

VIRULENCE FACTORS ASSOCIATED WITH INTRACELLULAR GROWTH OF *FRANCISELLA*

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**Intracellular nutrition and *F. tularensis* pathogenesis**A. Charbit<sup>1</sup><sup>1</sup>INSERM U570, Université Paris Descartes, Faculté de Médecine Necker-Enfants Malades, Paris, France

The role of nutrient acquisition systems in survival of intracellular bacterial pathogens within infected cells is yet poorly understood. We recently adapted a cefotaxime-based negative selection to isolate intracellular growth-deficient mutants of *F. tularensis* LVS. This procedure allowed us to select one mutant in a gene (*FTL\_0766*) encoding a putative  $\gamma$ -glutamyl transpeptidase (GGT). The mutant strain showed severe intracellular growth defect and was strongly attenuated for virulence in mice. *F. tularensis* requires cysteine for growth and the specific requirement for cysteine has been attributed to a nonfunctional pathway for sulfate assimilation. We found here that *F. tularensis* GGT activity allowed utilization of glutathione ( $\gamma$ -glutamyl-cysteinyl-glycine, GSH), and of  $\gamma$ -glutamyl-cysteine dipeptide as cysteine sources to ensure bacterial growth.

GSH is the most abundant source of cysteine in the host cytosol, and the cleavage of cysteine-containing peptide by GGT activity thus provides the essential source of cysteine required for intracellular multiplication. This is the first demonstration of the essential role of a nutrient acquisition system in the intracellular multiplication of *F. tularensis*.

These data will be integrated in the more general frame of how *F. tularensis* adapted its metabolic needs to the nutrients available (nature and concentration), to multiply efficiently and simultaneously to avoid a premature death of the host cell.