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Togaviridae[1]

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Summary. The family ***Togaviridae*** comprises four genera: *Alphavirus* (with 26 species), *Rubivirus* (one species), *Pestivirus* (three species), and *Arterivirus* (one species). The main characteristics of the member viruses are: (i) the virus particles are spherical, 50–70 nm in diameter, including an envelope with surface projections that incorporate two or three polypeptides, usually glycosylated; (ii) the nucleocapsid comprises a core protein and a single strand of positive-sense RNA, molecular weight about 4×10^6; where characterized, the RNA has an m^7G 'cap' at the 5′ end and is polyadenylated at the 3′ end; (iii) maturation occurs by budding of spherical nucleocapsids 30–35 nm in diameter, with proven or presumed icosahedral symmetry, through cytoplasmic membranes. Where characterized, translation of structural proteins occurs on subgenomic messenger RNA(s); these appear to represent the 3′ end of the genome. Nearly all alphavirus species are transmitted by mosquitoes. Transmission also occurs transovarially (*Alphavirus*) or transplacentally (*Rubivirus* and *Pestivirus*). Members of a genus are serologically related, but are not related to members of other genera.

The ***Togaviridae*** are a family of spherical, enveloped, positive-stranded RNA viruses; the single piece of RNA has a molecular weight of about 4×10^6 [1]. The name 'togavirus' refers to the envelope and is derived from the Latin 'toga' – a Roman mantle or cloak. In 1978 the Arbovirus Study Group defined four genera in the family ***Togaviridae:*** *Alphavirus*, *Flavivirus*, *Rubivirus*, and *Pestivirus* [2]. At that time, the strategy of replication had been characterized only for the *Alphavirus* genus. The subsequent acquisition of additional molecular data on the other genera has led to a taxonomic revision of the family. Recently, the ***Togaviridae*** Study Group submitted two proposals to the International Committee on Taxonomy of Viruses, and

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these proposals were approved in 1984. Accordingly, the *Flavivirus* genus has been elevated to the status of a family, the ***Flaviviridae*** [3]; the members differ from togaviruses in regard to molecular structure of the virion, gene sequence and replication strategy, and probably in mode of morphogenesis. The other taxonomic change is the creation within the ***Togaviridae*** of a new genus, *Arterivirus*, based on the possible togavirus member specified previously, equine arteritis virus [1]. At present, *Arterivirus* is a monospecific genus, like *Rubivirus*, whereas the *Alphavirus* and *Pestivirus* genera currently comprise 26 and 3 species, respectively.

Members of the four genera that now comprise the ***Togaviridae*** have a diameter of 50–70 nm and mature by budding of nucleocapsids through plasma membranes or intracytoplasmic membranes (evidence for budding is still elusive for the *Pestivirus* genus) [4]. The virus envelope carries surface projections associated with two proteins (E1 and E2, sometimes also an E3) that are usually glycosylated. E1 is the functional hemagglutinin for alphaviruses and probably for rubella virus [5–8]. The envelope encloses the spherical nucleocapsid (diameter 28–35 nm) with proven or presumed icosahedral symmetry [4]; the nucleocapsid comprises the single strand of positive-sense RNA and the core protein C. Where characterized, the RNA has an m^7G cap at the 5′ end and is polyadenylated at the 3′ end. Although not yet established for the *Pestivirus* genus, a common replication strategy of the family appears to be the use of one or more polyadenylated subgenomic messengers. The major family criterion is probably the gene sequence. This is known in complete detail only for the *Alphavirus* genus [9], in which the genes for nonstructural proteins are located at the 5′ end of the genome and those for the structural proteins are located towards the 3′ end.

Icosahedral symmetry has been reported for the capsid in the *Alphavirus* genus [see discussion in 10]; in highly purified preparations, the envelope proteins appear to be arranged in trimer clusterings, forming an icosahedron for which T = 4 [10]. On the surface of *Pestivirus* and *Arterivirus* species are ring-like subunits, 10–12 or 12–15 nm in diameter, respectively [4, 11, 12]. The *Pestivirus* virions have a lower buoyant density than other togaviruses (1.12–1.13 g/cm^3 in sucrose as compared with 1.17–1.19 g/cm^3) and a lower sedimentation coefficient (S_{20w} = 140 as compared with 220–280) [13].

The chemical structure and composition of members of the *Alphavirus* genus are well documented [6, 14–16]. The molecular weights of the structural proteins are: E1 and E2, $(50–59) \times 10^3$; E3 (when present), 10×10^3; C, $(30–34) \times 10^3$ [6]. The gene sequence is 5′nsP1-nsP2-nsP3-nsP4-C-E3-E2-E1-3′, confirmed from the complete nucleotide sequence of Sindbis virus RNA [9]. The alphavirus replication strategy was reviewed recently [14, 17]. The four nonstructural (ns) proteins are translated directly from the genomic RNA; complementation assays with RNA$^-$ temperature-sensitive mutants suggest a polymerase role for each nonstructural protein [9, 14]. Synthesis of a subgenomic 26S messenger RNA is initiated internally on a full-length, minus-strand template, and it is capped and polyadenylated. Translation of the amplified 26S RNA is initiated at a single site, commencing with the C protein, which is cleaved first from the nascent polyprotein. The translation sequence continues as P62 (subsequently cleaved to E3 and E2), 4,200 dalton (4.2K) or 6K, and E1 polypeptides;

E2 and E1 are inserted via amino-terminal signal sequences in the endoplasmic reticulum and are later glycosylated en route to the Golgi apparatus and plasma membrane. The polyprotein precursor of the structural proteins is as much as 75% homologous between species [9]. At least 22 of the 26 species are transmitted by mosquitoes, infect a wide range of vertebrates and produce various febrile diseases, some with rash, arthritis or encephalitis. The species comprise six serologic complexes [18] which are based largely on the antibody reactions associated with E1 (hemagglutinin-inhibition) and E2 (neutralization) [5].

Rubella virus (*Rubivirus* genus) RNA is polyadenylated and sediments more slowly than alphavirus RNA [19, 20]; it differs also in base composition [21]. The sizes of the structural proteins, the lipid content, the gene sequence, and the replication strategy all appear to be very similar to those of alphaviruses [7, 8, 22–25]. The envelope glycoproteins and core protein are translated as a polyprotein from a polyadenylated subgenomic 24S messenger RNA and are posttranslationally cleaved in the sequence NH_2–C–E2–E1–COOH [23]. E2 is heterogeneous due to variable glycosylation [7, 8, 25, 26]. Virions mature by budding through membranes (Golgi, vacuoles, plasma membrane) [4]. Man is the only host.

Pestivirus species possess at least two envelope glycoproteins, E1 and E2, and a core protein C [27, 28]; their sizes are similar to their counterparts in the *Alphavirus* and *Rubivirus* genera. Larger structural proteins also have been reported [29]. Very little information is available on their replication; only a single species of virus-specific RNA [relative molecular mass (M_r) about 3×10^6] with anomalous sedimentation behavior and unusual RNase resistance was identified in cells infected with mucosal disease virus [30]. Virions accumulate within the cisternae of membranous organelles [4, 11, 12, 31]. The three species in the genus show antigenic relationships by immunodiffusion, antibody neutralization, and fluorescence [11, 12]. The natural hosts worldwide are swine and ruminants in which generalized infections and transplacental transmission occur [11, 12].

The structural proteins of equine arteritis virus (*Arterivirus* genus) are all much smaller than those of the other togaviruses. Of the two envelope proteins E1 and E2 (M_r 21×10^3 and 14×10^3, respectively), only E1 is glycosylated; the core protein C (M_r 12×10^3) is the smallest [32]. A genomic sized RNA and five subgenomic RNA species (M_r range from 0.2×10^6 to 1.3×10^6) are specified in infected cells; these are all polyadenylated, and the subgenomic species may be derived from a larger precursor [33, 34]. Virus particles bud from and accumulate within cytoplasmic vesicles [4, 11, 12].

Possible members of the ***Togaviridae*** include lactic dehydrogenase virus and an enveloped plant virus, carrot mottle virus [1, 2]. The latter is classified mainly on morphological criteria [35]. Lactic dehydrogenase virus has morphological and physicochemical properties similar to equine arteritis virus [11, 12] but is unrelated to it serologically [36]. Replication occurs only in mouse macrophages, and virions mature by budding through intracytoplasmic membranes [11, 12]. Attempts to detect subgenomic RNA were unsuccessful [37]. In the absence of further information, this interesting virus remains classified as a possible togavirus.

In summary, the ***Togaviridae*** comprise four genera and two possible members. The spherical, enveloped virions are of proven or

presumed icosahedral symmetry, 50–70 nm in diameter, with peplomers comprised of at least two different proteins, usually glycosylated. They contain infectious single-stranded RNA of molecular weight about 4×10^6. Where characterized, the RNA is capped at the 5′ end and polyadenylated at the 3′ end. The gene sequence commences with the genes for the nonstructural proteins, which are translated directly from the genomic RNA, whereas the structural proteins are translated from at least one subgenomic RNA. Morphogenesis occurs by budding of preformed nucleocapsids through cytoplasmic or plasma membranes. The host range for the mosquito-transmitted members of the *Alphavirus* genus includes a wide range of vertebrates, whereas the host range for the other genera is restricted to only one or a few mammals. Transplacental transmission occurs in the *Rubivirus* and *Pestivirus* genera. A wide range of asymptomatic infections and varied clinical symptoms are produced. Species within a genus are serologically related to each other but are not related to members of other genera.

Togaviridae, Genus *Alphavirus*

1 Taxonomy
1.1 Family: ***Togaviridae.***
1.1.1 Genus: *Alphavirus.*
1.2 Taxonomic status: Genus in family ***Togaviridae.***
1.3 Relationships with other groups: Some similarities to flaviviruses.
2 The virion
2.1 Chemical composition
2.1.1 Nucleic acid
2.1.1.1 RNA
2.1.1.2 Single-stranded
2.1.1.3 Linear
2.1.1.4 Number of pieces: One.
2.1.1.5 Sedimentation coefficient(s): 42–49S (best value, 49S – Sindbis).
2.1.1.6 Molecular weight: 4×10^6.
2.1.1.7 Percentage weight of virion: 6%.
2.1.1.8 Base composition: A, 28; G, 25; C, 26; U, 21 [Sindbis, from known nucleotide sequence of 11,703 bases, excluding the 3′ poly(A) tract].
2.1.1.9 Nearest neighbor analysis: Not known.
2.1.1.10 Homology studies: Conserved sequences of 19 nucleotides or less occur near both termini of the genome and at the start of the subgenomic 26S RNA [Sindbis, Highlands J, Semliki Forest virus (SFV)].
2.1.1.11 Infectivity: RNA is infectious.
2.1.1.12 Other features: 49S RNA serves as a messenger; type O cap and polyadenylated.
2.1.2 Proteins
2.1.2.1 Percentage weight of virion: 62%.
2.1.2.2 Number of polypeptides: 3 in Sindbis and several other species, 4 in SFV.
2.1.2.3 Molecular weights of polypeptides: E1 and E2, $(50–59) \times 10^3$; C, $(30–34) \times 10^3$; E3, 10×10^3.
2.1.2.4 Number of protein subunits in virion: 240 (SFV).
2.1.2.5 Enzymes: None.
2.1.2.6 Other functional proteins: Envelope glycoprotein E1 functions as a hemagglutinin. E2 fixes complement and induces production of neutralizing antibody.
2.1.3 Lipids
2.1.3.1 Percentage weight of virion: 26%.
2.1.3.2 Composition is host dependent.
2.1.4 Carbohydrates

2.1.4.1 Percentage weight of virion: About 6%.

2.1.4.2 Other features: Composition is host dependent; envelope glycoproteins incorporate complex or complex and high mannose glycans.

2.2 Physicochemical properties

2.2.1 Density: 1.18–1.19 g/cm^3 (in sucrose).

2.2.2 Sedimentation coefficient: 286S ± 22S.

2.2.3 Weight in daltons: 5×10^7.

2.2.4 Stability of infectivity

2.2.4.1 pH: Stable at pH 6.5–9.0.

2.2.4.2 Heat: Rapidly inactivated at 50°; more slowly at 37°.

2.2.4.3 Lipid solvents: Sensitive to lipid solvents.

2.2.4.4 Radiation: Rapidly inactivated by UV light.

2.2.4.5 Other agents: Very sensitive to ionic and nonionic detergents; relatively resistant to trypsin.

2.3 Structure

2.3.1 Nucleocapsid

2.3.1.1 Symmetry: Cubical.

2.3.1.2 Diameter and number of capsomeres in icosahedral form: 12–14 nm diameter (number = 32 or 42, indeterminate at present).

2.3.2 Envelope

2.3.2.1 Dimensions: 50 nm external diameter, excluding surface projections.

2.3.2.2 Composition: Lipid bilayer membrane containing 2–3 viral specific glycoproteins organized in trimer clusters with T = 4 (42 subunit) surface lattice symmetry.

2.3.3 Cores

2.3.3.1 Dimensions: 35 nm, 140S.

2.3.3.2 Composition: Ribonucleoprotein containing a single protein and 49S RNA; 240 protein subunits of molecular weight $(30–34) \times 10^3$ in core.

2.4 Morphology

2.4.1 Overall shape: Spherical, with spikes.

2.4.2 Dimensions: 50–55 nm in ultrathin sections; 60–65 nm in negatively stained preparations.

2.4.3 Surface projections: 6–10 nm long.

2.4.4 Special features in thin sections: Bilayer membrane with projections. Some have electron-lucent areas within the nucleocapsid.

2.4.5 Other features: Not established.

3 Replication

3.1 Site of accumulation of viral proteins: Cytoplasm, cytoplasmic and plasma membranes.

3.2 Nonstructural proteins

3.2.1 Number and molecular weight of polypeptides: 3 precursors to 3 or 4 viral structural proteins and 3 precursors to 4 nonstructural proteins. Molecular weights of structural precursors: 62×10^3, 98×10^3 and 130×10^3; nonstructural precursors: 150×10^3, 230×10^3 and 270×10^3 (Sindbis).

3.2.2 Virus-induced enzymes: RNA polymerase – probably 4 viral specified polypeptide components. Molecular weights: 60×10^3, 72×10^3, 76×10^3, 89×10^3 (Sindbis). An autocatalytic protease is apparently encoded in the nascent structural polyprotein.

3.3 Mode of nucleic acid replication

3.3.1 General account: Replication complex includes membranous cytoplasmic structures and viral specified polymerase. Input positive-strand 49S RNA is transcribed by

polymerase into complementary minus-strand 49S RNA, which serves as a template for subgenomic 26S and progeny 49S RNA.

3.3.2 Effects of inhibitors: Insensitive to actinomycin D. Guanidine – Sindbis relatively insensitive, SFV sensitive.

3.4 Site and mechanism of maturation: Intracellular formation of nucleocapsids; infectious virus released by budding through virus-modified host cell plasma membrane.

3.5 Other features: Viral 26S RNA represents the 3′ end of the genome and codes for structural proteins only, in the sequence 5′–C–E3–E2–E1–3′. 49S RNA codes for nonstructural proteins. Latent period is about 4 h. Translation of host messenger is blocked late in infection.

4 Cooperative interactions

4.1 Recombination: No.

4.2 Multiplicity reactivation: No.

4.3 Phenotypic mixing: Yes, among themselves, and with lactic dehydrogenase (LDH) virus.

4.4 Other interactions: Complementation with temperature-sensitive mutants; at least 7 complementation groups (4 RNA^-, 3 RNA^+).

5 Host range

5.1 Natural: Wide range of vertebrates and invertebrates (mosquitoes) and cimicids (2 viruses from swallow-bugs, Colorado, USA).

5.2 Experimental

5.2.1 In vivo: Wide range of vertebrates and invertebrates.

5.2.2 In vitro: Wide range of vertebrate and invertebrate cells.

6 Pathogenicity

6.1 Association with diseases: Mer - bers of genus cause varied clinic l syndromes including undiffere - tiated febrile illness, fever with ras , arthritis and encephalitis.

6.2 Tissue tropisms: Pantropic.

6.3 Cytopathology: In most vertebra e cells, not in invertebrate cells exce t in some instances with SFV in *Aed s aegypti*.

7 Geographic distribution: World-wide.

8 Transmission

8.1 Vertical: No [transplacental trans-mission, Venezuelan equine en-cephalitis (VEE)].

8.2 Horizontal: No (exceptionally, in VEE epidemics, by droplets).

8.3 Vectors

8.3.1 Biological: Yes.

8.3.2 Mechanical: Possibly.

9 Antigenic properties

9.1 Number of distinct antigenic mol - cules in virion: At least 3 – E1, E , and C.

9.2 Antigen(s) involved in virus neutra - ization: Envelope protein E2.

9.3 Number of distinct nonstructur l antigens: Probably 4.

9.4 Specificity of different antiger : Sindbis envelope protein, E2, is - rus-specific; E1, subgroup reacti ; core proteins, broadly cross-re - tive. Antisera prepared against c e and envelope do not cross-react. 2 and C are major complement-fixi g antigens.

9.5 Antigenic properties used for cl s-sification: Complement fixati n, hemagglutination inhibition, n - tralization, immunofluorescen e, solid-phase binding assays.

10 Classification

10.1 Brief definition of genus: Enveloped RNA viruses 60–65 nm in diameter. Contain a single linear molecule of single-stranded, polyadenylated and infectious RNA of molecular weight 4×10^6, with a capsid of cubic symmetry 35–39 nm in diameter which is enclosed within a lipoprotein envelope 50 nm in diameter. The gene sequence is 5′–nsP1–nsP2–nsP3–nsP4–C–E3–E2–E1–3′; the nonstructural proteins are associated with the RNA polymerase. Molecular weights of structural proteins are $(50–59) \times 10^3$ (E1 and E2), $(30–34) \times 10^3$ (C), and 10×10^3 (E3, if present), and these are translated from a 26S subgenomic mRNA. Envelope protein E1 functions as a hemagglutinin. Alphaviruses are serologically related to each other but are unrelated to other ***Togaviridae***; they multiply in the cytoplasm and mature by budding from cytoplasmic membranes; nearly all have mosquitoes as invertebrate hosts.

10.2 Genus: *Alphavirus*.

10.2.1 Type species: Sindbis virus, strain AR 339.

10.2.2 Other members: Aura, Barmah Forest, Bebaru, Cabassou, Chikungunya, eastern equine encephalitis, Everglades, Fort Morgan, Getah, Highlands J, Kyzylagach, Mayaro, Middelburg, Mucambo, Ndumu, O'Nyong-nyong, Pixuna, Ross River, Sagiyama, Semliki Forest, Tonate, Una, Venezuelan and western equine encephalitis, Whataroa.

Togaviridae, Genus *Rubivirus*

1 Taxonomy

1.1 Family: ***Togaviridae.***

1.1.1 Genus: *Rubivirus.*

1.2 Taxonomic status: Genus in family ***Togaviridae.***

1.3 Relationship with other groups: None.

2 The virion

2.1 Chemical composition

2.1.1 Nucleic acid

2.1.1.1 RNA

2.1.1.2 Single-stranded

2.1.1.3 Linear

2.1.1.4 Number of pieces: One.

2.1.1.5 Sedimentation coefficient: 40S.

2.1.1.6 Molecular weight: $(3.2–3.8) \times 10^6$.

2.1.1.7 Percentage weight of virion: About 3%.

2.1.1.8 Base composition: A, 22; G, 31; C, 34; U, 13.

2.1.1.9 Nearest neighbor analysis: Not known.

2.1.1.10 Homology studies: Not known.

2.1.1.11 Infectivity: RNA is infectious.

2.1.1.12 Other features: Poly(A) tract required for infectivity.

2.1.2 Proteins

2.1.2.1 Percentage weight of virion: 75%.

2.1.2.2 Number of polypeptides: 3.

2.1.2.3 Molecular weights of polypeptides: E1, $(58–59) \times 10^3$; E2, $(42–48) \times 10^3$; C, $(33–34) \times 10^3$. E2 is heterogeneous due to variable glycosylation.

2.1.2.4 Number of protein subunits in virion: Not known.

2.1.2.5 Enzymes: None.

2.1.2.6 Other functional proteins: E1 functions as hemagglutinin.

2.1.3 Lipids

2.1.3.1 Percentage weight of virion: 19% dry weight.
2.1.3.2 Other features: Phospholipid 69% and fatty acids 23% of total lipid.
2.1.4 Carbohydrates
2.1.4.1 Percentage weight of virion: 4%.
2.1.4.2 Other features: Both high mannose and complex glycans are incorporated in E1 and E2.
2.2 Physicochemical properties
2.2.1 Density: 1.19 g/cm^3.
2.2.2 Sedimentation coefficient: 286S ± 22S.
2.2.3 Weight in daltons: Not known.
2.2.4 Stability of infectivity
2.2.4.1 pH: Stable between pH 6.8 and 8.1.
2.2.4.2 Heat: Rapidly inactivated at 56°; more slowly at 37°.
2.2.4.3 Lipid solvents: Sensitive to lipid solvents.
2.2.4.4 Radiation: Rapidly inactivated by UV light.
2.2.4.5 Other agents: Thermal stabilization by $MgSO_4$.
2.3 Structure
2.3.1 Nucleocapsid
2.3.1.1 Symmetry: Probably cubic.
2.3.1.2 Diameter and number of capsomers in icosahedral forms: Not known.
2.3.2 Envelope
2.3.2.1 Dimensions: 60 nm external diameter.
2.3.2.2 Composition: Lipid bilayer membrane containing glycoproteins E1 and E2.
2.3.3 Cores
2.3.3.1 Dimensions: 30–35 nm, 160S.
2.3.3.2 Composition: Ribonucleoprotein containing protein C and 40S RNA.
2.4 Morphology
2.4.1 Overall shape: Spherical, with occasional protrusions.
2.4.2 Dimensions: 60 ± 8 nm.
2.4.3 Surface projections: Present; 6 nm long with enlarged ends.
2.4.4 Special features in thin sections: Not known.
2.4.5 Other features: Some virus particles are pleomorphic (elongated, or with multiple cores).
3 Replication
3.1 Site of accumulation of viral proteins: Cytoplasm.
3.2 Nonstructural proteins
3.2.1 Number and molecular weight of polypeptides: Several reported in molecular weight range from 13×10^3 to 200×10^3.
3.2.2 Virus-induced enzymes: Not known.
3.3 Mode of nucleic acid replication
3.3.1 General account: Input positive-strand 40S RNA is copied by virus-specified polymerase into complementary minus-strand 40S RNA which serves as template for synthesis of progeny 40S RNA and subgenomic 24S mRNA.
3.3.2 Effects of inhibitors: Not inhibited by DNA inhibitors or actinomycin D.
3.4 Site and mechanism of maturation: Assembly and maturation both intracytoplasmic and in the plasma cell membrane. Budding through cellular membranes.
3.5 Other features: Latent period is 8 h or greater. Structural proteins are translated from a subgenomic 24 S mRNA as a polyprotein which is posttranslationally cleaved in the sequence NH_2–C–E2–E1–COOH. Cell protein synthesis continues throughout infection.
4 Cooperative interactions

4.1 Recombination: No.
4.2 Multiplicity reactivation: No.
4.3 Phenotypic mixing: No.
4.4 Other interactions: No.
5 Host range
5.1 Natural: Man.
5.2 Experimental
5.2.1 In vivo: Narrow range of vertebrates. Possibly teratogenic in rabbits.
5.2.2 In vitro: Moderate range of vertebrate cells.
6 Pathogenicity
6.1 Association with diseases: In postnatal infection ranges from asymptomatic infection to exanthematic disease, exceptionally encephalitis. Teratological effects and fetal death in developing embryo.
6.2 Tissue tropisms: Pantropic. Replicates in human T cells, persists in B cells.
6.3 Cytopathology: Noncytopathic in most vertebrate cells; cytopathic in RK13, BHK21, SIRC, and Vero cells and in human primary cultures.
7 Geographic distribution: Worldwide.
8 Transmission
8.1 Vertical: Yes.
8.2 Horizontal: Yes.
8.3 Vectors
8.3.1 Biological: No.
8.3.2 Mechanical: Probably not.
9 Antigenic properties
9.1 Number of distinct antigenic molecules in virion: E1 (probably the hemagglutinin) and E2; complement-fixing and two precipitating antigens. Platelet agglutinin.
9.2 Antigen(s) involved in virus neutralization: E1 or E2.
9.3 Number of distinct nonstructural antigens: Not known.
9.4 Specificity of different antigens: E1 is immunoprecipitated by monoclonal antibody to hemagglutinin.
9.5 Antigenic properties used for classification: Complement fixation, hemagglutination inhibition, neutralization, immunofluorescence, immunoprecipitation.
10 Classification
10.1 Brief definition of genus: Enveloped RNA virus about 60 nm in diameter which multiplies in the cytoplasm and matures by budding through intracytoplasmic membranes or through plasma membrane. RNA is infectious and polyadenylated. A subgenomic 24S RNA codes for the structural proteins; their molecular weights are $(58–59) \times 10^3$ (E1), $(42–48) \times 10^3$ (E2), and $(33–34) \times 10^3$ (C). Serologically unrelated to other ***Togaviridae***. No invertebrate host. Vertebrate host: confined to man.
10.2 Genus: *Rubivirus*.
10.2.1 Type species: Rubella virus.
10.2.2 Other members: None.

Togaviridae, Genus *Pestivirus*

1 Taxonomy
1.1 Family: ***Togaviridae***.
1.1.1 Genus: *Pestivirus*.
1.2 Taxonomic status: Genus in family ***Togaviridae***.
1.3 Relationships with other groups: None.
2 The virion
2.1 Chemical composition

2.1.1 Nucleic acid
2.1.1.1 RNA
2.1.1.2 Single-stranded
2.1.1.3 Linear
2.1.1.4 Number of pieces: One.
2.1.1.5 Sedimentation coefficient(s): 38–40S.
2.1.1.6 Molecular weight: About 4×10^6.
2.1.1.7 Percentage weight of virion: Not known.
2.1.1.8 Base composition: Not known.
2.1.1.9 Nearest neighbor analysis: Not known.
2.1.1.10 Homology studies: Not known.
2.1.1.11 Infectivity: RNA is infectious.
2.1.1.12 Other features: None.
2.1.2 Proteins
2.1.2.1 Percentage weight of virion: Not known.
2.1.2.2 Number of polypeptides: 3.
2.1.2.3 Molecular weights of polypeptides: Envelope – glycoproteins E1, $(55–57) \times 10^3$ and E2, $(44–46) \times 10^3$; core – C, $(34–36) \times 10^3$. Larger proteins also reported.
2.1.2.4 Number of protein subunits in virion: Not known.
2.1.2.5 Enzymes: None.
2.1.2.6 Other functional proteins: None.
2.1.3 Lipids
2.1.3.1 Percentage weight of virion: Not known.
2.1.3.2 Other features: None.
2.1.4 Carbohydrates
2.1.4.1 Percentage weight of virion: Not known.
2.1.4.2 Other features: None.
2.2 Physicochemical properties
2.2.1 Density: 1.12–1.15 g/cm^3.
2.2.2 Sedimentation coefficient: 138S ± 11S.
2.2.3 Weight in daltons: Not known.
2.2.4 Stability of infectivity
2.2.4.1 pH: Stable at pH 6–9.
2.2.4.2 Heat: Rapidly inactivated at 56 ; more slowly at 37°.
2.2.4.3 Lipid solvents: Sensitive.
2.2.4.4 Radiation: Rapidly inactivated by UV light.
2.2.4.5 Other agents: Very sensitive to ionic and nonionic detergents; sensitive to trypsin.
2.3 Structure
2.3.1 Nucleocapsid
2.3.1.1 Symmetry: Probably icosahedral.
2.3.1.2 Diameter and number of capsomeres in icosahedral form: Surface ring-like structures 10–12 nm in diameter; number not known.
2.3.2 Envelope
2.3.2.1 Dimensions: 50–60 nm external diameter.
2.3.2.2 Composition: Lipid bilayer containing the glycoproteins E1 and E2.
2.3.3 Cores
2.3.3.1 Dimensions: 27–35 nm.
2.3.3.2 Composition: Ribonucleoprotein containing protein C and 38–40S RNA.
2.4 Morphology
2.4.1 Overall shape: Spherical.
2.4.2 Dimensions: 50–60 nm.
2.4.3 Surface projections: Present; projections probably lost from smooth particles.
2.4.4 Special features in thin sections: Smooth bilayer membrane; core is spherical, 25–35 nm in diameter.
2.4.5 Other features: None.
3 Replication
3.1 Site of accumulation of viral proteins: Cytoplasm.
3.2 Nonstructural proteins

.2.1 Number and molecular weight of polypeptides: Not known.
.2.2 Virus-induced enzymes: Not known.
.3 Mode of nucleic acid replication
.3.1 General account: Not known.
.3.2 Effects of inhibitors: Insensitive to actinomycin D; inhibited by proflavine.
.4 Site and mechanism of maturation: In cytoplasmic vesicles, presumably by budding.
.5 Other features: Latent period 8–10 h.
4 Cooperative interactions
4.1 Recombination: No.
4.2 Multiplicity reactivation: No.
4.3 Phenotypic mixing: No.
4.4 Other interactions: Intrinsic interference with Newcastle disease virus.
5 Host range
5.1 Natural: Swine (hog cholera) or ruminants (other virus species).
5.2 Experimental
5.2.1 In vivo: Narrow range of susceptible vertebrates.
5.2.2 In vitro: Narrow range of vertebrate cells.
6 Pathogenicity
6.1 Association with diseases: Ranges from asymptomatic infection to fatal disease; teratological and fatal effects on the developing embryo.
6.2 Tissue tropisms: Pantropic.
6.3 Cytopathology: Noncytopathic strains are frequent in bovine virus diarrhea and are usual in hog cholera.
7 Geographic distribution: Worldwide.
8 Transmission
8.1 Vertical: Yes.
8.2 Horizontal: Yes.
8.3 Vectors
8.3.1 Biological: No.
8.3.2 Mechanical: Possible.
9 Antigenic properties
9.1 Number of distinct antigenic molecules in virion: Three.
9.2 Antigen(s) involved in virus neutralization: Probably E1 or E2.
9.3 Number of distinct nonstructural antigens: Not known.
9.4 Specificity of different antigens: Not known.
9.5 Antigenic properties used for classification: Neutralization, immunoprecipitation, immunofluorescence.
10 Classification
10.1 Brief definition of genus: Enveloped RNA viruses 50–60 nm in diameter which multiply in the cytoplasm and accumulate in cytoplasmic vesicles. Molecular weights of structural proteins most uniformly reported are $(55–57) \times 10^3$ (E1), $(44–46) \times 10^3$ (E2), and $(34–36) \times 10^3$ (C). The virions have a significantly lower buoyant density and sedimentation coefficient than the other togaviruses. Serologically interrelated but unrelated to other ***Togaviridae***. No invertebrate host. Vertebrates affected are bovines, swine, sheep and goats. Vertical transmission is common.
10.2 Genus: *Pestivirus.*
10.2.1 Type species: Mucosal disease-bovine virus diarrhea virus, strain Oregon C24V.
10.2.2 Other members: Hog cholera virus (swine fever virus), border disease virus.

Togaviridae, Genus *Arterivirus*

1 Taxonomy
1.1 Family: ***Togaviridae.***
1.1.1 Genus: *Arterivirus.*
1.2 Taxonomic status: Genus in family ***Togaviridae.***
1.3 Relationship with other groups: The structural proteins of lactic dehydrogenase virus, a possible member of the ***Togaviridae***, are in the same size range but there is no antigenic relationship.
2 The virion
2.1 Chemical composition
2.1.1 Nucleic acid
2.1.1.1 RNA
2.1.1.2 Single-stranded
2.1.1.3 Linear
2.1.1.4 Number of pieces: One.
2.1.1.5 Sedimentation coefficient: 48S.
2.1.1.6 Molecular weight: $(4.1–4.3) \times 10^6$.
2.1.1.7 Percentage weight of virion: Not known.
2.1.1.8 Base composition: Not known.
2.1.1.9 Nearest neighbor analysis: Not known.
2.1.1.10 Homology studies: Not known.
2.1.1.11 Infectivity: RNA is infectious.
2.1.1.12 Other features: Polyadenylated, probably at 3′ terminus.
2.1.2 Proteins
2.1.2.1 Percentage weight of virion: Not known.
2.1.2.2 Number of polypeptides: Three.
2.1.2.3 Molecular weights of polypeptides: E1, 21×10^3; E2, 14×10^3; C, 12×10^3. (E1 is a glycoprotein.)
2.1.2.4 Number of protein subunits in virion: Not known.
2.1.2.5 Enzymes: None.
2.1.2.6 Other functional proteins: None known.
2.1.3 Lipids
2.1.3.1 Percentage weight of virion: Not known.
2.1.3.2 Other features: Not known.
2.1.4 Carbohydrates
2.1.4.1 Percentage weight of virion: Not known.
2.1.4.2 Other features: None.
2.2 Physicochemical properties
2.2.1 Density: 1.15–1.17 g/cm^3 in sucrose.
2.2.2 Sedimentation coefficient: 224S ± 8S.
2.2.3 Weight in daltons: Not known.
2.2.4 Stability of infectivity
2.2.4.1 pH: Sensitive to acid pH.
2.2.4.2 Heat: Rapidly inactivated at 57°, more slowly at 37°.
2.2.4.3 Lipid solvents: Sensitive to lipid solvents.
2.2.4.4 Radiation: Not known.
2.2.4.5 Other agents: Sensitive to detergents; resistant to trypsin.
2.3 Structure
2.3.1 Nucleocapsid
2.3.1.1 Symmetry: Probably icosahedral.
2.3.1.2 Number of capsomeres: Not known.
2.3.2 Envelope
2.3.2.1 Dimensions: 60 nm external diameter.
2.3.2.2 Composition: Includes one glycoprotein (E1) and one nonglycosylated polypeptide (E2).
2.3.3 Cores
2.3.3.1 Dimensions: 35 nm in diameter; 158S.
2.3.3.2 Composition: Ribonucleoprotein containing protein C and 48S RNA.
2.4 Morphology
2.4.1 Overall shape: Spherical.
2.4.2 Dimensions: 60 ± 13 nm.
2.4.3 Surface projections: 12- to 15-nm ring-like surface units.

2.4.4 Special features in thin sections: Spherical particles with a diameter of 43 ± 2 nm containing an electron-dense core of 35 ± 2 nm.
2.4.5 Other features: None.
3 Replication
3.1 Site of accumulation of viral proteins: Cytoplasm and cytoplasmic membranes.
3.2 Nonstructural proteins
3.2.1 Number and molecular weight of polypeptides: Not known.
3.2.2 Virus-induced enzymes: Not known.
3.3 Mode of nucleic acid replication
3.3.1 General account: A genomic sized RNA and five smaller polyadenylated RNAs, which probably are derived by splicing or cleavage from a larger precursor, are found in infected cells.
3.3.2 Effects of inhibitors: Insensitive to actinomycin D.
3.4 Site and mechanism of maturation: Morphogenesis occurs on intracytoplasmic membranes; particles accumulate in cytoplasmic vesicles and cisternae as a result of budding.
3.5 Other features: None.
4 Cooperative interactions
4.1 Recombination: Not known.
4.2 Multiplicity reactivation: Not known.
4.3 Phenotypic mixing: Not known.
4.4 Other interactions: Not known.
5 Host range
5.1 Natural: Equines.
5.2 Experimental
5.2.1 In vivo: Equines.
5.2.2 In vitro: Wide range of vertebrate cells.
6 Pathogenicity
6.1 Association with diseases: Necrosis of the muscle cells in the small arteries, leading to a variety of clinical symptoms. In pregnant mares abortion occurs in about 50% of the exposed animals.
6.2 Tissue tropisms: Pantropic.
6.3 Cytopathology: In most vertebrate cells, not in invertebrate cells.
7 Geographic distribution: Worldwide (America, Africa, Eurasia).
8 Transmission
8.1 Vertical: Yes.
8.2 Horizontal: Yes.
8.3 Vectors
8.3.1 Biological: Not known.
8.3.2 Mechanical: Not known.
9 Antigenic properties
9.1 Number of distinct antigenic molecules in virion: At least three: E1, E2, C.
9.2 Antigens involved in virus neutralization: Not known.
9.3 Number of distinct nonstructural antigens: Not known.
9.4 Specificity of different antigens: Specific antisera against E1 and E2 do not cross-react. C binds specifically to protein A of *Staphylococcus aureus*.
9.5 Antigenic properties used for classification: Complement fixation, neutralization and radioimmunoprecipitation.
10 Classification
10.1 Definition of genus: Enveloped RNA virus about 60 nm in diameter which multiplies in the cytoplasm and matures by budding through intracytoplasmic membranes. Single strand of infectious polyadenylated RNA. Two envelope proteins of

molecular weights 21×10^3 (E1, a glycoprotein) and 14×10^3 (E2), and a core protein (C), 12×10^3. Several subgenomic RNAs found in infected cells. Serologically unrelated to other ***Togaviridae*** members. No invertebrate host.

10.2 Genus: *Arterivirus.*

10.2.1 Type species: Equine arteritis virus.

10.2.2 Other members: None.

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