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Review

Acid-dependent viral entry

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ABSTRACT

Virus infection of host cells requires that entry into the cell results in efficient genome release leading to translation and replication. These initial steps revolving around the entry and genomic release processes are crucial for viral progeny generation. Despite the variety of receptors used by viruses to initiate entry, evidence from both enveloped and non-enveloped viral infections is highlighting the important role played by intracellular acidic compartments in the entry of many viruses. These compartments provide connecting nodes within the endocytic network, presenting multiple viral internalization pathways. Endosomal compartments employing an internal acidic pH can trigger molecular mechanisms leading to disassembly of viral particles, thus providing appropriate genome delivery. Accordingly, viruses have evolved to select optimal intracellular conditions for promoting efficient genome release, leading to propagation of the infectious agent. This review will address the implications of cellular compartment involvement in virus infectious processes, and the roles played by the viruses' own machinery, including pH sensing mechanisms and the methodologies applied for studying acid-dependent viral entry into host cells.

Contents

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1. Introduction

Cells use a broad spectrum of mechanisms for internalizing substances in their environment (Benmerah and Lamaze, 2007; Conner and Schmid, 2003a; Mayor and Pagano, 2007; Sandvig and van Deurs, 2005). With viral infection being reproducible and readily measurable, viruses have become useful probes for the analysis of endocytic routes (Pelkmans, 2005; Pelkmans et al., 2005; Pelkmans and Helenius, 2003). Initially, two different routes for virus entry were distinguished, based on the morphology of the cellular vesicular structures into which the viruses were internalized. These structures are known as clathrin-coated vesicles and non-clathrin dependent vesicles (Marsh and Helenius, 1989). Indeed, our current knowledge of endocytic routes groups them as clathrin-dependent and clathrin-independent endocytosis; the latter includes micropinocytosis, macropinocytosis, phagocytosis and caveolae-dependent endocytosis (Brandenburg and Zhuang, 2007; Damm and Pelkmans, 2006; Gruenberg, 2009; Marsh and Helenius, 2006; Mercer et al., 2010a,b; Sieczkarski and Whittaker, 2005; Thorley et al., 2010; Tsai, 2007). The form taken by the endocytic process is dependent on the cellular machinery involved, and the type of material to be internalised. While micropinocytosis tends to involve relatively non-particulate material such as macromolecules, the other processes have all been linked to the uptake of different viruses. Phagocytosis is a rather loosely applied term, often referring to uptake of large particles and immune complexes. Nevertheless, it has much in common with macropinocytosis in terms of the signalling cascades and intracellular events which follow internalisation.

Recent studies on the routes and mechanisms of viral entry have demonstrated that the different endocytic processes cannot be regarded in isolation. It is now know that there are a number of interconnections among endocytic components and routes, observable as complex networks of internalisation pathways rather than simplistic "linear" routes. The present review will focus on showing how the growing evidence of the roles played by intracellular endocytic compartments is demonstrating the diversity of the processes and interactions involved. In particular, the importance of the low pH associated with maturing endosomes, and the connecting nodes within the endocytic network of multiple internalisation pathways, are of major importance in determining the outcome of virus entry into the host cell. Not only will the pH of the endocytic pathways relate to the success of the replicative cycle for many viruses, it will also determine the outcome of processing by cells of the innate immune system.

2. General concepts in viral entry

As a first requisite for infection, the virus must interact with the surface of the host cell in a process commonly referred as attachment. One general element therein is the ability of certain molecules and structures on the virus particle surface to act as ligands for particular cell receptors, which in turn gives rise to cell and host tropisms (Baranowski et al., 2001). The majority of viruses use specific cellular proteins as receptors, but viruses can also use lipids and sugars to this end. Examples of viruses in the latter category are vesicular stomatitis virus, which may interact directly with phosphatidylserine (Schlegel et al., 1983), and polyomaviruses, which attach to gangliosides (lipids with attached sugars) (Low et al., 2006; Magaldi et al., 2012; Tsai et al., 2003; Tsai and Qian, 2010).

When viral surface molecules bind to their cellular receptors, akin to the natural ligand binding, the receptor is modulated to initiate a cascade of events involving transposition of the receptor, and therefore the virus interacting with it. This is often regulated by kinase and phosphatase activities associated with that receptor. The consequence is activation of particular endocytic pathways associated with ligation of that receptor, promoting internalisation of the virus-receptor complex (Coyne et al., 2007a; Liberali et al., 2008; Pelkmans et al., 2005). There is quite some diversity in both receptor–ligand interaction and endocytic processing, as witnessed by the reports over 200 known cellular kinases involved in endocytosis mechanisms (Pelkmans et al., 2005).

A key point for viral entry, essential for successful virus infection and replication, is the release of viral genomic material at the appropriate site within the host cell. This process is important to enable both genome replication and synthesis of the encoded viral proteins, necessary for both replication and viral particle assembly (maturation). Although enveloped and non-enveloped viruses can share similar mechanisms of internalisation, one may already observe major differences between them. Enveloped viruses can release their genome either naked or associated with nucleocapsid components, via the fusion of viral envelope with a cellular membrane (Harrison, 2008b). This process can occur at the plasma membrane or inside endocytic compartments. In the case of non-enveloped virus, their lack of a viral envelope requires that membrane penetration be mediated through perturbation of the membrane structure, as witnessed with the formation of pores due to ion channel activities (Tsai, 2007), or disruption of endocytic vesicle membranes through modification of the membrane structure or adsorption of protons through the proton sponge effect. Despite such differences among enveloped and non-enveloped viruses, and important component is the role played by low pH inside endocytic compartments.

3. Endocytic pathways and low pH compartments

Virus entry, and involvement of the acidifying endosomal system therein, is dependent not only on the virus, but also on the cell receptor and signalling pathways involved (examples of viruses entering through different pathways, but having in common requirements for acidifying processes leading to initiation of their replicative cycle, are shown in Table 1). The characteristics of this relationship will also vary dependent on the cell type. For example, virus infection of an epithelial cell via clathrin mediated endocytosis may perfectly suit the virus. Therein, the endocytic pathway would acidify in a manner favouring virus uncoating and genome release into the cytosol before the maturing endosomes would become too degradative. In contrast, activated macrophages may present a less favourable intracellular environment for a virus, even when using the same endocytic processes as the epithelial cell; an activated macrophage can present a more rapidly acidifying endosomal pathway, and therefore maturing endosomes, particularly when linked to clathrin-mediated endocytosis. Such characteristics of different cell types is important when considering not only how a virus evolved to survive, but also how evolution developed a powerful acidifying endosomal system for