

ORT_19 - Murine model of *Mycobacterium kansasii* infection reproducing necrotic lung pathology reveals considerable heterogeneity in virulence of clinical isolates

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Introduction: The incidence of non-tuberculous mycobacteria (NTM) pulmonary infections in humans have raised in recent decades, among them *Mycobacterium kansasii* (Mkan) is one of the most pathogenic. Unlike most pathogenic NTMs, Mkan infects immunocompetent individuals as well, inducing a TB-like lung disease that leads to cavitory pathology in more severe cases. The lack of animal models that reproduce human-like lung disease, associated with the necrotic lung pathology, impairs studies of Mkan virulence and pathogenicity.

Objectives: Establish a new murino model that reproduces the main pathological elements of the disease caused by *Mycobacterium kansasii* in humans.

Methodology: In this study, we examined the ability of the C57BL/6 mice, intratracheally infected with highly virulent Mkan strains, to produce a chronic infection and necrotic lung pathology. As a first approach, we evaluated ten Mkan strains isolated from Brazilian patients with pulmonary disease and the reference strain Mkan ATCC 12478 for virulence-associated features in macrophages infected *in vitro*; five of these strains differing in virulence were selected for *in vivo* analysis.

Results: Highly virulent isolates induced progressive lung disease in mice, forming large encapsulated caseous granulomas in later stages (120–150 days post-infection), while the low-virulent strain was cleared from the lungs by day 40. Two strains demonstrated increased virulence, causing premature death in the infected animals. These data demonstrate that C57BL/6 mice are an excellent candidate to investigate the virulence of Mkan isolates. We observed considerable heterogeneity in the virulence profile of these strains, in which the presence of highly virulent strains allowed us to establish a clinically relevant animal model.

Conclusion: In conclusion, we propose the infection of resistant C57BL/6 mice with Mkan as a reliable model reproducing human-like necrotic lung pathology, therefore suitable for investigating Mkan virulence and pathogenicity, as well as an anti-mycobacterial or adjunct drug testing. Additionally, a macrophage infection model *in vitro* may be used to predict the virulence of Mkan strains.

Keywords: *Mycobacterium kansasii*, pathogenicity and animal model