is BAV-10 which was originally described as a member of subgroup 2 BAVs. Its genome analysis and the phylogenetic calculation clarified however that BAV-10 is a typical mastadenovirus, although distantly related to subgroup 1 BAVs.

An interesting example of the use of sequencing and phylogenetic calculations is a guinea-pig adenovirus which has never been isolated, yet partial amplification of its genome by polymerase chain reaction (PCR) was successful. The amplified partial hexon sequence could then be included into phylogenetic calculations, and the obtained distance (branch length) data confirmed that the virus is not closely related to any other known adenoviruses and will likely be a new type (Fig. 1).

Serologic Relationships and Variability

Typing of mammalian animal adenoviruses on the basis of neutralization has recognized at least 57 different types distributed as follows: simian (27), bovine (10), ovine (6), swine (5), equine (2), canine (2), caprine (1), murine (2), tree shrew (2). All are mastadenoviruses with the exception of BAV types 4 to 8 and OAV287 (showing one-way crossneutralization with BAV-7). Among the 21 avian adenoviruses there are fowl (12), turkey (3), goose (3), pheasant (1) and duck (2) serotypes (duck adenovirus type 1 being the EDS virus belonging to the proposed new genus). In addition to these type-specific antigens, there are group-specific antigens characteristic of the three genera as well as a variety of subgroup antigens which indicate more diverse antigenic relationships between the types. Panels of monoclonal antibodies have been produced which can further define these antigenic relationships, e.g. between the fowl serotypes. Most of these different antigenic sites appear to be associated with hexons, although some have also been ascribed to the fiber components (see earlier). Hemagglutination with rodent and monkey erythrocytes has proved to be a useful laboratory tool to establish serological groupings and inhibition and enhancement of hemagglutination can be used to make further serological refinements.

Epizootiology, Transmission and Tissue Tropism

The animal adenoviruses appear to be widely dispersed in their respective host species mostly in an

asymptomatic manner. Similarly to human adenoviruses, persistent infection might be established and the virus can be excreted to the environment from the respiratory and gastrointestinal tracts. Vertical (transplacental) spreading in cattle and swine, as well as egg transmission in poultry have also been described. There are several reports on fulminating diseases attributed to adenovirus infection (over a thousand Californian mule deer died of a disseminated hemorrhagic disease). In other cases of fatal hemorrhagic enteritis in cattle or epizootic lethal pneumonia in guinea pigs, low contagiousness and morbidity, but acute course and very high mortality (up to 100%) were observed. A very wide spectrum of tissue tropism among the animal adenoviruses is evident, e.g. porcine adenovirus type 3 shows a tropism for columnar epithelial cells whereas bovine adenoviruses prefer capillary endothelial cells; however, it is not clear how far tissue tropism relates to pathogenesis and disease. Nevertheless, it is known that for example canine adenovirus types 1 and 2 cause distinct pathology. The two murine adenovirus serotypes (MAV-1 and -2) also have very divergent pathogenic effects. Moreover, recent studies demonstrated that different inbred or outbred, but fully immunocompetent, murine strains show different susceptibility to MAV-1 and according to the presence of genetically determined cellular receptors the infection also has different manifestations.

There is some evidence that an adenovirus which is asymptomatic in its natural host can produce disease in another species. Thus epidemics of reduced laying and soft-shell or shell-less eggs in some flocks of chickens could be attributed to a duck adenovirus (EDS). Aviadenoviruses appear to require avian cells to replicate although they can abortively infect mammalian cells and under the appropriate conditions can transform them.

Pathogenicity and Clinical Features of Infection

Most adenoviruses can be isolated from tissues obtained from healthy animals, but isolations have been associated with respiratory, gastrointestinal and conjunctival diseases, particularly in intensively reared herds and flocks. There is also some evidence for disease etiology in natural infections in the wild. In the case of canine adenoviruses (CAV) the two serotypes, CAV-1 and CAV-2 do seem to have differing tropisms associated with disease patterns. Thus CAV-1 is the agent responsible for infectious canine hepatitis (Rubarth's disease) and along with CAV-2 contributes some of the viruses constituting the 'kennel cough' syndrome. CAV-1 also appears to

induce transient corneal opacity and may also cause encephalopathy. Epizootic infections with CAV-1 in foxes, bears, wolves, coyotes and skunks have also been reported. CAV-2 on the other hand appears to be confined to infections of the canine respiratory tract. Recently, an adenovirus was isolated in connection with the deaths of over a thousand mule deer in California. The virus seemed to be a subgroup 2 BAV. It is also notable that every isolate of BAV-10 has so far originated from diseased and subsequently dead animals showing intestinal hemorrhages. Retrospective *in situ* DNA hybridization of tissue sections from similar cases suggested that not only BAV-10 but the subgroup 2 BAVs may also be responsible for economic losses.

There is evidence that, as in humans, pre-existing adenovirus infection in animals can also develop into generalized disease in immunocompromised hosts. Disseminated adenovirus infection affecting the vascular endothelium was detected by electron microscopy in a cat that had a concomitant feline leukemia virus infection. The origin of the adenovirus infection has not been determined. Clinical manifestation of adenovirus infection was also described in horses with combined immunodeficiency syndrome and in a simian immunodeficiency virus (SIV)-infected rhesus monkey.

Avian adenoviruses have been associated with a wide range of disease patterns, e.g. haemorrhagic enteritis in turkey, bronchitis in quail, 'marble spleen' disease in pheasant, inclusion body hepatitis, pulmonary congestion and edema. Recent pathogenesis studies on turkey's hemorrhagic enteritis suggested that HEV has a tropism for the B lymphocytes and macrophages and that intestinal lesions are not induced by local cytopathic viral replication, but rather are immune mediated.

Several animal models have been used for the study of human adenovirus pathogenicity. Cotton rats, rabbits and chinchilla could successfully be infected with HAV-5 or HAV-1, and reproducible pneumonia, ocular infection and otitis media could be established, respectively.

Pathology and Histopathology

Animal adenoviruses infect susceptible cells and elaborate similar gross pathology to that seen with human adenoviruses, e.g. early rounding of cells and aggregation followed by the later appearance of characteristic basophilic nuclear inclusions. Examination by electron microscopy can also reveal crystalline assays of virus particles in the case of aviadenoviruses. 'Marble spleen disease' of chickens and pheasants induced by avian adenoviruses can be accompanied by

gross lesions including pulmonary congestion, splenomegaly, hepatomegaly and congestion of egg follicles. Microscopic lesions include multifocal pneumonia and edema and reticuloendothelial cell hyperplasia of the spleen with concurrent white-pulp neurosis and lymphocyte depletion. Many of the hyperplastic cells contain the basic intranuclear inclusions characteristic of adenovirus infection. However, there are conflicting reports on the nature of the etiological agents relating to pathologies seen in avian species and it has been suggested that concurrent infections with other microorganisms may play a synergistic role in tandem with adenovirus infection.

Immune Response, Prevention and Disease Control

Serological analyses of animal species have indicated that there is widespread natural infection demonstrated by the presence of antibody against the group antigens. In studies with murine adenoviruses a protective role for T cells was demonstrated but in other systems there have been very few definitive investigations of the nature of the immune responses to infection. On the other hand, vaccination programs have been successfully developed with bovine, ovine, canine, equine and avian adenoviruses. Live attenuated, inactivated and *ts* viruses have all been used in these programs. Inactivated combined bovine adenovirus vaccines exist consisting of one subgroup 1 and one subgroup 2 serotype, thereby conferring immunity to BAVs belonging to two different genera. Recently, there has been great interest in using animal adenoviruses themselves as viral vectors to express and deliver foreign antigens in cattle, sheep, swine, dog, poultry, etc. For the insertion of foreign genes, generally the E3 region is replaced. This region has been or is now being characterized in a number of animal mastadenoviruses (BAV-2, BAV-3, etc.). In addition a nonessential, deletable, putative E3 region has been identified in the OAV287 (a member of the proposed new genus) and a gene expression vector has already been developed from it and also from BAV-3.

See also: Adenoviruses (Adenoviridae): General features, Malignant transformation and oncology, Molecular biology; Vectors: Animal viruses.

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Malignant Transformation and Oncology

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Introduction

Adenoviruses (Ad) are double-stranded DNA viruses that cause a number of acute respiratory infections, in addition to some other types of infections, depending upon the cell type infected. They came to prominence in 1962 because they were shown to cause tumors in rodents. From this, they were considered DNA tumor viruses. The various serotypes have been classified into subgroups, which exhibit different degrees of oncogenic potential in rodent systems (Table 1). Subsequently, it was determined that induction of tumors is an alternative path followed when a productive lytic cycle cannot be completed. Adenovirus transformation has not been reported for humans, which are permissive for the genus Mastadenovirus of the adenoviridae family. Ad normally infects quiescent epithelial cells, but requires the host DNA synthetic machinery for its own replication, thus the virus has evolved mechanisms to reactivate quiescent cells into the cell cycle. It has been through the identification of these viral genes, which are