

Manipulation of macrophage innate immune responses by *Listeria monocytogenes*

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Listeria monocytogenes is a Gram positive, facultative intracellular pathogen of many mammalian species that has been used for decades as a model to study basic aspects of intracellular parasitism and cell-mediated immunity. Because *L. monocytogenes* induces a robust CD8⁺ T-cell response, attenuated strains of *L. monocytogenes* are being developed as live vaccine vectors for infectious disease and malignancies.

Virulent strains of *L. monocytogenes* secrete a pore-forming cytolysin (LLO) that allows the bacteria to access the host cell cytosol. LLO-minus mutants are absolutely avirulent, fail to grow intracellularly and do not provide protective immunity. In this study, we examined the macrophage transcriptional response to wild-type (cytosolic) and LLO-minus (vacuolar) bacteria. The macrophage response to *L. monocytogenes* was characterized by two dominant pathways: Bacteria trapped in a vacuole were recognized by a MyD88-dependent response. In contrast, the response to cytosolic bacteria was MyD88-independent, IRF-3-dependent and led to the production of IFN- β and a few dozen other co-regulated genes. To our surprise, mice lacking the IFN $\alpha\beta$ R were substantially more resistant to infection leading to a hypothesis that *L. monocytogenes* is actively stimulating a host pathway of innate immunity to promote its pathogenesis. The nature of the bacterial ligand(s) and host receptor(s) leading to IRF-3 activation are actively under investigation.

From these and other data, it was clear that macrophages possess a cytosolic microbial recognition system. However, other than cytosolic pathogens, it is not clear how microbial ligands are delivered to the cytosolic pathway. Here we provide some evidence that in activated macrophages, bacterial ligands generated in a phagosome are shuttled to the cytosol and recognized by the cytosolic innate immune response.

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