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EDITORIAL

ELMO1: More Than Just a Director of Phagocytosis

When one considers the significance of the word *phagocytosis* the first thought that mostly likely comes to mind is a process of uptake that evolved to engulf and destroy invading pathogens, as first described in 1882 by Metchnikoff. However, upon further examination, phagocytosis is a far more complex process. While primitive organisms commonly use phagocytosis as a means of nutrient uptake, phagocytosis in multicellular organisms such as metazoans is more often restricted to specialized phagocytic cells including macrophages, dendritic cells, and neutrophils. Over the past decade there has been a torrent of information showing that phagocytosis is not only the first step in a complex cascade of events that initiates host defense and inflammation but that it is also required for removal of senescent cells, embryonic development, and tissue remodeling.

Phagocytosis is a critical host defense mechanism used by macrophages and neutrophils to clear invading pathogens. Macrophages in particular are found in all tissues of the body, serving as sentinels lying in wait for pathogens. They possess an array of germline-encoded pattern recognition receptors/sensors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) and activate downstream effectors/pathways to help mediate innate immune responses and host defense. PRRs include Toll-like receptors (TLRs), scavenger receptors, C-type lectin receptors, and cytosolic sensors such as nucleotide-binding oligomerization domain-containing protein 1 (NOD1) and NOD2, which allow cells to recognize and clear unwanted or foreign materials. These receptors have evolved to recognize conserved motifs displayed by pathogens but not by tissues of higher eukaryotes. The motifs recognized by PRRs are essential to the biology of the invading organism and are therefore not subject to high mutation rates. PRR ligation activates innate immune responses, including rapid induction of transcriptional networks that trigger the production of cytokines, chemokines, and cytotoxic molecules; leukocyte mobilization; and pathogen phagocytosis.

Numerous studies have well documented the signaling and host responses triggered by TLRs such as TLR4, and TLR2, but the role of PRRs in regulating phagocytosis and subsequent inflammatory responses is far less appreciated. Brain angiogenesis inhibitor 1 (BAI1) is a pattern recognition receptor that recognizes the core carbohydrate of lipopolysaccharide (LPS) rather than the lipid A moiety which is bound by TLR4.[1] The intracellular domain of BAI1 interacts with engulfment and cell motility protein 1 (ELMO1) and dedicator of cytokinesis 180 (Dock180) to act as a bipartite guanine nucleotide exchange factor (GEF) for the small Rho GTPase Rac1. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Das et al[2] advance our understanding of BAII and ELMO function to show that internalization of *Salmonella* Typhimurium contributes to maximal cytokine production and that both ELMO1 and Ras-related C3 botulinum toxin substrate 1 (Rac1) are required for internalization and proinflammatory responses.

Their study provides the first line of evidence to suggest that the ELMO1 pathway has an important role in the contribution of phagocytes to the pathogenesis of disease after enteric infection with *Salmonella*, and they detail two important advances. First, the study suggests the importance of ELMO1 in the intracellular sensing of innate immune cues. The biological relevance of this observation was demonstrated by data showing that intestinal macrophages isolated from ELMO1 knockout (KO) mice failed to internalize *Salmonella*. Remarkably, when compared with wild-type mice, these ELMO1 KO mice displayed reduced tissue bacterial burden and attenuated tumor necrosis factor and monocyte chemoattractant protein-1 responses in the ileum, cecum, and spleen. These data suggest that proinflammatory cytokine induction by *Salmonella* after internalization into macrophages may be dependent on EMLO-Rac1 function. However, mice with tissue-specific ELMO1 knockout in myeloid cells, using LysM cre, were similar to the universal ELMO1 KO mice. Further, in vitro analyses showed that ELMO1 and Rac1 were required for nuclear factor κB and p38 mitogen-activated protein kinase activation and downstream cytokine production after *Salmonella* phagocytosis.

Studies of *Salmonella* pathogenesis have significantly contributed to our understanding of how pathogens are detected in the gut and also how they respond to innate immune defense mechanisms. Many receptors recognize bacterial ligands and stimulate host responses. Although surface PRRs are important in stimulating the host response to infection, the internalization of bacteria may modify the host response further as the bacterial PAMPs are displayed to intracellular sensing mechanisms. Thus, the data from this report show that ELMO1-stimulated responses occur largely from within the cell after phagocytosis engulfment of the target, resulting in an amplified signal from the concentration of bacterial PAMPs within phagosomes.

Overall, the study by Das et al introduces the novel concept that not only does the ELMO1/Rac pathway mediate the internalization of bacteria, but also this internalization is essential for the inflammatory response induced by *Salmonella* infection. However, as a consequence of coevolution, *Salmonella* has learned to adapt and thrive in the gut despite such adverse immune consequences. Thus, despite this new understanding of ELMO1 function, like all good studies this work may raise more questions than it answers. For example, the results from using KO mice made me wonder who benefits from phagocytosis and induction of cytokine production—the host or the pathogen? What bacterial virulence factors are necessary to initiate this

response? Can ELMO1 differentially regulate the immune response after sensing pathogens? Is there a role for commensal bacterial in these processes? I look forward to studies that build on their work by addressing these questions and thereby providing further insight into the mechanisms of innate immune responses.

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Conflicts of interest
The authors disclose no conflicts.

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