INFECTIOUS DISEASE

Hitching a ride with DCs

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Most lineages of the *Salmonella enterica* subspecies Typhimurium cause gastroenteritis in humans, but a recently emerged lineage found in sub-Saharan Africa causes systemic disease. Carden *et al.* now report that the hyperdissemination of this lineage arises as the result of pseudogenization of a bacterial effector protein that normally inhibits dendritic cell (DC) migration.

Salmonella enterica serovars can be classified as typhoidal or non-typhoidal (NTS) depending on the type of human disease they cause. NTS infections typically cause self-limiting gastroenteritis, but in sub-Saharan Africa these infections are the main cause of bloodstream *Salmonella* infections. Invasive African NTS infections are generally caused by *Salmonella* Typhimurium isolates of sequence type 313 (ST313), whereas gastroenteritis-inducing strains of *S. Typhimurium* are usually ST19 isolates. Compared with ST19 isolates, ST313 isolates show evidence of genome degradation, including pseudogene formation; the authors set out to determine how these genomic differences shape the ability of ST313 to induce systemic disease.

When antibiotic-treated mice were orally infected with either ST313 or ST19 *S. Typhimurium*, comparable levels of each isolate were detected in the small intestine, Peyer's patches and caecum at 2 days post-infection. By contrast, higher levels of ST313 were detected in the mesenteric lymph nodes (MLNs), spleen and liver. Mice infected intraperitoneally showed similar levels of ST313 and ST19 bacteria in the spleen and liver, suggesting that the ST313 isolates do not have a survival or replication advantage at systemic sites, but instead are more efficient at disseminating from the gut.

In mice that had been infected orally with ST19 or ST313, similar bacterial loads were detected in the blood between 30 minutes and 2 days post-infection; therefore, the initial hyperdissemination of ST313 from the gut does not occur via the bloodstream. Flow cytometry analyses of innate immune cells in the MLNs showed that ST313 infected higher numbers of migratory DCs than ST19, indicating that DCs may facilitate increased dissemination by transporting bacteria from the gut to the MLNs. Further

characterization of the migratory DC types targeted by ST19 and ST313 showed that both isolates infected equal numbers of CD103⁺CD11b⁻ and CD103⁺CD11b⁺ DCs, but ST313 infected higher numbers of CD11b⁺ DCs.

ST313 was not more efficient in infecting or surviving in DCs compared with ST19, and experiments with caspase-deficient mice indicated that differences in inflammasome-mediated cell death do not explain the hyperdissemination of ST313. However, when the authors orally infected mice deficient in the lymph node homing receptor CCR7 with either ST19 or ST313, they found similar levels of both isolates in the MLNs, liver and spleen. Therefore, CCR7-dependent migration of CD11b⁺ migratory DCs seems to be necessary for the hyperdissemination of ST313.

Previous work by the same group showed that ST19 produces seven *Salmonella* pathogenicity island 2 (SPI-2) effectors that inhibit DC migration towards the CCR7 ligand CCL19. One such SPI-2 effector, *Salmonella*-secreted effector I (Ssel), has been rendered a pseudogene in ST313 isolates; the authors reasoned that this may permit DCs infected with ST313 to more readily migrate to MLNs. In support of this idea, Ssel-deficient ST19 bacteria showed increased dissemination to MLNs compared with a wild-type ST19 strain. Comparison of various *S. Typhimurium* strains that either contained or lacked a functional Ssel confirmed that the absence of this effector is associated with increased numbers of *Salmonella*-infected DCs in MLNs following oral infection.

The authors propose that rapid dissemination of *Salmonella* may lead to faster induction of T cell responses and enhanced pathogen clearance in immunocompetent hosts. By contrast, in immunocompromised hosts, such as those often found in sub-Saharan Africa, hyperdissemination is less likely to be deleterious for *Salmonella*, potentially facilitating the loss of Ssel and evolution towards causing systemic disease.

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ORIGINAL ARTICLE Carden, S. E. *et al.* Pseudogenization of the secreted effector gene *ssel* confers rapid systemic dissemination of *S. Typhimurium* ST313 within migratory dendritic cells. *Cell Host Microbe* <http://dx.doi.org/10.1016/j.chom.2017.01.009> (2017)