mutant mice (Welch et al., 2007) share significant pathophysiological mechanisms with any disorders that produce compulsive behaviors in humans. However, these mutant mice should prove extremely useful as tools for neurobiological investigations. Analysis of *Hoxb8* mutant mice should help to illuminate such matters as the roles of different populations of microglia in the brain. Moreover, these mice could give rise to sorely needed new hypotheses about the mechanisms underlying human disorders characterized by compulsive behaviors. Although recent genetic animal models of disease have tended to move from the human to the mouse, it is equally important to find ways of following up in human patients on observations made originally in mutant mice. If we are to understand the basis of human neuropsychiatric disorders, we will need great ingenuity, and we will have to exploit unexpected findings from mutant mouse strains when they appear to be relevant to the human condition.

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Viral Houseguests Undertake Interior Redesign

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As part of their life cycle some single-stranded RNA viruses remodel host cytoplasmic membranes into specialized organelles. In this issue, Hsu et al. (2010) demonstrate how the viruses selectively co-opt host machinery to make this unique organelle, which has a lipid composition favorable to viral replication.

Viruses are obligatory intracellular parasites that depend on a living host for reproduction. They have continuously probed the machinery of the cell to find new ways of exploiting their hosts, ensuring their continued success and, as an unintended corollary, providing many insights into cellular function. There are over two thousand species of viruses, which are classified by the nature of their genomes. Among these groupings are the positive-sense single-stranded RNA (ssRNA) viruses whose genomes can be directly translated into proteins. This collection includes deadly pathogens that are threats to humans (for example, dengue virus, hepatitis C virus, and yellow fever virus), animals (foot-and-mouth disease virus), and plants (tobacco mosaic virus). Despite being highly divergent in genome organization, host range, and morphology, these RNA viruses share a common replication strategy—they remodel host cytoplasmic membranes into specialized organelles that foster their replication (Miller and Krijnse-Locker, 2008). In this issue, Hsu et al. (2010) reveal insight into how RNA viruses selectively recruit host factors to make a specialized organelle with a lipid composition that is favorable to virus replication.

These specialized virus-induced organelles can arise from endosomal or mitochondrial membranes but most commonly derive from membrane compartments of the secretory pathway, including the endoplasmic reticulum, Golgi, and trans-Golgi network (Figure 1; Miller and Krijnse-Locker, 2008). Although the exact function of these organelles remains speculative, the replication of positive-sense ssRNA viruses requires the targeting and anchoring of RNA-dependent RNA polymerase within their membranes. The specialized membranes may provide a stable microenvironment that facilitates viral RNA

replication by concentrating replication complexes. Alternatively, they may ensure protection from host proteins that would recognize the viral RNA and trigger an immune response.

Although there is agreement on the origin of the membranes for the replication complexes, little is known about how they form from the secretory pathway. How the RNA-dependent RNA polymerase, which is a soluble protein, anchors itself within the membrane of these organelles is also unclear. Much of our understanding of the secretory pathway is rooted in the beautiful electron microscopy of George Palade and colleagues (Palade, 1975). Unfortunately, these static images belie the dynamic nature of these organelles. Each of these membrane-bound organelles is actively exchanging molecules via membrane-bound vesicles. Thus, it is still hotly debated whether and to what extent these secretory organelles exist as static discrete entities or whether they exist only in a dynamic steady state (Simon, 2008). Either way, their dynamic exchange of membranes and cargo has not escaped the probing of viruses.

The new study by Hsu et al. reveals that three different positive-sense ssRNA viruses—coxsackievirus B3 (CVB3), poliovirus (PV), and the hepatitis C virus (HCV)—form these replication factories by exploiting host molecules that regulate membrane transport. The authors demonstrate that expression of the enteroviral protein 3A, a membrane-binding component of the replication complex (Wessels et al., 2006), is sufficient for membrane remodeling. Protein 3A targets the Golgi apparatus where it modulates the activities of proteins such as GBF1, a guanosine exchange factor for the small cellular GTPase Arf1. GBF1 and Arf1 together regulate the recruitment of COPI and other coat proteins to the membrane to regulate transport through the secretory pathway. Upon viral infection, GBF1 and Arf1 are co-opted to recruit other cellular proteins for the benefit of the replicating virus, resulting in a unique structure.

One of the proteins recruited is the phospholipid-modifying enzyme PI4KIIIβ, which catalyzes the production of phosphatidylinositol-4-phosphate (PI4P) lipids. This enzyme associates with the membranes of the CVB3- or PV-induced organelles and binds the viral proteins of the replication complex. The newly synthesized PI4P lipids, in turn, directly bind the viral RNA polymerase, which may assist in the recruitment of the polymerase to the membrane, as well as provide a niche that enhances viral RNA synthesis. The depletion of PI4P lipids from cells disrupts viral RNA synthesis.

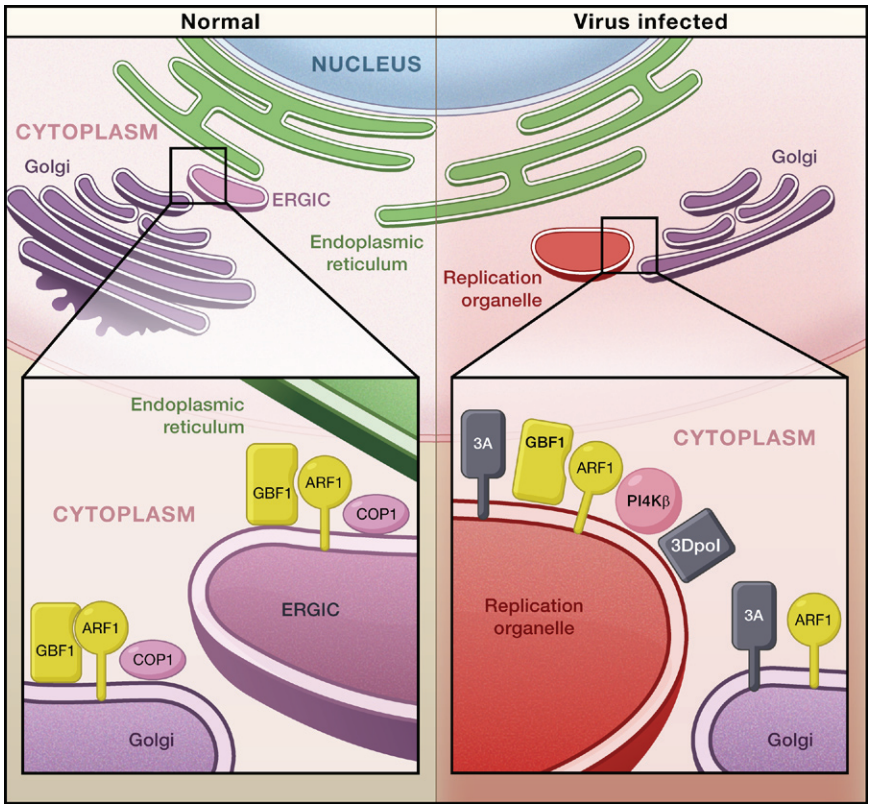

Figure 1. Secretory Pathway Manipulation by Viruses
In an uninfected cell (left) the guanosine exchange factor GBF1 and the small GTPase Arf1 recruit the coat protein COPI to the membrane for formation of transport vesicles between the Golgi and the ER-Golgi intermediate compartment (ERGIC). In a cell infected by a positive-sense single-stranded RNA virus (right) the virally encoded protein 3A utilizes GBF1 and ARF1 to recruit the phospholipid-modifying enzyme, phosphatidylinositol-4-kinase IIIβ (PI4KIIIβ). This enzyme catalyzes the production of phosphatidylinositol-4-phosphate (PI4P), which in turn binds the viral RNA polymerase leading to formation of the replication organelle.

As the infection progresses, the level of protein 3A rises, which facilitates the ongoing assembly of the viral replication complex onto these Golgi-derived membranes. This leads to the efficient production of viral RNA and viral proteins, providing a positive feedback loop. The hijacking of GBF1/ARF1 by the virus prevents the normal function of these proteins, the recruitment of COPI, thereby leading to a progressive disruption of the Golgi, which considerably attenuates the host's secretory pathway. The findings of Hsu et al. provide a clearer picture of these virally induced organelles: they both concentrate viral components of the replication complex and provide a lipid-enriched microenvironment, with PI4P as a key player, that enhances viral RNA replication.

They show that PI4P-enriched membranes are also required for infection of other viruses, such as HCV. HCV is not related to CVB3 or PV, and therefore it is tempting to speculate that such a use of PI4P is conserved among RNA viruses. Interestingly, a subclass of the positive-strand DNA viruses, which replicate in the cytoplasm, also remodel cellular membranes for their replication (Netherton et al., 2007). The function, once again, may be to produce a lipid niche favorable to their replication.

CVB3 and PV are lytic viruses and do not necessarily require the secretory pathway to escape their hosts. Other viruses, such as HCV, rely on the secretory pathway to exit the cell (Moradpour et al., 2007), and it is therefore difficult to imagine that their infection would lead to the complete destruction of the secretory pathway. It may be that in cells that are chronically infected, at least in the case of HCV, the level of viral protein expression is lower than in cell culture systems and therefore the balance between membrane hijacking and the maintenance of host integrity is more finely-tuned.

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