

Intracellular localisation and innate immune responses following *Francisella noatunensis* infection of Atlantic cod (*Gadus morhua*) macrophages.

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Source

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Abstract

The facultative intracellular bacterium *Francisella noatunensis* causes francisellosis in Atlantic cod (*Gadus morhua*), but little is known about its survival strategies or how these bacteria evade the host immune response. In this study we show intracellular localisation of *F. noatunensis* in cod macrophages using indirect immunofluorescence techniques and green fluorescent labelled bacteria. Transmission electron microscopy revealed that *F. noatunensis* was enclosed by a phagosomal membrane during the initial phase of infection. Bacteria were at a later stage of the infection found in large electron-lucent zones, apparently surrounded by a partially intact or disintegrated membrane. Immune electron microscopy demonstrated the release of bacterial derived vesicles from intracellular *F. noatunensis*, an event suspected of promoting phagosomal membrane degradation and allowing escape of the bacteria to cytoplasm. Studies of macrophages infected with *F. noatunensis* demonstrated a weak activation of the inflammatory response genes as measured by increased expression of the Interleukin (IL)-1 β and IL-8. In comparison, a stronger induction of gene expression was found for the anti-inflammatory IL-10 indicating that the bacterium exhibits a role in down-regulating the inflammatory response. Expression of the p40 subunit of IL-12/IL-17 genes was highly induced during infection suggesting that *F. noatunensis* promotes T cell polarisation. The host macrophage responses studied here showed low ability to distinguish between live and inactivated bacteria, although other types of responses could be of importance for such discriminations. The immunoreactivity of *F. noatunensis* lipopolysaccharide (LPS) was very modest, in contrast to the strong capacity of *Escherichia coli* LPS to induce inflammatory responsive genes. These results suggest that *F. noatunensis* virulence mechanisms cover many strategies for intracellular survival in cod macrophages.