

**THESIS TITLE: The role of follicular dendritic cells and persisting foot-and-mouth disease virus antigens as determinants of immune responses to the virus**

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**ABSTRACT**

Foot-and-mouth disease virus (FMDV) causes a highly contagious and economically important viral disease of cloven-hoofed animals. The disease is endemic in many countries in Africa and Asia and vaccination is considered a major tool for disease control in these areas. Effective control by vaccination is impeded by the FMDV carrier state and by the inability of current FMDV vaccines to induce a productive immune response lasting several years similar to the response induced by natural infection.

The FMDV carrier state in ruminants is primarily characterized by the persistence of the virus for prolonged periods in the lymphoid tissues that drain the oropharyngeal region. The persistence of FMDV in the lymphoid tissues of ruminants has been localized on follicular dendritic cells (FDCs) that reside in the light zone of the germinal centre (GC). These cells are able to retain antigens on their surfaces for prolonged periods and play a central role in generating and maintaining high antigen specific antibody titres. This study aimed to better characterize the role of FDCs and persisting viral antigens in the immune response to FMDV infection using the mouse as a model system. In this study, the mouse model was shown to mimic features of FMDV pathogenesis and persistence observed in natural hosts.

Mouse strains varied greatly in their susceptibility to intraperitoneal challenge with FMDV (C57BL/6 mice *vs* BALB/c mice). Virus strain influenced the susceptibility of mice to infection (FMDV/O/UKG/34/2001 *vs* FMDV/A/Arg/1/2000). Analysis of mouse spleen by immunohistochemical staining, laser capture micro-dissection-combined with quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) and FDC isolation and purification, also combined with qRT-PCR, indicated that FMDV antigens were retained in splenic GCs in association with FDCs for prolonged periods following infection. Effective temporary depletion of mouse splenic FDCs was achieved by administration of recombinant lymphotoxin beta receptor immunoglobulin fusion protein (LT $\beta$ R-Ig). Treatment affected viability and functionality of FDCs to trap and retain Peroxidase-anti-peroxidase immune complexes (PAP-ICs). Depletion of FDCs at different time points following FMDV infection affected the persistence of FMDV in the mouse spleen. There was a reduction in FMDV RNA copies in LT $\beta$ R-Ig- treated mice spleen samples compared to the control mice. The humoral immune response to FMDV was affected when depletion of FDC occurred before challenge with FMDV, suggesting a role for FDCs and an intact splenic marginal zone (MZ) structure in the early immune response to FMDV.

LT $\beta$ -deficient mice, which permanently lack FDC and normal splenic MZ, failed to trap and retain FMDV in the GC, failed to generate neutralizing antibodies to FMDV and showed impaired FMDV-specific humoral immune responses. In conclusion, FDCs are the major cells in the mouse lymphoid tissues that trap and retain FMDV antigens for prolonged periods of time up to 63 dpi. FDC and /or GC MZ, play an important role in induction of the humoral immune response to FMDV which appears to be predominantly T-cell independent.

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