Host-response to foot-and-mouth disease in cattle; possible implications for the development of persistently infected "carriers" - DTU Orbit (24/12/2018)

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General purpose and objectives Foot-and-mouth disease (FMD) is a viral infection of implicit financial importance for countries, such as Denmark, which rely on a significant trade in agricultural products. The disease is highly contagious with rapid spread amongst susceptible animals, causing substantial economical implications for farmers and live-stock industries of affected countries. The occurrence of persistently infected, so called "carriers" of FMDV (Foot-and-mouth disease virus) which may shed infectious virus for prolonged periods of time following exposure to the virus, causes significant complications for effective disease control. The main purpose of this PhD-project has been to investigate the host response to FMDV infection in cattle, with further objectives of elucidating any detectable differences in the measured immune response between animals that developed into FMDV carriers and those that did not. Experimental studies The thesis is based on results obtained from seven separate animal experiments with FMDV serotype O, which have been performed at DTU-Vet, Lindholm. In five out of the six experiments that were performed in cattle, animals were infected with FMDV O UKG 34/2001, representing the virus isolate responsible for the FMD outbreak in the UK and northern Europe in 2001. One cattle experiment was performed with an FMDV serotype O isolated from samples collected from a cattle farm in Uganda during an outbreak in 2006, whilst one additional experiment was designed to investigate the clinical course of infection with FMDV O UKG 34/2001 in sheep. An experimental study design involving endoscopical collection of small biopsies of pharyngeal mucosa from live cattle was developed. This technique enables collection of sequential tissue samples from infected animals, allowing investigation of the local tissue response to infection within this specific anatomical region of individual animals, at different time points following infection. This sampling system was used to investigate the pathogenesis of FMDV infection in cattle through quantification of the levels of FMDV RNA present within the pharyngeal epithelia during early infection. Similar analyses were performed on samples of pharyngeal epithelia and associated lymph nodes collected during post mortem examinations performed at around 32-35 days post infection in order to investigate possible sites of virus persistence. The early host response to FMDV O in cattle was investigated through measurements of systemic parameters consisting of the acute phase proteins, serum amyloid A (SAA) and haptoglobin (HP), as well as type 1 interferon (IFN). The local tissue response within the pharyngeal epithelia was investigated through measurements of mRNA levels of inflammatory cytokines in sequential biopsy samples. Structure of Thesis The first chapter contains general background information on the host response to virus infections, as well as characteristics of FMDV and the pathogenesis of the infection. Detailed aims and objectives of the project are stated at the end of chapter 1. Chapter 2 contains overall descriptions of the animal experiments included in the project. The general concepts of the experimental procedures are described, as well as the clinical characteristics of infection caused by the two different FMDV O isolates in cattle. The clinical description of the experiment performed with FMDV O UKG 34/2001 in sheep includes results of measurements of viremia and the development of specific anti-FMDV O antibodies, as these results are not presented in the included manuscripts. The third chapter of the thesis contains three manuscripts of research articles for publication in peer-reviewed scientific journals. The first manuscript is based on serological measurements of the acute phase proteins SAA and HP, together with the bioactivity of type 1 IFN, in three out of the performed cattle experiments. Measurements of the systemic response to early infection with FMDV is related to the observed development of clinical signs of infection as well as the occurrence of viremia and development of anti-FMDV antibodies. Observed variations in the acute phase response of HP between carriers and non-carriers are discussed. The second manuscript contains results from measurements of mRNA levels of inflammatory cytokines IFN-α and IFN-β as well as tumor necrosis factor –α (TNF-α), in collected biopsy samples. The type 1 interferon response in the analyzed tissue samples is discussed in relation to the previously reported systemic interferon response. The measured cytokine responses, as well as an observed variation in the TNF-α response between carriers and non-carriers, are discussed in relation to previous publications within the subject area. The third manuscript deals with investigations of possible sites of virus replication during early and persistent phases of infection. Levels of FMDV RNA was quantified in sequential biopsy samples of pharyngeal mucosa harvested during early infection, as well as in corresponding tissue samples collected post mortem. The final chapter of the thesis contains a general discussion of the obtained results, together with overall conclusions and future perspectives for continued research within the specific area.

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