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Consequences of *H. pylori* infection and its VacA cytotoxin on mitochondria and mitochondrial DNA: Impact on gastric pathogenesis

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Statement of the Problem: Mitochondria alterations and mitochondrial DNA (mtDNA) instabilities are a hallmark of cancer. Mitochondria represent strategic targets for pathogens also including *Helicobacter pylori.* This bacterium is a major risk factor for gastric cancer. Up to now, the cytotoxin VacA is the only one *H. pylori* factor known to target and damage mitochondria.

Methodology & Theoretical Orientation: By in vitro infection of gastric epithelial cells with wild-type and VacA-deficient *H. pylori* strains, treatment of cells with purified VacA proteins and infection of a mouse model, we show that *H. pylori* deregulates mitochondria by two novel mechanisms, both rather associated with host cell survival. First, early upon infection VacA induces transient increase of mitochondrial translocases and a dramatic accumulation of the mitochondrial DNA replication and maintenance factors POLG and TFAM. These events occur when VacA is not detected intracellularly, therefore do not require the direct interaction of the cytotoxin with the organelle. They occur independently of the VacA vacuolating activity. In vivo, these alterations coincide with the evolution of gastric lesions towards severity, concomitantly with the induction of mtDNA mutations and depletion of mtDNA content. Second, H. pylorus also induces VacA-independent alteration of mitochondrial replication and import components, suggesting the involvement of additional *H. pylori* activities in mitochondria-mediated effects.

Conclusions & Significance: Our findings reveal a novel and early inducer effect of *H. pylori* infection on mitochondrial translocases and the mtDNA replication/transcription machinery components POLG and TFAM. Moreover, we show that VacA does not account for all consequences of *H. pylori* infection at mitochondria, pointing to the involvement of other bacterial activities, yet to be determined. These effects of *H. pylori* infection are also relevant in vivo, suggesting that mitochondrial alterations impact H. pylori-induced gastric inflammation and pathogenicity.

Recent Publications

1. Chatre L, Fernandes J, Michel V, et al (2017) *Helicobacter pylori* targets mitochondrial import and components of mitochondrial DNA replication machinery through an alternative VacA-dependent and a VacA-independent mechanisms. Scientific Reports 7: 15901.
2. Majlessi L, Fadel Sayes F, Bureau JF, et al (2017) Colonization with *Helicobacter* is concomitant with modified gut microbiota and drastic failure of the immune control of *Mycobacterium tuberculosis*. Mucosal Immunology 10:1178-1189.
3. Matak P, Heinis M, Mathieu J, et al (2015) Myeloid HIF-1 is protective in *H. pylori* mediated gastritis. J of Immunology 194:3259-3266.
4. Fernandes J, Michel V, Carmolinga-Ponce M, et al (2014) Circulating mitochondrial DNA level as a potential non-invasive biomarker to the early detection of gastric cancer. Cancer Epidemiology, Biomarkers and Prevention 23:2430-2438.
5. Correia M, Casal S, Vinagre J, Seruca R, Figueiredo C, Touati E and Machado J C (2014) *H. pylori* cholesterol uptake impacts resistance to docosahexaenoic acid. Int. J of Medical Microbiology, 304: 314-320

Biography

Eliette Touati is currently working as a Senior Researcher at the Institut Pasteur in Paris. Her present work is dedicated to the study of the relationships between *H. pylori* infection and gastric cancer, focusing on the regulation of the host DNA damage and repair response. She works on translational projects to characterize gastric cancer biomarkers with the goal to develop non-invasive tests for the early detection/prevention of patients.

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