Separation of foot-and-mouth disease virus leader protein activities; identification of mutants that retain efficient self-processing activity but poorly induce eIF4G cleavage

Foot-and-mouth disease virus (FMDV) is a picornavirus and its RNA genome encodes a large polyprotein. The N-terminal part of this polyprotein is the Leader protein, a cysteine protease, termed Lpro. The virus causes the rapid inhibition of host cell cap-dependent protein synthesis within infected cells. This results from the Lpro dependent cleavage of the cellular translation initiation factor eIF4G. Lpro also releases itself from the virus capsid precursor by cleaving the L/P1 junction. Using site-directed mutagenesis of the Lpro coding sequence, we have investigated the role of 51 separate amino acid residues in the functions of this protein. These selected residues are either highly conserved or are charged and exposed on the protein surface. Using transient expression assays within BHK cells, it was found that residues around the active site (W52, L53 and A149) of Lpro and others located elsewhere (K38, K39, R44, H138 and W159) are involved in the induction of eIF4G cleavage but not in the processing of the L/P1 junction. Modified viruses, encoding such amino acid substitutions within Lpro can replicate in BHK cells but did not grow well in primary bovine thyroid cells. This study characterizes mutant viruses that are deficient in blocking host cell responses to infection (e.g. interferon induction) and can assist in the rational design of antiviral agents targeting this process and in the production of attenuated viruses.

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