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Current Opinion in Virology

Lipids and RNA virus replication

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Most viruses rely heavily on their host machinery to successfully replicate their genome and produce new virus particles. Recently, the interaction of positive-strand RNA viruses with the lipid biosynthetic and transport machinery has been the subject of intense investigation. In this review, we will discuss the contribution of various host lipids and related proteins in RNA virus replication and maturation.

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Current Opinion in Virology 2014, **9**:45–52

This review comes from a themed issue on **Virus replication in animals and plants**

Edited by **C Cheng Kao** and **Olve B Peersen**

For a complete overview see the Issue and the Editorial

Available online 28th September 2014

http://dx.doi.org/10.1016/j.coviro.2014.09.005

Introduction

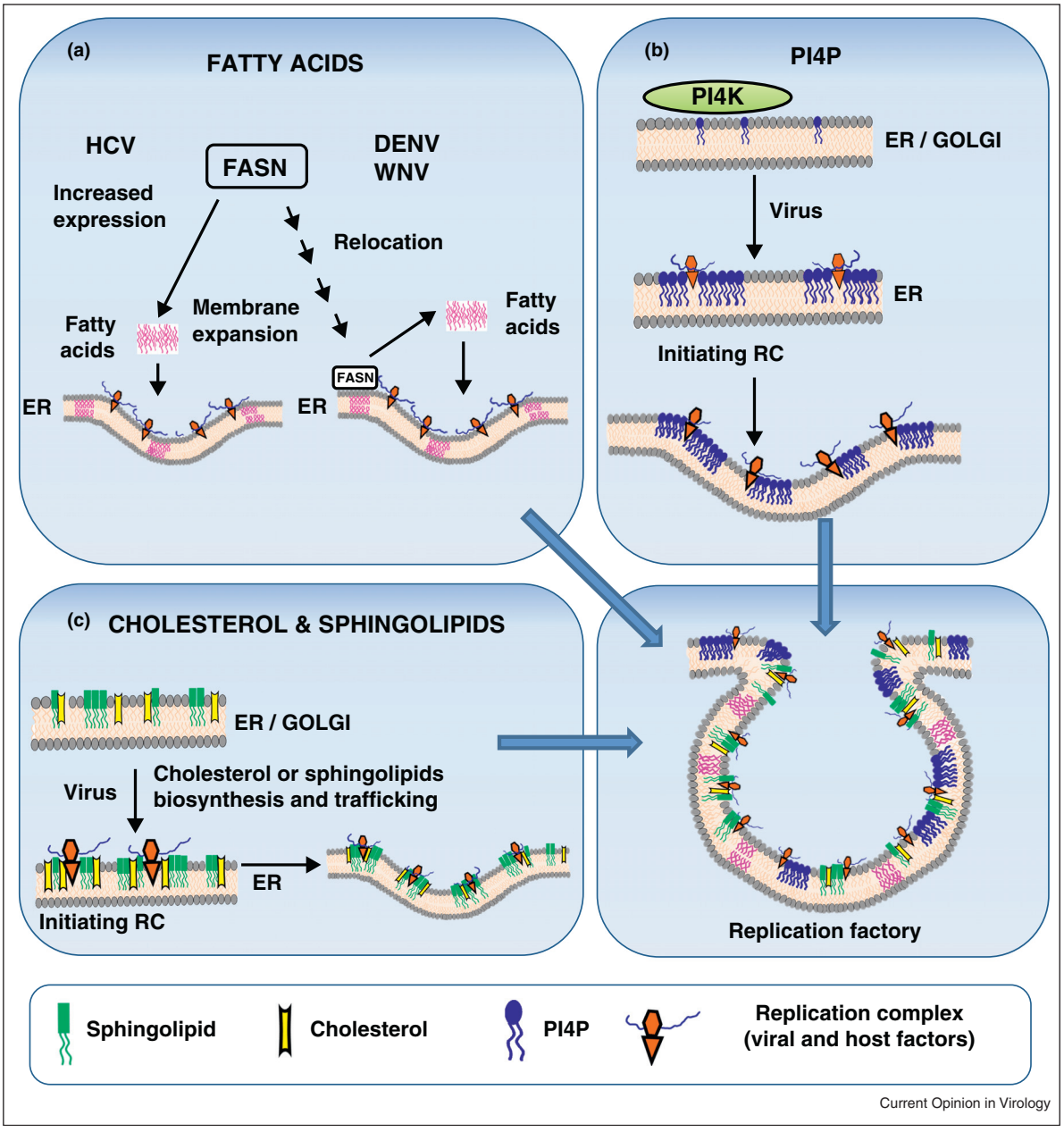
Viruses have evolved to utilize cellular membranes for entry, replication of their genome and production of nascent particles. Notably, positive-strand RNA viruses have developed this unique ability to co-opt cytosolic membranes to build a novel RNA replication factory. The factory contains the replicase complex, which includes viral RNA, proteins and host factors [1••,2]. Additionally, this platform is thought to protect the virus from host immune defenses. Previous reports indicate that the endoplasmic reticulum (ER), Golgi complex, mitochondria and endosome membranes are reorganized by various RNA viruses to build their replication complex [1••,2,3,4•,5•,6–8,9•]. For hepatitis C virus, the replication factory consists of double-membrane vesicles (DMVs) organized in a membranous web (MW) structure [10–14,15•]. Efforts to understand the organization and function of RNA virus replication platforms have initially focused on virus and host factors. However, there is overwhelming evidence that host lipids play a crucial role in the functioning of these replication factories. This review will underscore the recent findings on the roles that lipids play in virus RNA replication and particles production. Lipids are thought to help organize a functional virus replication factory by facilitating membrane curvature or binding to and stimulating the activity of the virus polymerase in the replication complex (Figure 1). Alternatively, lipids recruit core proteins to facilitate virus particles formation (Figure 2).

Lipids are essential for the integrity of cellular membranes and major alterations in lipid composition can negatively impact cellular homeostasis. However, subtle changes in membrane lipids pose a special challenge for RNA viruses that rely heavily on membranes for efficient genome replication and virus particles production. While these viruses need cytosolic membranes to replicate their genome, they all display specific lipid requirements. Hence, positive-strand RNA viruses employ multifaceted strategies to hijack host machinery involved in lipid biosynthesis and transport. This review will underscore the recent findings on the crucial roles of lipids in virus RNA replication and particles production. Due to space limitation, the review will feature the wealth of knowledge gained from studying the *Flaviviridae* and *Picornaviridae* families of viruses.

Fatty acids and virus genome replication

Fatty acids are constituents of triglycerides and phospholipids. They contribute to energy production and storage, generation of lipid droplets and structural integrity of membranes. Inhibitors of fatty acids synthesis (e.g. cerulenin, C75) severely impede the replication of enteroviruses (e.g. poliovirus), flaviviruses (e.g. West Nile virus or WNV) or hepatitis C virus (HCV) [16,17,18•,19••]. Fatty acid synthase (FASN) is a key lipogenic enzyme involved in fatty acids synthesis (Table 1 and Figure 1a). Indeed, FASN protein levels are increased in HCV-infected patients [20,21•] or HCV-infected cells [22•,23]. Notably, Nasheri *et al.* found that HCV NS4B was involved in FASN induction and concomitant increase in fatty acids production [23]. However, NS4B does not appear to bind to FASN protein or the regulatory sequences for FASN expression. Instead, NS4B activates the sterol regulatory element-binding protein (SREBP-1c), a major transcription factor for FASN expression [24,25]. Under this scenario, FASN-derived fatty acids, but not FASN itself, are recruited to build HCV replication factory [23], which consists of double-membrane vesicles (DMVs) organized into a membranous web [5•,11,12,14,15•,26]. The generation of DMVs likely requires additional phospholipids production to ensure minimal alteration in the lipid content of ER membrane. Indeed, HCV infection leads to increased levels of phosphatidylcholine and phosphatidylethanolamine [22•]. Thus, while fatty acids may be directly recruited to the HCV replication factory, they can be converted into

Figure 1



Lipids in virus RNA synthesis. **(a)** Fatty acids. The host protein, FASN, is a key enzyme in the biosynthesis of fatty acids, which are incorporated at sites of viral RNA replication and cause membrane expansion necessary to form the replication factory. FASN expression increases after HCV infection [23] while FASN is recruited to the sites of viral RNA replication after WNV or DENV infection [18•,19••,28•]. **(b)** PI4P. Following virus infection, PI4P is produced on ER membranes by PI4KIIIα or Golgi membranes by PI4KIIIβ. PI4P may bind to virus replicase proteins and contribute to membrane curvature. Alternatively, PI4P can recruit effector proteins via their PH domains, triggering a cascade of events which can lead to the organization of a functional replicase complex [101]. **(c)** Cholesterol and sphingolipids. Biosynthesis and trafficking of cholesterol or sphingolipids are essential for optimal functioning of virus replicase complex. By changing the membrane composition and fluidity, these lipids can contribute to membrane bending and stimulation of the replicase complex.

phospholipids to generate the DMVs. Alternatively, a recent report shows that FASN binds to, and stimulates HCV NS5B polymerase (RdRp) activity in the replication factory [27•]. While this report needs to be confirmed, it implies that FASN plays at least two different roles during HCV replication: providing the building block for phospholipids and stimulating virus polymerase.

FASN function is also required for WNV or dengue virus (DENV) RNA replication [18•,28•]. Nevertheless, these