

## ***Helicobacter suis* $\gamma$ -Glutamyl Transpeptidase Causes Glutathione Degradation-Dependent Gastric Cell Death**

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**Introduction:** *Helicobacter (H.) suis* is the most prevalent non-*H. pylori* *Helicobacter* (NHPH) species colonizing the stomach of humans suffering from gastric disease. This bacterium has only recently been isolated *in vitro* from the gastric mucosa of a sow, enabling us to investigate its possible virulence factors involved in human gastric pathology. We aimed to unravel the mechanism used by *H. suis* to induce gastric cell death, which is considered to be a major factor in the development of gastric ulcer, gastric atrophy, gastric cancer and gastritis. **Methodology and Results:** *H. suis* induced cell death was studied *in vivo* in mice and Mongolian gerbils and *in vitro* using AGS cells. Transmission electron microscopy revealed necrosis of gastric epithelial, mainly parietal cells both in mice and gerbils. Parietal cell loss was confirmed by immunohistochemistry, predominantly at the transition zone between fundus and antrum. *H. suis* whole bacterial cell lysate induced death of AGS cells. Incubation of AGS cells with active or inactivated purified recombinant *H. suis* GGT (rHSGGT) as well as inhibition of  $\gamma$ -glutamyl transpeptidase (GGT) activity of *H. suis* lysate showed that this enzyme plays an important role in *H. suis*-induced cell death. Supplementation of the AGS cultivation medium with glutathione strongly enhanced the observed increase of cell death, demonstrating that metabolites of *H. suis* GGT-mediated glutathione degradation play an active role in the induction of cell death. This effect was accompanied by an increase of the oxidative stress burden, reflected by an increase of extracellular H<sub>2</sub>O<sub>2</sub> concentrations. **Conclusions:** *H. suis* GGT mediates degradation of reduced glutathione, generating pro-oxidant metabolites of glutathione breakdown, which bring on cell damage and actively cause cell death. To our knowledge, this is the first report of a gastric pathogen abusing the antioxidative protection mechanism of the host by this means to damage the stomach.