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Disulfide bond formation in gastric pathogen *Helicobacter pylori*: An Achilles's heel for secretion of pro-inflammatory virulence proteins

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H. *pylori* causes gastritis, gastric ulcers and cancers but the mechanisms of virulence are not fully understood. It produces secreted proteins which may play a role in eliciting gastric inflammation, including the helicobacter cysteine rich protein HcpE (HP0235) whose biological function is unknown. Our goal was to investigate if HcpE is secreted by *H. pylori* and is involved in host/pathogen interactions, and identify components essential for its production. Using a combination of anti-HcpE ELISA and western blots, knockout mutagenesis, phenotypic analyses and biochemical assays, we demonstrate that HcpE is secreted by many strains as a soluble protein and in association with outer membrane vesicles. We show that infected patients produce anti-HcpE antibodies, indicating *in situ* HcpE production. We show that HcpE comprises many disulfide bonds and identify DsbK (HP0231) as a folding factor necessary for HcpE production, and show that recombinant DsbK can refold unprocessed, reduced HcpE *in vitro*. This highlights the first biologically relevant substrate for DsbK. Furthermore, we show that DsbK has disulfide bond (Dsb) forming activity on reduced

lysozyme and has DsbA-like activity upon expression in *E. coli*, despite its similarity with DsbG. Also, we show a role of DsbK in redox homeostasis in *H. pylori*. Finally, we show an important role for DsbK and HcpE in host-pathogen interactions, including murine gastric colonization and pro-inflammatory cytokine production in human gastric explants and in murine splenocytes. Both proteins will be investigated as therapeutic targets to treat *H. pylori* infections and prevent gastric ulcers and cancers.

Speaker Biography

Carole Creuzenet has completed her PhD in Biochemistry at the University of Nantes and The National Institute for Agronomical Research (France). She has completed her Post-doctoral studies at the Massachusetts Institute of Technology (USA) and the University of Guelph (Canada). She is Associate Professor at the University of Western Ontario (London, Canada) where her lab focuses on virulence factors from bacterial gastrointestinal pathogens such as *Campylobacter jejuni*, *Helicobacter pylori* and *Yersinia pseudotuberculosis*. Her focus is on glycolipids and glycoproteins as well as on novel secreted proteins and their folding partners. She has published 38 papers in reputed journals.

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