Chronic Infection and Competence: A New Mouse Model of Helicobacter Pylori

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Helicobacter pylori causes a chronic human infection, with symptoms appearing sometimes decades after infection. Natural infection is limited to humans and other primates; however, a handful of human isolates have been successfully adapted to infect mice. One strain (SS1) can chronically infect mice, but it is difficult to genetically manipulate. Another commonly used strain (NSH57) is genetically tractable, but it is cleared after only four weeks. These models have been useful for identifying *H. pylori* virulence factors and determinants of acute infection, but the genetic basis for chronic infection is difficult to address with the currently available strains. Dr. Nina Salama and Dr. Marion Dorer (Human Biology Division) have addressed this deficiency in a study recently published in*Infection and Immunity* by developing a genetically manipulable strain of *H. pylori* that persists in mice longer than 28 weeks.

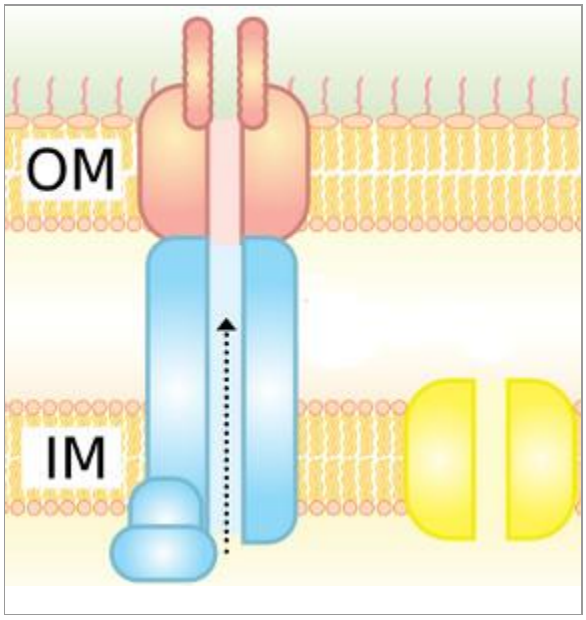
To generate their mouse model of chronic infection, the team serially passaged strain NSH57 in mice every four to nine weeks. After six rounds of infection, the team isolated strain MSD132, a clone that persists in the mouse stomach for at least seven months and is still genetically tractable.

Located in the genome of *H. pylori*, the Cag pathogenicity island (Cag PAI) encodes a Type IV secretion system (T4SS) which induces pro-inflammatory cytokine secretion by translocating cell wall fragments and the protein effector CagA into host cells. T4SS are specialized secretion systems that inject bacterial products into neighboring cells or take-up substrates from the environment. Although Cag-mediated inflammation does not lead to clearance during human infection, it is thought that this inflammation does inhibit chronic infection in the mouse. Therefore, the team asked whether or not the Cag T4SS is maintained in their passaged strains. They isolated two strains from passage 3; MSD86, which still induces inflammation; and MSD85, which has lost this ability and grows 20-fold better than MSD86. Sequencing identified a single nucleotide insertion in *cagY* which is predicted to truncate the protein. This mutation is sufficient to abolish T4SS activity. However, the team identified strains from passages 1 and 2 which also grow better than the parent strain and do not encode the*cagY* mutation, suggesting that Δc*agY* alone may not be sufficient to establish chronic infection in the mouse.

Most clinical isolates of *H. pylori* are naturally competent, meaning that they can take up and express DNA from other bacteria and the environment. Therefore, the team also tested the effect of competence on chronic infection in this model. Com is another T4SS responsible for DNA uptake from the environment, and Δ*comB10* abolishes this phenotype. After one week there was no difference in bacterial load between mice infected with a Δ*comB10* strain or the serially passaged MSD132 strain; however, after 8 weeks MSD132 had a significantly higher bacterial load ($p<0.01$). The results were similar when the team deleted drpA, a different gene involved in competence. Δ*drpA* bacteria can take up environmental DNA, but they cannot integrate it into their genomes. The observation that Δ*drpA* strains grow no better than Δ*comB10* strains suggests that the growth defect is not due to an inability to utilize exogenous nucleotides as an energy source, but is in fact attributable to the attenuation of natural competence in these bacteria. Taken together, these data confirm that natural competence is important for chronic colonization of mice by *H. pylori*.

The Salama Lab has previously shown that natural competence does not contribute to DNA repair mechanisms, and this current study suggests that DNA is not acquired from the environment as a source of nucleotides. The most compelling hypothesis, therefore, is that *H. pylori* natural competence provides an adaptive mechanism, allowing the bacteria to maintain genetically mixed populations and more rapidly adapt to selective pressure in the harsh environment they colonize. This new strain will be a powerful tool to investigate gene flow and adaptation during chronic *H. pylori* infection.

Dorer MS, Cohen IE, Sessler TH, Fero J, Salama NR. 2012. Natural competence promotes *Helicobacter pylori* chronic infection.*Infect. Immun.*, Epub ahead of print, doi: 10.1128/IAI.01042-12.



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Schematic representation of a type IV secretion system, similar to the Com and Cag apparatuses discussed in the paper. The complex spans the inner (IM) and outer (OM) membranes of H. pylori. Substrates are secreted or taken up through the central channel (arrow).