major determinant of cost-effectiveness in treating arthritis. We therefore performed a meta-analysis to compare rates of dyspeptic symptoms for two commonly used therapies in high-risk patients with arthritis: 1) Coxib alone, and 2) NSAID + PPI combination.
Methods: **We performed a structured search of MEDLINE and published abstracts to identify English-language randomized trials from 1990-2004 comparing either a Coxib *vs* NSAID or NSAID + PPI combination *vs* NSAID alone in chronic arthritis. Two reviewers independently selected studies that report incident dyspeptic symptoms, defined *a priori* as "epigastric pain," "dyspepsia," and "nausea." The reviewers independently abstracted data and assigned a quality score for each study. We performed meta-analysis with a fixed effects model to compare the relative risk reduction (RRR) and Absolute Risk Reduction (ARR) of dyspeptic symptoms for Coxib *vs* NSAID and NSAID + PPI *vs* NSAID, and performed an Egger's test to assess for publication bias.**
Results: We identified 840 titles, of which 37 were selected for final review (kappa>0.9 for agreement). Meta-analysis of 32 studies (N = 60,163 patients) comparing dyspeptic symptoms between Coxibs and NSAIDs revealed a 12% RRR for Coxibs (RR = 0.88; 95% CI = 0.85-0.90) with an ARR of 3.7%. Meta-analysis of 5 studies comparing dyspeptic symptom between the NSAID + PPI combination and NSAIDs alone revealed a 66% RRR for NSAID + PPI (RR = 0.34; CI = 0.22-0.54) with an ARR of 9%. There was no evidence of heterogeneity (p>0.05) or publication bias (p>0.05) in either analysis. Compared to the NSAID strategy, the number needed to treat in order to prevent a dyspeptic symptom was 27 for Coxibs and 11 for NSAID + PPI.
Conclusions: The NSAID + PPI strategy affords a greater risk reduction for dyspepsia than Coxibs alone when compared to the common baseline of NSAIDs alone. Because there are limited head-to-head data comparing Coxibs *vs* NSAID + PPI, these meta-analytic data provide the best indirect evidence that the NSAID + PPI strategy may be superior to Coxibs in minimizing incident dyspeptic symptoms during the treatment of chronic arthritis.

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Do Proton Pump Inhibitors (ppi) Infer Additional Gastrointestinal Protection in Patients Given Celecoxib? a Retrospective Cohort Study.
Elham Rahme, Alan Barkun, Youssef Toubouti, Sophie Rochon, Jacques LeLorier

Introduction: Proton pump inhibitors are prescribed with non-selective NSAIDs to prevent and treat NSAID-associated gastropathy. It is unclear whether the utilization of a PPI with celecoxib confers additional gastrointestinal (GI) protection in elderly patients.
Objectives: To assess the association between GI hospitalizations and the use of celecoxib & PPI, celecoxib alone, NSAID& PPI or NSAID alone and to identify patient subgroups in whom the addition of a PPI to celecoxib is beneficial.
Methods: We conducted a population-based retrospective cohort study using Quebec government administrative databases. Patients 66 years of age or older were included at the dispensing date of their first filled prescription (index date) for celecoxib or an NSAID between April 1999 and December 2002. They were followed from the index-date until the occurrence of a GI hospitalization, death or the last day of supplied medication for either celecoxib or an NSAID in the study period. Cox regression models with timedependent exposure were used to compare the hazard rates of GI hospitalization between the four groups: celecoxib & PPI, celecoxib alone, NSAID& PPI or NSAID alone, adjusting for patient characteristics at the index date.
Results: A total of 332,491 patients were included. The adjusted GI hospitalization hazard rate was significantly lower among patients given celecoxib & PPI compared to those given celecoxib alone (hazard ratio (HR) 0.69, 95% CI 0.52-0.93). The adjusted hazard rate among patients given NSAID & PPI was similar to that of patients given celecoxib alone (0.98, 0.67-1.45) while the rate among patients given NSAID alone was about twice as high as that of patients given celecoxib (2.18, 1.82-2.61). Stratified analyses showed that celecoxib alone was the GI-safest treatment option in patients 66-74 years of age, not taking aspirin and who did not have other GI risk factors. In all other groups the GI-risk associated with celecoxib seemed similar to that associated with NSAIDs & PPI. The results also showed that the use of a PPI with celecoxib may be beneficial in high-risk patients aged 75 or older and in patients using aspirin.
Conclusions: Celecoxib alone seemed as GI-safe as NSAIDs combined with a PPI in most patients. PPI conferred additional protection to celecoxib for older patients and for patients taking aspirin. The addition of a PPI to celecoxib did not seem beneficial for patients without these GI-risk factors.

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Identification of a Gastric Progenitor Cell
Xiaotan Qiao, Joshua Ziel, Blair Madison, Andrea Todisco, Linda C. Samuelson, Juanita Merchant, Deborah Gumucio

The stomach and intestine develop from a tube of endoderm surrounded by mesoderm that becomes regionally pattered during ontogeny. To trace the development of intestinal identity, we placed a β-galactosidase cDNA within an intestine-specific gene locus (villin) by homologous recombination. At E15.5, β-gal is expressed throughout the intestine and in the distal half of the stomach. At E16.6, a sharp epithelial border forms, and β-gal is robustly expressed in epithelial cells on the intestinal side of this border, but not in the adjacent stomach epithelial cells (Braunstein et al., Dev. Dyn. 2002). However, closer examination of the antrum of these mice reveals rare β-gal (+) cells within the stem cell zone. These cells are small and granule free with a prominent nucleolus; they are first seen in E16.5 animals, and still present in adults. Treatment of adult mice with interferon γ (IFNγ), which induces pseudopyloric metaplasia, results in a 5-10 fold increase in the number of these cells. We were intrigued by the fact that the number of β-gal (+) cells per gastric pit was always ≤ 1. Since they were located in the stem cell zone, and induced by INFγ, a cytokine known to expand stem cells in liver and pancreas, we speculated that the β-gal (+) cells may be progenitors whose daughter cells differentiate into gastric lineages, ceasing to express β-gal. To test this, we traced the progeny of the β-gal (+) cells. Villin-Cre mice were mated to the Rosa indicator strain, R26R (in the offspring, Cre expression results in β-gal activation). We expected that if β-gal (+) cells divide to give rise to gastric cells, then entire antral pits should be β-gal positive. This outcome was observed and cells within β-gal (+) pits expressed markers of gastric pit and neck cells. We are currently isolating and characterizing these progenitors from transgenic mice expressing Villin-EGFP, generated in our laboratory. These cells may represent the first prospectively identified gastric progenitor cells; it will be important to establish their possible links to intestinal metaplasia and gastric cancer.

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Gli3 Mediates Sonic Hedgehog Dependent Development of the Glandular Stomach
Jae H. Kim, Zhen Huang, Rong Mo

The role of the Hedgehog signaling pathway in various aspects of gut development is still poorly understood. In the developing stomach, secreted Sonic (Shh) and Indian hedgehog are expressed in both distinct and overlapping regions. The loss of function of Sonic hedgehog in the stomach results in a dramatic phenotype of intestinal transformation and glandular overgrowth. These changes are reminiscent of the pre-malignant lesion, intestinal metaplasia. Consistent with these findings, in adult forms of intestinal metaplasia, the expression of Sonic hedgehog is lost. In an effort to determine if the embryonic stomach would be a suitable model of intestinal metaplasia, we conducted a mutant analysis of glandular stomach from mice mutant in Hedgehog pathway molecules. METHODS: We studied mice mutant in Shh and the transcription factors, Gli2 and Gli3. Paraffin section slides generated from dissected stomachs at E18.5 days post coitum were subjected to immunohistochemical and transmission electron microscopic analysis. Antibodies and biotin-conjugated lectins studied were against gastric markers (H + /K + -ATPase, intrinsic factor, lectins AAA and GSII), tissue markers (alpha-smooth muscle actin, PECAM, beta-tubulin III), and proliferation markers (Ki67, phospho-histone H3). RESULTS: We discovered that striking glandular expansion occurred in both the Shh and Gli3 mutant stomachs but not the Gli2 mutant stomach. In the first two cases, such glandular expansion was mostly epithelial and gastric in nature and these changes arose from increased glandular branching. Increases in proliferation were not seen, however. All gastric cell markers tested were present in all wild-type and mutant stomachs but in the cases of Shh and Gli3 mutant mice, they co-existed with early features of intestinal metaplasia. CONCLUSIONS: These data strongly suggest that Gli3 is the primary mediator through which Shh negatively directs proper specification and control of growth of the glandular stomach. We suggest that this defines an uncommon example whereby full length Gli3 activator plays a dominant physiologic role. To our knowledge, this is the first instance where the full length Gli3 activator functions in gastrointestinal development. This study furthers our understanding of the role of Hedgehog pathway molecules in this model of intestinal metaplasia. The embryonic glandular stomach may assist in further illuminating the mechanisms of gastric carcinogenesis.

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Signal Transduction Pathways Regulating the Actions of Bmp-4 in Isolated Parietal Cells.
Andrea Todisco, Saravanan Ramamoorthy, Yinghua Xiao, Colin Delaney

BACKGROUND: BMP-4 is an important regulator of cellular growth and differentiation. Expression of BMP-4 has been documented in the gastric mucosa. We previously reported that incubation of purified (>95%)canine parietal cells in primary culture with BMP-4 (20 ng/ml)induces H + /K + -ATP-ase alfa subunit gene expression. In addition, we demonstrated that protein kinase B/Akt plays an important role in the regulation of parietal cell differentiation. AIM: To explore the signal transduction pathways mediating the actions of BMP-4 in the parietal cells. METHODS: H + /K + -ATP-ase alfa subunit gene expression was examined by Northern blot analysis. Akt activation was measured by immunoprecipitation and in-vitro kinase assay using GSK3 as substrate. Inhibition of Cdcd42 and Ras function was achieved by transduction of the parietal cells with 100 moi of adenoviral vectors expressing either dominant negative Ras or Green Fluorescent Protein-tagged dominant negative Cdc42. Expression of the proteins was documented by either western blots with anti-Ras antibodies or by examination of the parietal cells by fluorescent microscopy. Control experiments were performed with the adenoviral vector expressing beta-galactosidase. Inhibition of Akt was achieved by treatment of the cells with the specific Akt inhibitor 1L-6-Hydroxymethyl-chiro-inositol 2-(R)-2-O-methyl-3-O-octadecylcarbonate (5 micromolar). Cdc42 activation was measured by affinity precipitation and western blots with anti-Cdc42 antibodies. RESULTS: BMP-4 induced Akt after 48 h of incubation and it stimulated the activation of Cdc42. The stimulatory effects of BMP-4 on Akt activation and H + /K + -ATP-ase alfa subunit gene expression were blocked by either treatment of the cells with the Akt inhibitor or by expression of dominant negative Cdc42. The specificity of this effect was confirmed by the observation that dominant negative Ras failed to block BMP-4 induction of H + /K + -ATP-ase gene expression, while it reversed the inhibitory effect on the expression of the H + /K + -ATP-ase gene, seen after prolonged exposure (48 to 72h) of the parietal cells to EGF (10 nM). CONCLUSIONS: BMP-4 induces H + /K + -ATP-ase gene expression through a signal transduction pathway that requires the sequential activation of Cdc42 and Akt. These findings provide new clues for a better understanding of the mechanisms that regulate gastric epithelial cell differentiation.

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A Potential Interplay Between Gastrin and Hedgehog in Regulating Apoptosis in the Gastric Mucosa
Mo El-Zaatari, Andrew McKenzie, Susan A. Watson

Introduction: High gastrin levels have been implicated in regulating apoptotic activity and the development of cancer. Sonic Hedgehog (Shh) has been implicated in the maintenance of gastric cancer. In addition, Gastrin and Shh have been implicated in regulating proliferation and differentiation of stem cells within gastric glands. The aim of this study was to investigate the interplay between gastrin and Shh by using mice treated with lansoprazole (a proton pump inhibitor that increases gastrin levels) and cyclopamine (Shh pathway inhibitor).
Methods: Animals were treated for 28 days with lansoprazole, cyclopamine, a combination of lansoprazole and cyclopamine, and untreated (n = 3-4 per group). Serum was collected