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Tombusviruses orchestrate the host endomembrane system to create elaborate membranous replication organelles

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Positive-strand RNA viruses depend on intensive manipulation of subcellular organelles and membranes to create unique viral replication organelles (VROs), which represent the sites of robust virus replication. The host endomembrane-based protein-trafficking and vesicle-trafficking pathways are specifically targeted by many (+)RNA viruses to take advantage of their rich resources. We summarize the critical roles of co-opted endoplasmic reticulum subdomains and associated host proteins and COPII vesicles play in tombusvirus replication. We also present the surprising contribution of the early endosome and the retromer tubular transport carriers to VRO biogenesis. The central player is tomato bushy stunt virus (TBSV), which provides an outstanding system based on the identification of a complex network of interactions with the host cells. We present the emerging theme on how TBSV uses tethering and membrane-shaping proteins and lipid modifying enzymes to build the sophisticated VRO membranes with unique lipid composition.

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Introduction

Replication strategies of positive-strand (+)RNA viruses of plants and animals show many similarities likely due to their common origin as intracellular pathogens with simple genome organization and a limited coding capacity. These similarities provide a good interdisciplinary cross-talk among plant and animal virologists. This leads to accelerated progress in our understanding of RNA virus replication, deciphering the capabilities of these viruses to affect and rewire cell biology, and the infection-driven on-going discoveries on (+)RNA virus-host interactions are expected to facilitate future prevention of viral diseases of plants, animals and humans, and might also lead to more widespread cures of viral diseases.

Plant-infecting (+)RNA viruses are widespread and several of them cause significant losses in agriculture [8]. Similar to animal (+)RNA viruses, plant viruses not only rely on the expression of viral replication-associated proteins, but they need to co-opt numerous cellular factors in order to replicate their RNA genomes [9–14]. These viruses build large viral replication compartments or replication organelles (VROs) inside the infected cells. The VRO biogenesis is vital for (+)RNA viruses to sequester all the required viral components, including the (+)RNA genomes, and co-opted host factors into an optimal microenvironment that can support robust RNA virus synthesis. VROs are also critical for temporal and spatial organization of various viral processes, such as (−) and (+)-strand RNA synthesis, subgenomic RNA synthesis (in case of a large number of RNA viruses), viral RNA encapsidation, maturation and so on. As importantly, VROs provide critical protection of viral components from recognition by the host antiviral surveillance apparatus, such as RNA sensors (RIG-I, MDA5 or DICER), and from destruction by cellular antiviral nucleases and proteases [5,15–20]. Therefore, deciphering the mechanism of VRO biogenesis is a major topic in current virology research.

Because many viral processes depend on the interactions between the viral components and subverted cellular proteins, major research efforts have aimed at dissecting of viral-host protein interactomes [2,21–24]. However, virus replication process also depends on the intensive manipulation of subcellular organelles and membranes as well as re-wiring of metabolic processes, which create VROs representing a subcellular environment suitable for virus replication [11,25–29]. The host endomembrane-based protein-trafficking and vesicle-trafficking pathways are specifically targeted by many (+)RNA viruses to take advantage of the rich resources provided by these pathways and to affect host anti-viral responses, which depend on the intact endomembrane system of the cells.

In this short review, we summarize the critical roles of the co-opted subdomains of the endoplasmic reticulum (ER)