The best studied model for coronavirus replication and pathogenesis has been the group 2 murine coronavirus, mouse hepatitis virus, and much of what is known of the stages of the coronavirus life cycle has been determined in animals and in culture using this virus. Thus this discussion will focus on MHV with comparisons to SCoV and other coronaviruses. This is appropriate because bioinformatics analyses suggest that SCoV, while a distinct virus, has significant similarities in organization, putative protein functions, and replication to the group II coronaviruses, particularly within the replicase gene. Excellent, detailed reviews of MHV and coronavirus replication are available elsewhere.

The coronavirus virion is an enveloped particle containing the spike (S), membrane (M), and envelope (E) proteins. In addition, some strains of coronaviruses, but not SCoV, express a hemagglutinin protein (HE) that is also incorporated in the virion. The genome of coronaviruses is a linear, single-stranded RNA molecule of positive (mRNA) polarity, and from 28 to 32 kb in length. Within the virion, the genome is encapsidated by multiple copies of the nucleocapsid protein (N), and has the conformation of a helical RNA/nucleocapsid structure. The S protein has been a focus of pathogenesis studies in mice because it appears to be the critical determinant of cell tropism, species specificity, host selection, cell tropism, and disease.

Virus replication is initiated by binding of the S protein to specific receptors on the host cell surface. For MHV, the primary receptor has been shown to be the carcino-embryonic antigen–cell adhesion molecule (CEACAM), and for the human coronavirus, HCoV-229E, and other group 1 coronaviruses, the receptor is aminopeptidase N. The precise mechanisms of entry and uncoating have yet to be defined, but likely occur by either fusion from without or viroplexis through endocytic vesicles. For wildtype MHV, entry and uncoating constitute a pH independent process that is probably direct fusion mediated by a fusion peptide in the S protein. The understanding of the region of the S1 component of coronavirus that binds to receptors was the basis for studies leading to the very recent and very rapid identification of angiotensin converting enzyme 2 (ACE 2) as a receptor for SCoV.

The next discrete stage in the life cycle is translation and proteolytic processing of viral replicase proteins from the input genome RNA, followed by formation of cytoplasmic replication complexes in association with cellular membranes. Replication complexes are thought to be sites of

all stages of viral RNA transcription and replication, and possibly assembly of nascent viral nucleocapsids. Viral assembly occurs both temporally and physically distinct from viral replication complexes in the endoplasmic-reticulum-Golgi-intermediate compartment (ERGIC), a transitional zone between late ER and Golgi. Although the mechanisms by which replication products are delivered to sites of assembly remain to be determined, it has been shown that subpopulations of replicase proteins and the structural nucleocapsid (N) translocate from replication complexes to sites of assembly and may mediate the process in association with cellular membrane/protein trafficking pathways. Virus assembly in the ERGIC involves interactions of genome RNA, N, the membrane protein (M), and the small membrane protein (E), resulting in budding of virions into the lumen of ER/Golgi virosomes. Further maturation of virus particles occurs during movement through the Golgi, resulting in virosomes filled with mature particles. Trafficking of the virosomes to the cell surface has not been well characterized, but is presumed to occur via normal vesicle maturation and exocytic processes. The outcome is the nonlytic release of the vast majority of mature virions into the extracellular space. For MHV and several other coronaviruses that can directly fuse with cells, there is a characteristic and rapidly detectable cytopathic effect of cell-cell fusion into multinucleated syncytia. Production of infectious virus continues even after the majority of cells are fused. Syncytia were recently reported as a readout of SCoV receptor expression and cell infection.