



Modelling the interactions between the Porcine Respiratory and Reproductive Syndrome Virus (PRRSV) and its target cells: conditions for virus clearance.

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TITLE : Modelling the interactions between the Porcine Respiratory and Reproductive Syndrome Virus (PRRSV) and its target cells: conditions for virus clearance.

Efficient vaccines are lacking for the control of Porcine Respiratory and Reproductive Syndrome Virus (PRRSV) infection, a major concern for swine industry. The interactions between the virus and the immune system are only partially understood. The first steps of the innate immune response seem crucial for the infection outcome. The PRRS virus replicates mainly in the pulmonary macrophages which play a key role in the innate immunity mechanisms. They are responsible for inflammation and viral destruction by phagocytosis and they participate in the induction and orientation of the adaptive immune response. During a PRRS infection, macrophages also act as target cells for the virus, which can hamper the immune response. To explore these complex mechanisms and test biological hypothesis, we propose an original model centred on macrophage - virus interactions in the lung. Comparatively to previous modelling studies we highly detail the temporal dynamics of the innate immune response to better understand the influences of the macrophage-virus interactions on the viral clearance. We use a system of eighteen state variables: the viral particles, the four macrophage states (healthy, phagocytizing, infected non excreting and infected excreting), the nine major cytokines involved in the macrophage dynamics (IL_1 , IL_6 , IL_8 , IL_{10} , IL_{12} , TNF_α , IFN_α , IFN_γ , TGF_β) and four other immune cells (natural killers, cells involved in the humoral and cellular adaptive immune responses and regulatory cells). Cytokine productions by the immune cells are represented. The macrophages interactions with the viral particles are regulated by the cytokines. Activation/inhibition effects of the cytokines are included. These numerous interactions result in a complex non-linear model. To calibrate our model, we combined data from experimental and modelling studies on the PRRS virus and similar pathogens. To explore the relative influence of the immune mechanisms on the virus clearance we conducted a

multivariate sensitivity analysis using the R package *multisensi*. We showed that the first steps of macrophage-virus interactions are crucial for the outcome of the PRRS virus infection. As expected, the promoting of the cellular response favoured the viral clearance. In further studies we will use the model in order to test control measures to resolve the infection. Moreover, our model can be easily adapted and applied to other pathogens infecting macrophages.

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