mig-14 is important for *Salmonella* resistance to IFN-_ mediated responses to bacterial infection

Igor E. Brodsky[1], Eric R. Schurr[2], Carol Clayberger[2], Stanley Falkow[1], and Denise M. Monack[1]
[1]Department of Microbiology and Immunology, and [2]Department of Cardiothoracic Surgery and Pediatrics, Stanford University, Stanford, CA 94305

Salmonella species are responsible for hundreds of thousands of cases of human morbidity and mortality worldwide that result from ingestion of contaminated food and water products. Although infection of immunocompetent individuals by *Salmonella typhimurium* typically causes self-limiting gastroenteritis, in mice *S. typhimurium* causes a systemic disease that closely resembles human typhoid fever caused *Salmonella typhi*. Systemic salmonellosis in mammalian hosts is the result of bacterial invasion of macrophages and dendritic cells within the Peyer's patches of the small intestine, and subsequent spread to mesenteric lymph nodes, liver, and spleen, where bacteria replicate within host phagocytes. The ability of *Salmonella* to survive and replicate in macrophages is necessary for systemic disease. We previously identified a macrophage-induced gene of *Salmonella*, designated *mig-14*, that is required for replication of bacteria specifically at later times post-infection in the liver and spleen. We recently demonstrated that expression of *mig-14* can be induced by antimicrobial peptides and that *mig-14* is required for bacterial resistance to killing by antimicrobial peptides *in vitro*. Here, we show that unlike wild-type bacteria, a *mig-14* mutant strain of *S. typhimurium* is unable to replicate in tissue culture macrophages that have been previously activated by treatment with IFN-_ and LPS. *mig-14* mutant bacteria replicated in the liver and spleen of IFN-_$^{-/-}$ mice, resulting in killing curves that are indistinguishable from those caused by infection of these mice by wild-type bacteria. We also demonstrate that *mig-14* mutant bacteria are more sensitive to killing by a synthetic derivative of the human microbicidal protein granulysin. Therefore, although mice lack a direct granulysin homologue, it seems likely that *mig-14* promotes *Salmonella* virulence by protecting bacteria from the antimicrobial effector mechanisms of activated macrophages *in vivo*.