Interplay between Foot-and-Mouth Disease Virus 3D polymerase and the type I interferon response: a contribution to viral persistence?

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Foot-and-mouth disease (FMD) is a highly contagious viral animal disease with considerable socio-economic impact in case of outbreak. One of the major problems associated with this disease is the ability of FMDV (Foot-and-Mouth Disease Virus) to persist for several months in a high proportion of infected animals. While persistence of FMDV has been reported in ruminants, it has not been described in pigs. This differential persistence provides an opportunity to compare virus-host interactions between species, to determine their host specificity and to identify potential links between protein-protein interactions (PPI) and viral persistence. Although the underlying mechanisms remain unknown, we have shown in a previous collaborative project, that persistent infection in primary bovine cells is associated with a long-lasting but attenuated and ineffective innate antiviral response. Modulating this response could thus contribute to the establishment and/or maintenance of a virus-host equilibrium through PPI. In this project we focused on the interplay between FMDV proteins and 16 cellular proteins belonging to the type I interferon (IFN I) pathway, which are described as involved in more than 75% of virus-host PPI. Plasmids expressing these 16 proteins from cattle, pig, sheep and goat, as well as expression vectors for 15 FMDV O-type proteins were constructed. PPI were identified by NanoLuc-2-Hybrid screening. The most promising results concern the 3D polymerase for which no interaction with the IFN pathway has been described so far. This protein was used to screen the cattle, sheep, goat and pig NanoLuc plasmid libraries. When comparing the results of these screens, it appears that most of the interactors are shared with relative strength across species. The FMDV-host PPI, have been confirmed by affinity chromatography GST Pull-Down for the four species and functional validation of these PPI is ongoing. Furthermore, we have demonstrated by luciferase reporter assays (Bright-Glo® Luciferase Assay System and Renilla-Glo Luciferase Assay System) the inhibitory effect of 3D polymerase on the induction phase of the IFN response. These combined results strongly suggest that 3D could play an unsuspected part in the escape of FMDV from the host IFN response and potentially in its persistence.