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The Type III Secretion System Cleans up Its Act(in)

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Inflammasome-associated innate immune receptors sense host-cell targeting by the type III secretion system (T3SS) of pathogenic Yersinia. In this issue of Cell Host & Microbe, Chung et al. (2016) show that the Yersinia T3SS effector protein YopM counteracts this recognition pathway by restricting the pyrin inflammasome, thus increasing bacterial fitness.

The mammalian immune system and bacterial pathogens are locked in an evolutionary battle for survival. Phagocytosis and killing by neutrophils and macrophages represents a primary mechanism of host defense. To survive and grow in the face of this aggression, bacterial pathogens have evolved an arsenal of virulence factors to subvert these defenses. For example, pathogenic Yersinia, including the plague agent Y. pestis and the enteropathogens Y. pseudotuberculosis and Y. enterocolitica, block host actin polymerization, thereby evading phagocytosis and subsequent killing by phagocytes. As a result, Yersinia are found largely extracellularly within host tissues. Yet ~30% of bubonic plague patients and the vast majority of otherwise healthy people infected with enteropathogenic Yersinia recover without treatment. Over the last decade, it has become clear that inflammasome-associated innate immune receptors recognize these bacteria, contributing to their clearance.

Like many other Gram-negative pathogens, Yersinia use a specialized appendage called a type III secretion system (T3SS) to subvert host defenses. The T3SS is a syringe-like apparatus that forms a pore in target host cell membranes to deliver effector proteins directly into the host cytoplasm. Recent studies have suggested that host Nlrp3 and Nlrc4 inflammasomes are involved in sensing this membrane perturbation and subsequent cytosolic entry of T3SS structural components, enabling recognition of T3SS deployment by pathogens (reviewed in Shin and Brodsky, 2015). In addition, the protein pyrin forms an inflammasome following modification of the actin cytoskeletal GTPase RhoA by bacterial toxins such as the Rho-glucosylating cytotoxin TcdB of Clostridium difficile (Xu et al., 2014). In this issue of Cell Host & Microbe, Bliska and colleagues demonstrate that the Rho GTPase-targeting activity of the Yersinia T3SS effector proteins YopE and YopT triggers inflammasome activation and pyroptotic host cell death (Chung et al., 2016). Therefore, mammalian cells use the inflammasome signaling platform to mediate a host cell response to the activities of both the T3SS injectisome apparatus and T3SS effector proteins. The latter is reminiscent of the "altered self" or guard hypothesis describing how plant cytosolic innate immune receptors recognize the enzymatic activity of T3SS effector proteins used by plant pathogens to launch a protective response.

Despite this seemingly redundant strategy for host cell recognition of the T3SS, infection with wild-type Yersinia leads to relatively little inflammasome activation. This is because Yersinia encodes additional proteins that dampen inflammasome activity through distinct pathways. For example, the translocated protein YopE inhibits pyrin inflammasome activity after translocation via the T3SS. YopE from Y. pseudotuberculosis 32777 contains 21 LRRs and does not possess caspase-1 binding activity (Chung et al., 2014; LaRock and Cookson, 2012). RhoA-activated PRK was recently shown to phosphorylate pyrin, thereby enabling binding of 14-3-3 proteins that negatively regulate pyrin activity (Park et al., 2016). Now, Chung et al. (2016) show that YopM from Y. pseudotuberculosis 32777 enhances pyrin phosphorylation by its interactions with PRK2. Therefore, the authors propose a model in which YopE and YopT target RhoGTPases to prevent phagocytosis, and the associated inhibition of RhoA activity prevents activation of PRK, resulting in pyrin inflammasome formation (Figure 1A). YopM, however, dampens this immune response by triggering PRK-mediated pyrin phosphorylation (Figure 1B). Importantly, Chung et al. (2016) show that although a Y. pseudotuberculosis 32777 yopM mutant is attenuated in wild-type mice, it is fully virulent in mice lacking pyrin. Furthermore, YopE and YopT catalytic activity determines whether the absence of YopM is associated with decreased virulence in mice. Previous data suggest that Gr1+ cells, which include neutrophils, inflammatory monocytes, and several other cell types, are important for Y. pestis disseminated infection only when yopM is absent (Ye et al., 2009). Therefore, YopM may contribute to pathogenesis by dampening pyrin inflammasome activity critical for neutrophil or monocyte-mediated control of Yersinia.
YopM inhibition of pyrin activation that is triggered by the phagocytosis inhibitors YopE and YopT demonstrates beautifully the selective pressure reciprocally imposed by bacterial pathogens and the mammalian innate immune system over the course of evolution. But YopM may have other functions. In addition to interacting with inflammasome components in the host cytoplasm, YopM is also found in the nucleus. Recently, Berneking et al. (2016) provided evidence that Y. enterocolitica WA314 YopM (20 LRRs) interacts with the DEAD-box helicase DDX3 and that this interaction mediates its exit from the nucleus via the CRM1 export pathway. This YopM nuclear shuttling may collaborate with downmodulation of the pyrin inflammasome, as it modulates RSK1 phosphorylation and transcription of the anti-inflammatory cytokine IL-10 as well as other genes related to inflammation and immunity.

A number of questions remain about how YopM modulates innate immunity and enhances Yersinia virulence. Is maintaining the proper balance of cytosolic and nuclear YopM important for Yersinia pathogenesis? Is this balance altered in different host cell types and under specific inflammatory context? What is the significance of YopM heterogeneity among pathogenic Yersinia? In addition, gain-of-function mutations in the mfev gene, which encodes pyrin, cause a hereditary autoinflammatory disease called Familial Mediterranean fever and are carried by as many as one out of five people of Mediterranean origin. The present study by Chung et al. (2016) suggests the intriguing possibility that such mutations may have provided a selective advantage during plague pandemics that killed hundreds of millions of people living around the Mediterranean Sea over the last ~1,500 years.

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**REFERENCES**


