PERSPECTIVES: VIROLOGY

Rafting with Ebola

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One of the most fascinating aspects of virology is that distantly related viruses often use common strategies and host cell machinery to replicate themselves. Evidence has been accumulating that a diverse group of enveloped viruses use small regions of the cellular plasma membrane known as lipid "rafts" both to assemble new virus particles and to enter susceptible host cells. In a recent issue of the *Journal of Experimental Medicine*, Bavari *et al.* (*1*) present compelling evidence that filoviruses, including the deadly human pathogens Ebola and Marburg, enter and exit host cells using lipid rafts.

Originally, it was believed that the plasma membrane of living cells was a uniform and highly fluid sea in which lipid and protein components were free to diffuse rapidly in the plane of the membrane. Within the past decade an alternative concept has emerged: Rather than being homogeneous in nature, biological membranes in fact contain microdomains that have distinct lipid and protein compositions. One particularly intriguing type of microdomain, the lipid raft, is heavily enriched in cholesterol and saturated fatty acids and is therefore more tightly packed than the surrounding membrane (*2*). Lipid rafts appear to be involved in a variety of biological processes including signal transduction, protein sorting, and cell movement. A number of specific cellular proteins are targeted to lipid rafts, whereas other proteins are excluded from these microdomains.

Viruses are obligate parasites that rely heavily on the host cell for their survival. The structural proteins of several enveloped viruses, including measles, influenza, and HIV-1, are targeted to raft-rich regions of the host cell plasma membrane during virion assembly (*3*–*8*); disruption of rafts can impair virus production (*7*). These findings suggest that distantly related viruses use rafts to target their structural proteins to the cell surface and to promote the assembly of a new generation of virus particles. Rafts also appear to be necessary for viruses to enter host cells. The receptors for several classes of enveloped viruses reside in these microdomains, and disruption of rafts impairs virus infectivity (*9*).

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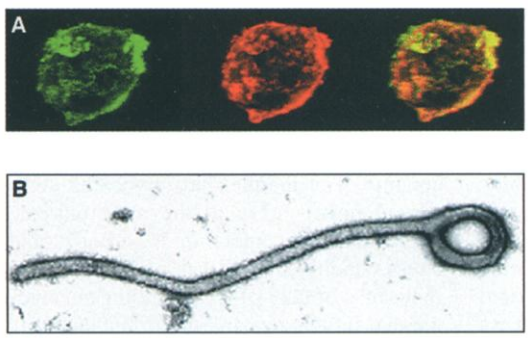
To gain new insights into filovirus replication, Bavari and co-workers asked whether the filovirus glycoprotein (GP), which is responsible for receptor binding and virus entry, and the Ebola matrix protein VP40, which is important for virus assembly in the host cell, are associated with lipid rafts (*1*). Using a variety of biochemical techniques, they demonstrate that filovirus GP, and to a lesser extent Ebola VP40, are targeted to lipid rafts during virus assembly. They also observe that Ebola and Marburg virions incorporate a raft marker, the ganglioside GM1, into their lipid envelopes. With confocal microscopy, the authors were able to visualize the colocalization of filovirus proteins with GM1 (see the figure, panel A). The considerable degree of colocalization is consistent with filovirus assembly and release taking place in raft-rich domains at the host cell surface. Finally, the authors examined whether filovirus entry is a raft-dependent process. Because rafts are so highly enriched in cholesterol, they can be disrupted with compounds that bind or extract cholesterol or prevent its biosynthesis. Treating target cells with two cholesterol-binding compounds, nystatin and filipin, significantly inhibited filovirus infectivity, suggesting that viral invasion of host cells depends on lipid rafts. Thus, as with HIV-1, both virion assembly and host cell entry by filoviruses take place in raft-rich domains of the plasma membrane.



Catching a ride on a lipid raft. Ebola particle assembly in lipid raft–rich domains of the host cell plasma membrane. **(A)** Colocalization of Ebola virus proteins and raft markers: The raft marker GM1 is shown in green and Ebola GP in red; the overlay of GM1 and GP appears in yellow. **(B)** Visualization by electron microscopy of Ebola virus–like particles formed by coexpression of GP and Ebola matrix protein VP40 in a human cell line. The length of the particle is ~2 μm. [Reprinted with permission from (*1*)]

The Ebola and Marburg filoviruses are among the most virulent of human pathogens. About 75% of infected individuals die of severe hemorrhagic fever within 10 days of infection. Ebola and Marburg outbreaks have so far been brief and geographically contained. However, the potential exists for much broader dissemination, particularly in the context of a bioterrorist attack. Because of the deadly outcome of Ebola and Marburg infections, filovirus research is generally restricted to high-containment "biosafety level 4" facilities.

Bavari and colleagues demonstrate that coexpression of GP and VP40 in a human cell line drives the formation of filamentous particles that appear by electron microscopy remarkably similar to bona fide Ebola virions (see the figure, panel B). The formation of virus-like particles with this genome-free approach will greatly facilitate future Ebola virus research by allowing studies of virus assembly to be performed without the need for biosafety level 4 containment. In addition, these virus-like particles could serve as a safe source of antigen for filovirus vaccine studies.

The Bavari *et al.* work adds Ebola and Marburg filoviruses to the growing list of viruses that use lipid rafts for their replication and propagation. Evidence has also come to light that viruses such as Ebola and HIV-1 use some of the same host proteins to facilitate the budding-off of new virus particles from infected cells (*10*, *11*). These studies enhance our understanding of enveloped virus replication at the molecular level, knowledge that may ultimately pave the way for the development of new antiviral strategies to combat these human pathogens. Perhaps it is not too optimistic to imagine that the elucidation of shared replication strategies will lead to common therapeutic approaches to combat diseases caused by distantly related viruses.

References

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