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**Analysis of the phenotype associated with the disruption of *mgIA* in *Francisella tularensis* LVS underlines its central role in manifestation of virulence**

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**Aims:** MglA is a pleiotropic transcription factor controlling the expression of more than 100 genes in *F. novicida*, including the ORFs located on the pathogenicity island. In this study, we further probe the role of MglA in the pathogenicity of the related strain *F. tularensis* LVS.

**Method:** A mutant strain in which the *mgIA* locus was disrupted was generated in the LVS background, by insertion of a non-polar selectable marker cassette. The phenotype associated with the *mgIA* null mutation in comparison to the isogenic parental strain was analysed *in-vitro* and *in-vivo*.

**Results:** The  $\Delta mgIA$  mutant:

- (I) cannot multiply *in-vitro* in macrophages,
- (II) is severely attenuated in a murine model of infection, exhibiting over 10<sup>4</sup> fold decrease in virulence by intra-nasal (IN) administration, and over 10<sup>7</sup> fold decrease by the intra-peritoneal (IP) route of infection,
- (III) unlike the wild type LVS strain, following IP administration, the mutant cannot multiply in the lungs, liver and spleen of infected animals,
- (IV) following IN administration  $\Delta mgIA$  bacteria do not disseminate to target organs (e.g. liver and spleen). Infection by  $\Delta mgIA$  bacteria elicit a significant humoral response, but does not appear to induce a cellular immune response, judging by the levels of INF $\gamma$  and IL-2 in an *in-vitro* stimulation assay. High doses of  $\Delta mgIA$  bacteria can protect mice against a lethal IP challenge of the wild-type LVS strain.

**Conclusion:** The results indicate that MglA plays a major role in *F. tularensis* LVS virulence as shown previously for *F. novicida*. Our studies suggest that inactivation of *mgIA* may serve as a platform for the development of improved attenuated vaccine of virulent *F. tularensis* strains.