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Preface

Mechanisms of enveloped virus release

Enveloped viruses must traverse the plasma membrane of the host cell twice during the viral replication cycle: initially during virus entry and again during particle release. Entry is typically achieved by means of a membrane fusion reaction, occurring either directly at the cell surface following particle binding, or in low-pH endosomes after endocytosis of bound virions. Enveloped viruses have evolved a diversity of strategies for release from the cell. For some enveloped virus families, the viral determinants of release have been well characterized and significant progress has been made in defining the host cell machinery that participates in the release process. For other families, a large cast of viral players appears to be required for efficient egress, and the role of cellular proteins in particle release remains to be elucidated.

The assembly and release of retroviral particles are mediated by the Gag protein, though in some retroviral genera the Env glycoproteins play a major role in directing Gag to the cell surface. Advances in the study of retrovirus release and the cell biology of protein sorting into the multivesicular body (MVB) pathway have revealed that viral sequences known as "late" domains promote particle release by interacting with components of the cellular endosomal sorting machinery. This so-called "class E Vps" machinery, originally defined in yeast as being critical for the formation of vesicles that bud inwardly into MVBs, has apparently been co-opted by retroviruses to promote virus particle release. Retrovirus budding can take place at the plasma membrane (upon recruitment of class E Vps proteins to the cell surface) or directly into MVBs. In the latter case, particle release from the cell is likely to occur in a manner analogous to exosomal release, in which vesicle-laden MVBs fuse with the plasma membrane and release their contents. Intriguingly, other enveloped virus families, most notably the filoviruses and rhabdoviruses, have evidently evolved a similar exit strategy, as the matrix proteins of these viruses also contain late domain motifs that interact with endosomal sorting machinery. Another common theme in the release of several enveloped viruses (e.g., the retroviruses, paramyxoviruses, orthomyxoviruses, and filoviruses) is the apparent association of viral structural proteins with plasma membrane microdomains known as lipid rafts. The role played by these domains in facilitating particle assembly and release, however, has not yet been clearly defined.

In several viral systems, different types of virus-like particles (VLPs) are produced depending on which viral proteins are expressed, and a clear synergy in virus release efficiency is observed upon coexpression of multiple viral proteins. For example, although expression of the hepatitis B virus (HBV) surface protein (S) induces the release of subviral particles, the production of authentic virions requires the capsid as well as the S and L glycoproteins. Expression of the filovirus glycoprotein (GP) or the matrix protein (VP40) generates amorphous VLPs with low efficiency; production of the characteristic filamentous filovirus particles requires the simultaneous expression of GP and VP40. In the case of the paramyxoviruses, both the matrix (M) and fusion glycoprotein (F) produce VLPs when expressed alone but release efficiency is enhanced by coexpression of these two proteins. The rhabdovirus G glycoprotein is not required for particle production but its expression markedly stimulates virus release. While the orthomyxovirus matrix protein (M1) produces VLPs in the absence of other viral proteins, the morphology of released particles and the efficiency of VLP production is strongly influenced by the neuraminidase (NA) envelope protein. In other systems (e.g., the alphaviruses), glycoprotein/nucleocapsid interactions are required for efficient envelopment and release. Tight interactions between the E2 glycoprotein and the capsid protein, and E2/E2 interactions at the site of alphavirus budding, largely exclude the packaging of host membrane proteins into virus particles. In contrast, retroviruses are rather promiscuous in their incorporation of host proteins.

Some enveloped viruses undergo multiple budding and fusion reactions as they assemble and exit the cell. For example, the herpesviruses assemble in the nucleus and undergo primary envelopment at the inner nuclear membrane and then secondary envelopment in Golgi-derived vesicles. Virus particles are released from the cell when virus-laden vesicles fuse with the plasma membrane. Poxvirus assembly takes place in putatively membrane-bounded cytoplasmic "virus

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factories" from which the first budding event is thought to occur. During transport of virus particles towards the cell periphery, additional envelopment is mediated by membranes derived from the Golgi or early endosomes. Release from the cell takes place upon fusion between the plasma membrane and the outer viral envelope. At this time little is known about cellular partners involved in the budding of these large DNA viruses.

This special issue on enveloped virus release brings together chapters focused on the retroviruses, rhabdoviruses, orthomyxoviruses (e.g., influenza), paramyxoviruses, filoviruses (e.g., Ebola), alphaviruses, herpesviruses, hepadnaviruses (e.g., hepatitis B), and poxviruses (e.g., vaccinia). The publication of chapters covering the release of these diverse enveloped viruses in one issue will serve to highlight both the significant differences and intriguing similarities in the molecular mechanisms by which enveloped viruses exit their host cells.

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