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Molecular call-and-response: how Salmonella learns the gospel from its host

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Host–microbe interactions are often portrayed as a game of molecular hide-and-seek or tug-of-war where one partner seeks to establish an upper-hand over the other. Perhaps a more useful analogy is the traditional call-and-response preaching method used so effectively in churches of the southern USA to encourage participation by the assembled parishioners. The preacher calls out a line of a gospel or hymn and the congregation responds as one to the cue. A recent paper identifies Nramp as a potential molecular preacher, and Salmonella, and probably other pathogenic bacteria, are singing back full-throated.

Salmonella enterica serovar Typhimurium normally causes self-limiting gastroenteritis. This pathogen uses type III pili to deliver effector proteins to its preferred host cell, the macrophage. The bacterial colony proliferates in an intracellular vacuole. As macrophages wander the body, the bacteria are disseminated by escape into various cellular compartments. Death can occur, but only in host mice that lack the product of the Nramp gene. Here, bacterial loads in the liver and spleen reach lethal levels. This Nramp loss-of-function mutation was first defined as a natural variation between strains of inbred mice. The strain lacking Nramp was killed by a variety of bacterial pathogens, including several species of Mycobacterium and Leishmania, and Candida albicans and Toxoplasma gondii (reviewed in Ref. [1]). In fact, Nramp, like many an itinerant preacher, went by several names in the inbred mouse strain literature (Ity/Bcg/Lsh). Nramp was cloned based on its genomic position in one of the earliest chromosome walks in mouse [2], and was subsequently shown to encode a protein that resides in an endocytic vacuole of macrophages, the same subcellular address inhabited by S. enterica Typhimurium. The function of Nramp is still somewhat unclear, but it is thought to pump divalent ions pleiotropically. It might also function to scavenge iron from dead red blood cells in the infected host.

Nramp gathers the congregation

A quirk of the cell biology edifice of Salmonella that has emerged over the past ten years is the heavy reliance on

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Nramp-defective mice (genotype nramp) or cell lines derived from them as experimental hosts. Among other things, this system has revealed that genes in the S. enterica Typhimurium SPI2 pathogenicity island are required for systemic proliferation. These genes include the type III structural genes and effectors delivered by it into the host cell. Although instructive for understanding how systemic disease results, and thus potentially a reasonable model for typhoid fever in humans, the ancestral wild-type allele must have been Nramp. Therefore, the interaction most reflective of the co-evolved ancestral wild-type allele must have been Nramp. How then does Nramp preach to the congregation of bacteria growing in the privileged confines of the late endocytic vacuole? And which Psalm do they sing?

Enter Zaharik and colleagues [3] who address the effects of Nramp on the growth and survival of S. enterica Typhimurium, and the effect of Nramp on a variety of pathogen genes involved in virulence. We know that intimate host–microbe associations result in signals being passed back-and-forth, and that these signals usually result in transcriptional re-programming in one or both partners. Therefore, if Nramp is a key molecule preaching a direct message to the pathogen, as opposed to simply a molecule whose presence conditions resistance independent of the bacterial genotype, its presence should generate a chorus of transcriptional 'amens' from the pathogen.

Choir soloists are virulence factors

First, Zaharik and colleagues demonstrated that S. enterica Typhimurium does indeed survive in Nramp-positive mice. Splenic bacterial numbers increase over the same four-day time-course that kills most of the Nramp-negative mice. This result indicates that Nramp is required to keep the slowly proliferating bacteria from growing uncontrollably. The growth observed in both Nramp-positive and Nramp-negative mice is eliminated by mutation in SPI2, proving that the type III system is key in this interaction. As the interaction in Nramp-negative mice is self-limiting, it would have been interesting to know the splenic bacterial titer at a time-point when infection is limited; presumably it drops to baseline levels.

Because the SPI2 system was required for bacterial survival in Nramp-positive mice, Zahari et al. postulated that genes in, or controlled by, SPI2 might respond to the presence of Nramp. They assayed promoter–reporter fusions for induction or repression in a macrophage-like cell line derived from an nramp mouse but complemented Nramp1 up-regulates the expression of pathogenicity island-2 virulence genes. Proc. Natl. Acad. Sci. U. S. A. 99, 15705–15710

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