Carcinogenic bacterial pathogen Helicobacter pylori triggers DNA double-strand breaks and a DNA damage response in its host cells.

Abstract:
The bacterial pathogen Helicobacter pylori chronically infects the human gastric mucosa and is the leading risk factor for the development of gastric cancer. The molecular mechanisms of H. pylori-associated gastric carcinogenesis remain ill defined. In this study, we examined the possibility that H. pylori directly compromises the genomic integrity of its host cells. We provide evidence that the infection introduces DNA double-strand breaks (DSBs) in primary and transformed murine and human epithelial and mesenchymal cells. The induction of DSBs depends on the direct contact of live bacteria with mammalian cells. The infection-associated DNA damage is evident upon separation of nuclear DNA by pulse field gel electrophoresis and by high-magnification microscopy of metaphase chromosomes. Bacterial adhesion (e.g., via blood group antigen-binding adhesin) is required to induce DSBs; in contrast, the H. pylori virulence factors vacuolating cytotoxin A, ?-glutamyl transpeptidase, and the cytotoxin-associated gene (Cag) pathogenicity island are dispensable for DSB induction. The DNA discontinuities trigger a damage-signaling and repair response involving the sequential ataxia telangiectasia mutated (ATM)-dependent recruitment of repair factors--p53-binding protein (53BP1) and mediator of DNA damage checkpoint protein 1 (MDC1)---and...
histone H2A variant X (H2AX) phosphorylation. Although most breaks are repaired efficiently upon termination of the infection, we observe that prolonged active infection leads to saturation of cellular repair capabilities. In summary, we conclude that DNA damage followed by potentially imprecise repair is consistent with the carcinogenic properties of H. pylori and with its mutagenic properties in vitro and in vivo and may contribute to the genetic instability and frequent chromosomal aberrations that are a hallmark of gastric cancer.