The composition and structure of rhabdoviruses

C.R. PRINGLE*

The composition and structure of rhabdoviruses

C.R. PRINGLE*

Summary: Within the family Rhabdoviridae, research has concentrated on two members — vesicular stomatitis virus (a vesiculovirus) and rabies virus (a lyssavirus). The former has been chosen as a reference virus in molecular biology on account of its unique morphology and the structure of its genome. It produces abundant defective interfering particles, which may contribute to modulation or self-limitation of the infection.

The genome of vesicular stomatitis virus has served as a model for the genetic analysis of non-recombinant viruses. The functions of its five genes have been elucidated — they provide information on the mechanisms of genetic variation among the rhabdoviruses, which apparently are mediated solely by mutation.

Further research is required on interactions between viral genes and host factors, and also on the evolutionary relationships between different rhabdoviruses. In this context, variations in rabies virus have important consequences for human and veterinary medicine.

KEYWORDS: Composition - Lyssavirus - Molecular biology - Rhabdoviridae - Vesiculovirus.

INTRODUCTION

The Animal Virus Research Institute (AVRI) has played an important role in the development of understanding of the nature of rhabdoviruses, especially vesicular stomatitis virus (VSV). The first research in the UK involving VSV was carried out at Mill Hill by F.M. Burnet in collaboration with I.A. Galloway, who later became the first Director of the precursor of the AVRI, and this work was published in 1934. Ten years later a number of field strains of VSV were imported into Pirbright by Dr Galloway, initiating a comprehensive programme of research on this virus. At first interest centred on the practical goal of developing serological methods of discrimination of vesicular stomatitis disease from foot-and-mouth disease by J.B. Brooksby and others. This phase was followed by pioneering work by C.J. Bradish and J.B. Brooksby on the morphology and biophysical properties of VSV, and some of the first electron micrographs of VSV were produced in the Institute. About the same time Hubert Skinner began exploring the disease-producing potential of VSV in domestic and laboratory animals and developed a modified strain of the Indiana-C strain which no longer produced vesicular lesions in cattle. The subsequent biochemical work of Fred Brown, Joan Crick, Ben Cartwright, Dave Rowlands and others made Pirbright an internationally recognised

* Biological Sciences Department, University of Warwick, Coventry CV4 7AL, United Kingdom.
centre of virological research at a time when interest in foot-and-mouth disease was still confined almost exclusively to veterinary research workers. More recently the Biochemistry Department at Pirbright has conducted a series of far-reaching studies on the physical nature of rabies virus. With the imminent retirement of Joan Crick the Pirbright connection with rhabdovirology is severed. This is a matter of regret at a time when there is a resurgence of interest in these viruses as evidenced by the significant advances reported at the Sixth Negative Strand Virus Meeting organised by Brian Mahy and Dan Kolakofsky in Cambridge in September 1985.

THE FAMILY RHABDOVIRIDAE

At present the Rhabdoviridae family of viruses comprises two recognised genera of related viruses and a large assemblage of uncharacterised viruses linked by a common bullet-shaped or bacilliform morphology (2, 10). The genus Vesiculovirus includes VSV and nine viruses directly or indirectly related to VSV (i.e. Chandipura, Cocal, Isfahan, Jurona, La Joya, Perinet, Piry, Porton-S and Yug Bogdanovac viruses). The genus Lyssavirus includes rabies virus and five rabies-related viruses (Duvenhage, Kotonkan, Lagos Bat, Mokola and Obodhiang viruses). Most of the vesiculoviruses infect arthropods as well as vertebrates, whereas the lyssaviruses infect vertebrates only, with the exception of Kotonkan virus which has been isolated from Culicoides spp. only.

The taxonomy and basic physical and biological properties of rhabdoviruses have been dealt with comprehensively in a three volume monograph edited by D.H.L. Bishop (1). This review will deal only with a few salient developments since that time.

VSV AND THE RISE OF MOLECULAR VIROLOGY

Vesicular stomatitis virus (VSV), the prototype rhabdovirus, as well as causing a troublesome animal disease, has been prominent in the development of molecular virology. The discovery by David Baltimore of an RNA-dependent RNA-polymerase activity associated with the VSV virion followed on the discovery by Kates and McAuslan of the vaccinia virus DNA-dependent RNA-polymerase and just preceded the discovery by Baltimore and Temin and Mitzutani independently of the RNA-dependent DNA-polymerase (reverse transcriptase) of retroviruses. The classification of viruses devised by Baltimore on the basis of the type and polarity of the nucleic acid of viruses which followed from this work has become the basis of the teaching of molecular virology, and VSV has come to be regarded as the prototype for all viruses with negative strand RNA genomes whether segmented or unsegmented. Subsequent research has reinforced the key position of VSV in molecular virology. VSV is still at the forefront of virus research, currently being used to produce VSV (HTLV) pseudotypes which are being used as a rapid assay and detection system for the human T-cell leukaemia viruses (3).

THE UNIQUE MORPHOLOGY OF RHABDOVIRUSES

VSV is only one of more than 50 named animal rhabdoviruses, and a larger number of plant rhabdoviruses. This family of viruses is unique in the manner in which it overrides taxonomic boundaries. The host organisms for these viruses include protozoa (an entamoeba), plants, invertebrates and vertebrates, including man. All the other negative strand viruses are more restricted in their hosts; even
the bunyaviruses which are probably the most diverse of all the families of negative strand viruses are represented outside the animal kingdom only by a single presumptive plant virus.

Undoubtedly the unique morphology of the virion contributes both to its isolation from this diversity of hosts and to its prominence in molecular virology. The characteristic bullet-shaped particle is illustrated in Fig. 1a. Because of this unique morphology discrete particle types can be discriminated by sucrose gradient velocity sedimentation and when virus is passaged at high multiplicity of infection in cultured cells, defective interfering (DI) particles tend to accumulate. Initially it was considered that there was a single standard type of DI particle (Fig. 1b). However, later it became apparent that each independent induction of DI particles generates a unique type of DI particle. There is no single standard DI particle, therefore, but rather a series ranging from particles with half-length genomes (Fig. 1c) to particles with one-tenth of the standard particle genome (Fig. 1d). The latter form small circular DI particles and are exceptional in that so far they have been associated only with temperature-sensitive (ts) mutants of Complementation Group III of VSV Indiana. The majority of DI particles have genomes derived from the 5′-end sequences of the molecule with the remainder deleted. The particles contain the same protein components as the virion in approximately the same proportions. DI particles exhibit the property of specific interference with the replication of normal infectious virus. One unique type of DI particle of VSV Indiana in which the 5′-end sequences are deleted and the 3′-end sequences retained is distinctive in its ability to interfere with virions of heterologous serotype as well as with those of the homologous serotype (15). Although DI particles with more-complex genome structures have recently been found in VSV New Jersey (14), the origin of all DIs can be explained by a “leaping or jumping replication complex” and copy-back or more probably copy-choice synthesis (10). The mechanism of specific DI particle-mediated interference appears to be at the level of competition for replication complexes.

It is considered that DI particles play an important role in the modulation or self-limitation of infection according to a theory originally expounded as long ago as 1970 by Huang and Baltimore (8). Definitive evidence in support of this is still lacking, however, because of failure to recover DI particles directly from infected animals.

**STRUCTURAL PROTEINS OF RHABDOVIRUS**

Although large and distinctive in dimensions (175 x 68 mm for VSV), rhabdoviruses are structurally simple. There are only five gene products and all are structural components of the virion. Much of the work elucidating the structure of VSV and rabies virus has been carried out at Pirbright, initially in the Biophysics Department under Dr Claude Bradish and later in the Biochemistry Department under Dr Fred Brown. Table I lists the properties and principal functions of the five proteins of VSV. Several of the proteins have multi-functional roles.

**THE RHABDOVIRUS GENOME**

The total sequence of the San Juan strain of VSV Indiana has been determined (16) and a good part of the genome of the Indiana C strain. The significant feature of the VSV genome is its economy; ninety-nine per cent of the genome is transcribed, and eighty-five per cent translated. There are five genes encoding the five
The virion and three morphological types of defective interfering (DI) particles of VSV Indiana serotype

1a. The virion.
1b. The standard DI particle.
FIG. 1 (cont.)
The virion and three morphological types of defective interfering (DI) particles of VSD Indiana serotype

1c. The long DI particle associated with certain ts mutants and similar to the heterotypically interfering DI particle of the Toronto HR-strain.
1d. The small DI particle associated with the group III mutants of VSV Indiana.
### TABLE I

The organisation of the genome of VSV Indiana

<table>
<thead>
<tr>
<th>Regions</th>
<th>Untranscribed (No. of nucleotides)</th>
<th>Transcribed sequences (No. of nucleotides)</th>
<th>Polypeptide-coding sequences (No. of nucleotides)</th>
<th>Gene product</th>
<th>Inferred MW of polypeptides (No. of amino acids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3'-terminal leader</td>
<td></td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leader:N junction</td>
<td>3(AAA)</td>
<td></td>
<td></td>
<td>(Leader RNA)</td>
<td></td>
</tr>
<tr>
<td>N gene</td>
<td>1333</td>
<td>1266</td>
<td>Nucleocapsid protein (N)</td>
<td>47,355 (422 amino acids)</td>
<td></td>
</tr>
<tr>
<td>N:NS junction</td>
<td>2(GA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS gene</td>
<td>822</td>
<td>666</td>
<td>Core-ancillary</td>
<td>25,110 (222 amino acids)</td>
<td></td>
</tr>
<tr>
<td>NS:M junction</td>
<td>2(CA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M gene</td>
<td>838</td>
<td>687</td>
<td>Non-glycosylated membrane protein (M)</td>
<td>26,064 (229 amino acids)</td>
<td></td>
</tr>
<tr>
<td>M:G junction</td>
<td>2(GA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G gene</td>
<td>1672</td>
<td>1533</td>
<td>Glycosylated membrane</td>
<td>57,416 (511 amino acids)</td>
<td></td>
</tr>
<tr>
<td>G:L junction</td>
<td>2(GA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L gene</td>
<td>6380</td>
<td>6327</td>
<td>Core-polymerase protein (L)</td>
<td>241,012 (2109 amino acids)</td>
<td></td>
</tr>
<tr>
<td>5'-terminal tail</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total No. of nucleotides in genome = 11,162
proteins with intergenic junctions of no more than 2-4 nucleotides. The features of the sequence are summarised in Table I. This is the pattern for the Indiana serotype of VSV and probably the other members of the genus Vesiculovirus, but new data indicate that the order of the genes may be different in the fish rhabdoviruses spring viraemia of carp (9) and infectious haematopoietic necrosis virus. In the rabies virus genome there is a long intercistronic sequence between the G and L genes in place of the intercistronic dinucleotide in the VSV genome. This sequence is sufficient to accommodate an additional gene (21). This extra sequence may represent either an evolving gene or a relict gene, since all three reading frames are interrupted. In infectious haematopoietic necrosis virus-infected cells there is clear evidence of a sixth gene product.

As sequence information accumulates it will become possible to deduce the evolutionary relationships of rhabdoviruses. Fig. 2 illustrates diagrammatically a comparison of the 3'-terminal regions of the genomes of the four vesiculoviruses, VSV Indiana, VSV New Jersey, Cocal virus and Chandipura virus. The sequences show varying degrees of relationship corresponding to the extent of serological divergence, coupled with conservation of sequence at strategic points such as the extreme termini. Sequence analyses of ts mutations in the G, NS and M genes have confirmed that phenotypic changes can result from substitution of single nucleotides (5, Gallen et al., in prep.; Elliott et al., in prep.), i.e. changes equivalent to approximately 0.01% of the genome. Laboratory strains of the same serotype differ in 1-2% of their nucleotides, whereas all serotypes differ in 40% or more of their nucleotides. More distantly related members of the Vesiculovirus genus differ in 80% or more of their nucleotides, although, as shown in Fig. 2, there may be localised regions of greater homology. Comparison of the sequences of the Indiana and New Jersey serotypes of VSV have also revealed differences between individual genes, e.g. the G, M and N genes all show greater than 50% homology, whereas the NS genes appear to be more variable and have only 41% of their nucleotides in common. Significant homologies have even been reported between VSV and the paramyxovirus Sendai virus, suggesting a common evolutionary origin for these two families of negative stranded RNA viruses (6).

THE CONTRIBUTION OF VSV TO THE DEVELOPMENT OF ANIMAL VIRUS GENETICS

Conventional genetic analysis is limited by the apparent inability of rhabdoviruses in common with other unsegmented negative strand RNA viruses to undergo genetic recombination. Sensitive experiments using parental viruses with mutations affecting the properties of four of the five structural proteins of the virion have failed to yield any evidence of exchange of genetic material during mixed infection. Complementation analysis, on the other hand, has been particularly effective in determining the functions of the rhabdovirus genome and has provided a model for genetic analysis of non-recombining viruses (12). The initial choice of VSV Indiana for genetic analysis proved to be fortunate because five non-overlapping groups of complementing temperature-sensitive (ts) mutants were defined at an early stage, and subsequent work confirmed that these complementation groups correspond to the five viral genes. (A sixth group defined later now appears to represent intracomplementation between mutants of one of the five original groups). Table II lists the general properties of these ts mutants and their gene assignments.
FIG. 2

Comparison of sequences at the 3'-termini of four vesiculovirus genomes

For pairs of sequences, and for all four, regions of homology are represented by a heavy line. Where necessary realignment has been carried out to accommodate different leader-N gene junction lengths.

TABLE II
Gene assignment of Indiana and New Jersey VSV serotypes

<table>
<thead>
<tr>
<th>Virus</th>
<th>Group</th>
<th>Assignment</th>
<th>Critical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSV Indiana</td>
<td>I</td>
<td>L</td>
<td>Thermolability of L in <em>in vitro</em> polymerase reconstitution.</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>NS</td>
<td>Partial proteolysis; tryptic peptide mapping.</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>M</td>
<td>Partial proteolysis; tryptic peptide mapping; RNA heteroduplex mapping.</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>N</td>
<td>Partial proteolysis; tryptic peptide mapping.</td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>G</td>
<td>Rescue by pseudotype formation; G protein <em>in vivo</em> instability; nucleotide sequencing and expression <em>in vitro</em>.</td>
</tr>
<tr>
<td></td>
<td>(VI)</td>
<td>(NS)</td>
<td>Phenotypic resemblance to group II in UV-inactivation experiments; reconstitution-infectivity assay.</td>
</tr>
<tr>
<td>VSV New Jersey</td>
<td>A</td>
<td>N</td>
<td>Thermolability; aberrant electrophoretic mobility.</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>L</td>
<td><em>In vitro</em> polymerase reconstitution; reversible thermolability <em>in vitro</em>.</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>M</td>
<td><em>In vivo</em> degradation; peptide mapping.</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>(G)</td>
<td>None. Assignment by exclusion only.</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>NS</td>
<td>Aberrant electrophoretic mobility; <em>in vitro</em> polymerase reconstitution; tryptic peptide maps; nucleotide sequencing.</td>
</tr>
<tr>
<td></td>
<td>(F)</td>
<td>L</td>
<td><em>In vitro</em> polymerase reconstitution.</td>
</tr>
</tbody>
</table>

The L gene mutants of VSV Indiana (Complementation Group I) have been instrumental in confirming by dissociation and reconstruction experiments that the L protein represents the virus-specified RNA-dependent RNA polymerase, and establishing that it has multiple roles in multiplication being concerned in replication, transcription and maturation. The L gene mutants have not yet been mapped in molecular terms because of the large size of the L gene which embraces more than half the genome (Table I), but this will be an important factor in locating the different functional domains of the L protein. Two of these mutants have recently found a novel use in detecting expression of a DNA copy of the VSV L gene incorporated into a vaccinia virus vector by complementation of the gene product (17).

The G gene mutants (Complementation Group V) have been useful in elucidating the steps involved in the biosynthesis and post-translational modification of
glycoprotein. The VSV Indiana mutants are defective for different stages of G protein transport because of either incomplete glycosylation or defective fatty acid acetylation. Gallione and Rose (pers. comm.) found that surface expression of the G protein in Cos-1 cells carrying the ts 045 (V) gene in an expression vector was temperature-sensitive whereas it was not with the wild type or a revertant gene in the same vector. The site of the ts mutation was located to a single substitution of phenylalanine by serine at position 204. This change is sufficient to prevent transport of the G protein to the cell surface. A ts mutant of VSV Cocal has been characterised which is partially defective in glycosylation at the permissive temperature and totally deficient in glycosylation at the restrictive temperature (Ghosh et al., in prep.), revealing that the presence of only one of the two oligosaccharide chains associated with the normal G protein is sufficient to allow transport of the G protein to the plasma membrane and normal maturation.

The M gene mutants (Complementation Group III) have contributed to analysis of the role of the M protein, confirming its involvement in transcription in addition to its role as a structural protein.

The NS gene mutants (Complementation Group II) of VSV Indiana have helped to clarify the role of this protein in biosynthesis; however, the corresponding mutants of the New Jersey serotype (Complementation Group E) have been characterised in great detail (12). The mutation in all three of the mutants making up this complementation group have been located to a six amino acid stretch of the 222 amino acid polypeptide. Each of the mutants appears to affect a different aspect of the replication cycle, but the phenotypes observed are consistent with the current interpretation of the role of this protein as an ancillary protein responsible for transport of the N protein within the cell to the site of nucleocapsid formation (22).

The N gene mutants (Complementation Group IV) are the least characterised, possibly reflecting the dominant structural role of this protein, although they have been used extensively in studying replication because certain group IV mutants have properties which allow them to be used experimentally to separate mRNA synthesis and genome template synthesis.

MECHANISM OF GENETIC CHANGE IN RHABDOVIRUSES

Sufficient sequencing of individual ts mutants has been carried out to confirm the prediction that base analogue-induced mutations are predominantly single base changes, whereas spontaneous mutants are more complex. Remarkably it has been established that single amino acid changes in the G polypeptide of rabies virus can drastically alter the virulence for the adult mouse of this otherwise apparently biologically very stable virus (4). Although strains of rabies virus appear to undergo genetic drift and gradual alteration of phenotypic properties while still retaining full virulence, reversion to virulence of apparently fully attenuated fixed virus can occur during a single or a few passages in cultured neuroblastoma cells. This paradox remains to be fully explored, although it is apparent that the critical mutation involves a receptor-binding site.

Because of the absence of recombination, genetic variation appears to arise solely by mutation. The frequency of single site mutation in the VSV genome has been estimated from the overall frequency of occurrence of the ts phenotype, or the frequency of monoclonal antibody resistant clones, indicating that the frequency is high (circa 10⁻⁴), although no higher than in other negative strand RNA viruses (11). Steinhauer and Holland (19) have developed a procedure for direct measure-
ment of the frequency of mutation of individual nucleotides in the VSV genome. This has revealed that even in evolutionary conserved regions of the genome such as the leader sequence the mutation frequency of individual nucleotides is very high and in the range 2-3 × 10⁻⁴. The rhabdoviruses are thus highly mutable agents with the potential to change very rapidly in the face of varying selective forces. Although essentially stable under normal conditions of lytic infection, Holland and colleagues (7) have shown that the genome of VSV propagated at high multiplicity or under conditions of persistent infection undergoes rapid and progressive change.

Another factor which determines genetic variability is the fidelity of transcription of the virion polymerase. High mutability is associated with the tsD1 mutant of VSV New Jersey and mutations can be induced in heterologous rhabdoviruses replicating in the same cells. These data are consistent with the existence of a transacting “mutator” polymerase in mutant tsD1 (13).

OUTSTANDING PROBLEMS AND TARGETS FOR FUTURE RESEARCH

Great progress has been made in definition of the genome of VSV and the functions of the gene products. But other problems remain to be tackled. It is clear that the whole biology of VSV is driven by the characteristics of the virion polymerase. Now that the sequence of the gene encoding the L protein, which comprises more than half the entire genome, is known, analysis of L gene function is open to experimental analysis. The existence of conditional lethal mutants of the L gene affecting host range indicates that host factors interact with the virion polymerase; the identity and precise role of these host factors have to be established for full understanding of rhabdovirus replication. Dissociation of the host component in replication could open the way to design of effective antiviral compounds.

Another question of great interest is the evolutionary relationship of the rhabdoviruses to other negative strand RNA viruses, and of the different members of the rhabdovirus group to one another. An increasing number of viruses from animals as diverse as bats and insects which show serological relationships with the classical strains of rabies virus are being identified, and the use of monoclonal antibodies is revealing unexpected variation among rabies viruses. The origin and the nature of the variability of these viruses are important issues for human and veterinary medicine.

Notwithstanding the dramatic progress in the understanding of the molecular biology of rhabdoviruses, many of the viruses in this group continue to cause disease problems (e.g. vesicular stomatitis, bovine ephemeral fever, and certain infections producing serious economic losses in fish farming). Rabies remains an important problem in both veterinary and human medicine, and much current research in rhabdoviology is focused on production of cheaper rabies virus vaccines by recombinant DNA technology. The recognition of an increasing number of rabies-like viruses may necessitate development of a corresponding range of vaccines.

The interpretation of mutational change in terms of the secondary (and eventually tertiary) structure of proteins, in the manner currently applied to analysis of the structure and function of the haemagglutinin and neuraminidase of influenza virus and the coat protein of FMDV and other picornaviruses, will be an important step towards elucidating the pathogenesis of rhabdovirus-induced disease in molecular terms and devising other strategies for disease control. Wunner et al. (22)
have identified a single amino acid substitution in the G protein of rabies virus which alters conformation of the polypeptide allowing glycosylation to occur at an adjacent site. This represents the first successful attempt to assess the precise effect of an amino acid substitution on the conformational state of a rhabdovirus protein and is likely to be the forerunner of a future trend.

ACKNOWLEDGEMENT

I am indebted to Dr J.B. Brooksby FRS for information on the history of VSV research in the UK.

*  
*  

COMPOSITION ET STRUCTURE DES RHABDOVIRUS. — C.R. Pringle.

Résumé : Dans la famille des Rhabdoviridae, deux virus ont fait l’objet de recherches particulières : un vésiculovirus, agent de la stomatite vésiculeuse, et un lyssavirus, agent de la rage. Le premier a été choisi comme virus de référence en virologie moléculaire en raison de sa morphologie unique et de la structure de son génome. Il produit un grand nombre de particules interférentes défectueuses qui pourraient contribuer à la modulation de l’infection chez l’hôte.

L’auteur décrit le génome du virus de la stomatite vésiculeuse et son intérêt comme modèle pour l’analyse génétique des virus non-recombinants. Les fonctions de ses cinq gènes sont précisées : elles permettent notamment de comprendre les mécanismes des variations génétiques chez les rhabdovirus, qui semblent se produire uniquement par mutation.

Les objectifs de recherche pour l’avenir portent sur les interactions entre les gènes viraux et les facteurs de l’hôte ainsi que sur les relations évolutives entre les différents rhabdovirus. Dans ce contexte, les variations du virus rabique ont des conséquences très importantes en médecine humaine et vétérinaire.


*  
*  

COMPOSICIÓN Y ESTRUCTURA DE LOS RHABDOVIRUS. — C.R. Pringle.

Resumen : En la familia de los Rhabdoviridae, se han investigado especialmente dos virus : un vesiculovirus, agente de la estomatitis vesicular, y un lyssavirus, agente de la rabia. Se adoptó el primero como virus de referencia en virología molecular debido a su morfología única y a la estructura de su genoma. Produce gran número de partículas interferentes defectuosas que podrían contribuir a la modulación de la infección en el huésped.

Describe el autor el genoma del virus de la estomatitis vesicular y su interés como modelo para el análisis genético de los virus no recombinantes. Se consignan las funciones de sus cinco genes : permiten especialmente comprender
los mecanismos de las variaciones genéticas en los rhabdovirus que según parece, se producen únicamente por mutación.

Los objetivos de investigación para el futuro se refieren a las interacciones entre los genes viricos y los factores del huésped, así como a las relaciones evolutivas entre los distintos rhabdovirus. En este contexto, las variaciones del virus rábico tienen consecuencias de suma importancia en medicina humana y veterinaria.


* *

REFERENCES


