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Poster Session V
Immunology, vaccination and host defences

TRANSCRIPTIONAL RESPONSE OF CHRONIC Q FEVER PATIENTS' MONONUCLEAR CELLS UPON C. BURNETII STIMULATION REVEALS INTACT INTERFERON-GAMMA RESPONSE PATHWAY

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Objectives: Q fever is a highly contagious zoonotic disease caused by *Coxiella burnetii*. The presentation of Q fever in humans is variable, from asymptomatic to acute or chronic infection. Chronic Q fever has significant mortality, presenting as *C. burnetii* endocarditis, mycotic aneurysm or infection of a vascular graft, months to years after initial infection. It is generally assumed that an adequate Th1 immune response is a requisite for *C. burnetii* clearance and that chronic Q fever is related to a suboptimal Th1 response to C*. burnetii.* However, we previously showed that chronic Q fever patients produce large amounts of *C. burnetii*-specific interferon(IFN)-gamma. Therefore, we investigated the immune transcriptional response to *C. burnetii* stimulation *in vitro* in patients with chronic Q fever and in healthy controls.

Methods: Peripheral blood mononuclear cells (PBMCs) of six chronic Q fever patients and four healthy controls were isolated. The PBMCs were stimulated *in vitro* with phase I *C. burnetii* Nine Mile (the virulent reference strain) or *E. coli* LPS, or were left unstimulated. After eight hours, cells were collected and RNA was extracted. Gene expression was assessed using whole genome microarrays (Agilent Technologies). The data were analyzed with R and the Bioconductor software suites with Linear Models for Microarray Analysis (limma) and a multiclass model integrating the experimental design. Functional enrichment analysis was performed with the DAVID bioinformatics tool.

Results: In patients' PBMCs stimulated with *C. burnetii,* we found a strong upmodulation of IFN-gamma (FC 54.7, $P<0.001$). Moreover, the signature was enriched in genes containing IFN-gamma related transcription factors binding sites. Finally, a large set of genes known to be modulated by IFN-gamma was specifically upmodulated. This suggests that the IFN-gamma response pathway to *C. burnetii* is not defective in chronic Q fever patients. Q fever patients also exhibited a strong humoral response, as illustrated by the upmodulation of i.e. XBP1, IRF4 and BLIMP1, which are implicated in plasmocyte differentiation. This is in accordance with the high antibody titres found in chronic Q fever.
Using *E. coli* LPS stimulation as a control for specificity, we identified the genes upmodulated by *C. burnetii* in healthy volunteers but not in patients. Overall, these genes were involved in immune/inflammatory response and, interestingly, in lipid metabolism pathways. Confirmation and investigation of these genes/pathways are currently ongoing.

Conclusion: We identified and compared the *C. burnetii*-specific immune profile in chronic Q fever patients and healthy controls. The IFN-gamma response pathway appeared to be intact in chronic Q fever patients. However, we found several genes and pathways upmodulated by *C. burnetii* in healthy volunteers but not in patients. These genes provide new insights in immune responses induced by *C. burnetii* and potential defects which may be responsible for progression to chronic Q fever.