Modifications to the foot-and-mouth disease virus 2A peptide; influence on polyprotein processing and virus replication - DTU Orbit (16/12/2018)

Foot-and-mouth disease virus (FMDV) has a positive-sense ssRNA genome that includes a single, large, open reading frame encoding a polyprotein. The co-translational "cleavage" of this polyprotein at the 2A/2B junction is mediated by the 2A peptide (18 residues in length) using a non-proteolytic mechanism termed "ribosome skipping" or "StopGo". Multiple variants of the 2A polypeptide with this property among the picornaviruses share a conserved C-terminal motif (D(V/I)E(S/T)NPG↓P). The impact of 2A modifications within this motif on FMDV protein synthesis, polyprotein processing and virus viability were investigated. Amino acid substitutions are tolerated at residues E₁⁴, S₁⁵ and N₁⁶ within the 2A sequence of infectious FMDVs despite their reported "cleavage" efficiencies at the 2A/2B junction of only ca. 30-50% compared to wt. In contrast, no viruses were rescued containing substitutions at residues P₁⁷, G₁⁸ or P₁⁹ that displayed little or no "cleavage" activity in vitro, but wt revertants were obtained. The 2A substitutions impaired the replication of an FMDV replicon. Using transient expression assays, it was shown that certain amino acid substitutions at residues E₁⁴, S₁⁵, N₁⁶ and P₁⁹ resulted in partial "cleavage" of a protease-free polyprotein indicating that these specific residues are not essential for co-translational "cleavage". Immunofluorescence studies, using full-length FMDV RNA transcripts encoding mutant 2A peptides, indicated that the 2A peptide remained attached to adjacent proteins, presumably 2B. These results show that efficient "cleavage" at the 2A/2B junction is required for optimal virus replication. However, maximal StopGo activity does not appear to be essential for the viability of FMDV.

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