Lymphotoxin α receptor signalling executes Helicobacter pylori-driven gastric inflammation in a T4SS-dependent manner.

Abstract:
Lymphotoxin α receptor (LTαR) signalling has been implicated in inflammation-associated tumour development in different tissues. We have analysed the role of LTαR and alternative NF-κB signalling in Helicobacter pylori-mediated gastric inflammation and pathology. We analysed several ligands and receptors of the alternative NF-κB pathway, RelB, p52 nuclear translocation and target genes in tissue samples of H. pylori-infected patients with different degrees of gastritis or early gastric tumours by in situ hybridisation, immunohistochemistry, Western blot and real-time PCR analyses. Molecular mechanisms involved in LTαR activation by H. pylori were assessed in vitro using human gastric cancer cell lines and distinct H. pylori isolates. The effects of blocking or agonistically activating LTαR on gastric pathology during challenge with a human pathogenic H. pylori strain were studied in a mouse model. Among the tested candidates, LT was significantly increased and activated alternative NF-κB signalling was observed in the gastric mucosa of H. pylori-infected patients. H. pylori-induced LTαR-ligand expression in a type IV secretion system-dependent but CagA-independent manner, resulting
in activation of the alternative NF-κB pathway, which was further enhanced by blocking canonical NF-κB during infection. Blocking LT?R signalling in vivo suppressed H. pylori-driven gastritis, whereas LT?R activation in gastric epithelial cells of infected mice induced a broadened pro-inflammatory chemokine milieu, resulting in exacerbated pathology. LT?R-triggered activation of alternative NF-κB signalling in gastric epithelial cells executes H. pylori-induced chronic gastritis, representing a novel target to restrict gastric inflammation and pathology elicited by H. pylori, while exclusively targeting canonical NF-κB may aggravate pathology by enhancing the alternative pathway.