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Publication date:
2015

Document Version
Peer reviewed version

MICRORNA REGULATION OF TLRS IN A POST-INFLUENZA ANIMAL MODEL

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Introduction

Substantial morbidity and mortality is caused by secondary bacterial infections occurring in individuals after influenza A virus (IAV) infection. Results from studies in mice suggest that this may in part be due to a lack of responsiveness to Toll-like receptor (TLR) ligands in the post-IAV infected individual. Using the pig as an animal model, we have identified microRNAs (miRNAs) that are differentially expressed in lung tissue two weeks after challenge compared to uninfected controls, i.e. well after the infection has cleared. The role for differential expression of miRNA at this late time point remains unclear. We therefore seek to examine the potential involvement of miRNAs in the translational regulation of TLRs and associated proteins, thus contributing to the lowered responsiveness to bacterial TLR ligands at this late time point, making the individual vulnerable to secondary infections.

Methods and outcome

Pigs were experimentally challenged with a Danish reassortant IAV strain (A/sw/Denmark/12687/03(H1N2)). Lung tissue was harvested 14 days after challenge, as well as from uninfected control animals. Using RNAseq and high-throughput RT-qPCR, we quantified the expression of relevant miRNAs (e.g. miR-335 and miR-146a-5p) and mRNA levels of relevant miRNA targets.

Transcriptional analysis at the site of infection reveals a set of miRNAs to be regulated one week after the pigs had cleared the IAV infection (i.e. two weeks after challenge). This set included miRNAs experimentally validated or *in silico* predicted to bind to and regulate transcripts of TLRs and relevant co-factors and transcription factors (online tools). The antiviral immune response elicited by IAV infection thus includes late miRNA regulation, which in turn may be at the expense of host responsiveness to bacterial TLR ligands.