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CLASSICAL AND ALTERNATIVE PATHWAY NUCLEAR FACTOR- κ B SIGNALLING DIFFERENTIALLY REGULATE GASTRIC EPITHELIAL RESPONSES TO *HELICOBACTER FELIS* INFECTION

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Introduction Classical pathway NF- κ B signalling is implicated in the pathogenesis of several inflammation associated cancers, including colitis associated colon cancer and *Helicobacter* associated gastric cancer. However, the role of individual NF- κ B family members and the function of alternative pathway NF- κ B signalling have not previously been assessed in this context. We have therefore investigated whether abrogation of classical and alternative pathway NF- κ B signalling altered murine responses to *Helicobacter felis* infection.

Methods 6-week-old female NF- κ B1 null (p50^{-/-}), NF- κ B2 null (p52^{-/-}), c-Rel null and C57BL/6 mice were infected with *H. felis* by oral gavage and culled 6 weeks later. Tissues were processed for histological analysis and immunohistochemistry.

Results *H. felis* infection of wild-type mice resulted in gastric atrophy (29% fewer parietal cells were observed in infected than in control mice (p < 0.05, 1-way ANOVA and Holm Sidak post hoc test)), a 1.5-fold increase in the number of Ki67 positive proliferating cells and no significant change in the number of active caspase 3 positive apoptotic cells. Animals with abrogated classical pathway NF- κ B signalling also developed gastric atrophy after *H. felis* infection. However, whereas infected c-Rel null animals showed similar parietal cell, proliferation and apoptotic indices to infected wild-type mice, p50^{-/-} animals

developed more severe pathology with significantly increased inflammation scores (p < 0.05, Mann-Whitney U) and a more marked 62% reduction in parietal cell number (p < 0.05, 1-way ANOVA). This was associated with significant 2.1-fold and 7.6-fold increases in the number of proliferating and apoptotic cells, respectively (p < 0.05, 2-way ANOVA). By contrast, infected p52^{-/-} mice showed much lower inflammation scores than wild-type mice (p < 0.05, MWU) following *H. felis* infection and did not develop gastric atrophy, with only 3% parietal cell loss (p < 0.05, 1-way ANOVA). In addition, these mice showed no significant changes in proliferation or apoptosis following infection with *H. felis*, and demonstrated similar proliferation and apoptotic indices to untreated wild-type mice.

Conclusion NF- κ B1 mediated signalling protects the gastric mucosa from *Helicobacter* induced atrophy, whereas alternative pathway NF- κ B signalling is required for the development of both inflammation and atrophy following infection with this organism. This supports the hypothesis that classical and alternative pathway signalling differentially affect long-term outcomes, including carcinogenesis, following *H. felis* infection in C57BL/6 mice.

Competing interests None.

Keywords gastric atrophy, *H. pylori*, NF- κ B.