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Dynamic lipid landscape of picornavirus replication organelles

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Picornavirus infection induces rapid reorganization of the cellular membrane architecture and appearance of novel membranous structures associated with the viral RNA replication and virion assembly — replication organelles. Recent studies significantly advanced our understanding of their lipid composition and cellular mechanisms involved in their development. Picornaviruses activate synthesis of both structural and signaling lipids and reroute cellular cholesterol trafficking pathways to create unique membranous domains favoring viral replication. Rapidly replicating picornaviruses rely on posttranslational activation and/or specific recruitment of cellular proteins rather than on modulation of expression of cellular genes to create favorable membrane microenvironment. At the same time picornaviruses demonstrate remarkable adaptability to changes in the lipid landscape which should be taken into account when developing novel antiviral strategies.

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Introduction

Picornaviruses are ubiquitous positive strand RNA (+RNA) viruses infecting vertebrate hosts. They include many well-known and emerging pathogens of humans and animals. Poliovirus, diverse enteroviruses and rhinoviruses, foot and mouth disease virus continue to represent significant health and economic problems worldwide. Genome RNA of poliovirus, the prototype member of the *Picornaviridae* family, is ~7500 nt long and encodes one polyprotein which undergoes proteolytic processing generating a dozen of mature peptides and intermediate products (Figure 1a). Only the P2-P3 region is required to sustain viral RNA replication and to induce dramatic changes in the metabolism of an infected cell, including total reorganization of the intracellular membranes.

Replication of picornaviruses is intimately associated with membranes. Poliovirus-infected cells display rapid development of novel membranous structures which occupy almost all the cytoplasm by the end of infection (Figure 1b). This dynamic membrane environment provides anchoring sites for the viral replication complexes and facilitates virion maturation and release [1–4]. Recent research firmly established that these membranes represent *bona fide* novel organelles with unique lipid and protein composition. Here we will discuss progress in our understanding of how picornaviruses divert lipid synthesis and trafficking pathways to build their replication organelles (RO). We will also focus on how the lipid microenvironment may support the replication process and the feasibility of controlling cellular lipid metabolism as an antiviral strategy.

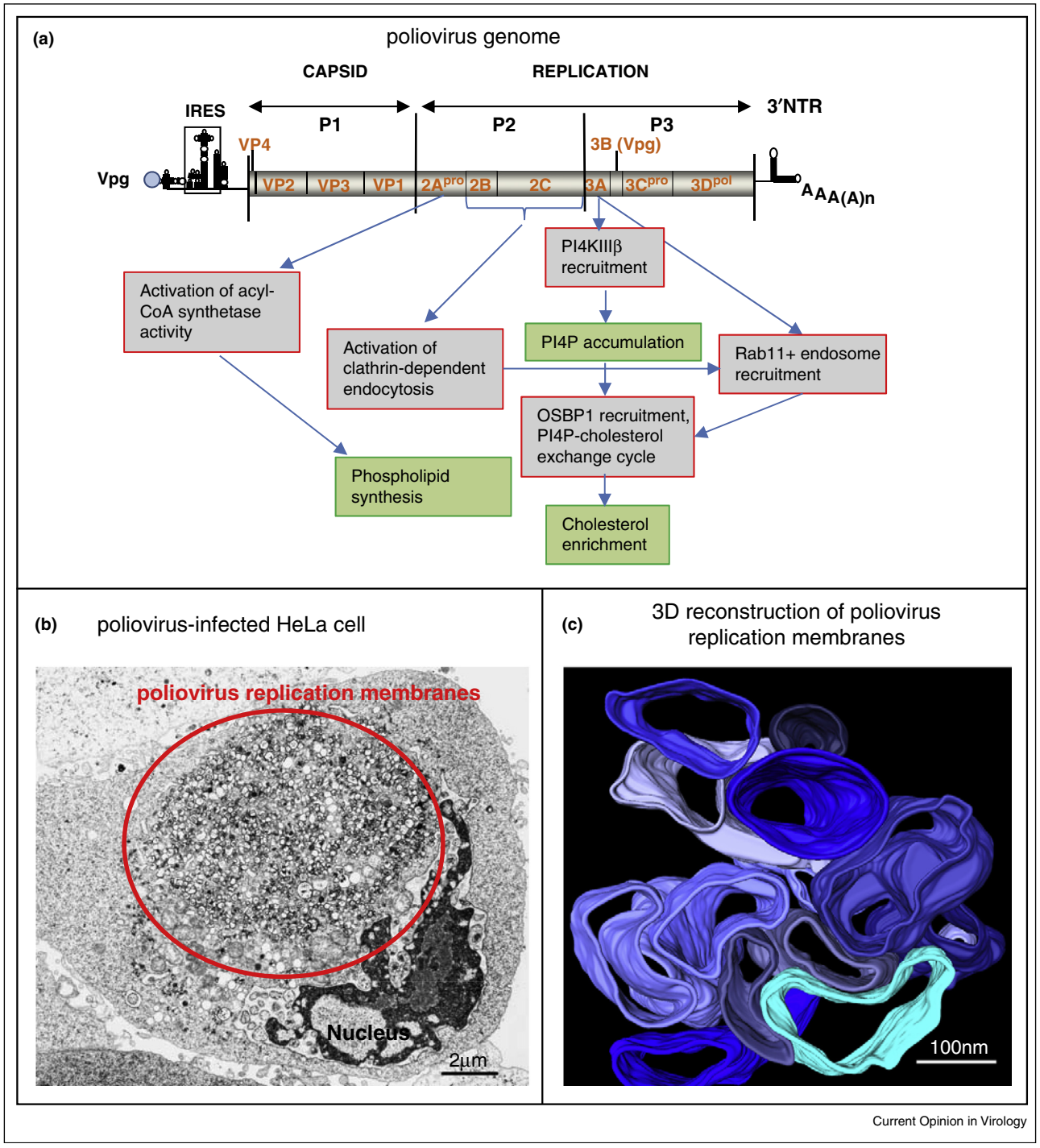
Development of picornavirus replication organelles

Most of our knowledge of picornavirus biology comes from studies of the members of the *Enterovirus* genus infecting humans, especially poliovirus, and murine picornaviruses from the *Cardiovirus* genus. In spite of adaptation to diverse hosts and cell types, these viruses demonstrate overall similar dynamics of development, morphology, and lipid composition of the replication membranes [5,6,7•,8••] suggesting that diverse picornaviruses share similar replication requirements. In poliovirus-infected cells, virus-induced membranous structures appear at ~2–3 h post infection; on electron microscopy (EM) images they look like clusters of loosely associated single-membrane vesicles. These clusters develop in close proximity to the Golgi membranes and/or the dilated ER tubules that are clearly recognizable at this stage of infection [9,10]. Later these clusters grow in complexity and volume, and the Golgi and ER membranes disappear. The EM tomography of enterovirus replication membranes revealed complex membranous agglomerates with no obvious homology to membranes found in uninfected cells (Figure 1c). Finally, the single-membrane replication structures collapse into double-membrane vesicles [10,11]. Thus, picornavirus infection results in rapid replacement of cellular organelles with virus-specific membranous structures.

Unique lipid signature of picornavirus replication organelles

The basic structural elements of biological membranes are glycerophospholipids with phosphatidylcholine accounting

Figure 1



Picornavirus infection induces the development of unique membranous structures — replication organelles. **(a)** Scheme of poliovirus genome RNA indicating involvement of the viral proteins in rerouting of the cellular lipid synthesis and trafficking pathways resulting in expansion of membranes enriched in cholesterol and PI4P. **(b)** An EM image of a poliovirus-infected HeLa cell at the end of infectious cycle (8 h post infection). The image is courtesy of Prof. Kurt Bienz, University of Zurich, Switzerland. **(c)** Electron tomography reconstruction of poliovirus replication membranes at the middle of infectious cycle (4 h post infection).
Source: Modified from [10].