Modulation of Nrf2-dependent antioxidant response after infection with *Helicobacter pylor*i may contribute to gastric cancer

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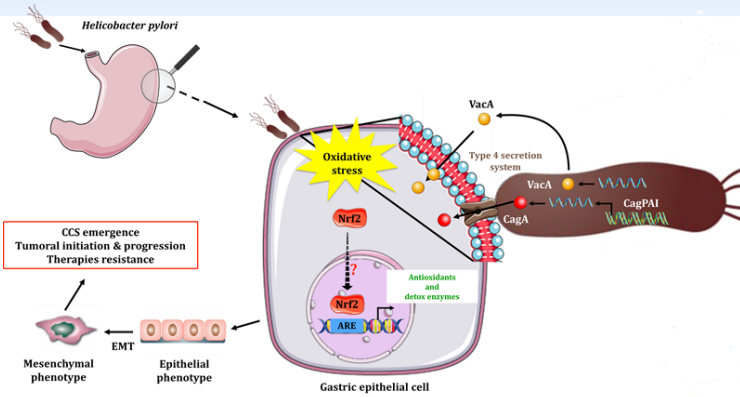
Background

- Gastric cancer (GC): 4th leading cause of mortality by cancer worldwide
- Major risk factor of GC: chronic infection with *Helicobacter pylori*
- *H. pylori* induces an epithelial-to-mesenchymal transition (EMT), first step of GC
- Nrf2: transcription factor, main regulator of cellular redox homeostasis



Objectives

1) To assess the modulation of the Nrf2 pathway after infection with *H. pylori*
2) To decipher the role of Nrf2 in *H. pylori*-induced EMT

Material & Methods

Objective 1: 3 gastric epithelial cell lines HFE-145 (non cancerous), AGS (cancerous diffuse subtype), MKN74 (cancerous intestinal subtype) co-cultured with *H. pylori* for 1, 5 or 24h

Objective 2: 4 gastric epithelial cell lines (AGS and MKN74) WT or Nrf2-KO by CRISPR-Cas9 co-cultured with *H. pylori* for 24h

Results

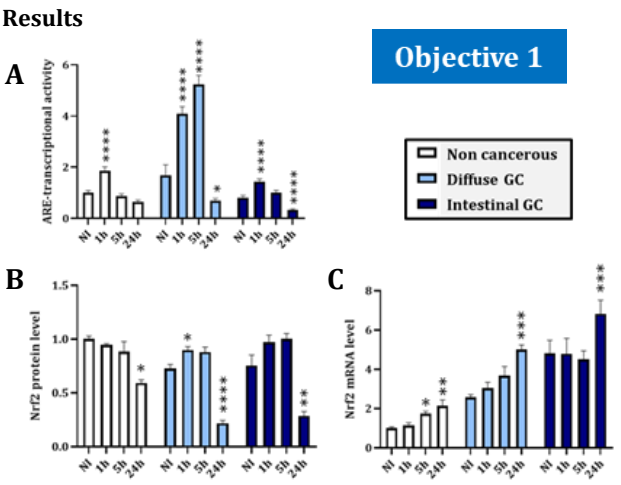


Figure 1: Non cancerous (white), cancerous diffuse subtype GC (light blue) and cancerous intestinal subtype GC (dark blue) cell lines were colcutured with *H. pylori* for 1, 5 and 24h. ARE-transcriptional activity **(A)** and Nrf2 protein **(B)** and mRNA **(C)** levels were assessed.

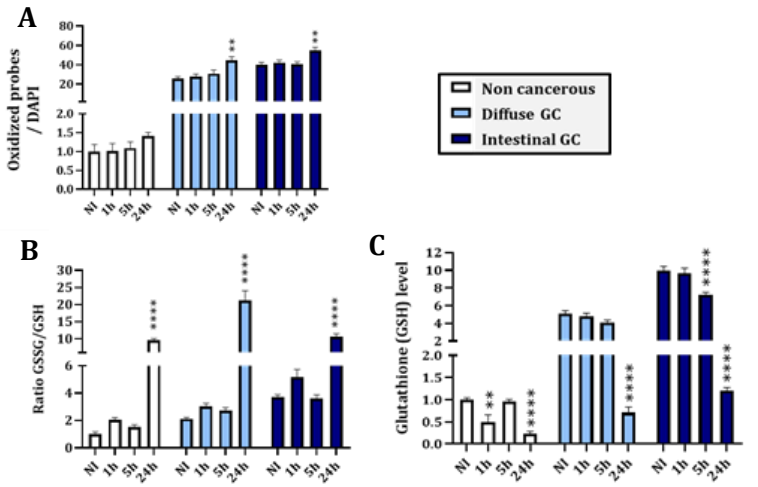


Figure 2: Non cancerous (white), cancerous diffuse subtype GC (light blue) and cancerous intestinal subtype GC (dark blue) cell lines were colcutured with *H. pylori* for 1, 5 and 24h. Intracellular level of ROS **(A)**, ratio between oxidized glutathione (GSSG) and total glutathione (GSH) **(B)** and level of total glutathione **(C)** were assessed.

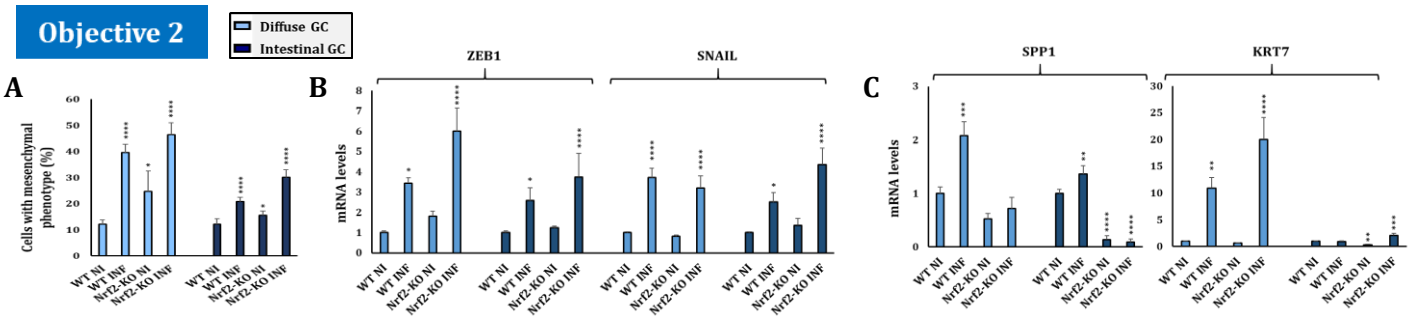


Figure 3: Cancerous diffuse subtype GC (light blue) and cancerous intestinal subtype GC (dark blue) cell lines either WT or Nrf2-KO were colcutured with *H. pylori* for 24h. Percentage of cells with a mesenchymal phenotype **(A)** and mRNA levels of mesenchymal **(B)** and epithelial **(C)** markers were assessed.

Conclusions

Objective 1: Upon infection with *H.pylori*, Nrf2 pathway is activated in the early phase while inhibited after 24h, the late inhibition is associated with an increased oxidative stress and a depletion of glutatione.

Objective 2: Nrf2 seems to be a guardian of the cellular epithelial phenotype integrity and *H. pylori*-induced EMT is increased when cells are deleted for Nrf2

Nrf2 could play a key role in *Helicobacter pylori*-induced gastric carcinogenesis