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Review

Viruses of the family *Bunyaviridae*: Are all available isolates reassortants?

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ABSTRACT

Viruses of the family *Bunyaviridae* (the bunyaviruses) possess three distinct linear, single-stranded, negative sense or ambisense RNA segments (large, medium, and small). Dual infections of arthropod and perhaps vertebrate and plant hosts provide substantial opportunity for segment reassortment and an increasingly recognized number of the nearly 300 viruses in this family have been shown to be reassortants. Reassortment of RNA segments (genetic shift) complements genetic drift (accumulation of point mutations) as a powerful mechanism underlying bunyavirus evolution.

Here we consider the possibility, if not likelihood, that most if not all bunyaviruses currently recognized may represent reassortants, some of which may be reassortants of existing viruses, and some of which may be reassortants of extinct viruses. If this hypothesis is correct, then the roots of the family and genus trees of bunyaviruses as currently described (or ignored) are incomplete or incorrect.

Contents

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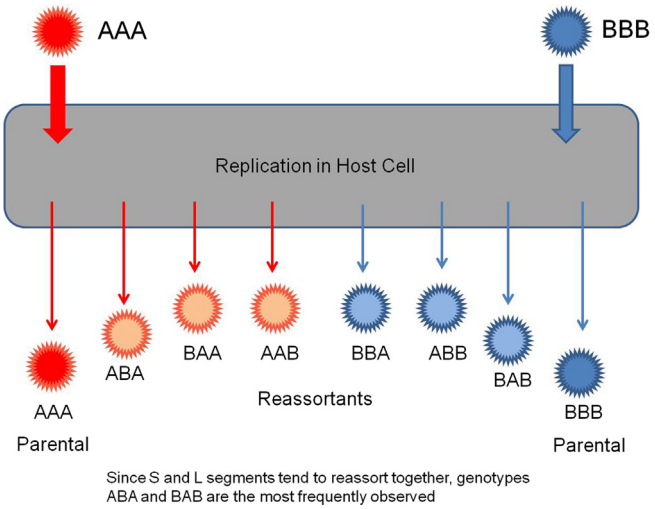

Fig. 1. Potential reassortants resulting from the dual infection of a cell by two different "parental" bunyaviruses: virus A (genome S_A, M_A, L_A), and virus B (genome S_B, M_B, L_B). Color indicates segment origin – A=red; B=blue – and intensity corresponds with the predominating genome origin: 2 segments from A=light red; 2 segments from B=light blue (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

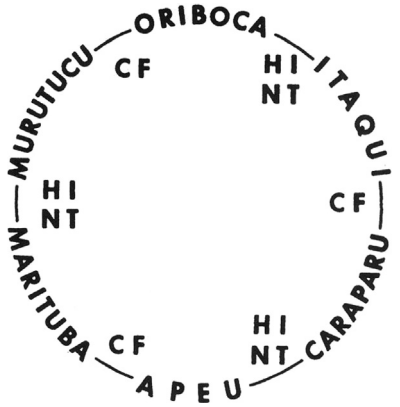

Fig. 2. Antigenic reactivity of six Group C orthobunyaviruses as determined by hemagglutination-inhibition, neutralization and complement-fixation (figure courtesy of the American Journal of Tropical Medicine and Hygiene).

Introduction

Viruses of the family *Bunyaviridae* (the bunyaviruses) possess three distinct linear, single-stranded, negative or ambisense RNA segments (large, medium and small). The small (S) RNA codes for the nucleocapsid protein, and in viruses of several genera also for a non-structural protein, NSs, which interferes with innate immunity. The surface spikes of the virions comprise two glycoproteins, Gn and Gc, embedded in a lipid bilayer. The glycoproteins are coded by the medium (M) RNA that generates a polyprotein, which is proteolytically processed, and in viruses of some genera also includes a non-structural protein (NSm) of unknown function. The large (L) RNA codes for the transcriptase and replicase protein, the large RNA-dependent RNA polymerase (RdRp or L protein). Bunyaviral L proteins, in addition to polymerase activity, have an endonuclease activity that cleaves cellular messenger RNAs for the production of capped primers used to initiate transcription of viral messenger RNAs (a feature known as 'cap snatching').

When two closely related bunyaviruses infect the same susceptible cell at the same time, their genome segments may be variously incorporated into the progeny viruses. For example, should two bunyaviruses, A and B, each with three genomic segments, co-infect a cell, progeny viruses may variously comprise a mixture of the L RNAs, M RNAs, and S RNAs of the two parent viruses, as well as progeny identical to the infecting parental viruses (Fig. 1). However, sequence relationships in natural reassortants may become diluted by longer periods of genetic drift, and putative assignments of "parent" and "reassortant" may be ambiguous, especially when a supposed parent can itself have been a reassortant. Another obvious possibility is that sequences may recombine to generate chimeric segments formed from homologous portions of homotypic or possibly heterotypic bunyaviruses, although this has so far only been described for a few viruses, most recently for the newly emerging severe fever with thrombocytopenia syndrome virus from China (He and Ding, 2012; Lam et al., 2013) but was also suggested previously for Crimean-Congo hemorrhagic fever virus (Lukashev, 2005; Deyde et al., 2006) or more convincingly for hantaviruses (Zhang et al., 2010; Zuo et al., 2011).

Bunyaviruses share several molecular characteristics; but based on their differences, the International Committee on Taxonomy of Viruses has classified them into five genera: *Orthobunyavirus, Hantavirus, Nairovirus, Phlebovirus,* and *Tospovirus* (King et al., 2012). Nearly 300 viruses have been placed in these taxa, including 97 species, 81 possible species, and a large number of isolates, encompassing 19 viruses in seven groups of related viruses and dozens of ungrouped viruses.

In the past, bunyaviruses were classified in "serogroups" using antigenic relationships determined principally by hemagglutination-inhibition (M segment determined; group placement), complement-fixation (S segment determined; group or complex placement), and neutralization (M segment determined; specific identification) tests; serologic makers determined by the L segment are not identified. Infrequently, a virus in one antigenic group reacted to a virus assigned to a different group. Over time, this quandary was solved by recognition that these links between groups implied that the groups were closely or distantly related. When electron microscopy and molecular markers confirmed these relationships, general taxonomic groupings at family, genus, and species levels became possible.

By the late 1970s monoclonal antibodies and molecular tools sufficient to detect subtle differences between bunyaviruses had been developed. Further and innovative modifications made possible the discrimination of minor yet significant details regarding the RNAs of bunyaviruses and their structure–function relationships (Bishop et al., 1980). Iroegbu and Pringle concluded from their studies of laboratory-produced reassortants of Batai, Bunyamwera, and Maguari viruses (all Bunyamwera group orthobunyaviruses) that there is no genetic barrier to exchange of genetic material between these viruses and that viruses of this group may constitute a single gene pool, discounting geographical and ecological limitations (Iroegbu and Pringle, 1981).

Some relationships, however, remained unclear. In the classic and informative investigation of six Group C viruses (family *Bunyaviridae*, genus *Orthobunyavirus*), Oriboca, Itaqui, Caraparu, Apeu, Marituba, and Murutucu, were shown to be variously related to each other: Oriboca and Itaqui by hemagglutination-inhibition and neutralization, Itaqui and Caraparu by complement-fixation, Caraparu and Apeu by hemagglutination-inhibition and neutralization, Apeu and Marituba by complement-fixation, Marituba and Murutucu by hemagglutination-inhibition and neutralization, and Murutucu and Oriboca by complement-fixation, as shown in Fig. 2 (Shope and Causey, 1962). As other Group C viruses were isolated and identified, their relationships also were determined by then-standard antigenic tests. It seemed reasonable to expect that viruses shown to be related based on the results of one kind of test would cross-react to varying extents in other kinds of tests. How then could they react by one test and not by another test and still be related? Indeed, not only did some not cross-react