The viral transmembrane superfamily: possible divergence of Arenavirus and Filovirus glycoproteins from a common RNA virus ancestor

ABSTRACT

These findings indicate a common pattern of structure and function among viral transmembrane fusion proteins from a number of virus families. Such a pattern may define a viral transmembrane superfamily that evolved from a common precursor eons ago.

INTRODUCTION

Background Findings in a number of laboratories have indicated that the transmembrane (TM) proteins of a number of RNA viruses have common structural and functional elements critical for virus entry. These include a hydrophobic region designated a "fusion peptide", usually at or near the amino-terminus generated by cleavage of a precursor protein, together with fibrous structure defined by two antiparallel alpha helices. These general principles appear to apply to the Orthomyxoviruses, Paramyxoviruses, Retroviruses, Lentiviruses, and Filoviruses. In some cases, such as between Ebola and Rous sarcoma viruses, there is considerable sequence identity to facilitate a comparison between two specific viruses. In other cases, even within a single virus family such as the Retroviridae, both structural modeling and more limited sequence similarity must be combined to discern the relationship. The finding of close sequence or structural similarity among otherwise disparate virus families has given rise to the concept of a viral TM superfamily sharing common structural and functional motifs. Recent biophysical studies of entry protein structure have reinforced this concept. In this respect, a general model of the Arenavirus glycoproteins, based on extensive study of lymphocytic choriomeningitis virus (LCMV) has been presented based on their overall similarity in functional organization to influenza and to other enveloped viruses. The GP-C precursor is proteolytically cleaved near a polybasic site to yield GP-1, a globular surface glycoprotein which contains receptor-binding sites, and GP-2, a TM protein forming the stalk of the complex via a coiled coil of amphipathic helices and responsible for virus entry by acid-dependent membrane fusion. We present here a detailed model of GP-2 for Lassa fever virus, an Arenavirus associated with multiple epidemics of hemorrhagic fever with high morbidity and mortality in West Africa, and for the related lymphocytic choriomeningitis virus (LCMV) which has been associated with sporadic outbreaks of human disease in Europe and North America. This model demonstrates that Arenaviruses share a number of specific sequence and structural motifs with other RNA viruses in the TM superfamily. Regions of Arenavirus GP-2 can be directly related to corresponding regions of Ebola, another agent of African hemorrhagic fever, and to HIV-1. Examination of the comparable regions of TM proteins from several virus families provides evidence suggesting divergence from a common ancestor.

CONCLUSION

Conclusions The most likely explanation for such high levels of similarity among Arenaviruses and Filoviruses would be divergence of both of these agents from a common viral ancestor. Since both virus families exhibit type variation over large areas coupled with stability among isolates within a more limited geographical area over considerable periods of time (the Arenaviruses being the more widespread) such divergence must have occurred eons ago. The potential importance of such apparent

conservation in the biology of these agents is underscored by noting that of the corresponding peptide sequences within the TM superfamily of proteins, that for HIV-1 forms the center of a peptide analogue shown to inhibit fusion in the nanomolar range. Modeling studies begun in the late 1980s have thus revealed a number of common and sequence motifs, subsequently shown in several cases to have homologous biological roles in infection, that were not otherwise apparent in studies of sequence homology. These models may lead to a common strategy of antiviral inhibition preventing entry of virus into host cells that is broadly applicable over a broad range of very diverse virus families.