

Results When patients with metastatic disease were compared with 5-year survivors significant increased gene expression was noted for heat shock protein (HSP-90), $p=0.016$ and KRAS, $p=0.046$. When the pattern of gene expression between those who survived less than a year ($n=40$) and those surviving 5 years ($n=10$) was compared then HSP-90 and GHRL were shown also to have altered expression. A variety of genes including TFT1, HSPD1, BCAS1, CAPDH, GHRL were globally enhanced among virtually all samples.

Conclusion HSP-90 a gene encoding a chaperone protein implicated in carcinogenesis exhibited increased expression in metastatic disease. Up-regulation of HSP-90 should help cancer cells adapt to stress conferring a survival advantage. Thus finding relative over-expression in cancers which have progressed to metastatic disease suggests a possible role as a prognostic marker. This study has identified candidate genes that could contribute to a prognostic model for gastric cancer utilising qNPA technology and demonstrates the up-regulation of HSP-90 and KRAS in advanced gastric cancer.

Competing interests None declared.

OC-096 TH17 CELLS ARE INCREASED IN *HELICOBACTER PYLORI* INFECTION AND MAY BE ASSOCIATED WITH PEPTIC ULCER DISEASE

doi:10.1136/gutjnl-2012-302514a.96

E Staples, R J M Ingram,* K Hussain, D P Letley, J C Atherton, K Robinson. University of Nottingham, Nottingham, UK

Introduction *Helicobacter pylori* (*Hp*) persistently colonises the stomachs of half the world's population. The majority of hosts remain asymptomatic but 10%–15% will develop peptic ulcer disease (PUD) or gastric cancer. Disease is associated with an IFN γ -producing T-helper 1 (Th1) response. Pro-inflammatory IL-17-producing T-helper 17 (Th17) cells, which express the transcription factor RORC2, are also likely to be involved. The murine Th17 response to *Hp* has been characterised but the role of human Th17 responses remains unclear.

Aim To assess the importance of Th17 cells in *Hp*+ patients. We quantified Th17 cells in the human gastric mucosa, compared *IL17*, *RORC2* and *IFNG* transcription, and investigated correlations with PUD.

Methods Gastric biopsies were donated by patients undergoing routine upper GI endoscopy at Queen's Medical Centre in Nottingham with informed consent and ethical approval. Patient characteristics: 17 with *Hp*-associated PUD, 28 with *Hp*-associated gastritis and 17 uninfected (*Hp*-). Antral *IL17* and *RORC2* mRNA levels (all patient biopsies) and *IFNG* transcription (26 *Hp*+ and 9 *Hp*- biopsies) and were quantified by real time PCR (RT-qPCR) relative to a comparator prepared from a further 14 uninfected biopsies. Frequencies of IL-17-secreting CD4 $^+$ and CD8 $^+$ T-cells were assessed by flow cytometry in gastric biopsies donated by 12 *Hp*+ and 11 *Hp*- patients.

Analysis Comparisons between *Hp*+ and *Hp*- groups and patients with and without PUD used Mann-Whitney tests. Levels of mRNA expression for paired biopsies were compared with Wilcoxon signed rank tests. Spearman's rank correlation was used to analyse relationships.

Results Increased frequencies of CD4 $^+$ IL-17 $^+$ Th17 (3.0-fold, $p=0.001$) and CD8 $^+$ IL-17 $^+$ (Tc17) cells (3.3-fold, $p=0.01$) were present in *Hp*+ samples. RT-qPCR showed that infected patients have increased mucosal *IL17* (45.0-fold, $p<0.0001$) and *IFNG* expression (3.4-fold, $p=0.006$) and showed for the first time that *RORC2* expression was also higher (2.6-fold, $p<0.0001$). There was a trend towards a correlation between *IL17* and *IFNG* expression ($r=0.39$, $p=0.051$) and relative *IL17* expression was 3.1-fold higher

than *IFNG* ($p=0.0006$). Relative *RORC2* gene expression was also 35% higher in tissue from *Hp*+ patients with PUD than in those with gastritis alone but this did not reach statistical significance ($p=0.11$).

Conclusion

1. The *Hp*-infected human stomach has increased frequencies of Th17 and Tc17 cells, and increased expression of *IL17*, *RORC2* and *IFNG*.
2. *IL17* expression was significantly higher than *IFNG* expression, though the sources of *IL17* have yet to be fully characterised. There was a trend for increased *RORC2* expression in PUD. Our data suggest that Th17 cell responses may influence the clinical outcome of *Hp* infection in patients.

Competing interests None declared.

OC-097

THE NOVEL GASTRIN/CCK2 RECEPTOR ANTAGONIST YF476 INDUCES CLINICAL RESPONSES AND IS WELL TOLERATED IN PATIENTS WITH TYPE I GASTRIC NEUROENDOCRINE TUMOURS

doi:10.1136/gutjnl-2012-302514a.97

¹A R Moore, *²L Ball, ²M Boyce, ¹A Varro, ¹D M Pritchard. ¹Institute of Translational Medicine, University of Liverpool, Liverpool, UK; ²Hammersmith Medicines Research, London, UK

Introduction Autoimmune chronic atrophic gastritis causes loss of gastric parietal cells and results in achlorhydria, increased antral gastrin production and hypergastrinaemia. In some patients this hypergastrinaemia induces hyperplasia of enterochromaffin-like (ECL) cells and leads to type I gastric neuroendocrine (carcinoid) tumour (NET) development. Most type I gastric NETs behave in an indolent fashion, but a small proportion (<1%) grow more rapidly and metastasise. Surgical antrectomy has been shown to lead to resolution of hypergastrinaemia and regression of tumours in some patients. We therefore hypothesised that pharmacological inhibition of the gastrin/CCK-2 receptor using the novel orally bioavailable competitive antagonist YF476 would also lead to clinical regression of type I gastric NETs. The aims of this study were to assess (1) whether YF476 is an effective medical treatment for type I gastric neuroendocrine tumours; (2) the safety and tolerability of YF476 treatment and (3) the effects of YF476 on biomarkers of ECL cell activity.

Methods Following ethical committee and MHRA approval, six patients with small type I NETs secondary to autoimmune chronic atrophic gastritis and hypergastrinaemia have received a 12-week course of 50 mg/day YF476. Clinical responses were monitored by six weekly upper GI endoscopy with biopsy and three weekly measurement of fasting serum gastrin and chromogranin A (CgA) concentrations. Drug tolerability has been assessed by monitoring clinical adverse events and by assessing haematological, renal and hepatic blood parameters.

Results In all six patients the number and size of NETs decreased following 12 weeks of therapy (mean reduction in size of largest tumour = 39%, mean reduction in tumour number = 40%). However no patient showed complete tumour regression after 12 weeks' therapy. Serum CgA concentrations decreased in all subjects while receiving YF476, but increased to pre-treatment levels in the three subjects in whom measurements have to date been performed 12 weeks after completing therapy. Fasting serum gastrin concentrations did not significantly change while patients received YF476. YF476 was well tolerated in all patients; no serious adverse effects were reported and there was no evidence of haematological, renal or hepatic toxicity.